Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
Edited by Saul Patai
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Supplement E
The chemistry of ethers, crown ethers, hydroxyl groups and their sulphur analogues
Part 1

Edited by
SAUL PATAI
The Hebrew University, Jerusalem

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 1

Synthesis of crown ethers and analogues

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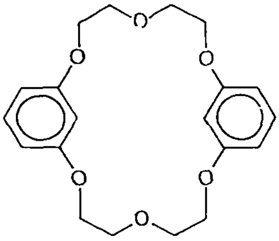
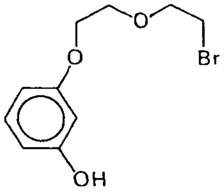
I. HISTORICAL BACKGROUND

It is interesting to reflect upon the fact that, although linear compounds containing sequential ether linkages[1-3] have occupied an important position in chemistry for many years, it is only during the last decade or so that macrocyclic polyethers and their analogues have made their major impact upon the scientific community. Alas, the fascinating complexing properties of macrocyclic polyethers were not anticipated from the comparatively mundane chemical behaviour of cyclic ethers containing up to seven atoms in their rings[4,5]. Indeed, as often happens in science, serendipity played[6] an important role in the discovery of the so-called crown ethers and the appreciation of their somewhat intriguing characteristics. Although the early literature was not devoid of reports on the synthesis of macrocyclic polyethers, their value and potential was not realized by those involved. It is easy to feel with hindsight that it should have been; but it is difficult to envisage how it could have been!

The first macrocyclic polyethers were reported by Lüttringhaus[7] in 1937 as part of an investigation of medium- and large-sized rings. For example, he obtained the 20-membered ring compound 1 in low yield after reaction of the monosubstituted resorcinol derivative 2 with potassium carbonate in pentan-1-ol. Later, the tetrafuranyl derivative 3 was isolated[8] after acid-catalysed condensation of furan with acetone and the cyclic tetramers 4 and 5 of ethylene[9] and propylene[10] oxides, respectively, were reported.



(1)



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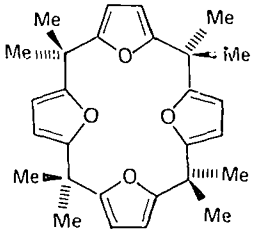

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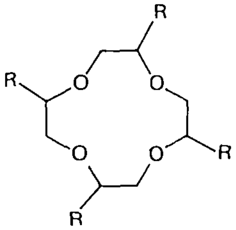
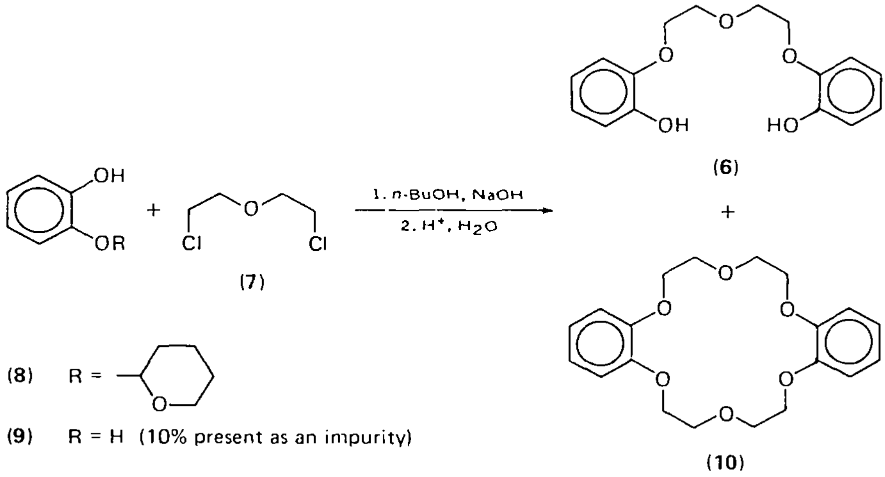


(4) R = H

(5) R = Me

Several acyclic polyethers, as well as compound (5), were found[10] to dissolve small quantities of potassium metal and sodium–potassium alloy giving unstable blue solutions of solvated electrons and solvated cations. However, it was not until 1967 that Pedersen[11] reported on the formation of stable complexes between macrocyclic polyethers and salts of alkali and alkaline earth metals. During an attempted preparation of the diphenol **6** from the dichloride **7** and the mono-protected catechol derivative **8**, the presence of 10% of catechol (**9**) as an impurity led[6] to the isolation (see Scheme 1) of the unexpected by-product which was identified as the macrocyclic polyether **10**. Given the trivial name dibenzo-18-crown-6 by Pedersen[6,12], it was found to be insoluble in methanol by itself, but became readily soluble on the addition of sodium salts. Furthermore, it was obtained in 45% yield when pure catechol (**9**) was employed[6,12] in its synthesis.



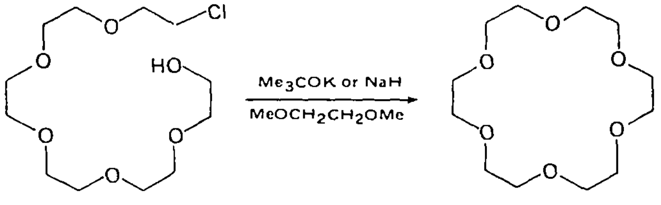
SCHEME 1.

This amazingly high yield for a macrocycle obtained on condensation of four molecules raises questions of fundamental importance which will be discussed in Section II. Following upon his initial discoveries, Pedersen[12] prepared more than 60 compounds in order to ascertain the optimum ring size and the preferred constitutional arrangement of oxygen atoms in the macrocycles for them to complex with a wide variety of cationic species. Those compounds which contain between five and ten oxygen atoms, each separated from its nearest neighbour by two carbon bridges, were found to be the most effective complexing agents. These observations have led to the synthesis of many crown ethers and analogues. This chapter is devoted to a review of the general principles and fundamental concepts governing this kind of macrocyclic ring formation as well as to a summary of the methodology and reaction types employed in the synthesis of these macrocycles.

II. FACTORS INFLUENCING YIELDS IN SYNTHESIS

A. The Template Effect

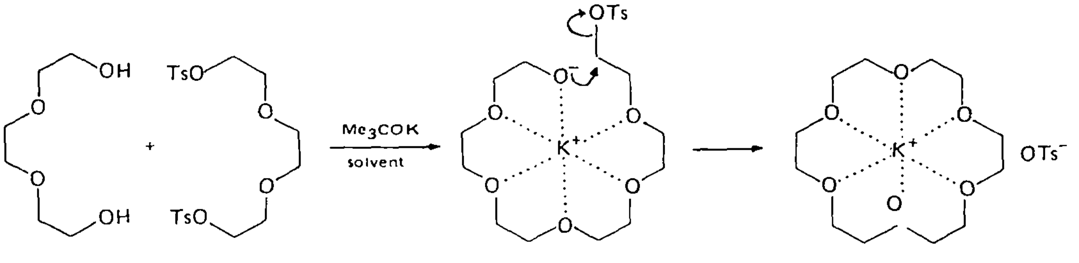
The isolation of dibenzo-18-crown-6 (**10**) in 45% yield under the conditions given in Scheme 1 prompted Pedersen[6] to observe that 'the ring-closing step, either by a second molecule of catechol or a second molecule of bis(2-chloroethyl) ether, was facilitated by the sodium ion, which, by ion–dipole interaction 'wrapped' the three-molecule intermediates around itself in a three-quarter circle and disposed them to ring-closure'. The isolation of numerous other macrocyclic polyethers in synthetically attractive yields by Williamson ether syntheses, as well as by other approaches, has led to the recognition of a template effect involving the cationic species present in the reaction mixture. Such a phenomenon is, of course, not unique to the synthesis of macrocyclic polyethers. Transition metal template-controlled reactions have been used extensively in the synthesis of (*a*) porphyrins from suitably substituted pyrroles[13,14], (*b*) corrin ring systems[15] leading to vitamin B_{12}, and more recently (*c*) large-ring lactones[16]. Evidence for the operation of a template effect in crown ether synthesis comes from a consideration of the published procedures for the preparation of 18-crown-6. Somewhat surprisingly, base-promoted cyclization of hexaethyleneglycol monochloride (**11**) in $MeOCH_2CH_2OMe$ using either Me_3COK or NaH as base led (equation 1) to very low (ca. 2% in each case) isolated yields of **12** in the first synthesis to be reported



(1)

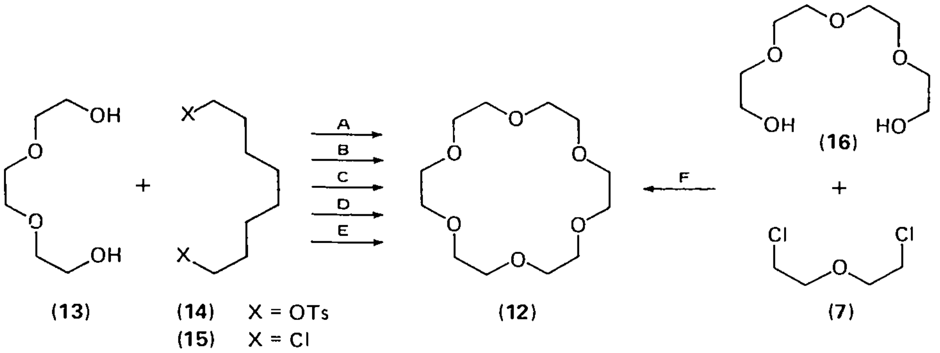
(11) (12)

by Pedersen[12]. Consequently, improved procedures were sought; these are summarized in Table 1. Depending upon the nature of the solvent, 18-crown-6 (**12**) can be obtained[17,18] in 33–93% yields from reaction of triethyleneglycol (**13**) with its ditosylate (**14**) in the presence of Me_3COK. By employing less expensive reagents, e.g. triethyleneglycol (**13**), its dichloride (**15**), and KOH in aqueous tetrahydrofuran[19] or tetraethyleneglycol (**16**), diethyleneglycol dichloride (**7**), and KOH in dry tetrahydrofuran[20] yields of 30–60% can be attained. In all these synthetic approaches to 18-crown-6 (**12**), a template effect involving the K^+ ion is an attractive proposition as, at least, a partial explanation for the high yields. In the reactions of **13** with **14** employing methods B–D in Table 1, a mechanism for cyclization (see equation 2) involving formation of an intermediate acyclic complex is envisaged[18]. The observations that (*a*) the macrocycle **12** can be isolated[17,18] as its potassium tosylate complex **12**·KOTs, (*b*) doubling the concentration of reactants in method C resulted[18] only in a decrease in the yield from 84 to 75%, and (*c*) when tetra-*n*-butylammonium hydroxide was used as the base the yield of



(13) (14) (12·KOTs)

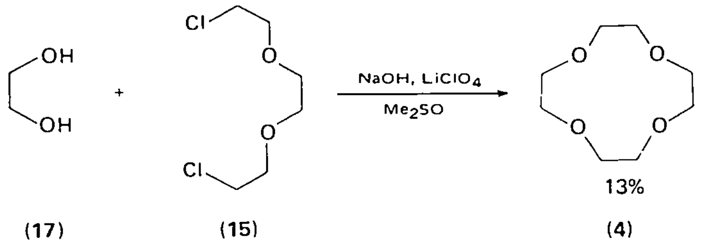
TABLE 1. 18-Crown-6 (12) syntheses


OH
O
O
OH
+
X
X
A
B
C
D
E
O
O
O
O
O
O
F
O
O
O
OH
HO
(16)
+
Cl
Cl
O
(13)
(14) X = OTs
(15) X = Cl
(12)
(7)

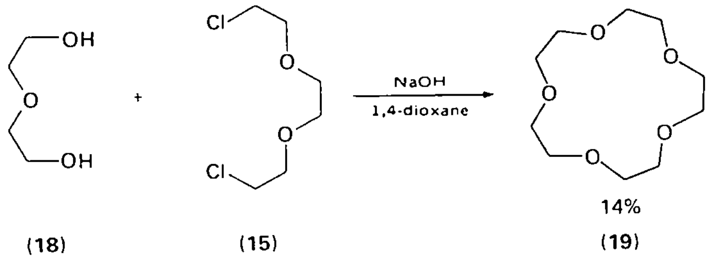
Method	X	Base	Solvent	Yield (%)	Reference
A	OTs	Me_3COK	Me_3COH/C_6H_6	33	17
B	OTs	Me_3COK	THF[a]	30–60	18
C	OTs	Me_3COK	DMSO[b]	84	18
D	OTs	Me_3COK	DME[c]	93	18
E	Cl	KOH	THF[a]/H_2O	40–60	19
F	Cl	KOH	THF[a]	30	20

[a] Tetrahydrofuran.
[b] Dimethyl sulphoxide.
[c] 1,2-Dimethoxyethane.

12 was reduced drastically[18], all support the operation of a template effect in the formation of 18-crown-6. The effect has generality. In reactions of ethyleneglycol (17) and diethyleneglycol (18) with 15 (equations 3 and 4, respectively), Li^+ and Na^+ ions have been shown[21] to template the formation of 12-crown-4 (4) and 15-crown-5 (19), respectively.

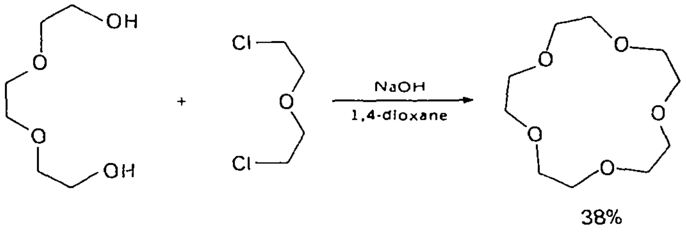

OH
OH
+
Cl
O
O
Cl
NaOH, LiClO4
Me2SO
O
O
O
O
13%
(17)
(15)
(4)

(3)


OH
O
OH
+
Cl
O
O
Cl
NaOH
1,4-dioxane
O
O
O
O
O
14%
(18)
(15)
(19)

(4)

Interestingly, however, a better yield of **19** is reported[20] for condensation (equation 5) of the diol **13** with the dichloride **7** under the same conditions as those employed in equation (4). It would be unwise to read too much into situations of this kind; isolated yields often reflect the skills of the experimentalist!

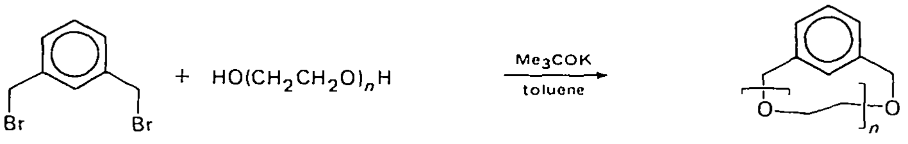


(5)

(13) (7) (19)

The optimization of template effects is probably achieved when the diameter of the cation corresponds most closely to the cavity diameter of the macrocycle being formed. Thus, for simple crown ethers, Li^+, Na^+ and K^+ ions are clearly suited to templating the syntheses of 12-crown-4 (**4**), 15-crown-5 (**19**) and 18-crown-6 (**12**), respectively. However, the effect is quite general. For example, in the acid-catalysed cyclic cooligomerization of furan and acetone to form the 16-crown-4 derivative (**3**), the addition of $LiClO_4$ to the reaction mixture increased[22] the yield of **3** from 18–20 to 40–45%. Also, large variations in yields (see Table 2) of the cyclic monomers **25**–**31** were observed[23] in condensations between the dibromide **20** and the dipotassium salts of $HO(CH_2CH_2O)_nH$ (n = 2–8). Significantly, the maximum yield (67%) occurred with the *meta*-xylyl-18-crown-5 derivative (**27**) and was virtually insensitive to variations in the rate of addition of the dibromide **20** to the glycolate derived from tetraethyleneglycol (**16**). This latter observation suggests that during the second stage of the reaction, intramolecular displacement of bromide ion to give **27** is very much faster than the competing intermolecular

TABLE 2. The dependence of isolated yields on ring size

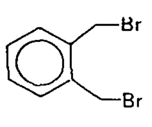


(20)

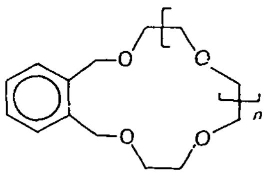
	n	Yield(%)	
(18)	2	2[a]	(25)
(13)	3	16[b]	(26)
(16)	4	67	(27)
(21)	5	49	(28)
(22)	6	18	(29)
(23)	7	21	(30)
(24)	8	21	(31)

[a] The cyclic dimer was isolated in 30% yield.
[b] The cyclic dimer was isolated in 9% yield.

reaction. A related investigation[24] on the cyclization of 1,2-bis(bromomethyl)-benzene (**32**) with polyethyleneglycolates revealed that the yields of cyclic monomers were not only dependent upon the chain length of the glycol but also on the nature of the cation present in the reaction mixture. For the 14-crown-4 (**33**), 17-crown-5 (**34**) and 20-crown-6 (**35**) derivatives, the optimum yields were obtained when Li^+, Na^+ and K^+ ions, respectively, were present with the appropriate polyethyleneglycolate. If a template effect operates in these reactions, then the comparative yields of crown ethers will reflect the relative stabilities of the cationic transition states leading to them. Perhaps, it is not surprising that, in competitive experiments, comparative yields of crown ethers reflect[24] their complexing ability towards the cation in question!

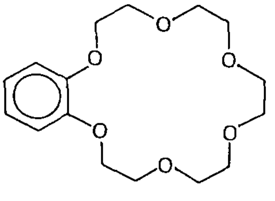


(32)

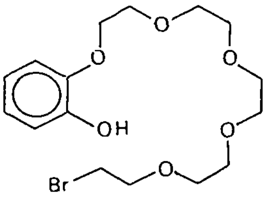


(33) $n = 1$
(34) $n = 2$
(35) $n = 3$

Kinetic evidence[25] for a template effect has also been presented recently. The influence of added Group IA and IIA metal ions upon the rate of formation of benzo-18-crown-6 (**36**) from the crown's percursor (**37**) in aqueous solution at +50°C was investigated with Et_4N^+ ions as the reference. The initial concentration (ca. 2×10^{-4} M) of **37** was made sufficiently dilute to make any contribution from second-order dimerization negligible. When the kinetics were followed spectrophotometrically by monitoring the disappearance of phenoxide ions, first-order behaviour was observed in all cases. Although Li^+ ions had a negligible effect upon the cyclization rate, significant rate enhancements were observed when Na^+ and K^+ ions were present at concentrations between ca. 0.1 and 1.0 M. Most strikingly, there were dramatic increases in cyclization rates when Ba^{2+} and Sr^{2+} ions were present in low concentrations (<0.1 M) indicating the remarkable templating properties of these Group IIA metal ions. Thus, it would appear that rates of cyclization reflect a close correspondence between the catalytic effect and the relative complexing ability of crown ethers towards the cations used in their synthesis.

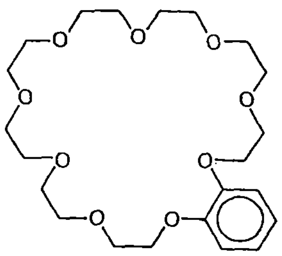


(36)



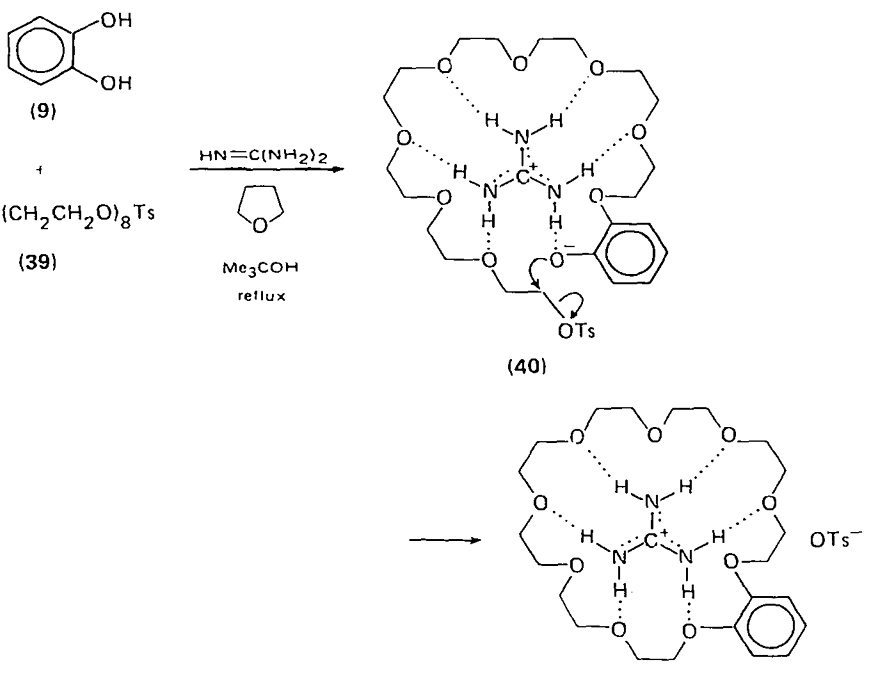
(37)

Organic cations can also act as templates for crown ether syntheses. The bases, Me_3COK, $HN{=}C(NH_2)_2$ and $HN{=}C(NMe_2)_2$ have all been examined[26,27] under similar reaction conditions for their comparative abilities to template the synthesis of benzo-27-crown-9 (**38**) from catechol (**9**) and octaethyleneglycol ditosylate (**39**).



(38)

Yields of 38 of 59, 23 and 2%, respectively, indicate that K$^+$ ion > H$_2$N=C(NH$_2$)$_2^+$ ion > H$_2$N=C(NMe$_2$)$_2^+$ ion in bringing together the reacting centres of the acyclic intermediate during the final cyclization step. In particular, the ten fold difference in yields between the condensations employing HN=C(NH$_2$)$_2$ and HN=C(NMe$_2$)$_2$ as bases suggests that in the former case an intermediate acyclic complex (**40**) involving six hydrogen bonds might stabilize the transition state leading to the complex 38 ·H$_2$N=C(NH$_2$)$_2$OTs of benzo-27-crown-9 as shown in equation (6).



(9)

+

TsO(CH$_2$CH$_2$O)$_8$Ts

(39)

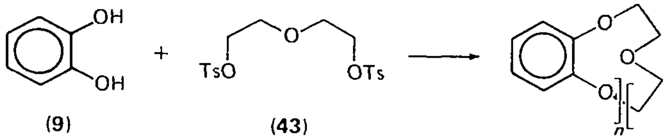
(40)

(6)

(38 ·H$_2$N=C(NH$_2$)$_2$OTs)

The abilities of Me$_3$COK, HN=C(NH$_2$)$_2$, HN=(NMe$_2$)$_2$ and (MeCH$_2$CH$_2$CH$_2$)$_4$-N$^+$OH$^-$ to produce benzo-9-crown-3 (41), dibenzo-18-crown-6 (10) and tribenzo-27-crown-9 (42) from catechol (9) and diethyleneglycol ditosylate (43) were also compared[27]. The results recorded in Table 3 show that the large nontemplating H$_2$N=C(NMe$_2$)$_2^+$ and (MeCH$_2$CH$_2$CH$_2$)$_4$N$^+$ ions favour the formation of **41** while K$^+$ ion > H$_2$N=C(NH$_2$)$_2^+$ ion > (MeCH$_2$CH$_2$CH$_2$)$_4$N$^+$ ion > H$_2$N=C(NMe$_2$)$_2^+$ ion in

TABLE 3. Effect of base on yields of crown ethers when catechol (9) was reacted with diethyleneglycol ditosylate (43) in tetrahydrofuran–Me_3COH under reflux[27]



(9) (43)

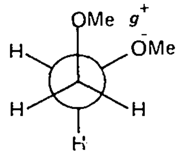
(41) $n = 1$
(10) $n = 2$
(42) $n = 3$

Base	Percentage yields based on catechol		
	(41)	(10)	(42)
Me_3COK	5	44	20
$HN{=}C(NH_2)_2$	4	25	11
$HN{=}C(NMe_2)_2$	11	6	0
$(MeCH_2CH_2CH_2)_4N^+OH^-$	15	23	5.5

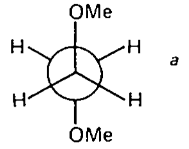
assembling four molecules to produce **10** and six molecules to produce **42**. The ability of the $H_2N{=}C(NH_2)_2^+$ ion to favour the formation of **10** and **42** suggests that it acts as a template during the final unimolecular reactions which produce dibenzo-18-crown-6 (**10**) and tribenzo-27-crown-9 (**42**) although it does so less effectively than K^+ ion.

B. The Gauche Effect

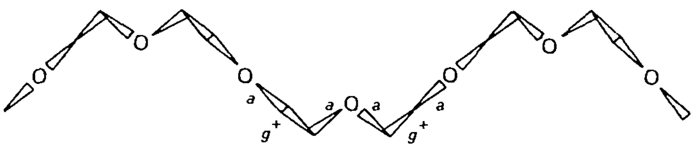
There is overwhelming physical and chemical evidence[28-31] that the C—C bond in $-OCH_2CH_2O-$ units prefers to adopt the *gauche* conformation. Infrared spectroscopy indicates[32] that, although the simplest model compound, 1,2-dimethoxyethane, comprises a range of conformational isomers including both *gauche* (**44a**) and *anti* (**44b**) conformations in the liquid phase at +25°C, it adopts only the *gauche* conformation in the crystal at −195°C. (The descriptors *g* and *a* are employed here beside formulae to denote *gauche* and *anti* torsional angles, respectively. In addition, *gauche* torsional angles are described as g^+ or g^--according as to whether they exhibit positive or negative helicities.) In the crystal, polyoxyethylene adopts[33] only *gauche* conformations about the C—C bonds with the expected *anti* preferences for the C—O bonds. A helical conformation (**45**) results. Comparisons between empirical and calculated physical properties indicate[34] that this is also the preferred conformation in solution.



(44a)

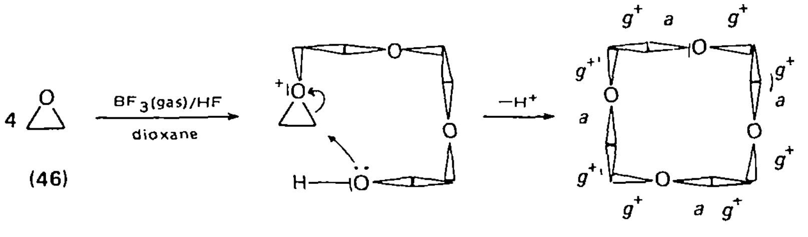


(44b)



(45)

The *gauche* effect would appear to play a significant role in crown ether syntheses in appropriate situations. For example, even though it is not the most stable product thermodynamically, 12-crown-4 (4) is the major product formed[35] from the cyclooligomerization of ethylene oxide (46) using BF_3 as catalyst and HF as cocatalyst. Crown ethers up to the undecamer (33-crown-11) have been separated and identified by gas–liquid chromatography. The product distribution recorded in Table 4 is not influenced markedly by changes in temperature or reactant concentrations. These observations suggest a mechanism for cyclooligomerization compatible with a helical shape for the growing oligooxyethylene chain (47), which brings the reactive centres, as shown in equation (7), into a good relative disposition for cyclization after addition of the fourth ethylene oxide residue.

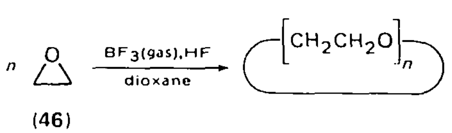


(7)

(47) (4)

Template effects can operate in conjunction with the *gauche* effect. Thus, the presence of certain suspended metal salts during BF_3-catalysed cyclooligomerization of **46** leads[35,36] to the exclusive production of 12-crown-4 (4), 15-crown-5 (19) and 18-crown-6 (12). In addition to other factors, the product distribution depends (see Table 5) upon the nature of the cation. The experimental procedure, which now forms the basis of a successful commercial route to crown ethers, involves the addition of **46** to a cold suspension of the insoluble metal salt in dioxane containing the catalyst (e.g. BF_3, PF_5 or SbF_5). As the salt dissolves, the metal ion–crown complexes either precipitate or afford a separate liquid phase. The complexes may be separated without prior neutralization leaving the mother liquors

TABLE 4. Product distribution[35] from the acid-catalysed oligomerization of ethylene oxide (46)



(46)

n	2	3	4	5	6	7	8	9	10	11	>11
Percentage yield	40	1	15	5	4	3	2	2	1	1	25

TABLE 5. The product distribution of crown ethers resulting from polymerization of ethylene oxide (46) by BF_3 as catalyst in 1,4-dioxane in the presence of suspended anhydrous salts[36]

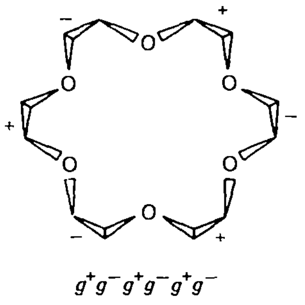
Salt	Ionic diameter of cation (Å)[b]	Cavity diameter (Å)[a] and product distribution (%)		
		12-Crown-4 (4) 1.2–1.4	15-Crown-5 (19) 1.7–2.2	18-Crown-6 (12) 2.6–3.2
$LiBF_4$	1.36	30	70	0
$NaBF_4$	1.94	25	50	25
KBF_4	2.66	0	50	50
KPF_6	2.66	20	40	40
$KSbF_6$	2.66	40	20	40
$RbBF_4$	2.94	0	0	100
$CsBF_4$	3.34	0	0	100
$Ca(BF_4)_2$	1.98	50	50	0
$Sr(BF_4)_2$	2.24	10	45	45
$Ba(BF_4)_2$	2.68	10	30	60
$AgBF_4$	2.52	35	30	35
$Hg(BF_4)_2$	2.20	20	70	10
$Ni(BF_4)_2$	1.38	20	80	0
$Cu(BF_4)_2$	1.44	5	90	5
$Zn(BF_4)_2$	1.48	5	90	5

[a] Estimated from Corey–Pauling–Koltun molecular models.

[b] Values taken from *Handbook of Chemistry and Physics* (Ed. R. C. Weast), 56th ed., Chemical Rubber Co., Cleveland, Ohio, 1975.

for use in further reactions. The crown ethers are most simply liberated from their complexes by pyrolysis under reduced pressure. The salt which remains behind may be reused without purification. The crown ethers are obtained pure (*a*) by fractional distillation, or alternatively (*b*) by fractional crystallization of their complexes prior to pyrolysis. The results in Table 5 show that, for the Group IA and IIA metal ions at least, the relative yield of a particular crown ether is highest when its cavity diameter corresponds most closely to the ionic diameter of the metal ion present during its synthesis. The cation seems to mediate the reaction by promoting appropriate folding of the growing polymer chain prior to cyclization (i.e. the *gauche* and template effects are operating in unison) as well as by protecting the crown ethers which are formed from subsequent degradation. The positive charge on the metal in the complex prevents the formation of the oxonium salt which would initiate degradation.

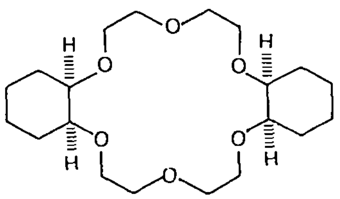
So far, we have seen that the *gauche* and template effects can operate together to increase the rate of cyclization by raising the probabilities that molecules are in favourable conformations and dispositions relative to each other to react. However, the implications of stereochemical control appear to go deeper than the *gauche* effect alone in the templated reactions of oligooxyethylene fragments to give crown ethers. The complete stereochemistry of the acyclic precursor can become important. In order to examine this claim, consider what is known about the structures of complexes of 18-crown-6 (12). There is evidence that they adopt the 'all-*gauche*-OCH_2CH_2O' conformation (12a) with D_{3d} symmetry in solution[37] as well as in the crystalline state[38–41]. Moreover, the association constants (K_a) and the corresponding free energies of association (ΔG) for the 1 : 1 complexes formed[42–44] between Na^+Cl^- and K^+Cl^- in MeOH and 18-crown-6 (12) are considerably greater (see Table 6) than the corresponding K_a and ΔG values for the



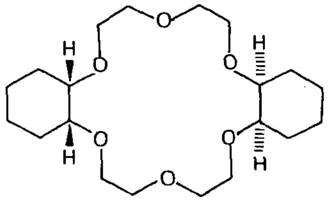
$g^+g^-g^+g^-g^+g^-$

(12a)

isomeric[43] dicyclohexano-18-crown-6 derivatives (48–51). Figure 1 shows that the *cis–cisoid–cis* (48a) and *cis–transoid–cis* (49a) isomers (*a*) can attain an 'ideal' complexing conformation and (*b*) are 'flexible' to the extent that the 18-membered ring can undergo inversion ($g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$); the *trans–cisoid–trans* (50a) and *trans–transoid–trans* (51a) isomers are 'rigid' to the extent that the 18-membered ring cannot undergo inversion and, whilst 50 can attain an 'ideal'



(48)



(49)

TABLE 6. The log K_a (based on K_a in M^{-1}) and ΔG values for the formation of 1:1 complexes with Na^+Cl^- and K^+Cl^- in MeOH

	Na^+			K^+		
Crown ether	log K_a^b	ΔG^c	$\Delta\Delta G^c$	log K_a^b	ΔG^c	$\Delta\Delta G^c$
18-Crown-6 (12)	$4.32^{d,e}$	-5.9^e	–	$6.10^{d,f}$	-8.3^f	–
cis–cisoid–cis-DCH-18-6[a] (48)	4.08^d	−5.5	0.4	6.01^d	−8.2	0.1
cis–transoid–cis-DCH-18-C-6[a] (49)	3.68^d	−5.0	0.9	5.38^d	−7.3	1.0
trans–cisoid–trans-DCH-18-C-6[a] (50)	2.99^g	−4.0	1.9	4.14^g	−5.6	2.7
trans–transoid–trans-DCH-18-C-6[a] (51)	2.52^g	−3.4	2.5	3.26^g	−4.3	4.0

[a] DCH-18-C-6 ≡ Dicyclohexano-18-crown-6.

[b] Obtained for the equilibrium, $M^+ n$MeOH + Crown $\rightleftharpoons$ M Crown$^+$ + nMeOH, at 20–25°C by potentiometry with ion selective electrodes.

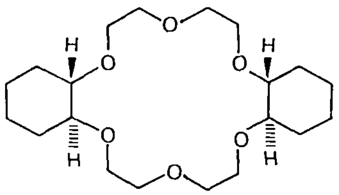
[c] In kcal/mol. The $\Delta\Delta G$ values correspond to the differences in the ΔG values between the particular crown ether and 18-crown-6 (12).

[d] Values from Reference 42.

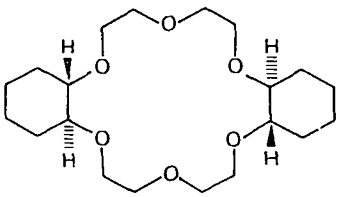
[e] Values for log K_a, ΔG, ΔH (kcal/mol), and $T\Delta S$ (kcal/mol) determined calorimetrically (Reference 44) at 25°C are 4.36, −6.0, −8.4 and −2.4, respectively.

[f] Values for log K_a, ΔG, ΔH and $T\Delta S$ determined calorimetrically (Reference 44) at 25°C are 6.05, −8.2, −13.4 and −5.2, respectively.

[g] Values from Reference 43.

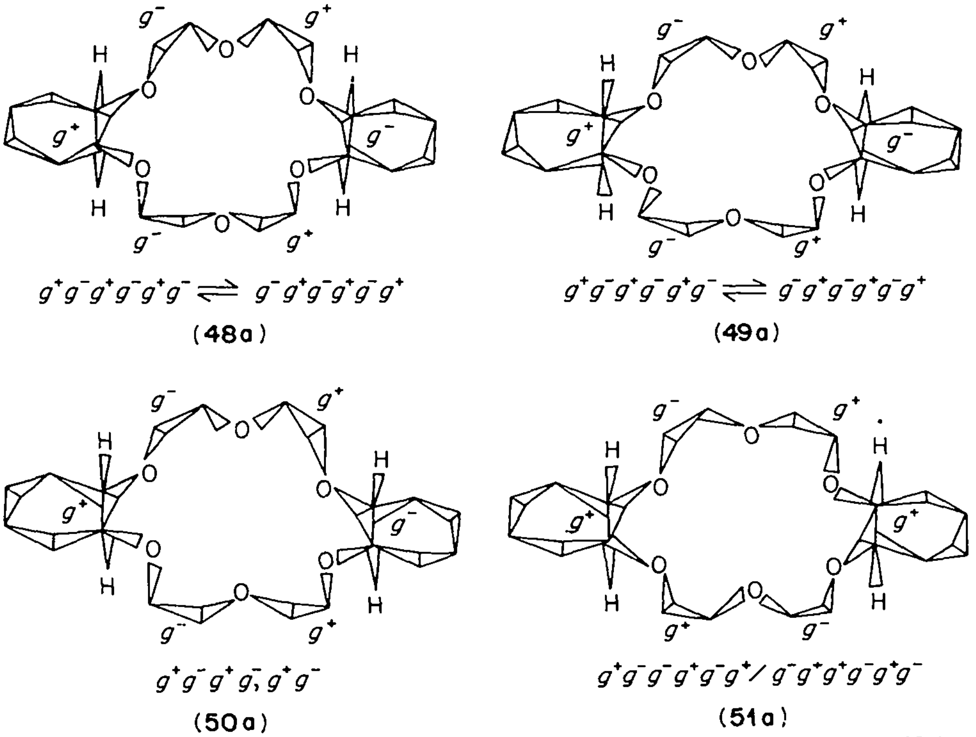


(50)



(51)

$g^+g^-g^+g^-g^+g^-$ conformation (**50a**), **51** is unable to adopt this 'ideal' complexing conformation. In view of the fact that it is a racemic modification[43], it has a $g^+g^-g^-g^+g^-g^+/g^-g^+g^+g^-g^+g^-$ conformation (**51a**). It is clear from the results in Table 6 and the stereochemical features highlighted in Figure 1 that a qualitative correlation exists[31,45,46] between the $\Delta\Delta G$ values and the conformation of the 18-crown-6 ring in **48**–**51**. Fine stereochemical differences involving only conformational features and gross stereochemical differences involving both configurational and conformational features can be differentiated. An example of gross stereochemical control in synthesis appears to be operative during the attempted preparation[47] as shown in Scheme 2 of **50** and **51** by condensation of (±)-*trans*-2,2′-(1,2-cyclohexylidene)dioxyethanol (**52**) with its ditosylate (**53**) in benzene in the presence of Me_3COK. Only **50** was isolated with a comment[47] about 'the marked tendency for pairing of (+) with (−) in the cyclization to give the *meso* form'. On formation of



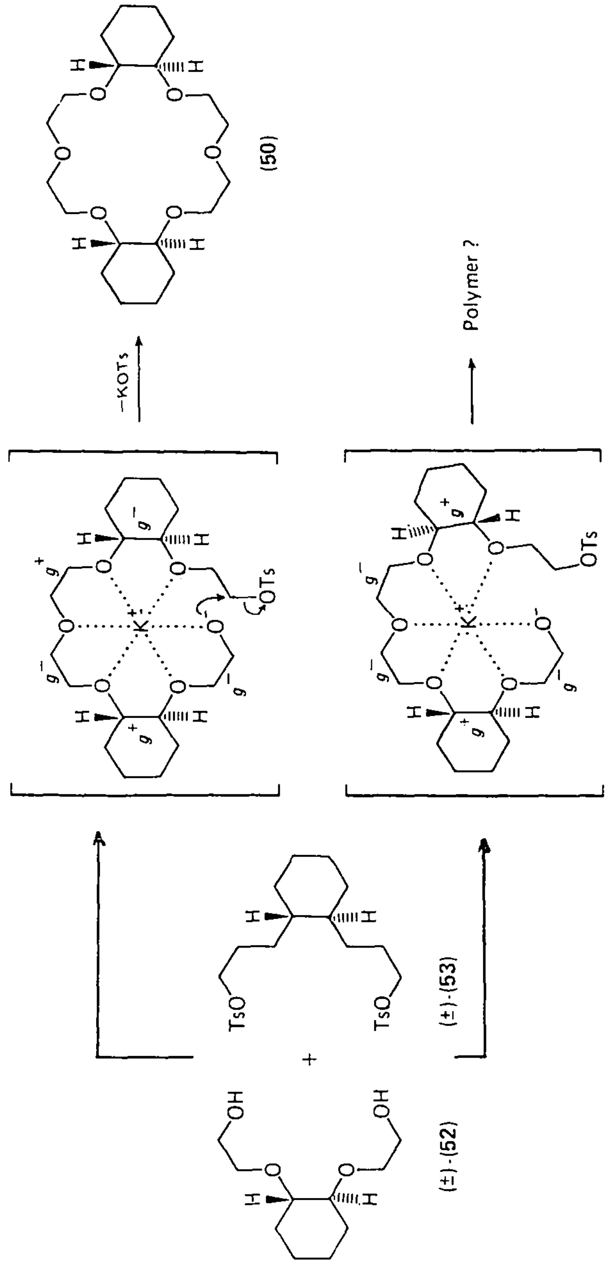
$g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$ (48a)

$g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$ (49a)

$g^+g^-g^+g^-g^+g^-$ (50a)

$g^+g^-g^-g^+g^-g^+/g^-g^+g^+g^-g^+g^-$ (51a)

FIGURE 1. The designations of conformational types for the di-*cis* (48a) and (49a) and di-*trans* (50a) and (51a) isomers of dicyclohexano-18-crown-6.


(±)-(52)
+
(±)-(53)
TsO
OH
−KOTs
OTs
K
(50)
Polymer ?
g+
g−

SCHEME 2.

the first C—O bond in both of the intermediates in Scheme 2, the relative configurations of the products are established. The observed steroselectivity ensues from the greater stabilization through efficient templating action of K^+ ions on the transition state leading to **50** than on the transition state leading to **51**. In the second instance, intermolecular reaction to give polymer is probably competing successfully with the intramolecular reaction. Thus, it would even seem to be possible to control diastereoisomeric ratios during cation-templated syntheses of chiral crown ethers. This possibility, which relates to the principle[31,45] that noncovalent bonds are highly directional in character, is capable of considerable exploitation.

C. Other Effects

The synthesis of medium- and large-sized ring compounds is usually a highly inefficient process. As we have seen in Sections II.A and II.B, success in crown ether syntheses depends strongly upon preorganized reactants being brought together under some external influence and then the acyclic precursor having the 'correct' stereochemical orientation in the final cyclization step. The operation of template and/or *gauche* effects helps to overcome unfavourable entropic factors which mitigate against the formation of highly ordered species. Rigid groups (e.g. benzo groups) can also increase[48] the rate of cyclization by reducing the number of conformational possibilities for the reactants and providing favourable stereochemistries for both inter- and intra-molecular reactions. Historically, reactions to form macrocyclic compounds have often been performed[49] under high dilution conditions. This meant that all reactions including cyclizations had to be fast in order to maintain very low concentrations of reactants and so suppress the formation of acyclic oligomers with respect to cyclic products. Although it is seldom possible to employ fast reactions to prepare crown ethers because C—O bond formation is relatively slow, it often proves[48] worthwhile to use high dilution conditions in the syntheses of aza- and thia-crown ethers. The ease of forming C—N and C—S bonds relative to forming C—O bonds makes the use of high dilution technology attractive from the point of view of obtaining higher yields for these derivatives than could be obtained by conventional means.

In this section on factors influencing yields in synthesis we have tried to highlight those areas which have particular relevance to crown ether syntheses. It is obvious that other factors such as (*a*) the nature of the leaving group in displacement reactions, (*b*) the solvent in which the reaction is conducted, (*c*) the temperature of the reaction mixture etc. will all have a bearing on the outcome of a particular synthetic step. Also, particular reaction conditions often pertain to the more specialized approaches to crown ether synthesis. These will be discussed as and when necessary in Section IV on syntheses exemplified.

III. DESIGN AND STRATEGY

The well-known receptor properties of crown ethers and their analogues provide one of the main incentives for their synthesis. Indeed, the design of receptor molecules for appropriate substrates is becoming more of a science than an art every day. During the embryonic phase of development of this science, the use of space-filling molecular models has become an indispensable adjunct and activity in the design stage and has generated a lot of new synthetic strategies and goals in different laboratories around the world. Nonetheless, it should be pointed out that, as far as molecular models are concerned, the framework variety have an important role to play in highlighting subtle stereochemical features such as those discussed in Section II.B. However, there is little doubt that design and strategy is going to rely more and more in future upon model building with the aid of high-speed electronic computers.

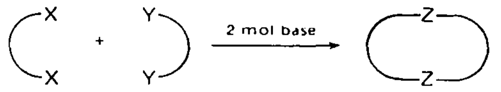
The design of synthetic receptor molecules which complex with (*a*) metal and other inorganic (e.g. H^+, NH_4^+ and H_3O^+ ions) cations and (*b*) inorganic anions (e.g. Cl^-, Br^- and N_3^-) has been extensively reviewed by Lehn[48,50,51]. Recommended strategies to be adopted in synthesis have also been outlined[48] in considerable detail. In several reviews[52-55], Cram has discussed the design of achiral and chiral crown ethers which complex with organic cations (e.g. RNH_3^+, RN_2^+ and $H_2N{=}C(NH_2)_2^+$ ions). He has appealed to axial chirality in the shape of resolved binaphthyl units in the elaboration of chiral crown ethers as synthetic analogues to Nature's enzymes and other receptor molecules. The attractions of utilizing natural products – and particularly carbohydrates – as sources of inexpensive chirality is one that the present authors[31,45,56] have championed.

IV. SYNTHESES EXEMPLIFIED

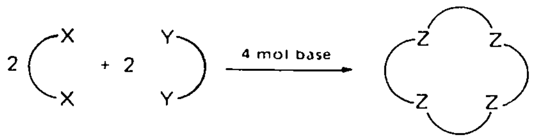
In this section, we shall deal with synthetic methods for preparing achiral crown compounds, chiral crown compounds, and macro-bi-, -tri- and -poly-cyclic ligands. We shall also include a brief mention of 'acyclic crown compounds'. Our treatment overall will be far from exhaustive! Fortunately, a number of lengthy reviews[57-60] have appeared which are highly comprehensive in their coverage of the literature.

A. Monocyclic Multidentate Ligands

Equations (8)–(11) illustrate the most common approaches (cf. Reference 48) employed in the preparation of monocyclic multidentate ligands. Experimentally, the approaches illustrated in equations (8) and (9) represent the most facile 'one-pot' methods. Depending upon the nature of X—X and Y—Y, two-molecule (equation 8) and four-molecule (equation 9) condensations may compete. The approach indicated in equation (10) suffers from the disadvantage that the intermediate X–Z–Y may undergo intramolecular cyclization as well as intermolecular



(8)



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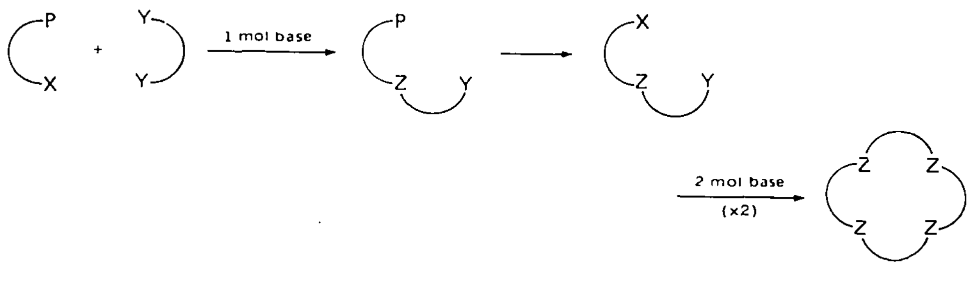
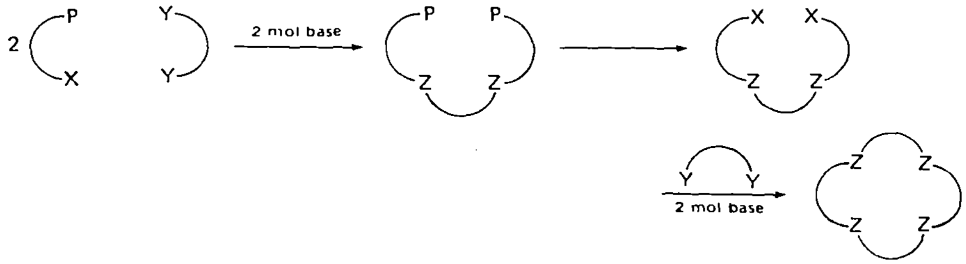


(10)

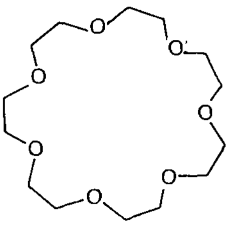


(11)

cyclization. The stepwise approach outlined in equation (11) is a versatile one and usually affords good yields of macrocyclic ligands. Despite the low yields in general, the approaches depicted in equations (8) and (9) are preferable for the synthesis of 'simple' monocyclic multidentate ligands. The approaches depicted in equations (10) and (11) are important in preparing macrocyclic ligands incorporating a variety of different structural features.

1. *All-oxygen systems*

The general method for preparing macrocyclic polyethers is the Williamson ether synthesis[61] which involves the displacement of halide ions from a dihaloalkane by the dianion derived from a diol. Common adaptions of this reaction utilize sulphonate esters – usually toluene-*p*-sulphonates – as leaving groups. Equations (8)–(11) illustrate (where —— = a carbon chain, X = a leaving group, Y = OH, Z = a heteroatom and P = a base-stable protecting group) the general approaches employed in the assembly of macrocyclic compounds. The base employed is typically NaH, NaOH, KOH or Me_3COK. The solvent is typically $Me(CH_2)_3OH$, Me_3COH, $MeOCH_2CH_2OMe$, Me_2SO or tetrahydrofuran. Reactions are usually conducted at room temperature or just above. The synthesis of 12-crown-4 (**4**), 15-crown-5 (**19**) and 18-crown-6 (**12**) have been discussed in considerable detail already in Section II.A. 21-Crown-7 (**54**) was obtained[17] in 26% yield when triethyleneglycol (**13**) was reacted with the ditosylate of tetraethyleneglycol (**16**) and Me_3COK in benzene. Using similar conditions, 24-crown-8 (**55**) was isolated[17] in 15% yield from condensation of tetraethyleneglycol (**16**) with its ditosylate. In tetrahydrofuran, reaction between tetraethyleneglycol (**16**) and triethyleneglycol ditosylate (**14**) in the presence of Me_3COK gave[18] **54** in 18% yield. Substituents can, of course, be introduced into the polyether ring with little difficulty. For example, the long-chain alkyl-substituted 18-crown-6 derivatives **56–58** can be obtained[62] in four steps from the corresponding alkenes as depicted in equation (12). This reaction sequence illustrates one method of preparing substituted 'half-crown' diols for use in crown ether syntheses. Double bonds can also be introduced into polyether rings. The stilbenediol dianion can be generated[63] by reaction of benzoin with NaOH in



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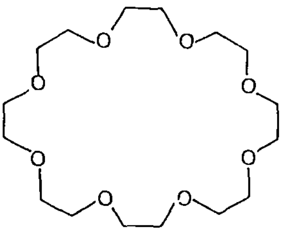
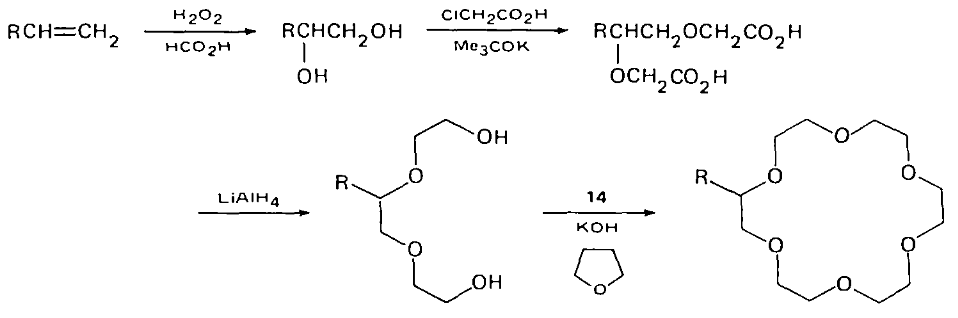


(55)

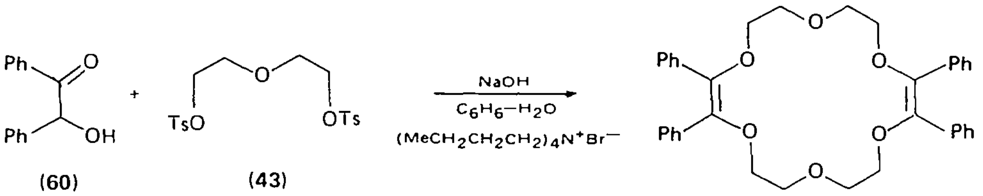


RCH=CH2
H2O2
HCO2H
RCHCH2OH
OH
ClCH2CO2H
Me3COK
RCHCH2OCH2CO2H
OCH2CO2H
LiAlH4
R
O
OH
14
KOH

(12)

(56) $R = (CH_2)_9Me$
(57) $R = (CH_2)_{13}Me$
(58) $R = (CH_2)_{20}Me$

water under phase-transfer conditions. Subsequent reaction of the dianion with difunctional alkylating reagents gives cyclic derivatives in which the double bonds have (*Z*) configurations. The 18-crown-6 derivative (**59**) has been prepared[63] (equation 13) in 19.5% yield by reaction of benzoin (**60**), NaOH and diethyleneglycol ditosylate (**43**) in a $C_6H_6-H_2O$ two-phase system using $(MeCH_2CH_2CH_2)_4N^+Br^-$ as a phase-transfer catalyst. The accessibility of the unsaturated 18-crown-6 derivative (**59**) and the possibility of chemical modification of the prochiral C=C double bonds could prove valuable in the synthesis of substituted 18-crown-6 derivatives.

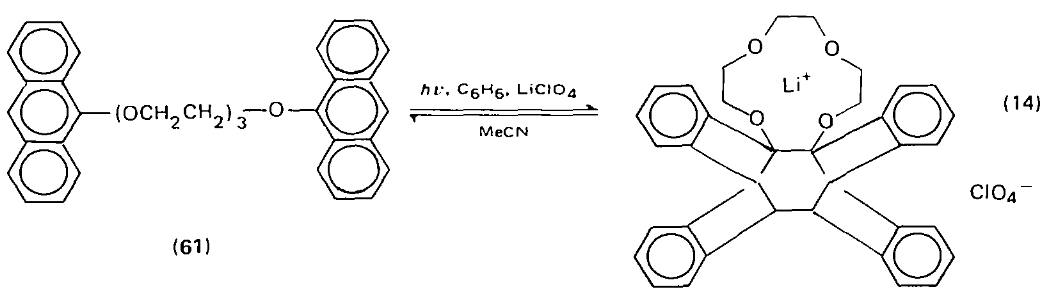


Ph
O
OH
+
TsO
OTs
NaOH
C6H6—H2O
(MeCH2CH2CH2)4N+Br−

(13)

(60) (43) (59)

Although alkylations to give macrocyclic polyethers provide the most important synthetic routes to the compounds, other approaches are available. As we have seen already in Section II.B, the acid-catalysed cyclooligomerization of ethylene oxide (**46**) is important[35,36] from a commercial angle. One report[30] of a photochemically generated, Li^+ ion-locked 12-crown-4 derivative is intriguing. Irradation of the bisanthracene **61** in benzene in the presence of $Li^+ClO_4^-$ yields the complex **62**·$LiClO_4$ which is thermally stable but dissociates easily on addition of MeCN



(OCH2CH2)3—O
hν, C6H6, LiClO4
MeCN
O
Li+
ClO4−

(14)

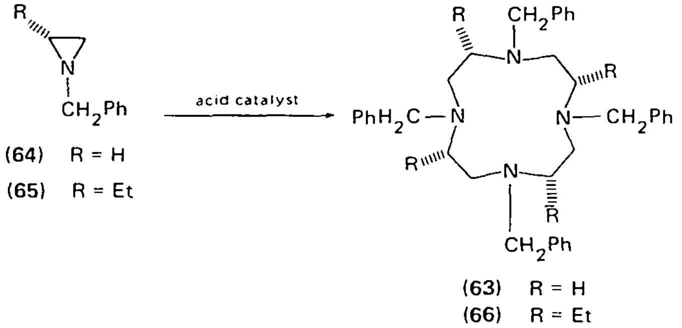
(61)

(62 · $LiClO_4$)

(equation 14). Finally, a method[64] of synthesizing macrocyclic polyethers by acid-catalysed insertion of an olefin into cyclic acetals in a one-step process lacks wide appeal because of (*a*) the mixtures of compounds which can result, and (*b*) the presence of three carbon units – which is generally detrimental to good complexing ability – in the products.

2. *All-nitrogen systems*

A wide variety of cyclic polyamines have been synthesized and listings of those prepared up to mid-1975 have been produced[57,59]. Several reviews have been published describing their synthesis[13,65,66] and the distinctive coordination chemistry and biological significance of their complexes[67]. Since cyclic polyamines are only distantly related to crown ethers, a detailed discussion is outside the scope of this review. A few examples will be cited, however. The tetraaza-12-crown-4 derivative **63** can be isolated[68] (see equation 15) in 96% yield from the reaction between *N*-benzylaziridine (**64**) and toluene-*p*-sulphonic acid in refluxing aqueous ethanol. It appears to be a unique reaction for **64** since aziridine itself and other *N*-substituted derivatives give only high molecular weight polymers. Chiral 1-benzyl-2-(*R*)-ethylaziridine (**65**) ring-opens[69] in the presence of BF_3-Et_2O at room temperature to give **66**. As a result of ring-opening exclusively at the primary centre only one constitutional isomer is produced (equation 15) in which the configurations at the chiral centres are preserved. A more general method of preparing aza-analogues of crown ethers has appeared[70]. The compounds **67–70** were synthesized by condensation of α,ω-ditosylates with the preformed sodium salts of appropriate α,ω-bissulphonamides in $HCONMe_2$ as shown in equation (16). The free amines can be obtained by acid-catalysed hydrolysis of the cyclic sulphonamides, followed by treatment of the salts with base. It does not appear that Na^+ ions act as templates since their replacement with Me_4N^+ ions did not lead to a



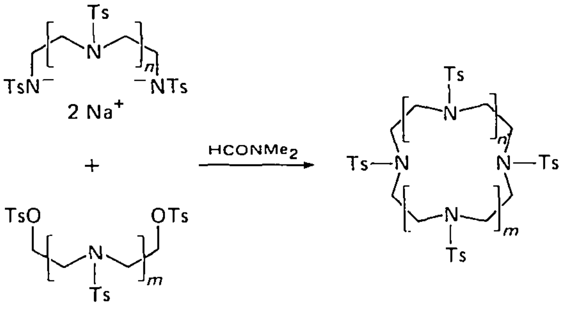
(64) R = H

(65) R = Et

(63) R = H

(66) R = Et

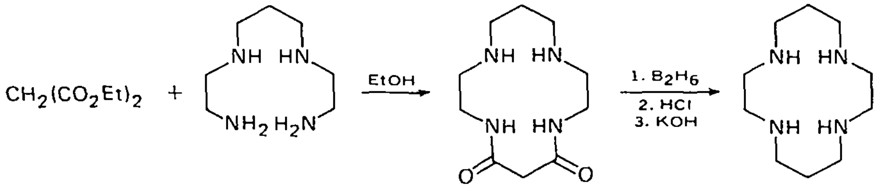
(15)



	n	*m*	Yield (%)
(67)	1	1	80
(68)	1	2	83
(69)	1	3	75
(70)	2	3	45

(16)

significant decrease in the yield of the cyclic tetramer. Macrocyclic polyamines can be obtained as shown in equation (17) by reduction of bislactam precursors which are readily available from the condensations of α,ω-diamines with diesters. For example, reaction of 71 with diethyl malonate (72) in ethanol under reflux gave[71] the cyclic bislactam (73) (30%) which afforded the tetraaza-14-crown-4 derivative (74) on diborane reduction.

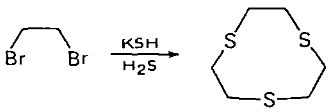


(17)

(72) (71) (73) (74)

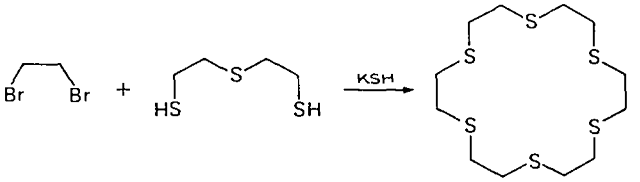
3. *All-sulphur systems*

The synthesis of polythiaethers is of interest in many areas of chemistry and has been the subject of an extensive review[72]. The first perthiacrown compounds were described over 40 years ago, some 30 years before the preparation of the oxygen analogues by Pedersen. The synthesis of trithia-9-crown-3 (75) as shown in equation (18) from $BrCH_2CH_2Br$ (76) and alcoholic KSH saturated with H_2S was described[73] in 1920. The isolation of hexathia-18-crown-6 (77) in very low yield (<2%) from the reaction (see equation 19) between the dimercaptan (78) and $BrCH_2CH_2Br$ (76) in the presence of KSH was reported[74] in 1934. More recently, 77, as well as tetrathia-12-crown-4 (79) and pentathia-15-crown-5 (80) were prepared[75] by reaction of the appropriate α,ω-dimercaptans with α,ω-dihalopolythiaethers in yields of 25–35, ca. 6 and 11%, respectively. Yields can be improved[76] by resorting to the use of high-dilution techniques.



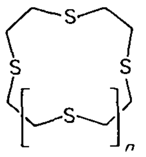
(18)

(76) (75)



(19)

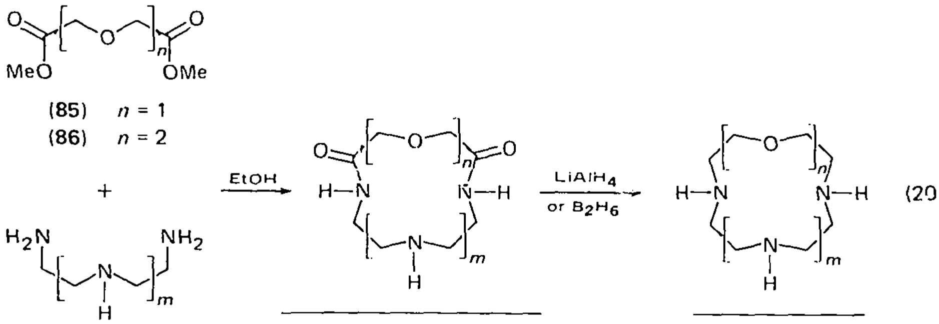
(76) (78) (77)



(79) $n = 1$
(80) $n = 2$

4. *Oxygen and nitrogen systems*

The variety and number of mixed heteroatom macrocycles that have been synthesized to date is immense. Fortunately, lists of mixed heteroatom macrocycles reported in the literature up to mid-1977 have been compiled[57,59]. These reviews also serve as excellent reference sources for their syntheses and properties. Macrocyclic aza polyethers have been prepared in good yields under high-dilution conditions by condensation of α,ω-diamines with α,ω-diacid dichlorides followed by hydride or diborane reduction of the key macrocyclic bislactam intermediates. The method has been exploited *par excellence* by Lehn[48,50,51] in the synthesis of macrobicyclic systems with nitrogen bridgeheads (see Section IV.G). An efficient flow synthesis of macrocyclic bislactams has also been developed[77]. However, a convenient synthesis of the aza polyethers **81**–**84** by cyclization of the readily available dimethyl esters of the α,ω-dicarboxylic acids **85** and **86** with the commercially available polyethylenepolyamines **87**–**89** in refluxing ethanol followed by reduction of the resulting cyclic amides **90**–**93** has been reported[78], which requires neither high-dilution techniques nor protection of the secondary amine functions in the starting polyethylenepolyamines. Although the yields recorded in equation (20) are lower than those obtained using high-dilution techniques, the method is much more convenient experimentally. Other researchers have prepared macrocyclic aza polyethers by alkylation. For example, reaction between *N*-benzyldiethanolamine (**94**) and tetraethyleneglycol ditosylate (**95**), followed by hydrogenolysis of the resulting *N*-benzylazacrown (**96**) gives[79] monoaza-18-crown-6 (**97**) as shown in equation (21). The diaza-12-crown-4 (**98**) and 18-crown-6 (**99**) derivatives have been prepared[70] in 80% yields by reaction of the **100** and **101** dianions derived from the appropriate α,ω-bissulphonamides with diethyleneglycol ditosylate (**43**) and triethyleneglycol ditosylate (**14**), respectively, in $HCONMe_2$. The corresponding free amines **102** and **103** were obtained (see equation 22) by acid-catalysed hydrolysis of the cyclic bissulphonamides followed by treatment of the salts with base. The diaza-18-crown-6 (**103**) was obtained[80] (see equation 23) in much lower yield by (*a*) reacting triethyleneglycol ditosylate (**14**) with the dianion derived from the α,ω-bistrifluoroacetamide (**104**) followed by alkaline hydrolysis of the trifluoroacetyl groups and (*b*) reacting the α,ω-dichloride (**15**) with excess of NH_3.



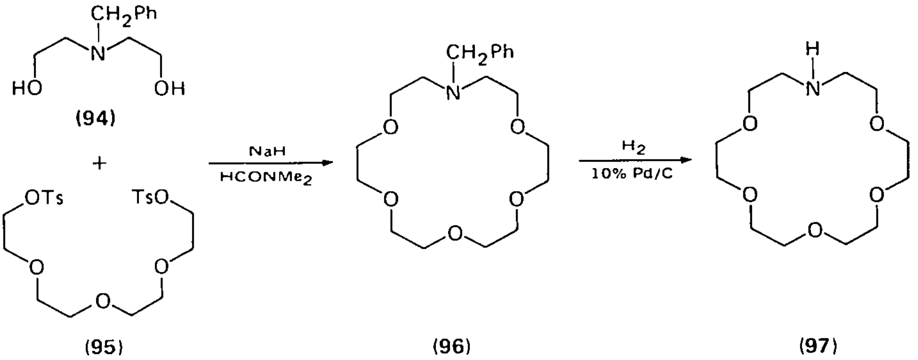
(20)

(85) $n = 1$
(86) $n = 2$

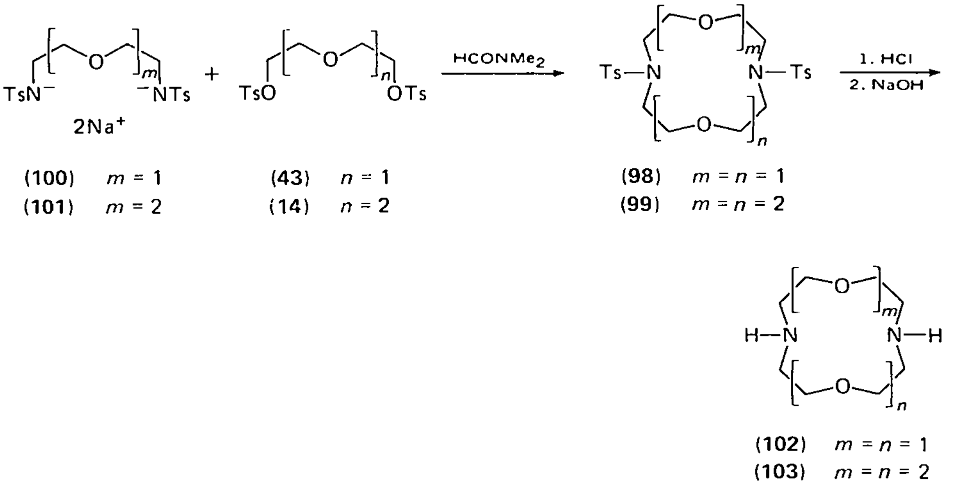
(87) $m = 1$
(88) $m = 2$
(89) $m = 3$

	n	*m*	Yield (%)
(90)	1	2	12
(91)	1	3	12
(92)	2	1	32
(93)	2	2	67

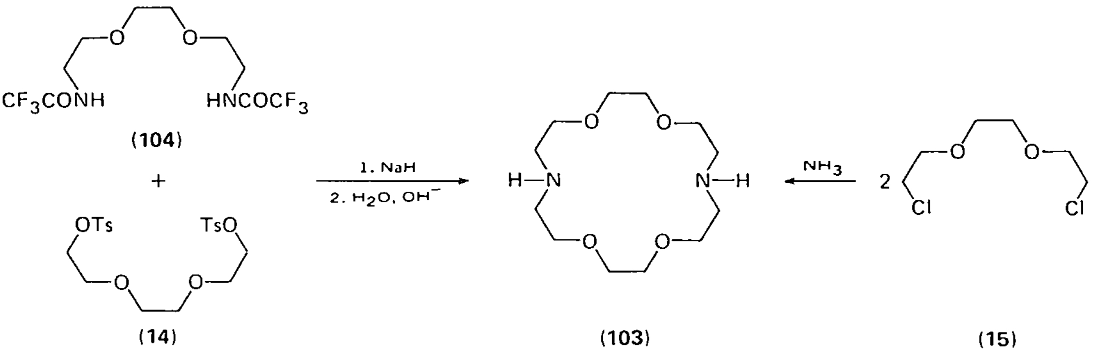
	n	*m*
(81)	1	2
(82)	1	3
(83)	2	1
(84)	2	2


(94)
(95)
NaH
HCONMe2
(96)
H2
10% Pd/C
(97)

(21)


2Na+
(100) m = 1
(101) m = 2
(43) n = 1
(14) n = 2
HCONMe2
(98) m = n = 1
(99) m = n = 2
1. HCl
2. NaOH
(102) m = n = 1
(103) m = n = 2

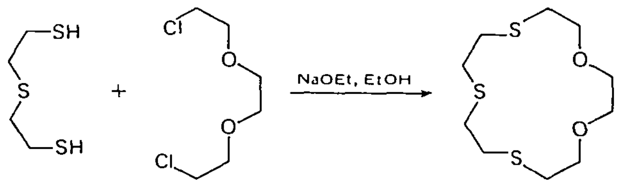
(22)


(104)
(14)
1. NaH
2. H2O, OH−
(103)
NH3
(15)

(23)

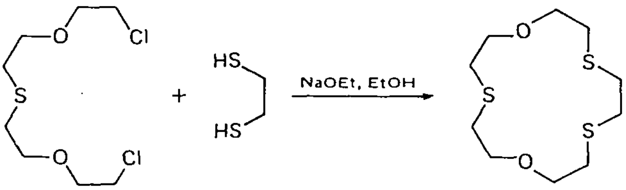
5. Oxygen and sulphur systems

Since the early reports[73,74] of macrocyclic compounds containing oxygen and sulphur atoms, a large number of simple thia polyethers have been synthesized[76,81-84]. Those reported in the literature up to mid-1975 have been the subject of two extensive reviews[59,72]. The most convenient method of synthesizing thiacrown ethers involves reaction of an appropriate α,ω-oligoethyleneglycol dichloride with either an α,ω-dimercaptan or sodium sulphide. These methods are illustrated by the preparations[83] of (*a*) 1,4,7-trithia-15-crown-5 (**105**) from the α,ω-dichloride (**15**) and the dithiol (**106**) (see equation 24), (*b*) 1,4,10-trithia-15-crown-5 (**107**) from the α,ω-dichloride (**108**) and ethanedithiol (**109**) (see equation 25), and (*c*) thia-18-crown-6 (**110**) from the α,ω-dichloride (**111**) and sodium sulphide (see equation 26).


SH
S
SH
+
Cl
O
O
Cl
NaOEt, EtOH
S
O
S
O
S

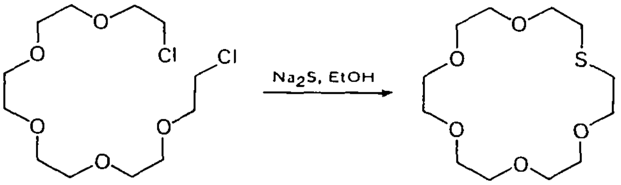
(106) (15) (105)

(24)


O
Cl
S
O
Cl
+
HS
HS
NaOEt, EtOH
O
S
S
S
O

(108) (109) (107)

(25)

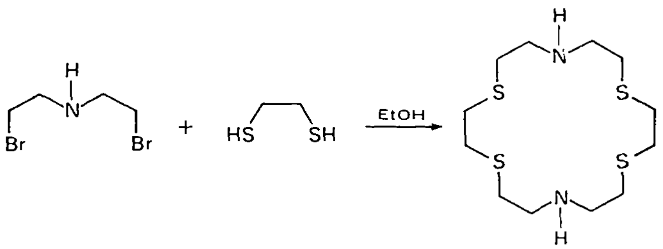

O
O
Cl
Cl
O
O
O
Na2S, EtOH
O
O
S
O
O
O

(111) (110)

(26)

6. *Nitrogen and sulphur systems*

Approaches involving both (*a*) alkylation and (*b*) acylation, followed by amide reduction, have been employed to obtain this series of crown compounds. The diazatetrathia-18-crown-6 derivative (**112**) has been isolated[85] from the reaction shown in equation (27) between the dibromide (**113**) and ethanedithiol (**109**) in ethanol under high dilution conditions. More recently, however, an acylation–reduction sequence has afforded better overall yields of **112**[86] and related crown compounds[78,87].

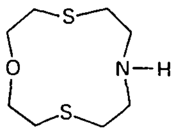

H
N
Br
Br
+
HS
SH
EtOH
H
N
S
S
S
S
N
H

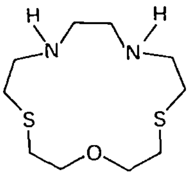
(113) (109) (112)

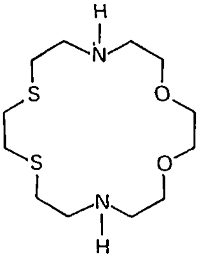
(27)

7. *Oxygen, nitrogen and sulphur systems*

Systems such as **114**–**116** have been synthesized using (*a*) the alkylation approach[85] and (*b*) the acylation–reduction sequence[86,87].


(114)

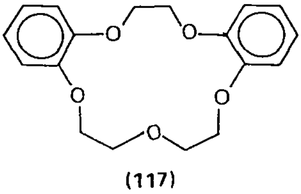

(115)

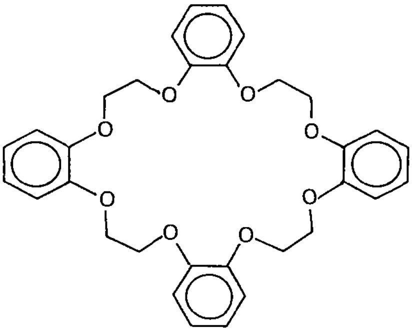

(116)

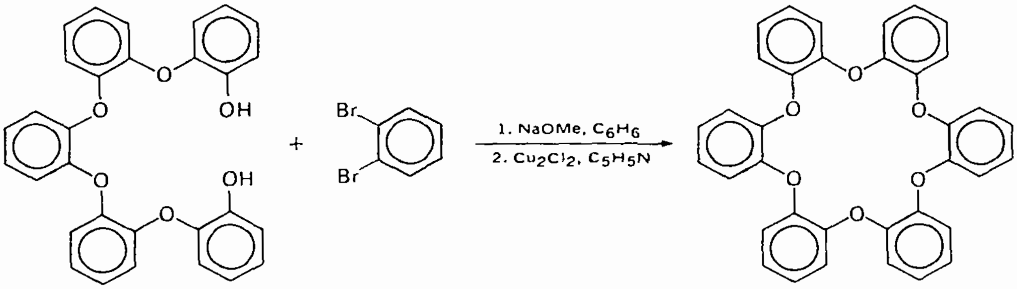
B. Crown Compounds Incorporating Aromatic Residues

1. *Systems fused to benzene rings*

Subsequent to his report of the accidental synthesis of dibenzo-18-crown-6 (**10**) in 1967, Pedersen[11,12] described the preparation of numerous other crown ethers, e.g. **117** and **118**, incorporating *ortho*-disubstituted benzene rings with both symmetrical and asymmetrical deployments around the polyether ring and with up to four aromatic rings fused to the macrocycle. More recently, the synthesis of hexabenzo-18-crown-6 (**119**) has been described[88]. A series of Ullmann-type condensations and de-*O*-methylations starting from 2,2′-oxydiphenol and *o*-bromoanisole afforded the diphenol (**120**) which was condensed with *o*-dibromobenzene (**121**) to give **119** (see equation 28). Alas, it does not complex with Group IA and IIA metal ions! Benzocrown ethers incorporating 4-methyl[89] and 4-*t*-butyl[12] substituents have been reported. 4-Vinyl-benzo-18-crown-6 (**122**) and -15-crown-5 (**123**) have been obtained[90] by cyclization of 3,4-dihydroxybenzaldehyde with the appropriate α,ω-dichloropolyethyleneglycol followed by reaction of the formyl group with a methyl Grignard reagent and dehydration of the resulting alcohol. The vinyl benzocrown ethers serve as important intermediates in the synthesis of polymer-supported crown ethers. A series of 4,4′-disubstituted dibenzo crown ethers have been prepared[91] from the constitutionally isomeric 4,4′-diaminodibenzo-18-crown-6 derivatives by condensation with aldehydes and isothiocyanates.

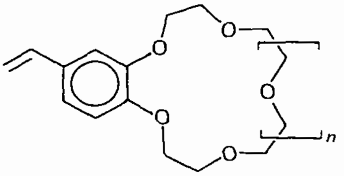

(117)


(118)



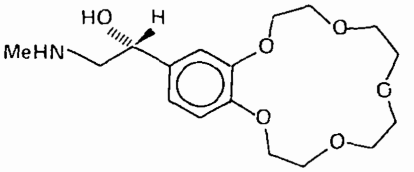
(120) (121) (119)

(28)

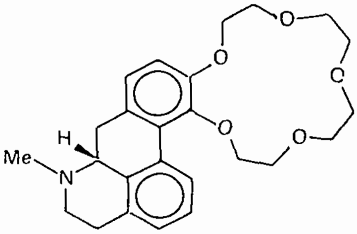


(122) $n = 2$
(123) $n = 1$

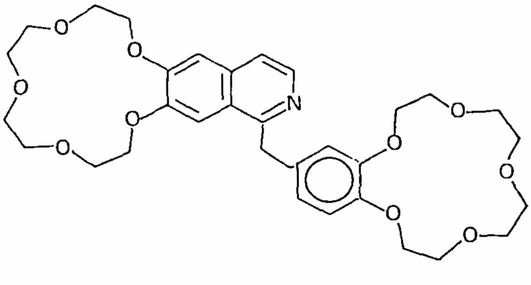
A diaminodibenzo crown ether was obtained by nitration of dibenzo-18-crown-6 (**10**) followed by reduction of the aromatic nitro groups to amino groups. Other interesting benzocrown ethers in which the aromatic ring carries functionality have been prepared. The 15-crown-5 derivatives (**124**) and (**125**) of adrenaline and apomorphine, respectively, were obtained[92] in one step from their physiologically active precursors. The bis-15-crown-5 derivative (**126**) incorporating a fully de-*O*-methylated papaverine residue has been reported[93]. Nitrogen atoms have been incorporated into the polyether rings of benzo and dibenzo crown ethers by employing (*a*) *o*-aminophenol[94,95] (*b*) *o*-amino aniline[94,95] and (*c*) *o*-nitrophenol[95] as readily available precursors. The syntheses[24] and detailed mass spectral analyses[96] of numerous crown ethers, e.g. **127**, containing one or two *ortho*-xylyl



(124)

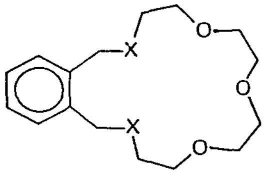


(125)



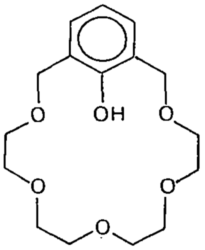
(126)

residues have been reported. The derivatives were obtained by reaction of *o*-xylylene dibromide with polyethyleneglycols in the presence of Me_3COK or NaH as base. *Ortho*-xylyldithiacrown ethers, e.g. **128**, are also known[97,98].



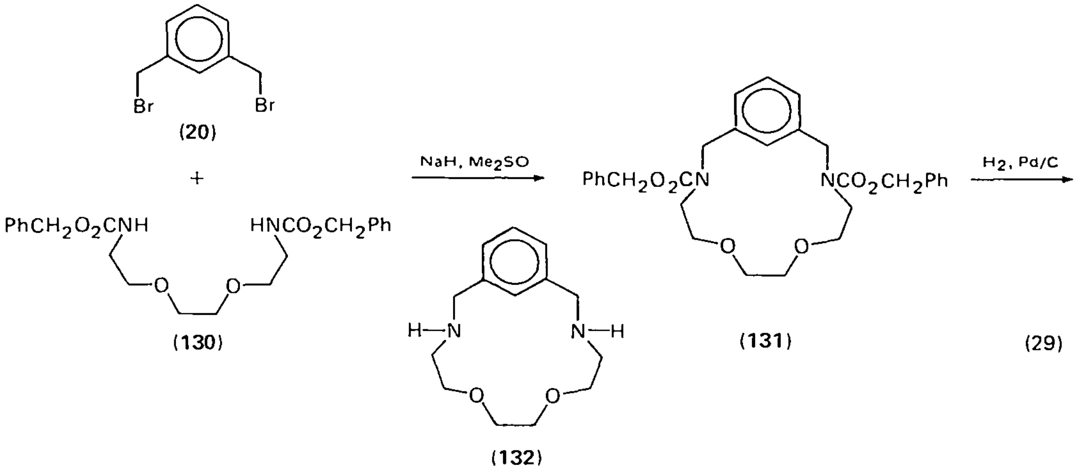
(127) X = O
(128) X = S

We have already discussed the synthesis of *meta*-xylyl crown ethers, i.e. **25–31**, in Section II.A. In addition to these investigations by Reinhoudt and his collaborators[23], Cram and his associates[99] have prepared numerous *meta*-xylyl-18-crown-6 derivatives with substituents at $C_{(2)}$ and $C_{(5)}$. Recently, phenolic crown ethers, such as **129**, have been obtained[100] in greater than 90% yield by de-*O*-methylation



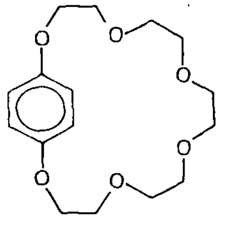
(129)

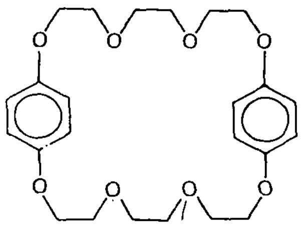
of the corresponding methyl ethers upon exposure to anhydrous LiI in dry C_5H_5N at 100° for 10 h followed by acidification. The success of these deetherifications has been attributed to intramolecular crown ether catalysis, as neither anisole nor 2,6-dimethylanisole furnish the corresponding phenol when subjected to similar treatment. *Meta*-xylyl-diaza-15-crown-5 derivatives have been synthesized[101] by reaction of *m*-xylylene dibromide with dianions generated from α,ω-bisurethanes on treatment with base. For example, when the α,ω-bis-*N*-benzyloxycarbonyl derivative (**130**) was treated with NaH in Me_2SO and *m*-xylylene dibromide (**20**) added, the macrocyclic bisurethane (**131**) was obtained as shown in equation (29).



Removal of the benzyloxycarbonyl protecting groups affords the free amine (**132**) which is a useful synthetic intermediate. *Meta*-xylyl-18-crown-5 derivatives containing sulphur atoms have also been reported[97,98].

para-Phenylene units have been incorporated into a wide range of crown compounds. Standard synthetic approaches have led to the preparation of (*a*) **133** and **134** from *p*-hydroquinone and the appropriate polyethyleneglycol ditosylate[102], (*b*) **135** and **136** from *p*-xylylene dibromide and the appropriate diol[23] or dithiol[98], and (*c*) **137** from *p*-phenylene-β,β'-diethylamine and triethylene glycol ditolsylate[103]. Recently, the synthesis of some anion receptor molecules incorporating *para*-phenylene units and guanidinium groups has been described[104]. For example, reaction of the diamine (**138**) with the bisisothiocyanate (**139**) affords the macrocyclic bisthiourea (**140**), which can be converted (see equation 30) into the bisguanidinium bromide, **141**·2Br$^-$, by treatment with EtBr in EtOH followed by reaction of the bis-*S*-ethyl thiouronium derivative with NH$_3$ in EtOH.


(133)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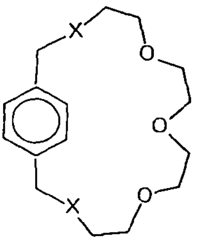
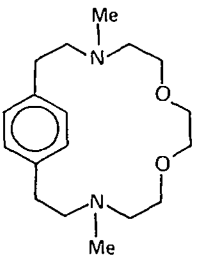

(135) X = O

(136) X = S

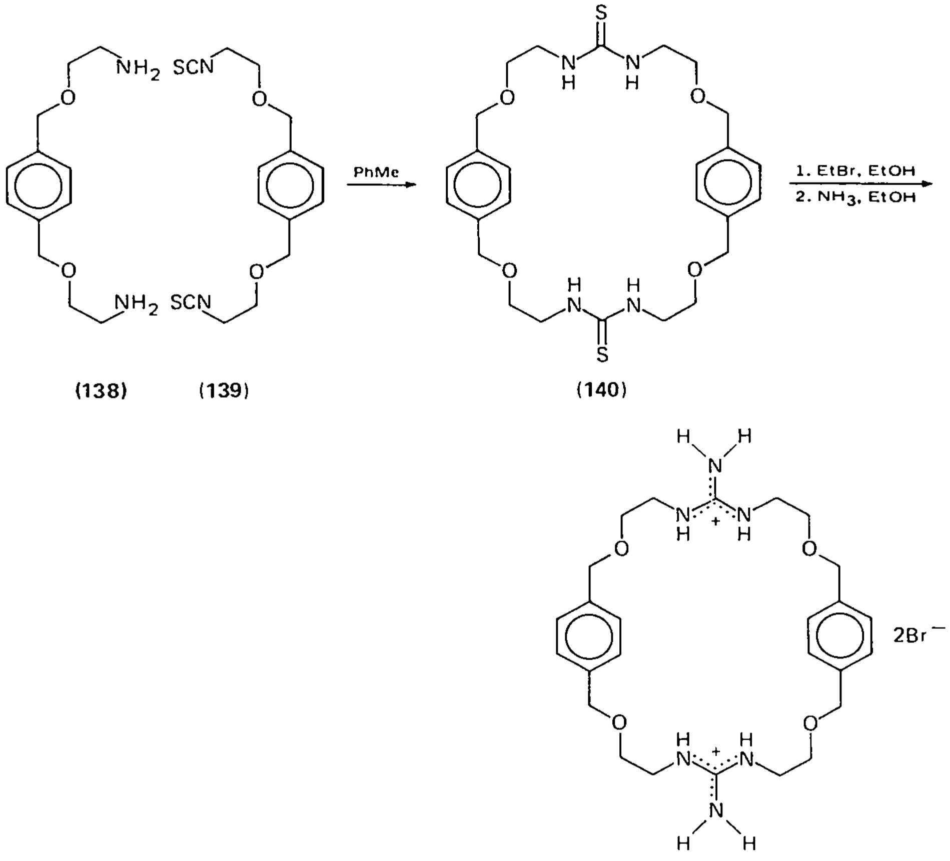


(137)

Polycyclic compounds which incorporate (*a*) aryl groups of the [2.2]-paracyclophane nucleus[102] and (*b*) naphthalene-1,5, -1,8 and -2,3-dimethylyl[105] units into crown-6 macrocycles have also been reported. Finally, biphenyl residues have been included[106] as aromatic subunits – exhibiting both 2,2' and 3,3' substitution patterns – in various macrocyclic compounds.

2. *Systems fused to furan rings*

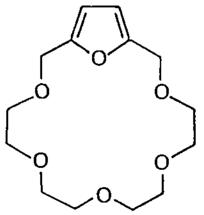
Furan-2,5- and -3,4-dimethylyl units have been incorporated[23,24] into crown ethers by at least two groups of investigators. A series of 18-crown-6 derivatives, e.g. **142**–**144**, containing one, two and three furano residues deployed around the macrocyclic ring have been reported[107]. The key starting material in their synthesis is 5-hydroxymethyl-2-furaldehyde which can be obtained[108] from sucrose. This hydroxy aldehyde (**145**) can be converted into the diol (**146**), the dichloride (**147**), the extended diol (**148**) and chloro alcohol (**149**), and the bisfuran diol (**150**) and


PhMe
1. EtBr, EtOH
2. NH_3, EtOH
2Br⁻

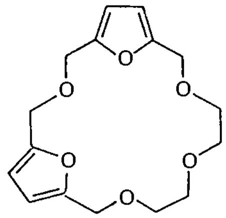
(138) (139) (140)

(30)

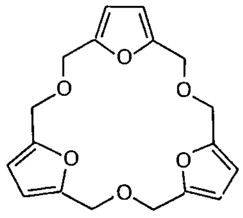
(141.2Br)



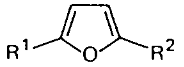
(142)

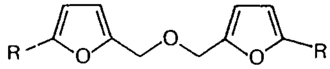


(143)



(144)

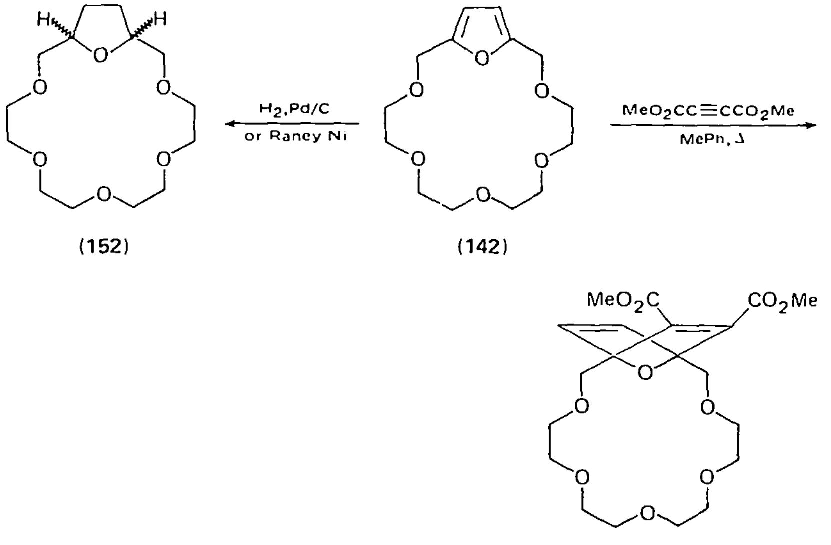




(145) $R^1 = CH_2OH$; $R^2 = CHO$
(146) $R^1 = R^2 = CH_2OH$
(147) $R^1 = R^2 = CH_2Cl$
(148) $R^1 = R^2 = CH_2OCH_2CH_2OH$
(149) $R^1 = CH_2OH$; $R^2 = CH_2OCH_2CH_2Cl$

(150) $R = CH_2OH$
(151) $R = CH_2Cl$

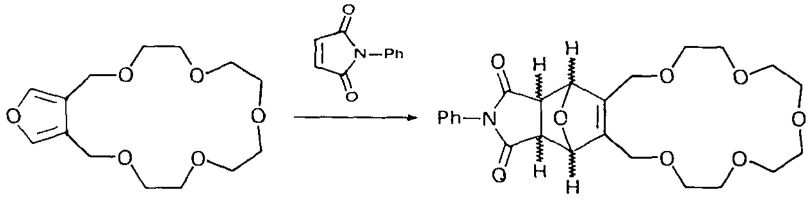
dichloride (**151**) by conventional methods. The compounds can then be employed as immediate precursors to **142**–**144** and other furan-containing cycles. Since furan rings lend themselves to chemical modification, macrocycles containing them have the potential to serve as precursors in the synthesis of receptor molecules whose perimeters are lined with a variety of shaping and binding residues. The monotetrahydrofuranyl-18-crown-6 derivative **152**, for example, is obtained on catalytic hydrogenation of **142** (see equation 31). When Pd on C was used as catalyst, **152** was obtained as a 1 : 1 mixture of *cis* and *trans* isomers; however, in the presence of Raney nickel as catalyst, only the *cis* isomer was isolated. When **142** was heated in refluxing toluene with an excess of $MeO_2CC{\equiv}CCO_2Me$, the [4 + 2] cycloaddition product (**153**) was obtained (see equation 31) in virtually quantitative yield. In addition to forming an adduct with $MeO_2CC{\equiv}CCO_2Me$, the monofuranyl-17-crown-6 derivative (**154**) incorporating a furan-3,4-dimethylyl unit undergoes[34,96] a Diels–Alder reaction with *N*-phenylmaleimide to form the adduct **155** as shown in equation (32).



(152) (142)

(153)

(31)

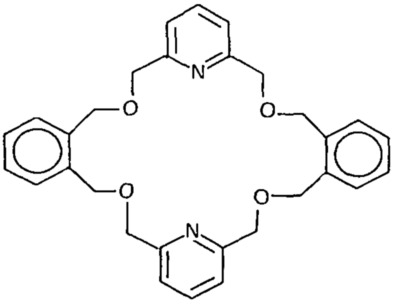


(154) (155)

(32)

3. *Systems fused to pyridine rings*

The pyridine-2,6-dimethylyl unit is another one which has been widely employed as a heterocyclic subunit in crown compounds. In this work, the key starting material has been 2,6-bis(bromomethyl)pyridine. In 1973, Newkome and Robinson[109] isolated 22-, 33-, 44-, and 55-membered ring compounds after reaction of this dibromide with 1,2-di(hydroxymethyl)benzene in $MeOCH_2CH_2OMe$ with NaH as base. An example of the smallest kind of macrocycle is provided by **156**. A series of crown compounds, e.g. **157**–**159**, containing between 12 and 24 atoms in the macroring and incorporating between 1 and 4 pyridine-2,6-dimethylyl units have been synthesized[110] by conventional means. Diaza, e.g. **160**, and dithia, e.g. **161**, derivatives have also been reported[97,98,111], and, in some cases, e.g. **161**, the preparation of the *N*-oxide has been accomplished. The pyridine ring is found in other guises in a few macrocycles reported in the literature. Base-promoted reaction of 2,6-bisbromopyridine with the appropriate polyethyleneglycol has yielded[112] **162** and **163**, for example, whilst incorporation of the 2,2′-bipyridyl unit into heteroatom-containing macrocycles through its 3,3′- and 6,6′-positions has been achieved[58,113].



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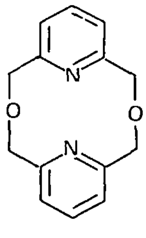

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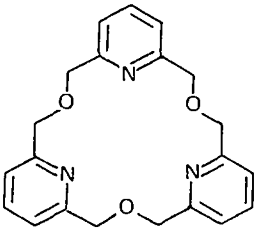

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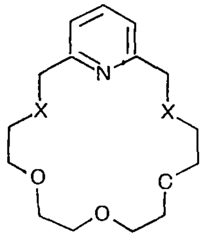
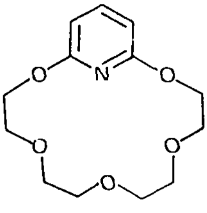


(159) X = O
(160) X = NTs
(161) X = S



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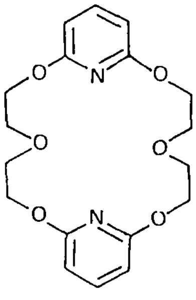


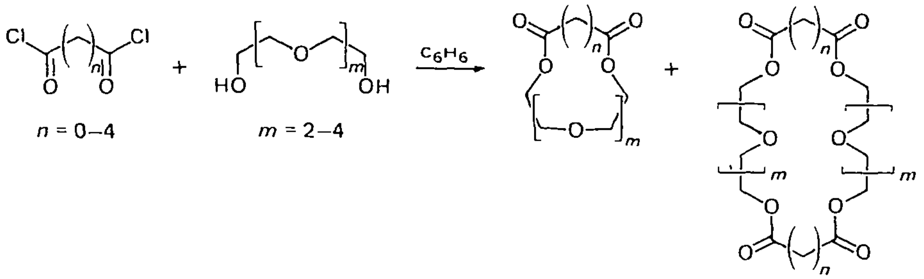
(163)

4. Systems fused to thiophene rings

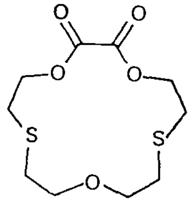
Both thiophene-2,5- and -3,4-dimethylyl units have been incorporated[24,96,97,111] into crown compounds.

C. Macrocyclic Diester, Dithioester and Diamide Compounds

Macrocyclic diesters have been synthesized by condensation of α,ω-diacid dichlorides and polyethyleneglycols in benzene using high-dilution techniques. Using this simple procedure without the addition of any base, macrocycles containing between 4 and 6 ether oxygen atoms and incorporating 1 or 2 residues derived from oxalic[114], malonic[115–118], succinic[116,117,119], glutaric[114,117] and adipic[117] acids have been prepared in good yields according to equation (33). Several methyl-, phenyl- and perfluoro-substituted diester crown compounds have also been reported[117] as well as macrocycles incorporating fumaric[117] and maleic[119] acids. The syntheses of several macrocyclic thia polyether diesters[114,116], e.g. **164**, aza polyether diesters[119] e.g. **165**, polyether dithioesters[114,116] e.g. **166** and thia polyether dithioesters[114] e.g. **167** derived from oxalyl, malonyl, succinyl and glutaryl dichlorides have also been described. In addition, a series of macrocyclic diesters have been synthesized[118,120,121], as shown in equation (34), by the



(33)



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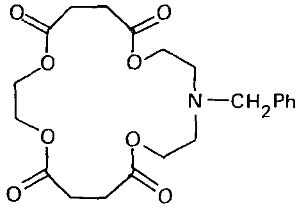

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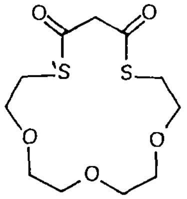

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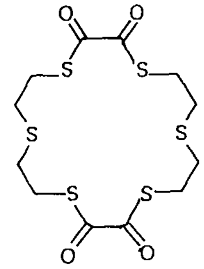

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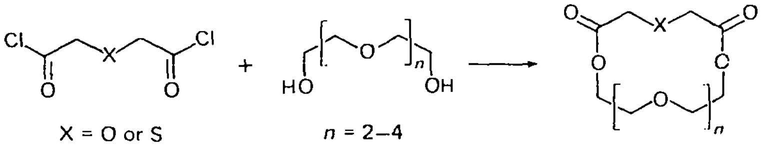
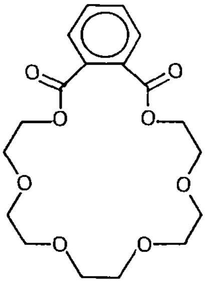


(34)

condensation of α,ω-diglycolic acid dichloride and α,ω-thiodiglycolic acid dichloride with various polyethyleneglycols. Macrocyclic diesters e.g. **168**–**171**, incorporating aromatic diacids have also been prepared[122,123]. In particular, 2,6- and 3,5-pyridine dicarboxylate residues have been introduced[123–125] into a variety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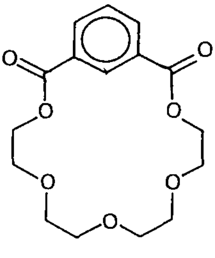
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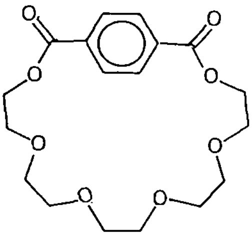
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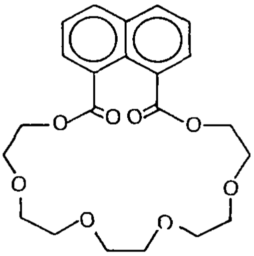
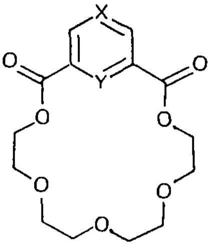

(171)

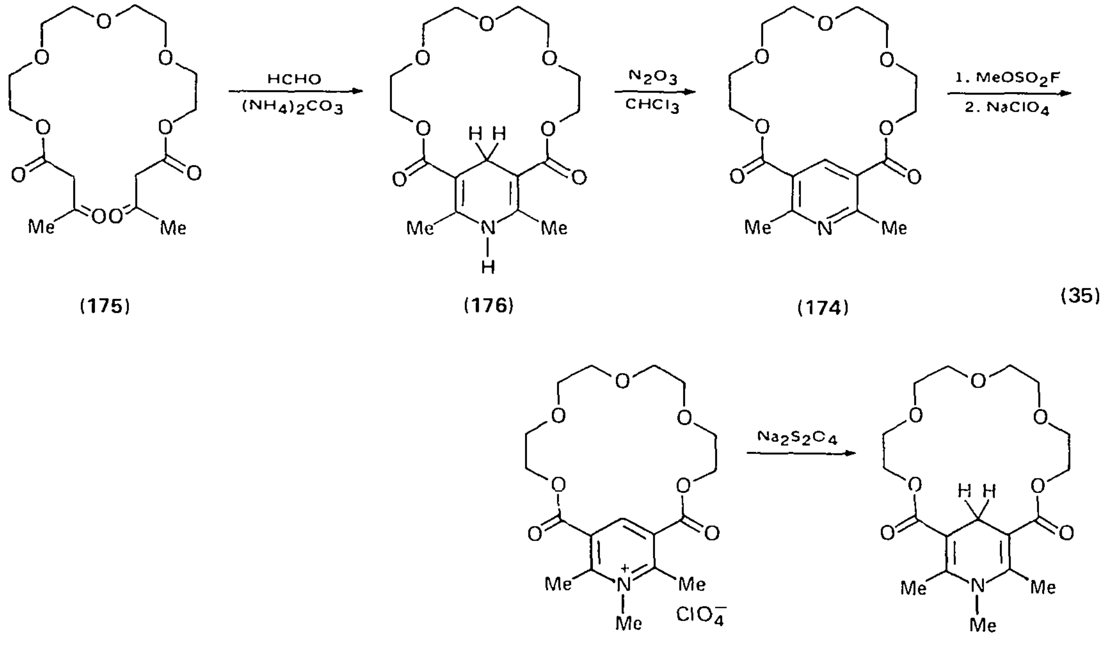
of macrocyclic compounds, e.g. **172** and **173**, by reaction of the diacid dichlorides derived from the pyridine dicarboxylates with polyethyleneglycols. In the case of **172**, a high yield (78%) was obtained from the reaction despite the absence of



(172) X = CH; Y = N
(173) X = N; Y = CH

metal ions. It has been suggested[124] that the high yield could arise from protonation of the nitrogen atom by HCl and the consequent ability of the pyridinium ion to act as a template for ring-closure.

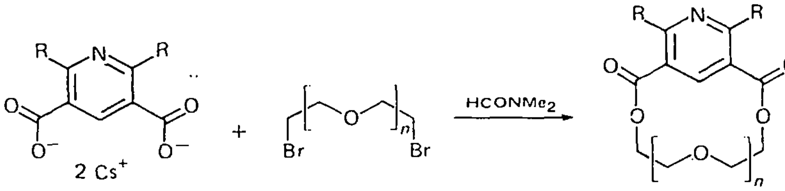
Several new crown ethers, e.g. **174**, containing the 3,5-di(alkoxycarbonyl)-pyridine ring system have been prepared[126] by an approach which is novel to crown ether synthesis. It relies upon a Hantzsch-type condensation of the α,ω-bis(acetoacetic ester) (**175**) of tetraethyleneglycol with HCHO and an excess of $(NH_4)_2CO_3$ in an aqueous medium followed by dehydrogenation of the intermediate 1,4-dihydropyridine derivative **176** as shown in equation (35). The macrocyclic and heterocyclic rings are thought to be generated simultaneously during the



(175) (176) (174) (35)

(178) (177)

course of this reaction. The pyridyl derivative **174** by methylation affords the pyridinium salt **178** which in turn can be converted into the *N*-methylhydropyridine derivative **177** by reduction with $Na_2S_2O_4$. The potential of **177** as a model for NAD(P)H has been demonstrated[127] by its ability to transfer hydride readily to sulphonium salts. Attempts to extend this type of synthesis to systems other than **174** have met with only limited success and alternative procedures have been sought. Reaction of the dicesium salts of 3,5-pyridinedicarboxylic acid (**179**) (R = H or Me) with α,ω-polyethyleneglycol dibromides in $HCONMe_2$ gives (see equation 36) cyclic 3,5-di(alkoxycarbonyl)pydridine derivatives (**180**) (R = H or



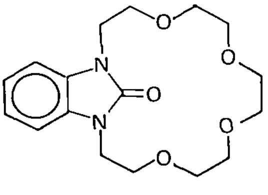
(179) (180) (36)

R = H or Me $n = 2$–5

Me) in yields of between 20 and 90% depending upon the chain length of the glycol. Cs^+ ions play a virtually irreplaceable role in the formation of **180** (R = H, $n = 3$) since the yield of macrocycle decreases drastically when Cs^+ ions are replaced by Rb^+, K^+ or Na^+ ions. It has been suggested that the Cs^+ ion acts as a template during the early stages of the reaction.

Several groups of investigators have prepared macrocyclic compounds incorporating the ubiquitous amide functional group. For example, macrocyclic peptides have been synthesized and investigated[128] for their cationic binding properties. In addition, macrocyclic diamides prepared by the approaches outlined in Section IV.A.4 have served as important intermediates in the synthesis of macrobiocyclic diaza polyethers (see Section IV.G). The preparation of several macrocyclic diamides incorporating 2,6-disubstituted pyridine bridges have also been reported[98,111].

Benzimidazolone has been reacted[129] with α,ω-polyethyleneglycol dichlorides in $HCONMe_2$ in the presence of LiH or NaH to afford a series of novel monomeric and dimeric derivatives, e.g. **181** and **182**. Interestingly, benzimidazolethione undergoes[129] alkylation firstly at sulphur and then at nitrogen to yield nitrogen–sulphur-bridged compounds, e.g. **183**. Quinoxaldione and 5-methyluracil have also been incorporated[129] into macrocyclic polyethers.



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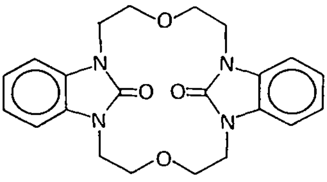

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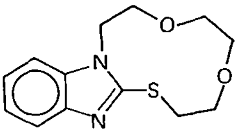
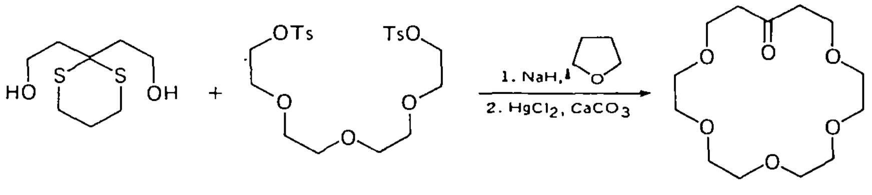


(183)

D. Crown Compounds Containing Carbonyl Groups

1. *Oxocrown ethers*

The carbonyl group has been introduced into crown ethers both as a direct replacement for an ether oxygen atom and as a formal insertion into an OCH_2CH_2O fragment. The oxo-18-crown-5 derivative **184** has been prepared[130] by base-promoted condensation of the dithiane **185** with tetraethyleneglycol ditosylate (**95**) followed by regeneration of the masked carbonyl group from the spiro intermediate as shown in equation (37). Reaction of tetraethyleneglycol (**16**) with NaH and 1,1-bis(chloromethyl)ethylene (**186**) gave[131] the methylene-16-crown-5 derivative **187**, which, on ozonolysis and decomposition of the ozonide, afforded (see equation 38) the oxo-16-crown-5 derivative **188** in nearly quantitative yield. Oxocrown ethers promise to be valuable synthetic intermediates. The novel dioxodithia-18-crown-6 derivative **189** has been obtained[132] recently from reaction of 1,9-dichloroanthraquinone with the appropriate polyethyleneglycol dithiol.

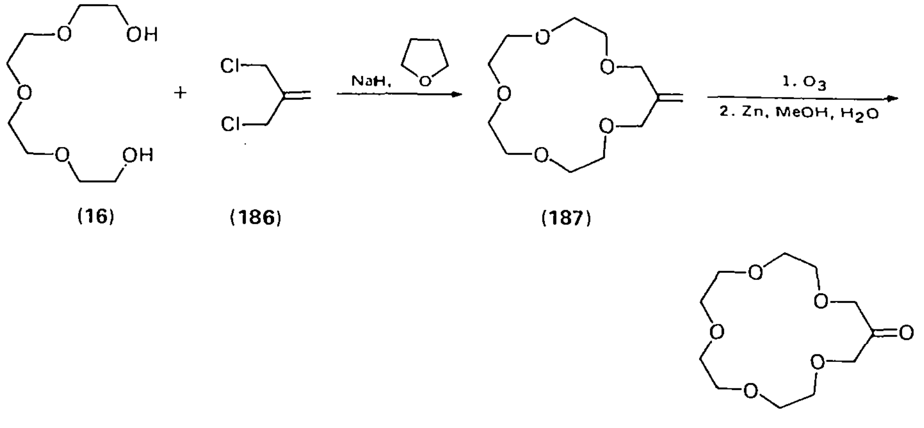


(37)

(185) (95) (184)

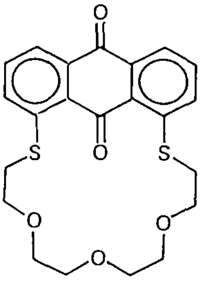
2. *Crown ethers incorporating β-diketone residues*

Since enolizable β-diketonates, such as acetylacetone, form stable complexes with both metal ions[133] and nonmetallic[134] elements, it is of interest to incorporate them into macrocyclic polyethers. Macrocyclic polyethers, e.g. **190**–



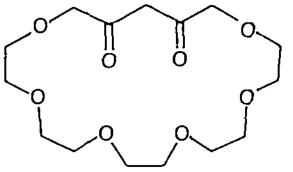
(16) (186) (187) (188)

(38)



(189)

192, which contain 1,2 and 3 β-diketone units in the ring have been made[135] from reaction of the key starting material (193) with NaH and (*a*) pentaethyleneglycol ditosylate – to give the β-diketone 190 after regeneration of the carbonyl groups – or (*b*) diethyleneglycol ditosylate – to give a mixture of the bis(β-diketone) (191) and the tris(β-diketone) (192) after regeneration of the carbonyl groups. The templated syntheses of acyclic and cyclic acetylacetone derivatives have been investigated[136] as well. The macrocycle 194 was produced in 13% yield from the reaction of the magnesium salt – but not the calcium salt – of 195 with bis(bromomethyl)benzene (20) under similar reaction conditions (see equation 39). In addition, the disodium salt of 195 was noted to give only polymer when cyclization



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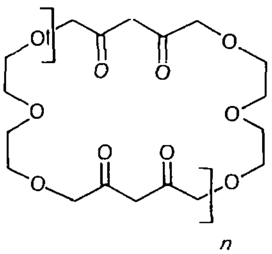
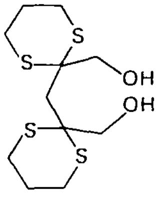


(191) $n = 1$
(192) $n = 2$



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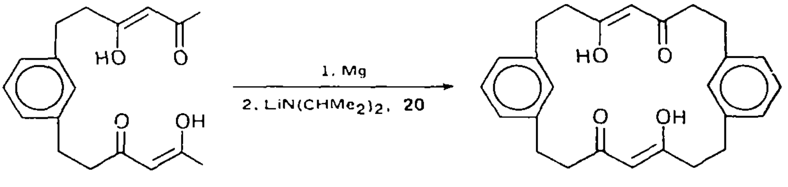


(195) (194)

(39)

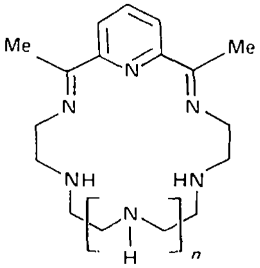
with the dibromide **20** was attempted. These experimental observations demonstrate that the cyclizations are templated selectively by metal ions.

E. Crown Compounds Incorporating Imine and Oxime Functions

1. Macrocycles from Schiff-base condensations

The Schiff-base condensation between a CO and an NH_2 group to form a C=N linkage forms the basis of many successful macrocyclic ligand syntheses. The use of alkaline earth and transition metal ions to control cyclizations and form *in situ* Schiff-base complexes is well established[137]. Two types of template effect have been recognized[13,66] in this area. According as to whether the metal ion lowers the free energy of (*a*) the transition state in an irreversible reaction or (*b*) the product in a reversible reaction, a 'kinetic' or 'thermodynamic' template effect is operative[138]. Although a 'kinetic' template effect clearly operates (see Section II.A) during the irreversible crown ether syntheses, many of the templated reactions involving the formation of imine functions probably rely upon[138] a 'thermodynamic' template effect.

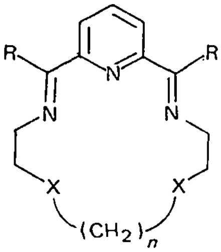
The 2,6-diiminopyridyl moiety has enjoyed popular application in the *in situ* synthesis of metal complexes of both macrocyclic polyamines and aza polyethers. The isolation of crystalline iron (III) complexes of the pentadentate 15-membered ring (**196**) and hexadentate 18-membered ring (**197**) compounds after Schiff-base



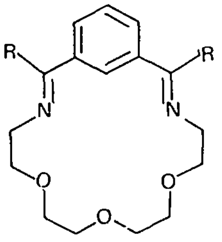
(196) $n = 0$
(197) $n = 1$

condensation of 2,6-diacetylpyridine with the appropriate polyamine in the presence or iron (II) salts has been reported[139]. Other investigators[140-142] have prepared similar types of complexes *in situ*. They have varied the nature of the coordinated metal ion, the size of the macrocycle and the nature (O, N and S) of the heteroatoms in the rings. In some instances, benzene rings have also been fused on to the macrocycle.

In view of the relatively high abundance of Mg^{2+} ions in Nature – and particularly their occurrence in chlorophylls – the effectiveness of Mg^{2+} as a templating ion in the synthesis of planar nitrogen-donor macrocyles is of considerable biological interest. The Mg^{2+} ion-templated syntheses of the macrocycles **198** and **199** and their isolation as hydrated $MgCl_2$ complexes has been reported[143]. More recently, the magnesium (II) complexes of the 2,6-diiminopyridyl polyethers **200** and **201** have been prepared[144]. A Group IV.B cation has been utilized[145] in the templated Schiff-base condensation of 2,6-pyridinedicarbonyl derivatives with α,ω-diamines and lead (II) thiocyanate complexes of the macrocyclic imino polyethers **202** and **203** have been isolated.

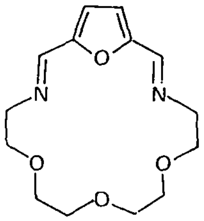


	R	X	*n*
(198)	Me	NH	2
(199)	Me	NH	3
(200)	Me	O	2
(201)	H	O	2



(202) R = H
(203) R = Me

Recently, the first reported syntheses of alkaline earth metal complexes of macrocycles containing 2,5-diiminofuranyl units have appeared[146] in the literature. Schiff-base condensation of furan-2,5-dicarboxaldehyde with the appropriate α,ω-diamino polyethers in the presence of either Ca, Sr of Ba thiocyanates as templates led to the isolation of the metal ion thiocyanate complexes of **204** and **205**.



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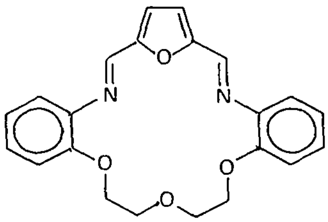
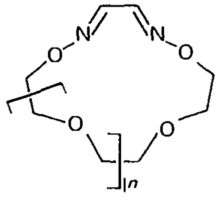
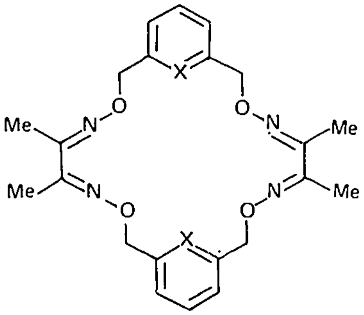


(205)

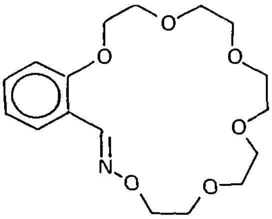
2. Oxime linkages in macrocycles

Oxime functions have recently been incorporated into multiheteromacrocyclic structures. The syntheses of the dioximes **206** and **207** and the tetraoximes **208** and **209** have been accomplished[147] by reaction of diacetyldioxime with either the appropriate polyethylene glycol ditosylate, 2,6-bis(bromomethyl)pyridine or 1,3-bis(bromomethyl)benzene in anhydrous $HCONMe_2$. In addition, the cyclic oxime **210** was prepared in ca. 28% yield from salicylaldoxime and pentaethyleneglycol dibromide. In all these macrocycles, the oxime linkage has the (*E*)-configuration. Novel multiheteromacrocycles, e.g. **211**, have been isolated[148] by polymerization of acetonitrile oxide in the presence of nucleophilic catalysts. Several of the compounds, including **211**, form crystalline complexes with KSCN.


(206) $n = 1$
(207) $n = 2$



(208) X = N
(209) X = CH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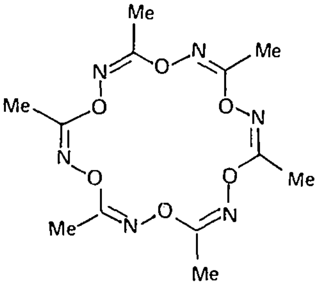
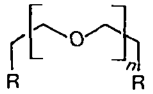


(211)

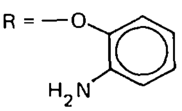
F. Acyclic Crown Compounds

The solvating power of polyethyleneglycol ethers (glymes) toward alkali metals and their salts was first recognized by Wilkinson and his collaborators[10] in 1959. They investigated the solubility of sodium and its potassium alloy in various glymes and observed that the intensities of the blue-coloured metal solutions increased with the number of oxygen atoms in the glyme. Since Pedersen's discovery[11,12] of cyclic crown compounds in 1967, there have been numerous reports of 'acyclic crown compounds'. We shall limit our brief discussion of these compounds to those examples where the $-OCH_2CH_2O-$ repeating unit is the predominant constitutional feature. For the most part, they have been synthesized by alkylations involving monoprotected polyethyleneglycol derivatives. The terminal residues in these so-called ‘octopus’ molecules may be introduced in the form of the original blocking group or they may be inserted in the final step of the synthesis with the penultimate step involving the removal of a temporary protecting group. Examples (*a*) based on polyethylene glycol chains, e.g. **212**–**216**, (*b*) emanating from aromatic rings, e.g. **217**–**221** and (*c*) emanating from nitrogen atoms, e.g. **222**–**224**, have been reported[149] in the literature. The triethanolamine tripod ligands can be viewed as analogues of the diazamacrobicyclic polyethers (see Section IV.E).



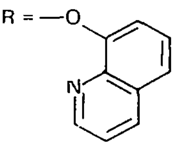
(212) R = OMe; $n = 4$
(213) R = $CONH_2$; $n = 5$
(214) R = CO_2Et; $n = 5$

(215) R =

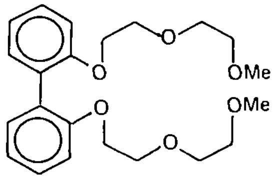


; $n = 5$

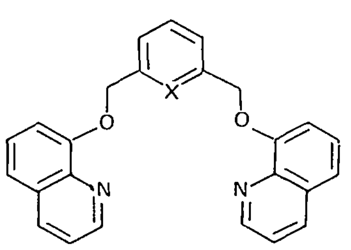
(216) R =



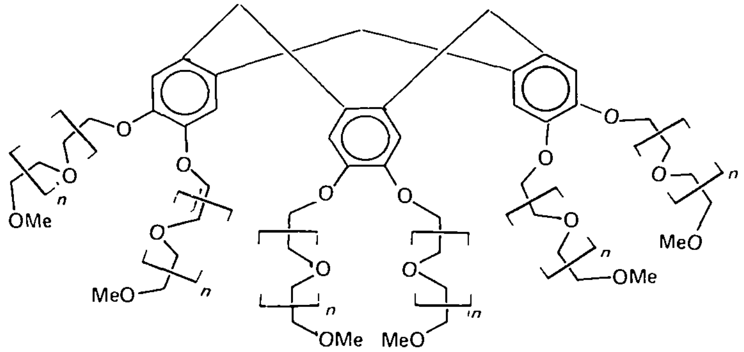
; $n = 3$



(217)

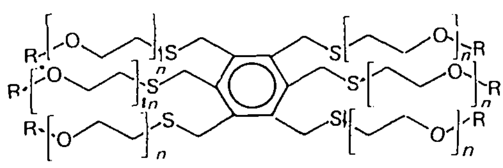


(218) X = COMe
(219) X = N

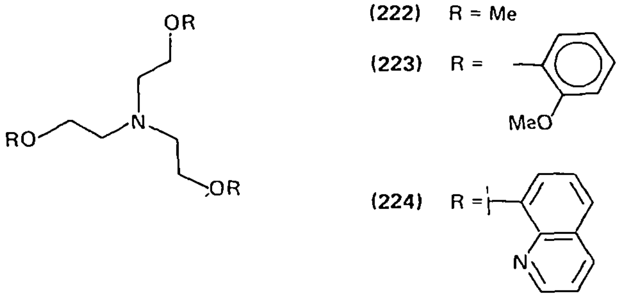


$n = 3$

(220)



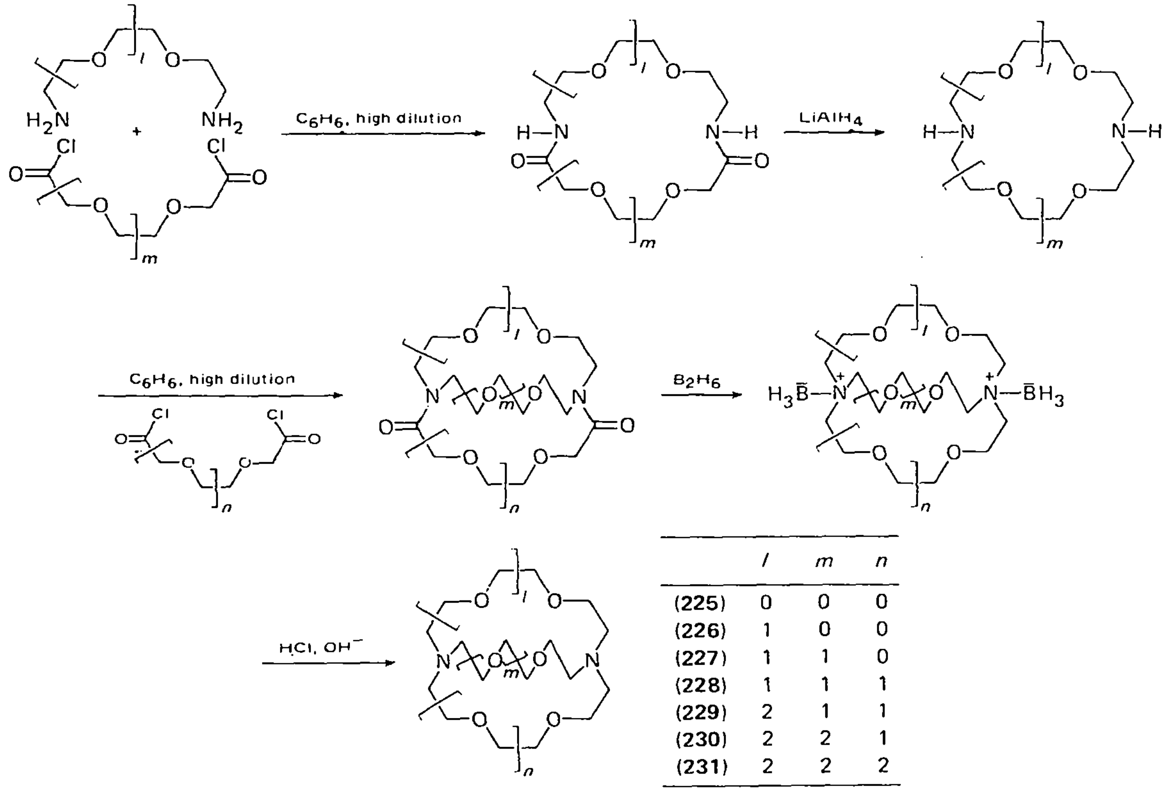
(221) R = $Me(CH_2)_3$; $n = 2$


(222) R = Me
(223) R =
MeO
(224) R =
N

G. Macrobicyclic, Macrotricyclic and Macropolycyclic Ligands

1. *Systems with nitrogen bridgeheads*

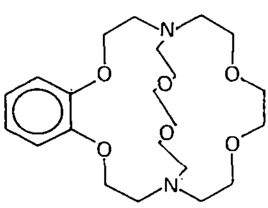
The inspired association by Lehn and his collaborators[48,50,51,150] of the synthetic accomplishments of Pedersen[6,11,12] on crown ethers and Simmons and Park[151] on macrobicyclic diamines led to the realization of diaza macrobicyclic polyethers in 1969. These ligands which can *encapsulate* metal cations in spherical holes usually form very strong complexes. A generalized scheme of reactions employed[150] in the synthesis of the macrobicyclic ligands **225–231** is portrayed in


C_6H_6, high dilution
LiAlH$_4$
C_6H_6, high dilution
B_2H_6
HCl, OH$^-$

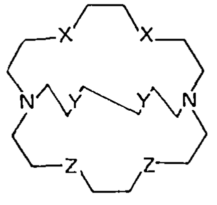
	l	*m*	*n*
(225)	0	0	0
(226)	1	0	0
(227)	1	1	0
(228)	1	1	1
(229)	2	1	1
(230)	2	2	1
(231)	2	2	2

SCHEME 3.

Scheme 3. Reaction of an α, ω-diamino polyether with an α, ω-diacid dichloride ($l = m$ or $l \neq m$) under high-dilution conditions (cf. Section IV.A.4) gives a macrocyclic diamide which can be reduced to the corresponding diamine. Condensation of this macrocycle with the same (i.e. $m = n$) or a different (i.e. $m \neq n$) α, ω-diacid dichloride under high-dilution conditions gives a bicyclic diamide which can be reduced with B_2H_6 to afford the corresponding bis(boraneamine). Acid-catalysed hydrolysis followed by passage of the bishydrochloride salts through an anion-exchange resin affords the diaza macrobicyclic polyethers. As part of an investigation into the factors that control the selectivity of macrobicyclic ligands toward binding of various metal ions, the Strasbourg group have synthesized compounds, e.g. 232–237, in which (*a*) *ortho*-disubstituted benzene rings have been incorporated[152] and (*b*) the ether oxygen atoms have been replaced progressively either by secondary and tertiary amine groups[153] or by sulphur atoms[86]. More recently, *meta*-xylyl, pyridyl, and 1,1′-bipyridyl residues have been introduced into the side-arms. Finally, macrobicyclic polyethers have also been covalently bound[155] to a polystyrene support. Macrotricyclic ligands can assume[48,50,51] at least two types of topology – identified by (a) and (b) in Figure 2 – which are distinct. Type (a) ligands may be considered to be cylindrical and are formed when two monocycles are linked by two bridges. A synthetic approach – involving the established routine of sequential condensations and reductions – which allows[154,156] construction of cylindrical macrotricyclic ligands, e.g. 238–242, with the same or different sizes of monocycles and the same or different lengths of bridges between them is based upon the following three-stage strategy: (*a*) the synthesis of a monocyclic diaza crown ether which is then monoprotected at nitrogen before (*b*) forming a bis-(monocyclic) crown ether and removing the protecting groups on the nitrogens and



(232)



	X	Y	Z
(233)	NMe	O	O
(234)	NMe	NMe	O
(235)	S	O	O
(236)	S	S	O
(237)	S	S	S

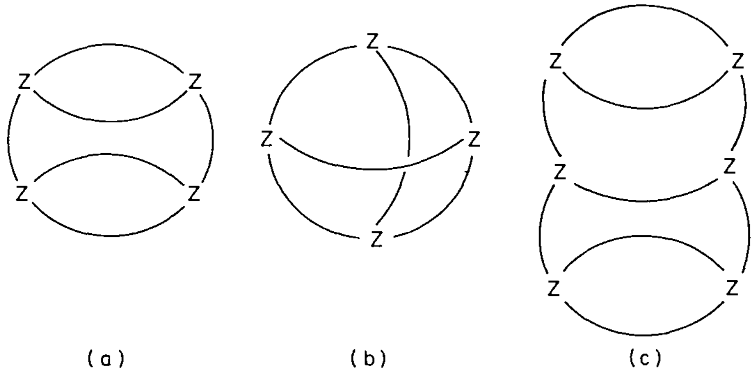
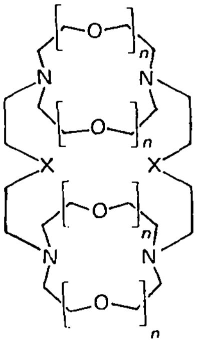
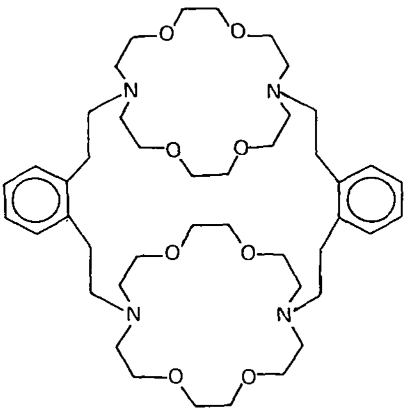


FIGURE 2. Topological representations of (a) cylindrical macrotricylic, (b) spheroidal macrotricyclic, and (c) cylindrical macrotetracyclic ligands.

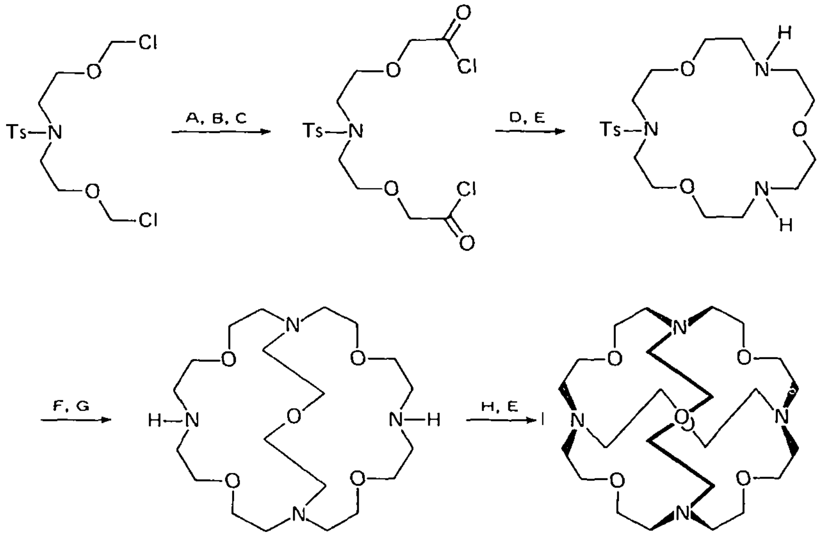


(238) X = O; *n* = 1
(239) X = O; *n* = 2
(240) X = NH; *n* = 2
(241) X = CH_2; *n* = 2



(242)

(*c*) inserting the second bridge to afford the macrotricyclic ligand. If the bridging units are chosen to incorporate nitrogen atoms, then a third bridge can be introduced[156] to give a macrotetracyclic ligand with the topology represented under type (c) in Figure 2. Returning to macrotricyclic ligands, the spheroidal topology belonging to type (b) in Figure 2 has also been realized[157] (see Scheme 4) in the



(243)

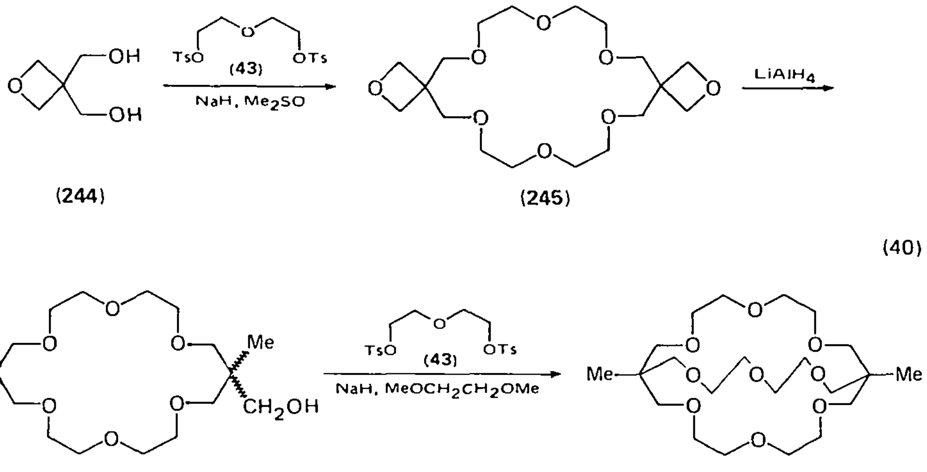
Reagents A: NaCN, $HCONMe_2$; B: $Ba(OH)_2$, H_2O then HCl; C: $(COCl)_2$, C_6H_6;
D: $H_2NCH_2CH_2OCH_2CH_2NH_2$, C_6H_6; E: B_2H_6; F: $TsN(CH_2CH_2OCH_2COCl)_2$, C_6H_6;
G: $LiAlH_4$; H: $ClCOCH_2OCH_2COCl$, C_6H_6

SCHEME 4.

shape of 243 with four identical faces. The use of the protected tosylamides is the key to this elegant synthesis conceived and accomplished by Graf and Lehn[157].

2. *Systems with carbon bridgeheads*

In principle, any atom of valency three or higher can occupy the bridgehead positions. Macrobicyclic polyethers with bridgehead carbon atoms have been synthesized[158] in a number of different ways from diethyleneglycol ditosylate (43) and either pentaerythritol or 1,1,1-tris(hydroxymethyl)ethane. For example, pentaerythritol can be converted[158] into the oxetanediol 244 by known reaction procedures. Reaction of 244 with NaH and 43 in Me_2SO afforded the dispiro-20-crown-6 derivative[159] (245) as shown in equation (40). The diastereoisomeric diols 246, obtained on reductive ring-opening of the oxetane rings in 245, gave the macrobicyclic polyether 247 on reaction with NaH and 43 in $MeOCH_2CH_2OMe$.

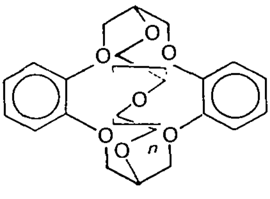


(244) (245)

(40)

(246) (247)

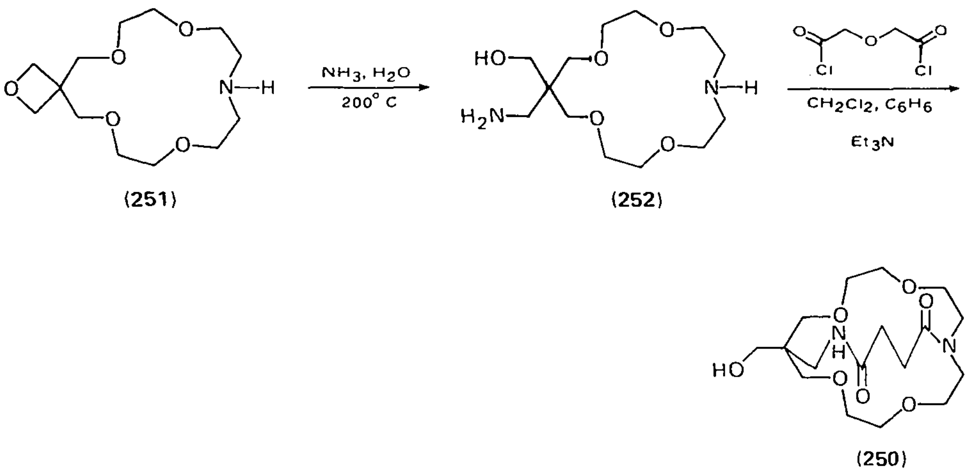
This ligand forms extemely weak complexes with alkali metal cations! More recently, 1,3-dichloropropan-2-ol has been employed[160] as the source of bridgehead carbon atoms in a four-step synthesis of the macrobicyclic polyethers 248 and 249. These derivatives of glycerol preserve the —O—C—C—O— unit throughout their constitution and hence it is not surprising that they bind Group IA metal cations strongly.



(248) $n = 2$
(249) $n = 3$

3. *A system with nitrogen and carbon bridgeheads*

A novel macrobicyclic polyether diamide (250) containing both nitrogen and carbon bridgehead atoms has been prepared[161] from the spiro compound 251 by opening of the oxetane ring with NH_3 to give the amino alcohol 252 which was then condensed with diglycolyl dichloride as shown in equation (41).

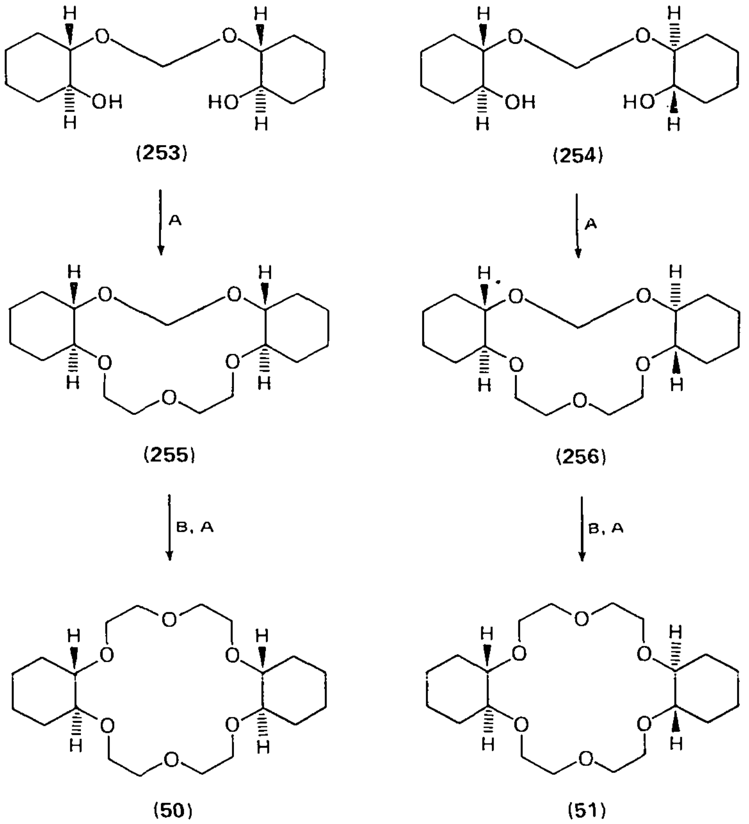


(251) (252) (250) (41)

H. Chiral Crown Ethers

1. Meso *compounds and racemic modifications*

Four, namely **48**–**51**, of the five possible configurational diastereoisomers of dicyclohexano-18-crown-6 are known. The two di-*cis* isomers **48** and **49** and the *trans–cisoid–trans* isomer (**50**) are *meso* compounds; the *trans–transoid–trans* isomer (**51**) belongs to a chiral point group (D_2) and so can be obtained optically active or as a racemic modification. Pedersen[12,162,163] isolated two crystalline isomers of dicyclohexano-18-crown-6 after hydrogenation of dibenzo-18-crown-6 (**10**) over a ruthenium on alumina catalyst followed by chromatographic separation on alumina[42,163,164]. They were designated[42,163,164] as Isomer A (m.p. 61–62°C) and Isomer B (m.p. 69–70°C). After a period of some confusion in the literature (cf. Reference 43), Isomer A was identified as the *cis–cisoid–cis* isomer (**48**) on the basis of an X-ray crystal structure analysis[165] of its barium thiocyanate complex. Similarly, an X-ray crystal structure determination of the sodium bromide dihydrate complex of Isomer B established[166] that it is the *cis–transoid–cis* isomer (**49**). More recently, X-ray crystallographic data on the uncomplexed ligand has confirmed that Isomer A is the *cis–cisoid–cis* isomer (**48**). Isomer B exists[164] in a second crystalline form, Isomer B′, with m.p. 83–84°C. In solution, the two forms are identical. A ready separation of Isomer B′ from Isomer A takes[168] advantage of the large differences in solubility in water between the lead and oxonium perchlorate complexes of the two isomers. X-ray crystallography has revealed[167] that Isomer B′ like Isomer B has the *cis–transoid–cis* configuration. Whilst it is generally believed[164] that Isomers B and B′ in the crystalline states are polymorphs, it is possible (cf. Reference 43) that they are conformational isomers differing in the relative conformations of the cyclohexane rings fused to the 18-membered ring. The stereospecific synthesis of the *trans–cisoid–trans* (**50**) and *trans–transoid–trans* (**51**) isomers from the methylenedioxydicyclohexanols[169] has been achieved[43,170]. Scheme 5 illustrates the synthetic route employed. Treatment of **253** and **254** in turn with diethyleneglycol ditosylate (**43**) under basic conditions gave the cyclic acetals **255** and **256**, respectively. Acid-catalysed hydrolysis afforded diols, which following further base-promoted condensations with **43** gave the two di-*trans* isomers **50** and **51** stereospecifically. A one-step synthesis

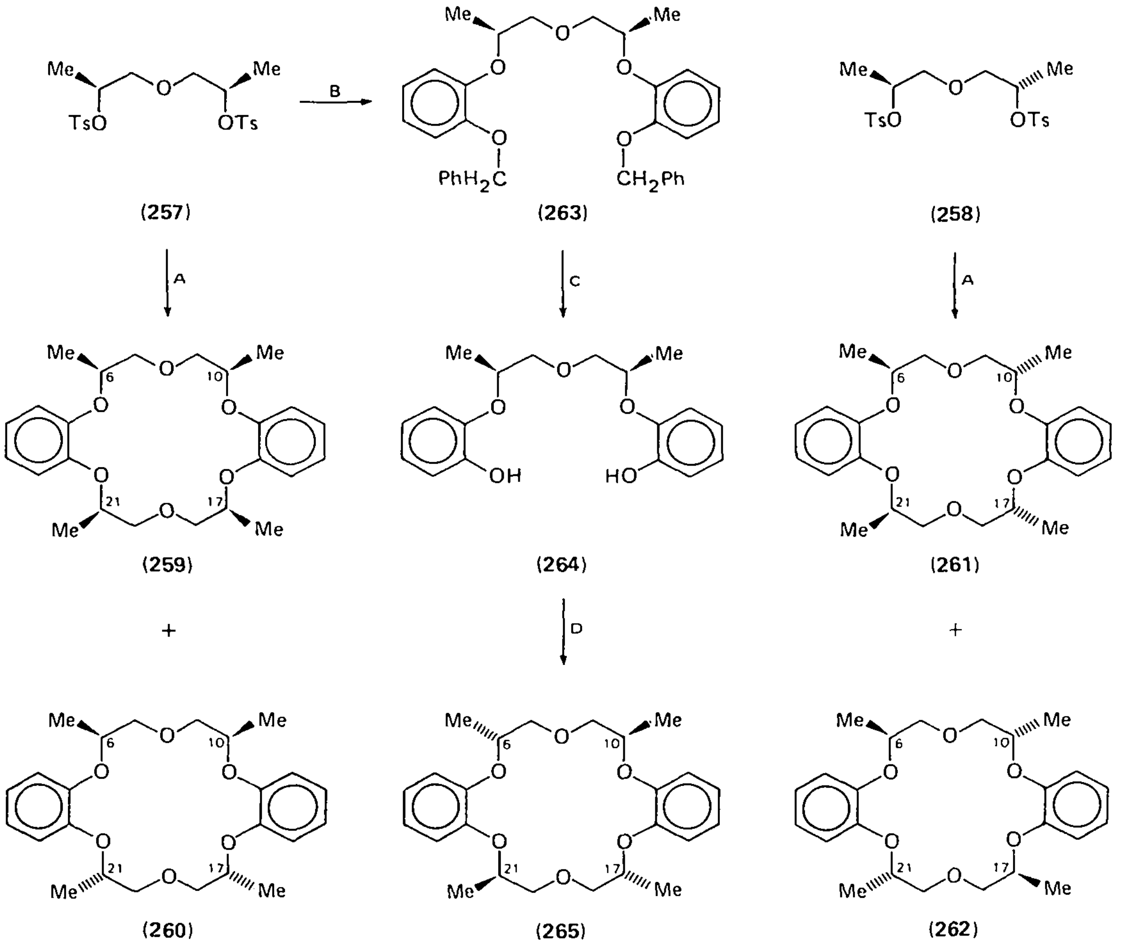


Reagents A: $TsOCH_2CH_2OCH_2CH_2OTs$, NaH, $Me_2SO/(MeOCH_2)_2$; B: H^+/H_2O

SCHEME 5.

of **50** and **51** from (±)-cyclohexane-*trans*-1,2-diol was accompanied by the formation of some (±)-*trans*-cyclohexano-9-crown-3.

The formal location of four constitutionally equivalent chiral centres at either $C_{(6)}$, $C_{(10)}$, $C_{(17)}$ and $C_{(21)}$, or $C_{(7)}$, $C_{(9)}$, $C_{(18)}$, and $C_{(20)}$ on the macrocyclic framework of dibenzo-18-crown-6 (**10**) generates five possible diastereoisomers in each series. The synthesis and separation of all ten configurational isomers of the constitutionally symmetrical tetramethyldibenzo-18-crown-6 derivatives have been described[171]. On the basis of stereochemically-controlled reactions and X-ray crystal structure analyses relative configurations have been assigned[171,172] to four of them. Scheme 6 outlines the preparation of the five diastereoisomers of the 6,10,17,21-tetramethyl derivative. A mixture of *meso*- and (±)-1,1′-oxydipropan-2-ol was prepared by reacting propylene oxide with (±)-propan-1,2-diol. The *meso*-isomer can be fractionally crystallized from the (±)-isomer. Tosylation of both the *meso*- and (±)-diols in turn afforded the *meso*-**257** and (±)-**258** ditosylates. Base-promoted condensation of **257** with catechol (**9**) gave a mixture of diastereoisomers **259** and **260**, which were separated by fractional crystallization. Similarly, reaction of the racemic ditosylate **258** with catechol (**9**) under basic conditions led



Reagents A: $o\text{-}C_6H_4(OH)_2$ (9), NaOH, $Me(CH_2)_3OH$; B: $o\text{-}PhCH_2OC_6H_4OH$, NaOH, $Me(CH_2)_3OH$; C: H_2, Pd; D: 258, NaOH, $Me(CH_2)_3OH$

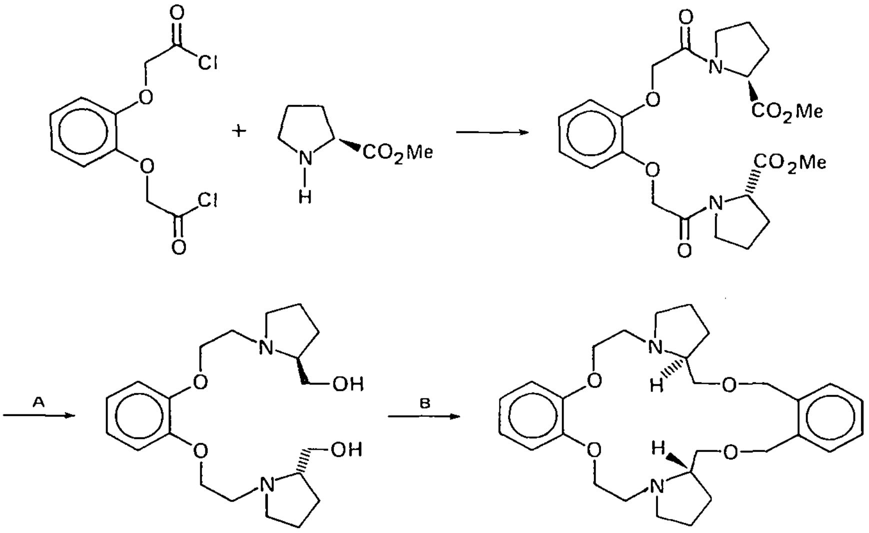
SCHEME 6.

to the isolation of a pair of diastereoisomers **261** and **262** which were separated by solvent extraction. The final diastereoisomer (**265**) was obtained by a three-stage procedure. The monobenzyl ether of catechol was condensed with **257** to give the dibenzyl ether **263**. After removal of the protecting groups to afford the diol **264** condensation with **258** led to ring-closure and isolation of **265**. The configuration of **265** follows from its mode of synthesis. The relative configurations of **259** and **260**, and **261** and **262**, have not been determined.

Catalytic hydrogenation of macrocyclic polyethers containing furan residues has led[107,173] in most cases to mixtures of diastereoisomers which have not been separated.

2. *Optically-active crown ethers from natural products*

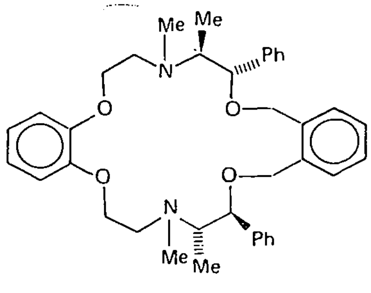
The first crowns incorporating optically-active residues were described by Wüdl and Gaeta[174] in 1972. L-Proline was introduced into the macrocyclic diaza polyether LL-266 by the procedure outlined in Scheme 7. D-ψ-Ephidrine was incorporated into DD-267 by a similar approach. In principle, a whole range of natural products including alkaloids, amino acids, carbohydrates, steroids and terpenes can be viewed[56] as chiral precursors. In practice, carbohydrates lend[31] themselves to the most detailed exploitation. For example, treatment of the bis(N,N'-dimethylamide) (L-268) of L-tartaric acid with two equivalents of thallium (I) ethoxide in anhydrous OHCNMe$_2$, followed by an excess of diethyleneglycol diiodide (269) in a modification[175] of the Williamson ether synthesis, afforded[176] (see equation 42) the tetracarboxamide 18-crown-6 derivative LL-270. This compound can be hydrolysed to the tetracarboxylate which can be converted into the tetraacid chloride, a key compound[177] in the preparation of derivatives with a



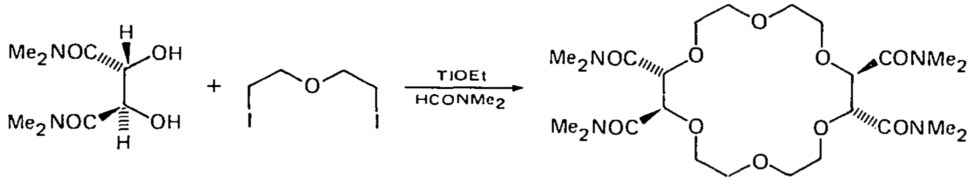
(LL-266)

Reagents A: LiAlH$_4$ B: o-C$_6$H$_4$(CH$_2$Br)$_2$ (32), NaOH, Me$_2$SO

SCHEME 7.



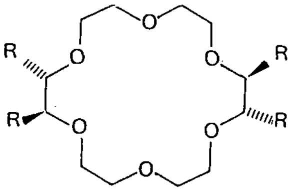
(DD-267)



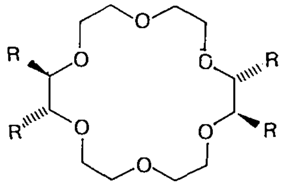
(42)

(L-268) (269) (LL-270)

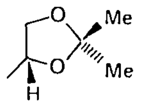
whole range of side-chains where the functionality has catalytic potential. The synthesis of LL-270 illustrates the attractions of employing chiral sources with C_2 symmetry. *Two* such residues are incorporated into *one* macrocycle which has D_2 symmetry. The same principle was relied upon in the synthesis of chiral 18-crown-6 derivatives, e.g. LL-271, LL-272, DD-273 and DD-274, incorporating L-threitol[178],

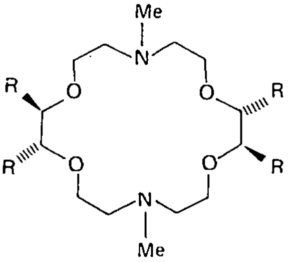


(LL-271) R = CH_2OH

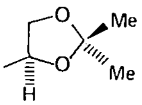


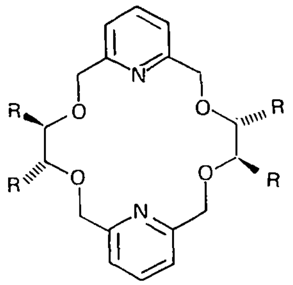
(LL-272) R =



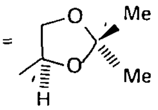


(DD-273) R =

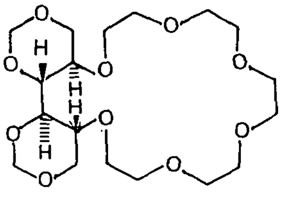




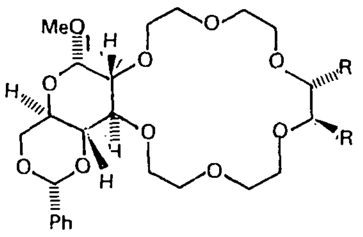
(DD-274) R =



L-iditol[179], and D-mannitol[178,180], all of which have C_2 symmetry. The key diols employed in these preparations were 1,4-di-*O*-benzyl-L-threitol and the 1,2:5,6-di-*O*-isopropylidene derivatives of L-iditol and D-mannitol. More recently, 1,3:4,6-di-*O*-methylene-D-mannitol has been incorporated[181] into a 20-crown-6 derivative D-275. Chiral asymmetric 18-crown-6 derivatives, e.g. D-276 and DD-277 have also been synthesized with D-glucose[182], D-galactose[182], D-mannose[183], and D-altrose[183] as the sources of asymmetry. In these cases, chain-extensions to give 'half-crown' diols through the sequence[47] of reactions, (*a*) allylation, (*b*) ozonolysis and (*c*) reduction, on the 4,6-*O*-benzylidene derivatives of methyl glycosides proved invaluable. Although only one compound results from condensations involving two chiral precursors, one with C_1 and the other with C_2 symmetry, two constitutional isomers, e.g. DD-278 and DD-279 result[184,185]. when two asymmetric residues are incorporated into an 18-crown-6 derivative.

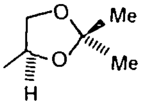


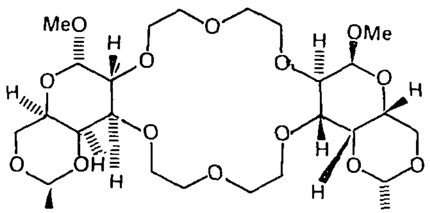
(D-275)



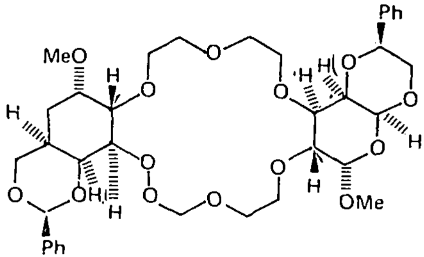
(D-276) R = H

(DD-277) R =



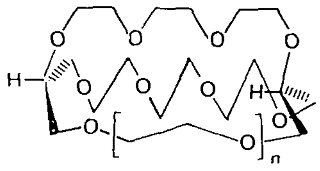


(DD-278)



(DD-279)

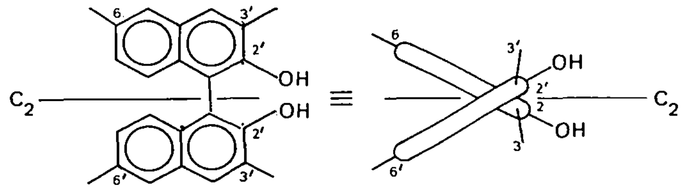
Finally, 2,3-*O*-isopropylidene-D-glycerol has been utilized[186] in an elegant synthesis of the chiral macrobicyclic polyethers DD-**280** and DD-**281**. One of the novelties of the preparative route is that it affords a stereospecific synthesis of *in–out* isomers of bicyclic systems.



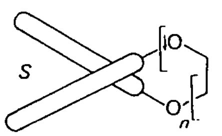
(DD-280) $n = 2$
(DD-281) $n = 3$

3. Optically active crown ethers from resolved precursors

The syntheses of (+)-(*SSSS*)-*trans–transoid–trans*-dicyclohexano-18-crown-6 as well as (+)-(*SS*)-*trans*-cyclohexano-15-crown-5 and (+)-(*SS*)-*trans*-cyclohexano-18-crown-6 have been reported[47] starting from optically pure (+)-(1*S*,2*S*)-cyclohexane-*trans*-1,2-diol resolved via the strychnine salts of the hemisulphate diester. However, it is the 1,1′-binaphthyl residue with axial chirality which has been utilized so elegantly by Cram and his associates[52–55,106,187–189] that has found its way into a whole host of optically active crown ethers! 2,2′-Dihydroxy-1,1′-binaphthyl is the key starting material in the syntheses. The fact that this diol is easily accessible from 2-naphthol and can then be resolved readily through either its monomenthoxyacetic ester or through the cinchonine salt of its phosphate ester to give, for example, (−)-(*S*)-**282** with C_2 symmetry accounts for its unique status. A range of macrocycles incorporating one, e.g. (+)-(*S*)-**283** to (−)-(*S*)-**287**, two, e.g.

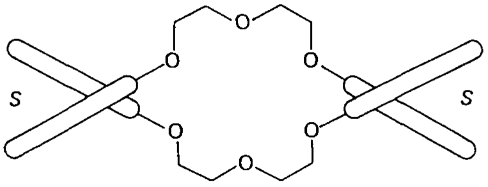


[(−)-(*S*)-282]

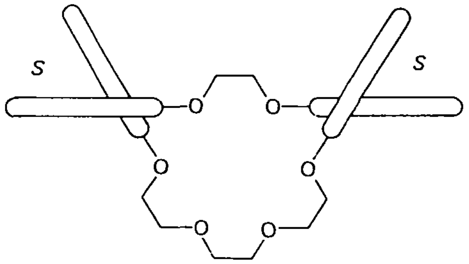


	n	Yield (%)
(+)-(*S*)-283	1	23
(+)-(*S*)-284	2	2
(−)-(*S*)-285	2	65
(−)-(*S*)-286	4	52
(−)-(*S*)-287	5	64

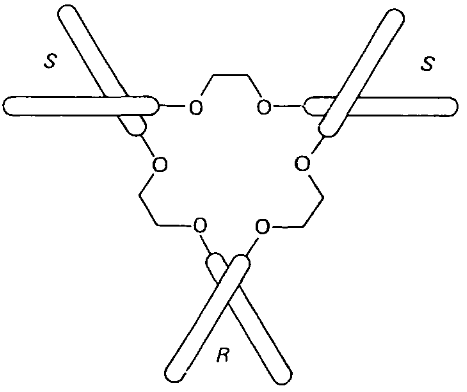
(−)-(*SS*)-288 and (−)-(*SS*)-289, and three, e.g. (−)-(*RSS*)-290, binaphthyl moieties have been synthesized by reactions involving base-promoted substitutions on RCl,



[(−)-(*SS*)-288]

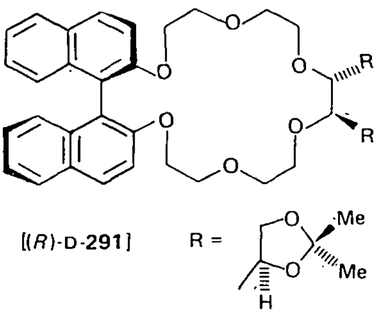


[(−)-(*SS*)-289]

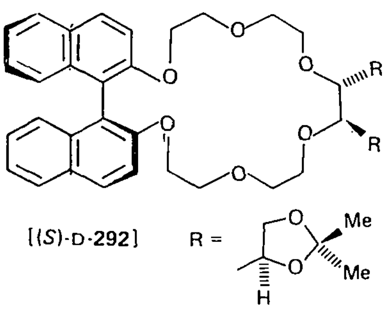


[(−)-(*RSS*)-290]

RBr or ROTs. Substituents, some containing functional groups have been incorporated at positions 3, 3′, 6, and 6′, and other residues and heteroatoms have been built into the macrocyclic ring. 'Resolution' of the 1,1′-binaphthyl unit has also been achieved[190] by employing (*RS*)-binaphthol, (*RS*)-282, and 1,2:5,6-di-*O*-isopropylidene-D-mannitol in the syntheses of the diastereoisomeric macrocyclic

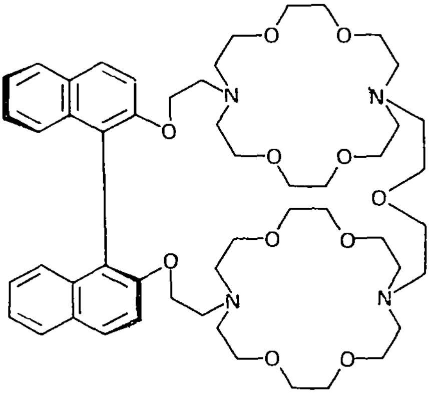


[(*R*)-D-291]



[(*S*)-D-292]

polyethers (*R*)-D-291 and (*S*)-D-292. Finally, it should be mentioned that (*S*)-282 has been incorporated[191] into the chiral macropolycyclic ligand (*S*)-293.



[(*S*)-293]

V. TOXICITY AND HAZARDS

Despite the large number of crown compounds synthesized during the past decade, comparatively little information is available in the open literature relating to their physiological properties. In his early papers, Pedersen[6,12,163] reported that dicyclohexano-18-crown-6 is toxic towards rats. The lethal dose for ingestion of this crown ether was found to be approximately 300 mg/kg of body weight. In ten-day subacute oral tests, the compound did not exhibit any cumulative toxicity when administered to male rats at a dose level of 60 mg/kg/day. Dicyclohexano-18-crown-6 was also found to be a skin irritant and generalized corneal injury, some iritic injury and conjunctivitis occurred when it was introduced into the eyes of rats as a 10% solution in propyleneglycol. Leong and his associates[192] have published toxicological data for 12-crown-4 (**4**) and other simpie crown ethers. Rats exposed to **4** at concentrations between 1·2 and 63·8 p.p.m. in air suffered loss of body weight. They also developed anorexia, asthenia, hindquarter incoordination, testicular atrophy, auditory hypersensitivity, tremors, convulsions and moribund conditions. Oral adminstration of **4** to rats in a single dose of 100 mg/kg of body weight produces effects upon the central nervous system in addition to causing testicular atrophy. Acute oral toxicity investigations on 15-crown-5 (**19**), 18-crown-6 (**12**) and 21-crown-7 (**54**) revealed that these compounds also produce effects upon the central nervous system of rats although higher dosages were needed than those required with **4**. It is clear that crown ethers should be handled with caution and respect!

There has been a report[193] of an explosion during one particular experimental manipulation[19] to obtain pure 18-crown-6 (12) from a reaction mixture. In one step of the isolation procedure, it is necessary to decompose thermally under reduced pressure the 18-crown-6-KCl complex formed during the reaction. However, at the temperatures of 100–200°C necessary to decompose the complex, decomposition may occur at the distillation head with the production of 1,4-dioxane. Breaking of the vacuum at >100°C can lead to autoignition of air–1,4-dioxane mixtures and hence explosions. Experimental procedures have been suggested[194] to reduce the risk of these as a result of distilling 18-crown-6 (12) from its KCl complex at high temperatures. Constant vigilence is essential!

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 2

Crown ethers—complexes and selectivity

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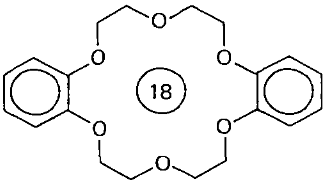
I. INTRODUCTION: CROWN ETHER TYPE NEUTRAL LIGAND SYSTEMS

Since the discovery of *dibenzo[18]crown-6* (1)[1], *[18]crown-6* (2)* and other cyclic polyethers[2] together with the knowledge that these potentially exolipophilic compounds selectively complex alkali and alkaline earth metal cations in their endopolarophilic cavity[3], efforts have continued to modify the widely useful properties[4–6] of such crown ethers by variation of all possible structural parameters in order to make accessible new ligand systems and to study the relationship between structure and cation selectivity as well as their complex chemistry[7].



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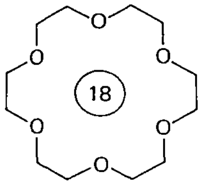

(2)

Variable parameters included the number of ether oxygen atoms, ring size, length of the $(CH_2)_n$ bridge, substitution by other heteroatoms (N,S), introduction of aromatic (benzene, biphenyl, naphthalene) and heteroaromatic systems (pyridine, furan, thiophene) in the ring[8,9]. Figure 1 shows some such crown ethers (*coronands*: the corresponding complexes have been called *coronates*)[10].

The possibilities of structural variation are still not exhausted. An important development in the neutral ligand topology is linked with the ability of large-ring bicyclic diamines (*catapinands*, see **17** in Figure 2) to take up protons and anions inside their three-dimensional cavity (*catapinates*)[11]. This has led to the design of *cryptands* – three-sidedly enclosed endopolarophilic/exolipophilic cavities – in

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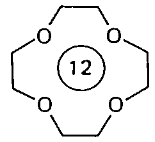
*Crown ether nomenclature: In square brackets the total number of atoms in the polyether ring is given (see encircled numbers in the formulae), followed by the class descriptor 'crown' and the total number of donor atoms in the main ring. Condensed rings are designated by prefixes 'benzo', 'cyclohexano' etc., sulphur or nitrogen donor centres by 'thia' and 'aza'.



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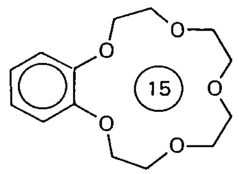

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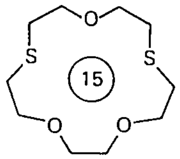

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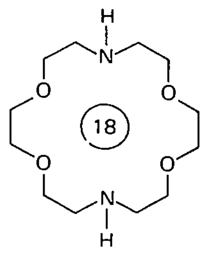

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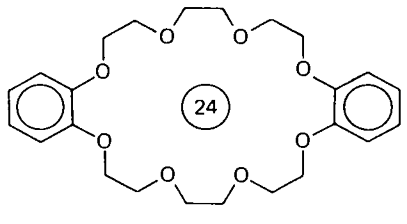

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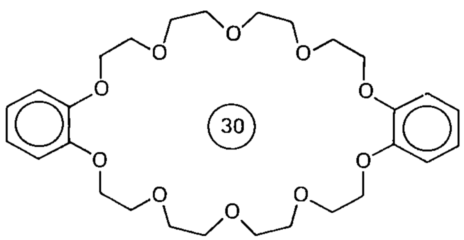

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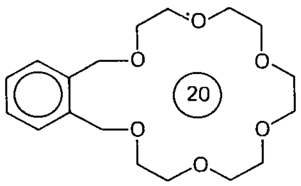

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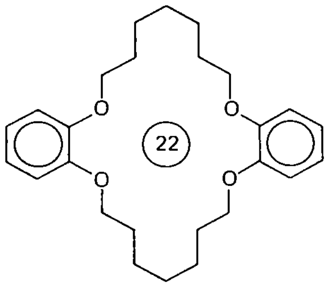

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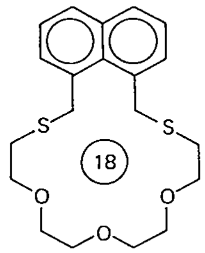

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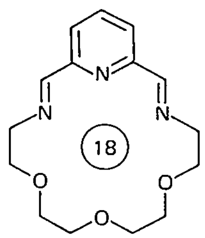

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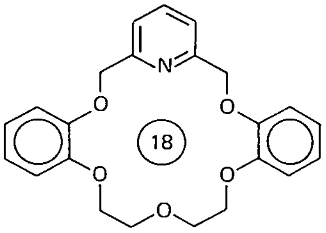

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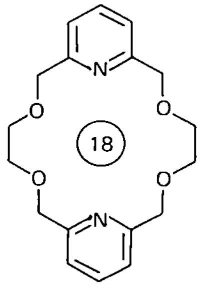

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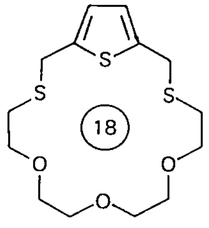

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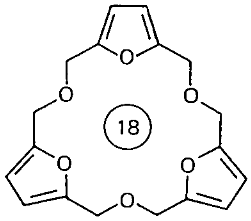

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FIGURE 1. Some monocyclic crown ether type neutral ligands (coronands).

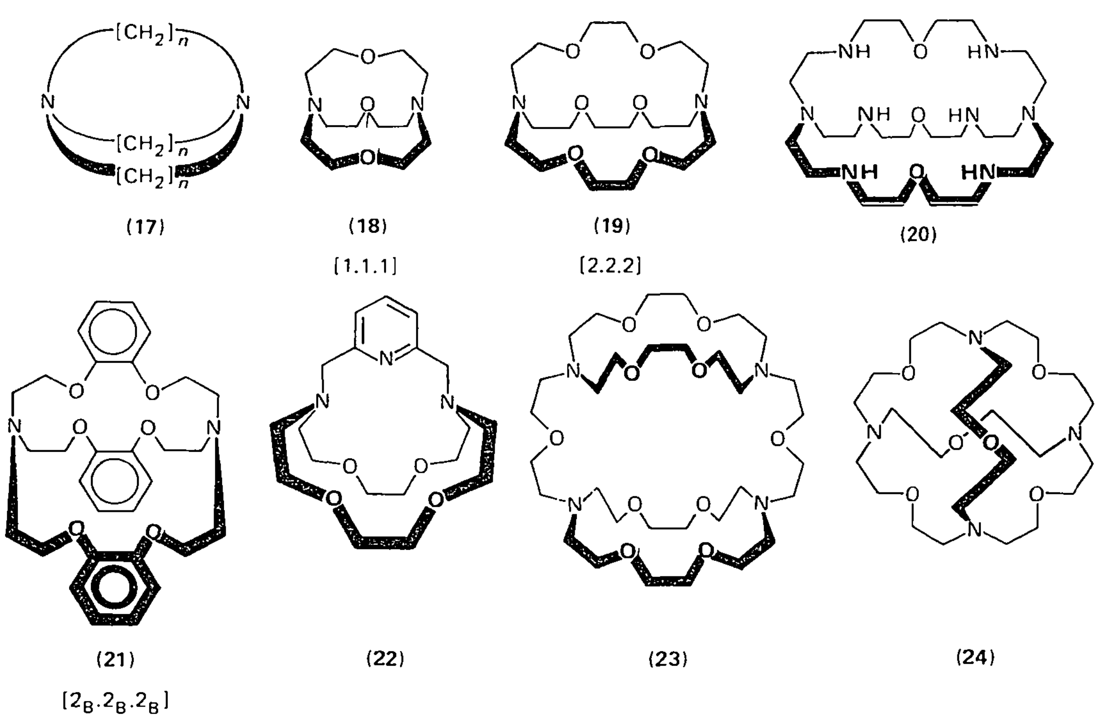


FIGURE 2. A catapinand 17 and some selected cryptand molecules 18–24.

which metal cations can be firmly trapped[12]. The complexes are called *cryptates*[13]*. Numerous structural variations are also possible here,[14,15] as shown in Figure 2†.

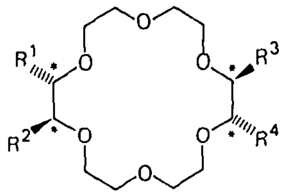
The chemistry of the neutral ligands was essentially enriched by the incorporation of chirality elements into the ring skeleton leading to the formation of *chiral* or optically active crown host compounds[16,17] (Figure 3) capable of differentiating between enantiomeric guest molecules, e.g. amino acids, as shown by some examples (chiroselectivity)[18].

After strong neutral ligands like the cryptands had been more accurately examined, interest grew in the study of *open-chain* ligand topologies[19], which, despite their weaker complexing ability, efficiently discriminate, as has been shown, between different cations[20]. Here the development proceeded with *many-armed* ligand systems (Figure 4) – where profitable use was made of the cooperative effect of piled up donor atoms (*'octopus molecules'*)[21] – ranging from phase-transfer catalytically active analogous triazine compounds[22] and similar *'hexahost'*-type molecules[23] to open-chain skeletons with rigid *terminal donor group systems* (*open-chain crown ethers* and *cryptands*, Figures 5 and 6)[24,25]. Relatively simple donor

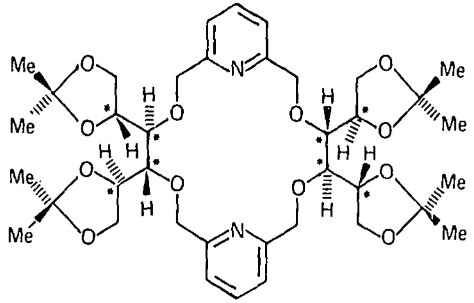
---

*Sometimes '⊂' is used to distinguish a cryptate from a cryptand, e.g. $[K^+ \subset 2.2.2]$.

†Every cipher in square brackets represents one bridge and gives the number of its donor atoms. [2.2.2]cryptand (or only [2.2.2]) is a cryptand with three bridges with two oxygen atoms in every one subscripts, e.g. 2_B, 2_C, 2_D, refers to benzo or cyclohexano condensation and to a decyl residue on the respective bridge.



(25) (a) R^1, R^2 = H; R^3, R^4 = COOEt
(b) R^1, R^2, R^3, R^4 = COOEt
(c) R^1, R^2, R^3, R^4 = $C(=O)NMe_2$



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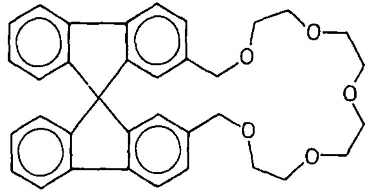

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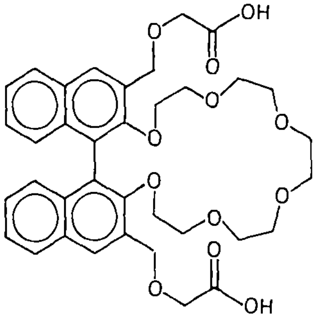

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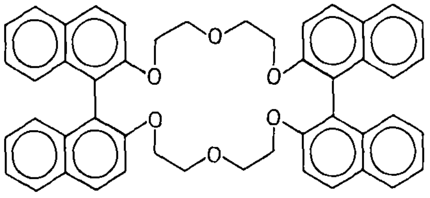

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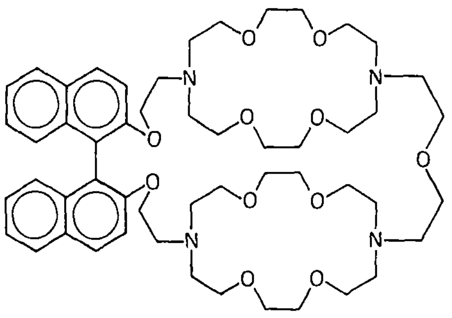
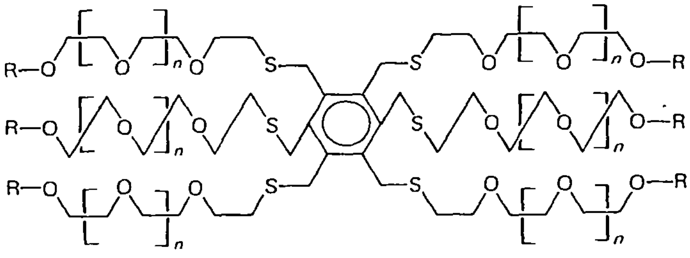


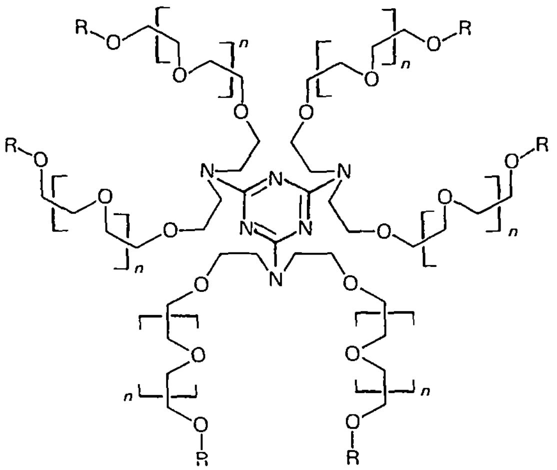
(29)

FIGURE 3. Selected chiral crown ethers.



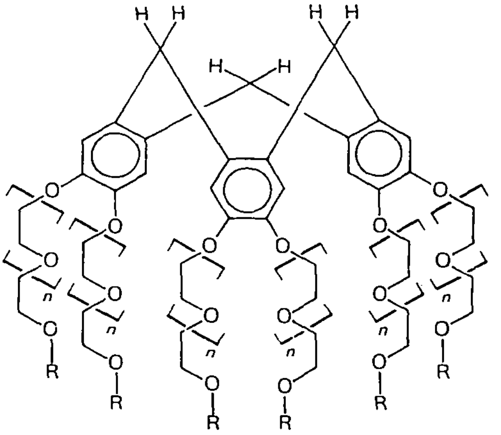
(31)

R = Me, Et, n-Bu



(32)

R = n-Bu, n-Oct



(33)

R = Me, Et, n-Bu

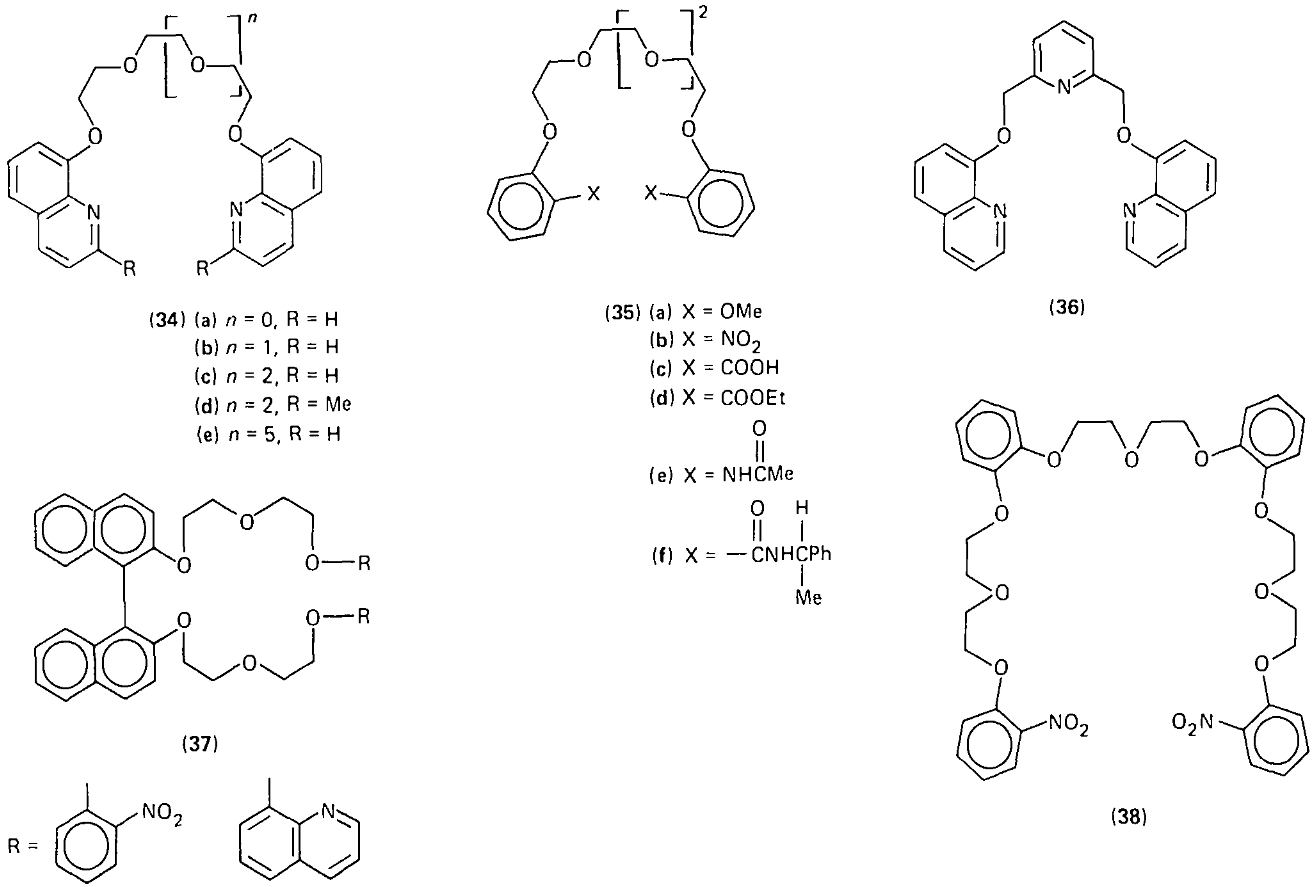
FIGURE 4. Octopus molecules as noncyclic neutral ligand systems.

endgroup-containing *glyme-analogous* compounds easily form crystalline complexes with alkali and alkaline earth metal ions[25,26].

Studies by Simon and coworkers show that on account of their high ion selectivity, weaker open-chain ligands like 42, and 43 (Figure 7) are of analytical value for microelectrode systems[27].

Interesting are the ligands in the marginal zone between cyclic and open-chain compounds[26b,28], which find their natural counterparts in the nigericin antibiotics[29] and as 'ionophores' are capable of transporting ions across lipophilic media (cell membranes)[30]. Essentially open-chained, they can create a *pseudocyclic* cavity of definite geometry via attractive interaction between their end-groups (see 35c, Figure 5 and 46, Figure 7), thereby achieving a higher ion selectivity than common noncyclic ionophores[7b].

With the isolation of crystalline complexes of glyme-type *short-chain oligoethers* (47)[31] possessing only one donor end-group as well as those of longer chain *classical glymes* (49) and glyme analogous ligands (48)[32] and even those of simple glycols (50) such as ethylene glycol ($n = 0$)[33a] (Figure 7) and ethanolamines[33b], the



(34) (a) $n = 0$, R = H
(b) $n = 1$, R = H
(c) $n = 2$, R = H
(d) $n = 2$, R = Me
(e) $n = 5$, R = H

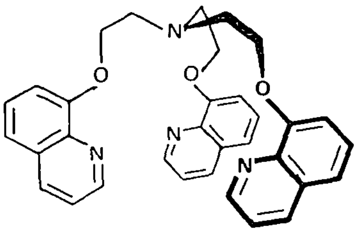
(35) (a) X = OMe
(b) X = NO_2
(c) X = COOH
(d) X = COOEt
(e) X = $NH\overset{O}{\overset{\|}{C}}Me$
(f) X = $-\overset{O}{\overset{\|}{C}}NH\underset{Me}{\overset{H}{C}}Ph$

(36)

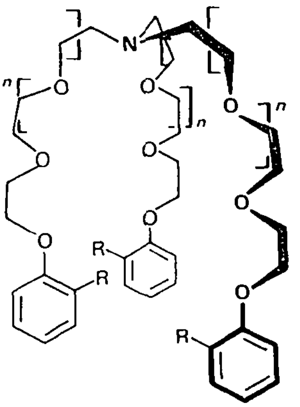
(37)

(38)

FIGURE 5. Open-chain crown-type ligands (X = donor centre).

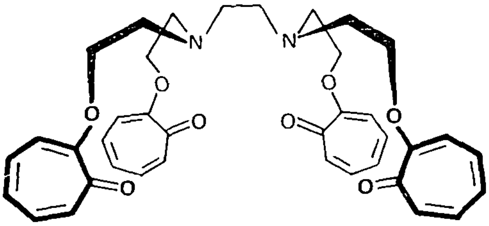


(39)



(40)

R = H, OMe, NO_2



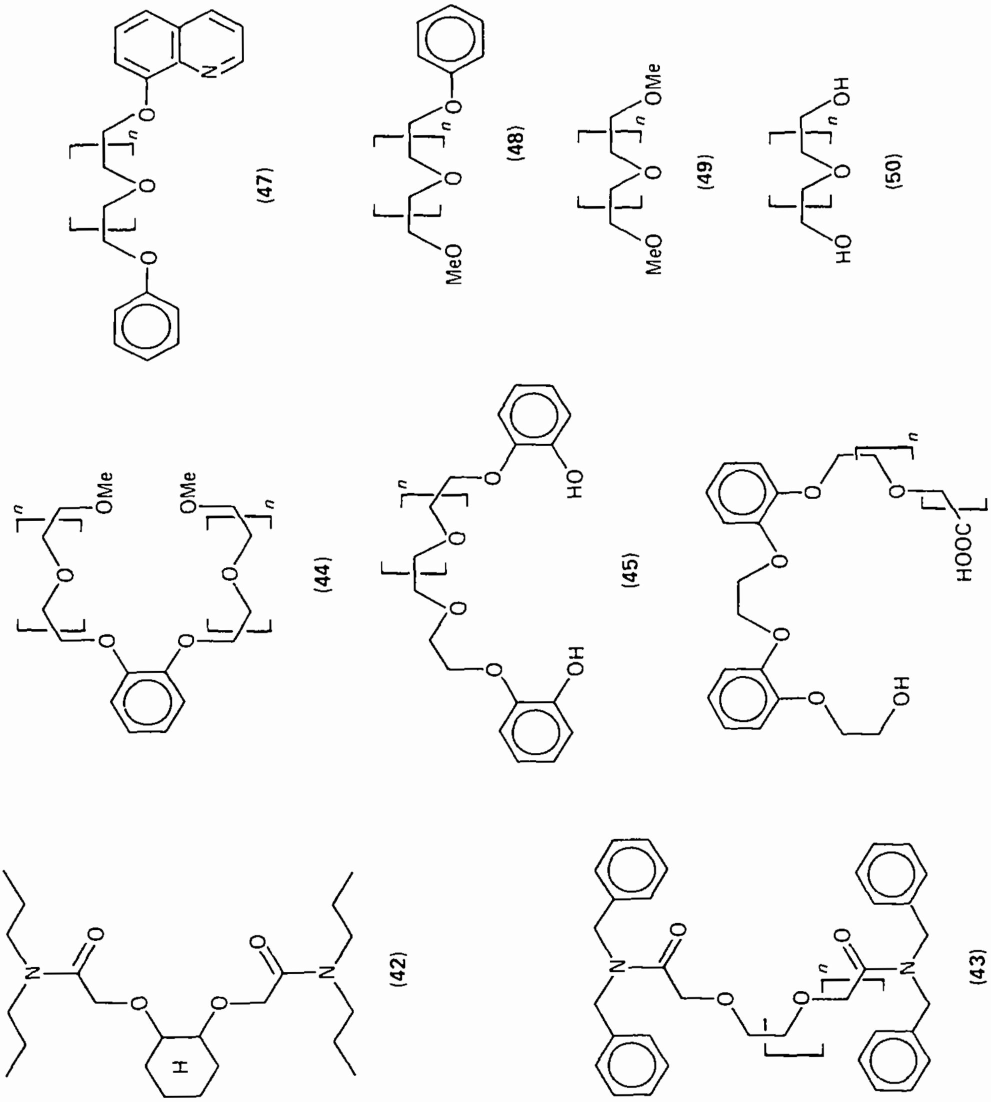
(41)

FIGURE 6. Open-chain-type cryptands (tripodands, tetrapodands).

whole range of crown type compounds is covered, extending from the original monocycles via the topologically notable polycyclic analogues to the relatively simple structural open-chain ligand systems with and without donor end-groups.

Investigations on the complexation of glymes and glyme analogues allow the study of the fundamental processes of complexation by neutral ligands with only a few donor centres and binding sites; the latter may be considered to be the most simple model substances for studying complexation processes of biomolecules and biochemical enzyme/substrate or receptor/substrate interactions[34].

It is remarkable that the historical development could equally well have originated with the open-chain glyme analogues to spread via the more complicated monocyclic crown ethers to the ultimate polycyclic cryptands. Apparently, it was only with the discovery of the very clear complexation behaviour of cyclic systems that interest arose in the alkali/alkaline earth complexation which might be exhibited by open-chain neutral ligands of the glyme type.



(42)

(43)

(44)

(45)

(46)

(47)

(48)

(49)

(50)

FIGURE 7. A few weaker complexing neutral ligand systems, glymes and oligoethylene glycols.

II. FUNDAMENTALS OF THE CROWN ETHER COMPLEXATION

A. General Remarks

Stability and *selectivity* of crown ether complexes cannot be properly or significantly understood without first considering the principles of the *kinetics* of complexation (‘*dynamic stability*’ of complexes).

A different approach to the problem is by determination of *thermodynamic* data pertaining to the system in an equilibrium state (‘*static complexation constants*’), omitting consideration of the mechanistic steps of the complexation reaction. Both methods allow the determination of the complex stability constants (K_S values), but significantly differ in points which may be important for the practical use of a particular crown ether. These points will be discussed in detail in Section III, following the general theoretical description of the crown ether complexation.

B. Kinetics and Mechanism of Complexation

1. Introduction[7b,d]

Molecular kinetics, i.e. the dynamic behaviour of a system – composed of ligand, cation and solvent – in the sense of a forward (*complexation*) and a reverse (*decomplexation*) reaction (equation 1), give information about the lifetime of a

$$M^{+}_{\text{solv.}} + \text{Ligand}_{\text{solv.}} \underset{\overleftarrow{k}}{\overset{\overrightarrow{k}}{\rightleftharpoons}} [M^{+}\,\text{Ligand}]_{\text{solv.}} \qquad (1)$$

complex. The ratio of the rate constant of complexation ($\overrightarrow{k}$) to that of decomplexation ($\overleftarrow{k}$) is thus directly connected with the stability of (K_S) of the crown ether complex ($K_S = \overrightarrow{k}/\overleftarrow{k}$, see Section II.C). Since the rate constants of the forward and reverse reactions depend on the corresponding activation energies (E_A), complex and selectivity constants are in fact results derived from thermodynamic data, composed of an enthalpy ($\Delta H^{\neq}$) and an entropy ($\Delta S^{\neq}$) part. Elucidation of the complexation reaction by consideration – albeit thorough – of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ is not always possible.

2. Interpretation of the complexation/decomplexation phenomena (desolvation, ligand exchange and diffusion processes)

Metal complexation in solution is generally a very quick reaction[35]. Nuclear magnetic resonance[36] and relaxation curves[37] have shown, however, that complex formation does not occur instantaneously, and it is not a simple one-step reaction between ligand and cation. Often complexation includes a series of intermediate steps like substitution of one or several solvent molecules from the inner coordination shell of the metal ion and/or internal conformational rearrangements of the ligand, in particular, when the ligand is a multidentate one (crown ether, cryptand, podand)[7b].

The ‘complexation reaction’ can occur essentially by two border mechanisms[38]:

(1) The solvent molecule leaves the cation, decreasing its coordination number, prior to entry of the ligand: S_N1*-type mechanism.*

(2) The ligand forces its way through the solvent envelope of the cation, increasing the coordination number of the latter and then displaces a solvent molecule: S_N2*-mechanism*.

In the first case, the rate of substitution depends only on the solvated metal ion; in the latter case it is also ligand-dependent.

In aqueous solution, solvent/ligand exchange reactions with many main-group metal ions proceed via the S_N1 mechanism[39], whilst S_N2 mechanisms are mostly associated with metal ions having deformed coordination envelopes[40]. In reality, a *hybrid mechanism* resembling more a 'push–pull' type process must be taken for granted[7b].

In order for a reaction between ligand and metal ion to occur, both partners must collide after diffusing to within critical distance of each other[41]. Thus the following overall system (equation 2) is derived from equation (1):

$$M^+_{\text{solv.}} + \text{Ligand}_{\text{solv.}} \underset{k_{2/1}}{\overset{k_{1/2}}{\rightleftarrows}} \underset{\text{(within critical distance)}}{[M^+\ldots\text{Ligand}]} \underset{k_{3/2}}{\overset{k_{2/3}}{\rightleftarrows}} [M^+\,\text{Ligand}]_{\text{solv.}} \qquad (2)$$

where $k_{1/2}$, $k_{2/1}$ are the rate constants of forward and reverse diffusions and $k_{2/3}$, $k_{3/2}$ the rate constants for (stepwise) ligand exchange. The rate constants for the whole complexation ($\vec{k}$) and decomplexation ($\overleftarrow{k}$) reactions can then be expressed by the following quotients (3) and (4):

$$\vec{k} = \frac{k_{1/2} \cdot k_{2/3}}{k_{2/1} + k_{2/3}} \qquad (3) \qquad\qquad \overleftarrow{k} = \frac{k_{2/1} \cdot k_{3/2}}{k_{2/1} + k_{2/3}} \qquad (4)$$

If the reverse diffusion ($k_{2/1}$) is quicker than the ligand exchange reaction, more encounters between the partners are required before a ligand exchange can occur; $\vec{k}$ will then be determined by equation (5). When the reaction step $k_{2/3}$ is rapid

$$\vec{k} = k_{2/3} \cdot \frac{k_{1/2}}{k_{2/1}} \qquad (5)$$

relative to the reverse diffusion, every encounter between the partners leads to the desired product and the whole process can be considered to be *diffusion-controlled* with $k_{1/2}$ as the overall rate constant.

The values for $k_{1/2}$ and $k_{2/1}$ are of the order of 10^9 to 10^{10} (l/mol/s) or (l/s); they depend on the charge and size of the partners as well as on the solvent used[42]. The following sections deal with the comparison and characterization of the various polyether families (natural ionophores, coronands, cryptands, podands) according to their kinetics of complexation.

3. *Kinetics of complexation of a few types of crown ether*

a. Natural ionophores. Open-chain antibiotics like *nigericin* show rate constants k of about 10^{10}/mol/s (Table 1)[7b,43] for recombination (complexation reaction) with alkali metal cations, as is expected for a diffusion-controlled reaction (see above) between two univalent oppositely charged ions[44]. Since the nigericin molecule wraps round the cation, it may be taken for granted that the substitution can be extremely rapid, occurring, however, by a stepwise mechanism. In other words, the solvent molecules are displaced one after the other; in each substitution step, solvation energy is compensated for by ligand binding energy.

The overall rate of complex formation for *valinomycin* depends on the radius of the cation (Table 1)[45,46]: Rb^+ ions complex more rapidly than K^+, Na^+ and Cs^+ ions. The rate of dissociation is, on the other hand, lowest for Rb^+. For this ionophore, exact rate constants of the single reaction step defined by equation (2) are also known (Table 2)[45b].

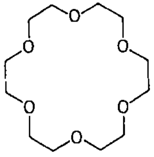
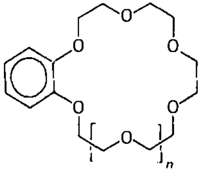
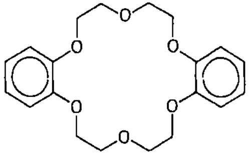
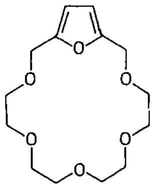
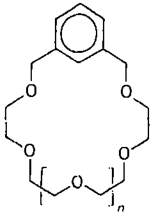
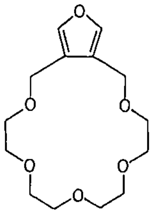
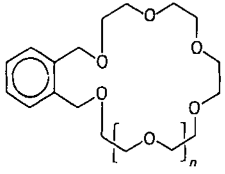
TABLE 1. Kinetic parameters ($\vec{k}$, $\overleftarrow{k}$) for the formation of cation complexes with some natural ionophores

Ligand	Solvent [temp.]	Cation	$\vec{k}$ (1/mol/s)	$\overleftarrow{k}$ (1/s)	Reference
Nigericin	MeOH[25°C]	Na^+	1×10^{10}	1.1×10^5	43
Nonactin	$MeOH/CDCl_3$ [4:1; 21°C]	K^+	1.6×10^5	32	46
Valinomycin	MeOH[25°C]	Na^+	1.3×10^7	1.8×10^6	45a
		K^+	3.5×10^7	1.3×10^3	
		Rb^+	5.5×10^7	7.5×10^2	
		Cs^+	2.0×10^7	2.2×10^3	
		NH_4^+	1.3×10^7	2.5×10^5	

TABLE 2. Rate constants for single steps of the complexation of valinomycin with Na^+ and K^+ (in MeOH, 25°C)[45b]

Cation	$k_{1/2}$ (1/mol/s)	$k_{2/1}$ (1/s)	$K_{1/2} = k_{1/2}/k_{2/1}$ (1/mol)	$k_{2/3}$ (1/s)	$k_{3/2}$ (1/s)	$K_{2/3} = k_{2/3}/k_{3/2}$
Na^+	7×10^7	2×10^7	3.5	4×10^6	2×10^6	2
K^+	4×10^8	1×10^8	4.0	1×10^7	1.3×10^3	7.7×10^3

TABLE 3. Kinetic data and K_S values of t-BuNH$_3^+$PF$_6^-$ complexes of some crown ethers (CDCl$_3$, 20°C)[36]

Crown	 (2)	 (4) $n = 0,1$	 (1)	 (51)	 (52) $n = 1,2$	 (53)	 (9) $n = 0,1$
$\overrightarrow{k}$ (l/mol/s)	1.49×10^9	7.75×10^8	1.02×10^9	1.43×10^9	1.19×10^9	7.7×10^8	1.26×10^9
$\overleftarrow{k}$ (l/s)	65	155(n = 1)	850	1100	5400(n = 1)	7000	9000(n = 1)
$\Delta G_1^{\neq}$ (kcal/mol) (kJ/mol)	14.7 61.53	14.2 59.44	13.2 55.26	13.0 54.42	12.1 50.65	12.0 50.23	11.8 49.49
E_A (kJ/mol)	19.3 80.79	18.0 75.35	13.0 54.42	15.2 63.63	12.2 51.07	10.5 43.95	9.9 41.44

b. Monocyclic crown ethers. Kinetic investigations of the alkali metal complexation of crown ethers are generally impeded by the following factors[7d]: the complexes are relatively weak and must, therefore, be studied at high metal ion concentrations; the rate constants are very high usually and the experimental difficulties encountered with the higher concentrations required are greater; the complexes often do not display any light absorption in measurable zones, so that spectroscopic determinations of reaction rate constants are usually not possible.

^{1}H-NMR spectroscopic investigations of the complexation kinetics of various *crown ethers* and *t*-butylammonium hexafluorophosphate showed that the rates of complex formation ($\vec{k}$) for all studied ligands are approximately the same, 0.8–1.5 $\times 10^9$/mol/s[36], and are probably, diffusion-controlled[47]. Hence, the differences in complex stabilities must be caused by different rates of decomplexation ($\overleftarrow{k}$), which vary between 10^2 and 10^4/s (see Table 3).

In Table 4 are listed the rate constants ($\vec{k}$, $\overleftarrow{k}$) of *dibenzo[30]crown-10* (8) and various alkali metal ions (Na^+...Cs^+) or NH_4^+[48], measured in methanol according to the temperature jump method[49]. These practically diffusion-controlled $\vec{k}$ values are only possible with appreciable conformational ligand flexibility[50]. A less flexible ligand would require total desolvation of the cation before complexation, leading to an essential decrease of the reaction rate constant. During the complexation of the conformationally very flexible dibenzo[30]crown-10, a solvent molecule is replaced by a crown ether donor location via a low activation energy barrier, i.e. the cation is simultaneously desolvated and complexed.

For *dibenzo[18]crown-6* and Na^+, a rate constant of $\vec{k} = 6 \times 10^7$/mol/s[51] has been found by ^{23}Na-NMR measurements[52] in DMF (Table 4); the value is much greater than that for the complexation of Na^+ ions by a macrobicyclic ligand in water, for example (see Section II.B.3.c).

c. Cryptands. Cryptands with comparably rigid structures should exchange cations more slowly, as has been confirmed experimentally (see Table 5). In the case of these ligands, a slightly modified stepwise mechanism of metal ion complexation is taken for granted, whereby it is again not required that all solvent molecules simultaneously leave the coordinated shell[7b].

The kinetics of complex formation were first measured for the *[2.2.2]cryptand*, **19**; with the help of potentiometry, ^{1}H- and ^{23}Na-NMR spectroscopy, the overall dissociation rates of the complexes have been determined[14c,53,54].

Temperature jump relaxation methods, which allow the determination of rate constants of complex association and dissociation, gave $\vec{k}$ values of $10^5 - 10^7$/mol/s and $\overleftarrow{k}$ values between 10 and 10^3/s for reaction between cryptands [2.1.1] (**54**), [2.2.1] (**55**), [2.2.2] (**19**) (in H_2O, not or singly protonated) and Na^+, K^+[37]. From these results it follows that after the diffusion-controlled formation of the encounter complex, the coordinating atoms of the ligand replace the water molecules of the inner hydrate shell of the metal ion in a stepwise way.

The pronounced selectivity of the cryptands (in MeOH) for alkali metal cations is reflected in the dissociation rates; the formation rates increase only slightly with increasing cation size[55] (Table 5). The specific size-dependent interaction between the metal ions and the cryptands must occur subsequent to the formation of the transition state in the complex formation reaction. For a given metal ion, the formation rates increase with increasing cryptand cavity size; for the [2.2.2] cryptand they are similar to the rates of solvent exchange in the inner sphere of the cations. This suggests that during complex formation, particularly for the larger cryptands, interactions between the cryptand and the incoming cation can compensate effectively for the loss of solvation of the cation[56].

TABLE 4. Overall rate constants for complexation ($\overrightarrow{k}$) and dissociation ($\overleftarrow{k}$) of some alkali metal ions with dibenzo[18]crown-6 (1) and dibenzo[30]-crown-10 (8) and values for the complex formation constant K_S

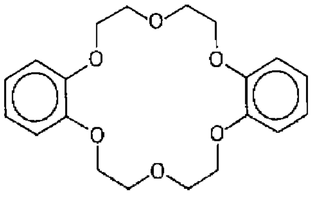
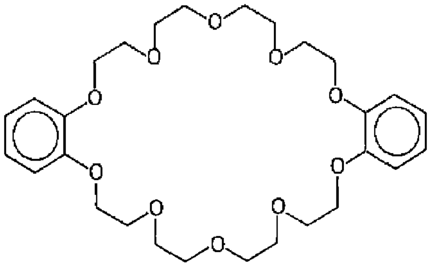
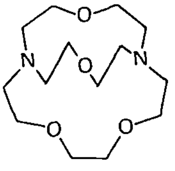
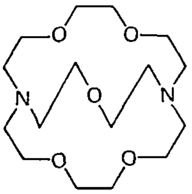
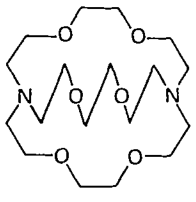
Ligand	Solvent [temp.]	Cation	$\overrightarrow{k}$ (1/mol/s)	$\overleftarrow{k}$ (1/s)	K_S	Reference
 (1)	DMF [25°C]	Na^+	6×10^7	1×10^5	600	51
 (8)	MeOH [25°C]	Na^+ K^+ Rb^+ Cs^+ NH_4^+	1.6×10^7 6×10^8 8×10^8 8×10^8 $>3 \times 10^7$	$>1.3 \times 10^5$ 1.6×10^4 1.8×10^4 4.7×10^4 $>1.1 \times 10^5$	1.3×10^2 3.7×10^4 4.4×10^4 1.7×10^4 2.7×10^2	48

TABLE 5. Overall rates and log K_S values for complex formation between bicyclic cryptands and alkali metal cations (MeOH, 25°C)[55]

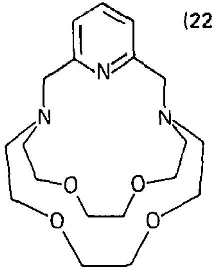
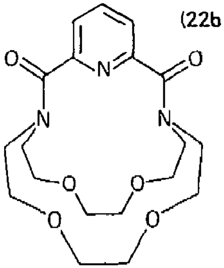
Ligand		Cation	$\vec{k}$ (1/mol/s)	$\overleftarrow{k}$ (1/s)	K_S[7b,14c]
 [2.1.1]	(54)	Li^+	4.8×10^5	4.4×10^{-3}	$>16^6$
		Na^+	3.1×10^6	2.50	1.3×10^6
 [2.2.1]	(55)	Li^+	1.8×10^7	7.5×10	$>10^5$
		Na^+	1.7×10^8	2.35×10^{-2}	$>10^8$
		K^+	3.8×10^8	1.09	$>10^7$
		Rb^+	4.1×10^8	7.5×10	$>10^6$
		Cs^+	$\approx 5 \times 10^6$	$\approx 2.3 \times 10^4$	$\approx 1.0 \times 10^5$
 [2.2.2]	(19)	Na^+	2.7×10^8	2.87	$>10^8$
		K^+	4.7×10^8	1.8×10^{-2}	$>10^7$
		Rb^+	7.6×10^8	8.0×10^{-1}	$>10^6$
		Cs^+	$\approx 9 \times 10^8$	$\approx 4 \times 10^4$	2.5×10^4

Pyridinophane cryptands of type 22 have been particularly well studied[57]. The first step of the complexation mechanism consists in the diffusion-controlled recombination of both reactants and the stepwise substitution of the water molecules of inner hydration sphere by the cryptands. The overall rate of complex formation is determined by structural changes of the ligand occurring at a frequency of approximately 10^4/s subsequent to the encounter and the substitution step. During this slow step, there is either rotation of the ether oxygen atoms into the ligand interior toward the incorporated metal ion or a shift of the *exo/endo* equilibrium at the bridgehead nitrogens of the ligand in favour of the *endo* conformation. Owing to steric restrictions, the latter structural change can be very slow.

At first sight, it may seem surprising that the relatively big potassium cation is more strongly bound by the diamide ligand 22b than by the less rigid diamine 22a (see Table 6), while the affinity of the sodium ion for both ligands remains approximately the same.

This apparent inconsistency has been elucidated by kinetic studies. Comparison of the single rate constants of corresponding reaction steps (Table 6) shows that the difference in the stability of the two complexes is particularly exhibited in the dissociation rate $k_{2/1}$ of the first step with all the other rate constants remaining very similar. This can be attributed to the fact that the diamine does not possess

TABLE 6. Rate constants k and log K_S values for the complexation of pyridinophane cryptands 22 (in H_2O, 25°C)[57]

Ligand	Cation	$k_{1/2}$(1/mol/s)	$k_{2/1}$(1/s)	$k_{2/3}$(1/s)	$k_{3/2}$(1/s)	log K_S
 (22a)	Na^+ K^+	3×10^8	7×10^3	8×10^3	2.0×10^4	4.89 4.78
 (22b)	Na^+ K^+	3×10^8 5×10^8	1.5×10^4 3×10^3	1.4×10^4 5×10^3	1.4×10^4 1.8×10^4	4.58 5.25

any electronegative carbonyl oxygen atoms on the surface of the molecule. Hence the rate of association $k_{1/2}$ to the intermediate decreases, while the dissociation rate $k_{2/1}$ increases.

The crystalline *Eu(III)* and *Gd(III) cryptates* of [2.2.1] display a remarkable kinetic stability in water and appear to be the first substitutionally inert lanthanide complexes[58]. Neutral solutions show no metal hydroxide precipitate, even after several days of ageing. In strongly basic solution, the complexes are stable for hours. No dissociation of the complex is seen even after several days in aqueous perchloric acid. This inertness renders the $[Gd(2.2.1)]^{3+}$ ion useful as a T_1 (shiftless) relaxation reagent for NMR in polar inorganic solvents or in aqueous solutions.

The kinetics of *protonation and deprotonation* of cryptands have also been studied in detail[59], particularly, with [1.1.1] (**18**), possessing a cavity, into which a proton just fits, and which cannot be totally removed even by boiling for hours with concentrated alkali hydroxide[60]. For the reaction $H_2O + [2.2.2] \underset{\leftarrow}{\overset{\rightarrow}{\rightleftarrows}} [2.2.2.H]^+ + OH^-$, the following rate constants are found: $\overleftarrow{k} = 10^7$/mol/s and $\overrightarrow{k} = 10^3$/s[59a]. The ligand is protonated inside the ligand cavity. The rates of protonation are at least two orders of magnitude smaller than those of proton-transfer reactions of simple tertiary amines.

In *[3]cryptates* an *intramolecular* cation exchange process can be observed by means of ^{13}C-NMR spectroscopy; a cation is transferred from one of the two diazacrown ether rings via a process of type **56** → **58** (Figure 8) to the other ring[61]. The activation energy ($\Delta G^{\neq}$) of this exchange reaction decreases with increasing size and decreasing hydration energy of the cation ($\Delta G^{\neq}$:$Ca^{2+} > Sr^{2+}$), i.e. in the

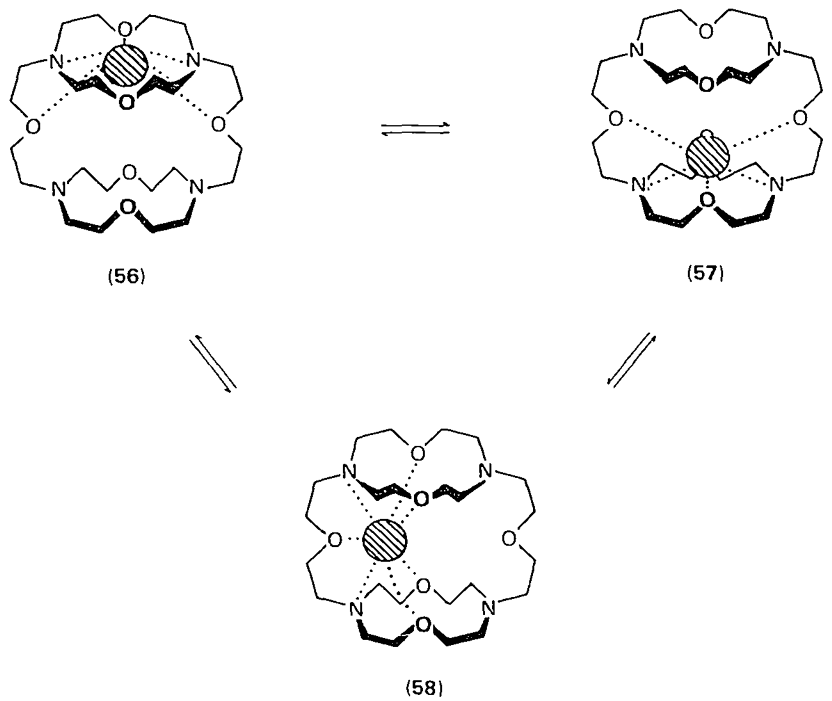


FIGURE 8. Possible intramolecular cation exchange in [3]cryptates.

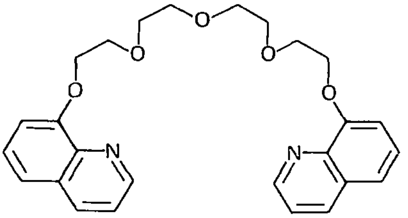
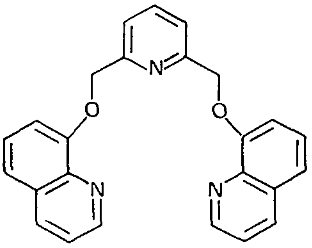
reverse order to that found for the slow *intermolecular* cation exchange in this system.

d. Podands. The results on the *open-chain* ligands agree well with similar studies on other simple chelating agents as NTA and EDTA[62] as well as on various macrotetrolide systems[63]. Both of the open-chain *quinoline polyethers* 34c and 36 show – as revealed by temperature-dependent UV absorption measurements of the complexation[57] (the stepwise binding of the metal ion induces a bathochromic shift of the absorption maximum of the ligand and a decrease of the absorption coefficient in methanol) – recombinations between ion and ligand (Table 7) that are slower by one order of magnitude than diffusion-controlled processes (10^9 – 10^{10}/mol/s, see Section II.B.2). This points to a stepwise replacement of the solvation sphere of the metal ion by the chelating atoms of the multidentate complexones.

A comparison with the *oligoethylene glycol ethers* of types 35 and 47, in which donor groups containing aromatic units or simple benzene nuclei replace the quinoline rings, proves to be interesting. The rate constants $\overrightarrow{k}$ for recombination between metal ion and ligand are – as determined by temperature jump–relaxation experiments – of the order of 3×10^7 to 4×10^8/mol/s[64]; such values are relatively high, but still lower than those found for diffusion-controlled recombinations in methanol, as e.g. the recombination of the negatively charged, open-chain nigericin antibiotic with Na^+ ions ($\overrightarrow{k} = 10^{10}$/mol/s, in methanol, Table 1).

The diminished rates are, as described above, a result of the stepwise replacement of the solvent molecules in the inner coordination sphere of the metal ion by

TABLE 7. Overall rate constants k and log K_S values of alkali metal ion complex formation with some open-chain oligoethers (in MeOH, 25°C)[57]

Ligand	Cation	$\overrightarrow{k}$ (1/mol/s)	$\overleftarrow{k}$ (1/s)	log K_S
 (34c)	Li^+	3×10^7	4.3×10^4	2.37
	Na^+	1×10^8	3.4×10^4	3.22
	K^+	1.1×10^8	4×10^3	3.51
	Rb^+		$\approx 10^5$	3.06
 (36)	Na^+	4×10^8	2.5×10^4	3.65
	K^+		$\gtrsim 10^5$	2.75

the chelating atoms of the multidentate complexones. In order to account for the high overall rates every single substitution process has to occur with a rate constant of the order of 10^8 to 10^9/s. In general, the rate of solvent substitution decreases with decreasing ionic radius of the metal ion, because the solvent molecules of the inner solvation shell are more strongly bound due to the strong, electrostatic interaction. This is particularly noted in the case of the quinoline polyether **34c** (see Table 7). Furthermore, the stability of the complexes increases with decreasing $\bar{k}$ values, i.e. the most stable K^+ complex of the series dissociates with the lowest frequence. The dependency of the association and dissociation rate constants of ligand **34c** on the metal ion radius is thus in agreement with results found for cyclic complexons like valinomycin [45a] and dibenzo[30]crown-10 (8)[48].

4. *Comparison of the different ligand systems*

The results obtained for the various ligands described above show that in no case does a one-step reaction between ligand and cation occur.

As a rule, substitution of one or several solvent molecules in the inner coordination shell of the metal ion as well as conformational changes of the ligand take place during complexation at a rate of 10^9 to 10^{10}/mol/s (nigericin 10^{10}) for *open-chain* ligands; these reactions are practically diffusion-controlled (see Tables 1 and 7).

With *monocyclic* crown ethers the rates of alkali metal ion complexation are only slightly smaller (values of about 10^9/mol/s, see Tables 3 and 4), supposing that the ligand is flexible.

For more rigid *cryptand* systems, the results may be summarised as follows (see Tables 5 and 6):

(a) The rates of formation with values between 10^4 and 10^7/mol/s are much slower than the exchange of the hydration shell, but appear to follow the same order.

(b) The transition state lies on the side of the starting materials, i.e. it is accompanied by considerable solvation of the cation.

(c) The dissociation rates of the most stable complexes are slower ($10-10^3$/s) than those of macromonocyclic coronands or antibiotic complexones and decrease with increasing stability constants.

(d) The dissociation can proceed via an acid-catalysed pathway at low pH.

(e) Rapid exchange rates require small cation solvation energies, ligand flexibility and not too high complex stabilities. Conformational change can occur during the process of complexation; the most stable cryptates are *cation receptor complexes*, which release the cation again only very slowly. The less stable ones exchange more rapidly and can, therefore, serve as *cation carriers*.

C. Thermodynamics of Complexation

1. *Introduction*

Thermodynamics of complexation[65,76] is synonymous with the discussion of the *free enthalpy change* ΔG^0, which accompanies the formation of the complex. The latter is expressed by the Gibbs–Helmholtz equation (equation 6) which

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \tag{6}$$

consists of an enthalpy and an entropy term, the relative importance of each depending on the type of ligand and cation.

There are altogether four possible combinations of the thermodynamic parameters leading to stable complexes ($\Delta G^0 < 0$):

$\Delta H^0 < 0$ and dominant, $\Delta S^0 > 0$ (*a*)
$\Delta H^0 < 0$ and dominant, $\Delta S^0 < 0$ (*b*)
$\Delta S^0 > 0$ and dominant, $\Delta H^0 < 0$ (*c*)
$\Delta S^0 > 0$ and dominant, $\Delta H^0 > 0$ (*d*)

From (*a*) and (*b*) *enthalpy*-stabilized complexes result, from (*c*) and (*d*) *entropy*-stabilized ones and from (*a*) and (*c*) enthalpy- *as well as* entropy-stabilized complexes. All four types of complexes are found among the coronates, cryptates and podates discussed here.

Combination of a charged ligand with a hard A-type* metal ion to form a complex of *electrostatic* nature is preferentially entropy-driven, while on the other hand, recombination of an uncharged ligand with a soft B-type* metal ion to form a complex of *covalent* nature is preferentially enthalpy-driven[66]. Unfortunately, this empirical rule cannot be used to predict complexation reactions between alkali metal ions and noncyclic crown ether type polyethers, because alkali metal ions belong to group A of the hard, unpolarizable cations while the noncyclic ligands belong to the group of uncharged ligands.

The free enthalpies themselves result from the superposition of several different, partly counteracting increments of ΔG^0:

(*a*) the binding energy of the interaction of the ligand donor atoms with the cations;
(*b*) the energy of conformational change of the ligand during complexation;
(*c*) the energies of metal ion and ligand.

2. *Significance of ΔH^0, ΔS^0, ΔG^0 and ΔC_p^0 for complexation*

a. Free enthalpy changes. ΔG^0 values are a direct measure of the degree of complexation in solution, and these values are used for comparison of the complex stabilities and cation selectivities of crown ethers. In Tables 8–10 are listed the ΔG^0 values of a few typical ligand/salt combinations. Enthalpy changes of a cation–ligand reaction in solution allow conclusions about the binding energy of cation–donor atom bonds and the hydration energies of reactants and products.

b. Enthalpies. ΔH^0 values of the above ligand/salt combinations are also given in Tables 8–10. The magnitudes of the ΔH^0 values are indicative of the type and number of binding sites (e.g. O,N,S etc.). As a rule, the ΔH^0 values are solvent-dependent. Thus, they often reflect (more accurately than other thermodynamic parameters) the energy changes that accompany bond formation and bond cleavage in cases where the solvent is changed or donor atoms are substituted.

c. Entropies. When ΔG^0 and ΔH^0 values of the complexation reaction are known, the corresponding ΔS^0 values (see Tables 8–10) can be calculated. The value of ΔS^0 mostly depends on electrostatic factors such as the relative hydration, and number of product and reactant species. As a rule, one obtains significant ΔS^0 contributions with macrocyclic ligands only when strong conformational changes are present during formation of the complex. So the magnitudes of the ΔS^0 values are indicative of solvent–solute interaction and supply information about the relative degrees of hydration of the metal ion, macrocycle and complex, the loss of degrees of freedom of the macrocycle when complexed with the metal ion and the charge-types involved in the reaction.

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*'A-type' cations have d_0 configuration. In typical 'B-type' cations d-orbitals are fully occupied; for more details see Section III.D.1.a(1) and References 66, 94 and 95.

d. C_p changes. Only a few ΔC_p^0 values for the complexation of crown ether type neutral ligands are known so far[8b,64]. They may give information about the conformational change of the ligand. Such conformational changes play a significant role, for instance during the formation of the K^+ complex of valinomycin and nonactin as well as that of the K^+ complex of [30]crown-10 (8) (see Figure 23, Section IV.B.1.a).

3. Thermodynamics of a few selected crown ethers

The thermodynamic parameters of the complexes of the A isomer (*cis–syn–cis* isomer) of *dicyclohexano[18]crown-6* (59a) (see Table 8) have been most thoroughly examined[67]. Favourable ΔS^0 values (positive) are found with cations having a pseudoinert gas configuration, e.g. Ag^+ (ΔS^0 = 11.02 cal/deg/mol) and Hg^{2+} (10.2). Since the ΔH^0 values here are very small (ΔH^0 = 0.07 and −0.71 kcal/mol), complexation with these metal ions is almost/solely entropy-driven. Also in the case of Sr^{2+}, a positive entropy change (ΔS^0 = 2.5 cal/deg/mol), albeit smaller, is measured together with a strongly negative ΔH^0 (−3.68 kcal/mol); hence the complexation of many double-charged cations (alkaline earth ions) is a result of favourable ΔH^0 as well as ΔS^0 values.

The entropy of formation ΔS^0 depends mostly on the change of the number of degrees of freedom of the particles during complex formation, taking participating water into consideration also. The biggest term normally represents the translational entropy of released water molecules, so that highly charged smaller cations, which are more strongly hydrated, should give bigger values of ΔS^0. This is experimentally confirmed, for instance, on going from K^+ to Ba^{2+}: the ΔS^0 value of Ba^{2+} (−0.20 cal/deg/mol) is much more favourable than that of K^+ (−3.80), whilst the enthalpy changes do not differ as much ($\Delta H^0{}_{Ba} = -4.92$, $\Delta H^0{}_K =$ −3.88 kcal/mol), a fact attributable to stronger cation–ligand interactions and bigger entropy gain during displacement of the solvent shell. From these results, it can be seen that the type of cation as well as its charge plays an important role in the thermodynamics of complexation (for more details see Section III.D).

Of interest in the case of *[18]crown-6* (2), apart from the complexation thermodynamics of the alkali/alkaline earth ions (see Table 8), is that of the rare earth ions La^{3+} to Gd^{3+}, measured in methanol by titration calorimetry[68]. Three features of the results are significant: (*a*) no heat of reaction is found with the *post*-Gd^{3+} lanthanide cations; (*b*) all reaction enthalpies are positive and thus the observed stabilities of entropic origin; (c) with increasing atomic weight, the complex stabilities decrease, contrary to those of the triple-charge lanthanide complexes of most other ligands. The results have been interpreted in such a way as to reflect the balance among ligand–cation binding, solvation and ligand conformation. UO_2^{2+} and Th^{4+} give no measurable heats of reaction with [18]crown-6 in methanol under similar conditions[68]. It seems that complex formation does not

TABLE 8. Thermodynamic data for the interaction of several macrocyclic [18]crown-6-type ligands with various metal ions at 25°C

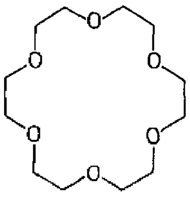
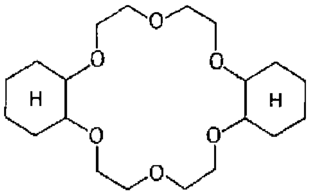
Ligand	Cation	Solvent	ΔH^0 (kcal/mol) [kJ/mol]	ΔS^0 (cal/deg/mol) [J/deg/mol]	log K_S	Reference
 (2)	Na^+	H_2O	−2.25 [− 9.42]	− 3.7 [−15.49]	0.80	67b
	K^+	H_2O	−6.21 [−25.98]	−11.4 [−47.52]	2.03	
	Rb^+	H_2O	−3.82 [−15.98]	− 5.8 [−23.86]	1.56	
	Cs^+	H_2O	−3.79 [−15.86]	− 8.1 [−33.91]	0.99	
	Ag^+	H_2O	−2.17 [− 9.08]	− 0.4 [− 1.67]	1.50	
	Ca^{2+}	H_2O			<0.50	
	Sr^{2+}	H_2O	−3.61 [−15.11]	0.3 [1.26]	2.72	
	Ba^{2+}	H_2O	−7.58 [−31.73]	− 7.9 [−33.07]	3.87	
	Pb^{2+}	H_2O	−5.16 [−21.60]	2.2 [9.21]	4.27	
	Hg^{2+}	H_2O	−4.69 [−19.63]	− 4.7 [−19.67]	2.42	

TABLE 8 – continued

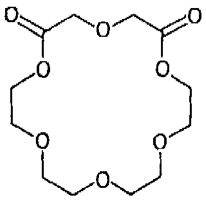
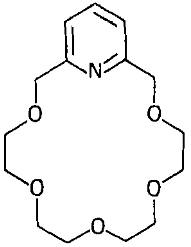
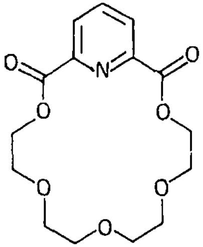


(59)

(a) *cis–syn–cis* isomer

(b) *cis–anti–cis* isomer

Li^+	H_2O		–	–	0.60	67b
Na^+	H_2O	(a)	0.16 [0.67]	6.1 [25.53]	1.21	
		(b)	–1.57 [– 6.57]	– 2.1 [– 8.79]	0.69	
K^+	H_2O	(a)	–3.88 [–16.24]	– 3.8 [–15.91]	2.02	
		(b)	–5.07 [–21.22]	– 9.6 [–40.18]	1.63	
Rb^+	H_2O	(a)	–3.32 [–13.90]	– 4.2 [–17.58]	1.52	
		(b)	–3.97 [–16.62]	– 9.3 [–38.92]	0.87	
Cs^+	H_2O	(a)	–2.41 [–10.09]	– 3.7 [–15.49]	0.96	
		(b)	–	–	0.90	
Ag^+	H_2O	(a)	0.07 [0.29]	11.0 [46.05]	2.36	
		(b)	–2.09 [– 8.75]	0.3 [1.26]	1.59	
Tl^+	H_2O	(a)	–3.62 [–15.15]	– 1.0 [– 4.19]	2.44	
		(b)	–4.29 [–17.96]	– 6.0 [–25.12]	1.83	
Hg_2^{2+}	H_2O	(a)	–2.16 [– 9.04]	1.6 [6.70]	1.93	
		(b)	–4.29 [–17.96]	– 7.4 [–30.98]	2.57	
Sr^{2+}	H_2O	(a)	–3.68 [–15.40]	2.5 [10.47]	3.24	
		(b)	–3.16 [–13.13]	1.5 [6.28]	2.64	
Ba^{2+}	H_2O	(a)	–4.92 [–20.60]	– 0.2 [– 0.84]	3.57	
		(b)	–6.20 [–25.95]	– 5.8 [–24.28]	3.27	
Pb^{2+}	H_2O	(a)	–5.58 [–23.36]	3.9 [16.33]	4.95	
		(b)	–4.21 [–17.62]	6.2 [25.95]	4.43	
Hg^{2+}	H_2O	(a)	–0.71 [– 2.97]	10.2 [42.70]	2.75	
		(b)	–2.55 [–10.67]	3.3 [13.81]	2.60	

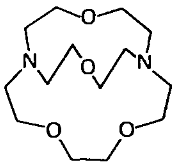
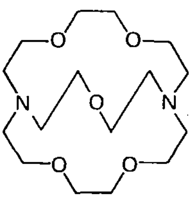
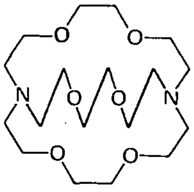
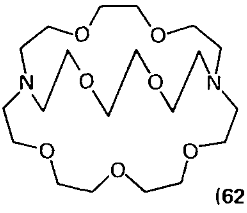
 (60)	Na$^+$	MeOH	−2.27 [− 9.50]	1.1 [4.60]	2.5	70
	K$^+$	MeOH	−5.87 [−24.57]	− 2.06 [− 8.62]	2.79	
	Ba^{2+}	MeOH	−0.46 [− 1.93]	3.8 [15.50]		
 (61a)	Na$^+$	MeOH	−5.44 [−22.77]	0.14 [0.59]	4.09	70
	K$^+$	MeOH	−9.11 [−38.09]	− 1.8 [− 7.53]	5.35	
	Ba^{2+}	MeOH	−7.72 [−32.32]	0.5 [2.09]	>6	
 (61b)	Na$^+$	MeOH	−6.19 [−25.91]	− 0.34 [− 1.42]	4.29	70
	K$^+$	MeOH	−9.3 [−38.93]	− 2.9 [−12.14]	4.66	
	Ba^{2+}	MeOH	−6.03 [−25.24]	− 0.11 [− 0.46]	4.34	

occur under these conditions; this is emphasized by the fact that apart from cocrystallisates (see Section IV.B.1.b), no solid uranyl complexes of [18]crown-6 have been discovered so far.

Thermodynamic data of the complexation of heavy metal ions (Ag^+, Hg^{2+}, Pb^{2+}) have been obtained for crown ethers of various ring size including exchange of oxygen centres by *sulphur*[69].

The thermodynamic origin for differences in complexation between the [18]crown-6-type macrocycles containing *carbonyl oxygen* and those, that do not, seems to vary (see Table 8)[70]. Comparing the two *pyridine-containing* ligands 61a

TABLE 9. Free energies, enthalpies and entropies of complexation by bicyclic ligands in water at 25°C[75]

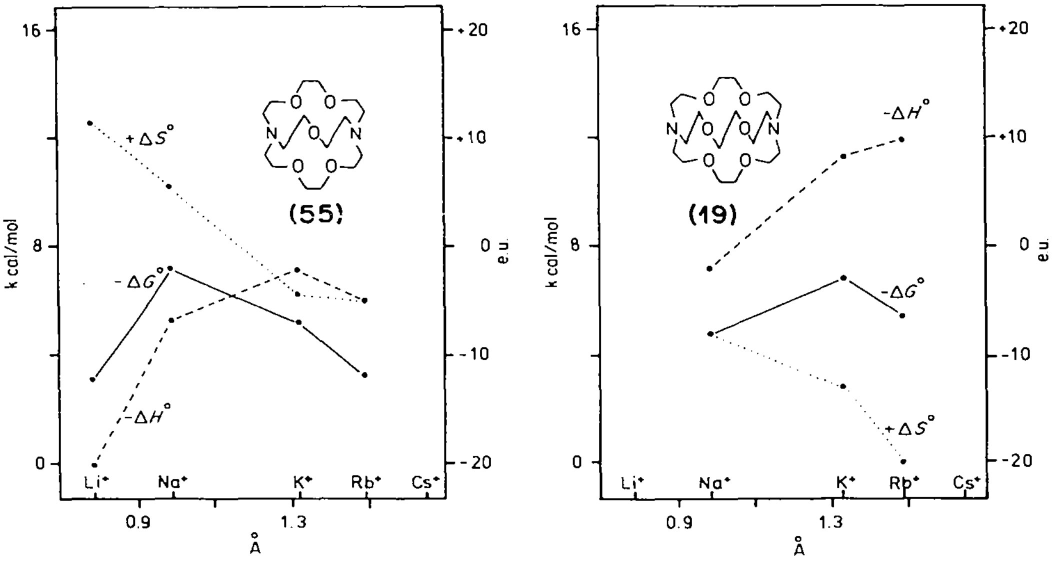
Ligand	Cation	ΔG^0 (kcal/mol) [kJ/mol]	ΔH^0 (kcal/mol) [kJ/mol]	ΔS^0 (cal/K/mol) [J/K/mol]
 (54) [2.1.1]	Li^+	− 7.5 [−31.4]	− 5.1 [−21.35]	8 [33.5]
	Na^+	− 4.5 [−18.8]	− 5.4 [−22.60]	− 3 [−12.6]
	Ca^{2+}	− 3.4 [−14.2]	− 0.1 [− 0.42]	11.1 [49.4]
 (55) [2.2.1]	Li^+	− 3.4 [−14.2]		11.4 [47.7]
	Na^+	− 7.2 [−30.1]	− 5.35 [−22.40]	6.2 [25.9]
	K^+	− 5.4 [−22.6]	− 6.8 [−28.47]	− 4.7 [−19.7]
	Rb^+	− 3.45 [−14.4]	− 5.4 [−22.60]	− 6.5 [−27.2]
	Ca^{2+}	− 9.5 [−39.8]	− 2.9 [−12.14]	22 [92.1]
	Sr^{2+}	−10.0 [−41.9]	− 6.1 [−25.95]	13.1 [54.8]
	Ba^{2+}	− 8.6 [−36.0]	− 6.3 [−26.37]	7.7 [32.2]
 (19) [2.2.2]	Na^+	− 5.3 [−22.2]	− 7.4 [−30.98]	− 7 [−29.3]
	K^+	− 7.2 [−30.1]	−11.4 [−47.72]	−14.1 [−59.0]
	Rb^+	− 5.9 [−24.7]	−11.8 [−49.40]	−19.8 [−82.9]
	Ca^{2+}	− 6.10 [−25.1]	− 0.2 [− 0.84]	19.5 [81.6]
	Sr^{2+}	−10.9 [−45.6]	−10.3 [−43.12]	2 [8.4]
	Ba^{2+}	−12.9 [−54.0]	−14.1 [−59.02]	− 4.0 [−16.7]
 (62) [3.2.2]	K^+	− 3.0 [−12.6]	− 3.0 [−12.56]	0 [0]
	Rb^+	− 2.8 [−11.7]	− 4.2 [−17.58]	− 4.7 [−19.7]
	Cs^+	− 2.45 [−10.3]	− 5.4 [−22.60]	− 9.9 [−41.4]
	Ca^{2+}	− 2.7 [−11.3]	0.16 [0.67]	9.6 [40.2]
	Sr^{2+}	− 4.6 [−19.3]	− 3.3 [−13.81]	4.4 [18.4]
	Ba^{2+}	− 8.2 [−34.3]	− 6.2 [−25.95]	6.7 [28.0]

and **61b**, in all cases the stability of complexes of the ligand without carbonyl groups is entropy-favoured. ΔH^0 varies little with no systematic trend. Comparison between **2** and **60** shows that the entropy term favours complexes of the ligand with carbonyl groups, while the enthalpy term for this ligand is comparatively very unfavourable. As Table 8 shows, the increased stability of complexes of **61b** over that of complexes of the parent macrocycle **60** is due almost entirely to the enthalpy term in the case of the monovalent cations. However, a significant drop in entropy stabilization for the Ba^{2+} complex of **61b** from that of **60** results in the reversal of the K^+/Ba^{2+} selectivity sequence between these two ligands.

Cram and coworkers studied the free energies of association between polyethers and *t*-butylammonium salts[71]. For thirteen different eighteen-membered crown ether rings in chloroform (at 24°C) ΔG^0 values lying between -9.0 and -2.9 kcal/mol and depending on the structure of the crown ether were found. Furthermore, *ab initio* molecular orbital calculations of the relative values of the binding energies were drawn up[71,72] and shown to be in qualitative agreement with experimental results.

Regarding the thermodynamics of protonation of the cyclic *oligooxadiaza ligand* **6**[73], the bicyclic **19** and the corresponding open-chain diamine analogue with typical primary, secondary and tertiary amines, the data obtained for the substituent effect[74] cannot be simply correlated. This is understandable, since in the cyclic systems the N atoms can no more be arranged strain-free and the N—N distance is greatly reduced. It can be taken for granted that both H atoms of the diprotonated cyclic ligand are located inside its cavity. This desolvates the protons very strongly, particularly in the case of the bicyclic ligands, thereby causing an increase of ΔS^0 and ΔH^0 compared to normal diamines.

Calorimetric measurements of alkali and alkaline earth metal complexation by *macrobicyclic cryptands* show that here also enthalpy and entropy changes play an



(a) (b)

FIGURE 9. Free energies $-\Delta G^0$, enthalpies $-\Delta H^0$ and entropies $+\Delta S^0$ of cryptate formation by several alkali cations with (a) [2.2.1]- and (b) [2.2.2] cryptands in water at 25°C.

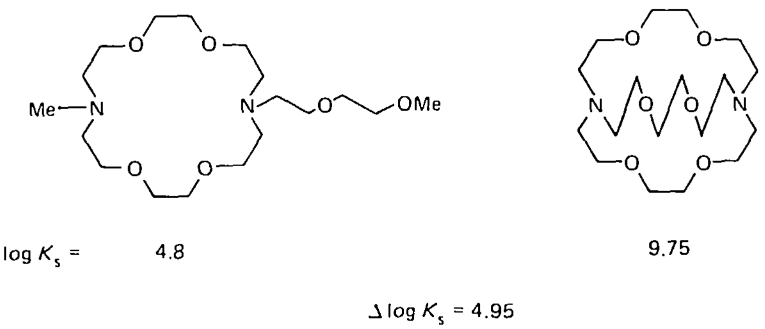


FIGURE 10. Stability constants ($\log K_S$) of K^+ complexation in $MeOH/H_2O$ (95 : 5)[14d]: *macrobicyclic effect* ([2] cryptate effect).

important role[75]. Particularly noteworthy are the high enthalpies and the negative entropies of the complexes with alkali cations such as Na^+, K^+, Rb^+ and Cs^+ (see Table 9). Alkaline earth cryptates (Sr^{2+}, Ba^{2+}) just like the Li[2.1.1] and Na[2.2.1] complexes are marked by dominant enthalpy changes apart from a similarly favourable entropy change. The Ca^{2+} cryptates (and the Li[2.2.1] complex), with a heat of reaction of nearly zero, are completely entropy-stabilized.

The complexation enthalpies show selectivity peaks for various cations in contrast to the entropies (Figure 9)[75]. The entropy term may nevertheless lead to marked differences between enthalpy and free energy selectivities. Thus the selectivity peaks observed in the stability constants of cryptates are intrinsically of enthalpic origin.

The high stability of macrobicyclic complexes compared with analogous monocyclic complexes (Figure 10) is caused by a favourable enthalpy, and is termed the '*macrobicyclic*' or '*cryptate effect*', or more specifically the '*[2]cryptate effect*'[14c,d]. In the case of the topological tricyclic cryptands, one similarly speaks of a *macrotricyclic* or *[3]cryptate effect* etc.

The cryptate effect is enthalpy-influenced[75], which is attributable to the strong interactions of the cation with the poorly solvated polydentate ligand of macrobicyclic topology.

Open-chain podands usually show smaller ΔG^0 or K_S values of complexation than macrocyclic crown ethers[76] (Figure 11, $\Delta \log K_S = 3-4$) or bicyclic cryptands

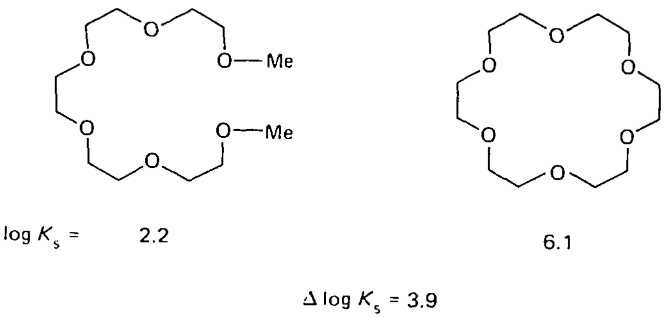


FIGURE 11. Stability constants ($\log K_S$), of K^+ complexation in MeOH[76]: *macrocyclic effect* ([1] cryptate effect).

(Figure 10, Δ log $K_s = 7-9$)[14d,65]. With reference to the effective [2]cryptate effect of bicyclic cryptands, a so-called *macrocyclic* (or *[1]cryptate*) effect[14c] for monocyclic crowns has been defined.

More thorough investigations reveal that this is partly caused by a loss of degree of freedom of the open-chain ligand, but more often by a weaker solvation of the complexed cyclic ligand[14d,65,77]. A more accurate elucidation of these results from the point of view of enthalpic and entropic contributions due to solvation and conformation is experimentally difficult[78].

The still effective '*chelate effect*'[14c,79] of open-chain multidentate podands compared with simple monodentate compounds such as ROR and R_3N is often entropy-influenced, though the complexation entropies may differ a great deal according to the type of the podand (see below).

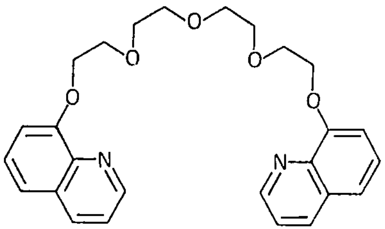
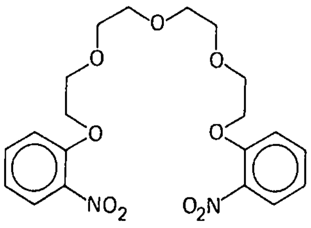
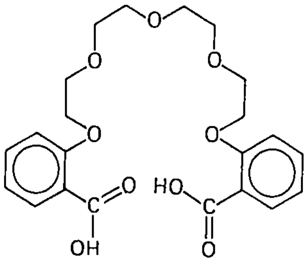
Since the complexation of *podands* has only recently been investigated and detailed results are meanwhile available[64], but still not summarized, it seems proper at this point to give a more thorough description of the subject.

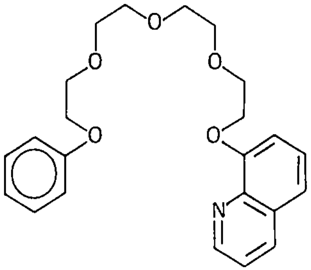
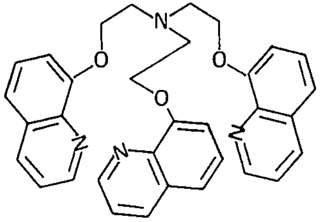
Table 10 shows that the complex stability (ΔG^0) of the noncyclic ligands **34c**, **35b**, **35c**, **39** and **47** is entirely of enthalpic origin accompanied by an unfavourable loss of entropy. The ΔH^0 values of the noncyclic compounds between -20 and -70 kJ/mol are comparable to the values obtained for cyclic complexones in methanol (cf. Table 8); however, for some complexes the decrease of entropy is remarkably high. The largest negative entropies of complexation among the aromatic tetraethylene glycol ethers were found for the lithium complex of **34c**, the sodium complex of **35c** and the potassium complex of **47**. Maximum values of ~ -200 J/K/mol are reached with the rubidium and caesium complexes of the tripodand **39**.

Table 10 also illustrates the influence of the cation size on ΔG^0, ΔH^0 and ΔS^0 of the ligands measured. The dependency of open-chain ligand **34c** regarding the ionic radius is opposite to that of the tripodand **39**, for which values of reaction enthalpy and entropy decrease on going from the lithium complex to the rubidium-complex. For the K^+ and Rb^+ complexes of **34c** the entropy loss is practically zero, while the enthalpic terms reach a negative plateau for the bigger K^+, Rb^+ and Cs^+ cations. In the case of complexones **34c** and **35c** the heat of reaction and the loss of entropy decrease with increasing ionic radius. The reaction enthalpies of the lithium and sodium complexes of **35c** are strongly temperature-dependent, as shown by the large values of the molar heat capacities: ΔC_p^0 (Li^+) = 1 kJ/K/mol and ΔC_p^0 (Na^+) = 4 kJ/K/mol. Ligand **39**, however, behaves like the cyclic complexones; the values of ΔH^0 and ΔS^0 become more negative with increasing ionic radius.

These experimental results have been discussed in the light of different intrinsic contributions to enthalpy and entropy[64]. The *complexation enthalpy* can be split into the contributions from the *cation* and those from the *ligand*. The bonds of the metal ions with the solvent molecules are partly or totally substituted by the bonds to the polar groups of the ligand. Also, the difference between the solvation enthalpies of the solvent molecules outside the complex and outside the first solvation shell of the free metal ion has to be taken into consideration. The changes of the enthalpy of the ligand by complexation are mainly due to the changes of solvation, intramolecular ligand–ligand repulsions, to the stacking of the aromatic residues and the steric deformation of the ligand induced by the bound metal ion. In methanol, the electrostatic interaction between the metal ion and the coordinating sites of the ligand represents one of the important driving forces of the complexation enthalpy, because the counteracting interaction with solvent mole-

TABLE 10. Thermodynamics of alkali metal ion complex formation with open-chain ligands at 25°C in MeOH[a, 4]

Ligand	Cation	ΔG^0 (kJ/mol)	ΔH^0 (kJ/mol)	ΔS^0 (J/K/mol)	ΔC_p^0 (J/K/mol)
 (34c)	Li^+ Na^+ K^+ Rb^+ Cs^+	−13.4 −18.4 −20.1 −17.6 −15.0	−63 −36 −21 −20 −25	−170 − 59 − 3 − 7 − 33	4 x 10² 1.2 x 10²
 (35b)	K^+	− 9.2	−29	− 67	–
 (35c)	Li^+ Na^+ K^+ Rb^+ Cs^+	−19.7 −19.7 −20.1 −18.4 −11.0	−41 −68 −33 −25 −24	− 70 −160 − 22 − 23 − 40	1.1 x 10³ 3.8 x 10³ 6.7 x 10² 0.6 x 10² 1.3 x 10²

 (47)	K^+	−10.5	−59	−	1.6×10^2	−
 (39)	Li^+ Na^+ K^+ Rb^+ Cs^+	−13 −20.9 −14.6 −11.7 − 8.8	−29 −35 −50 −66 −50	− 20 − 46 −119 −184 −140		− − − 6×10^2 8×10^2

cules is relatively small, as compared to the corresponding interactions in aqueous solution. If the solvent molecules are not too tightly bound, the uptake of the small cations by the ligand should be favoured. The tripodand **39**, however, prefers the large cations as far as the enthalpies are concerned. This may be due to the fact that binding of the small ions leads to an unfavourable conformation of the ligand. In contrast, ligand **34c** prefers the small cations, because the electrostatic attraction is the dominant increment of the negative complexation enthalpy. Because of the high flexibility of the open-chain compounds, sterically unfavourable conformations can be avoided. Furthermore, the stacking energy of the terminal aromatic moieties contributes to the negative ΔH^0 values.

The complex formation for the glyme-analogous **34c**, **35b**, **35c** and **47** and tripodand **39** is enthalpically favoured but entropically disfavoured (see Table 10).

As in the discussion of the enthalpy values a more thorough understanding of the *entropy values* is achieved considering the various intrinsic contributions: for the linear ligands **34c** and **35c** the dependence of the complexation entropy on the ionic radius is opposite to that of the cyclic (Table 8) and bicyclic complexones (Table 9). Here, the release of the solvation shell has to be overcompensated by the other contributions to the complexation entropy. The metal ion may not be completely desolvated. The change of the topology of ligand from a linear conformation in the uncomplexed state to a helical conformation in the complex state leads to a large loss of entropy. This is supported by the experimental finding that the decrease of entropy due to complexation is smallest for the uptake of those cations which do not induce steric deformations of the ligand structure: K^+ and Rb^+ ions fit well into the sterically optimum cavity of ligand **34c**. Thus, the favoured stability of the K^+ complex of ligand **34c** is the consequence of the absence of a destabilizing loss of entropy, and correspondingly the lability of the Li^+ complex is due to the entropy-unfavourable conformational changes of the ligand. Addition and/or variation of the donor groups in the *ortho* position of the terminal aromatic moiety shift the complexation entropy of the K^+ complexes by nearly two orders of magnitude (see Table 10). The podand **39** is much more restricted in its conformational flexibility than the compounds **34c** and **35c**. Thus, the differences of the solvation and of the internal entropies of the ligand between the free and the complexed state are comparably small, and, instead, the difference of the translational entropy due to the release of the solvation shell controls the dependence of the complexation entropy on ionic radius[64].

Recent ^{23}Na-NMR investigations[80] about the thermodynamics of complexation of open-chain podand **35e** with Na cations in pyridine as solvent gave the following results: $\Delta H^0 = -17$ kcal/mol (-71 kJ/mol), $\Delta S^0 = -48$ cal/K/mol (-201 J/K/mol). The very negative ΔS^0 value points to a cyclization or/and polymerization entropy. For a discussion of the X-ray analysis of the K^+ complex of **35e** see Section IV.B.3.b(1). The Na^+ complexation forces the podand to adopt a particularly well-arranged conformation, in which most (or all) of the oxygen donor atoms form van der Waals' bonds to the enclosed sodium ion, thus causing the relatively big enthalpy change. The complexation of **35e** in solution is enthalpy-driven. From ^{23}Na-NMR results, it is to be concluded that the interaction of the open-chain podand **35e** with sodium can best be described by a successive wrap of the sodium cation by the heptadentate ligand.

Thus, with the help of a few concrete examples, it is shown how the various ligand, cation and medium parameters of single thermodynamic data like ΔG^0, ΔH^0, ΔS^0 and ΔC_p^0 are differently influenced, the effects being reflected in the complex stabilities and particularly also in the complexation selectivities.

III. COMPLEX STABILITIES AND SELECTIVITIES

A. General Remarks

The formation of a 'complex' by association of two or more chemical units is one of the most basic molecular processes and of utmost importance in chemistry, physics and biology.

A *host–guest complex*, unlike covalent bonds, arises mostly through weak bond interactions (hydrogen bonding, metal-to-ligand bonding, pole–dipole binding forces, dipole–dipole binding forces, hydrophobic bindings etc.)[81]. Such relatively weak molecular interactions should be a subject of intensified research on the basis of molecular recognition between two chemical units in future, since molecular information is transferred during the process of complexation[14c].

In living creatures, highly specific and complicated molecular aggregates play an important role in *enzyme–substrate interactions*, the *replication of nucleic acids*, the *biosynthesis of proteins*, in *membranes* and in *antigen–antibody reactions*[34]. Their stability, selectivity, structure and reactivity are complicated functions of many variables.

There is a striking similarity between the metal ion selectivity of some antibiotics and certain macrocyclic ligands[7b]. It has proved, therefore, important to synthesize simpler host molecules as model substances and study their analogous interactions with substrates[14e,16g,16m,16n,18b,18c,82]. These investigations have led to a series of results concerning the ligand structure, complex stability and selectivity with diverse guest molecules in various solvents. In this way, it has been possible to separate various variables and achieve an analysis of structural interactions. The different variables can then not only be analysed, but also be controlled[14c,81].

B. Definition of the Complex Stability Constant and of the Selectivity of Complexation

The complexation process between a ligand L and a cation M^{n+} in solvent S may be represented by the general equation (7), where $\vec{k}$, $\overleftarrow{k}$ are defined as the rate

$$(L)_{solv.} + (M^{n+},mS) \underset{\overleftarrow{k}}{\overset{\vec{k}}{\rightleftharpoons}} (L,M^{n+})_{solv.} + mS \tag{7}$$

constants of formation and dissociation of a complex (see Section II.B.1 and II.B.2). The quotient of $\vec{k}/\overleftarrow{k}$ gives the *stability constant* K_s (kinetic derivation of the stability, cf. Section II.B.1). The *thermodynamic* stability constant K_{th} can be given by equation (8), where f_C, f_L and f_M are the activity coefficients of the three

$$K_{th} = \frac{f_C[L,M^{n+}]}{f_L[L]f_M[M^{n+}]} \tag{8}$$

species present (complex, ligand, cation). Since these coefficients are generally unknown, however, the stability constants K_s (equation 9), based on the concentrations, are usually employed. K_s is an average stability constant for the system in

$$K_s = K_{th}\frac{f_L f_M}{f_C} = \frac{[L,M^{n+}]}{[L][M^{n+}]} \tag{9}$$

thermodynamic equilibrium on the basis of ligand conformation and complexation[14c].

The relationship between K_s and the free enthalpy of formation ΔG^0 of a complex is given by the following equation (10)[7b]:

$$\Delta G^0 = -RT \ln K_s \tag{10}$$

K_s values are known for many complexes[8b] and a list is given in Tables 4–8, 11, 12, 15. These values also reflect the socalled selectivities of complex formation of the ligands.

'*Selectivity* is concerned with the ability of a given ligand to discriminate among the different cations'[14c]. A measure for the selectivity of a particular ligand with respect to two different metal ions M_1 and M_2 is, per definition (equation 11), the ratio of the stability constants of the complexes LM_1 and LM_2 (L = ligand, M = metal cation). High complex stability, often desirable, does not necessarily mean high selectivity. Crown ethers with low complex stability constants may be highly selective; thus this knowledge has proved to be very valuable for the design of carrier molecules for use, e.g. in ion-selective electrodes[27,83].

$$\text{Selectivity} = \frac{K_s(\mathrm{LM_1})}{K_s(\mathrm{LM_2})} \tag{11}$$

C. Methods for Determination of Complex and Selectivity Constants

The following methods or devices have been employed for the experimental determination of the complex stability constants K_s : *cation selective electrodes*[76a,84], *pH-metric* methods[33b,85], *conductometry*[51,86], *calorimetry*[67–70,87], *temperature jump* measurements[7b,37,49,57,64], *NMR*[80,88], *ORD*[89], *solvent extraction*[90] and *osmometry*[91]. These methods have been discussed in several reviews[7a,b,d]. It is to be mentioned that cation selective or cation specific organic neutral ligand systems of the crown ether type have proved to be useful in ion-selective electrode systems themselves[6c,6d,27,92].

An advantage and at the same time a drawback associated with the numerous possibilities of measurement is that the complex constants listed in the Tables 4–8, 11, 12, 15 have been obtained according to different methods (often in different solvents) and therefore, cannot be readily compared with one another.

D. Factors Influencing Stability and Selectivity

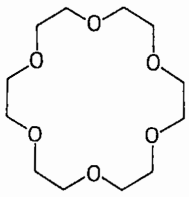
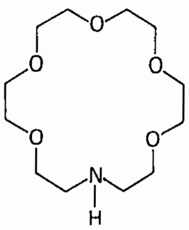
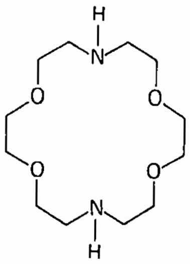
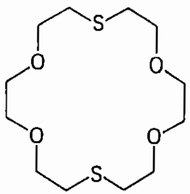
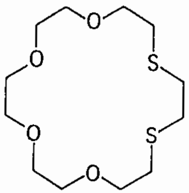
In the following, an attempt is made to discuss the different factors in order to work out their specific influences on the complexation. In reality the several parameters are often strongly connected with each other.

1. Ligand parameters

a. Binding sites. A crown ether may be considered to be a collection of donor heteroatoms (O,N,S,P) distributed strategically. It is clear that the kind of donors employed has a big influence on the complexation behaviour.

(1) *Donor atom type.* In classical crown ethers, *ether oxygens* have been used as donor site[93] As *A-type donors*[66,94], they should most favourably combine with, *A-type metal ions* (alkali/alkaline earth, lanthanide ions) according to the 'hard and soft acid–base' principle[95]. Thus, complexes of purely oxygen crown ethers such as 1, 2 and 8 with salts of the above cations tend to give high K_s values[8b] (see

TABLE 11. Comparison of log K_S values for the complexation of [18]crown-6 and of some aza and thia analogues with K^+ and Ag^{+}[69,76a]

Cation	Ligand				
	 (2)	 (63)	 (6)	 (64)	 (65)
$K^{+\,a}$	6.10	3.90	2.04	1.15	–
$Ag^{+\,b}$	1.60	3.30	7.80	4.34	3.0

[a] In CH_3OH.
[b] In H_2O.

Sections II.B.3.b and II.C.3, Table 4). *B-type cations* (Cu^{2+}, Ag^+, Co^{2+}, Ni^{2+}, etc.) should less compatibly combine with the 'hard' ether oxygens, thereby resulting in lower stabilities of the complexes, as shown in practice (cf. 2 in Table 11).

On the other hand, such cations interact favourably with 'soft' *B-type donors* like N,S[94]. Investigations on the stepwise substitution of *nitrogen* or *sulphur* atoms in crown ether skeletons and about their stabilizing/destabilizing influences on complexation have already been carried out[76a].

The K_s values of a series of *thia analogues* with [9]crown-3, [12]crown-4, [15]crown-5, [18]crown-6 and [24]crown-8 skeletons have been determined[69,70b] (e.g. 64 and 65; see Table 11). They are, as expected, very low for alkali/alkaline earth ions, but high for transition metal ions. Substitution of an oxygen in benzocrown ethers by an *NH group* reduces their ability to extract alkali picrates into organic phases[96].

The complex constants of *bicyclic systems* are likewise influenced: The *polyaza ligands* **66**–**68** show lower K_s values for alkali/alkaline earth ions compared to the parent compound, [2.2.2]cryptand (**19**) (Table 12)[85b,97]. The effect is particularly pronounced for the K^+ complexes of the methylaza cryptands **66**–**68**, the complex stabilities constantly diminishing by a factor of ~10 upon successive substitution of an O by an NCH_3 binding site. Since the dipole moment of the NCH_3 group is smaller than that of O, the substitution of O by NCH_3 leads to a decrease of the electrostatic interaction between cation and ligand. Moreover, the van der Waals' diameter of N is somewhat bigger than that of O (1.5, compared to 1.4 Å), so that the cavity formed by a polyaza cryptand should be a bit smaller [see Section III.D.1.b(1)]. The different hydration of N- compared to O-binding sites should also play a role.

The *selectivities* of complexation are influenced by the substitution of O by N or S donor sites. For instance, the peak selectivity for K^+ flattens increasingly on going from **19** to **67** or **68**[85b]. While **66** still shows comparable selectivities, **67** hardly shows any.

The experimental results may essentially be summarized as follows[14c,14d,76a] (see Tables 11, 12):

(a) Substitution of ether oxygen atoms by *sulphur* generally reduces the binding ability toward alkali/alkaline earth metal ions, leaving it unchanged or causing it to increase toward Ag^+, Pb^{2+}, Hg^{2+} and similar ions.

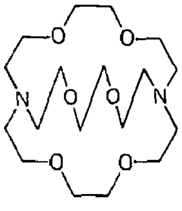
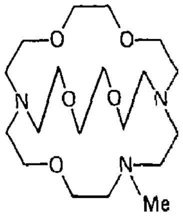
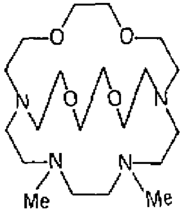
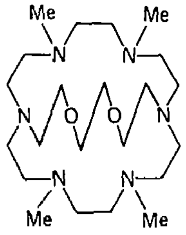
(b) Incorporation of *nitrogen* atoms has a favourable influence on the complexation of B-type ions; the coordination of alkali metal ions is much less weakened.

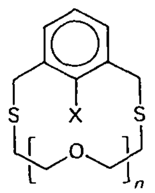
O and N donor atoms, that are integrated in *functional groups*, partly cause other gradations of complex stability and selectivity: Thus *acetal oxygen* atoms, for example, are less effective than $O-CH_2-CH_2-O-$ groups[2,98].

For macrocyclic systems containing one to three *β-diketone* units, constants of complex formation lying $10^{1.8}-10^{6.3}$ times higher than for the corresponding open-chain model substances are found[99].

The influence or coordinating ability of *intraannular functional groups* in cyclic crown ethers **69** was first described by Weber and Vögtle[100]. Cram and coworkers[101] investigated systematically the characteristics (association constants) of the intraannularly substituted macrocyclic polyethers **70** containing *halogen, OH, OMe, CN, COOMe, COOH* as donor groups X.

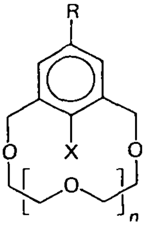
TABLE 12. Stabilities ($\log K_S$) of [2.2.2] and some aza analogues [2.2.2] cryptands with alkali/alkaline earth and heavy metal ions (in H_2O at 25°C)[85b,97]

Cation	 (19)	 (66)	 (67)	 (68)
Li^+	<2	1.5	2.4	–
Na^+	3.9	3.0	2.5	–
K^+	5.4	4.2	2.7	1.7
Rb^+	4.3	3.0	2.3	–
Cs^+	<2	<2	<2.0	–
Mg^{2+}	2	1.9	2.6	–
Ca^{2+}	4.4	4.6	4.3	1.5
Sr^{2+}	8.0	7.4	6.1	1.5
Ba^{2+}	9.5	9.0	6.7	3.7
Ag^+	9.6	10.8	11.5	13.0
Co^{2+}	⩽2.5	5.2	4.9	5.3
Ni^{2+}	⩽3.5	5.0	5.1	5.7
Cu^{2+}	6.8	9.7	12.7	12.5
Zn^{2+}	⩽2.5	6.3	6.0	6.8
Cd^{2+}	7.1	9.6	12.0	10.7
Hg^{2+}	18.5	21.7	24.9	26.1
Pb^{2+}	12.7	14.1	15.3	15.5



(69)

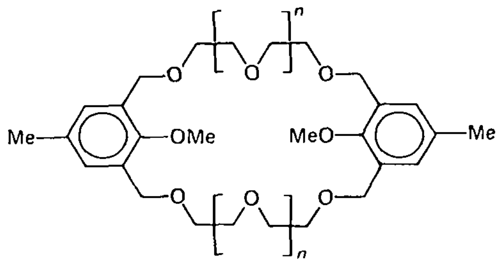
X = H
Cl
Br
OH
SH
NH_2
OMe
CN
COOH
COOMe



(70)

R = H
Me
t-Bu
NO_2
CN
COOEt

(n = 1–4,7)



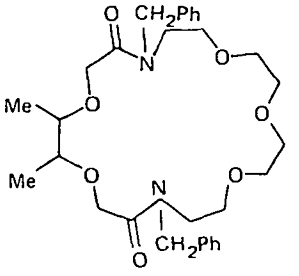
(71)

n = 0,1

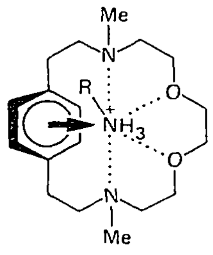
In the case of the eighteen-membered rings **70** (n = 3, R = Me) the K_s values are in the order of $CO_2Me > OMe > H$ for all cations examined, apart from K^+, for which the order of $OMe > CO_2Me > H$ is found[101b]. According to molecular models, the conformation of the complexes should be such that the plane of the benzene ring is rotated approximately 30–60° out of plane of the macro ring (X-ray structure of an analogous *t*-butylammonium salt complex, see Figure 25 in Section IV.B.1.a). Owing to two opposing methoxyphenyl units in **71**, a series of degrees of freedom of the ligand are frozen; thus, formation of cavities for guest molecules is encumbered (see Section III.D.1.c) and the complex constants are comparably low[101b]. In the series of **70** the phenol (X = OH) represents the worst ligand, since the compound forms transannular hydrogen bonds which must be cleaved during cation complexation[102]. Intraannular donor centres may also consist of acidic groups suitable for salt formation. Thus the carboxylic acid **70** (n = 3, X = COOH), in particular, forms a crystalline 1 : 1 salt with *t*-butylamine in cyclohexane/dichloromethane[18c]. These inwards directed substituents act as additional binding sites for cationic guests. The possibility, that they can also act as catalytic sites, is being explored[101a].

Suitably located *pyridine-nitrogen, furane-oxygen, thiophene-sulphur* atoms[8f] (see Figure 1) coordinate as a rule[18a,71,81,103]. They may be useful in achieving particular selectivities, e.g. in increasing the Na^+ selectivity[100,104].

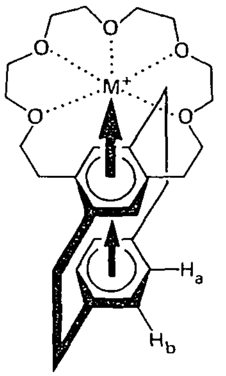
In cyclic and open-chain crown ethers, containing *amide* (**42** and **43**, see Figure 7; **72**) and *ester* functions (**60** and **61b**, see Table 8), the carbonyl groups can cooperatively act as donor centres[105]. Thus ligand **72** is ten times more selective for Ca^{2+} than for Ba^{2+} [106]. Substitution of the coordinating methoxy end-groups of open-chain crown ethers **35a** by primary amide (**35e**, **35f**) or ester groups (**35d**) (Figure 5) reduces the complexing ability of the ligand skeleton[107].



(72)



(73)



(74)

R = Me, *i*-Pr, *t*-Bu, CH_2Ph, CHMePh

Stoichiometric alkaline earth salt complexes of oligoethylene glycols have only lately been systematically synthesized[33]. Thus, it has been shown that even ethylene glycol itself forms a crystalline 1 : 1 complex with Ba$(SCN)_2$[33a]. Similar complexes are formed by 2,6-pyridine dimethanol, diethylene glycol and (several) oligoethylene glycols[33b].

Molecular models of the complexes of primary and secondary alkylammonium salts with *diazaparacyclophane* crown ethers 73 suggest that the *π-electron system* of the aromatic ring should participate in the binding of *p*-alkylammonium cations[108]. Dynamic ^{1}H-NMR spectroscopy is consistent with chiral asymmetric complexes in solution, represented by the stabilizing interaction between the π-electron system of the phenylene ring and the alkylammonium cation, which accounts for the hindered rotation of the phenylene rings in the complex. The aromatic protons H_a and H_b of the outer benzene nucleus 74 show reasonable downfield shifts[109]. This can be explained by a *transannular π-electron release* from the outer benzene ring to the complexed inner benzene nucleus to enhance the π-complexing ability. This effect probably contributes to the high yield of the synthesis.

(2) *Donor atom number.* Since a crown ether in a cation complex is comparable to the inner solvation sphere of a metal ion (see Figure 12), the number of available donor atoms in the crown ether skeleton should, as far as possible, match the *coordination number* of the particular cation[110]. Reference points for the optimum coordination numbers of cations in the complex are provided by their

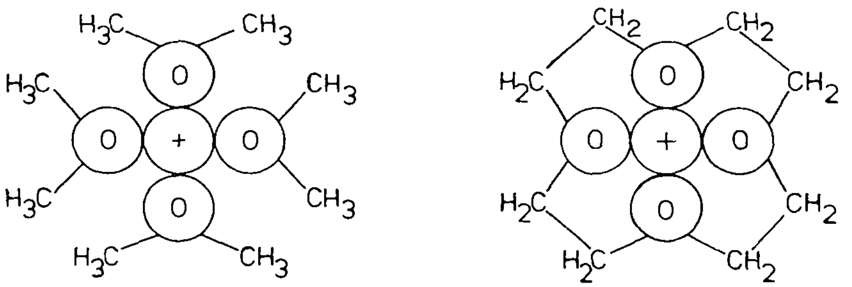
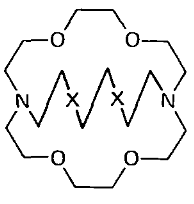


FIGURE 12. Comparison of ion solvation by dimethyl ether to ion solvation by a polyether.

coordination numbers with water molecules[111] : 6 for alkali metal ions, 4 for Be^{2+}, 6 for Mg^{2+}, and 8 for Ca^{2+}, Sr^{2+}, and Ba^{2+} respectively[112].

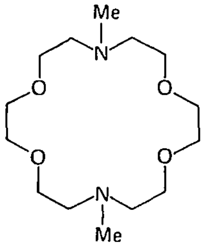
The influence of this factor is clearly revealed by a comparison of [2.2.2] *cryptand* (**19**) and [2.2.C_8] (**75**) with approximately similar size; ligand **75** differs from **19** only in the lack of a pair of O-donor sites in one of the three bridges of the [2.2.2] skeleton[113]. This leads to a reverse of the Ba^{2+}/K^+ selectivity of the order of 10^6. Thus the Ba^{2+}/K^+ ratio is 10^4 for **19**, but $<10^{-2}$ for **75**.

The fact, that *monocyclic* **76** with the same number of donor atoms as bicyclic **75** displays a Ba^{2+}/K^+ selectivity comparable to that of the octadentated cryptand **19**, could be explained by the easier accessibility of the complexed cation in **76** to solvent molecules which can saturate its unoccupied coordination sites[113].



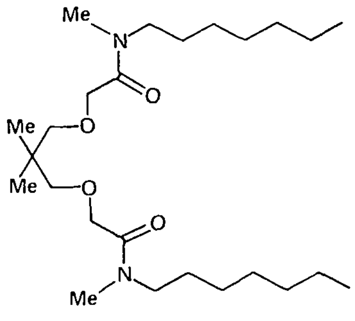
(**19**) X = O

(**75**) X = CH_2

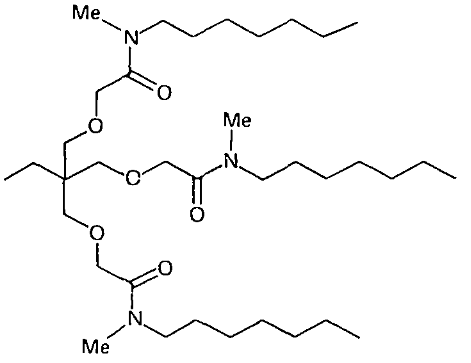


(**76**)

The 1 : 1 association constants of a few *open-chain* oligoethylene glycol ethers with different donor numbers have been determined for various metal ions potentiometrically as well as conductometrically[86b]. The K_s values and the selectivity ratio K^+/Na^+ rise with increasing number of coordination sites. The tetradentate ligand **77**, used as an ionophore in liquid membrane electrodes, shows the selectivity sequence $Li^+ > Na^+ > K^+$. By connecting another complexation arm as in tripodand **78**, the donor atom number can be increased to a total of 6 and the ligand rendered Na^+-selective[27k].



(**77**)



(**78**)

In general, *double-valent cations* should, as molecular models show, selectively be complexed by uncharged ligands with mostly big coordination numbers[112]. However, since the stoichiometry of the complex formation reaction is not known *a priori* consideration of this parameter for the design and choice of ligands remains intrinsically problematic. Other possibilities of influencing the monovalent/divalent selectivity are considered in Section III.D.1.d(1).

(3) *Arrangement of donor atoms.* The symmetrical arrangement of the donor sites in a crown ether skeleton does not seem to play an aesthetic role only[7]. Every deformation of the inner 'charge-shell', which is not in keeping with the geometry of the guest, reduces the binding ability of the ligand and the stability of the complex (host–guest relationship)[18c,81].

For *spherical* metal ions, the optimum charge-shell should also have a spherical form (see 'soccer molecule' 24, Figure 2); for the *rod-like* azide ion, on the other hand, it should be stretched so as to look like a 'baseball' (see Section III.D.3)[14d]. Crown ethers, in which the oxygen dipole ends are not ideally located in the ring centre (cf. Figure 1), clearly show lower complex stabilities for cations[7,113]. This applies to coronands (Tables 8, 11) as well as cryptands (Tables 9, 12) and less particularly to open-chain podands.

Thus, the K^+ complexation of [18]crown-6 falls to about half on replacing a C_2H_4 by a C_3H_6 unit and again by replacement of another C_2H_4 unit[7a,7d,15d]. A more pronounced *spatial stretch* of individual donor atom pairs, e.g. through insertion of four to seven CH_2 groups (see **10**, Figure 1)[7d] or aromatic units (*o*-, *m*-, *p*-xylylene, naphthalene, biphenylene)[7d,36], leads to more unfavourable complexation (see Table 3). An overall similar effect is noted when individual donor sites are *brought together* within the crown ether skeleton as with acetal ether moieties[7d,98].

Even with a cyclic symmetrical alternating combination of ethano and propano moieties or with only propano units[114], strong stability losses of the complexes result, compared with corresponding ethanocrown ethers[7d], thus revealing the particular role played by *ethyleneoxy groups* in crown ethers[7a]. It is well known that in *five-membered* ring chelates containing a pair of binding sites (X = O,N,S), the intervening $-CH_2-CH_2-$ fragment and the coordinated metal ion are more stable than *six-membered* and *four-membered* ones[85a] (see 'chelate effect', Section II.C.3). Thus $X-CH_2-CH_2-X$ arrangements are preferable to the homologous $X-(CH_2)_{2+n}-X$ and $X-CH_2-X$ ones.

Since every unsymmetry of charge distribution in crown ethers disturbs the complexation of spherical metal ions[15d,113] – apart from donor atom specific interactions – the partial incorporation of other types of donor atoms must also be viewed within this framework. This may be quite particularly useful for gradation of selectivity [see Section III.D.1.a(1)].

b. Shape and topology. (1) *Cavity size and shape.* As was often pointed out earlier, the ratio of cation volume to crown ether/cryptand cavity plays an important role (see also Section IV.B, complex structures). Since spherical cavities, which can enclose cations, can best be formed by *cryptands*, particularly marked effects are observed here[14c].

Figure 13 shows, for instance, the results of measurements of complex constants of cryptands [2.1.1] to [3.3.3] for alkali metal ions ranging from lithium to caesium as well as for the alkaline earth metal ions Mg^{2+} to Ba^{2+} [14d,85a]. Therefore it follows that macrobicycle [2.1.1] **54** with the smallest inner volume possesses the highest K_S value for Li^+, while the cryptands [2.2.1] (**55**) and [2.2.2] (**19**) are best suited to complex Na^+ and K^+ respectively. The very big macrobicycles [3.2.2] (**62**), [3.3.2] (**79**) and [3.3.3] (**80**) combine progressively better with Cs^+ in the order given. For alkaline earth cations cavity size affects the stability constants, as in the case of alkali cations. However, the selectivity peaks (Figure 13) are much less sharp than for the alkali cryptates (see also Section III.D.1.c).

The general point, which can be derived, is that the K_S value is principally

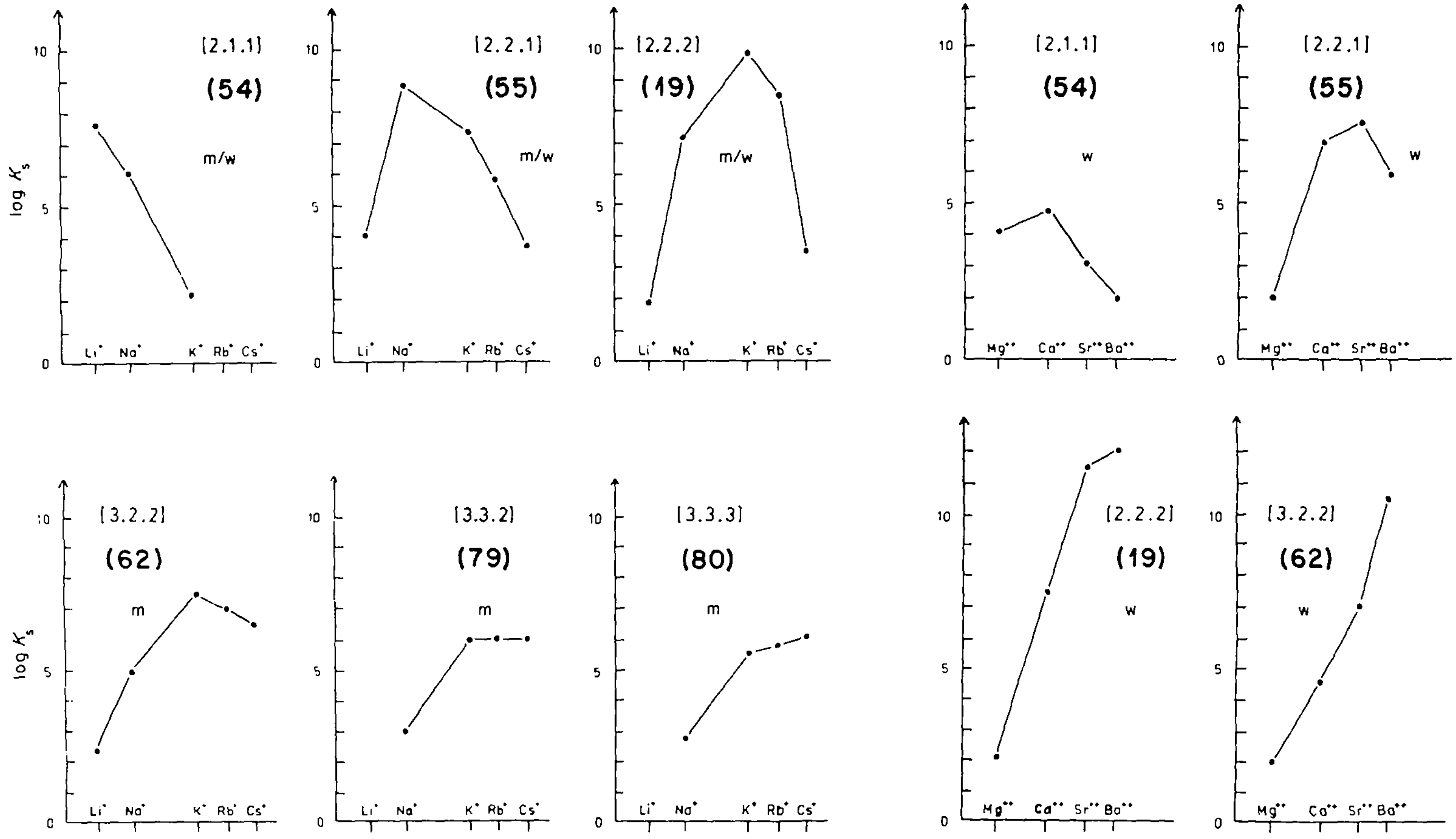


FIGURE 13. Plots of stability constants (log K_S) of various cryptates as a function of the ionic radii of alkali/alkaline earth metal cations at 25°C in 95 : 5 methanol/water (m/w) or pure methanol (m) or in water $(w)^{85a}$.

highest (Figure 13) and the cation fit particularly good, when the diameter of the *metal cation* roughly matches the hole diameter of the *host*[65] (see Table 13).

Similar rules apply to *coronates*[8b,c,e], as can be seen from Table 4[48], 8[67,69] and Figure 16 (Section III.D.1.c). [12]crown-4 (**81**) corresponds best with Li$^+$, [15]crown-5 (**82**) with Na$^+$, [18]crown-6 (**2**) with K$^+$ etc. (see Table 13).

An example for the influence of slightly differing cavity sizes and shapes on the complexation is given by the four isomers (*trans–anti–trans, trans–syn–trans, cis–anti–cis, cis–syn–cis*) of *dicyclohexano[18]crown-6* ligands (**59**)[113]. They display different complex constants for alkali metal ions like Na$^+$, K$^+$, Rb$^+$ and Cs$^+$ (Table 14). Thus the stabilities of the complexes of the *trans–anti–trans* and *trans–syn–trans* isomers with the three metal cations Na$^+$, K$^+$ and Cs$^+$ are lower than those of the corresponding complexes of the *cis–anti–cis* and *cis–syn–cis* isomers (see also Table 8[67b]).

With Na$^+$, K$^+$, Rb$^+$ and Cs$^+$ ions, the stability constants are higher for the *trans–syn–trans* isomers than for the *trans–anti–trans* isomers. The four isomers of dicyclohexano[18]crown-6 (**59**) differ most significantly in their complexing ability toward K$^+$ ions; log K_S values are 3.26, 4.14, 5.38 and 6.01 for the *trans–anti–trans, trans–syn–trans, cis–anti–cis* and *cis–syn–cis* isomers respectively.[115]. The fact that large ΔK_S values are observed for metal ions and also for *t*-Bu$\overset{+}{N}H_3$ suggests that the contributions from ion–dipole interactions as well as those from hydrogen bonding, are sensitive to small conformational differences in the host[113] (cf. Section III.D.1.c).

Thus *cavity selectivity* may be used as an operational criterion for predicting selectivity of complexation.

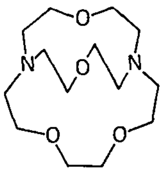
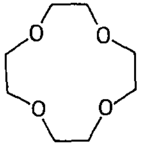
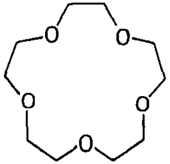
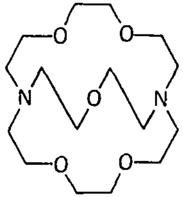
(2) *Ring number and type (ligand constitution).* The overall ligand topology (connectivity, cyclic order, dimensionality)[14c] determines the way in which ligand and cation interact and defines the type of complex formed (*podate, coronate, cryptate*). A selection of possible ligand topologies is given in Figure 14[14c] ranging from a *linear* ligand **A** (mono- or di-podand) to *cylindrical* and *spherical* cryptands **I,K**[116,117], but other systems may be imagined (see 'multi-loop crowns'). Examples are represented in the Figures 1–7.

The ligand should be able to replace as completely as possible the solvation shell of the cation during the complexation steps. Thus the stability of a complex is higher the better the ligand can envelope the cation and replace its coordination shell [see Section III.D.1.a(2), (3)]. On going from *open-chain* oligoethylene glycol ether neutral ligands of the dipod type **A** (Figures 5 and 7) via noncyclic tripod **B**, hexapod ligands (Figures 4 and 6) to *monocyclic* crown ethers **D** (Figure 1) and further to *bi-* and *oligo-cyclic* cryptands **G**, **I** and **K** (Figure 2), a considerable increase of the complex stability up to 10^9 (see Figures 10, 11) and often of the selectivity also (*toposelectivity*) is observed as a rule[7,8,14,85a].

An optimum ligand (receptor, see Section II.B.4) for *cations* should be fairly rigid and held in a conformation defining a spherical cavity such as the 'soccer'-like cryptand **24**[117] (see Figure 2), possessing ten binding sites and a rigid cavity (diameter ~3.6 Å) practically ideal for complexing Cs$^+$ ions (diameter 3.38–3.68 Å). Thus up until now, this aesthetic ligand of high topology, **I**, is the best one for complexing selectively Cs$^+$ metal ions (log $K_S = 3.4$, in H_2O at 25°C)[117].

An interesting topology is shown by ligands of types **84–86**, combinations of several crown ethers with different ring size and donor atom distribution being connected by *spiro* carbon atoms[118]. Such 'morefold crown ethers' as a rule show the *multiple* selectivity of the combined crown ether rings – **85** being selective for

TABLE 13. Correlation of cation and cavity radii (Å) of alkali/alkaline earth metal ions and of some crown ethers and cryptands

Cryptand	Cavity radius	Cation radius	Cation	Cation radius	Cavity[a] radius	Coronand
 (54)	0.8	0.78	Li^+ Mg^{2+}	0.78	0.72	 (81)
					0.92	 (82)
		0.98	Na^+	0.98		
		1.06	Ca^{2+}	1.06		
 (55)	1.15					
		1.27	Sr^{2+}	1.27		

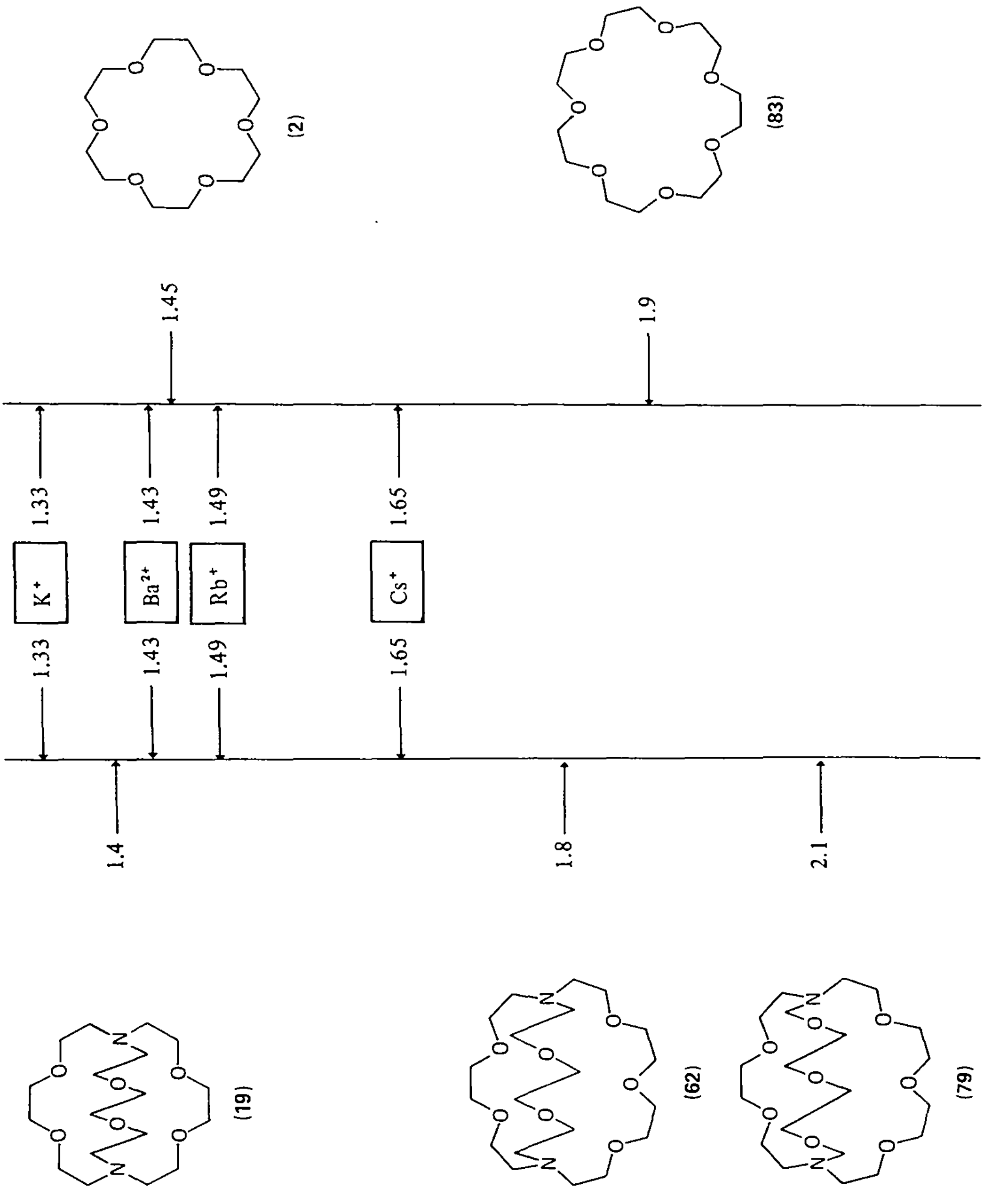
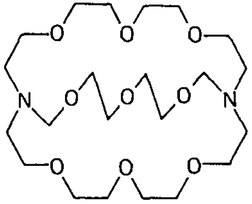
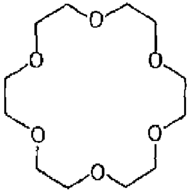
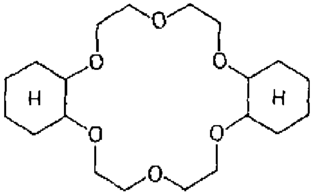

(2)
(83)
1.45
1.9
K⁺
Ba²⁺
Rb⁺
Cs⁺
1.33
1.43
1.49
1.65
1.4
1.8
2.1
(19)
(62)
(79)

TABLE 13 – continued

 (80)	2.4 →		

[a] Average values.

TABLE 14. Complex stabilities (log K_S) of dicyclohexano[18]crown-6 isomers and [18]crown-6 with alkali cations (in MeOH at 25°C)[113]

Cation	Ligand				
					
	(2)	*cis–syn–cis* (59a)	*cis–anti–cis* (59b)	*trans–syn–trans* (59c)	*trans–anti–trans* (59d)
Na^+	4.32	4.08	3.68	2.99	2.52
K^+	6.10	6.01	5.38	4.14	3.26
Rb^+	5.35	–	–	3.42	2.73
Cs^+	4.70	4.61	3.49	3.00	2.27

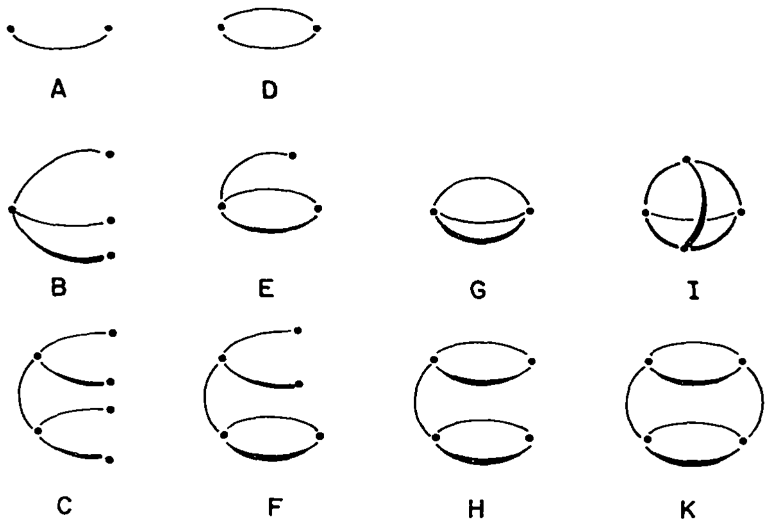
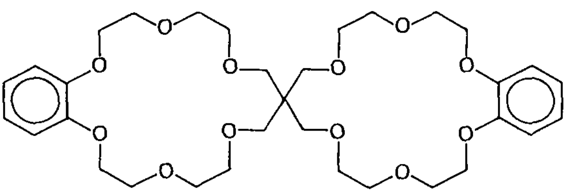
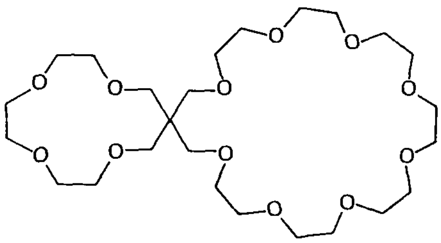


FIGURE 14. Topological representation of various types of organic ligands[14c]. A–C: acyclic (podands); D–F: monocyclic (coronands); G–H: bicyclic (coronands, cryptands); I–K: tricyclic (cryptands).

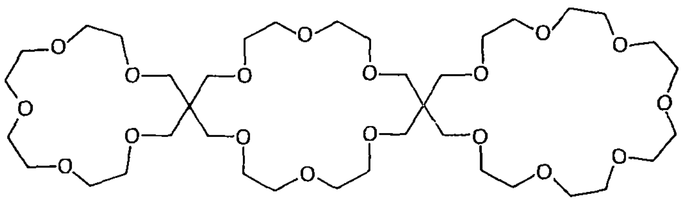
Li^+ and Cs^+, 86 for Na^+, K^+, Rb^+ etc. – but on the other side they may exhibit unexpected selectivities regarding the precipitation of ions from mixtures, that may be explained by the receptor cavities being near enough to each other for interactions between intramolecularly complexed cations.



(84)



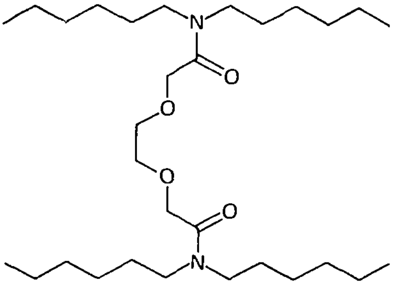
(85)



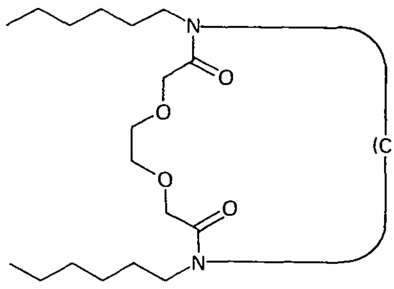
(86)

For the 3,6-dioxaoctane dicarboxamides 87 and 88 investigations have been carried out concerning the influence of *ring-closure* and *ring-size* on the ion-selectivity of a ligand-impregnated PVC/*o*-nitrophenyl octyl ether membrane and the ability to extract alkali/alkaline earth metal ions, including NH_4^+ and H^+ from an aqueous into an organic phase[119]. The results show that because of ring-closure in

88, the selectivity and extractive ability are more strongly reduced with narrowing ring, in comparison to the open-chain compound 87.



(87)



(88)

$n = 2, 6, 10$

A deeper analysis of the origin of such ring formation and (topological) ring number effects ('macrocyclic' and 'cryptate' effect') in terms of enthalpy/entropy contributions was given in Section II.C.3.

(3) *Chiral configuration.* Recognition requires the careful design of a receptor molecule presenting intermolecular complementarity[14c,14d,14e,18,81]. In particular, it involves discerning the proper interactions which will lead to substrate binding and inclusion.

Chiral recognition might be obtained by incorporating a *chiral unit* in the ligand skeleton. To this end, the ligand may contain lateral cavities serving as anchoring sites for polar groups of the substrates and a central cavity large enough for including a molecular ion[14e,81] (cf. Figure 15, 'host'). The complexation of an optically active substrate (e.g. ammonium salt) (+)-S or (−)-S by a chiral ligand (+)-L is represented by the following equations[120]:

$$(+)\text{-L} + (+)\text{-S} \rightleftharpoons [(+)\text{-L}, (+)\text{-S}] \qquad (12)$$

$$(+)\text{-L} + (-)\text{-S} \rightleftharpoons [(+)\text{-L}, (-)\text{-S}] \qquad (13)$$

The two *diastereomeric* complexes obtained have in principle different association constants. The resulting chiral discrimination may be evaluated by the difference (in percentage) of the two diastereomers formed, i.e. the *enantiomeric excess* (e.e.)[121].

In order to obtain specific ligands for sophisticated chiral guest molecules one is faced up with the task of synthesizing highly structural cavities that will tailor-fit the guests ('moleclar architecture')[18a–c], so that out of two enantiomeric guest molecules only one is able to enjoy the particularly tight, energetically favourable interaction with the host ('host–guest chemistry')[81,122]. Out of this conception arose a series of crown ether and cryptand systems[5b,18] with *chiral centres* (marked with asterisks, Figure 3) in definite arrangement (25 and 26)[16a,e–o,124] or with *chirality axes* in the form of binaphthyl units (27–29)[16b–d,17,122,125] or *spiro* groups (30)[18d].

By means of the *binaphthyl crown ether* 28, Cram and coworkers succeeded in *separating racemates* of amino acids in the enantiomers[122a,126]. The separation of the racemic amino acid cations is possible on account of the different stability of the diastereomeric crown ether complexes[123] (Figure 15): for instance, the crown ether 28a with (*S,S*)-configuration and having two 1,1′-binaphthyl units as chirality barriers preferentially complexes the (*R*)-enantiomer of *methylphenylglycinate*

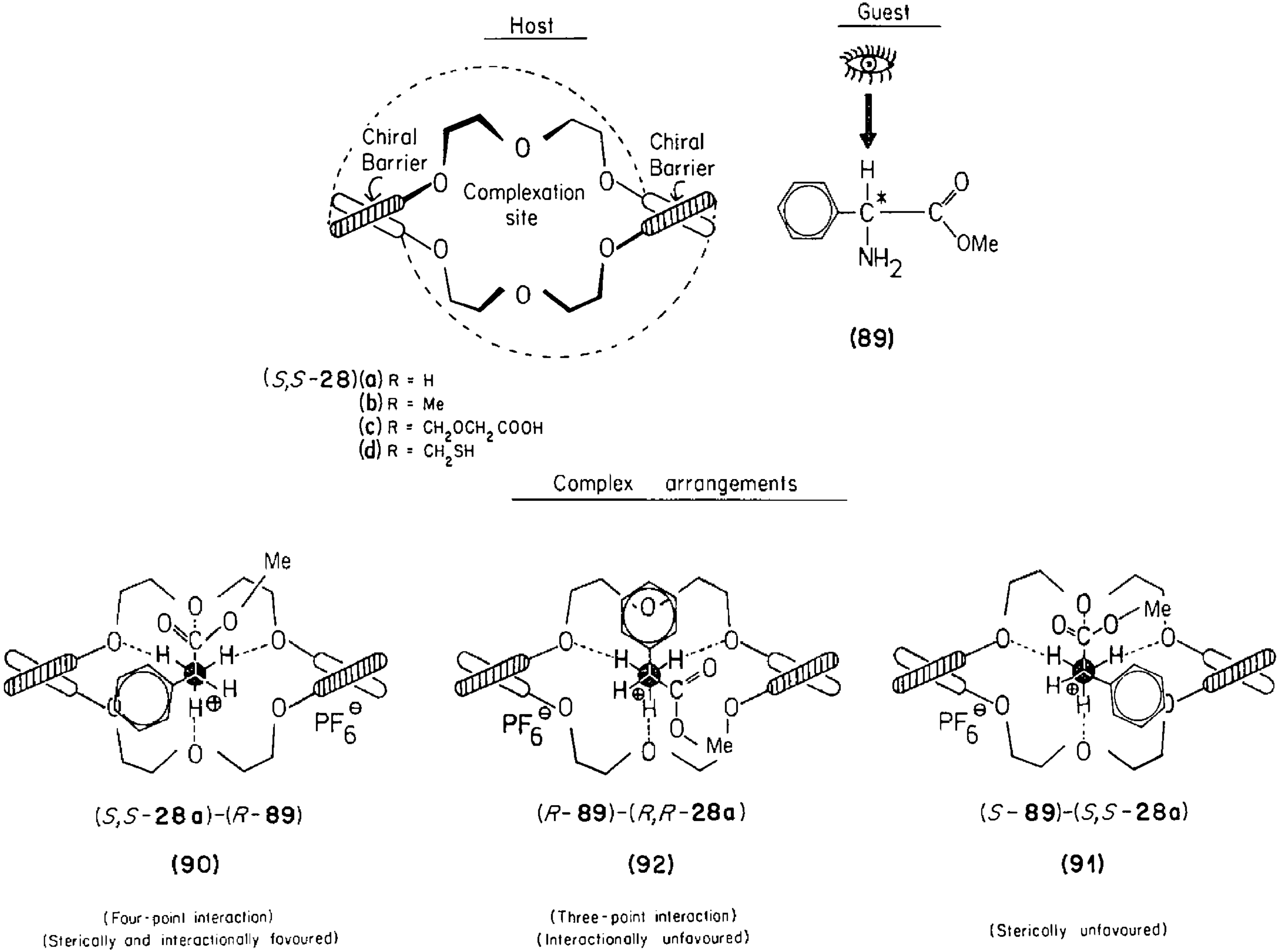

Host
Guest
Chiral Barrier
Complexation site
Chiral Barrier
(89)
(S,S-28)(a) R = H
(b) R = Me
(c) R = CH2OCH2COOH
(d) R = CH2SH
Complex arrangements
(S,S-28a)-(R-89)
(90)
(Four-point interaction)
(Sterically and interactionally favoured)
(R-89)-(R,R-28a)
(92)
(Three-point interaction)
(Interactionally unfavoured)
(S-89)-(S,S-28a)
(91)
(Sterically unfavoured)

FIGURE 15. Chiral recognition between host 28 and guest 89 in various arrangements. Binaphthyl unit as chiral barrier.

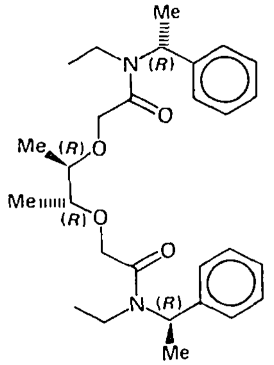
ammonium ion (89)[127]. Thus, when an aqueous solution containing the hydrochloride of *racemic* methylphenylglycinate (89) and LiPF$_6$ is shaken with a solution of (*S*,*S*)-28a in chloroform, 63.5% (*R*)- and 36.5% (*S*)-amino ester can be isolated from the organic phase and 56% (*S*)- and 44% (*R*)-amino ester from the aqueous phase. The projection **90** illustrates the interaction of (*S*,*S*)-28a with the preferred enantiomer (*R*)-89 in the complex, in comparision to the unfavourable arrangement of **91** with (*S*,*S*)-28a–(*S*)-89 geometry[128]. Elusion of the spatial constraint (phenyl nucleus/binaphthyl joint) in **91** through conformational change in the guest molecule reduces the optimum *4-point interaction* in **90** to a less stabilizing *3-point interaction* [see arrangement **92** for the combination of (*R*)-89/(*R*,*R*)-28a].

Through variation of structural units[122f,g] for specific incorporation of *steric barriers* (alkyl groups as in 28b)[129] or *functional complexing groups* as in 27 and 28c,d[125a,130], the chiral cavity can be more strongly subdivided, the chirality barrier raised and the chiral separation increased further. The optically active crown (*S*)-27 with two additional carboxyl functions as donor centres complexes, for example, (*S*)-valine in preference to the (*R*)-isomer (factor of 1.3)[130a].

Conversely, it has also been possible to carry out the enantiomeric separation of *crown ether racemates* by means of enantiomeric amino acids[130a].

Similar polyethers have been used for the total optical separations of *amines* by chromatographic methods[16i,124b,125b,126a]. The difficulty usually encountered here is the preparation of the free crown ether ligand in optically pure form. Taking advantage of the ready availability of natural compounds, Lehn and coworkers[16f], starting from L-*tartaric acid*, as well as Stoddart and coworkers[124] starting from (D)-*mannitol*, (L)-*threitol*, (D)-*glucose* and (D)-*galactose*, synthesized a few optically pure [18]crown-6 analogous ring skeletons (like 25b,c and 26; see Figure 3) containing several chirality barriers which recently also included binaphthyl[125b] or pyridino units (26)[16i]. Macrocyclic polyethers of this type form complexes with metal ions and primary alkylammonium cations, and show enantiomeric differentiation in the complexation of (±)-(R,S)-*α-phenylethylammoniumhexafluorophosphate*[124b].

An enantiomeric differentiation has also been observed in transport through liquid *membranes* containing crown 28[131] or podand 93[132]. Thus it is proved that



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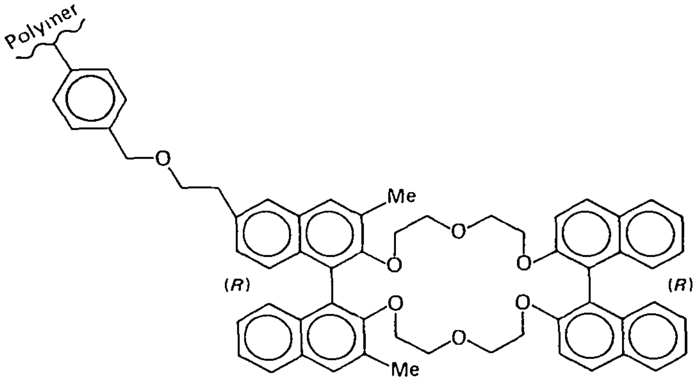
the *chiroselective transport* of ions across a membrane can be effected by means of chiral complexation compounds, i.e. out of a racemic mixture it is possible, by using a suitable crown ether as carrier molecule, to transport one particular enantiomer preferentially from one side of a membrane to the other.

The separation of guest racemates is more economical and at the same time essentially easier, while the optical separation factors are strongly raised, when the chiral crown ethers or cryptands are bound to a *polymeric* supporting material (styrene resin 94, silica gel, etc.) and used as the stationary phase in the form of column fillings[133]. Thus was achieved the total chromatographic enantiomeric resolution of *α-amino acids* and their ester salts via chiral recognition by a host crown ether covalently bound to a polystyrene resin[133b] or on silica gel[122a]. The separations were carried out on a preparative as well as on an analytical scale. The values of the separation factors (α) vary between 26 and 1.4 depending on the structure of the guest molecule; the resolution factors R_S have values between 4.5 and 0.21. Here also, a reasonable relationship could be established between the available cavity of the 'isolated' ligand and the size of the substituent in the guest amino acid.



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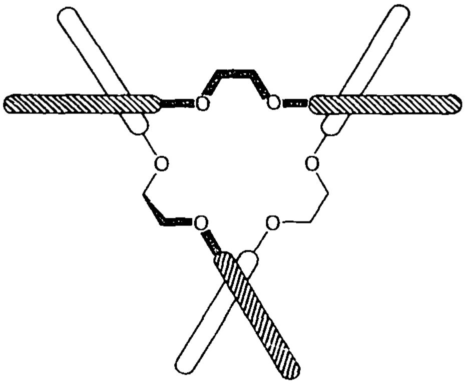
The incorporation of additional chirality barriers in the model system 28 was lately accomplished by the synthesis of 95 with *three* binaphthyl units[16d]. However, no particular results concerning the enantiomer-selective complexation behaviour of these ligands have yet been reported.



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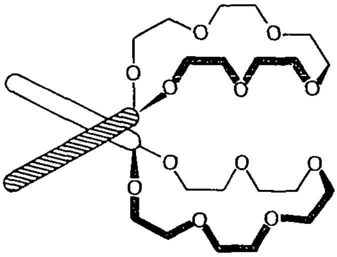

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A new possibility or type of complexation and enantiomer selection is '*cascade binding*'[14e], involving complexation of an alkali cation followed by pairing with an organic molecular anion, e.g. mandelate anion[120]. Compounds of this type may be considered as metalloreceptor model systems, where binding of an anion substrate is dependent on initial binding of a cation. A weak resolution of chiral racemic substrates has been observed by extraction and transport (through a bulk liquid membrane) experiments[120]. The resolution achieved with the cryptand 29 for the (±)-*mandelate anion* is markedly affected by the nature of the complexed cation.

Semirigid molecular skeletons 96, in which *two* crown ether units are held together through a binaphthyl joint, represent another topical development on the way to abiotic model systems for biological multifunctional molecular receptors[134]. The fundamental importance here lies in the fact that highly selective molecular complexations between organic molecules must have played a central role in the molecular evolution of biological systems[81]. In other words, the molecular basis for the natural selection of the species depends directly on the selection of partners in molecular complexation based on structural recognition.

c. Conformational flexibility/rigidity. Rigidity, flexibility and conformational changes of a ligand skeleton (*ligand dynamics*) often go hand-in-hand with cavity size in governing cation selectivities[14c,65,85a] [see Section III.D.1.b.(1)]. Ligands with small cavities are generally quite rigid, since a small cavity is delineated by short, relatively nonflexible chains. Larger ligands with cavities above a certain size are generally more flexible and may undergo more pronounced conformational changes. In other words, rigid ligands give definite and only slightly alterable coordination cavities, while flexible, conformationally labile ligands can form cavities of variable dimensions. Hence it follows that rigid skeletons should display higher cation selectivities, i.e. their ability to discriminate between ions, which are either smaller or larger than their cavities, should be better.

This is pictured in Figure 13[85a]. The *cryptands* of the *'rigid' type* [2.1.1] (54), [2.2.1] (55) and [2.2.2] (19) show a stability peak (*peak selectivity*) for the cation of optimum size (cf. Table 13). Ligands of the *'flexible' type* beginning with [3.2.2] (62), which contain large, adjustable cavities show *plateau selectivity* for K^+, Rb^+ and Cs^+, whereas K^+/Na^+ selectivity is large (Figure 13). Thus, while rigid ligands can discriminate between cations, that are either smaller or bigger than the one with the optimum size (peak selectivity), flexible ligands discriminate principally between smaller cations (plateau selectivity). That the stability plateau generally starts with K^+ is not too surprising since the largest relative change in cation radius occurs between Na^+ and K^+ (cf. Table 13). An important contribution to this peak–plateau behaviour also results from coordination property facts; the free energies of hydration change much less for K^+, Rb^+ and Cs^+ than for Li^+, Na^+, K^+[14c].

Many macrocyclic *antibiotics* (e.g. enniatin B and valinomycin) show a similar behaviour[7b].

Corresponding rules, though less rigid, apply to *coronands* apart from a few exceptions[65]. The data in Figure 16[76a] show the maximum log K_S value and peak selectivity in the case of K^+ to be reached with [18]crown-6 rings [cyclohexano[18]crown-6 (97), dibenzo[18]crown-6 (1)]. However, while the log K_S values for K^+-dibenzo[21]crown-7 (98) and K^+-dibenzo[24]crown-8 (7) interactions decrease as expected, a significant increase is seen in the case of dibenzo[30]crown-10 (8). The unexpectedly large stability of the *K^+-dibenzo[30]crown-10 complex*[48] is consistent with the observation based on X-ray crystallographic data (see Figure 23, Section IV.B.1.a), according to which the ligand is held in a conformation where all ten donor sites are 'wrapped' around the K^+ ion[135]. Such unusual ligand conformational change during complexation results from a

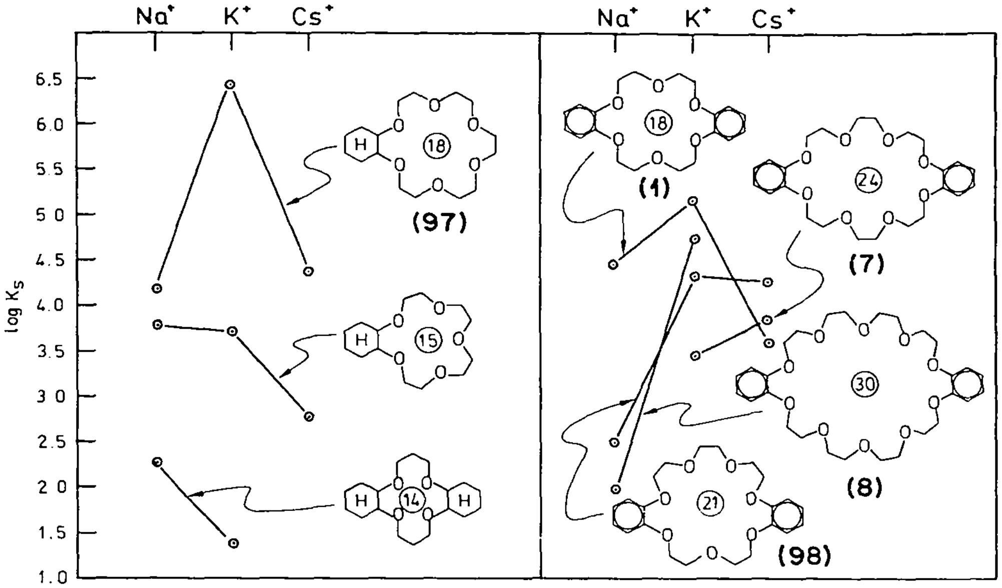


FIGURE 16. Plots of log K_S (in MeOH at 25° C) for complex formation between alkali metal cations and several cyclohexano- and dibenzo-crown ethers[65].

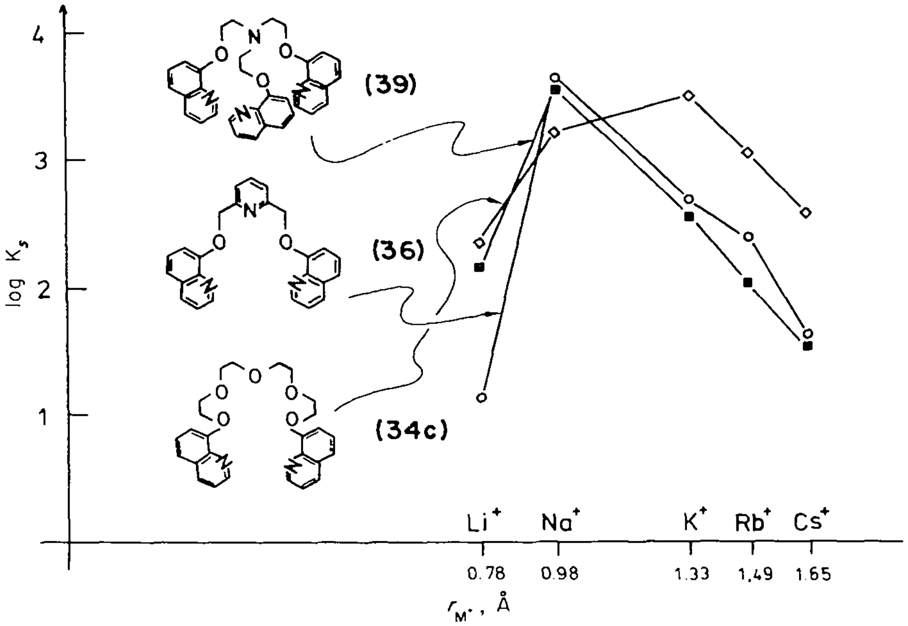
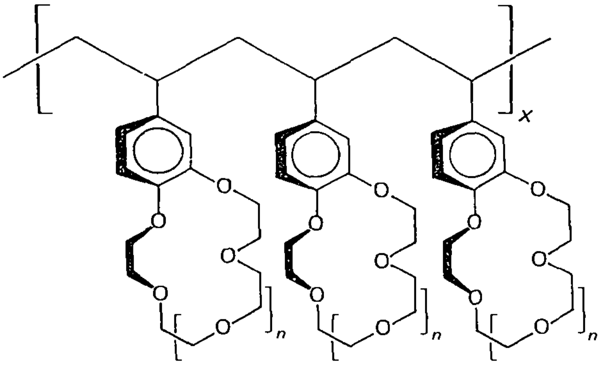


FIGURE 17. Plots of log K_S (in MeOH at 25°C) of complexes of open-chain crown ethers 34c and 36 and open-chain cryptand 39 as a function of the ionic radii of alkali metal cations[64].

stronger interaction of the K^+ ion with the donor atoms than might otherwise be expected. Similar conformational ligand arrangements are also found in the K^+ complex of antibiotics of large ring size (valinomycin, nonactin)[136].

Although *open-chain* ligands belong to crown ether types with the biggest flexibility and ability to adapt to cations of various size, they sometimes show remarkable peak selectivities (Figure 17), particularly when the oligoethylene glycol ether (middle section of **34c**) is partially stiffened by insertion of a pyridino nucleus as in **36**[57,64].

Polyvinyl macrocyclic polyethers **99** are more efficient in complexing cations than their monomeric analogues, especially in those cases where the diameter of the polyether ring is smaller than that of the cation[137] For example, log K_s for formation of the K^+–poly(4′-vinyl)benzo[15]crown-5 (**99**, $n = 1$) complex is found to be >5 (obtained by extraction of K^+–fluorenyl), whereas that for the corresponding monomer benzo[15]crown-5(**4**)–K^+ complex is 3.7. This can be explained by cooperative coordination effects, where two neighbouring crown ether rings combine with a single cation.



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That macrobicyclic ligands present better *overall selectivities* than all other types of ligands (monocyclic crown ethers, open-chain podands) may be related to their bicyclic topology[85a]. Cryptands have a higher 'connectivity', hence higher rigidity and 'dimensionality' [cf. Section III.D.1.b(2)] than simple monocyclic and open-chain ligands[14c]. The best overall selectivity for all metal ion pairs is displayed by the [2.2.2]cryptand (**19**). In an aqueous solution containing all alkali metal ions, for instance, [2.2.2] would complex K^+ strongly, Na^+ and Rb^+ slightly less, but leave Li^+ and Cs^+ completely uncomplexed[85a].

Pyridino rings lead to stiffening of the skeleton and selectivity shift in cryptand as well as in crown ether and podand systems (e.g. increase of Na^+ selectivity, cf. Figure 17)[57,64,85c].

Instead of the pyridino nucleus, *intraannularly*-substituted benzene rings may also be incorporated in open-chain and cyclic crown ether frameworks [see Section III.D.1.a(1)]. Model inspections show that crown ethers of type **70** adopt a conformation where the plane of the benzene ring is twisted approximately 30° out of the plane of the macro ring[101]. Two opposing methoxyphenyl rings in **71** lead to comparably low constants, since a series of rotational degrees of freedom are frozen, causing difficult formation of cavities for guest molecules[102].

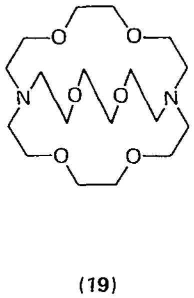
Added *benzene* or *cyclohexane* rings are able to alter the complex constants themselves as well as the selectivities[65]. This can be deduced from Figure 16, where various cyclohexano- and dicyclohexano-crowns are compared with the corresponding dibenzo derivatives[76a]. The decomplexation energy of the Na^+–dibenzo[18]crown-6 complex is the same in various solvents, about 12.6 kcal/mol, and is lowest for the dicyclohexano[18]crown-6-Na^+ complex (8.3 kcal/mol in methanol). The main barrier to removal of Na^+ from the cation complex of dibenzo[18]crown-6 and its derivatives seems actually to be the energy required for a conformational change. The smaller activation energy for the decomplexation of the Na^+-dicyclohexano[18]crown-6 complex is attributed to greater flexibility of the ligand. Addition of rigid benzene nuclei should also diminish the cavity size as is confirmed in several cases [see Section III.D1.b.(1)].

As mentioned above, complexation of conformationally labile ligands is usually accompanied by a stiffening or fixation of the ligand skeleton in the complex. In a few cases, this can be directly derived from the ^1H-NMR spectra of ligand and complex[15i,100b]. In the case of crown ethers and cryptands with ester or carbamide structure, complex stability and selectivity are also influenced by hindered rotation about the C–O or C–N bond[138].

d. Substituent effects. (1) *Lipophilicity.* Crown ethers as cation complexing ligands are of the *endopolarophilic/exolipophilic* type with polar binding sites turned inside and a surface formed by lipophilic hydrocarbon groups[4e,8e,18a] (cf. Figure 12). The lipophilic character of a ligand may be controlled by the nature of the hydrocarbon residues forming the ligand framework or attached to it.

Ligands with thick lipophilic shells shield the cation from the medium and decrease the stability of the complex[14c]; therefore very thick ligands cannot usually form stable complexes. Since this effect is four times more strongly felt by doubly charged alkaline earth metal ions than alkali cations, ligand lipophilicity influences in particular the *selectivity* between *mono* and *divalent* cations: the thicker the organic ligand shell (and the lower the dielectric constant of the medium, cf. Section III.D.4), the smaller the selectivity ratio for divalent M^{2+}/monovalent M^+ cations[20,112]. Competition between monovalent/bivalent cations plays a very important role in biological processes[139].

The selectivity between Ba^{2+}/K^+ serves as a test, since these cations have (almost) similar size (cf. Table 13). For instance, the addition of a first *benzene ring* as lipophilicity-enhancing element in the cryptand [2.2.2] (**19**) (see **100**) does not much affect the Ba^{2+}/K selectivity, probably because solvent approach to one side of the bicyclic system remains unhindered[140]. However, when a second benzene ring is added as in **101**, the stabilities of the Ba^{2+} and K^+ cryptates become nearly equal and the Ba^{2+}/K^+ selectivity is lost[140]. Analogously, the *NCH_3 group* in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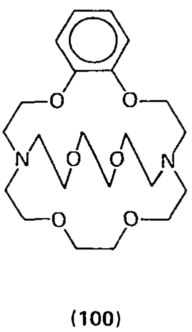
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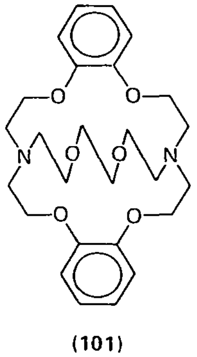
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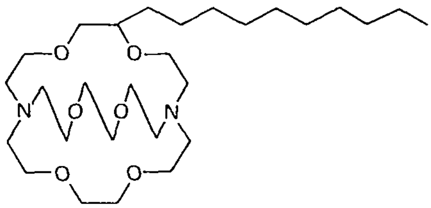
cryptands **66–68** (Table 12) – compared to **19** – thicken the ligand layer and have a destabilizing effect on doubly charged cations[85b,97]. Another influence on complexation selectivity between monovalent and bivalent ions caused by removal of binding sites is discussed in Section III.D.1.a(2).

Lipophilicity enhancement has also been studied in podands of the 3,6-dioxaoctanedioic diamide type **87**[141]: An increase in lipophilicity (lengthening of the N-*alkyl chains*) decreases the ionophoric behaviour of these ligands; at a chain-length of $(CH_2)_{17}-CH_3$, the ability to transport ions across a membrane is practically nil. Nevertheless, a complexation of Ca^{2+} in solution can be detected by ^{13}C-NMR spectroscopy[142]. To account for the surprising electromotoric behaviour, kinetic limitations at the phase boundary have been suggested.

In general, lipophilicity of a ligand and its complex plays a very important role whenever substances should be solubilized in organic media of low polarity[4,143]. This is the case with crown ethers as *anion-activating* agents[4] ('naked anions')[144] and *phase-transfer* catalysts[4,145] and of *cation transport* through lipid membranes[6a,b,7b,30]. In this connection, many crown ethers, cryptands and open-chain ligands fitted with benzene rings (e.g. **21**, **100** and **101**) or with long alkyl side-chains (e.g. **32**, Figure 4 and **102–104**) have been synthesized and used with success[22,146].



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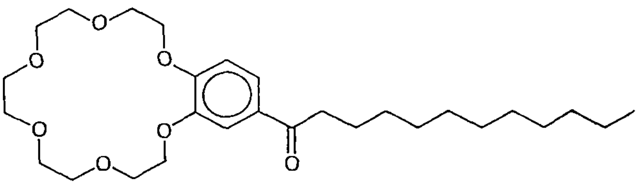

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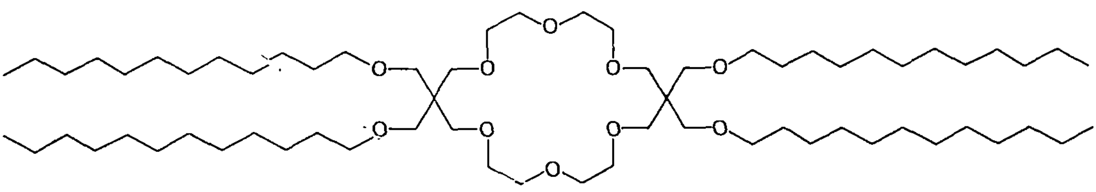
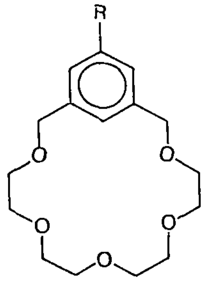


(104)

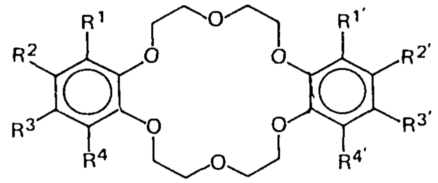
(2) *Electronic influences*. Experiments on the extraction of sodium and potassium salts in the two-phase system water/dichloromethane show a marked substituent effect for substituted *dibenzo[18]crown-6* ethers **105** (*cis*- and *trans*-dinitro, *cis*- and *trans*-diamino, tetrabromo, octachloro) as well as mono- and

bis-(tricarbonylchromonium) derivatives[147]; one observes a reverse of the usual selectivities of dibenzocrown ethers when strong, electron-withdrawing substituents are bound to the aromatic rings[148].

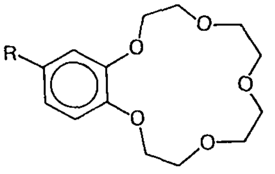
Analogous effects were investigated for *benzo[15]crown-5* systems **106** carrying various electron-donating and -withdrawing substituents in the benzene nucleus[149]. For example, 4'-amino- and 4'-nitro-substituted derivatives differ by a factor of 25 in K_S for complexation with Na^+ ions. Within the whole series of **106** a good *Hammett correlation* is obtained when log K_S is plotted vs. ($\sigma_p + \sigma_m$), the ρ value being −0.45. The substituent effect for the system of *benzo[18]crown-6*/Na^+ is much smaller and almost negligible with electron-withdrawing substituents[149]. For the K^+–benzo[18]crown-6 complexes, somewhat bigger effects are found, but no linear Hammett correlation. This could be attributed to the more flexible structure of benzo[18]crown-6. The results show that caution must be applied in extrapolating substituent effects found in one system to other crown–cation combinations.



(70)(a) R = H (−4.8)
(b) R = *t*-Bu (−5.1)
(c) R = CN (−2.7)
(d) R = COOEt (−3.8)



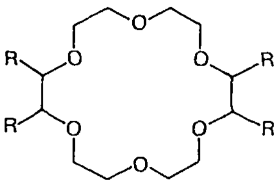
(105) $R^2, R^{2'} = NO_2, NH_2$
$R^2, R^{3'} = NO_2, NH_2$
$R^2, R^3, R^{2'}, R^{3'} = Br$
$R^1, R^2, R^3, R^4, R^{1'}, R^{2'}, R^{3'}, R^{4'} = Cl$



(106) R = H, Me, Br, NH_2, NO_2,
CHO, COOH, COOMe

Complexation of the *m-benzene-bridged* hosts **70** is found to be sensitive to substituents both the 2'- [see Section III.D.1.a(1)] and 5'-positions[18c]. The binding energies of **70a–d** for *t*-$BuNH_3^+SCN^-$ change between 5.1 kcal/mol and 2.7 kcal/mol, which can be explained by the affected electron density of the π-system and correlated by Hammett-type linear free energy relationships[150].

'*Lateral discrimination*' can be obtained by changing sidegroups (R) in the crown ether system **25**[14d]. Within the series **25c–f**, the tetracarboxylate **25d** forms – in accord with the strong electrostatic interaction with K^+ – one of the most stable complexes reported to date for a macrocyclic polyether (K_S = 300,000 in H_2O)[16g]. That the tryptophane derivative **25f** (K_S = 5500) complexes K^+ better than the glycinate **25e** (K_S = 200) might be related to the shielding effect of the lipophilic



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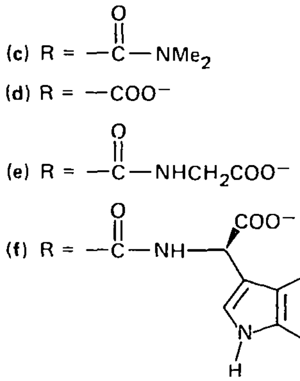


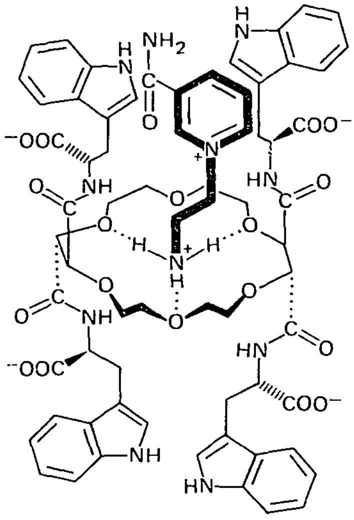
(c) $R = -C(=O)-NMe_2$

(d) $R = -COO^-$

(e) $R = -C(=O)-NHCH_2COO^-$

(f) $R = -C(=O)-NH-$

indole groups in the solvation of the carboxylate. Diammonium salts like the nicotinamide derivative in **107** are very strongly bound by the tryptophanate **25f**.



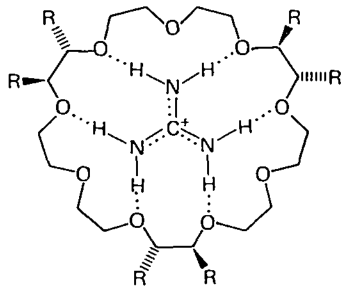
(107)

Thus, the guest is fixed at the NH_3^+ end inside the crown ether ring, and by electrostatic interaction of two carboxylate groups with the pyridinium unit. Moreover, donor–acceptor interaction between the indole and pyridinium groups are effective as shown by a charge-transfer absorption in the electronic spectrum[16g].

2. *Guest parameters: type, size and charge of guest ion*

An intramolecular complex compound is considered to be composed of a host and a guest component. While hosts are organic molecules or ions, whose binding sites converge, guests have divergent binding sites. In order to complex and to have a good fit, *host and guest* must possess a *complementary* stereoelectronic arrangement of binding sites and steric barriers[81].

Thus *guanidinium* ion as guest[151] well meets the requirements for coordination inside the circular cavity of the macrocycle **108** (*'circular recognition'*)[14e].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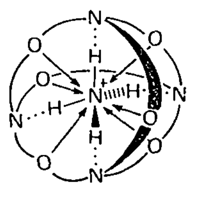
The spheroidal intramolecular cavity of macrobicyclic ligands is well adapted to the formation of stable and selective complexes with *spherical* cations [cf. Section III.D.1.b(1)]. Spherical macrotricycles of type 24 ('soccer molecule') should be most favourable for the recognition of spherical guest particles (*spherical recognition*)[14d].

Tetrahedral arrangement of nitrogen sites (cf. also 39, Figure 6) renders ligand 24 also an ideal receptor for the *ammonium* cation in arrangement **109** (*tetrahedral recognition*)[14d,e]. The NH_4^+ ion is fixed in a tetrahedral array by four $\overset{+}{N}$–H . . . N bonds (cf. Figure 30a, Section IV.B.2.b); also six electrostatic O → $\overset{+}{N}$ interactions are effective in addition to twelve hydrogen bondings $\overset{+}{N}$–H . . . O.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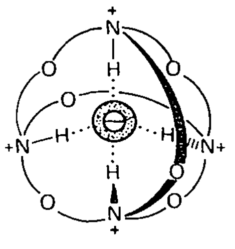
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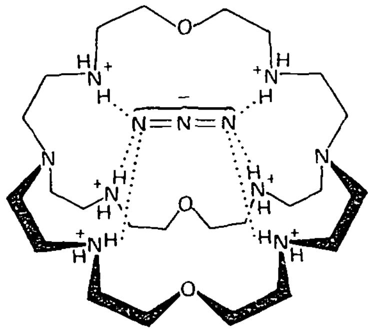
In its *tetraprotonated* form macrotricycle 24 represents a suitable receptor for spherical anions (*anion recognition*)[117,152]. With *halogenide* anions (chloride, bromide) cryptates (**110**) are formed which show similar cavity selectivities for anions of varying size as in the case of cation cryptates[153]. The selectivity of the anion cryptates **110** is highest for Cl^- as guest (log $K_S \geqslant 4.0$ in H_2O; Br: < 1.0; cf. catapinates, Reference 11b). Here it seems that the array of hydrogen bonds and the cavity size complement each other ideally.

Linear anionic species such as the triatomic *azide* ion require corresponding ellipsoidal cavities (*'linear triatomic receptor'*). A good example is furnished by the *hexaprotonated* bis-tren* ligand in **111**[154]: Addition of sodium azide to an aqueous solution of free ligand **20** at pH 5 yields a stoichiometric 1 : 1 azide cryptate in which the linear N_3^- ion is held within the molecular cavity by six hydrogen bonds, three on each terminal nitrogen of the guest ion. Thus this hexaprotonated ligand acts as a receptor for triatomic anionic species.

It may be deduced, therefore, that like the coordination chemistry for cations, a *coordination chemistry for anions* appears feasible[14d,e]. Biological systems often make use of charged receptors. An interesting case would be the complexation of the locally triatomic but nonlinear carboxylate group R–COO^- and of CO_2 and NO_2 molecules, whose stereochemistry are close to that of N_3^-.



(111)

The few examples above (related to the guest) make clear once again the importance of a defined interaction between host and guest for achieving a selective complexation between receptor and substrate. The ligand parameters, which have already been discussed thoroughly in Section III.D.1, must also be viewed in this complementary sense, so that further discussion here is superfluous.

Replacement of oxygen by nitrogen or sulphur in crown ethers and cryptands not only causes a rise in the stabilities of *heavy metal* complexes generally [see Section III.D.1.a(1)], but also markedly influences the cation selectivities in certain instances. Thus the Cd^{2+}/Zn^{2+} *selectivities* of the tetraaza 67 and hexaaza ligand 68 lie higher than those of any other known ligand[85b]. The Cd^{2+}/Co^{2+}, Ni^{2+} *and* Cu^{2+}/Zn^{2+}, Co^{2+} *selectivities* of 67 and 68 are similarly pronounced. On the whole, the aza cryptands offer a wide range of complexation selectivities, which are particularly interesting in the field of biological detoxication (decorporation and depollution), since they complex the toxic heavy-metal ions Cd^{2+}, Hg^{2+} and Pb^{2+} very strongly and the biologically important ions Na^{+}, K^{+}, Mg^{2+}, Ca^{2+} and Zn^{2+} rather weakly. The development of a 'cryptato therapy' based on the above selectivities has been suggested[14d,85b,155].

That the stability of sodium cryptates is dependent on *isotope effects* may find practical use in nuclear chemistry[14d]. In order to evaluate an isotope effect, the distribution of activity of $^{22}Na^{+}$ and $^{24}Na^{+}$ in the heterogeneous equilibrium mixture of a cationic cryptand exchange resin and an aqueous or methanolic solution was measured[156]. The results showed that changes in the isotopic composition occur only in methanolic solutions and not in water. This is surely related to greater solvation of the ions in water, so that mass differences between isotopes are not clearly felt therein. An explanation for the isotopic selective behaviour is that the Li^{+}-charged resin first takes up $^{22}Na^{+}$ and $^{24}Na^{+}$ unspecifically in exchange for Li^{+}. The enrichment of $^{24}Na^{+}$ follows in the backward-reaction, where Li^{+} displaces $^{22}Na^{+}$ preferentially from its binding on account of the lower weight and higher thermal lability of the $^{22}Na^{2+}$ in comparison to $^{24}Na^{+}$. The enrichment of the higher isotope $^{24}Na^{+}$, thus, can be exploited for practical use. Also, the isotope ^{44}Ca present at a 2% level in naturally occurring calcium could be separated from ^{40}Ca by multiple extraction with dibenzo[18]crown-6 (1) or dicyclohexano[18]crown-6 (59)[157].

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*Tren = tris(2-aminoethyl)amine.

Further, the enrichment of ^{235}U on the crown ether basis, reported recently by a French research group, marks a spectacular achievement of technical interest[158].

3. *Anion interactions, ion-pair effects*

While the foregoing sections have been limited to considerations of the ligand/guest complexation, the following deals with the aspect of guest–counterion (an anion usually) relationship.

Taken as a whole, the *ligand–cation unit* – as seen from its environment (solvent, anion) – is like a cationic species of very large size and of low surface charge density, in other words, like a 'superheavy' alkali or alkaline earth cation (about 10 Å diameter, Cs^+ : 3.3 Å)[159]. Accordingly, the electrostatic anion (and solvent) interactions are here much weaker than even with the largest alkali cation Cs^+. While the complexed cation can still be reached by the corresponding anion from 'top' and 'bottom' of the complex in the case of numerous crown ether and open-chain podand-type complexes (still better in the latter case, cf. Figures in Section IV.B), this is hardly possible in the case of spherical cryptates, depending on the degree of encapsulation. Thus, a more thorough *cation–anion separation* can be achieved by cryptates with a complete 'organic skin', and the latter are also more strongly dissociated in solvents of low polarity[159,160]. In the extreme case, one could speak of a 'gas-phase analogous chemistry in solution'[14d].

The interaction between the anion and the complexed cation may affect the stability of the complex[14d]. In highly solvating media, the charged complex and the counterion are *separately* solvated; no anion effect on complex stability is found. In poorly solvating media, however, *ion pairing* gains weight increasingly in the form of complexed or ligand-separated ion pairs; anion effects, that are controlled by the charge, size, shape and polarizability of the anion, can be observed[4e,161]. For instance, ion-paired complexes of *divalent* alkaline earth metal ions will be much more destabilized by an increase in anion size than those of alkali metal ions.

A dramatic and unusual type of cation–anion interaction is illustrated by the crystalline Na^+–[2.2.2]cryptate (or K^+–[2.2.2]cryptate) containing an *alkali metal anion* (Na^-, K^-) as counterion[162]. With Na^+–[2.2.2] as counterion it has also been possible to isolate polyatomic anions of the heavy post-transition metals (e.g. Sb_7^{3-}, Pb_5^{2-} Sn_9^{4-})[163].

Anion effects may also be responsible for the difference in the *exchange kinetics* of TlCl and $TlNO_3$ cryptates[53].

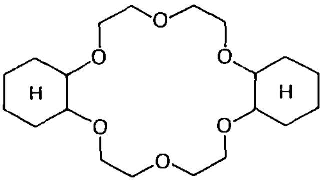
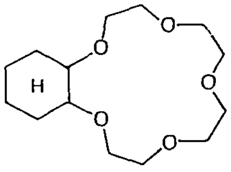
Chiral discrimination of molecular anions by ion pairing with complexed alkali cations via a two-step *cascade complexation* mechanism with chiral cylindrical cryptands (as 29) opens up a new concept of metal receptors where binding of an anionic substrate is dependent on the initial binding of a cation[120] [see Section III.D.1b(3)].

In general, the influence of the *lipophilicity* of the employed anion on the solubility of a complex is of utmost importance. Soft organic and inorganic anions (e.g. phenolate, picrate, tetraphenyl borate, thiocyanate, permanganate) greatly increase the solubility in solvents of low polarity, and this influences cation transport processes, properties and anion activation[4].

4. *Medium (solvent) parameters*

The stability and selectivity of a cation complex are determined by the interaction of the cation both with the solvent and with the ligand[164]. Thus a change in

TABLE 15. Comparison of log K_S values of Na^+ and K^+ complexation in water and methanol solutions at 25°C

	Na^+		K^+		Cation
Ligand	H_2O	MeOH	H_2O	MeOH	Solvent
 (59)	1.21	4.08	2.02	6.01	log K_S
 (112)	<0.3	3.71	0.6	3.58	

media effects *complex stabilities* and simultaneously *selectivities* of complexation, especially where cations are strongly solvated in one solvent but not in another[14c,65].

In *aqueous solution*, most ligands are less selective and the complexes less stable than in *less polar* solvents like MeOH (cf. Tables 4–12, Sections II.B.3, II.C.3 and III.D.1.a). The difference in stability in these solvents is of the order of 10^3-10^5 for cryptates[85a] and 10^3-10^4 for coronates (see Table 15)[65]. For example, the selectivity of benzo[15]crown-5 (4) for K^+ over Na^+ rises continuously as the percentage weight of methanol increases in the solvent system $MeOH/H_2O$ (Figure 18)[165].

The following K_S sequences have been found for [18]crown-6 alkali complexes in the nonaqueous solvents DMSO, DMF and PC (propylene carbonate)[166]:

DMSO: $K^+ > Rb^+ > Cs^+ \cong Na^+ \gg Li^+$
DMF: $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$
PC: $K^+ \gg Na^+ > Rb^+ > Cs^+ > Li^+$

In many cases the rise in selectivity is approximately proportional to the rise in stability of the complex, and for complexes of comparable stabilities *larger* cations are favoured over *smaller* ones. Furthermore, solvents of low dielectric constants favour complexes of *monovalent* ions over those of *bivalent* ones. This general trend allows new selectivity gradations, particularly for cryptates with a wide spectrum of K_S values[85a].

Thermodynamic measurements[75,165] for gaining information about the origin of the solvent effect show that the higher enthalpies of complexation found in

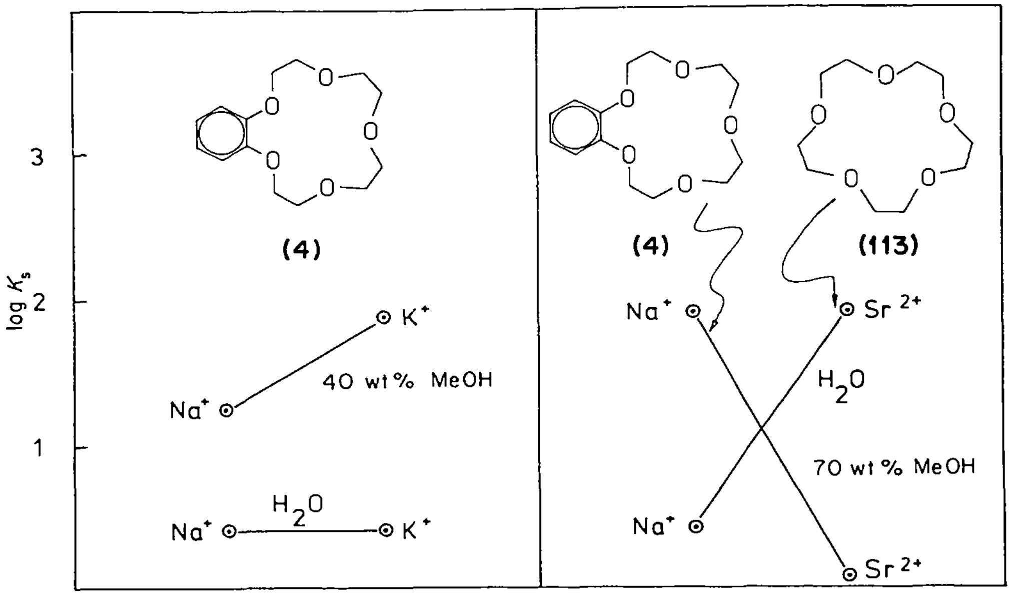


FIGURE 18. Stability constants (log K_S) of complexation for several cation pairs in H_2O and H_2O/MeOH (60 : 40, 30 : 70) as solvents[165].

MeOH/H_2O solutions may be due mostly to an increase of electrostatic interaction of the cation with the ligand and its smaller interaction with the solvent in media of lower dielectric constants. In poorly solvating media the effect becomes very large and complexes, which are soluble in solvents like chloroform or benzene, have extremely high stabilities. This may be important for the preparation of complexes with weakly complexing ligands in water or methanol (cf. Section IV.A).

It is interesting that *podand* 35e is able to compete so well against pyridine as solvent as to allow the determination of the thermodynamics of complexation by the ^{23}Na-NMR method ($K_S = 10^3 - 10$ l/mole in the range of 5–50 °C)[80]. The selectivities of open-chain ligands can be strongly altered, particularly, in such solvents as are used in ion-selective membranes for microelectrodes[27].

These results show that the selectivity of crowns toward alkali and alkaline earth ions is dependent on the physical properties of the solvent and mainly that the relative stability of a complex increases with decreasing solvating power of the medium. The presence of water in solvents may significantly influence the complexation and lead to inaccurate measurements of the complex constants. As Reinhoudt and coworkers showed, concomitant coordination of water molecules in the complex is also possible[167]. During the synthesis of complexes, water is often (inevitably) carried in by the salt employed or in the solvent used for recrystallization (cf. Section IV.A). Numerous crown ethers with water in stoichiometric amounts are known (see below).

IV. CRYSTALLINE COMPLEXES OF CYCLIC AND NONCYCLIC CROWN ETHERS

Having dealt with the more important crown ether skeletons and the stabilities and selectivities of the complexes *in solution*, we will turn now to *crystalline* complex formation by monocyclic, oligocyclic and noncyclic neutral ligands and discuss their stereochemical peculiarities.

A. Preparation of Crown Ether Complexes

Crystalline crown ether complexes can be prepared by several methods[1a,3c,168]. The choice depends essentially on the solubility behaviour of the complex and its components.

The easiest way is to dissolve the polyether and salt (in excess) in a very small amount of warm solvent (or solvent mixture). On cooling, the complex crystallizes slowly (*method 1*)[1a,168]. Sometimes precipitation of the complex is very slow or does not occur at all. In this case, the solvent is partially or totally removed *in vacuo* and the residue recrystallized (*method 2*)[1a,168]. If there is no appropriate solvent mixture common to both crown ether and salt, a suspension of crown ether and salt solution may be warmed. The free ligand then slowly reacts to form the crystalline complex, even in the absence of a homogeneous phase (*method 3*)[1a,168]. Reaction may also be carried out without a solvent. Both components are thoroughly mixed and heated to melting (*method 4*)[1a]. Under certain circumstances crown ether complexes can directly be formed during the ligand synthesis[169] through a '*template participation*'[151,170,171] of the cation. It is then sometimes even more difficult to obtain the free ligand than its complex[85c]

In all cases, complex formation favours salts with weaker crystal lattice forces[14c]. Thus, alkali metal fluorides, nitrates, and carbonates give complexes with polyethers in alcoholic solution; however, it is often difficult to isolate the complexes since concentration, on account of the high lattice energy, mostly leads to decomposition in the sense that the inorganic salt components assemble back to their stable crystal packing and precipitate uncomplexed out of solution[1a].

However, with *alkali* and *alkaline earth metal thiocyanates*[172], *chlorides*[9i], *bromides*[173], *iodides*[1a,100b,168,169], *polyiodides*[1a,168], *perchlorates*[174], *benzoates*[172a], *nitrophenolates*[172a], *tosylates*[169], *picrates*[172a,175], *tetraphenylborates*[176], *nitrites*[1a,100b]; various *ammonium salts*[1a,18c,26a,168] as well as *heavy metal halogenides*[177], *thiocyanates*[178], *nitrates*[100b,177b,c], *perchlorates*[177c] and *tetrafluoroborates*[177c], numerous well-defined, sharp-melting, crystalline crown ether complexes[179] can be obtained by the above methods 1–4.

Of the *lanthanide salts* coordination compounds with crown ethers and cryptands are also known[26a,180,181]. *Uranyl crown ether complexes*[182] are of interest with respect to isotope enrichment[158] (cf. Section III.D.2).

The stable *H_3O^+ complex* of one diastereomer of dicyclohexano[18]crown-6 represents quite a rare case[183].

Crystalline neutral complexes with *acetonitrile*[184], *malodinitrile*[184] and other *CH-acidic compounds*[184,185] are generally obtained by dissolving or warming the ligand in them. Recently, a stable *[18]crown-6 benzene sulphonamide molecule complex* could also be isolated[186]. With aromatic unit-containing polyethers like **1**, *bromine* forms crystalline complexes that partly have a stoichiometric (1 : 1, 1 : 2) composition[187]. *Thiourea* complexes of [18]crown-6 have already been synthesized by Pedersen[188], while those of open-chain crown ethers have been reported more recently[189].

Noncyclic neutral ligands with different numbers of arms and donor units often give analogous metal/salt and neutral particle complexes as easily as their cyclic counterparts[24].

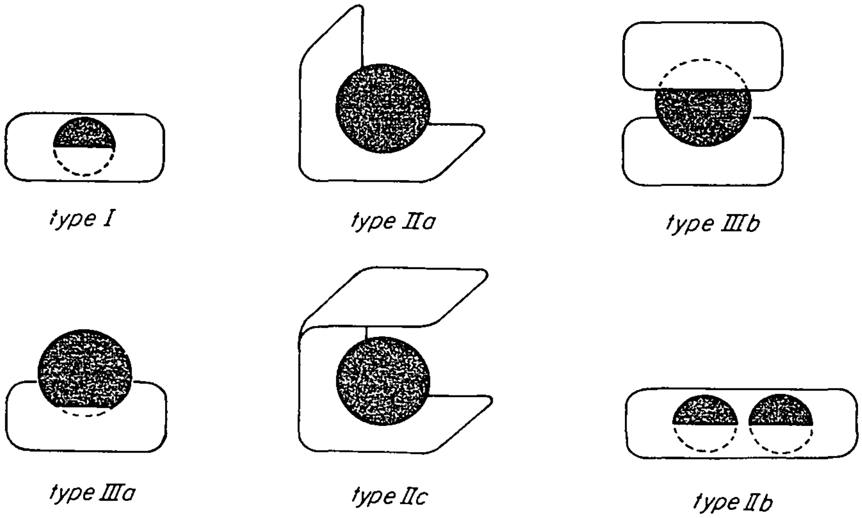
B. Selectivity of Crystalline Complex Formation and Ligand and Complex Structures

Stoichiometry and crystalline structure of crown ether complexes[130] are not always easy to predict, despite careful use of the rules derived in Section III.D[191–193]. Thus, monocyclic crown ethers may apparently have uneven stoichiometries also (cf. the RbSCN–dibenzo[18]crown-6 complex). Complicated stoichiometric compositions are particularly frequent in the case of open-chain polyoxa ligands[24], while mostly normal stoichiometries are found for cryptates[14a–c].

If the difference in cavity size and cation diameter is not too big, 1 : 1 (ligand : salt) complexes may nevertheless be formed. The cation then is either *shifted* from its ideal position (centred in the ring-plane of the crown ether, *type I*, Figure 19, or in the middle of the cavity of the cryptand) or the ligand is *wrapped* around the cation in a nonplanar way. These circumstances are shown in Figure 19 (*type IIa, type IIIa*) and are discussed in more detail at the appropriate place.

If the cavity is much too large for a cation, then *two* of them may be embedded therein (cf. Figure 19, *type IIb*); on the other hand, if the cation is much to large, a sandwich-type complex may be formed, where the cation is trapped between two ligand units (*type IIIB*). The formation of crystalline 1 : 1 complexes, nevertheless, despite unfavourable spatial requirements of ligand and cation, may be explained, at least in part, by the concomitant coordination of H_2O or other solvent molecules in the crystal lattice of the complexes[190] [see further details and compare also Sections III.D.1.a(2), III.D.3. and III.D.4.].

A general comparison of the structures of the *noncomplexed* ligand molecules with the same molecules in its *complexes* suggests types of conformational changes which may occur during complexation (see Figure 20, cf. also Section III.D.1.c). The number of possible structures of noncomplexed molecules that can be elucidated by X-ray structure analysis is limited, because many of the compounds have



type I

type IIa

type IIIb

type IIIa

type IIc

type IIb

FIGURE 19. Schematic representation of several types of crown ether complexes.

low melting points; a few noncomplexed cyclic polyether molecules have nevertheless been studied[190d]. These include *[18]crown-6* (2)[194], *dibenzo[18]crown-6* (1)[195], *dibenzo[30]crown-10* (8)[135] and some isomers of *dicyclohexano[18]crown-6* (59)[196]. The reported structures[197] have some features in common. None of them have the ordered conformations found in the complexes of groups one and two. Even though the molecules do not have highly ordered structures, there are several cases in which they are located about centres of inversion. This is the case for [18]crown-6, for example (see Figure 20a). In the absence of organizing metal ions, and because energy differences between some conformations may be small, the structures determined for these molecules in the solid state may be effected mainly be packing energies[198].

1. Monocyclic crown ethers (see Figure 1)

a. Alkali and alkaline earth metal ion complexes. The architecturally well-examined alkali metal ion complexes of cyclic crown ethers mostly display a 1 : 1 ligand/salt stoichiometry. In addition, there exist polyether/salt combinations of the following compositions: 1 : 2, 2 : 1, 3 : 2 etc.[190].

From the above comparision (Table 13), it follows that Na^+, for example, is too small, Rb^+ and Cs^+ are too big, while K^+ is more likely to be embedded in the cavity of [18]crown-6 (2). All four cations give crystalline, stoichiometric complexes with structures differing significantly, as shown schematically in Figure 19, according to the spatial requirements (*'structure-selectivity'*).

In the *NaSCN–H_2O–[18]crown-6 complex* (Figure 20b)[199] the Na^+ ion is coordinated by all six oxygen atoms of the ligand; while five of them lie in a plane

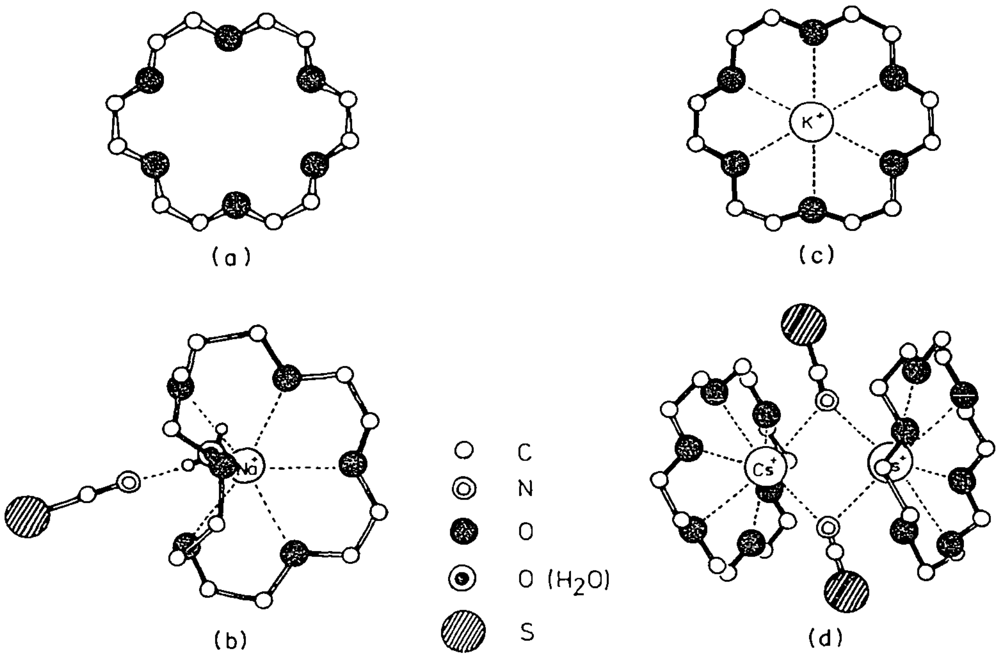


FIGURE 20. Structures of [18]crown-6 and some [18]crown-6 complexes with different alkali metal salts.

containing the cation, the sixth one is folded out of plane and partially envelopes the cation (*type IIA*, diameter ligand > diameter cation; cf. Figure 19). This type of complexation is typical of crown ether rings that are too big for the cation (cf. Table 13). A H_2O molecule additionally participates in the coordination of the Na^+ ion.

In the *KSCN complex of [18]crown-6* (Figure 20c)[200] all six oxygen atoms lie in an almost hexagonal plane coordinating the K^+ ion at the centre of the ring (*type I*, 'ideal' type, diameter ligand ≃ diameter cation). A weak bond to the SCN^- ion was established.

In the *RbSCN–*[201] *or CsSCN–[18]crown–6 complex* (Figure 20d)[202] the cation is situated above the plane of the polyether ring (*type IIIA* diameter ligand < diameter cation). Two cation/ligand units are bridged by two SCN^- ions which also serve to saturate each cation from the 'naked' side of its coordination sphere[203].

From the data given in Figure 13, it can be deduced that regarding the K^+ complex of *benzo[15]crown-5* (4) or *dibenzo[24]crown-8* (7), no ideal spatial conditions are fulfilled for a 1 : 1 stoichiometry of ligand to salt.

As in the combination of [18]crown-6/Rb^+ the cavity of the 15-membered ring 4 is too small for a K^+ ion. However, since the ligand here contains only relatively few donor sites (5 instead of 6), the *KI–benzo[15]crown-5* is formed as a 2 : 1 complex (Figure 21b)[204] with *'sandwich'*-type structure (*type IIIB*, Figure 19). The potassium ion is embedded between two ligand molecules. Both ligand units are arranged approximately centrosymmetrical with respect to each other, all ten oxygen atoms lying at the corners of an irregular pentagonal antiprism.

On the other hand with the fitting Na^+ ion, 4 forms a *sodium iodide complex* (Figure 21a)[205] present as a 1 : 1 monohydrate coordination compound of pentagonal pyramidal configuration, in which the Na^+ ion is coordinated by the five coplanar ligand oxygen atoms lying at an average distance of 2.39 Å and stands 0.75 Å out of the ring-plane. The sixth corner is occupied by a H_2O molecule bound to the Na^+ ion at a distance of 2.29 Å.

Ca^{2+} with a similar ionic radius as Na^+ (cf. Table 13) also gives a 1 : 1 complex with 4[206]; however, differences result in the crown ether structure, reflecting the influence of the cation charge on the ligand arrangement. In the *$Ca(SCN)_2 \cdot H_2O$*[206] or *$Ca(SCN)_2 \cdot MeOH$ complex of benzol[15]crown-5* (Figure 21c) the Ca^{2+} ion is irregularly eightfold coordinated by the crown ether ring on one side and both SCN ions as well as a H_2O and MeOH molecule on the other side. The structures of the H_2O and MeOH complexes differ only slightly by the steric arrangement of one of the two SCN groups. While the Na^+–[15]crown-5 complex displays a very regular crown ether conformation, strong distortions of the bond angles crop up in the calcium complexes. Moreover, the Ca^{2+} ion is displaced farther (1.22 Å) out of the plane of the crown ether.

In the *$Mg(SCN)_2$–[15]crown-5 complex* (Figure 21d)[206b] one notes, just as in the case of the Na^+ complex, the pentagonal bipyramidal structure as well as the high regularity of the crown ether framework. The Mg^{2+} ion is small enough to settle inside the crown ether ring where it is coordinated by the five ether oxygen atoms; two nitrogen atoms of the anion occupy the axial positions of the bipyramid.

Thus with benzo[15]crown-5 magnesium forms only a *1 : 1 complex,* calcium forms both *1 : 1 and 2 : 1 complexes*, and the larger cations (like potassium) form only *2 : 1 crown ether/metal salt complexes.*

Regarding its cavity geometry, the 24-membered cyclic *dibenzo[24]crown-8* (7)

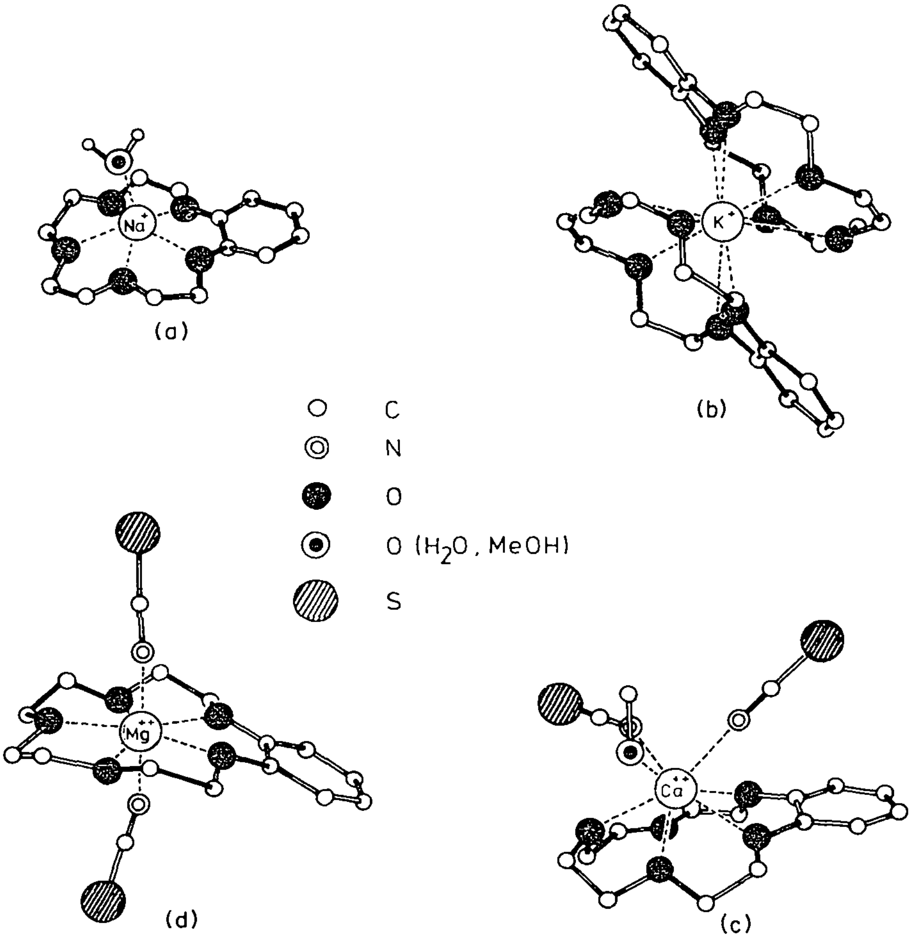


FIGURE 21. Different types of benzo[15]crown-5 alkali/alkaline earth metal ion complexes.

is suited to take up two K$^+$ ions, thus giving rise to a two nuclei-containing *KSCN complex (type IIB*, Figure 19). The eight oxygen donor sites, which are shared between two potassium ions, cannot completely saturate the coordination sphere of the central ions; thus the corresponding anions participate in the K$^+$ complexation. The 2 : 1 KSCN complex of dibenzo[24]crown-8 (Figure 22a)[207] shows a symmetry centre with K$^+$ ions almost coplanarly enclosed by the oxygen atoms. The thiocyanate anions are coordinated to the central ions via the nitrogen atoms; moreover benzene rings of neighbouring molecules seem to participate in the complexation.

The *di(sodium o-nitrophenolate)–dibenzo[24]crown-8 complex* (Figure 22b)[208] differs structurally from the KSCN complex in the sense that two ether oxygen atoms of the octadentate ligand do *not* participate in the coordination. Each Na$^+$ ion is bound to only three oxygen atoms of the ether. The *o*-nitro-

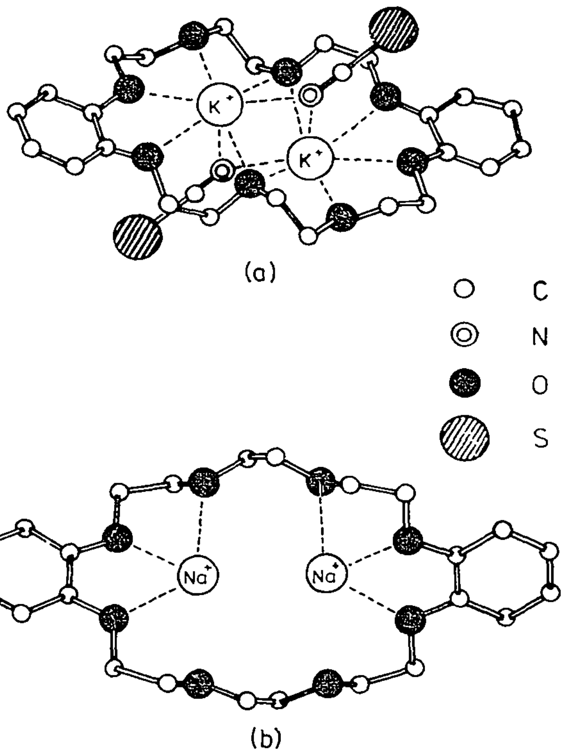


FIGURE 22. Structures of Na$^+$ and K$^+$ complexes of dibenzo[24]-crown-8.

phenolate ions serve to bridge both Na$^+$ ions and complete the coordination at the cation to six.

With the alkaline earth metal ions and dibenzo[24]crown-8, only 1 : 1 complexes have been obtained so far[209,210], although these ions have largely the same radii as the alkali ions. Apparently, the higher charge of double-valent ions prevents their juxtapositional settling within the same cyclic ligand as is possible with single-charged ions. In the *Ba(picrate)*$_2$*·2H*$_2$*O-dibenzo[24]crown-8 complex*[209] only *five* of all eight donor sites of the ligand are used for the coordination of the Ba^{2+} ion. The coordination number of ten of the Ba^{2+} ion is attained through a complex arrangement with two H_2O molecules, two phenolate oxygen atoms of the picrate and one oxygen of an *o*-nitro group. It is interesting to note that *one* of the two H_2O molecules is bound to the central Ba^{2+} ion as well as via hydrogen bridges to two unoccupied ether oxygen atoms of the crown ether ring. Up to date this is a unique case of a crowned 'hydrated cation', whereby the cation as well as a water molecule is coordinated by the crown ether.

Large polyether rings with an unfavourable ratio of ligand cavity to cation diameter can also use their numerous oxygen donor atoms to coordinate a single cation. Thus, for instance, the Ba^{2+} ion in the *1 : 1 Ba(ClO*$_4$*)*$_2$*–[24]crown-8 complex*[210] is altogether tenfold coordinated by the eight available ether oxygen atoms almost completely encircling the cation and by both perchlorate ions (one of which is possibly bidentated).

Finally the central ion can be completely wrapped up in a spherical ligand as was analogously observed in a few antibiotic complexes[211]. As a prerequisite the ligand must display high, conformational ring flexibility (cf. Section III.D.1.c).

In the *KI complex* of *dibenzo[30]crown-10* (8), the cyclic ligand tightly encloses the central K$^+$ ion in a 'tennis fissure'-like conformation so that an approximately closed basket structure results (Figure 23b)[135]. The relatively short K—O bond lengths determined by X-ray point to the fact that all ten donor atoms belong to the coordination sphere of the potassium ion.

The *free ligand* 8 (Figure 23a)[135] has a symmetry centre as symmetry element; the K$^+$ complex on the other hand, has a twofold crystallographic axis passing through the central atom. The coplanar arrangement of several oxygen atoms, which is typical of many crown ethers, is not found in the above complex.

In the *RbSCN complex* of *dibenzo[18]crown-6* (1), however, the six ether oxygen atoms are again coplanarly arranged, though a twisted and complicated structure is to be expected as a result of the uneven stoichiometric ratio of 2 : 3. The sandwich structure that was postulated at first could not be confirmed by X-ray analysis[212]. The unfavourable ligand/salt ratio is rather due to the fact that in the unit cell of the crystal lattice *uncomplexed molecules of* 1 are present besides the coordinating ligand. Thus, though the molecular architecture of crown ether complexes essentially obeys strict topological rules, it may show deviations from

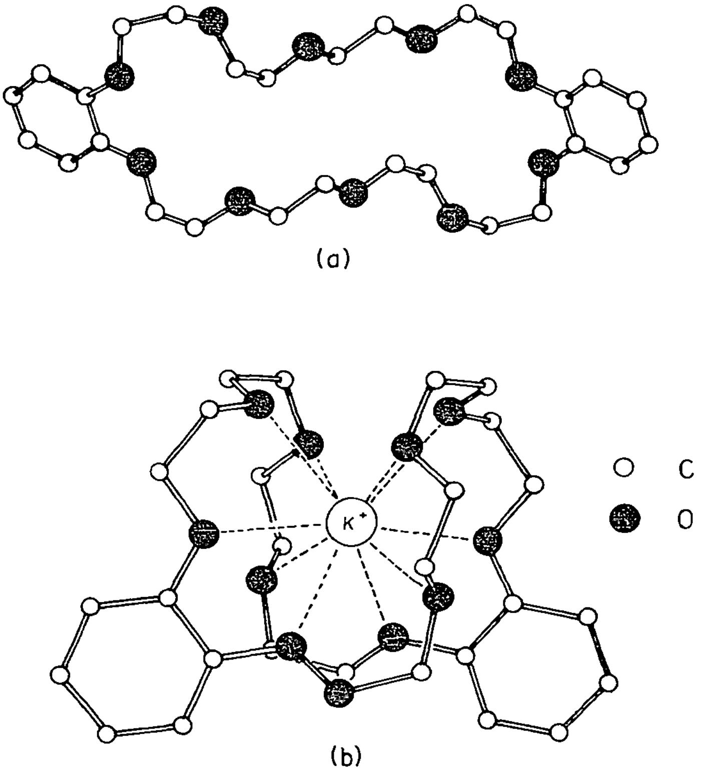


FIGURE 23. Molecular structure of dibenzo[30]crown-10 and of its potassium complex.

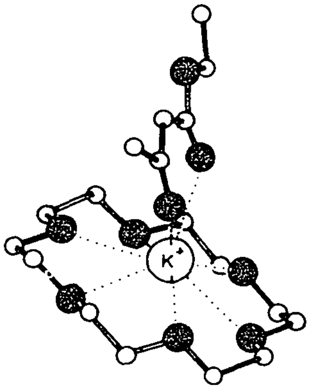


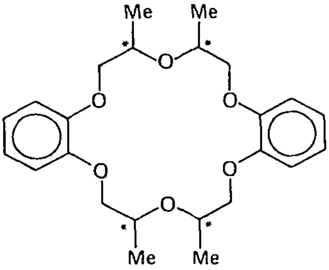
FIGURE 24. Structure of [18]crown-6 potassium ethyl acetoacetate enolate.

time to time[190]. The Rb^+ ion of the coordinately bound cation/ligand unit is expectedly displaced from the centre of the six ligand oxygen atoms; the SCN^- group stands approximately perpendicular to the polyether ring and shares (nitrogen-bonded) the seventh coordination site of the Rb^+ ion in the 'crowned RbSCN ion pair'[213].

A similar geometry is revealed by the *potassium acetoacetate–[18]crown-6 complex* (Figure 24)[214] in which the K^+ ion is coordinated to the six ring oxygen atoms and bound *chelate-wise* to both oxygen atoms of the acetoacetate anion[215].

In the same way that incorporation of benzo nuclei influences the 'crystalline structure selectivity' of cation complexes, alkyl substituents can also play an influential rule on the geometry and stoichiometry of the complex.

As an example *tetramethyldibenzo[18]crown-6* (114)[16e,197] with four chiral centres shows clearly how slight differences in the stereochemistry of a ligand (same number of donor sites) can influence the formation of a complex. While $Cs(SCN)_2$ and a *racemic* isomer of the five possible isomers of tetramethyldibenzo[18]crown-6 form a 2 : 1 sandwich complex, containing a *twelvefold* coordinated Cs^+ ion, a 1 : 1 complex is obtained with the *meso* configurated ligand (114)[216]. In the latter complex two Cs^+ ions are joined via a thiocyanate bridge (*N*-coordinated), so that the Cs^+ ion attains only an *eightfold* coordination, if any interaction with the aryl carbon atoms is neglected. When dibenzo[18]crown-6 is hydrogenated[1b], five isomers of *dicyclohexano[18]crown-6* (59) are, in



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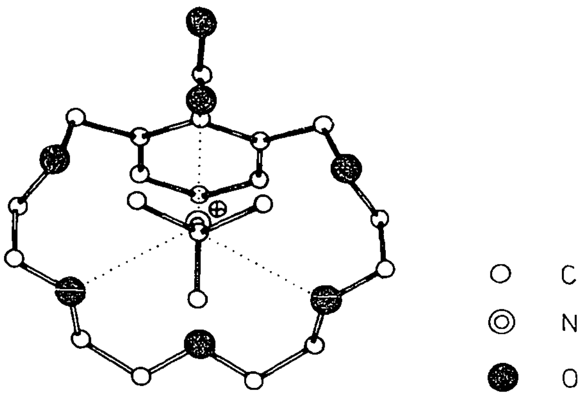


FIGURE 25. Structure of intraannularly substituted *m*-cyclophane crown ether (70)–$t\text{-BuNH}_3^+$ complex in the perching configuration; $NH\cdots O$ bonds as dotted lines.

principle, possible[217] cf. Section III.D.1.b, Table 14). The structure of the $Ba(SCN)_2$ complex obtained with **59a** establishes that it is the *cis–syn–cis* isomer[218]. **59b** is shown to be the *cis–anti–cis* isomer in the study of its $NaBr\cdot 2H_2O$ complex[219]. In the $Ba(SCN)_2$ complex, the Ba^{2+} ion is located on a twofold axis and fits in the cavity of the ligand. In the $NaBr\cdot 2H_2O$–**59** complex, the sodium ion has a hexagonal bipyramidal coordination with water molecules at the apices, and the structure is held in place by hydrogen bonding.

The structural skeletons of crown ether *ammonium salt complexes* are predominantly marked by *hydrogen bond*[18c,185]. An example of a crystalline complex of host–guest type involving a carboxylate ion and two ether oxygens as hydrogen bonding sites for a $t\text{-BuNH}_3^+$ ion is given in Figure 25[18c,220]. The X-ray structure indicates a *perching configuration* of the ligand [cf. Section III.D.1.a(1)]. Noteworthy is that the three $NH^+\cdots O$ hydrogen bonds are arranged in a tripod, that the *t*-Bu–N bond is only about 3° from being perpendicular to the least square plane of the binding oxygens, that these oxygens turn inward and somewhat upward toward the NH_3^+, and that the $H{-}\overset{+}{N}{-}C{-}C$ dihedral angles are about 60°, as predicted by inspection of CPK molecular models[18c].

b. Heavy metal ion complexes. Of the transition metals *lanthanide ions* as class A acceptors[94] show the strongest similarity to the alkali and alkaline earth ions (cf. ionic radii, electropositivities etc.[221]) and should be properly complexed by crown ethers containing five or six oxygen atoms.

The first complex of this group to be examined by X-ray, namely, the *$La(NO_3)_3$ cis–syn–cis isomer of dicyclohexano[18]crown-6* (Figure 26a)[222], was also the first example of a tripositive cation–crown compound and the first uncharged molecular *12-coordinated* complex to be described. The La^{3+} ion is bound to six ether oxygen atoms (La–O distances 2.61–2.92 Å) and to six oxygen atoms of the three bidentate nitrate ions (2.63–2.71 Å) (one on the sterically more hindered side of the crown ether ring and two on the more favourable side). The ether oxygen atoms are nearly coplanarly arranged and the cation is situated in the cavity.

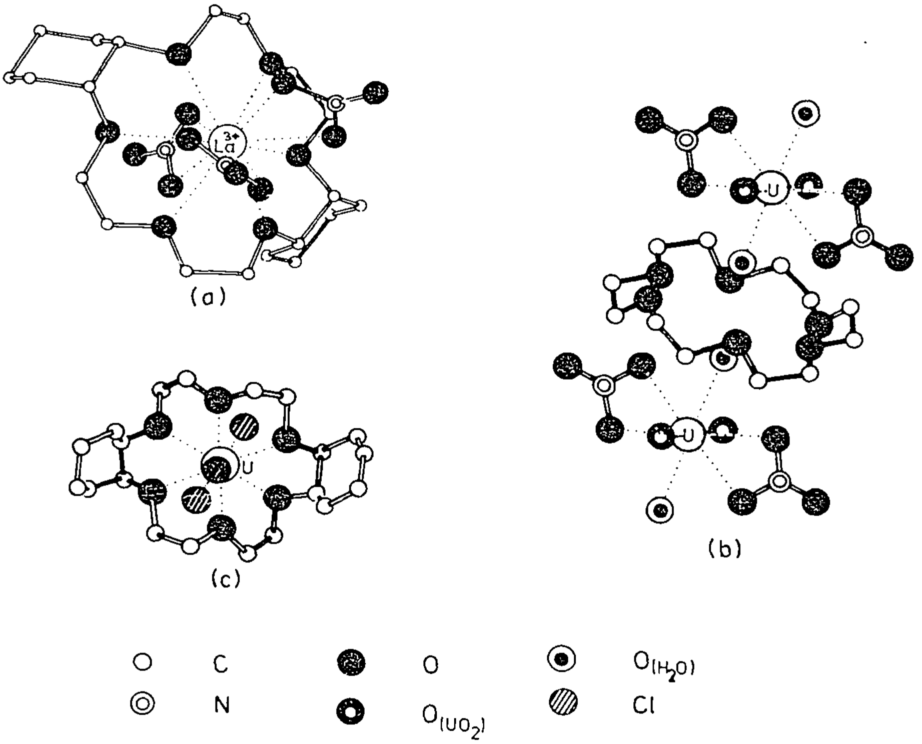


FIGURE 26. Structures of several crown ether complexes of lanthanum and uranium.

The *actinide salts* often consist of complex ions[79], which persist in crown ether aggregates and give rise to structures resembling much less the 'true' crown ether complexes than compounds of the *host–guest type* (cf. Section IV.B.1.c). In the *$UO_2(NO_3)_2 \cdot 2H_2O$–[18]crown-6 complex* (Figure 26b)[223], for example, there is *no* direct bond to the donor atoms of the polyether ligands, but very short H_2O-oxygen/ether oxygen atom distances can be established (2.98 and 3.03 Å). The linear uranyl group is coordinated *only* to the two bidentate nitrate ions and to the water molecules. Therefore the whole structure could be described in terms of polymeric chains with alternance of $UO_2(NO_3)_2 \cdot 2H_2O$ groups and [18]crown-6 molecules connected together through a system of hydrogen bonds. Remarkably the conformation of the ligand in this complex more strongly resembles that found in the KSCN[200] and RbSCN complexes[201] of [18]crown-6 than that of free [18]crown-6 in the crystal[194].

The recently described *UCl_4–dicyclohexano[18]crown-6 complex* (Figure 26c)[224] possesses a structure akin to that of the *true* crown ether complexes. A pair of the three uranium atoms in the unit cell of $UCl_6(UCl_3[18]crown\text{-}6)_2$ is directly bound to the crown ether ring, three chlorine atoms acting as neighbours. The third uranium atom is surrounded octahedrally by six chlorine atoms.

Only relatively few of the numerous crown ether complexes with typical heavy metal ions such as those of Fe, Co, Ni, Ag, Zn, Cd, Mg, Pd, Pt, etc.[225] have been structurally examined as yet[226]. In many respects, they resemble the foregoing lanthanide and actinide complexes.

Thus, the *$[MnNO_3(H_2O)_5]^+$–[18]crown-6-$NO_3]^-$·H_2O complex* (Figure 27a)[226b] displays a structure closely related to that of the $UO_2(NO_3)_2$·$2H_2O$–[18]crown-6 complex (cf. Figure 26b) with piled metal/H_2O/anion and crown ether rings connected together through hydrogen bonds.

As for the *$(CoCl)_2$–dicyclohexano[18]crown-6 complex*[226a], sandwich structures are discussed in which the metal ion makes direct contact with three crown ether oxygen atoms.

However, cases are also known, where, as in classical crown ether complexes (*type Ia*, Figure 19) heavy metal ions are located at the centre of the ring.

The [18]crown-6-analogous *triaza ligand* **12** encloses Pb^{2+} in the approximately coplanar arrangement of the ligand donor atoms (Figure 27b)[226e]. Both of the SCN ions serve to fill up the eight coordination sites of the Pb^{2+} ion; they lie above and below the ligand plane, being bound once through nitrogen and once through sulphur to the metal ion. The soft Pb^{2+} ion is *preferentially* coordinated to the softer nitrogen atom (Pb–O distances 3.07 Å, Pb–N 2.60 Å). In this respect, the heavy metal ion complex differs from the corresponding alkaline earth ion complexes of the same ligand, in which *all* donor atoms (N and O) are almost equidistant from the central ion[227].

The differentiation of the heavy metal ion between more (e.g. S, N) and less favourable donors (e.g. O) in substituted crown ethers may be marked to such an extent that whole ligand regions with their donor sites are displaced out of the influence sphere of the cation, thereby remaining uncoordinated (Figure 27c)[228]. Analogous alkali/alkaline earth complexes of *dithiapyridinocrown* (**115**)

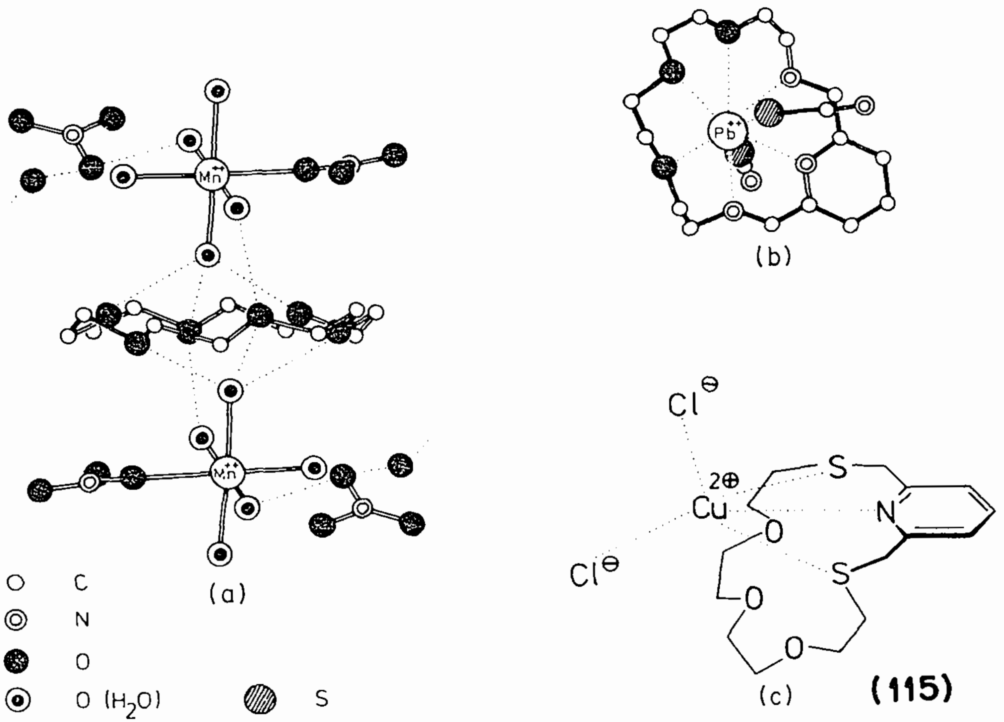


FIGURE 27. Several typical heavy metal ion complexes of [18]crown-6 and nitrogen and sulphur analogues.

show – in contrast to the $CuCl_2$ complex of **115** – nearly ideal proportions relative to all donor atoms[228,229] and this may be termed as a distinct stereochemical answer in the course of the molecular recognition of two ball-shaped cations by the same ligand.

c. Neutral molecule host–guest complexes. The existence of crown ether complexes composed solely of neutral (uncharged) molecules was recognized by Pedersen, who first isolated *thiourea complexes* of some benzocrown ethers[230].

Cram and Goldberg carried out a structural elucidation with the *dimethyl acetylenedicarboxylate [18]crown-6 complex* as example (Figure 28a)[185]. A remarkable feature of the complex is that all six oxygen atoms of each crown ether molecule participate on opposite sides of the crown by means of dipole–dipole interactions between the electronegative oxygen atoms of the crown and the electropositive carbon atoms (methyl groups) of the guest.

In the 1 : 2 host–guest complex of [18]crown-6 with *benzenesulphonamide* (Figure 28c)[186] strong and weak NH . . . O interactions are found, but the crown

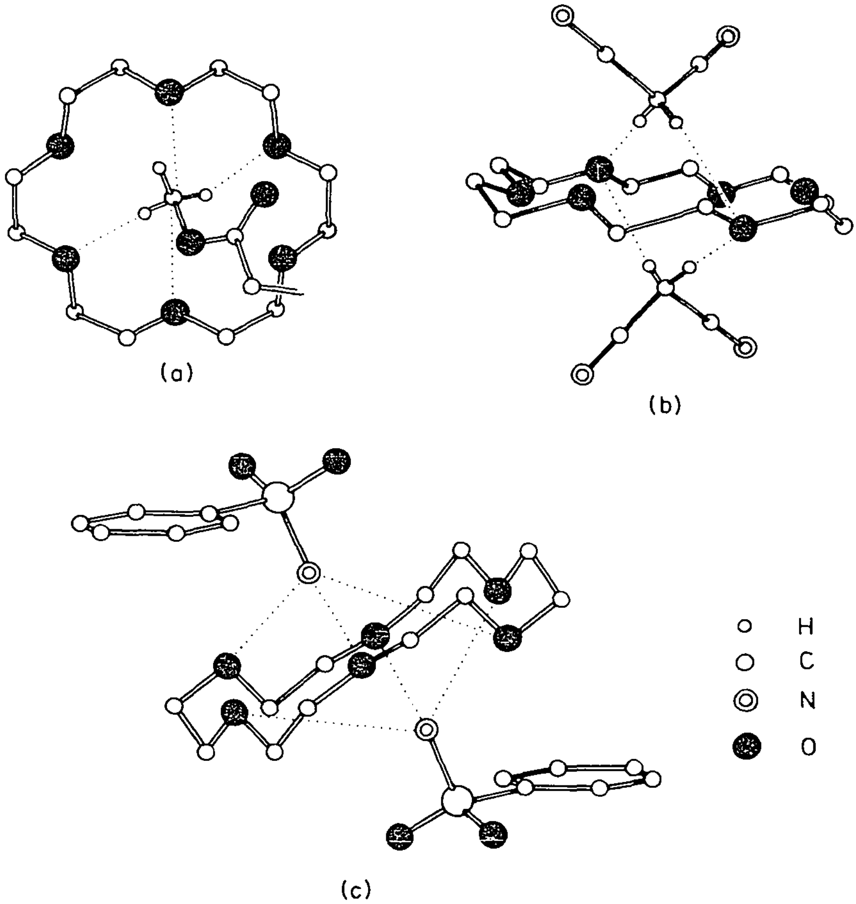


FIGURE 28. Complexes of [18] crown-6 with CH- and NH-acidic neutral guest molecules.

adopts nearly the same conformation as the uncomplexed hexaether (cf. Figure 20a).

Complexes formed by *CH-* (see Figure 28a[185], *malodinitrile–[18]crown-6 complex*, cf. Figure 28b[231]) and *OH-* and *NH-acidic* substrates (Figure 28c), usually show *layered* structures, in which crown ether host and guest molecule are held together through H-bonds and dipole–dipole interactions.

2. Bi- and poly-cyclic cryptates (see Figure 2)

a. Bicyclic ligands. X-ray structure analyses of uncomplexed cryptands and their cryptates allow interesting comparative studies of ligand conformation. The free ligands may exist in three forms differing in the configuration of the bridgehead nitrogen: *exo–exo* (out–out), *exo–endo* (out–in) and *endo–endo* (in–in)[11a,12b]. These forms may interconvert rapidly via nitrogen inversion[13c,53]. Crystal structure determinations[232–235] of a number of cryptands and cryptates showed that the alkali, alkaline earth and heavy metal cations were contained in the tridimensional molecular cavity[236] and that in all cases the ligand has the *endo–endo* configuration, even in the uncomplexed state[237].

Figure 29 shows the configuration of the *[2.2.2]cryptand*[237] and of its *Rb$^+$ complex*[233,234a]. Four ether oxygen atoms and the two nitrogen atoms participate in octahedral coordination of the cation. In both the complex and the free ligand, the two nitrogen atoms are in *endo–endo* configuration. Whereas the ligand is flattened and elongated when free, it has swollen up in the complex.

With increasing ion radius and coordination number of the embedded cation ($Na^+ < K^+ < Rb^+ < Ca^{2+}$) one observes a progressive opening-up of the molecular cavity of the [2.2.2]cryptand with torsion of the ligand around the N/N axis[234b]. Under such circumstances, possibilities of anion or solvent/cation contact are present[234a,234g,235] as, for example, in the *$Eu(ClO_4)[2.2.2]^{2+}$ cation*[238], where a pair of the ten coordination sites (eight being shared by the cryptand) of the europium is saturated by a bidentate ClO_4^- ion. The geometry of the coordination polyhedron can be described in terms of a bicapped square antiprism with two nitrogen atoms at the apices.

In the *bivalent* cation complexes anion and/or solvent coordinations are found apart from a few exceptions[234a,234g,235].

Two nuclei-containing complex structures, as are known for voluminous mono-

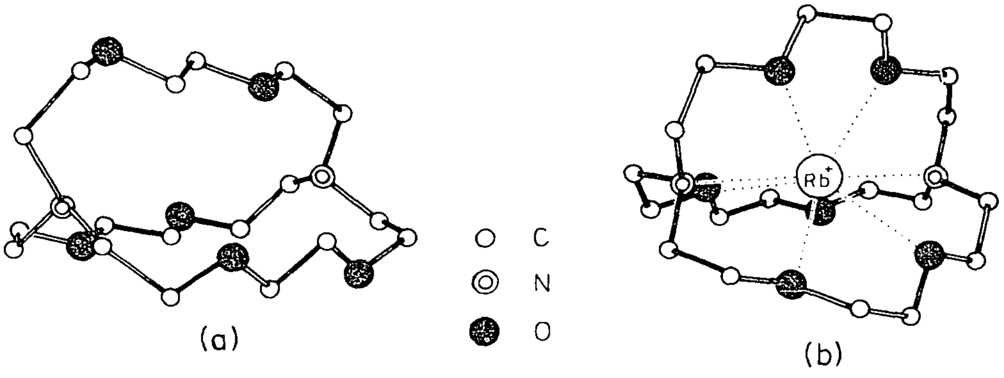


FIGURE 29. Molecular structures of [2.2.2] cryptand (19) and of the rubidium cryptate.

cyclic crown ethers (see Section IV.B.1.a), are nonexistent for bicyclic cryptands. On the whole, the known structures of bicyclic cryptates are not as varied as those of crown ethers.

b. Tricyclic cryptands. Complexes with *two* enclosed cations are, however, known for tricyclic cryptands like 23 (Figure 2). Figure 30a shows the structure of the 23–*NaI cryptate* in which each Na$^+$ ion is bound to two nitrogen atoms and five oxygen atoms of the ligand[239]. The lengths of the Na–N and Na–O bonds of both molecular single-cavities are approximately the same as in the [2.2.2]–NaI complex[234e]; the Na$^+$ ions of both hemispheres lie 6.4 Å apart.

The cation/cation separations of the two corresponding nuclei-containing *heavy metal complexes* of tricyclic ligands are of theoretical interest[240].

Recently two complexes of the spherical macrotricyclic ligand 24 ('soccer molecule', see Figure 2)[117], which contains four bridgehead nitrogens, all in the *in–in* conformations, were reported[241]. One complex (Figure 30b) consists of an *ammonium cation* in the molecular cavity, held in place by hydrogen bonds. In the latter complex (Figure 30c) the *tetraprotonated* ligand 24 forms an unusual *anion inclusion complex* (anion cryptate) with Cl$^-$ (cf. Section III.D.2). The four

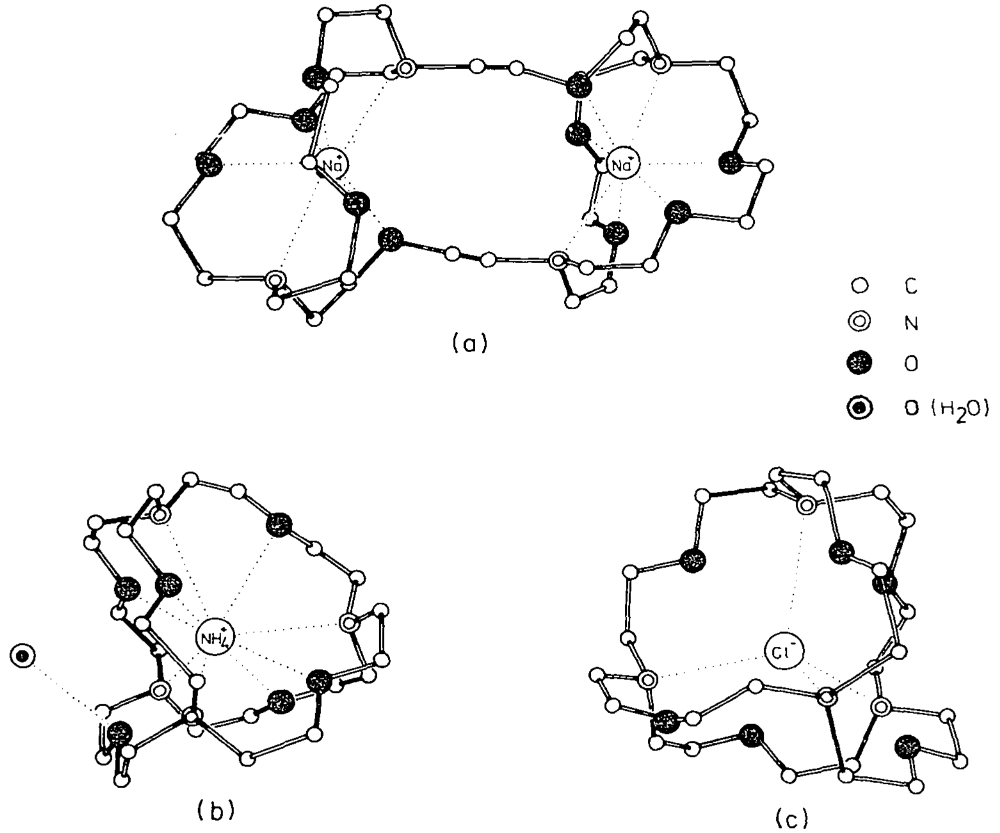


FIGURE 30. (a) Two nuclei-containing Na$^+$ complex of the tricyclic cryptand 23; (b) NH$_4^+$ complex of the soccer molecule 24; (c) anion cryptate of the tetraprotonated soccer ligand.

hydrogen-bonded nitrogen atoms of the ligand are located at the corner of a tetrahedron, and the six oxygen atoms are at the corner of an octahedron. Noteworthy are the short Cl—N distances of 3.09 Å, which are less than the sum of the van der Waals' radii.

3. Open-chain podates (see Figures 5–7)

a. Glymes, glyme-analogous and simple noncyclic ligands. Until recently little has been known about the synthesis of crystalline alkali complexes of glyme-type poly- and heteropoly-ethers[24]. Subject to better X-ray investigations, however, have been the glyme complexes of *transition metal ions* such as Fe^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} [242], and Hg^{2+} [243] and Cd^{2+} salts[244].

While several ligand units (three as a rule) are required in the case of *dimethoxyethane* (49) ($n = 0$) (monoglyme, see Figure 7)[242,245], longer polyether chains (hexaglyme) (49) ($n = 5$) sometimes form two nuclei-containing adducts also[243c].

The X-ray structure analysis of the *tetraethylene glycol dimethyl ether (TGM)* (49) ($n = 3$)*—$HgCl_2$ complex*[243a] (1 : 1 stoichiometry) shows the following ligand conformation[246] (Figure 31a): All $H_2C—O$ bonds are in antiperiplanar (*ap*) arrangement; the $CH_2—CH_2$ bonds in each following unit are oriented synclinal (*sc*) and (–) synclinal (–*sc*). In this way, the ligand is fixed in an unclosed circular form with the five oxygen atoms lying almost coplanarly inward and surrounding the Hg^{2+} ion at a short distance of 2.78–2.98 Å.

In the corresponding *tetraethylene glycol diethyl ether (TGE)—$HgCl_2$ complex*[243b] very similar Hg—O distances and bond angles are found. An *sc*-arrangement is present only at one end of the chain, where as such steric hindrance of the ethano groups in an *ap*/*ap*-conformation is avoided. Armed with seven potential coordination sites, *hexaethylene glycol diethyl ether (HGE)* is able to bind *two* Hg^{2+} ions at a relatively short Hg—O distance (2.66–2.91 Å) (Figure 31b)[243c]. The remarkable feature of the complex structure is the presence of two consecutive *sc*/*sc*-arrangements at the central oxygen atom, which causes a separation into two coordination cavity halves, each being outlined by four coplanar oxygen atoms and containing one Hg^{2+} ion. The central oxygen atom is coordinated by both Hg^{2+} ions.

The same structural principle is again found in the *tetraethylene glycol dimethyl*

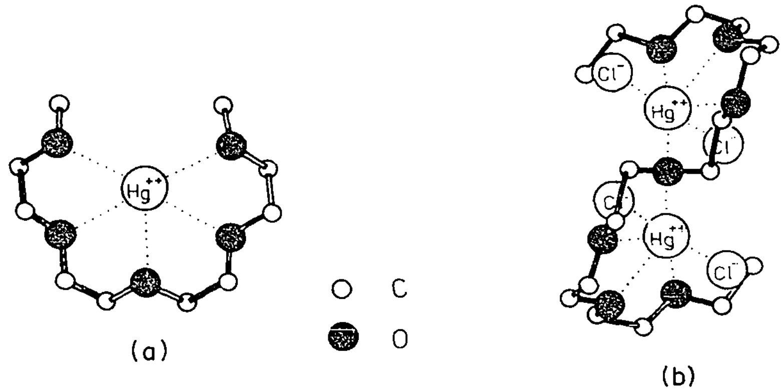


FIGURE 31. Oligoethylene glycol ether complexes of Hg^{2+} ions.

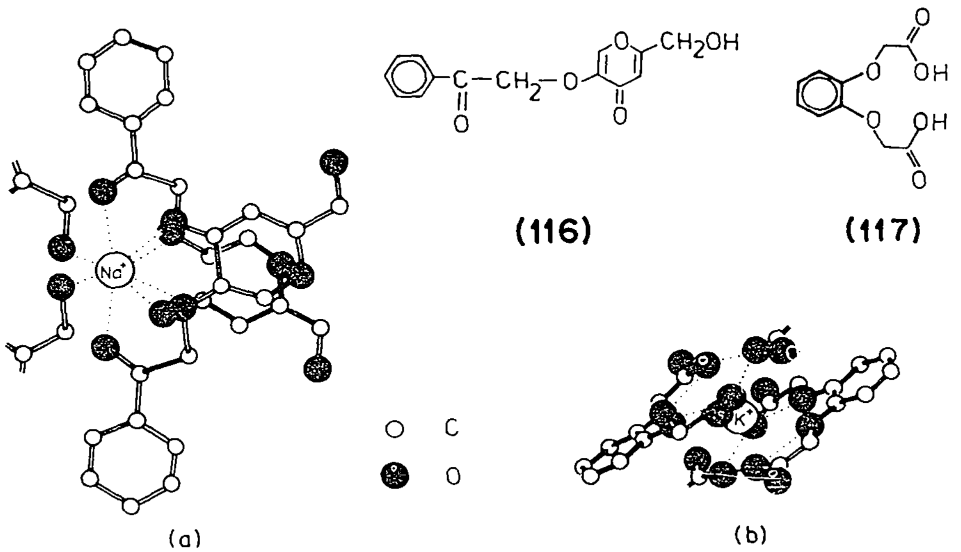
ether (TGM)–$CdCl_2$ complex[244]. Owing to the smaller number of available donor sites, however (five per glyme molecule), coordinating chlorine bridges additionally function to hold together two ligand units via four Cd^{2+} ions.

The synthesis of corresponding *alkali* and *alkaline earth complexes* met with difficulties for quite a long time[26a]. Meanwhile, success has been achieved with *glymes* of various chain-lengths (hexaglymes, heptaglymes)[32], glyme-analogous *oligoethylene glycol mono- and di-phenyl ethers* (47 and 48, see Figure 7)[32] and even with nonalkylated *oligoethylene glycols* (including ethylene glycol itself)[33a]. X-ray structure analyses of these simplest open crown type ether complexes remain to be done.

Crystalline 2 : 1 complexes of the crown ether related *phenacyl cojate* (116) (see Figure 32)[247] with sodium halogenides in methanol were isolated 25 years ago; their structures, however, could be investigated only lately[248].

The geometry of the *NaI complex* (Figure 32a)[248d] resembles that of [18] crown-6 with corresponding sodium salts[249]. Six oxygen donor centres (belonging to two phenacyl cojate units) display a planar arrangement around the sodium ion, while four of them are delivered by a carbonyl group in contrast to the crown ether complex. The crystal structure is held in place by hydrogen bonds between CO and OH groups as well as by H· · · O interactions.

A remarkably stable 2 : 1 complex is formed between *O,O'-catechol diacetic acid* (117) with KCl[250]. It shows a complicated layer structure stabilized by hydrogen bonds with the potassium ions enclosed sandwich-like between ten oxygen atoms (four ether and six carboxyl oxygen atoms) in an irregular pentagonal antiprismatic arrangement (Figure 32b). Corresponding coordination compounds are not obtained with lithium, sodium, caesium and ammonium salts. The observed 'precipitation selectivity' for K^+, which surpasses $NaBPh_4$, is unusual, since all precipitation reagents known so far for K^+ are also applicable to NH_4^+, Cs^+ and Rb^+[251].



(a) (b)

FIGURE 32. (a) Arrangement of Na^+ phenacyl cojate (116) complex; (b) K^+ complex of *O,O'*-catechol diacetic acid 117. Dotted lines in (b) indicate irregular pentagonal antiprismatic arrangement of the oxygen atoms.

b. Noncyclic crown ethers and cryptands. (1) *Alkali and alkaline earth metal ion complexes.* Despite the less strictly defined 'cavity geometry' of noncyclic crown ethers and cryptands to that of cyclic ones, complexes of *definite stoichiometric composition* are formed as a rule (ligand : salt = 1 : 1, 2 : 1, 3 : 2) and also in presence of a large excess of one component of the complex[24-26]. For instance, the open-chain ligand 34c (see Figure 5) reacts with KSCN to form exclusively the 1 : 1 complex independently of the stoichiometric amounts of ligand : salt (such as 2 : 1 or 1 : 2) used[26a]. Remarkably, water and anion participations in the metal coordination are hardly more frequent for these relatively 'open' ligand structures than for their cyclic counterparts[24].

For the 34c–*RbI complex*, the X-ray structure analysis (Figure 33a)[252] reveals a participation of all seven heteroatoms (5 O, 2 N) in the complexation and for the

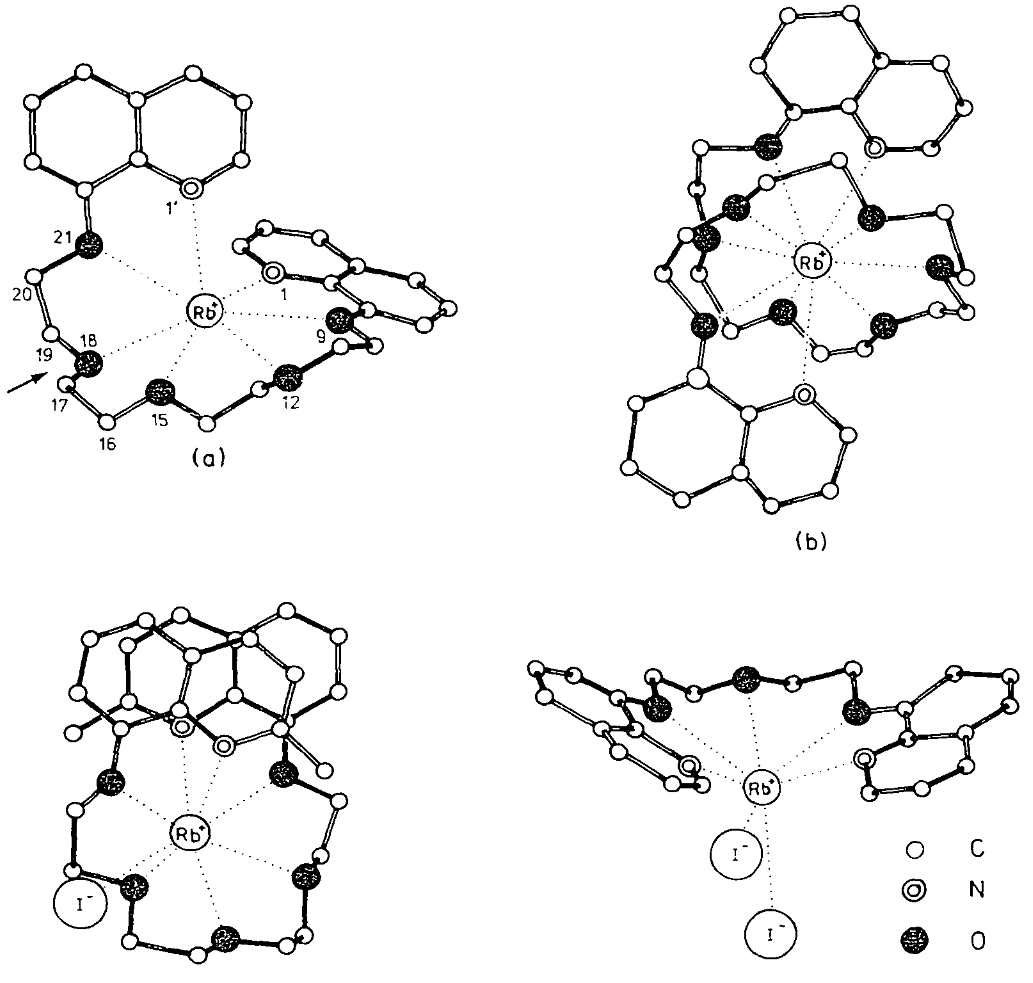


FIGURE 33. Rb$^+$ complexes of open-chain crown ethers with different numbers of oxygen donor sites.

first time a *helical structure* arrangement of a synthetic open-chain ionophore around an alkali metal ion (racemate of plus and minus helices). The iodide ion is, however, not included in the coordination sphere of the central ion; also it does not come in direct contact with any heteroatom of the quinoline ether. Though the bond lengths and angles between the various heteroatoms (O,N) and the Rb^+ ion differ from one another, they can be considered to be approximately symmetrical about an axis passing through the Rb^+ ion and the $O_{(15)}$ atom (cf. Figure 33a). The most remarkable structural feature is the angle – *sp* instead of *ap* (see arrow mark) – at the atoms $C_{(17)}-O_{(18)}-C_{(19)}-C_{(20)}$, which seems to be necessary for avoiding a collision between both terminal quinoline units. This evokes a fold of heteroatoms $O_{(21)}$ and $N_{(1')}$ together with the attached quinoline skeleton out of the plane of the remaining five donor sites and a 0.748 Å displacement of the Rb^+ ion in the direction of the folded quinoline nucleus, thereby imparting to the complex its particular helical structure.

The *decadentate* ligand 34e, *lengthened by three* oxaethane units, does not show any upfield shift of the quinoline protons during complexation of alkali metal cations in solution[107], as is observed for the shorter open-chain ligand 34c[26a]. This may suggest that either the two terminal groups do not participate in the complexation or that during the process of cation complexation, both quinoline moieties are far apart as shown by molecular models. The latter supposition has been confirmed in the RbI complex by X-ray analysis for the crystalline state (Figure 33b)[253]. The eight oxygen atoms are *helically coiled* around the central cation in the equatorial plane, while both of the quinoline moieties coordinate from *above* and *below*. Thus, we have a case of a novel complexation geometry of a decadentate ligand.

The helical skeleton of the 34c–RbI complex gives way to an approximately planar (butterfly-like folded) arrangement with mirror-image-wise symmetry in the *RbI complex* of ligand 34a, *shortened by two* oxaethane units (Figure 33c)[228]. In order to fill up the still unsaturated coordination sphere of the Rb^+ ion – five donor locations of the ligand are already involved in the coordination – two iodide ions per ligand unit alternately participate in the complexation.

The X-ray structure analysis of the 34d–*RbI complex*[228] reveals significant differences in the ligand conformation, compared with the 34c–RbI complex. While in the first case a discontinuous helix with a folded, but coordinated quinoline end-group is present, the bulky *(quinaldine)₂–ligand* 34d is arranged like a *continuous* screw in the complex (Figure 33d).

Also in the 35a–*NaSCN complex* the ligand forms a continuous helix with one OCH_3 group fixed above/below the other benzene ring[228].

An X-ray structure analysis of the *1 : 2 KSCN complex* of 38 (Figure 34a)[254] shows that the ligand adopts a *S-like coiled* structure with remarkable parallels to the Hg^{2+} HGE complex shown in Figure 31b (see Section IV.B.3.a).

The X-ray structure analysis of the *1 : 1 KSCN complex* of the amide ligand 35e reveals strikingly that *polymeric* ligand–cation chain structures are present (Figure 34b)[228]. The two carbonyl groups of the ligand do not coordinate the potassium cation enclosed by the five intramolecular ether oxygen atoms, but instead, share their coordination to the central ion of the next pair of ligands. The observation is in keeping with the high entropy of complexation found for the sodium ions, which may point either to a cyclization or/and to a polymerization entropy[80].

Interesting comparisons with structurally related carboxylic antibiotic ionophores (nigericin[7b,7c,29]) are brought about by the complexes of such types of ligands as 35c and 46, having potential *intramolecular attractive end-group inter-*

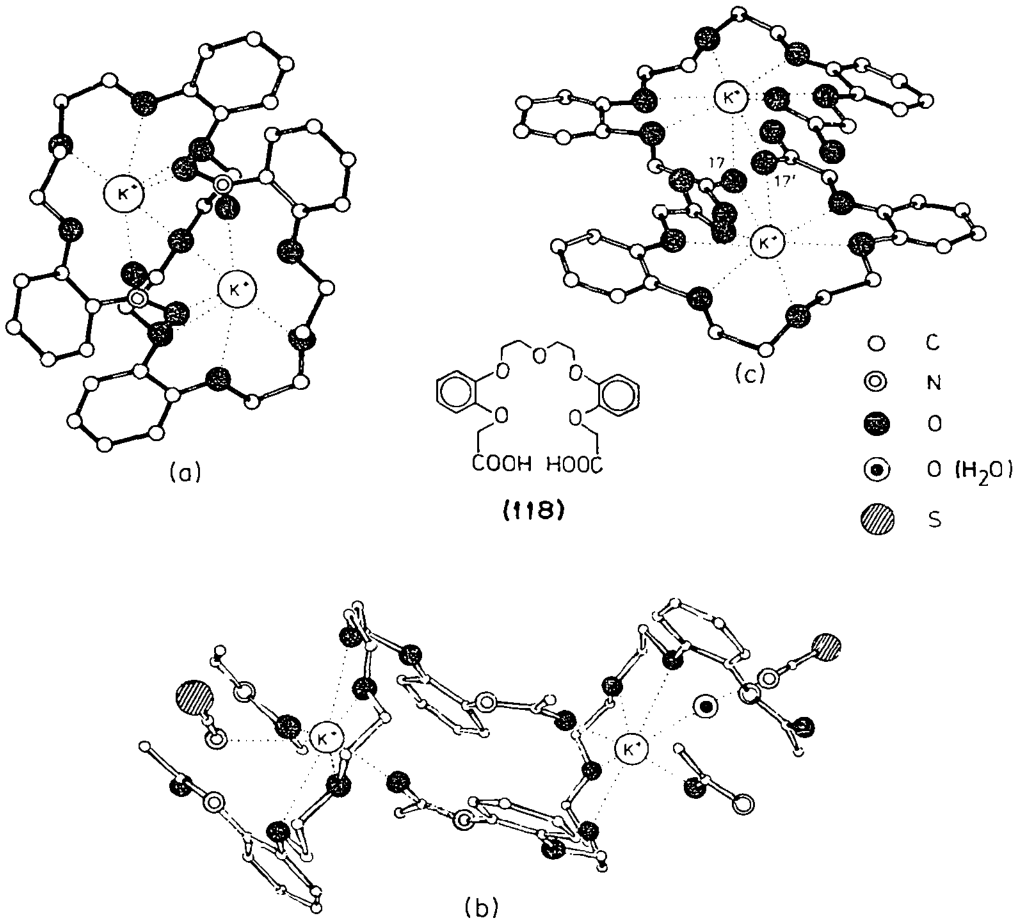


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FIGURE 34. (a,c) Two-nuclei K$^+$ complexes of open-chain polyethers 38 and 118; (b) section of the polymeric arrangement of the 1 : 1 KSCN complex of amide ligand 35e.

actions^{26b,29}. An X-ray structure analysis of the *potassium picrate complex* of the *polyether dicarboxylic acid* **118** (Figure 34c)^{28a,255} is known^{256}. Contrary to expectations, no intramolecular 'head-to-tail' hydrogen bonds, that should result in a pseudocyclic 1 : 1 complex unit, are observed. The most significant structural characteristic is rather the *dimeric* complex cation. Every single ligand is conformationally fixed by a potassium ion spiralwise. The end carbonyl oxygens (O_{17}, O_{17}') of the monomer function act as bridging atoms and are each additionally coordinated to a second potassium ion. Thus, each potassium achieves an irregular eightfold coordination. The two K$^+$ ions are separated by a distance of 4.74 Å.

The *three-armed decadentate* neutral ligand **40** ($n = 0$, R = OMe) reveals as the first example of an alkali metal ion complex of an *open-chain cryptand* (tripodand) a novel complexation geometry in its *KSCN complex* (Figure 35)^{228}. All of the ten donor centres and the three OMe terminal groups participate in the coordination of the central cation. In order to achieve this coordination, the three arms wrap

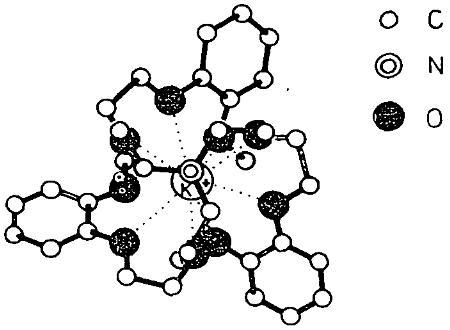

FIGURE 35. K$^+$ complex of open-chain cryptand 40.

around the cation in a *propeller-like* way. A particularly interesting fact is that coordination by the anion is totally hindered owing to complete envelopment of the cation; thus the anion remains outside the lipophilic periphery of the complex, in analogy to the bicyclic cryptates where the metal cations are also completely enveloped.

(2) *Heavy metal ion complexes.* A series of crystalline heavy metal ion complexes of open-chain crown ethers have been isolated[24-26], but relatively few have been structurally elucidated so far. Often it seems, as in the case of cyclic crown ethers, that water molecules are involved in the construction of a stable crystal lattice. The fact that carbonyl oxygen atoms participate as coordinating ligand locations not only in the undissolved form[257], but also in the crystal of open-chain crown ether complexes[278], has been confirmed by X-ray structure analysis of the *MnBr$_2$ complex* of 42 (Figure 36)[258].

In the above complex, the metal ion is coordinated by four *ether oxygen* atoms and four *carbonyl groups* of a pair of symmetrically equivalent ligands. The oxygen–metal ion distances are longer for the ether oxygens than for the carbonyl

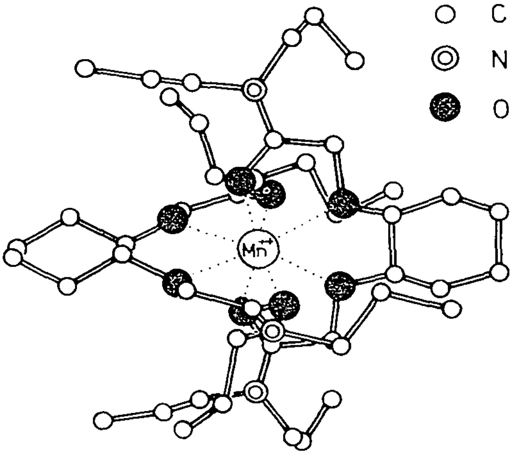

FIGURE 36. MnBr$_2$ complex of open-chain ligand 42.

groups; the latter distances (2.185 Å) are even shorter than the theoretically calculated ion–atom contact distances. (2.20 Å). The crystal lattice of 42–$MnBr_2$ (1 : 1 stoichiometry) contains *two sorts* of Mn^{2+} ions with different geometrical coordinations; thus one sort is coordinated by a pair of ligand molecules as in the corresponding $CaCl_2$ complex[258], while the other one is surrounded by four bromide ions at the corners of a square.

(3) *Neutral molecules as guests.* Open-chain crown ethers can form stoichiometrical host–guest neutral molecule complexes[189] just as do their cyclic counterparts (cf. Section IV.B.1.c). The X-ray structure of the 1 : 1 adduct of *thiourea* and 35a (see Figure 5) reveals remarkable characteristics (Figure 37)[259]. The conformation of the polyether host is such that it enables the thiourea guest to utilize all the possible multidentate interactions offered. Thus the thiourea molecule is hydrogen-bonded through NH· · ·O interactions with *all seven* oxygen atoms of the ligand, the central atom $O_{(10)}$ accepting two hydrogen bonds and the other six oxygen atoms accepting one hydrogen interaction each. This geometry gives rise to four *bifurcated hydrogen bonds*, which have previously been demonstrated certainly only in a very few cases[260].

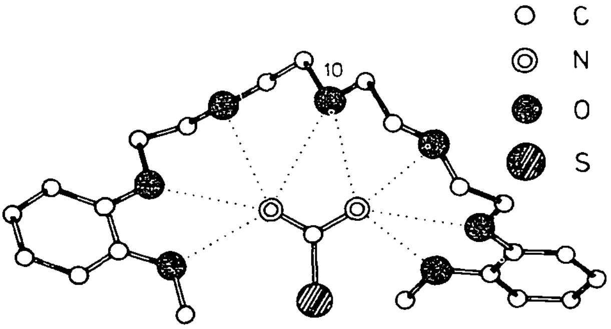

FIGURE 37. Thiourea complex of open-chain crown ether 35a. Dotted lines indicate NH· · ·O bifurcated hydrogen bonds.

V. OUTLOOK

The selectivity of crown ethers and cryptands toward alkali/alkaline earth and heavy metal cations will surely be exploited for *practical use* in many other cases[4-6]. New possibilites of development are to be expected with *anion receptors*[14d,e]. The intramolecular combination of crown ethers and other important molecular structures such as *dyes*[261], as well as that of *ionophoric* and *pharmaceutical*[262] or *polymeric* structures[137] showed other noteworthy trends of development. The field of organic receptor cavities may certainly be extended to include other very *voluminous*, *rigid* and *exohydrophilic/endolipophilic* host molecules that have hardly been investigated yet[263], and that can select between *neutral* organic guest molecules, the molecular properties of which are either masked or modified according to the peripheric structural features of the host envelope.

Perhaps, one day there will be concave host molecules with tailor-shaped endopolarophilic as well as endolipophilic cavities for many of the low molecular weight convex organic compounds.

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 3

Organic transformations mediated by macrocyclic multidentate ligands

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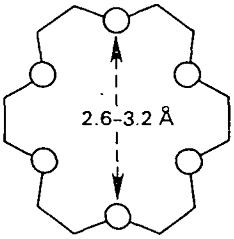
I. INTRODUCTION

With the advent of crown ethers and related macrocyclic and macrobicyclic multidentate compounds[1-4], simple and efficient means have become available for solubilizing metal salts in nonpolar and dipolar organic solvents where solvation of the anionic portion of the salt should be minimal[1,5-8]. Anions, unencumbered by strong solvation forces, should prove to be potent nucleophiles and potent bases and should provide the basis for the development of new and valuable reagents for organic synthesis. These weakly solvated anionic species have been termed naked anions[5-7].

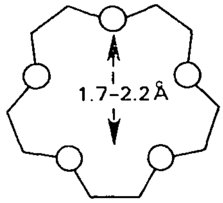
Figure 1 illustrates the structures and names of some synthetically useful crowns. The estimated cavity diameters of the crowns and the ionic diameters of some alkali metal ions are also included[6]. It is apparent that the potassium ion has an ionic diameter which will enable it to fit inside the cavity of 18-crown-6 while the sodium ion and the lithium ion have ionic dimensions which are compatible with 15-crown-5 and 12-crown-4, respectively. While this specificity has been experimentally demonstrated, it must be emphasized that 18-crown-6 will also complex sodium and caesium ions. In the application of crowns to organic transformations, exact correspondence between cavity diameter and ionic diameter is not always a critical factor.

The following four points will be addressed at this juncture:

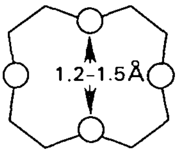
(1) The effect of a given crown in solubilizing metal salts (with a common cation) in nonpolar and dipolar aprotic media.
(2) The effect of various crowns in solubilizing a particular metal salt.



18-Crown-6
(1)



15-Crown-5
(2)



12-Crown-4
(3)

Ionic diameters (Å)	
K^+	2.66
Na^+	1.80
Li^+	1.20

FIGURE 1.

(3) The reactivity of anions solubilized as their metal salts by crowns.
(4) The reactivity of a particular anion solubilized as its metal salt by a variety of macrocyclic and macrobicyclic ligands.

Table 1 summarizes the solubilities of a wide variety of potassium salts in acetonitrile at 25°C in the presence and in the absence of 18-crown-6 (0.15M)[6]. The concentrations of potassium ion were determined using flame photometric techniques. Excellent solubility enhancements are achieved for all salts except for potassium chloride and potassium fluoride whose crystal lattice free energies are quite high. The concentration of potassium acetate in acetonitrile-d_3 and benzene has been determined from ^1H-NMR analysis as a function of 18-crown-6 concentration (Table 2)[9]. At least 80% of the crown was complexed with the potassium acetate. The solubility of potassium fluoride in acetonitrile has also been determined at various crown concentrations (Table 3) using flame photometry[5].

TABLE 1. Solubilities of potassium salts (M) in acetonitrile at 25°C in the presence and absence of 18-crown-6

Potassium salt	Sol. in 0.15M crown in acetonitrile	Sol. in acetonitrile	Solubility enhancement
KF	4.3×10^{-3}	3.18×10^{-4}	0.004
KCl	5.55×10^{-2}	2.43×10^{-4}	0.055
KBr	1.35×10^{-1}	2.08×10^{-3}	0.133
KI	2.02×10^{-1}	1.05×10^{-1}	0.097
KCN	1.29×10^{-1}	1.19×10^{-3}	0.128
KOAc	1.02×10^{-1}	5.00×10^{-5}	0.102
KN_3	1.38×10^{-1}	2.41×10^{-3}	0.136
KSCN	8.50×10^{-1}	7.55×10^{-1}	0.095

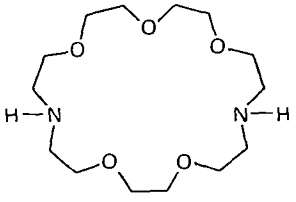
TABLE 2. Solubility of potassium acetate in solvents containing 18-crown-6

	18-Crown-6 (M)	Potassium acetate (M)
Benzene	0.55	0.4
	1.0	0.8
Acetonitrile-d_3	0.14	0.1

TABLE 3. Concentration of potassium fluoride at various crown concentrations at 25°C by flame photometry

	KF concentration (M)
1.01M 18-Crown-6-benzene	5.2×10^{-2}
0.34M 18-Crown-6-benzene	1.4×10^{-2}
0.16M 18-Crown-6-CH_3CN	3.5×10^{-3}

The solubility of potassium acetate in the presence of a variety of macrocyclic and macrobicyclic multidentate ligands has been reported. The following order of solubilization effectiveness was found[10]: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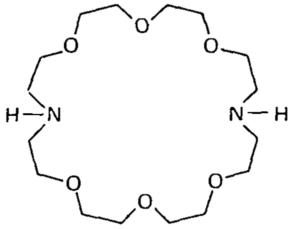
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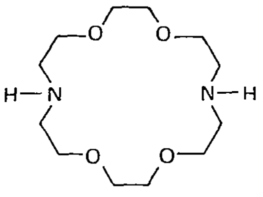
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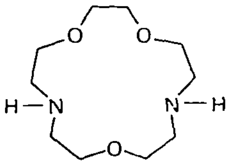
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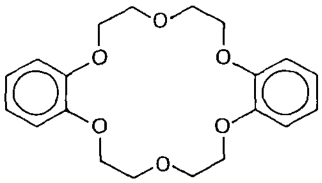
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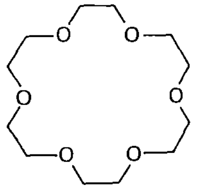
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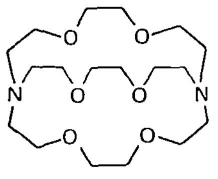
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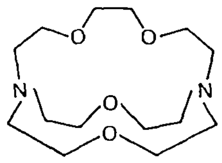

(10)

TABLE 4. Relative nucleophilicities of naked anions

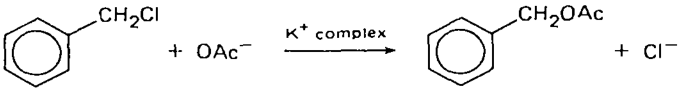
	Acetonitrile				Benzene		
Nucleophile	$k_{\mathrm{PhCH_2OTs}}$ ($M^{-1}\,s^{-1}$)	Rel. rates	$k_{n\text{-}\mathrm{C_5H_{11}Br}}$ ($M^{-1}\,s^{-1}$)	Rel. rates	$k_{n\text{-}\mathrm{C_5H_{11}Br}}$ ($M^{-1}\,s^{-1}$)	Rel. rates	Rel. rates in protic media
N_3^-	1.02	10.0	4.90×10^{-3}	7.5	1.04×10^{-4}	7.5	100
$CH_3CO_2^-$	0.95	9.6	1.66×10^{-3}	2.5	5.10×10^{-5}	3.7	5
CN^-	0.23	2.4	3.58×10^{-3}	5.5	3.12×10^{-5}	2.2	1250
Br^-	0.12	1.3	–	–	–	–	80
Cl^-	0.12	1.3	–	–	–	–	10
I^-	0.09	1.0	6.52×10^{-4}	1.0	1.39×10^{-5}	1.0	1000
F^-	0.14	1.4	–	–	–	–	1
SCN^-	0.02	0.3	3.28×10^{-5}	0.05	1.06×10^{-5}	0.76	625

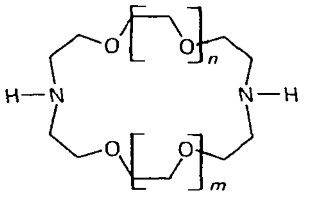
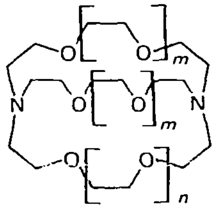
Arguments based upon cavity diameter, lipophilicity and rigidity of the macrocycle or macrobicycle were advanced to explain the observed order.

Studies related to the relative nucleophilicities of a series of naked anions toward benzyl tosylate in acetonitrile ($\epsilon = 37$) at 30°C[11] and toward 1-bromopentane in acetonitrile ($\epsilon = 37$) and benzene ($\epsilon = 2$) at 20°C[12] are summarized in Table 4. It is interesting to note that there appears to be a marked levelling effect in the nucleophilicities of naked anions toward a particular substrate in a particular solvent. The results are in direct contrast to the previously observed nucleophilicities in protic media[13]. Under naked anion conditions, nucleophiles which were considered poor (under protic conditions) become as active as nucleophiles which were considered excellent. This appears to be true irrespective of the substrate or solvent. Some recent evidence indicates that the superoxide radical anion is more nucleophilic than the anions in Table 4 by several orders of magnitude[14].

The effect of a wide variety of macrocyclic multidentate ligands on the activation of acetate (dissolved in acetonitrile as its potassium salt) toward benzyl chloride has been reported (Table 5). The characteristics of the ligand which influenced the rate were suggested to be (*a*) the stability of the metal–ligand complex, (*b*) the lipophilicity of the ligand, (*c*) the rigidity of the ligand, and (*d*) the reactivity of the ligand toward the substrate (aza crowns)[10].

TABLE 5. Effect of macrocyclic polydentate ligand on rate of reaction of potassium acetate with benzyl chloride in acetonitrile



Ligand		Approx. half-life (h)
None		685
18-Crown-6 (1)		3.5
Dibenzo-18-crown-6 (8)		9.5
Dicyclohexo-18-crown-6 (12)		1.5
	[2.1] (7) [2.2] (6) [3.2] (4) [3.3] (5)	700 65 75 100
	[2.1.1] (10) [2.2.1] (13) [2.2.2] (9)	8 0.8 5.5

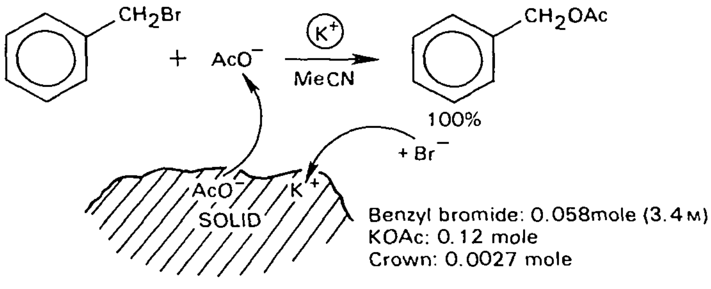
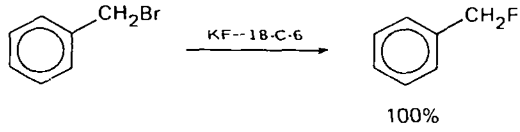


FIGURE 2.

The use of crowns to enhance the solubility of metal salts in nonpolar and dipolar aprotic solvents augmenting the reactivity of the anionic portions of the salts (naked anions) has prompted many investigators to use these novel ligands in catalysing organic reactions and in probing reaction mechanisms[6]. Reactions carried out under homogeneous conditions as well as those carried out under solid–liquid and liquid–liquid phase-transfer catalytic conditions have been reported[7]. To illustrate this latter techniques, consider the reaction between benzyl bromide (0.058 mole) and potassium acetate (0.12 mole) in acetonitrile containing only catalytic quantities (0.0027 mole) of 18-crown-6 (Figure 2). Since there is not enough crown present to dissolve all the potassium acetate present the reaction mixture is a two-phase system. Nevertheless, the reaction proceeds quantitatively to benzyl acetate. This result indicates that in priniciple the crown acts as a carrier of potassium acetate reactant from the solid phase to the liquid phase and also as a carrier of potassium bromide product from the liquid phase to the solid phase. In the absence of crown little reaction takes place during a comparable period of time. This technique of performing organic transformations has also been accomplished between two liquid phases[7]. Representative examples of crown-mediated reactions will be explored in the following sections. No attempt will be made to present an exhaustive survey. Only the general scope and flavour of this subject will be addressed.

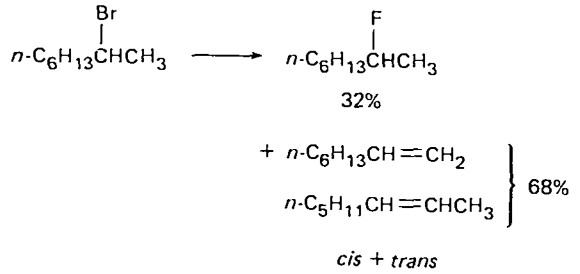
II. ORGANIC REACTIONS MEDIATED BY MACROCYCLIC AND MACROBICYCLIC MULTIDENTATE LIGANDS

In spite of the marginal solubilization of potassium fluoride by 18-crown-6 in actonitrile and benzene[5], enough anion is present in solution, even in the presence of catalytic quantities of crown, to allow facile transformations which introduce fluorine into organic molecules by simple displacement processes (reactions 1–8).



(1)

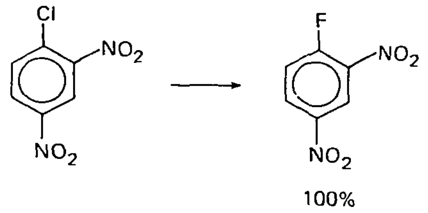
$$n\text{-}C_6H_{13}CH_2CH_2Br \longrightarrow n\text{-}C_6H_{13}CH_2CH_2F \; 92\% \; + \; n\text{-}C_6H_{13}CH{=}CH_2 \; 8\% \qquad (2)$$



$$n\text{-}C_6H_{13}CH(Br)CH_3 \longrightarrow n\text{-}C_6H_{13}CH(F)CH_3\ (32\%) + \left.\begin{array}{l} n\text{-}C_6H_{13}CH{=}CH_2 \\ n\text{-}C_5H_{11}CH{=}CHCH_3 \end{array}\right\}\ 68\%$$

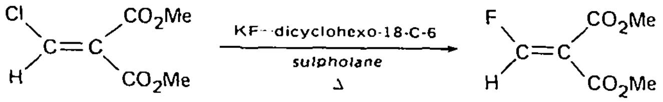
cis + trans

(3)

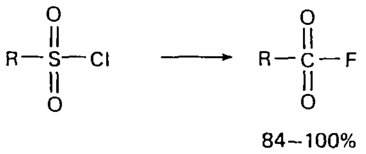


(4)

$CH_3COCl \longrightarrow CH_3COF$ 100% (5)



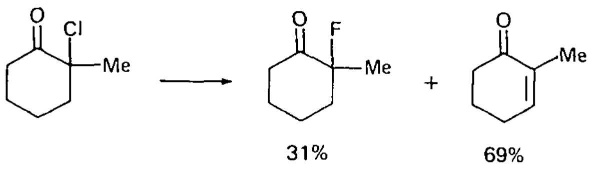
(Ref. 15) (6)



$$R{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}{-}Cl \longrightarrow R{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{C}}{-}F$$

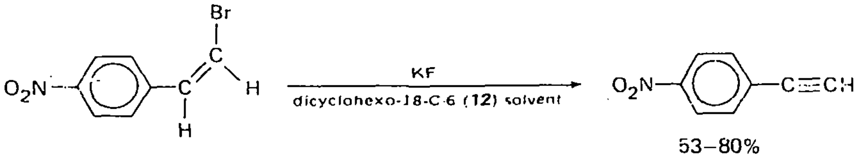
84–100%

(Ref. 16) (7)

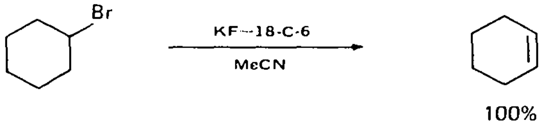


(8)

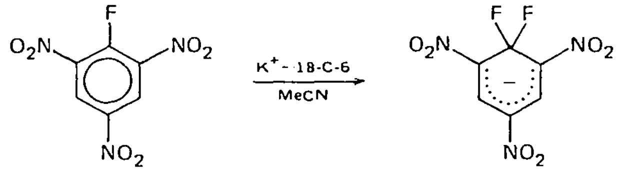
It is interesting to note that fluoride ion behaves as a dehydrohalogenating agent with certain substrates (reactions 2, 3, 8–10). The *gem* difluoro σ-anionic complex (reaction 11) was observed by means of ^{1}H- and ^{19}F-NMR spectroscopy. Naked fluoride has been reported to be an effective base catalyst in the deprotonation of the indole ring of tryptophan in the formation of *N*-benzyloxycarbonyl and *N*-2,4-dichlorobenzyloxycarbonyl derivatives[19].



(Ref. 17) (9)

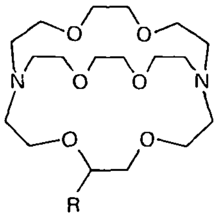


(Ref. 5) (10)



(Ref. 18) (11)

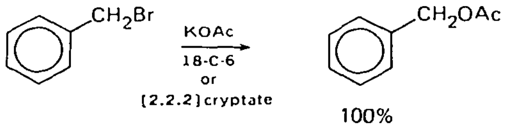
Nucleophilic substitution and elimination processes have been reported for chloride[15], bromide[20] and iodide[20] under solid–liquid phase-transfer catalytic conditions using dicyclohexo-18-crown-6 (12) and under liquid–liquid phase-transfer catalytic conditions using dicyclohexo-18-crown-6 (**12**), benzo-15-crown-5 (**11**), dibenzo-18-crown-6 (**8**), 1,10-diaza-4,7,13, 16-tetraoxacyclooctadecane (**6**) and **9a**, b and c[21,22].



(a) R = H
(b) R = $n\text{-}C_{11}H_{23}$
(c) R = $n\text{-}C_{14}H_{29}$

(9)

Acetate ion has always been considered a marginal to poor nucleophile in protic media (see Table 4). Nevertheless, when solubilized as its potassium salt in acetonitrile and benzene, it becomes an active nucleophilic species. Reactions of naked acetate with a wide variety of organic substrates (Figure 2, reaction 12; reactions 13–17)[19,23]. Indeed, carboxylate ions in general become quite reactive under naked anion conditions (reactions 18–21). It is interesting to note that acetate



(Refs. 9, 30) (12)

$$n\text{-}C_7H_{15}CH_2Br \xrightarrow[\text{18-C-6 or [2.2.2] cryptate}]{\text{KOAc}} n\text{-}C_7H_{15}CH_2OAc$$

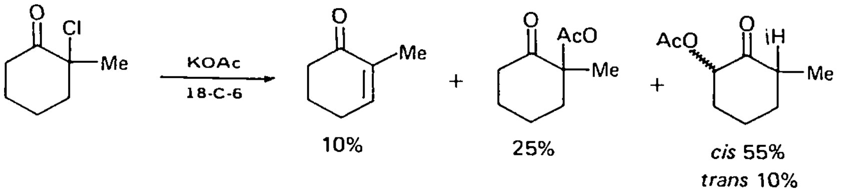
96% (Refs. 9, 30) (13)

$$n\text{-}C_6H_{13}CHBrCH_3 \xrightarrow[\text{18-C-6}]{\text{KOAc}} n\text{-}C_6H_{13}CH(OAc)CH_3 + \text{octenes}$$

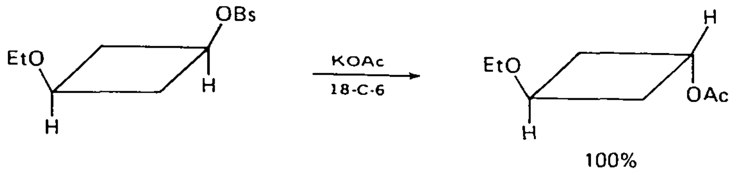
90% 10% (Ref. 9) (14)

$$BrCH_2CH_2Br \xrightarrow[\text{18-C-6}]{\text{KOAc}} AcOCH_2CH_2OAc$$

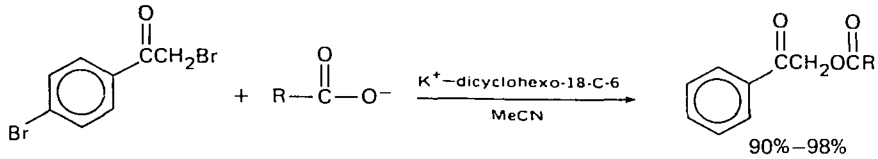
90% (Ref. 9) (15)


O
Cl
Me
KOAc
18-C-6
O
Me
10%
+
O
AcO
Me
25%
+
AcO
O
H
Me
cis 55%
trans 10%

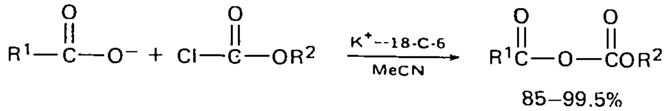
(Ref. 9) (16)


OBs
EtO
H
H
KOAc
18-C-6
H
EtO
OAc
H
100%

(Ref. 23) (17)

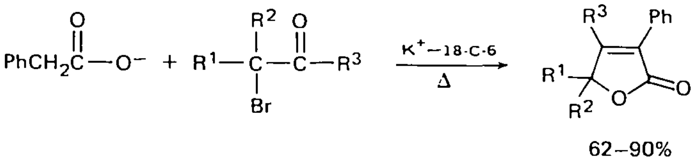

O
CCH2Br
Br
+
R—C—O⁻
O
K⁺—dicyclohexo-18-C-6
MeCN
O O
CCH2OCR
90%–98%

(Ref. 24) (18)

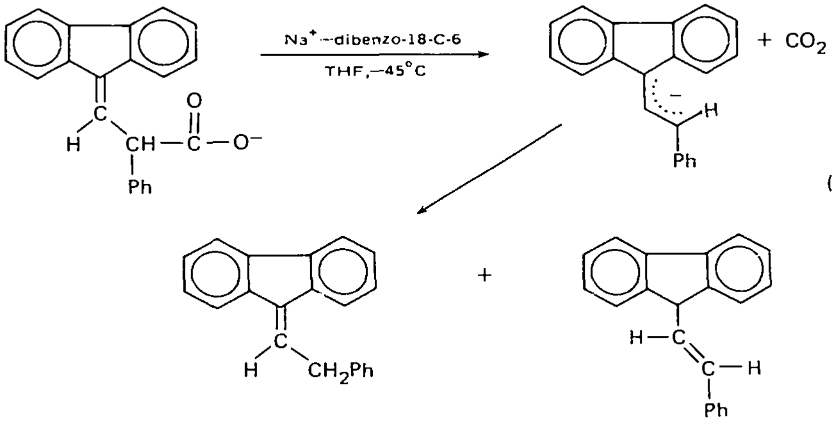


$$R^1-\overset{O}{\overset{\|}{C}}-O^- + Cl-\overset{O}{\overset{\|}{C}}-OR^2 \xrightarrow[\text{MeCN}]{K^+\text{—18-C-6}} R^1\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}OR^2$$

(Ref. 25) (19)


O
PhCH2C—O⁻
+
R2 O
R1—C—C—R3
Br
K⁺—18-C-6
Δ
R3
Ph
R1
R2
O
O
62–90%

(Ref. 26) (20)


C
H
CH—C—O⁻
O
Ph
Na⁺—dibenzo-18-C-6
THF, —45°C
+ CO2
−
H
Ph
C
H
CH2Ph
+
H—C
C—H
Ph

(Ref. 27) (21)

promotes less dehydrohalogenation compared to fluoride under comparable reaction conditions. The reaction of chloromethylated resin with the potassium salts of boc-amino acids in dimethyl formamide solution was shown to be facilitated by the presence of 18-crown-6[28] and the polymerization of acrylic acid has been reported to be initiated by potassium acetate complexed with crown[29].

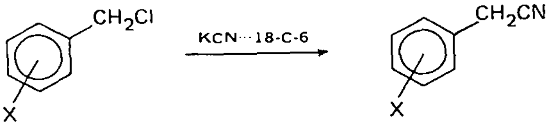
Cyanide ion, generated under solid–liquid and liquid–liquid phase-transfer catalytic conditions using crowns and cryptates, has been demonstrated to be a useful reagent in a wide variety of substitution, elimination and addition processes (reactions 22–35). It is interesting to note that in displacement reactions by

$$n\text{-}C_5H_{11}CH_2Br \xrightarrow[C_6H_6 \text{ or } MeCN]{KCN\text{—}18\text{-}C\text{-}6} n\text{-}C_5H_{11}CH_2CN \quad (22)$$

100%

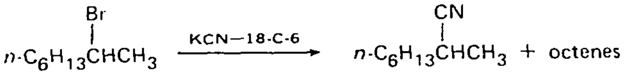
$$n\text{-}C_7H_{15}CH_2Cl \xrightarrow[\text{or DC-18-C-6}]{KCN,\ [2.2.2]\ \text{cryptate}} n\text{-}C_7H_{15}CH_2CN \quad \text{(Ref. 22) (23)}$$

93%


CH2Cl
X
KCN···18-C-6
CH2CN
X

80–95%

(Refs. 31, 32) (24)



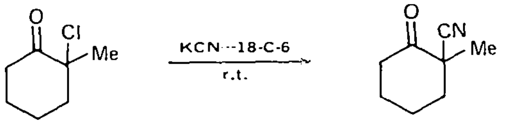
$$n\text{-}C_6H_{13}CH(Br)CH_3 \xrightarrow{KCN\text{—}18\text{-}C\text{-}6} n\text{-}C_6H_{13}CH(CN)CH_3 + \text{octenes} \quad \text{(Ref. 31) (25)}$$

70%

$$BrCH_2CH_2CH_2Br \xrightarrow{KCN\text{--}18\text{-}C\text{-}6} NCCH_2CH_2CN \quad \text{(Ref. 31) (26)}$$

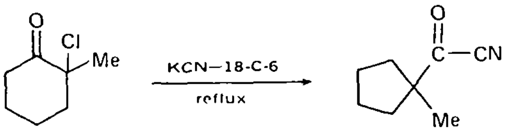
94–97%

$$Me_3SiCl \xrightarrow{KCN\text{-}\ 18\text{-}C\text{-}6} Me_3SiCN \quad \text{(Ref. 32) (27)}$$


O
Cl
Me
KCN--18-C-6
r.t.
O
CN
Me

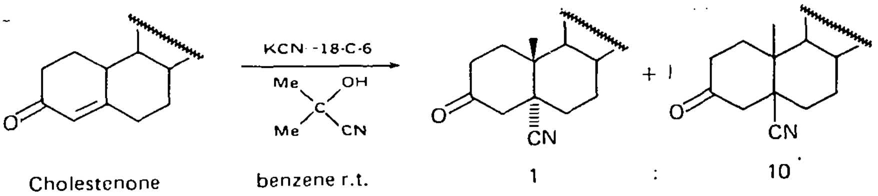
96%

(Ref. 6) (28)


O
Cl
Me
KCN–18-C-6
reflux
O
C—CN
Me

90%

(Ref. 6) (29)

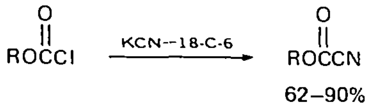

O
KCN -18-C-6
Me
OH
C
Me
CN
benzene r.t.
O
CN
+
O
CN

Cholestenone

1 : 10

86%

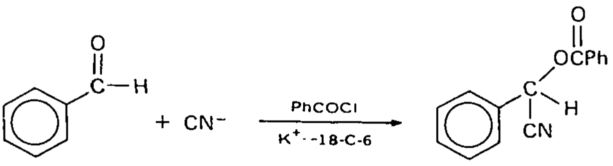
(Ref. 33) (30)



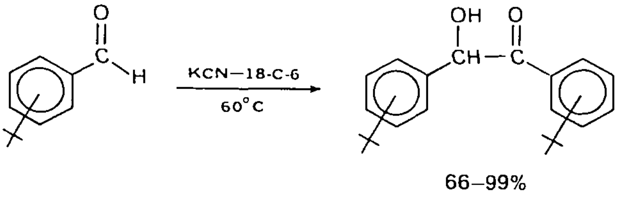
$$\mathrm{RO}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Cl} \xrightarrow{\text{KCN--18-C-6}} \mathrm{RO}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CN}$$

62–90%

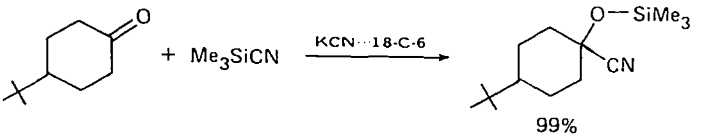
(31)



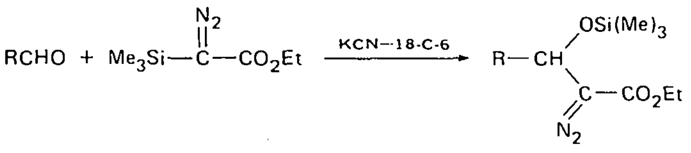
(Ref. 35) (32)



(Ref. 36) (33)



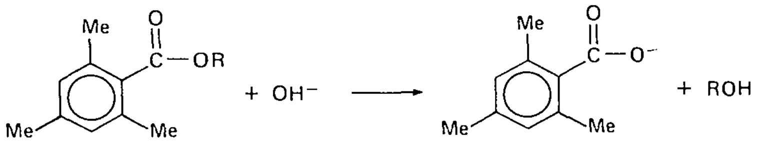
(Ref. 37) (34)



(Ref. 39) (35)

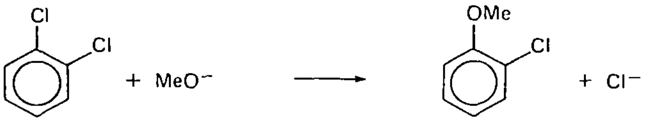
cyanide under solid–liquid conditions, primary chlorides react faster than primary bromides while secondary bromides react faster than secondary chlorides. 18-Crown-6 has been shown to facilitate the photochemical aromatic substitution by potassium cyanide in anhydrous media[40] and to enhance the nucleophilic displacement by cyanide on hexachlorocyclotriphosphazene[41].

Kinetic studies have shown that the presence of macrocyclic multidentate ligands increases the solubility and alters the ionic association of metal hydroxides and alkoxides in relatively nonpolar media and greatly increases the nucleophilic and basic strength of the oxy anions[42–44]. For instance, sterically hindered esters of 2,4,6-trimethylbenzoic acids easily undergo acyl-oxygen cleavage by potassium hydroxide in toluene containing dicyclohexo-18-crown-6 or the [2.2.2] cryptate (reaction 36)[45], chlorine attached to a nonactivated aromatic ring is readily displaced by methoxide ion dissolved as its potassium salt in toluene containing crown



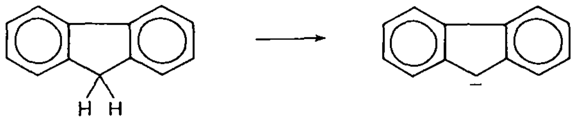
(Refs. 1, 45) (36)

by an addition–elimination mechanism (reaction 37), and carbanions are generated from weak carbon acids by hydroxide and alkoxide in nonpolar solvents containing



(Ref. 20) (37)

crowns and cryptates (reactions 38–40)[45]. Indeed, the regiochemical and stereochemical course of reaction in both substitution and elimination processes is

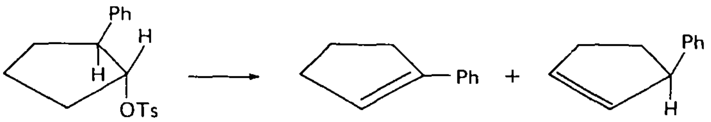


(38)

$$Ph_3CH \longrightarrow Ph_3C^- \qquad (39)$$

$$Ph_2CH_2 \longrightarrow Ph_2CH^- \qquad (40)$$

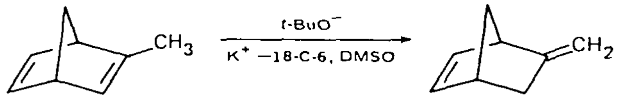
markedly altered by the presence of crown[46–50]. Reaction of 2-phenylcyclopentyl tosylate (reaction 41) with potassium *t*-butoxide in *t*-butyl alcohol produces two isomeric cycloalkene products[46]. In the presence of dicyclohexo-18-crown-6, 3-phenylcyclopentene is produced in greatest quantity while in its absence 1-phenylcyclopentene is the major product. This and other studies indicate that in nonpolar



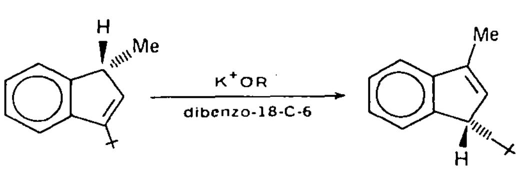
(Ref. 46) (41)

media metal alkoxides react as ion aggregates and promote elimination reactions via a *syn* pathway, while in the presence of a macrocyclic multidentate ligand, the aggregate is disrupted and the *anti* elimination pathway becomes dominant.

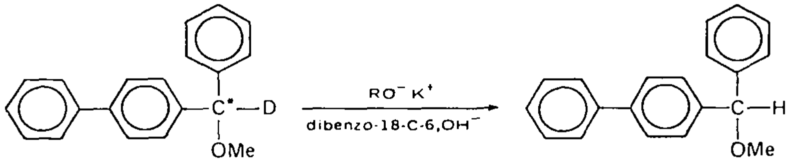
Isomerization reactions, reactions involving stereochemical course of isotope exchange, and fragmentation reactions promoted by metal alkoxides and rearrangements of metal alkoxides in the presence and in the absence of crowns have been reported (reactions 42–47). Enolates and related species and halomethylenes and



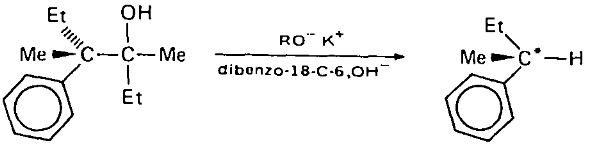
(Ref. 51) (42)



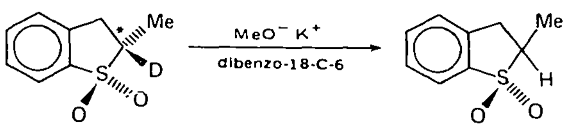
(Ref. 52) (43)



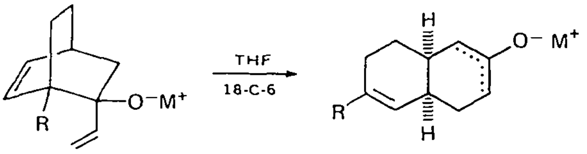
(Ref. 53) (44)



(Ref. 53) (45)



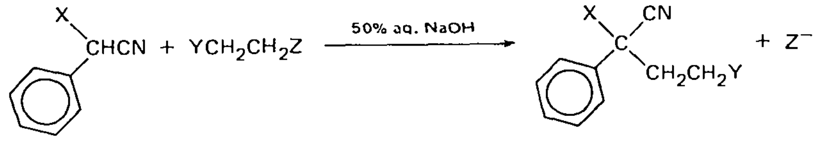
(Ref. 53) (46)



(Ref. 54) (47)

their carbanion precursors have been generated under liquid–liquid phase-transfer catalytic conditions using crowns and cryptates and effectively used in synthetic transformations (reactions 48–54)[55a–c]. Ambient ions such as 9-fluorenone oximate (**14**), and the enolates of ethyl malonate (**15**) and ethyl acetoacetate (**16**) have been generated in the presence of macrocyclic multidentate ligands in a variety of solvents. It has been demonstrated that the presence of a metal ion complexing agent greatly effects the rate of alkylation as well as the ratio of N/O and C/O allylation[6–60].

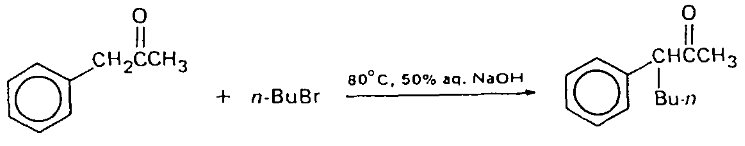
Potassium superoxide has been successfully solubilized in dimethyl sulphoxide, benzene, tetrahydrofuran and dimethylformamide containing 18-crown-6 and effectively used as a nucleophilic reagent for the preparation of dialkyl and diacyl



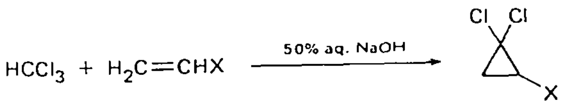
(Ref. 55a) (48)

X = H, Ph
Y = H, Br
Z = Br, Cl

Y = H 85%
Y = Br 75%

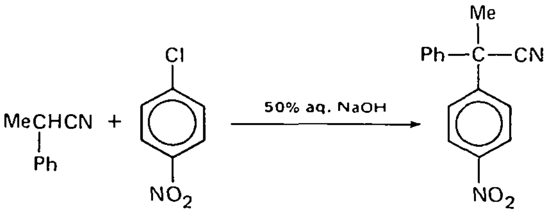


(Ref. 22) (49)



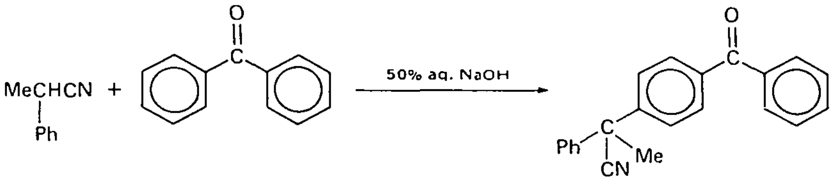
(Ref. 55a) (50)

X = Ph 87%
X = CN 40%



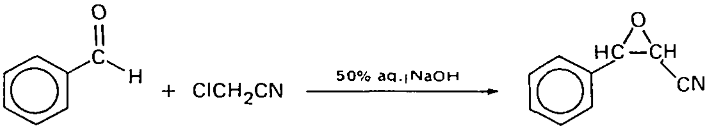
81%

(Ref. 55a) (51)



67%

(Ref. 55a) (52)



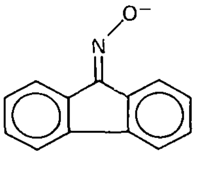
78%

(Ref. 55a) (53)

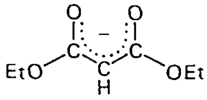
$$H_2N{-}NH_2 \xrightarrow[18\text{-}C\text{-}6]{CHCl_3,\ KOH} CH_2N_2$$

48%

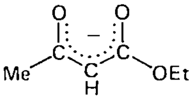
(Ref. 55b) (54)



(14)



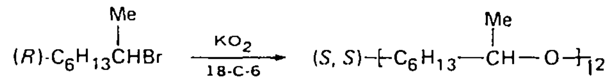
(15)



(16)

peroxides and alcohols (reactions 55 and 56)[14,60-64]. It has also been demonstrated that superoxide in benzene is an efficient reagent for cleavage of carboxylic esters[62,63] and for promoting the oxidative cleavage of α-keto, α-hydroxy and α-halo ketones, esters and carboxylic acids[65] and α,β-unsaturated carbonyl compounds[66] (reactions 57 and 58).

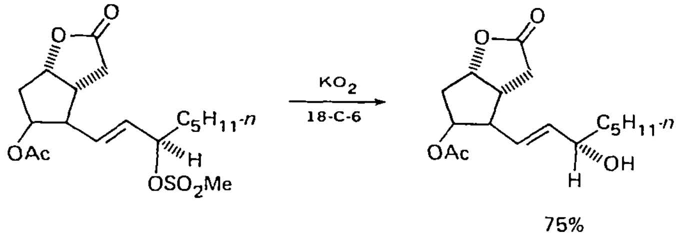
It has been demonstrated that potassium permanganate solubilized in benzene with crown provides a convenient, mild and efficient oxidant for a large number of



$$(R)\text{-}C_6H_{13}\overset{\text{Me}}{\overset{|}{C}}HBr \xrightarrow[18\text{-}C\text{-}6]{KO_2} (S,S)\text{-}[C_6H_{13}{-}\overset{\text{Me}}{\overset{|}{C}}H{-}O]_2$$

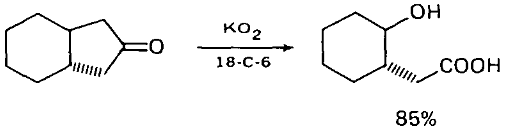
55%

(Ref. 61) (55)



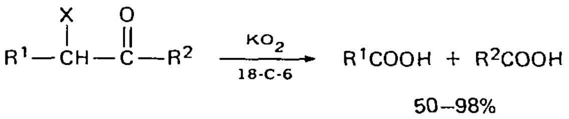
O
O
OAc
C_5H_{11}-*n*
H
OSO_2Me
KO_2
18-C-6
O
O
OAc
C_5H_{11}-*n*
OH
H
75%

(Ref. 62) (56)



O
KO_2
18-C-6
OH
COOH
85%

(Ref. 64) (57)

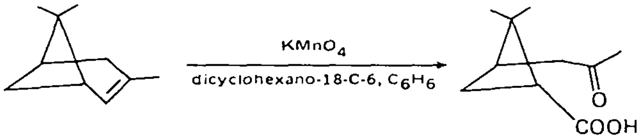


$$R^1-\overset{X}{\overset{|}{C}}H-\overset{O}{\overset{\|}{C}}-R^2 \xrightarrow[18\text{-C-6}]{KO_2} R^1COOH + R^2COOH$$

50–98%

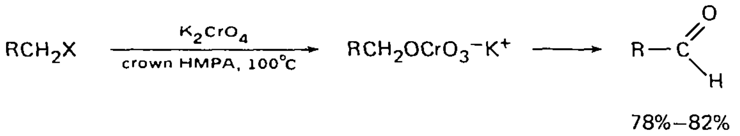
(Ref. 65) (58)

organic reactions (reaction 59)[20], while potassium chromate has been reported to react with primary alkyl halides at 100°C in hexamethylphosphoramide containing crown to produce good yields of alkehydes (reaction 60)[67]. Carbanions formed from reaction of weak carbon acids with potassium hydroxide in toluene containing crowns or cryptates are readily oxidized by molecular oxygen (reaction 61)[45] and the homogeneous photosensitization of oxygen by solubilizing the anionic dyes Rose Bengal and Eosin Y in methylene chloride and carbon disulphide using crown is reported to produce singlet oxygen (reactions 62 and 63)[68].



$KMnO_4$
dicyclohexano-18-C-6, C_6H_6
O
COOH

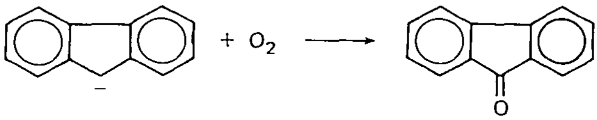
(59)



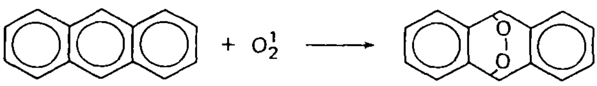
$$RCH_2X \xrightarrow[\text{crown HMPA, 100°C}]{K_2CrO_4} RCH_2OCrO_3^-K^+ \longrightarrow R-\overset{O}{\overset{\|}{C}}-H$$

78%–82%

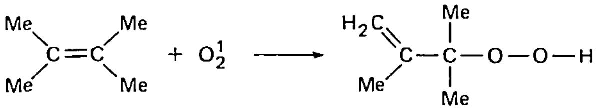
(60)



(61)

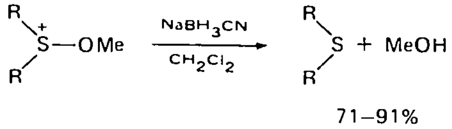


(62)



(63)

The action of reducing agents such as lithium aluminium hydride, sodium borohydride and sodium cyanoborohydride on organic substrates has been explored in the presence of macrocyclic and macrobicyclic polydentate ligands under homogeneous, solid–liquid and liquid–liquid phase-transfer catalytic conditions[22,69–72]. In the former cases, crowns and cryptates were used to elucidate the role of the metal cation as an electrophilic catalyst. Sodium cyanoborohydride in the presence of crown has been reported to reduce alkoxysulphonium salts to sulphides (reaction 64)[72].



(64)

Sodium, potassium and caesium anions have been generated in ether and amine solvents in the presence of crowns and cryptates[73] and sodium, potassium, caesium and rubidium have been reported to dissolve in benzene and toluene and in cyclic ethers containing these hydrocarbons in the presence of crowns and cryptates to produce the corresponding anion radicals[74].

Finally, macrocyclic multidentate ligands have been found to be a sensitive tool for exploring the mechanistic details in the reactions and rearrangements of carbanions[52–54,75–78] and in substitution and elimination processes[46–50]. Indeed, any reaction involving metal ion anion intermediates is, in principle, subject to mechanistic surgery with the aid of crowns and cryptates. It must be remembered that these macrocyclic and macrobicyclic species can be designed and synthesized specifically for a particular metal ion. Herein lies their potential power.

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 4

Geometry of the ether, sulphide and hydroxyl groups and structural chemistry of macrocyclic and noncyclic polyether compounds

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I. INTRODUCTION

Various diffraction and spectroscopic methods have proved particularly useful in the analysis of characteristic molecular dimensions and conformations of the compounds under discussion in this chapter. Most of the experimental techniques have been significantly improved in recent years and their application extended to numerous molecular structures of varying complexity. The mutually complementary tools of electron diffraction (ED) and microwave spectroscopy (MW) are suitable for the examination of simple and highly symmetric molecules which exist only in the vapour phase or can be vaporized easily. This applies for example, to the simplest of the title compounds such as dimethyl ether, dimethyl sulphide and methanol. Of special merit in the ED and MW methods is the fact that they directly yield detailed structural information about the shape of the molecules in the gaseous state where the intramolecular forces are exclusively responsible for the conformational choice. A major limiting factor of the ED technique itself lies in an inadequate treatment of the effects of thermal motion, and in order to determine a structure precisely one often has to calculate vibrational amplitudes from spectroscopic data. However, in favourable cases combination of ED with spectroscopy can readily lead to a reliable determination of exact atomic positions, including those of the light hydrogen atoms.

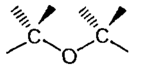
X-ray diffraction (XD) crystallography is at present the most convenient method for the study of moderately complex molecules that produce single crystals. The development of computer-controlled diffractometers for rapid acquisition of accurate X-ray intensity data and the enhanced efficiency of algorithms for the solution of the phase problem in diffraction have caused a sharp increase in the number of crystallographic determinations in organic and inorganic chemistry. It should be kept in mind, however, that the amplitudes of atomic thermal vibrations, and particularly the positions of hydrogen atoms, can be determined with a considerably greater accuracy by neutron diffraction than by XD cystallography. The neutron diffraction technique has therefore an important function in the study of hydrogen bonds and electron density distributions; it also is experimentally more difficult and its applicability requires the immediate neighbourhood of an atomic reactor.

The structural data are being presented in this article mainly in terms of geometrical factors such as bond lengths, bond angles and torsional angles (when available, the estimated standard deviations are expressed in parentheses in units of the last decimal place). It is important to emphasize here that the MW, ED and XD molecular dimensions are derived from observed quantities which are affected in different ways by molecular vibrations. The conventional results of XD (as well as neutron diffraction) experiments correspond to distances between average atomic positions in a molecular coordinate system, those obtained in the reduction of ED data usually refer to an average over the molecular vibrations, while the distance parameters in a MW study are calculated from ground-state rotational contants. Hence, a detailed comparison of the corresponding r value should be carried out with much care. These anticipated differences are generally small, and seem to be not significant with respect to the following discussion. Therefore, the literature values of bond parameters are quoted in this article without modification. Presently available structural information about ethers, crown ethers, hydroxyl groups and their sulphur analogues suffices to fill at least one separate volume on this matter. Hence, an attempt to cover the whole field adequately and to present a comprehensive survey of all structural properties within the scope of a single chapter would (obviously) be unsuccessful. In fact, a few relevant specific subjects, such as those dealing with stereochemistry of dioxanes and hydrogen bonding by hydroxyl groups, have already been reviewed in detail. In the present article we have chosen to confine the discussion to (*a*) the reference structural parameters of the title functions, and (*b*) the structural chemistry of crown ether compounds which has been developing significantly in the recent years. The subjects (*a*) and (*b*) are dealt with below, in Sections II and III respectively.

II. STRUCTURAL PARAMETERS OBTAINED FROM ELECTRON DIFFRACTION AND MICROWAVE STUDIES

A. The C—O—C Group

The geometry and conformation of a number of small organic species that contain the ether group were investigated by ED and MW methods. Two accurate and independent structure determinations of dimethyl ether (1), by Kimura and Kubo[1] from ED patterns and by Kasai and Myers[2,3] from MW spectra, provided reference structural parameters for the C(sp^3)—O—C(sp^3) moiety. The respective results of these two studies are very similar: 1.416(3) and 1.410(3) Å for the C—O bond distance, 111.5(15) and 111.4(3)° for the C—O—C bond angle. The experimental evidence showed conclusively that the dimethyl ether molecule has in the gas phase C_{2v} symmetry, the methyl groups being staggered with respect to the opposite C—O bonds. In the MW work the molecular dipole moment of $(CH_3)_2O$ was determined to be 1.31(1) D. The structure of monochlorodimethyl ether (2) was also examined by means of ED of the vapour[4], yielding an averaged C—O bond of 1.38 Å and a C—O—C angle of 113.2°. A careful analysis of the experimental radial distribution function for this molecule led, however, to the conclusion that the two C—O bonds are not equal; the best fit between the structural model and data was obtained with CH_2Cl—O and CH_3—O bond distances of 1.368 and 1.414 Å, respectively. It has been difficult to rationalize the significant difference between the two C—O bond distances without invoking interaction between the oxygen atom and the lone-pair electrons of the chlorine atom (see below).



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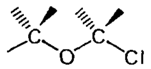
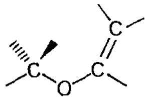


(2)

In unsaturated olefinic systems the C—O bond is also shortened considerably through influence of the double bond. This feature was observed in the structures of gaseous methyl vinyl ether (3), methyl allenyl ether (4) and 1-methoxycyclohexene (5). In the gas phase, methyl vinyl ether was found as a mixture of 64% of a *cis* form having a planar skeleton in which the methyl group is staggered with respect to the CH—O bond and 36% of a second conformer which has its CH_3—O bond approximately at right angles to the plane of the vinyl group[5]. The following parameters for the ether group structure were obtained: C(sp^3)—O = 1.424 Å, C(sp^2)—O = 1.358 Å and C—O—C = 120.7°. The molecule of methyl allenyl ether adapts an equilibrium planar *cis* conformation with C_s symmetry[6]. From inspection of the ED data it was concluded that at room temperature there is a large torsional motion of the OCH_3 group around the other ether linkage which



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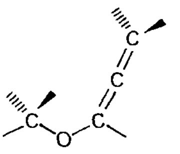

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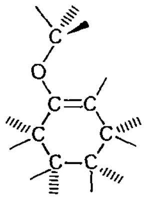
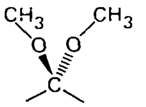


(5)

could be characterized by a displacement angle from planarity of about 23°. The reported results include the bond distances $C(sp^3)$—O = 1.427(8) and $C(sp^2)$—O = 1.375(7) Å and the bond angle C—O—C = 115.0(12)°. 1-Methoxycyclohexene is a substituted vinyl ether having a methoxyl group bonded to one of the double-bonded carbon atoms in the cyclohexene ring. In the gas phase, the molecule was also found to exist predominantly in the *cis* conformation[7]. The structural parameters associated with the methoxy group are C—O = 1.364(6) Å for the distance from the sp^2 carbon to the oxygen atom, C—O = 1.421(6) Å for the distance from the oxygen atom to the methyl carbon atom and C—O—C = 119.7(25)°. Evidently, the above data on the three alkenes are quite consistent with respect to the bond lengths; there is, however, a fairly severe disagreement between the refined magnitudes of the C—O—C angle.

Further information on the molecular geometry of simple acyclic ethers was obtained in the investigations (by ED) of dimethoxymethane[8] (6) and tetramethoxymethane compounds[9] (7). The diether molecule (6) has a C_2 symmetry.



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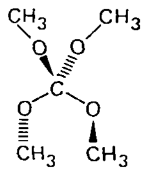

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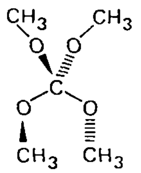


(7b)

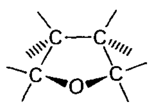
The *gauche* arrangement about the two C—O bonds apparently minimizes the repulsive interaction of lone-pair electrons on the oxygen atoms. In this conformation the molecular dipole moment was calculated to be 1.08 D. Two possible forms of tetramethoxymethane, with staggered methyl groups each belonging to a face of the oxygen tetrahedron, were considered as best models for this species. The diffraction study showed that the molecule has S_4 symmetry (7a); the D_{2d} model (7b) was estimated to be roughly 6 kcal/mol less stable than the S_4 rotamer. The conformation of the C—O—C—O—C sequence in the molecule is either *gauche–gauche* or *gauche–trans*, in good agreement with the observed geometry of dimethoxymethane. Relevant structural parameters of $CH_2(OCH_3)_2$ and $C(OCH_3)_4$ are compared in Table 1. The experimental findings clearly indicate that the central CH_2—O bonds are consistently shorter by 0.03–0.05 Å than the terminal

TABLE 1. Structural parameters of di- and tetra-methoxymethane

	$CH_2(OCH_3)_2$	$C(OCH_3)_4$
Bond lengths (Å)		
(C—O) av.	1.405	1.409
CH_3—O	1.432	1.422
CH_2—O	1.382	1.395
Bond angles (deg.)		
C—O—C	114.6	113.9
O—C—O	114.3	114.6
Methoxy torsional angle (deg.)		
C—O—C—O	63	63

ones. Similar shortening of the C—O bond was also observed in a number of other α-X substituted compounds containing the C—O—C—X moiety, where X is an atom bearing lone-pair electrons (X = OR, halogen, etc.)[10,11]; the monochlorodimethyl ether (2) provides a perfect example. This well-known aspect of the molecular structure has been explained in the literature by various considerations based on the anomeric effect[10,11], its most attractive interpretations involving dipole–dipole electrostatic interactions and n-electron delocalization into the adjacent antibonding orbital.

Tetrahydrofuran (8) is an example of a cyclic monoether compound. Its gas-phase molecular structure was investigated simultaneously and independently by two research groups[12,13]. The structural parameters resulting from both ED studies are identical within the experimental error. It was indicated that gaseous tetrahydrofuran undergoes essentially free pseudorotation between two conformational states, the 'half-chair' form with C_2 symmetry and the 'envelope' form with C_s symmetry. The average single C—O and C—C bond distances 1.428(3) and 1.537(3) Å, respectively, were assumed to be independent of the pseudorotation. The bond angles in the molecule were defined in three different ranges: C—C—C 101–104°, C—C—O 104–107° and C—O—C 106–110°. A MW study of tetrahydrofuran[14] confirmed that the C_2 and C_s conformers are almost equally stable at room temperature with an estimated barrier hindering pseudorotation of 20 cal/mol. The dipole moment of the molecule was determined from the Stark effect in the pure rotational spectrum, and was found to vary from 1.52 to 1.76 D depending upon the pseudorotational state.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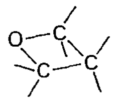
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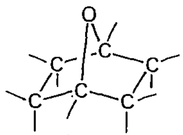
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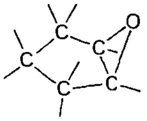
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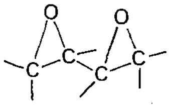
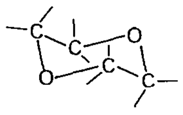
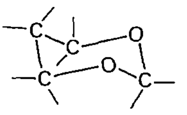
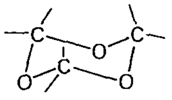

(12)

The effect of intramolecular strain on the geometry of the ether moiety is clearly demonstrated in the structures of trimethylene oxide (9), 7-oxanorbornane (10) and compounds containing a three-membered epoxide ring. The structure of **10** was investigated by making joint use of the experimental ED intensities and rotation constants determined from MW spectra[15]. The thermal-average parameters reported for the ether group are C—O = 1.442(10) Å and C—O—C = 94.5(22)°. From MW spectra of four isotopic species of trimethylene oxide it was deduced that the molecular framework is essentially planar but that the ring-puckering vibration is of a fairly large amplitude, of the order of 0.06 Å[16]. The preferred bonding parameters of this molecule include: C—O = 1.449(2) Å and C—O—C = 92.0(1)°. It is evident, therefore, that in the conformationally strained structures **9** and **10**, the C—O bond is about 0.02–0.03 Å longer and the C—O—C angle is about 17–18° smaller than the corresponding parameters in dimethyl ether and tetrahydrofuran. Long C—O bonds were also observed in the studies of gaseous cyclopentene oxide (**11**) (by a simultaneous least-squares analysis of ED and MW data)[17] and 1,2,3,4-diepoxybutane (**12**) (from ED patterns)[18]. The respectively reported values for the C—O bond distance, 1.443(3) and 1.439(4) Å, and for the ring C—C bond distance, 1.482(4) and 1.463(5) Å, are in good agreement with the corresponding early data obtained by Cunningham and coworkers for ethylene oxide, 1.436 and 1.472 Å[19].

1,4-dioxane, 1,3-dioxane and 1,3,5-trioxane are six-membered heterocycles that contain more than one ether group in the molecular ring. The molecular dimensions of 1,4-dioxane (**13**) obtained by Davis and Hassel[20] by ED differ only slightly from those of tetrahydrofuran. The observed structural parameters are C—C = 1.523(5), C—O = 1.423(3) Å, O—C—C = 109.2(5)° and C—O—C = 112.4(5)°. The latter value is larger than 'tetrahedral' (109.5°), and there is a certain flattening of the 'ideal-chair' structure. This could have been expected, since in 1,4-dioxane four oxygen lone electron pairs are present instead of C—H bonds as in cyclohexane. A chair conformation was also found in the structure of 1,3-dioxane (**14**) with ring angles close to the tetrahedral angle, the O—C—O angle of 115.0° being the only exception[21]. The C—O bonds separated by this angle are 1.393(25) Å long, substantially shorter than the other C—O bonds which are 1.439 (39) Å long. Perhaps, this comparison demonstrates again that where two oxygen atoms are attached to the same carbon atom, the C—O bond is shorter. The torsional angles for 1,3-dioxane range from 56 to 59°, and the C—C distance was found to be 1.528(13) Å.


(**13**)


(**14**)


(**15**)

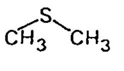
1,3,5-Trioxane (**15**), a cyclic trimer of formaldehyde, and its 2,4,6-trimethyl derivative have been extensively studied by several spectroscopic and diffraction (including X-ray) techniques. Even in the vapour state the trioxane species were found to exist in a stable chair configuration (**15**) characterized by a C_{3v} symmetry, the axial carbon-hydrogen bonds being nearly parallel to the threefold symmetry axis. The molecular dipole moment of 2.07(4) D was determined from a microwave spectrum[22]. The most recent investigations of the molecular structure of trioxanes by ED are those of Clark and Hewitt[23] (trioxane at 75°C) and Astrup[24] (trimethyltrioxane). In the substituted compound, the three methyl groups occupy equatorial sites with almost no distortion of the chair configuration of the molecule except for a slight flattening of the ring; the OCOC torsional angle is 55(1)°. The structural parameters obtained in several investigations of trioxanes are compared in Table 2, which shows that there is a considerable agreement between the various sets of results. The potential energy calculations from vibrational spectra by Pickett and Strauss[25] are of particular interest in this context. They indicate that in saturated oxanes the C—O—C angle is expected to be larger than the O—C—C angle, an argument rationalized by taking into account the repulsions between protons across the C—O—C angle that are absent for the O—C—C angle. Recent results of accurate XD studies on polyether compounds are in accord with this expectation (see below).

TABLE 2. Molecular dimensions of 1,3,5-trioxanes

Method	C—O (Å)	O—C—O (deg.)	C—O—C (deg.)	Reference
ED	1.410(4)	110.7(7)	112.3(8)	24
ED	1.411(2)	111.0(7)	109.2(10)	23
MW	1.411(10)	111.2(10)	108.2(10)	22
XD (at −170°C)	1.421(6)	109.6(3)	110.4(3)	55

B. The C—S—C Group

A considerable amount of work has also been performed on sulphides, the sulphur analogues of ethers. An early MW study of the molecular structure of dimethyl sulphide (**16**) in the gas phase yielded the following reference parameters for the sulphide moiety: C(sp^3)—S = 1.802(2) Å and C—S—C = $98.9(2)^{\circ}$[26]. The above values are very similar to the results obtained by Tsuchiya and Kimura[27] in a more recent ED work: C—S = 1.805(3) Å and C—S—C = $99.0(3)^{\circ}$. In the equilibrium conformation of gaseous $(CH_3)_2S$ both methyl groups are staggered with respect to the adjacent C—S bond axes. The estimated barrier of internal rotation of a methyl group in dimethyl sulphide (2.1 kcal/mol) is about 0.6 kcal/mol lower than the rotational barrier in dimethyl ether (2.7 kcal/mol)[28]. It was also observed that the symmetry axes of the two methyl groups form an angle of 104.4°, thus not coinciding with the C—S bond axes. The molecular dipole moment of dimethyl sulphide was found to be 1.50 D, 0.2 D greater than that of dimethyl ether. Reliable structural parameters of dimethyl disulphide (**17**) were determined by Beagley and McAloon from ED patterns[29]. The two methyl groups were established to be nearly staggered with respect to the S—S bond, the torsion angle about this bond being 83.9°. The C—S length in dimethyl disulphide, 1.806(2) Å, is very close to the ED value in $(CH_3)_2S$. The C—S—C angle and the S—S bond distance are $104.1(3)^{\circ}$ and 2.022(3) Å, respectively.



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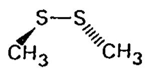
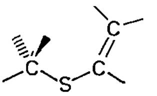


(17)

The geometry of unsaturated organic sulphides is probably affected to a certain extent by the involvement of sulphur d-orbitals in the π-system of the molecule. In methyl vinyl sulphide (**18**) the observed CH_3—S length of 1.806(6) Å is normal for a C(sp^3)—S single bond but, as expected, the =CH—S bond is 0.06 Å shorter, 1.748(6) Å. The observed angular values are C—S—C = $104.5(7)^{\circ}$ and C=C—S = $125.9(5)^{\circ}$. This ED work showed that the molecule exists as a mixture of at least two conformations. Molecular structures of methyl vinyl sulphide and methyl allenyl sulphide (**19**) were also investigated recently by Derissen and Bijen by means



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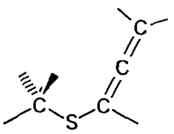


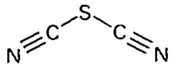
(19)

TABLE 3. Molecular dimensions of methyl vinyl sulphide and methyl allenyl sulphide

	Methyl vinyl sulphide		Methyl allenyl sulphide
	Reference 30	Reference 31	Reference 31
C(sp^3)—S(Å)	1.806(6)	1.794(12)	1.800(10)
C(sp^2)—S(Å)	1.748(6)	1.752(10)	1.745(10)
C—S—C (deg.)	104.5(7)	102.5(2)	98.1(8)
C=C—S (deg.)	125.9(5)	127.0(15)	125.4(6)

of ED[31]. The structural parameters obtained from their study at 40°C are summarized in Table 3. In contradiction with the previous suggestion of Reference 30, Derissen and Bijen concluded that the two compounds exist predominantly in the planar *syn* conformation, the nonplanar *gauche* conformers being less important. It is interesting to note that the barrier to free rotation of the methyl group in the *syn* form of methyl vinyl sulphide was found to be unusually large (about 3.2 kcal/mol)[32], probably in large part due to nonbonding interactions between the hydrogen atoms.

The structural effect of the interaction between bivalent sulphur and a carbon–carbon or carbon–nitrogen triple bond was investigated by means of the MW spectra of sulphur dicyanide (**20**), methyl thiocyanate (**21**) and methyl thioethyne (**22**). The following bond lengths and angles were observed for the sulphide moiety:



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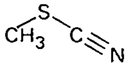

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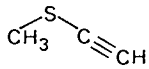
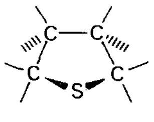


(22)

C(sp)—S = 1.701(2) Å and C—S—C = 98.4(2)° in $S(CN)_2$[33]; C(sp)—S = 1.684 Å, C(sp^3)—S = 1.820 Å and C—S—C = 99.9° in CH_3SCN[34]; C(sp)—S = 1.685(5) Å, C(sp^3)—S = 1.813(2) Å and C—S—C = 99.9(2)° in CH_3SCCH[35]. The results reported for molecule **21** are somewhat inferior in precision, and do not include estimated standard deviations of the parameters. It appears that the C(sp)—S bond distance is 0.10–0.12 and 0.05–0.06 Å shorter than the C(sp^3)—S and C(sp^2)—S bonds, respectively. The above range of the observed C—S values may thus correspond well to the differences in hybridization of carbon bonding orbitals in the respective molecules. Nevertheless, Pierce and coworkers indicated in their work on sulphur dicyanide that the ground electronic state of the molecule is probably also affected to a considerable extent by back-bonding by sulphur[33]. Accordingly, the structure of the —SCN fragment was described by resonance formulae $-S-C{\equiv}N \leftrightarrow -{}^{+}S{=}C{=}N^{-}$.

Turning to cyclic sulphides, the investigation of a gas-phase ED pattern obtained from tetrahydrothiophene (**23**) enabled a fairly reliable determination of its molecular structure[36]. While gaseous tetrahydrofuran was found to exhibit a free pseudorotation between two conformations with respective C_2 and C_s symmetries, the study of Reference 36 indicated strongly that tetrahydrothiophene exists preferentially in the C_2 conformation. In fact, by theoretical energy calculations, this conformation was found to be between 2 to 3 kcal/mol more stable than the C_s form. Strain in the five-membered ring is reflected in some of the bonding parameters. The C—S bond distance in **23** is 1.839(2) Å, 0.03 Å longer than the C(sp^3)—S distance found in dimethyl sulphide. Furthermore, the ring angles C—S—C = 93.4(5), S—C—C = 106.1(4) and C—C—C = 105.0(5)° are several degrees smaller than the corresponding bond angles in unstrained molecules. The observed C—C bond distance of 1.536(2) Å is essentially identical to that in tetrahydrofuran.

The strain effect is even more pronounced in the molecular structures of



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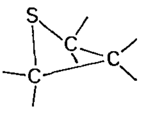

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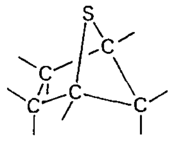

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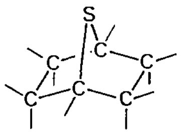

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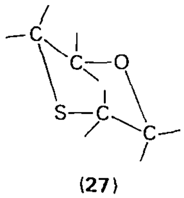
TABLE 4. Bond lengths and angles for 1,4-dioxane, 1,4-thioxane and 1,4-dithiane

	1,4-Dioxane (Reference 20)	1,4-Thioxane (Reference 39)	1,4-Dithiane (Reference 40)
C—C (Å)	1.523	1.521(6)	1.54
C—O (Å)	1.423	1.418(4)	
C—S (Å)		1.826(4)	1.81
C—C—O (deg.)	109.2	113.2(17)	
C—C—S (deg.)		111.4(10)	111
C—O—C (deg.)	112.5	115.1(22)	
C—S—C (deg.)		97.1(20)	100

trimethylene sulphide (24), 5-thiabicyclo[2,1,1]hexane (25) and 7-thiabicyclo [2,2,1]heptane (26). All of these structures were determined by an analysis of ED intensities[37,38]. The mean vibrational amplitudes of compounds 25 and 26 were estimated from the amplitudes found in norbornane; those of molecule 24 were derived from rotational spectra. Some skeletal parameters of the three molecules are listed below, the values identified with each parameter being referred to compounds 24, 25 and 26 respectively: C—S = 1.847(2), 1.856(4) and 1.837(6) Å, $C—C_{av}$ = 1.549(3), 1.553(3) and 1.549(3) Å, C—S—C = 76.8(3), 69.7(5) and 80.1(8)°. It is of particular interest to note that the C—S bond is longer and the C—S—C angle is smaller in the strained rings than in other environments. Analogous trends have been observed in related ethers and hydrocarbons.

1,4-Thioxane (27) is composed of one C—S—C and one C—O—C unit, thus exhibiting the structural features of both the ether and sulphide functional groups. The molecular structure, as determined by means of an ED study[39], shows a chair conformation with an average puckering angle of 58.3°. The parameters obtained for the 1,4-thioxane ring geometry are summarized in Table 4. Comparison of the results for 1,4-thioxane with those of vapour-phase studies of 1,4-dioxane[20] and 1,4-dithiane[40] reveals no major differences. However, while the C—O—C angle in 27 is 3.6° larger than that in dimethyl ether, the C—S—C angle is somewhat smaller than that in dimethyl sulphide; the opposite trends are probably effected by the structural asymmetry of the 6-membered ring.



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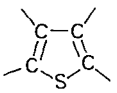

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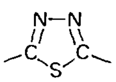


(29)

The final example refers to two pseudoaromatic compounds that contain a formally bivalent sulphur atom: thiophene (28) and diazathiophene (29). In the gas phase both molecules resemble each other by virtue of their planarity and geometry of the C—S—C fragment. The relevant parameters are C—S = 1.717(4) Å and C—S—C =91.9(3)° in 28[41], and C—S = 1.723(3) Å and C—S—C = 86.4(4)° in 29[42]. The above C—S lengths lie between those of the C(sp^2)—S (1.75 Å) and C(sp)—S (1.69 Å) single bond distances. This probably reflects a limited contribution of the sulphur heteroatom to the π-system of the thiophene-type species which is much less aromatic than is the benzene ring.

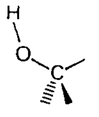
TABLE 5. Molecular dimensions of gaseous methanol

	Reference		
	43	1	44
C—O (Å)	1.427(7)	1.428(3)	1.425(2)
O—H (Å)	0.956(15)	0.960(15)	0.945(3)
C—H (Å)	1.096(10)	1.095(10)	1.094(3)
C—O—H (deg.)	109(2)	109(3)	108.5(5)

C. The C—O—H Group

Table 5 presents the molecular dimensions of gaseous methanol (30) as they were obtained from MW[43] and ED[1,44] data. The results of Reference 44 rely solely on experimental data, and no structural assumptions other than that of symmetry of the methyl group about its axis were made. The agreement between the three sets of parameters given in Table 5 is remarkable. Hence, the accurate structure of the —COH moiety can be reliably described by C—O = 1.426 ± 0.002 Å, O—H = 0.95 ± 0.01 Å and C—O—H = 108.5 ± 0.5°. Apparently, the C—O—H angle is larger by about 4° than the angle of the water molecule and smaller by about 3° than the C—O—C angle in dimethyl ether (see above). The experimental values for the total dipole moment of methanol and its projection along an axis parallel to the O—H bond were found to be 1.69 and 1.44 D, respectively[45]. The molecular structure of ethyl alcohol was investigated by Imanov and Kadzhar from MW spectra[46]. The Russian workers reported a rather low value for the C—O—H angle (104.8°), but their results for the C—O (1.428 Å) and O—H (0.956 Å): bond lengths are essentially identical to those in methanol.

The above reference geometry of the —COH functional group was found to be altered significantly in the presence of highly electronegative substituents in close proximity to the hydroxyl site, as well as by the hydroxyl group involvement in hydrogen bonds. The MW studies of the molecular structures of 2-chloroethanol (31)[47] and 2-aminoethanol (32)[48] provided relevant information. Reportedly, the most stable conformation of 31 and 32 is *gauche*, the O—C—C—X (X = Cl or N) torsion angles about the ethylenic bond being 63.2 and 55.4°, respectively. The molecular conformation was assumed to be stabilized by a dipole—dipole interaction between the nearly parallel O—H and C—Cl dipoles in 2-chloroethanol and by a stronger O—H···N hydrogen-bonding interaction in 2-aminoethanol. These interactions are also reflected in the respective H···Cl (2.61 Å) and H···N (2.14 Å) nonbonding distances that appear to be shorter by about 0.5 Å than the corresponding sums of van der Waals' radii. Furthermore, the main structural results summarized in Table 6 show that the alcohol part of both species has a structure significantly different (with consistently longer O—H bond, shorter C—O bond and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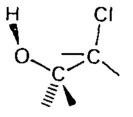
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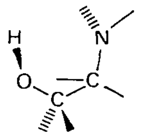
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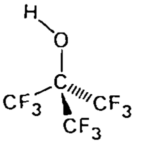
TABLE 6. Molecular geometry of substituted ethanols

	2-Chloroethanol[47]	2-Aminoethanol[48]
C—C (Å)	1.520(1)	1.526(16)
C—O (Å)	1.411(1)	1.396(10)
O—H (Å)	1.010(10)	1.139(10)
C—O—H (deg.)	105.8(4)	103.7(2)
C—C—O (deg.)	112.8(1)	112.1(1)

smaller C—O—H angle) from that of methanol. A relatively short C—O bond length of 1.414 Å was also found by Yokozeki and Bauer[49] in a recent least-squares analysis of intensities for perfluoro-*t*-butyl alcohol (**33**).

Another example of the structural effect of possible intramolecular interactions in alcohols has been provided by the structural analysis of glycol monoformate (**34**)



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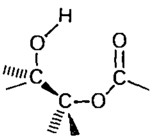
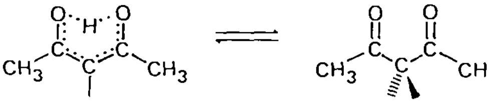


(34)

in the gas phase[50]. The molecule was found to be stable in two *gauche* conformations with respect to the central C—O bond, both with internal hydrogen bonds but involving different acceptor sites (the carbonyl oxygen atom in one rotamer and the ether oxygen atom in the second rotamer). The resulting geometry was defined by the following parameters: C—C = 1.525(4), C—O = 1.412(7), O—H = 1.18 Å and C—C—O = 109.4(7)°, which are in good agreement with those of 2-aminoethanol. Because of certain assumptions concerning the molecular geometry, the initially assumed value of 107° for the C—O—H angle was not refined in that work.

Finally, there is another group of interesting compounds, exemplified by acetylacetone (**35**), which exhibit distinct features of the molecular structure. Separate ED studies by Karle and collaborators (at 110°C)[51] and Andreassen and Bauer (at



enol (35) keto

room temperature)[52] showed that the molecule of acetylacetone exists in two tautomeric forms in dynamical equilibrium. In the gas phase, the enol species, which is characterized by a nearly linear intramolecular hydrogen bond, appears to be a predominant form. At 110°C the equilibrium mixture is composed of 65% of the enol form and 35% of the keto form, while at room temperature the relative amount of the enol tautomer is increased to about 97%. The two structure determinations led to essentially similar descriptions of the molecular geometry. The hydrogen bond in the enol is part of a planar ring in which the C—C bond distances (1.416[51] and 1.405 Å[52]) are close to aromatic values. Furthermore, the observed C—O bond lengths of 1.315[51] and 1.287 Å[52] are intermediate between

TABLE 7. The characteristic geometry of the ether, sulphide, hydroxyl and thiol groups

(*a*) *The C—O—C group*		(*b*) *The C—S—C group*	
1. C(sp^3)—O	1.42 Å	1. C(sp^3)—S	1.80 Å
2. Shortened in presence of electronegative substituent	$\leqslant$1.40 Å	2. Stretched in sterically strained molecules	$\geqslant$1.84 Å
3. Stretched in sterically strained molecules	$\geqslant$1.44 Å	3. C(sp^2)—S	1.75 Å
4. C(sp^2)—O	1.36 Å	4. C(sp)—S	1.69 Å
5. C(sp^3)—O—C(sp^3)	112°	5. C(sp^3)—S—C(sp^3)	99°
(*c*) *The C—O—H group*		(*d*) *The C—S—H group*	
1. C(sp^3)—O	1.43 Å	1. C(sp^3)—S	1.82 Å
2. Shortened in presence of electronegative substituent or hydrogen bond	$\leqslant$1.41 Å	2. Shortened in presence of electronegative substituent or hydrogen bond	<1.81 Å
3. O—H	0.95 Å	3. S—H	1.33 Å
4. Stretched in hydrogen bonded moieties	$\geqslant$1.00 Å	4. C(sp^3)—S—H	96°
5. C(sp^3)—O—H	109°		

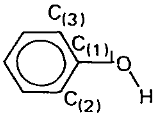
(*e*) *Molecular dipole moments*	
Dimethyl ether	1.31 D
Methanol	1.69 D
Dimethyl sulphide	1.50 D
Methanethiol	1.52 D

the double bond value in acetone (1.21 Å) and the single bond distances in methanol and dimethyl ether (1.42 Å; see above).

D. Comparison of Averaged Results

The characteristic average bonding parameters of the title species are summarized in Table 7. The structural chemistry of the thiol group, the sulphur analogue of hydroxyl, has recently been reviewed by Paul[53] in an earlier volume of this series; for the sake of completeness some of the relevant data including those on methanethiol (CH_3SH)[54] are also given in the Table. The following structural features emerge: The C(sp^3)—O single bond is consistently shorter in ethers than in alcohols. The C—O—C angle is about 3° greater than the C—O—H angle. This trend also appears to occur in the sulphide and thiol groups. As a result of the difference in hybridization of carbon and sulphur bonding orbitals the bond angles around sulphur are about 13° smaller than the corresponding bond angles around oxygen Apparently, due to the latter feature the conformational strain in sulphides is generally larger than in the corresponding oxygen analogues.

The above data should be supplemented by structural information on phenols (36) where the hydroxyl function is attached to an aromatic carbon atom. A large



(36)

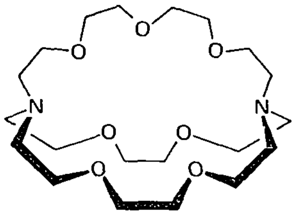
amount of relevant data is available from X-ray crystal structure determinations of a variety of phenol derivatives. Recently, a systematic review of phenol structures has been published by a French group[56], and some observations of general validity are summarized below. An obvious remark should be made. Although the hydroxyl hydrogen atom can often be located in a particular structure by means of difference electron density calculations, the determination of its position by conventional XD methods is in general inaccurate. An inspection of the molecular geometries of about 20 crystallographically independent phenol moieties points to the following features. The observed values (not corrected for the effects of thermal motion) of the C—O bond length range between 1.37 and 1.40 Å with an average near 1.38 Å. The benzene ring is planar in most of the compounds studied, but the three bond angles at $C_{(1)}$ are strikingly different. The average value of the internal $C_{(2)}$—$C_{(1)}$—$C_{(3)}$ bond angle is slightly larger than trigonal (121.4°); most probably, this is associated with the electron-withdrawing nature of the hydroxyl group. Moreover, the O—$C_{(1)}$—$C_{(2)}$ bond angle on the side of the H atom is usually larger by several degrees than the O—$C_{(1)}$—$C_{(3)}$ angle; the reported angular values which are scattered over a relatively wide range appear to cluster around 121.3 and 117.3° respectively. This difference could be interpreted in terms of steric repulsions between H and $C_{(1)}$ and $C_{(2)}$ that are absent for $C_{(3)}$ on the other side of the ring. Intermolecular hydrogen bonds involving the OH group are important in the various crystal structures of phenols, but their comprehensive discussion should be postponed at least until reliable positions of the H atoms have been determined by neutron diffraction. The $C(sp^2)$—O parameters in phenols are consistent with the data shown in Table 7.

As mentioned above, a structural anomaly occurs in compounds such as dimethyl ether and dimethyl sulphide; the axes of symmetry of the methyl groups were found to be inclined with respect to the O—CH_3 and S—CH_3 bonds. This effect was attributed by Hirshfeld[57] to the steric repulsion between the two methyl groups that cause the C—O and C—S bonds in $(CH_3)_2O$ and $(CH_3)_2S$ to be bent.

III. STRUCTURAL CHEMISTRY OF POLYETHER COMPOUNDS

Recent developments of macrocyclic polyethers (termed 'crown' ethers because of the appearance of their molecular models) pioneered by Pedersen[58] in 1967 have aroused considerable interest in several unique properties of these compounds. Their most outstanding feature is that they are capable of combining stoichiometrically with a variety of organic and inorganic species to form inclusion complexes which are stable both in the crystalline state and in a wide range of solvents[58,59]. Selected crown ethers, acting as host molecules, show in solution varying degrees of stereoselectivity in complexation of guest molecules and ions of appropriate size, and also appear to catalyse certain chemical reactions. Hence, they have been referred to as models for interacting biological systems[60,61]. Most recently, the multidentate polyethers have been the subject of an extensive, systematic research in which a series of *chiral* crown ether macrocycles are being designed and synthesized to exhibit properties of chiral recognition toward natural guest moieties[62]. X-ray structure analyses of the crown ethers and their host–guest-type complexes have been carried out in several laboratories to investigate the stereochemical relationships in these compounds, and in particular, the geometry of inclusion in relation to the stereospecificity of crown ether-catalysed reactions as well as crown ether–substrate interactions.

Numerous chemical studies have been reported in the literature on diaza macrobicyclic (37) and tricyclic (38) polyether ligands which also exhibit remarkable complexation properties toward alkaline earth, transition metal and toxic heavy metal cations[63]. These bicyclic and tricyclic cation inclusion complexes (called [2]-cryptates and [3]-cryptates respectively) have cylindrical or spherical topology, either one or two guest ions being enclosed within the central cavity of the ligand. The structures of several cryptates have been established by X-ray crystallography[64]. The cryptates and the macrocyclic crown complexes have in general different spatial geometries. However it seems that, apart from effects due to the bridging nitrogen atoms in the former compounds, the conformational behaviour and ligand–cation interaction modes in both systems are, at least in principle, controlled by similar factors which hold for all molecular structures of polyether compounds. A recent structural analysis of the tricyclic heterocrown 39 provided experimental evidence in support of this assumption[65]. Since a detailed description of both cryptates and crown ethers would exceed the scope of this article, the present discussion is limited to the sterically simpler class of macrocyclic crown compounds.



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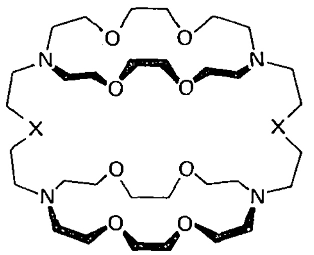

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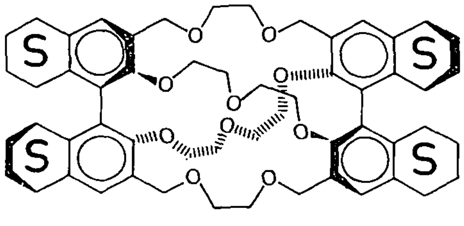

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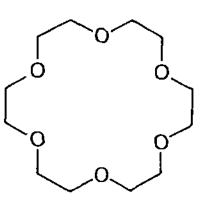
The next two sections deal with structural properties of cyclic polyethers. The third refers to several examples of noncyclic polyethers displaying similar cation-binding characteristics.

A. The Macrocyclic 18-Crown-6 System, and some General Considerations

The structural features of polyether macrocycles can be exemplified by systems containing the unsubstituted 1,4,7,10,13,16-hexaoxacyclooctadecane (40; 18-

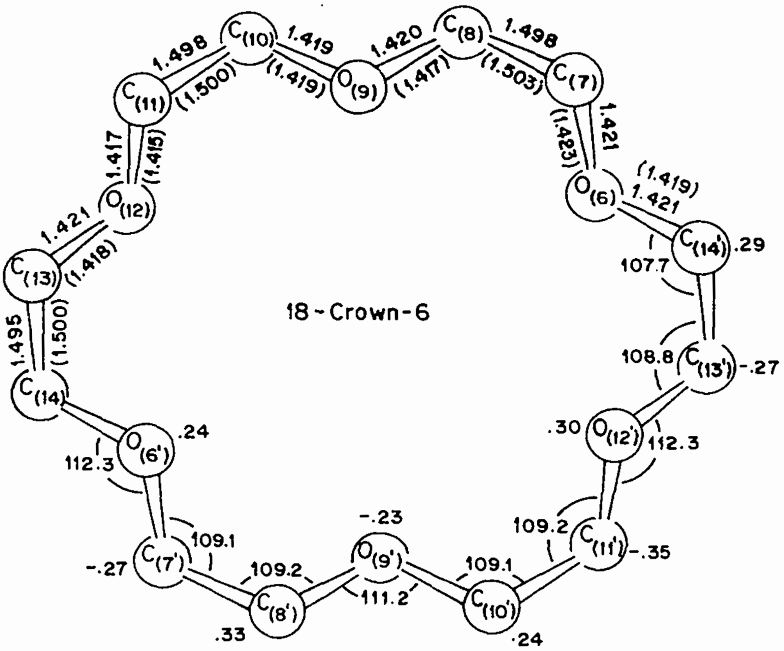


(40)

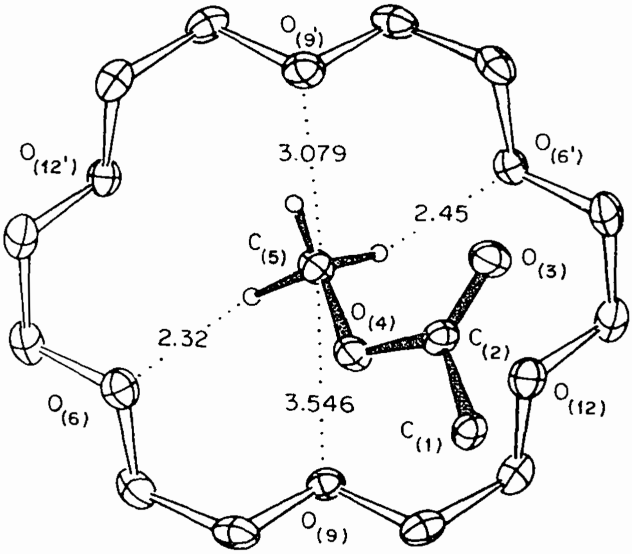
crown-6) ligand, an almost ideal molecular model of a crown ether. Crystal structure analyses of the uncomplexed hexaether and its complexes with NaNCS, KNCS, RbNCS, CsNCS[66], $UO_2(NO_3)_2 \cdot 4H_2O$[67], $NH_4Br \cdot 2H_2O$[68], $CH_2(CN)_2$ (malononitrile)[69], $C_6H_5SO_2NH_2$ (benzenesulphonamide)[70] and $CH_3OOCC\equiv CCOOCH_3$ (dimethyl acetylenedicarboxylate)[71] have recently been reported in detail. The latter structure was studied at low temperature (ca. −160°C), thus yielding more precise geometrical parameters (Figure 1a).

Figure 2 illustrates some characteristics of the molecular geometry of 18-crown-6 resulting from the ten independent structure determinations. In general, the distribution of bond lengths and angles in the 18-crown-6 ligand is very close to that found in previous studies of other moieties (see above). All observed C—O bond lengths are in the range 1.39–1.45 Å with a mean value near 1.42 Å. Most of the O—C—C angles are close to tetrahedral, while the C—O—C angles are about 3° larger averaging 112.6° (in agreement with the theoretical results of Pickett and Strauss[25]). The C—C single bond distances range from 1.46 to 1.52 Å, with an average of 1.495 Å, showing the characteristic shortening observed in all crystal structure analyses of the crown ethers so far published; the usually quoted reference value for a single aliphatic C—C bond is $\geqslant 1.53$ Å[72]. The apparent shortening of C—C bonds in crown ether moieties has been a controversial issue[66,73]. It was recently considered by Dunitz and coworkers as a spurious effect arising from inadequate treatment of molecular motion in crystallographic analysis[66]. However, in view of the continuously increasing evidence from low-temperature studies, it seems now that the short bonds indeed reflect a genuine feature of the molecular structure; the origin of this effect has not been clarified as yet. The structural investigations referred to above indicate that there are no *systematic* changes in bond lengths between the 18-crown-6 molecules given in different conformations. On the other hand, the dimensions of valency angles are clearly dependent on the local conformation within the macroring (see below).

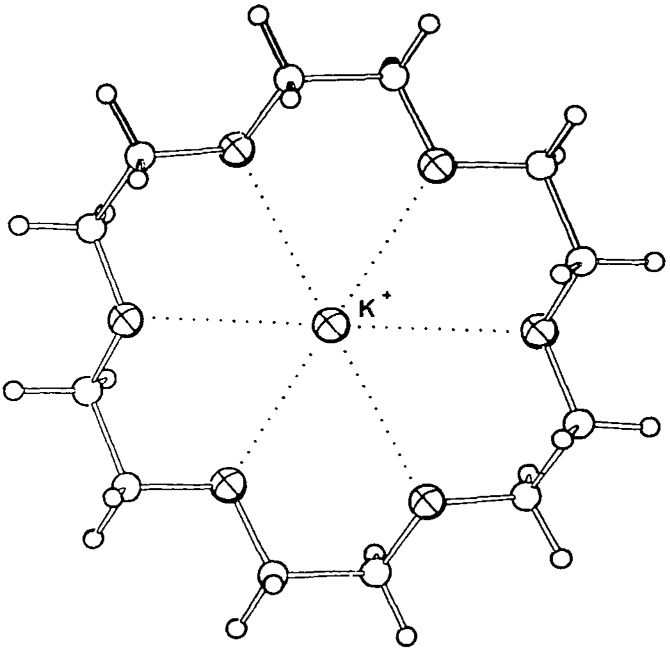
The detailed conformation of 18-crown-6 found in the various crystal structures is best described in terms of the torsion angles about the ring bonds (Table 8). In seven of the complexes the hexaether molecule has a remarkably similar and nearly ideal 'crown' conformation with approximate D_{3d} symmetry. All torsion angles about C—C bonds are *syn*-clinal and those about C—O bonds are antiplanar (Table 8, columns 1–7). The C and O atoms lie alternately about 0.2–0.3 Å above and below the mean plane of the ring. The six ligating oxygens are turned toward the centre of the macrocycle, forming a hexagonal cavity of side approximately 2.8 Å (Figure 1). Assumedly, the energetically favourable symmetric crown conformation of the ether ring is stabilized by effective pole–dipole and dipole–dipole interactions with the corresponding guest species. Except for the potassium ion the other guests are too large to fit in the cavity of 18-crown-6. Thus, within the KNCS complex K^+ occupies exactly the centre of the hexagon of the ether oxygen atoms (Figure 1c), but in the remaining structures the interacting guests are displaced


C(10)
C(8)
C(11)
O(9)
C(7)
O(12)
O(6)
C(13)
C(14')
18-Crown-6
C(13')
C(14)
O(6')
O(12')
C(7')
O(9')
C(11')
C(8')
C(10')
1.498
(1.500)
1.419
(1.419)
1.420
(1.417)
1.498
(1.503)
1.417
(1.415)
1.421
(1.423)
1.421
(1.418)
(1.419)
1.421
1.495
(1.500)
.29
107.7
108.8
-.27
.24
.30
112.3
112.3
-.23
109.2
-.35
109.1
-.27
109.2
109.1
111.2
.33
.24

(a)


O(9')
O(12')
O(6')
3.079
2.45
C(5)
O(3)
O(4)
C(2)
2.32
O(12)
O(6)
3.546
C(1)
O(9)

(b)



(c)

FIGURE 1. The 18-crown-6 ligand in a regular conformation with approximate D_{3d} symmetry. (a) Molecular dimensions[71]; (b) interaction of 18-crown-6 with dimethyl acetylenedicarboxylate[71] (only one half of the guest molecule is shown); (c) interaction of 18-crown-6 with K^+ guest ions[66].

from the mean oxygen plane by 1.00 Å ($-NH_3^+$), 1.19 Å (Rb^+), 1.44 Å (Cs^+), 1.50 Å ($\geq CH_2$) and 1.89 Å ($-CH_3$), in direct correspondence with their relative size. In the crystalline complex of 18-crown-6 with uranyl nitrate, the crown molecules are not bound directly to the uranyl group.

The 18-crown-6 framework when complexed with NaNCS or with benzenesulphonamide deviates markedly from the above described structure. The Na^+ and $R—NH_2$ substrates appear to be too small to 'fill' the annular space within the ligand cavity given in an unstrained conformation. In order to optimize the host–guest interactions the 18-crown-6 molecule is distorted, the deformation strain being preferentially accommodated in torsion angles about the C—O bonds without affecting the *gauche* arrangement of the OCH_2CH_2O units. At this point it is relevant to illustrate the effect of local conformation on bond angles. In the complex of benzenesulphonamide the torsion angle about the $O_{(7)}—C_{(8)}$ bond is *syn*-clinal (72.5°) rather than antiplanar[70]. Such deformation of the ring system introduces 1–4 steric repulsions between the $CH_2(6)$ and $CH_2(9)$ methylene groups, causing the bond angle at $C_{(8)}$ to assume value much greater than tetrahedral (113.3°). Similarly, the small torsion angles about the $C_{(9)}—O_{(10)}$ (70.5°), $O_{(13)}—C_{(14)}$ (76.8°) and $O_{(16)}—C_{(17)}$ (73.7°) bonds in the Na^+ complex cause short contacts between the $CH_2(8)$ and $CH_2(11)$, $CH_2(12)$ and $CH_2(15)$, and $CH_2(15)$ and $CH_2(18)$ methylene groups. This is reflected in a significant widening

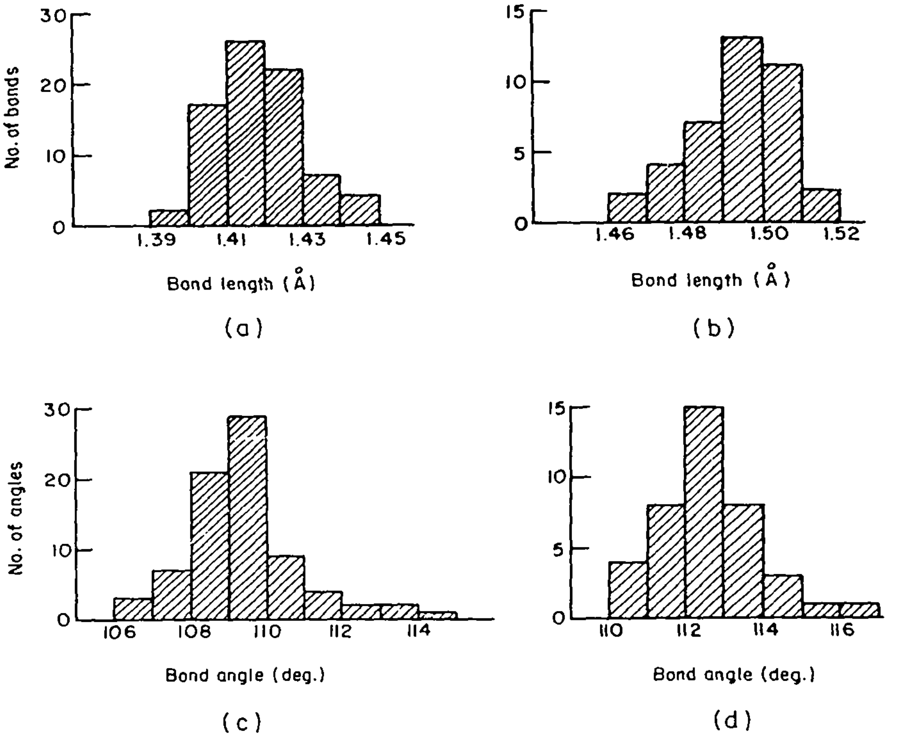


FIGURE 2. A distribution of the bonding parameters observed for 18-crown-6 in ten different structure determinations (References 66–71); (a) C—O bond length, (b) C—C bond length, (c) C—C—O bond angle and (d) C—O—C bond angle.

of bond angles at $C_{(9)}$, $C_{(14)}$, $O_{(16)}$ and $C_{(17)}$ to 112.4, 113.6, 116.5 and 112.1°, respectively[66].

The uncomplexed 18-crown-6 ligand adopts a different type of conformation in the solid. Figure 3 shows that the molecular framework has an elliptical shape because the arrangement about two of the ethylenic bonds becomes antiplanar rather than *gauche*. It appears that the empty space inside the molecule is filled by two H atoms that form transannular H···O contacts; a possible indication that intramolecular van der Waals' and C—H···O dipolar attractions play a major role in determining the overall shape of the uncomplexed macrocycle. This conclusion is consistent with recently published energy calculations of Truter[74]. Her results show that when only nonbonded intramolecular interactions are taken into account, the 18-crown-6 ring has a more favourable energy in the asymmetrical form corresponding to the uncomplexed molecule than in the one with approximately D_{3d} symmetry. An elliptical arrangement of the heteroatoms has also been observed in uncomplexed molecules of the 18-membered crown when two of the oxygen atoms were replaced by sulphur atoms. The interesting feature of the 1,10-dithio-18-crown-6 structure is, however, that the sulphur atoms are directed out of the cavity, while the four oxygen atoms remain turned inward[75].

The conformation of oxyethylene oligomers (chains and rings) has been investigated by various experimental and theoretical methods. References 76 and 77

TABLE 8. Torsion angles (deg.) in 18-crown-6 and its complexes

	Regular conformation							Irregular conformation		
Guest species	$C_6H_6O_4$	$CH_2(CN)_2$	NH_4Br	KNCS	RbNCS	CsNCS	$UO_2(NO_3)_2$	NaNCS	$C_6H_5SO_2NH_2$	none
	Ref. 71	Ref. 69	Ref. 68	Ref. 66	Ref. 66	Ref. 66	Ref. 67	Ref. 66	Ref. 70	Ref. 66
$C-O_{(1)}-C_{(2)}-C$	180	179	180	−171	−179	−178	180	173	177	−80
$O-C_{(2)}-C_{(3)}-O$	72	64	−67	−65	67	68	−63	61	−66	75
$C-C_{(3)}-O_{(4)}-C$	176	179	−174	179	−178	−177	175	−171	158	−155
$C-O_{(4)}-C_{(5)}-C$	179	−177	−175	178	179	179	179	−177	180	166
$O-C_{(5)}-C_{(6)}-O$	−76	−60	65	70	−61	−63	64	−59	−67	−68
$C-C_{(6)}-O_{(7)}-C$	177	179	−176	−176	−173	−173	−175	−173	180	176
$C-O_{(7)}-C_{(8)}-C$	−169	175	178	−177	176	177	−173	−174	−73	175
$O-C_{(8)}-C_{(9)}-O$	70	65	−71	−65	60	61	−72	52	−68	175
$C-C_{(9)}-O_{(10)}-C$	179	178	−171	−178	167	172	−178	71	173	170
$C-O_{(10)}-C_{(11)}-C$					175	174		−172		
$O-C_{(11)}-C_{(12)}-O$					−64	−66		63		
$C-C_{(12)}-O_{(13)}-C$					−176	−176		−176		
$C-O_{(13)}-C_{(14)}-C$	*a*	*a*	*a*	*a*	−172	−172	*a*	77	*a*	*a*
$O-C_{(14)}-C_{(15)}-O$					64	65		47		
$C-C_{(15)}-O_{(16)}-C$					172	173		115		
$C-O_{(16)}-C_{(17)}-C$					−178	−179		−74		
$O-C_{(17)}-C_{(18)}-O$					−64	−65		−59		
$C-C_{(18)}-O_{(1)}-C$					−179	180		167		

[a] In these structures 18-crown-6 is located on inversion centres or mirror planes.

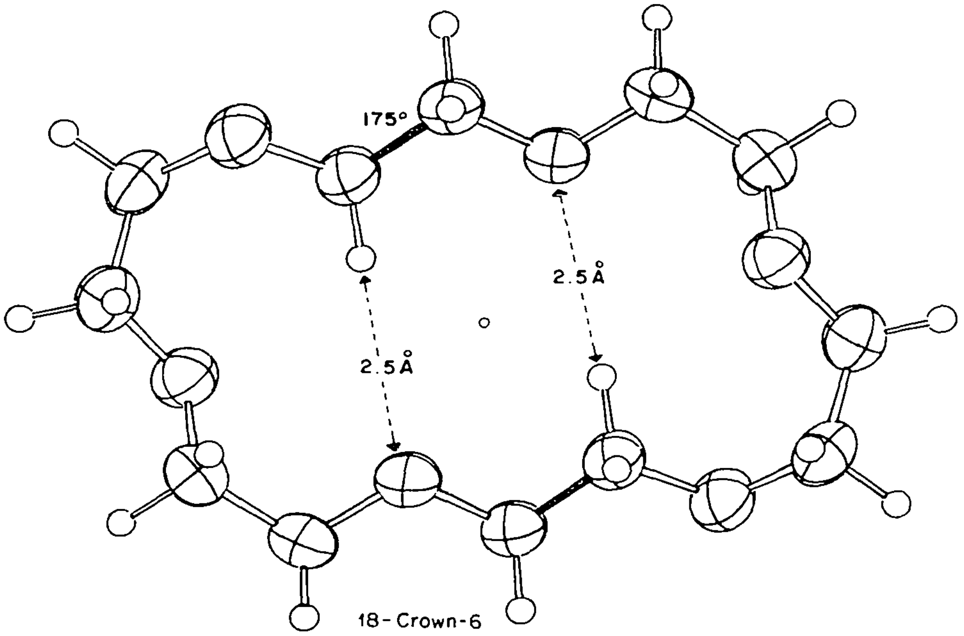


FIGURE 3. View of the conformation adopted by the uncomplexed 18-crown-6 hexaether[66].

report conformational analyses of ethers consisting of CH_2CH_2O units by spectroscopy; a *gauche* conformation was found to be 0.3–0.5 kcal/mol more stable than a *trans* form for a CH_2—CH_2 bond[76], whereas the *trans* form is 1.1 kcal/mol more stable than a *gauche* form for a CH_2—O bond[77]. The latter trend was interpreted in terms of a stabilizing interaction between the oxygen lone-pair orbitals and the nearest hydrogen atom of a methylene group. Indeed, the chemical shifts and vicinal coupling constants observed in n.m.r. spectrum of several cyclic ethers and their cation complexes indicated that the OCH_2CH_2O fragments have the same *gauche* structure in a number of solvents; in a solution there is a rapid interconversion between the *anti-* and *syn-gauche* rotamers[78]. The most recent Raman and infrared spectral observations, combined with the normal coordinate calculation, suggested that the stable form of 2,5-dioxahexane is that with a *trans* arrangement about the CO—CC axis and a *gauche* arrangement about the OC—CO axis[79]. Finally, potential functions for bending of some six-membered oxane rings were determined from vibrational spectra by Pickett and Strauss[25]. On the assumption that the methylene groups are constrained to move as units with constant geometry, the calculated torsional barriers for the OCCO and COCC fragments were 3.45 and 2.02 kcal/mol respectively. The general conclusion that the monomeric unit —O—CH_2—CH_2—O— has the preferred *trans–gauche–trans* conformation is consistent with XD measurements.

The structures of 18-crown-6 discussed above provide an excellent example of the most common features of conformation occurring in macrocyclic polyether species[80] (see below). Regular, energetically optimal, geometries corresponding closely to *syn*-clinal torsion angles about the C—C bonds and

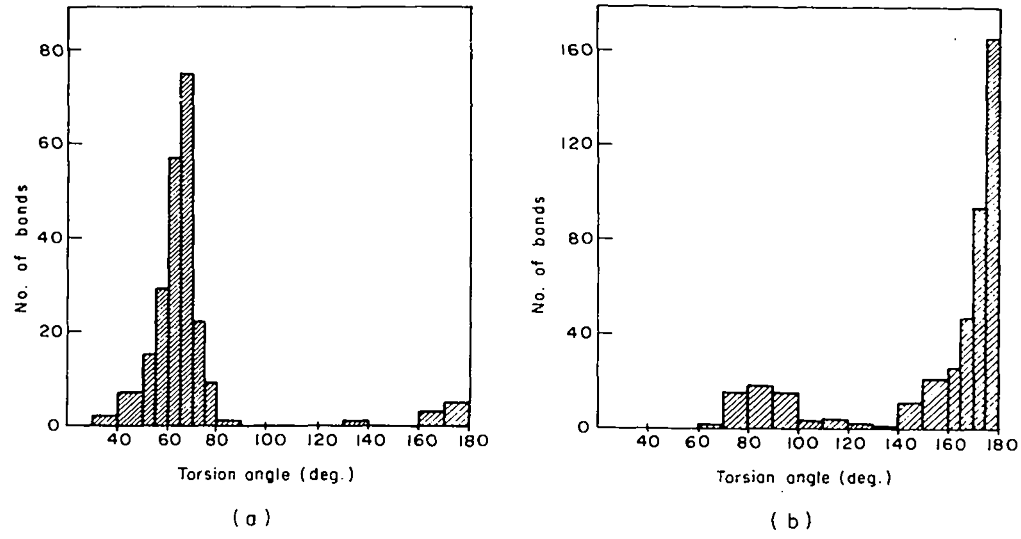


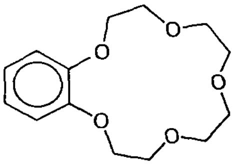
FIGURE 4. Histograms showing the characteristic distribution of (a) O—C—C—O and (b) C—O—C—C torsion angles in macrocyclic polyethers; they are based on data found in about 40 independent structure determinations[80].

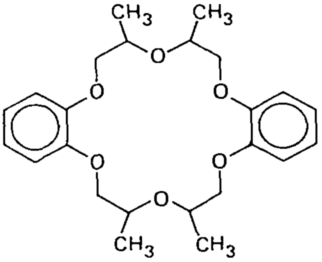
antiplanar torsion angles about the C—O bonds are attained for most of the conformational parameters in these macrorings. Irregular geometries containing an antiplanar arrangement of the O—CH_2—CH_2—O group, associated with the formation of transannular C—H···O contacts, have been found in several crystal structures of 'empty' ligands. In the various complexes, and particularly in those involving substrates too small to fit into the ligand cavity, conformational changes about the C—O bonds from antiplanar to *syn*-clinal arrangements occur more frequently; their apparent function is to optimize the specific interactions bonding the host to the guest species. Finally, crown ether macrocycles lacking a sufficiently extended pattern of stabilizing interactions of specific nature tend to be partially disordered in the crystal phase even at low temperatures. In such case the average conformation of the disordered fragment of the molecule is often characterized by torsion angles having magnitudes intermediate between *gauche* and *trans* geometries. It is of interest to note in this context that a survey of the structural details available from the work so far published on crown ethers suggests that the crystal forces acting on the ligands or on their complexes in the various structures usually have a minor effect on the molecular geometry. The above described stereochemical aspects of polyether macrocycles are illustrated by histograms in Figure 4 which were compiled from structural data of about 40 different polyether moities. A few of them will be described in more detail in the following section. The observed properties of the conformation support the view that the complexing capability of the crown ethers can in part be attributed to tendency of the $\leftarrow CH_2—CH_2—O \rightarrow$ units to assume an unstrained *gauche–trans* structure, and to the fact that only a limited number of degrees of freedom is usually involved in the conformational changes associated with the complex formation. Furthermore, host–guest complexes are expected to have a more stable conformation the more thoroughly filled are the macrocyclic cavities.

B. Structural Examples of Host—Guest Complexes with Crown Ethers

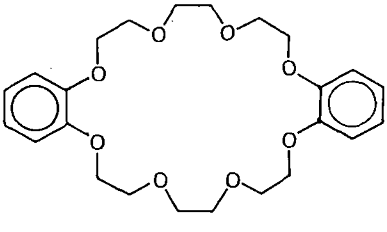
Representative examples of two different types of host–guest compounds are being discussed in this section. The first concerns complex formation between macrocyclic polyethers and metal cations, which is stabilized mainly by ion–dipole interactions; hitherto, no indications for *enantiomer* selectivity of chiral crown compounds with alkali and alkaline earth salts have been reported. The second involves crown ether complexes with organic guest moieties where hydrogen bonding is the main contributor to the intermolecular attraction. Chiral recognition properties of polyether macrocycles, containing steric barriers in the form of bulky rigid substituents, towards primary amine salts have been extensively investigated in the recent years[81].

Benzo-15-crown-5 (**41**) was found to form crystalline complexes with hydrated sodium iodide[82], potassium iodide[83], solvated calcium thiocyanate[84] and calcium 3,5-dinitrobenzoate trihydrate[85]. Apparently, the structural relationships between Na^+ and the 15-crown-5 derivative are more favourable than those in the 18-crown-6 complex. The 15-membered ring roughly preserves its crown conformation, the guest cation lying 0.75 Å above the mean plane of the pentagonal cavity of oxygen atoms. The Na···O(ring) distances, which range from 2.35 to 2.43 Å, are significantly shorter than the corresponding contacts in the sodium thiocyanate complex of 18-crown-6 (2.45–2.62 Å). In both structures the Na^+ is also coordinated to a water molecule at about 2.3 Å; as a result it is surrounded either by a pentagonal piramide or a pentagonal bipiramide of ligating sites. Potassium iodide forms a 1 : 2 adduct with the cyclic polyether. The potassium ion is located between two centrosymmetrically related host molecules, and consequently coordinated to the ten ether oxygens (Figure 5). It deviates 1.67 Å from each mean plane of the two enclosing ligand cavities as compared with 0.75 Å for Na^+ in the sodium iodide complex of **41**. This is consistent with the fact that the ionic radius of K^+ (1.33 Å) is considerably larger than that of Na^+ (0.95 Å). All K···O(ring) distances are within the range of 2.78–2.95 Å, and the iodide anions do not seem to affect the


(41)



(42)


(43)

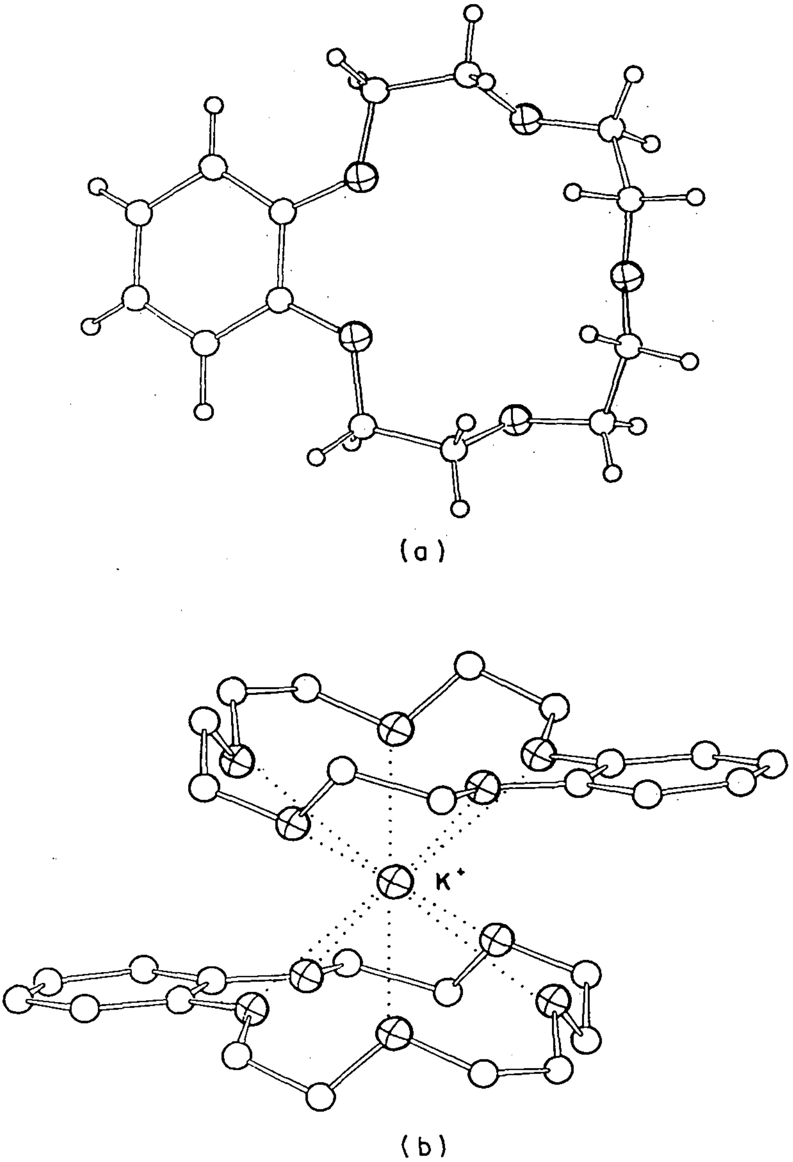


FIGURE 5. The structures of (a) benzo-15-crown-5[86] and (b) its complex with potassium cation[83].

configuration of the complexed entities. In the complex of benzo-15-crown-5 with $Ca(NCS)_2 \cdot CH_3OH$ and $Ca(NCS)_2 \cdot H_2O$ the metal cation interacts with the five ether oxygen atoms on one side and two isothiocyanate nitrogen atoms and an oxygen from the solvent on the other side[84]. In the crystalline complex of 41 with calcium dinitrobenzoate the guest ion is coordinated to the pentaether ring and four benzoate oxygen atoms[85]. The deviation of Ca^{2+} from the cross-section of the macroring cavity (1.23–1.38 Å), and its separation from the interacting oxygen sites (⩾2.52 Å) are intermediate between those observed in the sodium and potassium adducts. Cradwick and Poonia[85] rationalized the presence of direct cation–anion interactions in the complexes of calcium by the small size combined with relatively high charge density of the Ca^{2+} ion. However, similar associations have also been observed in a few structures with larger monovalent cations. Since, obviously, the mode of interaction between metal salts and crown hosts in the crystal phase depends on many factors, it seems difficult to predict for a particular structure whether the guest species will be completely enclosed within crown ether cavities or if it will directly coordinate with counterions as well.

The molecular structure of uncomplexed **41** was most recently investigated by Hanson at −150°C with the aid of photographically collected data[86]. The conformation of the free ligand was found to be somewhat different from any of the complexed structures. In the absence of an interacting substrate the pentagon defined by the oxygen atoms is contracted along the principal molecular axis (via deformation of two torsion angles about C—O bonds which assumed values of 81 and 85°) in order to reduce the empty space within the macroring (Figure 5). Moreover, even at the low temperature several atoms in the peripheral part of the ring have relatively large mean-square amplitudes of vibration and are possibly disordered.

Considerable changes in molecular conformation of the tetramethyldibenzo-18-crown-6 host (42) were observed to occur on complex formation with alkali metal salts. In the crystal of uncomplexed 42 the hexagon defined by the ether oxygen atoms is expanded along two diagonals and contracted along the third giving rise to an elliptical arrangement of the heteroatoms[87]. Since two of the methyl substituents are turned toward the centre of the molecule, it seems likely that the observed conformation is stabilized by transannular van der Waals interactions (Figure 6). Two out of the five configurational isomers of 42 were found to form two different crystalline complexes with caesium thiocyanate in which the ligand conformation is more regular, all C—O bonds being nearly *trans* and the C—C bonds *gauche*[88]. The isomer which has methyl groups configuration *cis, anti, cis* forms a 1 : 1 complex with CsNCS. The Cs ion lies 1.71 Å out of the mean oxygen plane, and is coordinated to the thiocyanate anions as 3.19 and 3.25 Å in addition to the six ether oxygens at 3.07–3.34 Å. The crystal structure is composed of centrosymmetrically related dimeric units of the complex (Figure 6). The ligand molecules with *trans, anti, trans* configuration of the methyl groups form 2 : 1 complex with CsNCS. As in the potassium iodide complex of **41**, the Cs^+ guest ion is completely surrounded by two hosts. All twelve Cs···O contacts again vary from 3.12 to 3.36 Å, this range being similar to that in the CsNCS complex with 18-crown-6.

Another interesting crown system is that of dibenzo-24-crown-8 (43)[89]. This macrocycle is large enough to complex simultaneously two small guest ions, as in its complexes with two molecules of sodium nitrophenolate[90] or potassium isothiocyanate[91]. Coordination modes of Na^+ and K^+ in the two crystal structures (Figure 7) are characterized by the following features. In the complex of KNCS the ligating ether oxygen atoms are almost coplanar. Each K^+ ion interacts with only five oxygens (at 2.73–2.98 Å), two of the bonding sites being shared between the two interacting cations. The potassium atoms lie 0.66 Å from each side of the cavity, and are in contact with the thiocyanate moieties. Somewhat different steric relationships were observed in the structure with sodium-nitrophenolate. The ligand molecule is folded around the two smaller Na^+ ions, each of them coordinating three ether oxygens (at 2.47–2.62 Å). The nitro group and the phenolate oxygen

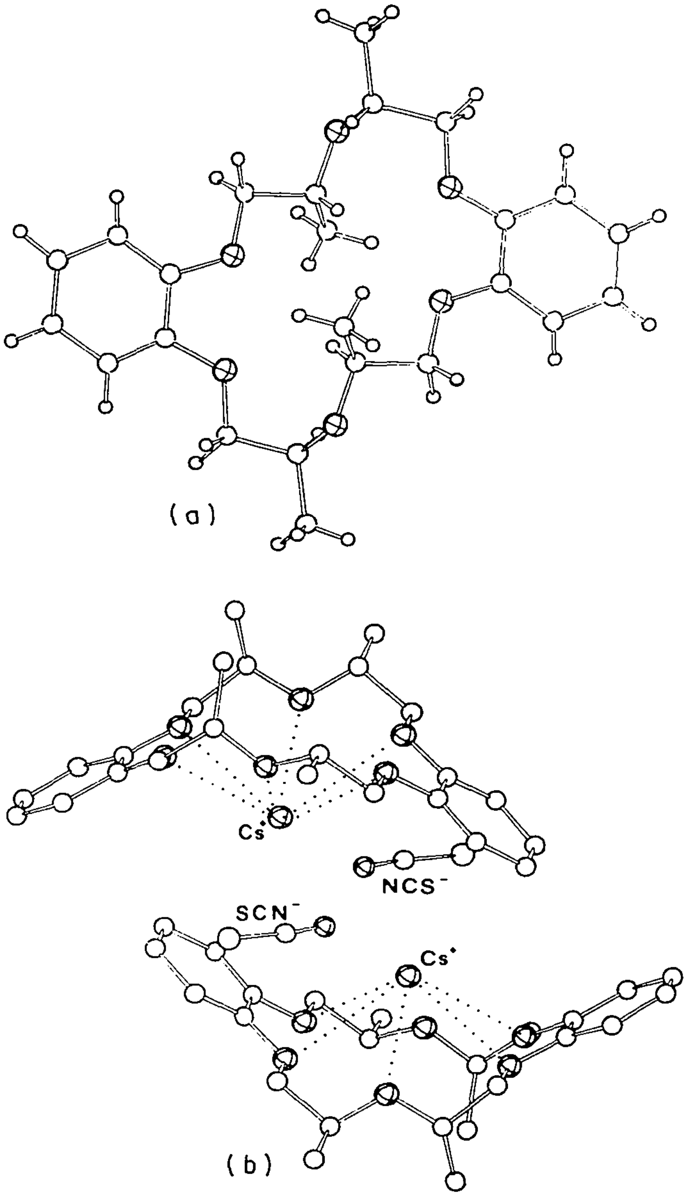


FIGURE 6. The structures of (a) one isomeric form of tetramethyldibenzo-18-crown-6[87] and (b) its complex with caesium thiocyanate salt[88]. Two centrosymmetrically related entities of the complex are shown.

atoms of chelating anions are included in the sphere of interaction around each cation. A small section of the macroring is not involved in direct coordination of the guest species, and has a partially disordered conformation. Host 43 also forms stable complexes of 1 : 1 stoichiometry with alkaline earth metal salts; reported

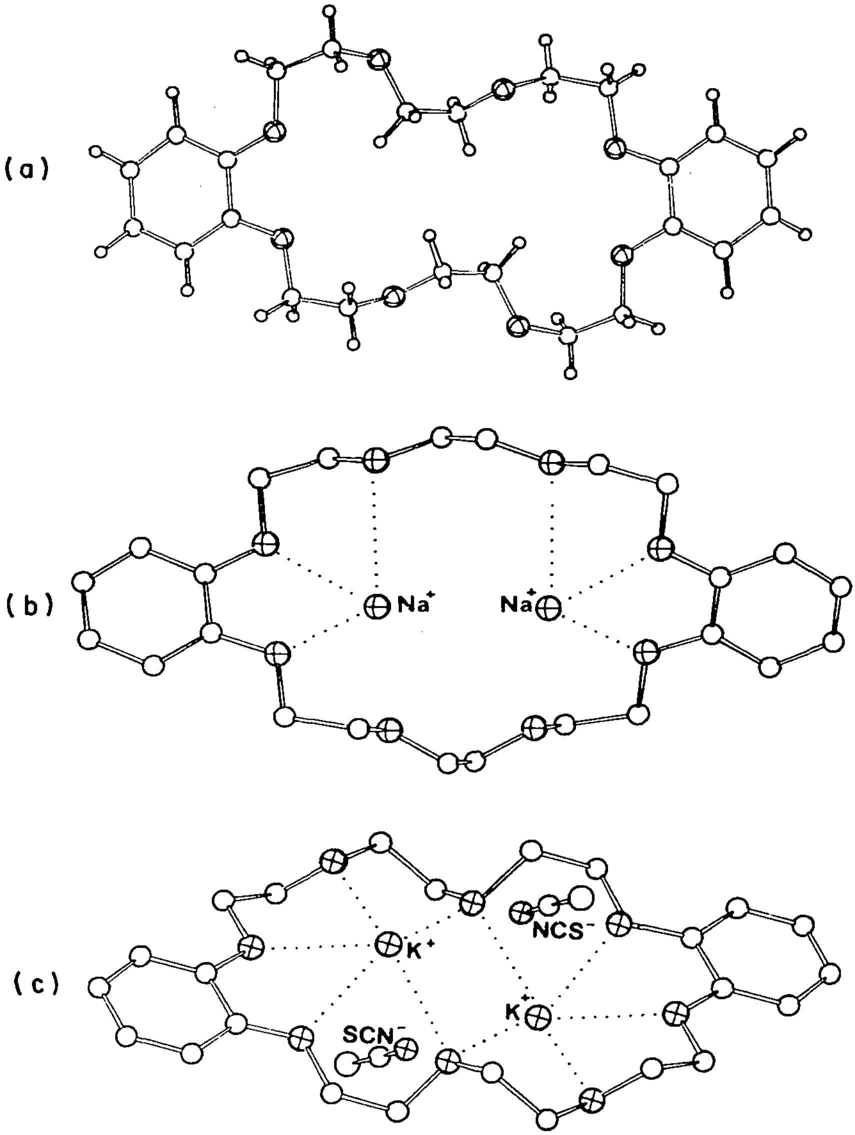
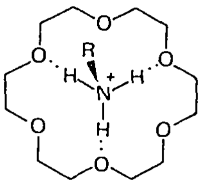


FIGURE 7. (a) Molecular conformation of dibenzo-24-crown-8[89]; (b) interaction of two Na^+ ions with this ligand[90]; (c) view of the complex with two molecules of potassium isothiocyanate[91].

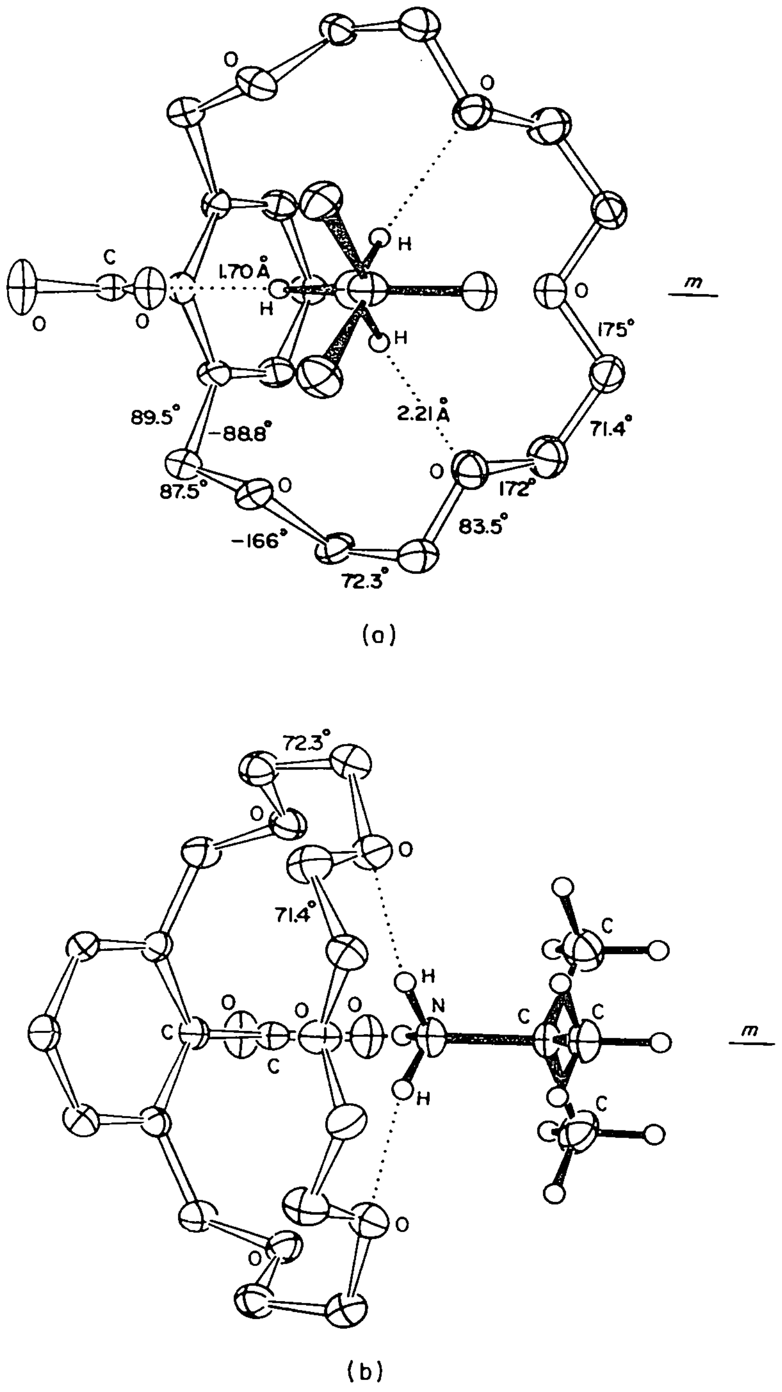
examples involve adducts with barium perchlorate[92] and barium picrate[93]. As in other 1 : 1 compounds involving metal guest species, the Ba^{++} cation interacts both with the macrocyclic ligand and the counterions and solvent molecules. Characteristic distances between barium and ligating oxygen atoms range from 2.7 to 3.1 Å. Some details of the molecular conformation of 43 in the five structures referred to above are considerably different.

Many effective syntheses of hydrogen-bonded complexes of alkylammonium ions and cyclic polyethers have been developed in recent years, with the host and guest species being subjected to a wide range of structural modifications[62,94]. An idealized scheme of the intermolecular association involving crown hexaethers suggests NH···O hydrogen bonding between the three acidic hydrogens of the NH_3^+ group and three alternate oxygens of the macroring, and direct polar N···O interactions in between the hydrogen bonds with the remaining ring-oxygen atoms (**44**). In sterically undistorted structures, as that of 18-crown-6 with NH_4Br[68], the ammonium ion is usually centred and tightly fitted within the hydrophilic macrocyclic cavity. The characteristic geometrical parameters of this interaction include N^+···O distances ranging from 2.9 to 3.1 Å, H···O distances from 1.9 to 2.1 Å and nearly linear NH···O bonds. Theoretical calculations on simple model systems (e.g. NH_4^+ with $(OCH_3)_2$) indicated that the energy of the hydrogen-bonding interaction is about three times that of the direct electrostatic interaction[95].



(**44**)

The first crystal structure of an alkylammonium crown ether adduct described in the literature is that of 2,6-dimethylylbenzoic acid-18-crown-5 with *t*-butylamine[96]. The 1 : 1 salt was analysed at 120 K, and its geometry is depicted in Figure 8. The host molecule contains a polar functional substituent which is directed towards the polyether cavity, and (after proton transfer) acts also as an internal counterion for the ionic guest. The complex is held together by hydrogen-bonding and ion-pairing interactions. Although the 18-membered ring contains only five oxygen atoms that are available for binding the guest ion, the ligand adopted a conformation in which a symmetric hexagonal cavity is formed with one of the carboxylate oxygen atoms. The carboxylate and ammonium moieties that ion-pair are on the same side of the macroring. The resulting coordination around the $-NH_3^+$ group in this structure includes, therefore, one very short (1.70 Å) NH^+···O^- and two longer (2.21 Å) NH^+···O(ring) hydrogen bonds in a tripod arrangement, the *t*-Bu—N bond being nearly perpendicular to the mean plane of the six ligating oxygens. (The second carboxylate oxygen atom takes part in lateral CH···O^- interactions that connect adjacent adduct entities related by a glide plane symmetry.) The observed geometry of the host–guest complex is characterized by a very high organization, and it has a higher degree of symmetry (the molecular units are situated on crystallographic mirror planes) than the constituents in their stable form. Correspondingly, the molecular structure of the uncomplexed ligand (Figure 9)[97] is different from that found in the complex with *t*-butylamine. The skeleton of 2,6-dimethylylbenzoic acid-18-crown-5 exhibits only approximate C_2 symmetry with the carboxyl group rigidly located in the centre of the ether ring. The overall conformation is uniquely stabilized by internal transannular hydrogen bonding and attractive dipole–dipole O(ring)···C=O interactions. In the complexed as well as uncomplexed ligand structures all ether oxygen atoms turn inward, the methylene atoms turn outward, and the OCH_2CH_2O fragments have *gauche* conformations.


O
O
C
1.70 Å
H
H
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C
O
O
m
175°
89.5°
−88.8°
2.21 Å
71.4°
87.5°
O
O
172°
83.5°
−166°
72.3°
(a)
72.3°
O
O
71.4°
H
C
O
O
O
N
C
C
C
C
C
m
H
C
C
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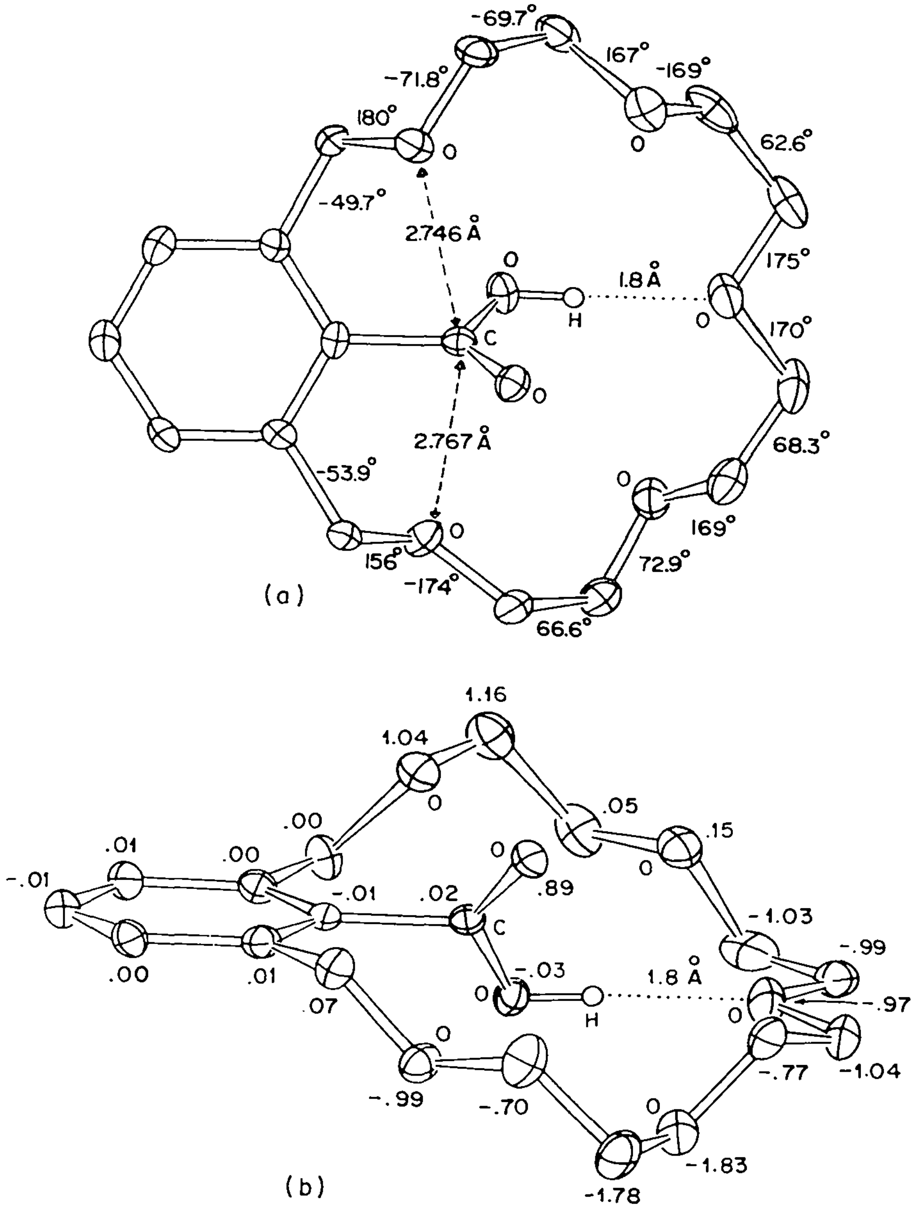
O
(b)

FIGURE 8. Two views of the molecular complex of 2,6-dimethylylbenzoic acid-18-crown-5 with *t*-butylamine[96].


-69.7°
-71.8°
167°
-169°
180°
O
O
62.6°
-49.7°
2.746 Å
O
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H
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170°
C
O
2.767 Å
68.3°
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O
169°
156°
-174°
72.9°
(a)
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O
-.01
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.89
-1.03
C
-.99
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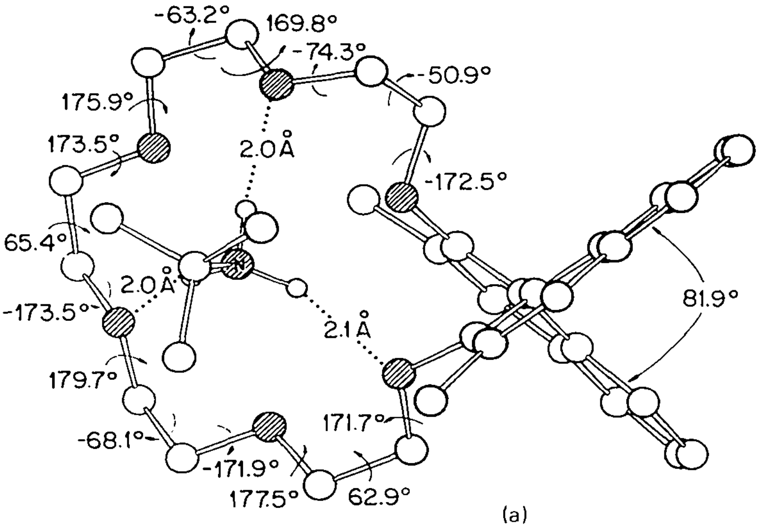
1.8 Å
O
.07
O
H
O
-.97
-.99
-.70
O
-.77
-1.04
-1.83
(b)
-1.78

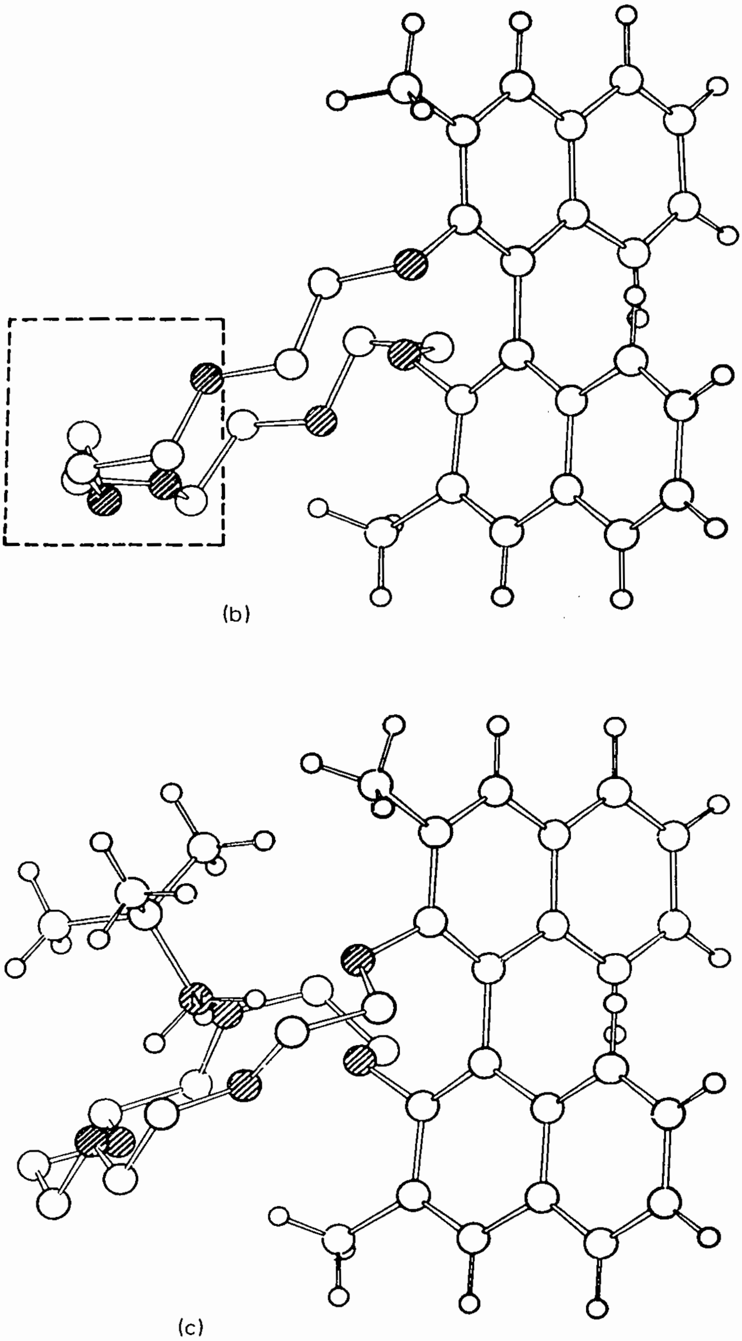
FIGURE 9. Two views of the molecular structure of uncomplexed 2,6-dimethylyl-benzoic acid-18-crown-5[97].

In the course of the author's investigation into the structural chemistry of crown compounds a hexaether system containing a 2,2′-substituted 3,3′-dimethyl-1,1′-dinaphthyl unit and its 1 : 1 inclusion complex with *t*-butylammonium perchlorate have recently been characterized by low-temperature X-ray analysis (Figure 10)[98]. Conformational properties of the macrocycle and the geometry of its binding to *t*-BuNH$_3^+$ are generally similar to those already described earlier in this article. The observed host–guest association is mainly due to complexation through a tripod arrangement of NH$^+$···O hydrogen bonds on one face of the macrocyclic cavity. The C—NH$_3^+$ bond is perpendicular to the complexation site of the crown, the ammonium hydrogen atoms being donated to three alternate ether oxygens in a favourable geometry. Furthermore, the structural data suggest that three donor oxygen atoms are involved in direct pole–dipole interactions with the substrate, one of their lone-pair orbitals pointing almost directly at the electrophilic N$^+$. Apparently, the spatial relationship between the host and the guest is free from severe steric constraints, which allows an undistorted complementary arrangement of the binding sites. The overall conformations of the complexed and uncomplexed ligand molecules are very similar, the macroring forming an angle of about 40° with the 1,1′-dinaphthyl bond. Consequently, one of the methyl substituents covers and directly interacts with one face of the cavity. This may lead to an interesting conclusion, that even in solution the two sides of the macrocycle are not necessarily equivalent with respect to complexation of guest species. The complexed host exists in an ordered and regular conformation with all oxygens turned inward, and with characteristic *syn*-clinal and antiplanar (with a single exception) torsion angles about the C—C and C—O bonds respectively. The conformation of one part of the uncomplexed molecule is disordered, and therefore exhibits (on the average) an irregular pattern of torsion angles. The remaining fragment of the ring is stabilized by an intramolecular CH···O attraction and has one OCH_2CH_2O group in an antiplanar arrangement.

Synthetic compounds containing more than a single macroring assembly of binding sites are of particular interest since they can act as potential hosts for a variety of bifunctional guest moieties such as dihydroxyphenylalanine, lysine, etc. A model system of this type consists of a chiral ligand, containing two 18-crown-6 rings connected by a 2,3- and 2′,3′-substituted 1,1′-dinaphthyl unit, that interacts with the bis(hexafluorophosphate) salt of tetramethylene diamine[99]. Evidently, the organic host complexed simultaneously the hydrogen-bonding parts of the guest, the two crown rings being thus held in a convergent relationship (Figure 11). The



(a)


(b)

(c)

FIGURE 10. A host–guest complex between a 1,1′-dinaphthyl-20-crown-6 ligand and a *t*-butylammonium ion (a). The overall conformations of the uncomplexed and complexed ligand are shown in (b) and (c) respectively[98]. The marked frame encloses the conformationally disordered part of the uncomplexed molecule.

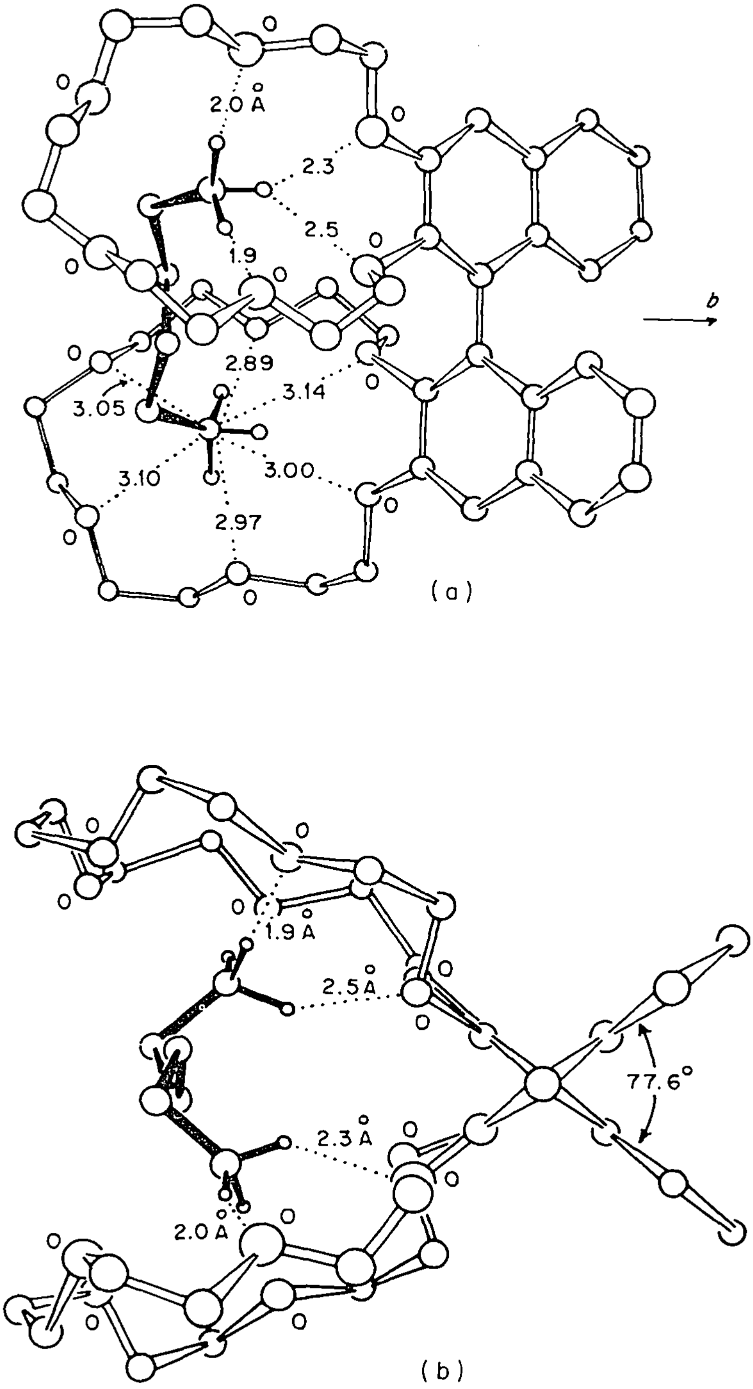
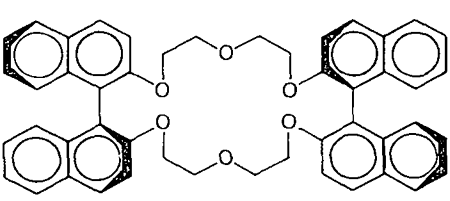

O
2.0 Å
2.3
2.5
1.9
O
2.89
3.14
3.05
3.10
3.00
2.97
O
(a)
b
O
1.9 Å
2.5 Å
O
77.6°
2.3 Å
O
2.0 Å
O
(b)

FIGURE 11. An illustration of a host–guest organic crown complex containing two assemblies of binding sites[99].

ammonium groups centre into the hydrophilic cavities, and the tetramethylene chain is strung between the two macrorings. The overall shape of this structure and the geometry of host-to-guest interaction are influenced by the relatively short dimension of the $(CH_2)_4$ bridge. Thus, in the observed conformation the dihedral angle between the planes of the naphthalene rings attached to one another is 77.6°; in the uncomplexed and isolated molecule of the host the dihedral angle can vary between extremes of about 60 to 120°. Moreover, the peripheral region of the 18-crown-6 unit is not directly involved in the hydrogen bonding, and its framework deviates significantly from the D_{3d} conformation. Nevertheless, the molecular dimensions of the crown ring preserve the characteristic features usually observed in structures of poly(ethylene oxide) compounds. It should be pointed out that the PF_6 counterions which fill the intercomplex cavities in the crystal structure seem to have little effect on the geometry of interaction between the host and the guest. Since the space group of these crystals is centrosymmetric, the two enantiomers of the complex were not resolved upon crystallization.

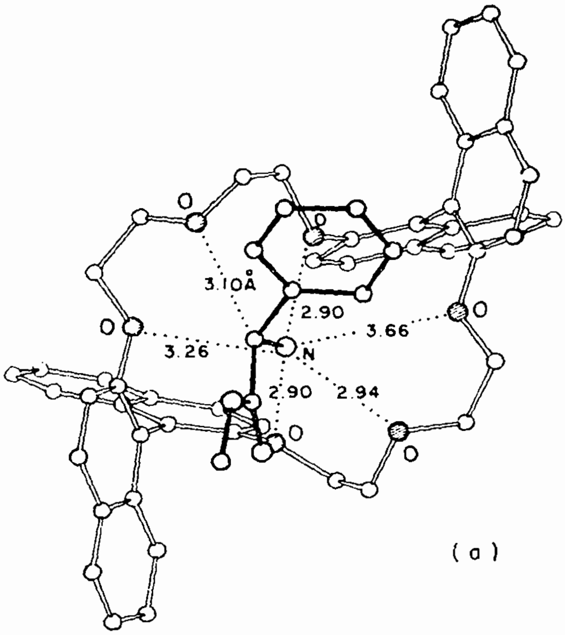
Chiral recognition in molecular complexation between multiheteromacrocycles containing 1,1′-dinaphthyl units as steric and chiral barriers and primary amine salts has been reported by Cram and coworkers[81], and to a lesser extent by other research groups. Suitably designed diastereomeric complexes were found to differ in their free energy of formation in solution by as much as 2 kcal/mol; consequently, a complete optical resolution of racemates of primary amine salts could be achieved[100,101]. From the structural point of view, the complexation stability of a given ligand–substrate system is closely related to the nature and geometrical details of the binding interactions, while stereoselectivity in the complex formation is associated with the degree of complementary structural relationships between the intervening species. The chemistry of ligands containing two chiral 1,1′-dinaphthyl units separated by a central macrocyclic binding site and bound to ether oxygen in their 2,2′-positions is particularly well known[81]. These compounds contain six hexagonally arranged and inward-turning oxygens positioned to hydrogen-bond the ammonium group of a potential guest. Unfortunately, to date it has been possible to crystallize very few diastereomeric complexes of this kind, and to our knowledge accurate structural results are available only for a single optically pure model compound[102]. A similar study was carried out on optical resolution of asymmetric amines by preferential crystallization of their complexes with the *naturally* occurring lasalocid antibiotic[103].

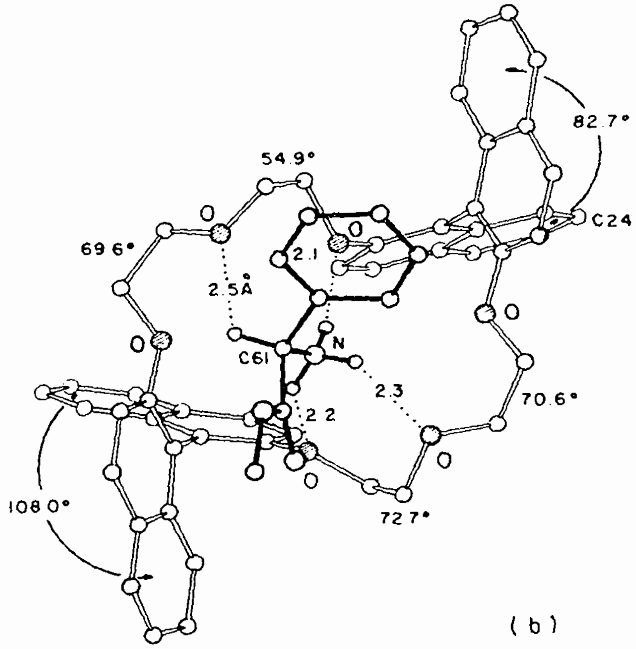
Figure 12 describes the structure of a complex between chiral (*S*,*S*)-host-45 and the hexafluorophosphate salt of (*R*)-phenylglycine methyl ester as determined by XD at −160°C[102]. From the two diastereomeric complexes resolved in solution,

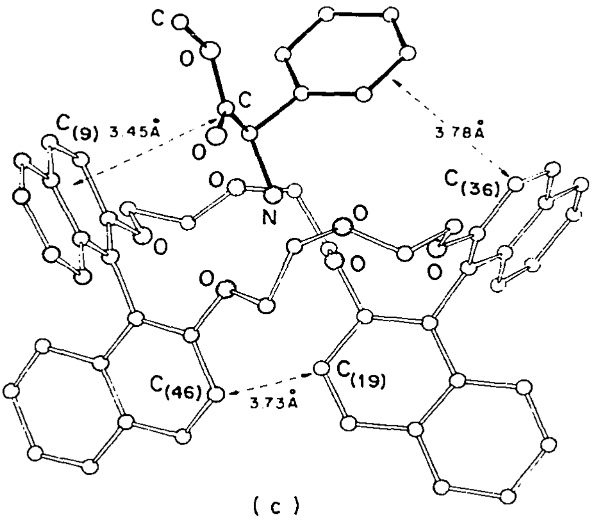


(45)

this structure corresponds to the less stable isomer. The observed attraction of an organic host to an organic guest via specific interaction of the NH_3^+ ion with the polyether cavity is similar, in general terms, to that described for other inclusion compounds. On an idealized molecular model of the ligand the rigid naphthyl


O
O
3.10Å
2.90
O
3.26
N
3.66
O
2.90
2.94
O
O
(a)


82.7°
54.9°
O
O
C24
69.6°
2.1
2.5Å
O
O
N
C61
2.3
70.6°
2.2
O
O
108.0°
72.7°
(b)



(c)

FIGURE 12. An illustration of the main attractive and repulsive interactions within the inclusion compound of phenylglycine methyl ester with a chiral ligand[102].

groups divide the space around the macroring into four equivalent cavities, two below and two above the ring. In actual structure, the host–guest interaction is confined to one face of the ligand. The three substituents attached to the asymmetric centre of the guest phenylglycine derivative are arranged in such a way that the large phenyl group and the small hydrogen atom are located in one cavity, while the medium ester group resides in the other site (Figure 12). In the more stable (*S*,*S*)–(*S*) diastereomer, these substituents are expected to be arranged more favourably with respect to the steric barriers of the ligand. It appears that the accommodation of the α-amino ester within the host requires some conformational adjustments and a partial reorganization of the ligand binding sites. This is reflected, for example, in the following structural features. The NH···O hydrogen bonds are far from linear, the nitrogen atom is in close contact with only three of the six ether oxygen atoms, and the naphthalene substituents on the interacting side of the ring are pushed away from each other. However, as in the former example, the PF_6 counterions appear to play no role in structuring the host–guest adduct. The complex crystallizes with 1 mol of chloroform solvent, and the charge separation in this structure is stabilized by delocalization of the negative charge in the relatively large anions as well as by their hydrogen bonding to chloroform. In spite of the fact that reliable structural data on the more stable diastereomer of this compound were not available, correlation of the crystallographic results with solution studies on chiral recognition led to some interesting interpretations. One striking example refers to a higher chiral recognition towards phenylglycine methyl ester observed when the bisdinaphthyl hexaether ligand was modified by introduction of two methyl groups in the 3-positions of one dinaphthyl unit (in Figure 12 this corresponds to $-CH_3$ substitutions on atoms $C_{(9)}$ and $C_{(46)}$ or $C_{(19)}$ and $C_{(36)}$)[100]. On the assumption that the overall structure of the corresponding compound is similar to that shown in Figure 12, the methyl substituents apparently increase the steric hindrance between the host and the guest as well as between the naphthalene rings on the noninteracting side of the cavity. The stronger repulsive interactions thus contribute to further destabilization of the less stable diastereomer of the modified system. Opposite reasoning could be applied to account (in part) for the decrease of stereoselectivity in complexation of smaller amino esters by the bisdinaphthyl polyether hosts.

C. Inclusion Compounds of Noncyclic Polyethers

A synthesis of noncyclic crown-type polyethers containing quinoline functions attached to terminal oxygens has recently been reported by Vögtle and his co-workers[104,105]. The open-chain polyether compounds were found to exhibit strong complexing properties as the crown ethers, forming stoichiometric crystalline adducts with a variety of alkali, alkaline earth and ammonium salts. Figure 13 illustrates the structure of a 1 : 1 complex between the heptadentate 1,11-bis(8-quinolyloxy)-3,6,9-trioxaundecane species and RbI[106]. The crystallographic analysis showed that the Rb^+ ion strongly interacts with all seven donor heteroatoms at characteristic distances between 2.9 and 3.1 Å. The host species is wrapped around the cation in a conformation resembling one turn of a helix, the conformational details being quite similar with those observed in the macrocyclic ethers; i.e. *gauche* torsion angles about all C—C bonds that vary from 59° to 69° and *trans* torsion angles about all but one C—O bonds. The iodine ions are located in spaces between molecules of the complex. Observations from u.v. spectra indicate that the molecular conformation of the ligand itself changes considerably upon inclusion complex formation with a magnesium salt[104]. Reportedly, further work is now in progress to investigate the conformational properties of complexes with longer-chain hosts; such compounds may form helices with more than one turn.

In correlation, a few earlier studies of ethylene oxide oligomers showed that a polyethylene oxide chain adopts a helical structure in the crystalline state[107]. Approximately the same conformation was found to represent the lowest energy form of the polymer in solution where the compound is probably an equilibrium mixture of conformers. Moreover, oligomers of oxyethylene seem to have a specific property of interaction with some alkali and heavy metal salts and ions. A detailed XD structural study of molecular complexes of tetraethylene glycol di-

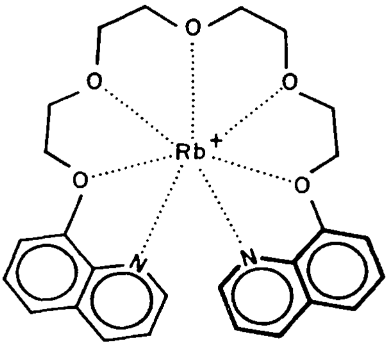


FIGURE 13. The complex of 1,11-bis(8-quinolyloxy)-3,6,9-trioxaundecane with RbI[106].

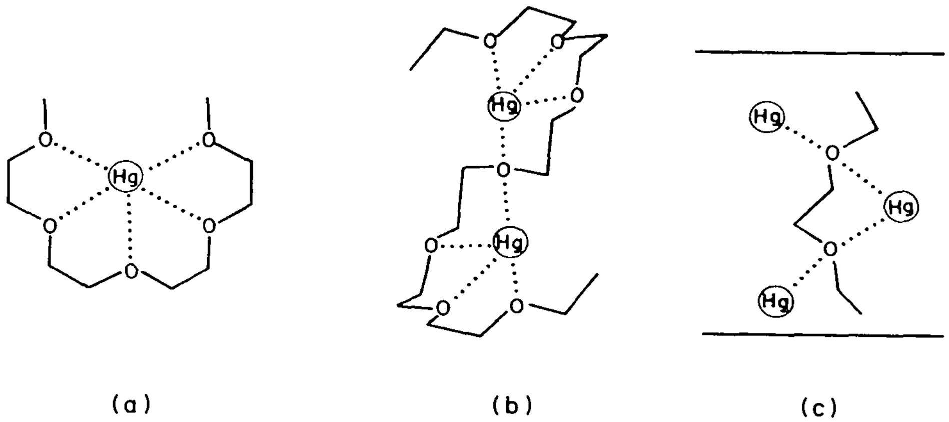


FIGURE 14. Modes of the interaction between the oxygen and mercury atoms in complexes of tetraethylene glycol dimethyl ether (a), hexaethylene glycol diethyl ether (b) and polyethylene oxide (c) with $HgCl_2$[108].

methyl and diethyl ethers and hexaethylene glycol diethyl ether with $HgCl_2$ and $CdCl_2$ have recently been carried out by Iwamoto and coworkers; less precise structural data are available for adducts between $HgCl_2$ and a polymer of oxyethylene[108,109]. In the complexes of tetraethylene glycol ethers with mercuric chloride the chain molecule exhibits a nearly circular conformation. The five ether oxygen atoms are nearly coplanar and turned inward to coordinate efficiently the mercury atom at distances between 2.8 and 3.0 Å. The larger ligand, hexaethylene glycol diethyl ether, was found to interact with two moles of $HgCl_2$. Three oxygens of either half of the molecule are coordinated with one mercury atom, the central oxygen being coordinated simultaneously to the two guest atoms. Interatomic distances between mercury and ligating oxygen are within 2.7–2.9 Å. Interestingly, the resulting molecular structure resembles a helix with two turns. The observed coordination modes between the oxygen and mercury atoms in the inclusion complexes are shown schematically in Figure 14[108]. The overall shape of the complex of tetraethylene glycol dimethyl ether and ionic $CdCl_2$ is different from that of covalent $HgCl_2$. The ligand is coordinated to two cadmium atoms and has an extended rather than a convergent conformation; the difference between the molecular conformations is probably due to the different coordination radii of Cd and Hg atoms. Relevant interaction distances are 2.4–2.5 Å for the Cd···O and 2.4–2.7 Å for the Cd···Cl contacts. The crystal structure consists of paired adduct entities that are linked to each other through Cl bridges[109]

In summary, the observed features of molecular conformation in the noncyclic oligomers are very consistent with the general characteristics of cyclic $(-CH_2CH_2O-)_n$ species reviewed in this article.

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Note Added in Proof

An interesting structural study on the 1 : 1 complex of monopyrido-18-crown-6 with *t*-butylammonium perchlorate has recently been published[110]. The host–guest association in this compound was found to be stabilized mainly by a tripod arrangement of hydrogen bonds between the alkylammonium ion and two oxygen atoms and the pyridine nitrogen atom in the crown ether ring. Interaction of the other three ether oxygen atoms with the ammonium nitrogen is less important. The results of the crystallographic study of cation complexes formed by long noncyclic polyethers have now appeared[111]. In the complex between 1,20-bis(8-quinolyloxy)-3,6,9,12,15,18-hexaoxaeicosane and RbI, the cation is spherically wrapped in the decadentate ligand with more than one turn. The 1 : 2 complex of 1,5-bis{2-[5-(2-nitrophenoxy)-3-oxapentyloxy]phenoxy}-3-oxapentane with KSCN has S-shaped arrangements, with one cation included in each S-loop of the polyether.

Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 5

Stereodynamics of alcohols, ethers, thio ethers and related compounds

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I. INTRODUCTION

There has been much research in recent years concerning the stereodynamics of acyclic and cyclic compounds containing oxygen and sulphur. Efforts have focused on determining conformational preferences, barriers to rotation about single bonds in acyclic systems, and barriers to ring stereomutation in heterocycles. Much of the recent progress in this area has been due to the rapid development of variable temperature or 'dynamic' nuclear magnetic resonance (DNMR) spectroscopy used in conjunction with complete theoretical DNMR line-shape analysis (Jackman and Cotton 1975). As a complement to these experimental studies, insight into molecular stereodynamics is also being gained from semiempirical molecular orbital calculations of energy as a function of molecular geometry. Chemical equilibration methods also continue to play a role in assessing conformational preferences in many ring systems.

The objective of this chapter is to summarize the salient stereodynamics of *acyclic* and *cyclic* systems containing oxygen and sulphur up to early 1978. We will focus on those ring systems which contain carbon and one or more of the *same* heteroatom. A discussion of cyclic systems containing more than one type of heteroatom, such as oxathiolanes and oxathianes, will be presented by Professor Pihlaja in another chapter of this volume. Due to restrictions on the length of this review, our approach will be illustrative and not exhaustive. We apologize for omitting much good research which might otherwise be included in a larger volume.

II. ACYCLIC SYSTEMS

A. Rotation about Bonds in Oxygen- and Sulphur-containing Compounds

In order to gain some insight into the stereodynamics of moderately large systems, it is instructive to examine pertinent conformational preferences and barriers to stereomutation in simple acyclic systems. However, it must be kept in mind that any extrapolation from acyclic to cyclic systems must be done with caution due to the possible significant intervention of *angle strain* in the stereodynamics of the cyclic molecules. However, with this in mind, it is useful to consider the rotational barriers in Table 1. All of the barriers compiled in Table 1 have been determined experimentally except those for hydrogen disulphide which were estimated using a theoretical approach.

For the first twelve compounds in Table 1, the energy surface for rotation may be assumed to have essentially *three-fold symmetry* analogous to ethane. For the peroxides and disulphides, the symmetry of the rotational energy surface is quite different and will be discussed below.

In perusing the data in Table 1, it is important to keep in mind the current state of understanding of the bond rotation processes in simple molecules. Although the barrier to rotation in ethane is well-established experimentally, an incisive theoretical description of the origins of the barrier remains elusive. Extended Hückel molecular orbital methods suggest that the energy increase in proceeding from staggered to eclipsed ethane arises mainly from a decrease in Mulliken p_π overlap populations associated with the *carbon–carbon bond* (Lowe 1973, 1974) while a frontier-orbital approach (Woodward and Hoffmann 1969) suggests that the origin of the barrier involves *repulsions between vicinal hydrogens*. A simple van der Waals' repulsion model accounts for only a small fraction of the barrier (Lowe 1973). Thus, the origin of the barrier to rotation in ethane appears to be a blend of van der Waals' repulsions and orbital-control considerations, but that blend is not yet quantitatively defined. In other theoretical studies, rotational barriers have been amenable to dissection into various energy components for simple molecules such as methanol and methylamine (Radom, Hehre and Pople 1972; see also Gordon and England 1973). Molecular mechanics or force field calculations have been successful in reproducing accurately various conformational and molecular parameters for alcohols and ethers (Allinger and Chung 1976) as well as alkanethiols and thia-

TABLE 1. Pertinent barriers to rotation in simple molecular systems

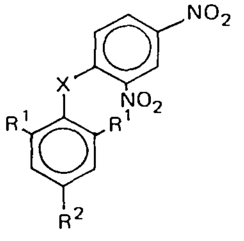
Compound	Barrier (kcal/mol)	Reference
CH_3CH_3	2.9	Kemp and Pitzer (1936), Weiss and Leroi (1968), Lowe (1973)
$CH_3CH_2CH_3$	3.3	Pitzer (1944)
CH_3OH	1.1	Ivash and Dennison (1953)
CH_3OCH_3	2.7	Blakis, Kasai and Meyers (1963)
CH_3SH	1.3	Kojima (1960)
CH_3SCH_3	2.1	Pierce and Hayashi (1961)
CH_3NH_2	2.0	Nishikawa, Itoh and Shimoda (1955)
CH_3NHCH_3	3.2	Wollrab and Laurie (1971)
$CH_3N(CH_3)_2$	4.4	Lide and Mann (1958a)
CH_3PH_2	2.0	Kojima, Breig and Lin (1961)
CH_3PHCH_3	2.2	Nelson (1963)
$CH_3P(CH_3)_2$	2.6	Lide and Mann (1958b)
H_2O_2 (*cis*-barrier)	7.0	Hunt, Leacock, Peters and Hecht (1965)
H_2O_2 (*trans* barrier)	1.1	
H_2S_2 (*cis* barrier)	9.3	Veillard and Demuynck (1970)
H_2S_2 (*trans* barrier)	6.0	

alkanes (Allinger and Hickey 1975). Recent Raman spectral studies of ethanol and ethanethiol (Durig, Bucy, Wurrey and Carreira 1975) as well as ethylamine (Durig and Li 1975) have provided valuable information regarding torsional motions and conformational preferences in these molecules.

A comparison of the barrier trends in Table 1 for molecules possessing the *same* heteroatom reveals an expected increase in the barrier to rotation about the carbon–heteroatom bond as steric crowding in the molecule increases (e.g. CH_3OH and CH_3OCH_3, CH_3SH and CH_3SCH_3, CH_3NH_2 and CH_3NHCH_3). These increases must be due in part to increasing van der Waals' repulsions in the transition state for rotation but one must not forget orbital-control considerations. A useful comparison can be made between the series of amines and phosphines in Table 1. In proceeding from CH_3NH_2 to CH_3NHCH_3 to $CH_3N(CH_3)_2$, a significant relative stepwise increase in the barrier to C—N rotation is observed. However, in the series CH_3PH_2, CH_3PHCH_3, $CH_3P(CH_3)_2$, the progressive increase in the barrier to methyl rotation is attenuated as compared to the amine series due most likely to smaller differential increases in nonbonded repulsions across the C—P bond due to the *longer* C—P bond (1.87 Å) as compared to the C—N bond (1.47 Å).

If the data in Table 1 were to be used to make predictions concerning the stereodynamics of *heterocyclic* systems (e.g. the rate of ring-reversal), selection of the *acyclic* models must be done with care. For example, if one were interested in comparing oxacyclohexane to cyclohexane, the appropriate acyclic models would be dimethyl ether and propane, *not* methanol and ethane. For thiacyclohexane versus cyclohexane, one would use dimethyl sulphide and propane, *not* methanethiol and ethane. However, in making such predictions regarding the relative stereodynamics of ring compounds, one must always be cognizant of a possible significantly greater role of *angle strain* in ring-reversal processes as compared to a simple rotation and care must be exercised in such an effort.

There have been very few reports of DNMR studies of restricted rotation about carbon–oxygen single bonds. In one instance, changes in the ^1H DNMR spectra of the diastereotopic isopropyl methyl groups of compound **1a** allowed a determination of the barrier to rotation about the phenyl–oxygen bond (equation 1; $\Delta G^{\ddagger} = 17.8$ kcal/mol at 57°C; Kessler, Rieker, and Rundel 1968). Similar symmetry characteristics allowed the determination of barriers to phenyl–sulphur rotation in **1b** ($\Delta G^{\ddagger} = 15.0$ kcal/mol at 12°C) and **1c** ($\Delta G^{\ddagger} = 15.1$ kcal/mol at 0°C). The faster rates of rotation in **1b** and **1c** as compared to **1a** are apparently a manifestation of a carbon–sulphur bond length (1.8 Å) which is longer than a carbon–oxygen bond (1.4 Å). In addition to the series **1**, ^1H DNMR evidence for restricted phenyl–sulphur rotation was obtained for **2a** ($\Delta G^{\ddagger} = 12.8$ kcal/mol at −27°C) and **2b** ($\Delta G^{\ddagger} = 11.7$ kcal/mol at −55°C; Kessler, Rieker and Rundel 1968).

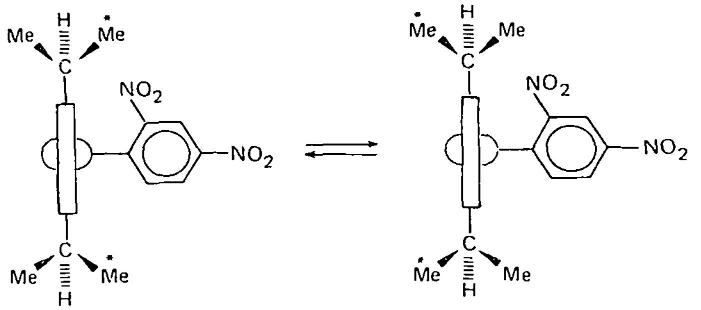


(a) X = O, R^1 = *i*-Pr, R^2 = H

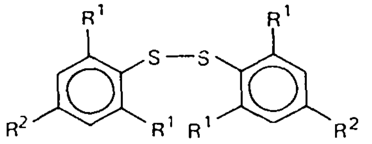
(b) X = S, R^1 = R^2 = *i*-Pr

(c) X = S, R^1 = Et, R^2 = H

(1)



(1)



(a) R^1 = R^2 = *i*-Pr

(b) R^1 = Et, R^2 = H

(2)

One recent elegant application of ^1H DNMR spectroscopy concerns chloromethyl methyl ether and restricted rotation about the chloromethyl carbon–oxygen bond (Anet and Yavari 1977). At temperatures above −165°C, the ^1H DNMR spectrum of $ClCH_2OMe$ consists of a downfield singlet ($ClCH_2$) and an upfield singlet (OMe). At temperatures below −165°C, the $ClCH_2$ resonance broadens and is separated into two signals of equal area at −182°C (Figure 1). The presence of two different methylene proton signals of *equal area* at −182°C is consistent with a strong dominance of the two enantiomeric *gauche* conformations (equation 2). The ^1H spectrum of the $ClCH_2$ group of either *gauche* rotamer would in principle be an AM-type spin system. The spin–spin coupling is not observed at

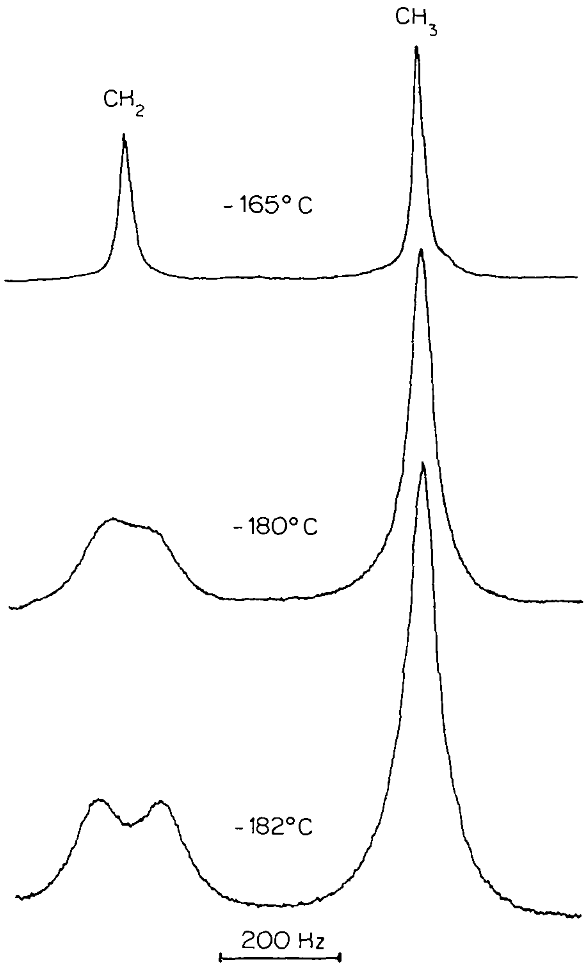
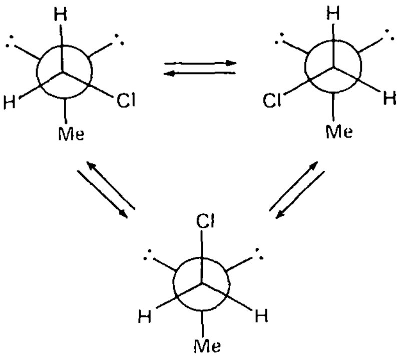


FIGURE 1. ^1H DNMR spectra (251 MHz) of $ClCH_2OCH_3$ in $CHFCl_2/CHF_2Cl$ (1 : 3 v/v) as solvent. Reprinted with permission from F. A. L. Anet and I. Yavari, *J. Amer. Chem. Soc.*, 99, 6752 (1977). Copyright by the American Chemical Society.

−182°C due to very broad lines in a very viscous solution and the fact that the rate constant for rotation probably still has a significant value even at −182°C. The *trans* rotamer (equation 2) would of course give a *singlet* resonance for the $ClCH_2$ group due to the presence of a plane of symmetry. Thus, the ^1H DNMR spectra in Figure 1 reveal only the slowing of the *gauche* to *gauche* equilibration on the DNMR time-scale. This equilibration could occur by a *direct gauche* to *gauche* process (chlorine and methyl eclipsed in the transition state) or via the *trans* form as an unstable intermediate *or* a transition state. The DNMR data (Figure 1) do not allow such a mechanistic distinction. From a complete ^1H DNMR line-shape analysis at −180°C, the free energy of activation ($\Delta G^\ddagger$) for *gauche* to *gauche* equilibration is calculated to be 4.2 kcal/mol. The strong preference of $ClCH_2OMe$ for the *gauche* rotamers is of course another manifestation of the *anomeric* effect (Lemieux 1971) or *rabbit ear* effect (Eliel 1972) or the *gauche* effect (Wolfe 1972) which will be discussed in more detail later in this chapter. No dynamic NMR effect was observed for bis(chloromethyl)ether or for fluoromethyl methyl ether down to −180°C.

These observations for $ClCH_2OMe$ are analogous to the strong preference of dimethoxymethane for the *gauche* conformation (3) and *not* the *anti* (4) (Uchida, Kurita and Kubo 1956). The anomeric effect manifests itself in a helical structure (all *gauche*) conformation for polyoxymethylene rather than the zig-zag or all *anti* geometry (Uchida and Tadokoro 1967). It should be noted at this point that it is not possible to apply the DNMR method to a study of dimethoxymethane because the C_2 symmetry of the *gauche* conformation (3) renders the methylene protons equivalent to each other and also the methyl groups are equivalent to each other. Theoretical calculations on simple acyclic molecules such as FCH_2OH as well as $(MeO)_2CH_2$ have also provided insight into the nature and magnitude of the anomeric effect (Wolfe 1972; Radom, Hehre and Pople 1972; Gorenstein and Kar 1977). A generalized anomeric effect plays a role in the conformational preferences of a variety of *heterocyclic* systems and examples will be discussed in due course below.



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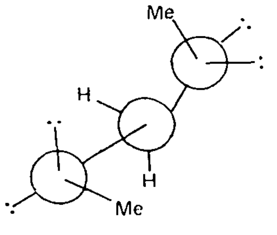
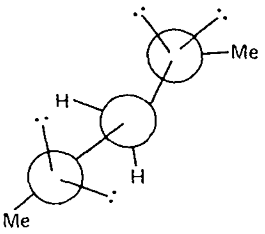
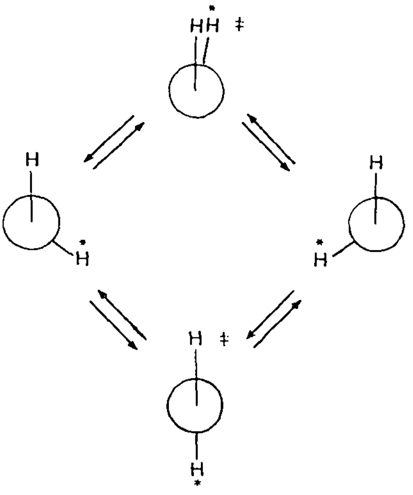


(3)



(4)

In considering those acyclic systems possessing oxygen–oxygen or sulphur–sulphur bonds, one encounters again some interesting conformational preferences. In the case of hydrogen peroxide, the preferred conformation has a dihedral angle between the two O—H bonds of 111° (Hunt and Leacock 1966; Olovsson and Templeton 1960) as seen in equation (3). Examination of equation (3) also reveals that equilibration between equivalent stable rotamers may occur by rotation about the O—O bond via two different energy surfaces one having the O—H bonds eclipsed (*cis* transition state; equation 3) and one having them *trans* (*trans* tran-

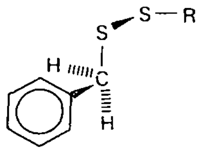


(3)

sition state). Indeed, many theoretical studies predict that the geometries of H_2O_2 having dihedral angles of 0° and 180° are maxima on the rotational energy surface for H_2O_2 but the heights of the two maxima are quite different. The *cis* transition state is consistently calculated to be of *higher* energy than the *trans* geometry (Radom, Hehre and Pople 1972; England and Gordon 1972). Indeed, experimental values for the *cis* and *trans* barriers are found to be 7.0 and 1.1 kcal/mol respectively (Redington, Olson and Cross 1962; Hunt, Leacock, Peters and Hecht 1965). It is obvious that the preferred rotational itinerary in H_2O_2 proceeds via the *trans* transition state. While interconversion via the *cis* transition state involves a barrier high enough to be detected by the DNMR method for a molecule of the requisite symmetry (e.g. RCH_2OOCH_2R), the *trans* barrier is well below the limit of DNMR detection (~4 kcal/mol) and DNMR studies of *acyclic* dialkyl peroxides may be precluded. We will, however, discuss DNMR studies of ring-flip processes in the cyclic 1,2-dioxanes later in this chapter.

For hydrogen disulphide (H_2S_2), the stereodynamics are somewhat different than for H_2O_2. The dihedral angle between the two S—H bonds in the stable geometry of H_2S_2 is about 90° (Winnewisser, Winnewisser and Gordy 1968). Theoretical calculations related to rotation about the S—S bond predict in a manner analogous to H_2O_2 a *cis* barrier of 9.3 kcal/mol and a lower *trans* barrier of 6.0 kcal/mol (Veillard and Demuynck 1970). While the barrier trend in H_2S_2 is the same as in H_2O_2, the magnitudes of the two different barrier heights are closer together in H_2S_2 than in H_2O_2 and both are apparently within the limits of DNMR detection. Indeed, an ^1H DNMR study of a series of acyclic disulfides capitalized on the diastereotopic characteristics of the benzyl protons of **5** (Table 2) which enabled the measurement of the rate of rotation about the S—S bond (Fraser, Boussard, Saunders, Lambert and Mixan 1971). An examination of Table 2 reveals interesting effects of structure on the barrier to S—S rotation. For example, the increasing barriers in proceeding from **5h** to **5g** to **5b** suggest strongly a *steric retardation* to rotation about the S—S bond. Since the DNMR method will be more sensitive to the *lower barrier pathway* for S—S rotation, the trend observed above is consistent with preferred rotation via the *cis* transition state, i.e. the route via the *cis* transition state involves a lower barrier than the *trans* route. Indeed, rotation via the *trans* transition state should be subject to *steric acceleration*. Thus, these experimental observations appear to be at odds with the theoretical calcu-

TABLE 2. Barriers to rotation about S–S bonds



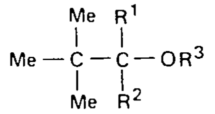
(5)

Compound	R	$\Delta G^{\ddagger}$ (kcal/mol)
5a	CCl_3	9.5 (−80°C)
5b	CPh_3	8.6 (−97°C)
5c	CF_3	8.3 (−104°C)
5d	C_6Cl_5	8.0 (−108°C)
5e	C_6F_5	7.9 (−109°C)
5f	Ph	7.7 (−115°C)
5g	*t*-Bu	7.9 (−113°C)
5h	$CH_2C_6H_5$	7.2 (−128°C)

lations for H_2S_2. However, it is quite possible that the relative barrier heights could be reversed by substitution of large groups for hydrogen. The CF_3 and CCl_3 groups are apparent deviates in this trend but they may be exerting strong inductive effects leading to a barrier increase. Additional insights into the nature of the S—S bond and associated rotational processes have been gained from semiempirical MO calculations (Boyd 1972; Snyder and Carlsen 1977) and molecular mechanics calculations (Allinger, Kao, Chang and Boyd 1976).

It is interesting to note from the point of view of comparison that hydrazines and diphosphines also prefer those conformations in which the vicinal lone pairs of electrons are *gauche* to one another which is analogous to H_2O_2 and H_2S_2 (Wolfe 1972). Indeed, even in the case of the highly encumbered tetra-*t*-butyldiphosphine, there is an essentially exclusive preference for the *gauche* conformation (Brunelle, Bushweller and English 1976; Lambert, Jackson, and Mueller 1970).

In this article so far, we have concentrated on the stereodynamics associated



$$\mathrm{Me{-}C(Me)_2{-}C(R^1)(R^2){-}OR^3}$$

(6) $R^1 = R^2 = Me, R^3 = D$

(7) $R^1 = CD_3, R^2 = CD_2CD_3, R^3 = D$

(8) $R^1 = R^2 = CD_2CD_3, R^3 = D$

(9) $R^1 = CD_3, R^2 = CH_2C_6H_5, R^3 = D$

(10) $R^1 = CD_3$, $R^2 =$ *t*-Bu, $R^3 = D$

(11) $R^1 = R^2 = CD_3, R^3 = Me$

(12) $R^1 = CD_3, R^2 = CD_2CD_3, R^3 = Me$

(13) $R^1 = R^2 = CH_2CD_3, R^3 = Me$

(14) $R^1 = CD_3$, $R^2 =$ *t*-Bu, $R^3 = Me$

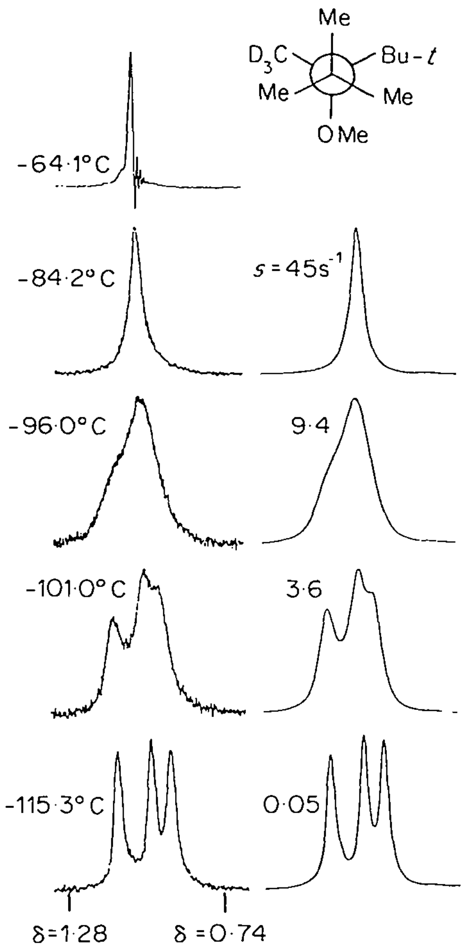
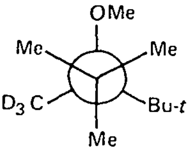


FIGURE 2. Experimental ^1H DNMR spectra (60 MHz) of the *t*-butyl group of **14** (5% v/v in vinyl chloride) (left column) and theoretical spectra calculated as a function of the rate of conversion of one *t*-butyl rotamer to another. Reprinted with permission from S. Hoogasian, C. H. Bushweller, W. G. Anderson and G. Kingsley, *J. Phys. Chem.*, 80, 646 (1976). Copyright by the American Chemical Society.

with bonds to oxygen or sulphur. There is available some data from ^1H DNMR studies regarding the effect of oxygen or sulphur on the rate of rotation about *other* bonds, specifically carbon–carbon single bonds. In one study, the barriers to *t*-butyl rotation in the series **6**–**14** were determined using complete ^1H DNMR line-shape analysis (Hoogasian, Bushweller, Anderson, and Kingsley 1976). As an example of the type of ^1H DNMR data obtained, consider the experimental and theoretical ^1H DNMR spectra of the *t*-butyl group of **14** illustrated in Figure 2. At

−64.1°C, the spectrum consists of a sharp singlet (δ = 0.995) consistent with rapid *t*-butyl rotation on the DNMR time-scale. At lower temperatures (Figure 2), the *t*-butyl resonance broadens and is separated at −115·3°C into three singlets of equal area (δ = 0.913, 0.983, 1.089) consistent with slow *t*-butyl rotation and the symmetry experienced by a static *t*-butyl group (see **15**). The activation parameters for *t*-butyl rotation in **6**–**14** are compiled in Table 3. A perusal of Table 3 reveals a relatively small range in barrier magnitudes and trends which can be correlated with the steric size of the alkyl groups, e.g. **6**, **7** and **9**. The 'abnormally' low barrier for **10** or **14** with two bulky *t*-butyl groups as compared to **6**, **7** or **9** is due most likely to nonstandard central CCC bond angles and the definite possibility of a concerted double gear-like rotation of the two *t*-butyl groups. It should be noted that the barrier to *t*-butyl rotation for **10** in a variety of solvent systems (Table 3) having different polarities and capacities to hydrogen-bond varies to only a small degree. A comparison of the alcohols in Table 3 (**6**–**10**) with the methyl ethers (**11**–**14**) shows hydroxyl to be roughly comparable to methoxyl in hindering *t*-butyl rotation. It is then interesting to compare various other groups on the same carbon skeleton to hydroxyl and methoxyl as compiled in Table 4. It is not surprising to note that hydrogen is the least effective of the groups in Table 4 in hindering *t*-butyl rotation while the trend for the halogens parallels van der Waals' radii. Hydroxyl and methoxyl are less hindering to rotation than all the halogens except fluorine.



(**15**)

An analogous DNMR study of the effect of oxygen or sulphur on the rate of *t*-butyl rotation has been done for the two series of cyclic compounds below (Stevenson, Bhat, Bushweller and Anderson 1974). Activation parameters for *t*-butyl rotation are compiled in Table 5. An examination of Table 5 shows clearly

TABLE 3. Activation parameters for *t*-butyl rotation in *t*-Bu(R^1)(R^2)COR^3

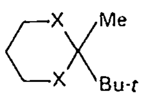
Compound	Solvent (v/v% of alcohol or derivative)	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ (e.u.)	$\Delta G^\ddagger$ (kcal/mol; −100°C)
6	CH_2CHCl (4%)	8.5 ± 0.4	−1.4 ± 2.7	8.76 ± 0.10
7	CH_2CHCl (4%)	8.7 ± 0.6	−1.4 ± 3.4	8.91 ± 0.10
8	CH_2CHCl (4%)	No DNMR effect observed		
9	CH_2CHCl (4%)	9.1 ± 0.4	0.8 ± 2.8	8.93 ± 0.10
10	CH_2CHCl (4%)	9.8 ± 0.8	1.5 ± 4.7	9.58 ± 0.10
	90:10 CH_2CHCl–MeOH (4%)	9.6 ± 0.2	−1.3 ± 1.2	9.77 ± 0.10
	75:25 CH_2CHCl–MeOH (4%)	9.9 ± 0.4	−0.6 ± 2.1	9.99 ± 0.10
	45:55 CH_2CHCl–MeOH (4%)	10.1 ± 0.7	0.6 ± 3.9	9.95 ± 0.10
	60:40 Me_2O–Me_2NCHO (4%)	9.6 ± 0.4	−0.1 ± 2.3	9.57 ± 0.10
11	CH_2CHCl (5%)			9.34 ± 0.40
12	CH_2CHCl (5%)	8.5 ± 0.4	0.0 ± 2.8	8.49 ± 0.10
13	CH_2CHCl (5%)	8.0 ± 0.2	0.2 ± 1.3	7.93 ± 0.10
14	CH_2CHCl (5%)	9.6 ± 0.6	0.8 ± 3.4	9.43 ± 0.10

TABLE 4. Free energies of activation for *t*-butyl rotation in *t*-BuCMe$_2$X

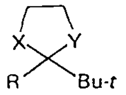
X	$\Delta G^{\ddagger}$ (kcal/mol)
H	6.9[a,b]
F	8.0[c]
Cl	10.4[a]
Br	10.7[a]
I	11.1[c]
OH	8.7[d]
OMe	9.3[d]

[a] Anderson and Pearson (1975).
[b] Bushweller and Anderson (1972).
[c] Anderson and Pearson (1972).
[d] Hoogasian, Bushweller, Anderson and Kingsley (1976).

the expected result that methyl is more hindering to rotation than hydrogen, e.g. compare **19** and **20** or **21** and **22**. Comparison of **16** and **17** or **18** and **19** reveals that sulphur is apparently more hindering to rotation than oxygen but the significant variation in the barrier differential between **16** and **17** in the 6-rings as compared to that between **18** and **19** in the 5-rings suggests that overall ring geometry can play an important role in the *t*-butyl stereodynamics.



(16) X = O
(17) X = S



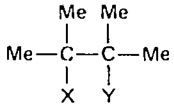
(18) X = Y = O, R = Me
(19) X = Y = S, R = Me
(20) X = Y = S, R = H
(21) X = O, Y = S, R = Me
(22) X = O, Y = S, R = H

The introduction of two vicinal electronegative substituents on a carbon–carbon single bond complicates the conformational picture but ^{1}H DNMR studies have been revealing for the series of haloalkoxy- and haloacetoxy-butanes **23**–**32** (Wang and Bushweller 1977).

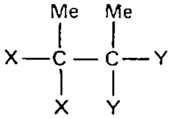
TABLE 5. Activation parameters for *t*-butyl rotation[a]

Compound	$\Delta H^{\ddagger}$(kcal/mol)	$\Delta S^{\ddagger}$(e.u.)	$\Delta G^{\ddagger}$(kcal/mol)
16	8.9 ± 0.3	1.4 ± 2.0	8.7 ± 0.1(−109.8°C)
17	9.9 ± 0.3	1.4 ± 2.0	9.6 ± 0.1 (−83.5°C)
18	7.5 ± 0.3	0.0 ± 2.0	7.5 ± 0.1(−124.7°C)
19	11.1 ± 0.3	2.5 ± 2.0	10.6 ± 0.1 (−70.2°C)
20	7.5 ± 0.4	0.0 ± 3.0	7.5 ± 0.2(−133.2°C)
21	10.8 ± 0.4	5.5 ± 4.0	9.8 ± 0.1(−101.2°C)
22	6.9 ± 0.4	−1.1 ± 2.0	7.0 ± 0.2(−139.6°C)

[a] Solvent: CH_2CHCl or $CBrF_3$.



$\mathrm{Me{-}\underset{X}{\overset{Me}{C}}{-}\underset{Y}{\overset{Me}{C}}{-}Me}$

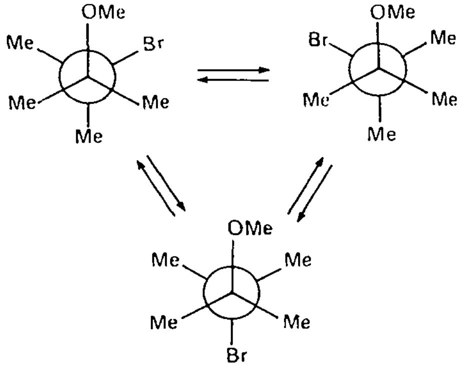


$\mathrm{X{-}\underset{X}{\overset{Me}{C}}{-}\underset{Y}{\overset{Me}{C}}{-}Y}$

(23) X = Br, Y = OMe
(24) X = Cl, Y = OMe
(25) X = Br, Y = OEt
(26) X = Cl, Y = OEt
(27) X = Br, Y = OAc
(28) X = Cl, Y = OAc

(29) X = Br, Y = OMe
(30) X = Cl, Y = OMe
(31) X = Br, Y = OEt
(32) X = Cl, Y = OEt

The ^1H DNMR spectrum (60 MHz) of 2-bromo-3-methoxy-2,3-dimethylbutane (23, 3% v/v in CH_2CHCl) at −39.8°C shows three singlet resonances at $\delta = 1.34$ (6H, $OCMe_2$), $\delta = 1.76$ (6H, $BrCMe_2$) and $\delta = 3.20$(3H, OMe) consistent with rapid rotation about the $C_{(2)}{-}C_{(3)}$ bond. Below −70°C, the $OCMe_2$ resonance broadens asymmetrically (see Figure 3) and is sharpened at −110.5°C into two small singlets of *equal area* at $\delta = 1.12$ and $\delta = 1.34$ as well as a large singlet at $\delta = 1.38$ (Figure 3). Such behaviour is consistent with slow rotation about the $C_{(2)}{-}C_{(3)}$ bond of 23 (equation 4) and with *both gauche* to *gauche* and *gauche* to *trans* processes being slow on the DNMR time-scale at −110.5°C (Figure 3). It is important to note at this point that if the *gauche* to *trans* process had slowed on the DNMR time-scale at −110.5°C and the *gauche* to *gauche* process remained *fast*, the spectrum would consist of a singlet for the *trans* and a *singlet* for the two time-averaged *gauche* methyl peaks. It is also important to note that if the *gauche* to *gauche* process were slow at −110.5°C and the *gauche* to *trans* equilibration were *fast*, the total spectrum of the $OCMe_2$ group would be a *singlet* because the *gauche* to *trans* to *gauche* itinerary is sufficient to average the environments of all the $OCMe_2$ methyl groups. The observation of singlet peaks for 23 at −110.5° is also consistent with *fast* rotation on the DNMR time-scale for the individual methyl groups of 23. The two small singlets of equal area at −110.5°C (Figure 3) are assigned to the two nonequivalent methyl groups of the $OCMe_2$ moiety in the two enantiomeric *gauche* rotamers (equation 4) and the larger singlet is assigned to the two equivalent methyl groups in the *trans* form. Such assignments are unequivocal and allow studies of both the rate of $C_{(2)}{-}C_{(3)}$ rotation as well as an accurate determination of the equilibrium constant for the *gauche* to *trans* equilibrium as a function of temperature. Some interesting results came out of both types of study.



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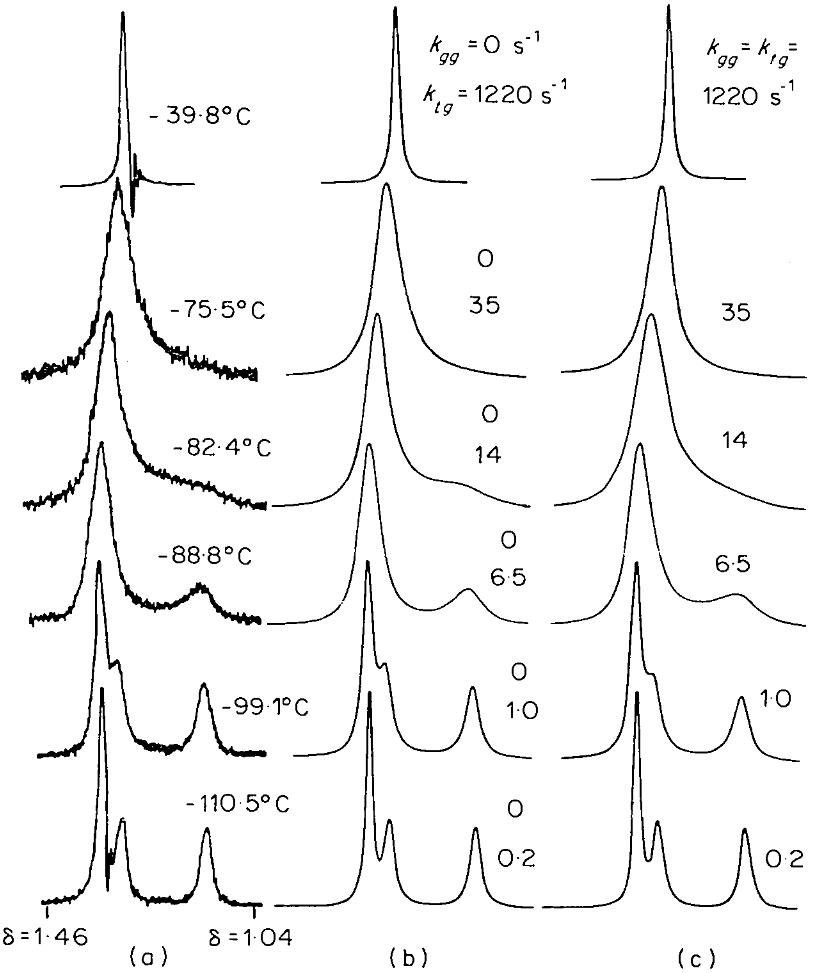
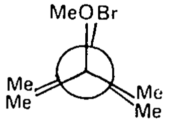


FIGURE 3. (a) Experimental ^{1}H DNMR spectra (60 MHz) of the $OCMe_2$ resonance of 23 (5% v/v in CH_2CHCl). (b) Theoretical spectra assuming no *gauche* to *gauche* exchange (k_{gg} and k_{tg} are the first-order rate constants respectively for the *gauche* to *gauche* and *trans* to *gauche* processes). (c) Theoretical spectra incorporating *equal* rates for *gauche* to *gauche* and *trans* to *gauche* processes. Reprinted with permission from C. Y. Wang and C. H. Bushweller, *J. Amer. Chem. Soc.*, 99, 314 (1977). Copyright by the American Chemical Society.

With regard to the dynamics of $C_{(2)}-C_{(3)}$ rotation, the best fits of theoretical to experimental DNMR spectra incorporated an effective rate constant of zero for the *gauche* to *gauche* process and the spectra were fit accurately by varying the rate of the *gauche* to *trans* equilibration (see Figure 3a and b). This does not mean that the rate of the *gauche* to *gauche* process is actually zero, but only that the process occurs at a significantly slower rate than the *gauche* to *trans* processes and therefore does not contribute to determining the DNMR line-shape. This observation indicates that the barrier to the *gauche* to *gauche* process is higher ($\geqslant$0.5 kcal/mol) than the *trans* to *gauche* or *gauche* to *trans* processes. The transition state for the *gauche* to *gauche* interconversion in 23 involves a maximum number of eclipsings of vicinal polar substituents and a maximum number of eclipsings of bulky methyl groups (33), while the transition state for the *gauche* to *trans* process (e.g. 34) has a



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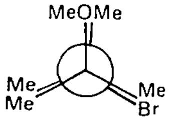


(34)

minimum number of vicinal polar eclipsings and a minimum number of vicinal methyl–methyl eclipsings. Indeed, the dynamics of $C_{(2)}-C_{(3)}$ rotation in 23 reflect the dynamics of the complete series 23–32, i.e. the barriers for the *gauche* to *gauche* processes are invariably higher than the *trans* to *gauche* processes. Pertinent activation parameters for the detectable *trans* to *gauche* process are compiled in Table 6. The enthalpies of activation ($\Delta H^{\ddagger}$) for the *trans* to *gauche* processes in 23–32 are all comparable (Table 6) revealing no significant substituent effects at least in this series. One other trend for compounds 23–32 is a *negative* entropy of activation ($\Delta S^{\ddagger}$) for the *trans* to *gauche* process (Table 6) consistent with increasing dipolar solvation of a transition state (e.g. 34) which has a higher dipole moment than the *trans* rotamer.

As stated above, DNMR spectra such as those illustrated in Figure 3 allow the measurement of the *gauche* to *trans* equilibrium constant in compounds 23–32 as a function of solvent and temperature thus giving ΔH^0 and ΔS^0 values for this equilibrium (Table 7). In perusing Table 7, it must be realized that these thermodynamic parameters refer to the *liquid phase* and probably do not reflect accurately gas-phase conformational preferences. The increased dielectric constant of the liquid phase usually leads to an increase in the concentration of more polar rotamers, i.e. *gauche* forms, due to increased dipolar solvation. Keeping this trend in mind, an examination of the solution data in Table 7 shows the *gauche* rotamer to be at *lower enthalpy* (ΔH^0) than the *trans* in every instance including two different solvents for compounds 23 and 24. However, entropy values [ΔS^0; corrected for the statistical preference for the *gauche* (R ln 2)] show the *trans* to

TABLE 6. Activation parameters for the *trans* to *gauche* rate process in 23–32

Compound	$\Delta H^{\ddagger}$(kcal/mol)	$\Delta S^{\ddagger}$(e.u.)	$\Delta G^{\ddagger}$(kcal/mol, −80°C)
23	8.7 ± 0.2^a	-6.3 ± 1.0	10.0 ± 0.1
24	8.6 ± 0.6^a	-5.9 ± 2.0	9.8 ± 0.1
25	8.1 ± 0.8^a	-9.9 ± 5.0	10.0 ± 0.1
26	7.9 ± 0.9^a	-10.0 ± 5.0	9.8 ± 0.1
27	8.7 ± 0.5^a	-6.4 ± 3.0	10.0 ± 0.1
28	7.8 ± 0.8^a	-10.0 ± 4.0	9.7 ± 0.1
29	8.9 ± 0.3^b	-4.6 ± 2.0	9.8 ± 0.1
30	8.2 ± 0.5^b	-4.0 ± 2.0	8.9 ± 0.1
31	8.5 ± 0.6^a	-7.8 ± 4.0	10.0 ± 0.1
32	8.6 ± 0.8^a	-1.7 ± 4.0	8.9 ± 0.1

[a] Solvent: CH_2CHCl.

[b] Solvent: $CBrF_3$.

TABLE 7. Thermodynamic parameters for *gauche* to *trans* equilibration[a]

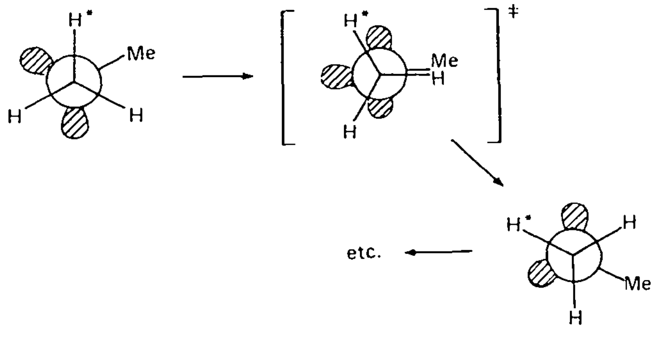
Compound	Solvent (% solute, v/v)	ΔH^0 (kcal/mol)	ΔS^0 (e.u.)	ΔG^0 (kcal/mol, −110°C)
23	CH_2CHCl(3)	0.89 ± 0.06	6.3 ± 0.1	−0.14 ± 0.02
	$CBrF_3$ (5)	0.50 ± 0.04	5.0 ± 0.2	−0.38 ± 0.02
24	CH_2CHCl(3)	0.52 ± 0.05	5.4 ± 0.2	−0.36 ± 0.02
	$CBrF_3$ (5)	0.24 ± 0.05	4.6 ± 0.2	−0.50 ± 0.02
25	CH_2CHCl(5)			−0.34 ± 0.04
26	CH_2CHCl(5)			−0.56 ± 0.04
27	CH_2CHCl(5)	0.75 ± 0.03	5.2 ± 0.4	−0.10 ± 0.02
28	CH_2CHCl(5)	0.72 ± 0.04	5.9 ± 0.4	−0.24 ± 0.02
29	$CBrF_3$ (5)	0.49 ± 0.04	5.5 ± 0.3	−0.41 ± 0.02
30	$CBrF_3$ (5)	0.42 ± 0.05	4.6 ± 0.2	−0.33 ± 0.02
31	CH_2CHCl(5)	0.40 ± 0.02	5.3 ± 0.4	−0.47 ± 0.02
32	CH_2CHCl(5)	0.30 ± 0.10	4.3 ± 0.6	−0.40 ± 0.04

[a] Corrected for statistical preference for *gauche*; K_{eq} = [*trans*]/[*gauche*].

be invariably *higher* in entropy than the *gauche*. ΔG^0 values calculated at −110°C (Table 7) show a preference in terms of free energy for the *trans*. It is noteworthy that the $T\Delta S^0$ term which favours the *trans* is large enough to overcome the enthalpy (ΔH^0) preference for the *gauche* at these temperatures (Table 7). Thus, the *trans* rotamer prevails at equilibrium. In addition, the solvent dependence of the ΔH^0 values for 23 and 24 in CH_2CHCl(μ = 1.45 D) and $CBrF_3$ (μ = 0.65 D), and the general trend in ΔS^0 values speak for increased dipolar solvation of the more polar *gauche* rotamer as compared to the *trans*. Therefore, in studying systems analogous to 23–32 one must be cognizant of the possibility that *gauche* forms may be at lower enthalpy than *trans* rotamers and that solvent polarity can play a role in conformational preference.

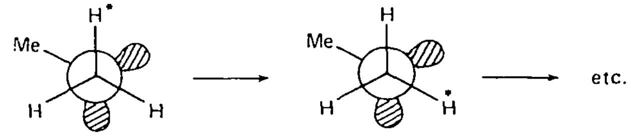
B. Inversion at Oxygen and Sulphur

For a simple molecule such as dimethyl ether (CH_3OCH_3), one can envisage an inversion process at oxygen illustrated in equation (5). The process involves a *concerted* inversion and rotation involving an sp^3 to sp^2 conversion at oxygen in the transition state and in the case of equation (5) a net 60° clockwise rotation of methyl with each completed inversion. The process is strictly analogous to the



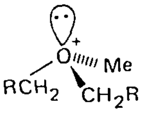
(5)

inversion–rotation process in tertiary amines (Bushweller, Anderson, Stevenson and O'Neil 1975). However, it should be noted that a simple *rotation* of methyl is also sufficient to achieve the same net change in environments for the methyl protons (equation 6). Indeed, it is apparent that the barrier to simple rotation (equation 6) is significantly lower than that for inversion at oxygen (e.g. equation 5) and that the preferred route for stereomutation about a C—O bond involves simple rotation (Truax and Wieser 1976).



(6)

Complexation of one of the lone pairs on oxygen by a Lewis acid produces a tricoordinate oxygen species isoelectronic with an amine. The subject of inversion at nitrogen, phosphorus and other tricoordinate centres has been reviewed by several authors (Lambert 1971; Rauk, Allen and Mislow 1970; Lehn 1970). A pyramidal geometry at tricoordinate oxygen has been established by X-ray crystallographic studies of $H_3O^+Cl^-$ in the solid (Yoon and Carpenter 1959). In principle, one could utilize the diastereotopic nature of the methylene protons in acyclic trialkyloxonium salts such as 35 to study the inversion–rotation process (e.g. equation 7) using ^1H DNMR spectroscopy. As a result of the specific inversion–rotation illustrated in equation (7), as well as many other such processes not illustrated, the two methylene protons can swap environments. Thus, this process is detectable by the DNMR method, at least in principle. However, there have been no reports of a DNMR measurement of the rate of inversion in an *acyclic* trialkyloxonium ion although the barrier to *nitrogen* inversion in dibenzylmethylamine (36, R = Ph) has been measured ($\Delta H^‡$ = 7.2 kcal/mol, $\Delta S^‡$ = 4 e.u., $\Delta G^‡$ = 6.6 kcal/mol at −141°C; Bushweller, O'Neil and Bilofsky 1972). The implication from this situation is that the barrier to inversion in trialkyloxonium ions may be lower than that in trialkylamines. This contention is supported by a DNMR study of the ring protons of 1-alkyloxiranium tetrafluoroborates (equation 8; R = Me, Et, *i*-Pr) for which a barrier (E_a) to inversion at oxygen of 10 ± 2 kcal/mol was



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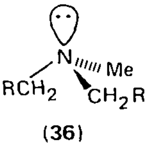

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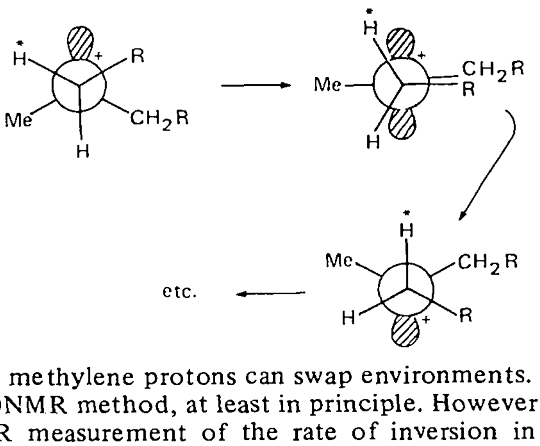

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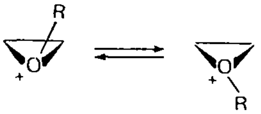
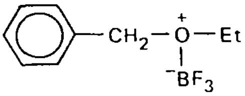


(8)

measured. This barrier is to be compared to the barrier to *nitrogen* inversion in *N*-ethylaziridine ($\Delta G^\ddagger$ = 19.4 kcal/mol at 108°C; Bottini and Roberts 1958) or *N*-*t*-butylaziridine ($\Delta G^\ddagger$ = 17.0 kcal/mol at 50°C; Brois 1967). The substantial reduction (7–9 kcal/mol) in the barrier to inversion in 1-alkyloxiranium ions as compared to *N*-alkylaziridines suggests that stereomutation at tricoordinate oxygen is much more facile than at tricoordinate nitrogen. It is noteworthy in this regard that alkyloxonium salts of oxacyclohexane show no DNMR effect down to −70°C consistent with *fast* oxygen inversion at this temperature. It is apparent that substantial angle strain in the transition state for inversion in the oxiranium salts (sp^2-hydridized oxygen) retards inversion effectively as compared to the larger rings.

In another report, the methylene protons of the ethyl group of the benzyl ethyl ether boron trifluoride complex (37) were observed to be nonequivalent at −65°C (Brownstein 1976). This observation is consistent with a pyramidal geometry at oxygen and slow inversion at oxygen with the expected diastereotopic methylene protons. From an analysis of changes in the ^{1}H DNMR spectra of 37, $\Delta H^\ddagger$ = 4.1 ± 0.3 kcal/mol. At the temperatures of interest in this report (−65°C and above), this $\Delta H^\ddagger$ value is associated with a $\Delta S^\ddagger$ of about −30 e.u. for the rate



(37)

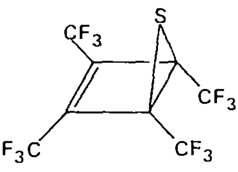
process observed and seems a bit large to be associated with a simple inversion process. The author of the paper states that the observed process must be assigned to inversion rather than a BF_3 exchange involving oxygen–boron bond cleavage, because only one type of complex is observed in the NMR spectrum. However, it is quite possible that a *bimolecular* transfer of BF_3 from one complex to another leading to net inversion at both oxygens could be occurring (Beall and Bushweller 1973). This kind of bimolecular rate process would indeed have a large negative $\Delta S^\ddagger$ value. Thus, while the ^{1}H DNMR spectrum of 37 at −65°C is consistent with slow inversion at oxygen, the activation parameters determined for 37 may not be associated with a simple inversion process but with some other chemical exchange process. However, it is apparent that the barrier to inversion at oxygen in 37 is higher than that in systems such as 35. LCAO–MO–SCF calculations indicate that the hydrosulphonium ion (H_3S^+) is pyramidal and the barrier to inversion is about 30 kcal/mol (Rauk, Andose, Frick, Tang and Mislow 1971). Indeed, appropriate trialkylsulphonium ions can be resolved into enantiomers and have barriers to inversion in the range of 26–29 kcal/mol (Scartazzini and Mislow 1967). Evidence for hindered inversion at sulphur has been obtained for the diethyl sulphide–borane complex (Coyle and Stone 1961) and dibenzyl sulphide–platinum chloride complexes (Haake and Turley 1967).

III. CYCLIC SYSTEMS

A. Perfluorotetramethyl Dewar Thiophene and the *exo-S*-oxide Derivative

Some interesting stereodynamical behaviour has been observed recently for two compounds which do not fit into any general category pertinent to this review. These two compounds will be discussed separately in this short section.

Since perfluorotetramethyl Dewar thiophene (38) is the only known Dewar isomer of a thiophene, it is an interesting compound from a structural viewpoint (Ross, Seiders and Lemal 1976). Indeed, ^{19}F DNMR studies of 38 and its *exo-S*-oxide (39) reveal a marked difference in dynamical behaviour. The ^{19}F DNMR spectrum (56.4 MHz) of 38 (1.0M in 1,2,4-trichlorobenzene) at 94°C consists of two quartets separated by 2.89 p.p.m. ($^{5}J_{\mathrm{FF}}$ = 2 Hz) as expected (Figure 4; Bushweller, Ross, and Lemal 1977). When the temperature is raised, the spectrum undergoes broadening and is coalesced near 190°C consistent with an increasing rate of exchange of trifluoromethyl groups among four sites (equation 9; X = lone pair). Activation parameters for automerization of 38 determined from complete ^{19}F DNMR line-shape analyses are $\Delta H^{\ddagger}$ = 18.8 ± 0.3 kcal/mol, $\Delta S^{\ddagger}$ = −7.7 ± 0.8 e.u. and $\Delta G^{\ddagger}$ = 22.1 ± 0.1 kcal/mol at 157°C. In contrast the ^{19}F DNMR spectrum of 39 (1.6M in 80% $CHCl_2F$/20% $CHClF_2$, v/v) is a *sharp singlet* even at −79°C. At −108°C, the spectrum begins to broaden and is separated at −160°C into two broad apparent singlets separated by 2.82 p.p.m. ^{19}F DNMR line-shape analyses for 39 gave $\Delta H^{\ddagger}$ = 6.6 ± 0.2 kcal/mol, $\Delta S^{\ddagger}$ = −0.5 ± 0.6 e.u. and $\Delta G^{\ddagger}$ 6.7 ± 0.1 kcal/mol at −136°C for automerization of 39 (equation 9; X = oxygen). The nature of the ^{19}F DNMR spectra for 38 and 39 do not allow a distinction to be made between a dynamical pathway involving a stepwise 'hopping' of the



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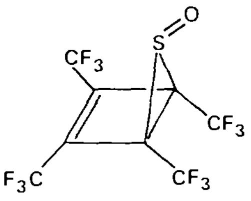

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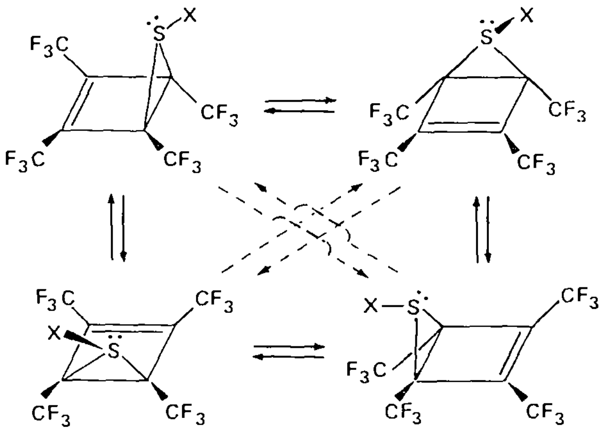

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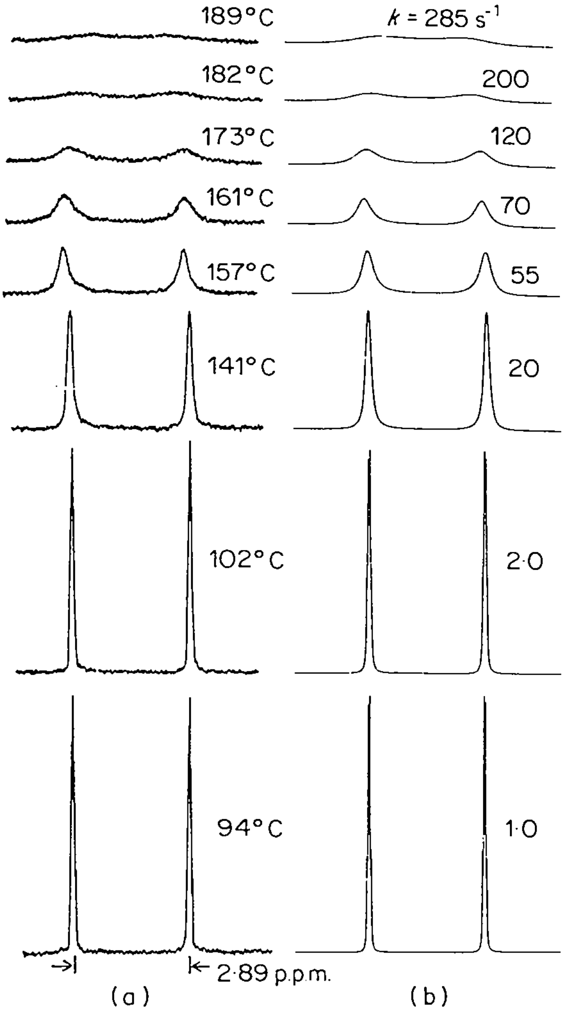
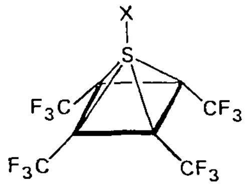


FIGURE 4. (a) Experimental ^{19}F DNMR spectra (56.4 MHz) of 38 (1.0M in 1,2,4-trichlorobenzene) at various temperatures, and (b) theoretical DNMR spectra calculated using a two-site exchange model with a trifluoromethyl group at each site and $^{5}J_{FF}$ = 2 Hz (k = first-order rate constant for disappearance of a trifluoromethyl group from one site). Reprinted with permission from C. H. Bushweller, J. A. Ross and D. M. Lemal, *J. Amer. Chem. Soc.*, 99, 630 (1977). Copyright by the American Chemical Society.

sulphur about the ring in 38 or 39 and a pathway involving a common intermediate such as the structure 40 having C_{4v} symmetry. Although the currently available DNMR data do not allow an incisive mechanistic picture for automerization of 38 and 39, it is clear that conversion of the sulphide (38) to the sulphoxide (39) leads



X = lone pair
or oxygen

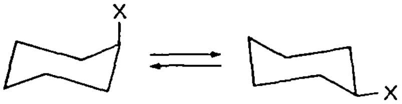
(40)

to a dramatic lowering ($\Delta\Delta H^{\ddagger}$ = 12.2 kcal/mol) of the barrier to conformational exchange.

B. Monosubstituted Cyclohexanes having Oxygen or Sulphur Substituents

Many different methods have been used to assess the steric requirements of a variety of substituents. One type of NMR technique involves a direct measurement of the axial–equatorial ratio in monosubstituted cyclohexanes under conditions of slow ring reversal on the DNMR time-scale (Table 8). In the axial conformation (Table 8) the substituent (X) experiences two *gauche*-butane-type repulsions which are relieved in the equatorial form. In general, there exists a preference for the equatorial form (Jensen and Bushweller 1971). The type of data obtained can be illustrated for trideuteriomethyl cyclohexyl ether in its axial (**41**) and equatorial

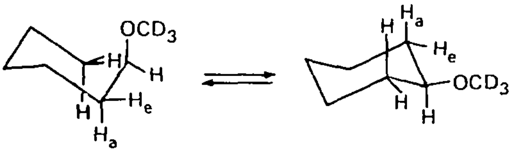
TABLE 8. Axial versus equatorial conformational preferences in monosubstituted cyclohexanes at −80°C[a]



X	ΔG^0 (kcal/mol)
$-OH$ (3M)	−1.08
$-OCD_3$	−0.55
$-OSO_2C_6H_5CH_3$	−0.52[b]
$-OSO_2CH_3$	−0.56[b]
$-\mathrm{O}\underset{\underset{\displaystyle\mathrm{O}}{\Vert}}{\mathrm{C}}\mathrm{H}$	−0.59
$-\mathrm{O}\underset{\underset{\displaystyle\mathrm{O}}{\Vert}}{\mathrm{C}}\mathrm{CH_3}$	−0.71
$-SH$ (2M)	−1.20
$-SCD_3$	−1.07
$-SCN$	−1.23
$-NCO$	−0.51
$-NCS$	−0.28
$-ND_2$	−1.2[c]
$-CH_3$	−1.6[d]

[a] Solvent: CS_2 unless otherwise indicated.
[b] Solvent: $CS_2/CDCl_3$.
[c] Solvent: pyridine/CH_2CHCl.
[d] Neat at −110°C.

(42) forms. Under conditions of fast ring-flip (on the DNMR time-scale) between 41 and 42, the HCO ring methine proton gives one time-averaged multiplet at $\delta = 2.50$. At lower temperatures, the HCO resonance broadens and is separated at -80°C into two resonances of unequal area at $\delta = 2.92$ and $\delta = 3.34$ (Figure 5a). Based on the well-established relationship between vincinal proton–proton coupling constants and dihedral angle, the resonance at $\delta = 3.34$ can be assigned unequivocally to the equatorial methine proton of 41 (axial methoxy). The methine



(41) (42)

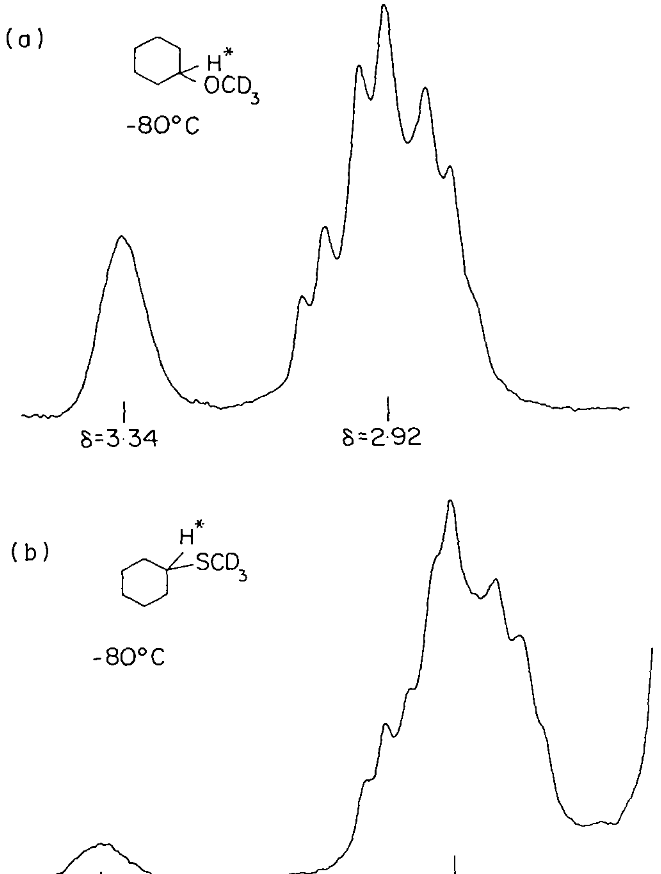
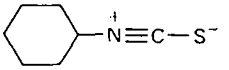


FIGURE 5. (a) The ^{1}H DNMR spectrum (100 MHz) of the HCO proton of trideuteriomethyl cyclohexyl ether at -80°C in CS_2. (b) The ^{1}H DNMR spectrum (100 MHz) of the HCS proton of trideuteriomethylcyclohexyl thioether at -80°C in CS_2.

proton of **41** will be coupled relatively weakly to the two vicinal equatorial protons (H_e of **41**; $^3J = 1-3$ Hz) and to the two vicinal axial protons (H_a of **41**; $^3J = 3-5$ Hz). The net result is a broad unresolved singlet resulting from overlap of many closely-spaced lines. The larger more resolved resonance at $\delta = 2.92$ (Figure 5a) also can be assigned unequivocally to the *axial* methine proton resonance of **42** (equatorial methoxy). While the axial methine proton of **42** will also be coupled weakly to the two vicinal equatorial protons ($^3J = 3-5$ Hz), it will be coupled strongly to the two vicinal *axial* protons ($^3J = 10-13$ Hz). The net result of this coupling pattern is essentially a resolved slightly overlapping triplet of triplets as observed for the resonance at $\delta = 2.92$ in Figure 5a. It is a simple matter to integrate the areas under the two resonances at −80°C (Figure 5a) and obtain the axial versus equatorial equilibrium constant directly. It is interesting to compare the HCO spectrum of the trideuteriomethoxycyclohexyl ether at −80°C (Figure 5a) to the HCS spectrum of the sulphur analogue (Figure 5b). The peak at $\delta = 2.93$ is assigned to the equatorial HCS proton (axial sulphur) and is clearly of a lower relative intensity than the equatorial HCO resonance of the ether (**41**) indicating a greater preference of sulphur for the equatorial conformer.

This ^1H DNMR technique has been used to measure the axial versus equatorial conformational preference in several monosubstituted cyclohexanes having sulphur or oxygen bonded to the cyclohexane ring (Table 8; Jensen, Bushweller and Beck 1969). The ΔG^0 value for methyl in Table 8 was obtained using ^{13}C DNMR spectroscopy at −80°C (Anet, Bradley and Buchanan 1971). *Other than hydroxyl,* the conformational preferences of oxygen-containing substituents for the equatorial conformer are very similar and in a range of 0.52 to 0.71 kcal/mol. The substantially larger preference of hydroxyl for the equatorial position can be ascribed to aggregation via hydrogen bonding and this preference is solvent-dependent as determined by ^1H DNMR measurements at about −80°C (Bushweller, Beach, O'Neil and Rao 1970). In contrast to the hydrogen-bonded value for hydroxyl in Table 8, an estimate of the ΔG^0 value for nonhydrogen-bonded hydroxyl is −0.6 kcal/mol (Hirsch 1967). A comparison of the oxygen-containing functionalities with the sulphur-containing groups (Table 8; $-SH$, $-SCD_3$, $-SCN$) reveals sulphur to be 'larger' than oxygen consistent with trends in van der Waals' radii. It is apparent also that the conformational preference of sulphydryl is not significantly solvent- or concentration-dependent as expected from a weakly hydrogen-bonded system. The large preference of the deuterioamino group for the equatorial form must be ascribed in part to intramolecular hydrogen bonding (Bushweller, Yesowitch and Bissett 1972).

It is interesting to compare the isocyanate and isothiocyanate groups in Table 8. The substantially lower conformational preference of isothiocyanate for the equatorial form as compared to isocyanate speaks for increased sp character at nitrogen (e.g. **43**) in the isothiocyanate, increased cylindrical symmetry and a resultant lower conformational size (Jensen, Bushweller and Beck 1969).



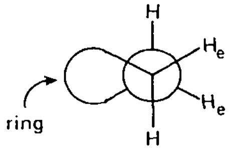
(43)

Finally, as part of this type of research it should be noted that it has been possible to isolate *in solution* at very low temperatures (−150°C) the conformationally pure equatorial form of trideuteriomethyl cyclohexyl ether (Jensen and Bushweller 1969).

C. Oxacyclohexanes and the Anomeric Effect

The presence of a heteroatom in a six-membered ring invariably causes distortion of the ring as compared to cyclohexane and affects conformational preferences and ring inversion processes.

The *R*-value method (Lambert 1967; Lambert, Keske and Weary 1967) uses vicinal ^1H NMR coupling constants to probe three types of six-membered ring conformation: an 'ideal' chair (**44**; e.g. cyclohexane), a conformation in which the equatorial hydrogens (H_e) are pushed more closely together than in cyclohexane (**45**), and a conformation for which the equatorial hydrogens are further apart than in cyclohexane (**46**). The *R*-value reflects changes in dihedral angles (see **44**, **45**, **46**) and is defined as the ratio of the time-averaged J_{cis} and the time-averaged J_{trans} for *vicinal* hydrogens in six-membered rings. Conformations of type **44** are represented by an *R* value of 2, conformations of type **45** have *R* values which are greater than 2, and conformations of type **46** have *R* values smaller than 2.



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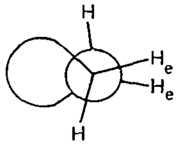

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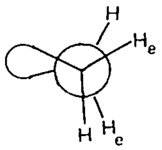
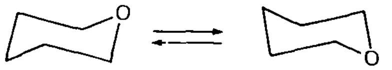


(46)

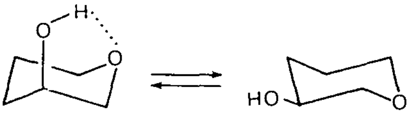
Oxacyclohexane exists as a slightly flattened chair conformation as evidenced by its *R*-value of 1.9 (Lambert 1967; Romers, Altona, Buys and Havinga 1969). The oxygen n-electrons are distributed so that the oxygen is approximately tetrahedral (Hoffman, David, Eisenstein, Hehre and Salem 1973) and, except for the short carbon–oxygen bond (1.41 Å) compared to the carbon–carbon bond (1.54 Å), the molecule resembles cyclohexane in geometry.

The dynamics of the chair-to-chair ring-reversal process in oxacyclohexane (equation 10) are very similar to cyclohexane. An ^1H DNMR study of oxacyclohexane-3,3,5,5-d_4 gave a $\Delta G^{\ddagger}$ for ring-reversal of 10.3 kcal/mol at $-61\,^{\circ}C$ and $E_a = 10.7 \pm 0.5$ kcal/mol (Lambert, Keske and Weary 1967). These values are very similar to the analogous parameters in cyclohexane for which $\Delta H^{\ddagger} = 10.8 \pm 0.1$ kcal/mol, $\Delta S^{\ddagger} = 2.8 \pm 0.5$ e.u. and $\Delta G^{\ddagger} = 10.2 \pm 0.1$ kcal/mol at $-65\,^{\circ}C$ (Anet and Bourn 1967).



(10)

The influence of the ring oxygen on conformational preference is readily demonstrated. The ΔG^0 for the axial to equatorial equilibrium in cyclohexanol is about -1.0 kcal/mol (Table 8) indicating preference for an equatorial hydroxyl group, whereas 3-oxacyclohexanol exists as a 50/50 mixture of axial and equatorial conformers with the axial hydroxyl group hydrogen-bonded to the ring oxygen as illustrated in equation (11) (Barker, Brimacombe, Foster, Whiffen and Zweifel 1959). In an analogous situation, a preference for the *axial* position (ΔG^0 = −0.41 kcal/mol) is also shown by the hydroxyl group in 5-hydroxy-1,3-dioxacyclohexane (Riddell 1967).

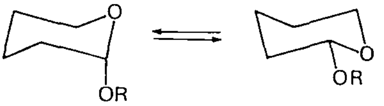


(11)

Oxacyclohexanes substituted in the 2-position with electronegative groups have received the greatest amount of attention because electronegative groups were found to prefer the *axial* position and in some cases, the preference was greater than 95% (Romers, Altona, Buys and Havinga 1969). The ring in the 2-halo-substituted oxacyclohexanes is flatter than the unsubstituted ring and the carbon–halogen bond is longer than the same bond in chlorocyclohexane. The carbon–halogen bond in the *axial* form is also somewhat bent away from the ring so that 1,3-*syn*-axial interactions are not as severe as in the corresponding cyclohexanes. Table 9 lists conformational free energy values, determined from coupling constant data, for a series of 2-alkoxyoxacyclohexanes (Pierson and Rumquist 1968). The data indicate that all 2-alkoxy groups prefer the axial position. This size of the R group makes only a minor change in the percentage of axial conformer probably because the alkyl part of the group is quite distant from the *syn*-axial hydrogens. As the group R increases in electronegativity there is also a greater preference for the axial position.

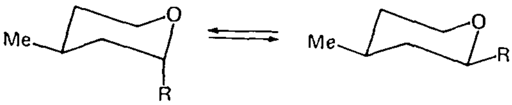
Equilibration studies (Booth and Ouellette 1966; Anderson and Sepp 1964; Anderson and Gibson 1967) on the 2-*R*-4-methyloxacyclohexanes also indicates a preference for the 2-axial position when R is electronegative (Table 10). There is a substantial solvent effect for the 2-methoxy derivative; ΔG^0 as defined in Table 10 is 0.34 kcal/mol in methanol, 0.71 kcal/mol in dioxane and 0.65 kcal/mol in acetic acid, suggesting that more polar solvents stabilize the equatorial conformation. The

TABLE 9. Conformational free energies for 2-alkoxyoxacyclohexanes at 38°C (Pierson and Rumquist 1968)



R	ΔG^0 (kcal/mol)
H	0.75
Me	0.58
Et	0.47
i-Pr	0.42
t-Bu	0.31
Ph	0.90
$ClCH_2CH_2$	0.75
Cl_2CHCH_2	1.2
Cl_3CCH_2	1.8
F_3CCH_2	1.5

TABLE 10. Conformational free energies for 2-*R*-4-Methyloxacyclohexanes (Booth and Ouellette 1966; Anderson and Sepp 1964; Anderson and Gibson 1967)

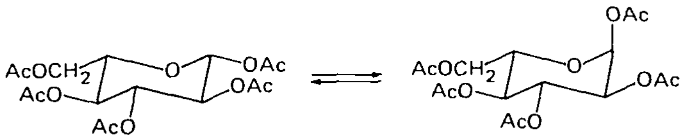


R	ΔG^0 (kcal/mol)
OMe	0.34(38°C)
OAc	0.65(38°C)
Cl	2.15(38°C)
Br	2.7 (38°C)
COOMe	−1.62(25°C)

value of acetoxy is smaller for the oxacyclohexanes than for the sugars. Equilibration of pentaacetyl-α-D-glucose and β-D-glucose reveals a 1.1 kcal/mol preference of the 2-acetoxy group for the axial position (equation 12).

Equilibration studies for a series of methyl-substituted oxacyclohexanes indicate that the methyl group generally prefers the equatorial position (Anderson and Sepp 1964).

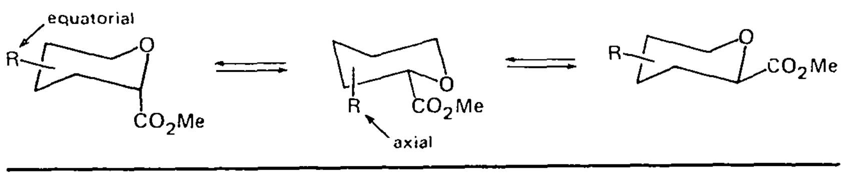
Table 11 gives conformational free energies for some 2-carbomethoxy-X-alkyloxacyclohexanes and Table 12 gives a summary of conformational free energy values for substituted cyclohexanes for purposes of comparison now and later.



(12)

Equilibration of 2-carbomethoxy-6-*t*-butyloxacyclohexane with base in methanol gave a ΔG^0 value of −1.22 kcal/mol (Table 11) indicating a stronger preference of carbomethoxy for the equatorial position than for the corresponding cyclohexane

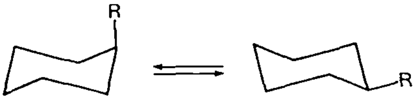
TABLE 11. Conformational free energies for 2-carbomethoxy-X-alkyloxacyclohexanes at 25°C (Anderson and Sepp 1964)



R	ΔG^0 (kcal/mol)[a]
4-Me	−1.70
5-Me	−1.27
6-Me	−1.70
6-Pr-*i*	−1.62

[a] For epimerization.

TABLE 12. Conformational free energies for some substituted cyclohexanes (Hirsh 1967; Jensen and Bushweller 1971)



R	ΔG^0 (kcal/mol)	R	ΔG^0 (kcal/mol)
OH	−1.0	F	−0.25
OMe	−0.56	Cl	−0.53
SMe	−1.07	Br	−0.48
SH	−0.90	CN	−0.25
Me	−1.70	COO^-	−1.96
Et	−1.75	Ac	−1.31
i-Pr	−2.15	COOMe	−1.1
t-Bu	−4.4	OEt	−0.9
Ph	−3.0	CH_2OH	−1.65
$HC\equiv C$	−0.41	CH_2OMe	−1.40
OAc	−0.60	NO_2	−1.05
NH_2	−1.20	SOMe	−1.9
		SO_2Me	−2.5

(Table 12). The smaller ΔG^0 value for the 5-methyl derivative (Table 11) reflects a reduced interaction between an axial methyl group and the oxygen which is apparently sterically 'smaller' than the methylene group in cyclohexane.

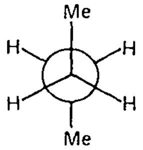
The preference of electronegative groups for the axial position in 2-substituted oxacyclohexanes is a manifestation of the *anomeric* effect. First discussed by Edward (Edward 1955; Edward, Morand and Pushas 1961) and rationalized by Lemieux (1964), the anomeric effect refers to the 'tendency of electronegative substituents at an anomeric centre ($C_{(1)}$) of a pyranose ring to exhibit a greater preference for the axial over the equatorial position than it does in cyclohexane' (Wolfe and Rauk 1971).

It was fortuitous and perhaps unfortunate that conformational analysis had its beginnings in carbocyclic rather than heterocyclic ring systems. Conformational preferences were rationalized in carbocyclic systems on the basis of 'effective size' and *n*-butane was used properly as a model for alkylcyclohexanes. In those instances in which unexpectedly low values of conformational free energies were found, as in bromocyclohexane, rationales were invoked based on the soft outer electron cloud for bromine and a long carbon–bromine bond. It is not surprising that the stronger axial preference of the anomeric hydroxyl in the pyranose sugars as compared to cyclohexanol (Table 12) was looked upon as a special effect since no argument which pertained to size could be sustained. It is now becoming increasingly clear that the special effect is in fact *normal* for carbocyclic systems with electronegative substituents and heterocyclic systems with electronegative ring atoms and/or substituents.

A major difficulty with the anomeric effect is an inability to create a clear physical picture for the phenomenon. The advent of machine calculations has made quantum mechanical explanations possible, but even those models are often in conflict. The recognition of what constitutes the anomeric effect has been extended beyond rings which contain two electronegative atoms attached to the same carbon.

The terms 'generalized anomeric effect' (Eliel 1972; Booth and Lemieux 1971), 'Edward–Lemieux effect' (Wolfe and Rauk 1971) and '*gauche* effect' (Wolfe 1972) have all been applied to the general phenomenon. Early ideas defined the origin of the phenomenon as an electrostatic interaction between the $C_{(5)}$—O ring bond and the $C_{(1)}$—OR bond of a pyranose structure.

An important simple model system for these studies has been dimethoxymethane discussed previously in the section on acyclic molecules. This system is analogous to the *n*-butane *anti* (47) and *gauche* (48) conformations used so extensively as models in cyclohexane studies. The initial surprise was that the *gauche* conformation **50** is preferred over the *anti* conformation **49**, whereas the *n*-butane *anti* conformation **47** is preferred over the *gauche* conformation **48**. Accordingly, the anomeric effect corresponds to a 'destabilization of a conformation (e.g. **49**) which places a polar bond between two electron pairs'. A model for 2-chlorooxacyclohexane is chloromethyl methyl ether (Anet and Yavari 1977) discussed previously in the section on acyclic molecules.



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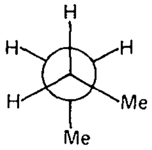

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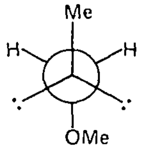

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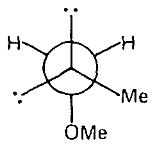
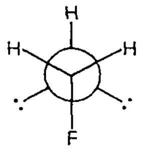


(50)

A more general statement of the anomeric effect is broadened to include a description of the effect on both static and dynamic stereochemistry as a result of having adjacent electron pairs, adjacent polar bonds or electron pairs adjacent to polar bonds in a molecule. Two general rules are proposed (Wolfe 1972): (1) 'electron pair–electron pair, electron pair–polar bond, or polar bond–polar bond interactions cause a significant increase in the rotation–inversion barriers of atoms bearing these substituents'; (2) 'when electron pairs or polar bonds are placed or generated on adjacent pyramidal atoms, *syn* or *anti* periplanar orientations are disfavoured energetically with respect to that structure which contains the maximum number of *gauche* interactions'. Rule (1) describes the dynamic properties of these systems and can be used to predict inversion pathways. For example, the energies for conformers **51** and **52** of fluoromethanol are calculated theoretically to be 12.6 and 8.25 kcal/mol above **53** which is the preferred conformation (Wolfe 1972). Conformations **51** and **52** are in fact potential *maxima* during rotation about the C—O bond.



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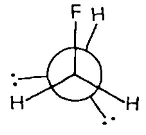

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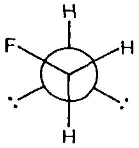
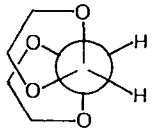


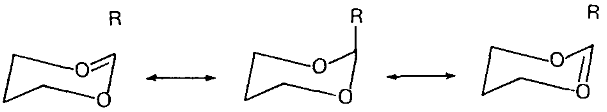
(53)

Rule (2) describes the thermodynamic properties of the system and so provides a rationale for conformational preferences. This rule is applicable to the report that bis-1,3-dioxacyclopentane adopts the *gauche* conformation 54 and that dimethoxymethane prefers the *gauche* conformation (50; see also 3).



(54)

Current interest in the physical origin of the anomeric effect is mainly the result of new capabilities for performing machine calculations and increasing confidence in molecular quantum mechanical calculations. Wolfe utilizes a model for which the total energy is a balance between attractive and repulsive forces and treats the system in terms of the interaction of bonded electron pairs and suggests that the nonbonded electrons on oxygen are essentially nondirectional and have no role other than to create a constant potential field through which the bonding electron pairs can move. He concludes that 'the physical origin of the Edward–Lemieux effect cannot be ascribed in any straightforward way to coulombic (dipole–dipole) interactions'. Altona (1964) suggests that donation from the axial lone pair of the ring oxygen into the $C_{(1)}$—X antibonding orbital stabilizes the axial conformation. A visual model of such an idea is described as double bond – no bond resonance (see 55; Bailey and Eliel 1974).

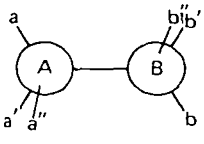


(55)

Baddeley suggested a description of the anomeric effect which is useful as a model with which to make predictions (Baddeley 1973):

> 'In each of the pairs of atoms Aa and Bb of the molecule 56, the larger amplitude of bonding orbital character is on the more electronegative atom and the larger amplitude of antibonding character on the less electronegative atom. Consequently, as shown in 57 which represents a system in which a is *anti* to b and the electronegativities of the atoms are in the order a > A and B > b, the best combination for an energy-lowering orbital interaction of the *Bb* bond and the unoccupied Aa antibonding orbital appears to involve the most electronegative ligand of A and the most electropositive ligand of B. The magnitude of this second-order stabilization will depend on the difference in energy between these two orbitals and the extent to which they overlap. The interaction will lower the electron density at b, increase the bonding A to B, partially neutralize the bond A—a and give preference to the configuration or

conformation which has the most elecropositive ligand (or lone pair of electrons) on B *anti* to the most electronegative ligand of A. Conversely, preference will be given to the most electropositive ligand of A being *anti* to the most electronegative ligand of B. These preferences have the same stereochemical implication as though given to placing the most electronegative (or electropositive) ligands of A *gauche* to the most electronegative (or electropositive) ligands of B. . . .'



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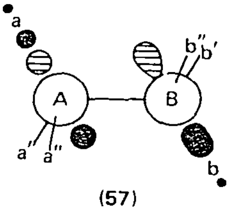


(57)

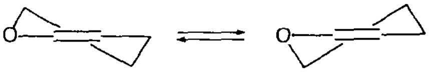
Gorenstein and Kar (1977) show by calculation that the O—C—O bond angle and the C—O torsional angle are coupled, i.e. the bond angle changes as the torsional angle changes. They caution that the prediction of torsional angles and calculation of barriers to internal rotation are sensitive to the initial choice of bond angle. For example, either a *gauche–gauche* or a *gauche–trans* conformation calculates to be of minimum energy for dimethoxymethane depending on the choice of bond angle for the O—C—O moiety. The coupling of the O—C—O bond angle to the C—O torsional angle plays an important role in optimizing energy. These calculations indicate that bond–bond interactions largely determine stereochemistry and that lone pair–lone pair effects are *not* responsible for the origin of the anomeric effect.

Others (Eliel, Kandasamy and Sechrest 1977; Kaloustian, Dennis, Mager, Evans, Alcudia and Eliel 1976) indicate that the Wolfe nulcear–electron attraction model and a classical electrostatic repulsion model both may be important in the anomeric effect each applicable more or less under different circumstances. Data from the study of solvent effects on the 1,3-dioxacyclohexanes with polar substituents at $C_{(5)}$ are rationalized on the basis of dipole–dipole interactions and solvation effects. Machine calculations do not at this time have the ability to predict the effect of solvent for these relatively large molecular systems and it is clear that a change in solvent can indeed affect conformational preferences.

However, the contribution that machine computations can make to our understanding of the origins of effects such as those discussed above is extremely important. It is generally held that those predictions which can be made from mathematical models are to be given the most confidence. There is however some reason for caution. All machine computation programs must incorporate assumptions which may or may not be critical in nature, e.g. the coupling of torsional angle and bond angle. The fact that the computations duplicate experimental data does not necessarily constitute best model knowledge and a continuing effort to develop more incisive theoretical approaches is required.

D. Dihydropyran

Analogous to cyclohexene, dihydropyran would be expected to adopt a half-chair geometry and be capable of undergoing a half-chair to half-chair interconversion (equation 13). Indeed, the rate of this process has been measured using



(13)

^{1}H DNMR spectroscopy and the $\Delta G^{\ddagger}$ value at −140°C is 6.6 ± 0.3 kcal/mol (Bushweller and O'Neil 1969). The rate of this half-chair ring-reversal process is slightly slower than the analogous process in cyclohexene ($\Delta G^{\ddagger}$ = 5.4 ± 0.1 kcal/mol at −165°C; Jensen and Bushweller 1969b), but substantially *faster* than the chair reversal process in oxacyclohexane (equation 10; $\Delta G^{\ddagger}$ = 10.3 kcal/mol at −61°C; Lambert, Keske and Weary 1967).

E. Thiacyclohexanes

Thiacyclohexane has an *R*-value of 2.6, indicating that it is distorted so as to push the *syn*-axial hydrogens closer together than in cyclohexane. The long carbon to sulphur bond (1.81 Å) spreads the molecule apart, while a C—S—C bond angle of 100° pushes the sulphur more out of the plane of the four carbon atoms than the corresponding carbon in cyclohexane (Kalff and Romers 1966). When the sulphur is protonated the *R*-value drops to 2.2 and the conformation is more like that of cyclohexane. The barrier for chair-to-chair ring reversal in thiacyclohexane-3,3,5,5-d_4 has been determined by ^{1}H DNMR spectroscopy ($\Delta G^{\ddagger}$ = 9.4 kcal/mol at −81°C; Lambert, Keske and Weary 1967).

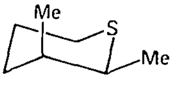
Low-temperature ^{13}C NMR spectra have been used to determine conformational preferences for a series of methyl-substituted thiacyclohexanes (Willer and Eliel 1977). These data are presented in Table 13. From perusal of Table 13, it is evident that the steric requirements for a methyl group at the 4-position of thiacyclohexane and for the methyl group in methylcyclohexane (ΔG^{0} = −1.7 kcal/mol) are very much alike as indicated by very similar ΔG^{0} values. The preferences of the methyl group for the equatorial position at the 2- and 3-positions of thiacyclohexane are somewhat smaller than the analogous value for methylcyclohexane. This is attributed to the absence of hydrogens on sulphur and an elongated CH_3—C—S—C *gauche* interaction.

The energy difference between the two conformers of *cis*-2,3-dimethylthiacyclohexane (−0.16 kcal/mol) and between the conformers of *cis*-3,4,-dimethylthiacyclohexane (−0.60 kcal/mol) in Table 13 is in contrast to the fact that the difference in energy between the two conformers of *cis*-1,2-dimethylcyclohexane is 0.00 kcal/mol. The presence of a ring heteroatom changes the conformational picture. The reason for the preferences shown by *cis*-2,3-dimethyl- and *cis*-3,4-dimethyl-thiacyclohexanes is in part related to the dihedral angle between the methyl groups. The dihedral angle between the equatorial 2-methyl and the axial 3-methyl groups of *cis*-2,3-dimethylthiacyclohexane (58) is 57° whereas the conformer with axial 2-methyl and equatorial 3-methyl has a dihedral

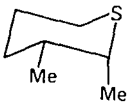
TABLE 13. Conformational free energies for methyl-substituted thiacyclohexanes (Willer and Eliel 1977)

Group	Preferred conformer	ΔG^{0} (kcal/mol)
3-Methyl	Equatorial	−1.40(−83°C)
cis-2,5-Dimethyl	e-2-Methyl, a-5-methyl	−0.02(−95°C)
trans-2,4-Dimethyl	a-2-Methyl, e-4-methyl	−0.38(−95°C)
cis-2,3-Dimethyl	e-2-Methyl, a-3-methyl	−0.16(−95°C)
cis-3,4-Dimethyl	a-3-Methyl, e-4-methyl	−0.60(−95°C)
2-Methyl	Equatorial	−1.42(calc.)
4-Methyl	Equatorial	−1.80(calc.)

angle of 52° (59). Accordingly, the energies for the *gauche* interactions between the two methyl groups are not equal; the *gauche* interaction with the greater dihedral angle is at lower energy (58). In addition, other types of interaction are different in the two conformations. Conformation 58 has two *gauche* butane-type interactions and one *gauche* CH_3—C—C—S interaction whereas conformation 59 has two *gauche* butane interactions and one *gauche* CH_3—C—S—C interaction.



(58)

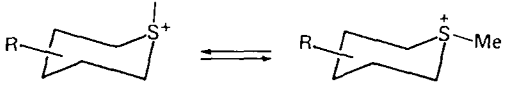


(59)

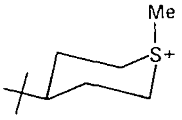
Following a similar argument, the dihedral angle for the axial 3-methyl and equatorial 4-methyl groups of *cis*-3,4-dimethylthiacyclohexane is 62° whereas the dihedral angle for the equatorial 3-methyl and axial 4-methyl isomer is 57°. The equatorial 4-methyl conformer has two butane *gauche* interactions and one CH_3—C—C—S *gauche* interaction as opposed to three butane *gauche* interactions for the axial 4-methyl conformer.

Protonated thiacyclohexane prefers a geometry in which the hydrogen adopts the axial conformation (Lambert 1967). The *R*-value (2.2) indicates that the conformation of the protonated species is more like cyclohexane than the unprotonated molecule. Accordingly, comparable conformational free energy values might be expected from the two systems. However, the equatorial preference of the methyl group in 4-*t*-butyl-*S*-methylthiacyclohexylium perchlorate is only 0.27 kcal/mol (Table 14). This value is considerably smaller than that for methylcyclohexane because the axial *S*-methyl group experiences reduced repulsions with *syn*-axial hydrogens due to a flattening of the ring near the sulphur atom. X-ray crystallographic data (Eliel, Willer, McPhail and Onan 1974; Gerdil 1974) reveal that the dihedral angle $C_{(3)}$—$C_{(2)}$—S—$C_{(6)}$ is 46° in 60 and 64° in 61. It follows that the

TABLE 14. Conformational free energies for some substituted *S*-methylthiacyclohexylium salts (Willer and Eliel 1977; Barbarella, Demback, Garbesi and Fava 1976)



R	X^-	ΔG^0 (kcal/mol) at 100°C
4-*t*-Butyl	ClO_4	−0.27
cis-3,5-Dimethyl	ClO_4	−0.32
4-Methyl	PF_6	−0.20
3-Methyl	PF_6	−0.08
2-Methyl	PF_6	−0.50
trans-2,5-Dimethyl	PF_6	−0.60
cis-2,4-Dimethyl	PF_6	−0.59
cis-2,6-Dimethyl	PF_6	−1.00
2,4,4-Trimethyl	PF_6	−0.48
3,3,5-Trimethyl	PF_6	−2.5
2,2,4-Trimethyl	PF_6	+0.10



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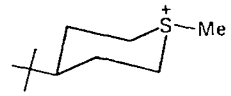


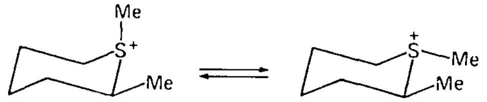
(61)

C—S—C bond angle in **60** is larger than in **61** since these bond angles are coupled to their respective dihedral angles (Gorenstein and Kar 1977). The realization that the C—X—C bond angle and the C—C—X—C dihedral angles may differ for each set of axial and equatorial conformers has not been exploited in conformational analysis but will certainly find greater application in the future.

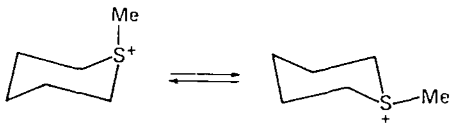
The data in Table 14 also show that although the conformational preference for the *S*-methyl group is small, there is considerable crowding from the methyl—methyl 1,3-*syn*-axial interaction in the 3,3,5-trimethyl derivative. The *syn*-axial *S*-methyl—*C*-methyl interaction is therefore in excess of 2 kcal/mol. The 2-methyl value (−0.50 kcal/mol) is higher than the 4-*t*-butyl value (−0.27 kcal/mol). The difference is attributed to a buttress effect from the equatorial 2-methyl group and the *S*-methyl. The equatorial 2-methyl group prevents ring-flattening to the same extent allowed in the 4-*t*-butyl derivative and makes the *S*-methyl axial conformation more crowded, i.e. the axial *S*-methyl group is pushed into the ring. The *trans*-2,5-dimethyl and *cis*-2,4-dimethyl derivatives show the same type of effect (Table 14). The *cis*-2,6-dimethyl derivative has an enhanced value due to the presence of a second equatorial group. In general, equatorial substituents at $C_{(2)}$ and $C_{(6)}$ increase the concentration of equatorial *S*-methyl by hindering ring-flattening. The effect is evident again in the ΔG^0 values available for 4-*t*-butyl-*S*-benzyl (−0.80 kcal/mol) and *cis*-2,6-dimethyl-*S*-benzyl derivatives (−1.50 kcal/mol).

Barbarella and coworkers (1976) report ΔG^0 values for 4-methyl, 3-methyl and *cis*-3,5-dimethyl-*S*-methylthiacyclohexylium salts which are considerably higher than those reported by Eliel. Solvent is believed to be the cause of the differences.

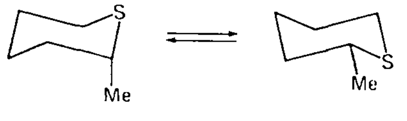
It is interesting to compare the results for the 1,2-dimethyl-thiacyclohexylium systems in Table 14 with other data. The equilibrium data from Table 14 reveal that the diequatorial geometry of the *trans* isomer (equation 14) is favoured over the *cis* with 2-methyl equatorial (ΔG^0 = −0.50 kcal/mol at 100°C). A low-temperature NMR study of 1-methylthiacyclohexylium hexafluorophosphate (Willer and Eliel, 1977) revealed *no* conformational preference for the *S*-methyl group at



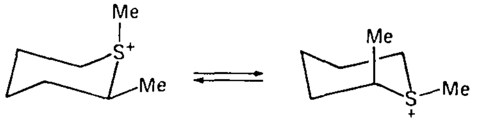
(14)



(15)



(16)



(17)

−90°C (equation 15; ΔG^0 = 0.0 kcal/mol). In contrast, the 2-methyl group of 2-methylthiacyclohexane strongly prefers the equatorial position (equation 16; ΔG^0 = −1.4 kcal/mol at 25°C; Willer and Eliel 1977). Thus, the fact that the *cis*-1,2-dimethyl derivative strongly prefers that geometry with an equatorial 2-methyl group (equation 17; ΔG^0 = +1.64 kcal/mol; Barbarella, Dembach, Garbesi and Fava 1976) reveals not unexpectedly that it is the 2-methyl group which is determining conformational preference in equation (17).

The preferred conformation of thiacyclohexane-1-oxide has been shown by DNMR studies to be that conformer which has an axial oxygen (ΔG^0 = 0.18 kcal/mol at −90°C; Lambert and Keske 1966). Equilibration of *cis*- and *trans*-4-*t*-butyl-thiacyclohexane-1-oxide also indicates a preference for axial oxygen. The 1,3-hydrogen–oxygen distance appears to be well within the range of the sum of the van der Waals' radii for hydrogen and oxygen and the attractive forces apparently outweigh repulsive forces for axial oxygen (Johnson and McCants 1964). Dipole moment studies also indicate that *cis*- and *trans*-4-chloro-thiacyclohexane-1-oxide prefer that conformation which has the oxygen in the axial position (Martin and Uebel 1964). The $\Delta G^\ddagger$ values for ring-reversal in thiacyclohexane oxide and thiacyclohexane dioxide are 10.1 kcal/mol (−70°C) and 10.3 kcal/mol (−63°C) respectively (Lambert, Mixan and Johnson 1973).

F. 1,3-Dioxacyclohexanes

1,3-Dioxacyclohexanes have been studied extensively by several groups. It is clear again that the presence of oxygen in the cyclic system makes analogy to the carbocyclic system problematical. The oxygen atoms affect the ring size and shape because of differing bond lengths, with the carbon–oxygen bond (1.41 Å) being shorter than the carbon–carbon bond (1.54 Å). As a result, the 1,3-dioxacyclohexanes are believed to be hyper (more puckered than cyclohexane) in the O—C—O portion of the molecule and hypo (less puckered than cyclohexane) in the C—C—C region of the molecule. In addition to this ring distortion the $O_{(1)}$ and $O_{(3)}$ positions have no hydrogens so that there are no 1,3-*syn*-axial hydrogen interactions with axial substituents at the $C_{(5)}$ position.

The barriers ($\Delta G^\ddagger$) for the chair-to-chair ring reversal process in 1,3-dioxacyclohexane, 2,2-dimethyl-1,3-dioxacyclohexane and 5,5-dimethyl-1,3-dioxacyclohexane, respectively, are 9.8, 7.9 and 11.2 kcal/mol (Anderson and Brand 1966; Friebolin, Kabuss, Maier and Lüttringhaus 1962). The significant drop in the barrier for 2,2-dimethyl-1,3-dioxacyclohexane as compared to 1,3-dioxacyclohexane may be attributed to increased 1,3-diaxial repulsions involving the axial methyl group and the 3,5-axial protons. This kind of interaction would lead to a flattening of the ring in the OCO region and a geometry closer to the transition state for ring-reversal. The increase in the barrier for the 5,5-dimethyl case as compared to the unsubstituted case may be due to more restricted rotation about the $C_{(4)}$—$C_{(5)}$ and $C_{(5)}$—$C_{(6)}$ bonds in the process of ring reversal.

The thermodynamic parameters for the chair–twist equilibrium in 1,3-dioxacyclohexane (Pihlaja 1968, 1974) and cyclohexane (Allinger and Freiberg 1960) are compiled in Table 15. It is expected that those interactions which cause cyclo-

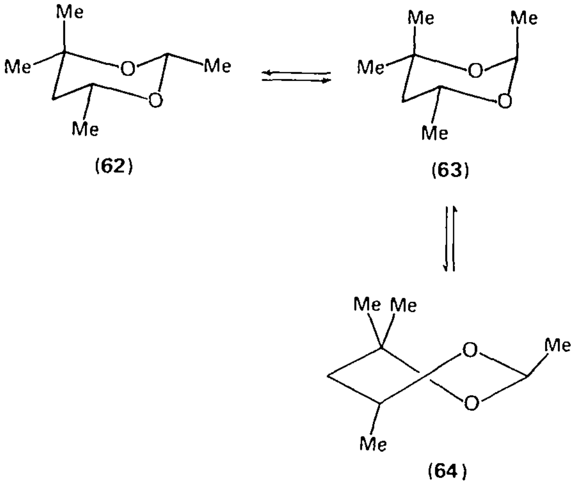
TABLE 15. Thermodynamic parameters for the chair-to-twist equilibrium (K_{eq} = [twist]/[chair]; Pihlaja and Pasanen 1974; Pihlaja and Nikander 1977; Allinger and Freiberg 1960)

	ΔG^0 (kcal/mol)	ΔH^0 (kcal/mol)	ΔS^0 e.u.
Cyclohexane	4.9	5.9	3.5
1,3-Dioxacyclohexane	8.0	8.6	2.2
1,3-Dithiacyclohexane	2.7	4.3	4.7

hexane twist conformations to be more stable than chair conformations will also cause the 1,3-dioxacyclohexanes to prefer the twist conformation over the chair.

Nonchair conformations have been detected by application of ^{13}C NMR substituent effects (Riddell 1970; Kellie and Riddell 1971; Jones, Eliel, Grant, Knoeber and Bailey 1971). A set of ^{13}C chemical shift substituent effects was derived for a series of 1,3-dioxacyclohexanes which were known to exist entirely in chair conformations. Predictions were then made by the appropriate addition of the chemical shift substituent parameter for the compounds under study. Any substantial discrepancy between the observed and predicted chemical shifts was then ascribed to nonchair or highly deformed chair conformations.

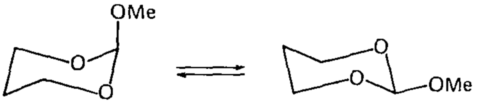
Those compounds that have 2–4, 2–6 or 4–6 diaxial substituent interactions gave the largest discrepancies and have been generally assigned to the twist family of conformations. These specific diaxial interactions are so severe that they raise the energy of the chair conformation above that of the twist. Compounds of this type include 2,2,4,4,6-pentamethyl, 2-2-*trans*-4,5-*cis*-pentamethyl, 2,2,4,4,6-hexamethyl, 2,2-*trans*-4,6-tetramethyl, 4,4,6,6-tetramethyl, 2,4,4,6,6-pentamethyl and 2,4,4,6-*trans*-tetramethyl-1,3-dioxacyclohexane. Equilibration of *cis*- and *trans*-2,4,4,6-tetramethyl-1,3-dioxane (equation 18) reveals that the *cis* epimer (62) is more than 5.6 kcal/mol more stable than the *trans* (63) which can exist to a large extent as a twist geometry (64). A study of the temperature-dependent ^1H NMR coupling constants for the *trans* isomer only indicates that the chair (63) to twist (64) ratio is 5 : 1 at room temperature and that the twist is the dominant conformer at 147°C (Nader and Eliel 1970).



(62) (63) (64)

(18)

Electrostatic interactions may play a major role in controlling conformational preferences in a heterocyclic system. For example, the ΔG^0 value for the axial to equatorial equilibrium for methoxycyclohexane is –0.60 kcal/mol at –80°C, (Jensen, Bushweller and Beck 1969), indicating a preferred equatorial methoxy conformation, whereas ΔG^0 for 2-methoxy-1,3-dioxacyclohexane is +0.62 kcal/mol, indicating a *preferred axial* conformation for the methoxy group (equation 19). Eliel describes electrostatic or polar effects in terms of an intramolecular dipole–dipole interaction (E_D) which is a maximum in the vapour phase and tends to zero in solvents of high dielectric constant, a solvation term (E_S) which is zero in the vapour phase and increases with the dielectric constant of the solvent and a steric compression term (E_{St}). In solution, that conformation which has the higher dipole moment is usually favoured (Kaloustian, Dennis, Mager, Evans, Alcudia and Eliel 1977). The total conformational energy is $E_T = E_{St} + E_D + E_S$.



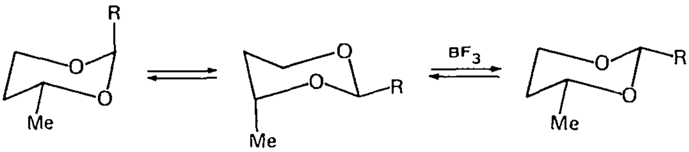
(19)

For 1,3-dioxacyclohexanes with electronegative substituents at $C_{(5)}$ the axial conformer has the greater dipole moment so that in solvents of high dielectric constant the axial conformation should be favoured over the equatorial conformation. The equilibration of *cis*- and *trans*-2-isopropyl-5-chloro-1,3-dioxacyclohexane in *carbon tetrachloride* indicates an equatorial preference for chlorine (ΔG^0 = –1.4 kcal/mol at 25°C) and a value of –0.25 kcal/mol in *acetonitrile* indicating a *greater* preference for the axial position in acetonitrile (Eliel, Kandasamy and Sechrest 1977). Other examples show an even more dramatic change in conformational preference with increasing dielectric constant. For example the corresponding 5-cyano group gives ΔG^0 values which range from –0.21 kcal/mol (favours equatorial cyano) in ether to +0.01 kcal/mol in acetonitrile (favours axial cyano slightly). A word of caution, however, is in order. Some solvents such as chloroform, benzene and toluene behave 'abnormally'. The abnormal behaviour may be related to the degree of penetration of the solvent into the cavity of the solute, the size of the solvent cage, and the orientation of the solvent about the solute which may change the bulk dielectric properties of the solvent system.

Steric effects are difficult to assess in this system. The $O_{(1)}$ and $O_{(3)}$ positions are devoid of hydrogens so that a substituent in the axial $C_{(5)}$ position experiences a different steric situation than the corresponding substituent in the $C_{(2)}$ axial position. The $C_{(2)}$ axial steric environment is much like that found in cyclohexane except that the 1,3-dioxacyclohexanes are hyperchair in this region (Eliel and Knoeber 1968; Pihlaja and Heikkila 1967). Accordingly, the preferences of a methyl group for the equatorial position at $C_{(2)}$ and $C_{(5)}$ of 1,3-dioxacyclohexanes are quite different, being –3.98 kcal/mol and –0.80 kcal/mol, respectively. The situation with an electronegative group is complicated by the anomeric effect. A 2-methoxy group favours the *axial* position by 0.41 kcal/mol (Nader and Eliel 1970) while a 5-methoxy group favours the *equatorial* position by 0.90 kcal/mol in the same solvent system.

A series of conformational free energy values are presented in Tables 16–18. Table 12 may be consulted for a list of values for substituted cyclohexanes for comparative purposes. The values in Tables 16–18 are taken from equilibrations in ether solvent or from nonpolar solvents when an ether value was not available. Values for other solvents may be found in the original literature. It is difficult to

TABLE 16. Conformational free energies for some 2-substituted 4-methyl-1,3-dioxacyclohexanes (Eliel and Knoeber 1968)



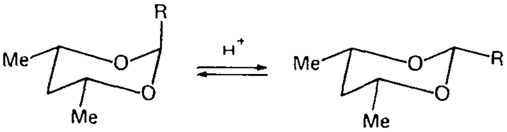
R	ΔG^0 (kcal/mol) at 25°C[a]
Me	−2.92
Et	−2.77
i-Pr	−2.73
t-Bu	−2.87
MeO	+0.36

[a] For the epimerization equilibrium.

make comparisons of ΔG^0 values from among the different systems in Table 16–18. For example, the ΔG^0 value for 2-methyl varies from 1.46 kcal/mol (Table 18) to 3.98 kcal/mol (Table 17) depending on the system equilibrated. A perusal of Table 16 indicates that the values for methyl, ethyl, isopropyl, and *t*-butyl are all smaller than the corresponding values from Table 17. The equilibrium for 2-substituted 4-methyl-1,3-dioxacyclohexanes (Table 16) is made up of at least a *three-component system* and the *trans* isomer exists predominantly in a conformation in which the $C_{(4)}$ methyl group is in the axial position. The epimerizations (e.g. with BF_3) in Table 16 are essentially those in which the $C_{(4)}$ methyl group is transferred from the axial to the equatorial position. The ΔG^0 values for methoxy in Table 16 indicates that the axial conformation is favoured. This is consistent with data for the equilibria depicted in Tables 17 and 18 and is another example of the role of the anomeric effect in heterocyclic systems (Eliel and Knoeber 1968).

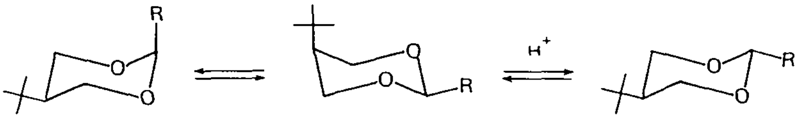
The conformational free energies obtained from the epimerization of *cis*- and

TABLE 17. Conformational free energies for some 2-substituted-4,6-dimethyl-1,3-dioxacyclohexanes (Eliel and Knoeber 1968)



R	ΔG^0 (kcal/mol) at 25°C
Me	−3.98
Et	−4.04
i-Pr	−4.17
Ph	−3.12
MeO	+0.41
HC≡C	+0.06
PhC≡C	0.00
$ClCH_2$	−4.19

TABLE 18. Conformational free energies for some 2-substituted-5-*t*-butyl-1,3-dioxacyclohexanes (Eliel and Knoeber 1968; Nader and Eliel 1970)



R	ΔG^0 (kcal/mol) at 25°C
Me	−1.46
Et	−1.43
i-Pr	−1.40
Ph	−1.38
MeO	+0.50

[a]For the epimerization equilibrium.

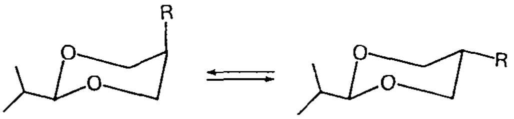
trans-2-substituted-5-*t*-butyl-1,3-dioxacyclohexanes (Table 18) are essentially the same for methyl, ethyl and isopropyl and indicate that the equilibrium biasing is determined essentially by the *t*-butyl group. The preference of a 2-methyl group for the equatorial position (−3.98 kcal/mol) has been measured from equilibration studies (Table 17) and a value of −4.01 kcal/mol was determined from calorimetric studies (Pihlaja and Luoma 1968). Equilibration of *cis*- and *trans*-2,5-di-*t*-butyl-1,3-dioxacyclohexane also reveals a relatively small preference for the equatorial 5-*t*-butyl group (ΔG^0 = −1.36 kcal/mol at 25°C; Pihlaja and Luoma 1968). Thus, the 4 kcal/mol preference for an equatorial *2-methyl* group on the 1,3-dioxacyclohexane ring (Table 17) is more than a sufficient amount of energy to ensure a preference for *axial* *t*-butyl in *cis*-2-methyl-5-*t*-butyl-1,3-dioxacyclohexane (Table 18). It is evident that the absence of 1,3-*syn*-axial hydrogens greatly reduces the steric requirements of an axial 5-*t*-butyl group as compared to the cyclohexane case.

The conformational free energies from the equilibration of *cis*- and *trans*-2-substituted-4,6-dimethyl-1,3-dioxacyclohexanes (Table 17) are useful to compare with those for the corresponding cyclohexanes. The equatorial preferences of 2-methyl, 2-ethyl and 2-isopropyl are almost twice as large as those for the corresponding cyclohexanes. On steric grounds this is attributed to the hyperchair in the O—C—O region of the molecule; the carbon—oxygen bond is shorter (1.41 Å) than the carbon—carbon bond (1.54 Å) and the distance from a $C_{(2)}$ axial alkyl group to the *syn* $C_{(4)}$ and $C_{(6)}$ positions is correspondingly shorter than in cyclohexane. The value for the CH_2Cl group is similar to values for the alkyl groups. The conformational preferences for methoxy, ethynyl and phenylethynyl (Table 17) are best explained by the anomeric effect. The value for phenyl is nearly the same as that reported for phenylcyclohexane (equatorial phenyl preferred) which is surprising given the hyperchair nature of 1,3-dioxacyclohexane. A rationale (Nader and Eliel 1970) is that the preference for the equatorial conformation in phenylcyclohexane is only partly due to the repulsion of the phenyl ring with the *syn*-axial hydrogens when the phenyl group is in the axial position. The axial phenyl group prefers a conformation with its flat side facing the *syn*-axial hydrogens of the cyclohexane ring. In this conformation there is a steric interaction between the *ortho* hydrogens of the phenyl ring with the equatorial hydrogens at positions $C_{(2)}$ and $C_{(6)}$ in the cyclohexane chair. This interaction disappears in 2-phenyl-1,3-dioxacyclohexane because oxygen atoms occupy these positions. The only significant difference between the conformers with equatorial and axial phenyl of 2-phenyl-1,3-dioxacyclohexane is the interaction of the axial phenyl ring with the *syn*-axial hydrogens. Although this interaction is more severe in the 1,3-dioxacyclohexane than in cyclohexane because of the shorter O—C—O bond distances, the absence of hydrogens on the oxygens compensates for the greater *syn*-axial compression with the result that conformational preferences are similar.

Calorimetric measurement (Bailey, Connon, Eliel and Wiberg 1978) of the heat of acid-catalysed isomerization of axial 2-phenyl-*cis*-4-*cis*-6-dimethyl-1,3-dioxacyclohexane to its equatorial epimer indicates that the conformational preference for the phenyl group is the result of a small conformational enthalpy ($\Delta H^0 = -2.0$ kcal/mol) and a large conformational entropy ($\Delta S^0 = 3.9$ e.u.) both favouring the *equatorial* isomer. The large entropy term is the result of the difference of freedom in the internal rotation about the $C_{(2)}$ to phenyl bond for each isomer, with the equatorial phenyl rotating freely while the axial phenyl librates about an average perpendicular orientation (flat face to the ring). The low ΔH^0 value is attributed to a small steric interaction present in the perpendicular conformation of an axial 2-phenyl group and also to the operation of the generalized anomeric effect.

The data in Table 19 related to 5-substituted-2-isopropyl-1,3-dioxanes is of special interest since it represents a system in which a double anomeric effect is

TABLE 19. Conformational free energies for some 5-substituted-2-isopropyl-1,3-dioxacyclohexanes at 25°C (Kaloustian, Dennis, Mager, Evans, Alcudia and Eliel 1976; Eliel, Kandasamy and Sechrest 1977)

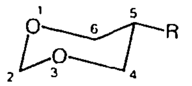


R	ΔG^0 (kcal/mol)	R	$-\Delta G^0$ (kcal/mol)
F	+0.62	CH_2SMe	−0.05
Cl	−1.20	CH_2CH_2SMe	−0.36
Br	−1.44	CH_2CH_2OMe	−0.53
CN	−0.21	SOMe	+0.60
COO^-	−1.11	CH_2SOMe	+0.14
COMe	−0.53	CH_2CH_2SOMe	−0.40
OCOMe	−0.00	CO_2Me	+1.16
OMe	−0.83	CH_2SO_2Me	+0.30
OEt	−1.05	$CH_2CH_2SO_2Me$	−0.12
CH_2OH	−0.03	$Me_2S^+OTs^-$	+2.0
CH_2OMe	−0.05	$Me_2SCH_2^+PF_6^-$	+0.60
NO_2	+0.38	$Me_2SCH_2CH_2^+PF_6^-$	−0.14
SMe	−1.73		
Me	−0.80[a]		
Et	−0.67[a]		
i-Pr	−0.98[a]		
t-Bu	−1.36[a]		
Ph	−1.03[a]		
OH	+0.41[a]		

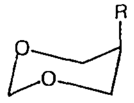
[a] Values from 2-*t*-butyl-5-substituted-1,3-dioxacyclohexanes.

operative. The 1,3-dioxygen orientation constitutes a dimethoxymethane geminal type of interaction while the R—$C_{(5)}$—$C_{(4)}$—O orientation constitutes a 1,2-vicinal dimethoxy ethane type of interaction. The geminal-type interaction is unfavourable in the chair conformation and the ring would have to twist to create a favourable geometry for orbital stabilization. It apparently requires more energy to twist the molecule than can be gained from a favourable anomeric effect since these molecules all exist in chair conformations. Therefore the data in this table is germane only to the dimethoxyethane type of anomeric effect. It should also be noted that the data in Table 17 reveal 2-isopropyl to be an effective conformational 'lock', i.e. the 2-isopropyl group is essentially exclusively equatorial.

The model for the anomeric effect as suggested by Romers, Altona and Baddeley discussed previously appears to explain most of the conformational preferences in this system (Table 19). The two relevant conformations are illustrated in **65** and **66**. Consider R a group which is more electronegative than $C_{(5)}$ and of course oxygen is more electronegative than $C_{(4)}$. When R is more electronegative than $C_{(5)}$, conformation **65** is destabilized with respect to that conformation in which R is *gauche* to oxygen (**66**). This is also consistent with the Wolfe rules discussed earlier.



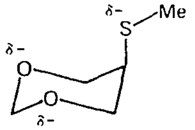
(65)



(66)

Those compounds which bear a substituent with a positive or partially positive charge are most stable with the substituent in the *axial* position. These groups include NO_2, SOMe, SO_2Me, CH_2SOMe, CH_2SO_2Me, SMe_2^+, NMe_3^+, $HNMe_2^+$, picrate, NH_3^+.

The following groups substituted at the 5-position of 1,3-dioxacyclohexane (Table 19) have a greater preference for the axial position than in the corresponding cyclohexanes: COOMe, Ac, CH_2OH, CH_2OMe. These groups also bear a partial positive charge on the carbon bonded to $C_{(5)}$ and aid in the destabilization of the equatorial (*anti*) conformer (**65**). The groups OMe, SMe, OEt, Cl, Br and CN all show a preference for the equatorial conformation in 5-substituted-1,3-dioxanes. Fluorine strongly prefers the axial position as predicted by the model. The values for CH_2SMe and CH_2OMe show a greater preference for the axial position than the corresponding group minus the CH_2 moiety because the methylene group bears a partial positive charge which destabilizes the equatorial conformation. As the strength of the positive charge diminishes, i.e. CH_2CH_2SMe, a greater preference for the equatorial position is found. Eliel favours an electrostatic attraction–repulsion model as depicted in **67** and **68**. Those groups which bear a partial negative charge prefer the equatorial position and those groups which bear a partial positive charge prefer the axial position. We note that neither the Eliel nor the Romers–Altona–Baddeley model makes all the correct predictions and that a composite model approach may need to be considered.



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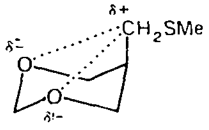
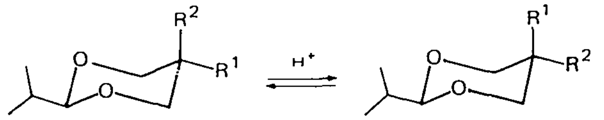


(68)

TABLE 20. Conformational free energies for 2-isopropyl-5,5-disubstituted-1,3-dioxacyclohexanes at 25°C (Eliel and Enanoza 1972)



R^1	R^2	ΔG^0(kcal/mol)
Me	Et	0.06
Me	*i*-Pr	−0.30
Me	*c*-Hex	−0.28
Me	*t*-Bu	−0.81
Me	MeO	−0.34
Me	Ph	−0.54
Et	*i*-Pr	−0.32
Et	Ph	−0.51
$HOCH_2$	Me	−0.68
$MeOCH_2$	Me	−0.63
OAc	Me	−0.09
HO	Me	−0.41
NO_2	Me	−0.62

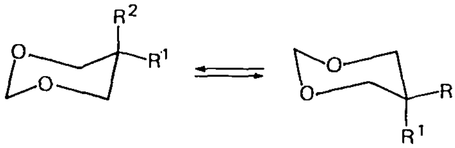
Equilibration data for 2-isopropyl-5-substituted-5-methyl-1,3-dioxacyclohexanes (Table 20) and low-temperature NMR data (Table 21) indicate that when size is a dominating factor in determining conformational preferences, the 5-substituents 'larger' than methyl generally prefer the equatorial position. This increased preference for the axial position by the methyl group is attributed to two possible causes: (*a*) the equatorial geminal substitute acts as a buttress preventing the axial substituent from bending outward, which is apparently more serious for an axial group larger than methyl and (*b*) the C—C—C bond angle is smaller (109·5° vs. 111°) and the ring more puckered when $C_{(5)}$ is quarternary than when it is tertiary (Eliel and Enanoza 1972).

When the anomeric effect intervenes, the presence of groups at $C_{(2)}$ more electronegative than alkyl all show a greater preference for the axial position when a geminal methyl group is present than when a geminal hydrogen is present. This implies that size is also an important consideration in the determination of conformational preference for these groups, and that electrostatic forces cannot be the sole factor.

Conformational free energies for a series of 2-substituted-2,*cis*-4,*cis*-6-trimethyl-1,3-dioxacyclohexanes were determined by equilibration studies (Table 22) (Bailey, Connon, Eliel and Wiberg 1978). The data show that all the alkyl groups prefer the equatorial position which is consistent with conformational principles that emphasize size relationships.

The ΔG^0 value for the 2-phenyl group (Table 22) indicates a stronger preference for the axial position than in phenylcyclohexane or in 2-phenyl-*cis*-4,*cis*-6-dimethyl-1, 3-dioxacyclohexane for which the phenyl group prefers the equatorial position by 3.0 and 3.1 kcal/mol, respectively. The increased preference for axial phenyl in the 2-methyl-2-phenyl derivatives can be attributed to entropy considerations when compared to the simple 2-phenyl derivative (i.e. no 2-methyl group).

TABLE 21. Conformational free energies in 5,5-disubstituted-1,3-dioxacyclohexanes by low-temperature NMR (ca. −55°C) (Coene and Anteunis 1970)

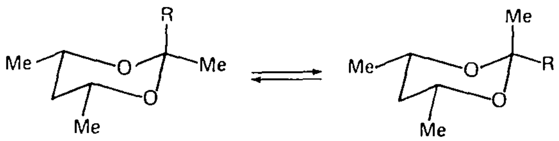


R^1	R^2	ΔG^0 (kcal/mol)
Me	NH_2	−0.16
Me	Ac	+0.91
Me	*i*-Pr	−0.19
Me	*i*-Bu	−0.03
Me	Ph	−0.32
Me	*s*-Bu	−0.18
Me	*c*-Pe	−0.12
Me	*c*-Hex	−0.19
Me	*n*-Pr	−0.29
Et	Ph	−0.38
Et	*i*-Pr	−0.17

The presence of a 2-methyl group restricts rotation of an equatorial phenyl group more than the case with *no* 2-methyl while rotation of an *axial* phenyl group is always restricted regardless of the absence or presence of a 2-methyl group. Such an effect will lower the entropy of any conformation having an equatorial phenyl and axial methyl on $C_{(2)}$.

Equilibration of 2-substituted-2,4-dimethyl-1,3-dioxacyclohexanes reveals an overwhelming preference for the axial position for CO_2Et (3.0 kcal/mol) while the values for CH_2Cl (0.06 kcal/mol) and CH_2Br (0.16 kcal/mol) indicate only a small preference for the axial position. The value for the chloromethylene group represents a dramatic increase in preference for the axial position in the above case when compared to equilibration data for *cis-* and *trans*-2-chloromethyl-*cis*-4, *cis*-6-dimethyl-1,3-dioxacyclohexane for which the chloromethyl group and the methyl group do not differ much in conformational preference. The greater

TABLE 22. Conformational free energies for some 2,2-disubstituted-1,3-dioxacyclohexane at 25° C (Bailey, Connon, Eliel and Wiberg 1978)



R	ΔG^0 (kcal/mol)
Et	−0.35
i-Pr	−0.62
Ph	+2.55

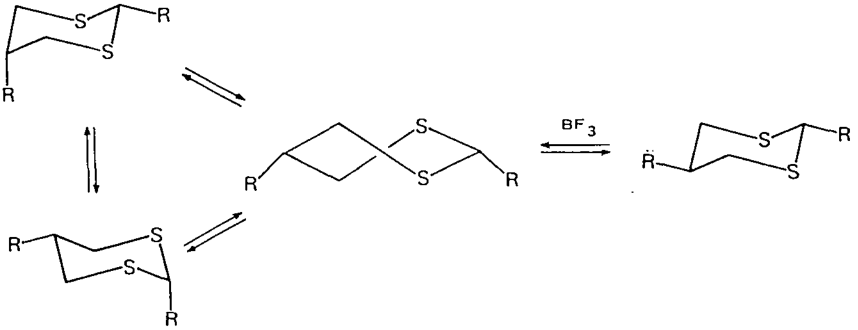
preference for the axial position shown by the bromomethylene over the chloromethylene group in the 2-substituted-2,4-dimethyl-1,3-dioxacyclohexanes is attributed to a reverse anomeric effect (Bailey and Eliel 1974).

G. 1,3-Dithiacyclohexanes

1,3-Dithiacyclohexane prefers the chair geometry as expected and the $\Delta G^{\ddagger}$ value for ring-reversal (9.4 ± 0.3 kcal/mol at −80°C; Friebolin, Kabuss, Maier and Lüttringhaus 1962) is not very different from 1,3-dioxacyclohexane (9.9 kcal/mol) or cyclohexane (10.3 kcal/mol). Barriers ($\Delta G^{\ddagger}$) to ring-reversal have also been determined for 2,2-dimethyl-1,3-dithiacyclohexane (9.8 ± 0.2 kcal/mol at −80°C) and 5,5-dimethyl-1,3-dithiacyclohexane (10.3 ± 0.2 kcal/mol at −65°C). The barrier trends parallel roughly those observed in the 1,3-dioxacyclohexanes discussed above.

A study of the equilibration between the *trans*- and *cis*-2,5-di-*t*-butyl-1,3-dithiacyclohexanes (Eliel and Hutchins 1969) as a function of temperature gave thermodynamic values of ΔG^0 (−1.82 kcal/mol at 25°C), ΔH^0 (−3.4 kcal/mol) and ΔS^0 (−5.3 e.u.) in Table 15. These values reflect the equilibrium between the chair (*trans* isomer) and twist (*cis* isomer) conformations of 1,3-dithiacyclohexane and indicate an energy preference for the chair. The corresponding values for cyclohexane and 1,3-dioxacyclohexane are considerably higher than these and suggest that 1,3-dithiacyclohexane can adopt the twist conformation much more readily than either of the others. Similar studies show that *cis*-2-phenyl-5-*t*-butyl- and *cis*-2,5-diisopropyl-1,3-dithiacyclohexane exist as mixtures of chair and twist conformations at room temperature. NMR data also establish *r*-2-*t*-butyl-*trans*-

TABLE 23. Conformational free energy differences for *cis*/*trans*-2,5-dialkyl-1,3-dithiacyclohexanes (Eliel and Hutchins 1969)



2-R	5-R	ΔG^0 (kcal/mol)[a]
t-Bu	Me	−1.04(69°C)
t-Bu	Et	−0.77(60°C)
t-Bu	*i*-Pr	−0.85(69°C)
t-Bu	*t*-Bu	−1.85(25°C)
i-Pr	*t*-Bu	−1.61(25°C)
Ph	*t*-Bu	−1.94(25°C)
i-Pr	*i*-Pr	−0.78(69°C)

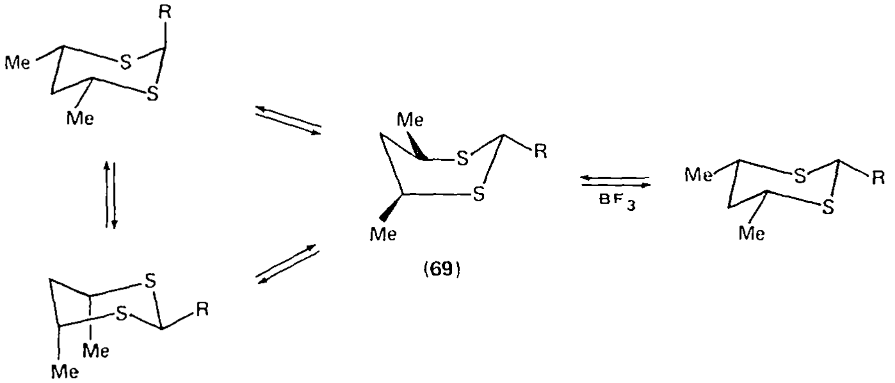
[a] For epimerization.

4,*trans*-6-dimethyl-1,3-dithiacyclohexane as a 'stiff' twist. The small difference in energy between the chair and twist conformations provides a reasonable alternative for this system to relieve itself of severe steric interactions in the chair geometry.

Conformational free energy values for the equilibration of *cis*- and *trans*-2,5-dialkyl-1,3-dithiacyclohexanes are given in Table 23. The ΔG^0 values for the first four compounds are smaller than the values for the corresponding cyclohexanes. The difference is attributed to a smaller space requirement for sulphur than for methylene. However, the *cis*-5-isopropyl-2-*t*-butyl and *cis*-2,5-di-*t*-butyl isomers exist as mixtures of chair and twist conformations. A contribution from the resulting entropy of mixing can account for some of the lower ΔG^0 values. With a *t*-butyl group at the 2-position, the ΔG^0 values for 5-methyl, 5-ethyl and 5-*t*-butyl are somewhat larger than the ΔG^0 values for the corresponding 1,3-dioxacyclohexanes (e.g. Table 19) and the isopropyl value is quite similar to that of the corresponding 1,3-dioxacyclohexane. The *cis*-5-isopropyl-2-*t*-butyl- and *cis*-2,5-di-*t*-butyl-1,3-dioxacyclohexanes have conformations in which the $C_{(5)}$ substituent occupies an *axial* position in the *chair* geometry whereas the corresponding 1,3-dithiacyclohexanes assume a *twist* conformation. It is important to note that one is dealing with two different equilibrium systems, the former a chair–chair equilibrium and the latter a chair–twist equilibrium. Caution is warranted when comparing conformational preferences in different systems; the number and types of each conformation present in the equilibrium may differ.

The ΔG^0 values for 2-alkyl-4,6-dimethyl-1,3-dithiacyclohexanes are given in Table 24. The preferences of the R group for the equatorial position at $C_{(2)}$ are quite similar to those reported for the corresponding cyclohexanes except for the 2-*t*-butyl derivative which is considerably lower than 4.9 kcal/mol established for the cyclohexanes. The *r*-2-*t*-butyl-*trans*-4,6-dimethyl-1,3-dithiacyclohexane has

TABLE 24. Conformational free energies for 2-alkyl-4,6-dimethyl-1,3-dithiacyclohexanes at 69°C (Eliel and Hutchins 1969)



(69)

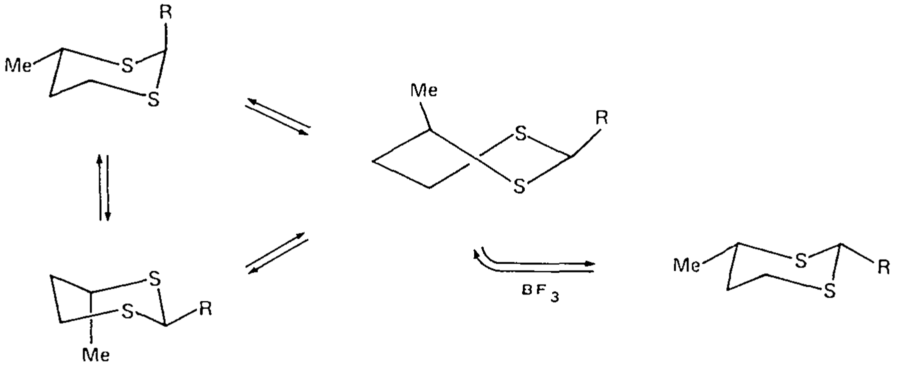
R	ΔG^0 (kcal/mol)[a]
Me	−1.77
Et	−1.54
i-Pr	−1.95
t-Bu	−2.72

[a] For epimerization.

been proposed to exist as a stiff boat (69) rather than as a chair conformation. Chair conformations for the *trans*-2-*t*-butyl epimer would probably require ΔG^0 values in excess of 4.9 kcal/mol. The preferences of 2-methyl, 2-ethyl and 2-isopropyl groups for the equatorial position on the 1,3-dithiacyclohexane ring (Table 24) are comparable to the values for the corresponding cyclohexanes but much smaller than for the analogous 1,3-dioxacyclohexanes (Table 17). The high values for the 1,3-dioxacyclohexanes can be attributed to a short C—O bond length (1.41 Å) which renders the *syn*-axial distances smaller than in the cyclohexane or 1,3-dithiacyclohexane systems. A model built for 2-phenyl-1,3-dithiacyclohexane from X-ray data (Kalff and Romers 1966) shows the $C_{(2)}$ to $C_{(4,6)}$ *syn*-axial distances to be only slightly smaller than the same distance in cyclohexane. The differences in conformational preferences for the substituted 1,3-dioxacyclohexanes compared to the cyclohexanes or 1,3-dithiacyclohexanes are similar. This is consistent with the ring inversion barriers for 2,2-dimethyl-1,3-dioxacyclohexane (7.9 kcal/mol; Anderson and Brand 1966), 2,2-dimethyl-1,3-dithiacyclohexane (9.4 kcal/mol; Friebolin, Kabuss, Maier and Lüttringhaus 1962), and 2,2-dimethylcyclohexane (10.4 kcal/mol; Müller and Tosch 1962). The values for the cyclohexanes and the dithiacyclohexanes are similar suggesting that there is approximately the same amount of ground-state compression for both compounds. The lower ring-inversion barrier for 2,2-dimethyl-1,3-dioxacyclohexane indicates considerably more ground-state compression due to the axial 2-methyl group and closer *syn*-axial hydrogens. This is also reflected in high equatorial alkyl conformational preferences in this system.

Conformational preferences for the 2-alkyl-4-methyl-1,3-dithiacyclohexanes are given in Table 25. The value for the 2-*t*-butyl group indicates that the predominant conformation for the *trans* isomer is one in which the 4-methyl group is axial. That

TABLE 25. Conformational free energies for 2-alkyl-4-methyl-1,3-dithiacyclohexanes (Eliel and Hutchins 1969; Pihlaja 1974)

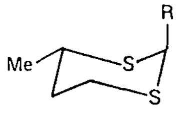


R	ΔG^0 (kcal/mol)[a]
Me	−1.26(25°C)
Et	−1.15(25°C)
i-Pr	−1.45(25°C)
t-Bu	−1.69(69°C)

[a] For epimerization.

conformation with the 4-methyl group equatorial (2-*t*-butyl axial) makes little or no contribution (Pihlaja 1974).

The *trans* isomers of 2,4-dimethyl-, 2-ethyl-4-methyl- and 2-isopropyl-4-methyl-1,3-dithiacyclohexane exist as a mixture of conformations **70** and 71. Based on the observed thermodynamic data (Eliel and Hutchins 1969), there is also reason to suspect the presence of a twist conformation (72). The values reported in Table 25 are also lower than the ΔG^0 values reported for the corresponding 1,3-dioxacyclohexanes (Table 16). Here again the longer carbon–sulphur bond and an entropy contribution may account for these differences. An investigation of the chair-to-chair equilibrium for *trans*-4,6-dimethyl-1,3-oxathiacyclohexane (Gelan and Anteunis 1968) reveals that the conformation 73 predominates to the extent of 85%, indicating that the 1,3-*syn*-axial interaction between axial methyl and $C_{(2)}$ across the C—S—C bonds is less severe than the corresponding interaction across the C—O—C bonds as in 74.



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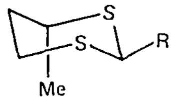
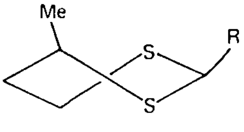


(71)



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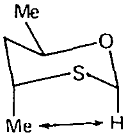
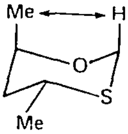


(73)

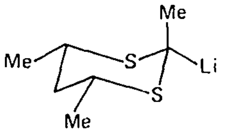


(74)

1. *Stereoselective reactions*

Treatment of the 2-lithium salt of *cis*-4,6-dimethyl-1,3-dithiacyclohexane with DCl, MeI and carbonyl compounds gives equatorial substitution with better than 99% isomeric purity. Reaction of the lithium derivative of *r*-2-*cis*-4,*cis*-6-trimethyl-1,3-dithiacyclohexanes (75) with HCl yields *r*-2-*trans*-4,*trans*-6-trimethyl-1,3-dithiacyclohexane (76). In a similar manner, the lithium derivative of *r*-2-*t*-butyl,*cis*-4,*cis*-6-dimethyl-1,3-dithiacyclohexane (77) and *cis*-2,4,4,6-tetramethyl-1,3-dithiacyclohexane give the contrathermodynamic isomers when treated with HCl indicating that for these compounds the preference for equatorial lithium (or carbanion electron pair) is overwhelmingly equatorial.

Lithiation followed by methylation of the two diastereoisomeric 2-deutero-*cis*-4,6-dimethyl-1,3-dithiacyclohexanes 78 and 79 shows that the equatorial hydrogen is abstracted only 8·6 times faster than the axial hydrogen. Stereospecificity therefore cannot be kinetically controlled because this rate difference is insufficient to account for stereoselectivities of greater than 99%. It was concluded that the process was thermodynamically controlled and the thermodynamic preference is for the lithium (or carbanion electron pair) equatorial (Eliel, Hartmann and Abatjoglou 1974).



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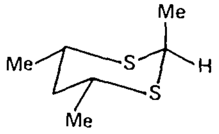
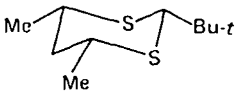


(76)



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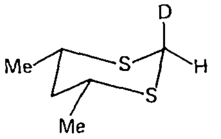

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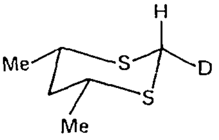
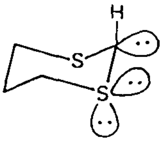


(79)

The most plausible explanation for the equatorial preference of the anion electron pair involves the anomeric effect. There is a second-order stabilization achieved by overlap of the carbon–sulphur antibonding σ^* orbital with the carbon to electron pair bonding orbital (Lehn and Wipff 1976) which is favoured in conformation **80**, for which the electron pair adopts the equatorial position. *Ab initio* calculations indicate that stabilization via an equatorial electron pair can amount to as much as 9 kcal/mol which is more than a sufficient amount of energy for control of the equilibrium. In the solvent tetrahydrofuran, 2-lithio-2-phenyl-1,3-dithiacyclohexane exists as a contact ion pair while in HMPA it exists as a solvent-separated ion pair. However, both types of ion pair react with electrophiles to give the same stereoselectivities. One concludes that the type of association between the carbanion and the lithium is unimportant and the preference of the carbanion electron pair for the equatorial position accounts for the stereospecificity (Abatjoglou, Eliel and Kuyper 1977; Eliel, Koskimies and Lohri 1978). The observation that electrophilic attack on 2-lithio salts of conformationally locked 1,3-oxathiacyclohexane like that on 2-lithio-1,3-dithiacyclohexanes leads exclusively to equatorially substituted products has been used to accomplish an asymmetric synthesis of (*s*)-(+)-atrolactic acid methyl ether (81) as illustrated in Scheme 1 (Eliel, Koskimies and Lohri 1978).



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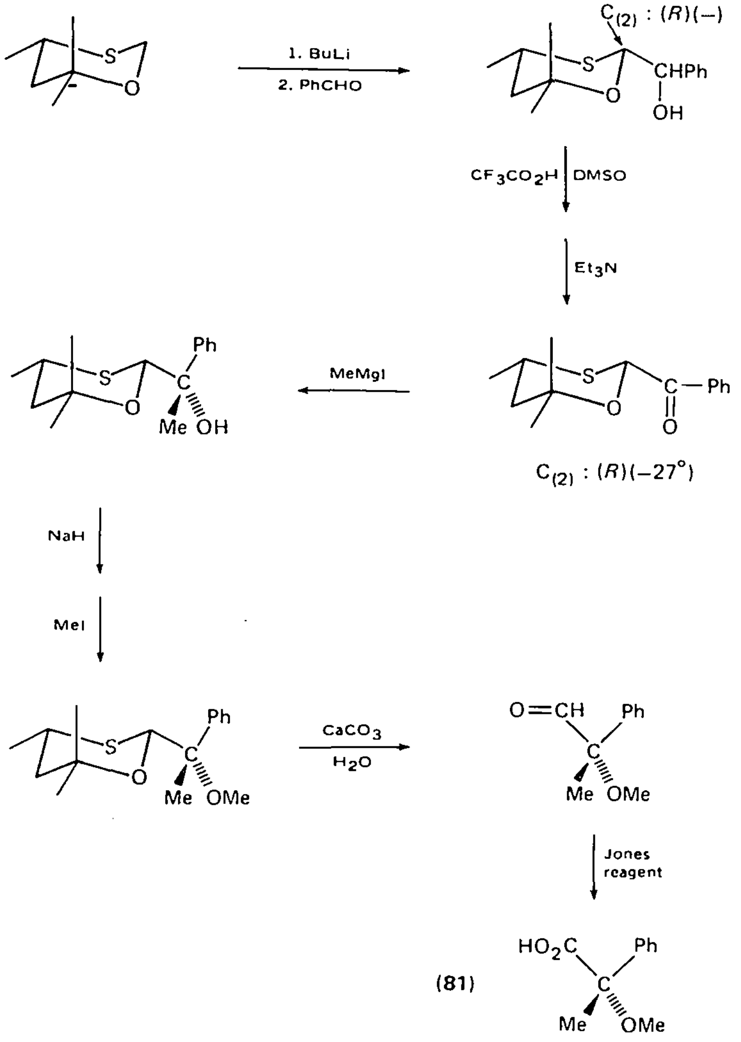


1. BuLi
2. PhCHO
$C_{(2)}$: (R)(−)
CHPh
OH
CF_3CO_2H
DMSO
Et_3N
C—Ph
O
$C_{(2)}$: (R)(−27°)
MeMgI
Ph
C
Me OH
NaH
MeI
Me OMe
$CaCO_3$
H_2O
O=CH
Jones reagent
HO_2C

(81)

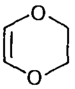
SCHEME 1.

H. Other Six-membered Rings containing Oxygen and Sulphur

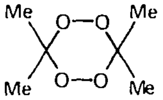
1,4-Dioxacyclohexane exists as a slightly puckered chair conformation as indicated by an R-value of 2.20 (Lambert 1967). The C—O—C bond angle is 112° and the C—O—C—C dihedral angle is 57.9° in contrast to cyclohexane which has a C—C—C—C dihedral angle of 54.5° (Romers, Altona, Buys and Havinga 1969). It is interesting to note that the ^{1}H NMR spectrum of 1,4-dioxacyclohexane is independent of temperature, i.e. remains a singlet, down to −166°C (Bushweller 1966). However, the ^{1}H DNMR spectrum of (*trans*-2,3-*trans*-5,6-d_4)-1,4-dioxacyclohexane separates into two singlets at low temperature separated by only 2.8 Hz at 100 MHz thus enabling the determination of a barrier ($\Delta G^{\ddagger}$) to ring-reversal of 9.7 kcal/mol at −94°C (Jensen and Neese 1975a).

The *trans*-2,3-dichloro- and 2,3-dibromo-1,4-dioxacyclohexanes have generated much interest in conformational studies in this class of compounds. Both of these prefer a chair conformation with *axial* halogens in both the solid state and in solution. In contrast, *trans*-1,2-dichlorocyclohexane exists as a mixture of conformers of which 48% occupy the diaxial position (Lemieux and Lown 1965). Diequatorial preferences are reported for *trans*-2,3-dimethyl-1,4-dioxacyclohexane (Gatti, Segre and Morandi 1967) and for the *trans*-2,5- and *cis*-2,6-dicarboxylic acid derivatives (Summerfield and Stephens 1954a,b). For these compounds there is no anomeric effect operating and 'conventional' preferences for the equatorial position are followed.

^{1}H DNMR methods have also been used to measure the rate of chair reversal in 3,3,6,6-tetramethyl-1,2-dioxane ($\Delta G^{\ddagger}$ = 14.6 kcal/mol; Claeson, Androes and Calvin 1961) and the rate of half-chair reversal in 1,4-dioxene (82; $\Delta H^{\ddagger}$ = 7.3 ± 0.2 kcal/mol, $\Delta S^{\ddagger}$ = 0.0 ± 1.0 e.u., $\Delta G^{\ddagger}$ = 7.3 ± 0.2 kcal/mol at −125°C; Larkin and Lord 1973). In 3,3,6,6-tetramethyl-1,2,4,5-tetroxane (83), it is apparent that there exists an expected essentially exclusive preference for the chair geometry and a substantial barrier to ring reversal ($\Delta G^{\ddagger}$ = 15.4 kcal/mol; Murray, Story and Kaplan 1966). This is in contrast to the all-sulphur analogue (*s*-tetrathiane) of 83, which as discussed below prefers the *twist* geometry.



(82)

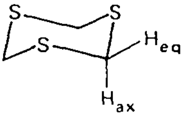


(83)

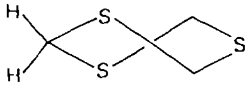
1,4-Oxathiacyclohexane exists as a distorted chair conformation as evidenced by an *R*-value of 2.77. The activation parameters for chair ring-reversal in 1,4-oxathia-cyclohexane have been determined by ^{1}H DNMR spectroscopy ($\Delta H^{\ddagger}$ = 8.8 ± 0.7 kcal/mol, $\Delta S^{\ddagger}$ = 0.5 ± 0.4 e.u., $\Delta G^{\ddagger}$ = 8.7 ± 0.3 kcal/mol at −96°C; Jensen and Neese 1975b). Conformational preferences in other substituted oxathia-cyclohexanes and oxathiolanes will be treated in detail by Professor Pihlaja in another chapter of this volume.

1,4-Dithiacyclohexane also exists as a chair conformation and the *trans*-2,3-dihalogen derivative also prefers a diaxial conformation due to the anomeric effect. An *R*-value of 3.38 suggests that the axial hydrogens are closer together than in cycloohexane, but X-ray analysis (Romers, Altona, Buys and Havinga 1969) indicates that the dihalogen dihedral angle is 165° rather than the expected 180°. This indicates that at least in the solid state the axial positions are splayed out from the ring. The barrier to chair reversal in 1,2-dithiacyclohexane-4,4,5,5-d_4 has been determined by the ^{1}H DNMR method ($\Delta G^{\ddagger}$ = 11.6 kcal/mol at −43°C; Claeson, Androes and Calvin 1961).

An ^{1}H DNMR study of 1,3,5-trithiane revealed spectral changes from a singlet at high temperatures to one AB spectrum at −80°C (Anderson 1971). This observation is consistent with a preference for the chair geometry (84) with non-equivalent axial and equatorial protons and not with the twist (85; all protons

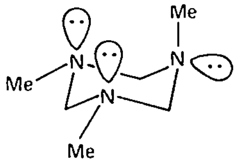


(84)



(85)

equivalent). As a comparison, ^{1}H DNMR studies indicate that *N,N',N''*-trimethyl-1,3,5-triazane also adopts a *chair* geometry for the ring but prefers, essentially exclusively, that conformation with one *N*-methyl group *axial* (86; Bushweller, Lourandos and Brunelle 1974).



(86)

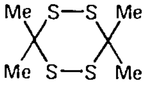
Barriers to chair reversal have also been measured for 1,2,3-trithiane ($\Delta G^{\ddagger}$ = 13.2 kcal/mol at −8°C) and 5,5-dimethyl-1,2,3-trithiane ($\Delta G^{\ddagger}$ = 14.7 kcal/mol at 6°C; Kabuss, Lüttringhaus, Friebolin and Mecke 1966).

I. *s*-Tetrathianes

It should be evident from the previous discussions of six-membered heterocycles in this article and the myriad studies of cyclohexane that the general preference for ring geometry in simple derivatives of these systems is the *chair* form. Boat and twist forms of simple derivatives are usually several kcal/mol higher in energy than the chair. Indeed, at least in the case of cyclohexane, the boat form is the *transition state* for pseudorotation of the twist.

The *s*-tetrathiane ring system is an interesting exception to the above trends both with respect to ring conformational preference and stereodynamics. Thus, we devote a separate section to this ring system.

Examination of the ^{1}H DNMR spectrum (60 MHz) of 3,3,6,6-tetramethyl-*s*-tetrathiane (87; 'duplodithioacetone', 15% by weight in Cl_2CCCl_2) at 80°C,



(87)

reveals a singlet resonance (δ = 1.73) consistent with rapid equilibration on the ^{1}H DNMR time-scale (Bushweller 1969). At lower temperatures in CS_2 as solvent, the spectrum broadens and is separated at −30°C into a large singlet at δ = 1.68 and two smaller singlets of *equal area* at δ = 1.53 and δ = 2.03 (Figure 6). If there were a strong conformational preference in 87 for the *chair* geometry (88; C_{2h} symmetry), the slow exchange spectrum would consist of just two singlets of equal area for axial and equatorial methyl groups. Indeed, these two singlets are present at −30°C at δ = 1.53 and δ = 2.03 (Figure 6) but the spectrum is dominated by a much larger singlet at δ = 1.68. The larger dominant singlet is consistent with the D_2 symmetry of the *twist* geometry (89) for which all methyl groups are equivalent. The area ratio of the large singlet (twist) to the total of the two small singlets (chair) is 2.3 at −15°C in CS_2 revealing that *the twist is favoured over the chair* (ΔG^0 = −0.43 kcal/mol). This observation is in clear contrast with cyclohexane and a host of six-membered heterocycles. Thus, it is apparent that 87 can equilibrate among two equivalent twist forms and two equivalent chair forms (equation 20).

From a cursory examination of the temperature range associated with changes in the ^{1}H DNMR spectrum of 87 (Figure 6), it was evident that the barrier to

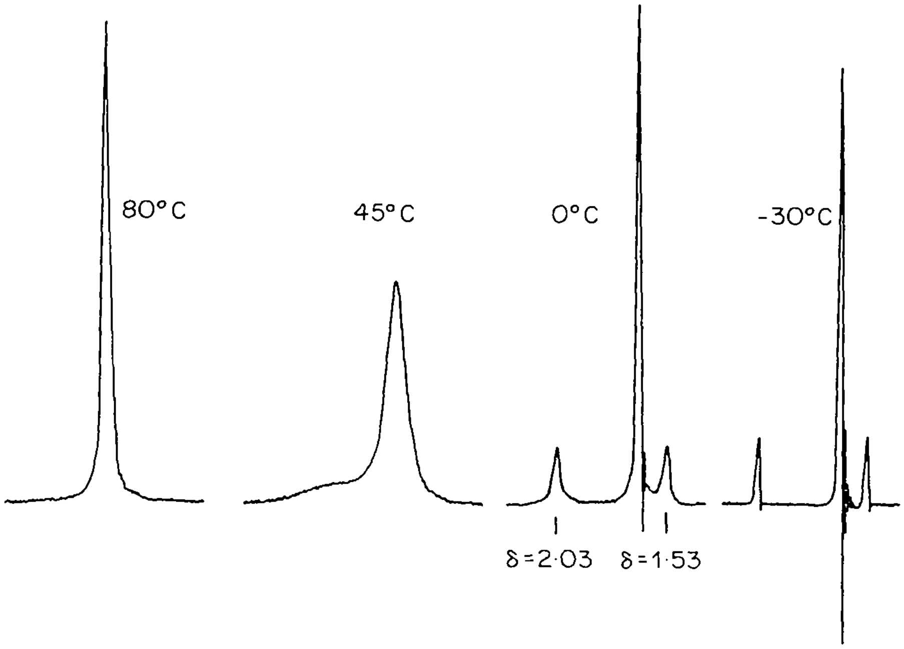
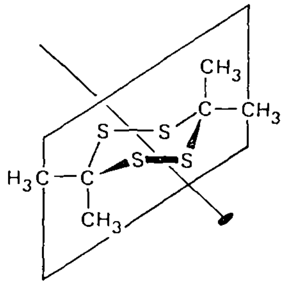
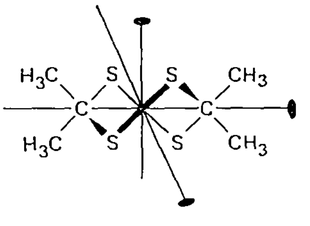


FIGURE 6. The ^{1}H DNMR spectra (60 MHz) of 3,3,6,6-tetramethyl-*s*-tetrathiane (87) in tetrachloroethylene (0–80°C) and in carbon disulphide (–30°C). Reprinted with permission from C. H. Bushweller, *J. Amer. Chem. Soc.*, 91, 6020 (1969). Copyright by the American Chemical Society.

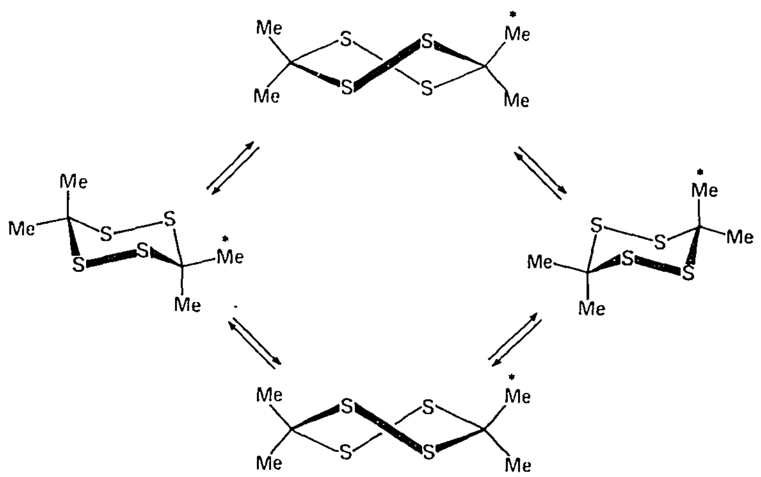


(88)



(89)

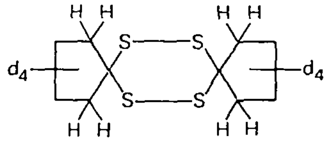
chair-to-twist exchange in 87 is about 16 kcal/mol. This would mean that the half-life of the chair or twist form at about -80°C would be long enough ($\sim$75 h) to permit *isolation* of either conformer using some technique. In addition, most crystalline compounds exist in a conformationally homogeneous state, e.g., all twist or all chair in the case of 87. Indeed, cooling a sample of crystals of 87 (m.p. 98°C) to -80°C and subsequent slow dissolution in CS$_2$ at -80°C produced a solution which gave *one* ^{1}H NMR singlet at $\delta = 1.70$, i.e. a solution of the conformationally pure twist form (89). The conclusion from this experiment is that 87 is indeed conformationally homogeneous in the crystal as the twist and this has been verified recently by X-ray crystallographic studies (Blocki, Chapuis, Zalkin and Templeton, unpublished data).



(20)

Isolation of the pure twist form of **87** allowed a study of the twist-to-chair equilibration by classical kinetic methods at low temperatures and by ^{1}H DNMR lineshape analyses at higher temperatures. The best dynamical model used to simulate the experimental ^{1}H DNMR spectra illustrated in Figure 6 incorporated no direct chair-to-chair equilibration, i.e. the observed rate process presumably involves a chair-to-twist to chair-to-twist stepwise itinerary (equation 20; Bushweller, Golini, Rao and O'Neil 1970). Apparently, there is no *direct* twist-to-twist equilibration in 87 (equation 20) but the fact that all methyl groups are equivalent in the twist form of **87** precludes the detection of a direct twist-to-twist process by the DNMR method. The activation parameters for the chair to twist process in **87** are $\Delta H^\ddagger = 15.9 \pm 0.4$ kcal/mol, $\Delta S^\ddagger = 1.2 \pm 1.0$ e.u. and $\Delta G^\ddagger = 15.6 \pm 0.1$ kcal/mol at 14°C.

A compound which revealed a more complete stereodynamical picture for the *s*-tetrathiane ring is **90**. Examination of the ^{1}H DNMR spectrum of **90** with ^{2}H decoupling reveals a broadened singlet at 82.7°C (Figure 7). At lower temperatures, the spectrum broadens and is separated into two large sharp singlets of *equal* area (δ = 1.73, 2.77) and a less intense AB spectrum (δ = 2.36, 1.78; $J = -14.2$ Hz) at −23°C (Bushweller, Bhat and coworkers 1975). The ratio of the total area of the two singlet resonances to the total area of the AB spectrum is 4.3 : 1.0 at −23°C. The two large singlet resonances for **90** may be assigned to the *chair* conformer for which rapid cyclopentane pseudorotation creates effectively C_{2h} symmetry and both protons on any given axial or equatorial methylene group are reflected through a time-average plane of symmetry and thus are equivalent to each other. Obviously, an axial methylene group is different from an equatorial methylene and two different *singlets* are observed for the chair geometry (equation 21). The AB spectrum at −23°C (Figure 7) is then assigned to the twist conformer of the *s*-tetrathiane ring of **90** (equation 21) but the observation of an AB spectrum for



(90)

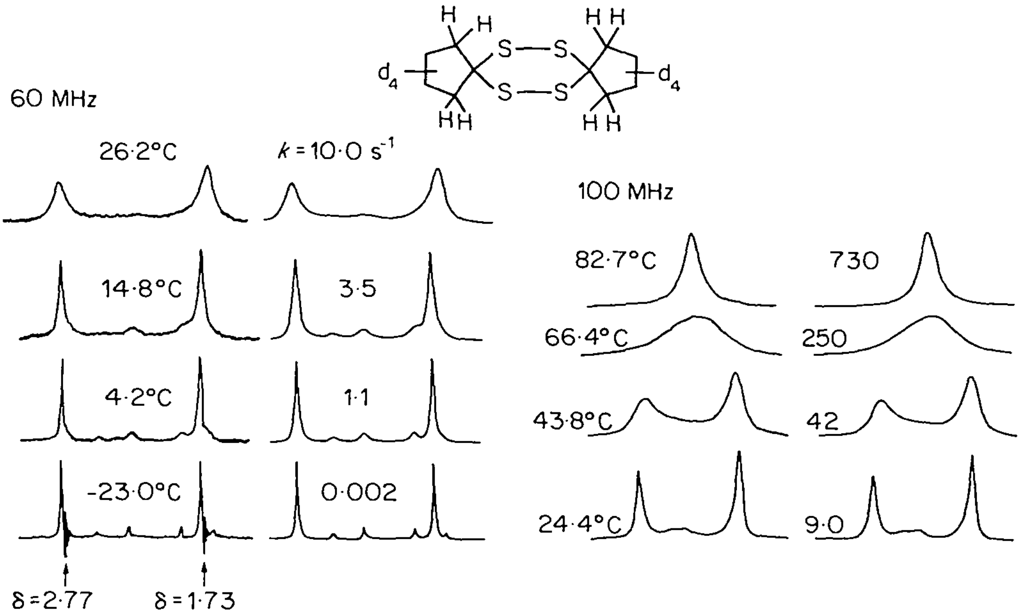
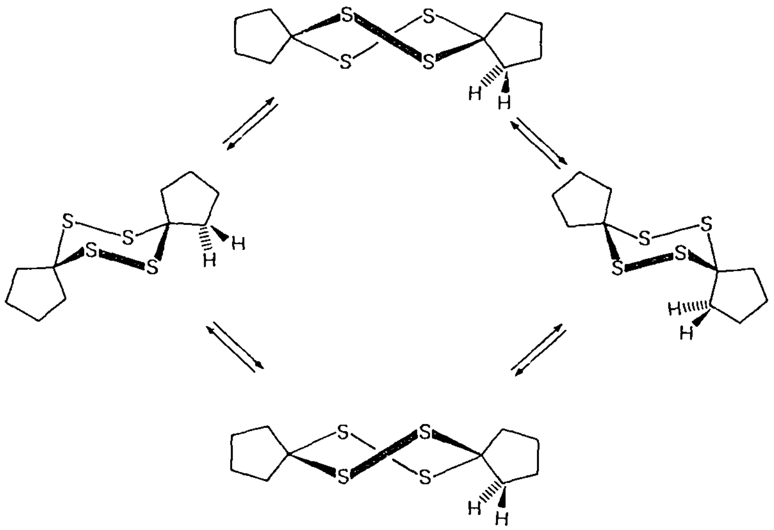
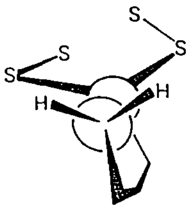


FIGURE 7. The experimental and theoretically calculated ^{1}H[^{2}H] DNMR spectra of **90** (60 MHz) in CS_2 as solvent and at 100 MHz in Cl_2CCCl_2 as solvent; k is the first-order rate constant for conversion of chair to twist. Reprinted with permission from C. H. Bushweller and coworkers, *J. Amer. Chem. Soc.*, 97, 66 (1975). Copyright by the American Chemical Society.



(21)

the twist implies a unique stereodynamical situation. Even in the event of fast cyclopentane pseudorotation for the twist form of **90**, the two protons of a given methylene group of a *static* *s*-tetrathiane twist geometry will be nonequivalent due to effective overall D_2 symmetry and respective proximate 'up' or 'down' sulphur—



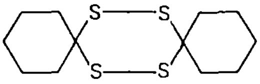
twist

(91)

sulphur bonds. This symmetry effect is illustrated in the projection (91) of a *partial* structure of a twist form of **90**. If the *s*-tetrathiane twist-to-twist process were fast at −23°C the AB spectrum would be time-averaged to a *singlet*. In the case of **90**, both the direct chair-to-chair process (exchange of the two singlets) and the direct twist-to-twist process (AB exchange) are DNMR-detectable (see equation 21). In fact, the dynamical model used to give the best DNMR simulation incorporated *no direct chair-to-chair processes and no direct twist-to-twist processes.* The preferred itinerary for conformational exchange in **90** involves the stepwise chair-to-twist-to-chair-to-twist pathway as illustrated in equation (21). The activation parameters for the chair-to-twist process in **90** are $\Delta H^{\ddagger} = 15.7 \pm 0.5$ kcal/mol, $\Delta S^{\ddagger} = -2 \pm 2$ e.u. and $\Delta G^{\ddagger} = 16.2 \pm 0.1$ kcal/mol at 26.2°C. The strong implication to be drawn from the above data is that the barrier for the twist-to-twist process in **90** (i.e. a process analogous to pseudorotation of the cyclohexane twist) is *higher than 16 kcal/mol.* The barrier to cyclohexane twist pseudorotation is about 1 kcal/mol (Pickett and Strauss 1970).

From an integration of ^{1}H NMR peak areas for **90** at −15°C discussed above, one may calculate that the *chair* geometry of **90** is favoured over the twist ($\Delta G^0 = -0.71$ kcal/mol at −15°C in CS_2). This is in contrast to the conformational preference in 87.

An analogous but more complicated ^{1}H DNMR study of deuteriated 92 revealed



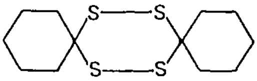
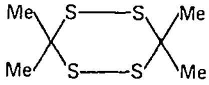
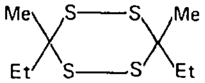
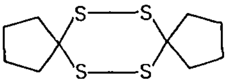
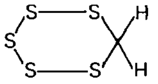
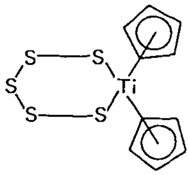
(92)

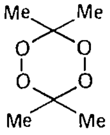
changes in the spectrum consistent with restricted twist-to-chair, chair-to-chair and twist-to-twist rate processes for the *s*-tetrathiane ring and slow cyclohexane ring-reversal on both the *s*-tetrathiane twist and chair conformers (Bushweller, Bhat and coworkers 1975).

For purposes of comparison, the chair-to-twist ratios for a number of multi-sulphur six-membered rings are compiled in Table 26 including data for pentathiane (Feher, Degen and Söhngen 1968) and a pentasulphur titanium complex (Köpf, Block and Schmidt 1968). The reasons for the conformational preferences in Table 26 and especially the low chair-to-twist energy difference in *s*-tetrathianes are not immediately evident. A rationale for the trend in *s*-tetrathiane conformational preferences is based on a combination of the *gem*-dialkyl effect and interactions between *syn*-axial lone pairs on sulphur (Bushweller 1969) but an alternative rationale could be founded on 1,3-interactions between axial alkyl groups and sulphur atoms of the tetrathiane chair.

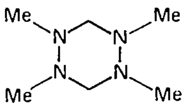
It is noteworthy that other heterocycles analogous to the *s*-tetrathianes such as 93 (Murray, Story and Kaplan 1966) and 94 (Anderson and Roberts 1968) show a strong ring conformational preference for the chair geometry although 94 displays an unusual *axial* preference for two methyl groups.

TABLE 26. Chair: twist ratios in solution for multisulphur heterocycles

Compound	Chair : twist ratio
	0.25(–15°C)
	0.43(–15°C)
 (*cis* and *trans*)	0.56(–15°C)
	4.0 (–15°C)
	>99
	>99



(93)

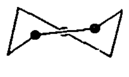


(94)

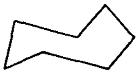
Molecular mechanics calculations have been applied to a series of six-membered rings containing different numbers of sulphur atoms (Allinger, Hickey and Kao 1976). Agreement with experiment is excellent in some cases and it is evident that these theoretical calculations do give accurate insight into the intimate stereodynamics of these sulphur heterocycles.

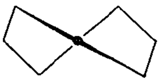
J. Medium Rings

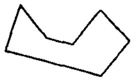
Calculations based on empirically determined potential functions have identified four potentially stable conformations of different symmetry for cycloheptane: the twist-chair (95), chair (96), twist (97) and boat (98) (Bocian and Strauss 1977a,b).


(95)

● = CH_2

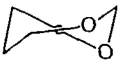

(96)

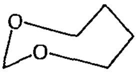

(97)


(98)

The energies of these conformations increase in proceeding from 95 to 98. There are multiple possibilities for conformational exchange itineraries in such *saturated* seven-membered rings. One type of process is pseudorotation which may be defined for a homocyclic system as a process which results in a new geometry which is superimposable on the original but rotated about one or more symmetry axes. No bond angle deformations occur during the course of a pseudorotation. Barriers to pseudorotation are usually very low. The other type of rate process is a ring-reversal process analogous to cyclohexane ring-flip. Much bond angle deformation may occur during the course of a ring-reversal. Barriers to classic ring-reversal processes are usually higher than those for pseudorotation. However, in some medium and large ring systems, pseudorotation can effect the same net conformational change as a ring-reversal (Hendrickson 1967; Dale 1969). Excellent reviews of research in the sterodynamics of medium rings have been published relatively recently (Anet and Anet 1975; Dale 1969; Friebolin and Kabuss 1965; Sutherland 1971; Tochtermann 1970). The reader should consult these articles for a more complete treatment than is possible here.

In the case of 1,3-dioxacycloheptane, theoretical calculations indicate that a twist-chair (**99**) is the most stable geometry analogous to cycloheptane but there are a series of chair forms (**100**–**103**), twist (**104**), and boat forms (e.g. **105**) of comparable stability (Bocian and Strauss 1977a,b). The barrier to conformational exchange in 1,3-dioxacycloheptane is estimated to be 4 kcal/mol and thus it is not surprising that no DNMR data are available for this system. Also, no DNMR spectra changes have been reported for cycloheptane (Anet and Anet 1975). ^{13}C NMR studies conducted at ambient temperatures on substituted 1,3-dioxacycloheptanes fail to indicate the presence of a single highly populous conformation (Gianni, Saavedra and Savoy 1973). The data do show that a conformational array is present at room temperature. ^{13}C NMR chemical shift substituent effects indicate that for *trans*-4,7-dimethyl-1,3-dioxacycloheptane a conformational mixture is present including chair forms such as **106** and **107** as well as twist-chairs (e.g. **108**). The ^{13}C NMR chemical shift trends indicate the presence of axial methyl groups consistent with **107**. Conformation **108** does not have methyl group with axial character but conformation **107** and its twist do have sufficient axial character to account for the ^{13}C NMR spectra (Gianni, Saavedra, Savoy and Kuivila 1974). The ^{13}C NMR data for the *cis* isomer indicates an array of four conformations (**109**–**112**) *or* their twist forms. Conformations **111** and **112** each have an axial


(99)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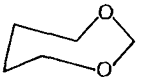
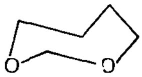

(101)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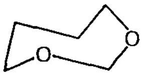
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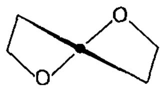
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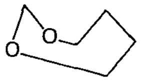
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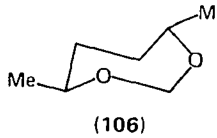

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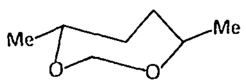

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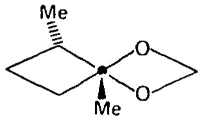

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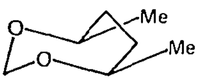

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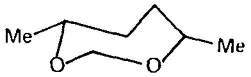

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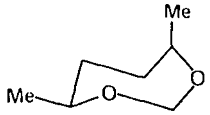

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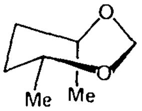


(112)

methyl group which accounts for the ^{13}C NMR chemical shift substituent effects observed for C$_{(5)}$.

Equilibration data for some substituted 1,3-dioxacycloalkanes are compiled in Table 27. The low ΔG^0 values for 2-*t*-butyl-4-methyl-1,3-dioxacycloheptane, 2-*t*-butyl-5-methyl-1,3-dioxacycloheptane and 2-*t*-butyl-4-methyl-1,3-dioxacyclopentane have been interpreted to indicate the presence of numerous conformations separated by small energy differences (Gianni, Saavedra and Savoy 1973; Willy, Binsch and Eliel 1970). This is consistent with theoretical calculations which indicate that 1,3-dioxacycloheptane has a twist conformation that is preferred by 4 kcal/mol over the most stable chair conformation and a series of chair and twist-chair conformations which differ in energy by less than 3 kcal/mol (Bocian and Strauss 1977a,b) However, these calculations give little or no weight to substituent or anomeric effects which as we have seen can play a major role in the determination of conformer stability. For example, the calculations predict that chair conformation **103** is more stable than **101** but the anomeric effect would favour **101** and disfavour **103**. The predicted energy difference between these

TABLE 27. Conformational free energies for some substituted 1,3-dioxacycloalkanes (Gianni, Saavedra and Savoy 1973; Willy, Binsch and Eliel 1970; Eliel and Knoeber 1966; Riddell 1967; Gianni, Cody, Asthana, Wursthorn, Patanode and Kuivila 1977)

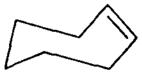
cis $\rightleftarrows$ *trans* or *exo* $\rightleftarrows$ *endo*	ΔG^0 (kcal/mol)
cis/*trans*-2-*t*-Butyl-5-methyl-1,3-dioxacycloheptane	−0.0 (80°C)
cis/*trans*-2-*t*-Butyl-4-methyl-1,3-dioxacycloheptane	−0.45(80°C)
cis/*trans*-2-*t*-Butyl-4-methyl-1,3-dioxacyclopentane	−0.27(25°C)
cis/*trans*-2-*t*-Butyl-4-methyl-1,3-dioxacyclohexane	−2.9 (25°C)
cis/*trans*-2-*t*-Butyl-5-methyl-1,3-dioxacyclohexane	−0.84(25°C)
exo/*endo*-4-Isopropyl-3,5-dioxabicyclo[5.1.0] octane	−0.12(80°C)

conformations is not very large so that even a small energy increase for **103** due to the anomeric effect could be important in determining the conformer populations.

The data in Table 27 are also consistent with conformational preferences found for cycloheptane derivatives. The enthalpy difference between *cis*- and *trans*-1,3-dimethylcycloheptane is approximately zero as is the enthalpy difference between *cis*- and *trans*-1,4-dimethylcycloheptane (Mann, Muhlstadt, Muller, Kern and Hadeball 1968).

The observed conformational parameters (e.g. ΔG^0) for the 1,3-dioxa*cyclohexanes* are due in part to the fact that there are only two low-energy chair conformations available for each pair of diastereoisomers in the case of disubstituted rings. For the five- and seven-membered rings there are many conformations of comparable energy available. The low ΔG^0 value for 4-isopropyl-3,5-dioxabicyclo[5.1.0]octane is due to the fact that the *exo* and *endo* isomers exist as chair and crown conformations which differ only slightly in energy.

Stable conformations of cycloheptene include the preferred chair (**113**), boat (**114**) and twist (**115**) forms (Emer and Lifson 1973). The boat form can be transformed to the twist by a local pseudorotation but conversion of the boat or the twist to the chair requires a ring-reversal. An ^{1}H DNMR study of cycloheptene indicates a low barrier to conformational exchange ($\Delta G^{\ddagger}$ = 5 kcal/mol; St. Jacques and Vaziri 1971). It should be noted that **113** is a rigid chair incapable of pseudorotation. A complete pseudorotation all the way around the ring involving **114** or **115** is also not possible due to the presence of the double bond. Thus, the presence of the double bond reduces stereodynamical possibilities as compared to the saturated ring cycloheptane.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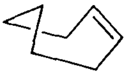
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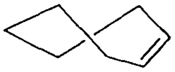
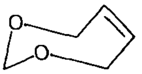

(115)

The presence of a double bond at $C_{(5,6)}$ also reduces the number of conformations which need to be considered for the 1,3-dioxacyclohep-5-enes to a chair (**116**), twist (**117**) and a boat (**118**). ^{13}C NMR substituent effects were used to assign preferred twist conformations to 2,2-dimethyl-1,3-dioxacyclohept-5-ene, *cis*- and *trans*-4,7-dimethyl-1,3-dioxacyclohept-5-ene and *r*-2-*t*-butyl-*cis*-4,*trans*-7-dimethyl-1,3-dioxacyclohept-5-ene (Gianni, Adams, Kuivila and Wursthorn 1975). *cis*-4,7-Dimethyl-1,3-dioxacyclohept-5-ene prefers the twist conformation (**119**) even though the chair conformation has two equatorial methyl groups while the twist has an axial methyl group. A twist conformation for the *trans* isomer (**120**) relieves a severe 1–3 methyl–hydrogen interaction which is present in the chair. This is also true for 2,2-dimethyl-1,3-dioxacyclohept-5-ene and 2,2-dimethyl-1,3-di-



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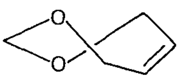

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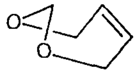

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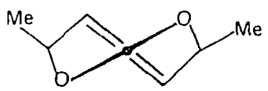
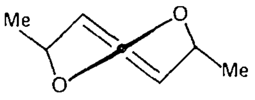


(119)



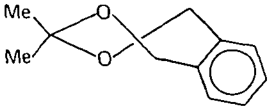
(120)

• = CH_2

oxabenzocycloheptane. In contrast, 1,2-benzocycloheptane, 5,5-dimethyl-1,2-benzocycloheptene, cycloheptene (Ermer and Lifson 1973) and 5,5-difluorocycloheptene (Knoor, Ganter and Roberts 1967) are most stable in chair conformations. Unfortunately, the preferred conformation for 1,3-dioxacyclohept-5-ene itself is unknown.

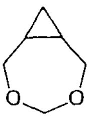
A generalized anomeric effect has been suggested as the driving force that makes the chair conformations less stable than the twist forms for the substituted 1,3-dioxacyclohept-5-enes (Gianni, Adams, Kuivila and Wursthorn 1975). The geometry of the chair conformation is such that the $C_{(4)}$—O and $C_{(7)}$—O bonds are *syn*-periplanar and each of these bonds is in turn *syn*(and *anti*)-periplanar to the p-orbitals of the π-bonds. The Wolfe rule indicates that these orientations are disfavoured with respect to those orientations which have *gauche* interactions between the p-orbitals and the $C_{(4)}$—O and $C_{(7)}$—O bonds as in the twist conformations. This also explains the preference for the twist conformation shown by 1,3-dioxacyclohept-5-ene oxide discussed below. In contrast, cycloheptene oxide in which there is no anomeric effect exists as a mixture of chair and crown conformations (Servis, Noe, Easton and Anet 1974).

^{1}H DNMR studies have been of some value in studying the stereodynamics of these systems. For example, the $C_{(4)}$ and $C_{(7)}$ proton resonances of 2,2-dimethyl-1,3-dioxabenzocycloheptene are transformed from a singlet at 25°C to an *AB spectrum* at −76°C. The 2,2-dimethyl resonance remains a *singlet*. Such a spectrum at −76°C is consistent with the symmetry of the twist (121) in which the two methyl groups are equivalent. The $\Delta G^{\ddagger}$ for ring-reversal is 9.7 kcal/mol (Friebolin, Mecke, Kabuss and Lüttringhaus 1964). No change in the ^{1}H NMR spectrum of the unsubstituted analogue was observed to −120°C. By way of comparison, the barriers to conformational exchange in benzocycloheptene-4,4,6,6-d_4 and 5,5-dimethylbenzocycloheptene are 10.9 kcal/mol at −56°C and 11.8 kcal/mol at −45°C, respectively (Friebolin and Kabuss 1965).



(121)

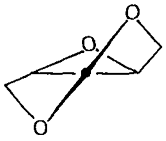
Stereodynamical restrictions analogous to those imposed by the double bond in the 1,3-dioxacycloheptene system may also be introduced by the presence of a three-membered ring. Indeed, the barrier for chair-to-chair ring-reversal in 122 is about 11 kcal/mol (Gianni, Cody, Asthana, Wursthorn, Patanode and Kuivila 1977). Conformational assignments are also reported for a series of 3,5-dioxabicyclo[5.1.0]octanes. A twist conformation (123) was assigned to 3,5,8-trioxabicyclo[5.1.0]octane on the basis of low-temperature ^{1}H NMR spectra. The anomeric effect is presumed to be important in establishing the twist conformational preference over that of either the chair or the crown conformations.



(122)

A twist is also reported as the preferred conformation for 4,4-dimethyl-*exo*-8-bromo-3,5-dioxabicyclo[5.1.0]octane (124; Taylor and Chaney 1976; Taylor, Chaney and Dick 1976). For this molecule, the chair and crown conformations have severe 1–3 methyl–hydrogen interactions which are relieved in the twist. The anomeric effect due to the oxygen atoms in the 1 and 3 positions is also more favourable in the twist than in either the chair or crown conformations.

In the solid state a crown conformation is preferred by 4-phenyl-8,8-dichloro [5.1.0] octane (Clark, Fraser-Reid and Palenik 1970). In solution, a preference for the crown conformation is also reported for 8,8-dichloro- and 8,8-dibromo-3,5-dioxabicyclo[5.1.0] octanes (**125**). The monohalogen analogues, *exo*-8-chloro- and *exo*-8-bromo-3,5-dioxabicyclo[5.1.0] octanes prefer the chair conformation (**127**) over the crown (**128**). The preference of **125** over **126** can be rationalized on the basis of a repulsive interaction between the *endo* halogens and 3 and 5 oxygen atoms in **126**. The absence of this type of interaction in **127** may play a role in its preference over **128**.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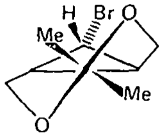
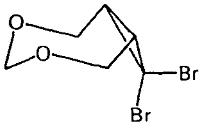


(124)



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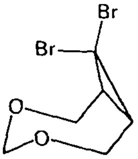

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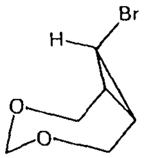

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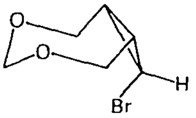
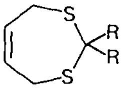


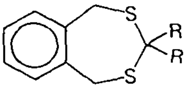
(128)

Several sulphur analogues of the 1,3-dioxacycloheptenes discussed above have been investigated by the ^{1}H DNMR method. In most cases, it is not possible to obtain a clear-cut conformational assignment. Some structures with associated free energies of activation are illustrated below. The data for **129** and **130** have been taken from Friebolin, Mecke, Kabuss and Lüttringhaus (1964).



(129)

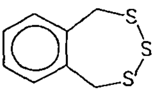
R	$\Delta G^{\ddagger}$(kcal/mol)
H	8.5(−100°C)
Me	8.2(−110°C)



(130)

R	$\Delta G^{\ddagger}$(kcal/mol)
H	10.9(−55°C)
Me	12.1(−33°C)

In at least one instance (**131**), evidence for a chair-to-twist interconversion ($\Delta G^{\ddagger} \cong 17$ kcal/mol) has been obtained directly from ^{1}H DNMR studies (Kabuss, Lüttringhaus, Friebolin and Mecke 1966). ^{1}H DNMR methods have also detected

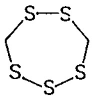


(131)

TABLE 28. Barriers to conformational exchange in 1,3-dioxacycloöctanes

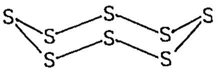
Compound	Rate process	$\Delta G^{\ddagger}$(kcal/mol)
1,3-Dioxacycloöctane	Pseudorotation	5.7
	Ring-inversion	7.3
2,2-Dimethyl-1,3-dioxacycloöctane	Pseudorotation	6.4
	Ring-inversion	11.0
6,6-Dimethyl-1,3-dioxacycloöctane	Pseudorotation	4.9
	Ring-inversion	6.4
2,2,6,6-Tetramethyl-1,3-dioxacycloöctane	Pseudorotation	5.8
	Ring-inversion	10.8

restricted conformational exchange in **132** (E_a = 12.9 kcal/mol; Moriarty, Ishibe, Kayser, Ramey and Gisler 1969).



(132)

The all-sulphur eight-membered ring (S_8) prefers the crown conformation (**133**; Abrams 1955). A limited amount of data regarding the stereodynamics of medium rings containing oxygen or sulphur is available. Substantial enhancements in barriers to ring-reversal may occur as a result of introduction of sulphur into an eight-membered ring. For example, the barriers ($\Delta G^{\ddagger}$) for ring-reversal in the series **134** (Lehn and Riddell 1966) range from 13.4 to 14.8 kcal/mol as compared to cycloöctane ($\Delta G^{\ddagger} \cong$ 8 kcal/mol; Bushweller 1966).



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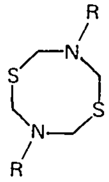

(134)

R = alkyl

The dynamics of some eight-membered rings containing oxygen are summarized in Table 28 (Anet, Degen and Krane 1976).

A more complete discussion of the stereodynamics of other medium and large rings may be found in the series of review articles cited above.

IV. ACKNOWLEDGEMENT

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER **6**

Chiroptical properties of alcohols, ethers, thio ethers and disulphides

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I. INTRODUCTION

The purpose of this chapter is to bring up to date and to extend to disulphides the review by Toniolo and Fontana[1]. Although chromophoric derivatives of alcohols will not be treated, the benzoate and dibenzoate chirality rules will be included owing to the particular interest of this topic.

II. ALCOHOLS

The optical activity of chiral alcohols has been widely studied since the period when the most important theoretical treatments in this field were described. Kuhn[2a], Boys[2b], Kirkwood[2c] and Eyring[2d,e], among others, have tried to predict the *R*-configuration of (+)-2-butanol by their theories of optical activity.

Some more recent studies on the hydroxyl chromophore, where the most consolidated theoretical treatments are applied, will be reported here, with particular attention to the reliability of the stereochemical data obtained in the different cases.

Organic chemists as a rule are not fully aware how safe and reliable the application of available CD information can be to the solution of stereochemical problems.

Direct MO calculations of optical activity, *ab initio* or otherwise, are more and more frequent, but the perturbative models are generally preferred by the experimental chemists owing to the size of the investigated molecules and to the fact that the descriptions obtained by these models are more pictorial and capable of generalization.

The 'dynamic coupling model' (electric–electric, electric–magnetic)[3] is now the most widely followed; it states in a general way that a transition of a symmetric chromophore, in order to be optically active, that is, to have associated collinear magnetic and electric dipole moments, must induce by its charge distribution the required electric dipole moments in the polarizable asymmetric chemical surrounding.

In order to obtain nonempirical sterochemical information from CD data, we must therefore know the electronic states of both the chromophore and its surrounding groups very well.

The CD studies of the hydroxyl chromophore in a saturated asymmetric carbon backbone[4,5] and the CD of benzoate derivatives of molecules containing either aromatic[6] or aliphatic[7] groups can clearly emphasize how the safety of the stereochemical data achieved by CD spectra increases when aromatic groups are present in the chiral molecule; in these cases, well-isolated and -studied transitions are involved.

The CD spectrum of (+)-2-butanol in the vapour phase was measured in the vacuum-UV[4] (Figure 1) and three bands centred at 180.8 nm, 161.3 nm and 149.3 nm have been clearly resolved.

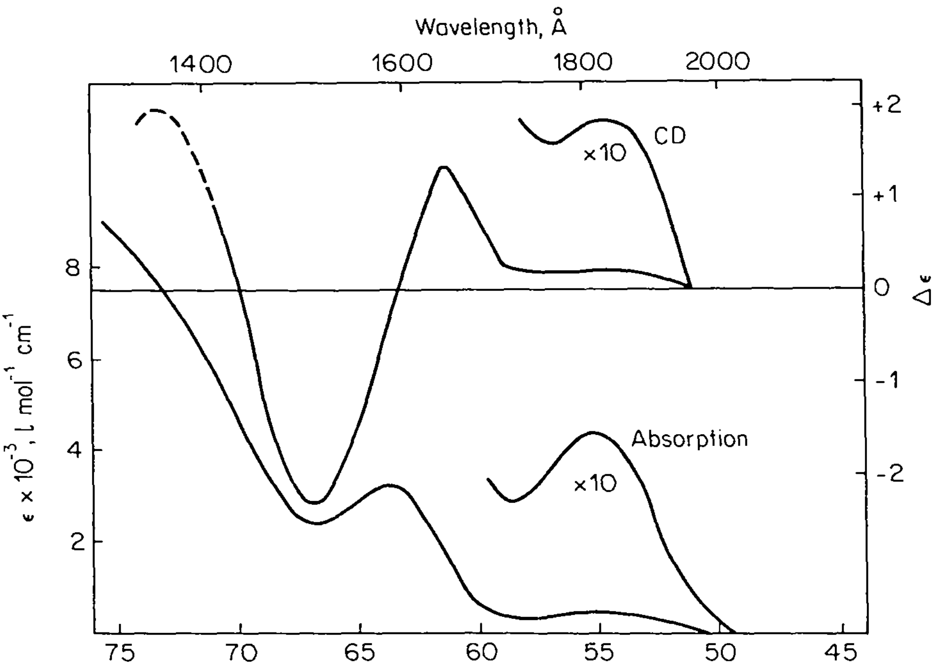


FIGURE 1. The absorption and circular dichroism spectra of (+)-(*S*)-2-butanol in the vapour phase. Reproduced from P. A. Snyder and W. C. Johnson, Jr., *J. Chem. Phys.* 59, 2618 (1973) with permission of the American Institute of Physics.

The advantage of the CD technique with respect to the isotropic absorption is shown by the resolution of the absorption band at 156.3 nm in the two opposite-signed bands at 161.3 nm and 149.3 nm. These three transitions were assigned as n → σ* (O–H), n → σ* (C–O) and n → 3s (–O–) respectively; the round brackets indicate the location of the transition in the chromophore. Starting from these very tentative assignments, the rotational strength (i.e. intensity of the optical activity) of the three transitions were calculated by a dynamic-coupling approach. The calculations were performed assuming that the staggered conformation with a methyl–hydroxyl interaction was the only conformation of the hydrocarbon backbone, and that the free rotation of the hydroxyl group is sterically restricted. Agreement between the experimental and the computed signs of the rotational strengths of the three transitions was achieved. However, the basis of this elegant theoretical treatment is very unsafe; besides the conformational mobility of the system, both the transitions of the hydroxyl chromophore and the polarizability of the carbon backbone have been only tentatively described. In fact, neither the quantitative values of the anisotropies of the polarizability nor their signs can be considered to be certain; that is, we still do not really know if an ethane molecule is more polarizable perpendicular to or along the C—C bond, and hence we do not know whether the electric dipole moments induced by the transition charge distribution of the hydroxyl group must be placed in the calculations along the C–C bond or perpendicular to it.

In order to eliminate at least the uncertainties of the conformation of the carbon backbone, the same authors have subsequently studied L-borneol[5] where the only conformational freedom is the hydroxyl rotation.

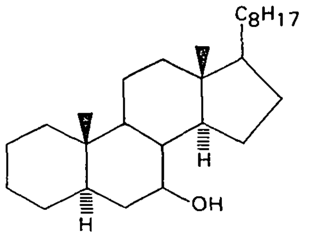
The same theoretical treatment was applied with three different sets of polarizabilities for the C—C and C—H bonds. The conformation which theoretically reproduces the negative sign of the two lower energy transitions is that reasonably expected from examining a space-filling model of L-borneol. Surprisingly, these theoretical results are, in this case, quite insensitive to the sign of the anisotropy of the polarizabilities chosen.

These results seem to confirm the assignments of the two lowest energy transitions as n → σ*(OH) and n → σ*(C–O), and to rule out the n → 3s assignment, recently proposed for the lowest energy transitions[8a,b], which does not give the same agreement between experimental and theoretical rotational strength. The possibility of discriminating between n → 3s and n → σ* transitions is due to the different origin of their optical activity.

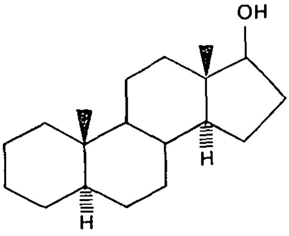
CD data of about thirty saturated hydroxy steroids and terpenes were reported by Kirk, Mose and Scopes[9], and the CD absorption maxima in the region 185–198 nm were assigned to the hydroxyl chromophore (Figure 2).

A very simple 'right–left' rule with respect to the C–O–H plane is proposed; only the contribution to the CD absorption of the bonds which project forwards towards the lone-pair orbitals of the oxygen atom has been considered. The contribution seems to change sign across the C–O–H plane (Figure 2). Such a simple rule could support a p → 3s assignment of this low-energy transition (as could be very easily demonstrated by symmetry considerations linked to the dynamic coupling approach). However, the weak experimental consistency of these data does not allow full confidence in the results (CD spectra were measured in solution with a commercial instrument down to 185 nm).

We can conclude at this point that the CD spectrum of the hydroxyl chromophore is not very useful in stereochemical determination; the spectroscopy of this group is not really known, and it starts to absorb at the lower limit of the near-UV,



(1)



(2)

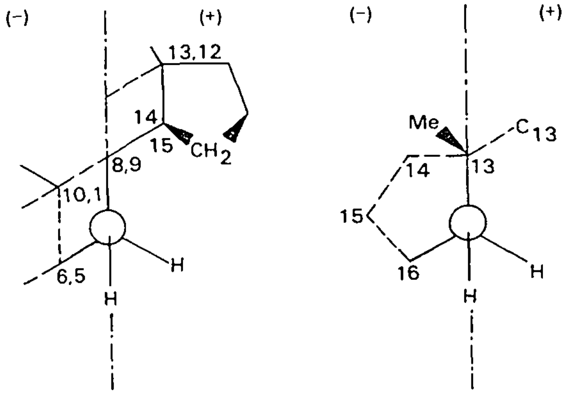


FIGURE 2. Sector projections of 5α-cholestan-7β-ol (1) and 5α-androstan-17β-ol (2). The molecules are viewed in a Newman projection in the preferred conformation and projected along the O–C bond. Experimentally, 1 and 2 have positive and negative Cotton effects respectively. Reproduced from D. N. Kirk, W. P. Mose and P. M. Scopes, *J. Chem. Soc., Chem. Commun.*, 81 (1972) with permission of the Chemical Society.

where any unsaturated chromophore could overlap its absorption and confuse the interpretation.

III. BENZOATE DERIVATIVES OF ALCOHOLS

CD studies of the benzoate derivatives of chiral alcohols have overcome the practical limitations mentioned in the previous section, and their interpretation is based on the knowledge of the electronic transitions of the benzoate chromophore in the near-UV region: 280 nm(ϵ = 1000) $^1A_{1g} \rightarrow {}^1B_{2u}$; 230 nm($\epsilon$ = 14,000) intramolecular charge transfer transition (CT) and 195 nm(ϵ = 40,000) $^1A_{1g} \rightarrow {}^1B_{1u}$.

The polarizations of the first and second transitions are along the short and long molecular axes respectively. The optical activity of the strong CT transition of the benzoate chromophore is due to its dissymmetric coupling with the electric dipole moments induced in the saturated or unsaturated carbon backbone (benzoate sector rule), or in another aromatic chromophore present in the molecule (aromatic chirality method), or in other benzoate chromophores in dibenzoate and tribenzoate derivatives of glycols and triols (dibenzoate method).

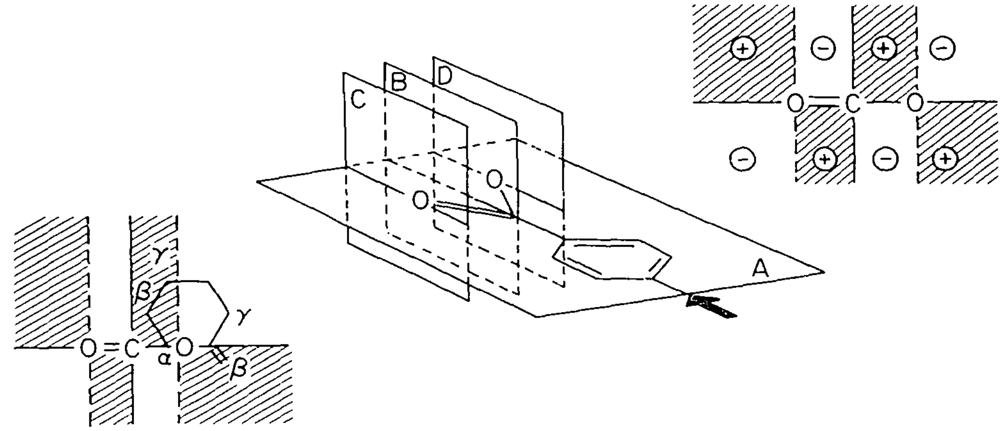


FIGURE 3. The benzoate sector rule: the projection is made in the direction of the arrow. Reprinted with permission from N. Harada, Mo. Ohashi and K. Nakanishi, *J. Amer. Chem. Soc.*, 90, 7349 (1968). Copyright by the American Chemical Society.

A. Benzoate Sector Rule

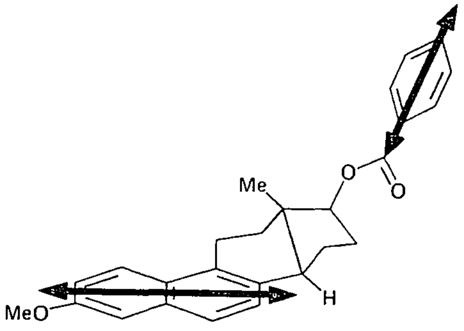
By symmetry theoretical considerations[7a], a sector rule was proposed and applied to cyclic secondary alcohols[7b,c]. This sector rule divides the space into eight sectors by nodal planes, A, B, C and D (Figure 3). The preferred conformation of the benzoyloxy group is assumed to be one in which it lies staggered between the carbinyl hydrogen and the smaller substituent, as already assumed by Brewster in his pioneering 'benzoate rule'[10].

The benzoate is looked at from the *para* position, and the rotatory contribution of α, β- and β, γ-bonds are considered; the sector rule states that bonds falling in the shaded and unshaded sectors in Figure 3 make positive and negative contributions respectively to the 230 nm Cotton effect. The contributions of a double bond would be greater than that of a single bond because of the greater polarizability. It should be pointed out, however, that as the wave functions used by the authors in defining this sector rule are extremely simple, it cannot be used very safely.

B. Aromatic Chirality Methods

The electrostatic interaction between the dipole moment of the CT transition of the benzoate chromophore and the induced dipole moments is greatly increased if a polarizable aromatic chromophore is also present in the molecule. In these cases, with the only exception being when stereochemical symmetry of conformational freedom cancels the exciton coupling between the transition dipole moments of the nonconjugated aromatic chromophores (see below in the dibenzoate and tribenzoate cases), the contribution of the polarizability of the carbon backbone can be neglected. This is a good achievement.

The theoretical optical activity of the coupled aromatic chromophores can be easily and very safely calculated if the sterochemistry of the molecule and the polarization of the coupled transitions are known. Conversely, if the polarizations are known, we can obtain from CD spectra the stereochemical arrangement of the aromatic groups.



(3)

This exciton approach has been very widely used and no failure of it has been recorded in stereochemical studies[11]. A selected example of application to a molecule when a benzoate chromophore is present is provided by 17β-dihydroequilenin-3-methyl ester 17-benzoate (3)[6].

The linear dichroism techniques using stretched films[12] or liquid crystals[13] are very useful for obtaining polarization data of chromophores not previously studied; this situation often occurs in studies of natural products with aromatic groups variously substituted[14].

C. Dibenzoate Chirality Rule

The optical activity of the CT transition of a dibenzoate derivative is mainly generated by the degenerate exciton coupling of the two identical aromatic groups.

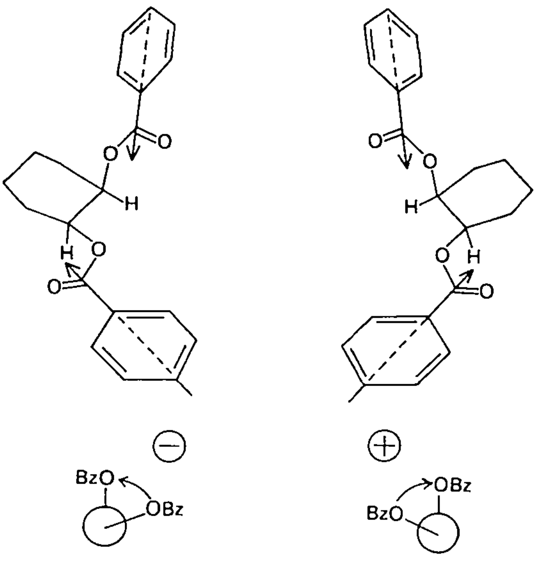
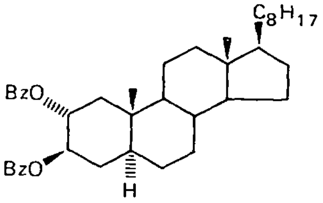


FIGURE 4. Chiralities of α-glycol dibenzoates. Reprinted with permission from N. Harada and K. Nakanishi, *Acc. Chem. Res.*, 5, 257 (1972). Copyright by the American Chemical Society.

The dissymmetric coupling of the intramolecular charge-transfer transitions at 230 nm of the two benzoate chromophores generates a very strong double-humped and conservative (equal intensity of the two opposite-signed components) CD curve. In this degenerate case, it is again very simple to calculate from the shape and intensity of the conservative bisignate spectrum the spatial orientation of the transition dipole moment of one chromophore with respect to that of the other. The spatial mutual orientation of the two transition dipole moments can be converted into stereochemical data. As the CT transition at 230 nm is polarized along the long axis of the benzoate chromophore, that is, approximately parallel to the alcoholic C—O bond, the stereochemistry of the starting glycol can be easily inferred.

The shape of the CD spectrum can also give directly, without any calculation, the chirality of the glycoldibenzoates, defined as positive or negative according to the sign of the low-energy component of the doublet and in correspondence to whether the dissymmetric dibenzoate two-bladed propeller is in the sense of a right- or left-handed screw (Figure 4). For example, the CD spectrum[6] of 2α, 3β-dibenzoyloxy-5α-cholestane (4) (Figure 5) exhibits the typical exciton doublet



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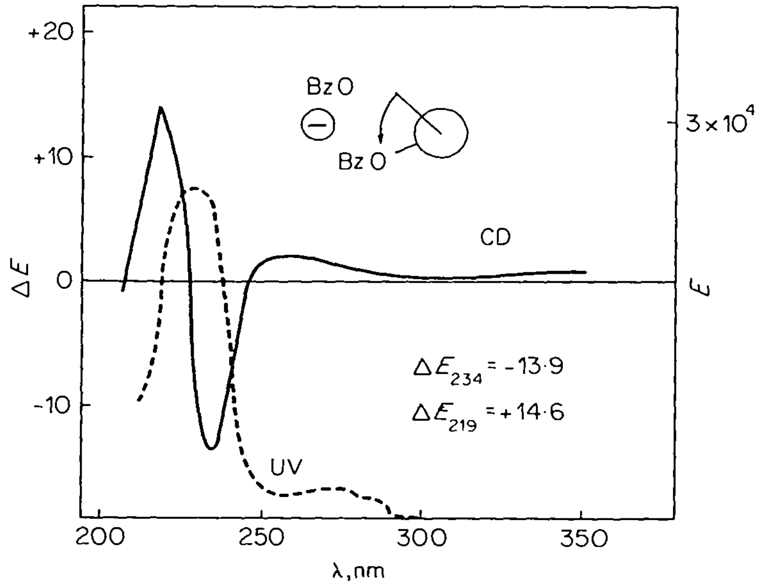
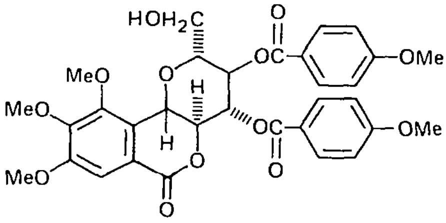


FIGURE 5. CD and UV spectra of 2α,3β-dibenzoyloxy-5α-cholestane (4) in ethanol–dioxane (9 : 1). Reprinted with permission from N. Harada and K. Nakanishi, *Acc. Chem. Res.*, 5, 257 (1972). Copyright by the American Chemical Society.

centred at 230 nm and a negative chirality is directly inferred from the negative sign of the low-energy band of the doublet. The intensity of the 280 nm ${}^1A_{1g} \rightarrow {}^1B_{2u}$ transition is very low and no splitting is apparent; the CD of this transition, which is polarized along the short axis of the two benzoate chromophores, owing to the rotational freedom around the alcoholic C–O bond and its low intensity, does not show an exciton-coupling, and its optical activity is probably generated by the stereochemistry of the atoms closest to the two aromatic rings.

The exciton CD doublets usually have a high intensity and other chromophores do not generally interfere because of the difference in energy and intensity of the CD bands; however, if necessary, the dibenzoate CD doublet can be shifted to lower energy by introducing suitable *para* substituents.

The doublet of the bis(*p*-methoxybenzoate)[6] located at 270 nm and 247 nm does not overlap the strong CD band at 224 nm of the gallate chromophore in dimethylbergenin bis(*p*-methoxybenzoate) (5) (Figure 6), which would instead over-



(5)

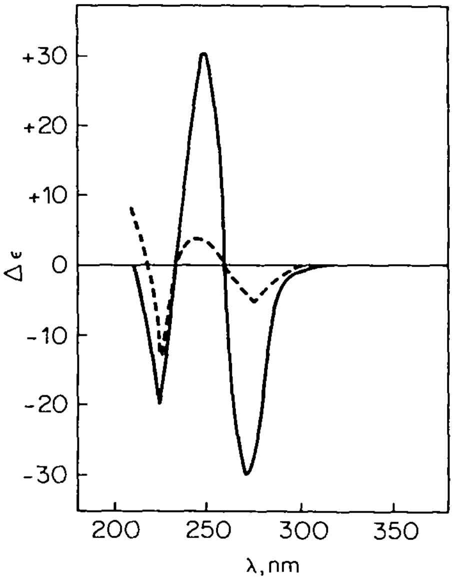
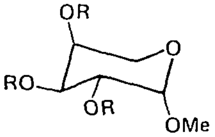


FIGURE 6. CD spectra of dimethylbergenin (– – –) and its bis(*p*-methoxybenzoate) (5) (———) in ethanol. Reprinted with permission from N. Harada and K. Nakanishi, *Acc. Chem. Res.*, 5, 257 (1972). Copyright by the American Chemical Society.

lap with the CD of the unsubstituted dibenzoate. The shift and the difference in the intensity of the CD couplets depend on the nature of the *para* substituent.

A linear relation has been found to exist between the amplitude of the conservative CD couplets and the square of the extinction coefficient maximum of the isotropic absorption[15]. This quadratic dependency holds only when exciton coupling is the main source of the Cotton effect and in ambiguous cases it could be a convenient test.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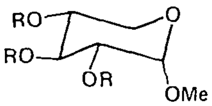
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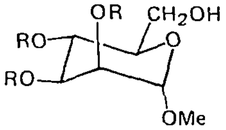

(8)

R = p-ClC$_6$H$_4$CO

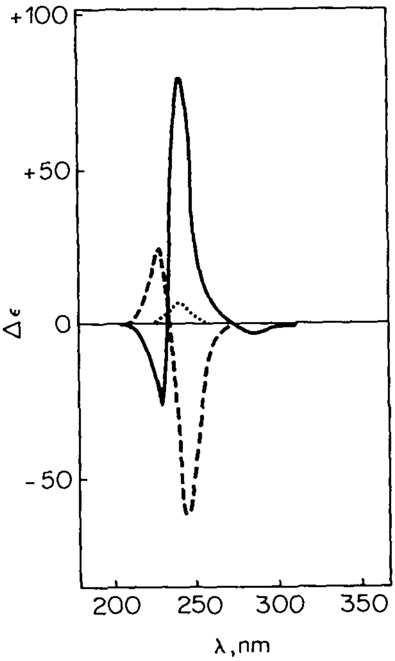


FIGURE 7. CD spectra of tris(p-chlorobenzoates) of sugars. (——) Methyl-α-L-arabinoside (6) [$\Delta\epsilon_{240} = +81.3$, $\Delta\epsilon_{230} = -25.6$ (in n-hexane)]; (··········) methyl-α-D-xyloside (7) [$\Delta\epsilon_{244} = +8.3$ (in EtOH)]; (----------) methyl-α-D-mannoside (8) [$\Delta\epsilon_{248} = -62.8$, $\Delta\epsilon_{230} = +24.7$ (in EtOH)]. Reprinted with permission from N. Harada and K. Nakanishi, *Acc. Chem. Res.*, 5, 257 (1972). Copyright by the American Chemical Society.

The dibenzoate method is not confined to the 1,2-glycol system, since it is based on a through-space electrostatic interaction. The stereochemistry of triols can be studied by the same method[6]. In the case of cyclic 1,2,3-triol tribenzoates, the exciton coupling is only a little more complicated. When the pair-wise chiralities between the 1—2, 2—3 and 3—1 benzoate groups are all positive, as in methyl-α-L-arabinoside 2,3,4-tri-*p*-chlorobenzoate (6) (Figure 7), a positive lower energy couplet results. A CD which is the mirror image of the former is expected and observed when the chiralities are all negative, as in methyl-α-D-mannoside 2,3,4-tris(*p*-chlorobenzoate) (8). In methyl-α-D-xyloside 2,3,4-tris(*p*-chlorobenzoate) (7), the exciton couplings of the three chromophores cancel out (a symmetry plane is present in their spatial arrangement) and the small CD band arises from different mechanisms.

This method was recently applied to polymeric systems[16]; the CD spectrum of poly(*O*-benzoyl-L-hydroxyproline), in the state where there is a right-handed helical conformation, is approximately the mirror image of the spectrum of the state where there is a left-handed helical geometry, and they both exhibit a clear exciton coupling of the benzoate chromophores around 232 nm where the sign of the low-energy exciton band again correlates with the handedness of the helix.

IV. ETHERS

The electronic absorption of ethers lies in the vacuum-UV, and unlike the case of alcohols, it is impossible to overcome this serious instrumental limitation.

The CD spectrum of propylene oxide in isooctane solution does not show a

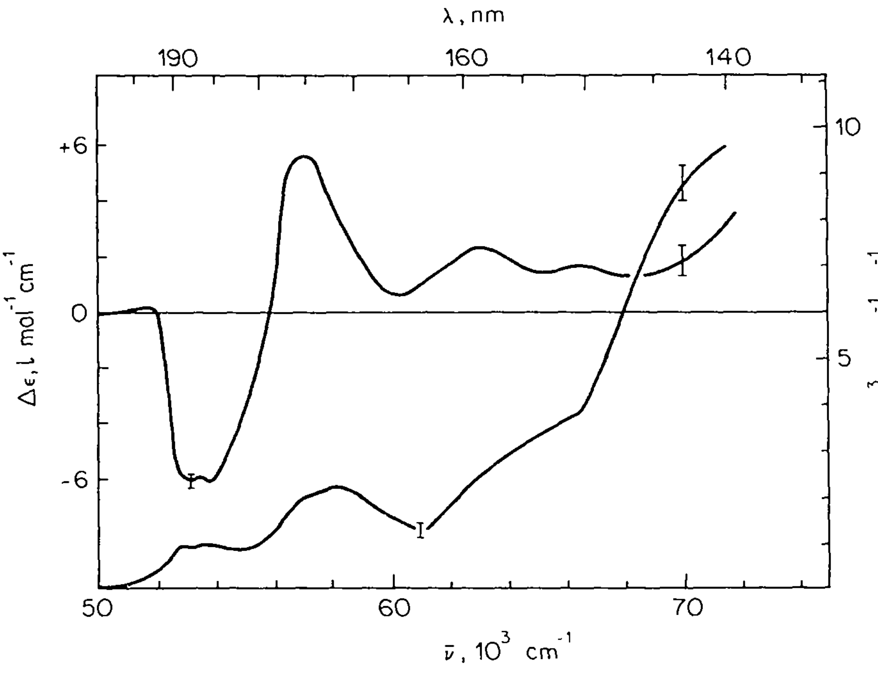


FIGURE 8. CD and absorption spectra in the vapour phase of (+)-*S*-*s*-butyl ethyl ether. Reproduced by courtesy of Prof. O. Schnepp.

maximum down to 185 nm[17]. ORD spectra of some ethers have been recorded in the past[18a,b].

The CD spectra of (+)-*S*-*s*-butyl ethyl, (+)-*S*-2-methylbutyl ethyl and (+)–*S*-3-methylpentyl ethyl ethers in the gas phase have been very recently recorded by Schnepp[19] (Figure 8). Three or perhaps four distinguishable absorption regions between 195 nm and 140 nm were detected. Following previous assignments, two possibilities are proposed for the low-energy transition: $n \rightarrow \sigma^*_{C-O}$ ($^1A_1 - {}^1B_1$ in C_{2v} symmetry) or pure Rydberg $n \rightarrow 3s$ giving the same symmetry as before. No solution spectra were measured to distinguish between valence and Rydberg transitions by shifting the latter ones with the density of the media[20]. The $^1B_1$ symmetry is supported by a high *g*-factor (ratio between circular dichroism and isotropic absorption[21]). The higher energy transitions have a *g*-value at least six times lower for (+)-*S*-*s*-butyl ethyl ether, but for the other two compounds the *g*-value is about the same as for the first transition. It is therefore not possible to obtain guidance for the assignments which remain uncertain.

The ether chromophore inserted in a sugar structure was studied by Nelson and Johnson[22a,b,c]. Unfortunately, the system is very complicated owing to both the equilibria of the sugars between the furanose–pyranose rings and anomeric α–β forms and the presence of many chromophores (hydroxyl, methoxyl, hydroxymethyl, hemiacetal and acetal) absorbing in the same region and probably having some mixing of their electronic states. Therefore, it seems impossible to base any interpretation of the CD of sugars on the specific knowledge of the spectroscopic properties of the different absorbing chromophores and to follow the nonempirical dynamic coupling of the different parts of the molecule. In this case, any safe theoretical approach should require the computing of the orbitals of the whole molecule.

A very effective but empirical approach based on the Kauzmann principle of pair-wise interaction[23] was applied in this field by Listowsky and coworkers[24] and by Nelson and Johnson[22b,c]. As the optical activity, according to this principle, is given as a sum of contributions from pair-wise interactions between the different groups of the chiral molecule, it is natural to divide the sugar into functional groups. The difference between the CD spectra ('difference spectra') of the two sugars which differ only at a single configurational centre, reveals the changes in the interactions involving the groups attached to this centre with the other groups in the molecule. Single pyranose[22b] and pyranoside[22c] anomers were selected by Nelson and Johnson in order to simplify the problem, avoiding, as much as possible, any complication arising from chemical equilibria. The CD spectra in the vacuum-UV to 165 nm of the investigated aldopyranoses are very different from the CD of the homomorphic methyl aldopyranosides, but their difference spectra (the computed difference of the intensities versus wavelength of the two derivatives) reveal many similarities. The substitution of a hydroxyl with a methoxy group on the anomeric carbon causes a negative CD contribution beginning at about 190 nm and having its maximum value at 170 nm for the β-anomers (Figure 9).

The changes are almost superimposible for all the pairs of sugars investigated, except for the D-galacto pair (suggesting some conformational difference between α-D-galactose and α-D-galactoside).

When a hydroxymethyl group is added to C_5, the difference spectra reveal an additional positive CD absorption irrespective of the configuration of the anomeric centre.

The effect of the C_4 and C_1 epimerization has also been investigated by the difference spectra technique. Following this approach, a method was developed[25]

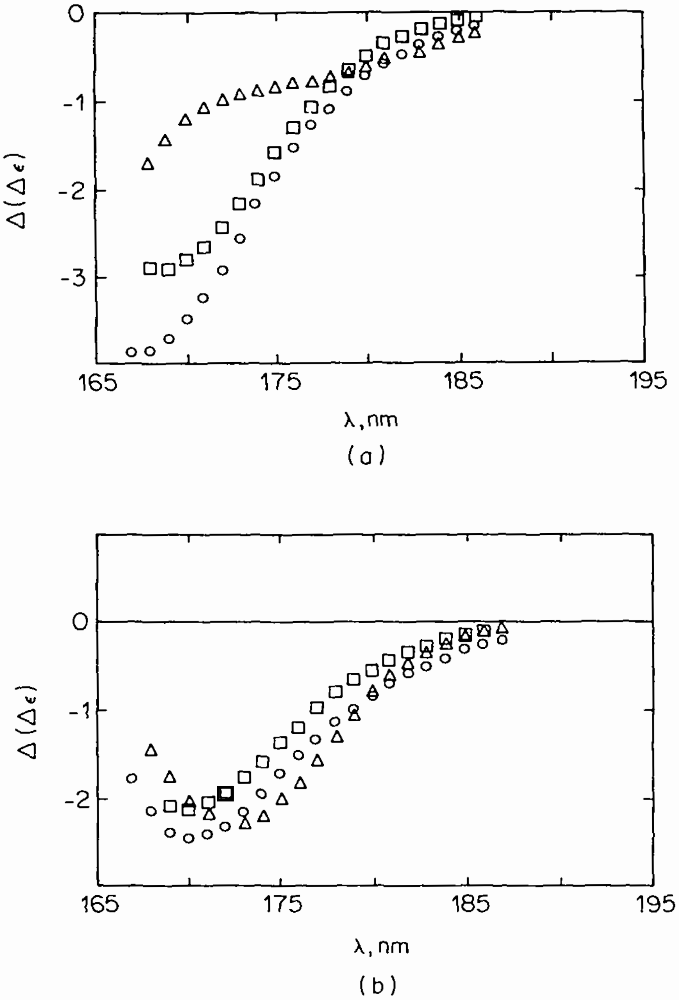


FIGURE 9. Difference CD spectra of methyl-aldopyranosides and -aldopyranoses. (a) α-Anomers: (△) α-D-galactoside minus α-D-galactose, (□) α-D-xyloside minus α-D-xylose, (○) α-D-glucoside minus α-D-glucose; (b) β-anomers: (△) β-D-galactoside minus β-D-galactose, (□) β-D-xyloside minus β-D-xylose, (○) β-D-glucoside minus β-D-glucose. D-Galactose and D-glucose spectra have been red-shifted 2 nm before subtraction from respective pyranoside spectra to account for solvent difference. D-Xylose spectra have been red-shifted 3 nm before subtraction from the D-xyloside spectra to account for solvent and temperature difference. Reprinted with permission from R. G. Nelson and W. Curtis Johnson, Jr., *J. Amer. Chem. Soc.*, 98, 4296 (1976). Copyright by the American Chemical Society.

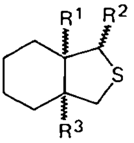
for predicting the CD spectra of pyranoid monosaccharides; the idea was to collect a catalogue of 'fragment CD spectra' that could be summed algebraically to predict the vacuum-UV CD spectra.

A tentative assignment of the transitions was proposed by the same authors[22c]. The first band (185 nm) in methyl pyranosides is due to the ring oxygen, the second (175 nm) to the methoxy group and the third (below 165 nm) at least in part to the methoxy group. The signs of the second and third bands are correlated to the configuration at the anomeric carbon. The first band in the pyranoses (180 nm) is apparently due to the ring oxygen.

V. THIO ETHERS

Since the work of Rosenfield and Moscowitz[26] on five- and six-membered ring thio ethers, few other papers have appeared on this subject.

Hagishita and Kuriyama[27] synthetized and studied the CD of several substituted 2-thiahydrindans (9). Rigid *trans* derivatives show two Cotton effects at ca. 245 and 215 nm, whilst in the *cis* derivative, 3α-methyl-2-thiahydrindan, other bands are present which by low-temperature measurements were shown to be due to conformational isomerism.



(9)

R^1 = α-Me, β-H
R^2 = H, α- or β-Me
R^3 = α- or β-H

By using the rule proposed by Kuriyama and coworkers for episulphides[28], the substituent effect could be predicted, except in the case of β-axial methyl. This discrepancy probably depends on the uncertain position of the nodal surfaces dividing the different sectors.

A theoretical work[29] based on nonempirical SCF-MO calculations substantially confirmed the assignment of $n \rightarrow \sigma^*$, previously proposed[26] for the low-energy transition of sulphides (at ca. 240 nm). However, on the low-energy side, a Rydberg type ($3p \rightarrow 4s$) transition also seems to be superimposed upon the magnetically allowed $n \rightarrow \sigma^*$. This Rydberg transition, however, gives negligible contributions to the optical activity.

Higher energy transitions were also discussed but the possible assignments are still uncertain.

A. Thio sugars

Recently, the α- and β- anomers of several l-thioglyco-furanosides[30] and l-thioglyco-piranosides[31] were studied by both ORD and CD techniques. While the CD revealed directly two weak bands at ca. 210 and 200 nm, the first of which is certainly connected with the C–S chromophore, ORD spectra by means of Drude-type plots allowed the identification of an intense band at ca. 150 nm. This band seems to be the one giving the dominant contribution to the optical rotation at the sodium-D line. While the first two bands are not 'diagnostic' of the anomeric configuration at C_1, the sign of the 150 nm band (connected to the ring oxygen?) was associated with the anomeric configurations; α gave positive signs and β negative, analogously to the Hudson isorotation rule.

Older work on methyl 5-thio-α- and -β-D-xylopyranoside based on ORD and Drude plots has led to analogous conclusions for a band at ca. 180 nm associated with the ring sulphur[32].

A study on alkyl-α- and -β-1-thiagalactopyranosides and their tetraacetates was recently communicated[33].

B. Episulphides

Considerable effort has recently been made to interpret the chiroptical properties of episulphides.

Ab initio calculations of the optical activity were performed on *R*-(+)-propylene sulphide[29]; from this study, the two absorptions observed at ca. 260 nm in the spectrum of episulphides were assigned as n → σ^* (higher energy) and n → 4s (lower energy) (Figure 10). These transitions correspond to those proposed for thio ethers[29], and only the first one plays a relevant role in determining the CD

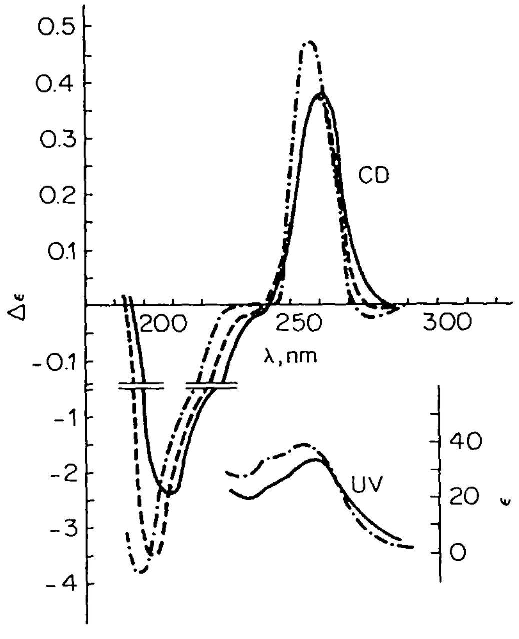


FIGURE 10. CD and UV spectra of (+)-*R*-*t*-butylthiiran in 3-methylpentane at +20°C (——), −90°C (– – –) and −180°C (· — · — ·). In the CD spectra the n → 4s transition is evident on the low-energy side of the intense n → σ^*. Reproduced from G. Gottarelli, B. Samorì, I. Moretti and G. Torre, *J. Chem. Soc., Perkin II*, 1105 (1977) by permission of the Chemical Society.

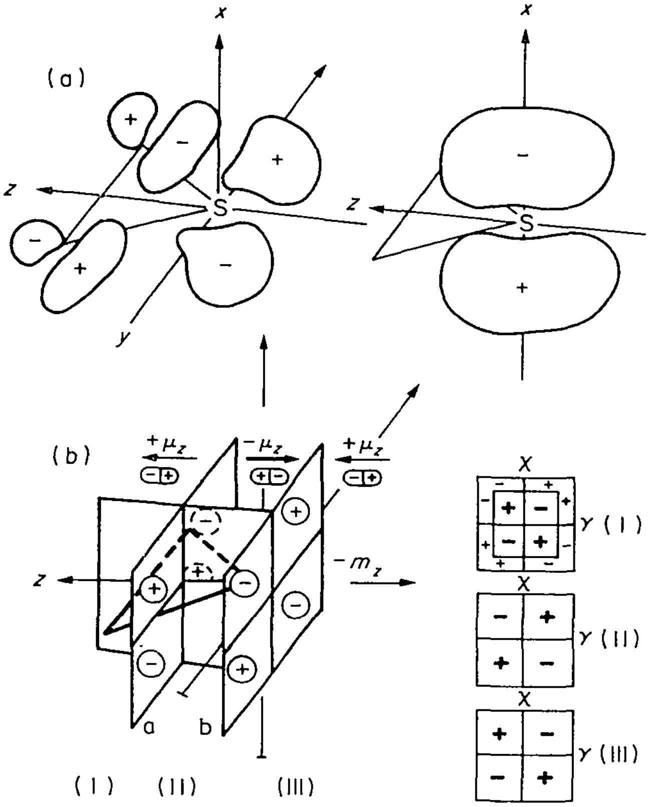


FIGURE 11. (a) Orbitals of the ground (right) and excited (left) states of the magnetically allowed n → σ* transitions. (b) The multipolar transition charge distribution resulting from the overlap of the ground and excited state orbitals; ⊕ and ⊖ represent real monopolar charges and not the signs of the overlap, $-m_z$ is the magnetic moment of the transition, μ_z (⊕⊖) represents the z-component of the dipoles induced by the transition monopoles in a polarizable perturber (i.e. chemical group or bond) in the different regions surrounding the chromophore (I, II, III). The signs of the contributions to the optical activity are depicted on the right. In region I the outer sector refers to groups not directly bonded to the thiirane ring (these contributions are very small). Reproduced from G. Gottarelli, B. Samorì, I. Moretti and G. Torre, *J. Chem. Soc., Perkin II*, 1105 (1977) by permission of the Chemical Society.

observed at ca. 260 nm. The charge distribution of the n → σ* transition was computed and used to perform dynamic coupling[34a,b] calculations of the optical activity of several simple episulphides. Still using the dynamic coupling mechanism, a general symmetry rule (Figure 11), correlating the stereochemistry around the episulphide group to the CD of the 260 nm transition, was deduced. This rule is for practical purposes similar to that proposed by Kuriyama and collaborators[28], but emphasizes the contributions of the region near the central part of the thiirane ring.

VI. DISULPHIDES

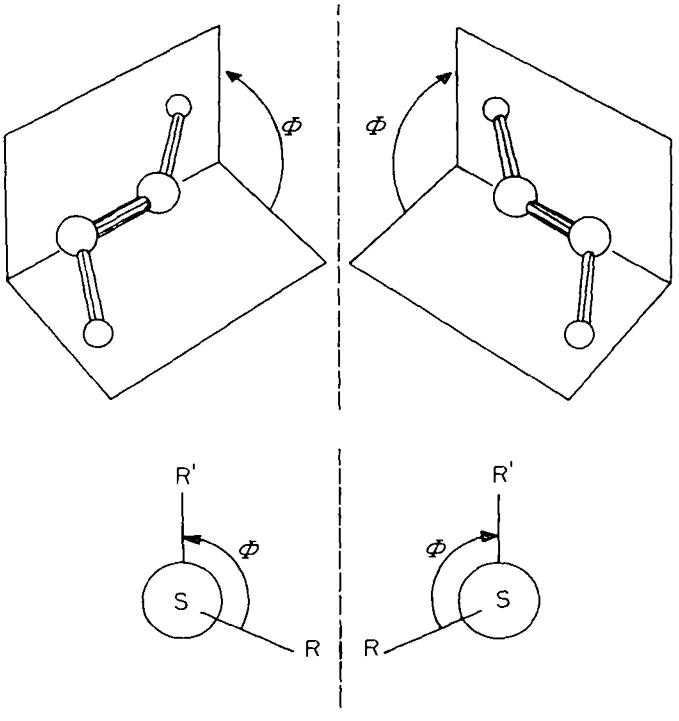
Considerable research has been devoted in recent years to the optical activity of the disulphide chromophore. The S–S bond length is about 2.04–2.06 Å and the R–S–S′ bond angle ranges between 100° and 108°[35].

Of primary importance with regard to the optical activity is the dihedral angle Φ formed by the intersection of two planes, one of which is defined by R–S–S′ and the other by S–S′–R′. For $\Phi \neq 0°$ and 180°, the disulphide group is dissymmetric and shows inherent optical activity distinct from contributions by external perturbations[36] (Figure 12).

The value of Φ in cyclic compounds is imposed by the ring size, and in open-chain derivatives by steric and electronic factors.

The disulphide linkage has characteristic absorption bands between 210 and 370 nm which show corresponding circular dichroism. The wavelength of maximum absorption, the extinction coefficients and the chiroptical properties are very sensitive to the value of the dihedral angle Φ[37].

Simple cyclic disulphides have been extensively investigated by several authors[36–42]. In these cases, the dihedral angle Φ ranges from about 60° in six-membered rings[43] to ca. 30° in five-membered rings[44]. In six-membered rings,



M-helix P-helix

FIGURE 12. The dissymmetric disulphide group. Reprinted with permission from J. Webb, R. W. Stickland and F. S. Richardson, *J. Amer. Chem. Soc.*, 95, 4775 (1973). Copyright by the American Chemical Society.

two optically active transitions are detected at 280–290 nm and at ca. 240 nm; in five-membered rings, the dihedral angle is reduced and the transitions are red-shifted to ca. 330 and 262 nm[37,45]. In all these cases the long-wavelength CD is negative for M-helicity ($\Phi < 0^\circ$) and positive for P-helicity[36,38–42].

The second UV band gives a CD with an opposite sign to the first band, but correlations based on this transition seem to be less reliable[38].

The apparently abnormal behaviour of *R*-(+)-α-lipoic acid[46] is reconciled with the general trend by considering the conformational equilibrium of two species having opposite chirality to the disulphide group[45].

Studies of disulphides with Φ close to 90° have led to quite a different picture. Coleman and Blout[47] studied the chiroptical properties of cystine and derivatives and found that the rotatory strength of the long-wavelength band at ca. 250–260 nm is low and is dominated by external perturbations rather than by the screw-sense of the disulphide linkage. Beychok and Breslow[48] found in several cyclic polypeptides that the first CD band was sensitive to minor structural changes and they did not find a correlation between its sign and the chirality of the disulphide group. A later study[49] on cyclo-l-cystine having Φ very near 90°, revealed no CD in the long-wavelength absorption region of the disulphide group.

(2,7-Cystine)-gramicidin-*S* constitutes an example[50] of a P-helical disulphide with $+90^\circ < \Phi < +180^\circ$ (*transoid*); here the long-wavelength absorption of the disulphide group (271.5 nm) has a negative CD, opposite to that found for *cisoid* disulphides.

All the data reported above were rationalized, and also in part anticipated, by the theoretical work of Linderberg and Michl[51]; this work is based on considerations of the simple Bergson model[52], together with empirical CD data of simple molecules. The picture is further confirmed by semiempirical CNDO calculations. The main results of this work can be summarized as follows.

The two transitions observed between 210 and 360 nm are from the highest occupied MOs (formed by symmetric or antisymmetric combinations, ψ_+ and ψ_-, of the lone-pairs of sulphur atoms, χ_A and χ_B)

$$\psi^+ = \frac{1}{\sqrt{2}}(\chi_A + \chi_B) \qquad \psi^- = \frac{1}{\sqrt{2}}(\chi_A - \chi_B)$$

to the same antibonding σ^*-orbital of the S–S group. Since the chromophore has C_2 symmetry, the excited states will be of A and B symmetry respectively. The energy of ψ_+ and ψ_- is strongly influenced by variations of Φ, whereas that of σ^* is not. For $|\Phi| < 90^\circ$ the first excited state is B; for $90^\circ < \Phi < 180^\circ$ the first exicted state is A. For $\Phi = 90^\circ$, A and B are degenerate and only one single absorption is detectable in the spectrum.

For an M-helix, B has negative rotatory strength and A positive. Therefore, for $0^\circ < \Phi < 90^\circ$ the M-chirality gives negative CD and P-chirality positive CD. Thus the inversion of sign for $90^\circ < \Phi < 180^\circ$ is explained by the fact that the low-wavelength transition is no more B but A. At $\Phi = 90^\circ$ the two degenerate rotatory strengths mutually cancel.

More complete MO calculations[53] of the optical activity of the disulphide group were recently performed and this basic picture was substantially confirmed. The elegant theoretical work of Woody[54] on the Bergson model does not change the above picture.

For practical purposes, a quadrant rule can be used to correlate the handedness of the twisted disulphide group to the sign of the long-wavelength CD observed both for *cisoid* and *transoid* disulphides[50] (Figure 13).

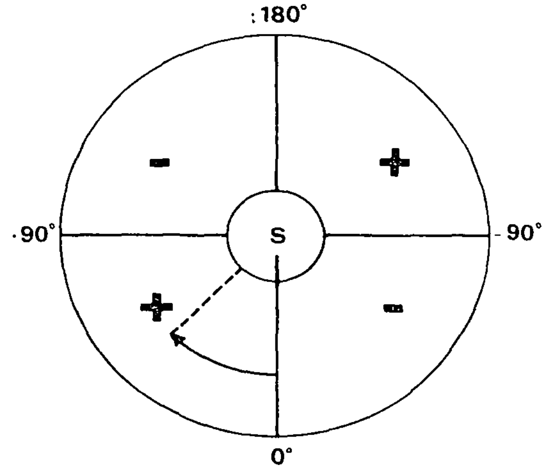


FIGURE 13. Quadrant rule for the inherent optical activity of the low-energy transition of the disulphide chromophore. Reproduced from U. Ludescher and R. Schwyzer, *Helv. Chim. Acta*, 54, 1637 (1971) by permission of the Schweiz. Chem. Gesellschaft.

In addition to the references quoted above, other studies have been reported on biomolecules; cystine has been extensively studied[55-58].

Several researches have been devoted to the CD of the disulphide group in complex biological molecules; these include (2-glycine)oxytocin[48], the trypsin inhibitor of adzuki beans[59], Neurophysin II[60], antibiotics[50,61,62], Somotropin[63] and Choriomammotropin[64].

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Note Added in Proof

The final interpretation of the spectra of (+)-*S*-*s*-butyl ethyl ether reported in Figure 8 has been recently published and assignments to Rydberg-type transitions are preferred.

Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 7

The mass spectra of ethers and sulphides

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I. INTRODUCTION

The last review[1] of the electron impact mass spectrometry of ethers and sulphides was published more than a decade ago and, except for biannual compilations[2] of selected references, no recent update is available. The tremendous growth and popularization mass spectrometry has undergone since then obviously is reflected in the amount of material covering a wide variety of aspects (e.g. analytical, mechanistic, thermochemical, theoretical) of the gas-phase ion chemistry of these compound classes. This review will outline recent advances but no attempt has been made to be exhaustive. Because of space limitations overlap with related interesting fields, such as, for example, carbohydrate analysis[3] and negative-ion mass spectrometry[4], has been avoided, particularly when recent reviews are available. Another

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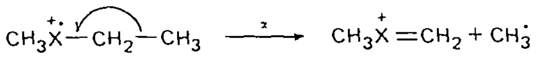
**Present address:* Agfa-Gevaert NV, Research and Development Laboratories, Chemistry Department, Septestraat, B-2510 Mortsel, Belgium self-imposed restriction is that only compounds containing C–O–C or C–S–C linkages are discussed: silyl ethers, for instance, are only occasionally treated. Compounds in which the ether or sulphide character is obscured by other structural features (e.g. aromatic heterocycles) have also been omitted. Except for these restrictions, literature coverage extends through early 1978. The symbolism of Budzikiewicz, Williams and Djerassi[1] (asterisk, singly and doubly barbed arrows) has been used throughout the text.

II. GENERAL CHARACTERISTICS OF THE MASS SPECTRA OF SATURATED ALIPHATIC ETHERS AND SULPHIDES

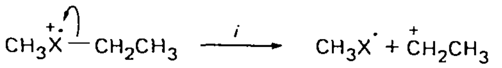
One of the most useful concepts to the organic mass spectrometrist is the concept of charge localization[1,5,6]: the removal of an electron from a molecule containing a heteroatom (or π-bond) will preferentially involve a lone-pair electron (respectively π-electron) of this heteroatom (respectively π-bond). In the case of a polyfunctional molecule, removal of an electron is then pictured as occurring predominantly from the function or atom having the lowest individual ionization energy. A particularly vigorous discussion of the validity of the concept has centred around the mass spectral behaviour of methionine and selenomethionine[7,8] but van den Heuvel and Nibbering[9] have confirmed its predictive capabilities in these instances. Budzikiewicz and Pesch[10] complemented these investigations in a study of α,ω-bifunctional alkanes in which amino groups were opposed to sulphide or selenide functions. They found (*i*) that the ionization energy of a polyfunctional molecule is indeed determined by the functionality of lowest ionization energy, and (*ii*) that the charge in the molecular ion can migrate to another site through space (rather than through σ-bonds) below the ionization energy of that other function. Thus apparent contradictions to the charge localization concept can be explained. Williams and Beynon[11] have recently reevaluated the concept and stress (*i*) that the most important aspect of a cation radical (e.g. a molecular ion) is the radical site, and (*ii*) that the available evidence points to the preferential localization of the unpaired electron in certain orbitals. In the case of ethers and sulphides removal of an electron then predominantly occurs from the heteroatom lone-pair orbitals, subsequent decomposition being initiated either by the radical site or by the charge. In the first case the unpaired electron will seek to pair with one of the electrons of an adjacent α-bond (equation 1) and as such lowers the dissociation



$$\mathrm{CH_3\overset{+\cdot}{X}{-}CH_2{-}CH_3} \xrightarrow{\alpha} \mathrm{CH_3\overset{+}{X}{=}CH_2 + CH_3^{\cdot}} \qquad (1)$$

X = O	702	660	138	$E_a = 96$
X = S	765	857	138	$E_a = 230$

energy for this bond. This also follows from quantitative data: assuming that simple cleavage reactions involve no reverse activation energy[12], the activation energy (E_a) for the forward reaction can be calculated from available[11,13-15] thermochemical data (ΔH_f values are given below each structure and are expressed in kJ mol^{-1}). It is clear that the dissociation energy for the C–C bond in both ether and sulphide molecular ions is substantially reduced relative to its value (~347 kJ mol^{-1}) in the neutral molecules: as a result radical site initiated decompositions mainly occur through α-cleavage. Charge-site induced fragmentation on the other hand, by attracting an electron pair, leads to heterolytic *ipso*-cleavage ('*i*-cleavage', equation 2). The activation energies are higher than those for α-cleavage (equation 1) and



$$\overset{+\cdot}{CH_3X}-CH_2CH_3 \xrightarrow{i} CH_3X^{\cdot} + \overset{+}{C}H_2CH_3 \qquad (2)$$

X = O 702 4 915 $E_a \sim 209$

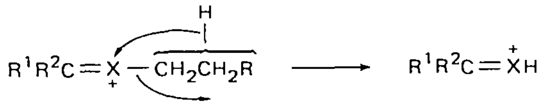
X = S 765 136 915 $E_a \sim 273$

hence the latter process will dominate (see below), although to a lesser extent in the case of the sulphides (as observed experimentally[16,17]). Note that the higher energy barriers to both reactions in sulphides must result in a decreased fragmentation and hence in increased parent ion abundances relative to the corresponding ethers (as observed)[17,18]. Also note that the higher energy requirement for α-cleavage in sulphides mainly reflects the different ability of the heteroatom to stabilize the positive charge in the product ion[14].

Several generalizations[17,18] hold for the α-cleavage reaction in the 70 eV spectra of both compound classes and are only briefly recapitulated: (*i*) α-cleavage occurs preferentially at the most substituted carbon provided the alkyl substituents on the other α-carbon are not too much larger; (*ii*) given an equal degree of substitution, loss of the larger alkyl group prevails. In the case of ethers the yield of α-cleavage products quickly drops with increasing molecular size as a result of enhanced competition of heterolytic *i*-cleavage (equation 2) and other hydrocarbon fragment producing reactions (see below). The reaction is however enhanced by α-branching and the presence of a vicinal functionality such as in vicinal diethers: the major fragments of these compounds arise though α-cleavage of the central C—C bond[19,20], which feature has been exploited in a method for the determination of double-bond positions in polyunsaturated fatty acids[21]. Other factors may also affect the propensity for α-cleavage as exemplified by allylic[22] and propargylic[23] ethers: loss of a vinyl or acetylenyl, respectively, radical is essentially absent.

When investigating the *intrinsic* preference of the cleavage process for loss of the larger (R_L) or the smaller (R_S) alkyl group, one should bear in mind that the associated fragment abundances in the 70 eV spectra are hardly useful since a substantial fraction of these α-cleavage products will have undergone subsequent decomposition. This problem is avoided by recording the mass spectra at sufficiently low ionizing energies. It was then observed[24,25] for several compound classes that loss of R_S becomes more important at lower energies, the differences residing in the actual values of the $[M - R_S]/[M - R_L]$ ratio. In persistent cases such as ethylene acetals and ketals[26] this value does not exceed unity at the lowest internal energies. However, by extending the range of observed internal energies through the observation of unimolecularly decomposing metastable molecular ions, it could be confirmed that at these lowest energy contents the smaller radical is preferentially lost as well[26].

Subsequent decomposition of α-cleavage products typically occurs through hydrogen rearrangement with concomitant olefin elimination[17,18,27,28] (equation 3). The reaction involves nonspecific hydrogen abstraction from all positions in the



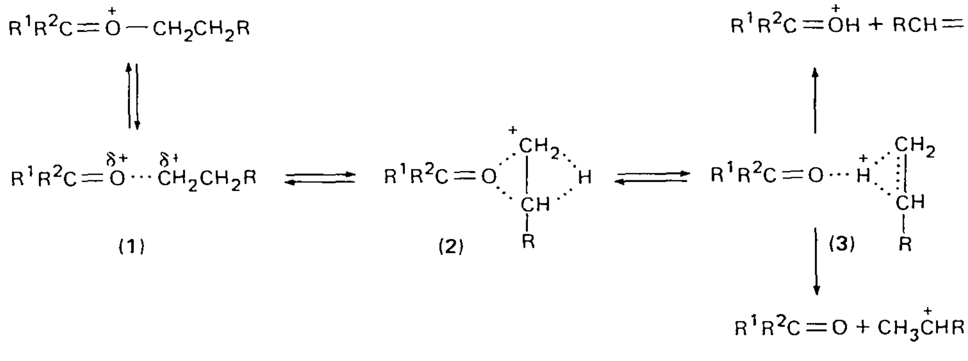
$$R^1R^2C{=}\overset{}{\underset{+}{X}}-CH_2CH_2R \longrightarrow R^1R^2C{=}\overset{+}{X}H \qquad (3)$$

remaining alkyl chain, the actual fractions being very much similar for ethers and sulphides[28]. This result was interpreted[27,28] in terms of competing specific mechanisms involving three-, four-, five-, six- and, if applicable, higher-membered cyclic transition states with the four-, five- and six-membered cases being about equally favoured, all other factors being equal. Abstraction from all possible positions also occurs in metastable decompositions of α-cleavage ions[29]. It was therefore argued[29] that for all competing abstraction routes comparable activation energies should be at hand which, at the time, was considered a highly unlikely situation. The increased β- and γ-hydrogen abstractions in metastable ions relative to their ion source decomposing analogues was therefore attributed[29] to a relatively rapid 1,2-exchange between β-and γ-hydrogens, the exchange reactions involving α- and δ-hydrogens being substantially slower. Actual hydrogen abstraction was thought to occur specifically from the β- or γ-position, or from both. More recent evidence[30] on other nonspecific hydrogen-transfer reactions, however, has revealed that situations involving several competing, specific hydrogen abstractions are possible, even at lowest internal energies. A corollary of the different energetical requirements for all pathways is then the increased specificity at lowest internal energies[30], and therefore the observations[29] made on metastable α-cleavage products cannot exclude such a situation! The available experimental evidence on ethers confirms that the hydrogen is transferred to the positive oxygen, as indicated in equation (3): ion cyclotron resonance[31] (ICR) and collisional activation[32] (CA) studies have established[32b,33,34] that the product of the reaction is identical to the α-cleavage product of the appropriate alcohol molecular ions and can also be generated through protonation of the appropriate carbonyl compound. The same conclusion is drawn from labelling and thermochemical data on the $C_2H_5O^+$ ion from diethyl ether[35]. More recent data[36,37] have confirmed that these observations can also be extended to sulphides (X = S in equation 3).

Loss of a carbonyl fragment by heterolytic bond fission has been reported[27,38-41] as an alternative pathway for decomposition of ether α-cleavage products, the appropriate metastable peak having been detected (equation 4). The

$$R^1R^2C{=}\overset{+}{O}{-}R^3 \longrightarrow R^1R^2C{=}O + R^{3+} \qquad (4)$$

competition between the two reactions (equations 3 and 4) strongly depends on the actual substituents R^1, R^2 and R^3 but can be predicted[42] using proton affinity data. Bowen and coworkers[42] propose that in fact equation (3) occurs in a relatively nonconcerted manner as shown in equation (5). Sufficient internal energy is available to stretch the *O*-alkyl bond with formation of the weakly coordinated cations **1** which then undergo isomerization of the alkyl chain by means of 1,2-hydride shifts. If the intermediate complexes (as **2**) are sufficiently loose to enable rotation to **3**, a potential carbonyl molecule and a potential olefin will



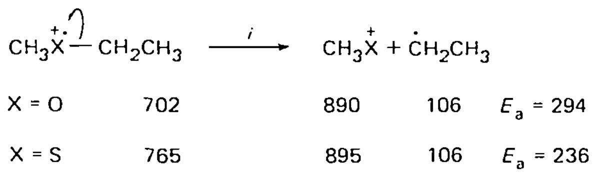
(5)

compete for the proton trapped between both. The outcome obviously depends on the proton affinities of the corresponding molecules, equation (4) being important when the olefin has the higher value (as observed!). Note that equation (4) is an alternative route to the products of heterolytic *i*-cleavage in ether molecular ions (equation 2) and partly accounts for the increased yields of alkyl cations from higher straight-chain ethers[42]. So far there is no evidence that the equivalent of equation (4) is operative in sulphide α-cleavage products. As was already mentioned in the discussion of equation (2), heterolytic carbon–sulphur cleavage in the molecular ions can compete far more effectively with α-cleavage and may well be the major route to alkyl cations.

A third, but generally less important breakdown mode of ions **1** involves the expulsion of water[29,38-40]. The reaction, if occurring, has the lowest activation energy and therefore competes more effectively at lowest internal energies (metastable ions). Labelling data[29] on the $[M - 15]^+$ ion from *n*-butyl isopropyl ether indicate that both hydrogens eliminated as water originate from the butyl chain only, but do not allow for more precise mechanistic inferences. A possible pathway emerges from an ICR study[43] on the ion chemistry of 2-propanol.

Sulphide α-cleavage products can undergo a second hydrogen rearrangement–olefin elimination reaction, which can be formally written as a McLafferty-type rearrangement[28]. Specific γ-hydrogen transfer does indeed occur, secondary hydrogens being preferred over primary ones whenever the choice arises[28]. Additional confirmation is provided in a recent CA investigation[36] of the product ion structures: the reaction does indeed yield species of the predicted structure.

In addition to α-cleavage and heterolytic *i*-cleavage there exists the possibility of homolytic *i*-cleavage (equation 6). In the case of ethers the energy requirement of



$$CH_3\overset{+\cdot}{X}{-}CH_2CH_3 \xrightarrow{i} CH_3\overset{+}{X} + \dot{C}H_2CH_3 \qquad (6)$$

X = O 702 890 106 E_a = 294

X = S 765 895 106 E_a = 236

294 kJ mol^{-1} largely exceeds the value for α-cleavage (96 kJ mol^{-1}), as expected For sulphides, however, the activation energies are virtually the same (236 and 230 kJ mol^{-1}, respectively) thus rendering homolytic *i*-cleavage a feasible alternative to α-cleavage. Confirmatory labelling evidence is available[14,28,36b]. Some attention has been devoted to $C_2H_5S^+$ and $C_3H_7S^+$ fragments formally generated through equation (6). Van de Graaf and McLafferty[36] point out that the virtually identical ΔH_f values[14] for $CH_3CH_2S^+$ and $CH_3CH{=}\overset{+}{S}H$ might be due to the threshold operation of anchimeric assistance instead of direct C–S cleavage, the available evidence (including labelling data) being inconclusive. At higher ionizing energies the bulk of $C_2H_5S^+$ ions might still be formed initially as $CH_3CH_2S^+$ but the CA spectrum clearly shows that isomerization to $CH_3CH{=}\overset{+}{S}H$ ensues. Migration of the α-methyl group has only been observed[36] when secondary methyl groups are involved, such as is the case in $(CH_3)_2CHS^+$ rearranging to $(CH_3)_2C{=}\overset{+}{S}H$ and (to a lesser extent) $CH_3CH{=}\overset{+}{S}CH_3$. Recent CA evidence[37] has established the thiomethoxide ion CH_3S^+ as a stable species which can be differentiated from protonated thioformaldehyde $H_2C{=}SH^+$. Again the data indicate that at threshold the reaction of equation (6) suffers strong competition from the anchimerically assisted process. The homolytic *i*-cleavage reaction is particularly enhanced for symmetrical sulphides in the $C_{10}{-}C_{14}$ range[17] and has been at-

tributed[44] to rearrangement of the initial product to stable protonated thiacycloalkanes.

The general observation that sulphides exhibit a wider variety of decomposition pathways than their oxygen analogues is exemplified by the β-cleavage reaction. Its product occurs (minor abundance) in *n*-butyl and *n*-pentyl ethers only and is only formally due to such cleavage as is clearly established by labelling experiments[45]. The reaction does however occur in sulphides, as CA measurements[36] confirm the cyclic nature of a fraction of the product ions. An independent study[46] revealing that such three-membered ring sulphonium ions are stable at lifetimes exceeding 10^{-5} s, the remainder cannot be due to isomerization of an initial β-cleavage product and therefore at least a second process must be operative. Other cleavages (γ, δ and ε) do also occur in sulphide molecular ions (albeit to a lesser extent[17]) and may well yield cyclic sulphonium ions on account of the larger δ-fission fragment abundance (presumably reflecting the enhanced stability of the five-membered ring). Note that these cleavages can be considerably enhanced if a stable radical (e.g. phenoxy instead of alkyl) is lost[46,47].

Analogously to the loss of water from alcohol molecular ions, ether and sulphide parent ions do lose a molecule of alcohol[27,41,48] or thiol[17,28], respectively, thereby formally producing olefinic fragments. At electron energies low enough to suppress alternative pathways, such fragments are formed by competitive 1,4-, 1,5- and 1,6-eliminations in ethers[48], in striking contrast to the high (>90%) specificity for the 1,4-elimination of water from alcohols. The possibility of interfering hydrogen randomization cannot, however, be excluded in these low-energy measurements. Even less is known about the analogous reaction in sulphides, as mixing of the hydrogens of the two alkyl groups occurs prior to the elimination reaction[28]. The complementary process (charge retention on the thiol fragment) also occurs and seems to involve preferential 1,2-elimination[28].

Reducing the electron energy helps considerably in the analysis of higher aliphatic ethers; the low-voltage spectra exhibit characteristic fragments corresponding to a protonated alcohol species[41], the yield of which increases with increasing molecular size. Deuterium labelling in ethyl *n*-hexyl ether demonstrates that the bulk of both hydrogens transferred to oxygen in the process arises from C_5 of the hexyl chain, indicating a preference for seven-membered intermediates in the reaction. These protonated alcohol ions readily decompose through loss of water, thus providing a third route (in addition to equations 2 and 4) to alkyl cations.

The fragmentation pathways of saturated aliphatic ethers and sulphides discussed in the preceding paragraphs of this section have been the basis of the heuristic Dendral program for the identification of compounds belonging to these classes[49,50]. With no more input than a tabulated mass spectrum (in the improved version[50]) and using algorithms which are a mathematical translation of most of the preceding observations, the program drastically reduces the list of structures fitting the deduced elemental composition in the case of di-*n*-decyl ether, for instance, the initial number of 11,428,365 isomers can be reduced to 22,366 and finally to 1 if NMR data are taken into account. Note that the computer always includes the correct answer in the final listing of candidates and generally performs better than an experienced mass spectrometrist!

Some comments must be made on the structures of oxygen- and sulphur-containing fragment ions. Of the possible $C_2H_5X^+$ and $C_3H_7X^+$ (X = O,S) structures, the acyclic onium ions are the most stable and hence most widely occurring species[34,36]. Resonance stabilization obviously operates, though less effectively in the sulphur-containing species[14], as is illustrated by the heat of formation data of

TABLE 1. Heat of formation data (kJ mol^{-1}) on $C_2H_5X^+$ ions

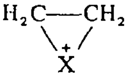
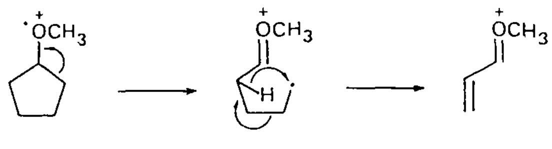
Ion	X = O	X = S
$CH_3\overset{+}{X}{=}CH_2$	660[13]	857[14]
$CH_3CH{=}\overset{+}{X}H$	585[13]	823[14]
	710[13]	803[51]

Table 1. Also, in contrast to their oxygenated analogues, three-membered ring sulphonium ions are energetically more attractive (relative to acyclic isomers) and are therefore frequently encountered. This is adequately illustrated in the $C_3H_7X^+$ series where stable *S*-methyl thiiranium ions are found[46], the corresponding *O*-methyl oxiranium species still eluding experimental characterization[34,46]. It has recently been demonstrated that the presence of a heteroatom, vicinal to a carbenium ion centre, brings about a substantial reduction in the degree of isomerization of the positive ion[52]. This is ascribed to an increased threshold for isomerization, relative to that for unimolecular decomposition, as a result of the predominant charge localization at the heteroatom[52]. If this were a general trend, the decreased ability (relative to oxygen) of sulphur to stabilize an adjacent positive carbon (see above), should result in a lower threshold for isomerization in $C_nH_{2n+1}S^+$ ions. The available evidence on these species does indeed reveal that all $C_2H_5S^+$ [53] and all but one $C_3H_7S^+$ species[46,54] have isomerized to a common structure or mixture of structures prior to unimolecular decomposition. The oxygen analogues on the contrary display a greater variety of different decomposing isomers or mixtures of isomers: at least two for $C_2H_5O^+$ [33], three for $C_3H_7O^+$ [38,55] and no less than five for $C_4H_9O^+$ [56], although some isomers may decompose via the same potential surface[40,57].

III. SPECIAL FEATURES OF OTHER ETHERS AND SULPHIDES

A. Cycloalkyl Ethers and Sulphides

Except for the negligible loss of an α-hydrogen, α-cleavage in the molecular ions of cycloalkyl compounds does not directly result in a fragment ion, further reaction of the resulting ring-opened molecular ions being required to achieve this. In cyclopropyl ethers loss of the $C_{(2)}$ or $C_{(3)}$ ring substituents by radical site initiated cleavage is the only feasible route[58,59] unless equation (3) can operate[60]. Methyl ethers of higher cycloalkanols yield a characteristic $C_3H_6O^{+\cdot}$ fragment through allylic-type cleavage[61-63] in the open parent ions. The high yield of this fragment for cyclobutyl methyl ether[61] has recently been exploited in a method[64] for double-bond location by means of ion molecule reactions. From cyclopentyl methyl ether onward[65] the complex mechanism (equation 7)[62] also observed for



(7)

cycloalkanols dominates. Low yields of the product are observed in the corresponding ethyl (or higher) ethers because of subsequent decomposition according to equation (3) and because of strong competition of heterolytic *i*-cleavage (equation 2) to yield dominating cycloalkyl ions[66]. Also note that a $C_{(2)}-C_{(3)}$ double bond[67] or an exocyclic double bond on $C_{(2)}$[68] effectively quench the process. A characteristic loss of methanol produces moderately abundant hydrocarbon fragments[62,65] from methyl ethers; the reaction has stereochemical implications and will therefore be treated in Section V. The reaction of equation (7) is of minor importance in the spectra of cyclopentyl and cyclohexyl sulphides, the bulk of the fragmentation involving formation of cycloalkene, alkyl (equation 2) and protonated alkylthiol fragments[69,70].

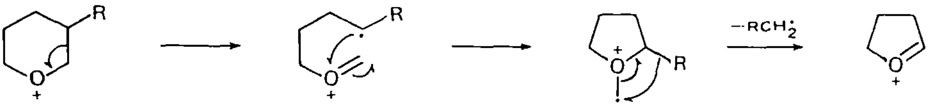
B. Unsaturated, Nonaromatic Compounds

The genesis of $C_2H_4O^{+\cdot}$ ions from lower alkyl vinyl ethers[71] involves nonspecific abstraction of hydrogen in the alkyl chain[72], indicating transfer to the ether oxygen (cf. equation 3) to yield enolic products, the structure of which has recently been confirmed[73,74]. Charge retention on the olefinic fragment increasingly competes in the higher homologues[75]. Hydrogen transfer via an eight-membered transition state, followed by cyclization to a tetrahydropyrane molecular ion has been revealed (deuterium labelling) to occur prior to loss of a methyl radical[72] in *n*-heptyl vinyl ether. The same cyclic intermediate is also involved in the formation of dominating hydrocarbon fragments in the spectra of such compounds. As soon as a pentyl group is present loss of ethanol is a striking feature[72], particularly at low ionizing energies, and is due to a triple hydrogen transfer. Since none of the large transition states are accessible to methyl enol ethers of aliphatic aldehydes, it is not surprising that these readily undergo allylic cleavage, a highly useful feature for the analysis of aliphatic aldehydes[76]. The spectra of alkyl vinyl thioethers[72] exhibit losses of all possible alkyl radicals, the base peak, however, always being due to $C_2H_4S^{+\cdot}$ fragments (m/z = 60). A substantial fraction of these is produced by a site-specific McLafferty rearrangement[72] and accordingly has the thioacetaldehyde structure[77]. Methyl vinyl sulphide[78] and phenyl vinyl sulphide[79] obviously cannot undergo such reactions and exhibit complex rearrangements, as exemplified by their facile loss of SH_n ($n = 1-3$) neutrals. Isomeric vinyl acetylene sulphides, however, can be differentiated[80].

Heterolytic *i*-cleavages to alkyl and allyl cations are important routes of allylic ethers[22]. Diagnostically very useful[22] is the formation of the ionized allylic alcohol by nonspecific hydrogen transfer from the alkyl group to the oxygen atom. Partial conversion of the allylic ether molecular ions to the isomeric vinylic species (by 1,3-hydrogen shift) accounts for the observation of some typical vinyl ether rearrangement products. This seems to be a general characteristic, since ionized allyl alcohol and 1-propen-1-ol cannot be distinguished by collisonal activation[81]. The scarce data on allylic sulphides[78,82] indicate important differences relative to their oxygen counterparts such as for example the occurrence of a McLafferty rearrangement with charge retention on the sulphur-containing fragment[82]. Note that McLafferty rearrangements are also important in δ-ethylenic ethers[22]!

C. Cyclic Ethers and Sulphides

Aliphatic epoxides exhibit a rich gas-phase ion chemistry[1,83] involving severa possible cleavages (α-, β- and particularly γ-cleavage), whereas a systematic study o their sulphur analogues is still lacking. Recent evidence confirms that epoxide molecular ions do indeed exist as stable species (relative to isomeric aldehydic or ketonic ions), at least in the cases studied so far[73,74,81]. The data cannot, however, rule out ring-opening prior to decomposition, nor can they exclude decomposition partly occurring via isomeric structures, which frequently are the only plausible intermediates for some spectral features[83,84]. The so-called *inside* McLafferty rearrangement does not occur as originally postulated, on account of its lack of site-specificity[84] and also because CA measurements[81] indicate a methyl vinyl ether product instead of the expected allyl alcohol species. These observations can be accommodated by reaction in ring-opened molecular ions, the hydrogen rearrangement then occurring to a radical site on a saturated functionality[81]. Pronounced transannular cleavages[84–86] are characteristic for epoxides and are very useful for the determination of epoxide position in long-chain compounds[85–87], which is a method for double-bond location. The fragmentations of alicyclic epoxides are exceedingly complex[83,88] and the reader is referred to the original literature. Partial rearrangement to carbonyl isomers has been established for aromatic epoxides[88,89] and occurs by 1,2-hydrogen or 1,2-phenyl shifts as verified for styrene and stilbene epoxides[89]. The spectra of 1,2-[90] and 2,3-epoxytetralin[91] clearly illustrate the pronounced effect of the aromatic nucleus in the former compound. Loss of a $C_{(2)}$ substituent is a minor process of oxetanes, presumably because of ring strain in the product ion[92–94]. Ring-opening is far more favourable and, if the substituent is an alkyl group, hydrogen rearrangement (equation 3) will ensue[92,94]. Aromatic $C_{(2)}$ substituents[93] as well as $C_{(3)}$ substitution[92] promote a retro-cycloaddition (as in the parent compound[75,83]), the charge generally residing on the olefinic fragment. Expulsion of formaldehyde is the dominant primary fragmentation of five-, six- and seven-membered cyclic ethers[95], unless $C_{(2)}$ substituents are present which induce pronounced α-cleavages[71,96]. Care is to be exercised as some of these are in fact rearrangements as revealed by the release of kinetic energy associated with the reaction : substitution of the methylene group at $C_{(4)}$ in 2-methyl- or 2,6-dimethyl-tetrahydropyran for an imino group causes ring-contraction to oxazolidines prior to methyl expulsion[97]! Introduction of a $C_{(3)}$ keto function in tetrahydrofuran strongly promotes CO loss as the primary pathway leading to all important fragments[98]. The presence of a $C_{(3)}$ hydroxy and particularly a $C_{(3)}$ mercapto substituent induces a now well-documented[99,100] ring-contraction in the tetrahydropyran ring (equation 8) which is also observed in



(4) (8)

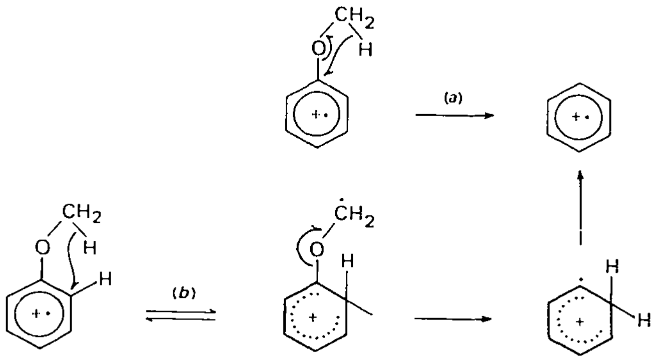
the acetylated derivatives (R = OAc, SAc). An additional alkoxy group at $C_{(2)}$ promotes additional decompositions of the intermediate 4[101]. Introduction of a double bond in the tetrahydropyran system induces retro-Diels–Alder reactions[83,102,103]. The retention of the charge as well as the abundance of the products are largely determined by the double-bond position, the location of the substituents and their number. 3,4-Dihydro-2*H*-pyrans are characterized by the formation of a protonated diene fragment[103], induced by allylic cleavage and subsequent hydrogen rearrangement.

The presence of a second oxygen atom in 1,3-dioxolanes and 1,3-dioxanes has a profound effect, loss of a $C_{(2)}$ substituent being particularly promoted[26,71,83,104]. Note, however, that a strong isotope effect discriminates against loss of D$^•$ from 4-methyl-1,3-dioxolane-2-d_2[105]. The occurrence of highly specific fragmentations (cf. equation 7) in ethylene ketals of cyclic ketones and their usefulness in the steroid field need not be recapitulated[71]. Ring-expansions and ring-contractions have recently been uncovered for cycloalkanone ethylene ketals[106]. Hexafluoroacetone ketals[107] have been proposed as suitable derivatives for the location of double bonds and offer an alternative to the older acetonide method[108]. Vinylic substituents on a 1,3-dioxolane moiety are not readily lost and induce ring-fissions followed by heterolytic cleavage (equation 4)[109]. Aryl substituents at $C_{(2)}$ lead to abundant benzoyl fragments and often result in discernible molecular ions[110,111]. The decomposition of alkyl substituted 1,3-dioxanes is dependent on the position of the substituent[104]. The availability of a tertiary hydrogen in the side-chains induces a highly characteristic pathway in 4,6-di-*i*-butyl-1,3-dioxane[112]. Appearance energies have been claimed[113] to be useful for differentiation of diastereosiomeric 4,6-dimethyl-1,3-dioxanes although the very small differences justify some scepticism as to their significance.

In five- and higher-membered cyclic sulphides there is a general trend towards enhanced formation of sulphur-containing ions produced by *i*-cleavages and subsequent losses of hydrocarbon fragments[70,83]. Alkyl substitution leads to loss of the alkyl group regardless of its position and this has been interpreted in terms of the bridging ability of a sulphur atom[83]. Ring-contractions and complex rearrangements (e.g. loss of SH_n neutrals, $n = 1-3$) have also been observed[114]. Ethylene thioketals have been investigated and are derivatives of cyclic ketones inferior to their ketal analogues[115]. The greater propensity for C—S cleavages (equation 6) is typical for 1,3-dithiolanes[116,117], 1,3-dithianes[116,118,119] and *s*-trithianes[120] and leads to the formation of particularly abundant thiocarbonyl fragments upon aryl[116,120] or vinyl[117,119] substitution.

D. Aromatic Compounds

Aryl methyl ethers are logically less prone to breakdown than their aliphatic analogues, losses of a methyl radical (followed by elimination of CO) or of formaldehyde being the most important pathways[71]. The latter route has been the subject of several mechanistic studies, the debate centring around the question of whether the reaction involves a four- or a five-membered transition state (equation 9). Originally route (*a*) was proposed[71], but more recent evidence[121], based on several ring-deuterated anisoles, reveals that hydrogen exchange occurs between the methyl group and the *ortho* positions only, as expected for the stepwise process of

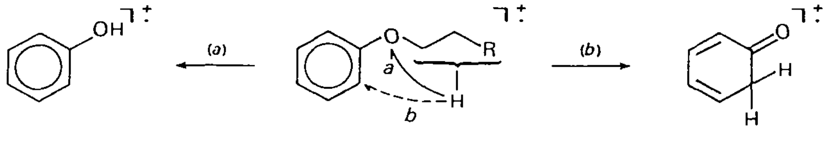


(9)

route (*b*). Also, the presence of an *ortho* nitrogen (as in 2-methoxypyridine[121], 2-methoxyquinoline[121] and 6-methoxypyrimidine[122]) strongly promotes formaldehyde loss and this has been invoked as supporting route (*b*). Metastable peak-shape analysis has finally confirmed that two processes are indeed at hand and related energy partitioning studies support the mechanism of equation (9)[123,124]. It could also be ascertained that for substituted anisoles positional identity was retained in these reactions, so as to exclude ring-expansions in the molecular ions prior to decomposition. Substituent effects on fragment abundances and appearance energies also indicate site retention during loss of CH_2O[125,126]. A similar observation has been made for the loss of a methyl radical from *m*- and *p*-substituted anisoles[127]. The reaction normally is less important than formaldehyde loss, and is increasingly outcompeted at low internal energies, as expected for a cleavage reaction[128]. The reaction sequence of successive losses of a methyl radical and carbon monoxide does however become important whenever a quinonoid fragment can be formed. Using this criterion, preferential loss of a $C_{(7)}$ methoxy group would be predicted in 6,7-dimethoxycoumarin, as confirmed by deuterium labelling[129]. This strong dependence of the reaction channel initiated by methyl loss on substituent position is of high analytical utility since it allows differentiation of isomeric compounds, as exemplified in the case of dimethoxynaphthalenes[130], dimethoxytoluenes[131] and dimethoxycoumarins[132]. In some cases loss of a methyl radical is only partially due to a simple cleavage reaction. Methylanisoles, for instance, exhibit composite metastables in contrast to other substituted anisoles[123,124]. The additional component has been attributed to ring-expansion prior to loss of $CH_3^{\bullet}$. Composite metastable peaks have also been observed[131] for the expulsion of $CH_3^{\bullet}$ from 2,4- and 2,6-dimethoxytoluene molecular ions, the extra component being ascribed to initial hydrogen transfer with formation of quinonoid products.

Minor decomposition reactions of anisole are the losses of formyl or methoxyl radicals. The former reaction is a characteristic feature of *m*-dimethoxy-substituted aromatics[71,131] and then frequently exceeds formaldehyde loss. Loss of a methoxyl radical can become important in *ortho*-substituted anisoles, as a result of functional group interaction[131,133]. Suitably positioned methoxy substituents can also promote reactions in other substituents: *ortho*- and *para*-methoxy substitution render benzylic cleavage particularly favourable[71,134].

As soon as the alkyl group in alkyl phenyl ethers is ethyl or larger, alkene elimination becomes the dominant feature[71]. The resulting fragments can have ionized phenol (5) or ionized cyclohexadienone (6) structure depending on the target of the hydrogen transfer (equation 10). The migrating hydrogen originates from all positions in the alkyl chain[135,136]. The increased site specificity of the process at lower internal energies (low eV and metastable ions) suggests the occurrence of several competing mechanisms (each involving abstraction from a particular position) rather than specific abstraction preceded by hydrogen exchange reactions[137]. This is confirmed by recent field ionization kinetics[138] measure-



(10)

(5) (6)

ments on labelled phenyl *n*-propyl ethers[30]. Substituent effects on the loss of ethylene from substituted phenetoles, though often very minor, are nevertheless real[139] and indicate retention of positional identity: the reaction can therefore be assumed to occur from unrearranged molecular ions. Virtually all ion structure probes have been applied to the problem of the $C_6H_6O^{+\cdot}$ ionic product from phenetole. First of all, the absence of a steric blocking effect upon *ortho* substitution strongly advocates against structure 6[136,140]. An important argument for route (*a*) in equation (10) is the observation of the same metastable ion characteristics (abundance ratios for competing metastable decompositions, metastable peak shapes and widths) for $C_6H_6O^{+\cdot}$ ions generated from phenetole and from phenol[139,141–143]. More direct evidence for the phenol-like structure (5) of the product is the observation that $^{13}C^{12}C_5H_6O^{+\cdot}$ ions from phenol-l-^{13}C and phenyl-1-^{13}C butyl ether both lose ^{13}CO only[144]. Also, CH_3OD only is lost subsequent to expulsion of C_2D_4 from *o*-$C_2D_5OC_6H_4COOCH_3$ molecular ions and this is only compatible with deuterium migration exclusively occurring to oxygen[145]. Isotope effects on competing metastable transitions of $C_6H_5BrO^{+\cdot}$ ions from *p*-bromophenol and *p*-bromophenetole also indicate initial formation of 5[146]. It has been pointed out that the available evidence can only confirm the existence of a common structure for decomposing ions generated from phenols and their alkyl ethers. Some arguments against 5 have been formulated and an acyclic structure was tentatively proposed[143]. Structural studies have also been extended to nondecomposing species. Structure 6 for instance was proposed on account of the higher heat of formation data for $[M - \text{alkene}]^{+\cdot}$ ions relative to ionized phenol[147]. However alkene loss necessarily involves a reverse activation energy which has been neglected in these calculations. Hence the ΔH_f values for rearrangement $C_6H_6O^{+\cdot}$ ions are too high by this amount and therefore are still compatible with a phenolic structure 5. This conclusion is reinforced by ICR[148,149] and CA[30,143,150,151] measurements. Moreover, the CA spectra of $C_6H_5DO^{+}$ ions generated from side-chain deuterated phenyl *n*-propyl ethers confirm the phenolic nature of the product, regardless of the site of hydrogen abstraction[30], thus disproving the earlier proposal[137] of different product ion structures depending on the origin of the abstracted hydrogen. A more refined picture emerges from a comparison of the EI and CI behaviour of phenyl *n*-propyl ether[136]: a stepwise mechanism involving reversible proton abstraction by the oxygen and subsequent rate-determining cleavage of the carbon–oxygen bond. Note that the system is sensitive to structural modifications as direct 1,2- and 1,3-hydrogen shifts to oxygen compete with 1,5-hydrogen transfer from $C_{(1)}$ to the *ortho* position in 2-phenoxyethyl halides[151,152]. Phenolic products are formed by all three routes, the fractional contributions of which depend on the nature of the halide present.

Loss of a sulphydryl radical is characteristic for all methylthio-substituted aromatics which otherwise exhibit similar reactions as their oxygen analogues[44]. Quinonoid stabilization, however, is no prerequisite for a pronounced loss of a methyl radical, although the reaction is enhanced in *ortho* and *para* substituted thioanisoles[44]. Also note that expulsion of thioformaldehyde is characteristic in unsubstituted and *meta*-substituted thioanisole only[44,153]. In thiophenetoles and higher alkyl aryl sulphides α-cleavages and *i*-cleavages are significant processes[71,153]. Unspecific hydrogen abstraction[135] has been observed in the formation of important[153] $[M - \text{alkene}]^{+\cdot}$ fragments and has been interpreted in terms of a thiol structure of the ionic product, in contrast to the earlier proposal based on energetic data[147]. Note however that the comment made for such data on $C_6H_6O^{+\cdot}$ ions could also be reiterated here. Also, the observation of an isotope effect on the subsequent loss of CS from $[M - C_2D_4]^{+\cdot}$ ions from d_5-ethylthiopyridines is indicative for a thiol structure as well[154].

As expected benzyl[71,155] and trityl[156] ethers, as well as the corresponding sulphides[156,157], are particularly prone to benzylic cleavage. *Para* substitution of the aryl group in aryl benzyl ethers with a strongly electron-donating substituent quenches the process in favour of abundant (quinonoidal) aryloxy cations[158]. Substituent effects and metastable ion data on aryl benzyl ethers have been interpreted in terms of tropylium ion formation for most substituents[159]. Ion kinetic energy data on the other hand seem to indicate a benzylic structure for $C_7H_7^+$ ions from benzyl methyl ether[124]. This assignment is challenged in a more recent analysis[160] of the $C_7H_7^+$ ion structure problem showing that, at the internal energies necessary for unimolecular metastable decomposition, such ions from benzyl ethers should be present as a mixture of equilibrating tropylium and benzyl species. The fraction of nonreactive benzyl cations increases in the aryl benzyl ethers relative to their alkyl analogues as the increased stability of the expelled radical lowers the activation energy for direct benzylic cleavage[160]. Benzyl radical loss is observed in benzyl cycloalkyl ethers and is reported to involve exchange of benzylic and aliphatic hydrogens[155]. The $C_7H_8^{+\cdot}$ ion from benzyl methyl ether has been shown to have ionized toluene structure[124] but no data are available on the $C_7H_8^{+\cdot}$ McLafferty rearrangement product of the higher homologues.

Particular attention has been devoted to the occurrence of ring contractions prior to decomposition of the molecular ions of chroman, tetrahydrobenzoxepine and their sulphur analogues[161–164]. The sole operation of the specific mechanism of equation (8) requires the presence of a $C_{(3)}$ substituent[163]. In all other instances[162,164] this mechanism, though still the major decomposition route, suffers competition of other pathways, initiated by benzylic cleavage. The mechanism of equation (8) very likely precedes the expulsion of a methyl radical from 2,3-dihydrobenzoxepine as it yields stable benzopyrylium ions for which there is some experimental evidence[165]. Ring contractions also intervene in the losses of a benzyl radical from 2,2-diphenylchroman and an ethyl radical from 2,2-dimethylchroman[162]. The formation of a protonated diene fragment (cf. dihydropyranes) occurs very frequently and is associated with equilibration of the molecular ions between two isomeric structures in the case of 2-substituted chroman-4-ones[166,167]. The retro-Diels–Alder reaction is on the average more pronounced in thiochromans than in chromans, a trend which is even more pronounced in the corresponding selenium compounds[168]. Introduction of a $C_{(4)}$ keto function drastically promotes the reaction, charge retention occurring on the diene fragment[169].

The electron impact behaviour of 1,3-benzodioxoles is rather unexceptional[170]. Aryl migration occurs in the molecular ions of the 2,2-bisaryl derivatives and is responsible for the formation of abundant aroyl cations, unless quinonoidal stabilization can operate subsequent to aroyl radical loss[171]. Benzo-1,4-dioxan and homologous catechol polymethylene diethers undergo ring contractions leading to benzo-1,3-dioxolanylium ions[172]. Labelling data indicate that reactions similar to equation (8) play an important role[163,172]. The yield decreases with increasing heterocyclic ring size, the exception being benzo-1,4-dioxan on account of a strongly competitive retro-Diels–Alder reaction[172]. Several studies have been devoted to the analysis of dibenzo-1,4-dioxins, particularly the polychlorinated derivatives on account of their high toxicity[173–176].

The absence of low-energy pathways in the molecular ions of diphenyl ether and diphenyl sulphide is reflected in the occurrence of substituent isomerization[177] as well as hydrogen randomization[178] prior to decomposition. CA measurements[179] indicate identical structures for the $[M - CO_2]^{+\cdot}$ ions from diphenyl carbonate and the molecular ions of diphenyl ether, thus removing the ambiguity left in a previous study[180]. *Ortho* effects have been observed in the spectra of diphenyl ethers[71,181,182] and Ar—O bond fissions become important upon *ortho* and *para* substitution with electron-donating groups[181]. Nitro substitution causes preferential charge localization on the other ring, but opposite conclusions have been reached concerning the possibility of charge migration[183,184]. Interannular interactions between two groups *ortho* to the ether linkage occur for 2′-isopropyl- and 2′-*t*-butyl-substituted 2,4-dinitrophenyl phenyl ethers[185].

E. Macrocyclic Compounds

There is a relative scarcity of mass spectral data on macrocyclic polyethers. The few electron impact spectra of aliphatic crown ethers (such as 12-crown-4[186,187], 15-crown-5[186] and 20-crown-4[188]) which have been published, clearly point to the absence of readily detectable molecular ions as the main reason for this lack of data and/or interest. Important fragments formally corresponding to the protonated lower homologues of the parent molecule are found in the low mass region only. Recent results[188,189] indicate that chemical ionization mass spectrometry[190,191], using isobutane as a reagent gas, produces abundant protonated molecular species allowing facile molecular weight determination of these so far elusive compounds. Methane causes increased fragmentation, predominantly through successive losses of the repetitive monomeric unit from both the protonated molecule and the $[M - H]^+$ ions[189].

More is known on the EI behaviour of benzocrown ethers[192–194] as well as oxygen-bridged aromatic macrocycles[195,196] in which the presence of the aromatic ring brings about enhanced molecular ion stability to yield detectable parent peaks. These are particularly abundant for dibenzocrown ethers[193,194] as well as aromatic macrocycles[195,196]. Deuterium labelling uncovered that catechol derived benzo-3*n*-crown-*n* compounds only formally decompose through successive losses of C_2H_4O and are in fact undergoing competitive losses of C_2H_4O and $C_4H_8O_2$. Moreover, part of the fragment ions generated in the latter reaction can undergo recyclization prior to further decomposition. Fragmentation apparently occurs by a variety of parallel pathways.

Few reports are available on sulphur-containing macrocycles[195–197]. Compounds containing 1,2- and 1,4-xylenyl units only, or mixed with aliphatic polymethylene bridges, all display parent peaks of appreciable abundance as well as characteristic low mass fragments[195,197]. Aromatic macrocycles containing disulphide bridges are more prone to fragmentation as a result of the facile S—S cleavage[195,196].

IV. FUNCTIONAL GROUP INTERACTIONS

The utility of mass spectrometry in structure elucidation depends largely on the applicability to polyfunctional molecules of the observations made on monofunctional compounds. Unfortunately the mass spectral behaviour of complex molecules is frequently inadequately described by the summed effects of its individual functionalities, the presence of several functional groups resulting in unique fragmentations due to direct interactions between two groups[198,199].

Several such effects have been observed in the spectra of polyfunctional ethers and sulphides.

Migration of an alkoxy group to a carbenium centre occurs frequently and yields abundant fragments provided a stable neutral can subsequently be eliminated. This is the case in acylium ions derived from 4-alkoxycyclohexanone (α-cleavage) which are converted into ionized δ,ε-unsaturated esters and logically undergo specific γ-hydrogen transfer[200]. The interaction is a sensitive function of the nature of the potential migrating group[200,201]. Loss of formaldehyde from α-cleavage products of formaldehyde acetals occurs largely via methoxyl migration to the carbenium centre, the contribution of alkyl migration being only minor at 70 eV but increasing at lower internal energies[202]. This situation is particularly unusual in that two routes from the same reactant to the same product are involved. Migration of methoxy groups to positive carbon is responsible for the formation of abundant dimethoxycarbenium ions ($m/z = 75$) in the spectra of permethylethers of aliphatic[203] and alicyclic polyols[63] (including sugars[3]). Several other alkoxy migrations to carbenium centres have been reviewed earlier[198,204] and more recent examples are found in the spectra of 3-methoxy fatty acid esters[205] as well as bifunctional ethylene ketals[206,207]. Migrations of alkoxy or aryloxy groups to positive silicon are characteristic features of bifunctional silyl ethers[208,209] and silanes[209]. In cyclic compounds the reaction is more pronounced if a *cis* configuration of the interactive functions is at hand[155] indicating an intact ring is at least partially involved.

Neighbouring-group participations have frequently been invoked to rationalize abnormal fissions in polyfunctional ethers, particularly in the case of bifunctional alkyl phenyl ethers of the general type $C_6H_5O(CH_2)_nX$[192,208,210]. These readily expel a phenoxy radical, the maximum product abundance for $n = 4$ according well with the expected formation of a five-membered ring. If the participation reaction does indeed occur, the activation energy should reflect the stability of the transition state and (assuming the Hammond postulate is applicable to the endothermic processes of electron impact mass spectrometry) of the cyclic product as well, as observed in all cases investigated so far[211]. The cyclic structure of the products has also been ascertained by deuterium and carbon-13 labelling, using the symmetry of these species[210]. Note however that a three-membered ring structure is only produced when the bridging heteroatom is sulphur[46], nitrogen[212] or chlorine[213], a competitive mechanism intervening when the heteroatom is oxygen[46]. Anchimeric assistance of silyl and germyl groups has been invoked to rationalize pronounced carbon–oxygen bond cleavages in the spectra of 9-silyl- and 9-germyl-, respectively, substituted fluorenyl ethers[214]. The expulsion of methoxy radicals from the molecular ions of *o*-methoxycinnamic acids[133] and *o*-methoxy-substituted triphenylphosphines[215] are examples of participation by carboxyl and aryl groups respectively. Also related is the time-dependent positional interchange of the phenoxy group and the halide atom in the molecular ions of 2-phenoxyethyl halides[216].

An important series of investigations has dealt with the pronounced loss of benzyl radicals from the molecular ions of α,ω-dibenzyloxyalkanes[217-219]. Migration of a benzylic hydrogen atom to the opposite ether function is followed by back-transfer of a benzyl cation. The feasibility of such benzyl cation transfer is supported by the demonstration of its intermolecular equivalent in ion–molecule reactions[218]. These studies adequately illustrate the general observation that hydrogen abstraction from a methylene group adjacent to an ether oxygen (or an aromatic ring) will occur readily on account of the reduced C–H bond dissociation energy of such activated hydrogens, provided a suitable receptor function is present and the necessary geometrical requirements are fulfilled. The ensuing radical centre may subsequently induce cleavage reactions. Such assisted carbon–oxygen bond cleavages have, for example, been observed in 4-alkoxybutyrates[220] and 3-methoxy fatty acid esters[205]. Alternately the protonated receptor function can be lost as a neutral molecule, as in the low-energy spectra of α,ω-dialkoxyalkanes[221]. Note that in these molecules the hydrogen transfer is highly regioselective, as was also observed for the reciprocal hydride transfer in $CH_3O(CH_2)_nCH{=}\overset{+}{O}CH_3$ fragment ions[222]. Finally hydrogen abstraction is also eased by an adjacent carbenium centre as observed in methoxy-substituted long-chain aliphatic esters[223].

A diagnostically very useful class of functional group interactions are the so-called *ortho* and *peri* effects observed in aromatic compounds[224]. These, for instance, are responsible for the pronounced elimination of $OH^{\bullet}$ and H_2O from the molecular ions of *ortho-* or *peri*-methoxy-substituted aromatic carbonyl compounds[225,226]. *Peri*-ethoxy-substituted naphthoquinones and anthraquinones exhibit a highly diagnostic loss of the terminal methyl in the ethoxyl group (presumably via a cyclization reaction)[226]. Aromatic carbonyl compounds with *ortho-* or *peri*-ethoxy substituents are characterized by the presence of $[M - H_3O]^+$ species which undoubtedly must result from complex skeletal rearrangements[227]. Mechanistically far more interesting are the *ortho* effects which have been uncovered in a series of *ortho*-substituted benzoic acid methyl esters[228-230]. The driving force in these reactions is the capability of the carboxyl function to abstract an activated (benzylic or carbinol, see above) hydrogen in the *ortho* substituent. Such a hydrogen transfer, for instance, precedes loss of the ester methyl in the molecular ions of *o*-methoxy[228,229] and *o*-ethoxy[145,150] derivatives. Activated hydrogens are also abstracted prior to loss of an ether methyl radical from the molecular ions of *o*-methoxymethyl methylbenzoate as well as loss of methanol from the molecular ions of the *o*-(β-methoxyethyl) derivative[230]. An *ortho*-positioned nitro group also has an intramolecular catalytic effect in the formaldehyde loss from *o*-nitroanisole molecular ions[231], the loss of methanol from *o*-nitrobenzaldehyde dimethyl acetal parent ions[232] and presumably also in the formation of cyclohexadienethione fragments from *o*-nitrobenzyl aryl sulphides[233].

V. STEREOCHEMICAL EFFECTS IN THE SPECTRA OF ETHERS

The usefulness of electron impact mass spectrometry as a stereochemistry probe has become increasingly apparent during the last decade, as reflected in two recent reviews on the subject[234,235]. Stereochemical effects most frequently operate in rearrangements as a result of the cyclic transition states involved in such processes. Indeed, provided the original stereochemistry is retained in the molecular ions of stereoisomers, one of these may well have a more readily accessible transition state for a given rearrangement, resulting in an increased rate constant. This is adequately illustrated by the preference for a transition state avoiding phenyl–phenyl eclipsing in the 1,2-elimination of methanol from the molecular ions 1,2-diphenylethanol methyl ether as revealed by diastereotopical labelling of the $C_{(2)}$ methylene hydrogens[236]. Stereochemical effects are nevertheless predominantly encountered in cyclic systems which decompose less through simple cleavages. These general observations unfortunately cannot be extended to sulphides for lack of available studies.

Both 1,3- and 1,4-elimination of methanol occur from cyclohexyl methyl ether molecular ions[62], with an increased preference for the former relative to the loss of water from cyclohexanol[237]. Labelling of diastereotopic hydrogens in the latter compound reveals a highly stereospecific 1,4-elimination and a total lack of specificity for the 1,3-process[237]. This has been explained in terms of a more distant hydrogen being involved in stereospecific 1,3-elimination: the reaction is energetically less favorable[238] and suffers strong competition of ring-opening. Elimination of water in the resulting acyclic molecular ions ensues but evidently cannot discriminate between diastereotopic hydrogens. Increasing the reach of the functionality as in cyclohexyl chloride promotes the occurrence of the stereospecific 1,3-process in intact molecular ions and stereospecific 1,3-elimination of hydrogen chloride results[237]. On account of the longer RO—H bond length relative to the HO—H distance, it then seems logical to assume at least an intermediate situation for methyl ethers. No diastereotopic labelling has been performed on cyclohexyl methyl ether, but the increased $[M - HX]/[M]$ ratio for *cis*-4-*t*-butylcyclohexyl methyl ether[239] ($X = OCH_3$; 0.68) relative to the corresponding alcohol ($X = OH$; 0.06)[240] is in agreement with this prediction (no stereospecific 1,4-reaction is possible in these compounds).

The alcohol elimination is a sensitive function of the bond strength of the C—H bond to be broken; a reduction of this parameter by alkyl or aryl substituents lowers the activation energy for abstraction from the site of substitution and promotes the reaction. Accordingly the $[M - CH_3OH]/[M]$ ratio is drastically increased relative to the unsubstituted compound (0.8[62]) for the *trans* isomers of 4-*t*-butyl-(7.5[239]), 4-aryl-(28.6[241]) and 3-aryl-(76[241]) substituted cyclohexyl methyl ethers. Moreover, deuterium labelling[241] in the aryl compounds has confirmed the high degree of regioselectivity brought about by such activating substituents. The *cis* isomers of the above-mentioned substituted cyclohexyl methyl ethers cannot undergo abstraction of activated hydrogen in an intact molecular ion and consequently are much less prone to loss of methanol[239,241]. A normal, energetically less favoured 1,3-elimination is then expected but labelling data indicate a strong involvement of benzylic hydrogens too. Evidently ring-opening has occurred prior to elimination, the increased mobility of the benzylic hydrogen apparently still providing the necessary driving force for the observed specificity of hydrogen abstraction in the acyclic species.

The preceding examples clearly illustrate that activating groups can be very effective in inducing spectral differences for stereoisomers through a promotion of regioselective and stereospecific hydrogen abstractions. This is particularly true for dimethoxy-substituted cycloalkanes[242,243] which have been studied by Grützmacher and collaborators. Their investigations reveal that intact molecular ions have to survive long enough if steric effects are to be observed. Vicinal alkoxy groups for instance destroy the stereochemistry by bringing about very rapid α-cleavages. Two important stereospecific processes have been uncovered. First of all, transannular hydrogen transfer from one methoxy group to the other, followed by consecutive elimination of formaldehyde and methanol, is observed whenever two *cis*-positioned methoxy groups can approach each other close enough in a particular conformation of the molecular ion. This is impossible for a *trans* configuration but then enhanced abstraction of an activated carbinol hydrogen by the other methoxy group leads to increased loss of methanol if a suitable conformation (chair for 1,3-isomers, boat for 1,4-isomers) is accessible. These observations require that molecular ions are still conformationally flexible and that energetically less favourable conformations (boat, diaxially substituted chair) are accessible within the ion source residence times (10^{-6} s) of these species. This is possible as sufficient energy is deposited in the molecular ions upon ionization, whereas conformational changes are fast enough ($\sim 10^{-8}$ s) to happen within the ion source. An experimental verification is provided by a study of anancomeric* 5-*t*-butyl-1,3-cyclohexanediol mono- and di-methyl ethers[244] which also led to following important generalizations: (*i*) if the ground conformation of the molecular ion has the substituents correctly positioned for stereospecific interaction, conformational changes are outcompeted, and (*ii*) if however conformational changes are required before a stereochemically controlled fragmentation can take place, then the overall process is slowed down and increased competition from unspecific reactions results. Unless the stereospecific step is fast, only small steric effects are observed. A careful analysis of the kinetics of competitive fragmentations in the EI-induced decay of 2- and 5-methyl-substituted 1,3-cyclohexanediols and their ethers confirms that 1,3-diaxial elimination of methanol (*trans* isomers) is instrinsically faster than conformational flipping, but also indicates that the converse holds for the formaldehyde elimination in the *cis* diethers[245].

Upon attachment of a second saturated ring to a dimethoxy-substituted cyclohexane ring, the conformational mobility is reduced and may therefore quench the stereospecific reactions observed in monocyclic compounds. Stereoisomeric 1,4-dimethoxy decalins are nevertheless readily differentiated[246]. Mass spectrometric identification of 1,3-dimethoxydecalins is also possible, but deuterium labelling indicates that the stereospecificity of the probe reactions is reduced when conformational changes are required prior to fragmentation[247]. In the case of 1,5-dimethoxy decalins an additional complication arises in that the substituents are located in different rings and therefore only one (out of the five) exhibits a clear steric effect[248]. Finally, incorporation of a dimethoxy-substituted cycloalkane ring into a rigid bicyclic system generally does not lead to pronounced steric effects, as a result of enhanced ring-cleavage reactions induced by bicyclic strain[249,250].

Note that stereochemical effects are not restricted to the interactions occurring between two alkoxy groups (see above) or an alkoxy and a silyloxy group (Section IV). Another useful stereochemistry probe is the hydrogen transfer from the *t*-butyl group to a *cis*-positioned ether oxygen (resulting in C_4H_8 and $C_4H_7^{\bullet}$ losses) observed in *cis*-4-*t*-butyl cyclohexyl methyl ether[239]. The effect can be used to differentiate epimeric 7-*t*-butyl-3-oxabicyclo[3.3.1]nonanes[251].

VI. CHEMICAL IONIZATION MASS SPECTROMETRY

Although approximate gas-phase proton affinities of oxygenated organic compounds have been known[252,253] for some time, accurate data[254-257] (Table 2) have only recently become available from measurements on thermal equilibria either in a pulsed ion cyclotron resonance instrument or in a pulsed electron beam high-pressure mass spectrometer. Both approaches involve the determination of the gas-phase equilibrium constant for proton-transfer reactions, and, after correction for entropy changes, lead to the reaction enthalpy, equal to the difference in proton affinity (PA) of the two bases involved in the reaction. An absolute PA-scale can then be built using isobutene as a reference since its absolute PA is accurately known from the heat of formation of the *t*-butyl cation[258]. The tabulated data (Table 2) clearly show the effect of a decreased electronegativity of the heteroatom

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*I.e. conformationally biased; designates structures for which the position of conformational equilibrium is so extreme that only one conformation is present in the neutral molecules.

TABLE 2. Gas-phase proton affinities, PA (kJ mol^{-1})

Compound	PA	Compound	PA
CH_4	531[253]	Tetrahydrofuran	821[255]
Oxirane	773[254]	Tetrahydropyran	824[255]
1,4-Dioxane	798[255]	Et_2O	825[255], 828[256]
Me_2O	795[256], 799[255]	Me_2S	826[255]
i-C_4H_8	807[256], 809[255]	PhOMe	833[257]
Oxetane	811[254]	NH_3	839[256], 846[255]

(Me_2O vs. Me_2S) as well as the internal inductive effect arising within the ring for cyclic ethers. Also note that alkyl substitution α to the ether oxygen atom leads to an increased PA (Et_2O vs. Me_2O) as had been observed earlier for alcohols[253]. Recently, linear relationships (correlation coefficients of 0.99) have been established between the PA of aliphatic ethers and their O(1s) core electron binding energies as well as their oxygen valence shell ionization energies[259]. These correlations are very useful as they allow the estimation of fairly accurate proton affinities for ethers when this parameter either is unknown or cannot be determined accurately.

The site of protonation in anisole has been the subject of several studies. A linear relationship between the proton affinities and substituent σ^+-values for a number of monosubstituted benzenes, including anisole, has been interpreted in terms of ring protonation[257], in agreement with predictions based upon molecular orbital calculations[260] for the three isomeric methylanisoles. The anisole O(1s) binding energy yields a PA-value (see above) substantially lower than the experimental value (Table 2) and confirms ring protonation as well[259]. Also consistent with this picture is the observation that the PAs of phenol and anisol differ much less than for example methanol and dimethyl ether[261]. The behaviour of anisole upon chemical ionization using water as a reagent gas, on the contrary, has been interpreted in terms of oxygen protonation[262], but it has been suggested[259] that in these non-equilibrium conditions kinetic control favours the less stable oxygen-protonated form.

The basic requirement for proton transfer chemical ionization is an exothermal protonation step or a product PA exceeding the PA of the conjugated base of the reactant species[190,191]. Hence methane and isobutane (see Table 2) are suitable for the analysis of most ethers. The ion–molecule complex being short-lived, the energy liberated upon protonation largely remains in the protonated molecule. Consequently the exothermicity of the protontransfer reaction (i.e. the PA difference of the two bases involved) will affect the extent of subsequent decomposition: isobutane is therefore advised for molecular weight determinations (e.g. aliphatic crown ethers[188,189] or permethylated sugars[263]). Subsequent decomposition of protonated aliphatic ethers generally occurs through alcohol loss[263–265]. Note that in the case of geometrical isomers of 2,3-dimethyl cyclopropyl ethers the relative yields are in accordance with the Woodward–Hoffman rules[58]. Recent labelling data disprove the apparent simplicity of the loss of alcohol from protonated 4-alkoxycyclohexanones: the direct cleavage seems to be in competition with a 1,3-hydrogen rearrangement and consecutive expulsion of alkene and water[266]. Cyclic ethers on the other hand exhibit reasonably abundant $[MH - H_2O]^+$ species[267] also found in the spectra of epoxides, epoxy esters and related compounds[268,269], but ring-cleavage products are analytically much more useful as they allow the determination of double-bond location in olefins. Loss of phenol is observed for protonated alkyl phenyl ethers[270] which also eliminate the aliphatic chain to yield characteristic protonated phenol fragments[136,270]. The data on labelled phenyl *n*-propyl ethers indicate hydrogen transfer from all alkyl positions to the oxygen atom prior to C–O bond cleavage in the latter reaction[136] (see also Section III.D).

Increasing the partial pressure of a monofunctional ether in and ICR spectrometer results in the formation of proton-bound dimers[271]. Competition from intramolecular coordination of the transferred proton occurs from their bifunctional $CH_3O(CH_2)_nOCH_3$ analogues as soon as $n > 3$ and effectively quenches cluster formation up to pressures as high as 10^{-3} torr for $n > 4$. Eight- or higher-membered rings are apparently preferred in the proton-bridged species, indicating a close to linear geometry for the intramolecular hydrogen bond. Similar conclusions have been reached from studies on α,ω-diaminoalkanes[272] and α,ω-diols[273]. The effect of proton bridging can be used for stereochemical assignments in bifunctional cyclic molecules since it requires a *cis* relationship between two groups: proton capture will ensue if two *cis*-related functions can approach each other close enough and yields abundant protonated species. No such effect is possible for the corresponding *trans* isomers which consequently are characterized by reduced MH^+ abundances (if observed at all). This criterion has been successfully applied to 2,7-dimethoxy-*cis*-decalins[274], 3-methoxycyclopentyl- and 3-methoxycyclohexyl-acetic acid esters[275], and 2-methyl-substituted 1,3-dimethoxycycloalkanes[276].

On account of the analogy between acid–base chemical ionization and condensed-phase cation chemistry it is no surprise that intramolecular substitution reactions have been observed upon methane or isobutane chemical ionization. Participation of methylthio groups has been recorded for β-methylthioethanol[51], *S*-methyl cysteine[277] and phenoxyalkyl methyl sulphides[278]. A methoxy group on the contrary is much less capable of such backside assistance but is readily displaced (subsequent to protonation) by ester groups, particularly at secondary positions[279]. In cyclic bifunctional compounds such displacement of protonated alkoxy groups is only possible if a *trans* relationship is at hand and occasionally the combined effects of proton bridging (*cis* isomer, see above) and S_Ni reactions (*trans* isomers) produce an all or none situation for the protonated molecule MH^+ [274-276]. Participation of ether oxygen has however been observed in the expulsion of phenol from protonated 4-(ω-phenoxyalkyl)-substituted tetrahydropyrans[210e], phenoxyalkyl ethers[278] and 1,3-dimethoxycycloalkanes[276].

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Note Added in Proof

Additional data have become available on $C_2H_5S^+$[280], $C_3H_7S^+$[281] and $C_6H_6O^{+\cdot}$[282,283] ions. Except for the cyclobutyl case, long-lived cycloalkyl methyl ether molecular ions have isomerized to linear alkene radical cations[284]. Information on the structure of triphenylsulphonium-type cations can be obtained by combined field desorption–collisional activation analysis of their salts[285,286]. Steric crowding effects are observed in the spectra of alkyl aryl sulphides[287]. Anchimeric assistance of silyl groups induces ether cleavages in alkyl silylmethyl ethers[288]. Functional group interactions are also responsible for the special behaviour of ω-alkoxy-alkylamines[289]. Methane CI data on sulphides[290] as well as additional data on cyclic ethers[291,292] have become available. Collisional activation has been used to unravel the fragmentation pathways of protonated ethers[293]. Allyl phenyl ether is reported to undergo a Claisen rearrangement under CI conditions[294]. A further comparison of leaving-group ability and anchimeric assistance under CI conditions has been made for methoxy and acetoxy groups[295]. Finally negative chemical ionization has been shown to be about three orders of magnitude more sensitive for the detection of polycholorodibenzo-*p*-dioxins than conventional positive CI[296].

Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 8

The electrochemistry of ethers, hydroxyl groups and their sulphur analogues

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I. INTRODUCTION

This review describes the reactions of ethers, hydroxyl groups or their sulphur analogues initiated by the electron transfer between electrode and the substrates, although the emphasis herein is mainly upon the organic reactions rather than upon electrochemical details. Since the electroorganic chemistry of ethers, hydroxyl groups and their sulphur analogues is rather a minor area in the electrochemistry of organic compounds, the reader is suggested to refer to texts[1-8] which are written for organic chemists unfamiliar with the electroorganic chemistry.

II. CATHODIC REDUCTION

In general, ethers, hydroxyl groups and their sulphur analogues are fairly stable under the reaction conditions of electrochemical reduction, so that the presence of a certain activating group is necessary to make these groups active for electrochemical reduction. The reduction of sulphoxides and sulphones is not included in this chapter, though they are electrochemically reducible.

TABLE 1. Polarographic reduction potentials of sulphides in DMF[9]

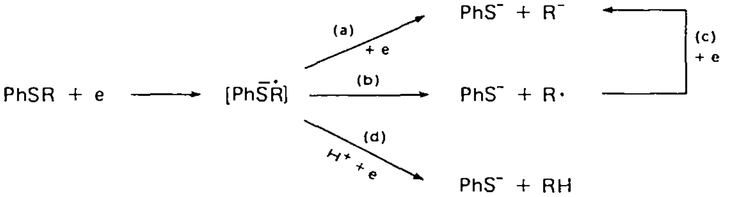
Ar in PhSAr	$-E_{1/2}$ (V)^a	R in RSPh	$-E_{1/2}$ (V)^a
Ph–	2.549	Me	2.751
2-MeC_6H_4–	2.571	Et	2.743
3-MeC_6H_4–	2.567	*i*-Pr	2.703
4-MeC_6H_4–	2.595	*t*-Bu	2.638
2,2'-$Me_2C_6H_3$–	2.588	$H_2C{=}CHCH_2$	2.655
3,3'-$Me_2C_6H_3$–	2.585	$PhCH_2$	2.569
4,4'-$Me_2C_6H_3$–	2.645	CH_2COOEt	2.455
		CH_2CN	2.351

^{a}Vs. Ag/Ag$^+$.

A. Sulphides

Simple dialkyl sulphides, such as dimethyl, diethyl sulphides etc., are not electrochemically reducible, probably because of their highly negative reduction potentials. Arylalkyl and diaryl sulphides, however, can be reduced, and the detail of the mechanism of the electroreduction of these compounds has been studied, though it has not been established yet. The polarographic reduction of arylalkyl and diaryl sulphides in anhydrous DMF shows generally a single well-defined irreversible wave, the half-wave potentials of which are shown in Table 1[9].

The controlled-potential electrolysis of diphenyl sulphide in anhydrous DMF yields equivalent amounts of thiophenoxide ion and benzene, so that the polarographic wave of most of the compounds shown in Table 1 can be associated with the two-electron fission of a S—C bond. The reduction of $PhSCH_2X$, where X is COOEt, COOH or CN, without the presence of a suitable proton donor such as phenol is assumed to be a one-electron process. Although the bond fission of a S–C bond is generally a two-electron process, the addition of the first electron is assumed to be the rate-determining step. The reaction pathways may be shown as in equation (1). The hypothetical electrode intermediate shown in the square bracket is generated at the initial potential-determining step.

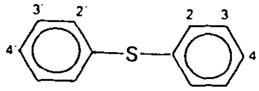


(1)

Most of the sulphides follow the pathways (a) or (b)–(c). In the first pathway, a second electron is transferred to the intermediate at the same potential before it can collapse into an anion and a radical. In the second case, a thiophenoxide anion rather than a thiophenoxy radical PhS· is yielded, and the generated radical R· is reduced to an anion at the electrode. If the process (c) is slow, the radical R· may behave as a free-radical species. Path (d) illustrates the case in which a suitable proton donor such as phenol exists in the reaction system.

A fairly good linear relationship is obtained by plotting the half-wave potentials shown in Table 1 against Tafts' σ^* parameters. The slope ρ^* is 0.286 ± 0.043 V. The structural effects on the half-wave reduction potential of sulphides are

TABLE 2. Half-wave potential shifts produced by methyl substitution on diphenyl sulphide[9]



	Shift (mV)
2-Me	22
3-Me	18
4-Me	46
2,2'-di-Me	39
3,3'-di-Me	36
4,3'-di-Me	96
2,4,6,2',4',6'-hexa-Me	189

essentially polar. The effect of methyl groups on the phenyl ring shows a good additive property as shown in Table 2[9].

The effects of substituents on the reduction potentials have also been studied on substituted diphenylmethyl phenyl sulphides, $X^1C_6H_4(X^2C_6H_4)CHSC_6H_4Y$. The half-wave potentials obtained in DMF are shown in Table 3[10].

The rate-determining step involves the addition of one electron. The plot of $E_{1/2}$ against σ shows two lines depending on substituents X or Y. The substituents (X^1, X^2) on the diphenylmethyl skeleton give a line of which slope (ρ_X) is 0.203 ± 0.008 V, whereas the slope (ρ_Y) obtained with substituents (Y) on the thiophenol ring is 0.386 ± 0.009 V. Thus, for both classes of substituent, electron-donating groups make the half-wave potential more negative while electron-withdrawing groups give the opposite effect on the reduction potential, the effect being much greater for substituents on the thiophenyl ring. If the rate-determining step involved the addition of two electrons instead of one forming a diphenylmethyl carbanion and a thiophenoxide anion, the substituents X would be supposed to be more efficient than substituents Y ($\rho_X > \rho_Y$). Therefore, the first

TABLE 3. Half-wave potentials of substituted diphenylmethylphenyl sulphides, $X^1C_6H_4(X^2C_6H_4)CHSC_6H_4Y$, in DMF[10]

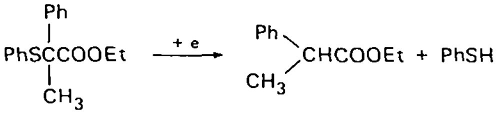
X^1	X^2	Y	$-E_{1/2}$ ± 0.003 (V)[a]
H	H	H	2.001
4-Cl	4-Cl	H	1.895
4-Cl	H	H	1.938
3-Cl	H	H	1.923
4-Ph	H	H	1.802
3-MeO	H	H	1.971
4-Me	H	H	2.022
3,4-di-Me	H	H	2.029
4-MeO	4-MeO	H	2.105
H	H	4-Cl	1.912
H	H	3-Cl	1.842
H	H	4-F	1.958
H	H	4-Me	2.061
H	H	4-MeO	2.089
Ph_3CSPh			1.930

[a] Vs. mercury pool.

active intermediate formed at the cathode is an anion radical in which the resonance formula with the negative charge on sulphur should contribute to a greater extent (equation 2). The Intermediate anion radical formed from diphenylmethyl-*p*-nitrophenyl sulphide has been detected by ESR spectrometry[11].

$$\mathrm{Ar_2CH{-}SAr \xrightarrow{+e} [Ar_2\bar{C}H\dot{S}Ar \longleftrightarrow Ar_2\dot{C}H\bar{S}Ar]} \qquad (2)$$

The optical activity is not retained in the electroreduction of optically active ethyl 2-phenylmercaptopropionate in ethanol (equation 3)[12]. This result may be in

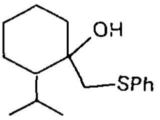
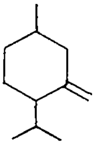
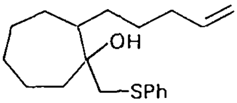
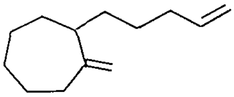
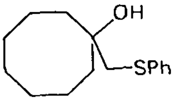
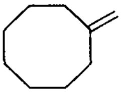
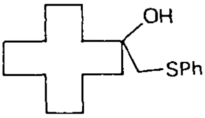
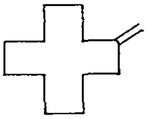
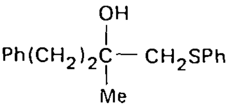
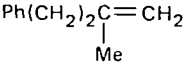
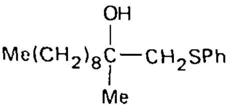
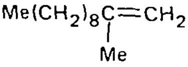


$$\mathrm{PhS\underset{CH_3}{\overset{Ph}{C}}COOEt \xrightarrow{+e} \overset{Ph}{\underset{CH_3}{>}}CHCOOEt + PhSH} \qquad (3)$$

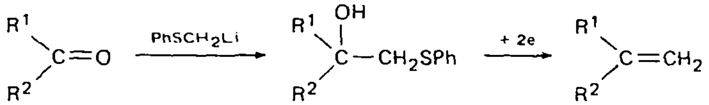
agreement with the idea that anion radicals formed from alkylphenyl sulphides collapse into alkyl radicals and thiophenoxide anion.

The electrochemical reduction of phenylalkyl sulphides having a hydroxyl group

TABLE 4. Cathodic elimination from β-hydroxysulphides[13]

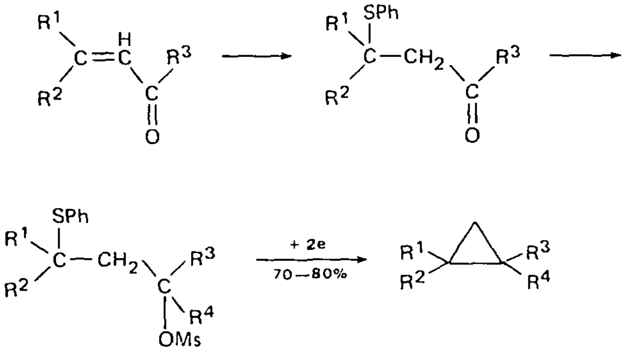
β-Hydroxysulphide	Product	Yield (%)
		80
		92
		68
		70
 $\mathrm{Ph(CH_2)_2\underset{Me}{\overset{OH}{C}}{-}CH_2SPh}$	 $\mathrm{Ph(CH_2)_2\underset{Me}{C}{=}CH_2}$	90
 $\mathrm{Me(CH_2)_8\underset{Me}{\overset{OH}{C}}{-}CH_2SPh}$	 $\mathrm{Me(CH_2)_8\underset{Me}{C}{=}CH_2}$	96

on the β- or γ-position of the alkyl moiety leads to elimination reactions useful in organic synthesis. The reduction of β-hydroxysulphides prepared from ketones yields olefins in high yields (equation 4) (Table 4)[13].


R1
R2
C=O
PhSCH2Li
OH
C—CH2SPh
+ 2e
C=CH2

(4)

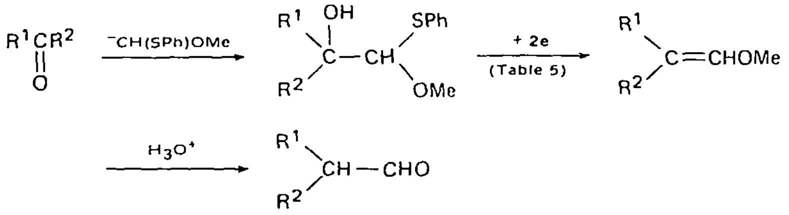
In the electroreduction of methanesulphonates of γ-hydroxysulphides, the corresponding cyclopropanes are formed in high (70–80%) yields (equation 5)[14].


R1
R2
H
C=C
R3
C
O
SPh
C—CH2
OMs
R4
+ 2e
70—80%

(5)

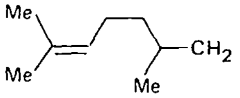
Ms = $MeSO_2$—

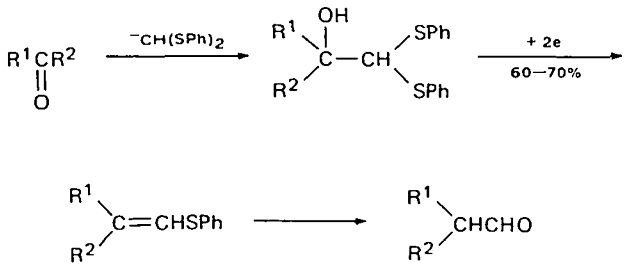
Homologation of aldehydes to the next higher members (Table 5) and transformation of esters or ketones to aldehydes can also be achieved by using this electroreductive elimination (equations 6–8)[15].


R1CR2
O
⁻CH(SPh)OMe
R1
R2
OH
SPh
C—CH
OMe
+ 2e
(Table 5)
C=CHOMe
H3O+
CH—CHO

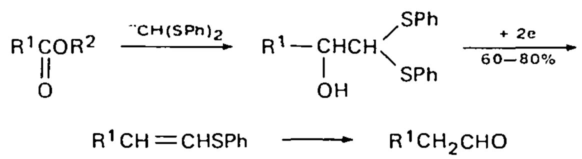
(6)

TABLE 5. Electroreductive formation of enol ethers ($R^1COR^2 \rightarrow R^1R^2C{=}CHOMe$)[15]

R^1	R^2	Yield (%)
$PhCH_2CH_2$	H	96
n-C_9H_{19}	H	98
n-C_6H_{13}	H	90
 Me Me CH2 Me	H	98
i-Bu	Me	91
$-(CH_2)_5-$		92



(7)



(8)

B. Other Sulphur Compounds

1. Thiols and disulphides

The electrochemical reduction of thiols (RSH) or their esters[16] to the corresponding RH-type compounds has not been achieved. The products obtained from the electroreduction of thiol esters are the corresponding thiols.

The sulphur–sulphur bond in disulphides is easily cleaved by electrochemical reduction. The reduction peak potential required for the transformation of PhSSPh to PhS^- is about – 1.8 V vs. SCE on platinum in DMF[17], whereas the disulphide can be reduced at about –0.5 V vs. SCE ($E_{1/2}$) on mercury in ethanol[18]. This relatively large anodic shift of the reduction potential of disulphides observed on a mercury cathode may be explained by the formation of $(RS)_2Hg$ being adsorbed on mercury through the reaction of RSSR with Hg^0 before the disulphides are electrochemically reduced, since the reduction potential of $(RS)_2Hg$ being adsorbed on mercury is almost the same as that of RSSR on mercury (equation 9)[19].

$$\mathrm{RSSR} + \mathrm{Hg}^0 \longrightarrow [(\mathrm{RS})_2\mathrm{Hg}]_{\text{adsorbed}} \tag{9a}$$

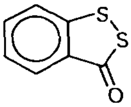
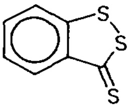
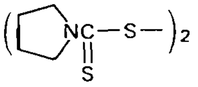
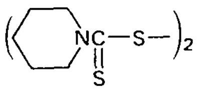
$$[(\mathrm{RS})_2\mathrm{Hg}]_{\text{adsorbed}} \xrightarrow[2\mathrm{H}^+]{2e} 2\,\mathrm{RSH} + \mathrm{Hg}^0 \tag{9b}$$

The thiolate anions formed from the electroreduction of disulphides may be trapped by a variety of electrophiles, so that this electrochemical reaction is a useful synthetic method of sulphide derivatives (equation 10). One of the advantages of this electrochemical method is that the derivatives can be prepared from the

$$\mathrm{R^1SSR^1} \xrightarrow{+\,2e} \mathrm{R^1S^-} \xrightarrow{\mathrm{R^2X}} \mathrm{R^1SR^2} + \mathrm{X^-} \tag{10}$$

disulphides of which corresponding thiols are unstable or not known. A restriction in this reaction is that the disulphides must be reduced prior to the reduction of the electrophiles. Table 6 shows reductive methylation of some disulphides with methyl chloride, and reactions with other electrophiles are shown in Table 7[20].

TABLE 6. Reductive methylation of disulphides with methyl chloride in DMF[20]

Disulphide	Cathode potential (–V)^a	Yield (isolated %)
$(PhCH_2S-)_2$	1.2	82
$(PhS-)_2$	0.85	83.5
$(p\text{-}MeC_6H_4S-)_2$	1.0	85.5
$(PhCOS-)_2$	0.8	70
$(o\text{-}NO_2C_6H_4S-)_2$	0.3	91
$(o\text{-}EtOCOC_6H_4S-)_2$	0.6	89
	0.15	85.5
	0.35	78
$(Me_2NCSS-)_2$	1.0	81
	0.8	88
	1.2	78

^{a}Vs. Ag/Ag$^+$.

TABLE 7. Reduction of disulphides in the presence of a variety of electrophiles in DMF[20]

Disulphide	Electrophile	Yield (isolated %)
$(MeS-)_2$	$PhCH_2Cl$	63
$(MeCOS-)_2$	$PhCH_2Cl$	76.5
$(PhS-)_2$	$PhCH_2Cl$	92
$(PhCH_2S-)_2$	MeCHClMe	75.5
$(PhCH_2S-)_2$	Ac_2O	89.5
$(o\text{-}NO_2C_6H_4S-)_2$	Ac_2O	68.5
$(o\text{-}NO_2C_6H_4S-)_2$	AcCl	39
$(o\text{-}NO_2C_6H_4S-)_2$	MeI	84
$(o\text{-}NO_2C_6H_4S-)_2$	$(MeO)_2SO_2$	91
$(o\text{-}NO_2C_6H_4S-)_2$	$(EtO)_2SO_2$	76.5
$(Me_2NCSS-)_2$	Me_2NCOCl	37
$(PhCOS-)_2$	CH_2Br_2	66
$(PhCOS-)_2$	CH_2Cl_2	34

2. *Sulphonium salts*

Sulphonium salts generally possess relatively anodic reduction potentials and are easily cleaved by the electrochemical reduction, so that their potentiality as supporting electrolytes is limited[1]. The electroreductive behaviour of sulphonium salts is, however, rather complicated[21]. The polarographic reduction of triphenylsulphonium bromide shows two reduction waves at −1.095 V vs. SCE and −1.33 V vs. SCE (pH 6). The first wave is independent of pH and shifts anodically with a slope of about 50 mV per tenfold change in concentration, while the second shows a slight nonlinear dependence on pH and shifts cathodically with a slope of about 60 m V per decade change in concentration. The number of electrons involved in the electrolysis is concentration-dependent: $n = 2$ at 0.46 ~ 0.79 mM, $n = 1.6$ at 8.4 mM.

The following reaction scheme has been proposed. The first electron transfer step is shown in equation (11). In the second step, the radical species accepts another electron and a proton (equation 12).

$$Ph_3S^{+}\cdots Hg + e \longrightarrow (Ph_3S\cdots Hg^{\bullet}) \qquad (11a)$$

$$2\,(Ph_3S\cdots Hg^{\bullet}) \longrightarrow 2\,Ph_2S + Ph_2Hg + Hg \qquad (11b)$$

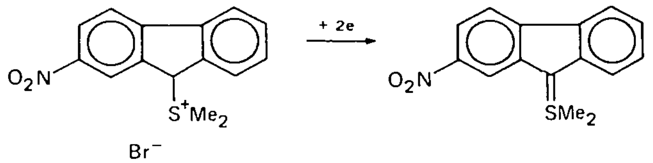
$$(Ph_3S\cdots Hg^{\bullet}) + e + H^{+} \longrightarrow Ph_2S + C_6H_6 + Hg \qquad (12)$$

In the polarographic and coulometric study of the reduction of cyanomethyl dimethylsulphonium ion in anhydrous DMSO, a wave corresponding to a single apparent one-electron transfer per molecule has been observed[22]. However, the polarographic study in the presence of acetic acid and the macroelectrolyses have suggested that the reduction is actually a two-electron process to form the cyanomethyl anion which reacts with the starting ion at the surface of electrode to form an ylid (equation 13).

$$Me_2\overset{+}{S}CH_2CN \xrightarrow{+\,2e} Me_2S + (CH_2CN)^{-} \qquad (13a)$$

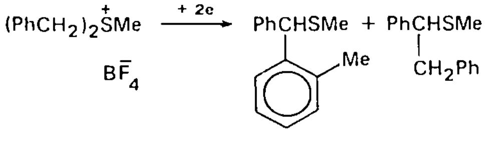
$$Me_2\overset{+}{S}CH_2CN + (CH_2CN)^{-} \longrightarrow Me_2\overset{+}{S}\overset{-}{C}HN + CH_3CN \qquad (13b)$$

The formation of ylids in the electroreduction of sulphonium salts has been clearly demonstrated[23] by the fact that the reduction of the aqueous solution of 2-nitrofluorenyl-9-dimethylsulphonium bromide gives immediately the corresponding ylid as a purple solid on the surface of cathode (equation 14).



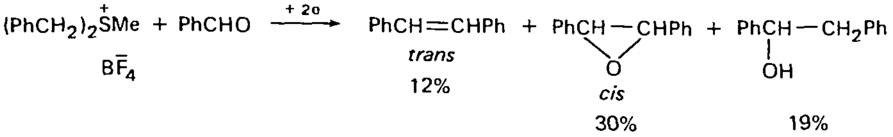
(14)

The cathodic reduction of dibenzylmethylsulphonium fluoroborate in DMSO at −1.6 V vs. SCE yields two products resulted from the rearrangement of the intermediately formed sulphonium ylid (equation 15).

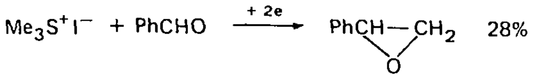


(15)

The electroreduction of some sulphonium salts in the presence of the acceptors of ylids such as benzaldehyde gives products which suggest the intermediary generation of sulphonium ylids (equation 16 and 17).

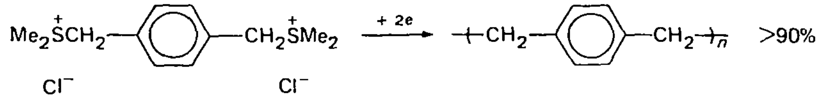

$(PhCH_2)_2\overset{+}{S}Me$ + PhCHO
$\bar{B}F_4$
+ 2e
PhCH=CHPh
trans
12%
PhCH—CHPh
O
cis
30%
PhCH—CH$_2$Ph
OH
19%

(16)


$Me_3S^+I^-$ + PhCHO
+ 2e
PhCH—CH$_2$
O
28%

(17)

Poly-*p*-xylene can be prepared in high yield by the electrochemical reduction of a solution of a *p*-xylenebissulphonium salt with a mercury cathode under an atmosphere of nitrogen (equation 18)[24].

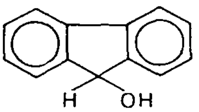
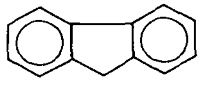
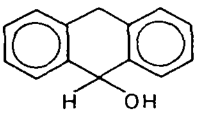
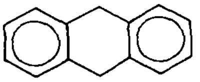

$Me_2\overset{+}{S}CH_2$
$CH_2\overset{+}{S}Me_2$
Cl^-
Cl^-
+ 2e
$-\!\!\!+CH_2$
$CH_2\!+\!\!\!-_n$
>90%

(18)

C. Hydroxyl Groups and Ethers

Hydroxyl groups and ethers which are not activated by any other functional group are not reducible by the electrochemical method. However, some benzylic, allylic and propargylic alcohols can be reduced on mercury to the corresponding saturated or unsaturated hydrocarbons at very negative potentials using DMF as solvent (Table 8)[25]. The reaction mechanism may be similar to that of the

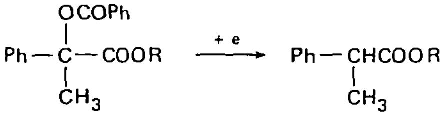
TABLE 8. Electroreduction of some activated alcohols[25]

Alcohol	Potential (–V)[a]	Product	Yield (%)
Ph_3COH	2.9	Ph_3CH	95
$PhCH{=}CHCH_2OH$	2.7	$PhCH{=}CHCH_3$ $PhCH_2CH_2CH_2OH$	70 30
$Ph_2\underset{\mathrm{OH}}{\underset{\mid}{C}}C{\equiv}CH$	2.7	$Ph_2CHCH_2CH_3$	95
$Ph_2\underset{\mathrm{OH}}{\underset{\mid}{C}}CH{=}CH_2$	2.8	$Ph_2CHCH_2CH_3$	90
$Ph{-}\underset{\mathrm{OH}}{\underset{\mid}{C}}H{-}Ph$	2.9	$PhCH_2Ph$	80
	2.6		50
	2.3		95

[a] Vs. SCE.

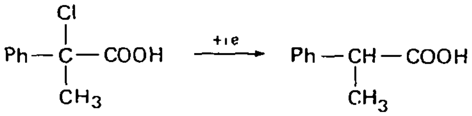
electroreduction of alkyl halides. $PhCH_2OH$, $PhCH(OH)C{\equiv}CH$, $Me_2C(OH)C{\equiv}CH$ and $PhCH(OH)CH{=}CHCH_3$ cannot be reduced.

Some esters such as benzoates, phosphates and methanesulphonates are reducible by the electrochemical method. The benzoate of atrolactic acid or its methyl ester, for instance, is reduced on mercury in ethanol, though this reduction has been reported to be nonstereospecific (equation 19)[26]. The reduction of the



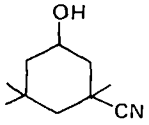
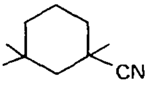
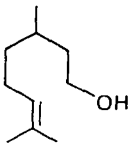
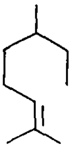
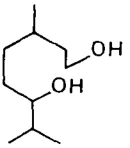
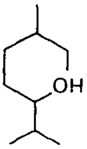
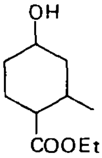
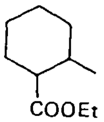
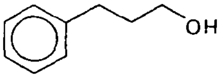
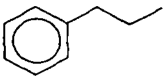
$$Ph{-}\overset{\overset{\displaystyle OCOPh}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}{-}COOR \xrightarrow{+e} Ph{-}\underset{\underset{\displaystyle CH_3}{|}}{C}HCOOR \qquad (19)$$

similar halide, however, has been known to proceed with 77–92% inversion of configuration (equation 20)[27]. This result may suggest that the mechanism of the



$$Ph{-}\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}{-}COOH \xrightarrow{+ie} Ph{-}\underset{\underset{\displaystyle CH_3}{|}}{C}H{-}COOH \qquad (20)$$

TABLE 9. Electrochemical reduction of methanesulphonates[28]

Alcohol	Product	Yield (%)
$C_8H_{17}CH{=}CH(CH_2)_8OH$	$C_8H_{17}CH{=}CHC_8H_{17}$	70
		84
		84
		72
		57
		50

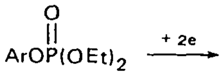
electrochemical cleavage of a certain carbon–oxygen bond is different from that of the corresponding carbon–halogen bond.

No carbon–oxygen bond cleavage has been observed in the cathodic reduction of esters of aromatic sulphonic acids, in which the products are the corresponding alcohols and sulphinic acids[1]. On the other hand, the electroreduction of esters of methanesulphonic acid on a lead cathode in DMF leads to carbon–oxygen bond fission yielding the corresponding hydrocarbons (equation 21) (Table 9)[28]. The

$$\mathrm{ROSO_2Me} \xrightarrow{+\,2e} \mathrm{RH} \qquad (21)$$

results shown in the Table 9 clearly suggest that the selectivity of this electrochemical method is superior to the reduction with lithium aluminium hydride.

The electroreductive elimination of hydroxyl groups from phenolic compounds is achievable by converting the hydroxyl groups to phosphates (equation 22) (Table 10)[29]. The reaction mechanism is probably complicated and may involve both anionic and radical intermediates.



$$\mathrm{ArO}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{(OEt)_2} \xrightarrow{+\,2e} \mathrm{ArH} \qquad (22)$$

Ethers are generally stable under the conditions of electrochemical reduction unless they are activated by other functional groups. Alkoxy groups existing on the α-position of aldehydes or ketones may be cleaved under acidic conditions. The cleavage of the carbon–oxygen bond of some benzylic or allylic ethers also takes place in both aprotic and protic solvents, the yield being higher in the latter solvent

TABLE 10. Electrochemical reduction of aryldiethyl phosphates on lead cathodes in DMF[29]

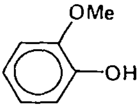
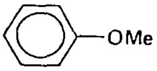
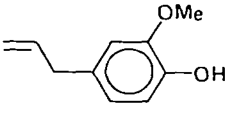
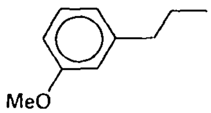
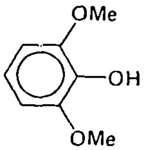
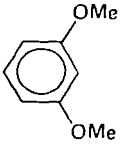
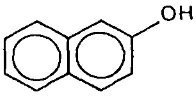
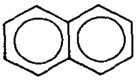
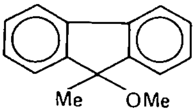
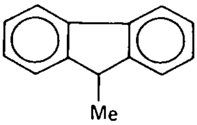
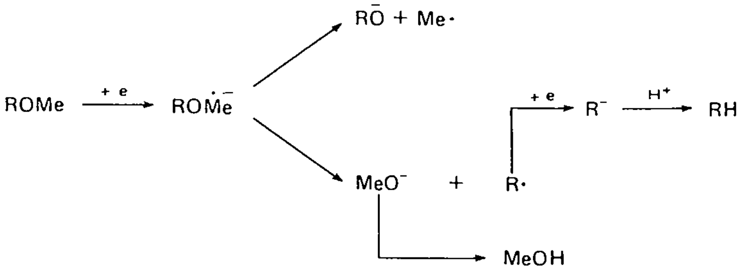
Parent phenol	Product	Yield (%)
		61
		90
		54
		59

TABLE 11. Electroreductive cleavage of ethers in DMF[30]

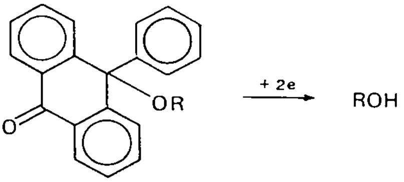
Ether	Product	Yield (%)	Medium	Potential (V)[a]
$(Ph_2CH{-})_2O$	Ph_2CHOH Ph_2CH_2	50 50	Aprotic	−2.4
Ph_2CHOMe	Ph_2CH_2	90	Protic[b]	−2.4
Ph_3COMe	Ph_3CH	100	Protic[b]	−2.3
$PhCH{=}CHCH_2OMe$	$PhCH{=}CHCH_3$ $PhCH_2CH_2CH_3$	65 18	Aprotic	−1.8
		90	Protic[b]	−1.9

[a] Vs. Ag/Ag$^+$.
[b] Phenol is added in DMF.

(Table 11)[30]. In case of unsymmetrical ethers such as ROMe, the reaction pathway yielding RH and MeOH as the products is the main route (equation 23).

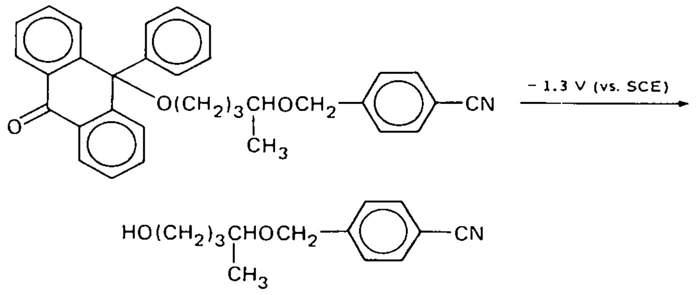

ROMe
+ e
ROMe
RO + Me·
MeO
+
R·
+ e
R
H+
RH
MeOH

(23)



(24)

R = *n*-Bu (85%); *n*-C_8H_{17} (84%); *n*-$C_{10}H_{21}$ (81%); *c*-C_6H_{11} (84%); cholesteryl (66%)


O
O(CH2)3CHOCH2
CH3
CN
− 1.3 V (vs. SCE)
HO(CH2)3CHOCH2
CH3
CN

(25)

The electrochemical cleavage of ethers is one of the useful methods of deblocking of protected alcohols. The cleavage of tritylon ethers by the usual chemical methods, for example, generally requires rather drastic conditions, whereas the ethers can be cleaved in high yield by the electrochemical reduction on mercury in neutral medium at room temperature (equation 24)[31]. Selective deblocking is achievable by this electrochemical method as shown in equation (25).

III. ANODIC OXIDATION

The initiation step of the anodic oxidation of ethers, hydroxyl groups and their sulphur analogues is generally the removal of an electron from the unshared electron pair on the oxygen or sulphur atom, so that the anodic oxidation of compounds having no unshared electron pair such as onium salts is difficult.

A. Thiols and Sulphides

Thiols are easily oxidized to disulphides by electrooxidation. The oxidation peak potential (E_p) of thiophenol on a platinum electrode in aqueous methanolic solution (50% v/v) exhibits its dependence on pH. The plot of E_p against pH gives a slope of 60 mV/pH where $pH < 8.2$. In alkaline medium, the oxidation peak potential is about 0.3 V vs. SCE. In a DMF solution, two oxidation peaks are observed on a platinum anode. The peak existing at about 0 V vs. SCE corresponds to the oxidation of PhS^- to PhSSPh, and the peak observed at about 1.1 V vs. SCE is attributable to the reaction shown in equation (26)[17]. The oxidation of thiols on a mercury electrode involves the formation of $(RS)_2Hg$ (equation 27).

$$2\,PhSH \longrightarrow PhSSPh + 2\,H^+ + 2\,e \qquad (26)$$

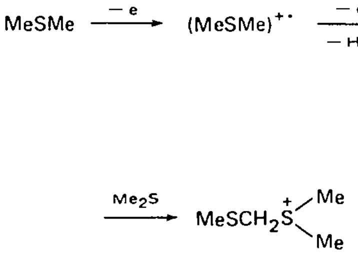
$$2\,RSH + Hg^0 \longrightarrow (RS)_2Hg + 2\,H^+ + 2\,e \qquad (27)$$

Further electrooxidation of disulphides may be achieved on a platinum electrode in acetonitrile using sodium perchlorate as a supporting electrolyte[32]. Diphenyl disulphide shows two oxidation peaks at about 1.2 V vs. Ag/Ag^+ and about 1.5 V vs. Ag/Ag^+. The first peak corresponds to the removal of one electron from a sulphur atom to yield a cation radical. The second peak may be attributed to the oxidation of an unknown intermediate probably formed through the reaction of the cation radical with solvent. The final product in this oxidation is sodium benzenesulphonate (equation 28) The supporting electrolyte plays an important

$$PhSSPh \xrightarrow{-e} (PHSSPh)^{+\cdot} \xrightarrow{NaClO_4} PhSO_3Na \qquad (28)$$

role in the determination of the reaction pathway, since sodium benzenesulphonate is obtained only in the case where sodium perchlorate is used as the supporting electrolyte, whereas the use of tetrabutylammonium tetrafluoroborate results in the formation of a complex mixture of products.

The oxidation of organic sulphides to sulphoxides or sulphones can easily be achieved in high yields by the electrochemical oxidation of the sulphides in aqueous solutions. Single sweep voltammetry of diphenyl sulphide with 0.18 M perchloric or sulphuric acid as supporting electrolyte shows a sharp oxidation peak at 1.30 V vs. SCE[33,34]. The controlled potential oxidation in perchloric acid at 1.10 V yields the corresponding sulphoxide in almost quantitative current yield without any contamination with diphenyl sulphone. Three reaction mechanisms have been proposed for this oxidation. The anodic oxidation of aliphatic sulphides on platinum anode under nonaqueous conditions has been studied to get insight into the mechanism[35]. For example, dimethyl sulphide is completely oxidized to dimethyl sulphone in acetonitrile containing only 1% of water. In anhydrous acetonitrile containing sodium perchlorate as a supporting electrolyte, the ultimate products are sodium methanesulphonate and carbon monoxide. The first step of the reaction involves one electron transfer from the sulphide to form a cation radical, which rapidly loses a proton and a second electron to produce a sulphonium derivative which upon reaction with the starting sulphide forms the dimethylmethylthiomethyl sulphonium ion as the immediate major product (equation 29). On the other hand,



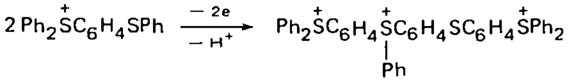
(29)

the reaction of sodium perchlorate with electrochemically generated protons forms perchloric acid which gives water and the anhydride of perchloric acid by equilibration (equation 30).

$$2HClO_4 \rightleftharpoons H_2O + Cl_2O_7 \qquad (30)$$

The anhydride and water contribute to the transformation of the sulphonium ion to sodium methanesulphonate and carbon monoxide. The formation of sulphonium ion in the oxidation of sulphides has been clearly demonstrated in the anodic oxidation of diphenyl sulphide in acetonitrile on a platinum electrode using sodium perchlorate as a supporting electrolyte[36]. Diphenyl sulphide shows three oxidation peaks at about 1.1 V (number of electrons, $n = 0.97$), 1.3 V ($n = 1.50$) and 1.6 V vs. Ag/Ag$^+$ ($n = 1.98$). On the basis of the analysis of products, the equations (31a and b) have been proposed for the first and second oxidation steps.

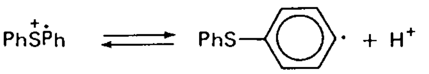
$$2\,PhSPh \xrightarrow[-H^+]{-2e} Ph_2\overset{+}{S}C_6H_4SPh \qquad (31a)$$



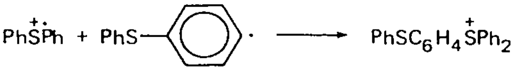
$$2\,Ph_2\overset{+}{S}C_6H_4SPh \xrightarrow[-H^+]{-2e} Ph_2\overset{+}{S}C_6H_4\underset{\displaystyle Ph}{\overset{+}{S}}C_6H_4SC_6H_4\overset{+}{S}Ph_2 \qquad (31b)$$

Three different mechanisms (equations 32–34) have been suggested for the formation of the first sulphonium ion.

$$2\,PhSPh \longrightarrow 2\,Ph\overset{+\bullet}{S}Ph \qquad (32a)$$

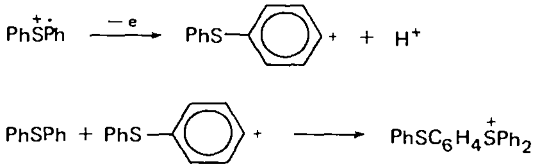


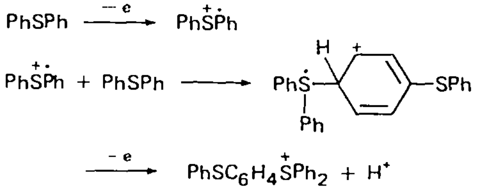
(32b)



(32c)

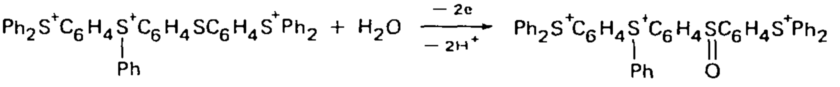
$$\mathrm{PhSPh} \xrightarrow{-e} \mathrm{Ph\overset{+\cdot}{S}Ph} \tag{33a}$$


(33b)


(34a)

(34b)

Formation of a sulphoxide has been suggested for the third oxidation step (equation 35), though it is not conclusive.


(35)

$$\mathrm{Ph_2S^+C_6H_4\underset{Ph}{S^+}C_6H_4SC_6H_4S^+Ph_2 + H_2O \xrightarrow[-2H^+]{-2e} Ph_2S^+C_6H_4\underset{Ph}{S^+}C_6H_4\underset{O}{\overset{}{S}}C_6H_4S^+Ph_2} \tag{35}$$

A different reaction pathway has been proposed for the formation of the trisanisylsulphonium cation by the anodic oxidation of dianisyl sulphide in the presence of anisole[37]. The anodic polarogram of dianisyl sulphide obtained at a rotating platinum electrode in acetonitrile with sodium perchlorate as a supporting electrolyte shows two oxidation waves with half-wave potentials of 1.075 V and 1.4 V vs. SCE. The first wave corresponds to the reversible or nearly reversible oxidation of dianisyl sulphide to dianisyl sulphide radical cation (equation 36a), which is remarkably more stable than diphenyl sulphide radical cation. The addition of anisole, however, does not show any influence on the polarogram. Therefore it has been concluded that the decay process which is responsible for the disappearance of the radical cation is not the addition of the radical cation to anisole but is its disproportionation to dianisyl sulphide and the dianisyl sulphide dication (equation 36b), with subsequent irreversible reaction of the dication with anisole to the final product (equation 36c).

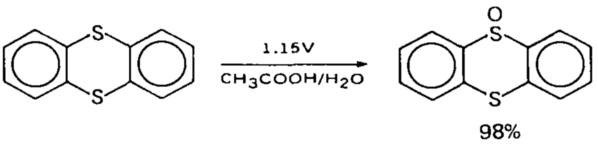
$$\mathrm{(MeOPh)_2S} \xrightarrow{-e} \mathrm{(MeOPh)_2S^{+\cdot}} \tag{36a}$$

$$\mathrm{2\,(MeOPh)_2S^{+\cdot}} \longrightarrow \mathrm{(MeOPh)_2S + (MeOPh)_2S^{2+}} \tag{36b}$$

$$\mathrm{(MeOPh)_2S^{2+} + MeOPh} \longrightarrow \mathrm{(MeOPh)_3S^+ + H^+} \tag{36c}$$

Cyclic voltammetry of dibenzothiophen in 0.18 M H_2SO_4 shows an oxidation peak at 1.44 V vs. SCE indicating that dibenzothiophen is more difficultly oxidized than diphenyl sulphide, since the oxidation peak potential for the latter sulphide under the same conditions is 1.36 V vs. SCE[38]. The greater difficulty in oxidation of dibenzothiophen than of diphenyl sulphide is attributable to the greater delocalization of the electrons on sulphur in dibenzothiophen.

Anodic oxidation of thianthrene is interesting because it has two sulphur atoms and is not planar. The oxidation in 80% acetic acid–water mixture containing perchloric acid at 1.15 V vs. Ag/Ag$^+$ gives the monoxide in almost quantitative yield (equation 37). A mixture of products consisting of 44% *cis*- and 28% *trans*-dioxide, 13% sulphone, 10% trioxide and 5% tetraoxide is obtained by the oxidation at 1.6 V (equation 38)[39]. Both ECC (equation 39)[40] and ECE (equation 40)[41] mechanisms have been proposed for the monoxidation of thianthrene (Th).



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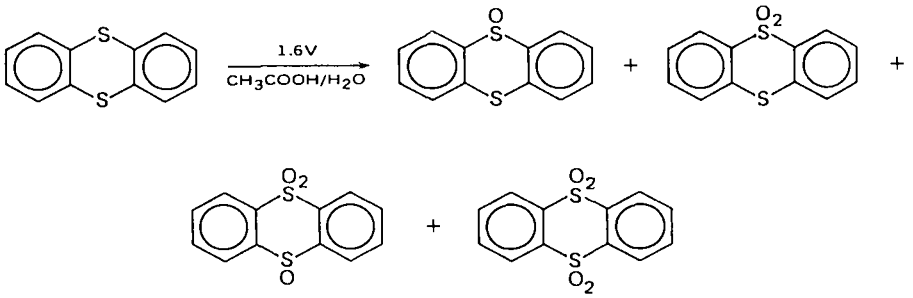


(38)

$$\mathrm{Th} \xrightarrow{-e} \mathrm{Th}^{+\cdot} \tag{39a}$$

$$\mathrm{Th}^{+\cdot} + \mathrm{Th}^{+\cdot} \rightleftharpoons \mathrm{Th}^{2+} + \mathrm{Th} \tag{39b}$$

$$\mathrm{Th}^{2+} + \mathrm{H_2O} \longrightarrow \mathrm{ThO} + 2\,\mathrm{H}^{+} \tag{39c}$$

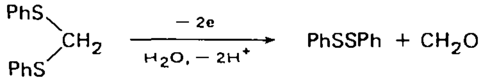
$$\mathrm{Th} \xrightarrow{-e} \mathrm{Th}^{+\cdot} \tag{40a}$$

$$\mathrm{Th}^{+\cdot} + \mathrm{H_2O} \rightleftharpoons (\mathrm{ThOH})^{\cdot} + \mathrm{H}^{+} \tag{40b}$$

$$(\mathrm{ThOH})^{\cdot} + \mathrm{Th}^{+\cdot} \rightleftharpoons (\mathrm{ThOH})^{+} + \mathrm{Th} \tag{40c}$$

$$(\mathrm{ThOH})^{+} \rightleftharpoons \mathrm{ThO} + \mathrm{H}^{+} \tag{40d}$$

Anodic bond cleavage of a carbon–sulphur bond has been observed in the oxidation of bis(phenylthio)methane in acetonitrile at a platinum electrode using sodium or tetraethylammonium perchlorate as the supporting electrolyte. This compound shows two oxidation peak potentials at 1.46 V and 1.57 V vs. SCE at slow sweep rates, and gives diphenyl disulphide and formaldehyde through the controlled potential oxidation at 1.38 V (equation 41)[42].

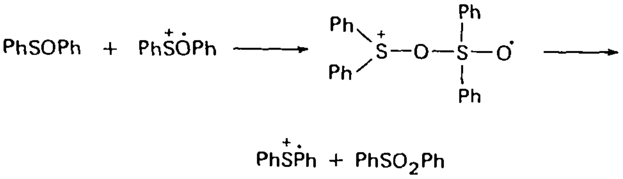


$$(\mathrm{PhS})_2\mathrm{CH_2} \xrightarrow[\mathrm{H_2O},\,-2\mathrm{H}^{+}]{-2e} \mathrm{PhSSPh} + \mathrm{CH_2O} \tag{41}$$

The further oxidation of diphenyl sulphoxide, the primary prouduct of the oxidation of diphenyl sulphide in acetonitrile, has been studied to determine the reaction mechanism[43]. The fact that diphenyl sulphoxide shows an anodic peak at 1.83 V vs. Ag/Ag$^+$ where the number of electrons involved is one for one molecule of the sulphoxide, and that the yield of the diphenyl sulphone in this oxidation is always about 50% suggests that the main oxygen source required for the oxidation must be the diphenyl sulphoxide itself according to the scheme shown in equation (42).

Each sulphoxide cation radical, the primary electron transfer product, reacts

$$PhSOPh \xrightarrow{-e} Ph\overset{+\bullet}{S}OPh \qquad (42a)$$



$$PhSOPh + Ph\overset{+\bullet}{S}OPh \longrightarrow Ph_2\overset{+}{S}{-}O{-}S(Ph)_2{-}\dot{O} \longrightarrow Ph\overset{+\bullet}{S}Ph + PhSO_2Ph \qquad (42b)$$

with one molecule of sulphoxide giving one molecule of sulphone and a new sulphide cation radical. This reaction mechanism coincides with the result that only half of the sulphoxide is oxidized to sulphone. In the benzene–acetonitrile mixed medium, the cation racial $Ph_2S^{+\bullet}$ is trapped by benzene giving triphenylsulphonium ions according to equation (43). In pure acetonitrile (equation 44), the

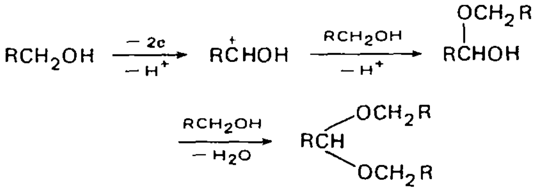
$$Ph_2S^{+\bullet} + C_6H_6 \xrightarrow{-e} Ph_3S^+ + H^+ \qquad (43)$$

$$Ph_2S^{+\bullet} + CH_3CN \longrightarrow Ph_2\dot{S}{-}N{=}\overset{+}{C}CH_3 \qquad (44)$$

cation radical reacts with acetonitrile to give another cation radical intermediate which in turn undergoes further anodic oxidation to make the overall reaction mechanism consistent with the coulometric results.

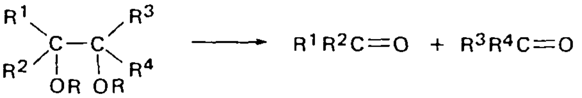
B. Hydroxyl Groups and Ethers

The anodic oxidation of hydroxyl groups and ethers is less facile than that of thiols and sulphides. The anodic potentials required for the oxidation of some saturated aliphatic alcohols are 2.5–2.7 V vs. Ag/Ag^+ in acetonitrile containing tetrabutylammonium tetrafluoroborate as a supporting electrolyte[44]. The electrochemical oxidation of methanol and ethanol gives the corresponding acetals in good yield in the presence of sodium perchlorate or tetrabutylammonium tetrafluoroborate as supporting electrolyes (equation 45), and aldehydes with sodium alkoxides as supporting electrolytes. The formation of acetals has been explained by



$$RCH_2OH \xrightarrow[-H^+]{-2e} R\overset{+}{C}HOH \xrightarrow[-H^+]{RCH_2OH} RCH(OCH_2R)OH \xrightarrow[-H_2O]{RCH_2OH} RCH(OCH_2R)_2 \qquad (45)$$

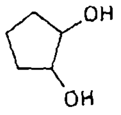
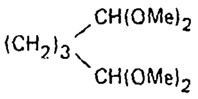
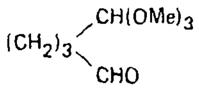
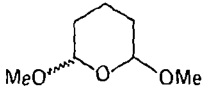
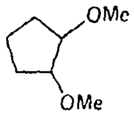
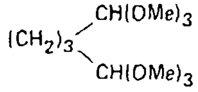
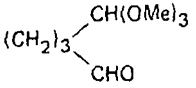
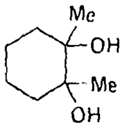
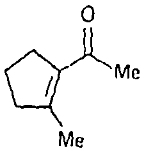
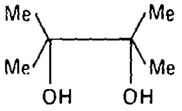
the initial formation of a carbonium ion[45]. The electrochemical method of the oxidation of alcohols is one of the most useful methods of the oxidative cleavage of glycols and related compounds to the corresponding carbonyl compounds (equation 46) (some examples are shown in Table 12)[46]. The advantage of the



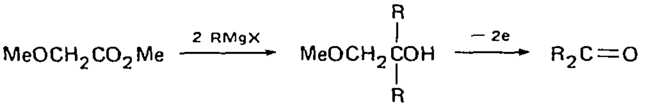
$$R^1R^2C(OR){-}C(OR)R^3R^4 \longrightarrow R^1R^2C{=}O + R^3R^4C{=}O \qquad (46)$$

anodic oxidation over the conventional chemical methods using oxidizing agents is that the former is a remarkably clean reaction which does not show any of the stereochemical limitations usually observed in the chemical methods and furthermore, glycol ethers are also oxidizable by the electrochemical method.

TABLE 12. Anodic oxidation of 1,2-glycols and related compounds in methanol

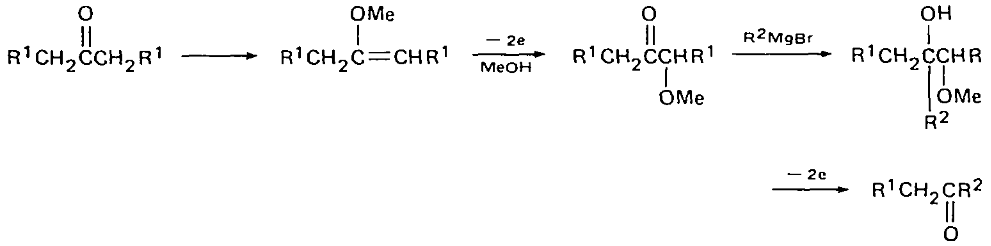
Glycol	Product and distribution (%)				Total yield (%)
	 $(\mathrm{CH_2})_3\begin{matrix}\mathrm{CH(OMe)_2}\\ \mathrm{CH(OMe)_2}\end{matrix}$	(56)	 $(\mathrm{CH_2})_3\begin{matrix}\mathrm{CH(OMe)_3}\\ \mathrm{CHO}\end{matrix}$	(14)	96
		(26)			
	 $(\mathrm{CH_2})_3\begin{matrix}\mathrm{CH(OMe)_3}\\ \mathrm{CH(OMe)_3}\end{matrix}$	(65)	 $(\mathrm{CH_2})_3\begin{matrix}\mathrm{CH(OMe)_3}\\ \mathrm{CHO}\end{matrix}$	(2)	67
	$\mathrm{MeCO(CH_2)_4COMe}$	(36)	$\mathrm{MeCO(CH_2)_4C(OMe)_2Me}$	(9)	61
		(16)			
	$\mathrm{Me_2C(OMe)_2}$	(11)	$\mathrm{Me_2C{=}O}$	(78)	89

This anodic cleavage is very useful for the general syntheses of carbonyl compounds such as symmetrical and unsymmetrical ketones, some of which are hardly accessible by the usual chemical methods[4 7]. Symmetrical ketones can be prepared according to equation (47). Since both the alkyl groups in the symmetrical ketones

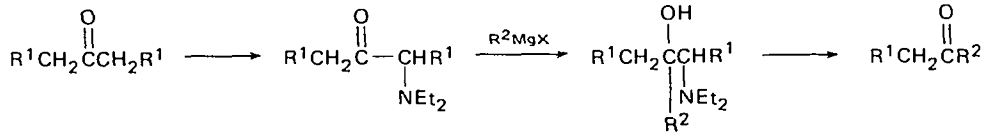


$$MeOCH_2CO_2Me \xrightarrow{2\ RMgX} MeOCH_2C(R)_2OH \xrightarrow{-2e} R_2C{=}O \qquad (47)$$

are derived from the Grignard reagent, this method is applicable to the synthesis of a variety of ketones from the single starting compound. The yield of anodic oxidation is about 80%. The transformation of symmetrical ketones to unsymmetrical ketones has also been achieved as shown in equations (48) and (49).

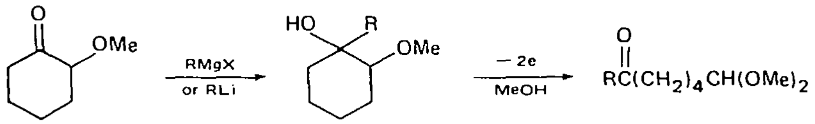


$$R^1CH_2COCH_2R^1 \longrightarrow R^1CH_2C(OMe){=}CHR^1 \xrightarrow[MeOH]{-2e} R^1CH_2COCH(OMe)R^1 \xrightarrow{R^2MgBr} R^1CH_2C(OH)(R^2)CH(OMe)R \xrightarrow{-2e} R^1CH_2COR^2 \qquad (48)$$



$$R^1CH_2COCH_2R^1 \longrightarrow R^1CH_2CO{-}CH(NEt_2)R^1 \xrightarrow{R^2MgX} R^1CH_2C(OH)(R^2)CH(NEt_2)R^1 \longrightarrow R^1CH_2COR^2 \qquad (49)$$

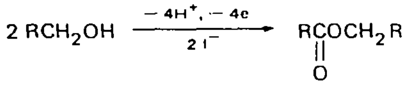
The electrochemical cleavage of glycols is also useful in the synthesis of some carbonyl compounds which are difficult to prepare by conventional chemical methods (equation 50).



(50)

R = Me, Bu, CH_2CN, CH_2CO_2Et

Although an exceedingly high electrode potential is required for the direct oxidation of alcohols, they are easily oxidized by using suitable catalytic homogeneous electron carriers such as iodine[4 8]. Anodic oxidation of alcohols in the presence of a small amount of KI gives the corresponding esters from primary alcohols (equation 51) and ketones from secondary alcohols (equation 52) in

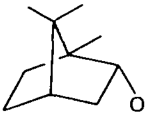
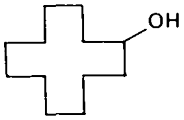
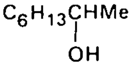
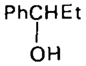
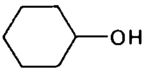


$$2\ RCH_2OH \xrightarrow[2\ I^-]{-4H^+,\ -4e} RCOCH_2R \qquad (51)$$

$$R^1R^2CHOH \xrightarrow[I^-]{-2H^+,\ -2e} R^1R^2C{=}O \qquad (52)$$

excellent yields (Table 13). The role of iodine as a catalytic homogeneous electron carrier is shown in the Figure 1.

TABLE 13. Anodic oxidation of alcohols in the presence of iodide[48]

Alcohol	KI/alcohol	Yield (%)[a]
	0.25	93
	0.25	91
 $C_6H_{13}CH(OH)Me$	0.1	92
 $PhCH(OH)Et$	0.25	100
	0.25	74
n-$C_6H_{13}OH$	0.1	83
$Ph(CH_2)_3OH$	0.25	84

[a]Based on the consumed alcohol.

Anodic oxidation of saturated aliphatic ethers in methanol containing sodium methoxide, tetraethylammonium *p*-toluenesulphonate or ammonium nitrate as a supporting electrolyte yields the corresponding α-methoxylated ethers, though the yields are low (Table 14)[49].

Two mechanisms are conceivable for the mechanism of the initiation step. One is the direct electron transfer from the unshared electron pair on oxygen to the anode (equation 53), while the other is the radical abstraction of a hydrogen from the α-position of the ether by a radical species generated by the anodic oxidation of the solvent or supporting electrolyte (equation 54).

$$RCH_2OR \xrightarrow{-2e} R\overset{+}{C}HOR + H^+ \tag{53}$$

$$RCH_2OR \xrightarrow{S^{\cdot}} R\dot{C}HOR \xrightarrow{-e} R\overset{+}{C}HOR \tag{54}$$

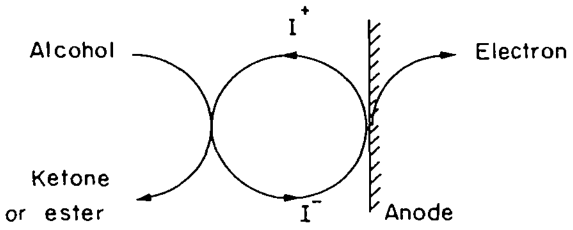
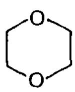
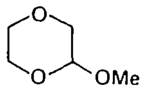
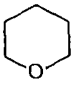
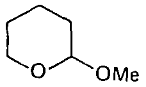
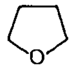
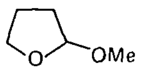
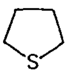
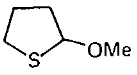
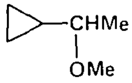
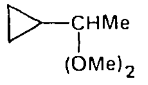
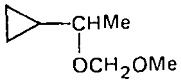
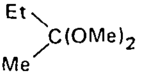
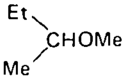


FIGURE 1. Iodine as a catalytic homogeneous electron carrier in the anodic oxidation of alcohols.

TABLE 14. Anodic methoxylation of ethers using MeONa as a supporting electrolyte[49]

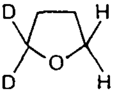
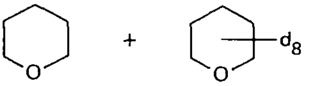
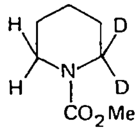
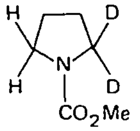
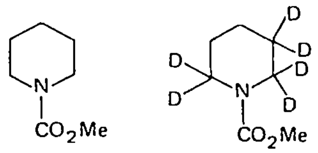
Ether	Product	Yield (%)
		28
		26
		16.3
		8.5
		24.3
		7.8
		21

In general, no oxidation peak nor current increment attributable to the direct oxidation of ethers has been observed. To get an insight into the mechanism, both intra- and inter-molecular isotope effects have been determined and compared with those obtained in the Kharasch–Sosnovsky reaction[50] and in the anodic oxidation of carbamates[51] (Table 15). If the mechanism of the initiation step is the hydrogen abstraction by a radical species, both intra- and inter-molecular isotope effects must be almost identical as shown in the case of Kharasch–Sosnovsky reaction, whereas in the direct electron transfer mechanism, the intermolecular isotope effect must be smaller than the intramolecular one.

Although it is not conclusive, the isotope effects shown in Table 15 may imply the advantage of the direct electron transfer mechanism, which has also been suggested in the anodic oxidation of 2-methoxyethanol[52].

Similarly to alcohols, some ethers are oxidizable by the anodic method using a

TABLE 15. Isotope effects (k_H/k_D)

Compound	Anodic reaction	Kharasch–Sosnovsky reaction
 [a]	2.1 (NaOMe) 2.0 (Et_4NOTs)	3.2
 [b]	1.5–1.6 (NaOMe) 1.6–1.7 (Et_4NOTs)	3.1–3.2
 [a]	1.81 ± 0.05 (Et_4NOTs)	
 [a]	1.84 ± 0.05 (Et_4NOTs)	
 [b]	1.59 ± 0.05 (Et_4NOTs)	
$Me_2NCOMe + (CD_3)_2COCD_3$ [b]	1.53 ± 0.05 (Et_4NOTs)	

[a] Intramolecular isotope effect.
[b] Intermolecular isotope effect.

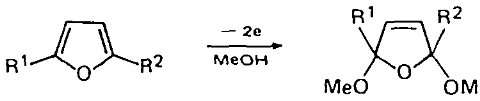
homogeneous electron carrier. The anodic oxidation of *p*-methoxybenzyl ethers in the presence of tris(*p*-bromophenyl)amine as the homogeneous electron carrier results in the clean cleavage of the C–O bond of ethers yielding alcohols and aldehydes in high yields (equation 55) (Table 16)[53].

In general, enol ethers are easily oxidized, since the cationic intermediates are stabilized by the alkoxyl groups to a certain extent. Anodic oxidation of furan derivatives (equation 56) or anodic coupling of enol ethers (equation 57) are the typical examples which are useful in organic synthesis[4].

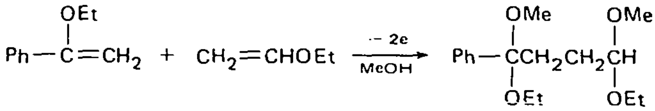
TABLE 16. Oxidative cleavage of ethers ($ROCH_2Ar$) using a homogeneous electron carrier[53]

R	Yield of ROH (%)
1-Octyl	95
2-Octyl	87
E-4-Hepten-1-yl	83
1-Methylcyclohexyl	94

$$\mathrm{ROCH_2Ar \longrightarrow ROH + ArCHO} \tag{55}$$

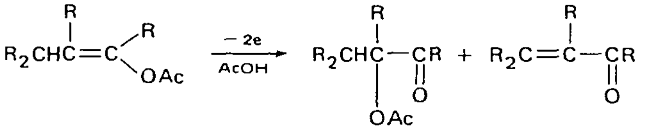


(56)

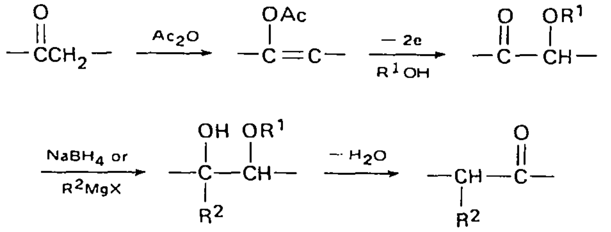


$$\mathrm{Ph{-}C(OEt){=}CH_2 + CH_2{=}CHOEt \xrightarrow[MeOH]{-2e} Ph{-}C(OMe)(OEt)CH_2CH_2CH(OMe)(OEt)} \tag{57}$$

Although the anodic oxidation of enols is not known, the oxidation of enol acetates is a useful reaction in organic synthesis[54]. The electrochemical oxidation of enol acetates in acetic acid yields α-acetyl and α,β-unsaturated carbonyl compounds (equation 58). The ratio of the two products can be modified by the control of reaction conditions[55]. One of the interesting applications of this reaction is 1,2-carbonyl transposition in aliphatic ketones (equation 59)[56].



$$\mathrm{R_2CHC(R){=}C(R)OAc \xrightarrow[AcOH]{-2e} R_2CHC(R)(OAc){-}C(R){=}O + R_2C{=}C(R){-}C(R){=}O} \tag{58}$$



$$\mathrm{{-}C({=}O)CH_2{-} \xrightarrow{Ac_2O} {-}C(OAc){=}C{-} \xrightarrow[R^1OH]{-2e} {-}C({=}O){-}CH(OR^1){-} \xrightarrow[R^2MgX]{NaBH_4\ or} {-}C(OH)(R^2){-}CH(OR^1){-} \xrightarrow{-H_2O} {-}CH(R^2){-}C({=}O){-}} \tag{59}$$

R^1 = Me, COMe; R^2 = H, alkyl or aryl

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 9

Electronic structures and thermochemistry of phenols

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I. ELECTRONIC STRUCTURES

A. Introduction

According to quantum mechanics the solution of the Schrödinger equation

$$H\psi = E\psi,$$

combined with the Pauli exclusion principle, provides all the information for the description of a chemical system.

The Hamiltonian operator, H, in atomic units, for an electronic system in a field of fixed nuclei (Born–Oppenheimer approximation) is given by

$$H = \sum_i \nabla_i^2 - \sum_\nu \sum_i \frac{Z_\nu}{r_{\nu i}} + \sum_{i<j} \frac{1}{r_{ij}},$$

where successive terms represent operators for the kinetic energy of the electrons i, the nuclear–electronic attraction (Z_ν is the atomic number of nucleus ν, $r_{\nu i}$ is the distance from this nucleus to the ith electron) and the repulsion between electrons (r_{ij} is the distance between electrons i and j).

Owing to mathematical difficulties, many simplifications have been proposed for carrying out calculations.

Hartree[1] and Fock[2] have proposed a treatment in which an electron is considered to move in the potential field of the nuclei and in the average potential of all of the other electrons in the molecule. This defines the *self-consistent-field (SCF) method*. The operator is a sum of one-electron terms and the solution is comparatively simple. Other 'semiempirical' methods are classified according to the level of sophistication chosen.

In the *π-electron approximation* the π-electrons of a molecule are treated apart from the rest. It is supposed that the effects of the σ-electrons can be lumped into the Hamiltonian for the π-electrons.

According to the *PPP (Pariser–Parr–Pople) method*[3,4], for a molecule having n π-electrons, the reduced Hamiltonian operator takes the form

$$H_\pi = \sum_{i=1}^{n} H_{\text{core}}(i) + \frac{1}{2} \sum_{i,j=1}^{n} \frac{1}{r_{ij}}.$$

The σ-electrons are taken into account through appropriate elucidation of the terms H_{core} (i) The evaluation of electronic repulsion integrals is greatly simplified by the introduction of a uniformly charged sphere representation of atomic orbitals. The wave function for the n-electron system is written as a normalized Slater determinant.

The *Hückel method*[5] makes the assumption that the potential of an electron is independent of the position of the others. H is the sum of operators H_{eff} (i) each containing the coordinates of only one electron.

$$H = \sum_i H_{\text{eff}}(i).$$

Furthermore the Hückel wave function is not even properly antisymmetrized. Despite these approximations, the Hückel Molecular Orbital (HMO) method has shown itself capable of explaining molecular properties with amazing consistency.

All-valence electron methods: The Extended Hückel Theory (EHT)[6] is an application of the Hückel treatment to all valence electrons. Pople[7] has described a simpler method for obtaining self-consistent molecular orbitals. This *CNDO/2* *method* involves the Complete Neglect of Differential Overlap. Pople has proposed also the *NDDO method* which involves the Neglect of Diatomic Differential Overlap only. Modifications of the CNDO/2 method, known as *INDO method* (Intermediate Neglect of Differential Overlap) have been proposed[8,9]. Del Bene and Jaffé[10] have described the *CNDO/S method* in order to compute spectroscopic transition energies and oscillator strengths.

Ab initio *method, STO-3G basis.* It is now possible to perform *ab initio* molecular orbital calculations with a modest-sized set of Gaussian orbitals. The basis set, STO-3G[11], consists of linear combinations of three Gaussian functions which are least-squares fitted to exponential Slater-type atomic orbitals.

B. Physical Characteristic Indexes

1. *Charge densities and bond orders*

A large number of calculations have been performed for phenols. The principal results of these calculations are given in Table 1 and Figure 1. It is of interest to note that Grabe[16] has discussed the necessity of varying parameters $W\mu\mu$ with charge of phenolic oxygen in the PPP method.

The charge densities of phenol show π-donation from the oxygen p-type lone pair into the ring, combined with σ-withdrawal. The increase in π-electron density is greater at the *ortho* position than at the *para* position. For the σ-electrons, the calculations predict a long-range inductive effect resulting in a considerable positive charge at the *para* position. This positive *para* σ-charge ($\Delta q = +0.018$) is about half the size of the π-electron density and opposite in sign ($\Delta q = -0.039$) and consequently has an important effect on the magnitude of the total charges.

Concerning the influence of substituents, we have made several studies[17,18] showing the inductive effect of alkyl groups fixed at various positions in the phenolic ring. A conclusion of these studies is the strong inductive effect of the methyl group. The π-electron release modifies the charges of the aromatic ring as shown in the Table 2.

TABLE 1. Charge densities on phenol by various methods

	HMO[12]	PPP[13]	CNDO/2[14]		STO-3G[15]
	π	π	σ	π	π
C_1	0.955	0.976	2.797	0.951	0.975
C_2	0.960	1.064	2.999	1.059	1.068
C_3	0.998	0.994	2.995	0.977	0.976
C_4	1.029	1.036	2.982	1.039	1.039
0	1.94	1.872	4.485	1.937	–

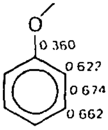

FIGURE 1. Bond orders calculated by the PPP method.

TABLE 2. Charges and reactivity indexes for methylphenols

		2-Methylphenol				3-Methylphenol				4-Methylphenol	
		3	4	5	6	2	4	5	6	2	3
Total charges CNDO		3.990	4.018	3.980	4.058	4.069	4.039	3.965	4.072	4.057	3.986
σ-Charges CNDO		2.994	2.985	2.904	2.995	2.979	2.972	3.005	2.985	1.996	2.993
π-Charges	CNDO	0.996	1.033	0.986	1.062	1.090	1.067	0.960	1.087	1.061	0.993
	PPP	0.999	1.022	0.998	1.042	1.045	1.024	0.997	1.044	1.041	0.998
	HMO	1.030	1.043	1.019	1.061	1.093	1.074	0.995	1.082	1.059	1.027
Charges in the HOMO	CNDO	0.001	0.206	0.101	0.041	0.043	0.277	0.014	0.185	0.092	0.058
	PPP	0.017	0.275	0.103	0.061	0.060	0.307	0.030	0.163	0.100	0.067
	HMO	0.000	0.207	0.101	0.056	0.079	0.293	0.012	0.212	0.103	0.064
Free valence indexes	CNDO	0.409	0.403	0.401	0.418	0.433	0.418	0.397	0.426	0.419	0.409
	PPP	0.404	0.402	0.393	0.417	0.423	0.409	0.397	0.419	0.416	0.404
	HMO	0.409	0.407	0.401	0.425	0.439	0.421	0.395	0.431	0.426	0.410
Electrophile surperdelocalisability[a] HMO		0.911	1.004	0.914	1.007	1.083	1.080	0.830	1.086	1.015	0.919

[a] Electrophile superdelocalisability is a reactivity index, introduced by Fukui and coworkers[18a], defined as

$$S = 2 \sum_{j=1}^{m} C_{jr}^2 / m_j$$

Yeargers[19] has used the 'variable electronegativity SCF' method to calculate the net π-electron charges for phenol, in the first excited singlet (S_1) and first excited triplet states (T_1). The calculations indicate that the hydroxyl oxygen becomes more positive upon excitation. The net π-charge densities on the oxygen are in the order $S_1 > T_1 > S_0$. This is consistent with the order of the p*K* values.

2. *Dipole moments*

The results[20-22] concerning dipole moments of phenols are reported in Table 3. They have been obtained in solution by Guggenheim and Smith's method and by Onsager's method from physical constants of the pure compounds. The differences between these two values show the importance of the association by hydrogen bonds in liquid phenols. All phenols substituted in the *meta* or *para* position are more strongly associated by hydrogen bonds than *ortho*-substituted ones. Consequently their 'Onsager' dipole moments are greater than those measured in solution.

The dipole moments calculated by the CNDO/2 method are always greater by 0.2–0.3 D than the measured ones in solution. This fact stems from a CNDO/2 artefact (cf. Reference 23); the electron-releasing effect of the alkyl or hydroxyl group is always exaggerated. The calculated values for phenol emphasize this fact; they are $\mu = 1.76$ by the CNDO/2 method[23], $\mu = 1.22$ by the STO-3G method, $\mu = 1.27$ by Del Re's method[24], while the experimental value is 1.47.

3. *Ionization potentials*

There is no good correlation between experimental ionization potentials and energies of the highest occupied molecular orbital[23].

4. *Conformation*

Phenol is predicted to be planar by the CNDO/2[25,26], NDDO[27] and STO-3G[15] methods. The theoretical barrier of O–H rotation around the C–O bond in phenol

TABLE 3. Observed and calculated dipole moments of some substituted phenols

Compound	Solution (*T*)	Onsager (*T*)	Calculated
Phenol	1.47 (20°C)	2.20 (40°C)	1.72
2-Methylphenol	1.41 (20°C)	1.64 (30°C)	1.63
3-Methylphenol	1.48 (20°C)	2.48 (20°C)	1.60
4-Methylphenol	1.46 (20°C)	2.36 (40°C)	1.76
2-Isopropylphenol	1.36 (25°C)	1.47 (25°C)	1.53
3-Isopropylphenol	1.53 (25°C)	2.39 (25°C)	1.63
4-Isopropylphenol	1.60 (25°C)	2.26 (70°C)	1.84
2,3-Dimethylphenol	1.23 (20°C)	1.53 (70°C)	1.45
2,4-Dimethylphenol	1.40 (20°C)	1.70 (20°C)	1.55
2,5-Dimethylphenol	1.45 (20°C)	1.66 (70°C)	1.81
2,6-Dimethylphenol	1.40 (20°C)	1.46 (40°C)	1.68
3,4-Dimethylphenol	1.56 (20°C)	2.33 (70°C)	1.60
3,5-Dimethylphenol	1.55 (20°C)	2.29 (60°C)	1.79
2,4-Diisopropylphenol	1.50 (25°C)	1.47 (30°C)	1.63
2,5-Diisopropylphenol	1.52 (25°C)	1.47 (30°C)	1.80
2,6-Diisopropylphenol	1.43 (25°C)	1.46 (30°C)	1.76
3,5-Diisopropylphenol	1.50 (25°C)	2.04 (60°C)	1.88

(5.16 kcal mol^{-1}, calculated by the STO-3G method) is considerably higher than the experimental values : 3.37 (microwave), 3.47 (infrared) kcal mol^{-1} . However, the changes in barrier with *para*substitution (OH, F, Me, CHO, CN and NO_2) are in close agreement with spectroscopic measurements[28].

C. Theoretical Study of Electrophilic Substitution on Phenols

1. Delocalized model

The classical reactivity indexes (electron density, free valence, polarizability) are based on the isolated molecule approximation. They do not take into account the nature of the reagent and this procedure fails to reproduce the changes in relative reactivity of various positions of attack. Klopman has developed a perturbation method which takes into account the influence of the attacking species on the reactivity[29]. Chalvet and coworkers[30]. have developed a theoretical treatment ('delocalized model') of the transition state. In this model, the reagent is represented by an orbital containing two or no electrons depending on the nucleophilic or electrophilic nature of the reagent. The energy of this orbital is given by

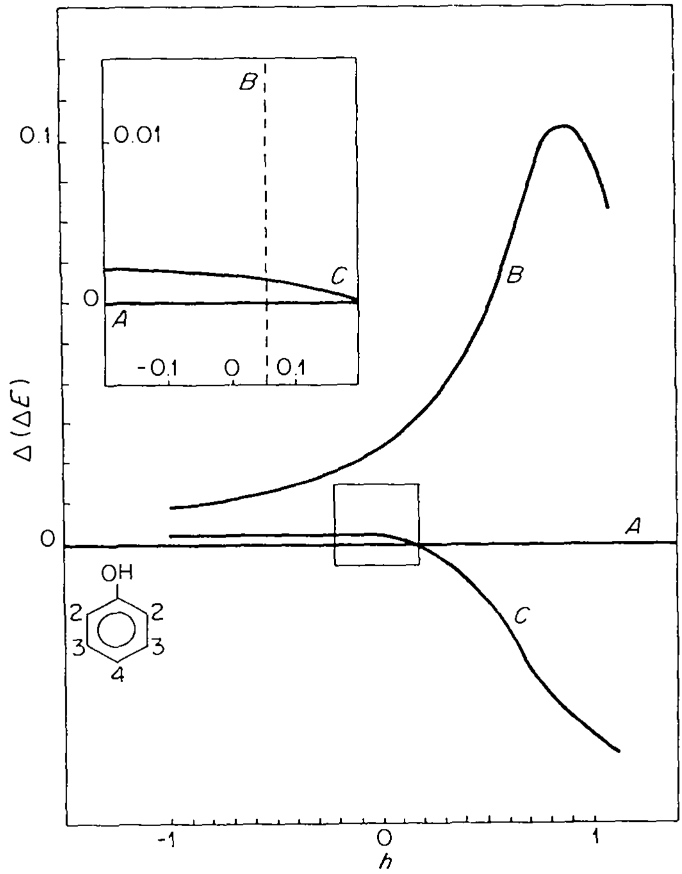

FIGURE 2. Reactivity of phenol by delocalized model of transition state.

$E = \alpha + h\beta$ (Hückel method). According to an extension of Koopman's theorem, the energy level of this orbital reflects the electron affinity or the ionization potential of the reagent. The energy difference $\Delta E = E_{\pi(\text{transition})} - [E_{\pi(\text{substrate})} + E_{\pi(\text{reagent})}]$ is determined. $E_{\pi(\text{transition})}$ is the π-energy of the transition state, $E_{\pi(\text{substrate})}$ and $E_{\pi(\text{reagent})}$ the π-energy of the reagents. The closer the electron affinity of the reagent (substrate) and the ionization potential of the substrate (reagent) is, the greater is the energy ΔE, this energy being a stabilization energy. This model has been used to study electrophilic substitution on aminophenols[31] and phenols[17,18].

For example, we have reported in Figure 2 the results obtained by using the delocalized model in the study of the alkylation, under kinetic conditions, of phenol by isopropyl alcohol. For reagents characterized by values between -1 and 0.2 the reactivity of the *ortho* position is greater than that of the *para* position. On the other hand for values included between 0.2 and 1 the reactivity of the *para* position becomes the greater. The experimental reactivity is in very good agreement with the calculated one for the value $h = 0.1$.

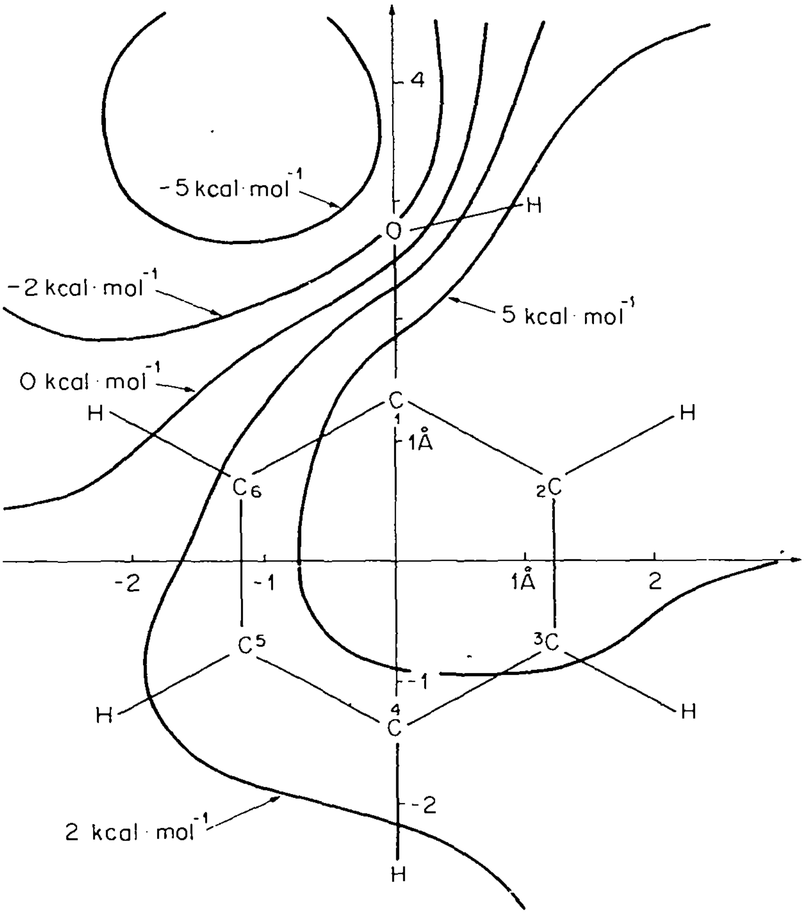

FIGURE 3. Phenol isopotential curves in a plane parallel to the ring at 2.2 Å.

Such theoretical calculations with the delocalized model allow us to understand the nature of the transition state. In particular, the relative importance of charge transfer and polarization in the transition state is reached by such calculations. Predictions by the Wheland model and other structure indexes are also discussed in References 17 and 18.

2. *Isopotential curves*

Bonaccorsi and collaborators[32] have proposed for the study of chemical reactivity another approach based on the calculation of the potential due to the nuclear and electronic charges. Since this potential is observable, in the quantum-mechanical meaning, this approach is particulary useful since it represents a better model of the system as seen from the approaching reactant. The interaction energy of a charge q with this potential is qV. A plot of the isopotentials obtained in this way gives the energy of interaction of an isolated proton and enables one to predict

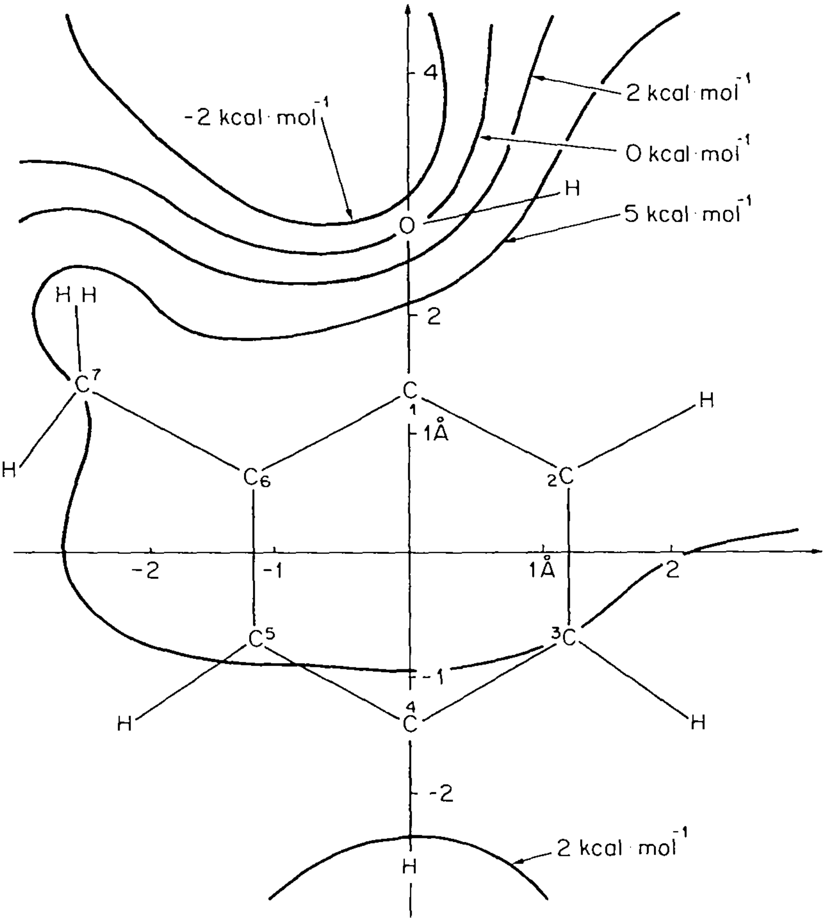

FIGURE 4. 2-Methylphenol isopotential curves in a plane parallel to the ring at 2.2 Å.

the point of attack of various electrophiles. Such maps[33] are given for phenol and 2-methylphenol in Figure 3 and 4. The curves are plotted in a plane parallel to the ring at a distance of 2.2 Å from it. The electrostatic potential is repulsive for an electrophilic reagent, except around the oxygen lone pairs.

It is interesting to note that these electrostatic potentials are more and more repulsive when the electrophile is brought nearer the aromatic ring. But during the electrophilic attack, as suggested by Politzer and Weinstein[34], a hydrogen can be moved out of the plane of the ring by interaction with the reactant. In fact, the plot of the isopotential curves, where the *ortho* or the *para* hydrogen have been moved out of the ring plane, shows an attractive potential for an electrophilic reagent, approximately centred on the direction of the vacant tetrahedral position. Although the charge on the *para* carbon is lower than that of the *ortho*, the attractive potential turns out to be greater at the *para* carbon. These conclusions are identical with that of the protonation study of toluene[35] and show the interest of electrostatic potentials in discussion of electrophilic substitution reactions.

D. Spectra and Quantum Calculations

1. Electronic spectra

The π-electron SCF theory in its PPP formalism has been applied to calculate the spectra of phenol. Mishra and Rai[36] performed calculations with the variable electronegativity SCF method in which the valence-state ionization potentials and electron affinities of the atoms are taken as parabolic functions of Slater's effective nuclear charges on the atoms. This modified PPP method brings an improvement in the calculation of excitation energies which are presented in Table 4. The excitation energy values, oscillator strengths and directions of the transition moments are in satisfactory agreement with the experimental observations.

2. Magnetic resonance spectra

Schaefer and coworkers[37] have analysed the proton magnetic resonance spectra of phenol in the absence of intermolecular proton exchange for different concentrations of phenol in CCl_4. The long-range coupling $^5J_{H,OH}$ between the hydroxyl and *meta* ring protons is estimated as 0.33 ± 0.01 Hz for a phenol molecule at 32 °C and as 0.20 ± 0.01 Hz for the trimer. This decrease in the coupling on trimerization is found in CNDO/2 and INDO MO FPT calculations.

The ^{13}C chemical shifts of substituted benzenes have been the subject of much work concerning qualitative correlations between parameters and experimental

TABLE 4. Singlet excitation energies, oscillator strengths and angles of polarization (ϕ) for phenol

Calculated excitation energies (eV)	Experimental excitation energies (eV)	Calculated oscillator strengths	Experimental oscillator strengths	ϕ (degrees)	Symmetry of state
4.73	4.50	0.026	0.0154	90	$^1B_2$
5.96	5.64	0.0656	–	0	$^1A_1$
6.85	6.53	1.2343	–	0	$^1B_2$
6.86	–	1.0838	–	90	$^1A_1$

data. The CNDO/2 method[23] and Del Re's method[24] have been used to reproduce ^{13}C and ^{1}H chemical shifts for these molecules. The correlations of ^{13}C and ^{1}H chemical shifts show that, for all positions in monosubstituted benzenes, the chemical shift is mainly determined by changes in charge density.

E. Molecular Orbital Studies in the Pharmacology of Phenols

The purpose of the pharmacologist is to discover molecules which will produce desired biological effects without any undesirable ones. Quantum chemistry has been introduced into the area of biochemistry to select such molecules. The physiological properties of phenols were theoreticaly studied[38]. It seems that an increase in activity may be associated with a decrease in the highest occupied molecular orbital energy and with an increase of the reduced Mulliken overlap populations relative to the oxygen atom.

F. Theoretical Study of Inter- and Intra-molecular Hydrogen Bonds in Phenols

The CNDO/2 calculations for phenol– and *p*-nitrophenol–ammonia complexes give energy minima for the O· · ·H distance in both complexes as 2.6 Å[39]. For the O· · ·H distance in the ground and excited states, a potential minimum at 1.0 Å due to H-bonded species and a minimum at 1.8 Å due to an ion pair are found. This ion pair is unstable in both the ground and excited states but is more stable in the first excited singlet state than in the first excited triplet state. This finding is in qualitative agreement with the experimental results.

The 'anomalous' order of intramolecular hydrogen bonding strengths in the *o*-halophenols $Cl > F > Br > I$ is explained by CNDO/2 and *ab initio* calculations[40]. The cause of this 'anomalous' hydrogen-bond order lies in the deviations from optimal hydrogen bonding geometries and in the repulsive halogen–oxygen and halogen–hydrogen 'interorbital' interactions. The *ab initio* calculations provide also insight into the reasons for the usual blue shift of the O· · ·H hydrogen-bonded IR stretching frequency for *o*-trifluoromethylphenol.

II. THERMOCHEMISTRY OF PHENOLS

A. Introduction

Thermochemistry is concerned with energy changes associated with physical transformations (melting, vaporization) and chemical reactions of substances. In this chapter we have collected thermodynamic data relating to phenols. When possible, we have attempted to link together the physical and chemical properties of these substances. All units will be kcal mol^{-1} for energy (enthalpy, free energy, resonance energy, activation energy) and cal mol^{-1} K^{-1} for entropy and heat capacity.

B. Thermodynamic Properties of Phenol Molecules

The thermodynamic properties of the different phases depend essentially on the heat capacity and the thermodynamic functions which can be calculated from it.

At constant pressure, the heat capacity is defined by

$$C_p = \left(\frac{\partial H}{\partial T}\right)_p$$

where H is the enthalpy. Hence, C_p is the quantity of heat ∂H necessary to increase the temperature of a substance by ∂T. For solids, the heat capacities are established experimentally from calorimetric measurements or theoretically, at low temperature, from Einstein and Debye's equations. For liquids, only experimental values are valid, since no theory of the liquid state is satisfactory. For gases, the heat capacity values can be established either from experimental measurements by Raman and infrared spectroscopies or theoretically from statistical mechanics. For a detailed study of these methods the remarkable book of Stull, Westrum and Sinke[41] should be consulted. Over a large temperature range, the variation of the heat capacity cannot be represented by a single mathematical expression and it is necessary to determine a great number of values for different temperatures. Thus it is possible to calculate the entropy at T_2 and T_1 from

$$S_{T_2} - S_{T_1} = \int_{T_1}^{T_2} \frac{C_p\,\mathrm{d}T}{T}.$$

In the same manner, it is possible to calculate the enthalpy according to the expression

$$H_{T_2} - H_{T_1} = \int_{T_1}^{T_2} C_p\,\mathrm{d}T$$

and the free energy (in United States) or free enthalpy (in Europe) from:

$$\Delta G = \Delta H - T\Delta S$$

It is usual to give the following expressions:

$$H_T^\circ - H_{298.15}^\circ \text{ and } (G_T^\circ - H_{298.15}^\circ)/T.$$

$H_T^\circ - H_{298.15}^\circ$ is the difference between the enthalpy in the standard state at temperature T, and the enthalpy in the standard state at 298.15 °K. $(G_T^\circ - H_{298.15}^\circ)/T$ is the free enthalpy in the standard state at temperature T less the enthalpy in the standard state at 298.15 K divided by T. This expression is equal to

$$(H_T^\circ - H_{298.15}^\circ)/T - S_T^\circ,$$

where S_T° is the entropy in the standard state at temperature T. The function

$$(G_T^\circ - H_{298.15}^\circ)/T$$

varies only slightly with the temperature so the interpolation is easy. In the literature we also find

$$(G_T^\circ - H_0^\circ)/T$$

and we have

$$(G_T^\circ - H_{298.15}^\circ)/T = (G_T^\circ - H_T^\circ)/T - (H_{298.15}^\circ - H_0^\circ).$$

In the gaseous state, for phenol[42] and the three isomeric cresols[43], Green has determined these different properties. In the solid and liquid states, Andon and collaborators have determined the heat capacity and the thermodynamic functions for phenol[44] and the three isomeric cresols[45]. Values for some simple phenols are given in Table 5.

TABLE 5. Heat capacity values for some simple phenols

		C_p(cal K^{-1} mol^{-1})		
Phenol	T(K)	Solid	Liquid	Ideal gas
Phenol	300	30.72		
	314.06	32.73	48.14	24.90
2-Methylphenol	300.00	37.17		31.31
	304.20	37.69	55.67	
3-Methylphenol	285.40	35.65	52.33	
	300.00		53.96	29.91
4-Methylphenol	300.00	36.13		29.91
	307.94	37.09	54.36	

Pentafluorophenol has been well studied in American[46] and Russian[47] laboratories in the solid and liquid state, and recently by an English group[48] in the gaseous state. Phenol-d$_1$ and phenol-d$_5$ have been studied in the gaseous state by Sarin and coworkers[49]. Verma and collaborators[50] have determined, in the gaseous state, the molar thermodynamic functions for the three isomeric methoxyphenols. Ramaswamy[51] has calculated, by the group equation method, the thermodynamic properties of *n*-alkylphenols.

As a general rule, it is possible to determine C_p° and S° or the ideal gaseous state from Benson and coworkers' systematic additive rules[52,53] For example in the case of *m*-cresol at 300 K we find 30.06 cal K^{-1} mol^{-1} while the expemental value is 29.91 cal K^{-1} mol^{-1}.

C. Physical Transformations

The following symbols are used for the physical transformations:

enthalpy and entropy of melting	ΔH_m	and	ΔS_m,
enthalpy and entropy of vaporization	ΔH_v	and	ΔS_v,
enthalpy and entropy of sublimation	ΔH_s	and	ΔS_s,
enthalpy and entropy of transition	ΔH_t	and	ΔS_t,

These enthalpies are defined as the heats exchanged with surroundings at the transformation temperature and usually at the atmospheric pressure. Entropies are the same quantities divided by the transformation temperature. The differences between these quantities and those concerning standard reference states are insignificant, except at high pressures for ΔH_m and ΔH_t and for some associated vapours for ΔH_v and ΔH_s as well.

In the past, ΔH_m did not have much interest for the interpretation and prediction of chemical results. However, we think that this information becomes more and more important as the chemistry of molecular organic solid state is advancing[54-59]. Thus, when examining reactions in the solid state, we must take into account the energy necessary to destroy crystal lattices. On the relation between crystal structure and the melting process interesting information can be found in the books by Bondi[60] and Ubbelhode[61]. Besides, ΔH_m is a datum[60,61] necessary to determine ΔH_s using

$$\Delta H_{sT} = \Delta H_{vT} + \Delta H_{mT}.$$

ΔH_s may be used to calculate the enthalpy of formation of a gas-phase chemical, starting from the enthalpy of formation of this product in the solid state,

$$\Delta H_{fT}(g) = \Delta H_{fT}(s) + \Delta H_{sT}.$$

Enthalpies of transition and melting may be directly determined by adiabatic calorimetric procedures. Enthalpies of melting may be also determined by cryoscopic methods. Enthalpies of vaporization can be obtained with a flow calorimeter, or by measurement of the vapour pressure and the application of the Antoine and the Clausius–Clapeyron equations, or by using the additive method of Laidler, Lovering and Nor[62–64].

The heat of melting (ΔH_m, kcal mol^{-1}) of phenol was found to be: 2.752 ± 0.002 [65], 2.74 ± 0.02 [66] and 2.5 ± 0.3 [67]. The same references provide values for other phenols too. Values for methylphenol isomers are given by Andon and coworkers[68]. The vaporization enthalpies of various phenols are available as follows: phenol, cresol and xylenols[69], ethylphenols[70], 3-ethyl-5-methylphenol, *o*-*s*-butylphenol and *p*-*t*-butylphenol[71] and many other phenols[72]. Transition enthalpies of *p*-halophenols have been determined by Bertholon and coworkers[73].

D. Physical Interactions with other Substances

Inter- and intra-molecular H-bonding and ionization of phenols in water were reviewed in 1971 by Rochester[74]. More recently, the enthalpies of dimerization in CCl_4 and C_6H_{12} have been determined for various phenols carrying chlorine, methyl and *t*-butyl groups by Baron and Lumbroso-Bader[75–77]. Rochester and coworkers have determined the thermodynamic functions for the ionization of some phenols in methanol[78] and in mixed aqueous solvents[79,80]. The thermodynamic functions of halophenol dissociation in dimethylformamide have been calculated[81]. The enthalpy and entropy values are linear functions of the dipole moments of these compounds.

Another physical interaction parameter, the free energy of solution, is given by

$$\Delta G° = -RT \ln (Cs)$$

where Cs is the solubility of the phenol in the solvent, assuming that the activity coefficient of the neutral phenols in the saturated phenol solution is one. The entropies of solution are deduced from the free energies and the calorimetrically determined enthalpies. Rochester and coworkers[82,83] have determined these thermodynamic parameters for solutions of 4-, 3- and 3,5- substituted phenols in water at 25 °C. Liotta and coworkers[84] have calculated the thermodynamic parameters for solutions of *meta*- and *para*-substituted nitro-, cyano- and formylphenols. They have also given the free energy of solution for 3-nitrophenols.

Rochester[82,83] and Liotta[84] have also evaluated free energies, enthalpies and entropies of hydration for phenols; i.e., thermodynamic parameters corresponding to the transfer of phenol from the gaseous state to aqueous solution. The free energies of hydration conform to a linear free-energy relationship of the form of the Hammett equation which for 2-cresol, phenol and 4-substituted phenols may be written as follows:

$$\Delta G_{hyd}\ (\mathrm{kcal\ mol^{-1}}) = -3.50\,\sigma - 4.72.$$

TABLE 6. Complexes or adducts with phenols and their corresponding enthalpies

Phenol	Additive	Solvent	ΔH (kcal mol^{-1})	Ref.
4-ClC_6H_4OH	CH_3COOEt	CCl_4	5.0	86
4-ClC_6H_4OH	CH_3CONMe_2	CCl_4	7.3	86
4-ClC_6H_4OH	C_5H_5N	CCl_4	7.0	86
4-ClC_6H_4OH	C_5H_5N	C_6H_{12}	8.1	86
4-ClC_6H_4OH	Et_3N	C_6H_{12}	9.5	86
3-$CF_3C_4H_4OH$	CH_3COOEt	C_6H_{12}	6.8	86
3-$CF_3C_6H_4OH$	$(CH_2)_5C{=}O$	C_6H_{12}	7.4	86
3-$CF_3C_6H_4OH$	CH_3CONMe_2	C_6H_{12}	10.3	86
3-$CF_3C_6H_4OH$	CH_3CONMe_2	CCl_4	7.3	86
3-$CF_3C_6H_4OH$	C_5H_5N	C_6H_{12}	8.5	86
4-t-BuC_6H_4OH	CH_3CONMe_2	CCl_4	6.4	86
4-t-BuC_6H_4OH	CH_3CONMe_2	C_6H_{12}	8.1	86
4-t-BuC_6H_4OH	C_5H_5N	C_6H_{12}	7.2	86
4-t-BuC_6H_4OH	Et_3N	C_6H_{12}	8.3	86
2,6-$Me_2C_6H_3OH$	Et_3N	C_8H_{18}	5.4	87
		C_6H_6	8.4	87
2,6-$Me_2C_6H_3OH$	C_5H_5N	C_8H_{18}	6.6	87
		C_6H_6	4.9	87
3,4-$Me_2C_6H_3OH$	Et_3N	C_8H_{18}	7.2	87
		C_6H_6	8.8	87
3,4-$Me_2C_6H_3OH$	C_5H_5N	C_8H_{18}	7.2	87
		C_6H_6	5.9	87
4-ClC_6H_4OH	Et_3N	C_8H_{18}	9.9	87
		C_6H_6	9.3	87
4-ClC_6H_4OH	C_5H_5N	C_8H_{18}	9.4	87
		C_6H_6	6.5	87
4-BrC_6H_4OH	Et_3N	C_8H_{18}	10	87
		C_6H_6	9	87
4-BrC_6H_4OH	C_5H_5N	C_8H_{18}	8	87
		C_6H_6	6.9	87
3,4-$Me_2C_6H_3OH$	$(C_7H_{15})_4NI$	CCl_4	3.8	88
4-MeC_6H_4OH	$(C_7H_{15})_4NI$	CCl_4	3.7	88
PhOH	$(C_7H_{15})_4NI$	CCl_4	3.9	88
4-FC_6H_4OH	$(C_7H_{15})_4NI$	CCl_4	4.0	88
4-ClC_6H_4OH	$(C_7H_{15})_4NI$	CCl_4	4.4	88
4-BrC_6H_4OH	$(C_7H_{15})_4NI$	CCl_4	4.7	88

For 3- and 3,5-substituted phenols the free energies deviate from the linear plot. However the deviations are insufficient to influence the general observation that the electron-withdrawing substituents decrease the free energy of hydration of phenols whereas electron-donating substituents increase it.

Huyskens and coworkers[85] have determined for various phenols the transfer energies between cyclohexane and water. The transfer enthalpies and the transfer free energies depend on the pK_a values and the position of the substituents.

Table 6 shows substances which form complexes or adducts with phenols, together with their corresponding enthalpies.

For a given donor, the enthalpy of adduct formation with this series of phenols correlates with the Hammett substituent constant of the phenol. Drago and Epley[86] have reported a procedure which makes it possible to predict enthalpies of

Phenol	Additive	Solvent	ΔH (kcal mol^{-1})	Ref.
4-IC_6H_4OH	$(C_7H_{15})_4NI$	CCl_4	4.1	88
3-BrC_6H_4OH	$(C_7H_{15})_4NI$	CCl_4	4.3	88
3,4-$Cl_2C_6H_3OH$	$(C_7H_{15})_4NI$	CCl_4	4.7	88
3,5-$Cl_2C_6H_3OH$	$(C_7H_{15})_4NI$	CCl_4	4.9	88
3,4-$Me_2C_6H_3OH$	Bu_4NCl	CCl_4	7.1	88
4-MeC_6H_4OH	Bu_4NCl	CCl_4	5.0	88
PhOH	Bu_4NCl	CCl_4	8.5	88
	C_5H_5N	CCl_4	7.2	89
	2-$(C_6H_4N)Me$	CCl_4	6.9	89
	3-$(C_6H_4N)Me$	CCl_4	7.4	89
	4-$(C_6H_4N)Me$	CCl_4	7.3	89
	C_5H_5N	C_6H_{12}	7.2	90
		CS_2	5.9	90
		CCl_4	5.7	90
		C_6H_6	5.0	90
		$Cl_2C_2H_4$	5.5	90
		$CHCl_3$	5.1	90
2-$(MeO)C_6H_4OH$	C_5H_5N	C_6H_{12}	2.8	90
		CS_2	3.2	90
		CCl_4	2.8	90
		C_6H_6	2.9	90
		$Cl_2C_2H_4$	2.4	90
		$CHCl_3$	2.2	90
PhOH	Me_2SO	C_6H_{12}	8.9	90
		CS_2	7.0	90
		CCl_4	6.3	90
		C_6H_6	5.1	90
		$Cl_2C_2H_4$	6.0	90
		$CHCl_3$	3.1	90
2-$(MeO)C_6H_4OH$	Me_2SO	C_6H_{12}	3.7	90
		CS_2	4.5	90
		CCl_4	3.0	90
		C_6H_6	3.8	90
		$Cl_2C_2H_4$	3.4	90
		$CHCl_3$	2.0	90

adduct formation for any *meta*- or *para*-substituted phenol whose Hammett substituent constant is known, with any donor that has been incorporated into the *E* and *C* correlation*.

Lambert[91] has studied the phenol complexes of pyridine, tetrahydrofuran, acetone and *p*-dioxane. Martin and Oehler[92] have determined the enthalpies, free energies and entropies of association between RC_6H_4OH (R = H, Me, MeO, Cl,

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*E and C correlation is defined as follows:

$$-\Delta H = E_A E_B + C_A C_B$$

where ΔH is the enthalpy of adduct formation, E_A and C_A two constants assigned to an acid and E_B and C_B two constants assigned to a base[86a].

NO_2, CO_2Me) and *N*-methylaniline, *N,N*-dimethylaniline and mesitylene. These authors found that the complexes are bonded by the delocalized π-electron system and not by the electron pair at the N atom.

E. Chemical Transformations

1. *Enthalpies of formation and heat balance*

For a chemical process, at constant pressure,

$$\nu_A\ A + \nu_B\ B + \cdots \rightarrow \nu_X\ X + \nu_Y\ Y + \cdots \qquad (1)$$

the heat of reaction ΔH_{rT} equals

$$\Delta H_{rT} = \sum_{\text{products}} \nu_i H_i - \sum_{\text{reactants}} \nu_i H_i .$$

At constant volume, the energy of reaction, ΔU_{rT}, is related to ΔH_{rT} by

$$\Delta H_{rT} = \Delta U_{rT} + P\Delta V_{rT}, \qquad (2)$$

where ΔV_{rT} is the difference, at constant pressure P, in molar volume between products and reactants. If all products and reactants are in their standard state, the heat of reaction involved is the standard heat of reaction ΔH°_{rT}.

The application of the first law of thermodynamics to reaction (1) gives:

$$\Delta H^\circ_{rT} = \sum_{\text{products}} \Delta H^\circ_{fT} - \sum_{\text{reactants}} \Delta H^\circ_{fT} \qquad (3)$$

where

$$\sum_{\text{products}} \Delta H^\circ_{fT} = \nu_A\ \Delta H^\circ_{fT}(A) + \nu_B\ \Delta H^\circ_{fT}(B) \ldots$$

and

$$\sum_{\text{reactants}} \Delta H^\circ_{fT} = \nu_X\ \Delta H^\circ_{fT}(X) + \nu_Y\ \Delta H^\circ_{fT}(Y) + \ldots$$

Equation (3) can be used to calculate ΔH°_{rT} for all reactions in which ΔH°_{fT} is known for all participants, therefore the standard heat of formation appears as an interesting way of obtaining the heat of reaction.

The most important method of determining the enthalpy of reaction or formation is the measurement of the enthalpy of combustion in oxygen. Experiments at constant volume lead to the energy of combustion which is converted to enthalpy by equation (2), assuming that the gaseous products are in the ideal state. From these measurements and by use of Hess' law, it is possible to obtain the standard heat of formation.

Other experiments also lead to the determination of the heat of formation : enthalpy of combustion from flame calorimetry, direct measurements of enthalpy of reaction by carrying out experiments in a calorimeter and determination of the equilibrium constants[41,93]:

$$d(\ln K_p)/dT = \Delta H^\circ_{rT}/RT^2$$

The thermodynamic function that is a true index of the feasibility for a given chemical process is the free energy function or Gibbs energy ΔG_{rT} involving both enthalpy and entropy functions. Like enthalpy and entropy, G is also an extensive property of the system. The appropriate equations are the same as those for enthalpy function:

$$\Delta G^\circ_{rT} = \sum_{\text{products}} \nu_i G_i - \sum_{\text{reactants}} \nu_i G_i$$

$$\Delta G^\circ_{rT} = \sum_{\text{products}} \Delta G^\circ_{fT} - \sum_{\text{reactants}} \Delta G^\circ_{fT}.$$

At equilibrium, $\Delta G_{rT} = 0$ and the expression $\Delta G_{rT} = \Delta G^\circ_{rT} + RT \ln K$ becomes:

$$\Delta G^\circ_{rT} = -RT \ln K_p.$$

$\Delta G^\circ_{rT} = 0$ corresponds to a reaction for which K_p is unity. When $\Delta G^\circ_{rT} < 0$, the reaction is thermodynamically favourable, and when $\Delta G^\circ_{rT} > 0$ it is thermodynamically unfavourable. From the knowledge of ΔG°_{rT} for a chemical process it is possible to calculate the equilibrium composition[94].

Heats of reaction have been studied for the combustion of phenolic compounds in oxygen. The combustion enthalpy for phenol, methylphenols and dimethylphenols has been determined[69-71]. Bertholon and coworkers[95] have studied many substituted phenols and conclude that the Kharasch method[96] of estimation of ΔH°_c (liq.) is a good one in spite of its simplicity. Table 7 shows the very good agreement between measured and calculated values. The Kharasch rule gives the combustion enthalpy of phenols with a maximum error of 0.6%. From the heat of reaction so measured and from the enthalpy of vaporization or sublimation, the authors have computed the standard heat of formation in the gaseous state. From these and other papers, Cox[97] has recently proposed a method for estimating the enthalpy of formation of benzene derivatives in the gaseous state.

There is great interest in computations of heat balances, equilibrium yields and thermodynamical feasibilities of processes. For example in the alkylation of 3-methylphenol by propene, yielding 3-methyl-6-isopropylphenol (thymol), it is possible to estimate the enthalpy of reaction at 0 K, 298 K and 600 K. Table 8 shows the standard enthalpies of formation of the compounds involved, computed by Franklin's method[98]. Hence, the standard heats of reaction ΔH°_{rT} are -22.95, -23.34 and -23.48 kcal mol^{-1} at 0, 298 and 600 K, respectively. The reaction is exothermal (i.e. thermochemically favourable) and the heat balance does not vary greatly with the temperature in the range 0–600 K. The values are in good agreement with those obtained by Kukui and coworkers[99] for alkylation of phenol with normal 1-alkenes

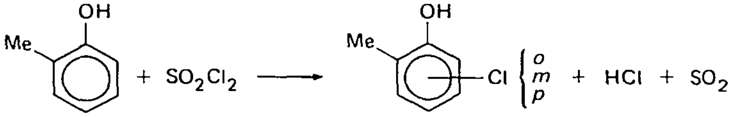
TABLE 7. Experimental and calculated values of enthalpies of combustion for some phenols

Compound	ΔH°_c(liq.) measured at 298 K	ΔH°_c(liq.) calculated at 291 K
Phenol	732.3	732.9
2-Methylphenol	886.32	885.7
2-Ethylphenol	1044.07	1042.0
2-Isopropylphenol	1200.5	1198.3
2-*t*-Butylphenol	1352.8	1354.6

TABLE 8. Standard enthalpies of formation of the compounds involved in the alkylation of 3-methylphenol by propene

Compound	ΔH°_f(0 K)	ΔH°_f(298 K)	ΔH°_f(600 K)
3-Methylphenol	−24.64	−32.08	−34.24
Propene	8.47	4.88	1.98
3-Methyl-6-isopropylphenol	−39.12	−50.54	−55.74

We can also calculate the thermodynamic values for the isothermal chlorination of 2-methylphenol by sulphuryl chloride (equation 4). By the Van Krevelen and



(4)

Chermin method[41,133], for inorganic products, we can compute the values of ΔG°_f, ΔH°_f and ΔS°_f for all participants of the reaction (Table 9). From these data, we can obtain the thermodynamic values of the three reactions giving the three isomers:

	ΔG°_r	ΔH°_r	ΔS°_r
6-Chloro	−23.72	−13.22	−55.55
m-Chloro*	−25.05	−14.55	−55.55
4-Chloro	−23.81	−13.31	−55.55

Since the values of ΔG°_{rT} are strongly negative, at the thermodynamic equilibrium, the chlorination products are greatly favoured. The reaction is also thermochemically favourable as shown by the values of the heat balances.

2. *The Planck function and relative stability of phenols*

The application of thermodynamics to organic reactions is particularly useful for the prediction of the feasibility of a given process. Considering the isothermal

TABLE 9. Thermodynamic values for the reaction participants in equation (4) at 298 K

Compound	ΔG°_f (kcal mol^{-1})	ΔH°_f (kcal mol^{-1})	ΔS°_f (cal mol^{-1} K^{-1})
2-Methylphenol	− 5.33	−29.94	8.26
Sulphuryl chloride	−74.80	−85.40	−35.57
Chloro-2-methylphenol:			
6-chloro	− 9.34	−35.55	−87.89
m-chloro*	−10.67	−36.88	−87.89
4-chloro	− 9.43	−35.64	−87.89
HCl	−22.77	−22.06	2.38
SO_2	−71.74	−70.95	2.65

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*By the calculation method used it is not possible to distinguish between the 2-methyl-3 and the 2-methyl-5-chlorophenol.

reaction of formation for a phenol

$$aC(g) + b/2H_2(g) + c2O_2\ (g) \leftrightharpoons C_aH_bO_c\ (g)$$

(all compounds in their standard state); the equilibrium constant K_p gives the thermodynamic yield, at the equilibrium, for the formation reaction.

A typical thermodynamic function for graphical representation of this equilibrium constant is the Planck function Γ. Indeed, if the formation reaction is an

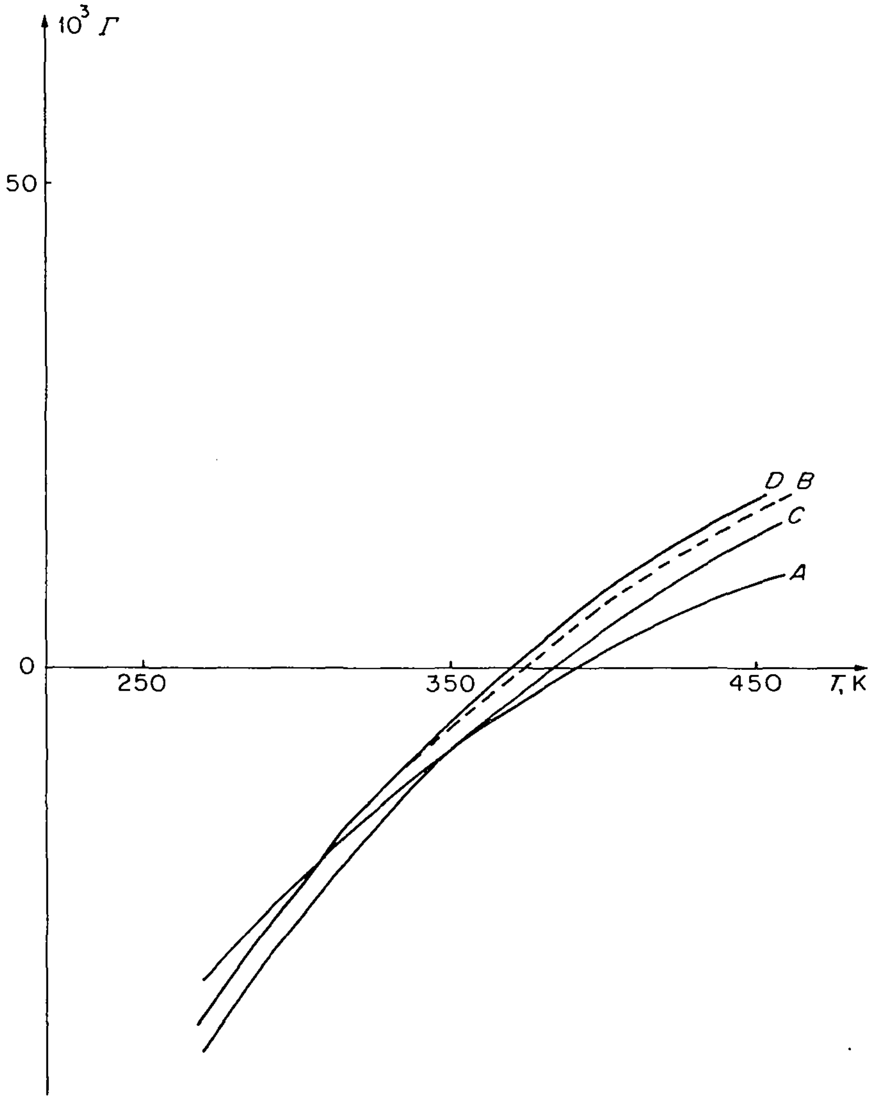


FIGURE 5. Plot of the Planck function vs. the temperature for phenol and methylphenols; *A*: phenol, *B*: 2-methylphenol, *C*: 3-methylphenol, *D*: 4-methylphenol.

equilibrium, the free enthalpy change becomes zero:

$$\Delta G_{TP} = \Delta G^\circ + RT \ln K_p = 0$$

$$\Delta G^\circ = -RT \ln K_p = \sum_{\text{product}} \Delta G_f^\circ - \sum_{\text{reactants}} \Delta G_f^\circ$$

$$\Gamma = \Delta G^\circ / T = -R \ln K_p.$$

The study of the variation of the Planck function with the temperature for isomeric compounds leads to a comparison of the relative thermodynamic stabilities.

The values of $(\Delta G^\circ$ must be calculated by group additivities if no experimental determinations are obtainable. Ciola[100] proposed an additivity method for the estimation of log K_f. This quantity can lead to the Planck function.

Bertholon[101] calculated the values of the Planck function at different temperatures for several series of phenolic isomers such as methylphenols, isopropylphenols and methylisopropylphenols. Figure 5 shows the variation of the function with temperature for phenol and methylphenols. The most stable compound has the greatest equilibrium constant of formation and consequently the lowest values of Γ. At 450 K the stability of methylphenols can be shown in the order methyl-3 > methyl-2 > methyl-4 phenol, whereas at 273 K the order is methyl-3 > methyl-4 > methyl-2 phenol.

It has been demonstrated[102-105], that the system $AlCl_3$–HCl allows migration of the alkyl groups around phenolic rings. For isopropylphenols and methylisopropylphenols, such a system leads rapidly to the thermodynamical equilibrium at room temperature.

It must be noted that Γ is calculated for molecules in their ideal gaseous standard state, which is not the usual one for real chemical reactions. Nevertheless, for isomeric compounds, it is possible to compare the relative stabilities in the same conditions.

The experimental and calculated stability orders for isopropyl- and diisopropylphenols are in good agreement (Table 10). These studies confirm the results obtained on various hydrocarbon series, particularly on alkylbenzenes, by Rossini and coworkers[106] and recently by Olah and Kaspi[107].

3. *Thermochemistry and kinetics*

Thermodynamics deals with the energy of the initial and final states of a system and the variations of energy between them, whereas kinetics concerns the rates at which the final states are reached. The empirical Arrhenius equation gives the activation energy E_a, i.e. the temperature dependence of the rate.

Only the theory of activated complexes leads to the thermodynamic quantities

TABLE 10. Stability orders for isopropyl- and diisopropyl-phenols

	Stability order at 298 K	
Compound	Experimental	Calculated (gasous state)
Isopropylphenols	*meta* > *para* > *ortho*	*meta* > *para* > *ortho*
Diisopropylphenols	3,5 > 2,5 > 2,4 > 2,6	3,5 > 2,5 = 2,4 > 2,6

directly related to kinetic ones. This theory links the rate constant k to the activation free enthalpy $\Delta G^{\circ\neq}$ by the relation

$$k = K\frac{RT}{N_A h}\exp(-\Delta G^{\circ\neq}/RT),$$

where K is the transmission coefficient (generally taken equal to unity), R is the ideal gas constant, T is the absolute temperature N_A is the Avogadro number and h is the Planck constant. In the Arrhenius relation

$$k = A\exp(-E_a/RT)$$

A is the pre-exponential factor, and E_a and A can be calculated from the experimental. Since we have

$$\Delta G^{\circ\neq} = \Delta H^{\circ\neq} - T\Delta S^{\circ\neq}$$

it can be shown[108] that

$$E_a = \Delta H^{\circ\neq} + RT \text{ and } A = \frac{eRT}{N_A h}\exp(\Delta S^{\circ\neq}/R)$$

Therefore, three thermodynamic quantities of activation $\Delta H^{\circ\neq}$, $\Delta S^{\circ\neq}$ and $\Delta G^{\circ\neq}$ can be obtained from the determination of rate constants and the application of the Arrhenius equation. These quantities are characteristic of a molecule, the 'activated complex', which corresponds to the state of maximum energy for the reacting system.

For an equilibrated reaction, we have[109]:

$$A + B \underset{(2)}{\overset{(1)}{\rightleftarrows}} C + D,$$

$$\begin{aligned}\Delta S^{\circ}_{r_1}/R &= \Delta S^{\circ\neq}_1/R - \Delta S^{\circ\neq}_2/R,\\ \Delta H^{\circ}_{r_1} &= \Delta H^{\circ\neq}_1 - \Delta H^{\circ\neq}_2,\\ \Delta G^{\circ}_{r_1} &= \Delta G^{\circ\neq}_1 - \Delta G^{\circ\neq}_2.\end{aligned}$$

Therefore:

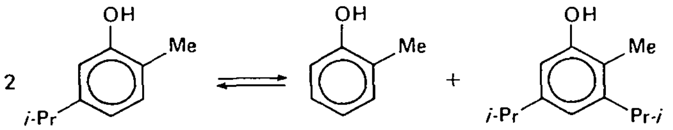
$$\begin{aligned}\Delta S^{\circ}_{r_1}/R &= \ln(A_1/A_2),\\ \Delta H^{\circ}_{r_1} &= E_{a_1} - E_{a_2},\\ \Delta G^{\circ}_{r_1} &= E_{a_1} - E_{a_2} - RT\ln(A_1/A_2).\end{aligned}$$

Therefore, if the Arrhenius parameters concerning the forward reaction are known, those of the reverse reaction can be calculated from the thermochemical properties of reactants and products.

For a suitable use of these equations, a good knowledge of the conditions of the studied reaction is necessary (see Reference 109).

It would be extremely interesting to be able to calculate thermodynamic parameters of activation. This kind of work is just starting now but studies to obtain experimental results sufficient to make fruitful comparisons are time-consuming and laborious. Hence, satisfactory examples are scarce in the organic chemistry literature. In the useful book written by Benson[110] only gas-phase reactions are considered; the case of condensed phases is not treated.

With regard to phenols, few thorough studies have been made. As an example, we shall cite the kinetic study of disproportionation of carvacrol or 2-methyl-5-isopropylphenol (equation 5) with aluminium chloride, in 1,2-dichloroethane[111].



(5)

The equilibrium constant of this reaction is equal to 0.105, and does not vary between 10 and 50 °C. Under these conditions, the variation of enthalpy is null, since

$$\frac{d(\ln K_p)}{dT} = \frac{\Delta H}{RT^2} .$$

For the forward reaction the activation energy, 12.7 kcal mol^{-1} is equal to that of the reverse reaction. Hence, rates of the reverse raction are readily calculated. A similar study has been done on the isomerization of 4-methyl-2,5-diisopropylphenol[112]. For these reactions the difference in the rates in the two directions is due to the difference in the entropy terms. Various kinetic studies on phenols are reported in the books of Bamford and Tipper[113] and Koptyug[114]. Claisen rearrangements have also been extensively studied[115], and their activation parameters have been determined. The cyclic nature of the transition states is confirmed by the sign and magnitude of the activation entropy $\Delta S^{\neq}$. For example, the $\Delta S^{\neq}$ value is -12 cal deg^{-1} mol^{-1} for the *ortho* rearrangement of *o*-allylphenyl ether in diphenyl ether[116].

With a knowledge of the activation parameters one can define the nature of the transition state. Very recently, Dutruc-Rosset[117] determined the activation parameters of the parallel *ortho* and *para* chlorination of 2-methylphenol by sulphuryl chloride in carbon tetrachloride. The activation entropies obtained favour on activated complex which is better organized than the initial reactants. The activated complex relating to the formation of the *para*-chlorinated derivative is better organized than that relating to the *ortho*-chlorinated one. The value of $\Delta S^{\circ\neq}$ is -25.9 and -36.9 cal mol^{-1} K^{-1} for the *ortho* and for the *para* chlorination, respectively, both values favouring a concerted mechanism.

4. *Resonance energy and reaction orientation*

Resonance energy, E_R, or delocalization energy, is the difference in energy between that of the actual molecules and that of the hypothetical molecules (pictured for example by Kekulé structures). Since the latter are not real, their energies can only be estimated from additive systematics. Nevertheless it is possible to obtain interesting results within a series of substances, like phenols, by using the same method for the resonance energy determinations. Indeed it is possible to estimate resonance energy by the quantum-mechanical theory, from heats of hydrogenation, from bond energies[118], from the enthalpy of combustion[119,120]. On this subject various books should be consulted[121-123,132].

In the case of phenols, an important application of resonance energy is the prediction of the keto–enol equilibrium. It is possible to predict that phenol has exclusively, and α-naphthol mainly, the enolic form, 9-anthrol is an approximately equal mixture of the enolic and ketonic forms, and 11-naphthacenol has mainly,

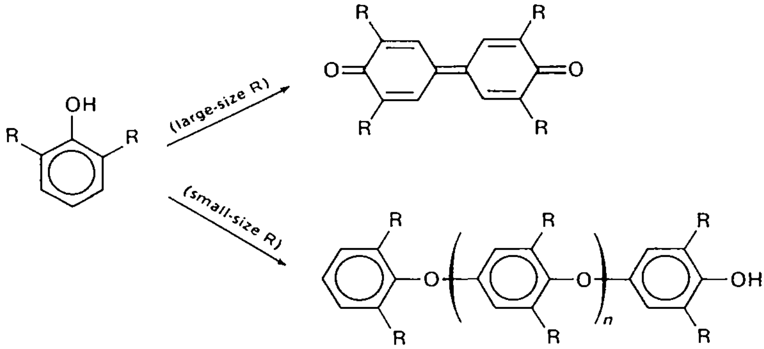
TABLE 11. Values of resonance energy for some phenols (calculated by Franklin's method)

Compound	E_R (kcal mol^{-1})
Phenol	39
2-*t*-Butylphenol	35
2,4-Di-*t*-butylphenol	28
2,4,6-Tri-*t*-butylphenol	23
2,4,6-Trimethylphenol	35
2,4,6-Triisopropylphenol	28
2,4,6-Tri-*t*-butylphenol	23

and 13-pentacenol exclusively, the ketonic form[124]. Similarly, phloroglucinol, a triphenol, and resorcinol a diphenol, are in equilibrium between two tautomeric forms[125]. Similarly, phloroglucinol gives with hydroxylamine a trioxime corresponding to triketocyclohexane and thus behaves like a cyclic triketone. However, its crystal structure determined by X-ray diffraction[126] shows that the average bond distances are C–C = 1.38 Å and C–OH = 1.37 Å corresponding to an enolic structure; hence it seems to attain the ketonic form only *during* the reaction, and particularly in the transition state.

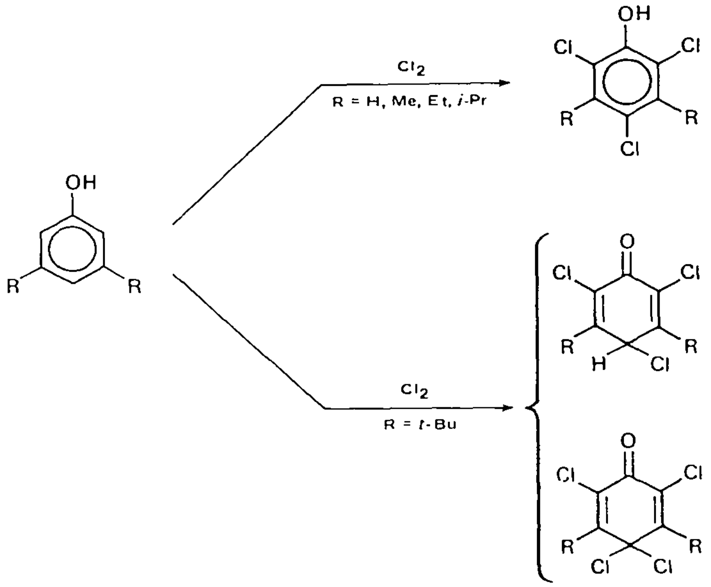
Bertholon and coworkers[127] have determined the resonance energy for many alkyl-substituted phenols. They have measured the heat of combustion and used the Pauling, Klages and Franklin methods to calculate the resonance energy. It appears that the resonance energy decreases both with an increasing number of alkyl substituents and with the number of carbons of the ramified substituents. The results shown in Table 11 illustrate these conclusions.

The decrease of the resonance energy with the number of carbons of the ramified alkyl group seems to be a measure of the inductive effect of these substituents which increases in the series: Me < Et < *i*-Pr < *t*-Bu. It has also been shown that a phenol can react either in its phenolic or in its quinonoid form acccording to its resonance energy. For example, oxidative coupling[128] leads either to polyethers (when the substituents in positions 2 and 6 are small) or to diphenoquinones (when the substituents are large) (equation 6). While it is possible to explain these results by steric hindrance, Lamartine and coworkers[129] have shown that when a phenol is substituted in the 3- and 5-positions by groups like methyl,



(6)

ethyl or isopropyl, chlorination by molecular chlorine leads largely to chlorophenols (equation 7a) while with *t*-butyl groups chlorocyclohexadienones are mainly formed (equation 7b). In equation (7) the substituents are in the same positions in both (a) and (b), and as these positions are far from the OH group it is not possible to explain the different results by steric hindrance. A study[130] of a large number of phenols which react in the solid state with chlorine has shown that the nature of the products is greatly dependent on the ramified alkyl substituents of the phenol ring. For these reactions Lamartine[131] has found a practically linear relationship between the resonance energy of the considered phenol and the ratio of chlorohexadienone formed. In order to explain these results it is necessary to note that the phenols studied in the ground state are in the enolic form, and only in the transition state is it possible to imagine them as being either in the enolic or ketonic form or in a mixture of these two forms.



(7a)

(7b)

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER **10**

Syntheses and uses of isotopically labelled ethers and sulphides

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I. SYNTHESES OF LABELLED ETHERS AND SULPHIDES

The desire to understand on the atomic and molecular level the mechanisms of action of ethers and their sulphur analogues, widely used in medical practice, dentistry, agriculture, radiation biology, chemical research and chemical industry (Meyers and coworkers 1977; Aleksandrov 1978), created the immediate need for the corresponding isotopically labelled compounds. This task has been accomplished by utilizing the well-established methods of classical organic chemistry such as Williamson synthesis (Fieser and Fieser 1975; O'Leary 1976; Baumgarten 1978; Le Noble 1974; March 1977; Perekalin and Zonis 1977) or by invoking more elaborate isotopic and nuclear techniques (Murray and Williams 1958; Miklukhin 1961; Evans 1966; Vdovenko 1969; *J. Labelled Compounds*, 1965–1978). Reactions of organic halides with alkoxide and hydroxide ions have been the subject of numerous investigations (Stothers and Bourns 1962; Fry 1970; Norula 1975; Williams and Taylor 1974; Julian and Taylor 1976; Sims and coworkers 1972). Routes leading to the formation of ethers and thio ethers are reviewed in the following sections.

A. Syntheses of Labelled Ethers

1. Synthesis of dimethyl ethers

a. Methyl methyl-^{14}C ether. ^{14}C-labelled dimethyl ether was prepared from ^{14}C-labelled methanol (equation 1) (Zieliński 1968). In a typical run ^{14}C-labelled

$$^{14}CH_3OH + CH_3OH \xrightarrow[-H_2O]{H_2SO_4} {}^{14}CH_3{-}O{-}CH_3 \qquad (1)$$

methanol was added gradually to concentrated sulphuric acid. The volatile gaseous ether was absorbed in a trap with ice-cold H_2SO_4. This complex of $^{14}CH_3{-}O{-}CH_3$ with sulphuric acid was then added dropwise to ice water, and the evolving dimethyl ether was collected in a cold trap immersed in liquid air. The crude radioactive product was purified by vacuum low-temperature distillations*.

b. Deuterated analogues of chloromethyl methyl ether. Deuterium was introduced into chloromethyl methyl ether (CMME), a potent human lung carcinogen, by reacting deuterated aqueous formaldehyde and methanol with hydrogen chloride (Gal 1975). Chloromethyl methyl-d$_3$ ether was obtained in 26.4% yield by bubbling hydrogen chloride gas through a vigorously stirred mixture of methanol-d$_4$ and paraformaldehyde cooled in an ice bath (equation 2).

$$CD_3OD + (CH_2O)_n \xrightarrow[1\ h]{HCl} CD_3OCH_2Cl \qquad (2)$$

Chloromethyl-d$_2$ methyl ether was synthesized in 22.5% yield from paraformaldehyde-d_2 and methanol using a similar procedure (equation 3). It was also

---

*In a similar manner tritium-labelled dimethyl ether was obtained using tritium-labelled methanol synthesized by reduction of tritium-labelled methyl formate with tritiated aluminium hydride (Zieliński 1962).

$$CH_3OH + (CD_2O)_n \xrightarrow{HCl} CH_3OCD_2Cl \qquad (3)$$

obtained in a three-step sequence by D-exchange of the hydrogen atoms adjacent to P of the intermediate phosphonium salt $[Ph_3P^+CH_2OCH_3]Cl^-$ with D_2O using Na_2CO_3 or $NaHCO_3$ as basic catalyst (Schlosser 1964). Thermal decomposition of the selectively deuterated compound yielded $ClCD_2OCH_3$ (75%) (equation 4).

$$Ph_3\overset{+}{P}CD_2OCH_3\cdot Cl^- \longrightarrow CH_3OCD_2Cl + Ph_3P \qquad (4)$$

Reaction of $ClCD_2OCH_3$ with Ph_3CNa in dry Et_2O gave, after hydrolysis, $Ph_3CD_2OCH_3$.

2. *Synthesis of simple and substituted ethyl ethers*

a. Ethyl ether-^{18}O. This synthesis was carried out according to the scheme shown in equation (5). Heating of ethyl bromide with an isotopically equilibrated

$$C_2H_5Br \xrightarrow[110^\circ C,\ 3-7\ days]{Mg(^{18}OH)_2} C_2H_5{-}^{18}OH \xrightarrow{NaOH,\ (C_2H_5O)_2SO_2} C_2H_5{-}^{18}O{-}C_2H_5 \qquad (5)$$

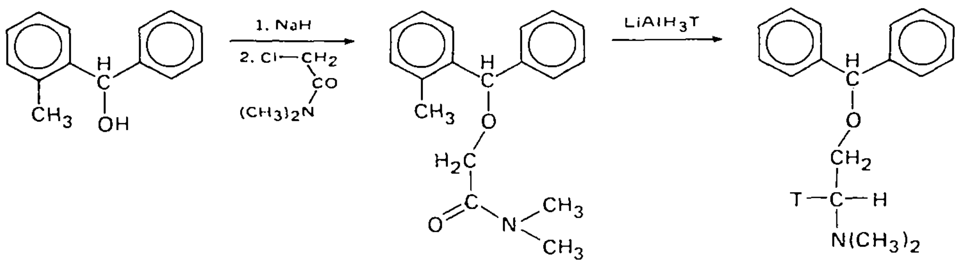
mixture of magnesium oxide and $H_2{}^{18}O$ in a sealed tube produces ethyl alcohol-^{18}O. The fraction distilling up to 100°C was treated with ethyl sulphate in the presence of sodium hydroxide. After completion of the etherification the flask was cooled to −60°C and the labelled ether distilled off under vacuum (Lauder and Green 1946).

b. Ethyl ethyl-1-^{14}C ether. This was synthesized using the modified Williamson synthesis (Burtle and Turek 1954) (equation 6).

$$C_2H_5ONa + CH_3{}^{14}CH_2I \xrightarrow[70-75^\circ C,\ 92\%]{abs.\ ethenol} CH_3{}^{14}CH_2{-}O{-}C_2H_5 \qquad (6)$$

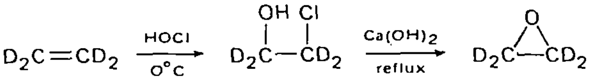
c. 2-Haloethyl-1-^{14}C ethyl ethers. This synthesis was carried out in 55–65% yield by reacting $XCH_2{}^{14}CH_2OH$ (X = Cl, Br) with $Et_3O^+BF_4^-$. Ethers of general formula $XCH_2{}^{14}CH_2OEt$ were produced (Shchekut'eva, Smolina and Reutov 1976).

d. Orphenadrine hydrochloride. This and related ethers of therapeutic interest labelled with tritium in the 2-(dimethylamino)ethyl moiety were synthesized by coupling *o*-methyl-α-phenylbenzyl alcohol with 2-chloro-*N*,*N*-dimethylacetamide and reduction of the resulting amide with tritiated aluminium hydride (Hespe and Nauta 1966). Hydrolysis of the labelled ethers with hydrochloric acid afforded tritiated 2-(dimethylamino)ethanol in 80% yield (equation 7).



$$\xrightarrow{HCl} (CH_3)_2NCTHCH_2OH \qquad (7)$$

e. Deuterium-labelled 1,2-epoxyethane-$^2H_4$. This was obtained by passing equivalent amounts of deuterated ethylene and chlorine into water at 0°C and subsequently treating with calcium hydroxide a 5% water solution of the ethylene-$^2H_4$ chlorohydrin obtained in the first step (equation 8). The product contained 87.5% of ethylene-$^2H_4$ oxide (Leitch and Morse 1952). C_2D_4O was also prepared by reacting ethylene-d_4 with HOCl and heating the ethylene chlorohydrin with KOH (equation 9) (Cunningham and coworkers 1951). Deuterated ethylene oxide synthesized directly by passing $C_2D_4Br_2$ over Ag_2O was contaminated with vinyl bromide (equation 10).



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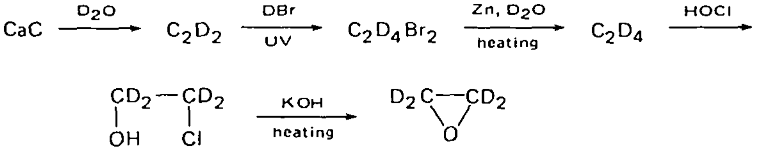

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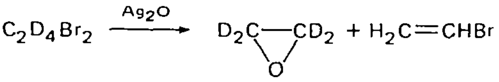
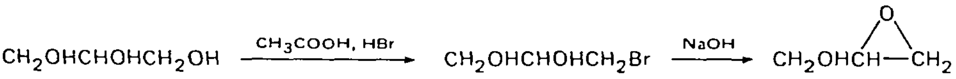


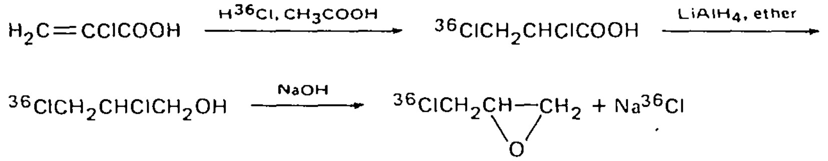
(10)

f. u-^{14}C-labelled 2,3-epoxypropan-1-ol. This was obtained in 99.5% yield from 3-bromo-1,2-diol labelled with carbon-14 (equation 11) (Jones 1973).



(11)

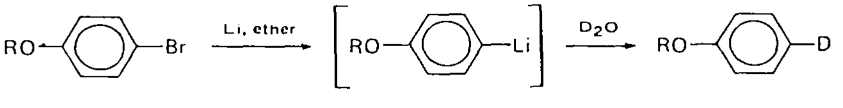
g. Epichlorohydrin labelled with ^{36}Cl. This was synthesized according to equation (12). 2,3-Dichloropropionic-3-^{36}Cl acid, obtained by reaction of 2-chloroacrylic acid with $H^{36}Cl$ in acetic acid, was reduced with lithium aluminium hydride in ether to 2,3-dichloro-1-propanol-3-^{36}Cl, which when subsequently treated with sodium hydroxide yielded epichlorohydrin-^{36}Cl. Sodium chloride formed in the reaction was partly radioactive (de la Mare and Pritchard 1954).



(12)

3. *Synthesis of phenyl alkyl ethers*

a. Deuterium- and tritium-labelled alkyl phenyl ethers. Anisole-4-^{2}H, anisole-2-^{2}H, phenetole-4-^{2}H, phenyl-4-^{2}H propyl ether and phenyl-4-^{2}H isopropyl ether were synthesized with D_2O and the corresponding intermediate organolithium compounds formed from 2- or 4-bromophenyl alkyl ethers (equation 13). (Lauer



(13)

and Day 1955). *p*-Deuteration was also effected by treating *p*-$MeOC_6H_4MgBr$ with D_2O (Oae, Ohno and Tagaki 1962).

Ethyl-1,1-d_2 phenyl ether and ethyl-1,1-d_2 p-t-butylphenyl ether were prepared according to equation (14) (R = H or *t*-Bu). 1-Iodoethane-1,1-d_2 and *p-t*-butylphenol gave 48% of the pure deuterated ether. Phenyl ethyl-1,1-d_2 ether was synthesized in a similar manner (Letsinger and Pollart 1956).

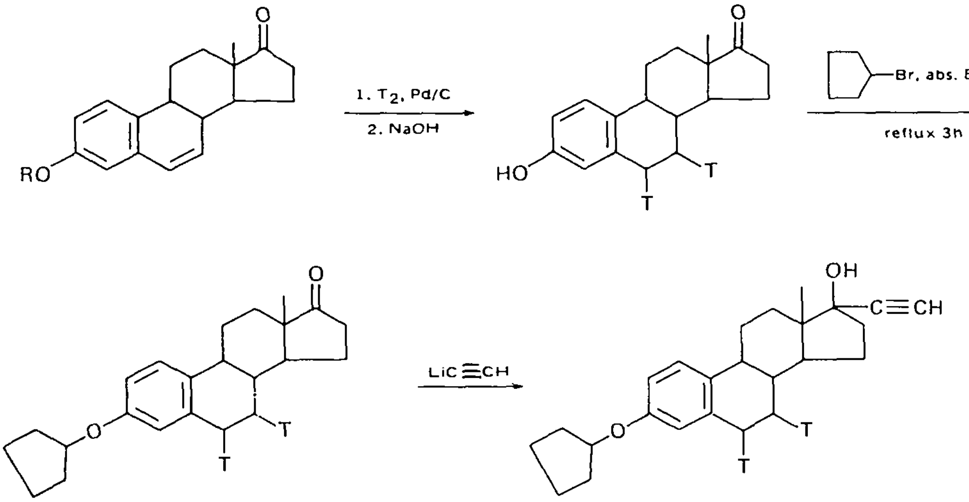
$$RC_6H_4{-}OH + CH_3CD_2I \xrightarrow{C_2H_5ONa} RC_6H_4OCD_2CH_3 \tag{14}$$

Ethyl benzyl-α,α-d_2 ether was obtained from benzyl-α,α-d_2 bromide and ethanol in which sodium had been dissolved. 70% of the deuterated ether was recovered (equation 15) (Letsinger and Pollart 1956). Benzyl-α,α -d_2 bromide was synthesized

$$C_6H_5CD_2Br + C_2H_5ONa \xrightarrow{\text{abs. ethanol}} C_6H_5CD_2OC_2H_5 \tag{15}$$

by reduction of ethyl benzoate with lithium aluminium deuteride in boiling ether solution and subsequent bromination of the benzyl-α,α-d_2 alcohol.

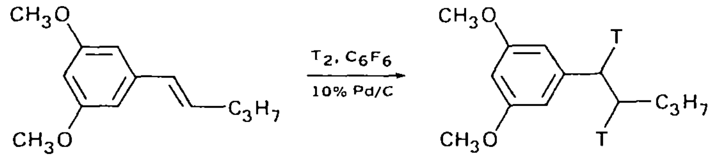
Oestrone-6,7-^3H,3-cyclopentyl ether prepared by etherification of oestrone-6,7-^{3} H, obtained by catalytic tritiation of 6-dehydroestrene acetate, with cyclopentyl bromide (equation 16) (Merrill and Vernice 1970, 1973).



(16)

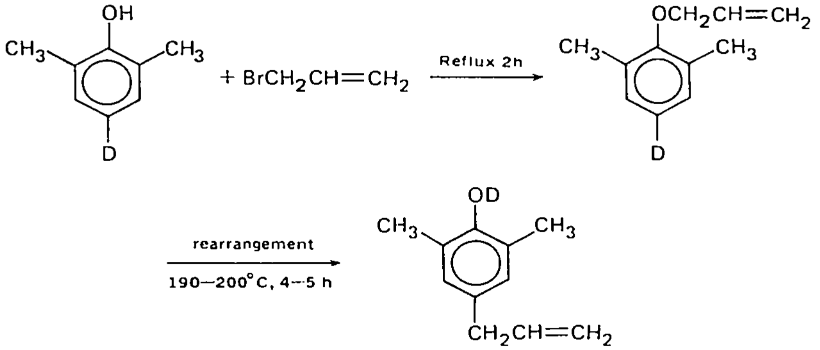
Oestradiol-3-methyl ether-6,7-^3H was obtained by etherification of oestradiol-6,7-^{3}H with dimethyl sulphate in 92% yield (Kepler and Taylor 1971).

Tetrahydrocannabinols labelled with tritium were prepared by 'a non-exchange synthesis' (Gill and Jones 1972).



(17)

4-Allyl-2,6-xylyl-4-^2H ether was synthesized by the reaction of 2,6-dimethyl-4-deuterophenol with allyl bromide. The ether rearranges thermally to 4-allyl-2,6-xylenol-^{2}H (equation 18) (Kistiakowsky and Tichenor 1942).



(18)

Several deuterium-labelled ethers useful for investigation of reaction mechanisms or as high-temperature solvents, lubricants or reagents for further syntheses were obtained by catalytic (5% Ru/C) deuterium exchange at 150–250°C, without cracking or isomerization (Atkinson and Luke 1972). Also no ether bond rupture, rearrangement or polymerization was observed during exchange of tritium on prereduced PtO_2 up to 130°C (Garnett, Law and Till 1965). Tritium-labelled phenyl allyl ether was obtained by exposure of the unlabelled compound to tritium gas. Various tritium-labelled compounds, including ethers, have been prepared by exchange reaction with the powerful acid complex $TH_2PO_4 \cdot BF_3$ (Hamada and Kiritani 1970). After 20 hours anisole was tritiated in about 33.5%, diphenyl ether in 40.5% and *p*-methoxynaphthalene in 36.3% yield. Investigation of the intramolecular distribution of tritium within the anisole molecule showed that 64.0% of

$$\mathrm{HOCH_2CH_2Cl + K^{14}CN \xrightarrow[83\%]{} HOCH_2CH_2{}^{14}CN \xrightarrow[71\%]{HCl} CH_2ClCH_2{}^{14}COOH}$$

$$\mathrm{\xrightarrow{CH_2N_2} CH_2ClCH_2{}^{14}COOCH_3 \xrightarrow[78\%]{LiAlH_4} CH_2ClCH_2{}^{14}CH_2OH}$$

$$\underset{(1)}{\mathrm{CH_2ClCH_2{}^{14}CH_2OH} + p\text{-}\mathrm{CH_3C_6H_4OH}} \xrightarrow{\mathrm{NaOH,\ H_2O}} \underset{85\%}{p\text{-}\mathrm{CH_3C_6H_4OCH_2CH_2{}^{14}CH_2OH}}$$

$$\xrightarrow{\mathrm{SOCl_2,\ pyridine}} \underset{85\%}{p\text{-}\mathrm{CH_3C_6H_4OCH_2CH_2{}^{14}CH_2Cl}} \xrightarrow{\mathrm{NaI}}$$

$$\underset{88\%}{p\text{-}\mathrm{CH_3C_6H_4{-}O{-}CH_2CH_2{}^{14}CH_2I}} \xrightarrow{\mathrm{Me_3N,\ EtOH}}$$

$$\underset{93\%}{[p\text{-}\mathrm{CH_3C_6H_4{-}O{-}CH_2CH_2{}^{14}CH_2\overset{+}{N}Me_3]\ I^-}} \xrightarrow{\mathrm{AgOH,\ H_2O}}$$

$$\underset{83.5\%}{[p\text{-}\mathrm{CH_3C_6H_4{-}O{-}CH_2CH_2{}^{14}CH_2\overset{+}{N}Me_3]\ OH^-}} \xrightarrow[\mathrm{90\text{-}\ 140^\circ C}]{\mathrm{pyrolysis}}$$

$$p\text{-}\mathrm{CH_3C_6H_4{-}O{-}CH_2CH{=}{}^{14}CH_2 + NMe_3}$$

SCHEME 1.

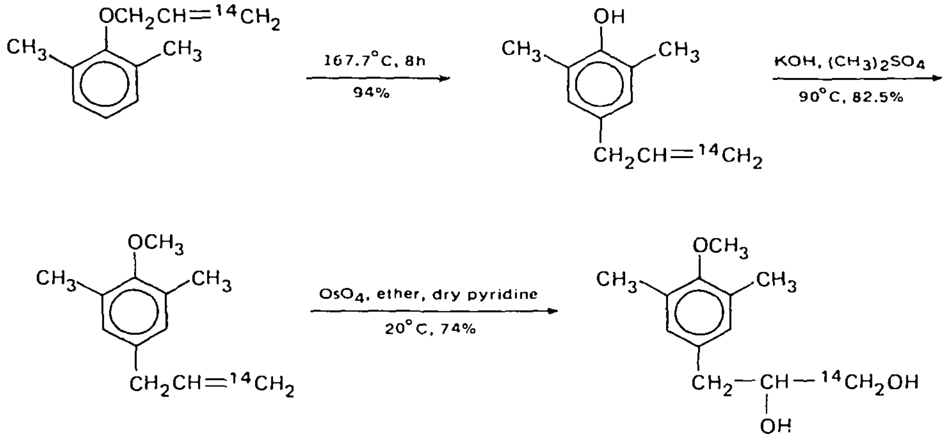
the radioactivity is located in two *ortho* positions, 5.7% in two *meta* positions, 28.9% in the *para* position and less than 2% in the side-chain. These and other observations indicate that the acid-catalysed hydrogen exchange of aromatic compounds is a typical electrophilic substitution reaction.

b. Carbon-14-labelled alkyl phenyl ethers. Allyl-3-^{14}C p*-tolyl ether* and other intermediate *p*-tolyl ethers have been synthesized according to Scheme 1. The starting labelled substrate, 3-chloro-1-propanol-1-^{14}C (1), was obtained in a standard manner by reacting ethylene chlorohydrin with potassium cyanide-^{14}C, hydrolysis of the nitrile, methylation of the 3-chloropropionic-1-^{14}C acid with diazomethane and reduction of methyl 3-chloropropionate-1-^{14}C with lithium aluminium hydride to the ^{14}C-labelled propanol. Oxidation of the obtained ^{14}C-labelled olefin with potassium permanganate gave 3-*p*-tolyloxy-1,2-propanediol-1-^{14}C and *p*-tolyloxyacetic acid (equation 19) (H. Schmid and K. Schmid 1952).

$$p\text{-}CH_3C_6H_4{-}O{-}CH_2CH{=}^{14}CH_2 \xrightarrow{KMnO_4\cdot} p\text{-}CH_3C_6H_4{-}O{-}CH_2CHOH^{14}CH_2OH$$

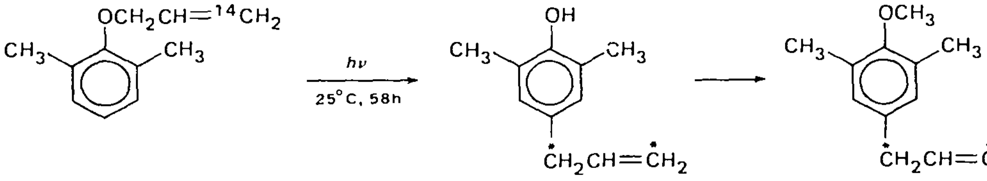
$$+\ p\text{-}CH_3C_6H_4{-}O{-}CH_2COOH \qquad (19)$$

4-Allyl-3-^{14}C-2,6-dimethylanisole was synthesized by heating allyl-3-^{14}C 2,6-xylyl ether in a sealed tube and by subsequent methylation of the obtained phenol with methyl sulphate. Oxidation of the methyl ether with osmium tetroxide yielded 3-(4-methoxy-3,5-xylyl)-1,2-propanediol-1-^{14}C (equation 20) (H. Schmid and K. Schmid 1953).

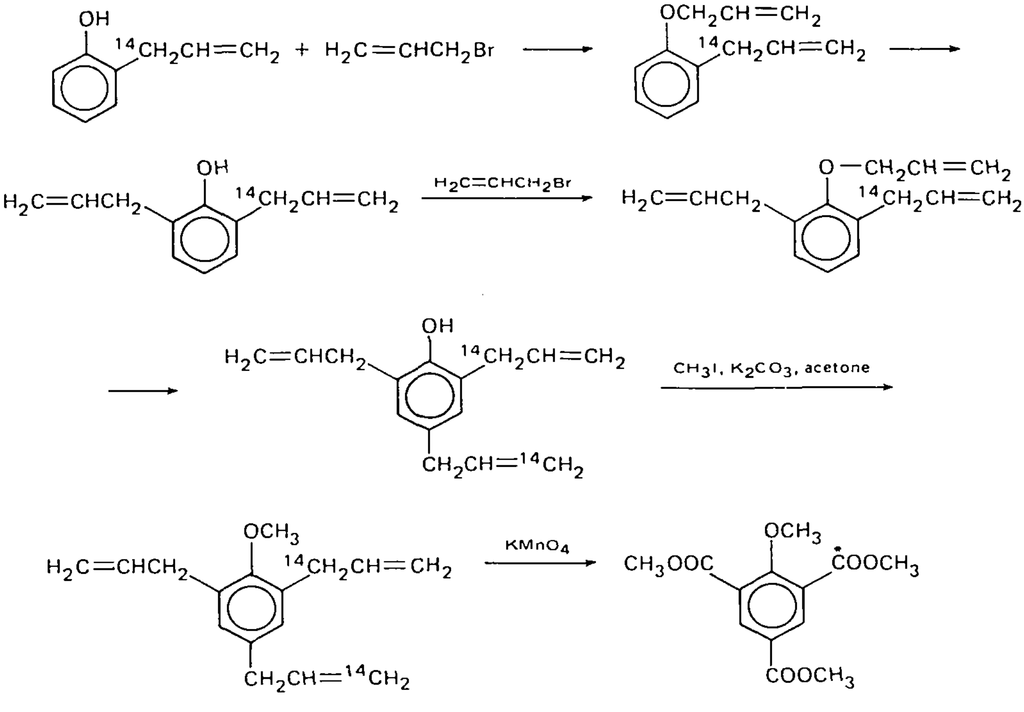

OCH2CH=14CH2
CH3
CH3
167.7°C, 8h
94%
OH
CH3
CH3
CH2CH=14CH2
KOH, (CH3)2SO4
90°C, 82.5%
OCH3
CH3
CH3
CH2CH=14CH2
OsO4, ether, dry pyridine
20°C, 74%
OCH3
CH3
CH3
CH2—CH—14CH2OH
OH

(20)

4-Allyl-1,3-^{14}C$_{1/2}$-2,6-dimethylanisole was obtained by photochemical *para* rearrangement of the allyl-3-^{14}C 2,6-xylyl ether to 4-allyl-1,3-^{14}C$_{1/2}$-2,6-xylenol, which in turn was methylated with methyl sulphate (equation 21) (K. Schmid and H. Schmid 1953). About 53% of the isotopic carbon is located at $C_{(1)}$. The


OCH2CH=14CH2
CH3
CH3
hν
25°C, 58h
OH
CH3
CH3
CH2CH=CH2
OCH3
CH3
CH3
CH2CH=CH2

(21)



SCHEME 2.

mechanism of the rearrangement involves the resonance forms of the free radical: $^{14}\dot{C}H_2-CH_2=CH_2 \longleftrightarrow {}^{14}CH_2=CH-\dot{C}H_2$.

The sequence of reactions given in Scheme 2 illustrates the synthesis of *2-allyl-1-^{14}C -4-allyl-3-^{14}C-6-allylanisole*. 2-Allyl-1-^{14}C-phenol was reacted with allyl bromide. The resultant allyl 2-allyl-1-^{14}C-phenyl ether was mixed with *N,N*-diethylaniline and thermally rearranged at 200°C to 2-allyl-1-^{14}C-6-allylphenol. Allyl 2-allyl-1-^{14}C-6-allylphenyl ether, obtained by heating labelled phenol with allyl bromide and sodium ethoxide in absolute ethanol, was rearranged to the corresponding phenol by heating in diethylaniline and the phenol was methylated with methyl iodide. 70% of the carbon-14 was found at the allyl-1-^{14} C position (K. Schmid, Haegele and H. Schmid 1954).

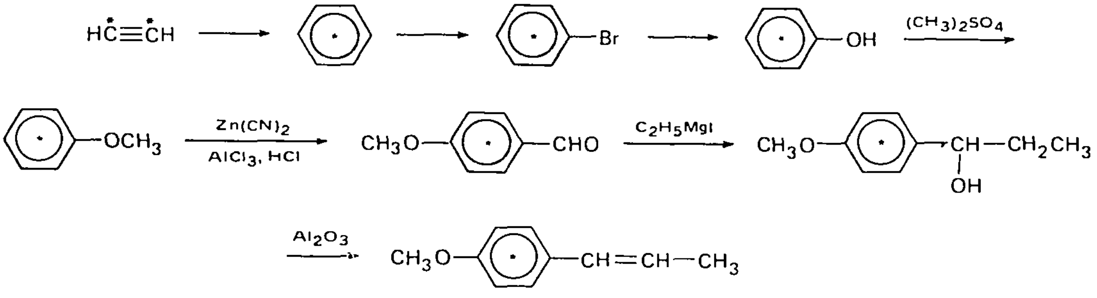
p-*Methoxyphenyl-1-propene-1-^{14}C-3* (*trans*-anethole-3-^{14}C) was obtained in 20% yield as shown in equation (22) (Herbert, Pichat and Langourieux 1974).

$$p\text{-}CH_3OC_6H_4-C\equiv CH \xrightarrow{BuLi} p\text{-}CH_3OC_6H_4-C\equiv CLi \xrightarrow{^{14}CH_3I}$$

$$p\text{-}CH_3OC_6H_4-C\equiv C-{}^{14}CH_3 \xrightarrow{LiAlH_4} CH_3OC_6H_4-CH=CH-\overset{14}{C}H_3 \qquad (22)$$

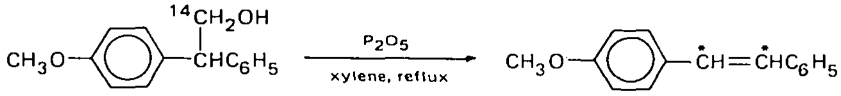
Scheme 3 illustrates the synthesis of uniformly ^{14}C-ring-labelled *trans*- (80%) and *cis*-anethole (ring-^{14}C-u) (20%) (Herbert, Pichat and Langourieux 1974).

4-Methoxystilbene-α,α′-^{14}C$_{1/2}$ was prepared by boiling 2-(*p*-methoxyphenyl)-2-phenylethanol-1-^{14}C with a suspension of phosphorus pentoxide in xylene (equation 23) (Burr and Ciereszko 1952; Bailey and Burr 1953). Degradation of the


HC≡CH
Br
OH
(CH3)2SO4
OCH3
Zn(CN)2
AlCl3, HCl
CH3O
CHO
C2H5MgI
CH—CH2CH3
OH
Al2O3
CH=CH—CH3

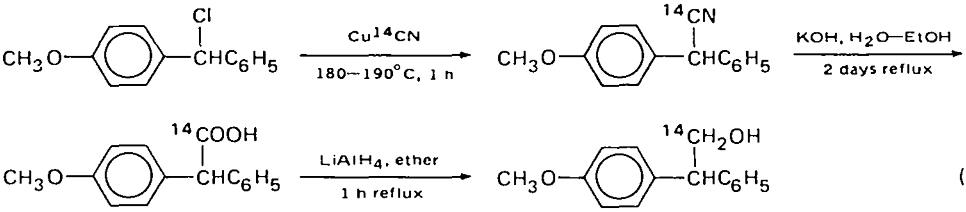
trans + *cis*

SCHEME 3.


14CH2OH
CH3O
CHC6H5
P2O5
xylene, reflux
CH=CHC6H5

(23)

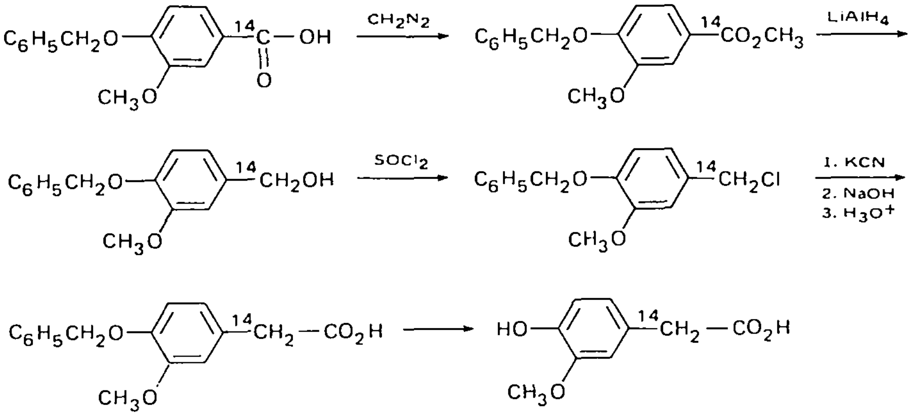
labelled methoxystilbene showed that 95.5% of the activity is located at the carbon adjacent to the *p*-methoxyphenyl group. 2-Phenyl-2-mesityl ethanol-1-^{14}C has been obtained according to equation (24) (Murray and Williams 1958).


Cl
CH3O
CHC6H5
Cu14CN
180–190°C, 1 h
14CN
KOH, H2O—EtOH
2 days reflux
14COOH
LiAlH4, ether
1 h reflux
14CH2OH

(24)

*Di(3,5-di-*t*-butyl-4-hydroxybenzyl-^{14}C) ether* was utilized to synthesize some phenolic antioxidants (Figge 1969).

Several intermediate ^{14}C-labelled alkyl phenyl ethers have been obtained in the course of the synthesis of *homovanillic acid-2-^{14}C* (Scheme 4) (Liebman and coworkers 1971).

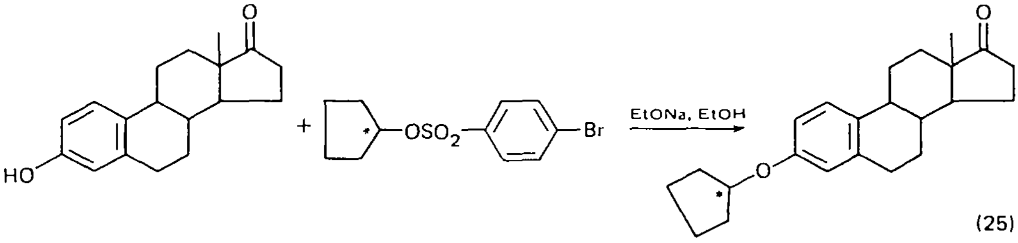

C6H5CH2O
14C—OH
O
CH3O
CH2N2
14CO2CH3
LiAlH4
14CH2OH
SOCl2
14CH2Cl
1. KCN
2. NaOH
3. H3O+
14CH2—CO2H
HO

SCHEME 4.

^{14}C-labelled methyl D*-glucopyranosides* were obtained by heating methyl α- and β-D-hexopyranosides, methyl tetra-*O*-acetyl-α- and -β-D-glucopyranosides and the D-galactose and D-mannose analogues in ^{14}C-labelled methanol containing 1% HCl. Exchange of the methoxyl groups was achieved under these conditions (Swiderski and Temeriusz 1966).

Methyl-^{14}C-bornesitol was synthesized by methylation of 1,4,5,6-tetra-*O*-benzyl-DL-myoinositol with methyl-^{14}C iodide and potassium hydroxide in benzene. Removal of the benzyl substituents from the methylated inositols by hydrogenolysis gave 1-*O*-methyl-^{14}C-DL-myoinositol. In a similar manner methyl-^{14}C-sequoyitol was obtained (Shah and Loewus 1970).

Oestrone-3-cyclopentyl-1-^{14}C ether was obtained by room-temperature reaction of unlabelled oestrone with cyclopentyl-1-^{14}C *p*-bromobenzenesulphonate (equation 25) (Merrill and Vernice 1970).



(25)

B. Synthesis of Labelled Sulphides

1. *Introduction: key compounds*

Labelled thio ethers are usually obtained by a modified Williamson method from potassium or sodium salts of thiols and alkyl halides, or by direct nucleophilic displacement of thiols with alkyl halides (equation 26).

$$R^1{-}S{-}M + R^2{-}X \xrightarrow[-MX]{} R^1{-}S{-}R^2 \tag{26}$$

The key compounds, sulphur-labelled thiols, monosulphides and disulphides have been synthesized according to equations (27)–(29) where RX denotes an alkyl

$$RX + M{-}\overset{*}{S}{-}H \longrightarrow R{-}\overset{*}{S}{-}H + MX \tag{27}$$

$$2\,RX + M_2\overset{*}{S} \longrightarrow R{-}\overset{*}{S}{-}R + 2\,MX \tag{28}$$

$$2\,RX + M_2\overset{*}{S}_2 \longrightarrow R{-}\overset{*}{S}{-}\overset{*}{S}{-}R + 2\,MX \tag{29}$$

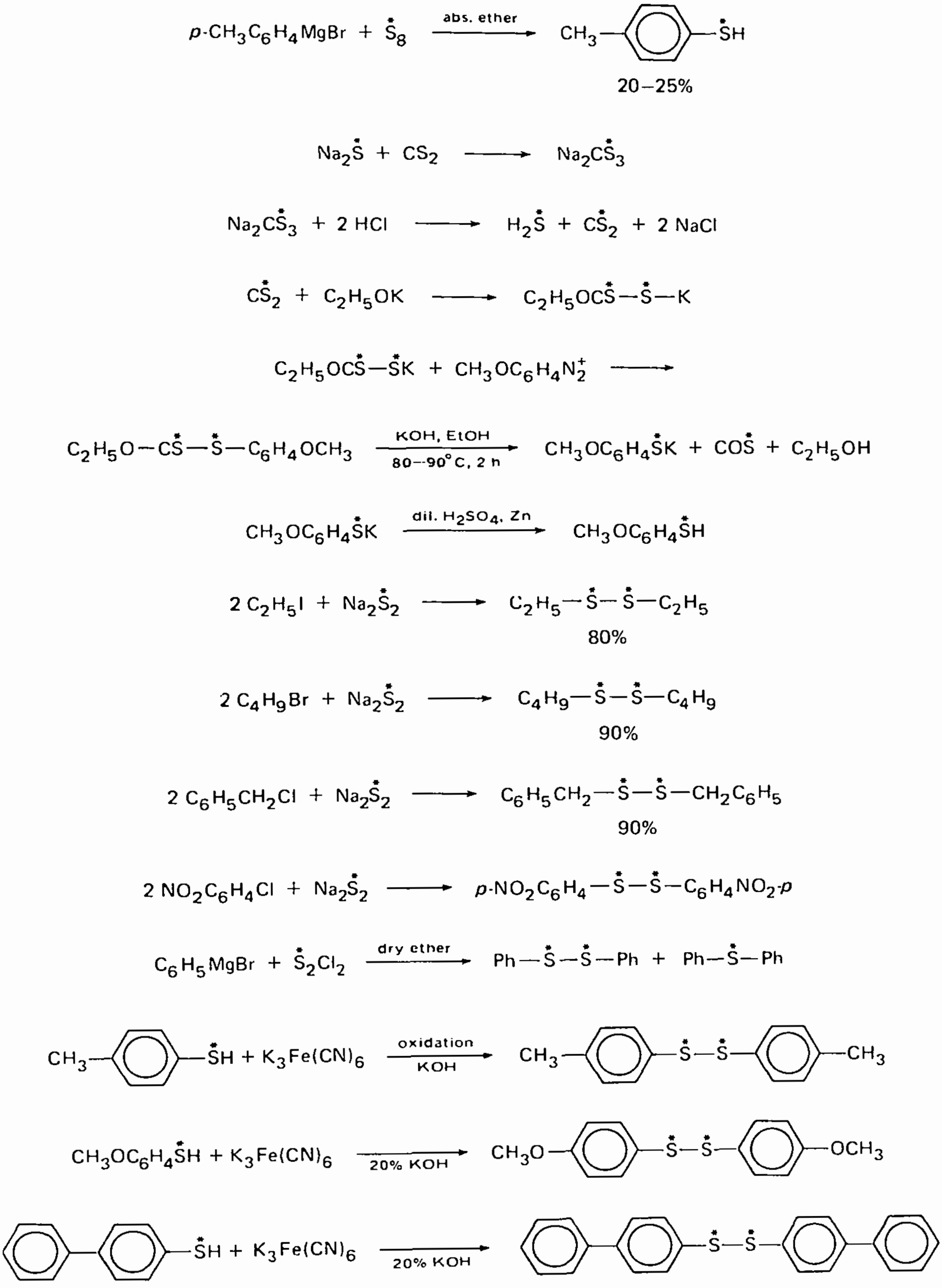
halide and M is a monovalent metal (Na,K etc.). In the case of aromatic compounds X is not labile and ArMgX and diazo compounds are used as substrates of reaction. Thus, numerous ^{35}S-labelled sulphides and disulphides have been obtained (Scheme 5) (Vasil'eva and Gur'yanova 1956).

$$C_4H_9Br + Na\overset{*}{S}H \xrightarrow{C_2H_5OH} C_4H_9\overset{*}{S}H$$

80%

$$C_6H_5CH_2Cl + Na\overset{*}{S}H \xrightarrow{C_2H_5OH} C_6H_5CH_2{-}\overset{*}{S}H$$

75%


abs. ether
20–25%
KOH, EtOH
80–90°C, 2 h
dil. H2SO4, Zn
80%
90%
90%
dry ether
oxidation
KOH
20% KOH
20% KOH

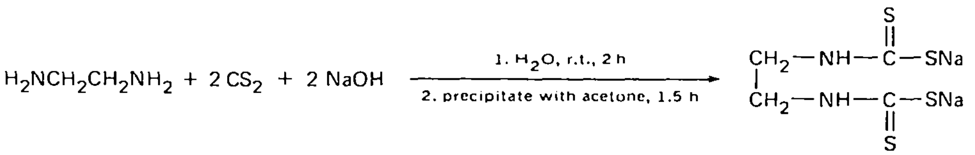
SCHEME 5.

Synthesis of the key compounds, *phosphorus pentasulphide-^{35}S* and *carbon disulphide-$^{35}S_2$* is as shown in equation (30). P_2S_5 was obtained in 89.4% yield by

$$^{35}S \xrightarrow[\text{fused}]{\text{red P}} P_2\overset{*}{S}_5 \xrightarrow[300-325^{\circ}C,\ 7\ h]{CCl_4} C^{35}S_2 \qquad (30)$$

fusing sulphur-35 with red phosphorus under carbon dioxide (Markova and coworkers 1953). P_2S_5 labelled with ^{32}P was obtained by irradiation of crystalline sulphur with reactor neutrons using the reaction $^{32}S(n,p)^{32}P$ (Bebesel and Turcanu 1967). Carbon disulphide-$^{35}S_2$ was synthesized from phosphorus pentasulphide-^{35}S with carbon tetrachloride in a sealed tube (77.3% yield). Labelled carbon disulphide was also synthesized by ^{35}S exchange between carbon disulphide and an aqueous solution of sulphide-^{35}S ions (Edwards, Nesbett and Solomon 1948), by passing sulphur-35 vapours over hot charcoal in a quartz tube (Busing and coworkers 1953) and by direct radiochemical methods (Edwards, Nesbett and Solomon 1948), utilizing the (n,p) reaction with ^{35}Cl to obtain ^{35}S.

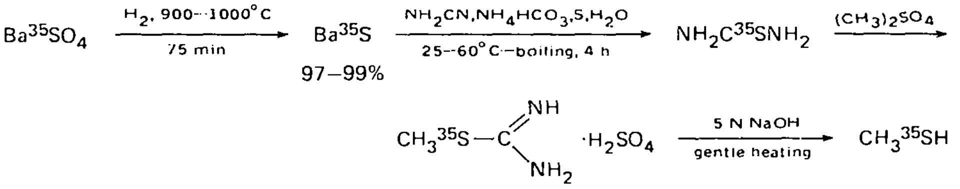
^{14}C-labelled disodium ethylenebisdithiocarbamate was obtained from ethylenediamine and carbon disulphide (equation 31) (Selling, Berg and Besemer 1974).



$$H_2NCH_2CH_2NH_2 + 2\,CS_2 + 2\,NaOH \xrightarrow[\text{2. precipitate with acetone, 1.5 h}]{\text{1. }H_2O\text{, r.t., 2 h}} \begin{array}{l} CH_2-NH-\overset{\overset{\displaystyle S}{\|}}{C}-SNa \\ | \\ CH_2-NH-\underset{\underset{\displaystyle S}{\|}}{C}-SNa \end{array}$$

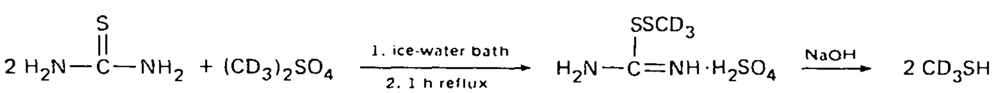
(31)

Methanethiol-^{35}S was synthesized from barium sulphate (equation 32) (Maimind, Shchukina and Zhukova 1952).



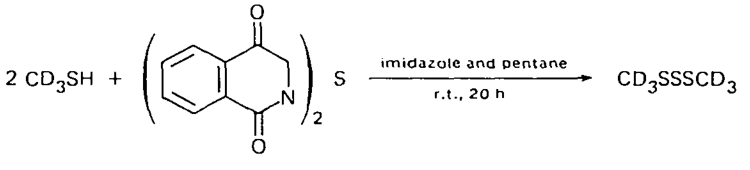
(32)

Methanethiol-d_3 and *dimethyl trisulphide-d_6* have been obtained as shown in equations (33) and (34) (Harpp and Back 1975). Methanethiol-d_3, generated *in situ*



$$2\,H_2N-\overset{\overset{\displaystyle S}{\|}}{C}-NH_2 + (CD_3)_2SO_4 \xrightarrow[\text{2. 1 h reflux}]{\text{1. ice-water bath}} H_2N-\overset{\overset{\displaystyle SSCD_3}{|}}{C}{=}NH\cdot H_2SO_4 \xrightarrow{NaOH} 2\,CD_3SH$$

(33)

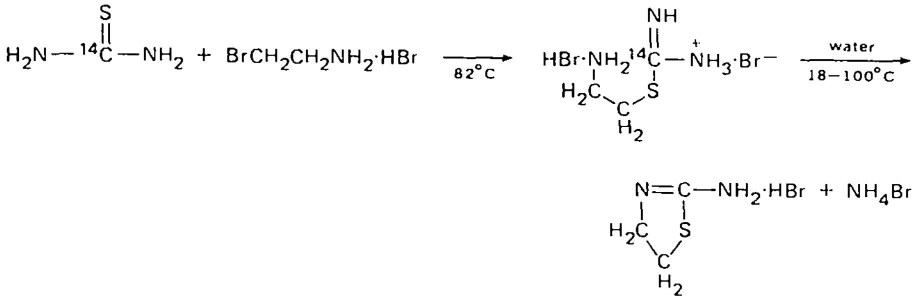


(34)

was passed into a pentane solution of bisphthalimido sulphide, an efficient sulphur-transfer reagent converting thiols to trisulphides.

Dimethyl sulphoxide-d_6 (*DMSO-D_6*) has been used for synthesis of d_3 analogues of methyl-substituted aromatic hydrocarbons by methyl-exchange (Chen, Wolinska-Mocydlarz and Leitch 1970).

S-Aminoethylisothiouronium bromide hydrobromide-^{14}C (AET), one of the most efficient radioprotective substances, was prepared by heating thiourea-^{14}C with 2-bromoethylamine hydrobromide in isopropyl alcohol (equation 35). In



(35)

aqueous solution AET-^{14}C yielded 2-aminothiazoline, (2-AT-^{14}C) (Kronrad and Kozak 1973). In a similar manner, Se-*aminoethylisoselenouronium bromide hydrobromide*-^{75}*Se*, A gamma emitter, suitable for scintigraphic detection of ischaemic heart disease, was prepared by condensation of selenourea-^{75}Se with 2-aminoethyl bromide.

Selenourea-^{75}*Se* was obtained by reduction of the neutron-irradiated SeO_2 to selenium hydride-^{75}Se, which with ammonia and cyanamide yielded the desired labelled compound (Kronrad and Kozak 1973).

Sulphur-35-labelled *methyl isothiocyanate* was obtained directly by irradiating methyl isothiocyanate–CCl_4 mixtures in sealed quartz ampoules in a neutron flux of 10^{11} n/cm^2 s at 50°C for 20–30 hours. 10–15% of the induced radioactivity was found in the form of $CH_3{-}N{=}C{=}^{35}S$ (Dzantiev, Shishkov and Kizan 1968). The mechanism of radioprotection by AET was investigated by Grigorescu and coworkers (1967) and Cier, Maigrot and Nofra (1967).

2. Synthesis of aliphatic sulphides

Addition reaction of hydrogen sulphide and thiols to unsaturated hydrocarbons (Jones and Reid 1938) is a useful method of preparation of *doubly labelled thio ethers* (Kanski, Borkovski and Pluciennik 1970). *Ethyl mercaptan* and *diethyl sulphide doubly labelled with carbon-14 and sulphur-35.* was synthesized as shown in equation (36). ^{35}S-labelled hydrogen sulphide was obtained by reduction of

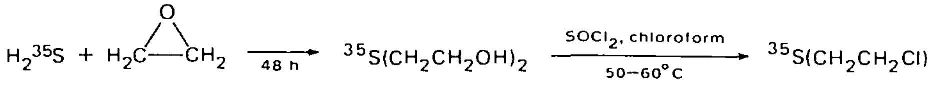
$$\begin{gathered} Ba^{14}CO_3 \xrightarrow[\text{heat}]{\text{metallic Ba}} Ba^{14}C_2 \xrightarrow{H_3O^+} {}^{14}C_2H_2 \xrightarrow[H_2O]{Cr^{++}} \\ {}^{14}C_2H_4 \xrightarrow{H_2{}^{35}S} {}^{14}C_2H_5{}^{35}SH + ({}^{14}C_2H_5)_2{}^{35}S \end{gathered} \tag{36}$$

sulphur-35 with hydrogen in a sealed glass ampoule at 500 °C. High-yield addition of labelled hydrogen sulphide to the olefinic double bond was achieved by heating in an ampoule a mixture of the ethylene and $H_2{}^{35}S$ at 310°C. The yield of $({}^{14}C_2H_5)^{35}S$ rises with increasing pressure of the gas in the ampoule, while the yield of ${}^{14}C_2H_5{}^{35}SH$ passes through a maximum at about 20 atm. Further increase of the pressure of the reacting mixture decreases the yield of ethanethiol, since it adds to a second molecule of ethylene to form diethyl sulphide (equation 37). The separation of the ^{35}S- and ^{14}C-labelled ethanethiol and ethyl sulphide was carried out by preparative gas chromatography. According to earlier investigations

$${}^{14}C_2H_5{}^{35}SH + {}^{14}C_2H_4 \longrightarrow {}^{14}C_2H_5{-}{}^{35}S{-}{}^{14}C_2H_5 \tag{37}$$

(Ipatieff and Friedman 1939) an excess of hydrogen sulphide favoured the production of thiols whereas excess of olefin led to formation of thio ethers. It has also been found that thiols are more reactive than hydrogen sulphide. The above described method should therefore be applicable also to synthesis of isotopic carbon-, hydrogen- and sulphur-labelled higher thiols and thio ethers.

Bis(2-chloroethyl) sulphide-^{35}S has been prepared in two steps (equation 38).



(38)

2,2-Thiodiethanol was obtained in quantitative yield (Bournsnell, Francis and Wormall 1946) and the bis(2-chloroethyl) sulphide-^{35}S in 74% yield. The latter was oxidized to bis(2-chloroethyl) sulphoxide-^{35}S, and further to bis(2-chloroethyl) sulphone-^{35}S (equation 39). Deuterium-labelled mustard gas was obtained by combination of deuteroethylene with sulphur chloride at 60°C. ^{35}S-labelled mustard gas was also obtained (Kronrad 1966) by reacting $Na_2{}^{35}S{\cdot}9H_2O$ with ethylene chlorohydrin and treating the intermediate β,β'-thiodiglycol-^{35} S with $SOCl_2$. *Carbon-14-labelled 2,2′-thiodiethanol-1,1′*-^{14}C was obtained in the reaction (equation 40) (Figge and Voss 1973). Sulphides and elemental sulphur labelled with ^{35}S are usually prepared from neutron-irradiated potassium chloride and by reducing the $Ba^{35}SO_4$ thus prepared with metallic Cr and H_3PO_4 to $H_2{}^{35}S$ (Suarez 1966).

$$^{35}S(CH_2CH_2Cl)_2 \xrightarrow{HNO_3} O^{35}S(CH_2CH_2Cl)_2 \xrightarrow[4-6\ h]{CrO_3,\ H_2SO_4} O_2{}^{35}S(CH_2CH_2Cl)_2 \tag{39}$$

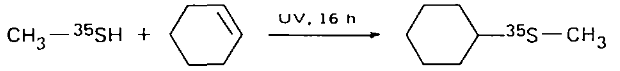
$$2\ ClCH_2{}^{14}CH_2OH + Na_2S \xrightarrow[2\ NaCl]{} (HOCH_2{}^{14}CH_2)_2S \tag{40}$$

Butyl 2-hydroxyethyl sulphide-^{35}S has been synthesized according to equations (41) and (42) (Wood and coworkers 1948).

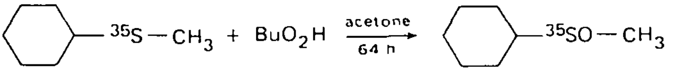
$$C_4H_9MgX + {}^{35}S \xrightarrow{\text{xylene—benzene}} C_4H_9{}^{35}SMgX \xrightarrow{5\ N\ HCl} C_4H_9{}^{35}SH \tag{41}$$

$$C_4H_9{}^{35}SH + ClCH_2CH_2OH \xrightarrow[\text{r.t.}]{1\ N\ NaOH,\ ether} C_4H_9{}^{35}SCH_2CH_2OH \xrightarrow[65^\circ C,\ 24\ h\ \ 44-62\%]{HCl} C_4H_9{}^{35}SCH_2CH_2Cl \tag{42}$$

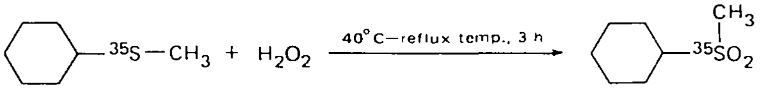
Cyclohexyl methyl sulphide-^{35} *S* was obtained by ultraviolet irradiation of a mixture of an excess of cyclohexene in acetone with methanethiol-^{35}S (equation 43) (Ayrey, Barnard and Moore 1953). The labelled sulphide was oxidized with butyl hydroperoxide at 50°C to *cyclohexyl methyl sulphoxide*-^{35} *S* (equation 44). The same sulphide with hydrogen peroxide yields *cyclohexyl methyl sulphone*-^{35} *S* (86%) (equation 45).



(43)

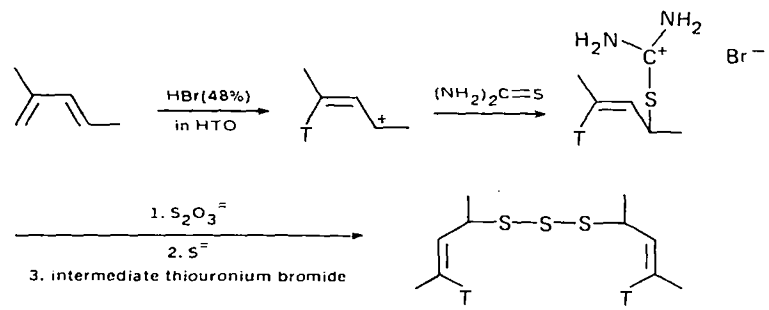


(44)



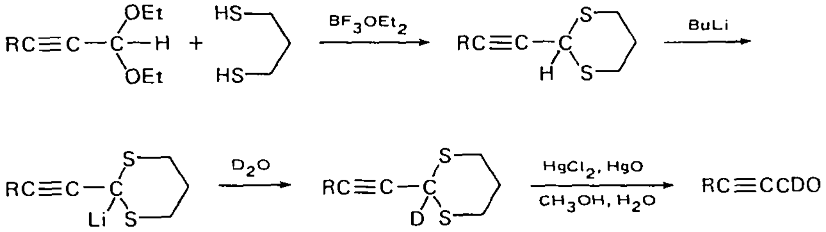
(45)

Tritium-labelled dialkenyl mono-, di- and tri-sulphides, structurally related to sulphur crosslinks in vulcanized natural rubber, have been synthesized from 2-methylpenta-1,3- and -2,4-dienes via the intermediate *S*-(1,3-dimethylbutyl-2-enyl)-[4-$^3H_1$] thiouronium bromide (equation 46) (Ayrey, Barnard and Housman 1974).


HBr(48%)
in HTO
$(NH_2)_2C{=}S$
H_2N
NH_2
C+
Br⁻
S
T
1. $S_2O_3^{=}$
2. $S^{=}$
3. intermediate thiouronium bromide
S—S—S

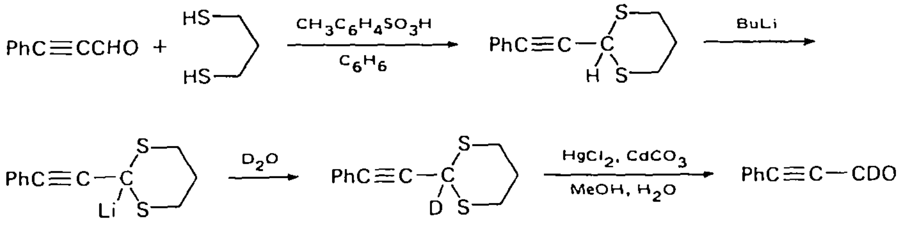
(46)

In the course of the synthesis of α-acetylenic aldehydes, deuterium-labelled *dithianes* have been obtained (equation 47) (Vallet, Janin and Romanet 1968). The

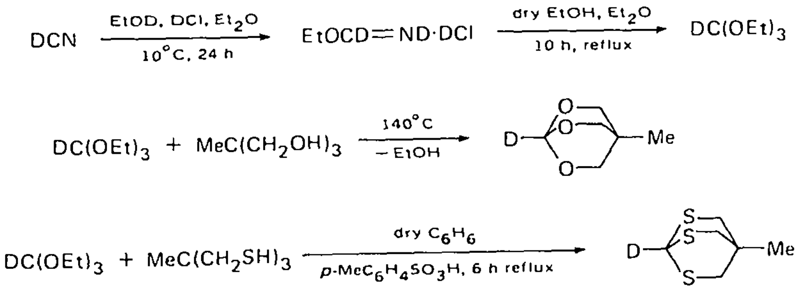

OEt
RC≡C—C—H
OEt
HS
HS
BF_3OEt_2
BuLi
D_2O
$HgCl_2$, HgO
CH_3OH, H_2O
RC≡CCDO

(47)

method was later improved (Vallet, Janin and Romanet 1971) by reacting the aldehyde with 1,3-propanedithiol in the presence of $CH_3C_6H_4SO_3H$ (equation 48).


PhC≡CCHO
HS
HS
$CH_3C_6H_4SO_3H$
C_6H_6
BuLi
D_2O
$HgCl_2$, $CdCO_3$
MeOH, H_2O
PhC≡C—CDO

(48)


DCN
EtOD, DCl, Et_2O
10°C, 24 h
EtOCD=ND·DCl
dry EtOH, Et_2O
10 h, reflux
$DC(OEt)_3$
$DC(OEt)_3$ + $MeC(CH_2OH)_3$
140°C
−EtOH
D
Me
$DC(OEt)_3$ + $MeC(CH_2SH)_3$
dry C_6H_6
p-$MeC_6H_4SO_3H$, 6 h reflux

SCHEME 6.

The reactions shown in Scheme 6 have been used to synthesize *4-methyl-2,6,7-trithiobicyclo[2.2.2] octane* (Oae, Tagaki and Ohno 1964a). In a similar manner, $TC(OEt)_3$ was obtained, which on reaction with EtMgI or PhMgBr gave $EtCT(OEt)_2$ or $PhCT(OEt)_2$. Reaction of $PhCT(OEt)_2$ with EtSH in the presence of anhydrous $ZnCl_2$ or $p\text{-}MeC_6H_4SO_3H$ as catalysts yields $PhCT(SEt)_2$. $EtCD(SEt)_2$ was obtained similarly.

Benzyl 2-hydroxyethyl sulphide-^{35}S was prepared from α-toluenehiol-^{35}S with ethylene chlorhydrin (equation 49) (Wood and coworkers 1948). α-Toluenethiol-^{35}S was prepared by reacting radioactive sulphur with benzylmagnesium bromide (equation 50).

$$C_6H_5CH_2{}^{35}SH + ClCH_2CH_2OH \xrightarrow[\text{ether}]{\text{NaOH}} C_6H_5CH_2{}^{35}SCH_2CH_2OH \tag{49}$$

$$C_6H_5CH_2MgBr + {}^{35}S \longrightarrow C_6H_5CH_2{}^{35}SMgBr \xrightarrow{H_3O^+} C_6H_5CH_2{}^{35}SH \tag{50}$$

Benzyl 2-chloroethyl sulphide-^{35}S was synthesized by treating a mixture of α-toluenethiol-^{35}S and sodium methoxide in methanol with ethylene chloride (equation 51) (Seligman, Rutenburg and Banks 1943).

$$C_6H_5CH_2{}^{35}SH + ClCH_2CH_2Cl \xrightarrow{CH_3ONa,\ CH_3OH} \underset{90\%}{C_6H_5CH_2{}^{35}SCH_2CH_2Cl} \tag{51}$$

Benzyl sulphide-^{35}S was obtained in 92% yield by heating hydrogen sulphide-^{35}S and benzyl chloride with potassium hydroxide in ethyl alcohol and water, in a sealed tube (equation 52) (Henriques and Marguetti 1946). Oxidation of the labelled benzyl sulphide with hydrogen peroxide gives labelled benzyl sulphoxide in 75% yield (equation 53). Further oxidation with chromic acid anhydride in glacial acetic acid produces labelled benzyl sulphone in 23.7% yield. Treatment of sulphoxides, R^1SOR^2, with P_4S_{10} in CH_2Cl_2 at 25°C leads to formation of sulphides R^1SR^2, in 45–99% yield (Still, Hasan and Turnbull 1977).

$$H_2{}^{35}S + C_6H_5CH_2Cl \longrightarrow (C_6H_5CH_2)_2{}^{35}S \tag{52}$$

$$(C_6H_5CH_2)_2{}^{35}S \xrightarrow[\text{r.t., 48 h}]{30\%\ H_2O_2} (C_6H_5CH_2)_2{}^{35}SO \xrightarrow[\text{15 min reflux}]{CrO_3,\ CH_3COOH} (C_6H_5CH_2)_2{}^{35}SO_2 \tag{53}$$

In the synthesis of *deuterated dimethyl(phenethyl)sulphonium bromides* (Blackwell and Woodhead 1975; Blackwell 1976) sodium salts of various phenylacetic acids have been repeatedly refluxed in D_2O until a satisfactory level of deuteration was obtained. The deuterated acids have been converted to the corresponding phenethyl bromides, which with CH_3SH in ethanolic sodium hydroxide yielded substituted phenethyl methyl sulphides. The latter have been converted to the corresponding dimethyl(phenethyl)sulphonium bromides by treatment with methyl bromide in nitromethane (equation 54). In the course of the synthesis of methyl[2,2-$^2H_2$]-*p*-nitrophenethyl sulphide from [2,2-$^2H_2$]-*p*-nitrophenethyl bromide an extensive exchange of deuterium atoms with the hydrogens of the

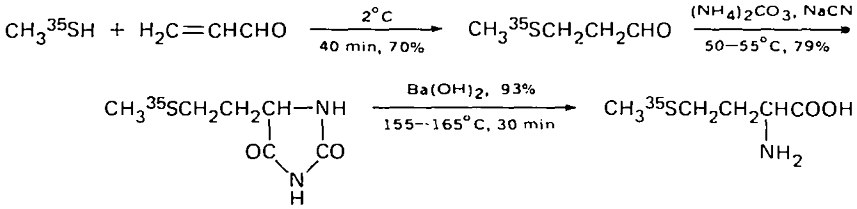
$$ZC_6H_4CD_2CH_2Br + MeSH \xrightarrow{NaOH,\ EtOH} ZC_6H_4CD_2CH_2SMe \xrightarrow[\text{nitromethane}]{MeBr} ZC_6H_4CD_2CH_2\overset{+}{S}Me_2\cdot Br^- \tag{54}$$

$$Z = H,\ p\text{-}MeO,\ p\text{-}Cl,\ m\text{-}Br,\ p\text{-}Ac,\ p\text{-}NO_2$$

solvent has been observed. *(Methylthio-$^{2}H_3$)acetic acid* was prepared in two steps. First methyl-$^{2}H_3$ iodide was added dropwise to mercaptoacetate in a solution of sodium in absolute methanol. The ethyl (methylthio-$^{2}H_3$)acetate so obtained was hydrolysed with a 15% solution of potassium hydroxide, acidified, extracted with ether and purified by distillation (equation 55) (Maw and du Vigneaud 1948).

$$CD_3I + HSCH_2COOC_2H_5 \xrightarrow[-10^{\circ}C]{CH_3ONa,\ CH_3OH} CD_3SCH_2COOC_2H_5 \longrightarrow CD_3SCH_2COOH \qquad (55)$$

Synthesis of methionine-^{35}S was carried out according to equation (56) (Pierson, Giella and Tishler 1948; Maimind, Shchukina and Zhukova 1952). Hydrogen peroxide oxidizes L-methionine-^{35}S, dissolved in concentrated hydrochloric acid and methanol to L-methionine-^{35}S sulphoxide in 95% yield (equation 57). In an early study (Seligman, Rutenburg and Banks 1943) methionine-^{35}S was prepared in 21% yield from methyl iodide and 2-amino-4-mercaptobutyric-^{35}S acid, which in turn was obtained by reduction of 2-amino-4-(benzylthio)butyric-^{35}S acid with sodium in refluxing butanol (equation 58).



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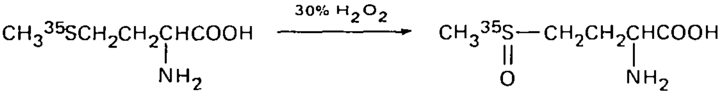
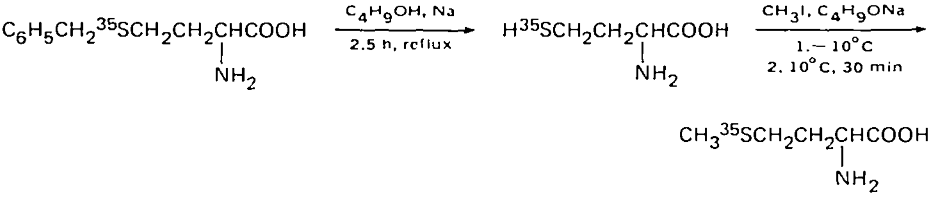
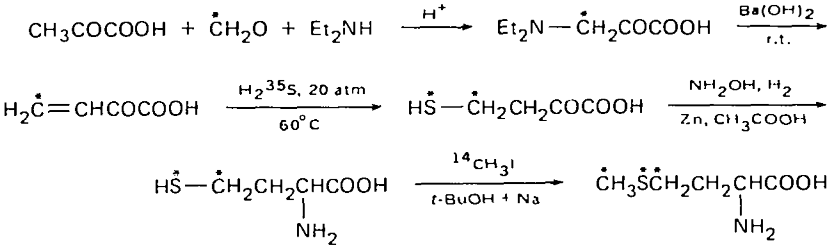


$$CH_3{}^{35}SCH_2CH_2\underset{NH_2}{\underset{|}{C}}HCOOH \xrightarrow{30\%\ H_2O_2} CH_3{}^{35}\underset{O}{\underset{\|}{S}}—CH_2CH_2\underset{NH_2}{\underset{|}{C}}HCOOH \qquad (57)$$



$$C_6H_5CH_2{}^{35}SCH_2CH_2\underset{NH_2}{\underset{|}{C}}HCOOH \xrightarrow[2.5\ h,\ reflux]{C_4H_9OH,\ Na} H^{35}SCH_2CH_2\underset{NH_2}{\underset{|}{C}}HCOOH \xrightarrow[2.\ 10^{\circ}C,\ 30\ min]{CH_3I,\ C_4H_9ONa\quad 1.-10^{\circ}C} CH_3{}^{35}SCH_2CH_2\underset{NH_2}{\underset{|}{C}}HCOOH \qquad (58)$$

^{35}S- and ^{14}C-labelled methionine has been prepared in 17% yield according to equation (59) (Samochocka and Kowalczyk 1970).



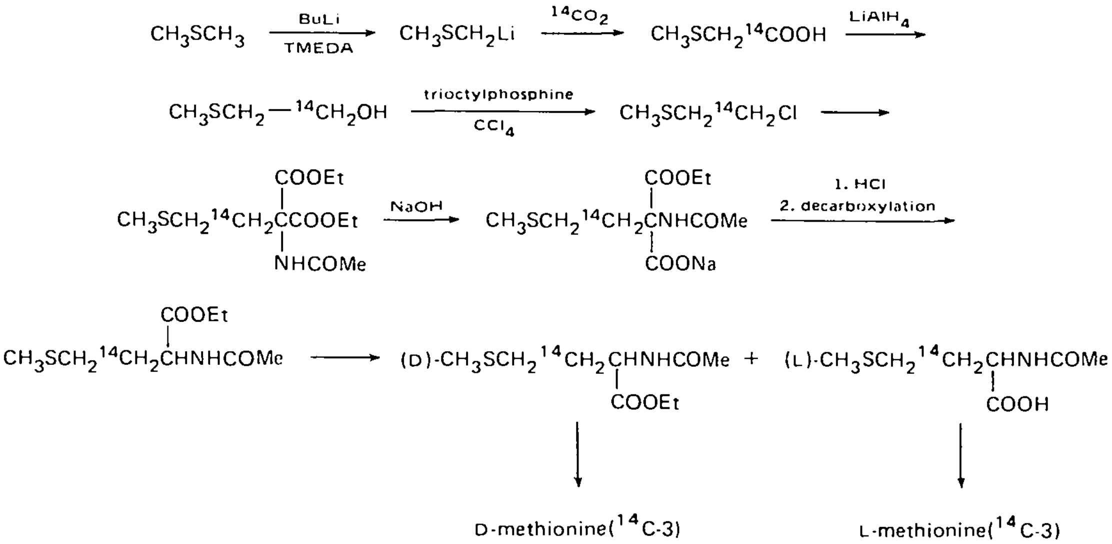
$$CH_3COCOOH + \overset{*}{C}H_2O + Et_2NH \xrightarrow{H^+} Et_2N—\overset{*}{C}H_2COCOOH \xrightarrow[r.t.]{Ba(OH)_2}$$

$$H_2\overset{*}{C}=CHCOCOOH \xrightarrow[60^{\circ}C]{H_2{}^{35}S,\ 20\ atm} H\overset{*}{S}—\overset{*}{C}H_2CH_2COCOOH \xrightarrow[Zn,\ CH_3COOH]{NH_2OH,\ H_2} \qquad (59)$$

$$H\overset{*}{S}—\overset{*}{C}H_2CH_2\underset{NH_2}{\underset{|}{C}}HCOOH \xrightarrow[t\text{-}BuOH + Na]{^{14}CH_3I} \overset{*}{C}H_3\overset{*}{S}\overset{*}{C}H_2CH_2\underset{NH_2}{\underset{|}{C}}HCOOH$$

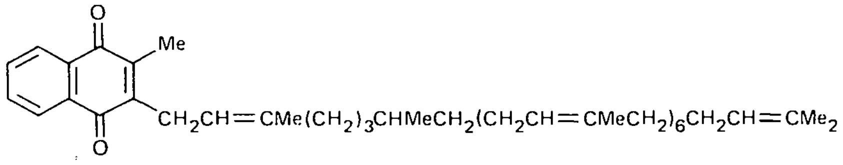
Methionine(^{14}C-3) has been obtained in an elegant reaction sequence: (Scheme 7) (Pichat and Beaucourt 1974).

^{35}S-labelled methionine has been used for selective labelling of milk proteins. (Pereira, Harper and Gould 1966). Incubation of *Mycobacterium phlei* cells with


BuLi
TMEDA
¹⁴CO₂
LiAlH₄
trioctylphosphine
CCl₄
NaOH
1. HCl
2. decarboxylation
D-methionine(¹⁴C-3)
L-methionine(¹⁴C-3)

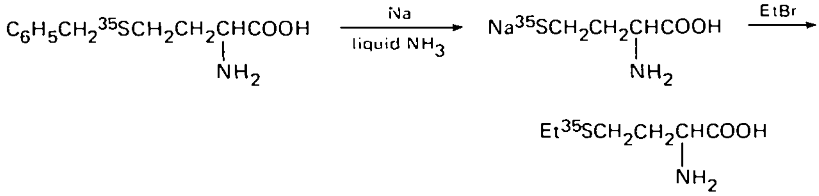
SCHEME 7.

^{14}C and tritium double-labelled L-methionine led to the formation of double-labelled dihydromenaquinone (2) with the $^{14}C/^{3}H$ ratio identical to that of methionine (Scherrer and Azerad 1970).



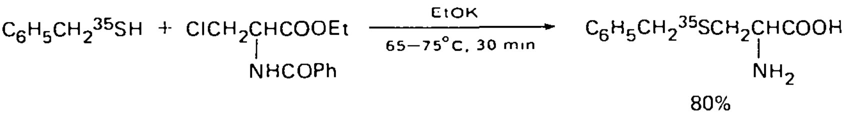
(2)

Ethionine-^{35}S was prepared in 75% yield by reduction of 2-amino-4(benzylthio)butyric-^{35}S acid with sodium in liquid ammonia and treating the intermediate sodium salt with ethyl bromide (equation 60) (Stekol and Weiss 1950).

 (60)

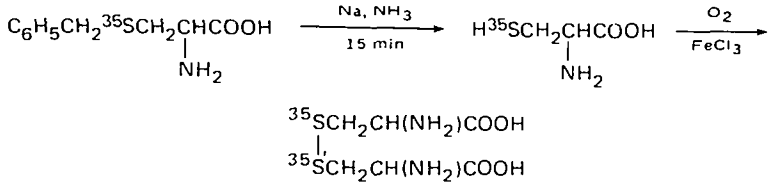
$$\underset{\displaystyle NH_2}{C_6H_5CH_2{}^{35}SCH_2CH_2CHCOOH} \xrightarrow[\text{liquid } NH_3]{Na} \underset{\displaystyle NH_2}{Na^{35}SCH_2CH_2CHCOOH} \xrightarrow{EtBr} \underset{\displaystyle NH_2}{Et^{35}SCH_2CH_2CHCOOH} \qquad (60)$$

S-*Benzylcysteine* was synthesized from α-toluenethiol-^{35}S and ethyl 2-benzamido-3-chloropropionate (equation 61) (Melchior and Tarver 1947).

 (61)

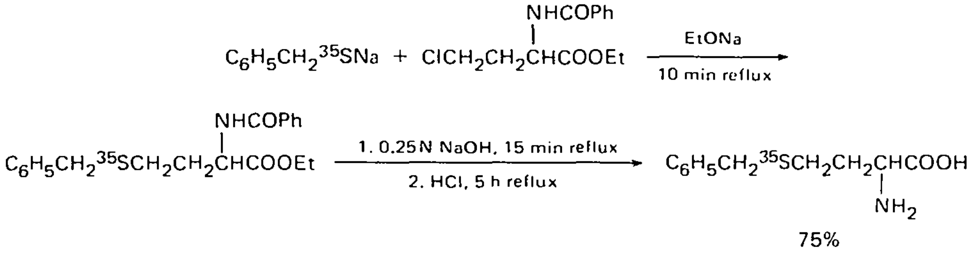
$$C_6H_5CH_2{}^{35}SH + \underset{\displaystyle NHCOPh}{ClCH_2CHCOOEt} \xrightarrow[65-75^{\circ}C,\ 30\ min]{EtOK} \underset{\displaystyle \underset{80\%}{NH_2}}{C_6H_5CH_2{}^{35}SCH_2CHCOOH} \qquad (61)$$

3-(Benzylthio)alanine was reduced with sodium in liquid ammonia to *cysteine-*^{35}S, which in turn was oxidized with air, in the presence of ferric chloride, to *cysteine-*$^{35}S_2$ in 75% yield (equation 62).



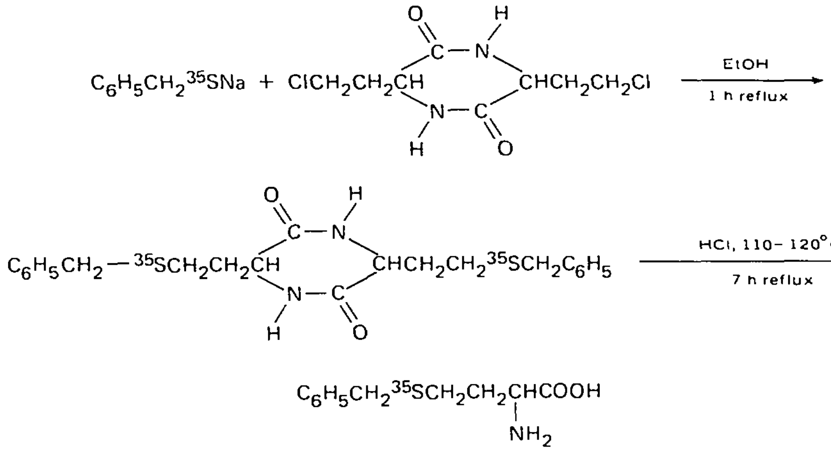
$$\underset{\displaystyle NH_2}{C_6H_5CH_2{}^{35}SCH_2CHCOOH} \xrightarrow[15\ \text{min}]{Na,\ NH_3} \underset{\displaystyle NH_2}{H^{35}SCH_2CHCOOH} \xrightarrow[FeCl_3]{O_2} \begin{array}{l} {}^{35}SCH_2CH(NH_2)COOH \\ | \\ {}^{35}SCH_2CH(NH_2)COOH \end{array} \qquad (62)$$

S-Benzylhomocysteine-^{35}S, used in the synthesis of labelled methionine, ethionine and other amino acids containing sulphide bonds, has been prepared from sodium α-toluenethiolate-^{35}S with ethyl 2-benzamido-4-chlorobutyrate (equation 63) (Tarver and Schmidt 1942). Reaction of sodium benzylthiolate-^{35}S with



$$C_6H_5CH_2{}^{35}SNa + \overset{\displaystyle NHCOPh}{ClCH_2CH_2CHCOOEt} \xrightarrow[10\ \text{min reflux}]{EtONa} \overset{\displaystyle NHCOPh}{C_6H_5CH_2{}^{35}SCH_2CH_2CHCOOEt} \xrightarrow[2.\ HCl,\ 5\ h\ \text{reflux}]{1.\ 0.25N\ NaOH,\ 15\ \text{min reflux}} \underset{\displaystyle NH_2}{C_6H_5CH_2{}^{35}SCH_2CH_2CHCOOH}\ \ 75\% \qquad (63)$$

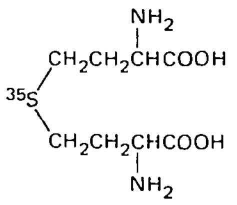
3,6-bis(2-chloroethyl)-2,5-piperazinedione in absolute ethanol and hydrolysis of the intermediate diketopiperazine also gives *S*-benzyl-DL-homocysteine-^{35}S (equation 64) (Wood and Gutmann 1949). The L-isomer was removed from the DL mixture by three consecutive recrystallizations after addition of a ten-fold excess of unlabelled *S*-benzyl-D-homocysteine to the labelled product.



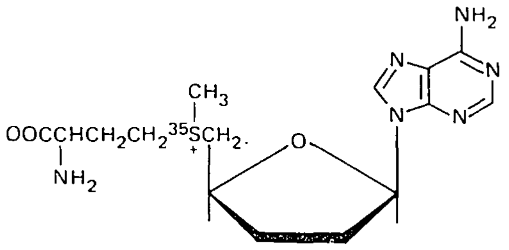
(64)

Reaction of *S*-benzylhomocysteine and 3,6-bis(2-chloroethyl)-2,5-piperazinedione with liquid ammonia and sodium yields *homolanthionine-*^{35}S (3) (Stekol and Weiss 1949).

^{35}*S-adenosylmethionine* (4), important in transmethylation and methionine biosynthesis, was isolated in useful yields from yeast cells cultivated in a medium



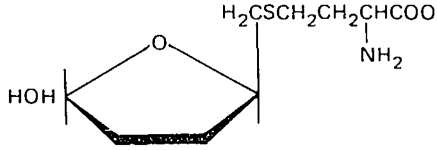
(3)



(4)

containing $^{35}SO_4^{2-}$ (Schlenk and Zydek 1966). *S*-Adenosylmethionine ^{15}N-labelled in the adenine part has been obtained by yeast biosynthesis in the presence of $^{15}NH_4^+$ as a source of isotopic nitrogen (Zappia and coworkers 1968).

S-*Ribosyl*-L-*homocysteine* (5) labelled in specific moieties has been prepared by



(5)

enzymatic hydrolysis of the glycosyl bond of *S*-adenosyl-L-homocysteine labelled with ^{35}S or tritium, yielding adenine and *S*-ribosylhomocysteine (Duerre and Miller 1968).

S-*Adenosylhomocysteine* has been synthesized enzymatically from adenosine and L-homocysteine by *S*-adenosyl-L-homocysteine hydrolase from rat liver (Duerre and Miller 1968).

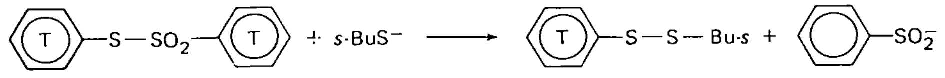
3. *Synthesis of aromatic and heterocyclic sulphides and disulphides*

Deuterium-labelled thioanisoles, $PhSCD_3$, and thioanisoles labelled with deuterium in *o*-,*m*- or *p*-position of the ring have been synthesized by methylation of PhSH with $(CD_3)_2SO_4$ or decomposition of $MeSC_6H_4MgBr$ isomers with D_2O (Shatenshtein, Rabinovich and Pavlov 1964a,b).

Ph^{35}*SPr* was prepared in 50–60% yield by treating PhMgBr with ^{35}S, hydrolysing $Ph^{35}SMgBr$, and alkylating Ph^{35} SNa with PrBr (equation 65) (Fischer, Reihard and Schmidt 1971).

$$\begin{gathered} PhBr + Mg \longrightarrow PhMgBr \xrightarrow{^{35}S} Ph^{35}SMgBr \longrightarrow Ph^{35}SH \longrightarrow \\ Ph^{35}SNa \xrightarrow{PrBr} Ph^{35}SPr \end{gathered} \tag{65}$$

A radical acceptor, *phenyl* ^{3}*H*-s-*butyl disulphide* was obtained by Wilzbach tritium irradiation of unlabelled phenyl benzenethiosulphonate followed by the reaction of the radioactive product with *s*-butanethiol in sodium ethoxide solution (equation 66) (Ayrey 1966).



(66)

Phenyl s-*butyl* $^{35}S_1$-*disulphide* was also synthesized in 20% yield, using elemental sulphur-35 (equations 67 and 68).

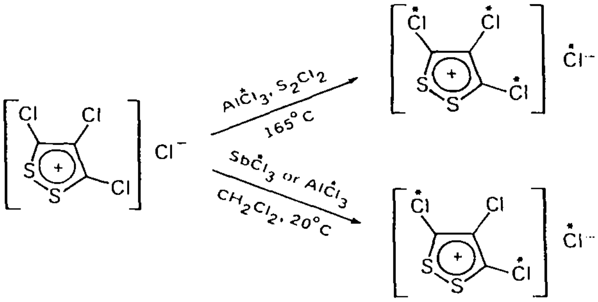
$$s\text{-BuMgBr} + {}^{35}\text{S} \longrightarrow s\text{-Bu}^{35}\text{SH} \qquad (67)$$

$$s\text{-Bu}^{35}\text{S}^- + \text{PhS—SO}_2\text{Ph} \longrightarrow s\text{-Bu—}^{35}\text{S—SPh} + \text{PhSO}_2^- \qquad (68)$$

Phenyl ^3H-s-*butyl* $^{35}S_1$-*disulphide* was also obtained.

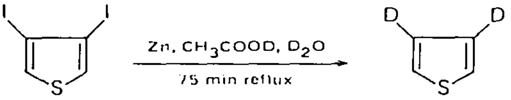
p-MeC$_6$H$_4$SO$_2$^{35}SC$_6$H$_4$NO$_2$-p was obtained by decomposition of p-MeC$_6$H$_4$SO$_2$-S^{35}SC$_6$H$_4$NO$_2$-p. The reaction of PPh$_3$ with ^{35}S-labelled p-toluenesulphonyl o- and p-nitrophenyl disulphides showed that the central sulphur atom of these sulphonyl disulphides was removed (Abe, Nakabayashi and Tsurugi 1971).

3,4,5-Trichloro-1,2-dithiolium chloride-(3,5-^{36}*Cl)* and *-(3,4,5-*^{36}*Cl)* have been synthesized by exchange reactions between 3,4,5-trichloro-1,2-dithiolium chloride and AlCl$_3$-(^{36}Cl) or SbCl$_3$-(^{36}Cl) (equation 69) (Boberg, Wiedermann and Kresse 1974).



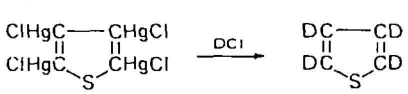
(69)

3d-Thiophene, *3,4-d*$_2$*-thiophene* and *tetradeuterothiophene* have been prepared by boiling under reflux the compound to be deuterated (3-iodothiophene, 3,4-diiodothiophene or tetraiodothiophene), zinc dust and a solution of CH$_3$COOD in D$_2$O (equation 70) (Bak 1956). Thiophene-d$_4$ was also synthesized by heating



(70)

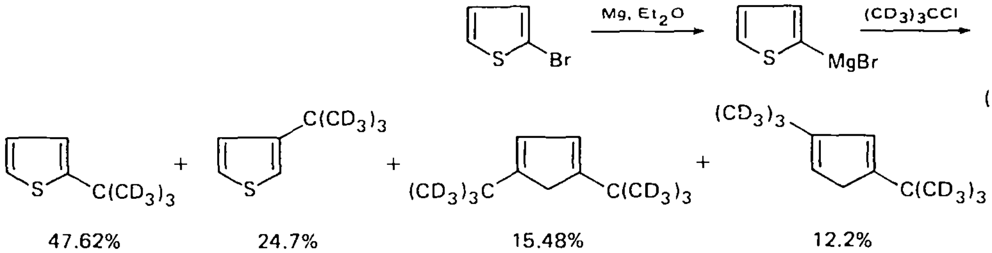
tetrakis(chloromercuri)thiophene with hydrochloric acid-d (equation 71) (Steinkopf and Boëtius 1940). Partially deuterated thiophenes have also been prepared by



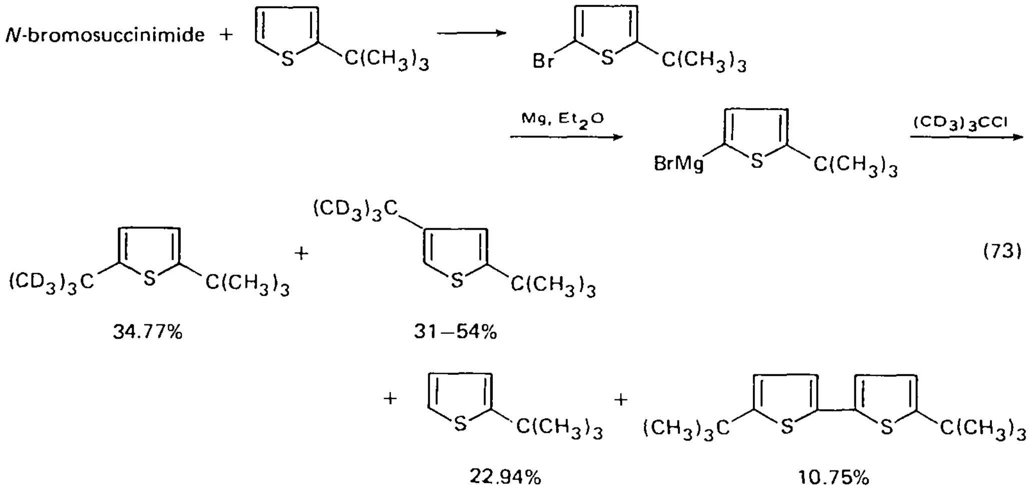
(71)

treatment of the corresponding chloromercuri compounds with deuterium chloride (Schreiner 1951). Fully deuterated thiophene was obtained by exchange with 69% aqueous sulphuric acid-d$_2$ (Schreiner 1951).

Deuterium-labelled *mono-*t*-butylthiophenes* and *di-*t*-butylthiophenes* have been synthesized by treating 2-thienylmagnesium bromide (equation 72) and 5-t-butyl-2-thienylmagnesium bromide with t-butyl-d$_9$ chloride (Fowler and Higgins 1970). Reaction of 5-t-butyl-2-thienylmagnesium bromide with t-butyl-d$_9$ chloride yielded 2,4-di(t-butyl-4-d$_9$)thiophene and 2,5-di(t-butyl-5-d$_9$)thiophene (equation 73). The labelled t-butylthiophenes have been separated by preparative gas chromatography.

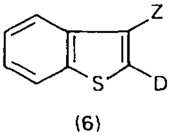

Mg, Et$_2$O
(CD$_3$)$_3$CCl
47.62%
24.7%
15.48%
12.2%

(72)

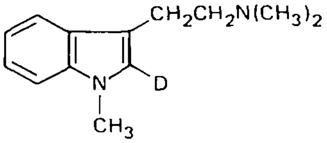

N-bromosuccinimide
Mg, Et$_2$O
(CD$_3$)$_3$CCl
34.77%
31–54%
22.94%
10.75%

(73)

Deuterium and tritium have been introduced into the 2-position of *benzo(b)thiophene* (6) and *1-methylindole* (7) analogues of biologically active



(6)



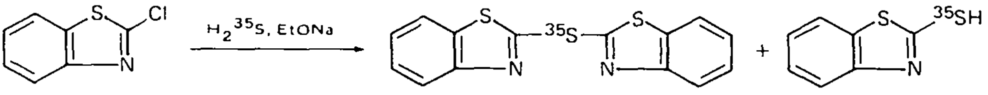
(7)

Z = $CH_2CH_2NH_2$, CH_2COOH, $CH_2CH_2N(CH_3)_2$

indole derivatives by metalation of the 2-position of these heterocycles with *n*-butyllithium and subsequent reaction with ^2H_2O or ^3H_2O (Bosin and Rogers 1973).

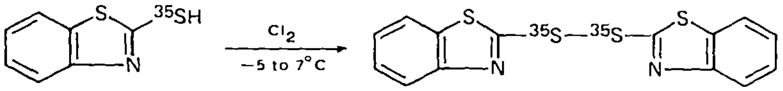
Investigation of the uncatalysed isotope exchange between *2,3-dimethylbenzothiazolium iodide* and D_2O revealed that deuteration took place exclusively at the methyl group in the 2-position (Bologa and coworkers 1967).

2,2'-Thio-^{35}S-bisbenzothiazole was prepared in 20–25% yield from 2-chlorobenzothiazole with hydrogen sulphide-^{35}S dissolved in a solution of sodium ethylate in ethanol (equation 74). The yield of the second product, 2-mercapto-^{35}S-benzothiazole, was 60–65% (Gur'yanova and Kaplunov 1954).


H$_2$^{35}S, EtONa

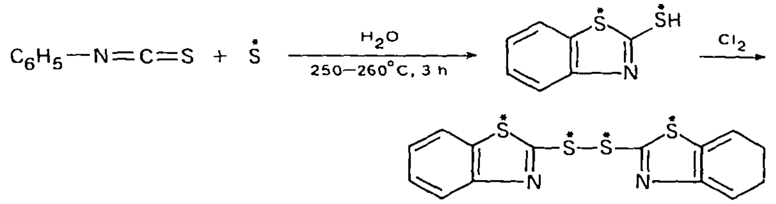
(74)

2,2'-Dithio-$^{35}S_2$-bisbenzothiazole was obtained by passing chlorine through 2-mercapto-^{35}S-benzothiazole (equation 75) (Gur'yanova and Kaplunov 1954).



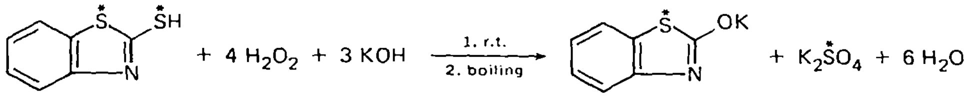
(75)

Uniformly labelled 2-mercaptobenzothiazole-$^{35}S_2$ was obtained in 80–85% yield by heating a mixture of phenyl isothiocyanate, sulphur-35 and water in a sealed tube (equation 76).



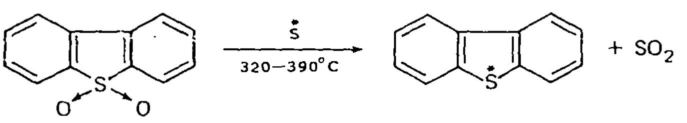
(76)

Quadruply labelled 2,2'-bis(benzothiazolyl) disulphide was obtained by oxidation of 2-mercaptobenzothiazole-$^{35}S_2$ with chloride. The uniform distribution of sulphur in 2-mercaptobenzothiazole-$^{35}S_2$ was revealed by oxidizing it with hydrogen peroxide and determining the activity of the degradation products (equation 77). Similarly it has also been shown that at 250–260° sulphur-35 exchange reaction takes place.



(77)

Sulphur-35-labelled dibenzothiophene was synthesized in 31% yield by heating a mixture of labelled sulphur with dibenzothiophene-5,5-dioxide under dry nitrogen (equation 78) (Brown and coworkers 1951). Dibenzothiophene-^{35}S was the starting material in the synthesis of sulphur-35-labelled carcinogenic compounds, e.g., *3-acetaminodibenzothiophene-^{35}S* was obtained in four steps with an overall yield of about 50% (equation 79) (Brown, Christiansen and Sandin 1948).

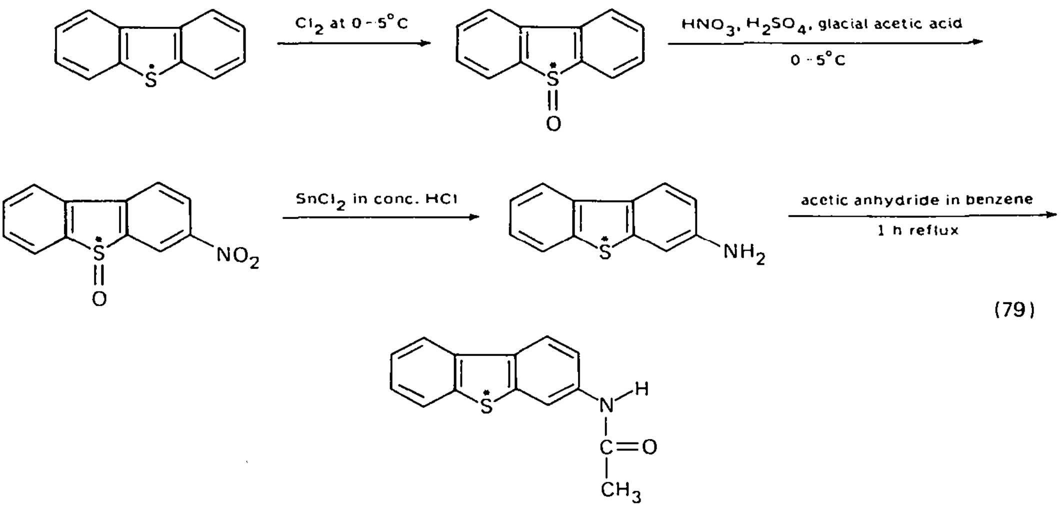


(78)

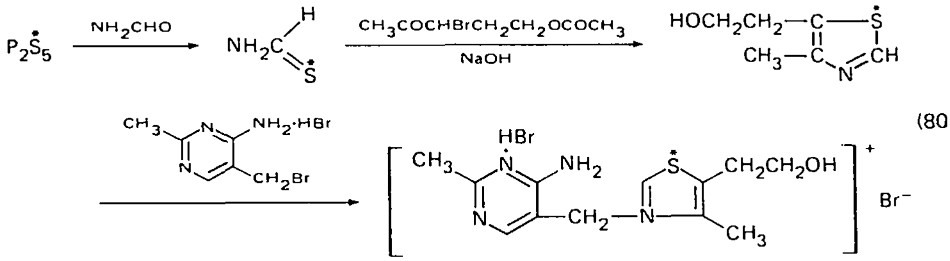
Vitamin B_1 labelled with ^{35}S has been synthesized according to equation (80) (Markova and coworkers 1953).

^{35}S-labelled thioxanthine, thioguanine and *2-thiouracil* have been obtained by exchange with radiosulphur in pyridine solution at 116°C or with molten ^{35}S at 200°C. In the case of 2-thiouracil a much higher yield (86%) has been achieved by heating the exchanging compounds in naphthalene (Chiotan and Zamfir 1968).

3,5-Disubstituted tetrahydro-1,3,5-thiadiazine-2-thiones labelled with ^{35}S have been prepared by direct exchange of sulphur atoms of thiadiazines with elemental sulphur-35 in xylene at 140°C (mainly the thione sulphur should have been replaced). In thiadiazines obtained from 4-bromophenyl isothiocyanate-^{35}S, $4\text{-BrC}_6H_4NC^{35}S$, both sulphur atoms are radioactive (Augustin and coworkers 1971). 3-Benzyl-5-carboxymethyl-^{14}C-tetrahydro-1,3,5-thiadiazine-2-thione was synthesized from benzylamine, sodium carbonate, carbon disulphide, formaldehyde and glycine-^{14}C.



(79)



(80)

^{35}*S-labelled aromatic thio ethers* can be obtained in high yield by reacting halogenated aromatic compounds with alkali metal thiophenolates in the presence of an active solvent at elevated (160–260°C) temperatures (Monsanto Company 1970), by gas-phase reaction of RCl with H_2S at 430–600°C and by liquid-phase reaction of RBr with H_2S in an inert solvent at 180–230°C (Voronkov and coworkers 1977; Irkutsk Institute of Organic Chemistry 1976).

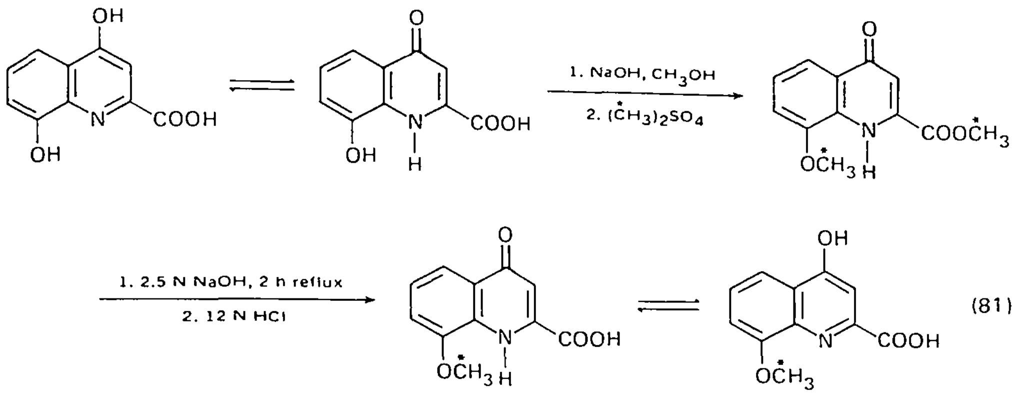
C. Synthesis of Ethers and Thio Ethers Used in Biology, Medicine and Agriculture

During the last decade the main efforts of synthetic radiochemists have been directed to the preparation of radioactive drugs and biologically active substances. In this section recent syntheses of such labelled compounds containing ether and sulphide bonds are briefly reviewed.

1. Compounds containing the ether bond

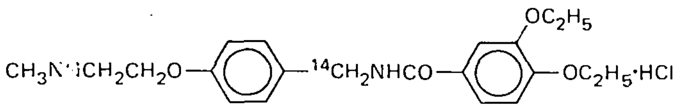
The *8-methyl ether of xanthurenic acid-methoxy-^{14}C*, which has been shown to have carcinogenic activity, was synthesized by selective *o*-methylation of the 8-hydroxyl group of xanthurenic acid (equation 81) (Lower and Bryan 1968).

The antiemetic compound, *N-[4-(2-dimethylaminoethoxy)benzyl-α-^{14}C]-3,4,5-trimethoxybenzamide hydrochloride*, has been synthesized in 29% yield according to Scheme 8 (Wineholt and coworkers 1970). The same synthetic route has been used to prepare *N*-[4-(2-benzylmethylaminoethoxy)benzyl-α-^{14}C]-3,4-diethoxy-



(81)

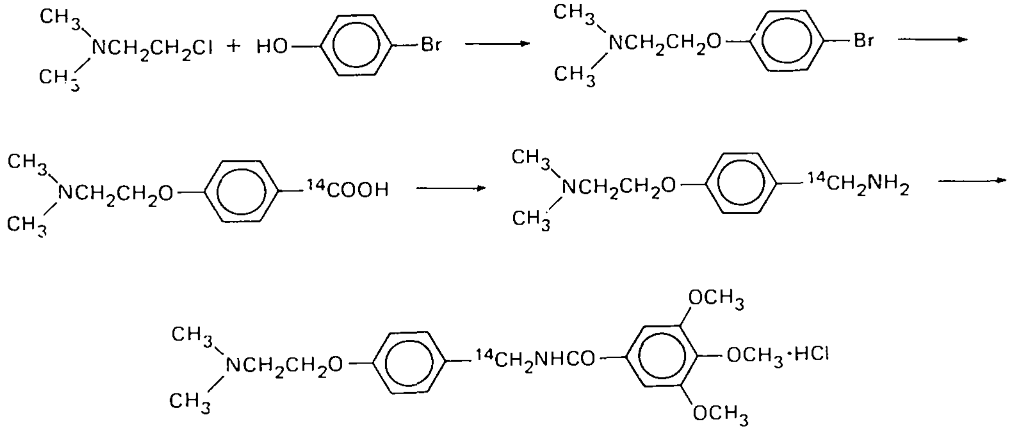
benzamide, which after debenzylation furnished N-*[4-(2-methylaminoethoxy)-benzyl-α-^{14}C]-3,4-diethoxybenzamide hydrochloride* (8).



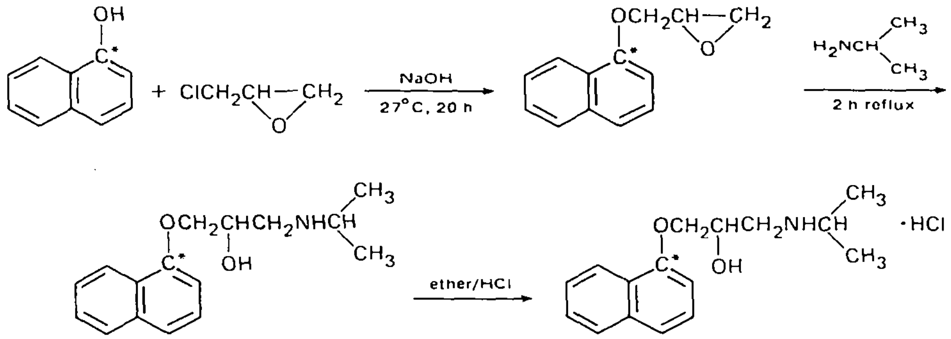
(8)

Several other compounds of potential biological interest containing –O– or –S– bonds, such as morphine derivatives (Lane, McCoubrey and Peaker 1966), *d,l*-3(2′-furyl)alanine (Tolman, Hanuš and Vereš 1968), *p*-methoxyphenylacetaldehyde oxime and *p*-hydroxyphenylacetaldehyde oxime (Shiefer and Kindl 1971), phenoxyacetic acid and promethazine (Telc, Brunfelter and Gosztonyi 1972) have also been labelled with carbon-14 or tritium.

Carbon-14- and tritium-labelled 1-isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride, '^{14}C-propranolol hydrochloride', an adrenergic blocking agent, has been obtained by condensing 1-naphthol-1-^{14}C with epichlorohydrin (equation 82) (Burns 1970). Propranolol has been used for the treatment of cardiac arrythmias,



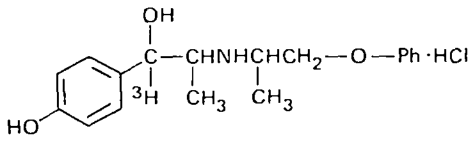
SCHEME 8.



(82)

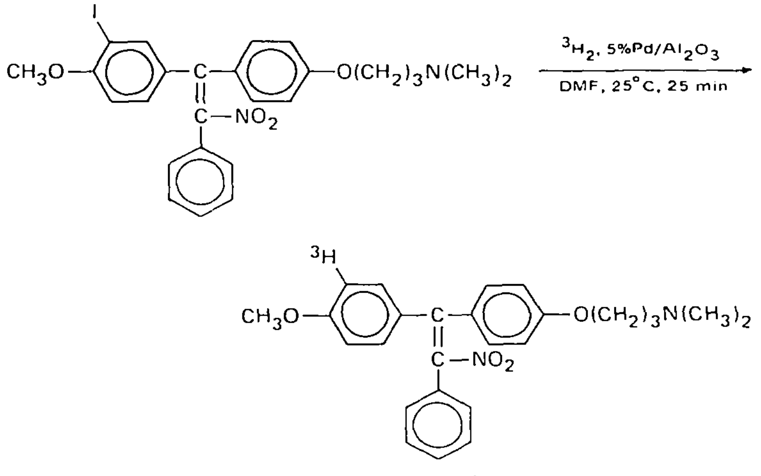
angina pectoris and hypertension. ^3H-labelled propranolol was synthesized by boiling unlabelled propranolol with acetic acid containing tritium.

Tritium-labelled isoxsuprine hydrochloride (9), a peripheral vasodilator and bronchodilator, has been prepared by catalytic tritiation of the corresponding ketone (Madding 1971).



(9)

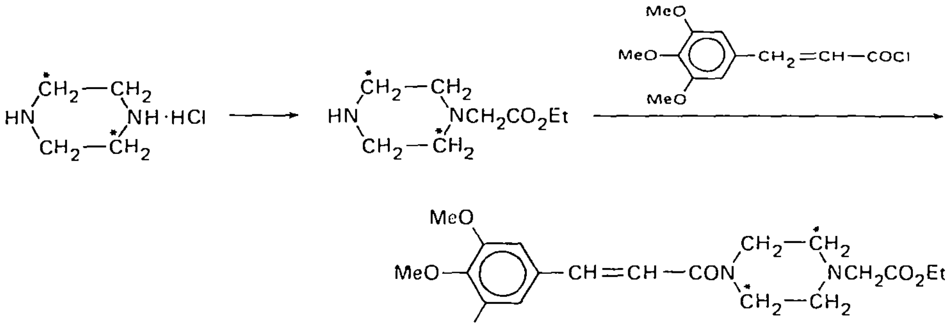
Tritium-labelled α-(p-*methoxyphenyl)*-α′-*nitro-4[3-(dimethylamino)propoxy]-stilbene*, the antiprogestational, hypocholesteramic drug with antifertility activity, has been prepared by catalytic deiodotritiation (equation 83) (Blackburn 1972).



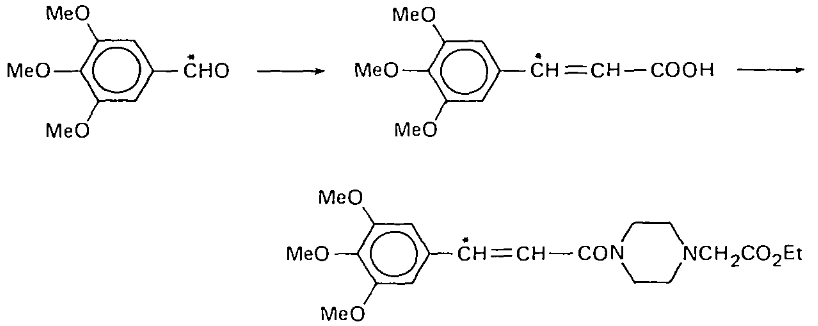
(83)

Ethyl 4-(3,4,5-trimethoxycinnamoyl)-[2,5-^{14}C]piperazinyl acetate and *ethyl 4-(3,4,5-trimethoxy[β-^{14}C]cinnamoyl)piperazinyl acetate*, a new potent coronary dilator, have been prepared according to equations (84) and (85) (Hardy, Sword and Hathway 1972).

^{14}C-labelled o-*(β-morpholinoethoxy)diphenyl ether hydrochloride* has been synthesized starting with uniformly labelled C_6H_5Br (Horie and Fujita 1972). ^3H-MPE-HCl (MPE = morpholinoethoxydiphenyl ether) was obtained by heating a



(84)



(85)

mixture of tritium water, 10% palladium on charcoal and a methanolic solution of MPE-HCl at 120°C for 15 hours in a sealed ampoule.

(N-C^3H_3)-Morphine has been synthesized by reductive methylation of normorphine with ^{3}H-paraformaldehyde and formic acid (equation 86) (Werner and

$$\mathrm{{>}N{-}H + CH_2O + HCO_2H \longrightarrow {>}N{-}CH_3 + CO_2 + H_2O} \qquad (86)$$

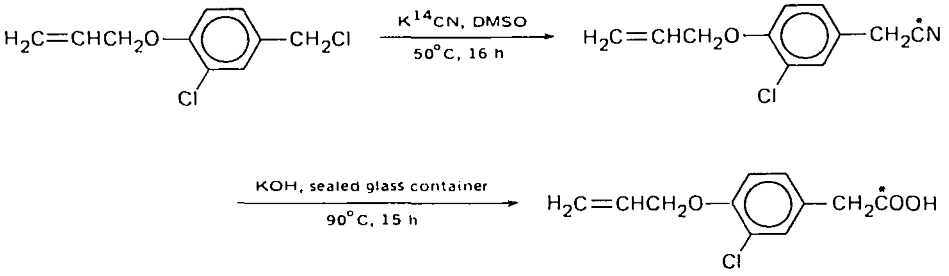
von der Heyde 1971). *Morphine-^3H* has also been prepared by microwave discharge activation of tritium gas (Fishman and Norton 1973).

Eugenol and *isoeugenol* have been labelled with carbon-14 in the methoxy position (Rabinowitz and coworkers 1973). Treatment of catechol with allyl bromide yielded *o*-allyloxyphenol (44%), which with ^{14}C-methyl iodide gave ^{14}C-*o*-allyloxyanisole. Rearrangement of the latter to ^{14}C-eugenol and isoeugenol has been performed using boron trifluoride etherate and glacial acetic acid catalyst. The overall yield of ^{14}C-labelled eugenol and isoeugenol based on ^{14}C-methyl iodide was 16% and 10% respectively.

*2,6-Di-*t*-butyl-*p*-cresol-$^{14}C_6$*, used in the chemical and food industry, has been found to also be a very active antioxidant in living biological systems. It was synthesized from *p*-cresol-$^{14}C_6$ and isobutylene (Shipp, Data and Christian 1973).

4-Allyloxy-3-chlorophenylacetic-1-^{14}C acid with low toxicity and showing strong analgesic and antipyretic properties has been prepared in a two-step reaction (equation 87) (Gillet and coworkers 1973) with 75% radiochemical yield.

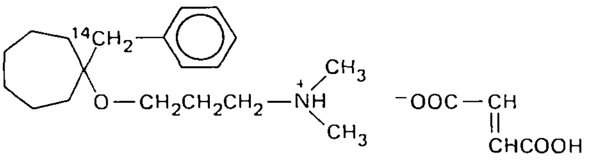
The widely used drugs *papaverine* and *quinopavine* and their derivatives have been labelled with ^{14}C to study their mode of action, distribution and metabolism (Ithakissios and coworkers 1974). Papaverine has been labelled with ^{14}C in the benzyl and 4-carbon position. Quinopavine has been isotopically labelled in the 1- or 4-position of the isoquinoline ring, or in the 4-methoxyphenyl position.



(87)

3,4-Dimethoxylbenzoic acid (carboxyl-^{14}C) and 4-^{14}C-methoxybenzoic acids have been used as the precursors in their synthesis. Papaverine labelled with ^{14}C in the benzyl position has been prepared by using $^{14}CO_2$ in the synthesis of 3,4-dimethoxybenzoic acid, an intermediate in the papaverine reaction sequence. Quinopavine labelled with ^{14}C in the 4-position has been obtained using the intermediate (3,4-dimethoxyphenyl)acetic acid-2-^{14}C as a precursor. Synthesis of quinopavine-1-^{14}C was carried out by using carboxyl-labelled 3,4-dimethoxybenzoic acid, and in a similar manner quinopavine labelled in the 4-methoxyphenyl position has been obtained from the same acid labelled in the 4-methoxy position. Papaverine labelled with ^{14}C in the 4-carbon position has been synthesized in a five-step reaction sequence starting with 3,4-dimethoxybenzaldehyde(carbonyl-^{14}C) which in turn was prepared by reduction of 3,4-dimethoxybenzoyl-^{14}C chloride.

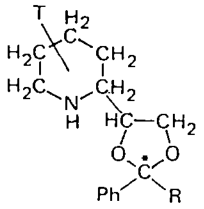
1-Benzyl(7-^{14}C)-1-(3'-dimethylaminopropoxy)cycloheptane fumarate (**10**), the active substance of the drug Halidor, has been produced from α-labelled benzyl chloride, in a sequence involving cycloheptanone, 3-dimethylaminopropyl chloride and fumaric acid (Banfi and Volford 1971). The same drug having carbon-14 in the dimethylamino moiety has also been obtained, in a different reaction sequence with $^{14}CH_3I$ as the source of the labelled group. 1-Benzyl-1-(2'-^{3}H-3'-dimethylaminopropoxy)cycloheptane fumarate and 1-(benzyl-4-^{3}H)-1-(3'-dimethylaminopropoxy)-cycloheptane fumarate have also been synthesized (Banfi, Zolyomi and Pallos 1973). The same compound has also been prepared carrying tritium labels in the side-chain, the aromatic ring or the cycloheptane ring (Banfi, Zolyomi and Pallos 1973).



(10)

An analgesic and anaesthetic compound, affecting the central nervous system, the d- and l-*2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride* (**11a**), has been labelled with carbon-14 at $C_{(2)}$ of the dioxolane ring and with tritium at the 4,5- and/or 3,4-positions of the piperidine ring (Hsi and Thomas 1973). The anaesthetic *2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride* (**11b**) has been labelled similarly (Hsi 1974).

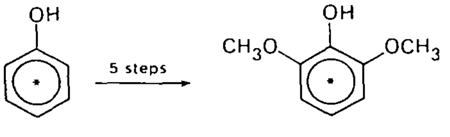
2,6-Dimethoxy(u-^{14}C-phenol) has been synthesized in five steps from (u-^{14}C)phenol (equation 88) (Miller, Olavesen and Curtis 1974).


T
H2
H2C
CH2
H2C
CH2
N
H
HC
CH2
O
O
C
Ph
R

[f. 43]

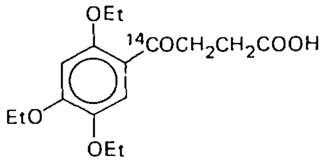
(11)

(a) R = Ph
(b) R = Et


OH
5 steps
OH
CH3O
OCH3

(88)

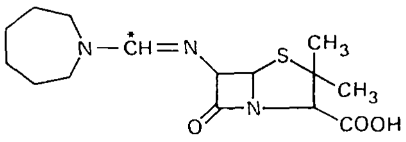
3-[2',4',5'-Triethoxybenzoyl(carbonyl-^{14}C)]propionic acid (12), a new spasmolytic agent for the bile duct, possessing a potent smooth muscle-relaxing activity


OEt
14COCH2CH2COOH
EtO
OEt

(12)

on Oddi's sphincter and the gall bladder, has been synthesized (Hayashi, Toga and Murata 1974).

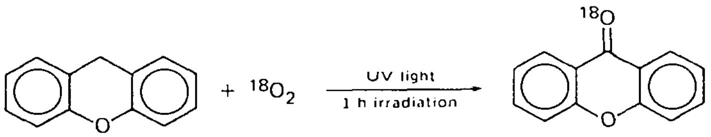
*6-(*N,N*-1',6'-Hexyleneformamidine-^{14}C)penicillanic acid* (13), exhibiting strong


N
CH=N
S
CH3
CH3
N
O
COOH

(13)

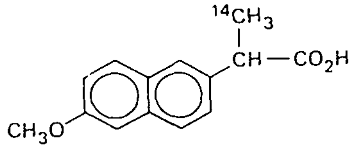
bacteriostatic action, particularly against *E. coli* species, has been prepared (Zupańska and coworkers 1974). Preparation of 9α,11ξ-tritiated oestrone-3-methyl ether has also been reported (Ponsold, Römer and Wagner 1974).

Carbonyl-labelled xanthone-^{18}O has been obtained by photooxidation of xanthene with oxygen-18 (equation 89) (Pownall 1974).

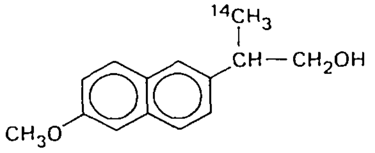

O
+ 18O2
UV light
1 h irradiation
18O
O

(89)

D-*2-(6'-Methoxy-2'-naphthyl)propionic acid* ('Naproxen') and L-*2-(6'-methoxy-2'-naphthyl)propanol*('Naproxol'), potent antiinflammatory and analgesic agents, have been labelled with carbon-14 (**14** and **15** respectively) and with tritium (Hafferl and Hary 1973). Naproxen labelled with tritium in the 1,4,7-positions of the naphthalene ring was obtained from the unlabelled drug with $BF_3 \cdot T_3PO_4$.

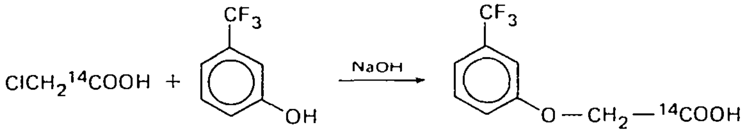


(14)



(15)

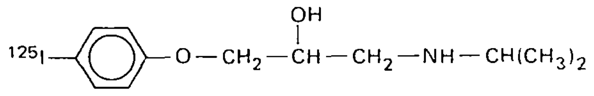
2-(3-Trifluoromethylphenoxy)-1-^{14}C acetic acid, used in the synthesis of prostagladin analogues, has been prepared in 78% yield from chloro-1-^{14}C-acetic acid and *m*-trifluoromethylphenol (equation 90) (White and Burns 1977).



(90)

(4′-Acetamido-2′, 6′-di-^{3}H-phenoxy)-2,3-epoxypropane was obtained in 64% yield from tritiated 4-acetamidophenol and epichlorohydrin (Shtacher and coworkers 1977).

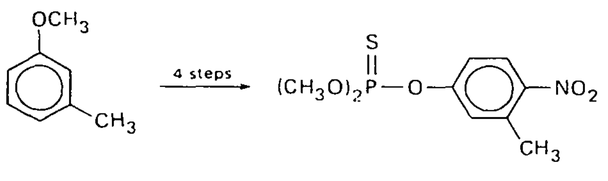
3-(4-Iodophenoxy)-1-isopropylamino-2-propanol-^{125}I (**16**), an adrenergic antagonist, has been prepared in 20–30% yield from the corresponding amine (Bobik and coworkers 1977).



(16)

^{14}C-labelled nonionic aryl surfactants (detergents) have been synthesized by Williamson coupling of chloroacetic-^{14}C-1 acid with *t*-octylphenol (TOPOH) followed by reduction of the aryloxyacetic acid with diborane, conversion of the $TOPOCH_2{}^{14}CH_2OH$ to $TOPOCH_2{}^{14}CH_2Cl$ with thionyl chloride and final Williamson coupling of the chloride obtained with pentaethylene glycol to yield $TOPOCH_2{}^{14}CH_2(OCH_2CH_2)_5OH$ (Tanaka and Wien 1976). Using octaethylene glycol in the last step $TOP(OCH_2CH_2)_9OH$ was also prepared. The authors have also synthesized the ^{14}C-labelled homogeneous surfactants derived from 2,6,8-trimethyl-4-nonanol(TMNOH), of the general structure $TMNOCH_2\overset{*}{C}H_2(OCH_2CH_2)_n$-OH (Tanaka, Wien and Stolzenberg 1976).

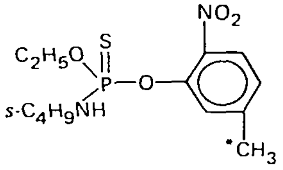
1-Methoxy-3-methylbenzene, the starting material in the synthesis of the organophosphorus insecticide 'Sumithion' (equation 91), labelled with ^{14}C at the 3-methyl group or in the phenyl ring, has been obtained respectively by coupling 3-methoxyphenylmagnesium bromide with methyl-^{14}C iodide and by *o*-methylation of 3-bromophenol-$^{14}C_6$ with dimethyl sulphate in 10% sodium hydro-



(91)

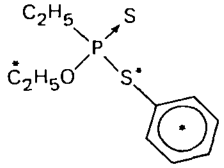
xide, followed by Grignard reaction with Mg and CH_3I (Yoshitake, Kawahara and coworkers 1977).

The ^{14}C-labelled herbicide, *O-ethyl O-(5-methyl-2-nitrophenyl)phosphoramidothioate* ('Cremart', **17**) has also been synthesized (Yoshitake, Shono and coworkers 1977).



(17)

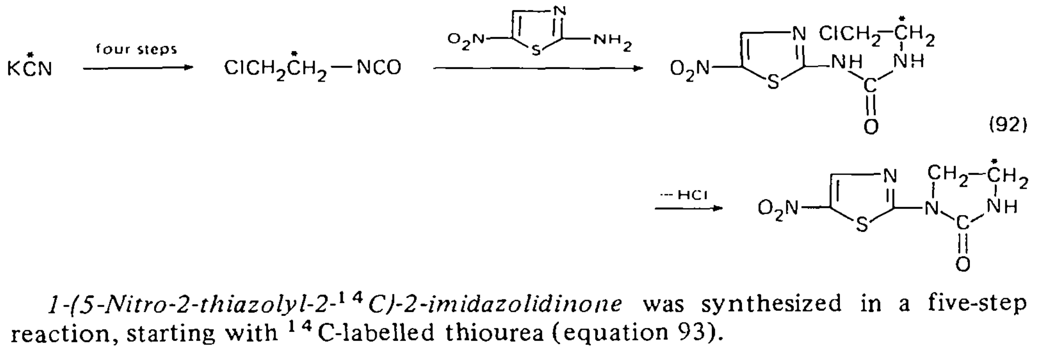
The soil insecticide, *O-ethyl S-phenyl ethylphosphonodithioate* (**18**), has been labelled with carbon-14 in the ethoxy moiety and in the benzene ring and with sulphur-35 in the thiophenyl moiety (Kalbfeld, Gutman and Hermann 1968; Kalbfeld, Pitt and Hermann 1969).



(18)

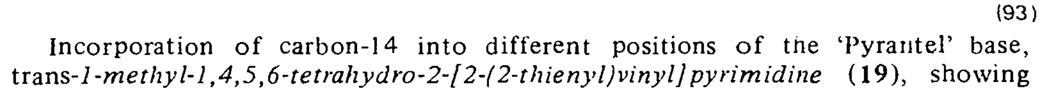
2. *Compounds containing the sulphide bond*

1-(5-Nitro-2-thiazolyl)-2-imidazolidinone-4-^{14}C, a drug used to treat patients suffering from bilharziasis and other diseases due to infestations with parasites ('Ambilhar'), has been obtained according to equation (92) (Faigle and Keberle 1969).



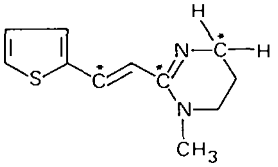
(92)

1-(5-Nitro-2-thiazolyl-2-^{14}C)-2-imidazolidinone was synthesized in a five-step reaction, starting with ^{14}C-labelled thiourea (equation 93).



(93)

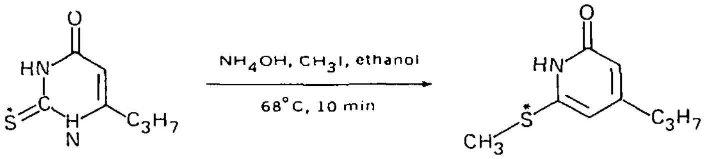
Incorporation of carbon-14 into different positions of the 'Pyrantel' base, trans-*1-methyl-1,4,5,6-tetrahydro-2-[2-(2-thienyl)vinyl]pyrimidine* (**19**), showing


H
N
C
H
S
C
C
N
CH3

(19)

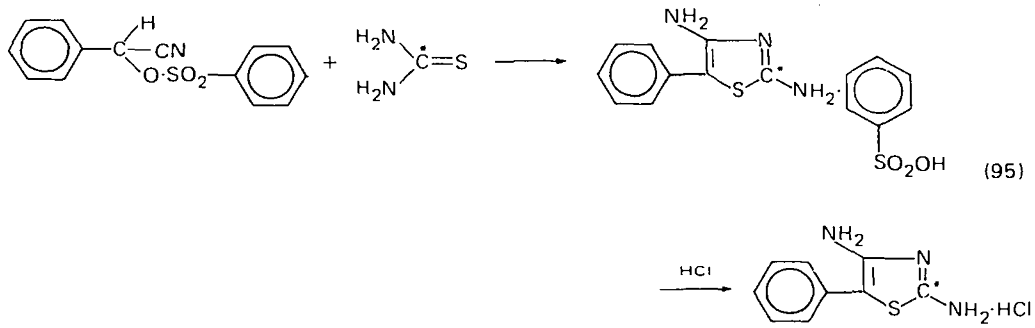
anthelmintic activity, has been achieved by using K^{14}CN or CH$_3$^{14}CN at various stages of the synthesis of the intermediate tetrahydropyrimidine (Figdor and coworkers 1970). Tritium-labelled pyrantel base has also been synthesized.

S-*Methyl-6-propyl-2-thiouracil-*^{35}*S*, one of the metabolites of the antithyroid drug 6-propyl-2-thiouracil, has been obtained as shown in equation (94) (Aboul-Enein 1974).


O
HN
S
C
H
N
C3H7
NH4OH, CH3I, ethanol
68°C, 10 min
O
HN
S
CH3
C3H7

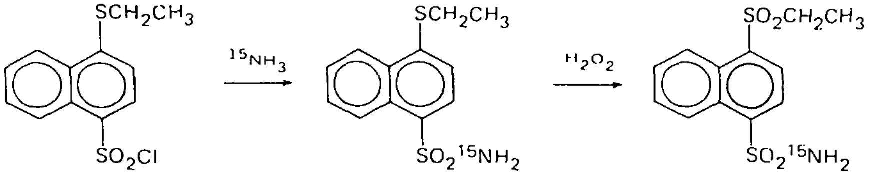
(94)

^{14}*C-labelled 2,4-diamino-5-phenylthiazole hydrochloride* (amiphenazole) exhibiting pharmacological activity free from undesirable side-effects and successfully used in the management of respiratory depression caused by narcotic analgesics (morphine), has been synthesized by condensing α-benzenesulphonylbenzyl cyanide with ^{14}C-thiourea (equation 95) (Adams, Nicholls and Williams 1976).


H
C
CN
O·SO2
+
H2N
C=S
H2N
NH2
N
C
S
NH2·
SO2OH
NH2
HCl
N
C
S
NH2·HCl

(95)

4-Ethyl sulphonyl-1-naphthalenesulphonamide-^{15}*N* (ENS), promoting experimental bladder carcinogenesis, has been prepared from 4-ethylthio-1-naphthalenesulphonyl chloride (equation 96) (Whaley and Daub 1977).

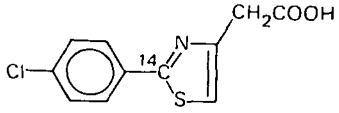

SCH2CH3
SO2Cl
15NH3
SCH2CH3
SO2 15NH2
H2O2
SO2CH2CH3
SO2 15NH2

(96)

Cysteine^{35} *S-sulphate*, which destroys neurons in the rat central nervous system, was obtained by an exchange reaction between cysteine-*S*-sulphate and cysteine-^{35}S (equation 97) (Misra and Olney 1977).

$$R^{35}SH + 2\,R{-}S{-}SO_3^-Na^+ \longrightarrow R{-}S{-}S{-}R + R{-}^{35}S{-}SO_3^- \qquad (97)$$

2-(4-Chlorophenyl)-2-^{14}C-thiazole-4-acetic acid (**20**), a drug tested for the treatment of rheumatoid arthritis, has been prepared from potassium^{14}C-cyanide in a multistep synthesis (White and Burns 1977).



(20)

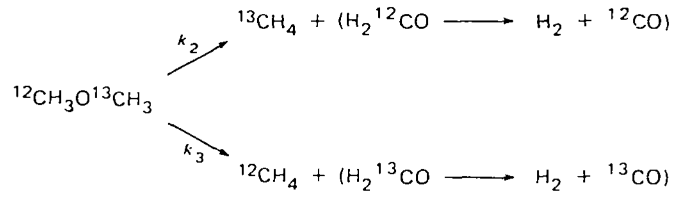
II. TRACER AND ISOTOPE EFFECT STUDIES WITH ETHERS

A. Isotopic Studies of the Thermal Decomposition and Rearrangement of Ethers

1. *Gas-phase decomposition of ethers*

A preliminary investigation of the gas-phase pyrolysis of *dimethyl ether* has been carried out at 505–532°C using labelled Me_2O (Zieliński 1968, 1979). It has been found that unlabelled ether molecules decompose at about 1% higher rate than $^{14}CH_3{-}O{-}CH_3$. The ^{14}C kinetic isotope effect was consistent with the free-radical mechanism of the dimethyl ether decomposition, and is determined by the isotope effect in the $^{14}C{-}H$ and $^{12}C{-}H$ bond rupture. It has also been concluded that there is no fast hydrogen migration in the $\cdot CH_2OCH_3$ free radical. The uninhibited pyrolysis of dimethyl ether is the one of the best behaved of all complex pyrolysis systems (Benson 1960). Therefore it was decided to undertake a further investigation of the ^{13}C kinetic isotope effects in the pyrolysis (Zieliński, Kidd and Yankwich 1976) at temperatures of 451–550°C (equations 98 and 99). The intermolecular, k_1/k_3, and intramolecular, k_2/k_3, ^{13}C kinetic isotope

$$^{12}CH_3O^{12}CH_3 \xrightarrow{k_1} {}^{12}CH_4 + (H_2{}^{12}CO \longrightarrow H_2 + {}^{12}CO) \qquad (98)$$



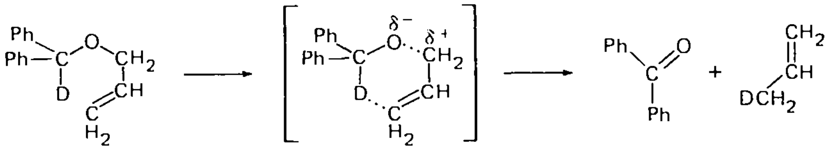
$$^{12}CH_3O^{13}CH_3 \begin{cases} \xrightarrow{k_2} {}^{13}CH_4 + (H_2{}^{12}CO \longrightarrow H_2 + {}^{12}CO) \\ \xrightarrow{k_3} {}^{12}CH_4 + (H_2{}^{13}CO \longrightarrow H_2 + {}^{13}CO) \end{cases} \qquad (99)$$

effects have been found to be of the order of 1% and to decrease with increasing temperature. No significant pressure effects were found. The ^{13}C isotope effects arise in the destruction of the symmetry of the dimethyl ether in hydrogen transfer reactions $R + C_{(2)}H_3OC_{(1)}H_3 \rightarrow RH + C_{(2)}H_2OC_{(1)}H_3$, where $R = CH_3$, H or NO. The best fit of the theoretically calculated isotope effecgs to the experimental results was obtained for reaction coordinates in which displacements in $R\cdots H$ and $H\cdots C_{(2)}$ are large and displacements in $C_{(2)}\cdots O$ is small, that is for nearly product-like transition states.

In the thermal decomposition of a 50 : 50 mixture of perhydro, CH_3OCH_3, and perdeutero, CD_3OCD_3, dimethyl ethers it was found (McKenney, Wojciechowski and Laidler 1963; McKenney and Laidler 1963) that the average ratio CD_3H/CD_4 equals 2.49 ± 0.04 for uninhibited runs and 2.44 ± 0.03 for pyrolysis carried out in the presence of a sufficient amount of NO ensuring maximum inhibition. It has been concluded that both the uninhibited and inhibited reactions are almost entirely chain processes. The temperature dependence of the kinetic isotope effects in the reaction of hydrogen and deuterium atoms with dimethyl ether, $H + Me_2O \rightarrow H_2 + CH_2OMe$, and with methanol has been investigated by the flow-discharge method (Meagher and coworkers 1974). The effects were found to be similar with Me_2O and with MeOH, indicating a comparable extent of bond breakage and formation in the activated complexes.

An inverse deuterium isotope effect, $k_D/k_H = 1.072 \pm 0.009$, was found in the cyclopentane-inhibited pyrolysis of Me_2Hg and $(CD_3)_2Hg$ at 366°C. The ^{13}C isotope effect at 366°C is $k_{12}/k_{13} = 1.0386 \pm 0.0007$ (Weston and Seltzer 1962). The inverse deuterium isotope effect was attributed to an increase of the C—H stretching frequencies in going from the initial to the transition state. Mass spectrometric investigations of the rearrangement and fragmentation of deuterium-labelled ethers have been carried out by Djerassi and Fenselau (1965), MacLeod and Djerassi (1966) and Ian and Dudley (1971).

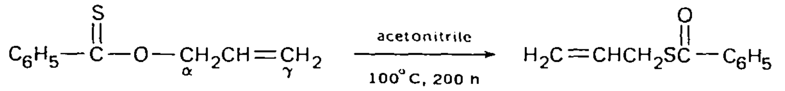
The gas-phase decomposition of *allyl ethers* at 500°C yields a carbonyl compound and propene, with the double bond shifted from the 2,3- to the 1,2-position of the allyl system. It has been observed that allyl α-deuteriodiphenylmethyl ether (equation 100) decomposes about 10% slower than the undeuterated compound (Cookson and Wallis 1966). The validity of this result was questioned by Kwart Slutsky and Sarner (1973). The details of the reaction were studied by investigating carbon-14 isotope effects in the decomposition of an allyl ether successively labelled at the benzhydryl carbon and the three carbons of the allyl group (Fry 1972).



(100)

A temperature dependence study of k_H/k_D in the gas-phase thermolysis of unsaturated ethers such as α, α′-dideuteriobenzyl allyl, $H_2C{=}CHCH_2OCD_2C_6H_5$, benzylpropargyl, $C_6H_5CD_2\text{-}O\text{-}CH_2\text{-}C{\equiv}CH$, and isopropyl allyl, $H_2C{=}CHCH_2OCD(CD_3)_2$, ether showed no evidence for proton tunneling. The maximum theoretical isotope effect has been realized in each case suggesting fully symmetrical bond formation and bond breaking in the activated complexes (C· · ·H· · ·C) (Kwart, Slutsky and Sarner 1973). Activation parameters of the vapour-phase thermolytic β-elimination of *t*-butyl-1, 1-d_2 ethyl ether, $(CH_3)_3COCD_2CH_3$, at 516–585°C are very similar to those of the $Me_3COC_2H_5$ reaction, but $(CD_3)_3COC_2H_5$ exhibits large differences, which are explained by a quantum-mechanical tunnel effect in the linear hydrogen transfer. A triangular transition state for thermal β-elimination reactions has been proposed (Kwart and Stanulonis 1976).

The secondary α-deuterium isotope effect in the cyclic, intramolecular rearrangement of allyl-1,1-d_2 thionobenzoate to allyl-3,3-d_2 thiolbenzoate was found to be much smaller (6–7% per deuterium) than that observed in carbonium ion, carbanion or radical reactions (10–12%) (equation 101). The very small γ-



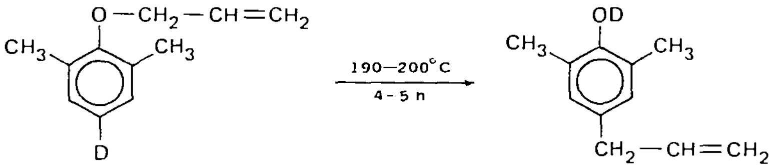
$$C_6H_5-\overset{\overset{S}{\|}}{C}-O-\underset{\alpha}{C}H_2CH=\underset{\gamma}{C}H_2 \xrightarrow[100^{\circ}C,\ 200\ h]{\text{acetonitrile}} H_2C=CHCH_2S\overset{\overset{O}{\|}}{C}-C_6H_5 \qquad (101)$$

deuterium effect of 0.97 (ca. 3% per deuterium) in the rearrangement of allyl-3,3-d_2 thionbenzoate to allyl-1,1-d_2 thiolbenzoate suggests a more reactant-like than product-like transtion state in such allylic rearrangements (McMichael 1967).

Allylic ethers, 4-$RC_6H_4CH_2OCMe_2CH{=}CH_2$, where R = H, Br, Me, MeO, Cl, Me_3Si etc., undergo redox fragmentation, in the presence of $(Ph_3P)_3RuCl_2$ accompanied by allylic transposition of the C=C double bond, with formation of 4-RC_6H_4CHO and $Me_2C{=}CHMe$. Benzylic deuterium substitution in the ether has no appreciable effect on the rate of the catalysed fragmentation and the cleavage of the allylic C–O bond is the rate-determining step (Salomon and Reuter 1977). Barroeta and Maccoll (1971) found that in the gas-phase thermolysis of ethyl-1,1-d_2 thiocyanate, $CH_3CD_2{-}S{-}C{\equiv}N$, $H_2C{=}CD_2$ is produced. Pyrolysis of ethyl-d_5 thiocyanate has also been studied.

2. Isotopic studies of the mechanism of the Claisen rearrangement

In early investigations of the Claisen rearrangement it was supposed that the hydrogen atom displaced by the migrating allyl group finally appeared in the phenolic OH group. This assumption has been confirmed by isotopic studies of the thermal rearrangement of the allyl ethers of 4-deutero-2,6-dimethylphenol (equation 102) and of 2,4,6-trideuterophenol (equation 103) (Kistiakovsky and Tichenor 1942). In equation (102) the *para* deuterium displaced by the migrating allyl group becomes the phenolic deuterium of the product. The acetate of the product of the rearrangement showed no detectable deuterium content. In equation (103) the displaced *ortho* deuterium becomes the phenolic deuterium. The authors envisage the movement of hydrogen in the course of the rearrangement not as a 'direct jump' but rather as the 'displacement of the proton', which finally reaches the oxygen anion. First-order kinetics suggests that *ortho* rearrangement proceeds by an intramolecular cyclic mechanism (equation 104). For the *para* rearrangement,



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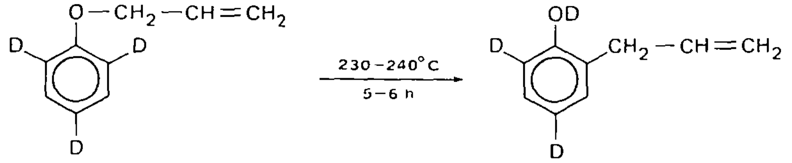

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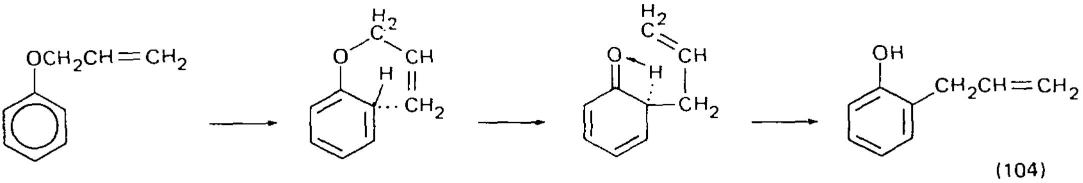
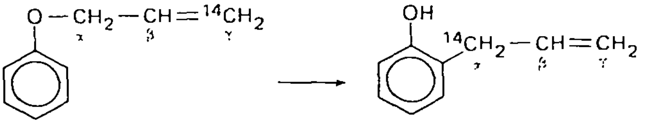


(104)

two mechanisms have been proposed. In the 'two-cycle mechanism' the allyl group first migrates with inversion to the *ortho* position and then rapidly rearranges to the *para* position (also with inversion) through two intermediate six-membered transition states. In the 'π-complex' mechanism a relatively free allyl group interacting with the π-electron cloud of the aromatic system migrates to the *para* position. The above conclusions have been corroborated by investigating ethers labelled with carbon-14 in the γ-position of the allyl group (Ryan and O'Connor 1952). Assay of stepwise degradative oxidation products of the *ortho* and *para* rearrangements has shown that in the course of the *ortho* rearrangement carbon-14 appears in the α-position of the *o*-allylphenol recovered (equation 105). In the case of *para* rearrangement ^{14}C occurs in the γ-position of the product (equation 106) and no $\alpha-\gamma$ inversion was observed. Hence, *ortho* rearrangement is cyclic and intramolecular, with inversion of the allyl group, while in the *para* rearrangement the isotopic carbon retains its original γ-position in the final product and no $\alpha-\gamma$ inversion occurs in accord with the double-cycle mechanism (Conroy and Firestone 1953), or with the π-complex mechanism in which the migrating allyl group preserves its original structure (Rhoads, Raulins and Reynolds 1953). The *ortho*-Claisen rearrangement of 2,4-disubstituted phenyl allyl ether (Fahrni and coworkers 1955) was studied. 2,6-Diallylphenol obtained in the course of rearrangement of 4,2-Me($CH_2=CH-^{14}CH_2$)$C_6H_3OCH_2-CH=CH_2$ was free of $H_2{}^{14}C=CH-CH_2$. The thermal behaviour of 2-(α-^{14}C)-6-diallylphenyl allyl ether, 2,6-$R^1R^2C_6H_3$ $OCH_2CH=CH_2$, where $R^1 = {}^{14}CH_2-CH=CH_2$, $R^2 = CH_2CH=CH_2$ (Haegele and Schmid 1958), 2,4,6-trimethylphenyl allyl ether-γ-^{14}C (Fahrni and Schmid 1958), *cis*-4-$MeC_6H_4OCH_2CH=CH$-$^{14}CH_3$ (Habich and coworkers 1962) and crotyl propenyl ethers (Vittorelli and coworkers 1968) has been investigated by Fahrni and Schmid (1958), Habich and coworkers (1962), Haegele and Schmid (1958) and H. Schmid and K. Schmid (1952, 1953) who found that 2,6-disubstituted phenyl allyl ethers rearranged to the corresponding 4-allylphenols. The specific rate constants for this isomerization have been determined and an intramolecular mechanism was proposed (Fahrni and Schmid 1959). *cis*-4-$MeC_6H_4OCH_2CH=CH-{}^{14}CH_3$ in PhCl in the presence of BF_3 at $-30°C$ gave only 4-methyl-2-(α-methylallyl)phenol, 4-Me(HO)$C_6H_3CH(^{14}CH_3)CH=CH_2$ (normal product). In the thermal rearrangement at about 200°C the 'normal' path was about 60% only and the 'abnormal' one amounted to about 40%, yielding Me(HO)$C_6H_3CHMeCH={}^{14}CH_2$, which was produced in the thermal isomerization of the primary normal product (equation 107) (Habich and coworkers 1962). The stereochemistry of the chair-like transition state in the aliphatic Claisen rearrangement of crotyl propenyl ether, $CH_3-CH=CH-CH_2-O-CH=CH-CH_3$, has been established by Vittorelli and coworkers (1968). A pronounced solvent effect in the Claisen rearrangement of allyl-^{14}C *p*-tolyl ether



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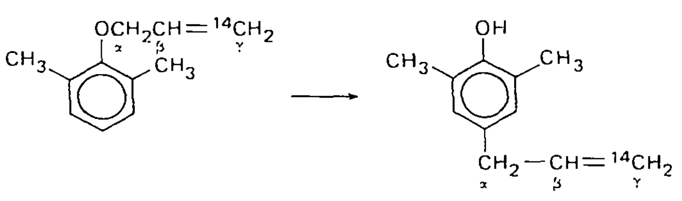

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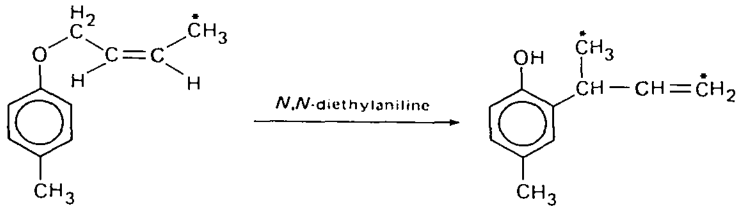


(107)

and other p-$RC_6H_4-O-CH_2CH{=}CH_2$ ethers, where R is NO_2, Br, Me and OMe has been observed (White and Wolfarth 1970a). The reaction rates are higher in polar solvents and electron-donating groups increase the reaction rate (White and Wolfarth 1970b). A deuterium solvent isotope effect has been observed in the acid-catalysed *ortho*-Claisen rearrangement of allyl ethers in '$CDCl_3-CF_3CO_2H$' solvents. The first-order rate constant increased exponentially with increase of the acid fraction. A highly polar transition state was postulated (Svanholm and Parker 1974). An unusually facile thermal Claisen-type rearrangement was observed with allyl and benzyl ethynyl ethers (Katzenellenbogen and Utawanit 1975).

B. Isotopic Studies of Reactions with Ethers

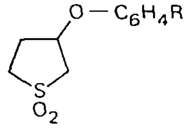
1. *Isotopic studies with vinyl ethers*

The mechanism of hydrolysis of vinyl ethers, $H_2C{=}CHOR$, has been investigated using $H_2{}^{18}O$ (Kiprianova and Rekasheva 1962). The reaction was catalysed by H_2SO_4 and $HgSO_4$. Isopropyl vinyl ether was also hydrolysed without catalyst at 140–50°C. The ROH obtained is not enriched in ^{18}O, therefore the cleavage occurred at the vinyl group through formation of hemiacetals and the attack on the vinyl group is the primary act in the hydrolysis. The kinetics of acid-catalysed hydrolysis of diethyleneglycol monovinyl ether has been investigated in $4-8 \times 10^{-4}$ N HCl in H_2O and DCl in D_2O (Shostakovskii and coworkers 1965). The authors concluded that the hydrolysis of simple vinyl ethers proceeds according to equation (108). The mechanism of the rate-determining proton transfer in vinyl

$$\begin{aligned}&CH_2{=}CHOR \xrightarrow[\text{slow}]{H^+} CH_3-\overset{+}{C}HOR \xrightarrow[\text{fast}]{H_2O}\\ &CH_3CH(OR)-\overset{+}{O}H_2 \longrightarrow CH_3CHO + HOR + H^+\end{aligned} \tag{108}$$

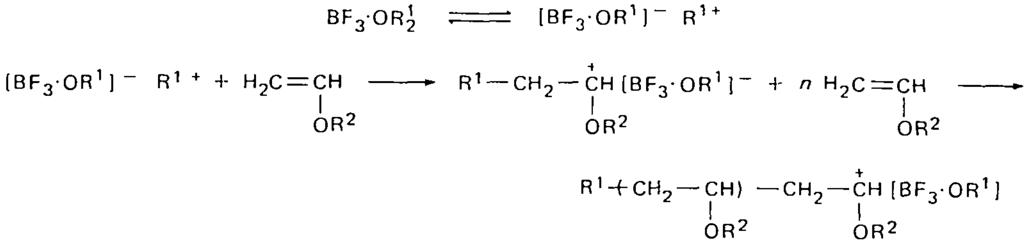
ether hydrolysis was investigated by Kreevoy and Williams (1968), who showed that in various media and even in pure water, direct proton transfer from a strong acid to a carbon atom is possible without involving water molecules. The primary isotope effect, $(k_H/k_D)_I$, is 4.8 and the secondary solvent isotope effect $(k_H/k_D)_{II}$ is 0.66. The measured tritium isotope effect obeyed Swain–Schaad relations (Kreevoy and Eliason 1968). The kinetic deuterium solvent isotope effect, k_{D_2O}/k_{H_2O}, in the mineral acid-catalysed hydrolysis of phenyl orthoformate, $(PhO)_3CH$, was about 2, and this was used as evidence that the hydrogen ion transfer is the rate-determining step (Price and coworkers 1969). Trifluoroacetolysis of 1-anisyl-2-methyl-1-propenyl tosylate or brosylate was investigated by Rappoport and Kaspi (1971). The deuterium isotope effect in the hydration of p-$MeOC_6H_4CMe{=}CH_2$, at 25°C in H_2O-D_2O medium in the presence of H_2SO_4, was $k^H_{H_3O^+}/k^D_{D_3O^+} = 3.15$ and was interpreted as a rising from a slow transfer of the acid proton to the olefin, with the transition state being 'halfway between products and substrates' (Simandoux and coworkers 1967). For p-$MeOC_6H_4-CHMe{=}CH_2$ the deuterium isotope effect k_H/k_D = 3.15 is approximately equal to that observed in proton transfer to $EtOCH{=}CH_2$ (k_H/k_D = 3.0) but is much larger than the isotope effect (k_H/k_D = 1.45) observed in the case of isobutene (Williams 1968). Deuterium primary isotope effects in the hydrofluoric acid-catalysed hydrolysis of vinyl ethers ($EtOCH{=}CH_2$, $PhOCMe{=}CH_2$, methyl-1-cyclohexenyl ether, HF in H_2O and DF in D_2O at 25°C) were found to be in the range $k_H/k_D = 3.3-3.5$. These relatively small effects were attributed to strong hydrogen bonding vibrations ($\omega = 1325-1450\ cm^{-1}$) in the proton-transfer transition state and lack of such compensatory mode of vibrations in the diatomic proton donor (Kresge, Chen and Chiang 1977; Kresge, Chiang and coworkers 1977). Earlier in this series (Kresge and Chiang 1967a,b,c; Kresge, Chiang and Sato 1967) the authors have found that the deuterium isotope effect of proton transfer from hydronium ion to ethyl vinyl ether is 2.95 and from formic acid to ether 6.8. The secondary deuterium isotope effect was about 0.65. A regular increase of the isotope effect, $k_{H_3O^+}/k_{D_3O^+}$, in the hydrolysis of 17 vinyl ethers in aqueous solution at 25°C, with log $k_{H_3O^+}$ up to a value of about 3.5 has been noticed (Kresge, Onwood and Slae 1968; Kresge, Sagatys and Chen 1968). Introduction of phenyl substituents at the β-position of the vinyl ether might shift the mechanism of hydrolysis from 'proton transfer from catalyst to substrate' being the rate-determining step, to rapidly reversible protonation followed by rate-determining hydration of the alkoxycarbonium ion intermediate (Kresge and Chen 1972). Cooper, Vitullo and Whalen (1971) have shown that there is a change in the rate-determining step in the hydrolysis of vinyl and related ethers with changing buffer concentration. It should be noted that complementary investigations of oxygen-18 isotope effects could possibly help to solve the problem of the rate-determining step in vinyl ether hydrolysis.

The hydrolysis of methyl pseudo-2-benzoylbenzoate in aqueous sulphuric acid and in D_2O was investigated by Weeks, Grodski and Fanucci (1968). The kinetics and mechanism of the hydrolysis of 4-ethoxy-2,6-dimethylpyrylium tetrafluoroborate using deuterium was studied by Salvadori and Williams (1968). Kinetic oxygen-18 and deuterium isotope effects in the hydroxide-ion-catalysed reaction of $2,4\text{-}(O_2N)_2C_6H_3OPh$ with piperidine in the presence of varying concentrations of hydroxide ion has been measured and it has been concluded that the reaction proceeds through the intermediate complex mechanism, with nucleophilic attack of OH ion yielding $2,4\text{-}(O_2N)_2C_6H_3OH$ (Hart and Bourns 1966). Analysis of rate coefficients and deuterium isotope effects in the alkaline hydrolysis of substituted 2-methoxytropones in aqueous dioxane and aqueous Me_2SO at 30–70°C indicated that in strong basic media the reaction proceeds through an addition–elimination mechanism with direct attack of OH^- at the 2-position as rate-determining step (Bowden and Price 1971). Second-order rate constants, activation parameters and isotope effects in the hydroxide-catalysed hydrolysis of phenyl sulpholan-3-yl ethers (21; R = H, 4-Me, 3-Me, 2-Me, 4-Br, $4\text{-}NO_2$), proceeding according to the ElcB



(21)

mechanism, have been determined (Bezmenova and coworkers 1974). The rates of acid-catalysed hydrolysis of alkyl vinyl sulphides, $H_2C = CHSR$ (where R = Me, Et, *i*-Pr, *t*-Bu) in 10% aqueous CH_3CN were found to be smaller in a deuterium



SCHEME 9.

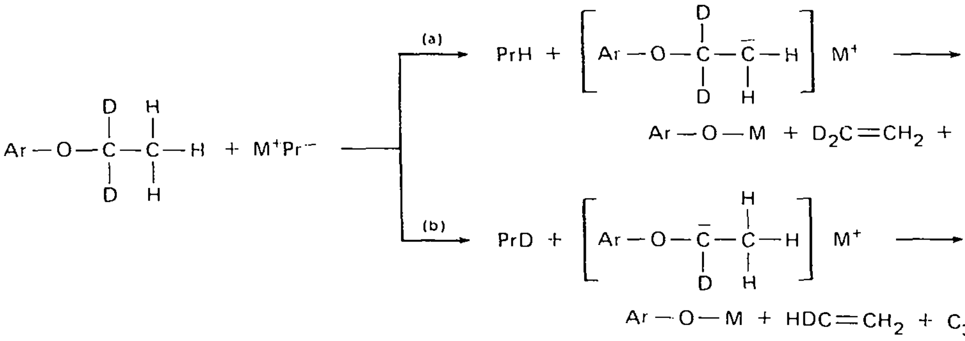
medium, $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 2.94$ (Okuyama, Nakada and Fueno 1976). No deuterium exchange between sulphide and deuterated solvent was detected during hydrolysis. The rate constant of the hydrolysis of the propenyl sulphides, $CH_3CH{=}CHSR$ (R = Et, *i*-Pr, *t*-Bu) have also been determined.

The electrophilic addition of ROH to $RO{-}CH{=}CH_2$ in C_6H_6, cyclohexane and octane was investigated by Vylegzhanin and Trofimov (1971). In octane, k_H/k_D = 2.00 at 25°C, in cyclohexane k_H/k_D = 2.18 at 40°C and 1.84 at 25°C and in benzene k_H/k_D = 1.4, 3.70 and 4.14 at 10°C, 25°C and 40°C, respectively. The large temperature dependence of k_H/k_D in C_6H_6 was explained by specific interaction between the vinyl ether and benzene. In the addition of EtOH or EtOD to $ClCH_2CH_2OCH{=}CH_2$ catalysed by HCl (Trofimov, Atavin and Vylegzhanin 1968), the obtained relation $k_H/k_D = \exp(32.7/R).\ \exp(-9600/RT)$ was interpreted by the authors as the result of two competing mechanisms, namely catalysis by nonionized HCl molecules in EtOD with concerted cyclic or acyclic hydrogen transfer and catalysis by ion pairs $[H_2O^+Et]Cl^-$ or $[H_2C{=}CH\overset{+}{O}HCH_2CH_2Cl]Cl^-$.

^{14}C-labelled boron trifluoride etherate, obtained from diethyl-1-^{14}C ether and BF_3, has been used to study the mechanism of isobutyl vinyl ether polymerization in liquid propane at −75°C (Kennedy 1959). Initially it had been supposed that the complexing ether originating from the BF_3 complex, participated intimately and directly in the polymerization and the growing chain contained an alkyl group on the end of the chain (Scheme 9). The radioactivity measurements of the product showed that 0.71% of the chains originated from ethyl groups and 99.29% by chain transfer. Thus the proposed mechanism could be operative, but the chain-transfer step plays the predominant role in the polymerization. Isobutyl vinyl ether and *t*-butyl vinyl ether polymerization was also investigated by Imanishi and coworkers (1962) and Higashimura and Suzuoki (1965). Polymerization of 2,2-dideutero-*p*-methoxystyrene was studied by Brendlein and Park (1975).

2. *Reactions of ethers with organoalkali metal compounds; elimination reactions.*

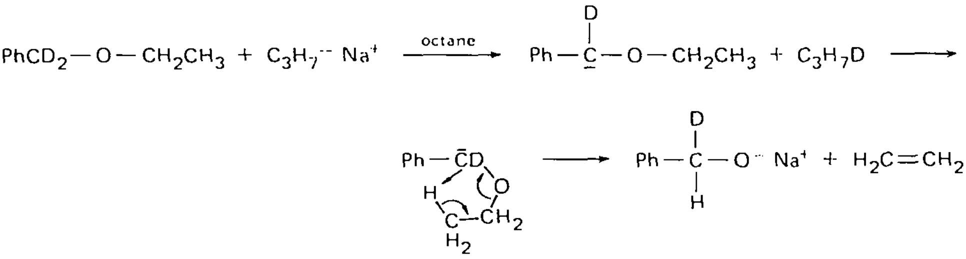
Ethers treated with organoalkali metal compounds yield olefins. The course of these reactions was investigated by studying the cleavage of deuterium-labelled ethyl-1,1-d_2 aryl ethers with propylsodium (Letsinger and Pollart 1956). In the reaction of ethyl-1,1-d_2 phenyl ether with propylsodium 28.2% of deuteroethylene, 15.2% of propane and less than 2.5% of propane-d was obtained. With ethyl-1,1-d_2 *p*-*t*-butylphenyl ether metalation of the aromatic ring was less and the yield of propane was smaller (11.2%); about 42% of deuteroethylene and no more than 1.3% of propane-d were obtained. Hence, production of ethylene proceeds according to path (a) in equation (109) (β-elimination). The contribution of path (b) (α-elimination), which postulates the removal of the α-proton from the ethyl group,



(109)

to the overall yield of ethylene is negligible, if any. The above conclusion was also confirmed by the absence of deuterated phenoxide in the products.

Ethyl benzyl-α,α-d$_2$ ether reacts readily with propylsodium yielding ethylene (91%), propane-d (81%) and nondeuterated propane (21%). The recovered benzyl alcohol showed strong IR absorption characteristics for aliphatic C–H and C–D bands. The above results indicate that the propyl group of the reagent removes deuterium from the α-position of the ether (equation 110) (Letsinger and Pollart 1956). The amount of nondeuterated ordinary propane was greater than the amount of hydrogen present in aluminium deuteride (used for the synthesis) which contained at least 92.5% of deuterium. The authors explained their observation by assuming that the propane resulted also from metalation of the aromatic ring, from traces of moisture or from some direct β-elimination of the ether.



(110)

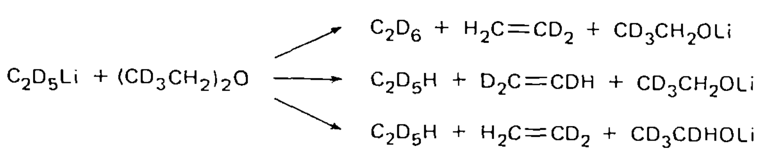
α-Elimination was also found in the reaction of 2-phenyltetrahydrofuran with propylsodium at about −40°C leading to high yields of ethylene and acetophenone (after hydrolysis). Tetrahydrofuran itself is relatively unreactive. The mechanism of the reaction of diethyl ether with alkyllithium compounds, which proceeds according to equations (111a) and (111b), has been investigated using ethers deuterated in

$$\mathrm{RLi + (C_2H_5)_2O \longrightarrow RH + H_2C{=}CH_2 + C_2H_5OLi} \tag{111a}$$

$$\mathrm{RLi} + n\,\mathrm{H_2C{=}CH_2 \longrightarrow R(CH_2{-}CH_2)_{\mathit{n}}Li} \tag{111b}$$

α- and β-positions (Maercker and Demuth 1973). In the case of α-deuterated diethyl ether the labelled products obtained suggest the reaction scheme as shown in equation (112), while in the case of β-deuterated diethyl ether the kinetic deuterium isotope effect operates and the isotopic reactions as shown in equation (113) take place.

$$\mathrm{C_2D_5Li + (CH_3CD_2)_2O \longrightarrow C_2D_5H + CH_2CD_2 + CH_3CD_2OLi} \tag{112}$$

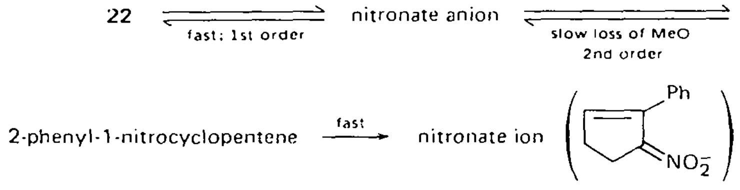

$C_2D_5Li + (CD_3CH_2)_2O$
$C_2D_6 + H_2C{=}CD_2 + CD_3CH_2OLi$
$C_2D_5H + D_2C{=}CDH + CD_3CH_2OLi$
$C_2D_5H + H_2C{=}CD_2 + CD_3CDHOLi$

(113)

Reactions of organolithium compounds with ethers have been reviewed by Baryshnikov and Vesnovskaya 1975). The deuterium kinetic isotope effect in the reaction of Cl_2CHOCH_3 and Cl_2CDOCH_3, with base, *i*-PrOK in *i*-PrOH and KSPh at −12°C, after correction for protium impurity, equals 5.4 ± 2 (Hine, Rosscup and Duffey 1960). This value has been used to support the conclusion that α-dehydrochlorination leading to methoxychloromethylene is the initial step of the reaction.

Rate constants of the phenoxide elimination reactions of β-substituted aryl ethyl ethers, XCR_2CH_2OPh (where R is H and D), have been determined and an E1cB mechanism has been proposed (Grosby and Stirling 1968, 1970). Rate constants for the bis-β-deuterio substrates, XCD_2CH_2OPh, in D_2O (NaOD) are about 1.5 times larger. Reactions with thiolate are slower and there is little change in the thiolate–ethoxide rate ratio as the activating group is changed: $k(t\text{-BuS}^-)/k(\text{EtO}^-) = 0.23$–$0.26$ when R = H and X = Ac, $PhSO_2$, CO_2Et, $p\text{-}ZC_6H_4SO_2$, $p\text{-}ZC_6H_4SO$. The deuterium isotope effects, k_H/k_D, in elimination of phenoxide from 2-phenoxyethylsulphonium salts and sulphoxides at 25.4°C, are 0.66 and 0.78 respectively. The observed isotope effects have been rationalized in terms of general equilibria of the type: $SH + HO^- \rightleftharpoons S^- + H_2O$, $SH + H_2O \rightleftharpoons S^- + H_3O^+$, $2H_2O \rightleftharpoons H_2O^+ + OH^-$.

The deuterium isotope effect in the methoxide-ion initiated β-elimination of CH_3OH from 2-phenyl-*trans*-2-methoxy-1-nitrocyclopentane (22a) and its *cis* isomer (22b) allowed the evaluation of rate constants for the forward and reverse steps in the reaction sequence (equation 114) (Bordwell, Yee and Knipe 1970).



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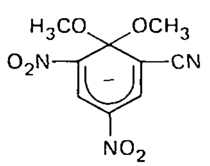
A very small secondary α-deuterium isotope effect has been observed in the ethanolysis of 4-methoxypentyl *p*-toluenesulphonate with deuterium on $C_{(1)}$ of the pentyl group, and in the acetolysis of 2-norbornen-7-yl *p*-toluenesulphonate with deuterium on $C_{(7)}$ of the bicyclo group, indicating that α-effects are less sensitive to changes in the geometry than are β-effects (Eliason and coworkers 1968).

Deuterium solvent kinetic isotope effects and α-methylene proton exchange in D_2O were used to support the suggestion that β-elimination of methoxide ion from 4-methoxy-4-methyl-2-pentanone, yielding α, β-unsaturated ketones, proceeds via rapid base-catalyzed formation of enolate anion, followed by rate-determining loss of methoxide ion from the latter (Fedor 1969).

A significant deuterium isotope effect was observed in the formation of the 1,1-dimethoxy Meisenheimer complex (22 and 23) formed in the reaction of MeO^- with 2-cyano-4,6-dinitroanisole or 2,4,6-trinitroanisole, respectively, in MeOH and MeOD solvents (equilibrium constant ratio $K_H/K_D = 0.45$). The reaction of methoxide ions with di- and tri-nitroanisole was also carried out in $(CD_3)_2SO$ solution and the formation of unstable transients was observed. The initial attack of MeO^- on the dinitroanisole yields 1,3-dimethoxy-2-cyano-4,6-dinitrocyclohexadienylide (24) (Fendler, Fendler and Griffin 1969).



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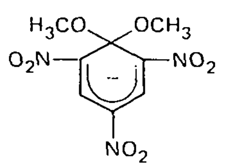

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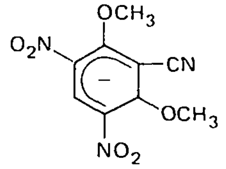
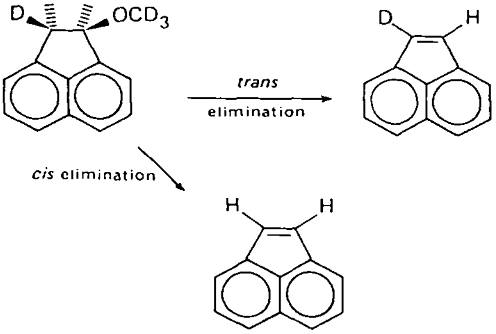


(24)

The stereochemistry of the alkoxide-catalysed (24) elimination reaction of *cis*- and *trans*-2-deuterio-1-trideuteriomethoxyacenaphthenes, leading to the formation of acenaphthylene (equation 115), was investigated by Hunter and Shearing (1973)



(115)

in *t*-butyl alcohol and methanol. The primary and secondary kinetic deuterium isotope effects, k_H/k_D, for the preferential initial *cis* elimination in potassium *t*-butoxide/*t*-butyl alcohol at 64.3°C were found to be in the range 1.04 (secondary)–1.40 (primary). The leaving group $-(OCD_3)$ isotope effect, $k_H/k_D = 1.20$, was attributed to an inductive effect analogously to trideuterioactic acid, which is 18% less acidic than acetic acid. These isotope effects are consistent with the Elcb mechanism but an E2 process cannot be ruled out, for which low k_H/k_D in the range 1.62–1.92 have been observed for *syn* elimination of cyclopentyl ammonium salts.

The isotope effect, k_H/k_D, in the enzymatic demethylation of *o*-nitroanisole-Me-^{2}H by a liver microsome preparation was about 2 (Mitoma and coworkers 1967). Binding of the deuterated *o*-nitroanisole to the enzyme was stronger and the observed isotope effect apparently reflects the differences in the rates of C–H and C–D bond breaking. Deuterium isotope effects of about 2 were also found for the enzymatic *O*-demethylations of *p*-nitroanisole, *p*-methoxyacetanilide and *p*-dimethoxybenzene and their trideuteromethyl derivatives by rat liver microsomes (Foster and coworkers 1974). Deuterium isotope effect studies in the dealkylation by rat liver microsomes of *p*-nitrophenyl alkyl ethers and their α-deuterated analogues led to the conclusion that the C–D bond breakage is the rate-determining step. A free-radical mechanism was proposed to explain the observations (Al-Gailany, Bridges and Netter 1975).

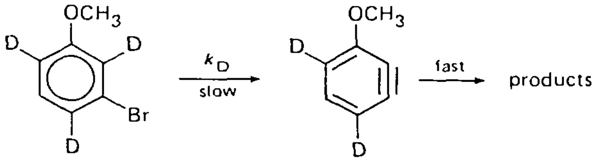
3. *Other reactions with ethers*

In the addition of 1-ethoxy-1-alkynes and 1-ethoxyvinyl esters to carboxylic acids in non-aqueous solvents (Zwanenburg and Drenth 1963a,b) HC≡COEt reacted at 25°C about three times slower with $MeCO_2D$ than it did with $MeCO_2H$.No incorporation of deuterium into unreacted alkyne occurred in benzene and sulpholane, but it did in dioxane. It was concluded that hydrogen-ion transfer and intermediate ion-pair formation is the rate-determining step, preceded by an initial equilibrium in which the alkyne is solvated by acid molecules. Similar results were obtained in the reaction of RCO_2H with ethoxyvinyl esters in benzene, dioxane and sulpholane at 25°C, which proceeded four times more slowly with $MeCO_2D$. No deuterium was incorporated into the unreacted vinyl ester.

The deuterium isotope effect in the reaction of 2,4-dinitrophenyl phenyl ether with piperidine, $C_5H_{10}ND$, in benzene at 25°C was found to be 1.27. It was suggested that this may arise from a rate-limiting proton transfer from the intermediate complex to a base (Pietra 1965).

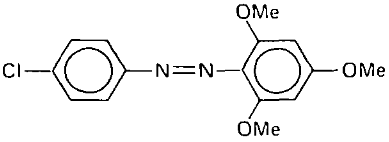
The deuterium isotope effect in the reaction of p-$MeOC_6H_4ND_2$ with $2,4$-$(O_2N)_2C_6H_3F$ and $2,4$-$(O_2N)_2C_6H_3Cl$ in benzene was between 0.95 and 1.05 and between 0.80 and 0.94 respectively, depending on the conditions (Bernasconi and Zollinger 1966).

The isotope effects in the amination of 3-BrC_6H_4OMe-2,4,6-d_3 were used as evidence for the benzyne intermediate postulated in the amination of iodobenzene-1-^{14}C-2,4,6-d_3 with KNH_2 in liquid NH_3 (equation 116) (Panar and Roberts 1960). The relatively low isotope effect [$k_H/k_D = 1.9 \pm 0.1$ for KNH_2 in NH_3 solvent and 3.1 ± 0.1 for $LiN(Et)_2$ in ether] suggests that considerable deuterium exchange takes place prior to the loss of bromine to form 3- methoxybenzyne.



(116)

An attempt to determine the deuterium and tritium fractionation in the course of the coupling of $1,3,5$-$(MeO)_3C_6D_3$ and 1,3,5-trimethoxybenzene-2-t with p-chlorobenzenediazonium ion, yielding 2,4,6-trimethoxy-4′-chloroazobenzene (25),



(25)

was made and yielded $k_T/k_H = 1.13 \pm 0.03$. Deuterium fractionation was found to be within the experimental error (Helgstrand and Lamm 1962).

Deuterium isotope effects in the reaction of p-methoxybenzenediazonium–BF_4 with deuterated amines such as dimethylaniline-2,4,6-d_3, m-toluidine-2,4,6-d_3, α-naphthylamine-2,4-d_2 and β-naphthylamine-1-d were investigated by Sziman and Messmer (1968) and it was found that the k_H/k_D ratios were 1.5, 1.0, 3.3 and 4.4 respectively. The reactions with weak bases exhibited considerable deuterium isotope effects, but the reactions with strong bases showed no isotope effect.

The deuterium kinetic isotope effect in the triphenylmethyl hexafluoroarsenate-catalysed disproportionation of substituted α, α-dideuteriobenzyl trityl ethers in CH_2Cl_2 to triphenylmethane and benzaldehydes was 9.74. The corresponding deuterium isotope effect with triphenylmethyl tetrafluoroborate was 3.56. These results have been used to show that the extent of hydrogen transfer in the rate-limiting step of the ether disproportionation depends on the type of trityl salt ion pair and not solely on the trityl cation (Doyle and Siefried 1976).

2,4,6-Trimethoxybenzaldehyde undergoes decarbonylation in deuterium acids (DCl, DBr, $DClO_4$) with slower first-order rates than in the corresponding hydrogen acids (Burkett and coworkers 1966). The rate of oxygen-18 exchange between $H_2{}^{18}O$ and the carbonyl oxygen of the aldehyde is at least 100 times faster than the rate of decarbonylation. Thus it has been concluded that acid-catalysed hydration of the aldehyde group and protonation of the ring carbon having the aldehyde group precedes the rate-controlling step of the decarbonylation reaction.

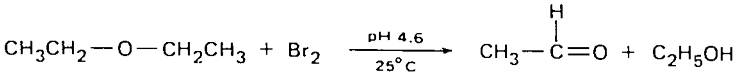
The reduction of ethylene oxide with $LiAlH_4$ was investigated with deuterated reagents and it was concluded that the reduction proceeds along several reaction paths. In one the intramolecular disproportionation of deuterium, in the product ethanol proceeded with k_H/k_D equal to about 2 (Bengsch and coworkers 1974).

Analysis of the product yields from the γ-radiolysis of $(C_2H_5)_2O$, $(CD_3CH_2)_2O$, $(CH_3CD_2)_2O$ and $(C_2D_5)_2O$ revealed that the cleavage of the α-C—H bond is the most important process in the course of hydrogen and methane formation, while β-C—H cleavage is the most important in ethylene formation. Both types of bond rupture contribute significantly to the formation of all three products of radiolysis (Ng and Freeman 1965a,b). The mechanism of the Al_2O_3-catalysed dehydration of alcohols and ethers at 316–320°C was investigated by Vasserberg, Balandin and Levi (1961) using ^{14}C-labelled dimethyl ether.

4. *Bromination and oxidation of ethers*

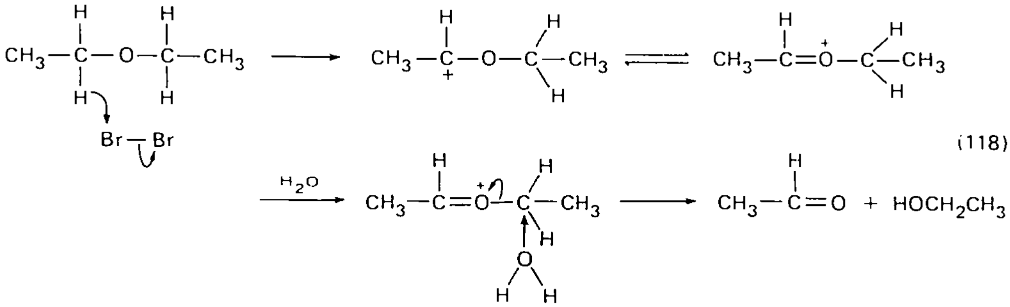
a. Bromination of ethers. No tritium isotope effect was observed in the bromination of 1,3,5-trimethoxybenzene with *N*-bromosuccinimide in dimethylformamide (Helgstrand 1964). Thus it has been concluded that the formation of free bromine from *N*-bromosuccinimide and hydrogen bromide is the rate-determining step in the formation of 1,2,4,6-$Br(MeO)_3C_6H_2$ and hydrogen bromide. No primary isotope effect was found in the bromination of partially deuterated 1,3,5-trimethoxybenzene, but a significant deuterium isotope effect was observed in the bromination of its 2-bromo derivative ($k_D/k_H = 0.28 \pm 0.08$ at 25°C), and of its 2,4-dibromo derivative ($k_D/k_H = 0.21 \pm 0.04$ at 65°C), caused by proximity effects of bromine (Helgstrand 1965). Bromination of 1,3,5-trimethoxy-2-methylbenzene and 1,3,5-trimethoxy-2,4-dimethylbenzene at −20°C in $HCONMe_2$ showed primary hydrogen isotope effects ($k_D/k_H = 0.49 \pm 0.04$ and 0.34 ± 0.04 respectively) (Helgstrand and Nilsson 1966). Deuterium isotope effects, k_H/k_D, in the bromination of anisole and anisole-2,4,6-d_3 by Br_2 and Br_3^- were found to be 1.16 and 2.6 respectively (Nandi and Gnanapragasam 1972) Br_3^- was only about 5% as reactive as Br_2 in the above reaction. The mechanisms of bromination of substituted methoxybenzenes were discussed by Aaron and Dubois (1971). The k_H/k_D in the bromination of thiophene in aqueous acetic acid was found to be 1.3. This was interpreted as a secondary effect, not representing slow proton loss. This and other studies (salt effect, activation parameters) indicate that the mechanism of bromination of thiophene is essentially the same as that of benzene derivatives (Butler and Hendry 1970). A substantial primary deuterium isotope effect was observed in nitrosation reactions of PhOH and PhOMe and their *p*-deuterium derivatives with $NaNO_2$ in aqueous $HClO_4$, proceeding via an S_E2 mechanism (Challis and Lawson 1971).

b. Oxidation of ethers. Isotopic studies of diethyl ether oxidations by chlorine and by bromine (equation 117), were undertaken by Kudesia (1975). The oxidation of $(C_2H_5)_2O$ in acetate buffer has been carried out both in H_2O and D_2O at



$$CH_3CH_2{-}O{-}CH_2CH_3 + Br_2 \xrightarrow[25^\circ C]{pH\ 4.6} CH_3{-}\overset{H}{\overset{|}{C}}{=}O + C_2H_5OH \quad (117)$$

25°C. In the case of bromine $k_2(H_2O)/k_2(D_2O) = 2.8$ and in the case of chlorine $k_2(H_2O)/k_2(D_2O) = 5.3$. Removal of hydride ion by molecular Br_2 has been proposed as the first step in the reaction (equation 118). A deuterium isotope



(118)

effect of 3.9 was observed in the oxidation of 2-methoxyethanol-1,1-d_2 to methoxyacetic acid by HNO_3 in sulphuric acid at 4–27°C. It has been proposed that

$$3\,CH_3OCH_2CD_2OH + 4\,HNO_3 \longrightarrow 3\,CH_3OCH_2CO_2H + 4\,NO + 5\,H_2O \quad (119)$$

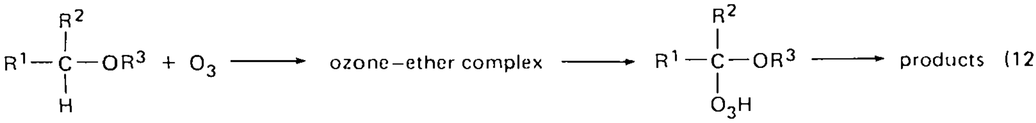
nitrosonium ion NO^+ is the active oxidizing agent and the rate-determining step of the reaction involves the cleavage of the 1-C–H bond (Strojny, Iwamasa and Trevel 1971).

The kinetics and the electron-transfer mechanism of the oxidation of *p*-methoxytoluene and other aromatic ethers and amines by manganese(III) acetate in acetic acid was investigated by Andrulis and coworkers (1966) (equation 120). The

$$MeOC_6H_4CH_3 + 2\,Mn(OAc)_3 \longrightarrow MeOC_6H_4CH_2OAc + AcOH + 2\,Mn(OAc)_2 \quad (120)$$

effectiveness of the deuterated aliphatic amines, $MeCD_2NH_2$, as inhibitors in the oxidation of Et_2O has been compared with that of undeuterated ones ($EtNH_2$) and an isotope effect of 6 : 1 was found (Jones and Waddington 1969).

Isotope effects were studied in the ozonation of ethers (Erickson, Hansen and Harkins 1968), which was found to be a complicated free-radical chain process. An unstable intermediate is formed by attack of ozone on the carbon–hydrogen bond in an insertion reaction (equation 121). The deuterium isotope effect depends on



$$R^1{-}\underset{H}{\underset{|}{\overset{R^2}{\overset{|}{C}}}}{-}OR^3 + O_3 \longrightarrow \text{ozone–ether complex} \longrightarrow R^1{-}\underset{O_3H}{\underset{|}{\overset{R^2}{\overset{|}{C}}}}{-}OR^3 \longrightarrow \text{products} \quad (121)$$

the ozonation conditions. At 0°C $k(CH_3CH_2O\text{-}t\text{-}Bu)/k(CH_3CD_2O\text{-}t\text{-}Bu) = 4.5 \pm 0.4$ (for O_3–O_2 in acetone), 2.4 ± 0.1 (for O_3–He in acetone) and 2.6 ± 0.1 (for O_3–O_2 in pyridine). At −78°C the deuterium isotope effects were larger.

Very large deuterium isotope effects have been observed in the autooxidation of the following benzyl ethers: $PhCD_2OC(CH_3)_3$ (k_H/k_D = 20.5 at 70°C), $PhCD_2O(CH_2)_3CH_3$ (5.5), $PhCD_2OCD_2(CH_2)_2CH_3$ (11.9), $PhCD_2OCD_2Ph$ (30.1) and $PhCD_2OPh$ (40.4 at 157°C). The relative reactivities for this reaction increase in the order: *n*-$BuOCH_2Ph$ < *t*-$BuOCH_2Ph$ <$(PhCH_2)_2O$ (Weisflog, Krumbiegel and Hübner 1970).

III. TRACER AND ISOTOPE EFFECT STUDIES INVOLVING SULPHIDES

A. Isotopic Studies of Decompositions and Rearrangements

The method of double-labelled molecules has been applied to the study of the gas-phase conversion sulphur-35 incorporated into diethyl sulphide and thiol molecules (Kański and Płuciennik 1972a,b). It has been found that 68 ± 11% of the primary molecular ions formed according to equation (122) stabilize in the form of

$$({}^{14}C_2H_5)_2{}^{35}S \xrightarrow{\beta^-} [{}^{14}C_2H_5{}^{35}ClC_2H_5]^+ \qquad (122)$$

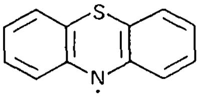
C_2H_5Cl at 0.5 mm Hg pressure. In the case of double-labelled thiol molecules (equation 123) 47 ± 3% of the primary ions originating in the β-decay of ${}^{35}S$

$${}^{14}C_2H_5{}^{35}SH \xrightarrow{\beta^-} [{}^{14}C_2H_5{}^{35}ClH]^+ \qquad (123)$$

stabilize in the form of C_2H_5Cl at 0.5 mm Hg pressure. In the presence of water vapour the yield of ${}^{14}C$-labelled $^*C_2H_5Cl$ molecules rises to 83 ± 8%.

Replacement of the H by D in methanethiol caused a significant increase in the probability of C—S bond cleavage in the photolysis of MeSD leading to formation of hydrogen and methane (Kamra and White 1977).

A primary deuterium isotope effect was observed in the formation of the radical **26** in the course of pulse radiolysis of phenothiazine (Burrows, Kemp and Welbourn 1973).



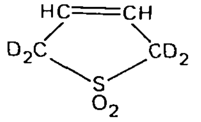
(26)

The mechanism of radioprotection has been investigated by studying the internal distribution of *S*-(2-aminoethyl)isothiuronium-${}^{35}S$ bromide hydrobromide given to rats and by observing its effect on the ${}^{32}P$ and triiodothyrosine-${}^{131}I$ uptake in various tissues (Grigorescu and coworkers 1967).

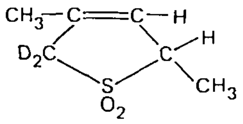
Secondary deuterium isotope effects (β and γ) in the thermal *thioallylic rearrangement* of $PhSCHMeCH{=}CH_2$ to $PhSCH_2CH{=}CHMe$ were found to be k_H/k_D = 0.936 and k_H/k_D = 0.918. These values have been interpreted in terms of a cyclic intermediate (Kwart and George 1977). The results eliminate a chain mechanism for the rearrangement and are in agreement with the interpretation of the high-precision measurements of the ${}^{32}S/{}^{34}S$ isotope effect (1.0040 ± 0.0016 at 198°C) on the thioallylic rearrangement studied earlier (Kwart and Stanulonis 1976a).

A normal secondary deuterium kinetic isotope effect was observed in the thermal rearrangement of 2-allyl-1,1-d_2-oxybenzothiazole and an inverse kinetic isotope effect for the corresponding 3,3-d_2 derivative. Introduction of a γ-Ph or a γ-Me group in the allylthio moiety of the 2-allylthiobenzothiazole caused retardation of the thermal rearrangement (Takahashi, Kaji and Hayami 1973; Takahashi, Okaue and coworkers 1973). The rearrangement proceeds with inversion of the allylic moiety and according to the concerted thio-Claisen pathway, with a transition state of a very low polar character.

Deuterium isotope effects, k_H/k_D, in the thermal decomposition of 2,5-dihydrothiophene-2,2,5,5-d_4 1,1-dioxide (27) at 120°C and 2,4-dimethyl-2,5-dihydrothiophene-5,5-d_2 1,1-dioxide (28) at 105°C were found in the melt to be 1.094 ± 0.014 and 1.054 ± 0.019, respectively. The ${}^{34}S$ isotope effect, $k({}^{32}S)/$



(27)



(28)

$k(^{34}S)$, in the decomposition of undeuterated 2,5-dihydrothiophene 1,1-dioxide was 1.009 at 99.5°C. Both deuterium and ^{34}S isotope effects were interpreted in terms of a concerted mechanism (Asperger and coworkers 1972). The maximum $^{32}S/^{34}S$ isotope effect in the C–S bond rupture equals 1.28% at 99.5°C if the value $\omega = 700\ cm^{-1}$ is taken for the C–S stretching frequency.

B. Reactions of Sulphides

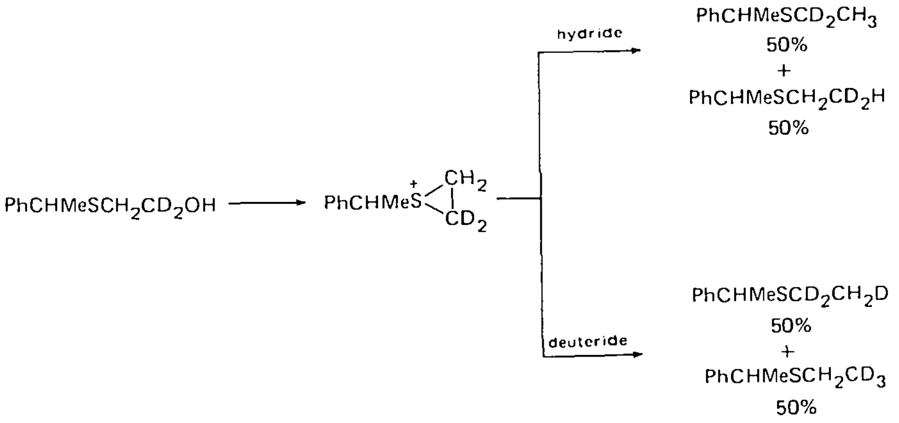
1. Cleavage and elimination reactions

Model calculations of the TIF (temperature-independent factor), TDF (temperature-dependent factor) and isotope effects, (k_{32}/k_{34}), in the carbon–sulphur bond rupture gave the values: 1.0102, 1.0083, 1.0186 and 1.0081, 1.0053, 1.0134 for the Me_3S^+ and C–S models, respectively (Saunders 1963).

The ^{34}S isotope effect in the E2 elimination of 2-phenylethyldimethylsulphonium bromide, $PhCH_2CH_2\overset{+}{S}Me_2Br^-$, with EtO^- in absolute ethyl alcohol was found to be 1.11% at 20.1°C (Hegedic 1977). It has been concluded that the carbonium character of the transition state of this reaction with ethoxide ion is greater than that in the reaction of sulphonium bromide with hydroxide ion. A large ^{14}C isotope effect has been observed in the methyl transfer from S-butyldimethylsulphonium ion, $EtCHMe\overset{+}{S}Me_2$, to p-thiocresolate ion, $4\text{-}MeC_6H_4SNa$ (Grue-Sorensen, Kjaer and Wieczorkowska 1977).

In the alkaline hydrolysis of S-adenosylmethionine in tritiated water, the uptake of tritium into the carbohydrate moiety was used as evidence of an 'ethylenic intermediate' formation (Schlenk and Dainko 1962).

The hydrogenolysis of β-hydroxyethyl thio ethers, which involves a rate-determining formation of a cyclic sulphonium ion, followed by a rapid hydrogenolysis, was studied, using β β-dideuterio-β-hydroxyethyl α-phenetyl sulphide with $LiAlH_4-AlCl_3$ and $LiAlD_4-AlCl_3$ (Eliel, Pilato and Badding 1962). The reaction with deuterium-labelled compounds proceeded according to equation (123). Thus the



(123)

existence of the cyclic sulphonium intermediate was confirmed and a convenient route of synthesis of thio ethers from carbonyl precursors and hydroxythiols established.

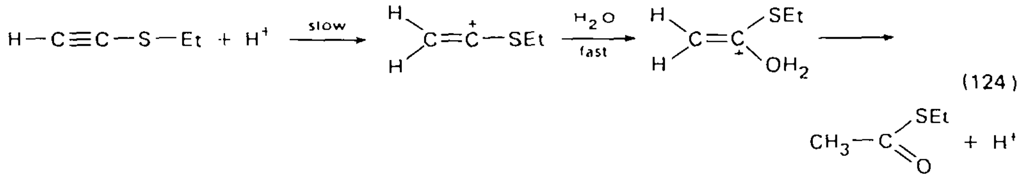
Cleavage of *p*-tolyl allyl-1-^{14}C sulphide was investigated by Chandra (1961). Treatment of the sulphide with lithium in boiling $EtNH_2$ gave 10.2% of propylene. In $MeNH_2$ only traces of propylene were noticed. Ozonation of the propylene gave a mixture of $H\overset{*}{C}HO$ and $A\overset{*}{c}H$. $H\overset{*}{C}HO$ contained 3.3–13.5% more ^{14}C than $A\overset{*}{c}H$. The presence of NH_4Cl, MeOH or the use of *i*-PrOH as solvent lowered the radioactivity of the HCHO by 2–9.8%. A similar investigation was carried out by Grovenstein (1965), who found that cleavage of the ^{14}C-labelled *p*-tolyl allyl sulphide synthesized from allyl-1-^{14}C alcohol by sodium or lithium in liquid ammonia in the presence of an excess of NH_4Cl or CH_3OH yielded propylene with ^{14}C almost equally distributed at $C_{(1)}$ and $C_{(3)}$. It has been concluded that the allyl group cleaves as the allyl-1-^{14}C carbanion. In the absence of NH_4Cl or CH_3OH the cleavage leads to the formation of propylene with preferential concentration of ^{14}C at $C_{(1)}$. Carbon–heteroatom bond cleavage has also been investigated by Curphey, Hoffman and McDonald (1967), Raj and Hutzinger (1970), Itoh and coworkers (1976) and Krawczyk and Wróbel (1977).

The mechanism of cleavage and α-substitution of dibenzylhalosulphonium salts formed in the reaction of benzyl sulphide with chlorine, bromine, *N*-chloro- and *N*-bromo-succinimide has been investigated by the competitive isotope effects method in $CDCl_3$ and CCl_4 (Wilson and Huang 1970). At low concentrations of halogen and sulphide the rate-determining step of the reaction involves halide ion attack on a single intermediate, but at initial concentrations higher than 0.3M, the decomposition of aggregates determines the ratio of cleavage to α-halogenated product formation.

Isotope effect studies have indicated that the rate of rearrangement of *N*-aryl-*S*,*S*-dimethyl sulphimides to *o*-methylthiomethylanilines is determined by the rate of proton abstraction from the S–Me group and by the equilibrium for protonation of the nitrogen atom (Claus and Rieder 1972). The mechanism of the C—S bond cleavage with deuterated acetylenes was investigated by Trofimov and coworkers (1968). $EtSCD{=}CD_2$ was obtained in the reaction of $DC{\equiv}CD$ with $EtSCH_2CH_2OD$.

2. *Reactions with sulphides*

Acid-catalysed addition of H_2O to *acetylenic thio ethers* (equation 124) proceeds in D_2O slower by a factor of 0.47 at 25°C (Drenth and Hogeveen 1960). The thio ether recovered from acidic D_2O after one half-lifetime did not contain $D{-}C{\equiv}C{-}S{-}Et$ (Hekkert and Drenth 1963). Addition of H_2O to $H{-}C{\equiv}C{-}S{-}Et$ and $D{-}C{\equiv}C{-}S{-}Et$ proceeds with an inverse secondary deuterium isotope effect, $k_D/k_H = 1.03$ (Hogeveen and Drenth 1963). It was concluded therefore that protonation of the alkynyl thioethylene is the rate-controlling step of the reaction. The correct sign of the secondary deuterium isotope effect has been qualitatively



(124)

explained by carrying out approximate calculations, based on the vibrational frequency alterations in going from the initial state to the transition state of the reaction and by considering the inductive electron-releasing effect of deuterium, which is a little larger than that of hydrogen. The acid-catalysed addition of water to the triple bond of *cis*-$MeC{\equiv}C{-}O{-}CH{=}CHMe$, in H_2O and D_2O with $HClO_4$ as catalyst, gave $k(H_2O)/k(D_2O) = 1.7$, in agreement with the calculation of deuterium solvent isotope effect by Willi. The reaction involves rate-determining proton transfer followed by addition of water (Stanhuis and Drenth 1963). Similar results, $k(H_2O)/k(D_2O) = 1.90$, have been obtained for the acid-catalysed hydration of 1-ethylthio-3-hydroxy-3-methyl-1-butyne with water (Hekkert and Drenth 1961). Drenth and Loewenstein (1962) estimated the rates of exchange of the acetylenic hydrogen in aqueous pyridine–D_2O,D_2O–Me_2CO and CH_3OD–D_2O at 21°C for $HC{\equiv}C{-}R$, where R and rate constants in $mole^{-1}\,s^{-1}$ are: $SCH{=}CH_2$, 430; *t*-BuS, 64; $O{-}CH{=}CH_2$, 60; OMe, 15; *t*-Bu, 0.8. The high rates in the thio ethers were explained by participation of sd orbitals in the transition state of the anion $^{-}C{\equiv}C{-}S{-}R$.

The mechanism of the reaction of $EtSCH_2CH_2OH$ (**29**) with $HC{\equiv}CH$, yielding at 150–200°C in the presence of KOH $EtSCH_2CH_2OCH{=}CH_2$, $EtSCH{=}CH_2$ (**30**) and $(CH_2CH_2O)_n$, was investigated by reacting $EtSCH_2CH_2OD$ with $DC{\equiv}CD$ and **29** with $PhC{\equiv}CH$. In the first isotopic reaction $EtSCD{=}CD_2$ was obtained, in the second $EtSCH{=}CHPh$. Thus it has been shown that cleavage of the C–S bond occurred in the reaction leading to $EtSCH{=}CH_2$, and the assumption that **30** was formed by dehydration of **29** was rejected (Trofimov, Atavin, Amosova and Kalabin 1968). The effect, $k_H/k_D = 1.22{-}1.40$, was found in the reaction of formaldehyde with diphenyl sulphide (and related compounds) catalysed by *p*-toluenesulphonic acid in benzene (Kunieda, Suzuki and Kinoshita 1973). The initial rate equation was $-d[CH_2O]/dt = k[\text{diphenyl sulphide}].[CH_2O].[H^+]$.

Enrichment of the heavy sulphur isotope in polysulphide and sulphide ions has been observed in the course of thiocyanation reactions (^{32}S leaves the polysulphide chain faster than ^{34}S) (Sakai 1966). The $^{32}S/^{34}S$ kinetic isotope effect in the reaction (equation 125) carried out at the natural isotope abundance level was established to be 1.022 at 24.8°C and it has been concluded that the rate-determining step should involve rupture of the S—S bond.

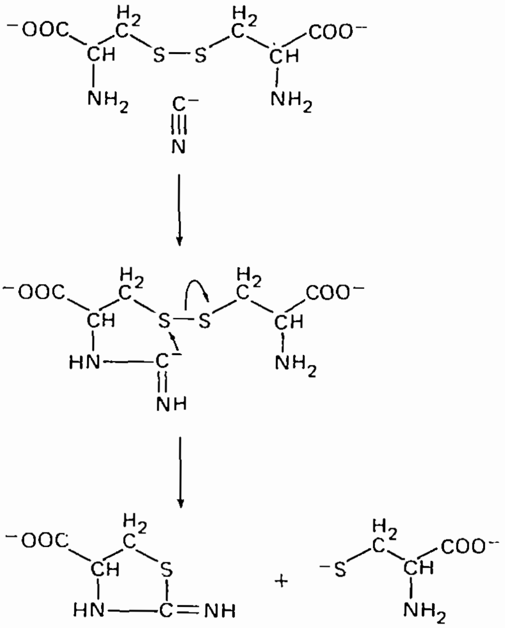
$$S_n^{2-} + (n-1)CN^- = S^{2-} + (n-1)SCN^- \qquad (125)$$

The nitrogen-15 kinetic isotope effect in the reaction of cyanide ions with ^{15}N-enriched cysteine was found to be 1.0094, demonstrating that the amino group is participating in the rate-determining step of the reaction of CN^- with the $-S-S-$groups of the amino acid (equation 126) (Wagner and Davis 1966).

The mechanism of chlorination of dimethyl sulphide with sulphuryl chloride was investigated using ^{36}Cl-labelled $SO_2\overset{*}{C}l_2$ (Schultze, Boberg and Wiesner 1959). The radioactivity was spread statistically between all chlorine atoms in the product and in the HCl evolved. Chlorolysis of the intermediate CCl_3SCH_2Cl produced CCl_3SCl and CCl_4. Analysis of the distribution of the radioactivity between the chlorolysis products showed that the cleavage of CCl_3SCH_2Cl was more important than that of CCl_3SCHCl_2.

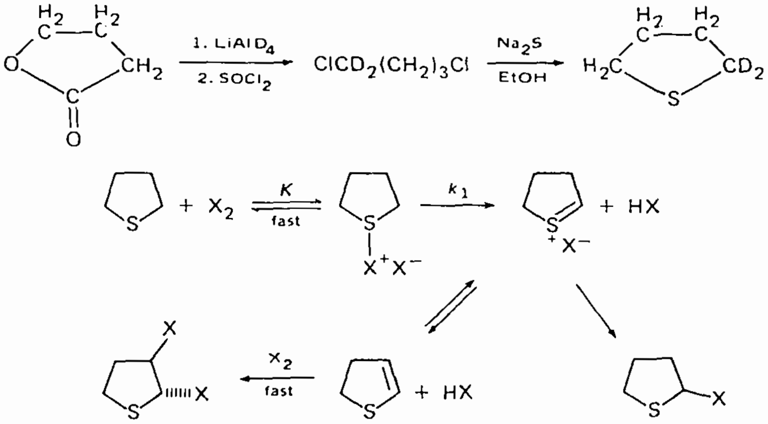
Isotope effects of 5.1 and 3.6 have been found in chlorination and bromination respectively of 2,2-dideuteriothiophane (Scheme 10) (Wilson and Albert 1973). The initial equilibrium is considered to be fast and the proton removal is considered rate limiting. Addition of CF_3CO_2H, *p*-$MeC_6H_4SO_3H$ and BF_3 to the reacting medium increased the amount of 2,3-dihalothiophane formation.

The mechanism of oxidation of S^{2-}, SO_3^{2-} and $S_2O_3^{2-}$ as well as that of Na_2S, H_2S and PbS with H_2O_2 using ^{18}O as a tracer has been investigated. It has been found that in the first case two atoms of oxygen from H_2O_2 enters into the oxidation reaction, while in the second case 90% of oxygen comes from H_2O_2 and 10% from H_2O (Burmakina-Lunenok 1964). Oxidation of organic sulphides and the syntheses of $Ph^{35}S(O)SPh$ and $Ph^{35}SS(O)Ph$ were investigated by Barnard and Percy (1962).


(126)

3. *Reactions leading to sulphides and ethers*

In a study of the Williamson synthesis of optically active ethers it has been found that the configuration of the alcoholate, attacking the alkyl halide at the side


SCHEME 10.

opposite the departing halogen, does not change (Norula 1975). Chlorine isotope effects, $k(^{35}\mathrm{Cl})/k(^{37}\mathrm{Cl})$, have been used to evaluate the transition-state structures of the S_N2 reaction of *n*-butyl chloride with thiophenoxide anion in MeOH (Julian and Taylor 1976). The central transition-state model results exactly fitted the observed values of 1.00898 and 1.00792 at 20 and 60°C, respectively. Calculated α-deuterium isotope effects for this model are also in good agreement with the experimental ones. Chlorine kinetic isotope effects, k_{35}/k_{37}, in model S_N2 reactions (i.e. *t*-butyl chloride solvolysis and reaction of *n*-butyl chloride with thiophenoxide anion) in anhydrous methanol have been investigated both experimentally and theoretically by several research groups (Turnquist and coworkers 1973, and others). The α-carbon ^{13}C isotope effect in the S_N2 reaction of benzyl bromide and 1-bromo-1-phenylethane with $\mathrm{EtO^-}$ was redetermined by Bron and Stothers (1968). The first data concerning the reaction of 1-phenyl-1-bromoethane with $\mathrm{EtO^-}$ in EtOH and of benzyl bromide with $\mathrm{MeO^-}$ in MeOH, ($k_{12}/k_{13} = 1.0531$) were reported by Stothers and Bourns (1962).

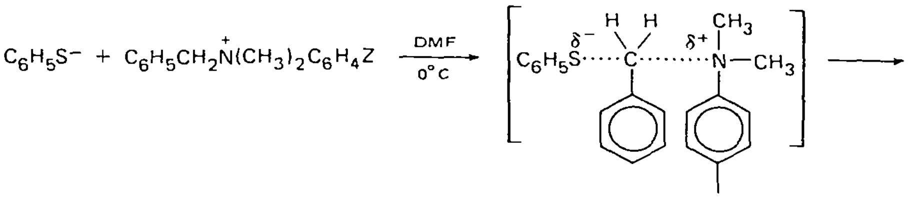
Comparative studies of the deuterium exchange (k_e) and of the epimerization (k_α) rate ratios for *dl*- and meso-α-methylbenzyl sulphones ($\mathrm{PhCH(Me)SO_2CH(Me)Ph}$), in MeOH showed that the ratios of rate constants for these two processes, k_e/k_α, are 196 (at 0°C), 90 (at 25°C), 27 (at 72°C) and 16 (at 100°C). The above results have been interpreted either as favouring an effectively planar structure of the α-sulphonyl asymmetric carbanion, with racemization by rotation, or as a measure of the relative rates of proton removal to form asymmetric or symmetric carbanions (Bordwell, Phillips and Williams 1968). The authors final conclusion was that $[\mathrm{PhCMeSO_2R}]^-$ carbanions are rapidly inverting (i.e. effectively planar).

In an investigation of the nucleophilic substitutions of *cis* and *trans* arylsulphonylhaloethylenes, $\mathrm{ArSO_2CH{=}CHX}$ and $\mathrm{ArSO_2CD{=}CHX}$, where X = Cl, Br, with $\mathrm{MeO^-}$ and $\mathrm{PhS^-}$ in MeOH no deuterium isotope effect was observed. Reaction of $\mathrm{ArSO_2CD{=}CHX}$ (X = Cl,Br) with MeONa in MeOH gave $\mathrm{ArSO_2CH{=}CHOMe}$, while with PhSNa $\mathrm{ArSO_2CH{=}CHSPh}$ was produced (Ghersetti and coworkers 1961). Similar results were obtained in the reaction of $\mathrm{ArSO_2CH{=}C(Me)X}$ with methoxide and phenoxide ions. The deuterium exchange rate of *trans*-$\mathrm{ArSO_2CH{=}CHBr}$ and *cis*- and *trans*-$\mathrm{ArSO_2CH{=}CHCl}$ was higher than the substitution rate. Absence of deuterium/hydrogen exchange in the reaction with $\mathrm{ArSO_2C(Me){=}CHX}$ and the high deuterium exchange rate and stereospecificity with $\mathrm{ArSO_2CH{=}CHX}$ and $\mathrm{ArSO_2CH{=}C(Me)X}$ suggested that the nucleophilic substitution in the last two proceeds according to equation (127).

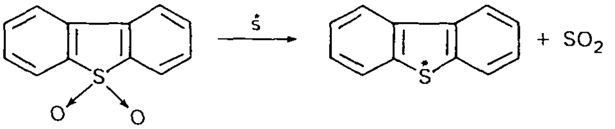
$$\mathrm{ArSO_2CH{=}CRX} \longrightarrow \mathrm{Ar{-}SO_2{-}\bar{C}{=}CRX} \longrightarrow \mathrm{ArSO_2C{\equiv}CR} \longrightarrow \textit{cis}\text{-}\mathrm{ArSO_2CH{=}CROMe}$$

$$\mathrm{R = H, Me} \tag{127}$$

A large nitrogen kinetic isotope effect $k_{14}/k_{15} = 1.0200 \pm 0.0007$ has been found in the nucleophilic substitution of phenylbenzyldimethylammonium nitrates with sodium thiophenoxide in *N,N*-dimethylformamide (equation 128) (Westaway and Poirier 1975), and it has been concluded that it proceeds according to the S_N2 mechanism with substantial simultaneous carbon–nitrogen bond rupture and carbon–sulphur bond formation in the transition state. This was confirmed (Westaway 1975) by further studies of the α-secondary deuterium kinetic isotope effect, which was found to be also large ($k_H/k_D = 1.19 \pm 0.01$, i.e. 1.09 per α-deuterium).


(128)

Dibenzothiophene-5-dioxide treated with sulphur yields dibenzothiophene at 320–390°C. The two possible reaction paths are either that sulphur removes oxygen

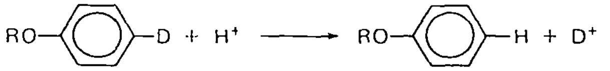

(129)

atoms from the sulphone group, or that it displaces the whole SO_2 group (equation 129). The problem was rigorously solved by using radiosulphur ^{35}S, and showing that the product contains radiosulphur. Thus it has been demonstrated that the process under study is an exchange reaction. This was additionally confirmed by measuring the radioactivity of the sulphur dioxide and small amounts of hydrogen sulphide, which were collected, oxidized to sulphate and radioassayed. The activity of these samples was less than 3% of that in the original ^{35}S-labelled sulphur (Brown and coworkers 1951). Earlier investigations of the nitrogen, oxygen, sulphur and chlorine isotope effects, have been reviewed by Fry (1970, 1972) and Maccoll (1974).

IV. ISOTOPE EXCHANGE STUDIES WITH ETHERS AND SULPHIDES

A. Deuterium and Tritium Exchange Studies

Lauer and Day (1955) have investigated the acid-catalysed exchange between deuterium in the *ortho* and *para* position of phenyl alkyl ethers (equation 130).


(130)

The data given in brackets are, k in s^{-1}, estimated at 80 and 100°C, respectively: *p*-deuteroanisole (0.88×10^{-4}, 3.0), *o*-deuteroanisole (0.29, 1.5), *p*-deuterophenetole (4.0 at 100°C), *p*-deutero-*n*-propyl ether (4.05 at 100°C), *p*-deuteroisopropyl ether (7.45 at 100°C). In the case of labelled anisole, the *ortho/para* ratio of exchange rates equals 0.5 at 100°C and 0.33 at 80°C, in qualitative agreement with data obtained in substitutions in phenols and their ethers. The deuterium exchange reaction studied is an electrophilic process, clearly influenced by the inductive effect of the alkyl groups in the alkyl phenyl ethers: The relative rates of exchange at 100°C are correspondingly: 1.00 (for methyl) $<$ 1.33 (for ethyl) $\leqslant$ 1.35 (for *n*-propyl) $<$ 2.48 (for isopropyl).

Nuclear deuteration was established in the majority of di- and tri-methoxybenzenes heated with D_2O–dioxan (3 : 1), at 95°C even in the absence of an acidic catalyst (Kolar 1971). No deuterium exchange was noticed in the case of methoxybenzene and of 1,2-dimethoxybenzene under mild experimental conditions, but with 1,3-dimethoxybenzene and 1,2,3-, 1,2,4- and 1,3,5-trimethoxybenzenes the exchanges were 36.2%, 21.5%, 16.1% and 100%, respectively, in agreement with the electron-releasing effect of the substituents. In the case of 1,3,5-methoxybenzene under similar conditions all nuclear hydrogens have been exchanged. Full deuterium exchange of both nuclear hydrogens of catechin 5,7,3′,4′-tetramethyl ether and of 5,7,3′,4′-tetramethoxyflavan was also achieved. However, dihydroquercetin 5,7,3′,4′-tetramethyl ether and 5,7,3′,4′-tetramethoxy-2,3-*trans*-flavan-3,4-*cis*-diol failed to undergo deuterium exchange.

The kinetics and mechanism of the aromatic hydrogen exchange in 1,3,5-trimethoxybenzene has been investigated by several research groups (Kresge and Chiang 1962; Kresge and Chiang 1967a,b; Kresge, Chiang and Sato 1967; Batts and Gold 1964). The reaction is subject to general acid catalysis and the mechanism is consistent with the schemes accepted for other electrophilic aromatic substitutions.

The rates of simultaneous loss of T and D from 1,3,5-trimethoxybenzene was studied by Batts and Gold (1964). In $D_2O-DClO_4$ solution the loss of T is 1.68 times faster than in $H_2O-HClO_4$ solutions of the same acid concentration. In deuterated acetate buffer solution the acetic acid-catalysed reaction is slower than in light medium. Three isotopes of hydrogen as tracers in different pairwise combinations have been used also by Kresge and Chiang (1967a) and Kresge, Chiang and Sato (1967) to study the acid-catalysed aromatic hydrogen exchange in 1,3-di- and 1,3,5-tri-methoxybenzene (Kresge and Onwood 1964). The medium D_2O effect on the detritiation of 1,3,5-trimethoxybenzene-2-t and azulene-1-t was also studied (Kresge, Sagatys and Chen 1977). The D–H isotope effects in reaction (131), with k_1 slow and ArH = 1,3,5-trimethoxybenzene, was found to be k_1^{H}/k_1^{D} =

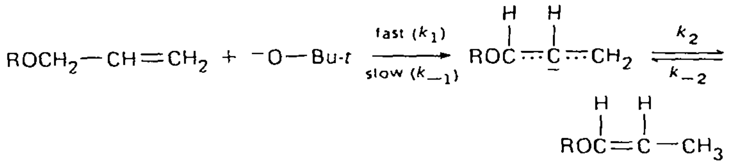
$$\mathrm{H'Ar} + \mathrm{H^+{-}(H_2O)}_n \xrightarrow{k_1} \mathrm{H'ArH^+} + n\,\mathrm{H_2O} \xrightarrow{k_2} \mathrm{ArH} + \mathrm{H'^+{-}(H_2O)}_n \qquad (131)$$

2.93 ± 0.07 and $k_2^{H}/k_2^{D} = 6.68 \pm 0.18$ (Kresge and Chiang 1962). The secondary hydrogen isotope effect on hydrogen ion transfer from the hydronium ion was found to be $(k_H/k_D)_{sec} = 0.59 \pm 0.01$ at 25°C (Kresge, Onwood and Slae 1968). Deuterium isotope fractionation between water and solvated protons was determined by Heinzinger and Weston (1964) (Kreevoy 1976). In a study of D–H exchange in $1,3,5\text{-}(MeO)_3C_6H_3$, Ph_2O, PhSMe, PhMe, PhEt, and *o*-, *m*- and *p*-xylene, catalysed by $MeSOCH_2-M$, where M = Li, K, Cs, the kinetics of isotopic exchange were found to depend on the size of the catalyst cation (Shapiro and coworkers 1976). Me_2S and Et_2S exchange readily their α-hydrogens with $(CD_3)_2SO$ in the presence of sodium at 100°C, while $Si(Me)_4$ did not exchange under similar conditions (Price and Sowa 1967). The catalytic deuterium exchange between ethers and deuterium on metal films was investigated by Forrest, Burwell and Shim (1959) and Clarke and Kemball (1959). The main exchange products of Et_2O and Pr_2O were $C_2D_5OC_2H_5$ and $C_3D_7OC_3H_7$ respectively.

The rate of OD^--catalysed exchange of protons of weak acids including $MeOC{\equiv}CH$ and $p\text{-}MeOC_6H_4C{\equiv}CH$ has been investigated in dimethylformamide solutions containing D_2O and Et_3N (Dessy, Okuzumi and Chen 1962). The literature concerning D/H and H/D exchange in methoxyacetone, $CH_3OCH_2COCH_3$, has been reviewed by Lamaty (1976). Titanium complex-catalysed hydrogen–deuterium exchange between gaseous D_2 and anisole was investigated by Shur and coworkers (1975). Infrared absorption of anisole-4d was studied by Thiers and Thiers (1952). In the course of isomerization of alkyl allyl ethers to alkyl *cis*-propenyl ethers in refluxing *t*-BuOD in the presence of potassium *t*-butoxide, the deuterium incorporates into the methyl position of the propenyl group (equation 132) (Broaddus 1965). Alkyl *cis*-propenyl ethers do not undergo deuterium

$$\mathrm{ROCH_2CH{=}CH_2 + KO{-}Bu\text{-}}t \xrightarrow{t\text{-BuOD}} \mathrm{ROCH{=}CHCH_2D} \qquad (132)$$

exchange under the same conditions. The exchange accommmpanying the isomerization proceeds through the allyl anionic intermediate which protonates yielding the more stable alkyl *cis*-propenyl ether (equation 133).

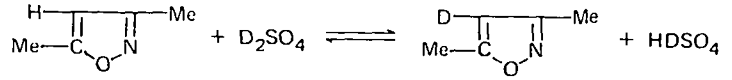


$$\mathrm{ROCH_2{-}CH{=}CH_2 + {}^{-}O{-}Bu\text{-}}t \underset{\text{slow }(k_{-1})}{\xrightarrow{\text{fast }(k_1)}} \mathrm{RO\overset{H}{C}{\cdots}\overset{H}{\underset{-}{C}}{\cdots}CH_2} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{RO\overset{H}{C}{=}\overset{H}{C}{-}CH_3} \qquad (133)$$

$k_1 > k_2; k_{-2} > k_{-1}$

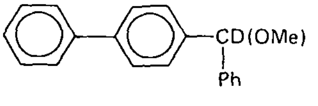
Detailed kinetic studies of deuterium exchange between fluorene-9d and p-$\mathrm{MeOC_6H_4COMe}$, t-BuOH and indene in the presence of t-BuOLi in different ethers have been carried out by Shatenshtein, Bessonov and Yakovleva (1965) and Shatenshtein and Gvozdeva (1965), with the aim of revealing the relative solvating capacities of the ethers and their effect on the polarity of the Li–O bonds. The kinetics of hydrogen–deuterium exchange of numerous ethers and sulphides having the general structure $\mathrm{RXCD_3}$, where X = S, O in liquid $\mathrm{NH_3}$ or $\mathrm{ND_3}$ as solvents and $\mathrm{KNH_2}$ as catalyst has been investigated by Shatenshtein, Rabinovich and Pavlov (1964a,b), Shatenshtein, Bessonov and Yakovleva (1965), Shatenshtein and Gvozdeva (1965) and Gvozdeva and coworkers (1969). In general the rates of deuterium exchange in $\mathrm{RSCD_3}$ compounds were much higher than in $\mathrm{C_6H_6}$ or in $\mathrm{PhOCD_3}$, $\mathrm{PhN(CD_3)_2}$ and p-$\mathrm{Me_2NC_6H_4OCD_3}$ due to expansion of the electron shell of sulphur by transfer of s electrons into the 3d orbitals. The deuterium exchange rates and acidities decreased in $\mathrm{RXCD_3}$ compounds in the order X = S > O > N. The rate constants of deuterium exchange of $\mathrm{Me_2S}$, $\mathrm{PhSCD_3}$, p-$\mathrm{Me_2NC_6H_4SCD_3}$, $\mathrm{PhSCD_2Me}$ and $\mathrm{PhSCDMe_2}$ with $\mathrm{KNH_2}$ in liquid $\mathrm{NH_3}$ are: $2 \times 10^{-4}\,\mathrm{s^{-1}}$ at 0°C, $1 \times 10^{-1}\,\mathrm{s^{-1}}$ at −60°C, $2 \times 10^{-3}\,\mathrm{s^{-1}}$ at −30°C, $3 \times 10^{-3}\,\mathrm{s^{-1}}$ at −30°C and $3 \times 10^{-5}\,\mathrm{s^{-1}}$ at −30°C. Further studies of the hydrogen exchange between sulphides $\mathrm{CD_3SR}$, where R = $\mathrm{PhCH_2}$, Me, t-Bu, c-Hex, c-Pe and Ph, in liquid $\mathrm{NH_3}$ catalysed by $\mathrm{KNH_2}$, showed that the relative rates of exchange are 2.3, 40, 550, 600 and 10^6 respectively (Gvozdeva and coworkers 1969). The fast exchange in the case of $\mathrm{CD_3SPh}$ was explained by phenyl participation on the carbanion stabilization. In a solution of $\mathrm{KNH_2}$ in liquid $\mathrm{NH_3}$ the D-exchange rate constants of o-, m- and p-$\mathrm{DC_6H_4SMe}$ were $2.2 \times 10^{-4}\,\mathrm{s^{-1}}$, $3.7 \times 10^{-4}\,\mathrm{s^{-1}}$ and $1.2 \times 10^{-4}\,\mathrm{s^{-1}}$ respectively. The D-exchange rate constants of o- and p-$\mathrm{DC_6H_4SMe}$ in glacial HOAc containing 2 mole % $\mathrm{H_2SO_4}$ were found to be $1.8 \times 10^{-6}\,\mathrm{s^{-1}}$ and $6.4 \times 10^{-6}\,\mathrm{s^{-1}}$, respectively, and the ratio of these rate constants to the corresponding rate constants for D-exchange in $\mathrm{C_6H_6}$ were 110 and 390, respectively. The rate of detritiation of the *ortho* position of PhSMe in $\mathrm{CF_3{-}CO_2H}$ at 70°C was investigated by Taylor and Bailey (1971). Deuterium and tritium isotope effects in the exchange reaction of $\mathrm{CF_3CO_2H}$ with durene, 1,2,4,5-$\mathrm{C_6H_2(CH_3)_4}$, and 2,5-di-t-butylthiophene have been determined in n-hexane, liquid $\mathrm{SO_2}$ and sulpholane and found to be in the range $k_\mathrm{D}/k_\mathrm{T} = 1.1{-}1.7$ (Serebryanskaya and coworkers 1973). Kinetic isotope effects, $k_\mathrm{T}/k_\mathrm{D}$, in the heterogeneous exchange of D and T in the 2- and 3-positions of thiophene with hydrogen in aqueous sulphuric acid are 0.51 ± 0.03 and 0.59 ± 0.04 correspondingly. The specific rate constants, expressed in $\mathrm{h^{-1}}$ for deuterium exchange in 57% aqueous $\mathrm{H_2SO_4}$ at 24.6°C are equal to 1.40 ± 0.03 for thiophene-2-d and 0.00134 for thiophene-3-d (Ostman and Olsson 1960).

The kinetics of hydrogen exchange at $C_{(4)}$ in 3,5-dimethylisoxazole was investigated in D_2SO_4 or CF_3CO_2D at 20–70°C (equation 134) (Setkina and Sokolov 1964). At 30°C and 50°C the rate constants of exchange are 4×10^{-7} s^{-1} and 60×10^{-7} s^{-1} respectively. The initial rates of deuterium reversible exchange between D_2 and hydrogen at the *para* position of $PhCN^{-}K^{+}$ ion radical salt, obtained in the reaction of benzonitrile (10^{-4}–10^{-2} M), with alkali metal in ca. 80 cc of dry tetrahydrofuran, monoethylene glycol dimethyl ether, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether or benzonitrile (in the temperature range from −20 to +50°C) were found to depend strongly on the nature of the ether (chelating solvents) used (Ichikawa and Tamaru 1971). The action of the chelating solvents was attributed to the solvation of alkali cations leading to a wide separation between anion and cation centres in the complex molecule and thus preventing the development of favourable conditions for the hydrogen activation.



(134)

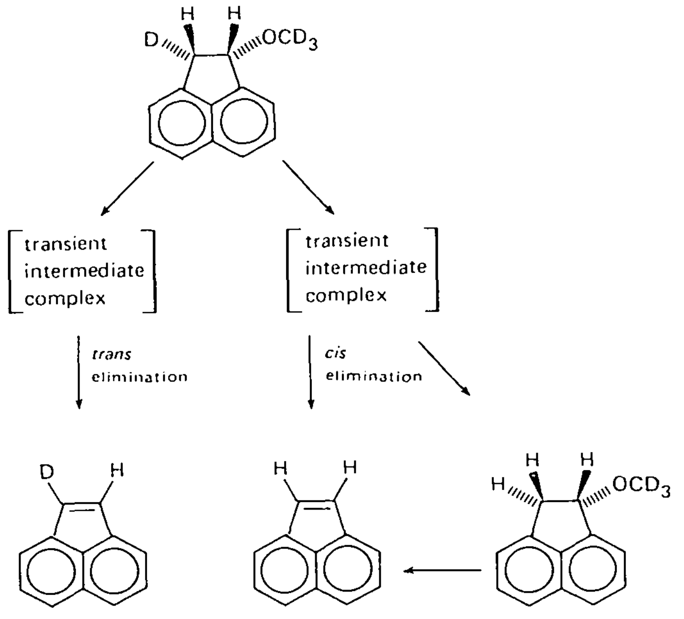
The kinetics of racemization and the kinetics of deuterium isotopic exchange of optically active 4-biphenylyldeuterio(methoxy)phenylmethane (31) in *t*-butyl alcohol—*o*-d-potassium *t*-butoxide have been investigated (Kollmeyer and Cram 1968). At 116°C the rate constant for isotopic exchange with retention was 33 times larger than that for isotopic exchange with inversion. The kinetic isotopic effect for racemization in deuterated solvent was $(k_H/k_D)_\alpha = 2.7$ at 116°C. The presence of a crown ether changed greatly the rate and the stereochemical course of the *t*-BuOK-catalysed reaction in *t*-BuOH solution, leading to H–D exchange (Cram and Roitman 1971). At 70°C in the presence of the crown ether $(k_{ex.}/k_{rac.}) = 1$, while in the absence of ether this ratio was 46.



(31)

The stereochemical course of the H–D exchange reactions of 2-phenylbutane, 2-phenylbutane-2-d, 1-phenyl-methoxyethane and 1-phenylmethoxyethane-1-d have been investigated by infrared analysis, with *t*-BuOK as base, in deuterated and ordinary *t*-BuOH (Cram, Kingsbury and Rickborn 1961). In *t*-BuOH the exchange proceeded with 97% net retention of configuration in contrast to Me_2SO where 100% racemization occurred. Substitution of sodium for potassium *t*-butoxide hardly changed the rate constant in *t*-BuOH but in Me_2SO depressed it by a factor of 100. The rates in *t*-BuOH were much slower than in Me_2SO.

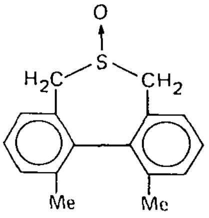
The stereochemistry of the base-catalysed H–D exchange and elimination of three D-labelled 1-methoxyacenaphthenes was also investigated (Scheme 11). In *t*-butyl alcohol with *t*-butoxide as base the sterochemistry of both exchange and elimination depends on the nature of the cation. Li^+ gave *cis* reaction only, while Me_4N^+ and K^+-crown ether gave *trans* reaction. Cs^+ and K^+ gave intermediate results, which were explained in terms of the coordination of M^+ cation–base ion pair of the oxygen of the methoxy group of substrate (Hunter and Shearing 1971, 1973). Both exchange and elimination proceed through a carbanionic intermediate. Exchange occurs predominantly at the 2-position. The kinetic isotopic effects, k_H/k_D, where k_H is the rate of elimination from 1-methoxyacenaphthene, and k_D


transient intermediate complex
transient intermediate complex
trans elimination
cis elimination

SCHEME 11.

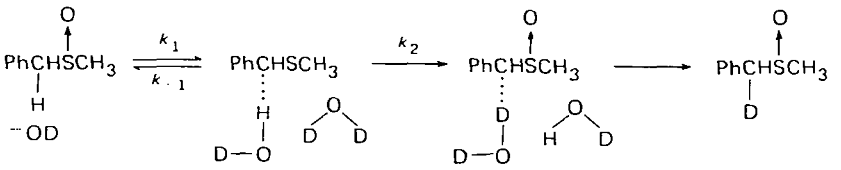
is that from 1-methoxy-d$_3$-1,2,2-trideuterioacenaphthene, in *t*-butyl alcohol with Cs$^+$, K$^+$ and K$^+$-crown ether fall in the range 1.6–1.8.

The Et$_3$N-promoted E1cB elimination of HF from PhSO$_2$CHD–CHF–SPh, was found to be *syn*-stereospecific and led to the formation of *trans*-PhSO$_2$CH=CHSPh and *trans*-PhSO$_2$CD=CHSPh(Fiandanese, Marchese and Naso 1972). Primary isotope effect (k_H/k_T and k_D/k_T) determinations showed that internal return is negligible in the isotopic exchange of the diastereotopic proton of PhCH$_2$SOMe (equation 135) and but is dominant in the bridged biaryl sulphoxide **32** (in



(32)

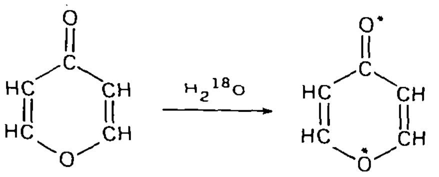
t-BuOD). The k_2^H/k_2^T ratio in benzyl methyl sulphoxide was found to be 3.2, while the low values for k_H/k_T of 1.21 and 1.41 were obtained for isotopic exchanges at H$_{(1)}$ and H$_{(2)}$ using stereoselectively tritiated samples of bridged biaryl sulphoxide (Fraser and Ng 1976).



(135)

B. ^{18}O, ^{35}S and ^{36}Cl Exchange Studies

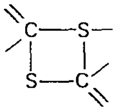
The exchange reaction between γ-pyrone and ^{18}O-enriched water has been studied in basic, neutral and acidic conditions (equation 136) (Beak and Carls 1964; Ichimoto, Kitaoka and Tatsumi 1966). In basic medium twice as much of the ^{18}O was incorporated into γ-pyrone as in neutral and acidic media. It has been concluded therefore that ^{18}O incorporates into the ring of γ-pyrone through a HOCH=CHCOCH=CHOH intermediate. To confirm the above assumption a similar ^{18}O-exchange study was carried out with 4-thio-γ-pyrone and the same profile of the ^{18}O content as a function of pH was obtained as in the previous study.



(136)

The rate of the thermal ^{35}S isotope exchange between organic sulphides and thiols, proceeding according to the radical mechanism, has been investigated (Obolentsev and Nikitin 1965). The rate of the RS radical exchange between sulphides and thiols depends only on the concentration of the sulphides. Fast exchanges occur between long-chain sulphides and normal thiols of low molecular weight. Secondary and tertiary thiols exchange at slower rates. Disulphides are formed during the heating of sulphides with thiols. The exchange between radioactive sulphur in xylene solution and tetramethyl thiuramdisulphide, tetramethyl thiurammonosulphide and 2-benzothiazolyl disulphide proceeds in two consecutive steps (Azami and Shizuka 1965). In the first step the S–S bonds dissociate into radicals which then react with *S atoms. In the case of the monosulphide the radicals are formed by dissociation of the C–S bond.

Isotopic exchange between ^{35}S-urea and *N*-substituted thioureas in EtOH and EtOH–C_6H_6 mixtures at 105°C on paper (Marcotrigiano and Battistuzzi 1968) proceeds through a cyclic arrangement (33) like the ^{35}S isotope exchange in thiurams and dithiocarbamic acid esters (Kuzina and Gur'yanova 1959). The exchange rate increases with the number of sulphur atoms in the polysulphide bridge. The two middle sulphur atoms in tetramethylthiuram tetrasulphide are more readily exchanged than the sulphur atoms bound also to carbon. Substitution of aliphatic radicals for phenyl radicals in thiuram disulphides lowers the exchange rate. The exchange of sulphur in ^{35}S-labelled polysulphides has also been studied by Koros and coworkers (1960). Hydrothermal exchange and fractionation of sulphur isotopes with inorganic sulphides was studied by Schiller, Von Gehlen and Nielsen (1970). Secondary deuterium isotope effects in the reaction of chloromethyl phenyl sulphides and ethers with labelled chlorides indicate the looseness of the transition state (Tanaka, Kaji and Hayami 1972). Substituted 2-phenylethyl chlorides seem to react through a more closely held transition state.



(33)

V. ISOTOPIC STUDIES OF COMPLEXES WITH ETHERS AND SULPHIDES

Polaczek and Halpern (1963) have shown that addition of diethyl ether and other electron-donor substances such as H_2O, EtOH, $BuNH_2$ caused strong blocking of isotopic exchange between $M^{131}I_3$ and RI, where M = Al, Ga or In and R = Me, Et or Pr, due to formation of complexes with MI_3. Infrared and Raman spectra of normal and perdeuterated complexes of *trans*-palladium(II)L_2X_2, where L = methyl sulphide and methyl-d_3 sulphide and X = chloride, bromide and iodide, have been studied and the distortion of the ligand around the PdS bond has been revealed (Tranquille and Forel 1975). It has also been found that thiomethyl ethers coordinate weakly to Fe(II) porphyrins (Castrio 1974).

Deuterium, chlorine and oxygen isotope effects in the isotope exchange distillation of dimethyl ether hydrochloride (equations 137–139) have been determined at

$$(CH_3)_2O{\cdot}HCl + DCl \rightleftharpoons (CH_3)_2O{\cdot}DCl + HCl \qquad (137)$$

$$(CH_3)_2O{\cdot}H^{35}Cl + H^{37}Cl \rightleftharpoons (CH_3)_2O{\cdot}H^{37}Cl + H^{35}Cl \qquad (138)$$

$$(CH_3)_2{}^{16}O{\cdot}HCl + (CH_3)_2{}^{18}O \rightleftharpoons (CH_3)_2{}^{18}O{\cdot}HCl + (CH_3)_2{}^{16}O \qquad (139)$$

−11 to 0°C. The separation factor α for deuterium equals $\ln\alpha = 0.432-(105.4/T)$; for oxygen-18 (which concentrates in the liquid phase) it is 1.006 ± 0.003, and for chlorine isotopes it is below 1.002, i.e. within the experimental error (Cuker and Ribnikar 1962).

Infrared spectra of DCl with various aliphatic ethers in the gas phase have been recorded and interpreted by Bertie and Millen (1965). Examination of the spectra of solutions of HNCS and DNCS in inert solvents with ethers revealed frequency shifts similar to those observed with HCl and HBr (Barakat, Legge and Pullin 1963).

Infrared spectra involving hydrogen bonding of MeOD with ethers such as Et_2O, $EtO(CH_2)_2OMe$, $MeO(CH_2)_2O(CH_2)_2OMe$, etc., have also been reported (Ginzburg, Petrov and Shatenshtein 1964). The enthalpies of formation of ether (Et_2O, Pr_2O, Bu_2O, etc.)–hydrogen halide (HCl, HF) complexes have been determined by calorimetry (Dunken, Fischer and Zahlten 1961).

Using already published vibrational frequencies it has been demonstrated that boron trifluoride coordination compounds with dimethyl ether and dimethyl sulphide can be used to separate oxygen and sulphur isotopes (Fonassier and Forel 1973). The calculated equilibrium constants K for (140), where n = 18 and 17, at

$$Me_2{}^{16}O{\cdot}BF_3(l) + Me_2{}^{n}O(g) \rightleftharpoons Me_2{}^{n}O{\cdot}BF_3(l) + Me_2{}^{16}O(g) \qquad (140)$$

250–400 K, are 1.017–1.039 and 1.008–1.019 for ^{18}O and ^{17}O respectively. In the case of dimethyl sulphide the equilibrium constants of the exchange reaction (141), where m = 34 and 33, respectively, are found to be K = 1.0035–1.0085 and

$$Me_2{}^{32}S{\cdot}BF_3(l) + Me_2{}^{m}S(g) \rightleftharpoons Me_2{}^{m}S{\cdot}BF_3(l) + Me_2{}^{32}S(g) \qquad (141)$$

1.0018–1.0043 in the same temperature interval. Calculated ^{10}B–^{11}B equilibrium separation factors for the reaction (142) are K = 1.029–1.048 and 1.018–1.041 for

$$Me_2X{\cdot}{}^{11}BF_3(l) + {}^{10}BF_3(g) \rightleftharpoons Me_2X{\cdot}{}^{10}BF_3(l) + {}^{11}BF_3(g) \qquad (142)$$

X = S and X = O respectively. Equilibrium constants for the exchange reactions of the type shown in equation (143) where D_0 = donor, have been extensively investigated by numerous research groups (Palko and Drury 1967; Nahane and Isomura

$${}^{10}BF_3(g) + {}^{11}BF_3{\cdot}D_0(l) \rightleftharpoons {}^{11}BF_3(g) + {}^{10}BF_3{\cdot}D_0(l) \qquad (143)$$

1966; Knyazev and coworkers 1970; Voloshchuk and coworkers 1973; Voloshchuk, Katal'nikov and Knyazev 1974; Voloshchuk, Karetnikov and coworkers 1974; Voloshchuk, Katal'nikov and coworkers 1974). The equilibrium constants for this reaction depend on the donor, and at 30°C the following order has been observed:

$$Et_2S > Me_2S > Me_2Se > Bu_2S > Et_2O > PhOMe > Me_2O > (CH_2)_4O > Ph_2O > Et_3N$$

(Palko and Drury 1964, 1967). Palko (1965) also investigated the coordination of compounds of Ph_2S with BCl_3, which was found to be stronger ($\Delta H = -8.7$ kcal/mol, T (K) = 311.2–325.3, m.p. = 42°C) than $BCl_3{\cdot}Ph_2O$ ($\Delta H = -5.32$ kcal/mol, m.p. = ca. 4°C). Boron trifluoride complexes with many aliphatic, haloaliphatic and aromatic ethers and other Lewis bases have been investigated isotopically by Katal'nikov and Kung (1965). Katal'nikov, Pisarev and Oistach (1971), Voloshchuk, Katal'nikov and Knyazev (1974), Voloschuk, Karetnikov and coworkers (1974) and Voloshchuk, Katal'nikov and coworkers (1974). In the case of the BF_3–$(FCH_2CH_2)_2O$ system the average boron distribution coefficients were found to be 1.048, 1.044 and 1.042 at 5, 15 and 25°C, respectively (Katal'nikov, Pisarev and Oistach 1971. The $^{11}B/^{10}B$ and $^{18}O/^{16}O$ separation factors were studied with $(CH_3)_2O{\cdot}BF_3$ (United Kingdom Atomic Energy Authority 1962). Elementary separation factors for the exchange distillation of the $Me_2O{\cdot}BF_3$ complex has also been determined by Kaminski, Karamyan and Partsakhashvili (1967), Bondarenko (1967), McGahan (1968), Palko, Begun and Landau (1962) and Riedel (1965); the equilibrium constant of the reaction (144) at 100°C is $K = 1.027$ (Vlasenko and coworkers 1964).

$$Me_2O.{}^{11}BF_3 + {}^{10}BF_3 \rightleftharpoons Me_2O{\cdot}{}^{10}BF_3 + {}^{11}BF_3 \qquad (144)$$

Boron isotope separations using boron trifluoride complexes with anisole and phenetole have been studied by Panchenkov, Makarov and Pechalin (1960, 1961, 1962), Makarov and Panchenkov (1961, 1963a,b), Makarov and coworkers (1968), Kulicke, Kretzschmann and Schmidt (1962), Katal'nikov and Paramonov (1966), Katal'nikov, Paramonov and Nedzvetskii (1967), Katal'nikov, Nedzvetskii and Voloshchuk (1969) and Katal'nikov, Dmitrevskaya and Voloshchuk (1970), Merriman, Pashley and Snow (1966), Merriman, Pashley and Smiley (1968), Pechalin and Panchenkov (1967), Voloshchuk, Katal'nikov and Knyazev (1974), Voloshchuk, Karetnikov and coworkers (1974) and Voloshchuk, Katal'nikov and coworkers (1974). The BF_3 complex with PhOEt was found to be more stable than that with PhOMe.

Boron tribromide has been used for demethylation of aryl methyl ethers (McOmie, Watta and West 1968). The deuterium isotope effect in the BF_3-catalysed rearrangement of 2-methyl-1,2-epoxypropane was 1.92 (Blackett and coworkers 1970). Titanium isotope effects in the distribution of Ti–HSCN complexes between water and ether were measured by Kuznetsova, Zakurin and Nikitin (1962).

VI. ISOTOPIC COMPOUNDS USED IN CANCER STUDIES

Sulphur-35-labelled methylene blue synthesized by Panasiewicz and coworkers (1978) has been applied by Link, Rydzy and Lukiewicz (1979) to cancer studies.

Polythiaether complexation and biotransport studies of radionucleide [$^{99}Tc^{+3}$, $^{111}In^{+3}$, $^{201}Tl^{+1}$, $^{203}Pb^{+2}$ and especially $^{203}Hg(II)$] purging ability by several side-chain-substituted tetrathiacyclohexadecane ligands have been undertaken recently by Ochrymowycz, Mak and Michna (1974) and Ochrymowycz (1978). Macrocyclic polythiaethers were found to have presumptive activity in the Leukaemia P338 test system.

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER **11**

Gas-phase thermal decompositions of simple alcohols, thiols and sulphides*

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*The terms, symbols, conventions and units used are those of Laidler and McKenney[1].

I. INTRODUCTION

Early work[2] on the thermal decomposition of alcohols consisted experimentally of passing the vapour through a hot tube or over heated solids, e.g. glass, pumice; alumina, etc. It seems likely that in these investigations reaction was taking place on the surface, or that because of the ubiquitous presence of oxygen, decomposition was to some extent being induced by a preliminary oxidation process. Reactions of alcohols on active surfaces have now been extensively investigated[3-5]. Metals and metal oxide semiconductors such as zinc oxide favour dehydrogenation, whilst metal oxide insulators such as alumina and acids such as phosphoric acid favour dehydration. Surface reactions in general have been discussed earlier in this series[5].

This review will be confined mainly to the homogeneous, gas-phase processes that occur in vessels whose walls have been suitably treated to suppress heterogeneous reaction (the 'static method'), and in flow systems and shock tubes[6a,b]. The static method, developed in the 1930s, involves conditioning of the surface by the reaction itself or by other suitable material until reproducible results are obtained. The reaction is often followed by pressure change detected by a sensitive membrane that also isolates the reaction from the measuring device. Mass spectrometry and gas chromatography in particular have made possible the numerous analyses necessary for a proper study of the mechanism, and have also led to the detection of products formed only in small amounts.

Recently the shock tube has led to the isolation of primary processes albeit at higher temperatures[7]. For example, in order to determine the effect of a neighbouring hydroxide group on the rate of C–C bond cleavage, Tsang has investigated the shock-tube decompositions of 3,3-dimethylbutan-2-ol and 2,3-dimethylbutan-2-ol and has derived the rate of primary bond fission for various primary processes.

The independent production of atoms or radicals and investigation of their reactions in flow systems has led to detailed information about the rates of elementary reactions, and facilitated the study of fast reactions. For example, at almost every collision and with little activation energy, oxygen atoms insert into the CH bonds of hydrocarbons to form alcohols[8]. As the reactions are exothermic the resulting alcohol molecules are 'hot', i.e. vibrationally excited and chemically activated, and decompose quickly unless stabilized by collisions. For $CH_3{-}OH$, $CH_3{-}CH_2OH$, $C_2H_5{-}CH_2OH$, $CH_3{-}CH(CH_3)OH$, $(CH_3)_2CH{-}CH_2OH$, $CH_3{-}C(CH_3)_2OH$, $(CH_3)_3C{-}OH$ and $\underline{CH_2CH_2CH_2CH_2CH}OH$ the kinetics of dissociation into two radicals at the bond indicated has been elucidated. The *A* factors, $10^{15}-10^{17}$ s^{-1}, are much higher than the normal value of 10^{13} s^{-1}, due to the formation of 'loose' activated complexes. For excited *t*-butanol the products, CH_3 and $(CH_3)_2COH$, are different from those of the thermal decomposition, viz. isobutene and water. This homolytic fission is considerably faster than the dehydration reaction, but calculations show that for thermally activated *t*-butanol at 700°C, fission into free radicals would be relatively unimportant. These insertion reactions are thus not representative of normal thermal decompositions. Sulphur atoms undergo similar insertion reactions with paraffins, olefins and acetylenes and these reactions and the decompositions of the excited species formed have been reviewed[9,10].

Under the normal conditions of thermal activation, in general primary alcohols undergo decomposition by radical or atom chain mechanisms. Usually initiation is rupture of the C–C skeletal structure and the chain carriers are methyl radicals or hydrogen atoms. Abstraction of hydrogen from the substrate may lead to aldehydic products, and these are generally less stable than the parent alcohols, so that carbon

TABLE 1. Activation energies for molecular elimination and bond strengths (kcal mol^{-1})

Compound	Activation energy for molecular elimination			Bond strength			
	Primary	Secondary	Tertiary	Bond broken	Primary	Secondary	Tertiary
Alkane	–	–	–	Alkyl–H	98	95	92
				Alkyl–CH_3	85	84	82
Alkanethiol	55	–	55	Alkyl S–H	92	87	84
				Alkyl–SH	69	69	69
Alcohol	67	65	60	Alkyl O–H	104	–	104
				Alkyl–OH	91	92	91
Alkyl chloride	55	50	45	Alkyl–Cl	81	81	81
Alkyl bromide	52	47	42	Alkyl–Br	68	68	67
α-Toluenethiol	53	–	–	Benzyl–SH	57	–	–

monoxide and hydrocarbon are the final products. For tertiary alcohols, molecular mechanisms compete with radical chains, and dehydration is the predominant process at moderate temperatures. Decompositions of secondary alcohols occupy an intermediate position.

Some of the differences between the reactivities of alkanethiols, alcohols and halides can be accounted for in terms of the thermochemical data listed in Table 1. In general, the greater tendency for thiols to decompose by radical rather than molecular mechanisms can be attributed to the relatively small C—SH bond energy. This enhances radical initiation. For instance, with primary alkanethiols and primary alkyl bromides the differences between activation energies for molecular elimination of H_2S and HBr, and the bond energies for C—SH and C—Br, are similar. Thus thiols may be expected to exhibit both molecular and radical mechanisms of pyrolysis as do primary alkyl bromides.

For alcohols and halides the trend of radical to molecular mechanism with change of primary to tertiary alkyl structure is a consequence of a lowering of the activation energy for molecular elimination without concommitant change in the energy necessary to initiate radical reaction. This lowering of molecular activation energy is not exhibited by thiols and this makes it more difficult to decide on the nature of the maximally inhibited reactions of these compounds.

Initiation of chains in alcohol decompositions is usually considered to arise from C—C rather than C—OH bond fission. For halides and thiols, however, decreased bond energies make C—X and C—SH fission the likely initiation reactions.

The course of radical decompositions of alcohols and thiols is governed by the rates of the various elementary processes. Ultimately the complete elucidation of these mechanisms will depend on a knowledge of the rates of the individual reactions involved. A substantial amount of information has been built up, particularly over the past twenty years and there are many reviews, some of which have been listed[11-28]. Isotopic labelling assists greatly in this work, for example rates of abstraction of H or D atoms from simple alcohols by CH_3 or CD_3 radicals have been listed in one review[24].

In the following sections individual decompositions are discussed in detail.

II. ALCOHOLS

A. Methanol

Since elimination of olefin is not possible and since there are no carbon—carbon bonds and no easily abstractable hydrogen atoms, methanol is stable to higher temperatures than other alcohols. Decomposition occurs above ca. 630°C to yield principally hydrogen and carbon monoxide in the ratio ca. 2 : 1. In 1934, using the static method, Fletcher[29] detected and measured small, almost stationary, amounts of formaldehyde present during decomposition and interpreted the results in terms of a two-stage process (equation 1). Only a small surface effect was observed and the activation energy was found to be 68 kcal mol^{-1}.

$$CH_3OH \longrightarrow H_2 + HCHO \longrightarrow 2H_2 + CO \tag{1}$$

Recently Aronowitz, Naegeli and Glassman[30], using an adiabatic turbulent flow reactor at 797–952°C have shown that in addition to formaldehyde small amounts of CH_4, C_2H_6, C_2H_4 and traces of C_2H_2 are formed in the decomposition. A 19-step, radical chain mechanism was proposed involving formaldehyde as an intermediate, abstraction by methyl radicals and hydrogen atoms as the main propagating steps, and CH_2OH and HCO as the principal μ-radicals. Initiation was considered to be bimolecular and termination to be through combination of methyl radicals at low temperatures and hydrogen atoms at high temperatures. Hydrogen was observed to promote and methane to inhibit reaction, both effects being consistent with the reaction scheme postulated.

The decomposition of methanol is not sensitized by decomposing acetaldehyde presumably because of the relative ease of abstraction of the aldehydic hydrogen atom. The decomposition is, however, sensitised by radicals produced from other sources, e.g. from ethylene oxide at 465°C[31]. Hydrogen chloride does not catalyse the radical decomposition of methanol as it does of dimethyl ether but forms methyl chloride at 450°C[32].

B. Ethanol

Homogeneous decomposition of ethanol occurs above ca. 520°C by a predominantly radical chain mechanism to give hydrogen, acetaldehyde, carbon monoxide, methane, water, ethylene and ethane as the major products. Acetaldehyde is unstable at these temperatures and rapidly breaks down to methane and carbon monoxide.

All of the three major studies reported were carried out in static systems with reaction followed by pressure increase and chemical analysis. The first, at 525°C only, was made by Freeman[33] in connection with his extensive study of the decomposition of diethyl ether where ethanol and ethylene were significant products, particularly in the inhibited reaction. The decomposition followed a first-order rate law. Products were analysed by mass spectrometry and gas chromatography and hydrogen, acetaldehyde, methane, carbon monoxide and ethylene found to predominate initially. The relative amount of ethylene was greatly augmented in the presence of nitric oxide. A chain reaction of the βμ-type with the various possible β-(CH_3, H, OH) and μ-(CH_3CHOH, CH_2CH_2OH, CH_2OH) radicals was inferred. Initiation by C—C fission was proposed and some molecular elimination was considered to occur.

A systematic study of the decomposition was made by Barnard and Hughes[34] in 1959 over the temperature range 576–624°C. Dehydration was unimportant. As a trace of formaldehyde was found in the products the authors chose for initiation the reaction shown in equation (2). Since methyl radicals from decomposing acetaldehyde did not sensitize the decomposition and methane was not an initial product whereas hydrogen was, a hydrogen atom chain was accepted (equation 3). Some polymer was also formed and it was suggested that this arose from an alternative decomposition of the μ-radical (equation 4). As the kinetic form was

$$CH_3CH_2OH \longrightarrow CH_3 + CH_2OH \tag{2}$$

$$H + CH_3CH_2OH \longrightarrow H_2 + CH_3CHOH \tag{3a}$$

$$CH_3CHOH \longrightarrow CH_3CHO + H \tag{3b}$$

$$CH_3CHOH \longrightarrow C_2H_4O + H \tag{4a}$$

$$C_2H_4O \longrightarrow \text{polymer} \tag{4b}$$

first order in initial pressure of ethanol, βμ-termination was inferred. The rate constant was given by $k = 10^{10.0} \exp(-46{,}200/RT)\ s^{-1}$.

The decomposition of ethanol in the presence of sufficient nitric oxide to produce maximal inhibition has been studied by Maccoll and Thomas[35]. Because acetaldehyde production was inhibited more than ethylene elimination and as this elimination accounted for 80% of the maximally inhibited reaction, they proposed a residual molecular reaction producing ethylene with rate constant $k = 1.1 \times 10^{-5}\ \mathrm{s}^{-1}$ at 525°C.

C. Propan-1-ol (*n*-Propanol)

The decomposition of *n*-propanol was investigated by Barnard and Hughes[36] over the temperature range 570–622°C and found to be a first-order process with rate constant given by $k = 10^{10.9} \exp(-49{,}950/RT)\ \mathrm{s}^{-1}$. The initial products were mainly methane and acetaldehyde with very little hydrogen and no propionaldehyde. Minor products were carbon monoxide, hydrogen, formaldehyde, ethane, ethylene, propane, propene and water. This indicates a complex chain reaction, in which the β-C—C bond must be broken. The chain process suggested was as shown in equation (5) with acetaldehyde subsequently decomposing to methane and carbon monoxide.

$$\mathrm{CH_3CH_2CH_2OH + H \longrightarrow CH_4 + CH_2CH_2OH} \tag{5a}$$

$$\mathrm{CH_2CH_2OH} \longrightarrow \begin{cases} \mathrm{CH_3CHO + H} \\ \text{polymer} + \mathrm{H} \end{cases} \tag{5b}$$

In view of recent values of bond energies, however, abstraction of methyl radical by a hydrogen atom may be unlikely and the chain process shown in equation (6) appears to be a possibility.

$$\mathrm{CH_3 + CH_3CH_2CH_2OH \longrightarrow CH_4 + CH_3CH_2CHOH} \tag{6a}$$

$$\mathrm{CH_3CH_2CHOH \longrightarrow CH_3 + H_2C{=}CHOH} \tag{6b}$$

$$\mathrm{H_2C{=}CHOH \longrightarrow CH_3CHO} \tag{6c}$$

For the decomposition in the presence of nitric oxide Maccoll and Thomas[35] found a homogeneous, molecular reaction of first-order kinetics with rate constant $k = 10^{13.64} \exp(-66{,}800/RT)\ \mathrm{s}^{-1}$.

D. Propan-2-ol (Isopropanol)

For isopropanol, studied by Barnard[37] over the temperature range 524–615°C, the pressure change corresponded to reactant lost over the initial 20% of decomposition. Plots of initial rate vs. pressure gave good straight lines with rate constants obtained from these slopes represented by $k = 10^{6.6} \exp(-34{,}000/RT)\ \mathrm{s}^{-1}$. The activation energy and A factor are much lower than those for primary alcohols. The initial products were mainly acetone and hydrogen, acetone subsequently decomposing to ketene and further products (equation 7). The decomposition is a radical chain process and for the propagating steps Barnard suggested that βμ-termination provided the first-order kinetic form.

$$\mathrm{H + CH_3CHOHCH_3 \longrightarrow CH_3COHCH_3 + H_2} \tag{7a}$$

$$\mathrm{CH_3COHCH_3} \longrightarrow \begin{cases} \mathrm{(CH_3)_2CO + H} \\ \text{Polymer} + \text{water} + \mathrm{H} \end{cases} \tag{7b}$$

Dehydration, which is not in large proportion when the isopropanol decomposes on its own, was observed by Barnard, and more recently by Maccoll and Thomas[35], to predominate in the presence of nitric oxide. Maccoll and Thomas considered the maximally inhibited first-order reaction to be molecular. Its rate constant was given by $k = 10^{13.70} \exp(-64{,}500/RT)\ \mathrm{s}^{-1}$.

E. Butan-1-ol (*n*-Butanol)

Barnard[38] also studied the decomposition of *n*-butanol which decomposed at 573–629°C in a first-order manner with $k = 10^{12.2} \exp(-56{,}700/RT)\ \mathrm{s}^{-1}$ to give principally carbon monoxide, formaldehyde, methane and hydrogen with smaller amounts of ethane, ethylene, propane and propene. Methyl radicals formed from the decomposition of *n*-propyl radicals carry on the chain and the presence of formaldehyde indicates the breaking of the α-C–C bond. The chain-carrying mechanism was considered to be as in equation (8).

$$CH_3 + CH_3CH_2CH_2CH_2OH \longrightarrow CH_4 + CH_3CH_2CH_2\underline{C}HOH \tag{8a}$$

$$CH_3CH_2CH_2CHOH \longrightarrow CH_3CH_2CH_2 + HCHO \tag{8b}$$

$$CH_3CH_2CH_2 \longrightarrow CH_3 + C_2H_4 \tag{8c}$$

F. 2-Methylpropan-2-ol (*t*-Butanol)

The gas-phase decomposition of 2-methylpropan-2-ol to 2-methylpropene and water was first investigated by Schultz and Kistiakowsky[39] in 1934 over the temperature range 487–555°C and found to be homogeneous and first-order with rate constants given by $k = 10^{14.68} \exp(-65{,}500/RT)\ \mathrm{s}^{-1}$. A unimolecular mechanism was proposed. Barnard[40] extended the temperature range to 620°C and carried out a careful analysis of the products. He observed products in addition to 2-methylpropene and water, but concluded that these arose from subsequent decomposition of the 2-methylpropene. He confirmed the first-order nature of the decomposition but obtained rates somewhat lower than those of Schultz and Kistiakowsky and accounted for this in terms of more complete ageing of the reaction vessel. Rate constants were given by $k = 10^{11.51} \exp(-54{,}500/RT)\ \mathrm{s}^{-1}$. Two further studies in static systems by Maccoll and Thomas[35] and by Johnson[41] have provided further evidence that the principal reaction is unimolecular decomposition. Molecular rate constants in these two studies were given by $k = 10^{13.2} \exp(-60{,}400/RT)\ \mathrm{s}^{-1}$ and $k = 10^{13.6} \exp(-64{,}000/RT)\ \mathrm{s}^{-1}$, respectively. Johnson also showed that a radical process with rate constant given by $k = 10^{11.0} \exp(-54{,}300/RT)\ \mathrm{s}^{-1}$ makes a small contribution to the overall reaction. For the free-radical component a hydroxyl radical chain mechanism was given as shown in equation (9).

$$(CH_3)_3COH \longrightarrow CH_3 + (CH_3)_2COH \tag{9a}$$

$$CH_3 + (CH_3)_3COH \longrightarrow CH_4 + (CH_3)_2C(OH)CH_2 \tag{9b}$$

$$(CH_3)_2C(OH)CH_2 \longrightarrow OH + (CH_3)_2C{=}CH_2 \tag{9c}$$

$$OH + (CH_3)COH \longrightarrow H_2O + (CH_3)_2C(OH)CH_2 \tag{9d}$$

$$OH + (CH_3)_2C(OH)CH_2 \longrightarrow \text{termination} \tag{9e}$$

Shock-tube studies of the decomposition have been made by Tsang[42] and by Lewis, Keil and Sarr[43] in the temperature ranges 777–1027°C and 647–902°C, respectively. Despite the higher temperatures results are in good agreement with those obtained by static methods. In the first of these studies Tsang determined reflected shock temperatures from measured incident shock velocities and obtained Arrhenius parameters log A/s^{-1} 13.4 and $E = 61.6$ kcal mol^{-1}. In the other investigation Lewis, Keil and Sarr used cyclohexene as internal standard to determine the experimental temperature and obtained log $A/\mathrm{s}^{-1} = 14.6$ and $E = 66.2$ kcal mol^{-1}. Tsang[7], who developed the comparative method used by Lewis and coworkers has subsequently acknowledged the latter's values as having resolved the previously discordant parameters. The measure of agreement of the values for 2-methylpropan-2-ol has led later workers to use this reaction as a standard for verifying the operation of the shock tube.

G. 2-Methylbutan-2-ol(*t*-Pentanol)

Schultz and Kistiakowsky[39] followed the first-order decomposition of 2-methylbutan-2-ol to olefin and water at 487–555°C by means of pressure change. The rate constant was given by $k = 10^{13.5} \exp(-60{,}000/RT)\ \mathrm{s}^{-1}$. As the products were simple they considered the reaction to be a molecular one.

In two other investigations, however, by Maccoll and Thomas[35] and by Johnson[44] a number of products other than methylbutenes and water were found. Thus, Maccoll and Thomas, at 525°C, noted methane, ethane, propanone and butanone. While nitric oxide reduced the overall rate, it did not reduce the rate of olefin elimination significantly. 2-Methylbut-1-ene and 2-methylbut-2-ene were produced in the ratio ca. 2 : 1, and the authors concluded that elimination was a molecular process and accounted for 80% of the inhibited reaction. The rate constant was given by $k = 10^{13.2} \exp(-60{,}400/RT)\ \mathrm{s}^{-1}$.

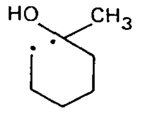
Johnson[44], who studied the decomposition both on its own in the temperature range 432–570°C and in the presence of toluene as inhibitor in the range 519–570°C, in a careful examination of the products noted little change in their distribution upon addition of toluene and specifically stated there was no evidence of butanone formed. He concluded that the initial dehydration was a molecular reaction, with $k = 10^{11.8} \exp(-54{,}800/RT)\ \mathrm{s}^{-1}$, and that the addition products came from the subsequent decomposition of the methylbutenes. Both 2-methylbut-1-ene and 2-methylbut-2-ene were found but as they isomerized under the reaction conditions, the proportion in which they were formed could not be determined. The absence of a radical component of the reaction would be in contrast with the decomposition of 2-methylbutan-2-ol where a small radical contribution was noted.

H. 1-Methylcyclohexanol

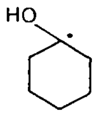
The decomposition of 1-methylcyclohexanol occurs in the manner typical of a tertiary alcohol. In a study at 448–506°C Garnett, Johnson and Sherwood[45] found the main initial reaction to be a unimolecular, gas-phase dehydration with $k = 10^{13.62} \exp(-57{,}800/RT)\ \mathrm{s}^{-1}$. A four-centre transition state was proposed.

A concurrent radical decomposition gave propanone and butanone with $k = 10^{14.0} \exp(-63{,}000/RT)\ \mathrm{s}^{-1}$. In the presence of a two-fold excess of toluene the rate of ketone formation in the early stages of reaction was approximately halved, whilst that of the dehydration was unaffected.

Initiation of the radical reaction was considered to occur by C–C bond fission at the tertiary carbon atom to give both the biradical **1** and the radical **2**. Subsequent



(1)



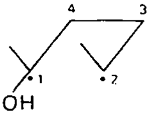
(2)

decomposition leads to the formation of propanone and butanone from 1 and butanone from 2. Propanone but not butanone can also be formed as a consequence of hydrogen abstraction from the parent alcohol.

I. *cis*-1,2-Dimethylcyclobutanol

In contrast with 1-methylcyclohexanol, *cis*-1,2-dimethylcyclobutanol is thought to decompose entirely by a biradical, nonchain mechanism. The decomposition was investigated by Feit[46] over the temperature range 372–394°C, the principal products being propanone and propene with smaller amounts of *trans*-1,2-dimethylcyclobutanol, ethylene and butanone, 2-hexanone and 3-methyl-2-pentanone.

1,2-Carbon–carbon fission gives



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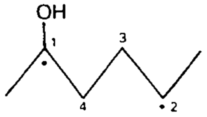
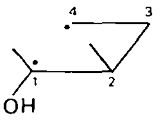


whilst 1,4-carbon–carbon fission gives



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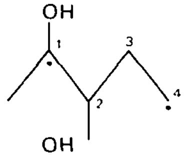
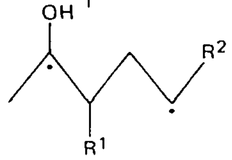


Representing both biradicals as



where R^1 = Me and R^2 = H for the former and R^1 = H and R^2 = Me for the latter case, subsequent hydrogen migration leads to formation of isomeric ketones whilst ring-closure leads to geometric isomerization. Further bond cleavage at the centre of the chain may also occur leading to olefinic products.

The activation energy for the ring-opening was found to be 58 kcal mol^{-1}, 3 kcal mol^{-1} less than for the parent hydrocarbon, *cis*-1,2-dimethylcyclobutane.

J. Other Alcohols

2-Chloroethanol decomposes at 430–496°C into acetaldehyde and hydrogen chloride, the acetaldehyde subsequently breaking down to methane and carbon monoxide[47]. The decomposition follows the pattern of an alkyl halide[48] rather than an alcohol with the rate slightly less than that for ethyl chloride. An interesting 1,2-shift of a hydrogen atom occurs.

Where the alcohol contains a suitably placed double bond, e.g. β-hydroxy

TABLE 2. Arrhenius parameters for β-hydroxy olefin decompositions[35]

Compound	E (kcal mol^{-1})	$\Delta S^{\neq}$ (cal k^{-1} mol^{-1})	Relative rates at 377°C
But-3-en-1-ol	41.0	−8.8	1
Pent-4-en-2-ol	40.9	−7.5	2.9
3-Methylpent-4-en-2-ol	40.7	−6.3	5.4
3-Phenylbut-3-en-1-ol	38.9	−7.8	9.9
4-Phenylbut-3-en-1-ol	42.8	−9.1	0.2
3-Ethyl-6-phenylhex-5-en-3-ol	41.8	−5.3	3.8

olefins, a concerted 6-membered ring transition state is possible; this leads to olefin elimination and ketone formation at the much reduced temperature of ca. 370°C[49]. Arrhenius parameters and relative rates for some such decompositions are given in Table 2. The cooperative electron movements in 6-centred transition states are similar to those considered responsible for the molecular gas-phase decompositions of esters and vinyl ethers.

This electronic effect is not available to α-hydroxy olefins. The decomposition of one such compound, 3-hydroxybut-1-ene, was studied by Trenwith[50] over the temperature range 500–560°C, the principal products being methane, butadiene and water. The latter pair were formed in a first-order, homogeneous reaction with rate constant given by $k = 10^{12.9} \exp(-55{,}700/RT)\ \mathrm{s}^{-1}$. Methane was considered to arise wholly from the reaction in equation (10) followed by abstraction from the

$$CH_3CH(OH)CH{=}CH_2 \longrightarrow CH_3 + CH(OH)CH{=}CH_2 \tag{10}$$

substrate. On the basis that this abstraction occurs at the same rate as CH_3 addition to the substrate, the rate constant $k = 10^{16.26} \exp(-69{,}200/RT)\ \mathrm{s}^{-1}$ was obtained from which a value for $D(H{-}CH(OH)CH{=}CH_2)$ of 80.1 kcal mol^{-1} was inferred.

K. Comparative Rates of Molecular Elimination Reactions

Much higher temperatures are needed to pyrolyse alcohols than halides or esters and insofar as a molecular elimination component can be isolated from the maximally inhibited reaction, the relative rates of dehydration of the lower alcohols

TABLE 3. Relative rates of elimination from chlorides, acetates and alcohols and the effect of α- and β- methyl substitution

R	Chloride at 400°C	Acetate at 326°C	Alcohol at 525°C
Ethyl	1	1	1
	(α-Methyl substitution)		
Isopropyl	96	31	10
t-Butyl	13000	3200	38
	(β-Methyl substitution)		
n-Propyl	3	.9	2
Isobutyl	3	.9	–

fall into a simple pattern (Table 3). In this table rates are relative to the rate of ethyl alcohol at 525°C(viz. $k = 1.1 \times 10^{-5}$ s^{-1}) and have been calculated from Arrhenius parameters listed by Maccoll and Thomas[35]. Temperatures have been chosen to give identical rates for ethyl chloride, ethyl acetate and ethyl alcohol. α-Methylation in the alcohol series is seen to lead to a moderate increase in rate and β-methylation to a small increase in rate. The trend is the same as in the elimination from chlorides but the size of the effect is very much less. The effect has been interpreted as due to strong heterolytic character in the halides' transition state, much weakened for the alcohols. The large effect of α-methylation and very small effect of β-methylation is also similar to the effects of these substitutions in elimination from esters. Esters, however, are considered to react by way of a six-centre, cyclic transition state[35].

As the thermodynamic proportions of the methylbutenes favour 2-methylbut-2-ene, the fact that 2-methylbut-1-ene is found to be the predominant alkene produced from the decomposition of *t*-pentyl alcohol, indicates that the elimination follows the Hoffman rule, as is the case with esters[44].

III. CATALYSED DECOMPOSITIONS

Early work on the acid-catalysed dehydration of alcohols was reviewed in this series in 1964 by Maccoll[108]. Initially the alcohols used were *t*-butanol and isopropanol with catalysts hydrogen bromide and hydrogen chloride. Trace products were generally absent, the catalyst was regenerated, the reactions followed the first-order form without induction periods, increased surface area caused no increase in rate, and recognized inhibitors of radical chain reactions gave no decrease in rate. The effective temperature was reduced by ca. 100°C below that of the uncatalysed, generally radical, decomposition, and the activation energy reduced to ca. 30 kcal mol^{-1}. Since that time the range of alcohols and catalysts has been extended (Table 4). In all cases the reaction is of the form in equation (11). Where

$$C_nH_{2n+1}OH + HX \longrightarrow C_nH_{2n} + H_2O + HX \qquad (11)$$

TABLE 4. Catalysed decompositions of alcohols

Substrate	Catalyst	$10^{-12}A$ ($cm^3 mol^{-1} s^{-1}$)	E (kcal mol^{-1})	T (°C)	Ref.
EtOH	HBr	–	--	472	52
i-PrOH	HCl	–	–	440	52
i-PrOH	HBr	1.0	33.2	369–520	52
i-PrOH	HI	1.7	31.9	356–457	53
S-BuOH	HBr	5.8	34.9	387–510	54
t-BuOH	HCl	2.0	32.7	328–454	55
t-BuOH	HBr	9.2	30.4	315–422	56
t-PeOH	HCl	6.7	34.0	370–503	57
t-PeOH	HBr	1.0	27.1	308–415	58
3-Methylbutan-2-ol	HBr	7.2	35.3	372–446	59
2, 3-Dimethylbutan-2-ol	HBr	0.68	26.5	303–400	60
Cyclopentanol	HCl	23	36.1	420–500	61
Cyclohexanol	HCl	25	38.9	420–500	61
Cycloheptanol	HCl	2.0	32.2	420–500	61

TABLE 5. Catalysed decompositions of ethers

Substrate	Catalyst	$10^{-12}A$ (cm^3 mol^{-1} s^{-1})	E (kcal mol^{-1})	T(°C)	Ref.
t-BuOMe	HCl	2.9	32.1	337–428	62
t-BuOMe	HBr	0.67	25.6	258–371	63
t-BuOEt	HCl	1.4	30.6	320–428	64
t-BuOEt	HBr	0.57	25.1	263–337	65
t-BuOPr-*i*	HCl	9.3	32.1	319–420	66, 67

several isomeric olefins result they are generally in their thermodynamic equilibrium proportions as HX also catalyses their isomerizations (cf. below). The kinetic form is of the first order in both the substrate and the catalyst. The order of catalytic effectiveness is

HI : HBr : HCl = ca. 150 : 25 : 1,

and for the alcohol, α-methylation produces a relatively large and β-methylation a relatively small increase in rate. Thus the rate relationships of this group of gas-phase reactions display the features of analogous reactions in solution.

This type of reaction is not confined to alcohols. Other compounds containing a basic oxygen atom behave similarly. Ethers (Table 5) with an alkyl group that provides some electron release give the analogous decompositions (equation 12). Carboxylic acids (Table 6) undergo a reversal of the Koch synthesis (equation 13), as is sometimes observed with Friedel–Crafts reagents in inert solvents. Their esters behave similarly (equation 14) and esterification and interchange of alkyl groups may also occur. Acetals (Table 7) decompose to alcohols and vinyl ethers (VOR^2) (equation 15).

$$\mathrm{R^1OR^2 + HX \longrightarrow Olefin + R^2OH + HX} \qquad (12)$$

$$\mathrm{RCOOH + HX \longrightarrow RX + CO + H_2O \longrightarrow Olefin + HX + CO + H_2O} \qquad (13)$$

$$\mathrm{R^1COOR^2 + HX \longrightarrow Olefin + CO + R^2OH + HX} \qquad (14)$$

$$\mathrm{R^1R^1C(OR^2)_2 + HX \longrightarrow VOR^2 + HX + R^2OH} \qquad (15)$$

TABLE 6. Catalysed decompositions of carboxylic acids and esters

Substrate	Catalyst	$10^{-12}A$ (cm^3 mol^{-1} s^{-1})	E (kcal mol^{-1})	T(°C)	Ref.
HCOOMe	HBr	3.2	32.2	390–460	68
CH_3COOH	HBr	0.4	30.4	412–492	69
CH_3COOMe	HBr	1.9	32.3	419–497	70
$MeCH_2COOH$	HBr	1.4	30.8	405–468	71
$Me_2CHCOOH$	HBr	7.4	33.1	369–454	72
Me_3CCOOH	HBr	1.9	31.6	340–460	73
$Me_3CCOOMe$	HCl	–	–	450–480	74
	HBr	–	ca. 30	370–442	74
c-C_5H_9COOH	HBr	1.5	29.5	369–434	75
c-$C_6H_{11}COOH$	HBr	36	34.4	369–430	75
c-$C_7H_{13}COOH$	HBr	31	34.5	369–434	75

TABLE 7. Catalysed decompositions of acetals

Substrate	Catalyst	$10^{-12}A$ ($cm^3 mol^{-1} s^{-1}$)	E ($kcal mol^{-1}$)	T (°C)	Ref.
$CH_3CH(OMe)_2$	HCl	13	26.7	254–322	76
$CH_3CH(OMe)_2$	HBr	13	22.1	233–322	77
	CF_3COOH	67	25.4	236–288	77
$CH_3CH(OEt)_2$	HCl	4.5	22.9	225–285	76
$(CH_3)_2C(OMe)_2$	HCl	23	22.2	226–364	78
	HBr	–	–	278	78
$(CH_3)_2C(OMe)_2$	HCOOH	0.0042	22.4	274–334	79
$(CH_3)_2C(OMe)_2$	CH_3COOH	7.9	30.8	314–400	80
$(CH_3)_2C(OMe)_2$	CF_3COOH	199	22.7	224–291	81
$(CH_3)_2C(OMe)_2$	C_2H_5COOH	2.75	29.7	335–389	79

TABLE 8. Catalysed isomerizations of olefins

Substrate	Catalyst	$10^{-12}A$ ($cm^3 mol^{-1} s^{-1}$)	E ($kcal mol^{-1}$)	T (°C)	Ref.
Cyclopropane	HBr	300	38.8	369–452	82
But-1-ene	HBr	0.72	26.3	310–380	83
Cyclopropane	BCl_3	0.22	25.5	360–470	84
Cyclopropane	BBr_3	0.0002	16.3	250–438	85
2-Methylbut-1-ene	BCl_3	0.0005	21.9	368–467	86

In particular 2,2-dimethoxypropane is a most labile substrate, and this has allowed extension of the catalyst used to carboxylic acids, viz. trifluoracetic, formic, acetic and propionic acids. Furthermore the isomerizations of cyclopropane and olefins have been effected by hydrogen halides and by Friedel–Crafts catalysts (Table 8). Hydrogen bromide, boron trichloride and boron tribromide also catalyse the laser-driven isomerization of cyclopropane[51].

Nitrogen may also act as a basic centre in this type of reaction (Table 9). Amines, *t*-butylamine and isopropylamine (equation 16), and the substituted amide, *N,N*-dimethylformamide (equation 17), undergo decompositions catalysed

$$RNH_2 + HBr \longrightarrow Olefin + NH_3 + HBr \tag{16}$$

$$HCONMe_2 + HCl \longrightarrow CO + Me_2NH + HCl \tag{17}$$

TABLE 9. Catalysed decompositions of amines and amides

Substrate	Catalyst	$10^{-12}A$ ($cm^3 mol^{-1} s^{-1}$)	E ($kcal mol^{-1}$)	T (°C)	Ref.
$EtNH_2$	HBr	–	–	460	87
i-$PrNH_2$	HBr	2.5	33.1	435–490	87
t-$BuNH_2$	HBr	1.6	29.3	395–460	88
$HCONMe_2$	HCl	0.38	24.0	335–415	89
$CH_3CONHBu$-t	HCl	–	–	380	90

by hydrogen bromide and hydrogen chloride, respectively, very like those of *t*-butanol and methyl formate.

All of these reactions seem to be akin, which suggests a polar-type transition state in the gas phase corresponding to acid catalysis in solution.

IV. THIOLS

The thermal decompositions of alkanethiols in the gas phase have not been studied as extensively as those of the corresponding alcohols, halides and esters. They are believed to occur by concurrent radical chain and unimolecular elimination mechanisms, the former predominating under most conditions.

The earliest quantitative investigations were undertaken about fifty years ago by Taylor and coworkers on ethanethiol and *n*-propanethiol at temperatures around 400°C in static[91,92] and flow systems[92]. They proposed a common complex mechanism involving (*a*) heterogeneous formation of the sulphide, R_2S, and hydrogen sulphide, which accounts for the marked induction periods observed, followed by (*b*) bimolecular formation of a sulphonium hydrosulphide intermediate, then (*c*) unimolecular, rate-determining decomposition to olefin and hydrogen sulphide. Activation energies for the reactions ensuing after the induction periods were ca. 40 kcal mol^{-1}. While the presence of radical chains in these decompositions now seems certain, diethyl sulphide has been found among the products of ethanethiol pyrolysis in uncoated vessels at high reactant pressures[93] and it is possible that molecular processes of type (*a*)–(*c*) above might contribute to some extent.

A. Methanethiol

Decomposition of methanethiol has been investigated by Sehon and Darwent[94] using the toluene carrier technique. Over the temperature range 732–829°C principal products were methane and hydrogen sulphide and the primary reaction was considered to be C–S homolysis (equation 18). With assumption of

$$CH_3SH \longrightarrow CH_3 + SH \tag{18}$$

$A = 3 \times 10^{13}$ s^{-1} first-order rate constants gave E = 67 kcal mol^{-1}. Benson and O'Neal[95] considered the rate constants obtained to be too low due to the process being in the unimolecular fall-off region and suggested corrected parameters $A = 10^{15.5}$ s^{-1} and $E = 76.6$ kcal mol^{-1}, respectively.

B. Ethanethiol

Sehon and Darwent[94] also studied the decomposition of ethanethiol. In a toluene stream at 512–665°C, evidence was found for two concurrent paths, (19) and (20), path (20) becoming increasingly significant at the higher temperatures.

$$C_2H_5SH \xrightarrow{k_1} C_2H_4 + H_2S \tag{19}$$

$$C_2H_5SH \xrightarrow{k_2} C_2H_5 + SH \tag{20}$$

Again, activation energies were obtained from assumed A factors and observed first-order rate constants. This gave $k_1 = 1 \times 10^{13} \exp(-55{,}000/RT)$ s^{-1} and $k_2 = 3 \times 10^{13} \exp(-63{,}000/RT)$ s^{-1}.

Benson and O'Neal[95] have commented that the reported parameters for the homolysis (path 20) are low and have suggested $k = 10^{15.5} \exp(-72{,}200/RT)$ s^{-1}

which is consistent with the rate constants obtained in the middle of the temperature range.

Heterogeneous decomposition of ethanethiol at 600–700°C also leads to ethylene and hydrogen sulphide as well as several side-products including diethyl sulphide[93]. Metal sulphides (copper, nickel, cadmium) facilitate this decomposition.

C. 2-Methyl-2-propanethiol

This alkanethiol has been studied more extensively than any of the others over the period 1952–1977.

Thompson, Meyer and Ball[96] used a quartz flow tube at 300–600°C without added inhibitor. They found hydrogen sulphide and isobutene as major products while minor products were isobutane, elemental sulphur and a polysulphide material. Induction periods were observed at the lower temperatures as well as secondary reactions leading to the minor products. The generalized mechanism, shown in equation (21), similar to that of Malisoff and Marks[97], was presented. No

$$(CH_3)_3CSH \longrightarrow (CH_3)_3C + HS \qquad (21a)$$

$$(CH_3)_3CSH + (CH_3)_3C \longrightarrow (CH_3)_2(CH_2)CSH + (CH_3)_3CH \qquad (21b)$$

$$(CH_3)_3CSH + HS \longrightarrow (CH_3)_2(CH_2)CSH + H_2S \qquad (21c)$$

$$(CH_3)_2(CH_2)CSH \longrightarrow (CH_3)_2C{=}CH_2 + HS \qquad (21d)$$

termination step was suggested and consideration of the kinetics was not pursued. Secondary reactions postulated to explain the formation of minor products were as shown in equation (22).

$$(CH_3)_2C{=}CH_2 + H_2S \longrightarrow (CH_3)_3CH + S \qquad (22a)$$

$$(CH_3)_2C{=}CH_2 + S \longrightarrow \text{polysulphides} \qquad (22b)$$

Tsang[42], using a single-pulse shock tube, studied the thermal decomposition in the presence of propylene at 687–957°C. The rate constant for the residual reaction, identified as unimolecular elimination, was given by $k = 2 \times 10^{13} \exp(-55{,}000/RT)\ s^{-1}$.

Recently Bamkole[98], using a static system and lower temperatures (424–589°C) than Tsang, observed a homogeneous radical chain process. Added cyclohexene lengthened the induction period in proportion to its partial pressure and almost eliminated sulphur formation. Initial reaction rates for the process occurring immediately after the induction period showed 3/2-order kinetics and the rate constant was given by $k = 10^{12.07} \exp(-40{,}600/RT)\ s^{-1}\ mol^{-1/2} cc^{1/2}$. The mechanism proposed by Bamkole was identical to that shown in equations (21) and (22) but with addition of the termination step (23). The overall reaction can be

$$2\,HS \longrightarrow H_2S + S \qquad (23)$$

classified as $^1\beta\beta_{3/2}$-type. Cyclohexene was suggested to be involved in suppressing an unspecified radical mechanism leading to sulphur formation.

While Bamkole attributed the difference in mechanism between his and Tsang's studies to the temperature ranges employed, the experimental results as originally reported by Emovon and Bamkole[99] appear to be in excellent agreement with Tsang's data. Emovon and Bamkole[99] considered the reaction as unimolecular with rate constant given by $k = 10^{13.4} \exp(-54{,}300/RT)\ s^{-1}$.

D. Butane-1-thiol and Butane-2-thiol

Pyrolyses of these thiols in a static system alone and in the presence of cyclohexene were also studied by Bamkole[98]. From butane-1-thiol the olefin formed was mainly butene-1, while from butane-2-thiol a mixture of butenes resulted. The two decompositions followed first-order kinetics with the constants given by $k = 10^{9.84}$ exp($-42.600/RT$) s^{-1} and $k = 10^{8.68}$ exp($-41{,}800/RT$) s^{-1}, respectively. The reactions were considered to occur by radical chain mechanisms of the type proposed for 2-methyl-2-propanethiol but with $\beta\mu$-termination involving combination of HS and an alkyl radical. The preliminary report* by Emovon and Bamkole[99] described these pyrolyses as fully inhibited unimolecular decompositions with Arrhenius equations $k = 10^{15.75}$ exp($-62.240/RT$) s^{-1} and $k = 10^{14.65}$ exp($-58{,}160/RT$) s^{-1} for butane-1-thiol and butane-2-thiol, respectively.

A study of butanethiol pyrolyses in a microflow system at 350–500°C has been reported by Sugioka, Yotsuyanagi and Aomura[100]. Butane-1-thiol and butane-2-thiol gave the various butenes while 2-methyl-2-propanethiol gave mainly isobutene. A radical mechanism based on SH was proposed.

E. Pentane-1-thiol

Using a flow system with a quartz tube Thompson, Meyer and Ball[96] studied the decomposition of this compound in the temperature range 350–500°C. The predominant sulphur-containing product was hydrogen sulphide, with small amounts of sulphur and sulphides, while the only hydrocarbon product was pentene. At the higher temperatures C_1–C_5 paraffins, C_2–C_4 olefins and C_4–C_5 diolefins were found as minor products. A molecular elimination of H_2S was postulated.

F. α-Toluenethiol (Benzylmercaptan)

Sehon and Darwent[94] studied the thermal decomposition of this compound in a toluene carrier system at 487–747°C. The principal products were hydrogen sulphide and bibenzyl in approximately equal quantities. Smaller amounts of hydrogen and methane were also found. The reaction was predominantly homogeneous and first order, and the mechanism postulated was as shown in equation (24). Hydrogen and methane production were attributed to secondary reactions

$$C_6H_5CH_2SH \longrightarrow C_6H_5CH_2 + SH \tag{24a}$$

$$C_6H_5CH_3 + SH \longrightarrow C_6H_5CH_2 + H_2S \tag{24b}$$

$$2\,C_6H_5CH_2 \longrightarrow (C_6H_5CH_2)_2 \tag{24c}$$

involving bibenzyl. Rate constants for the homolytic dissociation were given by $k = 3 \times 10^{13}$ exp($-53{,}000/RT$) s^{-1}. The C–S bond strength in $C_6H_5CH_2SH$, based on heats of formation of HS, $C_6H_5CH_2$ and $C_6H_5CH_2SH$ of 35.5, 45.0 and 21.9 kcal mol^{-1}, respectively, is 59.7 kcal mol^{-1} [95], which is higher than Sehon and Darwent's value of 53 kcal mol^{-1} [94] for the activation energy. However, it is possible that the preexponential factor may be low. Benson and O'Neal[95] suggest $A = 10^{15.1}$ s^{-1} and this is consistent with $E = 59.7$ kcal mol^{-1} and the observed rate constant in the middle of the temperature range.

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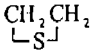
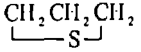
*In a recent private communication Professor Bamkole has indicated his preference for the results of the full investigation reported in Reference 98.

TABLE 10. Experimental studies of sulphide and disulphide decompositions

Compound	System	Temp. range (°C)	Arrhenius constants		Comments and reference
			log A (s^{-1})	E_a (kcal mol^{-1})	
$C_6H_5SCH_3$	Toluene carrier	550–706	14.48	60.0	103
$C_6H_5SCH_3$	VLPP	672–977	15.3	63.6	101
$C_6H_5CH_2SCH_3$	Toluene carrier	545–571	13.48	51.5	Full temperature range[104]
			14.1	53.8	Data from middle of temperature range of above study[95]
$C_6H_5CH_2SCH_3$	VLPP	564–866	14.7	56.0	101
CH_3SSCH_3	Static	316–373	13.3	45	Complex reaction initial products being methanethiol and thioformaldehyde polymer[105]
$C_2H_5SSC_2H_5$	Static	318	–	–	Rate constant at 318°C = 1.97 x 10^{-3} s^{-1} [105]
t-BuSSBu-*t*	Static	246–300	13.57	42.3	102
	Flow	328–400	14.6	44.0	102
 $\underbrace{CH_2CH_2}_{S}$	Static	>250	–	40.2	To ethylene thiol, pressure > 150 torr[106]
		<250	–	–	To ethylene and sulphur[106]
 $\underbrace{CH_2CH_2CH_2}_{S}$	Shock tube	707–767	13.0	48.2	To ethylene and thioformaldehyde[107]

V. SULPHIDES (THIO ETHERS) AND DISULPHIDES

Since bond strengths are ca. 74 kcal mol^{-1} for carbon–sulphur in sulphides[101] and of similar magnitude or smaller for sulphur–sulphur in disulphides[102] compared with 83–88 kcal mol^{-1} for carbon–carbon[103], cleavage in thermal decomposition of these compounds always occurs at the carbon–sulphur or sulphur–sulphur bond in preference to the carbon–carbon bond[103].

Only a few sulphides and disulphides have been investigated in any detail and these were generally studied under such conditions that only the initial homolysis was observed. The two techniques most commonly employed were the toluene carrier flow system and very low-pressure pyrolysis (VLPP). Results are summarized in Table 10. These indicate that, where alternatives are possible, the carbon–sulphur bond fission occurs in a manner that yields the most stable radical, e.g. benzyl and phenylthio radicals in the cases of benzyl methyl sulphide and phenyl methyl sulphide, respectively[101]. VLPP experiments, which produced results in good agreement with those of the toluene carrier technique[103,104], have led to the conclusion that the stabilization energy of the phenylthio radical (9.6 kcal mol^{-1}) is considerably smaller than that of the related benzyl (13.2 kcal mol^{-1}) and phenoxy (17.5 kcal mol^{-1}) radicals.

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 12

Oxidation and reduction of alcohols and ethers

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I. INTRODUCTION

This article reviews two rather different reactions (oxidation and reduction) of two even more different functional groups (alcohols and ethers). Since most of the material available from the recent literature concerns alcohol oxidations, this topic is given most extensive coverage. The approach is mechanistic; however, preparative applications are included whenever they appeared particularly illustrative or interesting. For reasons of space, a selection had to be made, so certain oxidizing agents could not be considered.

With respect to the other topics the literature is much less abundant. The reactions are less thoroughly investigated and their mechanisms only partly understood. This part of the article is essentially descriptive. In order to avoid overlap with other articles in this series, reactions of ethers, and in particular epoxides, with organometallic reagents and complex hydrides are not discussed in detail.

II. OXIDATION OF ALCOHOLS

A. General Aspects

Oxidation of an alcohol to an aldehyde or ketone may formally be considered as elimination of hydrogen at the C—O bond, resulting in overall transfer of two electrons from substrate to oxidant. These dehydrogenations proceed by a variety of pathways. Most frequently, the hydroxylic hydrogen is lost as proton, so that oxidation takes place with the alkoxide or with a complex or ester between alcohol and oxidant. The carbinolic hydrogen is lost as proton, hydrogen atom or hydride ion, depending on the oxidant used. Thus electron transfer is not necessarily associated with hydrogen transfer, but may proceed via breaking of the covalent bond between alcohol and oxidant or via electron transfer from intermediate free radicals. Since several pathways are sometimes available for one and the same oxidizing agent, reactions are often mechanistically complex, and accompanied by side-products.

B. Chromic Acid

Conversion of primary and secondary alcohols by chromium (VI)-derived reagents to aldehydes and ketones is not only a very frequently encountered reaction but also the most thoroughly investigated oxidation. Several reviews treating mechanistic and preparative aspects have appeared over the recent years.[1-6] The overall reaction may be formulated as equation (1). While alcohol oxidation

$$3\,R_2CHOH + 2\,CrO_3 + 6\,H^+ \longrightarrow 3\,R_2C{=}O + 2\,Cr\,(III) + 6\,H_2O \qquad (1)$$

involves transfer of two electrons for each molecule of substrate, reduction of chromium (VI) to chromium (III) requires three of them. As a consequence of this noncorrespondence of substrate and oxidant the oxidation mechanism comprises intermediate valence states of chromium, namely Cr(V) and Cr(IV) as well as organic free-radical intermediates. The latter frequently lead to side-products in the alcohol oxidation.

1. Mechanism

a. Preequilibria. Upon dissolution of chromic acid in water (25°C) the equilibria (2)–(6) may be observed[1,4]. In solutions below 0.05M in Cr(VI) the monomeric

$$H_2CrO_4 \rightleftharpoons H^+ + HCrO_4^- \qquad K_1 = 1.21\ \text{mol l}^{-1} \qquad (2)$$

$$HCrO_4^- \rightleftharpoons H^+ + CrO_4^{2-} \qquad K_2 = 3 \times 10^{-7}\ \text{mol l}^{-1} \qquad (3)$$

$$2\,HCrO_4^- \rightleftharpoons Cr_2O_7^{2-} + H_2O \qquad K_d = 35.51\ \text{mol}^{-1}\ (\mu = 0)^7 \qquad (4)$$

$$HCr_2O_7^- \rightleftharpoons H^+ + Cr_2O_7^{2-} \qquad K_2' = 0.85\ \text{mol l}^{-1} \qquad (5)$$

$$H_2Cr_2O_7 \rightleftharpoons H^+ + HCr_2O_7^- \qquad K_1' = \text{large} \qquad (6)$$

species predominate. Above this limit the dimeric dichromate ions become more and more important and, at still higher concentration polychromates are formed[8]. The rates of the reactions leading to these equilibria are several orders of magnitude faster than the rates of alcohol oxidation[9].

The oxidizing power of chromium (VI) solutions of constant acidity is dependent on the medium. Addition of acids leads to complex formation (equation 7)[10].

$$\mathrm{HCrO_4^- + AcOH \overset{K_e}{\rightleftharpoons} AcO{-}CrO_3H + H_2O} \quad K_e = 45 \tag{7}$$

The electron-attracting or -releasing effect of the complexing conjugate base changes the electron density at the central atom [Cr (VI)] which provokes shifts in the ultraviolet spectrum and reactivity changes.

Similarly alcohols react with chromic acid to form chromate esters (equation 8).

$$\mathrm{ROH + HCrO_4^- \overset{K}{\rightleftharpoons} RO{-}CrO_3^- + H_2O} \tag{8}$$

The equilibrium constant K is in the order of 1 to 10, and shows little variation with the structure of the alcohols[11]. The kinetics of ester formation between chromic acid and 2-propanol in 97% acetic acid (15°C, $[\mathrm{H}^+] = 0.0125$ M, $\mu = 0.184$ [$\mathrm{NaClO_4}$]) have been investigated by Wiberg and coworkers[12,13] with the results shown in Scheme 1. In this solvent system Cr(VI) is present mainly as mono- or di-ester at alcohol concentrations $> 5 \times 10^{-2}$ M. Under the same conditions mono- and di-ester decompose to ketone with rate constants of $k_{\mathrm{M}} = 0.294\ \mathrm{s}^{-1}$ and $k_{\mathrm{D}} = 0.174\ \mathrm{s}^{-1}$.[13] Although the formation of chromate esters during alcohol oxidation had already been reported near the end of the last century[14], their role in the reaction mechanism was not established until 1962. The first steps of the oxidation, according to Westheimer[15], are rapid and reversible ester formation, followed by slow decomposition to ketone and Cr(IV) (equations 13 and 14). The kinetic

$$\mathrm{AcOCrO_3H \overset{K_1}{\rightleftharpoons} AcOCrO_3^- + H^+} \tag{9}$$

$$\mathrm{R_2CHOH + AcOCrO_3H \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_2CHOCrO_3H + (AcOH)} \tag{10}$$

$$\mathrm{R_2CHOCrO_3H \overset{K_3}{\rightleftharpoons} R_2CHOCrO_3^- + H^+} \tag{11}$$

$$\mathrm{R_2CHOH + R_2CHOCrO_3H \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} R_2CHOCrO_2OCHR_2 + (H_2O)} \tag{12}$$

$$\begin{array}{llll}
K_1 & = 0.24\ \mathrm{M} & K_3 & = 0.019\ \mathrm{M} \\
k_2 & = 13{,}200\ \mathrm{M}^{-1}\mathrm{s}^{-1} & k_4 & = 710\ \mathrm{M}^{-1}\mathrm{s}^{-1} \\
k_{-2} & = 114\ \mathrm{s}^{-1} & k_{-4} & = 77\ \mathrm{s}^{-1} \\
K_2 & = k_2/k_{-2} = 115.4\ \mathrm{M}^{-1} & K_4 & = k_4/k_{-4} = 9.21\ \mathrm{M}^{-1}
\end{array}$$

SCHEME 1

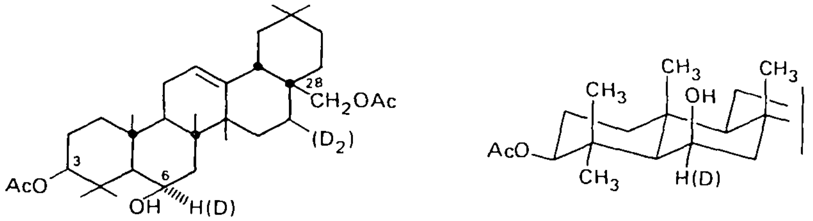
$$\mathrm{R_2CHOH + HCrO_4^- + H^+ \overset{fast}{\rightleftharpoons} R_2CH{-}OCrO_3H + H_2O} \tag{13}$$

$$\mathrm{R_2CH{-}OCrO_3H \xrightarrow{slow} R_2C{=}O + Cr(IV)} \tag{14}$$

isotope effect of 7, observed for oxidation of 2-propanol[16] indicates that the second step is rate-determining. In water and in organic solvents containing substantial quantities of water the ester is present only in low (steady-state) concentration, and the rate law is[17]

$$v = k_a[\mathrm{HCrO_4^-}]\,[\mathrm{R_2CHOH}]\,[\mathrm{H^+}] + k_b[\mathrm{HCrO_4^-}]\,[\mathrm{R_2CHOH}]\,[\mathrm{H^+}]^2 \qquad (15)$$

Eschenmoser[18] found for the oxidation of the sterically highly hindered alcohol, 3β,28-diacetoxy-6β-hydroxy-18β,12-oleanen (1) conditions where the isotope effect vanished ($k_H/k_D = 1$). 1 is still the only compound for which $k_H/k_D = 1$; in other cases abnormally low isotope effects have been attributed to partial rate-determining ester formation due to steric hindrance[19] or in strongly acidic solution, to unfavourable electrostatic interactions between the protonated alcohol and Cr(VI) species[20].



(1)

b. Oxidation steps. Watanabe and Westheimer[21] considered Schemes 2 and 3 for the conversion of Cr(VI) to Cr(III). P_4, P_5 and P_6 refer to the oxidation products of Cr(IV), (V) and (VI), respectively. In Scheme 2 2/3 of the reaction products are due to Cr(V) and in Scheme 3 each of the valence states forms 1/3 of the products. For most simple alcohols P_4, P_5 and P_6 are identical. However in some favourable cases the intermediate chromium species may lead to other

$$\mathrm{Cr(VI)} + \mathrm{S} \xrightarrow{\text{slow}} \mathrm{Cr(IV)} + \mathrm{P_6} \qquad (16)$$

$$\mathrm{Cr(IV)} + \mathrm{Cr(VI)} \longrightarrow 2\,\mathrm{Cr(V)} \qquad (17)$$

$$2\,\mathrm{Cr(V)} + 2\,\mathrm{S} \longrightarrow 2\,\mathrm{Cr(III)} + 2\,\mathrm{P_5} \qquad (18)$$

SCHEME 2

$$\mathrm{Cr(VI)} + \mathrm{S} \xrightarrow{\text{slow}} \mathrm{Cr(IV)} + \mathrm{P_6} \qquad (16)$$

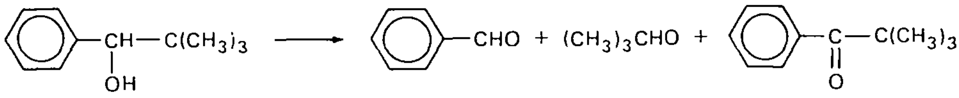
$$\mathrm{Cr(IV)} + \mathrm{S} \longrightarrow \mathrm{R^\bullet} + \mathrm{Cr(III)} \qquad (19)$$

$$\mathrm{Cr(VI)} + \mathrm{R^\bullet} \longrightarrow \mathrm{Cr(V)} + \mathrm{P_4} \qquad (20)$$

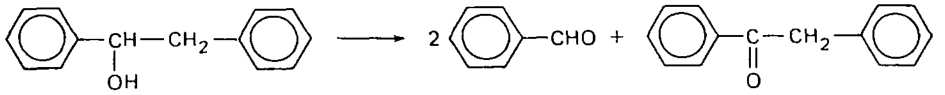
$$\mathrm{Cr(V)} + \mathrm{S} \longrightarrow \mathrm{Cr(III)} + \mathrm{P_5} \qquad (21)$$

SCHEME 3

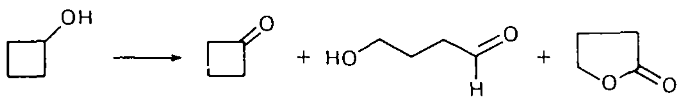
products than Cr(VI). For example, alcohols with quaternary α-carbons such as 2 afford not only ketones, but also cleavage products[22]. Cleavage has also been observed in the chromic acid oxidation of 2-aryl-1-phenylethanols (3)[23] and cyclobutanol (4)[24]. Although Westheimer[22] was able to demonstrate that cleavage of 2 was due to reaction of an intermediate chromium species, it could not be decided whether Cr(IV) or Cr(V) was involved. Two different approaches finally allowed this distinction to be made. Roček and collaborators[24,25] investigated the alcohol oxidation with chromic acid in the presence of V(IV)[26]. By doing so they were able to suppress oxidation by Cr(VI). As Cr(V) was found to be unreactive under their conditions, it could be shown that the relevant intervening species was Cr(IV). Scheme 2 was therefore rejected. Wiberg and collaborators[13,27] studied oxidation of 2-propanol and cyclobutanol (4) in 97% acetic acid. In this solvent system Cr(VI) is considerably more reactive than Cr(V) so that formation and disappearance of Cr(V) are experimentally observable. By analysing the yields of acetone relative to Cr(V) before oxidation by Cr(V) occurs, the authors arrived at the conclusion that only Scheme 3 was compatible with their experimental results.



(2) (22)



(3) (23)



(4) (24)

The complete reaction scheme may thus be formulated as shown in Scheme 4. Cr(V) is formed by reaction of Cr(VI) with the radicals generated in equation (25).

$$\mathrm{Cr(VI)} + \mathrm{S} \xrightarrow{\text{slow}} \mathrm{Cr(IV)} + \mathrm{P}_6 \qquad (16)$$

$$2\,\mathrm{Cr(IV)} + 2\,\mathrm{S} \longrightarrow 2\,\mathrm{Cr(III)} + 2\,\mathrm{R}^{\bullet} \qquad (25)$$

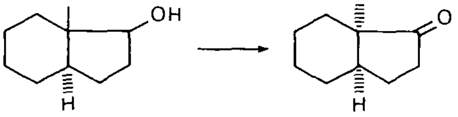
$$2\mathrm{Cr(VI)} + 2\,\mathrm{R}^{\bullet} \longrightarrow 2\,\mathrm{Cr(V)} + 2\,\mathrm{P}_4 \qquad (26)$$

$$2\,\mathrm{Cr(V)} \longrightarrow \mathrm{Cr(IV)} + \mathrm{Cr(VI)} \qquad (27)$$

$$\mathrm{S} + \mathrm{Cr(V)} \longrightarrow \mathrm{Cr(III)} + \mathrm{P}_5 \qquad (28)$$

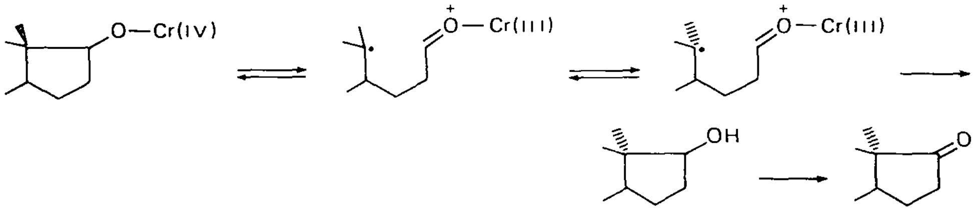
SCHEME 4

Depending on the reaction conditions it will either disproportionate (equation 27) or react with a molecule of substrate (equation 28). Radical formation as postulated in equation (25) has been demonstrated by trapping experiments with acrylonitrile and acrylamide[25,28] and for 3 with oxygen[23]. Fürst and collaborators[29] observed in the oxidation of a series of 8-methyl-*trans*-hydrindanoles (5) a side-reaction leading to isomerization at the tertiary α-carbon in up to 45% yield. The most likely reaction mechanism involves C—C cleavage by Cr(IV) leading to a radical, which after inversion, recyclizes before being oxidized to the ketone (equation 30).



(5) 45% *cis*

(29)



(30)

The oxidation of primary and secondary alcohols with Cr(IV) has been investigated by Rahman and Roček, using their Cr(VI)/V(IV) system[25]. In contrast to cyclobutanol (4) where cleavage to γ-hydroxybutyraldehyde is observed[30], simple alcohols react by C—H bond cleavage to yield aldehydes and ketones respectively. The oxidation of 2-propanol showed an isotope effect of $k_H/k_D = 1.9$, and the polar reaction constant ρ^* was found to be -0.84.

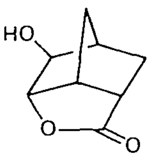
The cleavage reactions due to the intermediate Cr(IV) in alcohol oxidations may be suppressed by addition of scavengers such as Mn(II) or Ce(III) ions. Ce(IV) in catalytic quantities effects the same suppression of side-reactions, due to its catalytic effect on the disproportionation of Cr(IV) (equation 31)[31].

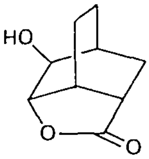
$$3\,\mathrm{Cr(IV)} \xrightarrow{\mathrm{Ce(IV)}} 2\,\mathrm{Cr(III)} + \mathrm{Cr(VI)} \qquad (31)$$

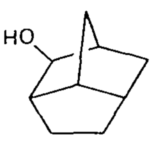
Oxidation by Cr(V) has been investigated by Wiberg and coworkers[13,27] in 97% acetic acid as well as by Hasan and Roček[32] in aqueous solution containing oxalic acid (see below). In both systems oxidation of cyclobutanol (4) afforded the ketone exclusively and no cleavage to γ-hydroxybutyraldehyde was observed. The kinetic isotope effects for the oxidation of 2-propanol was 3.3–4.3 (97% acetic acid)[27]; for cyclobutanol (water/oxalic acid) the value was 5.0[33]. The polar reaction constant ρ^* was found to be -0.80[33]. Thus Cr(V) oxidations of alcohols are mechanistically similar to oxidations of Cr(VI). Both reactions proceed via an intermediate ester, while for Cr(IV) oxidation ester formation appears not to be involved[25].

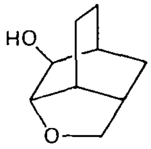
The reaction scheme described above has been investigated in aqueous solution and in aqueous acetic acid. The same general mechanism applies in aqueous acetone[10,34] and in aqueous trifluoroacetic acid[35]. However a different mechanism might operate in other solvents. For example, Cr(IV) is stable in acetic anhydride[36], and although the mechanism of alcohol oxidation has not been investigated, aldehyde oxidation proceeds by an entirely different mechanism in acetic anhydride than in aqueous acetic acid[37].

c. Cr(VI) oxidation. Chromate esters decompose in aprotic solvents slowly to ketone and Cr(IV)[38]. The reaction is accompanied by a kinetic isotope effect of 2 to 5[38,39]. The deuterium isotope effect for alcohol oxidation in protic solvents varies in the range 3.2–12.9[40]. The reaction is catalysed by picolinic acid[41] but not by pyridine[42], as originally suggested. Electron-withdrawing substituents lead to a decrease in reaction rate. The Hammett ρ-value for the oxidation of 1-phenylethanols in 30% acetic acid is -1.01[43]. Primary aliphatic alcohols are oxidized with $\rho^* = -1.06$[44] (aqueous solution). The abnormally low rates of oxidation of the hydroxylactones **6** and **7**[45,46] with respect to their hydrocarbon analogues **8** and **9** have been interpreted in terms of a polar effect of the electron-attracting substituents, leading to destabilization of the developing carbonyl group.



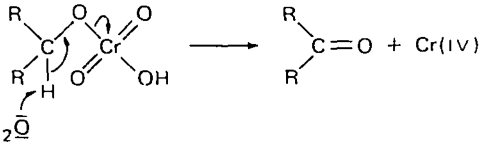




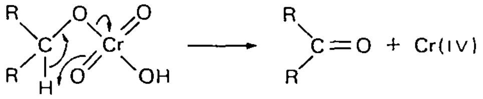


	(6)	(7)	(8)	(9)
k_{rel}	1.0	8.0	45.0	80.0

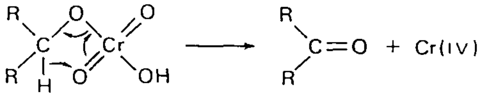
The mechanisms (32)–(36) have been considered for breakdown of the chromate ester[1]. Since general base catalysis could not be demonstrated, most authors favour


R
O
O
C
Cr
R
O
OH
H
$H_2\bar{O}$
R
C=O + Cr(IV)
R

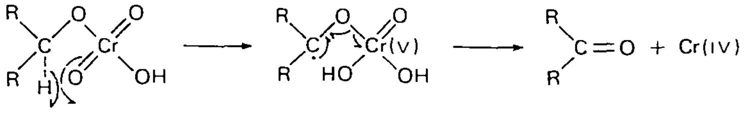
(32)


R
O
O
C
Cr
R
H
O
OH
R
C=O + Cr(IV)
R

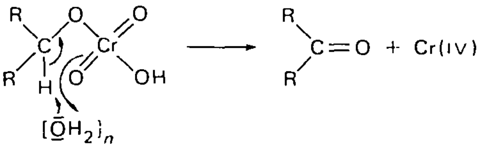
(33)


R
O
O
C
Cr
R
H
O
OH
R
C=O + Cr(IV)
R

(34)

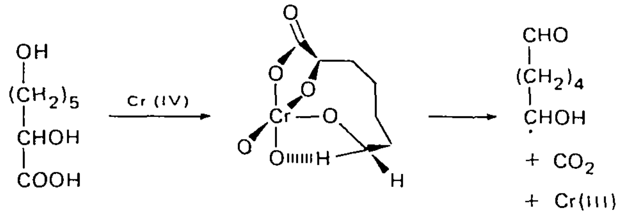

R
O
O
C
Cr
R
H
O
OH
R
O
O
C
Cr(V)
R
HO
OH
R
C=O + Cr(IV)
R

(35)


R
O
O
C
Cr
R
H
O
OH
$[\bar{O}H_2]_n$
R
C=O + Cr(IV)
R

(36)

cyclic mechanisms over mechanism (32). Hydrogen could be transferred as a proton (equation 33), a hydride anion (equation 34), or in a two-step process as a radical with either simultaneous or subsequent rapid electron transfer. Durand and coworkers[47] favour mechanism (33) on the grounds of an analysis of secondary isotope effects. On the other hand, Srinivasan and Roček[48] argued that hydrogen is transferred in an intramolecular mechanism as an atom or hydride anion (mechanism 34 or 35). They arrived at this conclusion by studying the intramolecular cooxidation of 2,7-dihydroxyheptanoic acid (**10**) according to equation (37). The



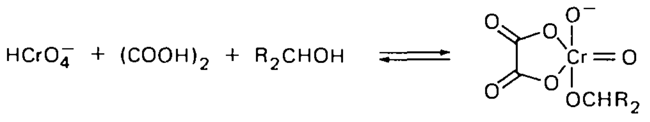
(37)

(10)

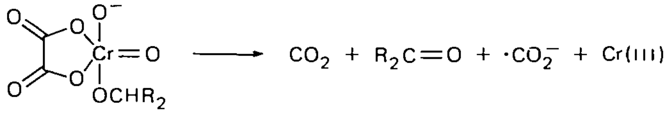
required geometry for intramolecular tranfer is rather hard to attain; nevertheless **10** reacts some 10^4 times faster than its higher or lower homologues, where other mechanisms are operative. It follows that the intramolecular pathway is an energetically very favourable process, and will also be favoured in Cr(VI) oxidation of simple alcohols. Proton transfer was ruled out because of the cyclic nature of the transition state. The Cr–O oxygen would have to be a better proton acceptor than water by 6 to 12 orders of magnitude in order to favour a cyclic proton transfer over an acyclic mechanism. The square-pyramidal geometry of the transition state is inferred by the steric hindrance to catalytic activity of picolinic acids in Cr(VI) oxidations upon substitution in the 6-position[41].

Mechanism (36) was proposed by Kwart and Nickle[49] for the oxidation of sterically highly hindered alcohols. The temperature dependence of the kinetic isotope effect for oxidation of di-*t*-butylcarbinol showed unusual variations in the energy of activation ($E_a^D - E_a^H$ up to three times as high as the difference in the zero-point energies of the C–D and C–H bond) and in the Arrhenius A-factor ($A_H/A_D = 0.12$–5.9) while unhindered alcohols have $A_H \simeq A_D$. The combination of these two factors resulted in a disappearance of the isotope effect at high acidity. Similar results were obtained for trifluoromethylcarbinol. These observations were explained by a change in mechanism from cyclic hydrogen transfer to transfer through a chain of solvent molecules accompanied by acid-catalysed tunnelling. Kwart suggested that steric effects on rates of alcohol oxidation might be due to variations in the degree of tunnelling, due to differences in the steepness of the energy barrier for hydrogen transfer. This proposal has been criticized. It has been argued that the abnormal activation parameters could as well indicate a change in the rate-determining step[41]. Müller and Perlberger[50] observed that the entropies of activation of sterically hindered alcohols such as di-*t*-butylcarbinol and 2,2,4,4-tetramethylcyclobutanol are significantly different from those of unhindered alcohols, the latter representing an isoentropic series. Thus, if di-*t*-butylcarbinol indeed reacts by a special mechanism, there is no evidence for tunnelling or mechanistic changes for normal, unhindered alcohols.

d. Three-electron oxidation. Hasan and Roček[51] investigated the Cr(VI) oxidation of 2-propanol in the presence of oxalic acid. The reaction is faster than the oxidation of either oxalic acid or 2-propanol alone. The mechanism in equations (38)–(40), involving the formation of a ternary complex and its decomposition by



(38)



(39)

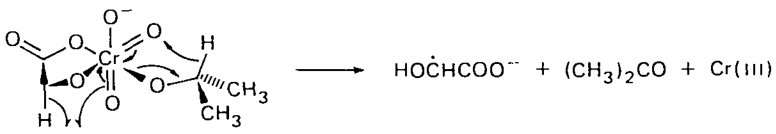
$$\mathrm{Cr(VI)} + \cdot\mathrm{CO_2} \longrightarrow \mathrm{Cr(V)} + \mathrm{CO_2} \qquad (40)$$

simultaneous transfer of three electrons, was proposed. Cr(V) produced in equation (40) may react with the alcohol or with oxalic acid to yield a ketone or carbon dioxide, respectively (equation 41). The yield of ketone relative to CO_2 therefore

$$\mathrm{Cr(V)} + \mathrm{R_2CHOH} \longrightarrow \mathrm{R_2C{=}O} + \mathrm{Cr(III)} \qquad (41a)$$

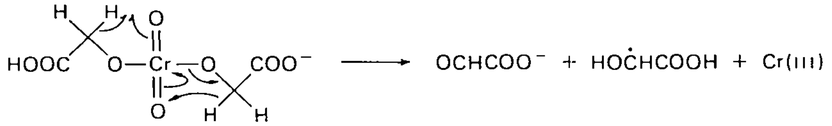
$$\mathrm{Cr(V)} + \mathrm{(COOH)_2} \longrightarrow 2\,\mathrm{CO_2} + \mathrm{Cr(III)} \qquad (41b)$$

provides a method of studying the reactivity of alcohols towards Cr(V)[32]. Similar results were obtained for the cooxidation of 2-propanol and glycolic acid[52]. When both alcohol and hydroxy acid were deuterium labelled, a kinetic isotope effect of 34.4 was obtained, confirming the breaking of two C—H bonds in the rate-limiting step (equation 42). Similarly, breakdown of the ternary complex of chromic acid



(42)

and of two molecules of glycolic acid is associated with an isotope effect of $k_H/k_D \geqslant 36.5$[53] (equation 43).



(43)

A three-electron mechanism has also been found in the oxidation 2-hydroxy-2-methylbutyric acid[54]. In the course of the reaction Cr(V) complexes of surprisingly high stability are formed. Krumpolc and Roček[55] isolated potassium bis(2-hydroxy-2-methylbutyrato)oxochromate (V) monohydrate from the reaction mixture and established the X-ray structure; the compound is not only of interest to chemists but also to high-energy physicists interested in the study of high-energy particle interactions[56].

During cooxidation of an alcohol and oxalic acid the only intermediate chromium species is Cr(V). This has been exploited by Krumpolc and Roček[57] to oxidize cyclobutanol (4) to the ketone under mild conditions and in high yield. Since Cr(IV) formation is avoided, no cleavage to γ-hydroxybutyraldehyde occurs. The method could be of interest in all alcohol oxidations, where Cr(IV) causes side-reactions.

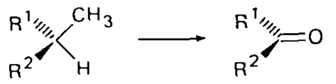
2. *Effects of structure*

a. Steric effects. The interpretation of the steric effects on the rate of oxidation of secondary alcohols has been the subject of much controversy over the recent years. Vavon[58] was the first to observe that sterically hindered alcohols are more reactive than their less hindered epimers. This appeared to be incompatible with the ester mechanism and was therefore explained by attack on the less hindered hydrogen[59]. Schreiber and Eschenmoser[18,60] found that the rate of oxidation was determined by release of steric strain in going from the sp^3-hybridized alcohol to a sp^2-hybridized ketone. Accordingly a late transition state was proposed[61]. Sicher postulated a linear free energy relationship between relative stability (ΔG°_{eq}) and reactivity ($\Delta\Delta G^{\neq}_{ox}$) for epimeric alcohols (equation 44). The relationship was tested

$$\Delta G^0_{eq} = ART \ln (k_a/k_e) = A\Delta\Delta G^{\neq}_{ox} \tag{44}$$

by various authors[62] and seems to hold fairly well, although the slope A varies from 0.8 to 1.0 depending on the author. This corresponds to an almost complete release of strain in going to the transition state. Accordingly, oxidations leading to strained ketones were expected to be particularly slow. However, it was found that cyclobutanol (4) is in fact more reactive than cyclopentanol[63] and 7-norbornanol only about 8 times less than 2-*exo*-norbornanol[64]. Therefore an early, rather sp^3-hybridized transition state was also proposed[40].

Müller and Perlberger[65] applied the method of molecular mechanics in order to rationalize the steric effects on rates of alcohol oxidation. The steric requirements of the OH groups were simulated by CH_3; the carbonyl group was used as a model reflecting the properties of the transition state. The calculated strain change in going from starting hydrocarbon to the transition state (equation 45) was then



(45)

$$\log k \sim E_{st}[R^1R^2CO] - E_{st}[R^1R^2CHCH_3] \tag{46}$$

correlated with the reaction rate. Figure 1 shows a plot corresponding to equation (46). Although there is considerable scatter due to various approximations which had to be made, the general trend shows that highly strained alcohols are the most reactive ones, while alcohols leading to strained ketones are unreactive. However, while ΔE_{st} spans a range of ca. 15 kcal mol^{-1}, the corresponding energies of activation cover only 6.7 kcal mol^{-1}. This indicates that the use of the ketone as a transition-state model leads to a substantial overestimation of strain in the transition state. Although alcohol strain, according to the Sicher correlation should be released to ca. 80% in going to the transition state, strain in the ketone will only be built up by about 1/3.

b. Primary alcohols. Oxidation of primary alcohols to aldehydes, although mechanistically analogous to that of secondary alcohols, is more complex because of further oxidation of the aldehyde to carboxylic acid or ester, the latter via hemiacetal formation[66] (equations 47 and 48). The subsequent oxidations may be suppressed if

$$RCH_2OH \longrightarrow RCHO \xrightleftharpoons{H^+} RCH(OH)_2 \longrightarrow RCOOH \tag{47}$$

$$RCHO \xrightleftharpoons{ROH/H^+} RCH(OH)OR \longrightarrow RCOOR \tag{48}$$

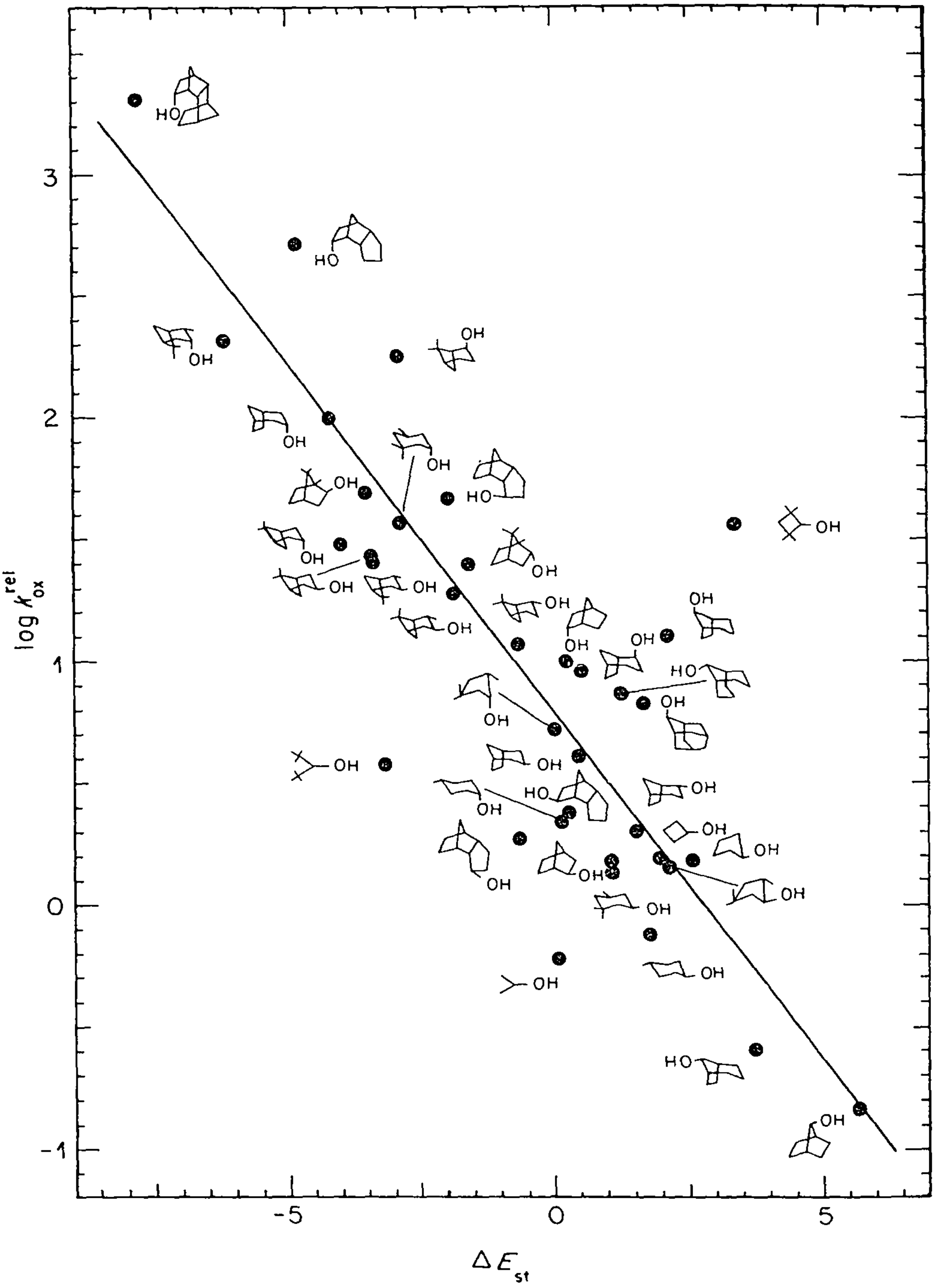
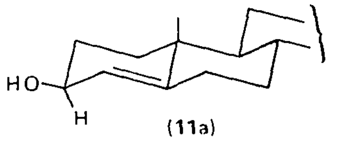


FIGURE 1. Rates for oxidation (log k_{ox}^{rel}) of alcohols as a function of ΔE_{st}. Reproduced from Reference 5 by permission of Schweizer Chemiker Verband.

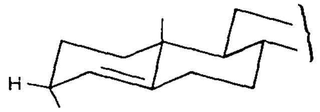
the aldehyde is continuously distilled out of the reaction mixture[67]. Lee and Spitzer[68] have exploited the fact that aldehyde oxidation takes place via the hydrate[69]. Hydration is acid-catalysed and may be suppressed under neutral conditions. Accordingly oxidation of primary alcohols with aqueous sodium dichromate at temperatures around 100°C leads to aldehydes. The reaction gives good yields for benzyl alcohols but is much less satisfactory for aliphatic alcohols. The latter have been converted by potassium dichromate in glacial acetic acid (100°C) to aldehydes in 40–80% yield[70].

c. Unsaturated alcohols. Allylic and benzylic alcohols react faster than their saturated analogues, because of conjugative stabilization between the developing carbonyl group and the π-system. For example α-tetralol is oxidized 17 times faster than cyclohexanol[71]. Burstein and Ringold[72] investigated a series of steroidal allylic alcohols. It was found that in the absence of substantial strain effects the (pseudo) equatorial alcohol **11a** was oxidized faster than the (pseudo) axial isomer **11b**, while in the saturated series the axial alcohol is more reactive than the equatorial epimer **12**. This observation was rationalized on the basis of better overlap of the departing axial hydrogen. Other structural effects on the oxidiation rates have been reported[73] (Table 1). The rate reduction observed for oxidation of

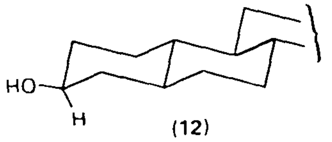
k_{rel}



(11a) 310



(11b) 54



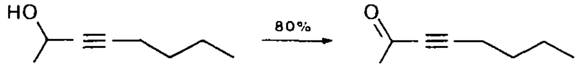
(12) 1.0

TABLE 1. Oxidation of benzylic alcohols with Cr(VI) (90% acetic acid, 0.01 M potassium acetate, 25°C)[73]

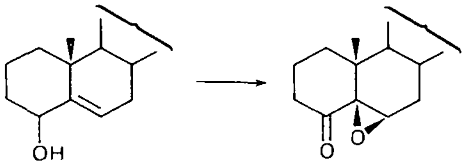
Alcohol	k_{rel}
1-Phenylethanol	1.0
1-Indanol	9.3
1-Tetralol	14.7
Benzocyclobutenol	1.7
1-(2-Methylphenyl)ethanol	0.30
1-(4-Methylphenyl)ethanol	1.75
1-Mesitylethanol	4.30

1-(2-methylphenyl)ethanol was interpreted by steric inhibition of resonance in the transition state. The low rate of benzocyclobutenol compared with indanol and 1-tetralol is believed to be due to a steric rate retardation.

Owing to their enhanced reactivity, allylic and benzylic alcohols may be oxidized selectively under mild conditions to aldehydes and ketones. Although many sophisticated reagents have been proposed for these transformations, chromic acid in acetone (Jones reagent)[74] often leads to comparable results. Cinnamaldehyde is obtained in 84% yield[75] from the alcohol. Geraniol and nerol give the aldehydes in 85–95% yield, although some isomerization occurs at the double bond. Similarly, acetylenic alcohols are converted to ketones in 80% yield[74] (equation 49). In some cases side-reactions have been observed owing to competing attack at the double bond. Glotter and collaborators[76] found formation of epoxy ketones in the oxidation of axial allylic steroidal alcohols with Jones' reagent (equation 50). Under the same conditions the equatorial alcohols afforded enones (equation 51). The OH group directs the approaching Cr(VI) species to attack from the same side of the molecule. Further complications may arise from allylic rearrangements prior to oxidation. In pyridine solution epoxidation was suppressed and even the axial alcohols gave enones. Similarly, oxidation of manool (**13**) with Jones' reagent led to a mixture of rearranged unsaturated aldehydes **14** and epoxy alcohol **15**[77]. Under the same conditions the corresponding secondary alcohol **16** gave enone **17**, epoxy ketone **18** and the rearranged epoxy ketone **19**. Interestingly no allylic rearrangement occurred with **16** under the reaction conditions in the absence of chromic acid. Modified Cr(VI) reagents produced similar results.



(49)



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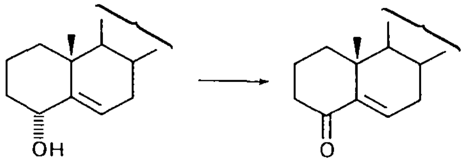

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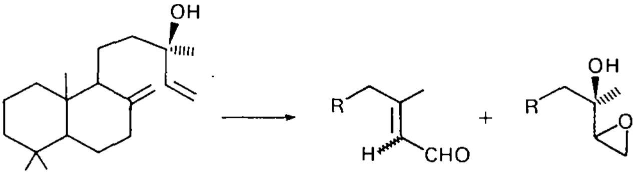
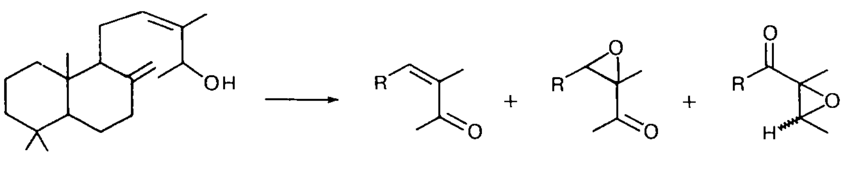


(13) (14) (15)

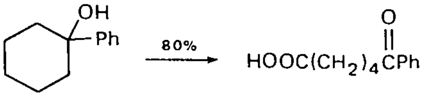
(52)

d. Tertiary alcohols and cyclopropanols. Although tertiary alcohols form chromate esters quite readily[78] their oxidation proceeds very slowly. The rates of oxidation are independent of the concentration of chromic acid, and correspond to

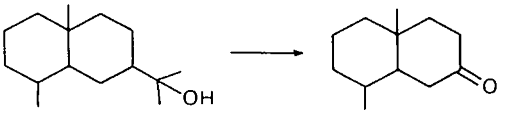


(16) (17) (18) (19) (53)

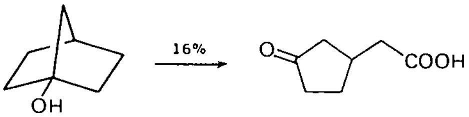
the rates of acid-catalysed dehydration of the alcohols[79]. Oxidation therefore takes place via alkene formation. The reaction has found some preparative applications as shown in equations (54)–(56). In the case of 1-norbornanol (equation 56) alkene formation is impossible. It has been suggested that this molecule reacts by direct C—C cleavage. Direct oxidation of a tertiary alcohol by Cr(VI) has been demonstrated for 1-methyl-1-cyclobutanol[83]. Cleavage of cyclobutanols has been exploited for the synthesis of a variety of 1,4-diketones (equation 57)[84]. Triarylcarbinols react also by direct C—C bond cleavage. A mechanism involving a 1,2-aryl shift has been proposed[85].



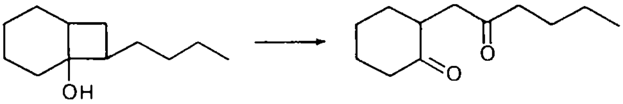
(Ref. 80) (54)



(Ref. 81) (55)



(Ref. 82) (56)



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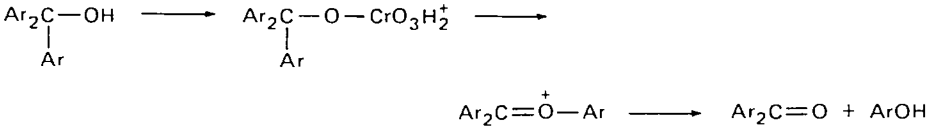
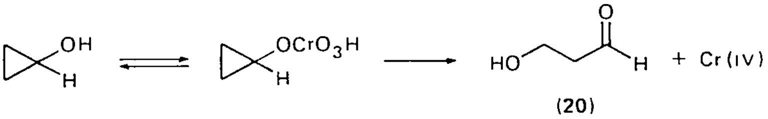
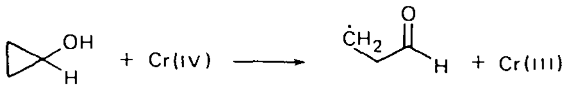


$$\begin{aligned}&\underset{\displaystyle Ar}{Ar_2\overset{|}{C}}\text{—OH}\longrightarrow \underset{\displaystyle Ar}{Ar_2\overset{|}{C}}\text{—O—}CrO_3H_2^+\longrightarrow\\&\qquad Ar_2C{=}\overset{+}{O}\text{—}Ar\longrightarrow Ar_2C{=}O + ArOH\end{aligned} \tag{58}$$

The chromic acid oxidation of cyclopropanols has been investigated by Roček and collaborators[86]. Cyclopropanols react 10^3-10^6 times faster than other secondary alcohols. Tertiary cyclopropanols are even more reactive. Both secondary and tertiary alcohols are oxidized by C—C cleavage. The mechanism proposed involves ester formation, followed by a two-electron oxidation to the hydroxyaldehyde **20** and Cr(IV). Cr(IV) oxidation leads to the radical **21** and Cr(III). The subsequent

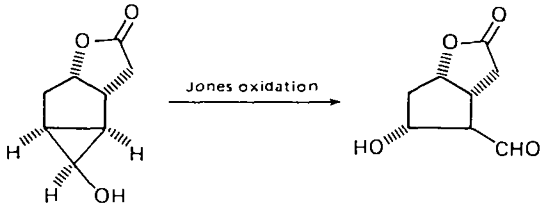


(20) (59)



(21) (60)

steps consist of oxidation of the radical with formation of Cr(V) which, in turn, reacts with cyclopropanol. The cyclopropanol oxidation is the only case where a secondary alcohol is oxidized by Cr(VI) via C—C bond cleavage. A practical application of cyclopropanol cleavage is shown in equation (61)[87].



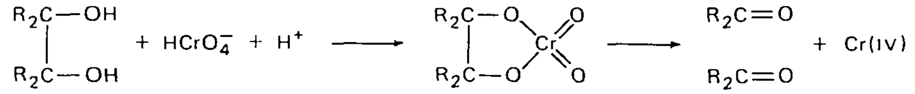
(61)

e. Diols. Oxidation of diols may proceed by two routes, either analogously to oxidation of simple alcohols to hydroxycarbonyl compounds or by C—C bond cleavage. The first pathway applies to ethylene glycol[88] for which the mechanism shown in equations (62) and (63) has been proposed[1]. Increasing alkyl substitution

$$\mathrm{HOCH_2CH_2OH + HCrO_4^- + H^+ \rightleftharpoons HOCH_2CH_2OCrO_3H + H_2O} \qquad (62)$$

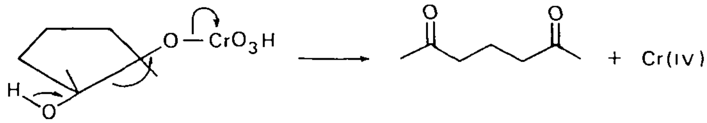
$$\mathrm{HOCH_2CH_2OCrO_3H \longrightarrow HOCH_2CH{=}O + Cr(IV)} \qquad (63)$$

increases the amount of cleavage (1—2% for ethylene glycol, 20—30% for 2,3-butanediol, exclusive cleavage for pinacol)[89]. Roček and Westheimer[90] proposed a cyclic chromate ester as an intermediate (equation 64), when they found that



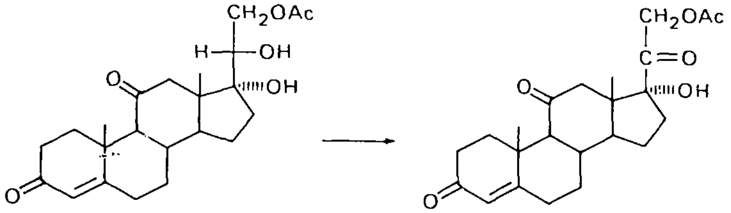
(64)

cis-1,2-dimethyl-1,2-cyclopentane-diol was oxidized to 2,6-hepanedione at a rate 17,000 times faster than the *trans* isomer. As in the normal oxidation of alcohols breakdown of the ester was considered to be rate-determining. For oxidation of the *trans* isomer the monoester 22 was proposed as intermediate, the breakdown of 22



(22) (65)

taking place with participation of the free OH group. The drastic difference in reactivity of *cis*- and *trans*-1,2-dimethyl-1,2-cyclopentanediol is not observed with secondary 1,2-diols; for example for 1,2-cyclopentanediol the *cis*/*trans* ratio is only 3, for 1,2-cyclohexanediol it is 6[91]. On thermodynamic grounds oxidation to hydroxy ketone or hydroxy aldehyde represents the favoured pathway[90], so that this reaction can be considered normal. The reason for the change in mechanism upon increasing methyl substitution is not yet clear. However, part of the cleavage reaction is probably due to Cr(IV). Walker[92] investigated the oxidation of the diol 23 in the presence and absence of Mn(II) or Ce(III). Glycol cleavage at the



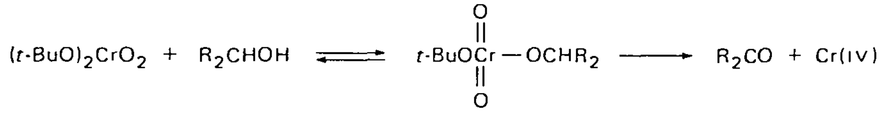
(23) (24) (66)

side-chains was the main reaction in the absence of Cr(IV) scavengers. When the reaction was run in the presence of Mn(II) the yield of cortisone acetate (24) rose from 30 to 48%.

3. *Modified Cr(VI) reagents*

a. t-*Butyl chromate and chromyl chloride.* The oxidation of alcohols with *t*-butyl chromate in a nonpolar solvent has been reported to afford aldehydes[93] and ketones[94] in 80–95% yield. However, Suga and Matsuura[95] found that the reaction has similar limitations as oxidation with chromic acit itself. Secondary alcohols lead to ketones in excellent yield and allylic or benzylic alcohols afford the corresponding aldehydes. However, with primary alcohols a mixture containing aldehyde, acid and ester, the latter formed via a hemiacetal, was obtained. Secondary 1,2-diols lead to cleavage.

The kinetics of the oxidation of secondary alcohols with *t*-butyl chromate has been studied[38]. The steric effects operating in the reaction follow the same trends as with chromic acid, but are less pronounced. The reaction mechanism involves transesterification followed by breakdown of the mixed ester 25 to ketone and a Cr(IV) species (equation 67). The latter is not further reduced to Cr(III) under the reaction conditions.



$$(t\text{-BuO})_2\text{CrO}_2 + \text{R}_2\text{CHOH} \rightleftharpoons t\text{-BuO}\overset{\overset{\text{O}}{\|}}{\underset{\underset{\text{O}}{\|}}{\text{Cr}}}\text{—OCHR}_2 \longrightarrow \text{R}_2\text{CO} + \text{Cr(IV)} \qquad (67)$$

(25)

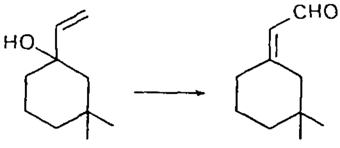
Chromyl chloride is a very vigorous oxidant lacking selectivity. However, adsorbed on silica–alumina it oxidizes primary alcohols to aldehydes and secondary alcohols to ketones in 75–100% yield[96]. Several functional groups such as esters, lactones, nitriles, ethers and halocarbons are inert to the reagent, while alkenes undergo oxidative cleavage. Sharpless and Akashi[97] moderated the activity of chromyl chloride by reacting it with pyridine and *t*-butanol. The structure of the reagent is not established. Sharpless proposed *t*-butyl chromate or its pyridine adduct as possible structures, but is clearly superior to the *t*-butyl chromate of Oppenauer and Oberrauch[93]. The Sharpless procedure offers advantages for large-scale oxidations of simple saturated primary alcohols to aldehydes.

b. Pyridine–chromium trioxide and related reagents. The pyridine–chromium trioxide complex[98] was introduced by Sarrett and collaborators[99] for the selective oxidation of allylic alcohols. The reagent dispersed in pyridine gives yields of 70–90% for steroids. For aliphatic alcohols yields are however considerably lower[100]. Several variations of the method are now available. In the Collins oxidation[101] the complex is dispersed in methylene chloride, in which it is slightly soluble. The Ratcliffe[102] procedure avoids the hazardous preparation of the hygroscopic complex by generating it *in situ* in methylene chloride. Cornforth[103] added an aqueous solution of chromium trioxide to pyridine and obtained results comparable to the Sarrett method. Other procedures use chromium trioxide in pyridine–acetic acid[104], pyridine dichromate[105] and Collins' reagent in the presence of celite[106].

Corey and Fleet[107] prepared a chromium trioxide–3,5-dimethylpyrazole complex by adding dimethylpyrazole to a suspension of chromium trioxide in methylene chloride. The reagent used in threefold excess converted a series of primary and secondary saturated and unsaturated alcohols to the corresponding aldehydes and ketones in 70–100% yield. The Sarrett and related procedures are of advantage for oxidation of acid-sensitive compounds. Their major drawback is the large (three- to six-fold) excess required to obtain acceptable yields.

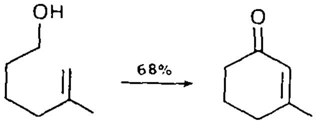
This problem may be overcome by using the more recently developed pyridinium chlorochromate[108], which requires only 1.5 equivalents of reagent. The reagent is slightly acidic, but the reaction mixture can be buffered by working in the presence of powdered sodium acetate.

Although the chromium–pyridine reagents are used under mild conditions, they may also lead to side-reactions with complex molecules. For example, oxidation of manool (15) with Collins reagent or pyridinium chlorochromate gave a complex mixture of products similar to that obtained with the Jones oxidation[77]. With tertiary allylic alcohol 26 oxidation was accompanied by rearrangement[109]. Allylic rearrangements have also been reported to occur during oxidation with the chromium trioxide–dimethylpyrazole complex[110]. The acidic nature of pyridinium chlorochromate has been exploited by Corey to form cyclohexenones by oxidative cationic cyclization from alcohols and aldehydes (equation 69)[111].



(26)

(68)



(69)

c. Miscellaneous. The need for chromic acid oxidations under mild conditions led to the development of other methods, some of them closely related to the Sarrett oxidation. Snatzke[112] oxidized steroidal alcohols with chromium trioxide in dimethylformamide containing small amounts of sulphuric acid in ca. 80% yield. Ketal groups remained intact under the reaction conditions. Similarly, sodium dichromate in dimethylsulphoxide and sulphuric acid has been used for oxidation of primary and secondary alcohols[113]. Chromium trioxide in hexamethylphosporic triamide converts activated primary and secondary alcohols in high yield; saturated secondary alcohols give less satisfactory results[114]. Alternatively two-phase systems of an organic solvent such as benzene[115] or ether[116] containing the substrate and chromic acid in water provide mild conditions for oxidations of sensitive alcohols. Chromium trioxide intercalated in graphite is a selective reagent for the conversion of primary alcohols to aldehydes[117]. Cainelli and collaborators[118] obtained a polymer-supported chromic acid reagent by treating an anion exchange resin with chromium trioxide. The reagent oxidized various alcohols to aldehydes and ketones in excellent yield.

C. Manganese and Ruthenium Oxides

1. Potassium permanganate

a. Mechanisms. Alcohol oxidation by potassium permanganate has been reviewed[3,4,119]. As with chromic acid the reaction mechanism must be complex, since intermediate valence states of manganese are involved. In acidic solution Mn(VII) is reduced to Mn(II) (equation 70)[120]. In neutral and basic solution reduction first proceeds to the manganate(VI) stage (equation 71)[121]. Manganate ion reacts ca. 40 times slower with the alcohol than permanganate. However, in all but very basic solutions it disproportionates to manganese dioxide and permanganate (equation 72). The formation of manganate (VI) may proceed by one-electron transfer from the substrate to Mn(VII). However, a two-electron transfer to manganese (VII) to yield Mn(V) followed by rapid oxidation with permanganate[122] would lead to the same result (equation 73). The oxidation of alcohols is thus mainly due to the Mn(VII) species, that is potassium permanganate.

$$2MnO_4^- + 5R_2CHOH + 6H^+ \longrightarrow 2Mn^{2+} + 5R_2CO + 8H_2O \qquad (70)$$

$$2MnO_4^- + R_2CHOH + 2OH^- \longrightarrow 2MnO_4^{2-} + R_2CO + H_2O \qquad (71)$$

$$3MnO_4^{2-} + 2H_2O \longrightarrow 2MnO_4^- + MnO_2 + 4OH^- \qquad (72)$$

$$MnO_4^- + MnO_4^{3-} \longrightarrow 2\,MnO_4^{2-} \qquad (73)$$

Much of the present knowledge of the reaction mechanism is due to the work of Stewart[121]. Benzhydrol was oxidized in basic solution with the rate law. A kinetic

$$v = k[MnO_4^-][R_2CHOH][OH^-] \qquad (74)$$

isotope effect of 6.6 was obtained with the deuterated compound, indicating C—H bond cleavage in the rate-determining step. Unusually high isotope effects (ca. 16) were observed for a series of aryltrifluoromethyl carbinols[123]. In acidic solution a value of $k_H/k_D = 2.1$ (50°C) was found for oxidation of cyclohexanol[124]. Similarly, ethanol gave $k_H/k_D = 2.6$ with acid permanganate[120]. In basic solutions reactions are much faster than under neutral or acidic conditions, and this has been shown to be due to ionization of the alcohol (equations 75 and 76). A small rate

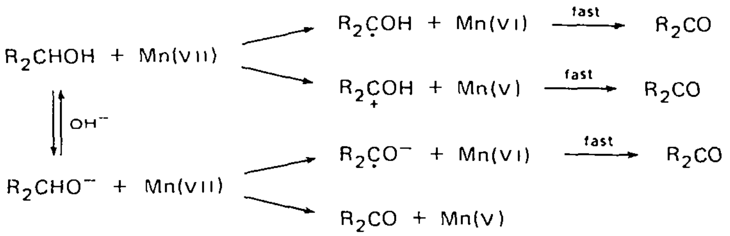
$$R_2CHOH + OH^- \rightleftharpoons R_2CHO^- + H_2O \qquad (75)$$

$$R_2CHO^- \xrightarrow{Mn(VII)} R_2CO \qquad (76)$$

increase is also observed with increasing concentration of acid because of protonation of permangante ion (equation 77)[124]. Part of the rate acceleration in acid

$$MnO_4^- + H^+ \rightleftharpoons HMnO_4 \qquad (77)$$

could however be due to induced oxidation by intermediate Mn(III) or Mn(IV) species[125], which cause an autocatalytic effect. The latter may be suppressed by adding fluoride or pyrophosphate ions to the solution, thereby stabilizing the intermediate valence states by complexation[120].



$$R_2\dot{C}OH + Mn(VI) \xrightarrow{fast} R_2CO \quad (78)$$

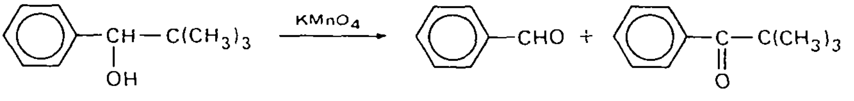
$$R_2\underset{+}{C}OH + Mn(V) \xrightarrow{fast} R_2CO \quad (79)$$

$$R_2\dot{C}O^- + Mn(VI) \xrightarrow{fast} R_2CO \quad (80)$$

$$R_2CO + Mn(V) \quad (81)$$

SCHEME 5.

Polar effects are more pronounced in the permanganate oxidation than in the oxidation with chromic acid. Banerji[120] found $\rho^* = -2.02$ for a series of primary alcohols. For a series of mandelic acids which are believed to react by the same mechanism as simple alcohols, ρ^* was -2.23[126]. Very little information is however available on structural effects. Cyclohexanol and 2-propanol react at about the same rate in both basic and acidic solutions[127], while diisopropyl ether is almost as reactive. On these grounds an intermediate permanganate ester formed in a pre-equilibrium can be ruled out. The mechanism of oxidation consists in removal of the carbinolic hydrogen either in a one-electron oxidation ($H^{\bullet}$ transfer) or in a two-electron oxidation (H^- transfer) in the rate-determining step (Scheme 5). Both mechanisms have been advanced, and although the question is not definitely settled, hydride transfer is preferred by most authors. Roček and Aylward[128] found that oxidizing agents capable of one-electron transfer can be distinguished from two-electron transfer reagents on the grounds of the oxidation products with cyclobutanol. The former yield cleavage products, while the latter afford the ketone, cyclobutanone. Potassium permanganate also gives cyclobutanone, and could therefore be considered a two-electron oxidant. On the other hand, with phenyl-*t*-butylcarbinol (2) potassium permanganate in acetic acid leads to cleavage products in high yield, a reaction considered to be typical for one-electron reagents[129]. However, as in the chromic acid oxidation, cleavage could be due to intermediate manganese species, such as Mn(IV) or Mn(III), so that their appearance might be irrelevant to the oxidation mechanism of Mn(VII).



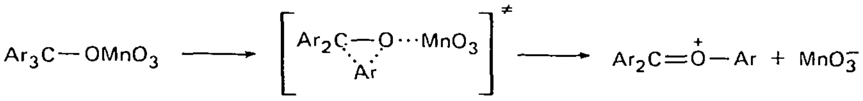
(82)

(2)

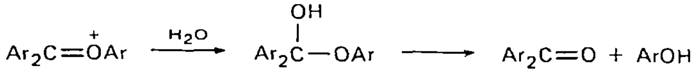
In more concentrated acid solution the reaction may take another course. Banoo and Stewart[130] investigated oxidation of secondary and tertiary aromatic alcohols in aqueous sulphuric acid and found a zero-order dependence in potassium permanganate. Under these conditions the rate-determining step consists in formation of the carbonium ion. The proposed mechanism is shown in equations (83) and (84). A permanganate ester $Ar_2CHOMnO_3$ is likely to be the first intermediate in the fast reaction steps. For tertiary alcohols a similar mechanism involving rearrangement of an aryl group was proposed (equations 85 and 86).

$$Ar_2CHOH + H^+ \underset{}{\overset{slow}{\rightleftharpoons}} Ar_2CH^+ + H_2O \quad (83)$$

$$Ar_2CH^+ + MnO_4^- \xrightarrow{fast} \text{products} \quad (84)$$

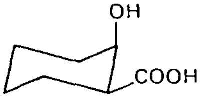


$$Ar_3C{-}OMnO_3 \longrightarrow \left[Ar_2C\overset{}{\underset{Ar}{\cdots}}O\cdots MnO_3 \right]^{\neq} \longrightarrow Ar_2C{=}\overset{+}{O}{-}Ar + MnO_3^- \quad (85)$$

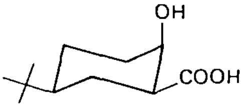


$$Ar_2C{=}\overset{+}{O}Ar \xrightarrow{H_2O} Ar_2\overset{OH}{\overset{|}{C}}{-}OAr \longrightarrow Ar_2C{=}O + ArOH \quad (86)$$

Although permanganate oxidations are in general slow in the intermediate pH range, pronounced rate accelerations were found for reaction of potassium permanganate with *cis*-2-hydroxycyclohexanecarboxylic acid (27) and its *cis*-5-*t*-butyl derivative 28 between pH 4 and 8, giving a typical bell-shaped curve, (Figure 2)[131].

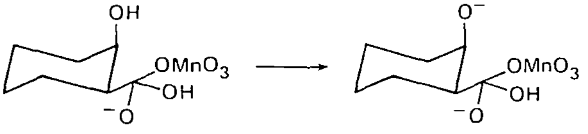


(27)



(28)

The reaction consists in oxidation of the hydroxy group to ketone, followed by slow decarboxylation. Such bell-shaped curves are well known in bioorganic systems and usually originate by the presence of two ionizable groups of different pK involved in the reaction mechanism. It was found that the *trans* isomers of 27 and 28 showed no sign of the phenomenon. Stewart and McPhee[131] proposed a mechanism in which the anion 29 is formed as a steady-state intermediate and then ionized to the dianion 30, the most reactive species involved.



(29) (30) (87)

This mechanism is however not entirely satisfactory. From the pH-rate profile the first ionizing group should have a pK_a of 4.7, just about the pK of a carboxyl group participating by general base catalysis. Furthermore, the mechanism does not

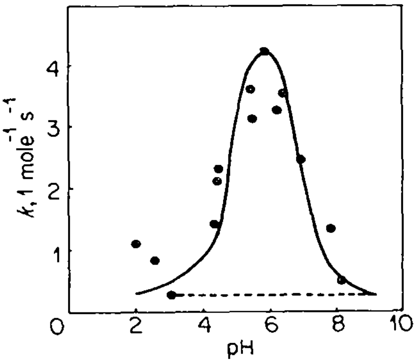
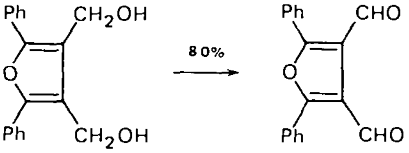


FIGURE 2. pH-rate profile for oxidation of 28 by potassium permanganate. Reprinted with permission from R. Stewart and J. A. MacPhee, *J. Amer. Chem. Soc.*, 93, 4271 (1971). Copyright by the American Chemical Society.

account for the rate decrease above pH 6. A second group or a pH-dependent equilibrium must be involved, capable of compensating for the catalytic effect of the first one. It was furthermore noted that the bell-shaped rate profile is not a general phenomenon. Neighbouring carboxylate groups produced no rate enhancement in the oxidation of benzhydrol[132].

The oxyanions of Mn(VI)[121] (manganate) and Mn(V) (hypomanganate) are also capable of oxidizing alcohols to ketones, but are considerably less reactive than permanganate. Mn(V) is more selective than permanganate and does not attack double bonds[133]. Solid barium manganate, suspended in methylene chloride converts alcohols and, more interestingly, diols to ketones and aldehydes in excellent yield (equation 88)[134].



(88)

b. Synthetic aspects. Potassium permanganate is a vigorous and relatively nonselective oxidant[3]. Primary alcohols give aldehydes, but the latter may be further oxidized to acids or be partly degraded via the enol form (equations 89 and 90)[119].

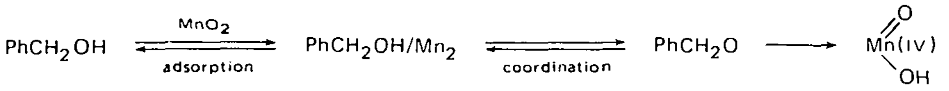
$$\begin{tikzcd}
\mathrm{RCH_2CH_2OH} \arrow[r, "\mathrm{Mn(VII)}"] & \mathrm{RCH_2CHO} \arrow[r, "\mathrm{Mn(VII)}"] \arrow[d, shift left] & \mathrm{RCH_2COOH} & (89) \\
& \mathrm{RCH{=}CHOH} \arrow[u, shift left] \arrow[r, "\mathrm{Mn(VII)}"] & \mathrm{RCOOH + CO_2} & (90)
\end{tikzcd}$$

Isolation of aldehydes as products of alcohol oxidation is impossible in neutral or weakly basic solution, but may be possible in strong base. Although organic solvents are attacked by potassium permanganate, oxidations are often carried out in acetic acid. In order to overcome solubility problems, Cornforth[135] used a two-phase petroleum ether–water system for oxidation of ethyl lactate to ethyl pyruvate. More recently potassium permanganate was solubilized in benzene by complexing it with a crown ether[136] (purple benzene). The reagent was found to react with alcohols, but also with alkenes, aldehydes and arylalkanes. An alternative method of solubilizing permanganate in benzene entails stirring an aqueous solution with a catalytic quantity of a quaternary ammonium salt to maintain a sufficiently high concentration of permanganate in the organic phase[137]. Regen and Koteel[138] activated potassium permanganate for oxidation in benzene by the process of impregnation onto inorganic supports such as molecular sieves, silica gel and certain clays. The procedure appears competitive with most other methods available for small-scale oxidations of secondary alcohols to ketones.

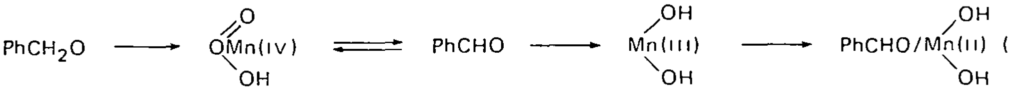
2. *Manganese dioxide*

Manganese dioxide, MnO_2, is the oxidant of choice for selective transformation of allylic and benzylic alcohols to aldehydes and ketones[139]. The reagent was discovered by Ball and collaborators[140] who found that MnO_2 converted Vitamin A almost quantitatively into retinene. Manganese dioxide is prepared by reaction of potassium permanganate with manganese sulphate or chloride[139], and activated by heating to 120–130°C or azeotropic distillation with benzene[141]. It is used as a suspension in a variety of solvents, and reactions are usually carried out by stirring a large excess of oxidant with the alcohol at room temperature for several hours. Gritter and Wallace[142] investigated the solvent effect on the yield of acrolein from allyl alcohols. Best results were obtained with petroleum ether or ethyl ether. With benzene, chloroform or carbon tetrachloride, yields dropped by 20–50%. Acetonitrile has been used for some MnO_2 oxidations[143], but it was later found to be hydrolysed by the reagent to the amide[144]. The method of preparation, the water content and the crystalline form are also of influence. It has been claimed that efficiency of the oxidation of benzyl alcohol proceeds in the order γ-MnO_2 > active manganese dioxide > α-MnO_2[145], and that the oxidizing power of active manganese dioxide depends on the content of γ-MnO_2 in the oxidant.

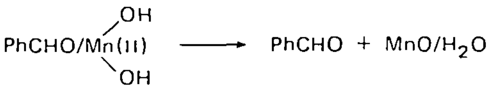
Owing to the heterogenous nature of the reaction, the mechanism is rather poorly understood. Oxidation of α-deuteriobenzyl alcohol showed an isotope effect of 14.2; in a competition experiment with benzyl alcohol and α,α-dideuteriobenzyl alcohol a value of $k_H/k_D = 18.2$ was obtained. On these grounds a reversible adsorption step prior to oxidation, followed by a radical pathway was proposed (equations 91–93)[146]. The high value for k_H/k_D was explained by a superposition of a normal primary isotope effect for C—H bond breaking and a steric isotope effect for the adsorption process. In the oxidation of benzenehexol a molecular surface complex with MnO_2 could be detected and the rate of adsorption monitored by X-ray diffraction[147]. Fatiadi[147] proposed decomposition of manganese dioxide to hydroxy radicals as a possible reaction pathway for the radical mechanism (equation 94). There is also evidence for ionic pathways. Oxidation of 7-norbornadienol (31) resulted in formation of benzaldehyde and the hemiacetal 32, which was explained by a carbonium ion rearrangement[148]. Although the ionic mechanism[149] cannot be ruled out, a radical mechanism could also be invoked to account for the rearrangement. The latter seems more likely in the light of the relative insensitivity of benzylic alcohols to changes in substitution during MnO_2 oxidation[150].



$$PhCH_2OH \xrightleftharpoons[\text{adsorption}]{MnO_2} PhCH_2OH/Mn_2 \xrightleftharpoons[\text{coordination}]{} PhCH_2O \longrightarrow O{=}Mn(IV){-}OH \quad (91)$$

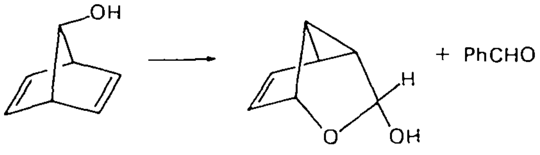


$$PhCH_2O \longrightarrow O{=}OMn(IV){-}OH \rightleftharpoons PhCHO \longrightarrow HO{-}Mn(III){-}OH \longrightarrow PhCHO/Mn(II)(OH)_2 \quad (92)$$



$$PhCHO/Mn(II)(OH)_2 \longrightarrow PhCHO + MnO/H_2O \quad (93)$$

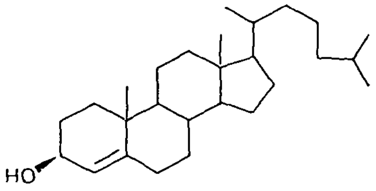
$$MnO(OH)_2 \longrightarrow 2\,{}^{\cdot}OH + Mn(II) \quad (94)$$



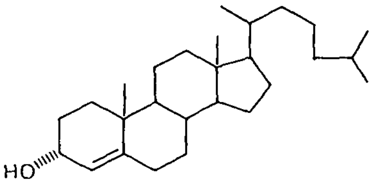
(95)

(31) (32)

Hydrogen abstraction in the slow step of the reaction may in part account for the stereoelectronic effects observed during oxidation of allylic alcohols. In the cyclohexenol series very often the pseudo-equatorial alcohols are much more reactive than their pseudo-axial epimers, for example cholest-4-en-3β-ol (33) is oxidized two to three times faster than the 3α-epimer 34[151]. The phenomenon is

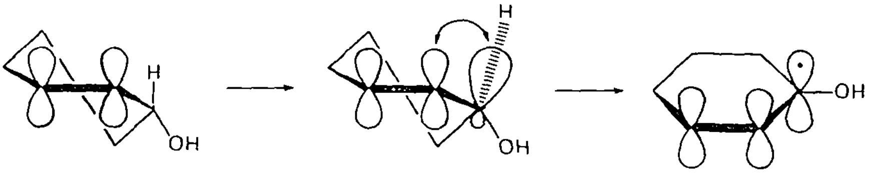


(33) fast



(34) slow

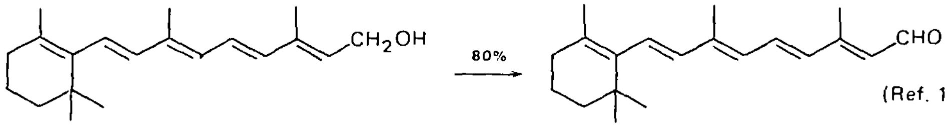
quite general and may be explained by better stabilization if the developing p-orbital is oriented parallel to the π-system (equation 96)[152]. In other cases,



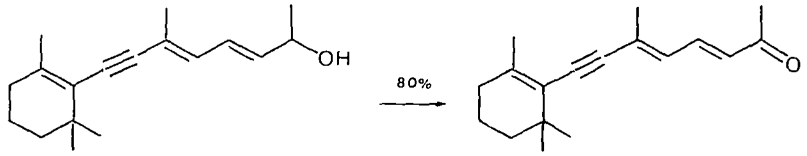
(96)

however, allylic steroid alcohols with both orientations have been converted to the corresponding ketones without difficulties[153].

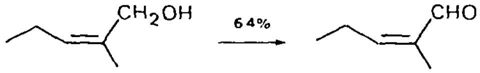
The scope of the oxidation with manganese dioxide is outlined in equations (97)–(102).


CH₂OH
80%
CHO

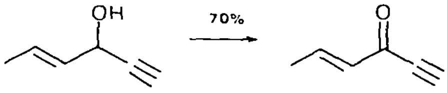
(Ref. 140) (97)



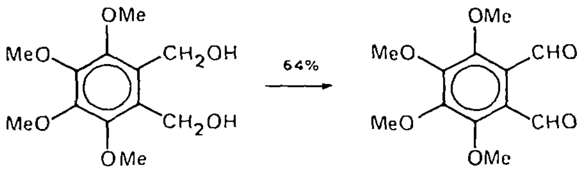
(Ref. 154) (98)


CH₂OH
64%
CHO

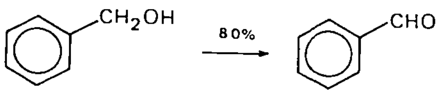
(Ref. 155) (99)



(Ref. 156) (100)

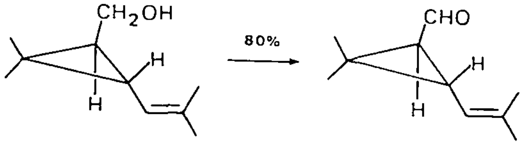

OMe
MeO
CH₂OH
MeO
CH₂OH
OMe
64%
OMe
MeO
CHO
MeO
CHO
OMe

(Ref. 157) (101)



(Ref. 150) (102)

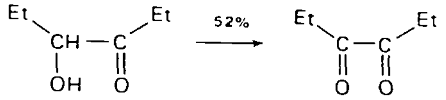
Adjacent cyclopropane rings also activate alcohols to allow oxidation; for example, Crombie and Crossley[158] oxidized *trans*-chrysanthemyl alcohol (35) to the aldehyde (36) in 62% yield at 20°C. Similarly, α-hydroxy ketones have been



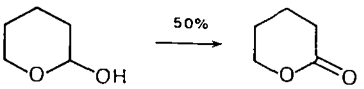
(35) (36)

(103)

oxidized to diketones (equation 104)[159], α-hydroxy esters to keto esters[160] and hemiacetals to lactones (equation 105)[161].

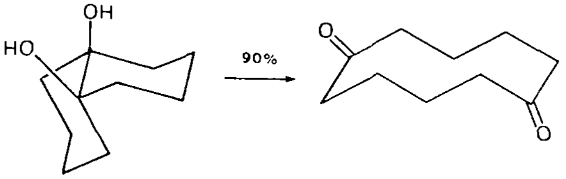


(Ref. 159) (104)



(Ref. 161) (105)

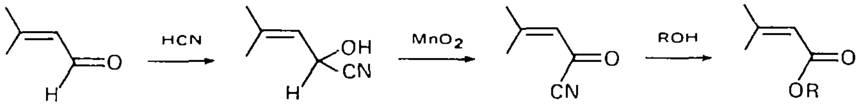
cis-1,2-Diols react preferentially by C—C cleavage, while the *trans* isomers are unreactive:



(Ref. 162) (106)

At elevated temperatures MnO_2 reacts even with saturated aliphatic alcohols to give aldehydes and ketones, respectively. The reaction may already proceed at room temperature, if a sufficiently high excess of oxidant is used[143].

Corey and collaborators[163] reported a simple procedure for the conversion of allylic alcohols to methyl esters with MnO_2 in the presence of HCN. The alcohol is first oxidized to the aldehyde which then reacts to the cyanohydrin. The latter is susceptible to further oxidation by manganese dioxide (equation 107). Furfural,



(107)

geranial and farnesal are transformed in 85–95% yield[163], and retinol affords methyl retinate by passing it through a column packed with an upper layer of MnO_2 and a lower layer with MnO_2/NaCN. Elution with methanol/acetic acid gives the ester in 50% yield[164].

3. *Ruthenium tetroxide*

a. Scope and applications. Ruthenium tetroxide is an extremely powerful, and therefore unselective, oxidizing agent[165]. It is conveniently prepared by reaction of hydrated ruthenium dioxide with an excess of sodium periodate in water, followed by extraction of the tetroxide with carbon tetrachloride[166]. Other procedures use ruthenium trichloride besides the dioxide and oxidants such as sodium hypochlorite[167], sodium bromate[168], chromic acid[169] etc. For synthetic procedures a two-phase system with use of a catalytic amount of ruthenium tetroxide in conjunction with a cooxidant such as aqueous sodium periodate is often employed. The organic substrate, dissolved in carbon tetrachloride or methylene chloride reduces the tetroxide to the insoluble dioxide. The latter is reoxidized by periodate and reextracted into the organic phase (equation 108)[170]. The stoichiometry of

$$RuO_2 \cdot 2H_2O + 2\,NaIO_4 \longrightarrow RuO_4 + 2\,NaIO_3 + 2H_2O \qquad (108)$$

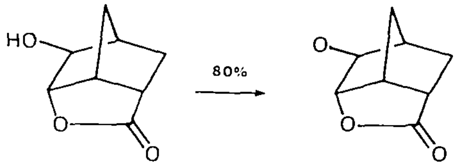
alcohol oxidation depends on the reaction conditions. In carbon tetrachloride the inorganic product is RuO_2 (equation 109)[170]. In perchloric acid, however, it

$$2\,PhCHOHPh + RuO_4 \xrightarrow{CCl_4} 2\,PhCOPh + RuO_2 + 2\,H_2O \qquad (109)$$

becomes Ru(III) (equation 110)[171]. Applications of ruthenium tetroxide to alcohol oxidation is somewhat limited owing to the high tendency of the oxidant to

$$5\,CH_3CHOHCH_3 + 2\,RuO_4 \xrightarrow{H^+/H_2O} 5\,CH_3COCH_3 + 2\,Ru^{3+} + 6OH^- + 2\,H_2O \qquad (110)$$

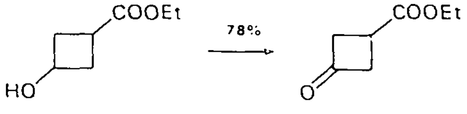
react with other functional groups such as double bonds, aromatic rings and ethers[165]. However, it is the reagent of choice whenever a vigorous oxidant and mild reaction conditions are needed. For example, Moriarty and collaborators[172] oxidized the hydroxylactone **6** to the ketone **37** in 80% yield, while over fifteen other standard methods failed. Yields of ketones from secondary alcohols are usually excellent, 2-propanol[173] and benzhydrol[166] being converted in practically quantitative yield.



(6) (37)

(111)

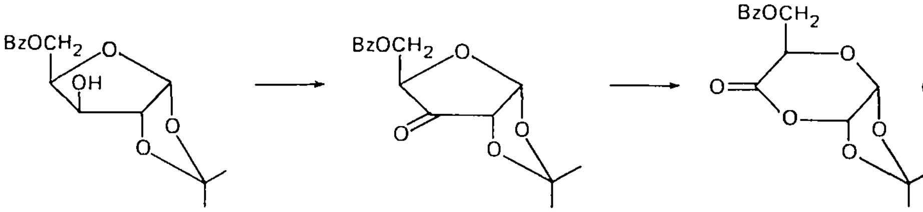
The oxidation of cyclobutanols to cyclobutanones is very often accompanied by cleavage products and, therefore, gives low yields with more conventional oxidants. Ruthenium tetroxide, however, converted ethyl-3-hydroxycyclobutanecarboxylate (**38**) to the ketone with a yield of 78% (equation 112)[174], while cyclobutanol (**4**) itself afforded the ketone exclusively with both ruthenium tetroxide and sodium ruthenate[175].



(38)

(112)

Primary alcohols are converted to aldehydes (40–70%)[168,170] and acids[174] while 1,2-diols give diketones[176] and, under alkaline conditions, mostly cleavage products[167]. A variety of steroidal alcohols have been oxidized by ruthenium tetroxide[177], but the most important application is found in the carbohydrate field[178]. Glycosidic linkages are unaffected during oxidation, and the conventional protecting groups remain intact. In some cases, prolonged treatment results in the formation of lactones (equation 113)[179].



(113)

b. Mechanism. The reaction mechanism has been investigated by Lee and van den Engh[173] for 2-propanol oxidation in aqueous perchloric acid. In solutions of moderate acidity the reaction was found to be first order in oxidant and substrate but inversely proportional to H_0. 2-Propanol showed a kinetic isotope effect of $k_H/k_D = 4.6$ and the activation parameters $\Delta H^{\neq} = 14.0$ kcal mol^{-1} and $\Delta S^{\neq} = -20.3$ e.u. The proposed mechanism is shown in equations (114)–(117). The rate-

$$CH_3CHOHCH_3 + H^+ \xrightleftharpoons{\text{fast}} CH_3CH\overset{+}{O}HCH_3 \qquad (114)$$

$$CH_3CHOHCH_3 + RuO_4 \xrightarrow{\text{slow}} CH_3\overset{+}{C}OHCH_3 + HRuO_4^- \qquad (115)$$

$$CH_3\overset{+}{C}OHCH_3 \xrightarrow{\text{fast}} CH_3COCH_3 + H^+ \qquad (116)$$

$$2\,HRuO_4^- + 3\,CH_3CHOHCH_3 \xrightarrow{\text{fast}} CH_3OCH_3 + 2\,Ru^{3+} \qquad (117)$$

determining step thus consists in transfer of hydride from the carbinolic carbon. This mechanism is based on the observation that electron-donating substitutents accelerate the reaction rate and that cyclobutanol gives only cyclobutanone, while cleavage products, typical for 1-electron oxidations, are absent[175]. Since ethers are oxidized almost as fast as alcohols[171] an ester mechanism similar to the one observed in chromic acid oxidation was ruled out. The rate decrease with increasing acidity was explained by protonation of the alcohol and by the reduced activity of water at high acidity, which would lead to less efficient solvation of the transition state.

At high acidity (7.5–10M $HClO_4$) the reaction becomes zero-order in ruthenium tetroxide, but first order in alcohol. The isotope effect disappears ($k_H/k_D = 1.3$), and two products, acetone and acetaldehyde, are formed. In this region, the reaction rate increases with increasing acidity. This was rationalized by rate-determining carbonium ion formation, followed by rapid oxidation or elimination (equations 118–120). Since ruthenium tetroxide is reduced to the dioxide

$$CH_3CHOH + H^+ \xrightarrow{\text{slow}} CH_3\overset{+}{C}HCH_3 + H_2O \qquad (118)$$

$$CH_3\overset{+}{C}HCH_3 \xrightarrow{\text{fast}} CH_3CH{=}CH_2 + H^+ \qquad (119a)$$

$$CH_3\overset{+}{C}HCH_3 \xrightarrow[\text{fast}]{RuO_4} CH_3COCH_3 \qquad (119b)$$

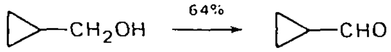
$$CH_3CH{=}CH_2 \xrightarrow[\text{fast}]{RuO_4} CH_3CHO \qquad (120)$$

during the reaction, a second oxidation step between ruthenium(VI) oxide and a molecule of alcohol must occur. Some reactions between sodium ruthenate and alcohols have been studied in basic solution and were found to yield ketones[180]. Cyclobutanol gives cyclobutanone. However, the Ru(VI) species cannot be observed in organic solvents, since it is only stable under strongly basic conditions, but it is believed to be much more reactive than ruthenium tetroxide. It appears thus that the intermediate ruthenium species reacts by hydride transfer, like ruthenium tetroxide itself.

D. One-electron Oxidants

1. Cerium(IV) and vanadium(V)

a. Oxidation with ceric ion. Cerium(IV) occupies a prominent position among the so-called one-electron oxidating reagents. A variety of interesting and in part preparatively useful reactions have been discovered over the last ten years. For example, benzyl alcohols are converted to the aldehydes by ceric ammonium nitrate in ca. 95% yield[181], and cyclopropylcarbinol leads to cyclopropylcarboxaldehyde (64%) (equation 121)[182]. Simple secondary alcohols are converted to ketones; thus 2-propanol and cyclohexanol give rise to acetone[183] and cyclohexanone[184] respectively. In many cases, however, the preferred pathway is not ketone formation, but rather C—C bond cleavage, as with Cr(IV). Typically, alkylphenylcarbinols[23,185] and 1,2-diarylethanols[23] are cleaved to various degrees, depending on the nature of the substituents present (equation 122). Similarly, cyclobutanol[186] reacts by cleavage to a variety of products and bicyclic alcohols such as isoborneol (39) lead to cyclopentene derivatives[187].



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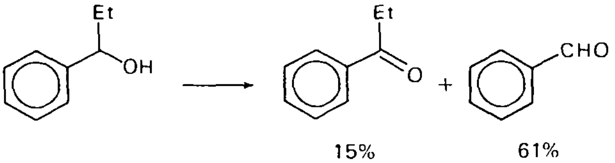

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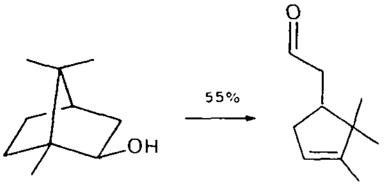
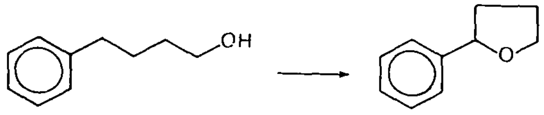


(123)

(39)

While oxidation of ethanol affords acetaldehyde (90% yield)[188], long-chain primary alcohols prefer still another pathway, namely formation of cyclic ethers. 2-Methyltetrahydrofuran is obtained in low yield from pentanol[189]. 4-Phenyl-1-butanol (40) gives 2-phenyltetrahydrofuran (58%, based on converted 40) (equation 124)[190]. Ether formation is rationalized by formation of an alkoxy radical undergoing a 1,5-hydrogen shift followed by further oxidation to a carbonium ion and subsequent cyclization (equation 125). This pathway is not available to the lower homologue, 3-phenyl-1-propanol, which undergoes attack on the phenyl ring by the alkoxy radical 42 to yield 4-chromanone (43) and chromone (44)[190]. Ceric ammonium nitrate cleaves tertiary alcohols to ketones at 80°C in aqueous acetonitrile (equation



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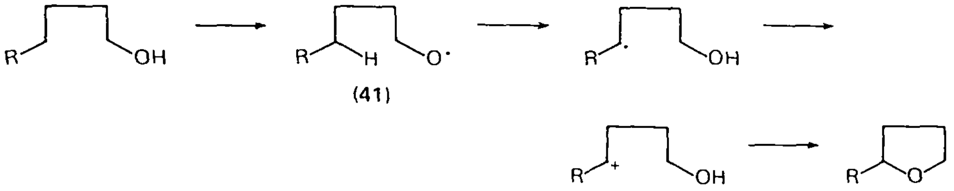
(124)



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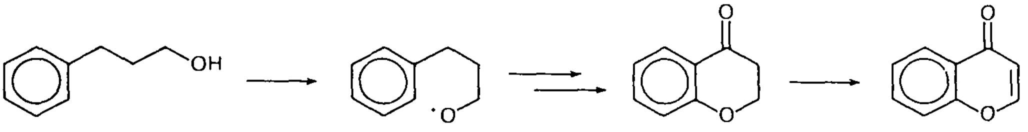
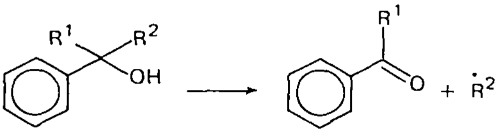
(125)



(42) (43) (44)

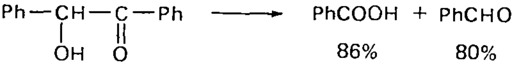
(126)

127)[23,191]. The radical produced in the cleavage step is further oxidized to alkyl nitrate by electron or ligand transfer[185]. From competition experiments the relative



(127)

rates of formation of the allyl : benzyl :: *t*-butyl radicals by oxidative cleavage were found to be 1 : 4.4 : 19.9–62.9[191]. Cleavage also occurs in the oxidation of benzoins (equation 128)[192], α-hydroxy acids[193] and 1,2-diols[184,194].



$$\underset{\text{OH}}{\text{Ph—CH}}\text{—}\underset{\text{O}}{\overset{}{\text{C}}}\text{—Ph} \longrightarrow \underset{86\%}{\text{PhCOOH}} + \underset{80\%}{\text{PhCHO}} \tag{128}$$

b. Mechanisms. Oxidation rates with Ce(IV) show a marked dependency on complexing anions present in solution; for example, reactions in sulphuric acid and acetonitrile are slower than in perchloric acid[194]. In many kinetic studies the precise nature of the reacting cerium species has not been established. Hanna and collaborators[195] recently proposed a system of $HClO_4$–Na_2SO_4–$NaClO_4$ which allows for variation and control of the various cerium complexes.

Alcohol oxidation with Ce(IV) proceeds via an intermediate Ce(IV)–alcohol complex[188]. Complexation results in a colour change of the cerium solution, and this allows for determination of the equilibrium constant K for complex formation. Young and Trahanovsky[196] have measured the equilibria of some 40 alcohols in 70% acetonitrile and found little variation of K with the alcohol structure (0.52 l mol^{-1} for methanol, 1.51 for 2-propanol and 4.73 for cyclohexanol). The complex, once formed is unstable and decomposes unimolecularly (equations 129 and 130).

$$\text{ROH} + \text{Ce(IV)} \rightleftharpoons \text{Ce(IV)}\cdot\text{ROH} \tag{129}$$

$$\text{Ce(IV)}\cdot\text{ROH} \xrightarrow{k} \text{products} \tag{130}$$

The reaction rate is therefore given by[197]

$$-\frac{d[\mathrm{Ce(IV)}]}{dt} = kK[\mathrm{Ce(IV)}][\mathrm{ROH}] \tag{131}$$

and the observed rate constant is

$$k_{\mathrm{obs}} = \frac{kK[\mathrm{ROH}]}{1 + K[\mathrm{ROH}]} \tag{132}$$

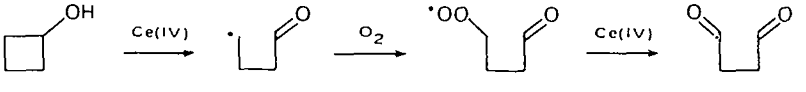
As a consequence of complex formation, k_{obs} shows a saturation effect at high substrate concentration, while plots of $1/k_{\mathrm{obs}}$ vs. $1/[\mathrm{ROH}]$ are linear. Wells and Husain[183] deduced from the acidity dependence of the 2-propanol oxidation in perchloric acid that two intermediate complexes, Ce(IV)$-$ROH$_{\mathrm{aq}}$ and Ce(IV)$-$RO$^-_{\mathrm{aq}}$ are involved.

With cyclohexanol as substrate, breakdown of the intermediate complex shows a kinetic isotope effect of $k_H/k_D = 1.9$[198], indicating C—H bond cleavage in the rate-determining step, with formation of a radical intermediate subject to further fast oxidation to ketone (equations 133 and 134). The hydrogen transfer as

$$\mathrm{R_2CHOH\cdot Ce(IV)} \xrightarrow{\text{slow}} \mathrm{R_2\underset{\bullet}{C}OH + Ce(III) + H^+} \tag{133}$$

$$\mathrm{R_2\underset{\bullet}{C}OH + Ce(III)} \xrightarrow{\text{fast}} \mathrm{R_2CO + Ce(III) + H^+} \tag{134}$$

opposed to hydride transfer mechanism is supported by the observation that Ce(IV) reacts with cyclobutanol (4) by ring-cleavage,[186] like other one-electron transfer



(4)

(135)

reagents, as well as by the cleavage reactions in equations (122) and (123). For cyclobutanol, the intermediate radical has been trapped with oxygen leading to succinaldehyde as the only isolable product[186]Similarly, radicals have been successfully trapped in oxidative cleavage of 1,2-diarylethanols[23]. The rates of this reaction correlate well with the σ^+ constant with $\rho = -2.00$, and this value was used to rule out a free alkoxy radical as reactive intermediate. In contrast, oxidation of primary aliphatic alcohols must proceed via alkoxy radicals (equation 124 and 125) so that tetrahydrofuran formation may occur.

c. Oxidation with vanadium(V). Oxidation of cyclohexanol in aqueous sulphuric acid has been investigated by Littler and Waters[199]. The rate law was found to be

$$v = k[\mathrm{ROH}][\mathrm{VO_2^+}][\mathrm{H_3O^+}] \tag{136}$$

and a mechanism involving fast formation of a vanadium(V)–alcohol complex, followed by slow decomposition with a kinetic isotope effect of 3.6–4.5 to a radical intermediate was proposed (equations 137–139). There is however some

$$\mathrm{VO_2^+ + H_3O^+} \rightleftharpoons \mathrm{V(OH)_3^{2+}} \tag{137}$$

$$\mathrm{V(OH)_3^{2+} + R_2CHOH} \rightleftharpoons \mathrm{[V(OH)_3\cdot R_2CHOH]^{2+}} \tag{138}$$

$$\mathrm{[V(OH)_3\cdot R_2CH_2OH]} \xrightarrow{\text{slow}} \mathrm{R_2\underset{\bullet}{C}OH + V(IV)} \tag{139}$$

discussion concerning the intermediacy of these complexes. In an investigation of the 2-propanol oxidation by vanadium(V) in aqueous perchloric acid, Wells and Nazer[200] found no evidence for complex formation, when kinetics were studies under anaerobic conditions. They proposed attack of $VO_{2\,aq}^{+}$ and $VO(OH)_{aq}^{2+}$ on the carbinolic hydrogen for the rate-determining step. On the other hand, Roček and Aylward[128] found that cyclobutanol (4) is ca. 10^4 times more reactive than its methyl ether, and they concluded that the O—H bond plays a vital part in the oxidation process. It must be broken either prior to or during the rate-limiting step. Therefore, they proposed an ester intermediate in a rapid preoxidation step, in analogy to the alcohol oxidation with Cr(VI). Both the rate law as well as these latter observations are compatible with an intermediate complex or ester in steady-state concentrations.

The reaction of cyclobutanol with vanadium(V) involves cleavage of the cyclobutane ring to γ-hydroxybutyraldehyde[128,200]. Other cleavage reactions have been observed during vanadium oxidation of 2-phenylethanol[201] (equation 140), α-hydroxy acids[202], carbohydrates[203], 1,2-diols[204] and α-hydroxyketones[205]. All these reactions proceed by C—H or C—C bond cleavage to radical intermediates.

$$PhCH_2{-}CH_2OH \longrightarrow PhCH_2^{\bullet} + CH_2O \longrightarrow PhCHO \qquad (140)$$

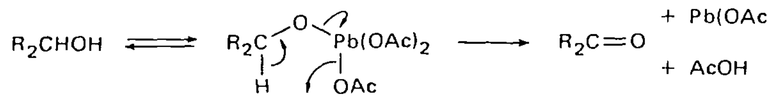
3. *Lead tetraacetate*

Alcohol oxidation with lead tetraacetate may give rise to a variety of different products[206] depending on the structure of the alcohol and the reaction conditions. For most reactions, homolytic mechanisms have been proposed. However, in some cases evidence for heterolytic pathways, where lead tetraacetate oxidations proceed by two-electron transfer, has also been presented.

The first step of the reaction consists in alcoholysis of the tetraacetate (equation 141). Breakdown of the intermediate lead alkoxide may then lead to ketones, ethers or fragmentation products.

$$ROH + Pb(OAc)_4 \rightleftharpoons ROPb(OAc)_3 + AcOH \qquad (141)$$

a. Formation of aldehydes and ketones. Alcohols are stable in lead tetraacetate–acetic acid solutions. They are oxidized in boiling benzene[207] or in pyridine[208] at room temperature to aldehydes and ketones in 60–90% yield. Criegee proposed a heterolytic reaction mechanism (equation 142)[206]. This

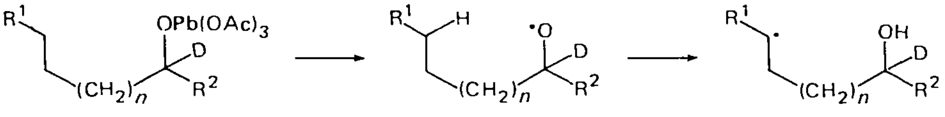


$$R_2CHOH \rightleftharpoons R_2C(H){-}O{-}Pb(OAc)_2(OAc) \longrightarrow R_2C{=}O + Pb(OAc)_2 + AcOH \qquad (142)$$

mechanism is supported by the observation of the kinetic isotope effects for oxidation of methanol ($k_H/k_D = 3.8$)[209] and benzhydrol ($k_H/k_D = 2.01$ in benzene and 4.87 in benzene–pyridine)[210]. The rate acceleration observed upon addition of pyridine to the solvent was interpreted as being due to formation of a complex with the structure $Pb(OAc)_4\ (C_5H_5N)$ rather than to base catalysis[210] These results are however also compatible with a two-step mechanism, where the carbinolic hydrogen is abstracted in a one-electron oxidation (equation 143). In

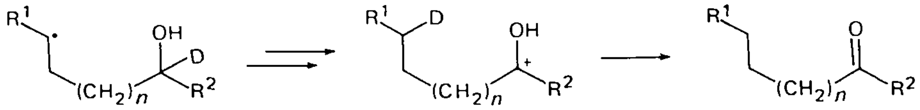
$$R_2CHOPb(OAc)_3 \longrightarrow R_2\dot{C}OH \longrightarrow R_2C{=}O \qquad (143)$$

reality, the reaction is more complex. Mihailović and collaborators[211] investigated the oxidation of a series of α-deuterium-labelled alcohols in boiling benzene and found substantial amounts (up to 60%) of D-incorporation in the δ- and ε-position, respectively. These oxidations are believed to proceed via alkoxy radical intermediates (**45**) undergoing 1,5- or 1,6-hydrogen shifts to carbon radical **46** (equation 144). The latter is oxidized to a carbonium ion prior to or after 1,4- or 1,5-hydride shift to give the carbonium ion **47** (equation 145). ESR spectroscopic evidence for the intermediacy of alkoxy radicals during lead tetraacetate oxidation of simple alcohols has been provided by spin-trapping with nitroso compounds[212] or nitrones[213] to yield nitroxides (equation 146). In all cases studied, only alkoxy radicals were observed, and there appears to be no evidence for a 1,2-hydrogen shift of the alkoxy radical. Since the path outlined in equations (144) and (145) accounts for only 60% of the ketone product even in the most favourable case, other mechanisms must be operative at the same time. The evidence available does not allow one to distinguish between the homolytic and heterolytic process at the present time.



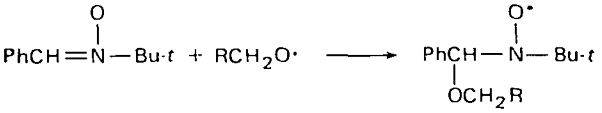
(45)

(144)



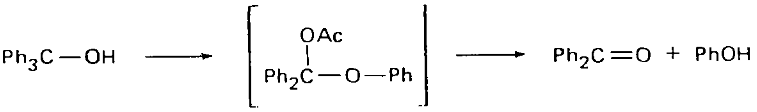
(46) (47)

(145)

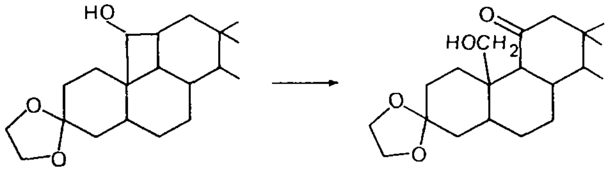


$$\mathrm{PhCH{=}\overset{\displaystyle O}{N}{-}Bu\text{-}\mathit{t} + RCH_2O^{\bullet} \longrightarrow PhCH(OCH_2R){-}\overset{\displaystyle O^{\bullet}}{N}{-}Bu\text{-}\mathit{t}} \qquad (146)$$

b. *β-Fragmentation.* One of the reactions competing with ketone formation during alcohol oxidation with lead tetraacetate consists in cleavage of the α,β-C—C bond. Such fragmentations occur with tertiary alcohols[214–216] and other alcohols[217] carrying quaternary β-substituents (equations 147–151). Although



$$\mathrm{Ph_3C{-}OH \longrightarrow \left[\, Ph_2\overset{\displaystyle OAc}{C}{-}O{-}Ph \,\right] \longrightarrow Ph_2C{=}O + PhOH} \qquad (147)$$



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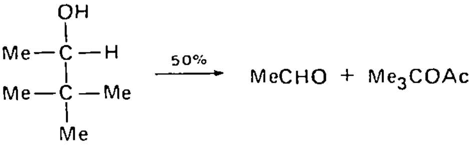
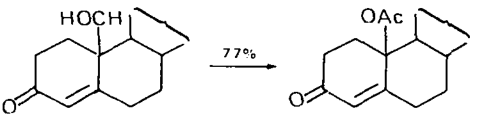


$$\mathrm{Me{-}\overset{\displaystyle OH}{C}H{-}C(Me)_2{-}Me \xrightarrow{50\%} MeCHO + Me_3COAc} \qquad (149)$$



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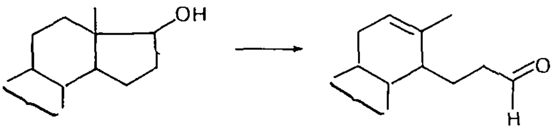
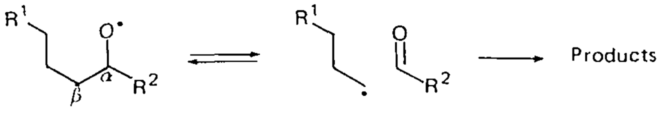


(151)

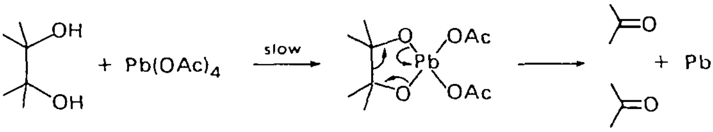
there is evidence that in some cases these reactions proceed by ionic mechanisms^{206,214} or via a cyclic transition state^{206} most authors assume a radical pathway where an initially generated alkoxy radical (48) undergoes reversible cleavage to a carbon radical (49) which is then stabilized either by loss of hydrogen, further oxidation to carbonium ion or hydrogen abstraction from the solvent to alkane (equation 152)^{218,219}. The reversible nature of the fragmentation is indicated by occurrence of isomerization in α- and β-positions^{220}. The amount of cleavage increases primarily with the stability of the alkyl radical formed, although the stability of the carbonyl fragment is of some importance too.



(152)

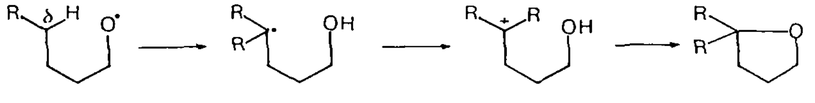
(48) (49)

In contrast, cleavage of *cis*-1,2-diols by lead tetraacetate is a two-electron oxidation which involves formation of a bidentate complex in the rate-determining step (equation 153)^{221}.



(153)

c. Intramolecular cyclization. Under favourable structural and stereochemical conditions alcohol oxidation with lead tetraacetate leads to cyclic ethers^{222}. The topic has been reviewed by Mihailović^{218}. The reaction proceeds either by hydrogen abstraction (equation 154) or addition to an unsaturated system (equation 155) of an alkoxy radical. Hydrogen abstraction may occur at the δ- or ε-position giving rise to formation of tetrahydrofurans and tetrahydropyrans, respectively, and it competes with β-fragmentation. Yields from primary and secondary alcohols are usually in the range of 40–55%. Hydrogen abstraction from the ε-position, which leads to tetrahydropyrans, becomes predominant when an ether oxygen is attached to the ε-carbon atom. In the cyclic systems with favourable geometry yields may be



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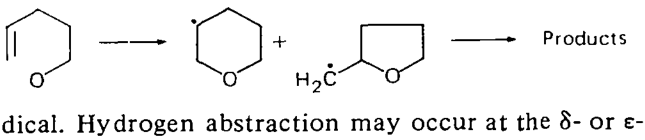
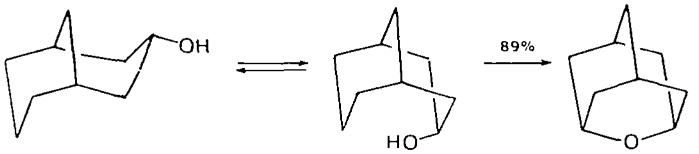
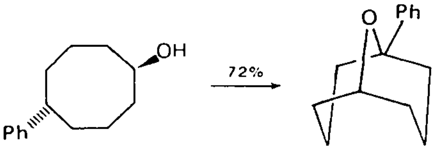


(155)

considerably higher (equations 156 and 157). The various factors controlling the proportion of ether and ketone formation and fragmentation have been discussed by Mihailović[218,225].

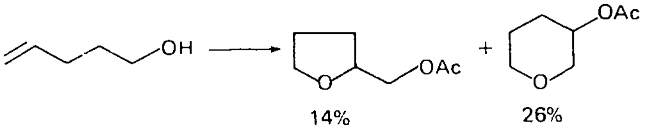


(Ref. 223) (156)

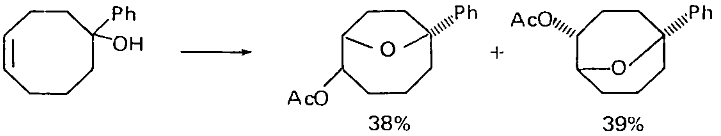


(Ref. 224) (157)

Intramolecular attack of an alkoxy radical on a double bond produces tetrahydropyran and tetrahydrofuran derivatives (equation 158)[226]. Yields of cyclization are in the range of 20–30% (equation 159), in exceptional cases up to 80%[227].

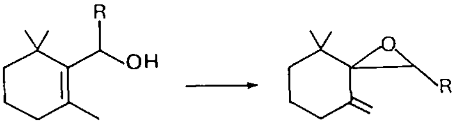


(158)



(159)

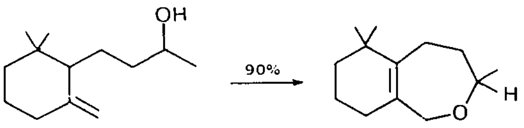
Oxidation of β-cyclogeraniol (**50a**) in boiling benzene affords the epoxide **51** (40%) as the main product (equation 160)[228]. Similar results have been obtained with the



(160)

(50a) R = H
(50b) R = Me
(51)

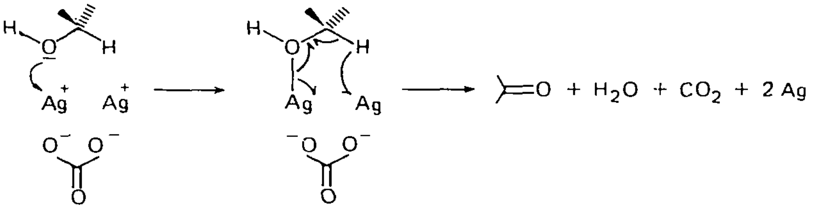
secondary alcohol **50b**. Another high-yield cyclization occurs during oxidation of dihydro-γ-jonol (equation 161)[229].



(161)

3. *Silver carbonate*

Although there are some alcohol oxidations known with silver(II) in the form of argentic picolinate[230] or argentic oxide[231], the main interest is in silver(I) carbonate, precipitate on celite (Fétizon reagent)[232]. The reagent, used in 5- to 30-fold excess, converts primary and secondary alcohols to aldehydes and ketones in excellent yield. Allylic alcohols are selectively oxidized in acetone or methanol solution. The reaction was investigated by Fétizon and collaborators who proposed the following mechanism in equation (162)[233]. The alcohol is reversibly absorbed

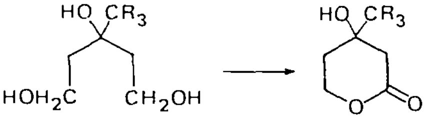


(162)

on the surface of the reagent. Coordination of oxygen with the silver ion facilitates concerted cleavage of the C—H and O—H bonds by a second silver ion. Evidence for the reversible nature of the adsorbtion and coordination steps is provided by the kinetic isotope effect (k_H/k_D = 1.9 for primary and 3.2 for secondary alcohols, measured with intermolecular competition experiments). From a stereochemical investigation it was concluded that the HCOH groups must be coplanar and perpendicular to the silver carbonate/celite surface. Molecules incapabe of attaining this required orientation for steric reasons are oxidized slowly.

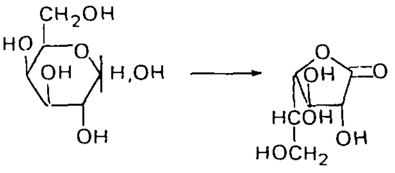
A reaction mechanism involving free carbon radical or carbonium ion intermediates was rejected because it was found that cyclopropylcarbinol was cleanly converted to the aldehyde. Cyclopropylcarbinyl radicals or cations would undergo ring opening or rearrangement.

1,2- and 1,3-diols generally are oxidized to hydroxy ketones[234]. An exception to this is found in the reaction of *threo*-1,2-arylethyleneglycols, where cleavage is predominant. The *erythro* isomers undergo cleavage only to the extent of 40%[235]. When the OH groups are separated by two, three or four carbon atoms, lactone formation via intermediate hemiacetals occurs (equation 163)[236].



(163)

Fétizon's reagent has found applications in carbohydrate chemistry. The high polarity of sugars allows for absorption on celite in polar solvents such as water, methanol and dimethylformamide[237]. Thus, galactose (52) was converted to galactonolactone (53) as the only product (equation 164). Similarly, *O*-methylated

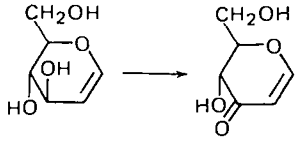


(164)

(52) (53)

xylose and glucose were oxidized to the corresponding aldono-1,5- or 1,4-lactones[238]. Selective oxidation of the allylic hydroxy group of D-glucal (54) has been reported by Tronchet (equation 165)[239].

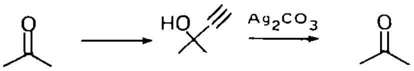
Propagylic alcohols and cyanohydrins are cleaved by Fétizon's reagent in



(54)

(165)

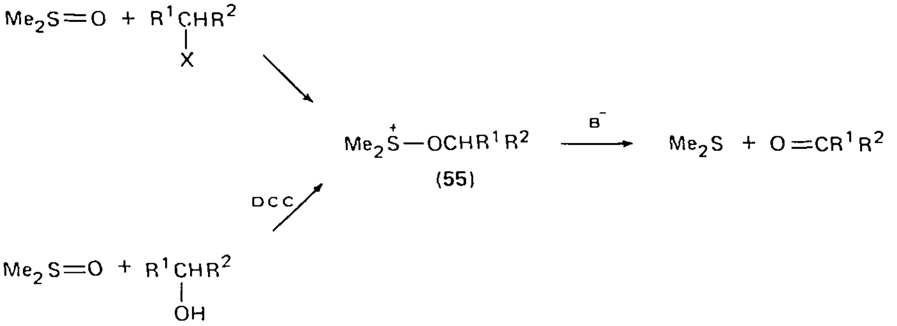
quantitative yield. The former reaction suggests the use of the ethynyl group for protection of ketones (equation 166)[240].



(166)

E. Dimethyl Sulphoxide and Related Reagents

Oxidation of alcohols by dimethyl sulphoxide (DMSO) was discovered by Pfitzner and Moffatt[241]. The Pfitzner–Moffatt oxidation entails the addition of the alcohol to be oxidized to a solution containing dicyclohexylcarbodiimide (DDC), DMSO and a proton source. The reaction (equation 167) is related to the

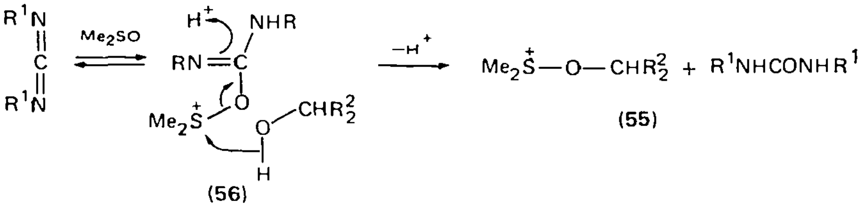


(167)

Kornblum oxidation of halides[242] and proceeds via the same dimethylalkoxysulphonium intermediate 55. The latter breaks down to ketone and dimethylsulphide in the presence of base. Several variations of this general approach exist, their main difference being in the preparation of the alkoxy intermediate 55.

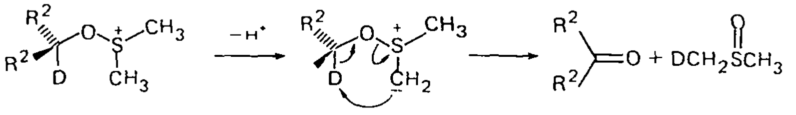
1. Pfitzner–Moffatt oxidation

The literature up to 1968 has been reviewed by Moffatt[243]. The reaction is initiated by acid-catalysed formation of a DMSO–DCC adduct 56 in low concentration[244]. Attack on sulphur by the alcohol gives rise to formation of the alkoxysulphonium intermediate 55 (equation 168). Formation of the adduct 56



(168)

was demonstrated by isolation of ^{18}O-dicyclohexylurea from an oxidation using ^{18}O-DMSO[245], while ^{18}O-labelled benzhydrol retained the label during oxidation[246]. Under the reaction conditions, neither 55 nor 56 could be observed directly. Abstraction of the carbinolic hydrogen in the alkoxysulphonium intermediate 55 proceeds by an intramolecular pathway (equation 169.



(169)

The oxidation of 1,1-dideuteriobutanol leads to the formation of 1-deuteriobutyraldehyde and monodeuteriodimethyl sulphide. Incorporation of deuterium is however only 70% which suggests that other, although less important, pathways may be operative[243].

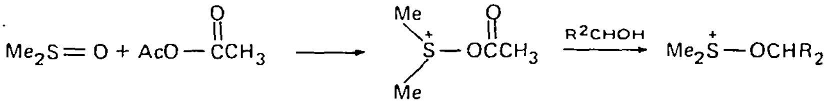
The Pfitzner–Moffatt oxidation has found wide application in the fields of steriods, carbohydrates[178] and alkaloids, giving good to excellent results. It is the method of choice whenever mild reaction conditions are required. In contrast to the trends observed in chromic acid oxidation, highly hindered axial hydroxy groups on the steroid skeleton are inert towards DMSO/DCC, or react by elimination, while the less hindered, equatorial epimers are smoothly converted to ketones[247].

Since the DMSO/DCC procedure requires nucleophilic attack of a free hydroxyl group as a prerequisite to oxidation, reaction of primary alcohols proceeds only to the aldehyde stage. Accordingly, a variety of aldehydes have been prepared by this route[243].

Weinshenker and Shen[248] have reported the synthesis of a carbodiimide linked to a crosslinked polystyrene matrix. This polymeric reagent in conjunction with DMSO and orthophosphoric acid has converted simple secondary alcohols, but also highly sensitive prostaglandine intermediates, to ketones.

2. *DMSO and acid anhydrides or chlorides*

The most frequently used variation of the DMSO/DCC oxidation is the combination of DMSO and acetic anhydride. This procedure, developed by Albright and Goldman[246], is related to the Pfitzner–Moffatt oxidation and proceeds by a similar mechanism. DMSO reacts with acetic anhydride to form the acetoxydimethylsulphonium ion (57). Attack of the alcohols leads to the alkoxysulphonium ion (55), which then collapses after proton loss as shown in equation (170).

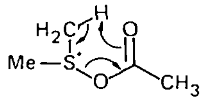


$$Me_2S{=}O + AcO{-}\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow Me_2\overset{+}{S}{-}O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{R^2CHOH} Me_2\overset{+}{S}{-}OCHR_2 \quad (170)$$

(57) (55)

The advantage of this method is to produce only water-soluble products which allows for more convenient work-up. The reagent is sterically less demanding than DMSO/DCC and therefore is better suited for oxidation of hindered alcohols. Unhindered alcohols, however, often lead to methylthio methyl ethers (58) and acetates as side-products. Ether formation is most likely due to reaction of an intermediate sulphonium ylid (59) with the alcohol (equation 171)[249,250]. This side-reaction also occurs to a small extent during Pfitzner–Moffatt oxidation.

In further variation, acetic anhydride has been replaced by phosphorus pentoxide[251] or pyridine–sulphur trioxide[252]. Both reagents have found wide application, in particular in carbohydrate chemistry[178]. Similarly, the combination of



$$\longrightarrow CH_3COOH + Me{-}\overset{+}{S}{=}CH_2 \xrightarrow{ROH} Me{-}S{-}CH_2OR \qquad (171)$$

(59) (58)

DMSO and trifluoroacetic anhydride effects formation of alkoxydimethylsulfonium salts below $-50°C$. Upon addition of triethylamine the salts are converted to carbonyl compounds[253]. This procedure gives excellent results in particular with hindered alcohols. Albright[254] investigated a series of sulphonic acid chlorides and anhydrides as well as cyanuric chloride in conjunction with DMSO in dichloromethane and hexamethylphosphoramide and obtained high yields of alcohols and ketones. Less satisfactory results were however obtained with trifluoromethanesulphonic anhydride[255]. Barton and collaborators[256], as early as 1964, prepared alkoxydimethylsulphonium salts from alcohols via displacement of chloroformate with DMSO (equation 172) with retention of configuration at carbon. Treatment of 55 with base affords the corresponding ketone.

$$R_2CHOH \xrightarrow{COCl_2} R_2CHO\overset{O}{\overset{\|}{C}}Cl \xrightarrow{DMSO} R_2CHO{-}\overset{+}{S}Me_2 \qquad (172)$$

(55)

3. *Sulphide-mediated oxidation*

Corey and Kim[257] discovered that alcohols are capable of reacting with complexes of chlorine or *N*-chlorosuccinimide and dimethyl sulphide to give alkoxysulphonium salts (equation 173 and 174). Aldehydes and ketones are obtained by

$$Me_2S + Cl_2 \longrightarrow Me_2\overset{+}{S}Cl\ Cl^- \xrightarrow{R_2CHOH} R_2CH{-}O{-}\overset{+}{S}Me_2 \qquad (173)$$

(55)

$$>N{-}Cl + Me_2S \longrightarrow Me_2\overset{+}{S}{-}N< \xrightarrow{R_2CHOH} R_2CH{-}O{-}\overset{+}{S}Me_2 \qquad (174)$$

(55)

subsequent treatment with base. The method has been applied to oxidation of *s,t*-1,2-diols to α-hydroxy ketones without C—C bond cleavage[258]. Oxidation with deuterium-labelled dimethyl sulphide [259] demonstrated that breakdown of the intermediate 55 proceeds in a cyclic mechanism via the ylid as in the Pfitzner–Moffatt oxidation (equation 69).

Subsequent investigations showed that the DMSO–chlorine complex is equally efficient[260]. The reaction is believed to proceed by the following mechanism shown in equation (175).

$$R_2CHOH \xrightarrow{Me_2SO_2Cl_2} R_2CH{-}O\overset{O}{\overset{\|}{\underset{+}{S}}}Me_2\ Cl^- \xrightarrow{Et_3N} R_2C{=}O + Me_2SO \qquad (175)$$

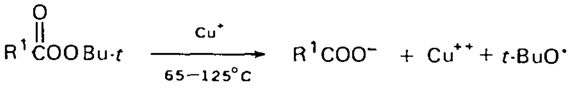
III. OXIDATION OF ETHERS

One of the most frequently observed pathways for oxidation of alcohols involves the formation of a covalent bond between the oxygen atom and the oxidizing agent with loss of the hydroxyl hydrogen. For structural reasons, this mechanism is obviously forbidden for ethers. As a consequence, oxidation of ethers is much less frequently encountered, and it is of minor synthetic importance. Although the oxidant may exceptionally coordinate with one of the lone pairs of oxygen, in most cases attack occurs at the α-C—H bond, leading to free radical or carbonium ion intermediates.

A. Free-radical Reactions

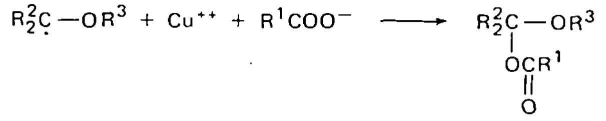
1. *Hydrogen abstraction by oxygenated species*

The copper-ion-catalysed decomposition of an organic peroxy ester produces alkoxy radicals capable of abstracting hydrogen α to an ether linkage (equations 176—178). The carbon radical is further oxidized to the cation by electron transfer to Cu^{++} and recombines with the carboxylate[261]. The topic has been reviewed[262]. Poor results are obtained when the reacting group is secondary alkyl or with dibenzyl ether. Initiation of the reaction occurs by heating or better by irradiation with UV light[263]. Similarly thermal decomposition of diacyl peroxides leads to α-acyloxy ethers (equation 179)[264-266].

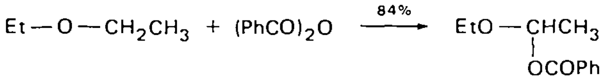


$$R^1\overset{\overset{O}{\|}}{C}OOBu\text{-}t \xrightarrow[65-125^\circ C]{Cu^+} R^1COO^- + Cu^{++} + t\text{-}BuO^\cdot \qquad (176)$$

$$t\text{-}BuO^\cdot + R^2_2CH{-}OR^3 \longrightarrow R^2_2\dot{C}{-}OR^3 + t\text{-}BuOH \qquad (177)$$

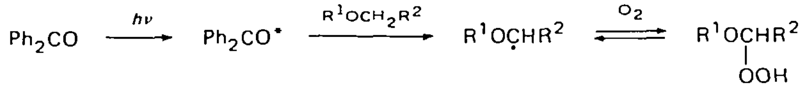


$$R^2_2\dot{C}{-}OR^3 + Cu^{++} + R^1COO^- \longrightarrow R^2_2\underset{\substack{|\\ O\underset{\substack{\|\\ O}}{C}R^1}}{C}{-}OR^3 \qquad (178)$$

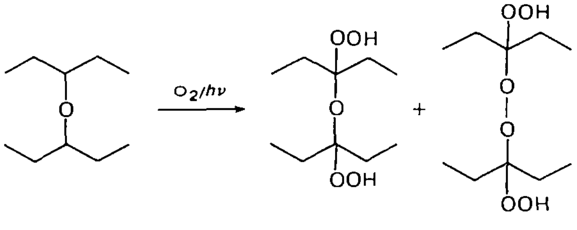


$$Et{-}O{-}CH_2CH_3 + (PhCO)_2O \xrightarrow{84\%} EtO{-}\underset{\substack{|\\ OCOPh}}{C}HCH_3 \qquad (179)$$

Irradiation of ethers in the presence of oxygen and benzophenone as photosensitizer gives rise to hydrogen abstraction. The incipient radicals combine with oxygen to yield hydroperoxides (equation 180)[267]. The oxidation of higher aliphatic ethers with oxygen and light gives dihydroperoxydialkyl ethers (**60**) and dihydroperoxydialkyl peroxides (**61**) (equation 181)[268].



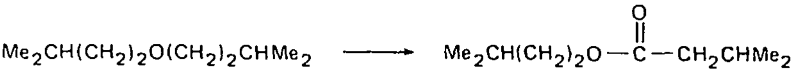
$$Ph_2CO \xrightarrow{h\nu} Ph_2CO^* \xrightarrow{R^1OCH_2R^2} R^1O\dot{C}HR^2 \overset{O_2}{\rightleftharpoons} R^1O\underset{\substack{|\\ OOH}}{C}HR^2 \qquad (180)$$



(181)

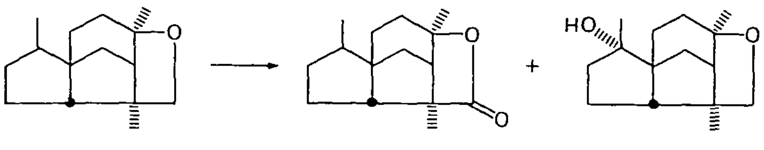
(**60**) (**61**)

Ozone reacts with ether to yield ester[269]. Thus isoamyl ether gave isoamyl isovalerate in over 70% yield (equation 182)[270]. Cedrane oxide (**62**) upon exposure



$$\mathrm{Me_2CH(CH_2)_2O(CH_2)_2CHMe_2} \longrightarrow \mathrm{Me_2CH(CH_2)_2O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_2CHMe_2} \qquad (182)$$

to ozone absorbed on silica gel afforded lactone **63** and, in lower yield, alcohol **64** (equation 183)[271]. Ozonation of ethers shows kinetic isotope effect of ca. 4 at 0°C

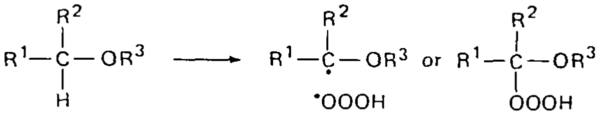


(183)

(62) (63) (64)

30% 10%

and up to 6.7 at −78°C. Polar effects are of little importance[272]. The reaction mechanism is complex. The initial step consists in hydrogen abstraction to yield either a trioxide (**65**) by insertion or a tight radical pair (**66**) (equation 184). On



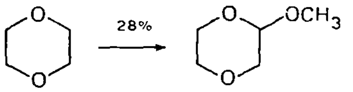
$$\mathrm{R^1{-}\underset{\displaystyle H}{\overset{\displaystyle R^2}{C}}{-}OR^3} \longrightarrow \mathrm{R^1{-}\underset{\displaystyle \cdot OOOH}{\overset{\displaystyle R^2}{\dot{C}}}{-}OR^3} \text{ or } \mathrm{R^1{-}\underset{\displaystyle OOOH}{\overset{\displaystyle R^2}{C}}{-}OR^3} \qquad (184)$$

(66) (65)

thermodynamic grounds the insertion product **65** should be favoured. Breakdown of the intermediates **65** or **66** then proceeds by radical mechanisms.

2. *Electrochemical oxidations*

Saturated aliphatic ethers may be oxidized to ketals by electrolysis in the presence of sodium methoxide (equation 185)[273]. The reaction proceeds via α-



(185)

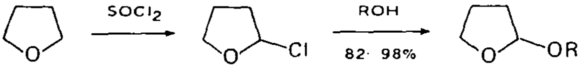
hydrogen abstraction by a radical generated from the supporting electrolyte. Better results are obtained in the electrolysis of benzyl[274] or *p*-anisyl[275] ethers, where alcohols may be recovered in yields of 74–98%. In contrast to the electrolysis of aliphatic ethers, their benzylic counterparts are oxidized by electron transfer from the organic moiety (equations 186 and 187).

$$\mathrm{ArCH_2OR} \xrightarrow{-e^-} \mathrm{\overset{+\cdot}{Ar}CH_2OR} \xrightarrow{-e^-} \mathrm{Ar\overset{+}{C}HOR} + \mathrm{H^+} \qquad (186)$$

$$\mathrm{Ar\overset{+}{C}HOR} + \mathrm{H_2O} \longrightarrow \mathrm{ArCHOHOR} \longrightarrow \mathrm{ArCHO} + \mathrm{ROH} \qquad (187)$$

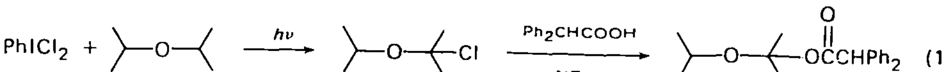
3. *Miscellaneous reactions*

Sulphuryl chloride reacts with tetrahydrofuran to yield the 2-chloro derivative, presumably via a radical pathway[276]. Upon addition of alcohols, the corresponding THF ethers are obtained in excellent yields (equation 188). α-Chlorination is also



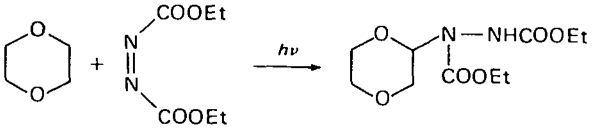
(188)

obtained by reacting iodosobenzene dichloride with ethers under irradiation[277]. The chloro ethers can be converted to acylals by reacting them with diphenylacetic acid and triethylamine (equation 189).



(189)

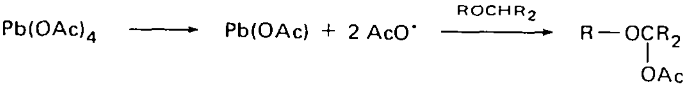
Photochemical decomposition of diethyl azodicarboxylate dissolved in various ethers leads to 1 : 1 adducts (67) (equation 190)[278].



(190)

(67)

Upon irradiation, lead tetraacetate decomposes to lead diacetate and acetoxy radicals[279]. The latter may decarboxylate or react with ether solvents to acetoxy ethers in 40–50% yield (equation 191).

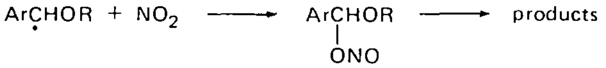


$$Pb(OAc)_4 \longrightarrow Pb(OAc) + 2\,AcO^{\bullet} \xrightarrow{ROCHR_2} R{-}O\underset{\substack{|\\ OAc}}{C}R_2 \qquad (191)$$

Oxidation of benzyl methyl ether with nitric acid is initiated by addition of a small amount of sodium nitrite and results in a high yield (95%) of benzaldehyde. (equations 192–194).[280] The reaction is first order in ether, but at acid concentrations over 0.5 M it is independent from both nitric or nitrous acid. The Hammett ρ constant is −1.9 determined by use of the σ^+ values. The slow step in the reaction scheme is believed to be hydrogen abstraction by HNO_2^+ at the benzylic position.

$$\begin{aligned} HNO_2 + HNO_2 &\rightleftharpoons 2NO_2 + H_2O \\ NO_2 + H^+ &\longrightarrow HNO_2^+ \end{aligned} \qquad (192)$$

$$ArCH_2OR + HNO_2^+ \longrightarrow Ar\dot{C}HOR + H_2NO_2^+ \qquad (193)$$



$$Ar\underset{\bullet}{C}HOR + NO_2 \longrightarrow Ar\underset{\substack{|\\ ONO}}{C}HOR \longrightarrow \text{products} \qquad (194)$$

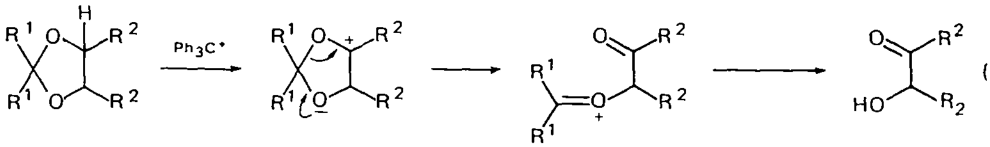
B. Hydride Transfer Reactions

1. Oxidation by cations

a. Triphenylmethyl cation. Alkyl ethers are hydride donors to carbenium ions to yield allehydes or ketones and the hydrocarbon derived from the cation used (equation 195)[281]. The synthetic utility of this reaction was not recognized until

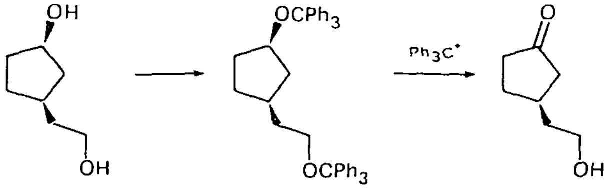
$$(R_2CH)_2O + Ph_3C^+ \longrightarrow R_2\overset{+}{C}{-}OCHR_2 + Ph_3CH \xrightarrow{H_2O} R_2C{=}O + R_2CHOH \qquad (195)$$

Barton[282] applied it to deprotection of alcohols masked by benzyl ethers, and to the deacetalization of ketone acetals[283]. Subsequently, Jung and Speltz[284] discovered that trityl, trimethylsilyl or *t*-butyl ethers of secondary alcohols react



(196)

faster with triphenylcarbenium salts than those of primary alcohols. A method for selective oxidation of secondary alcohols in the presence of primary alcohols was then developed (equation 197). Tritylalkyl and tritylbenzyl ethers undergo dis-

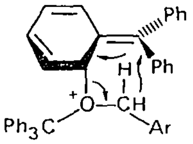


(197)

proportionation to triphenylmethane and substituted aldehyde when treated with catalytic amounts of trityl salts (equation 198)[285]. The reaction has a ρ value of

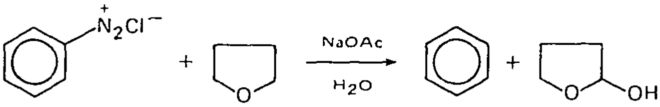
$$Ph_3C^+ + RCH_2-O-CPh_3 \longrightarrow RCHO + Ph_3CH + Ph_3C^+ \qquad (198)$$

−4.0 and a kinetic isotope effect of 9.7 with trityl hexafluoroarsenate and 3.6 with trityl tetrafluoroborate. Although direct hydride transfer appears possible, a mechanism involving association via a oxonium ion (**68**) was also suggested.



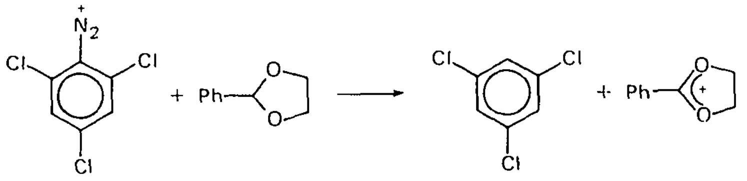
(68)

b. Diazonium and nitronium ions. The reaction of diazonium salts with ethers and dioxolanes has been reviewed by Meerwein[286]. In aqueous solution reaction products are aromatic hydrocarbons and α-hydroxylated ethers (equation 199). In



(199)

some cases the ionic nature of the hydrogen transfer step is clearly established. Thus treatment of 2,4,6-trichlorobenzenediazonium fluoroborate (**69**) with 2-phenyl-1,3-dioxolane (**70**) afforded phenyl-1,3-dioxolonium fluoroborate (**71**) in 80% yield (equation 200). Hydride transfer can occur before or after loss of



(200)

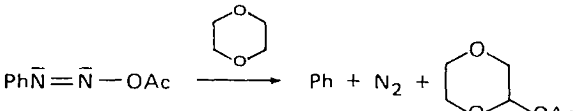
(69) (70) (71)

55% 80%

nitrogen. The most likely pathway involves formation of an intermediate aryldiimide (equation 201).

$$\mathrm{Ar{-}N{\equiv}\overset{+}{N}} \xrightarrow{\mathrm{H^-}} \mathrm{Ar{-}\bar{N}{=}NH} \longrightarrow \mathrm{ArH} + \mathrm{N_2} \qquad (201)$$

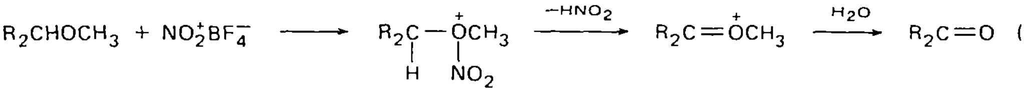
Other reactions show typical radical character. For example, aryldiazonium fluoroborates react with 2-methyl-1,3-dioxolane only after addition of a catalytic quantity of copper. Similarly, decomposition of phenyldiazoacetate (72) in the presence of dioxane affords benzene, nitrogen and 1-dioxanyl acetate (equation 202)[287]. Addition of acrylonitrile to the reaction mixture reduces the reaction


(72)

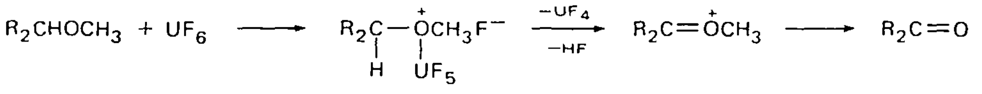
(202)

rate. When dioxane was replaced by benzene, biphenyl was obtained in 72% yield. These results have been interpreted in terms of an induced decomposition of 72 by a radical pathway.

Nitronium tetrafluoroborate is capable of cleaving alkyl methyl ethers (equation 203)[288]. Although the overall reaction corresponds to hydride abstraction from


$$\mathrm{R_2CHOCH_3} + \mathrm{NO_2^+BF_4^-} \longrightarrow \mathrm{R_2\underset{H}{C}{-}\underset{NO_2}{\overset{+}{O}}CH_3} \xrightarrow{-\mathrm{HNO_2}} \mathrm{R_2C{=}\overset{+}{O}CH_3} \xrightarrow{\mathrm{H_2O}} \mathrm{R_2C{=}O} \qquad (203)$$

the α-carbon, the mechanism suggests that the hydrogen might be lost as a proton. The reaction is regioselective; proton loss does not occur from the methyl group. A similar reaction takes place between ethers and uranium hexafluoride (equation 204)[289].

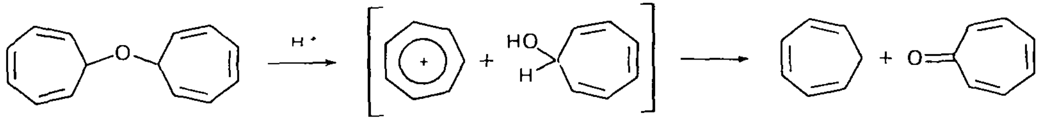

$$\mathrm{R_2CHOCH_3} + \mathrm{UF_6} \longrightarrow \mathrm{R_2\underset{H}{C}{-}\underset{UF_5}{\overset{+}{O}}CH_3F^-} \xrightarrow[-\mathrm{HF}]{-\mathrm{UF_4}} \mathrm{R_2C{=}\overset{+}{O}CH_3} \longrightarrow \mathrm{R_2C{=}O} \qquad (204)$$

2. *Pyrolytic ether cleavage*

Certain ethers, upon heating, undergo disproportionation to hydrocarbons and aldehydes or ketones. Thus, at 300°C, trityl alkyl ethers afford triphenylmethane and aldehydes (equation 205)[290]. The reaction is catalysed by protons and car-

$$\mathrm{Ph_3C{-}O{-}CH_2R} \xrightarrow{300^\circ\mathrm{C}} \mathrm{Ph_3CH} + \mathrm{RCHO} \qquad (205)$$

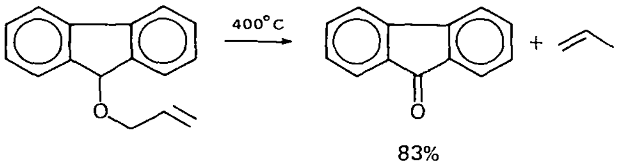
benium ions; this suggests that a mechanism as outlined in equation (198) might be operative. Heating ditropyl ether (73) with acid-treated silica gel gives tropone and cycloheptatriene (equation 206)[291]. Allyl ethers disproportionate at 400–600°C



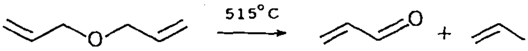
(73)

(206)

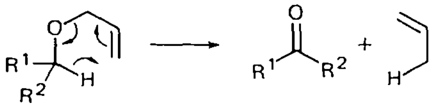
(equation 207 and 208)[292]. These reactions proceed via concerted mechanisms (oxy-ene reaction) (equation 209). Thermal disproportionation of allyl ethers,



(207)

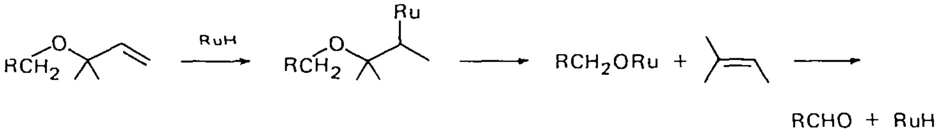


(Ref. 293) (208)


R1
R2
H
O
R1
R2
+
H

(209)

catalysed by tris(triphenylphosphine)ruthenium(II) dichloride occurs even at 200°C. The reaction is believed to proceed via addition of ruthenium hydride to the double bond, followed by rate-determining β-elimination of ruthenium alkoxide (equation 210)[294].

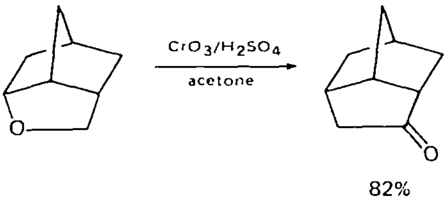

RCH2
RuH
Ru
RCH2
RCH2ORu +
RCHO + RuH

(210)

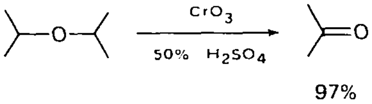
C. Metal Ions and Metal Oxides

1. Chromic acid

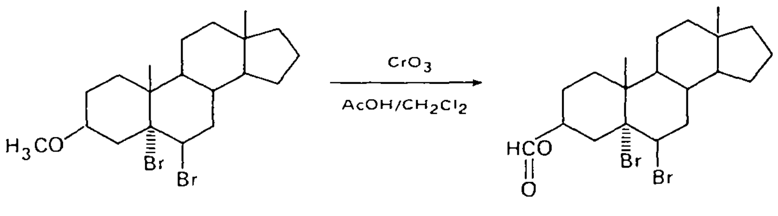
Oxidation of ethers with chromic acid can lead to a variety of products depending on the structure of the substrate. Thus ethers of primary alcohols afford lactones (equation 211)[295], ethers of secondary alcohols give ketones (equation 212)[296] and methyl ethers are converted to formates (equation 213)[297].


CrO3/H2SO4
acetone
82%

(211)

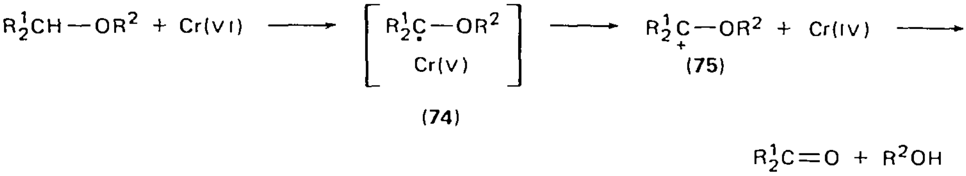

CrO3
50% H2SO4
97%

(212)


H3CO
Br
Br
CrO3
AcOH/CH2Cl2
HCO
O
Br
Br

(213)

The mechanism of the reaction with diisopropyl ether has been investigated by Westheimer[296]. A kinetic isotope effect of $k_H/k_D = 5.3$ was found with α,α'-dideuterioisopropyl ether and the reaction rate was 750 times slower than the rate for isopropanol oxidation. In the light of current knowledge on oxidation of C—H bonds with Cr(VI)[1] the most likely mechanism would include hydrogen abstraction in the rate-determining step to give a radical (**74**) associated with Cr(VI) (equation 214). Further oxidation of the radical by Cr(V) would lead to the carbenium ion

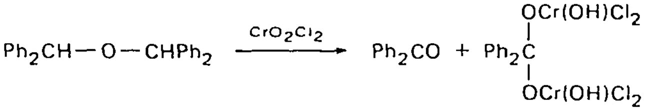


$$R^1_2CH{-}OR^2 + Cr(VI) \longrightarrow \left[\begin{matrix} R^1_2\dot{C}{-}OR^2 \\ Cr(V) \end{matrix}\right] \longrightarrow R^1_2\overset{}{\underset{+}{C}}{-}OR^2 + Cr(IV) \longrightarrow R^1_2C{=}O + R^2OH \qquad (214)$$

(74) (75)

75, which in turn would be converted to ketone and alcohol. Subsequent reactions of both Cr(IV) and alcohol are fast compared to ether oxidation.

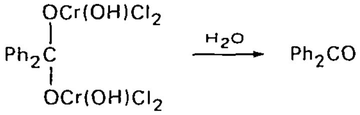
Chromyl chloride effects oxidative cleavage of dibenzhydryl ethers at room temperature[298]. First, one of the benzylic groups loses hydride to give the ketone, while the other one is oxidized to the Etard complex (**76**) (equation 215).



$$Ph_2CH{-}O{-}CHPh_2 \xrightarrow{CrO_2Cl_2} Ph_2CO + Ph_2C(OCr(OH)Cl_2)_2 \qquad (215)$$

(76)

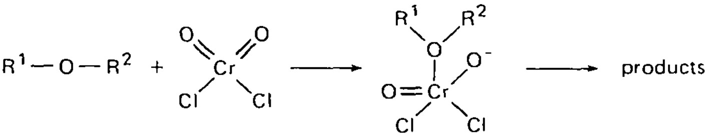
Hydrolysis of the Etard complex affords a second carbonyl compound (equation 216). The reaction is probably hydride transfer from ether to oxidant yielding a



$$Ph_2C(OCr(OH)Cl_2)_2 \xrightarrow{H_2O} Ph_2CO \qquad (216)$$

(76)

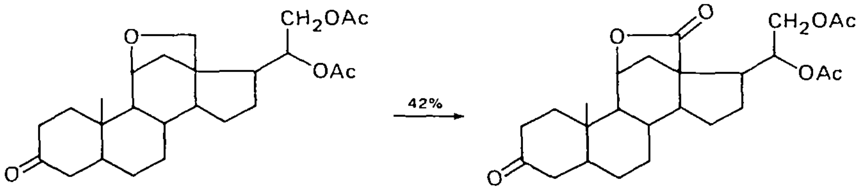
carbenium ion which then breaks down to ketone and the complex **76**. Association between a lone pair of oxygen and chromyl chloride has been invoked to explain oxidative cleavage of some secondary—tertiary or ditertiary ethers (equation 217).



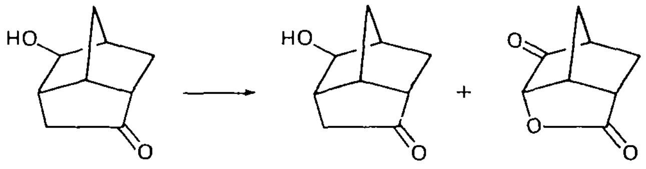
(217)

2. *Ruthenium tetroxide*

Ruthenium tetroxide is the most effective reagent for oxidation of ethers. It converts tetrahydrofurane to γ-butyrolactone in 100% yield[168]. The reagent has been used for conversion of tricyclic ethers[172] and for a synthesis of aldosterone (equation 218)[299]. Oxidation of ethers occurs at rates comparable to that of alcohols[165]. Hence, reaction of the hydroxy ether (**6**) affords a lactone and a ketone in similar amounts (equation 219). The kinetics of the oxidation of



(218)



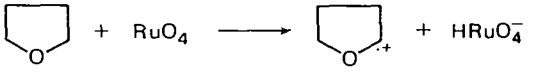
(6) 40% 30%

(219)

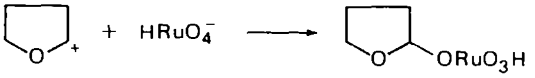
tetrahydrofuran by ruthenium tetroxide have been investigated[300]. The rate law for aqueous perchloric acid is

$$v = k[\mathrm{RuO_4}][\mathrm{THF}]h_0^{-0.22} \tag{220}$$

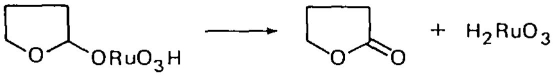
Substitution of the α-hydrogens by deuterium resulted in reduction of the reaction rate by 33%. A mechanism involving hydride transfer in the rate-determining step was proposed (equations 221–223).



(221)



(222)



(223)

3. One-electron oxidants

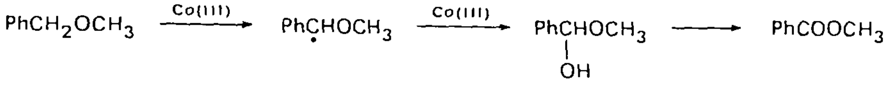
Reaction of lead tetraacetate with ethers has been reviewed[301]. Oxidation of dibenzyl[302] and diisopropyl ether[303] with cobalt (III) has been reported by Waters and collaborators. Dibenzyl ether is oxidized to benzaldehyde (80%) and to a smaller extent, benzoic acid[302]. Oxidation occurs by direct attack of Co(III) on the ether molecule rather than by hydrolysis of the ether prior to oxidation. The small quantities bibenzyl formed support the view that benzyl radicals are inter-

$$\mathrm{PhCH_2OCH_2Ph + Co(III)} \xrightarrow{\text{slow}} \mathrm{PhCH_2O\underset{\bullet}{C}HPh + Co(II)} \tag{224}$$

$$\mathrm{Ph\underset{\bullet}{C}HOCH_2Ph} \longrightarrow \mathrm{PhCHO + PhCH_2^{\bullet}} \tag{225}$$

$$\mathrm{PhCH_2^{\bullet}} \xrightarrow{\text{Co(III)}} \mathrm{PhCH_2OH} \xrightarrow{\text{2 Co(III)}} \mathrm{PhCHO} \tag{226}$$

mediates. The proposed mechanism is shown in equations (224)–(226). With benzyl methyl ether the radical formed by attack of Co(III) instead of breaking down as in equation (225) may be further oxidized to the hemiacetal and, finally, to methyl benzoate (equation 227). Oxidation of diisopropyl ether[303] proceeds about ten times slower than that of dibenyl ether and yields acetone. The mechanism is similar to that of dibenzyl ether oxidation. However, there is evidence for a competing acetone-forming chain reaction via attack by isopropyl radicals on the ether (equation 228 and 229).



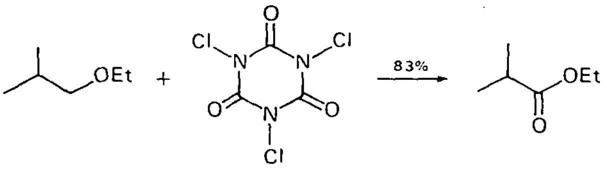
$$PhCH_2OCH_3 \xrightarrow{Co(III)} Ph\dot{C}HOCH_3 \xrightarrow{Co(III)} PhCH(OH)OCH_3 \longrightarrow PhCOOCH_3 \qquad (227)$$

$$Me_2CHOCHMe_2 + Me\dot{C}HMe \longrightarrow Me_2CHO\dot{C}Me_2 + MeCH_2Me \qquad (228)$$

$$Me_2CHO\dot{C}Me_2 \longrightarrow Me_2C{=}O + Me\dot{C}HMe \qquad (229)$$

D. Miscellaneous Reactions

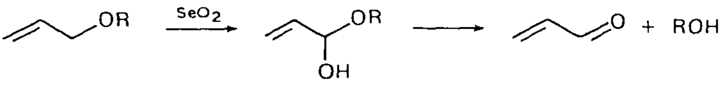
Trichloroisocyanuric acid (77) in the presence of water converts ethers to esters in yields ranging from 50 to 100% (equation 230)[304].



(77)

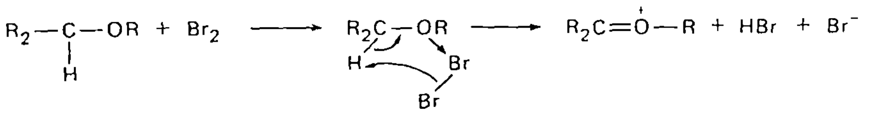
(230)

β,γ-Unsaturated ethers undergo oxidative cleavage with selenium dioxide in acetic acid[305]. The reaction has been investigated with allylic and propargylic ethers, and most likely consists of allylic oxidation of the α-methylene group by SeO_2 to a hemiacetal undergoing hydrolysis to aldehyde and alcohol (equation 231)[80].



(231)

Bromine reacts with ethers to give esters with primary alkyl groups and ketones with secondary ones[306]. In light it attacks selectively dibenzyl ether in the presence of diisopropyl ether, while the reverse is true in the dark. The light reaction has the characteristics of a radical pathway. For the dark reaction formation on an ether–bromine complex has been proposed. The latter breaks down by synchronous electron pair and proton loss (equation 232). An alternative mechanism where bromine attacks ethers by hydride transfer has been suggested by Barter and Littler[127].



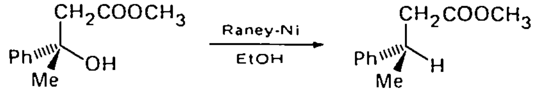
(232)

IV. REDUCTION OF ALCOHOLS

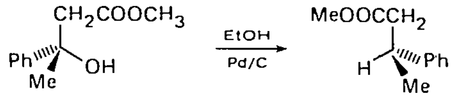
The direct reduction of alcohols to alkanes is difficult to accomplish and requires special reagents or particularly favourable structural features in the substrate. The poor leaving-group ability of the hydroxyl function almost entirely excludes pathways involving nucleophilic displacements. In most direct methods the alcohol is activated (protonation, complexation) prior to reduction. In comparison to oxidation, reduction of alcohols has been little studied, and the mechanisms are poorly understood.

A. Catalytic Hydrogenation

Benzyl alcohols are reduced to arylalkanes by catalytic hydrogenation. With unsymmetrically substituted alcohols the reaction generally shows a high degree of stereospecificity. Depending on the structure of the substrate it may proceed with retention (equation 233a)[307] or inversion (equation 233b)[308] of configuration.

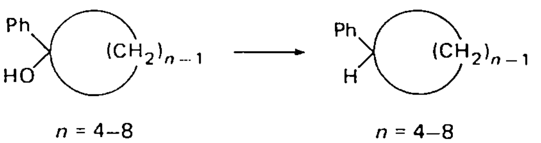

CH2COOCH3
Ph
OH
Me
Raney-Ni
EtOH
CH2COOCH3
Ph
H
Me

(233a)

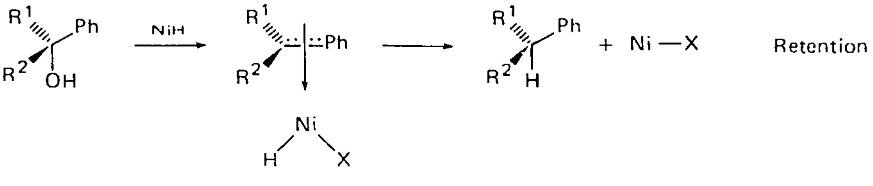

CH2COOCH3
Ph
OH
Me
EtOH
Pd/C
MeOOCCH2
H
Ph
Me

(233b)

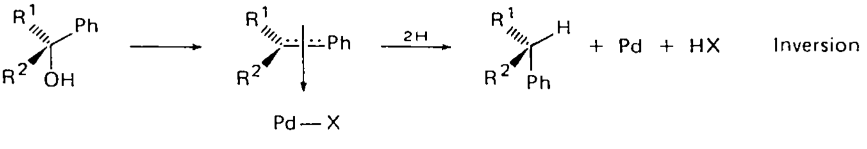
The rate profile for hydrogenolysis of the 1-phenylcycloalkanols (equation 234) is parallel to that of reactions where the reacting carbon atom undergoes hybridization change from sp^3 to sp^2 [309], while that for reduction of cyclanones follows the reverse order. The rate variations of these heterogenous reactions are however small in comparison to the related homogenous ones. The mechanisms in equations (235) and (236) have been proposed for retention and inversion of configuration during hydrogenolysis[309].


Ph
HO
(CH2)n−1
n = 4–8
Ph
H
(CH2)n−1
n = 4–8

(234)


R1
Ph
R2
OH
NiH
R1
Ph
R2
Ni
H
X
R1
Ph
R2
H
+ Ni —X
Retention

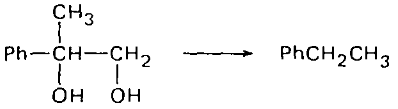
(235)


R1
Ph
R2
OH
R1
Ph
R2
Pd — X
2H
R1
H
R2
Ph
+ Pd + HX
Inversion

(236)

Hydrogenation of tertiary aliphatic alcohols in trifluoroacetic acid proceeds via elimination to form an alkene prior to reduction[310].

Under the conditions of catalytic hydrogenation some alcohols undergo C—C rather than C—OH bond cleavage[311]. For example, 2-phenyl-1,2-propanediol (78) upon treatment with Raney nickel in refluxing ethanol gave mainly ethylbenzene (equation 237). The principal structural requirement for this reaction is a hydroxyl



$$Ph{-}\overset{CH_3}{\underset{OH}{CH}}{-}\underset{OH}{CH_2} \longrightarrow PhCH_2CH_3 \qquad (237)$$

(78)

group adjacent to an aromatic ring. Hydrogenation of benzhydrol and related alcohols under hydroformylation conditions with dicolbalt octacarbonyl catalyst involves formation of complex 79 in the rate-determining step (equations 238 and 239)[312]. The homologous alcohol is not formed under the reaction conditions. In

$$Ph_2CHOH + HCo(CO)_4 \rightleftharpoons Ph_2CHOH_2^+\,Co(CO_4)^- \xrightarrow{slow} Ph_2CHCo(CO)_4 + H_2O \qquad (238)$$

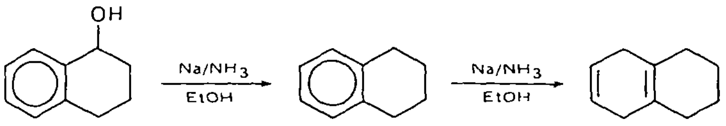
(79)

$$Ph_2CHCo(CO)_4 + H_2 \xrightarrow{fast} Ph_2CH_2 + HCo(CO_4) \qquad (239)$$

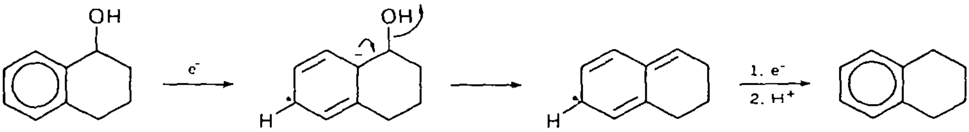
this respect benzhydrol differs from benzyl alcohol which gives a mixture of both toluene and 2-phenylethanol during the course of hydroformylation.

B. Dissolving Metal Reduction

The reducing of benzyl alcohols to the corresponding hydrocarbons has been reported by Birch[313]. The Birch procedure involves addition of small pieces of sodium to the benzyl alcohol and ethanol in ammonia. Since these are also the condition for reduction of the aromatic hydrocarbon to the dihydro derivative, some overreduction may be observed (equation 240)[314]. The latter is substantially lessened by carrying out the reduction with lithium in ammonia–THF and quenching the reaction mixture with ammonium chloride[315]. The reaction proceeds by electron transfer from the metal to the aromatic system to form the radical anion *80*. Loss of OH⁻ and further electron transfer followed by protonation afford the hydrocarbon (equation 241)[316].



(240)

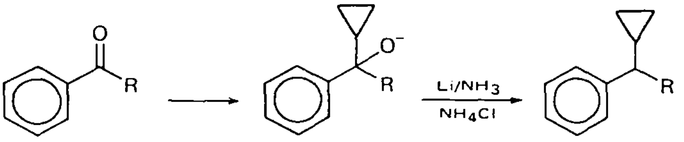


(241)

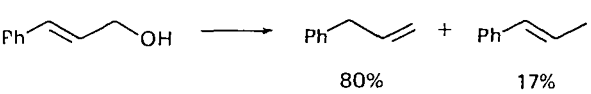
(80)

Benzyl alcohol can be protected from reduction via conversion to the corresponding benzylalkoxides[315]. Quenching of the reaction mixture with ammonium chloride in the presence of excess lithium results in protonation and reduction. This procedure has been used for the preparation of α-cyclopropyl aromatic hydrocarbons (equation 242)[317].

Some allylic alcohols have been reduced with zinc–HCl in ether in yields of 60–95% (equation 243)[318]. Isomeric allylic alcohols afford identical product

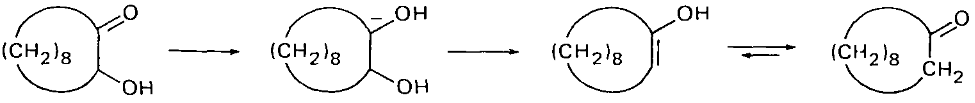


(242)



(243)

mixtures, the composition of which is not subject to thermodynamic control. The reaction is however not general. Saturated alcohols are not attacked under the conditions of the Clemmensen reduction (Zn–aqueous HCl), and therefore should not be intermediates during reduction of ketones to hydrocarbons. The reduction of α-hydroxy ketones by zinc in acetic acid is however possible[319]. This reaction is believed to proceed via electron transfer to the carbonyl group. The resulting anion **81** then expels the α-substituent and tautomerizes to the ketone (equation 244)[320].



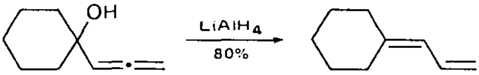
(81)

(244)

C. Hydride Reduction and Reductive Alkylation

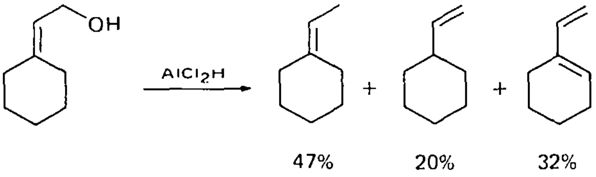
1. *Aluminium hydrides, silanes and boranes*

Simple alcohols react with lithium aluminium hydride via alkoxide formation rather than reduction. Propargylic[321] and cinnamyl[322] alcohols on the other hand undergo reduction at the triple and double bonds, respectively. Reduction of the OH group occurs with secondary and tertiary allenic alcohols, for example equation (245)[323].



(245)

The reactivity of alcohols toward hydride reduction is considerably enhanced in the presence of aluminium chloride. Thus benzylic alcohols can be reduced by $LiAlH_4$–$AlCl_3$ at 75°C to give the hydrocarbon in 48% yield; with *p*-methoxybenzyl alcohol reaction took place at room temperature[324,325]. Reduction of allylic alcohols gives the products expected for reduction of the allylic carbenium ion, for example equation (246).

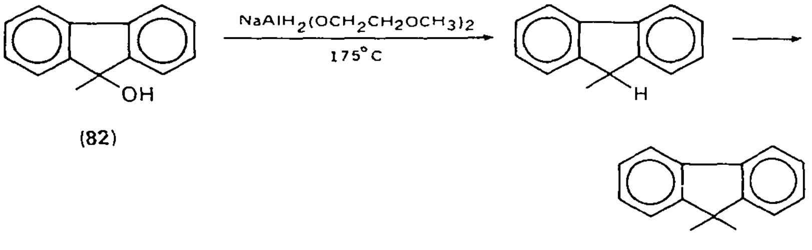


(246)

The reduction is sometimes accompanied by elimination. Saturated alcohols react at 60–80°C in higher boiling ethers to give hydrocarbons[326]. With aliphatic secondary and tertiary alcohols elimination becomes predominant, while β-phenyl alcohols undergo reduction at the OH group. Primary alcohols are however totally unreactive. These observations together with the appearance of rearrangement products strongly suggest a carbenium ion mechanism (equation 247). Similarly,

$$\mathrm{ROH} + \mathrm{HAlCl_2} \longrightarrow \mathrm{ROAlCl_2} + \mathrm{H_2} \xrightarrow{\mathrm{AlCl_3}} \mathrm{R^+} + \mathrm{Al_2OCl_5} \xrightarrow{\mathrm{HAlCl_2}} \mathrm{RH} \qquad (247)$$

carbenium ions generated from alcohols in methylene chloride–trifluoroacetic acid are reduced to alkanes by hydride transfer from alkyl silanes[327]. These reactions are of preparative interest unless the intermediate ions rearrange before being reduced. 9-Hydroxy-9-methylfluorene (82), upon reaction with sodium bis(2-methoxyethoxy)aluminium hydride at 175°C, is reduced to methylfluorene and subsequently alkylated to give the 9,9-dimethyl derivative 83, presumably via a homolytic pathway[328].

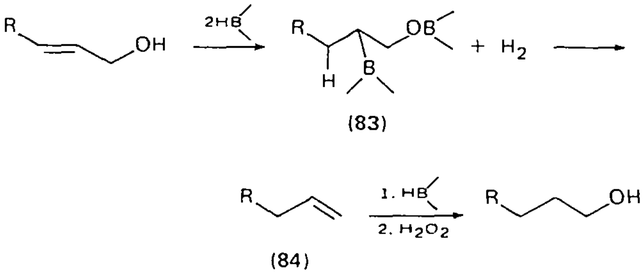


(82)

(83)

(248)

Diborane adds to the double bond of allylic alcohols in a regioselective manner to yield the β-substituted borane (equation 249)[329]. The latter undergoes elimination to an alkene (84), which may further react with excess borane. The

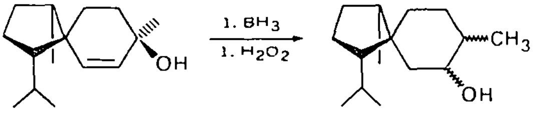


(83)

(84)

(249)

transformation of the allylic alcohol to 84 represents an overall reduction of the alcohol accompanied by rearrangement of the double bond. The sequence has been exploited for the synthesis of acorenone (equation 250)[330].



(250)

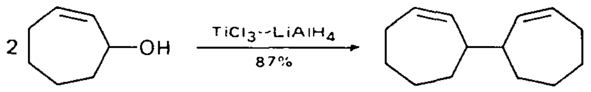
2. *Reductive alkylation*

Trimethylaluminium effects *C*-methylation with tertiary alcohols and arylalkyl carbinols[331]. Triarylcarbinols are particularly reactive and are methylated by excess trimethylaluminium at 80°C, while other alcohols require 120–130°C. The reaction proceeds via a dimethylaluminium alkoxide (equation 251). Pyrolysis of the alkoxide probably takes place by an autocatalytic pathway involving carbenium ions as intermediates (equation 252).

$$\mathrm{ROH} + \mathrm{Me_3Al} \longrightarrow \tfrac{1}{2}\,(\mathrm{Me_2AlOR})_2 + \mathrm{CH_4} \qquad (251)$$

$$\tfrac{1}{2}\,(\mathrm{Me_2AlOR})_2 \xrightarrow{\Delta} \mathrm{RMe}(+\mathrm{MeAlO}\ ?) \qquad (252)$$

Thermal fragmentation of titanium(II) alkoxides results in reductive coupling of allylic and benzylic alcohols equation 253)[332]. A more convenient procedure developed by McMurry[332a] uses $\mathrm{TiCl_3{-}LiAlH_4}$, presumably as a source for titanium(II) for the same reaction. For simple alcohols yields are in the range of 70–95%.



(253)

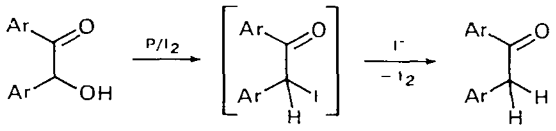
Reductive coupling of benzhydrol has been obtained in a-catalytic reaction in the presence of dichlorotris(triphenylphosphine)ruthenium and α-methylnaphthalene as solvent (equation 254)[333].

$$3\,\mathrm{Ph_2CHOH} \xrightarrow[190^\circ\mathrm{C}]{\mathrm{RuCl_2(PPh_3)_3}} \underset{93\%}{\mathrm{Ph_2CH{-}CHPh_2}} + \mathrm{Ph_2CO} + 2\,\mathrm{H_2O} \qquad (254)$$

D. Indirect Procedures

1. *Phosphorus—hydriodic acid*

Reduction of alcohols by red phosphorus in refluxing hydriodic acid represents a classical, although rather drastic procedure for degradation of natural products of unknown structure[334]. The OH groups undergo displacement to iodides which, in turn, are reduced by hydriodic acid. Milder conditions may be used for activated alcohols. Thus benzoins react with phosphorus and iodine at room temperature to yield the deoxygenated product (equation 255)[335].

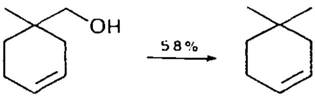


(255)

Allylic and benzylic alcohols are reduced in the presence of iodine and triphenylphosphine (diiodotriphenylphosphorane) as in equation (256)[336]. Primary

$$\mathrm{ROH} \xrightarrow{\mathrm{Ph_3P\cdot I_2}} [\mathrm{ROPPh_3}]^+\,\mathrm{I^-} + \mathrm{HI} \longrightarrow \mathrm{R{-}I} + \mathrm{Ph_3PO} \xrightarrow{\mathrm{HI}} \mathrm{RH} + \mathrm{I_2} \qquad (256)$$

alcohols may be converted to iodides by treatment with methyltriphenoxyphosphonium iodide. Sodium cyanoborohydride in HMPA reduces the iodides in excellent yield to alkanes[337]. A neopentyl alcohol has been reduced by this sequence in 57% yield (equation 257).



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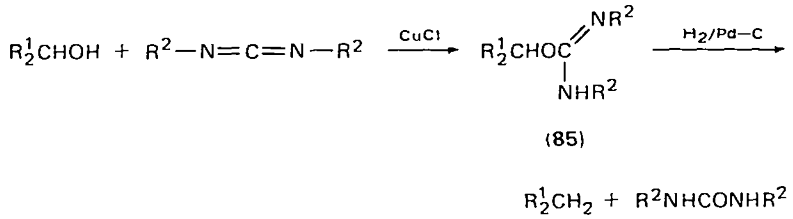
2. Reduction via sulphonate and sulphate esters

The most popular procedure for indirect reduction of primary and secondary alcohols consists in their conversion to tosylates or mesylates with subsequent treatment with lithium aluminium hydride[338] or sodium cyanoborohydride–HMPA[336] The method has some limitations. For example, deoxygenation is difficult when the hydroxy group is attached to carbon atoms at which S_N2 processes are hindered. With benzylic and allylic alcohols preparation of the sulphonate esters may be difficult owing to their high reactivity. The latter problem has been solved by conversion of the alcohol to sulphate monoester by means of the pyridine–sulphur trioxide complex[339]. The sulphate may be reduced without isolation with lithium aluminium hydride or $LiAlH_4$–$AlCl_3$ (equation 258).

$$\mathrm{ROH} \xrightarrow{\mathrm{SO_3-py}} \mathrm{ROSO_3^-\ C_6H_5NH^+} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{R{-}H} \qquad (258)$$

3. Reductions via isoureas, thiocarbamates and dithiocarbonates

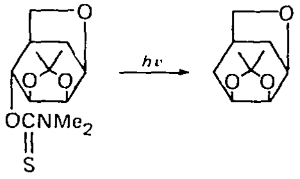
Primary, secondary and tertiary alcohols react with carbodiimides in the presence of CuCl to give *O*-alkylisoureas (85) in quantitative yield[340]. The isoureas may be reduced by catalytic hydrogenation to alkanes (equation 259). Yields are usually higher than 90%, except in cases where hydrogenolysis is severely hindered for steric reasons. *O*-Arylisoureas, obtained from phenols and carbodiimides, are more reactive than the alkyl derivatives and may therefore be selectively reduced.



(85)

$$\mathrm{R^1_2CHOH + R^2{-}N{=}C{=}N{-}R^2 \xrightarrow{CuCl} R^1_2CHOC({=}NR^2)NHR^2 \xrightarrow{H_2/Pd-C} R^1_2CH_2 + R^2NHCONHR^2} \qquad (259)$$

Upon photolysis dimethylthio carbamates of several sugar derivatives have been found to undergo reduction in ca. 40% yield to the corresponding deoxy sugar derivatives, for example (equation 260)[341]. The reaction probably proceeds via rearrangement to an *S*-dimethylcarbamoyl derivative which undergoes homolytic C–S bond cleavage. The radical then abstracts hydrogen from the solvent (equation 261).



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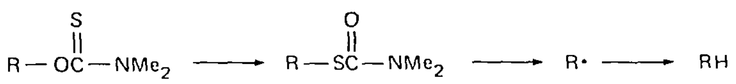
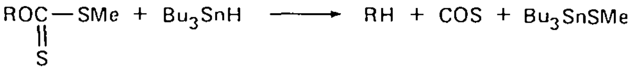


$$\mathrm{R{-}OC({=}S){-}NMe_2 \longrightarrow R{-}SC({=}O){-}NMe_2 \longrightarrow R\cdot \longrightarrow RH} \qquad (261)$$

A radical mechanism is also involved during reduction with tributylstannane of *O*-cycloalkylthiobenzoates and *O*-cycloalkyl-*S*-methyl dithiocarbonates (86) derived from secondary alcohols (equation 262)[342].

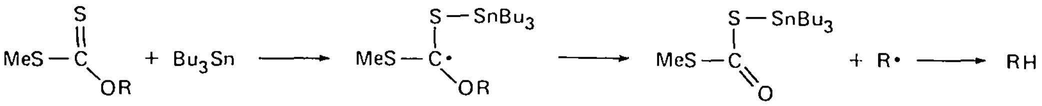
The radical pathway is to be preferred whenever S_N2-type processes, such as reduction of tosylates with $LiAlH_4$, are hindered or lead to rearrangements. The



$$\underset{\underset{S}{\|}}{ROC}\text{—SMe} + Bu_3SnH \longrightarrow RH + COS + Bu_3SnSMe \qquad (262)$$

(86)

reaction mechanism involves radical attack at the C=S double bond, followed by splitting off the alkyl radical (equation 263). Owing to the unstability of primary alkyl radicals, primary alcohols are not reduced by this procedure. In this case the intermediate radical (87) undergoes reduction instead of fragmentation.



(87)

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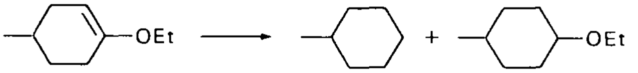
V. REDUCTION OF ETHERS

With the exception of epoxides and oxetanes, where ring-strain substantially enhances reactivity, ethers are in general as difficult to reduce as alcohols. The methods used for both kinds of substrate are to a large degree identical, although the absence of the acidic hydroxylic hydrogen allows for additional transformations with organometallic reagents.

A. Catalytic Hydrogenation

Cleavage of benzyl ethers by catalytic hydrogenation is a well established laboratory procedure. Cleavage occurs readily with Raney nickel or palladium–charcoal at room temperature and ordinary hydrogen pressure[308]. For this reason the benzyl group has been widely used for protection of alcohols during synthesis of a wide variety of compounds such as terpenes[343], steroids[344], carbohydrates[345], alkaloids[346] and glyceryl ethers[347]. As with alcohols, reduction of the C—O bond occurs with retention of configuration when Raney nickel is used as the catalyst, and with inversion in the presence of palladium–charcoal[308].

Hydrogenation of the 4-methyl-1-cyclohexenyl ether 88 with a series of catalysts has been investigated in detail[348]. The reaction proceeds by hydrogenolysis to methylcyclohexane and by hydrogenation of the double bond (equation 264). The



(88)

(264)

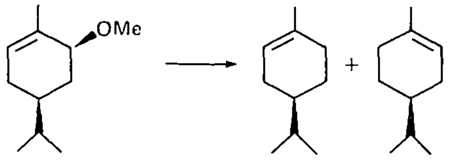
amount of hydrogenolysis was found to increase with the order of the catalysts $Pd \simeq Ru \ll Os < Rh < Ir \ll Pt$.

B. Dissolving Metal Reduction

Benzyl ethers undergo reductive cleavage when treated with sodium in *n*-butanol[349] or liquid ammonia[350]. The sodium–ammonia system has found application for detritylation of carbohydrate derivatives. Lithium cleavage of benzyl ethers in tetrahydrofuran has been used for preparation of benzyllithium (equation 265)[351].

$$PhCH_2{-}O{-}CH_3 \xrightarrow{2\,Li} PhCH_2Li + CH_3OH \qquad (265)$$

Allylic ethers are also reduced by metals. Thus optically active *cis*-carvotanacetol (**89**), upon reaction with lithium in ethylamine gives racemic *p*-menthene (equation 266)[352]. Allyl phenyl ether is cleaved by metallic magnesium to allylmagnesium phenoxide (equation 267)[353]. Reduction of allylic ethers has been obtained with zinc–HCl in ether[354]. As in the case of reduction of allylic alcohols (equation 243), the same product mixture is obtained from two allylic isomers, and the thermodynamically less stable alkene predominates (equation 268). This result has been rationalized by a mechanism where the ether is absorbed on the surface of the metal and protonated prior to reduction.



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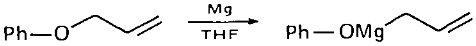

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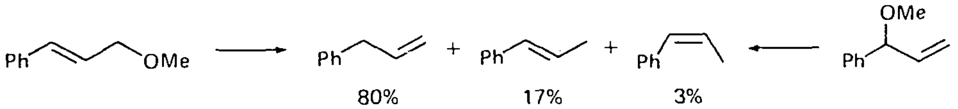
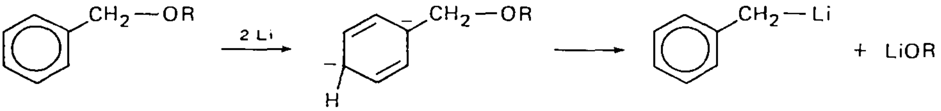


(268)

Reduction of benzyl and allyl ether by alkali metals proceeds via the dianion (equation 269)[354]. Similarly, diaryl- and aryl-alkyl ethers react with sodium in ammonia[355], ethylene diamine[356], pyridine[357] or lithium and potassium in hexamethylphosphoric triamide via the dianion (equation 270)[358]. The mechanism of cleavage by alkali metals in inert aliphatic ether solvents has been investigated by ESR techniques[359]. In the case of β-naphthyl ethers initial build-up of the orange, paramagnetic radical anion and its further reaction to the diamagnetic dianion could be directly observed. If the reduction is carried out in the presence of a proton donor, the radical anion undergoes protonation to yield a neutral radical, which after a second reduction step is converted to an enol ether (equation 271). Owing to the facile hydrolysis of enol ethers, this sequence provides a synthetically useful method for reductive deprotection of alcohols[360].



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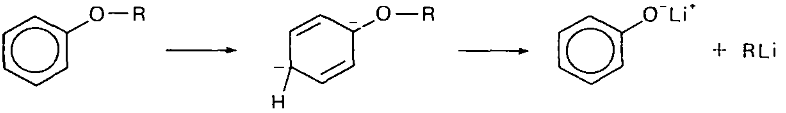
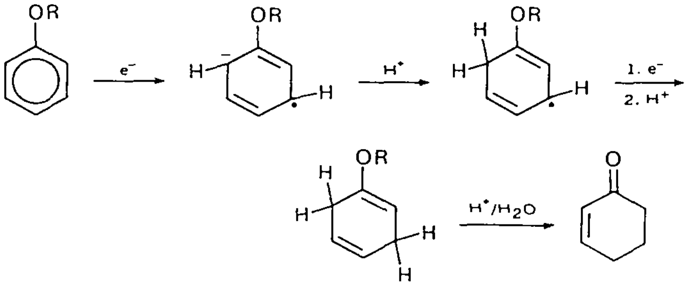


(270)

Alkyl ethers react with alkali metals at temperatures above 200°C[361]. However, the 2 : 1 lithium–biphenyl adduct (**90**) effects cleavage of tetrahydrofuran even at reflux temperature (equation 272). The adduct **90** serves as a homogeneous source of lithium. The reagent is considerably more reactive than metallic lithium itself[362].



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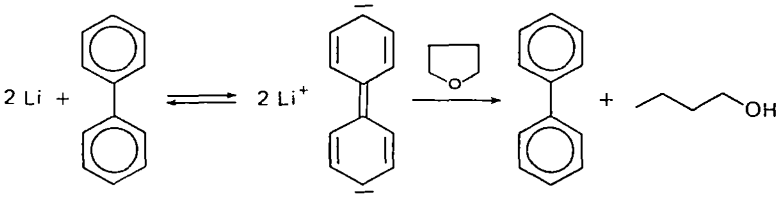

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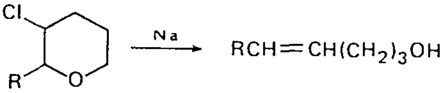
(272)

Aliphatic ethers with β-chloro or -bromo substituents readily undergo reductive elimination in the presence of zinc[363] or sodium[364] (equation 273). In contrast to



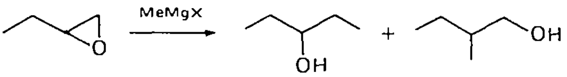
(273)

other β-eliminations, the reaction lacks stereospecificity. It has found application for deprotection of 3-bromotetrahydrofuran-2-yl and 3-bromotetrahydropyran-2-yl steroid ethers[365]. Similarly, zinc has been used for liberating phenols protected with the phenacyl group[366].

C. Organometallic Reagents

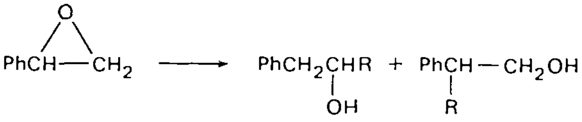
1. Organomagnesium compounds

Epoxides[367] and oxetanes[368] undergo reductive ring-opening when treated with Grignard reagents, organolithium and organocopper reagents. With unsymmetrically substituted epoxides the reaction may lead to two regioisomers, for example equation (274). The regioselectivity depends on the presence of halide



(274)

ions[367]. Only with chloride, 3-pentanol (45%) and 2-methylbutanol (22%) are obtained. With other halides present, the epoxide is converted to the corresponding halohydrines. Reductive ring-opening occurs however in excellent yields with dimethylmagnesium , methyllithium–LiBr and dimethylcopperlithium via attack at the secondary carbon. Similar results have been obtained for reaction of Grignard reagents with styrene oxide[369]. In the presence of magnesium halide the epoxide rearranges to phenylacetaldehyde, which is then attacked by organometallic reagent to afford the alcohol 91. Reaction with dimethylmagnesium, on the other hand, affords the alcohol 92, derived from attack at the benzylic carbon (equation 275).

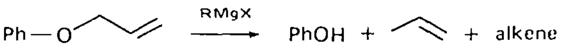


(275)

(91) (92)

Unstrained aliphatic ethers react with Grignard reagents only at elevated temperatures; for example, a 16% yield of methylcyclohexane was obtained upon heating methoxycyclohexane with methylmagnesium iodide in xylene[370].

Arylmethyl ethers are cleaved with methylmagnesium iodide at 100°C[371]. Reaction of Grignard reagents with arylalkyl and arylallyl ethers has been investigated by Kharasch[372]. A very strong accelerating effect of cobaltous chloride was observed. Benzyl ethers and diaryl ethers were cleaved at room temperature, but phenylalkyl ethers were found to be unreactive. Arylallyl ethers react already in the presence of a catalytic quantity of cobaltous chloride to give phenol, propylene and the alkene derived from the Grignard reagent (equation 276). During the uncatalysed reaction, The Grignard reagent couples with the allyl group (equation 277)[373].



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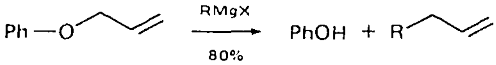
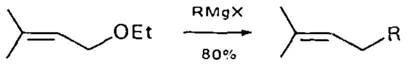


(277)

Organomagnesium compounds react with allylic ethers in the presence of cuprous bromide at 20°C[374]. Depending on the substitution pattern, displacement takes place via an S_N2 or an S_N2'-like pathway (equations 278 and 279). The allylic epoxide 93 reacts in an anlogous way with an organocopper reagent with 1,4-addition (equation 280)[375].



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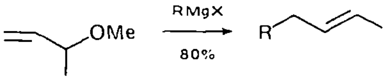

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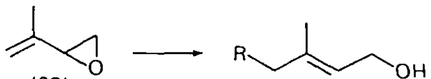
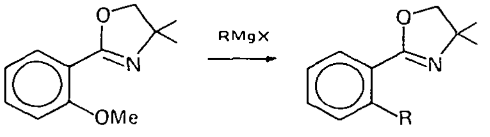


(280)

(93)

When 2-(*O*-methoxyphenyl)oxazolines (94) are treated with Grignard reagents or organolithium compounds, the methoxy substituent is replaced (equation 281)[376].



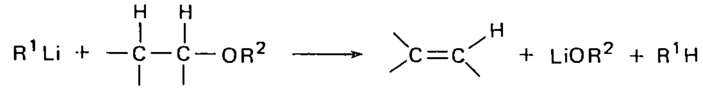
(281)

(94)

The oxazoline moiety serves to activate the aromatic ring toward nucleophilic aromatic substitution, and at the same time complexes with the metal of the attacking reagent.

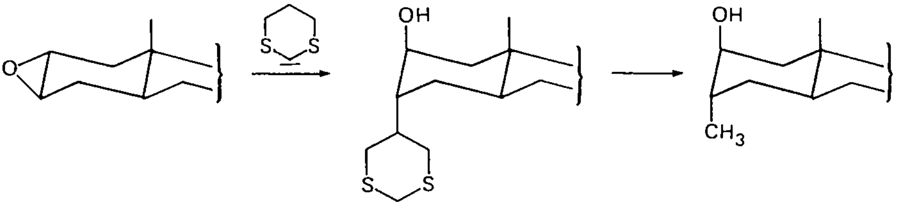
2. *Organolithium compounds*

The principal reaction of organolithium or sodium compounds with ethers is deprotonation at the α- or β-position leading to elimination products (equation 282)[377]. Nucleophilic attack by organolithium compounds is however possible



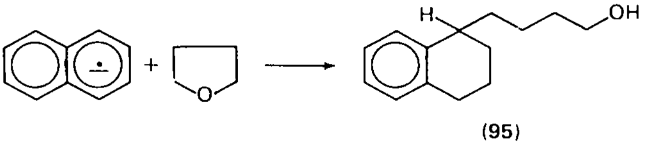
$$R^1Li + -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{H}{|}}{C}}-OR^2 \longrightarrow {>}C{=}C{<}^{H} + LiOR^2 + R^1H \qquad (282)$$

with oxetanes[378] and epoxides[379]. A synthetic application of the latter reaction is found in epoxide opening by 2-lithio-1,3-dithiane (equation 283)[380]. Lithium



(283)

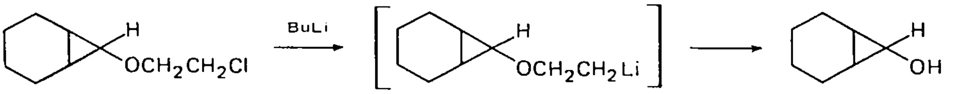
naphthalenide reacts with tetrahydrofuran at 65°C to give the α-substituted dihydronaphthalene **95** in 46% yield (equation 284)[381]. Köbrich and Baumann[382]



(284)

(95)

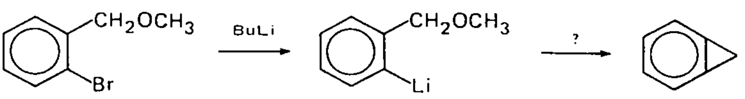
observed that 1,1-diphenylhexyllithium or benzhydryllithium are capable of nucleophilic ether cleavage. Epoxides and oxetanes as well as phenyl, allyl and vinyl ethers react at room temperature, while tetrahydrofuran requires heating to 70°C. In the case of phenyl alkyl ethers cleavage occurs at the alkyl–oxygen bond, but with vinyl ethers the vinyl oxygen bond is cleaved. This suggests an addition–elimination mechanism for cleavage of enol ethers. Intramolecular ether cleavage of organolithium compounds is also possible. Thus, *exo*/*endo*-7-norcaranol (**96**) is obtained via metalation of the chloro ether **97** with butyllithium (equation 285)[382].



(285)

(97) (96)

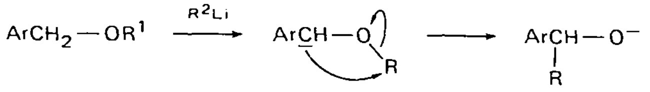
Radlick and Crawford[383] reported a benzocyclopropene synthesis via metalation of 2-bromobenzylmethyl ether (equation 286). However, subsequent work in the



(286)

author's and in other laboratories[384] showed that the reaction was difficult to reproduce.

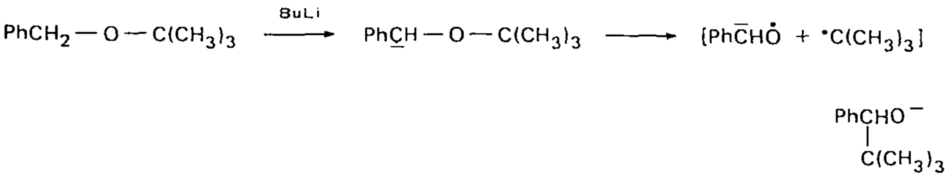
The Wittig rearrangement of benzyl or allyl ethers to alcohols[385] by means of organolithium compounds formally consists of an intramolecular, reductive ether cleavage by the α-metalated ether (equation 287). Mechanistically, the reaction is



$$ArCH_2{-}OR^1 \xrightarrow{R^2Li} Ar\underline{C}H{-}O(R) \longrightarrow ArCH(R){-}O^-$$

(287)

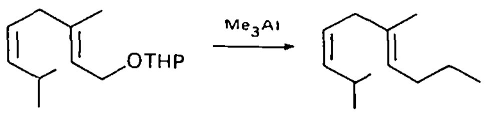
more complicated, and at least partially proceeds via radical pairs (equation 288)[386].



$$PhCH_2{-}O{-}C(CH_3)_3 \xrightarrow{BuLi} Ph\underline{C}H{-}O{-}C(CH_3)_3 \longrightarrow [Ph\bar{C}H\dot{O} + {}^{\bullet}C(CH_3)_3] \longrightarrow PhCH(C(CH_3)_3)O^-$$

(288)

Some other organometallic reagents are capable of reductive ether cleavage. Organocuprates open tetrahydrofuran to yield the corresponding alcohols in 60–70% yield, calculated on the amount of cuprate used[387]. Trimethylaluminium couples with allylic ethers. The corresponding methyl compound is formed in 80% yield (equation 289)[388]. In general, however, trialkylaluminium reagents are unreactive towards tetrahydropyranyl ethers, although they couple readily with allylic acetate, formate or carbonate esters.



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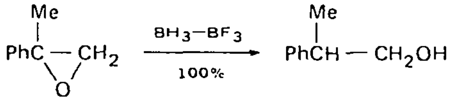
Addition examples of ether cleavage by organometallic reagents are reviewed in another volume of this series[389].

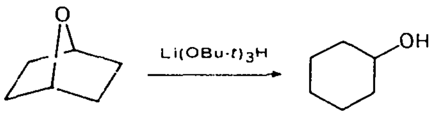
D. Complex Metal Hydrides

Reaction of epoxides and oxetanes with $LiAlH_4$ has been reviewed elsewhere[389]. In general, the ether linkage is resistant to this reagent, although some cleavage of tetrahydrofuran occurs with $LiAlH_4/AlCl_3$[386]. Epoxides undergo reductive anti-Markownikoff ring-opening in the presence of diborane and BF_3, for example equation (290)[390]. The same reagent may cleave benzyl ethers[391]. Some modified aluminium hydrides cleave aliphatic ethers efficiently. Tetrahydrofuran is converted to *n*-butanol by lithium tri-*t*-butoxyaluminium hydride in the presence of (equation 291) triethylborane at 25°C. 7-Oxabicyclo[2.2.1]heptane is converted to cyclohexanol (equation 291)[392]. Aliphatic ethers are stable towards diisobutylaluminium hydride at low temperature, but tetrahydrofuran is attacked by the reagent upon heating[393], and diglyme decomposes violently in the presence of dialkylaluminium hydride at room temperature[394]. Aromatic methyl ethers react with diisobutylaluminium hydride or triisobutylaluminium at 70–80°C with liberation of the corresponding phenols, for example equation (292)[395]. Di-



$$PhC(Me){-}CH_2\ (\text{epoxide, O}) \xrightarrow[100\%]{BH_3{-}BF_3} PhCH(Me){-}CH_2OH$$

(290)



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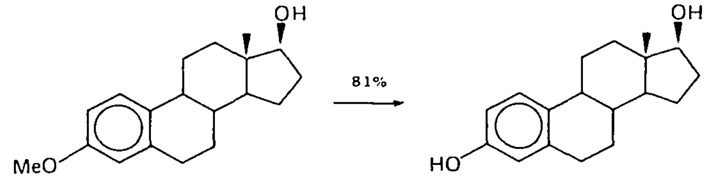
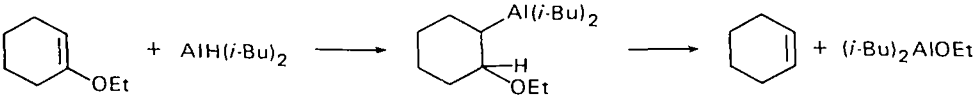


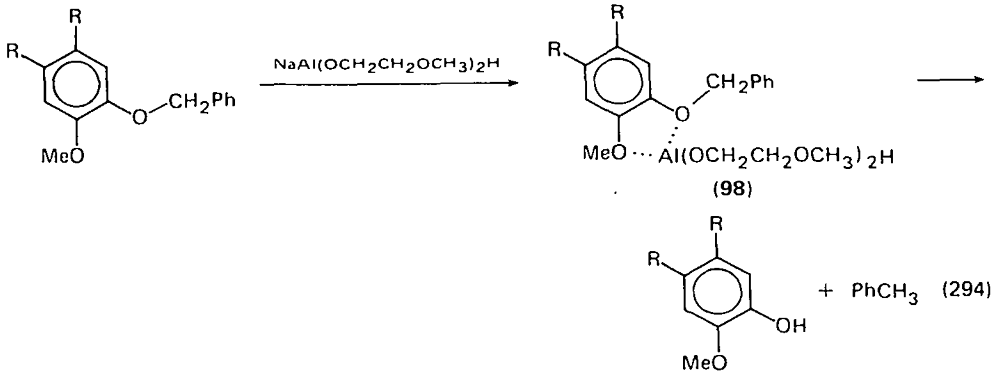
(292)

isobutylaluminium hydride cleaves vinyl ethers presumably via addition to the double bond, followed by alkene elimination (equation 293)[396].



(293)

Refluxing of benzyl aryl ethers of allyl aryl ethers with sodium bis(2-methoxyethoxy)aluminium hydride in xylene results in effective cleavage of the ether bond[397]. Debenzylation of ethers having an additional methoxy group at a vicinal carbon was found to proceed more smoothly than that of monofunctional compounds. This observation has been rationalized by formation of a complex (98) between the ether and the aluminium hydride (equation 294).



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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 13

Oxidation and reduction of sulphides

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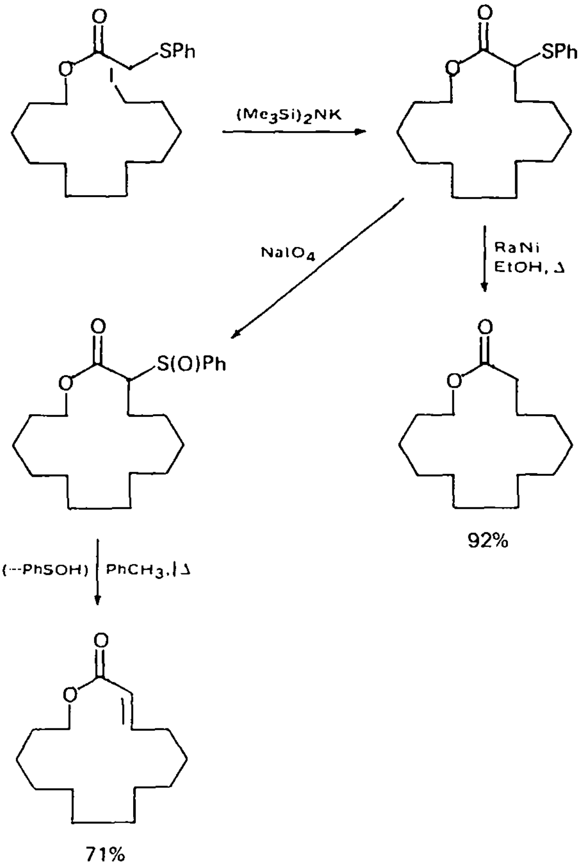
I. INTRODUCTION

One of the first reactions to be discovered in the field of organosulphur chemistry was the oxidation of sulphides to sulphoxides[1], a reaction which even today provides the principal means of synthesizing sulphoxides. Also discovered relatively early in the development of organosulphur chemistry was the ability of sodium in liquid ammonia[2] and Raney nickel[3] to reductively cleave C—S bonds in sulphides. In synthetic methods utilizing sulphur functions, oxidative and reductive procedures are of great value in the step involving removal of the sulphide or thioacetal sulphur, as illustrated by equations (1)[4], (2)[5] and (3)[6] for sulphides and (4)[7] and (5)[8] for



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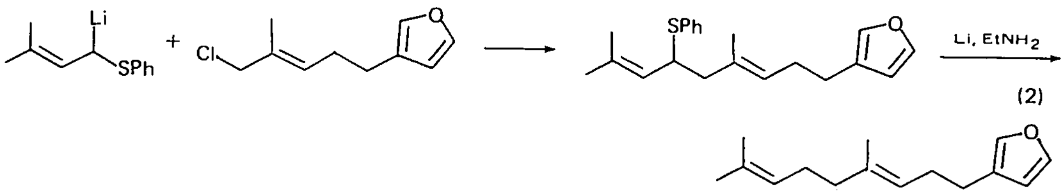

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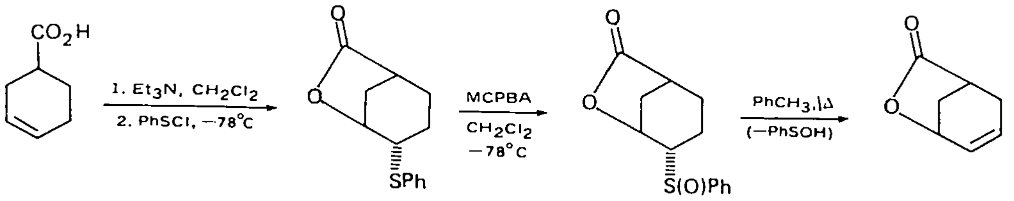

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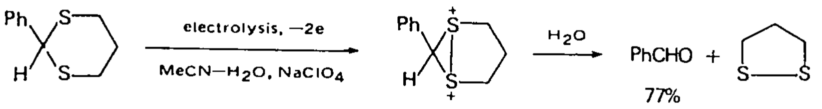

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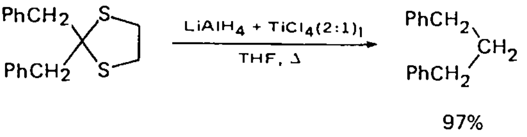


(5)

dithioacetals. Oxidative methods are often used in the hydrolysis of thioacetals with the purpose being to render the sulphur moiety a better leaving group and to remove the thiol irreversibly by converting it to other sulphur derivatives[9]. Among the reagents used for oxidative hydrolysis are chlorine, bromine, iodine, *t*-butyl hypochlorite, *N*-chloro- and *N*-bromo-succinimide, chloramine T, thallium (III) trifluoroacetate, lead tetraacetate and ceric ammonium nitrate as well as the electrochemical procedure shown in equation (4).

A large number of procedures for the quantitative determination of organic sulphides are based on the oxidation to sulphoxide followed by measurement of reagent consumption[10]. A number of analytical procedures involve reduction of sulphides with the product of analytical interest being a thiol (or thiolate ion), a hydrocarbon or hydrogen sulphide[10].

II. OXIDATION OF SULPHIDES

The oxidation of sulphides can lead under vigorous enough conditions to the formation of sulphuric acid via the stages indicated in equation (6). In this chapter we

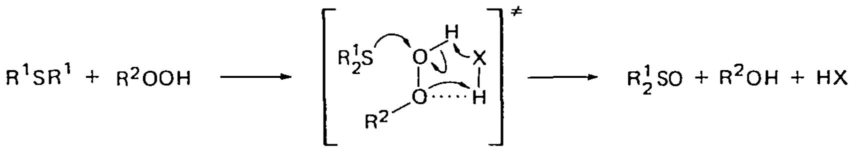
$$\mathrm{RSR} \xrightarrow{[\mathrm{O}]} \mathrm{RS(O)R} \xrightarrow{[\mathrm{O}]} \mathrm{RSO_2R} \xrightarrow{[\mathrm{O}]} \mathrm{RSO_3H} \xrightarrow{[\mathrm{O}]} \mathrm{H_2SO_4} \qquad (6)$$

shall be concerned primarily with the first, and most facile, stage in this process, namely the oxidation of sulphides to sulphoxides. A very limited number of cases are known in which sulphides are converted into sulphones by routes not involving sulphoxides; these reactions will also be discussed. There is great interest in the oxidation of sulphides as a means of synthesizing sulphoxides, in the use of sulphides as substrates for the study of oxidation mechanisms and in understanding how certain organosulphur compounds can function as antioxidants, in stereochemical studies involving selective oxidation at sulphur and in the *in vivo* oxidation of sulphides via the action of certain enzymes as well as under more destructive conditions involving the action of ozone, singlet oxygen and other exogenous oxidants. This chapter will provide a broad, albeit nonencyclopaedic, review of these and related areas with an emphasis on the current nonpatent literature up to November 1978 (a few more recent references have been added in proof; see p. 608). The earlier literature is covered more thoroughly in several older reviews[11-14].

A. General Methods

1. *Peroxy compounds: hydrogen peroxide, hydroperoxides, acyl peroxides, peracids and molecular oxygen*

One of the oldest, yet still widely used, procedures for the oxidation of sulphide to sulphoxide involves the addition of the theoretical amount of 30% H_2O_2 to a solution of the sulphide in sufficient acetic acid, acetone or alcohol to maintain homogeneity; the reaction mixture is then allowed to stand at room temperature overnight (or longer if necessary)[15,16]. In a related process an alkyl hydroperoxide such as *t*-butyl hydroperoxide is used instead of the hydrogen peroxide[11]. These reactions are strongly acid-catalysed and kinetically first order both in sulphide and peroxide. Catalysts and inhibitors of free-radical reactions, including O_2, are without effect. The role of the acid (HX) is apparently to facilitate loss of the leaving group (ROH) in the transition state (see equation 7)[11]. In nonprotic solvents a bimolecular dependence on peroxide is seen suggesting a transition state related to that shown in equation (8)[11]. An activation entropy $\Delta S^{\neq} = -33$ for the oxidation of 1,4-thioxane pictured in equation (9) is supportive of the highly ordered transition state depicted in equations (7) and (8)[11,17]. That hydrogen peroxide is ca. 20 times more reactive toward 1,4-thioxane than *t*-butyl hydroperoxide is consistent with the greater electronegativity of hydrogen than carbon[320].



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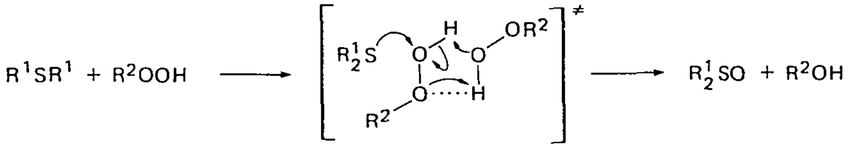

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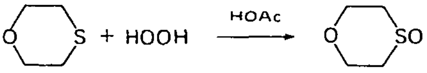
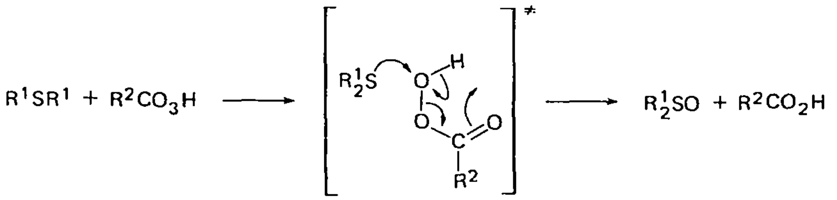


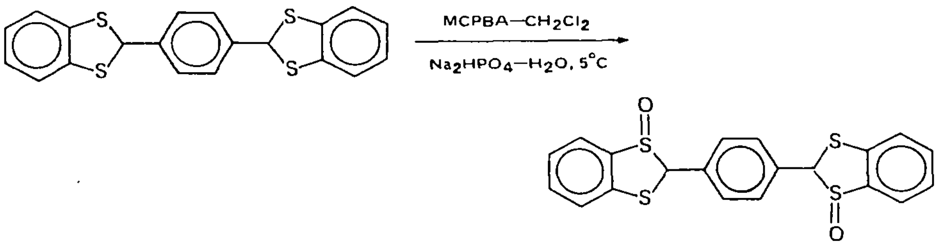
(9)

Peracids are even more powerful oxidants. Here the rate of oxidation depends on the electronegativity of the R group in RC(O)OOH with the approximate order of reactivity being $CF_3CO_3H > m\text{-}ClC_6H_4CO_3H$ (MCPBA) $> C_6H_5CO_3H > HCO_3H > CH_3CO_3H$. The transition state pictured for peracid oxidation is analogous to that involved for epoxidation of olefins (equation 10)[18]. In addition to depending on the nature of the R group in the peracid, the rate of oxidation of sulphides by peracids also depends on the nucleophilicity of sulphur and on the solvent.



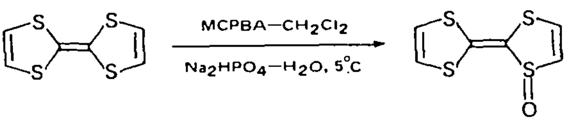
(10)

Electron-donating substituents on sulphur accelerate the reaction and the order of reactivity of sulphides is alkyl$_2$S > alkenyl$_2$S > aryl$_2$S[11]. As sulphoxides are much less nucleophilic at sulphur than sulphides, oxidation of sulphoxides is $10^{-2}-10^{-3}$ times slower than oxidation of the corresponding sulphides. Peracid oxidations are much faster in nonprotic solvents since the solvent does not compete with the internal hydrogen for bonding to the carbonyl oxygen and thus does not hinder oxygen transfer as do protic solvents. The Hammett ρ value for oxidation of substituted diaryl sulphides by perbenzoic acid in methylene chloride is -2.5, a value consistent with the electrophilic character of the oxidant[19]. By way of comparison, diaryl sulphides show a ρ value for oxidation by hydrogen peroxide in the presence of $HClO_4$ of -0.98[20]. With regard to oxidations by MCPBA a few additional points should be made. While the by-product of MCPBA oxidations, *m*-chlorobenzoic acid, is reportedly insoluble in chloroform and is thus removed, studies show that even at -5°C chloroform retains 1.5–2.5% (w/v) of this acid[21]. A useful way of removing residual acid is to bubble anhydrous ammonia into the reaction mixture and remove the precipitated ammonium *m*-chlorobenzoate by filtration through a bed of Celite[22,23]. Sometimes it is desirable to conduct MCPBA oxidations in the presence of a mild acid scavenger such as Na_2HPO_4 (used in a two-phase system; equations 11[24] and 12[25]). Through the use of MCPBA and related peracids, strained sulphoxides, such as thiiran 1-oxides (see Section L) and the *S*-oxide shown in equation (13)[26], can be readily prepared.



(11)

37%



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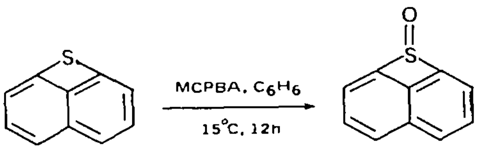
68%

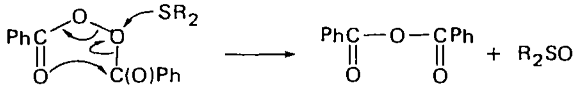


(13)

70%

Needless to say in the use of peracids caution should be exercised to avoid possible contamination by acetone which under certain circumstances can lead to the formation of explosive peroxides![27]

Diacyl peroxides can also be used to oxidize sulphides to sulphoxides (equation 14)[28]. Oxidations by H_2O_2 can be conducted under basic conditions (equation 15)[29] and can be dramatically accelerated by the addition of catalytic quantities of seleninic acids or selenium dioxide (the active oxidant is thought to be perseleninic acid;[321] equation 16)[30,31] and salts of W, Zr, Mo, V and Mn (in the case of tungsten a peroxy salt $WO_3(OOH)(OH)^{-2}$ is suggested to be the active oxidant)[21,322]. A particularly useful oxidant is the 'Milas reagent' H_2O_2–*t*-BuOH–V_2O_5 which can be used to oxidize thiirans, α-chlorosulphides[32], sulphides in the presence of disulphides[33] and vinyl sulphides (equation 17)[34]. Oxidation



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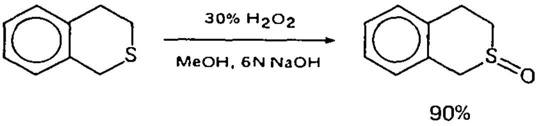


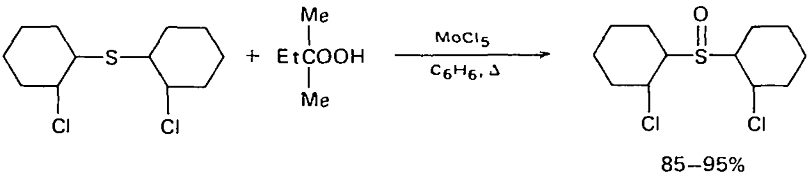
(15)

$$R_2S + 30\%\ H_2O_2 \xrightarrow[ArSeO_2H]{CH_2Cl_2,\ 25^\circ C} R_2SO \tag{16}$$

$$(CH_3)_3CSCH{=}CHCH_3 \xrightarrow[V_2O_5,\ 10^\circ C]{H_2O_2-t\text{-}BuOH} \underset{67\%}{(CH_3)_3CS(O)CH{=}CHCH_3} \tag{17}$$

using this reagent can be conducted as a titration since in the presence of hydrogen peroxide the reaction mixture is red–orange while in the absence of hydrogen peroxide a very pale yellow or green colour is observed. The *t*-butanol can be diluted with tetrahydrofuran to permit oxidations at −20°C[33,34].

There is also considerable interest in the catalysis of hydroperoxide oxidation of sulphides by salts of vanadium and molybdenum, e.g. as illustrated by equations (18)[35] and (19)[36]. With some sulphides no reaction occurred with H_2O_2, even



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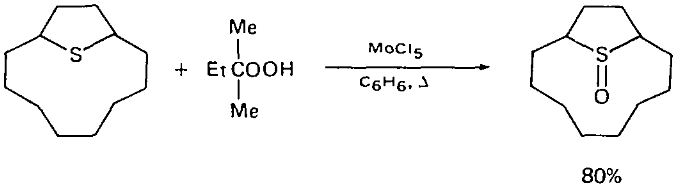
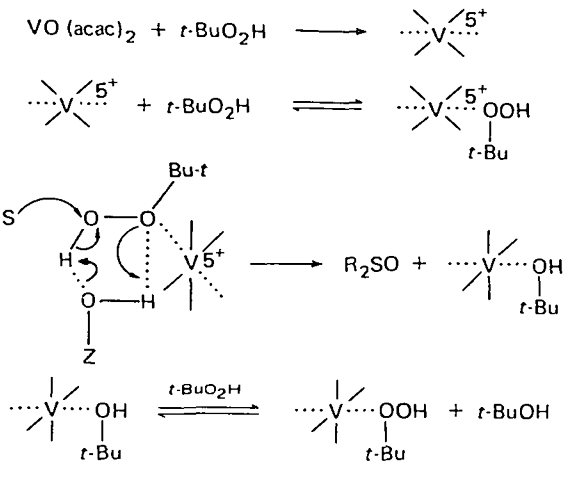


(19)

under drastic conditions, whereas oxidation proceeded easily with ROOH/$MoCl_5$[37]. The relative rates for oxidation by *t*-butyl hydroperoxide–$VO(acac)_2$ of di-*n*-butyl


VO (acac)2 + t-BuO2H
V5+
+ t-BuO2H
OOH
t-Bu
Bu-t
R2S
O—O
H
O—H
Z
R2SO +
OH
t-Bu
t-BuO2H
+ t-BuOH

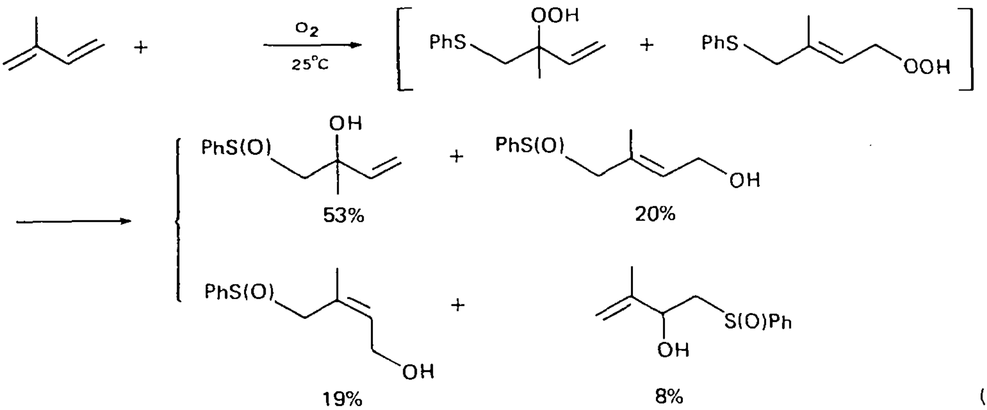
SCHEME 1.

sulphide, butyl phenyl sulphide, di-*n*-butyl sulphoxide and cyclohexene have been found to be 100, 58, 1.7 and 0.2, respectively[38], in a study which presents the is inorganic. Indeed, in the absence of special requirements it is still probably the absence of the vanadium catalyst the oxidation is very slow. An even more efficient catalyst than V(V) is Mo(VI), for example as dioxomolybdenum (VI) acetonate, $MoO_2(acac)_2$. This catalyst shows the selectivity Bu_2S (100) > Bu_2SO (0.15) > cyclohexene (<0.01) (relative reactivity in parenthesis) and is ca. 80 times more efficient than V(V), e.g. in the oxidation shown in equation (20)[39]. To rationalize

$$R_2S + t\text{-BuOOH} \xrightarrow[\text{EtOH, 25°C, 2h}]{4\%\ \text{MoO}_2(\text{acac})_2} R_2S{=}O \qquad (20)$$

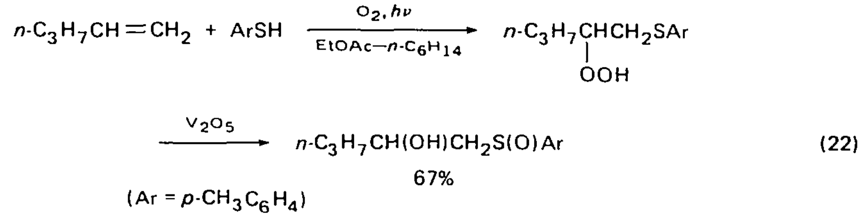
$$>98\%,\ R = Bu$$

the asymmetric oxidation that occurs when the *t*-butylhydroperoxide–$VO(acac)_2$ oxidation of sulphides is carried out in the presence of chiral alcohols, Modena, Edwards and coworkers postulate that a chiral vanadate ester $VO(OR)_3$ is the catalytic species[40]. Hydroperoxides are likely intermediates in the oxidative addition of thiophenol to olefins to give β-hydroxy sulphoxides (equation 21)[41].


+
O2
25°C
OOH
PhS
+
PhS
OOH
OH
PhS(O)
+
PhS(O)
OH
53%
20%
PhS(O)
OH
+
S(O)Ph
OH
19%
8%

(21)

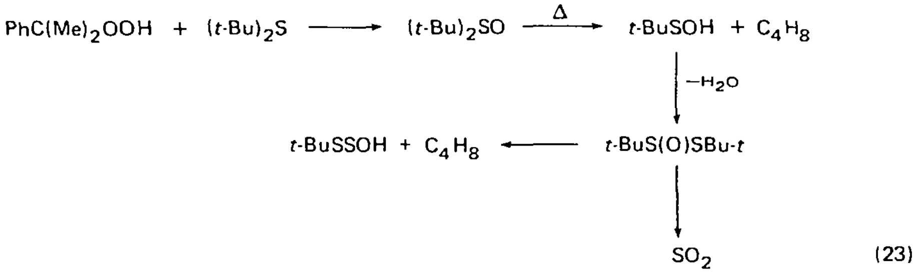
Indeed β-hydroperoxy sulphides have been isolated in certain cases. Conversion of β-hydroperoxy sulphides to β-hydroxy sulphoxides is achieved by simply stirring the reaction mixture in the presence of a catalytic amount of V_2O_5, oxobis(acetylacetonato)vanadium (IV), or dioxobis(acetylacetonato)molybdenum (VI) (equation 22)[42]. β-Hydroxy sulphoxides are synthetically useful intermediates[41,42].



$$n\text{-}C_3H_7CH{=}CH_2 + ArSH \xrightarrow[EtOAc-n\text{-}C_6H_{14}]{O_2,\,h\nu} n\text{-}C_3H_7\underset{\displaystyle OOH}{\underset{|}{C}}HCH_2SAr \xrightarrow{V_2O_5} \underset{67\%}{n\text{-}C_3H_7CH(OH)CH_2S(O)Ar} \qquad (22)$$

$(Ar = p\text{-}CH_3C_6H_4)$

Unsaturated sulphides undergo autooxidation presumably forming hydroperoxides as intermediates. The reactions are, however, quite complex showing both initial autocatalysis and later autoretardation and autoinhibition, indicative of the formation of oxidation inhibitors[11]. Illustrative of the types of antioxidants that can be generated on oxidation of sulphides and disulphides are *t*-butanesulphenic acid, *t*-butanethiosulphoxylic acid and sulphur dioxide, all of which could arise by initial oxidation of di-*t*-butyl sulphide by cumene hydroperoxide (equation 23)[43-45].



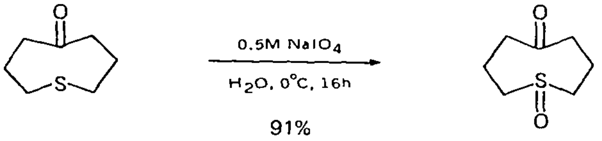
$$\begin{array}{ccccc} PhC(Me)_2OOH + (t\text{-}Bu)_2S & \longrightarrow & (t\text{-}Bu)_2SO & \xrightarrow{\Delta} & t\text{-}BuSOH + C_4H_8 \\ & & & & \Big\downarrow{\scriptstyle -H_2O} \\ & & t\text{-}BuSSOH + C_4H_8 & \longleftarrow & t\text{-}BuS(O)SBu\text{-}t \\ & & & & \Big\downarrow \\ & & & & SO_2 \end{array} \qquad (23)$$

The sulphur acids are very efficient radical scavengers while sulphur dioxide is known to catalytically decompose hydroperoxides.

Saturated alkyl, aralkyl and aryl sulphides do not react spontaneously with molecular oxygen at temperatures below about 100°C[46]. At elevated temperatures sulphides undergo oxidation by air or oxygen and this oxidation can be quite efficient in the presence of certain heterogeneous or homogeneous catalysts (e.g. $CuBr_2$ and $RuCl_3$)[47].

2. *Sodium metaperiodate*

Sodium metaperiodate, long used in the oxidative cleavage of vicinal diols was first popularized as a selective reagent for sulphide oxidation by Leonard and Johnson in 1962[48]. The reagent has much to commend it: it is safely handled and stored, it is readily available and requires mild conditions, it is quite selective and gives good yields, overoxidation is easily avoided, and the by-product (iodate) is in organic. Indeed, in the absence of special requirements it is still probably the reagent of choice for gentle conversion of a sulphide to a sulphoxide. It should be emphasised that temperature control is important (generally 0°C is used) as sulphone can be formed at higher temperatures. The principal difficulty with the reagent is the requirement for water as a solvent (or cosolvent) which limits applications to water-sensitive sulphides or to the preparation of sulphoxides which are difficult to isolate from water (or are difficult to dry). A cosolvent (generally methanol or occasionally dioxane or methanol–acetonitrile[49]) can be used to promote the reaction of insoluble sulphides. Oxidation of long-chain alkyl sulphides may still be difficult due to solubility problems. Selective examples of $NaIO_4$ oxidations are given in equations (24)[48], (25)[48], (26)[50], (27)[51] and (28)[52]. In the

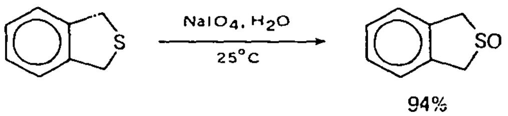


(24)

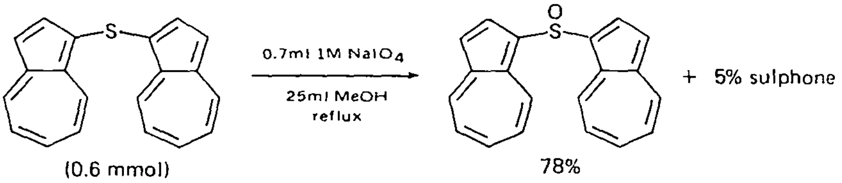
$$(Et_2NCH_2CH_2)_2S \xrightarrow[H_2O,\ 0^\circ C,\ 16h]{0.5M\ NaIO_4} (Et_2NCH_2CH_2)_2S{=}O$$

85%

(25)



(26)



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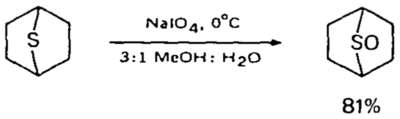
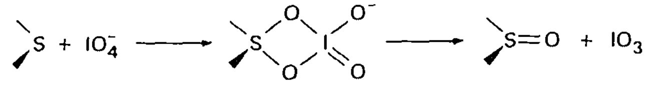


(28)

oxidation of dithioethers to monosulphoxides (see Section D) $NaIO_4$ is also the reagent of choice. The mechanism for sulphide oxidation probably involves a cyclic intermediate related to that proposed for glycol oxidation (equation 29)[48].



(29)

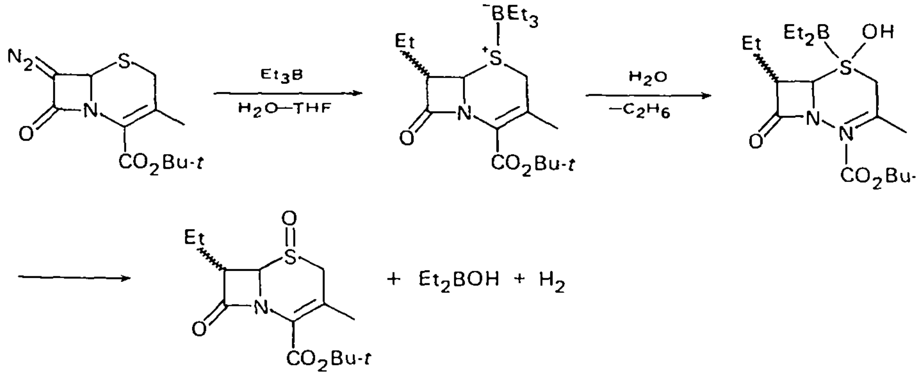
An interesting nonaqueous procedure involving $NaIO_4$ has been developed in which the reagent is adsorbed on acidic aluminium oxide[53]. Good yields of sulphoxides are obtained even with a twofold excess of oxidant; 95% ethanol is apparently the preferred solvent.

3. *Hypervalent iodine reagents*

Iodosobenzene (PhIO), iodosobenzene diacetate [$PhI(OAc)_2$] and iodobenzene dichloride ($PhICl_2$) have all been recommended as useful reagents for oxidizing sulphides to sulphoxides[12,54–57]. Acetoxylation and chlorination, however, are problems with the second and third reagent, respectively. Iodobenzene dichloride, requiring pyridine and small amounts of water as coreactant, oxidizes sulphides rapidly even at −40°C, giving over 90% yields of t-BuS(O)Ph, Ph_2SO and $PhS(O)CH_2CH_2S(O)Ph$ from the respective sulphides. If $H_2{}^{18}O$ is used, ^{18}O-labelled sulphoxides may be conveniently prepared[56]. Iodobenzene dichloride failed to give sulphoxide with PhSCH=CHR(R = PhS or CO_2H)[56].

4. Boranes

Wynberg has recently described what is reputed to be the first instance of oxidation of sulphur with a trialkylborane–water mixture (equation 30)[58]. The scope of this interesting reaction remains to be established.



(30)

5. Nitrogen oxides and nitric acid; organic compounds with N—O—C bonds

Nitric acid was the oxidant used to make the first known sulphoxide (dimethyl sulphoxide) in the 1860s[1] while Pummerer in 1910 reports the use of 'nitrous fumes' (NO_2)[59]. Today the major commercial route to dimethyl sulphoxide involves the air oxidation of dimethyl sulphide catalysed by NO_2 (equation 31)[60].

$$\begin{aligned} Me_2S + NO_2 &\longrightarrow Me_2SO + NO \\ 2\,NO + O_2(\text{air}) &\longrightarrow 2\,NO_2 \end{aligned} \qquad (31)$$

The NO_2 dimer, N_2O_4, is also an effective oxidant for sulphides. The oxidations are kinetically 1/2 order in N_2O_4, indicating the monomer NO_2 to be the active oxidant[61]. A Hammett ρ value of −2.7 has been determined for the reaction of N_2O_4 with aryl sulphides in CCl_4 suggesting the development of substantial positive charge on sulphur during the transition state[62,323].

In performing oxidations with N_2O_4, the reagents should be mixed at low temperatures and warmed carefully as NO evolution can be very vigorous; good yields of sulphoxides can be obtained although the first-formed product is a sulphoxide–N_2O_4 complex[63-65]. Nitric acid has been used as an oxidant on occasion[66,67]; with aromatic sulphides ring-nitration can be a competing side-reaction[68]. The active oxidant in the nitric acid oxidation of sulphides is said to be $N_2O_4H^+$[68]. A somewhat related oxidant involves the combination nitric acid–acetic anhydride. This combination forms acetyl nitrate which readily oxidizes thioanisole, for example, to the corresponding sulphoxide in 85% yield (equation 32)[69a]. Certain substituted oxaziridines (three-membered CNO heterocycles) have been found to be selective oxidants for sulphides[69b].

$$HNO_3(98\%) + Ac_2O \longrightarrow CH_3C(O)ONO_2$$

$$CH_3C(O)ONO_2 + PhSMe \longrightarrow \underset{85\%}{PhS(O)Me} \qquad (32)$$

6. *Oxidation of sulphides via halosulphonium salts*

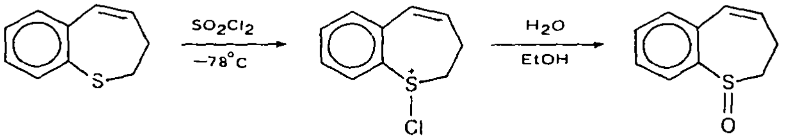
Hydrolysis of the complexes of sulphides with chlorine and bromine has long been used to prepare sulphoxides (see equation 33)[14,70]. Chlorine itself is not

$$R_2S + X_2 \rightleftharpoons R_2\overset{+}{S}-X\ X^- \xrightarrow{H_2O} R_2\overset{+}{S}O + 2H \qquad (33)$$

often used because of its excessive reactivity although this high reactivity can be used to advantage in the oxidation of poorly nucleophilic heavily chlorinated sulphides (see equation 34).[71] Another instance of preparation of a sulphoxide via a chlorosulphonium salt is indicated in equation (35)[72]. Here the source of

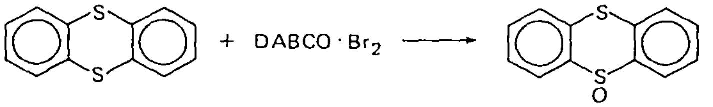
$$RSCH_2Cl \xrightarrow[3\text{ equiv. }H_2O]{HOAc,\ Cl_2} RS(O)CH_2Cl \qquad (34)$$

$$R = ClCH_2,\ 77\%$$
$$R = Cl_2CH,\ 65\%$$
$$R = Cl_3C,\ 50\%$$



(35)

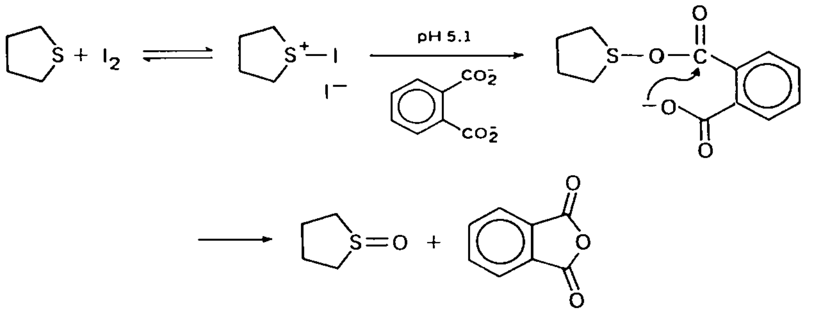
chlorine is sulphuryl chloride. The introduction and hydrolysis of the chlorine substituent can be conducted in a single step through use of wet silica gel with the SO_2Cl_2[73]. Bromine-mediated oxidation of sulphides of type MeSAr shows an unusually large Hammett ρ value of −3.2 (one of the largest values reported for a reaction of a sulphur centre) consistent with the development of considerable positive charge in the bromosulphonium ion intermediate (see equation 33)[74]. Steric effects are also seen in this oxidation, with methyl phenyl sulphide reacting 28 times faster than isopropyl phenyl sulphide[74]. Bromine may be conveniently introduced as the complex with DABCO (1,4-diazabicyclo[2.2.2]octane) as illustrated by the oxidation of thianthrene in equation (36)[75]. If $H_2{}^{18}O$ is introduced together with the amine–Br_2 complex, ^{18}O-sulphoxides may be prepared. Sulphides may be oxidized with iodine provided an additional reagent is added to trap the reversibly formed iodosulphonium complex. An interesting trapping agent is the phthalate anion which itself is transformed during the oxidation to phthalic anhydride (see equation 37)[76] Difluorosulphuranes, the covalent form of fluorosulphonium fluorides, may also be hydrolysed to sulphoxides as seen in equation (38)[77].



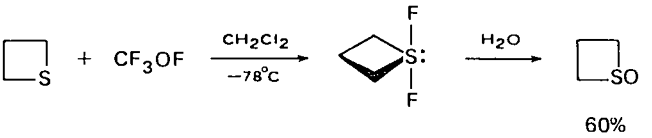
95%

(36)

The oxidation of sulphides to sulphoxides has also been realized with a variety of inorganic and organic bromine and chlorine compounds which form halosulphonium

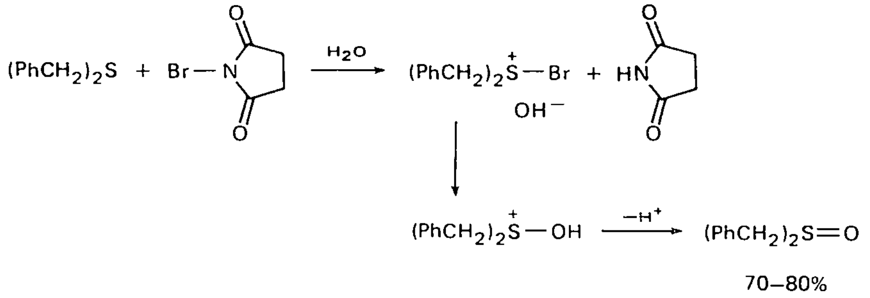


(37)



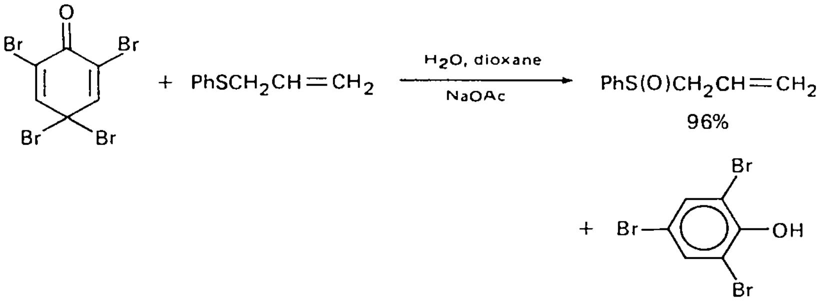
(38)

salts with sulphides. Among these reagents are *N*-bromosuccinimide (see equation 39; this reagent cannot be used with most aliphatic sulphides because of facile C—S



(39)

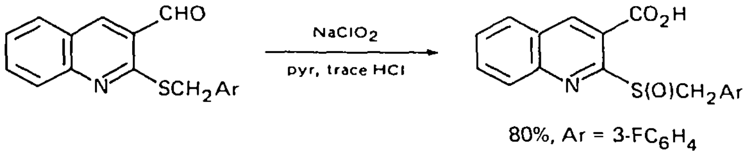
cleavage)[78] and *N*-chlorosuccinimide[79], 2,4,4,6-tetrabromocyclohexadienone (equation 40)[80], sodium hypochlorite (for example see equation 41)[81], sodium chlorite (equation 42; note cooxidation of the aldehyde group to a carboxylic acid function)[82], 1-chlorobenzotriazole (equation 43; gives C—S cleavage with di-*t*-butyl sulphide)[83], chloramine T(p-$CH_3C_6H_4SO_2NCl^-Na^+$; equation 44)[84,85] 'Halazone' (p-$HOOC$–$C_6H_4SO_2NCl_2$)[81] and *t*-butyl hypochlorite[86–89]. In many of these



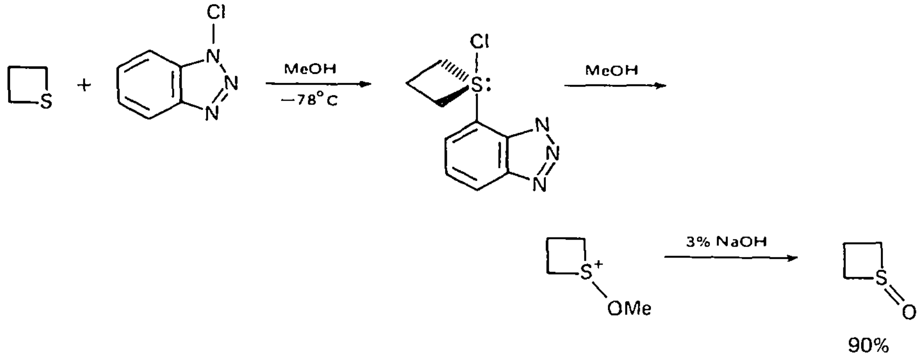
(40)

$$(ClCH_2CH_2)_2S \xrightarrow[H_2O\text{—}MeOH]{NaOCl,\ pH\ 7.5} (ClCH_2CH_2)_2SO \qquad (41)$$

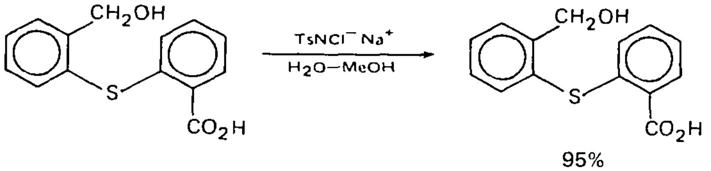
57%


CHO
SCH2Ar
N
NaClO2
pyr, trace HCl
CO2H
S(O)CH2Ar
80%, Ar = 3-FC6H4

(42)

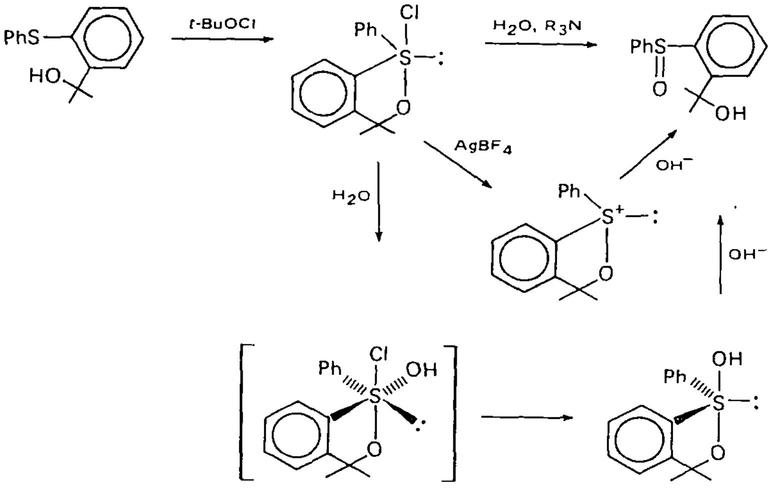

S
Cl
N
MeOH
−78°C
S:
MeOH
S+
OMe
3% NaOH
O
90%

(43)

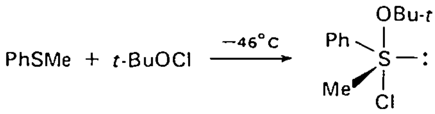

CH2OH
S
CO2H
TsNCl− Na+
H2O—MeOH
95%

(44)

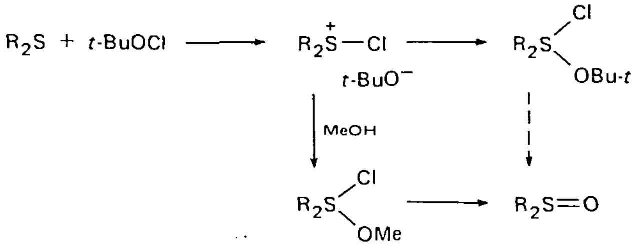
reactions σ-sulphuranes, tetracoordinate sulphur (IV) species, are thought to be involved as intermediates and are occasionally detected spectroscopically as in the work of Martin (equation 45)[90] and the earlier work of Johnson (equations 46 and 47)[89]. While the precise mechanism for hydrolysis or conversion to sulphoxide for these sulphuranes remains to be established, anions analogous to SF_5^- may be involved in some cases (see equation 45). However, with methanol-^{18}O as cosolvent it has been found that 69% of the original ^{18}O of the methanol is retained in the


PhS
HO
t-BuOCl
Ph
Cl
S
O
H2O, R3N
PhS
O
OH
AgBF4
OH−
H2O
Ph
S+
O
OH−
Cl
Ph
OH
S
O
OH
Ph
S
O

(45)

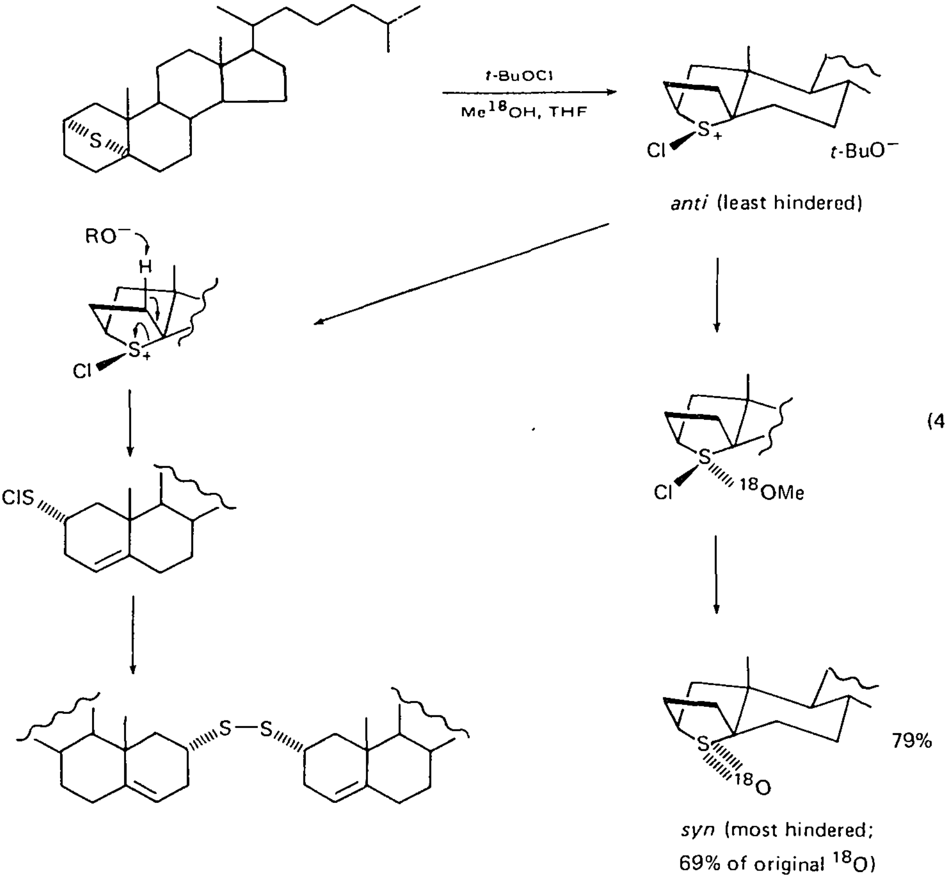

PhSMe + t-BuOCl
−46°C
OBu-t
Ph
S
Me
Cl

(46)


R2S + t-BuOCl
R2S—Cl
+
t-BuO−
MeOH
Cl
R2S
OBu-t
Cl
R2S
OMe
R2S=O

(47)

sulphoxide, indicating that C—O cleavage is also important (equation 48)[91]. With regard to oxidations by *t*-butyl hypochlorite it should also be noted that the most hindered sulphoxide generally predominates (formed from the least hindered chlorosulphonium salt) and that side-reactions such as *t*-butoxide-induced elimination (see equation 48; the amount of elimination product increases from 2.1 to 58.4% to 90.2 to 100% as the solvent is changed from methanol to ethanol to isopropanol to *t*-butanol)[91] and Pummerer-type rearrangement (equation 49)[92] can occur.


S
t-BuOCl
Me18OH, THF
S+
Cl
t-BuO−
anti (least hindered)
RO−
H
S+
Cl
S
Cl
18OMe
ClS
S—S
S
18O
79%
syn (most hindered;
69% of original 18O)

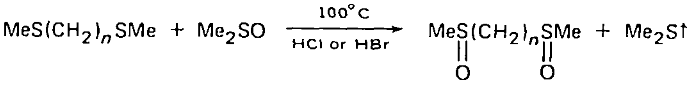
(48)

$$\mathrm{PhSCH_2C{\equiv}CH \xrightarrow[\text{MeOH, }-78^\circ\text{C}]{t\text{-BuOCl}} [PhS(O)CH_2C{\equiv}CH] \longrightarrow PhSCH(OMe)C{\equiv}CH} \quad (49)$$

78%

7. *Dimethyl sulphoxide as oxidant: oxygen transfer from sulphoxide to sulphide*

In 1958 Searles discovered that several simple dialkyl sulphides could be oxidized to the corresponding sulphoxides in 55–59% yields by heating with dimethyl sulphoxide at 160–175°C[93]. Recently it has been found that the yields can be improved and the temperature substantially lowered by the addition of catalytic amounts of HCl or HBr[94,95]. This procedure has been used in the synthesis of certain bissulphoxides (equation 50)[94] and methionine sulphoxide (equation 51)[96] and is apparently general for simple aliphatic sulphides although it fails with *t*-butyl or aryl sulphides. There is no overoxidation to sulphone with this procedure. The reaction is thought to involve bromo- or chloro-sulphonium salts as intermediates (see equation 52)[94]. Aryl alkyl sulphoxides can also serve as the source of oxygen in the oxidation of dialkyl sulphides (see equation 53)[97]. Under photochemical conditions diaryl selenoxides can also oxidize sulphides to sulphoxides in good yield[98].



$$\mathrm{MeS(CH_2)_nSMe + Me_2SO \xrightarrow[\text{HCl or HBr}]{100^\circ\text{C}} MeS(O)(CH_2)_nS(O)Me + Me_2S\uparrow} \quad (50)$$

n = 2–6

yields 52–73%

$$\mathrm{MeSCH_2CH_2CH(NH_2)COOH + Me_2SO \xrightarrow[\text{6N HCl, 5 min}]{100^\circ\text{C}} MeS(O)CH_2CH_2CH(NH_2)COOH + Me_2S\uparrow} \quad (51)$$

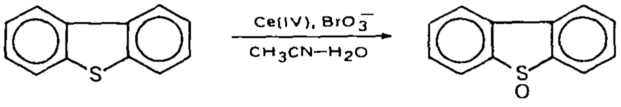
97%

$$\mathrm{Me_2SO \overset{2\,HCl}{\rightleftharpoons} Me_2\overset{+}{S}Cl\ Cl^- \underset{Me_2S}{\overset{R_2S}{\rightleftharpoons}} R_2\overset{+}{S}{-}Cl\ Cl^- \overset{H_2O}{\rightleftharpoons} R_2SO + 2\,HCl} \quad (52)$$

$$\mathrm{ArS(O)Me + Bu_2S \xrightarrow[\text{2:1 MeOH:H}_2\text{O, 2h, 25}^\circ\text{C}]{\text{4.1M HCl}} ArSMe + Bu_2SO} \quad (K_{eq} \geqslant 200) \quad (53)$$

8. *Cerium* (IV)

Ceric ammonium nitrate in the presence of sodium bromate oxidizes sulphides to sulphoxides in good yields (see equation 54). Catalytic quantities of cerium(IV) are used as the bromate serves as a cooxidant recycling the spent cerium(III)[99].



(54)

95%

9. *Chromium* (VI)

Chromic acid (CrO_3) in acetic acid or pyridine has long been used for the oxidation of sulphides[12,100–102] to sulphoxides. It is considered to be a more powerful oxidizing agent than peroxides and can be used for the oxidation of sulphides which resist milder reagents. It is a poor reagent for the oxidation of unsaturated sulphides. Examples appear in equations (55)[102] and (56)[101].

$$\mathrm{Ph_2CHSCH_2Ph} \xrightarrow[75^\circ\mathrm{C},\ 20\ \mathrm{min}]{\mathrm{CrO_3,\ HOAc}} \underset{58\%}{\mathrm{Ph_2CHS(O)CH_2Ph}} \qquad (55)$$

$$\mathrm{(PhCH_2)_2S} \xrightarrow[16\ \mathrm{h}]{\mathrm{CrO_3,\ pyr}} \underset{71\%}{\mathrm{(PhCH_2)_2SO}} \qquad (56)$$

10. *Gold* (III)

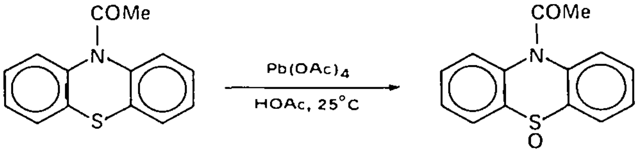
Gold (III) salts, known since 1905 to be effective oxidants for sulphides[103], have recently been found to quantitatively and stereoselectively oxidize methionine to its sulphoxide[104]. It is suggested that coordination of two methionine molecules to Au(III) occurs and is necessary for the reduction of Au(III) to Au(I). The stereospecificity seen in the oxidation [(*S*)-methionine gives (*S*)-methionine (*S*)-sulphoxide] is thought to arise from the interaction of two coordinated chiral centres when the second methionine becomes bonded to the gold.

11. *Lead* (IV)

Lead tetraacetate can convert sulphides to sulphoxides[12,105] but in nonpolar solvents such as benzene α-acetoxylation is a major side-reaction. For example dibenzyl sulphide gives predominantly α-acetoxylation (equation 57)[106] while

$$\mathrm{(PhCH_2)_2S} \xrightarrow{\mathrm{Pb(OAc)_4}} \underset{100\%}{\mathrm{PhCH_2SCH(OAc)Ph}} \qquad (57)$$

di-*n*-butyl sulphide affords moderate yields of the corresponding sulphoxide only with polar solvents (yield of di-*n*-butyl sulphide, solvent: 55%, CH_3CN; 36%, HOAc; 21%, nitrobenzene; 11%, CCl_4; 6%, benzene)[105]. Diaryl sulphides can be oxidized in good yield with lead tetraacetate (equation 58)[107].



70%

(58)

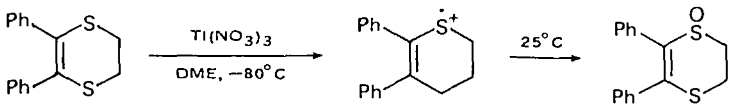
12. *Manganese* (IV)

Manganese dioxide will transform aliphatic sulphides to sulphoxides in moderate yields (equation 59)[101] though the reagent has seen very little use.

$$\mathrm{Bu_2S} \xrightarrow[\mathrm{pet.\ ether}]{\mathrm{MnO_2}} \underset{71\%}{\mathrm{Bu_2SO}} \qquad (59)$$

13. *Thallium* (III)

Thallium (III) nitrate oxidizes aliphatic sulphides to sulphoxides, probably by way of the sulphide cation radical (see equation 60)[108] in successive one-electron oxidation steps.



g value = 2.0070 72% (60)

14. *Organically-bound tin*

The combination hexabutyldistannoxane (HBD)—Br_2 is claimed to be a superior, selective oxidant which does not overoxidize sulphides even with excess reagent[109]. The commercially available tin reagent is used in nonprotic solvents and is effective even at low temperatures. Its drawback is that sulphoxides have to be separated from reagents and products by silica gel chromatography. Some examples of use are shown in equations (61)–(63). In the last equation (63) it should be noted that simultaneous oxidation at sulphur and at carbon has occurred giving a keto-sulphoxide.

$$CH_3SCH_2Cl + (Bu_3Sn)_2O + Br_2 \xrightarrow{-78^\circ C} \underset{78\%}{CH_3S(O)CH_2Cl} \tag{61}$$

$$(C_{16}H_{35})_2S + (Bu_3Sn)_2O + Br_2 \longrightarrow \underset{90\%}{(C_{16}H_{35})_2SO} \tag{62}$$

$$PhS(CH_2)_6CHOHPh + \underset{(2.5\text{ equiv.})}{(Bu_3Sn)_2O} + Br_2 \xrightarrow[-78^\circ C]{CH_2Cl_2} \underset{97\%}{PhS(O)(CH_2)_6COPh} \tag{63}$$

15. *Ozone*

Ozone was apparently first used for the oxidation of a sulphide to a sulphoxide by Böhme in 1942[110]. Since then it has been rather widely used with a variety of sulphides, such as β-chloro- and β-hydroxy-ethyl sulphides (equation 64)[81], aryl sulphides (equation 65)[111], penicillins[112], thietanes, thiolanes and thianes[113–117] and hindered sulphides (equation 66)[118], among other cases. The advantages of

$$(XCH_2CH_2)_2S \xrightarrow[H_2O\text{ or }H_2O/\text{Cellusolve}]{O_3} (XCH_2CH_2)_2S{=}O$$

X = Cl, 53%

X = OH, 95% (64)

$$PhSR \xrightarrow[C_2H_5Cl]{O_3} PhS(O)R \tag{65}$$

R = Me, 92%

R = Ph, 84%

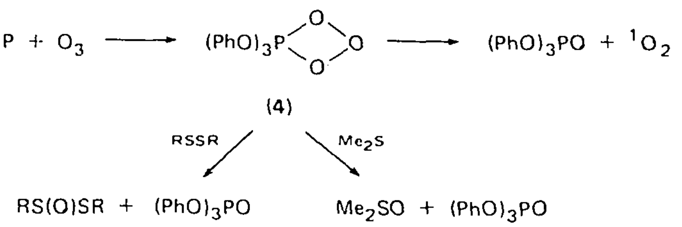
$$t\text{-}BuSCH_2Bu\text{-}t \xrightarrow[-70^\circ C,\ MeOH]{O_3} t\text{-}BuS(O)CH_2Bu\text{-}t \tag{66}$$

TABLE 1. Relative reactivity toward ozone[119,120]

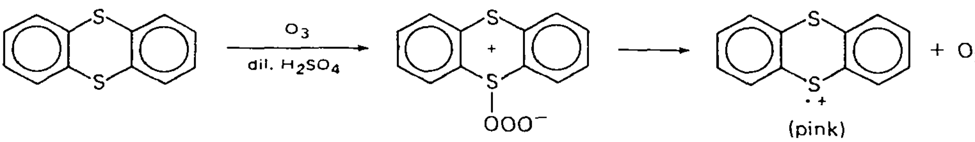
Compound	k_{rel}	Compound	k_{rel}
$Bu_2S{=}O$	ca. 1	Bu_2S	99
Ph_2S_2	1.6	$n\text{-}C_6H_{13}CH{=}CH_2$	ca. 5000
Bu_2S_2	2.5		

the reagent are its high reactivity allowing oxidation under very mild conditions and the ease of workup due to minimal side-products. The selectivity is quite good as indicated by the data in Table 1, which shows that sulphoxides and disulphides are 40–100 times less reactive than sulphides. Ozone cannot be used in the synthesis of unsaturated sulphoxides since carbon–carbon double bonds are much more reactive than sulphur. With certain substrates there are some troublesome side-reactions, as will be discussed below. There is interest in a practical aspect of the ozonation of sulphides, namely its application in the desulphurization of petroleum and petroleum products[120].

Scheme 2 summarizes the mechanism of ozonation of sulphides as proposed by Bailey[121], Razumovskii[120] and others. The initial intermediate **1** is reminiscent of the phosphite ozonide 4 first characterized by Thompson[122] and shown to oxidize sulphides[122] and disulphides[123] and to decompose to phosphate and singlet oxygen (equation 67)[124]. The formation of cation radicals by a one-electron oxidation process (step b) was established by ESR detection of the pink thianthrene cation radical in the ozonation of thianthrene (equation 68)[121]. Step (b′)[120] has precedence in the photosensitized oxidation of sulphides[125]. Steps (c) and (c′) are

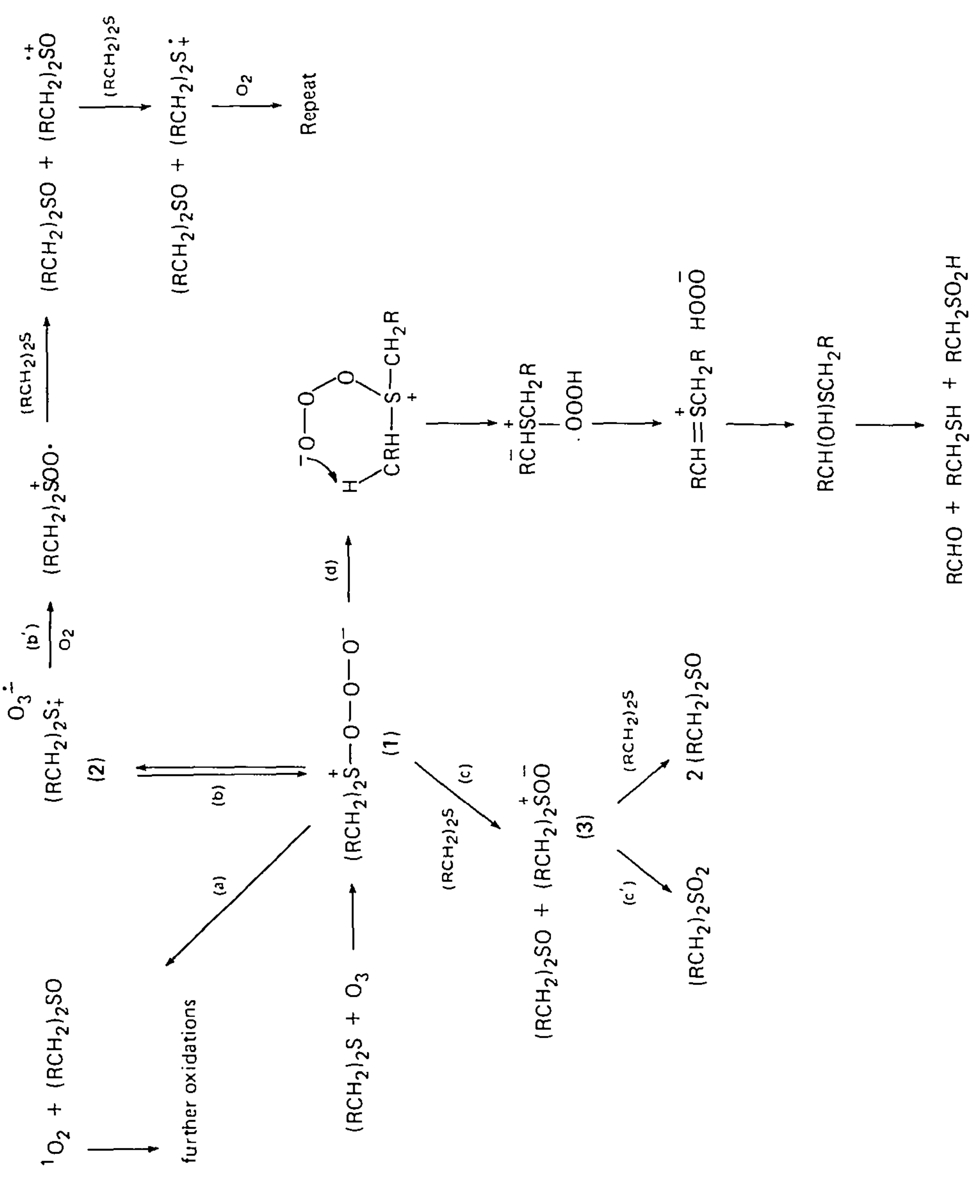


(67)



(68)

invoked in analogy to studies with singlet oxygen–sulphide reactions (see Section A16 below) to explain the formation of small amounts of sulphone simultaneously with sulphoxide directly from the intermediate products of reaction[120]. Step (d) is proposed[121] to account for benzaldehyde formation on ozonation of dibenzyl sulphide (equation 69a). Side-chain attack is apparently favoured by nonprotic solvents while sulphoxide formation is favoured by protic solvents (equation 69b)[121]. In the latter case the protic solvent may protonate the sulphide ozonide **1** and prevent the cyclodeprotonation process. An alternative route to benzaldehyde would involve singlet oxygen in the process proposed by Corey and Ouannès (see equation 73)[126].



$^1O_2$ + $(RCH_2)_2SO$
further oxidations
(a)
$(RCH_2)_2S$ + O_3
$(RCH_2)_2\overset{+}{S}—O—O—O^-$
(1)
$(RCH_2)_2S^{\cdot+}$ $O_3^{\cdot-}$
(2)
(b)
(b′)
O_2
$(RCH_2)_2\overset{+}{S}OO\cdot$
$(RCH_2)_2S$
$(RCH_2)_2SO$ + $(RCH_2)_2SO^{\cdot+}$
$(RCH_2)_2S$
$(RCH_2)_2SO$ + $(RCH_2)_2S^{\cdot+}$
O_2
Repeat
(c)
$(RCH_2)_2S$
$(RCH_2)_2SO$ + $(RCH_2)_2\overset{+}{S}O\overset{-}{O}$
(3)
(c′)
$(RCH_2)_2S$
$(RCH_2)_2SO_2$
$2\,(RCH_2)_2SO$
(d)
$\overset{-}{R}C\overset{+}{H}SCH_2R$ $\cdot OOOH$
$RCH{=}\overset{+}{S}CH_2R$ $HOO\overset{-}{O}$
$RCH(OH)SCH_2R$
RCHO + RCH_2SH + RCH_2SO_2H

SCHEME 2.

$$(\mathrm{PhCH_2})_2\mathrm{S} \xrightarrow[\text{pentane, 0°C}]{\mathrm{O_3}} \underset{76\%}{\mathrm{PhCHO}} + \underset{21\%}{(\mathrm{PhCH_2})_2\mathrm{SO}} \tag{69a}$$

$$(\mathrm{PhCH_2})_2\mathrm{S} \xrightarrow[\mathrm{CH_3OH},\ -40°\mathrm{C}]{\mathrm{O_3}} \underset{100\%}{(\mathrm{PhCH_2})_2\mathrm{SO}} \tag{69b}$$

16. Singlet oxygen

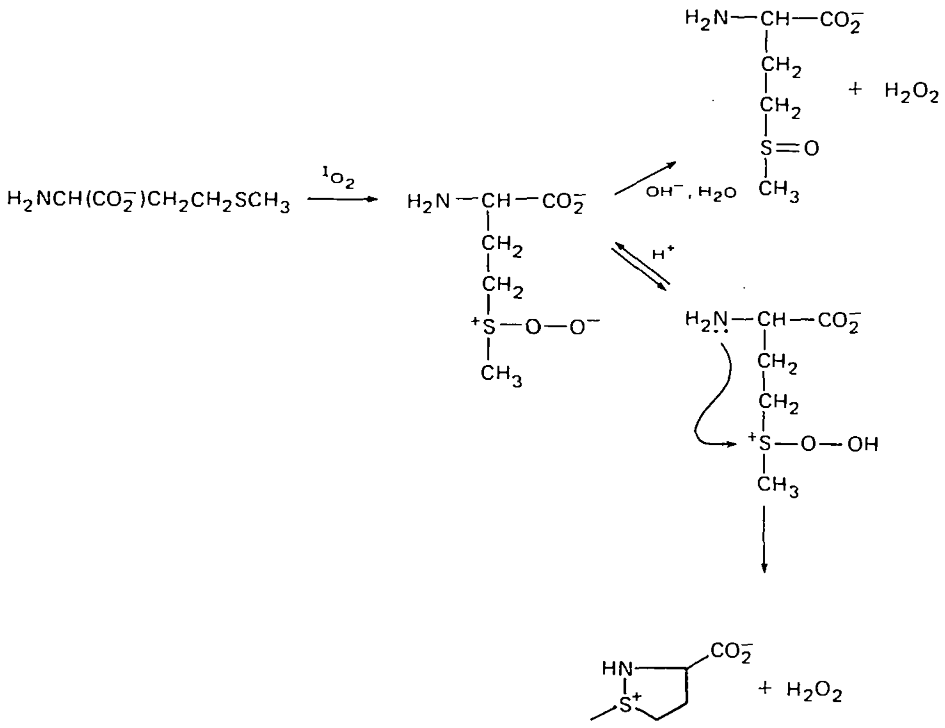
Sulphides are known to undergo photosensitized oxidation to their corresponding sulphoxides[127]. This oxidation, which has been found to be induced by singlet oxygen, is of particular interest because methionine is one of the amino acids which is attacked most rapidly in photodynamic action (the destructive action of dye sensitizers, light and oxygen on organisms)[128–130]. Other amino acids such as *S*-methylcysteine and lanthionine are also known to give sulphoxides on photooxygenation[131]. Since the photosensitized oxidation of disulphides has been shown to be quite facile (affording thiosulphinates as in equation 70)[123,132] it is

$$t\text{-BuSSBu-}t \xrightarrow[\text{senst.}]{h\nu,\ \mathrm{O_2}} t\text{-BuS(O)Bu-}t \tag{70}$$

likely that photodynamic action may also involve the disulphide bridges of natural polypeptides as well. Photooxidation can be used in the study of enzymes and other polypeptides. Thus Jori and coworkers have found protein elastase, which contains two methionine units (positions 41 and 172), to be unaffected under neutral pH photooxidation conditions 'owing to the location of the two methionyl side-chains in internal hydrophobic regions [where] there is a strong conformational screening of the interaction between them and the photooxidizing agent'[133]. At pH 3.5, methionine-172 undergoes photooxidation, presumably because at this pH the tertiary structure is loosened allowing access of the photooxidizing agent to the region containing this particular methionine. This monooxidized enzyme still displays practically 100% enzymic activity. At still higher pH values (2.5) both methionine-172 and -41 are oxidized and irreversible loss of enzymic activity occurs.

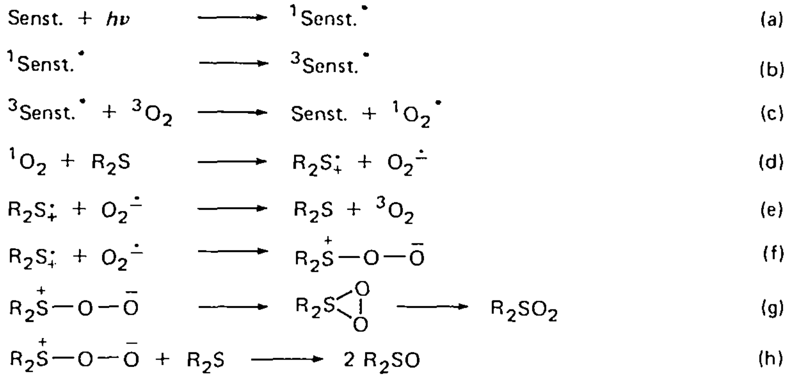
The formation of hydrogen peroxide and dehydromethionine in the photooxygenation of methionine has been rationalized in terms of respectively inter- and intramolecular displacement at sulphur in the intermediate persulphoxide (equation 71)[129].

As a result of substantial research, a general mechanism, summarized by equations (a)–(h) in Scheme 3, has emerged for the photosensitized oxidation of a sulphide[128,134–136]. We may indicate some of the experimental evidence supporting this mechanism. The dye-sensitized photooxidation of sulphides has been shown to involve singlet oxygen since it is competitively inhibited by singlet oxygen acceptors (diphenylanthracene) and quenchers (β-carotene). Electron-transfer step (d) is suggested by kinetic studies and by analogy to reactions of amines with singlet oxygen[137]. Subsequent interaction of the cation-radical–anion-radical pair leads either to quenching (equation e) or to formation of a zwitterionic persulphoxide (equation f). In ethanol the ratio of the rates for steps (e) and (f) for di-*n*-butyl sulphide has a value of about 0.7[136]. Earlier Foote concluded that no quenching occurs in methanol as solvent but that in benzene over 95% of the reactions of singlet oxygen lead to quenching and only a few percent lead to sulphoxide[128,135]. Further evidence for a zwitterionic persulphoxide comes from various studies


$H_2NCH(CO_2^-)CH_2CH_2SCH_3$
$^1O_2$
$H_2N-CH-CO_2^-$
CH_2
CH_2
$^+S-O-O^-$
CH_3
OH^-, H_2O
H^+
$S=O$
$+ H_2O_2$
$^+S-O-OH$
HN
S^+
CO_2^-
$+ H_2O_2$

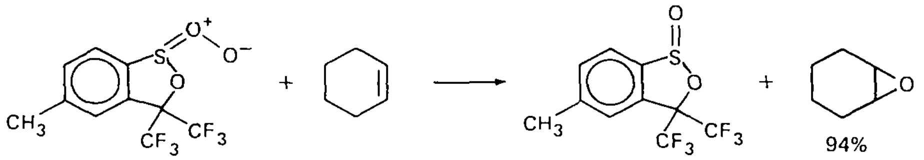
(71)

involving cooxidation of mixtures of sulphides, oxidation of certain bissulphides and activated sulphides, and studies of solvent effects. Foote has demonstrated that diphenyl sulphide reacts 2800 times slower than diethyl sulphide with singlet oxygen (diphenyl sulphide is only 1000 times less reactive than diethyl sulphide toward hydrogen peroxide) yet cophotooxidation of the two sulphides gives similar proportions of diphenyl and diethyl sulphoxides[128,135]. It is suggested that the oxidation of the normally unreactive diphenyl sulphide involves the persulphoxide as oxidizing agent (equation h). Recent studies by Martin indicate that the persulphoxide $Ph_2\overset{+}{S}OO^-$ is an electrophilic oxidant in its reaction with


$\text{Senst.} + h\nu \longrightarrow {}^1\text{Senst.}^\bullet$ (a)
${}^1\text{Senst.}^\bullet \longrightarrow {}^3\text{Senst.}^\bullet$ (b)
${}^3\text{Senst.}^\bullet + {}^3O_2 \longrightarrow \text{Senst.} + {}^1O_2^\bullet$ (c)
${}^1O_2 + R_2S \longrightarrow R_2S^{+\cdot} + O_2^{-\cdot}$ (d)
$R_2S^{+\cdot} + O_2^{-\cdot} \longrightarrow R_2S + {}^3O_2$ (e)
$R_2S^{+\cdot} + O_2^{-\cdot} \longrightarrow R_2\overset{+}{S}-O-\overset{-}{O}$ (f)
$R_2\overset{+}{S}-O-\overset{-}{O} \longrightarrow R_2S<\overset{O}{\underset{O}{|}} \longrightarrow R_2SO_2$ (g)
$R_2\overset{+}{S}-O-\overset{-}{O} + R_2S \longrightarrow 2\,R_2SO$ (h)

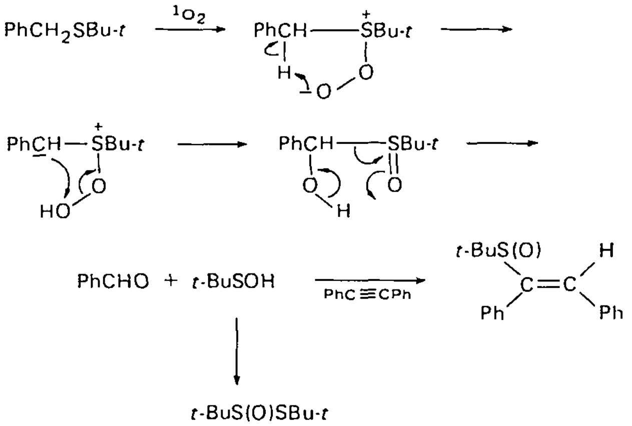
SCHEME 3.

diaryl sulphides with $\rho = -0.43$[138]. For comparison, the reaction of perbenzoic acid with diaryl sulphides gives $\rho = -2.5$[19] suggesting that there is more electrophilic character in oxidations involving perbenzoic acid than the persulphoxide. The persulphoxide $Ph_2\overset{+}{S}OO^-$ is incapable of expoxidizing cyclohexene; however a persulphoxide formally derived from a sultene has been found to be quite an effective oxidant (equation 72)[138].



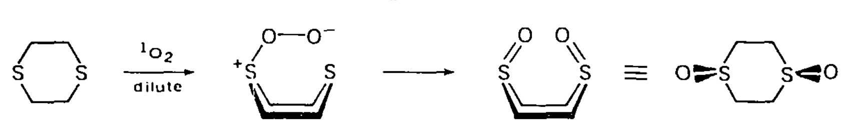
(72)

The persulphoxide has been assigned a zwitterionic rather than diradical or cyclic structure on the basis of the strong dependence of the quenching to oxidation ratio as a function of protic solvent. The protic solvent has been suggested to decrease the negative charge density on the zwitterion, thus promoting nucleophilic attack by a second sulphide to form two moles of sulphoxide[128,135]. In some cases the persulphoxide is postulated to act as a base as in equation (73)[126], to react intramolecularly in the case of bissulphoxides as in equation (74) and (75)[128,135], or to afford sulphone, as in equation (76)[128,135]. The latter process may involve a



(73)

[Other products: $PhCH_2S(O)Bu$-t + $PhCH_2SO_2Bu$-t]



(74)

$$CH_3S(CH_2)_nSCH_3 \xrightarrow[O_2,\ C_6H_6]{h\nu,\ \text{senst.}} CH_3S(O)(CH_2)_nS(O)CH_3 \qquad (75)$$

$$n = 2 \text{ or } 3$$

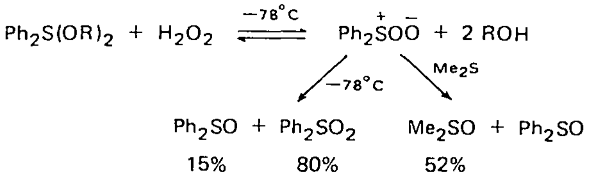
$$Et_2S \xrightarrow[O_2,\ Me_2O]{h\nu,\ \text{senst.},\ -78^\circ C} Et_2SO + Et_2SO_2 \qquad (76)$$

$$1 : 2.3$$

cyclic persulphoxide as shown in Scheme 3, equation (g). It was shown that sulphoxides are not oxidized to sulphones under the photooxidation conditions so that direct formation of sulphone at low conversion of sulphide is thought to provide further evidence for the presence of an intermediate containing two oxygens[128,135].

Unusually stable persulphoxides are thought to be formed from singlet oxygen and allyl sulphides[139]. While these persulphoxides do not apparently give rise to the corresponding allyl sulphoxides, they do transfer oxygen effectively to other sulphides. Thus, the yields of sulphoxides from sulphides such as thioanisole are doubled when reactions involving photochemically or thermally generated singlet oxygen are conducted in the presence of these allyl sulphides.

Martin has discovered a new route to persulphoxides via reaction of alkoxysulphuranes with hydrogen peroxide[138]. At −78°C the persulphoxide rearranges efficiently to sulphone or converts dimethyl sulphide to dimethyl sulphoxide (equation 77).



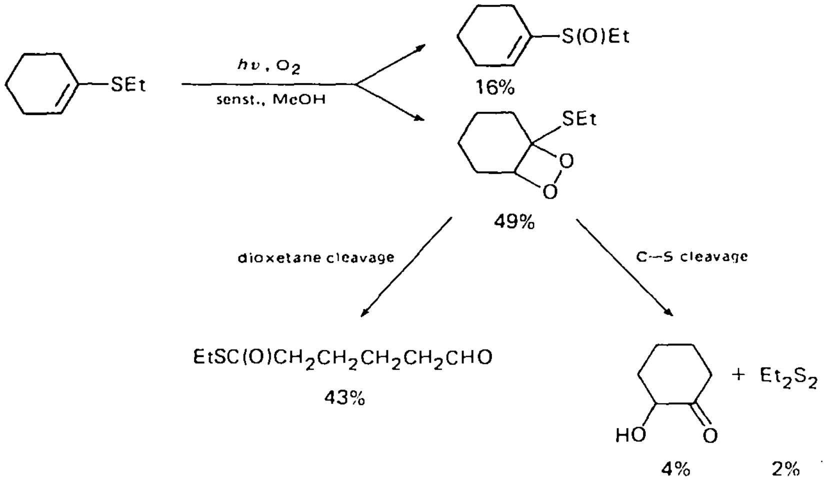
$$\mathrm{Ph_2S(OR)_2 + H_2O_2 \xrightleftharpoons{-78^\circ C} Ph_2\overset{+}{S}O\overset{-}{O} + 2\,ROH}$$

$$\mathrm{Ph_2\overset{+}{S}O\overset{-}{O} \xrightarrow{-78^\circ C} \underset{15\%}{Ph_2SO} + \underset{80\%}{Ph_2SO_2}} \qquad \mathrm{Ph_2\overset{+}{S}O\overset{-}{O} \xrightarrow{Me_2S} \underset{52\%}{Me_2SO} + Ph_2SO}$$

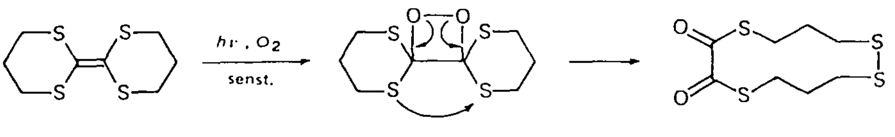
(77)

Vinyl sulphides, upon sensitized photooxidation, can undergo attack at both sulphur and at the double bond. From the published examples, attack at the carbon–carbon double bond seems to be significantly more favourable (see equations 78–80)[140–142]. Thiophenes and thiazoles also undergo reaction with singlet oxygen as will be discussed in Section II.K.

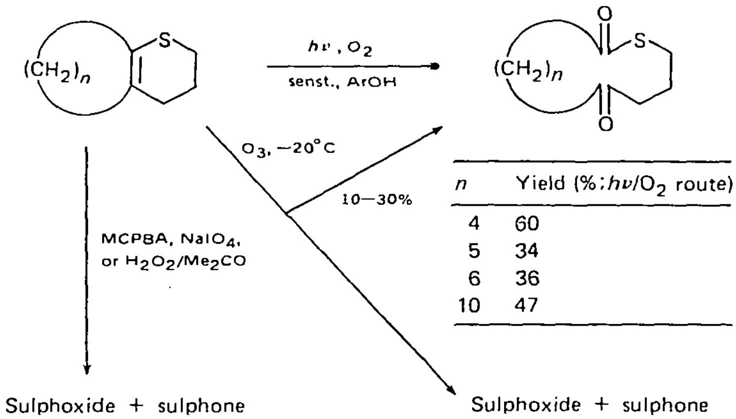
In some related singlet oxygen studies which might be regarded as intermolecular versions of the reactions in equations (78)–(80), Wasserman finds that 1,2-dioxetanes and carbonyl oxides formed by dye-sensitized photooxidation convert diphenyl sulphide to diphenyl sulphoxide[143].



(78)



(79)

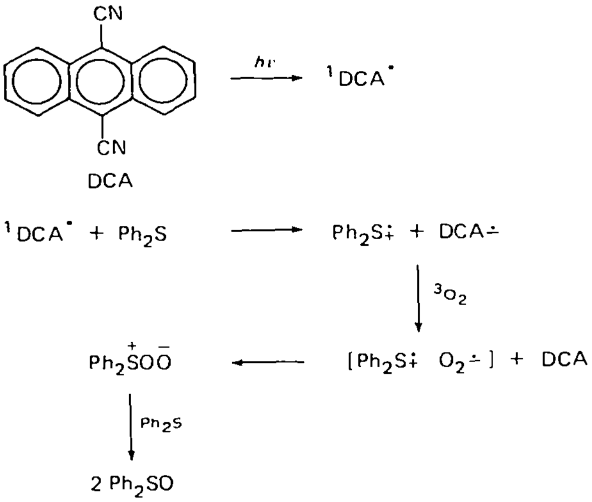


hν, O₂
senst., ArOH
O₃, −20°C
10—30%
MCPBA, NaIO₄, or H₂O₂/Me₂CO
(CH₂)ₙ
S
O
Sulphoxide + sulphone
Sulphoxide + sulphone

n	Yield (%: hν/O₂ route)
4	60
5	34
6	36
10	47

(80)

Recent research indicates that sensitized or nonsensitized photoxidation of sulphides can also occur via nonsinglet oxygen mechanisms. For example, Foote has observed that in 9,10-dicyanoanthracene-sensitized photooxidation, diphenyl sulphide is three times as reactive as diethyl sulphide (in striking contrast to the order of reactivity seen with other sensitizers) and that the photooxidation is not quenched by β carotene (an effective singlet oxygen quencher)[125]. Foote invokes cation and anion radicals intermediates in this oxidation, as indicated in Scheme 4. Direct irradiation of the sulphide—oxygen charge-transfer band (λ_{max} = 300—350 nm) in the absence of sensitizers can also lead to sulphoxide formation possibly by a process involving sulphide cation radicals and the superoxide anion, $O_2^{\dot{-}}$ (equation 81)[144]. Such unsensitized photoxidation of sulphides can even occur in the solid state[145a]. Finally, *even in the absence of oxygen*, certain sensitizers (acetone, biacetyl, cyclohexanone, acetophenone, 3-pentanone) can also function upon photoexcitation as oxidants for sulphides[145b].



CN
CN
DCA
hν
¹DCA*
¹DCA* + Ph₂S
Ph₂S⁺· + DCA⁻·
³O₂
Ph₂S⁺OO⁻
[Ph₂S⁺· O₂⁻·] + DCA
Ph₂S
2 Ph₂SO

SCHEME 4.

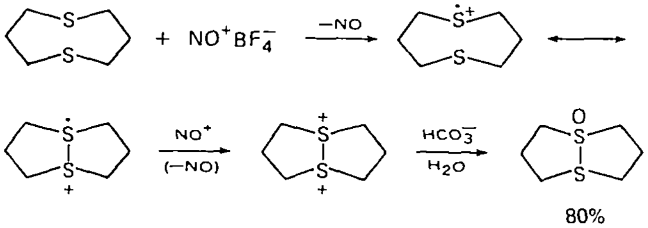
$$\mathrm{Ph_2S} + {}^{3}\mathrm{O_2} \longrightarrow [\mathrm{Ph_2S}\cdots\mathrm{O_2}] \xrightarrow[\text{5 h, MeOH}]{h\nu}$$

$$\lambda_{\max} = \text{ca. 350 nm}$$

$$[\mathrm{Ph_2S}\cdots\mathrm{O_2}]^{*} \longrightarrow [\mathrm{Ph_2S}^{\dot{+}}\ \mathrm{O_2}^{\dot{-}}] \longrightarrow \ \longrightarrow \mathrm{Ph_2SO}\ (17\%) \qquad (81)$$

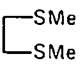
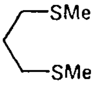
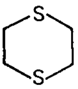
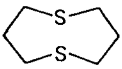
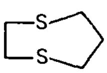
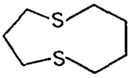
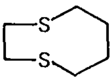
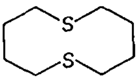
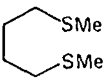
17. One-electron oxidations

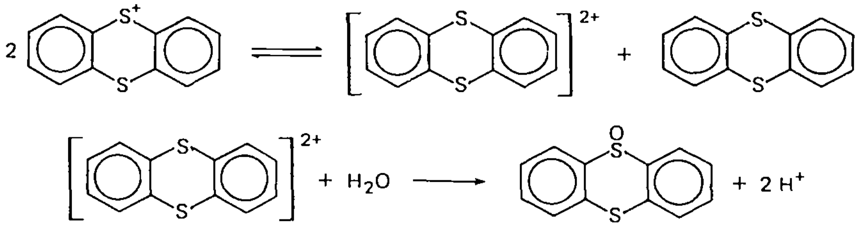
The majority of the oxidations of sulphides to sulphoxides with oxygen transfer agents (H_2O_2 MCPBA, $NaIO_4$, etc.) which we have considered involve a one-step two-electron process at sulphur. Sulphoxides also result from certain reactions which involve successive one-electron steps at sulphur, such as the conversion of acyclic and cyclic bissulphides to long-lived cation radicals and dications followed by hydrolysis of the latter which aqueous bicarbonate affording bissulphide *S*-monoxides in high yield (equation 82 and Table 2)[146]. Dications may also be involved in the reaction of the thianthrene cation radical with water to give equal amounts of thianthrene and thianthrene *S*-oxide (equation 83)[147]. The cation radicals may be formed by one-electron oxidation of sulphides with such agents as NO^+, con-



(82)

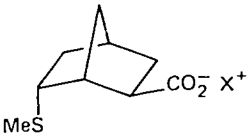
TABLE 2. Monosulphoxides from bissulphide dications[146]

Bissulphide	Yield of sulphoxide (%)	Bissulphide	Yield of sulphoxide (%)
	71		84
	60		80
	74		70
	72		85
			70

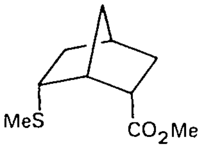


(83)

centrated H_2SO_4, $AlCl_3$, $SbCl_5$, Ti (III)–H_2O_2, $Tl(NO_3)_3$, or by electrochemical (anodic) oxidation[148,149]. The detailed mechanism of anodic oxidation of sulphides is unknown at present but it is known that electron transfer is facilitated by neighbouring lone-pair donors such as thioether, carboxylate and amino groups. Thus Glass and coworkers find the oxidation potential of *endo, endo*-sulphide **5** to be substantially lower than those of *endo, exo* compound **6** or ester **7** (0.65 V

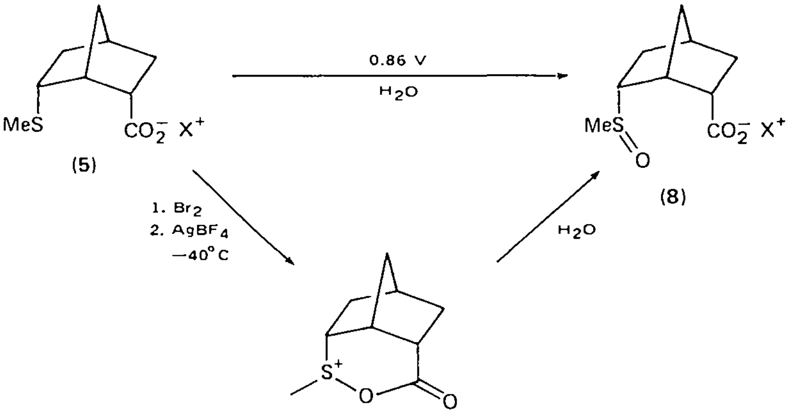


(6)



(7)

vs. 1.28 V and 1.21 V, respectively) in which electron transfer is unfavourable[150]. Electrolysis of **5** in water at a potential of 0.86 V affords a 78% yield of sulphoxide **8**, which sulphoxide also results from hydrolysis of sulphonium salt **9** (equation 84). It has not been established whether sulphonium salt **9** is actually an intermediate in the electrochemical oxidation of **5** in water[150].



(84)

(9)

In a process that may be considered to involve some form of intermolecular assistance in electron transfer at sulphur, it has been found that anodic oxidation of sulphides with chirally modified electrodes leads to optically active sulphoxides albeit in low optical yield[151,324].

The oxidation of methionine and other amino sulphides to sulphoxides by the Mn^{+2}-sulphite–O_2 system is also postulated to involve a sequence of one-electron oxidation steps as summarized in Scheme 5[152]. The extent of sulphoxide formation with a number of methionine analogues under identical conditions is summarized in

$$Mn^{+2} + O_2 \longrightarrow Mn^{+3} + O_2^{\cdot -} \qquad (a)$$

$$Mn^{+3} + SO_3^{-2} + H^+ \longrightarrow Mn^{+2} + HSO_3^{\cdot} \qquad (b)$$

$$SO_3^{-2} + O_2^{\cdot -} + 3H^+ \longrightarrow HSO_3^{\cdot} + 2\,HO^{\cdot} \qquad (c)$$

$$HSO_3^{\cdot} + O_2 \longrightarrow SO_3 + O_2^{\cdot -} + H^+ \qquad (d)$$

$$HSO_3^{\cdot} + HO^{\cdot} \longrightarrow SO_3 + H_2O \qquad (e)$$

$$2\,HSO_3^{\cdot} \longrightarrow SO_3 + SO_3^{-2} + 2H^+ \qquad (f)$$

$$SO_3 + H_2O \longrightarrow SO_4^{-2} + 2\,H^+ \qquad (g)$$

$$R_2S + O_2^{\cdot -} + 2\,H^+\ (\text{or } HO^{\cdot}) \longrightarrow R_2S^{\cdot +} + 2\,HO^{\cdot}\ (\text{or } OH^-) \qquad (h)$$

$$R_2S^{\cdot +} + HO^{\cdot} \longrightarrow R_2\overset{+}{S}{-}OH \longrightarrow R_2SO + H^+ \qquad (i)$$

$$R_2S^{\cdot +} + O_2^{\cdot -} \longrightarrow R_2\overset{+}{S}{-}O{-}\bar{O} \qquad (j)$$

$$R_2\overset{+}{S}O\overset{-}{O} + R_2S \longrightarrow 2\,R_2SO \qquad (k)$$

Overall reaction :

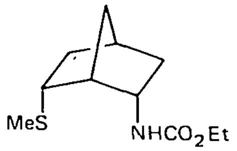
$$R_2S + 2\,SO_3^{-2} + \frac{3}{2}\,O_2 \xrightarrow{Mn^{+2}} R_2SO + 2\,SO_4^{-2} \qquad (l)$$

SCHEME 5.

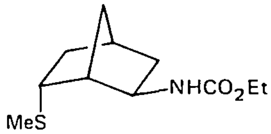
Table 3[152]. The data suggests that a γ-amino function is essential for efficient oxidation. The observation of Glass and coworkers[150] that di-*endo* bicyclic γ-amino sulphide **10** is oxidized electrochemically at a lower potential than *exo,endo*-amino sulphide **11** (0.98 V for **10** vs. 1.20 V for **11**) is also consistent with facilitation of sulphide oxidation by a suitably disposed neighbouring nitrogen, perhaps through a five-membered intermediate of type **12**[153] analogous to the intermediates from 1,5-bissulphides (see equation 82). Dehydromethionine **13** which has been identified as the product of anodic oxidation of methionine[154] and a by-product of the photooxidation of methionine[129], and which is easily hydrolysed to the sulphoxide in buffered solution[129], is a likely intermediate in the Mn^{+2}-sulphite–O_2 oxidation of methionine. It has been suggested that free-radical mechanisms of the type postulated for the Mn^{+2}-sulphite–O_2 oxidation may be responsible for the biological formation of sulphoxide *in vivo*[152], the subject of the next section of this chapter.

TABLE 3. Sulphoxide formation from various methionine analogues

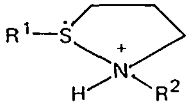
Substrate	Sulphoxide formation (%)
$CH_3SCH_2CH_2CH(NH_2)COOH$	80
$C_2H_5SCH_2CH_2CH(NH_2)COOH$	79
$CH_3SCH_2CH_2CH_2NH_2$	80
$CH_3SCH_2CH_2C(O)COOH$	0
$CH_3SCH_2CH_2CH(NHAc)COOH$	8
$CH_3SCH_2CH(NH_2)COOH$	2
$CH_3SCH_2CH_2COOH$	8


MeS
NHCO2Et

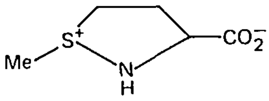
(10)


NHCO2Et
MeS

(11)



(12)



(13)

18. In vivo *oxidations*

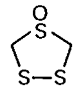
Studies on biological oxidations–reductions of sulphides are essential to gain an understanding of the metabolism of sulphur-containing L-amino acids, certain vitamins and drugs, solvents and even some toxic compounds. Various interesting naturally occurring sulphoxides such as **14**–**16**, compounds found in onions,

$CH_3CH{=}CHS(O)CH_2CH(NH_2)COOH$

(14)

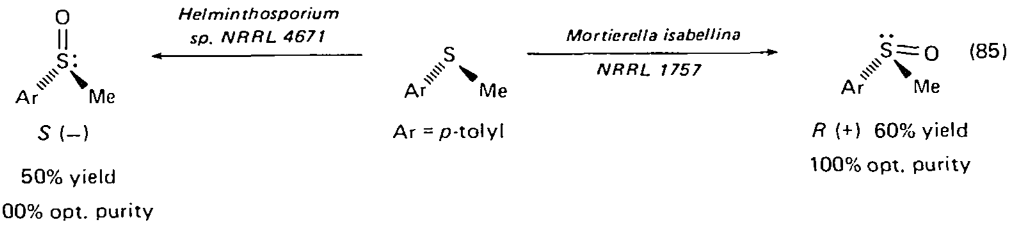
$CH_3S(O)CH{=}CHCH_2CH_2NCS$

(15)



(16)

radishes and the algae *Chondria californica*[149] respectively, are undoubtedly formed by *in vivo* oxidation of the respective sulphides. For example *S*-*n*-propyl-L-cysteine and various α-alkylthio- and α-arylthio-carboxylic acids are oxidized to the corresponding sulphoxides by microsomal fractions from rat liver homogenates[155,156]. Biotin, steroidal methylthioethers, the sulphur-containing antibiotics lincomycin and clindamycin, and various simple sulphides can be converted to their respective sulphoxides, often with high stereoselectivity, by microbiological oxidation using growing cultures or acetone powders (crude enzyme preparations)[157,158]. Unfortunately the yields of sulphoxides are often low in comparison to yields realized by chemical oxidations. In the best cases yields as high as 60% have been realized with 100% optical purity of either enantiomer being obtained depending on the choice of microorganism (equation 85)[159]. Bacterial luciferase will


O
S:
Ar
Me
S (−)
50% yield
100% opt. purity
Helminthosporium sp. NRRL 4671
S
Ar
Me
Ar = *p*-tolyl
Mortierella isabellina
NRRL 1757
S=O
Ar
Me
R (+) 60% yield
100% opt. purity

(85)

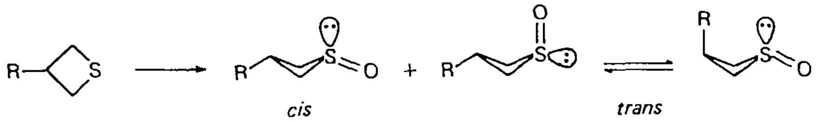
also convert certain dialkyl sulphides to sulphoxides in the presence of oxygen[160]. The stereoselectivity in the aerobic, microbial oxidation of sulphides and sulphoxides is dependent both on the species and the strain; substantial differences are even sometimes seen in results with different specimens of the same strain (subcultured in different locations)[161]. Other factors that effect the optical yield include the extent of preferential oxidation of one enantiomer of sulphoxide to sulphone (kinetic resolution) and preferential reduction of one sulphoxide enantiomer[161,325].

19. Polymer-supported oxidants

A novel solution to the problem of separation of oxidant and its reduction product from sulphoxide involves the use of insoluble polymeric oxidizing agents such as polymeric peracid and *N*-chloronylon 66. In the case of polymeric peracid, prepared from copolymers of styrene and 1–2% *p*-divinylbenzene, the sulphide in an appropriate solvent is treated with a suspension of the peracid or passed down a column of the peracid resin. The resin can be reactivated through treatment with 85% hydrogen peroxide and methanesulphonic acid. This oxidation procedure has been used to synthesize pencillin sulphoxides[162]. The stereoselectivity of oxidation is the same as that seen with the monomeric peracid. The *N*-chloronylon 66 reagent (NCN-66), prepared through action of *t*-butyl hypochlorite on nylon 66, gives good yields of sulphoxides, can be used to prepare ^{18}O-labelled sulphoxides and with optically active alcohols gives optically active sulphoxides, albiet in low (ca. 1%) optical yield[163,164].

B. Stereochemistry of Oxidation of Cyclic Sulphides: Comparative Studies with Different Oxidants

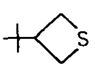
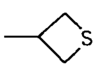
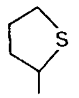
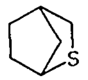
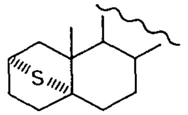
The stereoselectivity of the oxidation of a variety of thietane, thiolan and thiane derivatives with various oxidizing agents has been carefully examined by several research groups. It is generally assumed that oxidation of cyclic sulphides to their oxides by peroxy reagents (e.g. MCPBA, *t*-BuOOH, H_2O_2) proceeds preferentially on the sterically less hindered side of the sulphur atom, that oxidation with sodium metaperiodate generally provides the thermodynamically more stable sulphoxide as the major product and that oxidation with *t*-butyl hyprochlorite leads to a predominance of the more hindered sulphoxide[165]. Dinitrogen tetroxide is known to be capable of equilibrating sulphoxides although the sulphoxide mixture formed may not represent the true thermodynamic equilibrium composition because association between the sulphoxide and N_2O_4 is also involved[166]. Sulphoxides can also be equilibrated by treatment with hydrogen chloride in dioxane[167]. Table 4 summarizes much of this work on the stereoselectivity of oxidation of cyclic sulphides. 3-Substituted thietane *S*-oxides are known to be more stable in the *cis* than the *trans* configuration (equation 86)[116]. The stereoselectivity of the oxidation of 3-alkylthietanes as indicated in Table 4 is found to



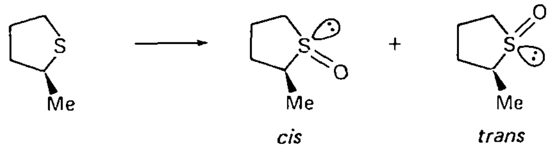
(86)

be less sensitive to the nature of the oxidant than with larger ring systems. The ratio of *cis*- to *trans*-1-oxide is greatest (3 : 1 to 4.6 : 1) with dinitrogen tetroxide as oxidant, and least (1 : 2) when *N*-chlorotriazole is used. *cis*-2-Methylthiolan *S*-oxide is more stable than the *trans* isomer (equation 87)[115]; similarly *cis*-4-substituted thiane *S*-oxides (oxygen axial) are found to be more stable than the *trans* sulphoxides (equation 88)[113]. *Exo*-2-thiabicyclo[2.2.1]heptane 2-oxide

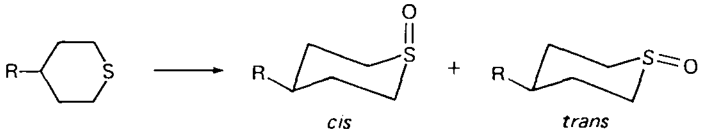
TABLE 4. Comparative stereoselectivity of oxidation of cyclic sulphides

Oxidant					
	cis : *trans*	*cis* : *trans*	*cis* : *trans*	*endo* : *exo*	*syn* : *anti*
t-BuOCl, ROH, – 70°C	59:41(0°C)	55:45(0°C)	65:35 (6:94)[f]	65:35	98.4:1.6[e]
N_2O_4, 0°C	82:18	75:25	62:38	18:82	8.4:91.6
$NaIO_4$, 0°C	51:49	59:41	43:57	24:76	1.4:98.6
H_2O_2, Me_2CO	43:57	46:54	56:44	15:85	2.3:97.7
MCPBA, CH_2Cl_2	45:55	45:55	54:46 (30:70)[b]	23:77	1.5:98.5[e]
CrO_3, py, 25°C	70:30	54:46	16:84	12:88	2.3:97.7[e]
HNO_3, Ac_2O, 0°C	Sulphone	Sulphone	–	25:75	–
PhIO, C_6H_6, 80°C	–	–	58:38	16:84	5.3:94.7
$PhICl_2$,py/H_2O	–	–	26:74	–	–
t-BuOOH, C_6H_6, 50°C	–	–	–	14:86	2.9:97.1[e]
t-BuOOH, MeOH, 50°C	–	–	–	11:89	–
H_2O_2, HOAc	43:57	46:54	–	18:82	–
O_3, CH_2Cl_2	–	41:59	23:77	8:92	–
Other	–	33:67[c]	–	–	–
Reference	116	116	115	114	91, 168

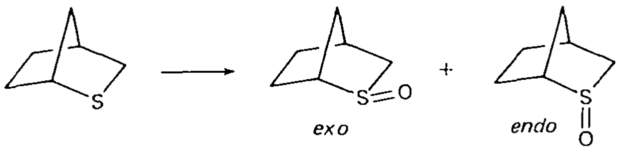
[a] In pyridine, 20°C. [b] In H_2O–dioxane, pH 12.0. [c] N-chlorotriazole, MeOH, – 78°C. [d] DABCO·2 Br_2, HOAc/H_2O. [e] Yield 80–100%. [f] *i*-PrOCl, CH_2Cl_2 – 78°C.



(87)

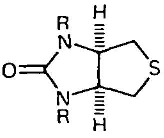
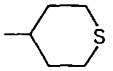
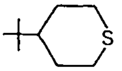
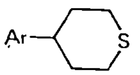
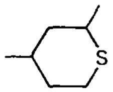
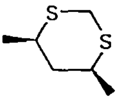


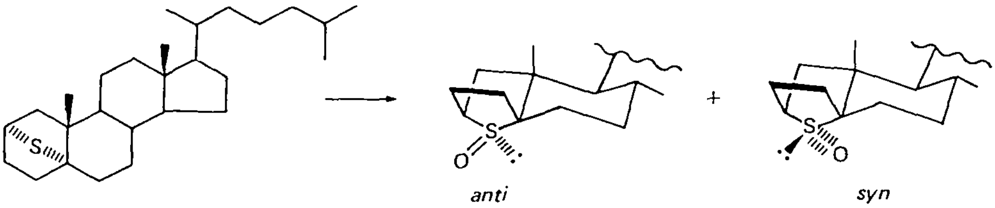
(88)



(89)

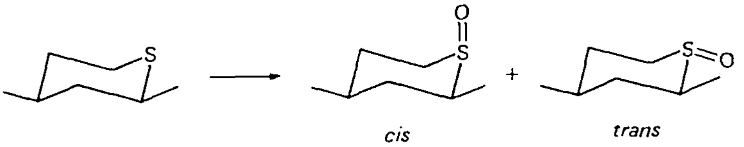
is more stable than the *endo* isomer (equation 89)[114] while in the ring-fused 7-thiabicyclo[2.2.1]heptane 7-oxide system the *anti* isomer is favoured over the *syn* (the equilibrium mixture is 92% *anti*, 8% *syn*; equation 90)[91,168]. Oxidation

					
cis : *trans*	*cis* : *trans*	*cis* : *trans*	*cis* : *trans*	axial O : eg. O	axial O : eg. O
–	89:11	100:0	98:2	63:37	4:96
–	76:24	81:19	81:19	74:26	43:57
90:10^{e}	72:28	75:25	76:24	57:43	13:87
–	40:60	37:63	30:70	32:68	2:98
85:15^{e}	30:70	36:64	33:67	–	–
–	–	27:73	–	–	–
–	–	67:33	–	–	–
–	49:51	46:54	51:49	–	–
			(17:83)^{a,e}		
55:45^{e}	–	–	5:95(−40°C)^{e}	–	–
–	35:65	36:64	35:65	–	–
–	32:68	27:73	–	–	–
80:20^{e}	–	35:65	–	–	–
90:10^{e}	15:85	10:90	16:84	–	–
–	–	–	14:86^{d,e}	–	–
117	113	113	113, 56	166	166



(90)

of 2-methylthiolane, while more selective than the 3-alkylthietanes, is less stereoselective than the bicyclic thiolans and the thianes, and shows some unusual patterns, e.g. both MCPBA and *t*-butyl hypchlorite gave mainly *cis*-2-methylthiolan 1-oxide while MCPBA in aqueous dioxane at pH 12 and isopropyl hypochlorite both gave predominantly *trans*-2-methylthiolane 1-oxide. 2,4-Dimethylthiane gives predominantly the *cis*-1-oxide with *t*-butyl hypochlorite, dinitrogen tetraoxide as well as sodium metaperiodate (in the latter case only by a slight margin), while hydrogen peroxide favours the *trans*-1-oxide (equation 91)[166]. In the case of 4,6-

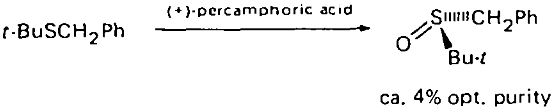


(91)

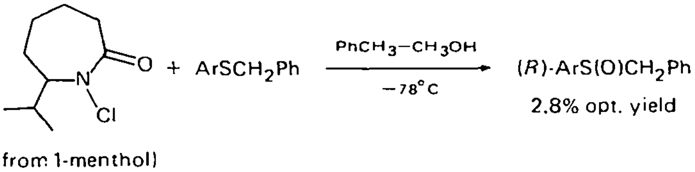
dimethyl-1,3-dithiane all oxidants tried favour the trans-1-oxide. While the course of oxidation of most of the other sulphides in the table follow the general trends on stereoselectivity enunciated at the beginning of this section, these common assumptions are clearly not universally valid and their use for assignment of configuration to cyclic sulphoxides is risky.

C. Asymmetric Oxidation

We have alread noted in Section II.A.18 that *in vivo* oxidation of sulphides with growing cultures or enzyme extracts can lead to optically active sulphoxides of high optical purity. Asymmetric oxidation of achiral sulphides can also be achieved with such reagents as (+)-monopercamphoric acid (equation 92)[169] and related chiral peracids[158], the chiral *N*-chlorocaprolactam (derived from (−)-menthol) indicated in equation (93)[170], chirally chemically modified electrodes[151], and with achiral oxidants in the presence of chiral solvents such as (−)-menthol (equations 94[171],


t-BuSCH₂Ph
(+)-percamphoric acid
S
CH₂Ph
O
Bu-t
ca. 4% opt. purity

(92)


O
N
Cl
(from l-menthol)
+ ArSCH₂Ph
PhCH₃—CH₃OH
−78°C
(R)-ArS(O)CH₂Ph
2.8% opt. yield

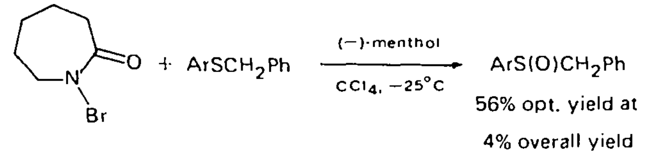
(93)

Ar = *p*-tolyl

$$\mathrm{Ar^1SAr^2} + t\text{-}\mathrm{BuOCl} \xrightarrow[\substack{\text{pyridine—CH}_3\text{CN}\\ -25^\circ\text{C}}]{(-)\text{-menthol}} \underset{\substack{85\%\ \text{yield}\\ 26\%\ \text{opt. yield}}}{(R)\text{-}\mathrm{Ar^1S(O)Ar^2}} \tag{94}$$

$\mathrm{Ar^1} = p$-tolyl

$\mathrm{Ar^2} = o\text{-}\mathrm{CH_3OC_6H_4}$


O
N
Br
+ ArSCH₂Ph
(−)-menthol
CCl₄, −25°C
ArS(O)CH₂Ph
56% opt. yield at
4% overall yield

(95)

Ar = *p*-tolyl

$$t\text{-}\mathrm{BuOOH} + \mathrm{ArSMe} \xrightarrow[\mathrm{VO(acac)_2,\ C_6H_6{-}C_6H_5CH_3}]{(-)\text{-menthol}} \underset{9.8\%\ \text{enant. excess}}{(R)\text{-}(+)\text{-}\mathrm{ArS(O)Me}} \tag{96}$$

Ar = *p*-tolyl

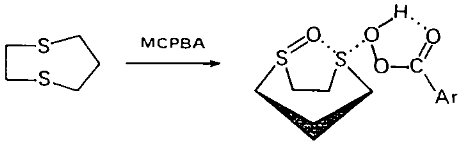
$$\mathrm{PhCH_2SMe} + \mathrm{I_2} + \underset{(S)\text{-}(+)}{{}^{-}\mathrm{O_2CCH_2\dot{C}HPhCO_2^-}} \longrightarrow \underset{6.4\%\ \text{enant. excess}}{(R)\text{-}(+)\text{-}\mathrm{PhCH_2S(O)Me}} \tag{97}$$

95[172] and 96[40,173]) or the chiral 2-phenylsuccinate buffer employed in equation (97)[174]. For a general discussion of transition-state models for asymmetric oxidation of sulphur in various sulphides the reader is referred to the excellent review of Morrison and Mosher[158].

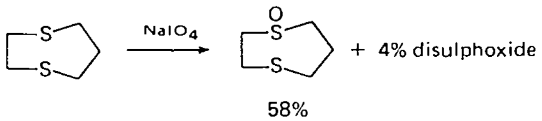
D. Selective Oxidations of Dithioethers

With compounds containing two (or possibly more) isolated sulphide groups there are problems associated with the preparation of pure monosulphoxide uncontaminated with one or both isomeric disulphoxides and sulphone, which undesired compounds would pose difficult separation problems. On other occasions pure monosulphone or bissulphoxide must be synthesized. This section will deal with aspects of the oxidation of dithioethers.

While early attempts to prepare the monosulphoxide of 1,4-dithiane led only to monosulphone and recovered dithiane[175], success in this effort was realized a few years later by Bell and Bennett who prepared both the monosulphoxide and the two ('α and β') bissulphoxides of 1,4-dithiane[176] using hydrogen peroxide. Attempts to oxidize the homologue of 1,4-dithiane, 1,4-dithiacycloheptane, with MCPBA gave rise to about 25% disulphoxide and unreacted starting material but very little monosulphoxide[22]. The authors conclude that 1,4-dithiacycloheptane 1-oxide is oxidized more rapidly than the dithio ether itself perhaps by the process shown in equation (98) where the alignment of the S—O dipole with the forming S—O dipole favours disulphoxide formation. A more satisfactory means of preparing 1,4-dithiacycloheptane 1-oxide involves use of sodium metaperiodate (equation 99); the method of choice involves sequential one-electron oxidations (see Table 2, Section II.A.17). 1,3-Dithianes are readily converted to their monosulphoxides with a variety of oxidants[49,177,178]. 2-Monosubstituted 1,3-dithianes preferentially form the *trans*(oxygen equatorial)-monosulphoxide[49,177] with either MCPBA or $NaIO_4$. Sodium metaperiodate is apparently not effective in oxidizing 3,5-dithiaheptane to its monosulphoxide (contrary to original claims) and MCPBA is recommended instead[179a]. Selective oxidation of an allylic thiophenyl group in the presence of a vinylic thiophenyl group can be accomplished in good yield with MCPBA[179b].

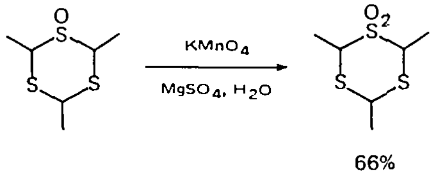


(98)

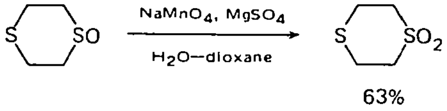


(99)

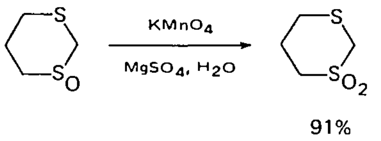
The selective oxidation of a dithioether monosulphoxide to a dithioether monosulphone was first accomplished using $KMnO_4/MgSO_4$ in 1930[180] (equation 100). Since then this procedure has proven successful in a number of other cases (equations 101[181], 102[182], 103[183]). Other oxidants which can be used for the selective oxidation of a sulphoxide in the presence of a sulphide group include OsO_4[181] $IrHCl_2$ and $RhCl_3 \cdot nH_2O{-}HCl$[184]. Potassium permanganate in acetone will also oxidize a thioacetal directly to the thioacetal *S,S*-dioxide(equation 104)[185].


KMnO4
MgSO4, H2O
66%

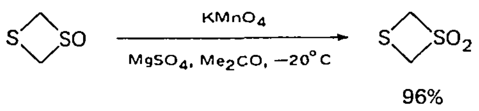
(100)


NaMnO4, MgSO4
H2O—dioxane
63%

(101)


KMnO4
MgSO4, H2O
91%

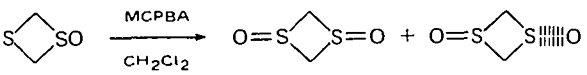
(102)


KMnO4
MgSO4, Me2CO, −20°C
96%

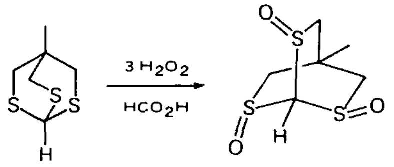
(103)

$$\mathrm{Me_2C(SMe)_2} \xrightarrow[\mathrm{Me_2CO,\ 0^\circ C,\ 8\ days}]{\mathrm{KMnO_4}} \underset{80\%}{\mathrm{Me_2C(SMe)(SO_2Me)}} \qquad (104)$$

Treatment of a dithioether monosulphoxide with MCPBA leads to the formation of a mixture of disulphoxides (equation 105)[183]. Oxidation of 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane with 3 moles of hydrogen peroxide in formic acid leads to a mixture of products including the 'propeller' trissulphoxide shown in equation (106)[186].


MCPBA
CH2Cl2

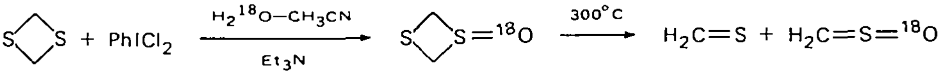
(105)


3 H2O2
HCO2H

(106)

E. Oxidative Methods for the Preparation of ^{18}O-Sulphoxides

In connection with mechanistic and structural studies involving sulphoxides or sulphoxide-derived compounds it is often necessary to prepare the ^{18}O-labelled sulphoxide. For example microwave structural studies on the short-lived molecules sulphine (equation 107)[183] and methanesulphenic acid (equation 108)[187] required the preparation of ^{18}O-labelled sulphoxide precursors. Among the various procedures


H2 18O—CH3CN
Et3N
300°C

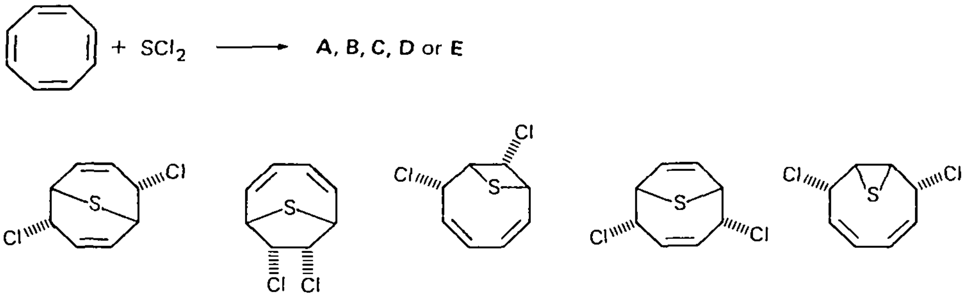
(107)

$$\text{MeSBu-}t + \text{PhICl}_2 \xrightarrow[\text{Et}_3\text{N}]{\text{H}_2{}^{18}\text{O}-\text{CH}_3\text{CN}} \text{MeS}(^{18}\text{O})\text{Bu-}t \xrightarrow{250°\text{C}} \text{CH}_3\text{S}-{}^{18}\text{O}-\text{H} + \text{C}_4\text{H}_8 \qquad (108)$$

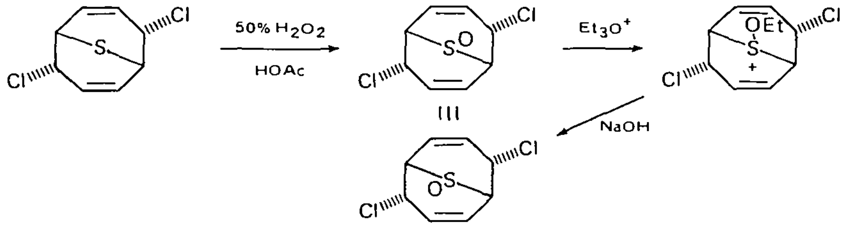
used to prepare ^{18}O-labelled sulphoxides are those involving ^{18}O-labelled water together with iodobenzene dichloride (see equations 107 and 108)[56], silica gel–sulphuryl chloride[188], bromine–DABCO[75], *N*-bromosuccinimide[78] and *N*-chloronylon 66[163]. In special circumstances ^{18}O-methanol can also be used (in conjunction with *t*-butyl hypochlorite)[91].

F. Oxidation to Sulphoxide as Proof of Structure for Sulphide; Rearrangement on Oxidation

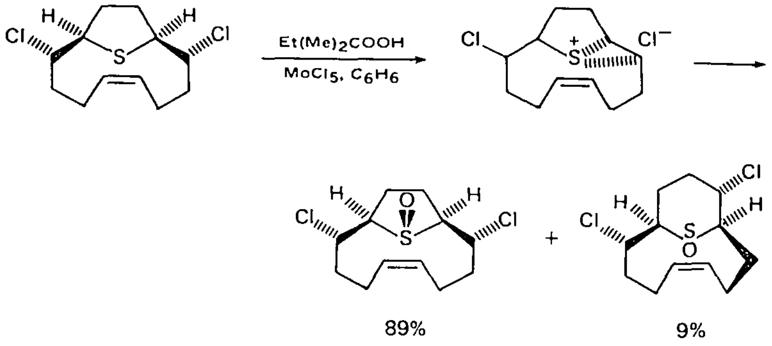
On occasion, oxidation of a sulphide to a sulphide can be useful in the determination of the structure of the original sulphide. For example cyclooctatetraene is known to give a single adduct on reaction with sulphur dichloride. Of the possible structures for the adducts A–E, (equation 109) only structure A is consistent with the oxidation of the adduct to a symmetrical sulphoxide (one that is transformed into itself on epimerization, as in equation 110)[189]. However, such structural evidence based on the structure of an oxidation product should be used with extreme caution as there are many examples of sulphides that undergo rearrangement on oxidation, for example equations (111)–(116). The first two examples, equations (111)[190] and (112)[191] illustrate the solvent-dependent rearrangement of β-chlorosulphides during the oxidation process, the next three examples, equations (113), (114)[192] and (115)[193] are consistent with the case of rearrangement of the intermediate thiirane *S*-oxides (see Section II.L), while the example in equation (116)[194] indicates the initiation of rearrangement by oxidation of a second functional group ($-CO_2H$) in a diaryl sulphide, and equation (117)[195] indicates the complex processes encountered in cephalosporin chemistry.



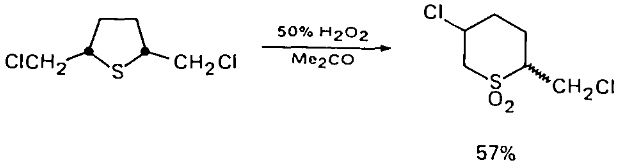
(A) (B) (C) (D) (E) (109)



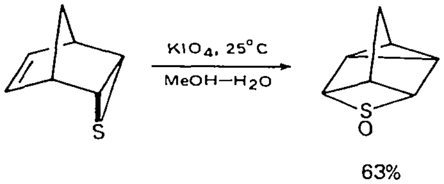
(110)



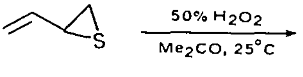
(111)



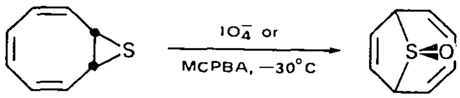
(112)



(113)



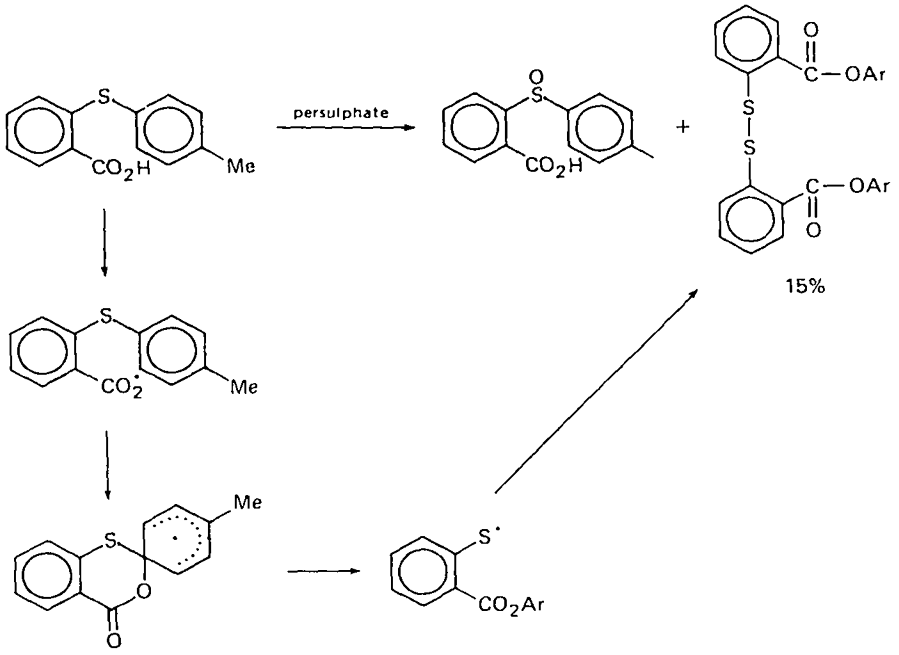
(114)



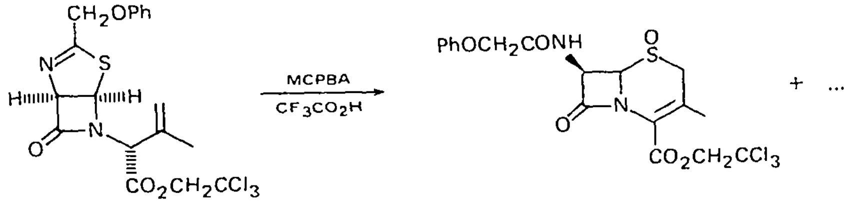
(115)

G. Oxidation of Sulphur in the Presence of various other Functional Groups

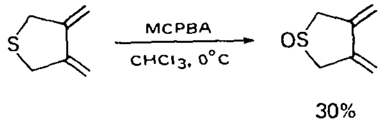
It is often necessary to selectively oxidize sulphur in molecules containing a variety of other functional groups. We have already seen some examples of selective oxidation at sulphur in previous sections of this chapter. With the proper choice of oxidant it is possible to oxidize sulphur in molecules containing amino and hydroxyl functions as well as carbon–carbon double and triple bonds, and disulphide linkages, among other easily oxidized groups. We shall also consider the oxidation of α-halosulphides because special oxidation conditions must be employed to avoid hydrolysis of these reactive compounds. Equations (118)[196] and (119)[197] indicate that readily polymerized, rearranged or aromatized substrates can be easily oxidized; equations (120)[197] and (121)[198] suggest that vinyl sulphides pose no special problems. Thiepin 1-oxides can also be prepared by direct oxidation (equation 122[199]) although product **17** has a lifetime of about one hour at 54°C. In equations


persulphate
15%

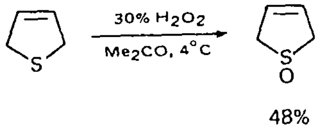
(116)


MCPBA
CF3CO2H
+ ...

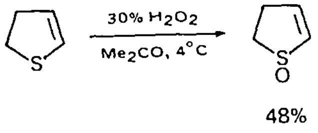
(117)


MCPBA
CHCl3, 0°C
30%

(118)


30% H2O2
Me2CO, 4°C
48%

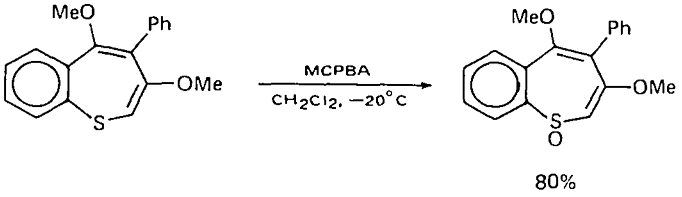
(119)


30% H2O2
Me2CO, 4°C
48%

(120)

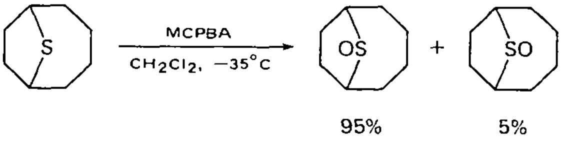
$$\mathrm{Ph_2C{=}CHSMe} \xrightarrow[\text{1 : 1 MeCN—H}_2\text{O}]{\text{NaIO}_4,\ -10^\circ\text{C}} \underset{96\%}{\mathrm{Ph_2C{=}CHS(O)Me}} \quad (121)$$

(123)–(126)[193] the preference for approach of the peracid from the (less congested) side of the two-carbon bridge suggests that directive influences associated with

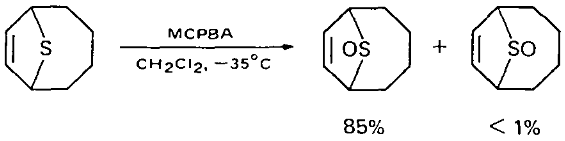

MeO
Ph
OMe
S
MCPBA
CH_2Cl_2, −20°C
MeO
Ph
OMe
S
O
80%

(17)

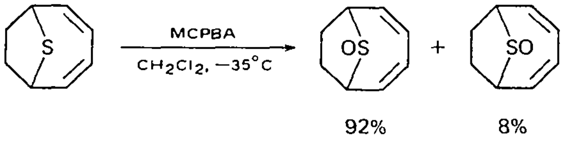
(122)


S
MCPBA
CH_2Cl_2, −35°C
OS
+
SO
95%
5%

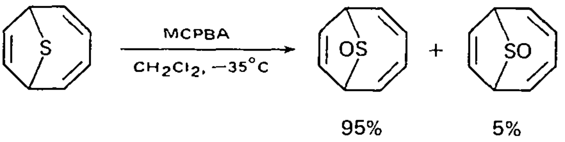
(123)


S
MCPBA
CH_2Cl_2, −35°C
OS
+
SO
85%
< 1%

(124)


S
MCPBA
CH_2Cl_2, −35°C
OS
+
SO
92%
8%

(125)


S
MCPBA
CH_2Cl_2, −35°C
OS
+
SO
95%
5%

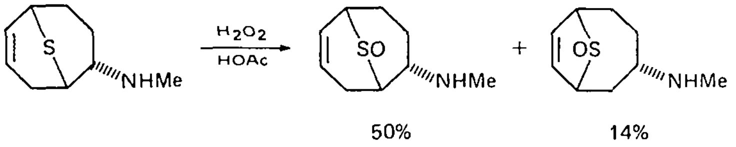
(126)

possible stabilizing complexation between the peracid and the π-systems are unimportant. Equations (127)[198] and (128)[200] indicate that alkynyl sulphides can

$$\mathrm{BuSC{\equiv}CH} \xrightarrow[\mathrm{Ac_2O,\ 0{-}20^\circ C}]{\mathrm{70{-}83\%\ H_2O_2}} \underset{46\%}{\mathrm{BuS(O)C{\equiv}CH}} \qquad (127)$$

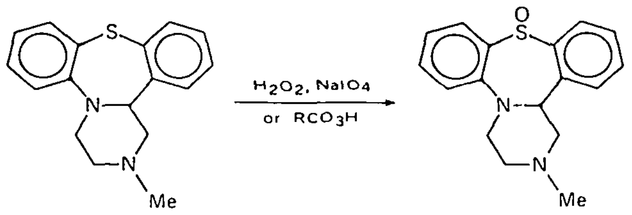
$$\mathrm{PhC{\equiv}CSMe} \xrightarrow[\mathrm{or\ (b)\ MCPBA,\ CHCl_3,\ -10^\circ C}]{\mathrm{(a)\ NaIO_4,\ 1:1\ MeCN:H_2O,\ -10^\circ C}} \underset{\substack{\text{(a) } 46\% \\ \text{(b) } 92\%}}{\mathrm{PhC{\equiv}CS(O)Me}} \qquad (128)$$

be oxidized to the corresponding sulphoxides although a stronger oxidant is required than with alkenyl sulphides. The resultant alkynyl sulphoxides are apparently much less stable than the analogous alkenyl sulphoxides. The oxidation of sulphur in the presence of amino and hydroxyl functions is shown by equations (129)[201] and (130)[202], and (131)[203]. Intermolecular competition studies have indicated that toward ozone, dialkyl disulphides are about 40 times less reactive than monosulphides. While the sulphide–disulphide shown in equation (132)[102]



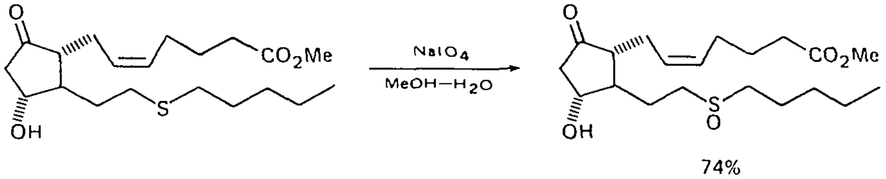
S
NHMe
H_2O_2
HOAc
SO
NHMe
+
OS
NHMe
50%
14%

(129)



S
N
N
Me
H_2O_2, $NaIO_4$
or RCO_3H
O
S
N
N
Me

(130)



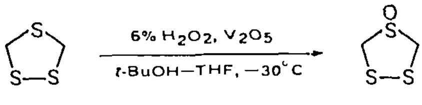
O
CO_2Me
S
OH
$NaIO_4$
MeOH—H_2O
O
CO_2Me
S
O
OH
74%

(131)

$$\mathrm{PhSS(CH_2)_2CONH(CH_2)_2SCHPh_2} \xrightarrow[\text{MeOH, 0°C}]{\mathrm{NaIO_4}} \mathrm{PhSS(CH_2)_2CONH(CH_2)_2S(O)CHPh_2} \qquad (132)$$

71%

could be selectively oxidized in good yield at the monosulphide sulphur with sodium metaperiodate, efforts to achieve similar selectivity with 1,2,4-trithiolane (to synthesize the antibacterial natural product **16**) led to mixtures[34,204]. However, good selectivity in the formation of **16** could be achieved at −30°C with H_2O_2—V_2O_5 in *t*-butanol–tetrahydrofuran[33,34].



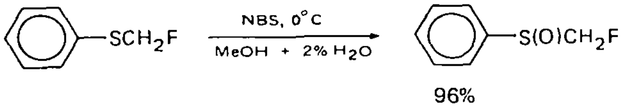
S
S—S
6% H_2O_2, V_2O_5
t-BuOH—THF, −30°C
O
S
S—S

(133)

(16)

60%

The oxidation of α-chloro-, α-bromo-, and α-iodo-sulphides pose special problems because of their ready hydrolysis and the reduced electron density at sulphur due to electron withdrawal by the halogen. α-Fluorosulphides are presumably less sensitive to hydrolysis and can be oxidized in methanol–water in high yield (equation 134)[205]. Perfluoroalkyl sulphides can be oxidized only under special conditions as will be discussed in Section II.J. Oxidants used to oxidize α-chlorosulphides include ozone (equation 135[110]), MCPBA (equation 136[206] and equation 137[207]), sulphuryl chloride–wet silica gel (equation 138[73]),



SCH_2F
NBS, 0°C
MeOH + 2% H_2O
$S(O)CH_2F$
96%

(134)

$$\mathrm{EtSCH_2Cl} \xrightarrow[\mathrm{CHCl_3}]{\mathrm{O_3}} \mathrm{EtS(O)CH_2Cl} \qquad (135)$$

$$PhSCH_2Cl \xrightarrow{MCPBA} PhS(O)CH_2Cl \qquad (136)$$

70%

$$PhCH_2SCCl_2Ph \xrightarrow{MCPBA} PhCH_2S(O)CCl_2Ph \qquad (137)$$

72%

$$PhSCH_2Cl \xrightarrow[\text{moist silica gel, } CH_2Cl_2]{SO_2Cl_2,\ 25^\circ C} PhS(O)CH_2Cl \qquad (138)$$

82%

$H_2O_2-V_2O_5$ (equation 139[32]), $(Bu_3Sn)_2O-Br_2$ (equation 140[109]) and chlorine–acetic acid–water (equation 141 and 142[71]). In the last reaction the

$$C_{12}H_{25}SCH_2Cl \xrightarrow[t\text{-BuOH}]{6\%\ H_2O_2-V_2O_5} C_{12}H_{25}S(O)CH_2Cl \qquad (139)$$

69%

$$CH_3SCH_2Cl \xrightarrow[-78^\circ C,\ CH_2Cl_2]{(Bu_3Sn)_2O-Br_2} CH_3S(O)CH_2Cl \qquad (140)$$

78%

$$RSCH_2Cl \xrightarrow[3\text{ equiv. } H_2O]{Cl_2,\ HOAc} RS(O)CH_2Cl \qquad (141)$$

$R = ClCH_2$ 77%
$R = Cl_2CH$ 65%
$R = Cl_3C$ 50%

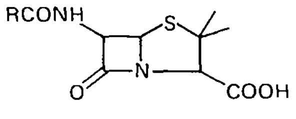
$$RSCCl_3 \xrightarrow[3\text{ equiv. } H_2O]{Cl_2,\ HOAc} RS(O)CCl_3 \qquad (142)$$

$R = Me$ 62%
$R = Ph$ 63%

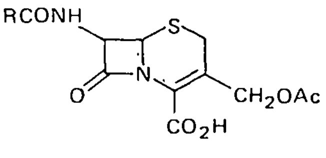
excessive reactivity of chlorine, which is normally a problem, is an advantage in the oxidation of poorly nucleophilic heavily chlorinated sulphides. The side-products of these reactions are sulphonyl chlorides which can be removed by washing with aqueous base.

H. Oxidation of Pencillin and Cephalosporin Derivatives

Great interest in the chemistry and biochemistry of the β-lactam antibiotics pencillin (18) and cephalosporin (19) has provided a stimulus for much new work



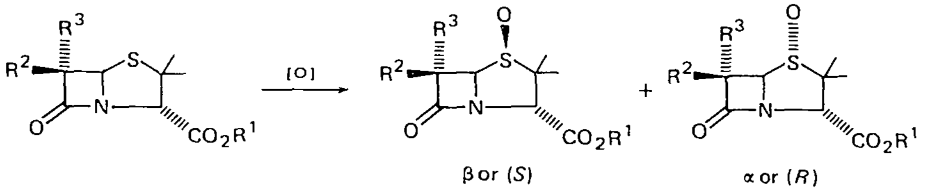
(18)

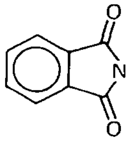
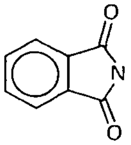
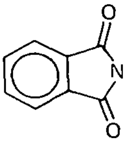


(19)

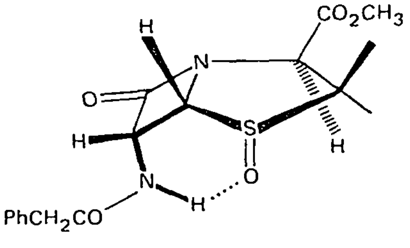
in the field of organosulphur chemistry. Oxidation of penicillins to their *S*-oxides is of particular interest because these *S*-oxides can be transformed into commercially important cephalosporin derivatives[208]. Generally the oxidation of penicillins with reagents such as peracids, sodium metaperiodate, hydrogen peroxide and ozone

TABLE 5. Stereoselectivity in oxidation of penicillins



Oxidant	R^1	R^2(β)	R^3(α)	%(*S*)	%(*R*)	Reference
Polymeric RCO_3H	H	$PhOCH_2CONH$	H	100	–	210
Polymeric RCO_3H	H	Br	Br	13	87	210
MCPBA	H	Br	Br	9	91	210
MCPBA	H	H	H	79	11	210
MCPBA	H	H	Cl	88	12	210
MCPBA	H	H	Br	92	8	210
MCPBA	Me	H		80	20	216
MCPBA	Me		H	0	100	216
$NaIO_4$	Me	$PhCH_2CONH$	H	100	0	217
$PhICl_2$	Me	$PhCH_2CONH$	H	50	50	217
H_2O_2/HCO_2H	H	$PhOCH_2CONH$	H	100	0	218
O_3	H	$PhOCH_2CONH$	H	50	50	112
O_3	H	NH_2	H	80	20	112
O_3	H		H	0	100	112

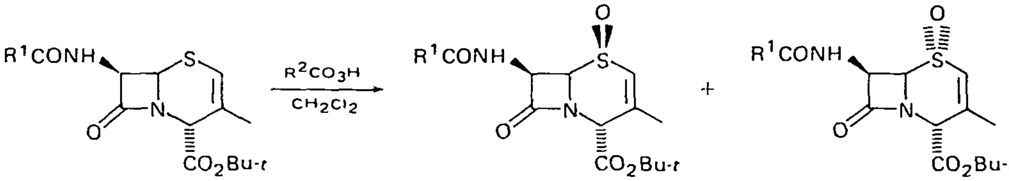
is quite stereoselective as seen from the data in Table 5. The steric effects of 6β-bromo and 6β-phthalimido groups are sufficient to favour oxidation from the sterically more accessible α-face giving the α- or (*R*)-sulphoxides. When there is a 6β-amino or 6β-substituted acetamido group, the NH group directs the oxidant to the β-face yielding β- or (*S*)-sulphoxide. Directing effects by hydrogen-bonding functions are of course well established in olefin epoxidation[209]. The 6β-NH group in penicillins can form a hydrogen bond with the incoming reagent or with the sulphoxide group of the product (see **20**) favouring the β-sulphoxide. When there



(20)

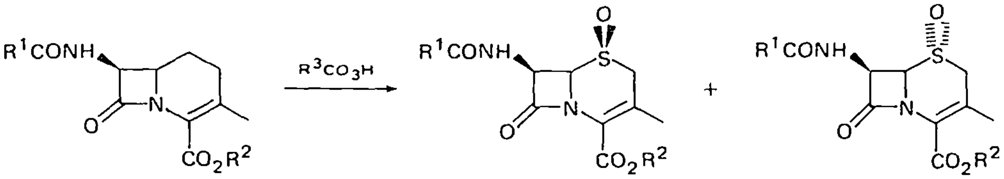
is no 6β-substituent as in methyl penicillinate and its 6α-bromo, 6α-chloro and 6α-phthalimido derivatives, the β-sulphoxide is also the major product[210]. An interesting method for oxidizing penicillin involves passage of an acetone solution down a column of polymeric peroxy acid at 40°C during 30 min giving a 91% yield of the (*S*)-sulphoxide on evaporation of the solvent[162].

Oxidation of Δ^2- and Δ^3-cephalosporins is also stereoselective as seen by the results in equations (143)[211] and (144)[212]. Hydrogen bonding by the 6β-NH group is thought to be responsible for the preference for the (*S*)- or β-form (see 21 and 22). When the oxidation of Δ^2-cephalosporins is conducted in hydroxylic solvents, rearrangement to the Δ^3-isomer occurs[213,214], reflecting the greater stability of β,γ-unsaturated sulphoxides compared to α,β-unsaturated sulphoxides[215]. This is a synthetically useful rearrangement because the


R¹CONH
S
N
O
CO₂Bu-t
R²CO₃H
CH₂Cl₂
O
+

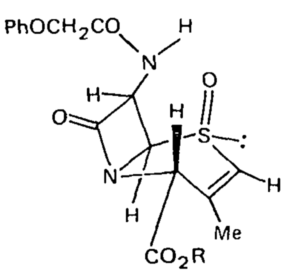
(143)

25 : 1

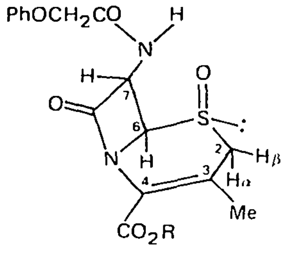

R¹CONH
N
O
CO₂R²
R³CO₃H
O
S
+

(144)

9 : 1


PhOCH₂CO
H
N
H
O
H
O
S
N
H
H
Me
CO₂R

(21)


PhOCH₂CO
H
N
H
7
O
6
O
S
N
H
2
Hβ
3
4
Hα
Me
CO₂R

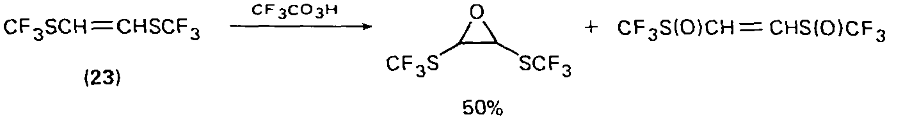
(22)

Δ^2-cephalosporins, sometimes produced in the penicillin to cephalosporin rearrangements, are inactive as antibiotics[212].

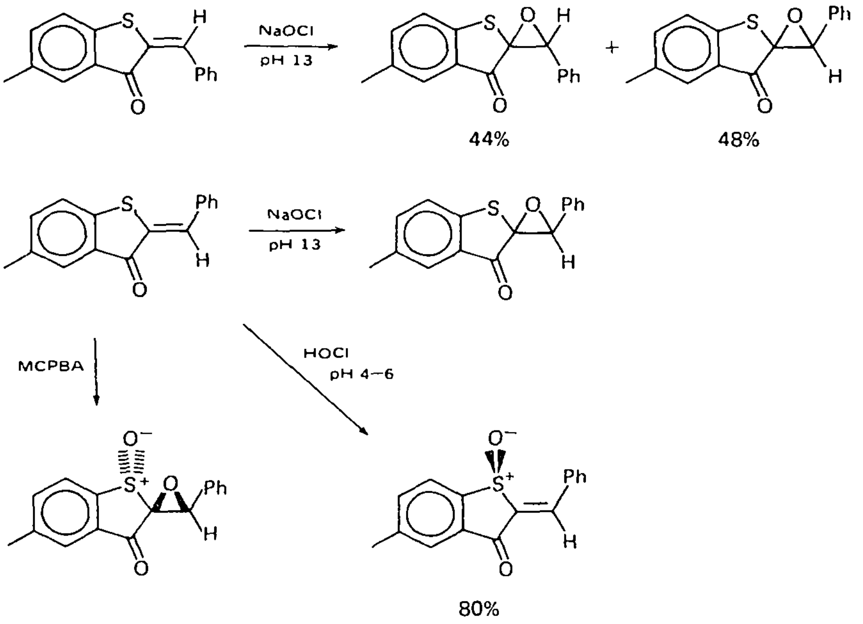
I. Oxidation of other Functionalities in the Presence of Sulphide Sulphur without Oxidizing this Sulphur

We have already seen that sulphide sulphur can be cleanly oxidized to sulphoxide sulphur even in the presence of a variety of reactive functionalities. It should therefore not be surprising that reversing the process so that other functionalities are oxidized without altering the oxidation level of sulphur is very difficult to achieve if one is limited to the types of oxygen transfer agents already considered (e.g. excluding hydride transfer processes such as the Oppenauer method which can be used with hydroxysulphides). We shall consider here a few representative examples of epoxidation and oxidative cleavage of carbon–carbon double bonds in divalent sulphur-containing compounds; selective oxidation of sulphoxides to sulphones in the presence of sulphides has already been considered in Section II.D.

Peracids cannot generally be used to epoxidize unsaturated sulphides because of the greater susceptibility of the sulphide group to electrophilic attack. For example even in the case of bis(trifluoromethylthio)ethylene (23) with diminished electron density on sulphur only a 50% yield of epoxide is realized with trifluoroperacetic acid, the remainder of the product being the bissulphoxide (equation 145)[219]. It is claimed that sodium hypochlorite at ca. pH 13 is a useful agent for the selective epoxidation of unsaturated sulphides as illustrated by equation (146)[220]. However, attempts to employ this reagent in the epoxidation of 4-thiacyclooctene have led

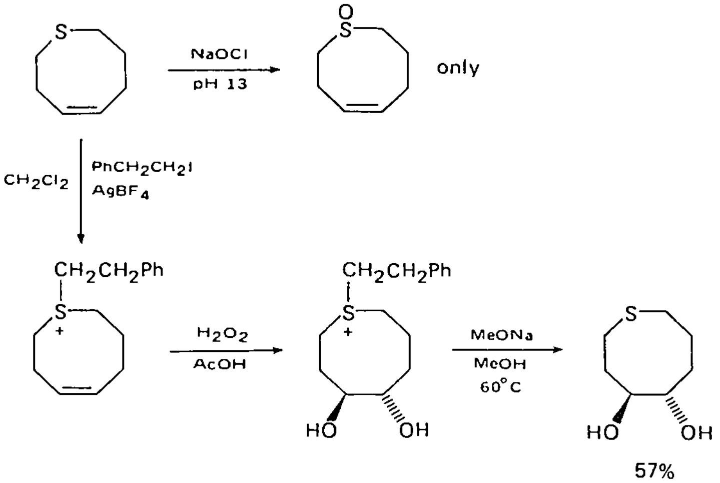


(145)



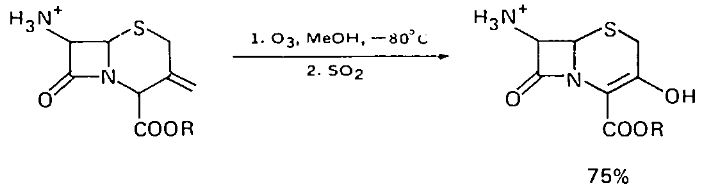
(146)

only to sulphoxide (equation 147)[221]. The oxidation of the double bond was finally accomplished by first protecting the sulphur as a sulphonium salt.



(147)

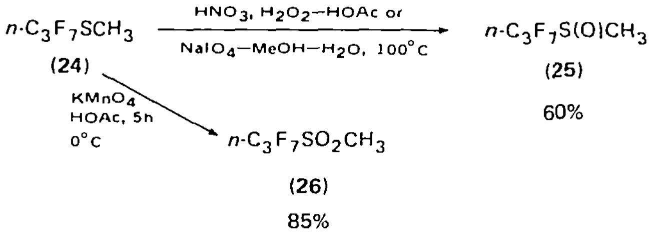
Reaction of certain thioethylenes with singlet oxygen leads to selective reaction at the double bond (see reactions in equations 79 and 80 in Section II.A.16). In the second example (equation 80) treatment with oxidants such as MCPBA, $NaIO_4$ or H_2O_2–acetone leads exclusively to oxidation at sulphur while treatment with ozone leads to attack both at sulphur and at the double bond. In other instances (equation 148)[222] ozone does react predominantly at the double bond of unsaturated sulphides.



(148)

J. Perfluoroalkyl Sulphoxides

The consequences of diminished nucleophilicity at sulphur on ease of oxidation are seen most dramatically in the case of perfluoroalkyl sulphides. Partially fluorinated alkyl sulphides require somewhat more drastic conditions for oxidation than their nonfluorinated counterparts, as illustrated by the use of 1 : 1 H_2O_2–HOAc at 100°C for 24 h, fuming HNO_3 at 100°C for 14 h or $NaIO_4$ in 50% aqueous methanol at 100°C for 24 h to convert methyl heptafluoropropyl sulphide **24** to the corresponding sulphoxide **25** in 60–70% yield (equation 149)[223]. In the $NaIO_4$ oxidation of **24** it is essential to use methanol as a cosolvent to prevent formation of sulphone **26**. In aqueous media sulphoxide **25** is much more soluble than sulphide **24** because of hydrogen bonding, so oxidation of sulphoxide to sulphone becomes competitive with sulphide oxidation despite the faster rate for the latter process. After 168 h at 100°C with aqueous $NaIO_4$, sulphone **26** is formed from sulphide **24** in 60% yield. A much more convenient preparation of sulphone **26** involves oxidation of **24** with $KMnO_4$ in acetic acid at 0°C for 5 h.


n-$C_3F_7SCH_3$
(24)
HNO_3, H_2O_2—HOAc or
$NaIO_4$—MeOH—H_2O, 100°C
n-$C_3F_7S(O)CH_3$
(25)
60%
$KMnO_4$
HOAc, 5h
0°C
n-$C_3F_7SO_2CH_3$
(26)
85%

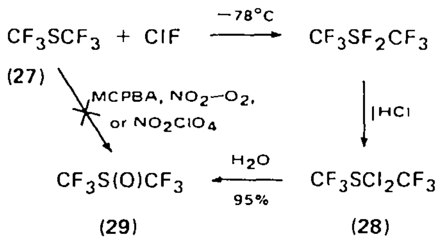
(149)

Other examples of oxidation of partially fluorinated alkyl sulphides are shown in equation (150) and (151)[224].

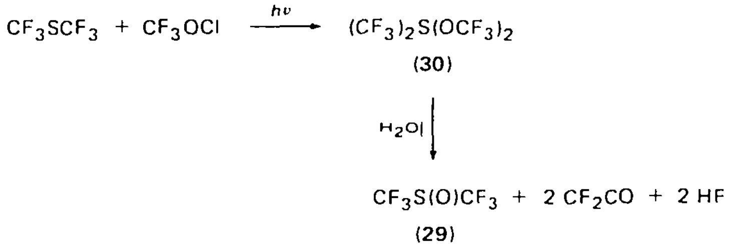
$$CF_3SCH_2SCF_3 \xrightarrow[\text{No solvent, 25°C, 4 days}]{\text{MCPBA}} CF_3S(O)CH_2SCF_3 \quad (150)$$

$$\begin{array}{l} CF_3SCH_3 \xrightarrow[\text{No solvent}]{\text{MCPBA, 0°C}} CF_3S(O)CH_3 \\ \qquad\qquad \xrightarrow{\text{MCPBA, 25°C}} CF_3SO_2CH_3 \end{array} \quad (151)$$

Unlike the cases depicted in equations (149)–(151), pentafluorodimethyl sulphide is unchanged after seven days exposure at room temperature to MCPBA[224] and perfluorodimethyl sulphide **27** is uneffected by heating with MCPBA in CCl_4 at 100°C for 2 h, exposure to NO_2ClO_4 at 25°C, irradiation in the presence of NO_2 or heating with a NO_2–O_2 mixture at 350°C[225]. The first successful preparation of a perfluoroalkyl sulphoxide (**29**) by Sauer and Shreeve involves oxidative fluorination of sulphide **27** with ClF, fluorine–chlorine interchange with HCl, and finally hydrolysis of sulphur (IV) dichloride **28**[226]. A more recent synthesis of **29** involves the hydrolysis of sulphurane **30** formed photochemically from bis(trifluoromethyl)sulphide as shown in equation (153)[227].


CF_3SCF_3 + ClF
−78°C
$CF_3SF_2CF_3$
(27)
MCPBA, NO_2—O_2,
or NO_2ClO_4
HCl
$CF_3S(O)CF_3$
H_2O
95%
$CF_3SCl_2CF_3$
(29)
(28)

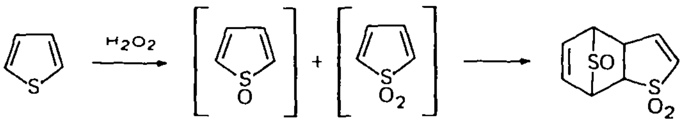
(152)


CF_3SCF_3 + CF_3OCl
$h\nu$
$(CF_3)_2S(OCF_3)_2$
(30)
H_2O
$CF_3S(O)CF_3$ + 2 CF_2CO + 2 HF
(29)

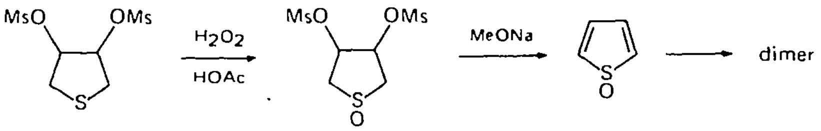
(153)

K. Thiophene 1-Oxides

Efforts to directly oxidize thiophene to its 1-oxide lead instead to dimeric Diels–Alder adducts (equation 154)[228]; a similar dimeric product is readily formed from thiophene 1-oxide generated by an elimination route (equation 155)[229].

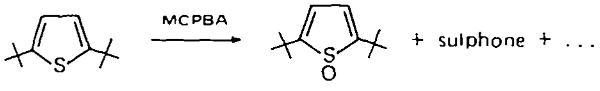

H2O2
SO
S
O
O2

(154)


MsO
OMs
H2O2
HOAc
MeONa
S
O
dimer

(155)

Oxidation of 2,5-di-*t*-butylthiophene (**31**) with one equivalent of MCPBA gives a stable crystalline thiophene 1-oxide (**32**) in low yield (equation 156)[230]. The

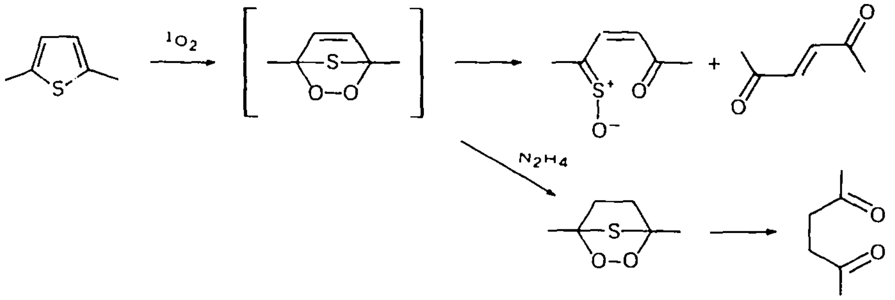

MCPBA
S
O
+ sulphone + . . .

(156)

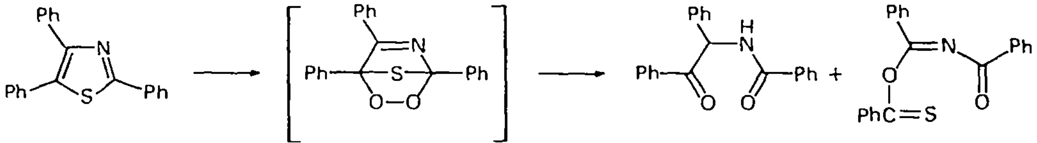
(31) (32)

5%

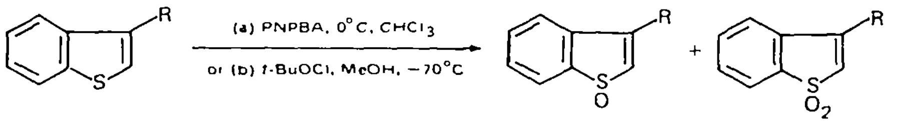
spectra of **32** are consistent with a pyramidal sulphinyl group with a rather low inversion barrier (14.8 kcal/mol compared to 36 kcal/mol for diaryl sulphoxides). It would appear that the high reactivity of the parent thiophene 1-oxide is a consequence of its lack of aromatic character. Reaction of thiophenes with singlet oxygen takes an entirely different course from oxidation with peroxides, namely


$^1O_2$
S
O—O
S+
O−
O
N2H4

(157)


Ph
N
S
O—O
H
PhC=S
O

(158)


R
S
(a) PNPBA, 0°C, CHCl3
or (b) t-BuOCl, MeOH, −70°C
O
O2

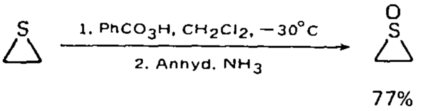
(159)

R = Me	(a)	70%	8%
	(b)	60%	–
R = iBr	(a)	40%	30%
	(b)	80%	–

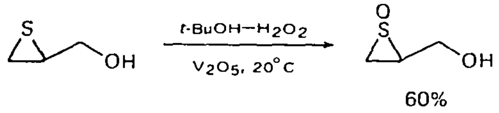
ring-opening via an intermediate Diels–Alder adduct with the oxygen (equation 157)[231,232]. A similar process occurs with thiazoles (equation 158)[233]. Benzothiophenes are normally oxidized to the corresponding *S*-oxide with *p*-nitroperbenzoic acid or *t*-butyl hypochlorite (equation 159)[234].

L. Thiiran 1-Oxides

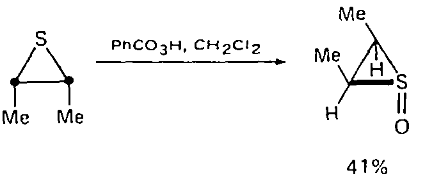
Thiiran 1-oxide, the simplest cyclic sulphoxide, and its substituted derivatives are of considerable interest as low-temperature sources of sulphur monoxide and various reactive ring-opened species and as compounds undergoing interesting rearrangements[149]. The original preparation from thiiran involving $NaIO_4$ in aqueous methanol[235] suffers from low yield and difficulty of isolation and has been supplanted by newer methods involving H_2O_2–*t*-BuOH–V_2O_5 (60% yield)[32] or better still perbenzoic acid in CH_2Cl_2 at –30°C followed by filtration of ammonium benzoate, formed through addition of gaseous ammonia (77% yield) (equation 160)[23]. The H_2O_2–V_2O_5 procedure has been used to prepare hydroxymethyl thiirane 1-oxide (equation 161)[32] while the perbenzoic acid has been used to make *anti*-2,3-dimethylthiirane 1-oxide (34) (equation 162)[23]. The *anti* stereochemistry of 34 reflects the approach of the peracid from the least hindered face of thiirane 33. Peroxytrifluoroacetic acid has been used in the oxidation of ring-fused thiiranes 35 and 36 (equation 163) while low-temperature oxidation of tricyclic thiirane 37 affords thermally labile sulphoxide 38 (equation 164)[236]. Efforts to prepare thiiran *S*-oxides 39 and 40 by low-temperature oxidation of the thiiran led instead to rearranged products said to be formed by 'pseudopericyclic' processes (equations 165 and 166)[193,236].



(160)



(161)

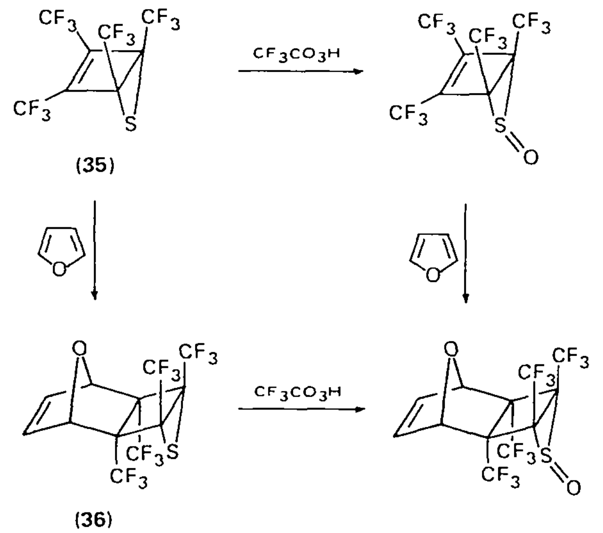


(162)

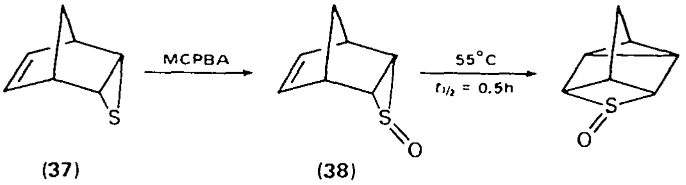
(33) (34)

III. REDUCTION OF SULPHIDES

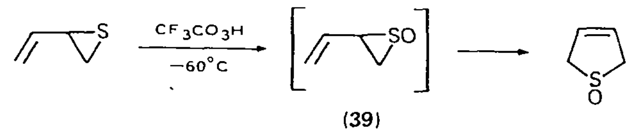
The products of reduction of sulphides are hydrocarbons and thiols or hydrogen sulphide, depending on the nature of the reducing agent and sulphide (equation 167). The rather strong C–S bond can be reductively cleaved by the alkali metals (and calcium) in liquid ammonia or alkylamines or in the presence of naphthalene or trimesitylborane, by sodium amalgam, by magnesium and by zinc with acetic



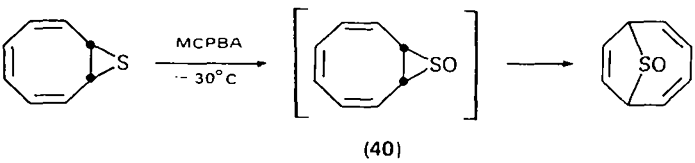
(163)



(164)



(165)



(166)

$$R-S-R \xrightarrow{[H]} RH + RSH \xrightarrow{[H]} RH + H_2S \qquad (167)$$

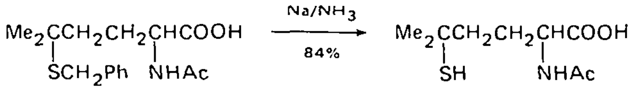
acid or trimethylsilyl chloride, by nickel boride, Raney nickel, Raney cobalt and cobaltous oxide–molybdic oxide–aluminium oxide catalyst and related hydrodesulphurization systems, by lithium aluminium hydride with added copper, zinc or titanium salts and in certain cases, by electrolysis or photolysis. The reductive cleavage of C–S bonds has been widely used in the structural elucidation of sulphides through identification of the hydrocarbons formed, an early example being the work by du Vigneaud and coworkers on the elucidation of the structure of biotin through desulphurization with Raney nickel[237]. The reductive cleavage of C–S bonds also provides a useful synthetic approach to certain thiols not readily available by other routes and finds considerable use, especially in peptide synthesis, in the regeneration of thiols following protection as benzylic or other related sulphides[238]. The desulphurization of thioacetals represents a useful alternative to Wolff–Kishner or Clemmensen reductions. Reductive desulphurization and the related methods of reductive alkylation, elimination and cyclization of sulphides are techniques of considerable utility in organic synthesis especially following the use of sulphur to assist cyclization (e.g. using thiophen as a template), alkylation (via an α-thio carbanion) or rearrangement (e.g. via the Stevens rearrangement)[149]. Finally, there is considerable commercial interest in the removal of organically-bound sulphur from coal and crude oil by the process of hydrodesulphurization.

This section will review all of the above areas with an emphasis on the current nonpatent literature up to November, 1978. Since there are good reviews on Raney nickel desulphurization[239] and other heterogeneous desulphurization procedures[240] coverage here will be abbreviated.

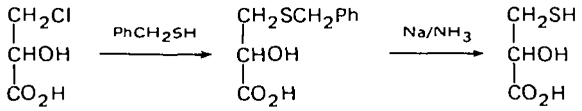
A. Group I and II Metals

It has been known since 1923[2] that organic sulphides can undergo C–S cleavage on treatment with sodium in liquid ammonia. The first synthetic use of this reaction was the removal of the *S*-benzyl group from an *S*-protected cysteine reported by du Vigneaud in 1930[241], a reaction which is now a standard process in peptide synthesis[238]. Some more recent examples of this reaction are shown in equations (168)[242], (169)[243] and (170)[244]. When the sulphur-free *benzyl* function is the desired end-product (e.g. in cyclophane syntheses) it is preferable to use Li/NH_3 for C—S cleavage rather than Na/NH_3 to minimize Birch reduction of the benzene rings[327].

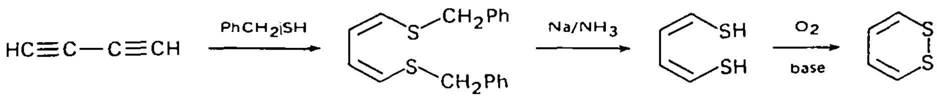
A general mechanism for alkali cleavage of sulphides is shown in equation (171)[245]. Evidence for formation of radical R• includes trapping with the acetone enolate (equation 172)[246] and isolation of dimers R–R (equation 173)[247]. While



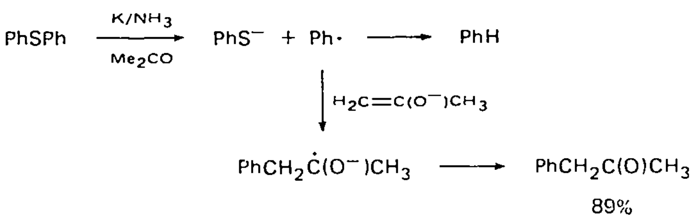
$$\underset{SCH_2Ph}{Me_2\overset{|}{C}}CH_2CH_2\underset{NHAc}{\overset{|}{C}}HCOOH \xrightarrow[84\%]{Na/NH_3} \underset{SH}{Me_2\overset{|}{C}}CH_2CH_2\underset{NHAc}{\overset{|}{C}}HCOOH \qquad (168)$$



$$\begin{matrix} CH_2Cl \\ | \\ CHOH \\ | \\ CO_2H \end{matrix} \xrightarrow{PhCH_2SH} \begin{matrix} CH_2SCH_2Ph \\ | \\ CHOH \\ | \\ CO_2H \end{matrix} \xrightarrow{Na/NH_3} \begin{matrix} CH_2SH \\ | \\ CHOH \\ | \\ CO_2H \end{matrix} \qquad (169)$$



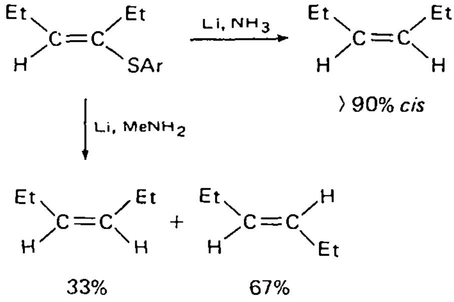
$$RSR + e^- \text{ (solv.)} \xrightarrow[NH_3]{(a)} [RSR]^{\dot{-}} \xrightarrow{(b)} RS^- + R\cdot \xrightarrow[e^- \text{ (solv.)}]{(c)} R^- \xrightarrow[-NH_2^-]{NH_3} RH \qquad (171)$$



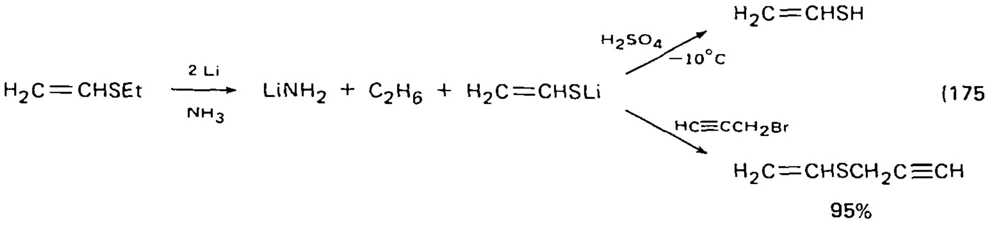
$$\begin{tikzcd}[column sep=small] PhSPh \arrow[r, "K/NH_3", "Me_2CO"'] & PhS^- + Ph\cdot \arrow[r] \arrow[d, "H_2C{=}C(O^-)CH_3"] & PhH \\ & PhCH_2\dot{C}(O^-)CH_3 \arrow[r] & \underset{89\%}{PhCH_2C(O)CH_3} \end{tikzcd} \qquad (172)$$

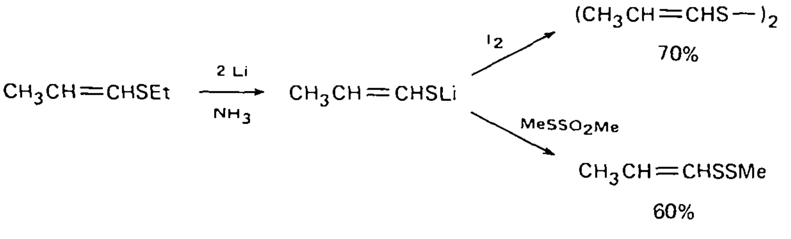
$$\underset{}{PhSC_{10}H_{21}\text{-}n} \xrightarrow{\text{Li/MeNH}_2} \underset{87\%}{PhSH} + \underset{71\%}{n\text{-}C_{10}H_{22}} + \underset{10\%}{n\text{-}C_{20}H_{42}} \qquad (173)$$

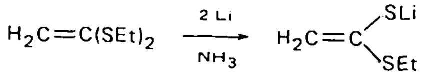
the mechanism of equation (171) is applicable to diaryl and alkyl aryl sulphides, it is not certain whether it also applies to dialkyl sulphides[248]. There are subtle differences in reductive cleavages conducted in ammonia compared to those performed in methylamine, as illustrated by equation (174)[249]. It is suggested that the rate of


Li, NH3
> 90% cis
Li, MeNH2
33%
67%
(174)

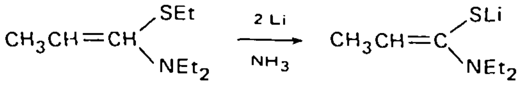
transfer of the second electron (step c, equation 171) is slower in methylamine than in liquid ammonia, thereby allowing the intermediate vinyl radical more time to isomerize in the former solvent[249]. With some unsymmetrical sulphides R^1SR^2 the direction of cleavage is thought to favour the most delocalized thiolate anion R^1SNa with R^2Na stability apparently irrelevant[250]. The tendency of thiolates to split in reductive cleavages with Na or Li/NH_3 is aryl—S^- > C=CS^- > C≡CS^- > alkyl—S^-[251]. Some illustrations of the synthetic utility of reductive cleavage of 1-alkenyl and 1-alkynyl sulphides are to be found in equations 175–180[250,251].


H2C=CHSH
H2SO4
−10°C
H2C=CHSEt
2 Li
NH3
LiNH2 + C2H6 + H2C=CHSLi
HC≡CCH2Br
H2C=CHSCH2C≡CH
95%
(175)


(CH3CH=CHS—)2
I2
70%
CH3CH=CHSEt
2 Li
NH3
CH3CH=CHSLi
MeSSO2Me
CH3CH=CHSSMe
60%
(176)


H2C=C(SEt)2
2 Li
NH3
H2C=C
SLi
SEt
(177)

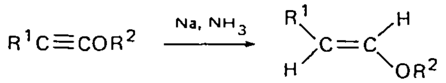
$$EtSCH{=}CHSEt \xrightarrow[NH_3]{2\ Li} LiSCH{=}CHSLi \qquad (178)$$



$$CH_3CH{=}CH(SEt)(NEt_2) \xrightarrow[NH_3]{2\,Li} CH_3CH{=}C(SLi)(NEt_2) \quad (179)$$

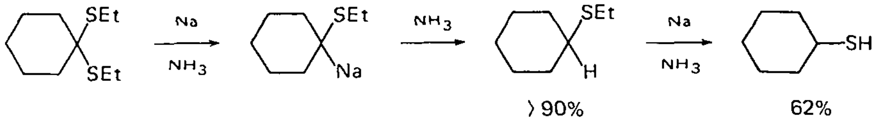
$$BuC{\equiv}CSEt \xrightarrow{2\,Li} BuC{\equiv}CSLi \xrightarrow[H_2C{=}CHCH_2Br]{} BuC{\equiv}CSCH_2CH{=}CH_2 \quad (180)$$

Alkenethiolates do not suffer reduction to saturated thiolates or loss of sulphur even in the presence of excess of alkali metal. Furthermore it is not necessary to use benzyl sulphides to get facile reductive cleavage. Even alkynethiolates can be readily prepared without the reduction of the triple bond that occurs, for example, with alkynyl ethers (equation 181)[250] or amines. In these reactions the alkali

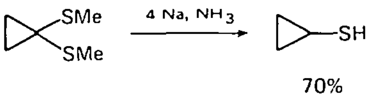


$$R^1C{\equiv}COR^2 \xrightarrow{Na,\,NH_3} (R^1)(H)C{=}C(H)(OR^2) \quad (181)$$

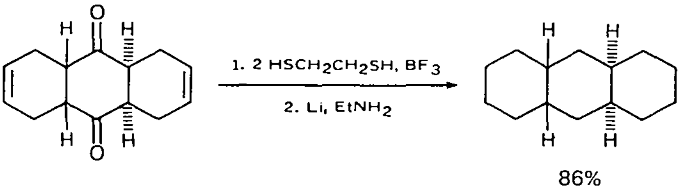
amide by-products must be neutralized with ammonium chloride or *t*-butanol (equation 189) to avoid complications. A convenient synthesis of cycloalkanethiols and cycloalkyl sulphides involves the reductive cleavage of cycloalkanone thioacetals (equations 182 and 183)[251]. Unsaturated 1,3-dithiolanes derived from ketones can be reduced to the hydrocarbons with (equation 184)[252] or without (equation 185)[253] concomitant reduction of the double bonds, providing an alternative to



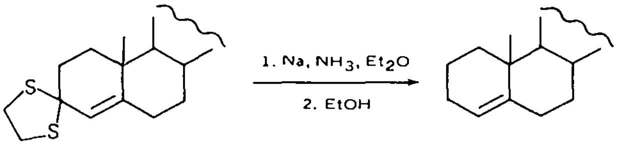
(182)



(183)

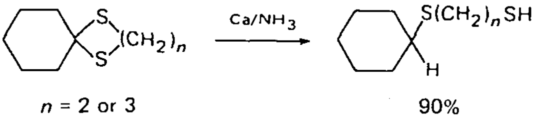


(184)

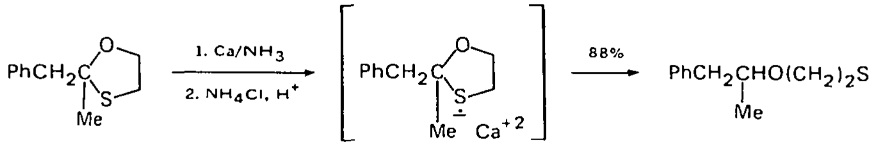


(185)

Raney nickel desulphurization. With calcium in liquid ammonia the reductive cleavage of 1,3-dithiolanes and 1,3-dithianes can be stopped with cleavage of one C—S bond (equation 186)[254] while under these same conditions 1,3-oxathiolanes afford β-mercapto ethers (equation 187[255]). The effectiveness of metals in these reductions in Ca > Li > Na > K and is thought to be related to ability to form ion



(186)

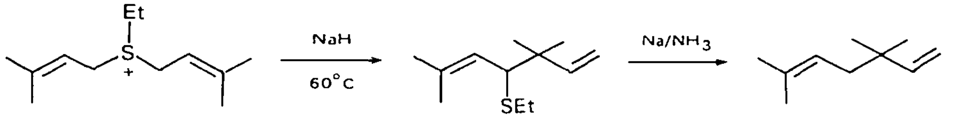

(187)

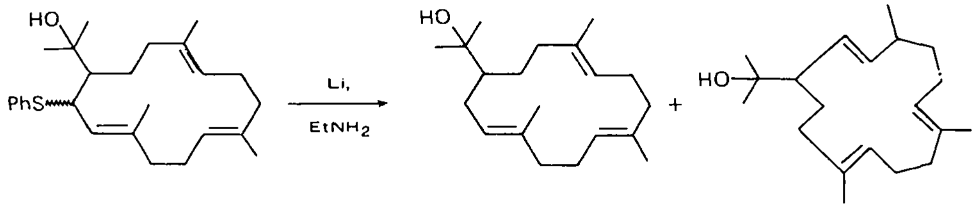
pairs with the intermediate anion radicals[255]. A useful application of reductive cleavage of simple dialkyl sulphides in the preparation of deuterated sulphur compounds is shown in equation (188)[256]. It should be noted that dimethyl sulphoxide also undergoes direct cleavage on treatment with Li/NH$_3$ (equation 189)[257].

$$\begin{tikzcd} (CD_3)_2SO \arrow[r, "PhSH", "85\text{--}95^\circ C"'] & PhSSPh + H_2O + (CD_3)_2S\ (90\%) \arrow[d] \\ \begin{array}{c} CD_3SSCD_3 \\ 88\% \end{array} & CD_3SNa + CD_3H + NaNH_2 \arrow[l, "{[O]}"'] \arrow[d, "H^+"] \\ & \begin{array}{c} CD_3SH \\ 75\% \end{array} \end{tikzcd} \quad (188)$$

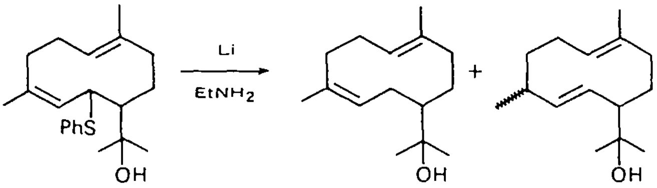
$$(CH_3)_2SO \xrightarrow[NH_3,\ t\text{-BuOH}]{2\ Li} CH_3Li + CH_3SOLi \xrightarrow{RBr} CH_3S(O)R \quad (189)$$

In some reductive cleavage processes involving unsymmetrical dialkyl sulphides it is clear that the stability of the carbon fragments R• and/or R– are important. Thus the conversion of thioacetals to dialkyl sulphides (equation 182) is more rapid than further reduction of the sulphides because of the stability of the intermediate α-thio carbanion (or α-thio radical). Alkyl allyl sulphides undergo preferential cleavage of the allylic bond as seen in equation (190)[258]. Complications with the reductive desulphurization of allylic sulphides using Li/EtNH$_2$ include positional isomerization involving the double bond (equations 191 and 192)[259] and partial reduction of double bonds (equation 193[260]). With regard to double-bond reduction it should be noted that, employing a mixture of 1-octene and *n*-decyl sulphide, Truce found C–S cleavage to occur ca. six times faster than C=C reduction[248].


(190)

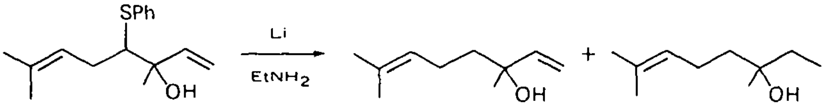

(191)

30% 20%



(192)

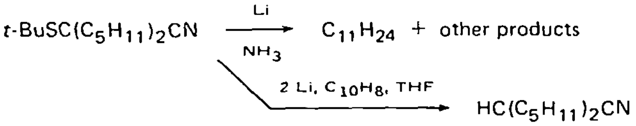
83% trace



(193)

87%

Another complication sometimes seen with alkali–ammonia desulphurizations is that other functional groups can be expelled as occurs with the nitrile in equation (194)[261]. In this case selective desulphurization was achieved by changing the electron-transfer medium to naphthalene or trimesitylborane in THF as solvent[261]

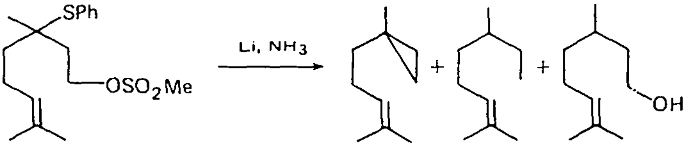


$$t\text{-BuSC}(C_5H_{11})_2CN \xrightarrow[NH_3]{Li} C_{11}H_{24} + \text{other products}$$

$$\xrightarrow{2\ Li,\ C_{10}H_8,\ THF} HC(C_5H_{11})_2CN$$

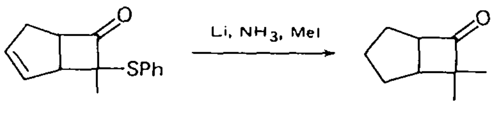
(194)

The carbanions resulting from reductive cleavage of sulphides are in general ammonolysed because they are much stronger bases than alkali amides. In some cases these carbanions can participate in intramolecular or intermolecular alkylation or elimination processes (equations 195[262], 196 and 197[263], respectively). A process termed 'reductive silylation' can be achieved through the combined action of sodium or zinc and trimethylsilyl chloride as illustrated by equations (198)[264] and (199)[265], respectively. Mechanistic details are not yet available for these reactions.

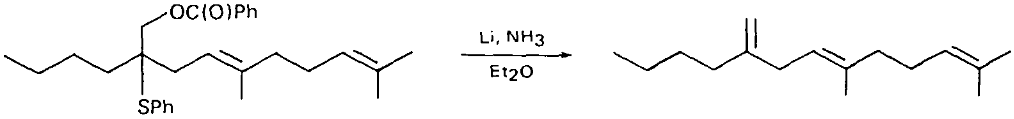


(195)

22% 22% 35%



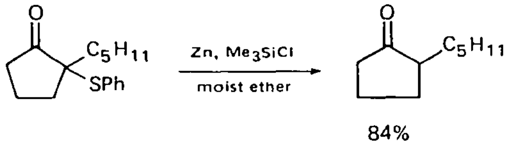
(196)



54% (197)

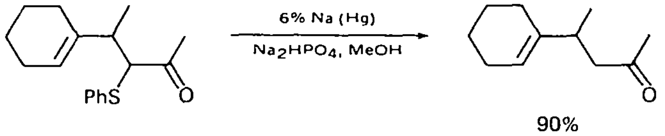
$$C_{10}H_{22}SPh \xrightarrow[Me_3SiCl]{Na,\ THF,\ \Delta} C_{10}H_{22}SiMe_3 \qquad (198)$$

85%

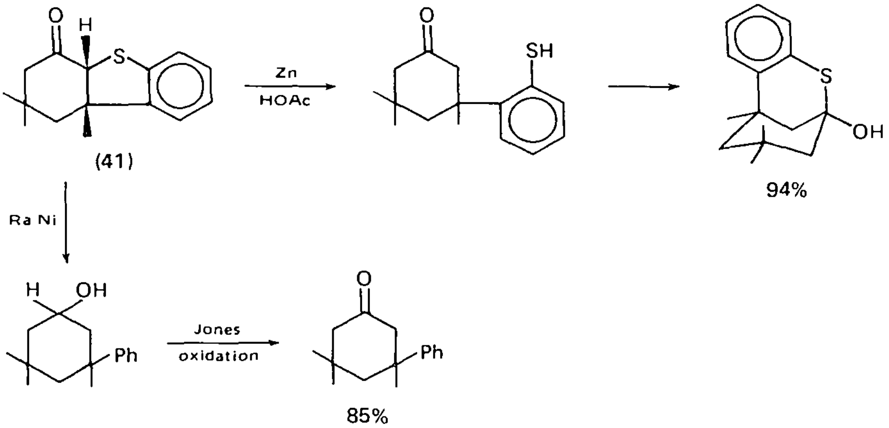

O
C5H11
SPh
Zn, Me3SiCl
moist ether
84%

(199)

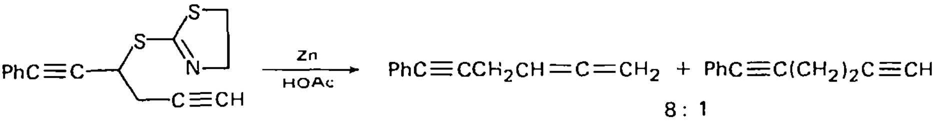
Other Group I/II reagents which have been used to effect C—S cleavage are sodium amalgam (equation 200[266]), zinc in acetic acid (equations 201[267] and 202[268]) and magnesium metal (equation 203[269]). In the last case C—S cleavage affords benzenethiolate and an allylic radical which either couples or undergoes one-electron reduction to the carbanion, which is then carboxylated.


PhS
O
6% Na (Hg)
Na2HPO4, MeOH
O
90%

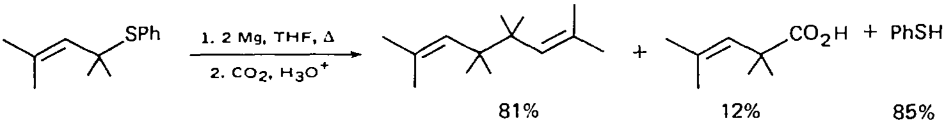
(200)


O
H
S
(41)
Zn
HOAc
O
SH
S
OH
94%
Ra Ni
H
OH
Ph
Jones
oxidation
O
Ph
85%

(201)


S
S
N
PhC≡C
C≡CH
Zn
HOAc
PhC≡CCH2CH=C=CH2 + PhC≡C(CH2)2C≡CH
8 : 1

(202)

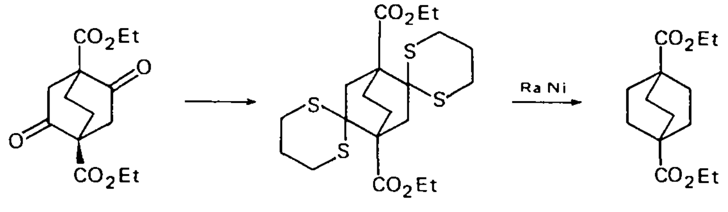

SPh
1. 2 Mg, THF, Δ
2. CO2, H3O+
+
CO2H + PhSH
81%
12%
85%

(203)

B. Raney Nickel and other Heterogeneous Catalysts

In 1927 Raney described a nickel catalyst prepared by the action of hot aqueous alkali on finely powdered nickel—aluminium alloy[270]. Twelve years later Bougault and coworkers reported the use of Raney nickel for desulphurization of organosulphur compounds and in particular proposed the use of Raney nickel for the commercial purification of benzene through removal of thiophene[3]. In the early

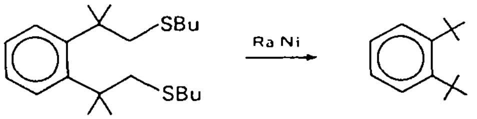
1940s Raney nickel was applied to structural investigations of sulphur-containing natural products such as biotin[237] and penicillin[271] while in the 1950s applications of Raney nickel desulphurizations in organic synthesis began to appear (for example the Raney nickel desulphurization of 1,3-dithianes and 1,3-dithiolanes represents a useful alternative to the Wolff–Kishner and Clemmensen reductions; equation 204[272]). In the intervening years innumerable applications of Raney nickel desulphurizations have been published. A number of comprehensive reviews have appeared summarizing these applications and considering the mechanisms of these processes[239,237a,b,274]. We shall in this section concentrate on a few of the recent, notable applications of this reaction in organic synthesis.



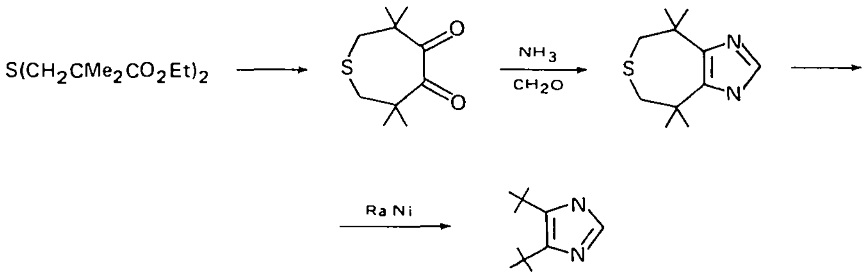
70%

(204)

Desulphurization is the final step in two syntheses of 1,2-di-*t*-butyl ring compounds (equations 205[275] and 206[276]). In the first of these reactions use of W-6 Raney nickel led to extensive reduction of the aromatic ring so that a modified preparation of Raney nickel was developed[277]. Woodward uses an isothiazole ring as a template in the construction of the ring system of colchicine. Raney nickel is used in one of the last steps of this synthesis to remove the sulphur after it has admirably served it purpose (equation 207[278]).

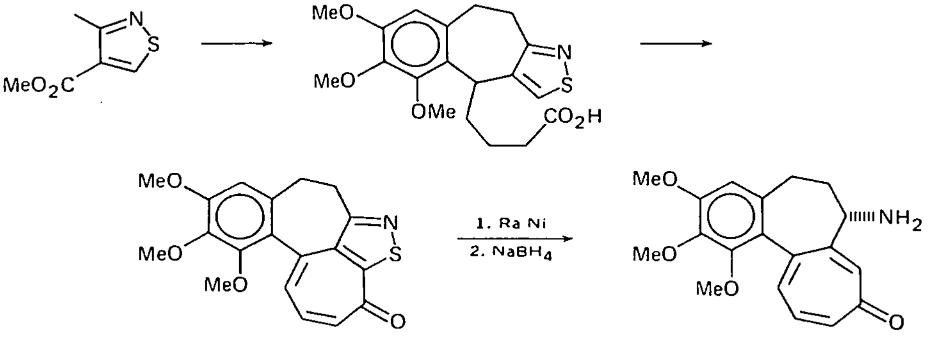


(205)



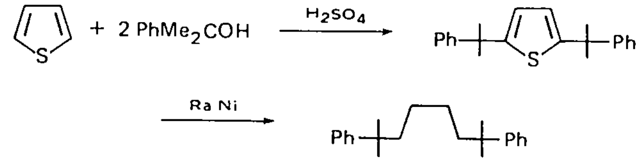
(206)

Thiophene, a reactive, readily derivatized heterocycle, is an especially useful template for the construction of organic molecules. Reductive desulphurization gives rise to a four-carbon unit. Goldfarb and others have employed the thiophene functionalization–Raney nickel reductive desulphurization procedure in syntheses of hydrocarbons, long-chain alcohols, ethers, ketones, mono-, di- and hydroxy-carboxylic acids, amines, amino alcohols, and amino acids and macrocyclic ketones and diketones[279-281] as illustrated by equations (208)[282], (209)[283], (210)[284], (211)[285], (212)[286], (213)[287] and (214)[288]. Dihydro- and tetrahydro-thiophene derivatives also serve as useful four-carbon templates as illustrated by equations (215)[289] and (216)[290]. Several interesting variants of the desulphurization of

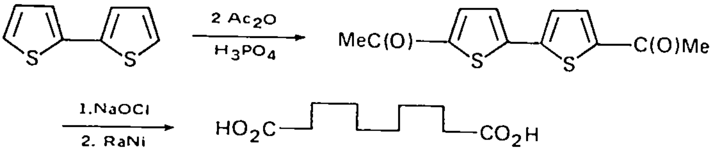

MeO
MeO
OMe
CO2H
MeO2C
N
S
1. Ra Ni
2. NaBH4
NH2
O

Desacetylcolchicine

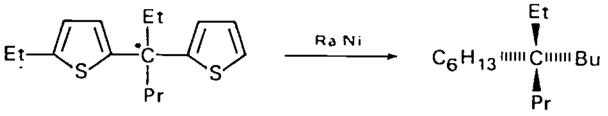
(207)


+ 2 PhMe2COH
H2SO4
Ph
S
Ra Ni

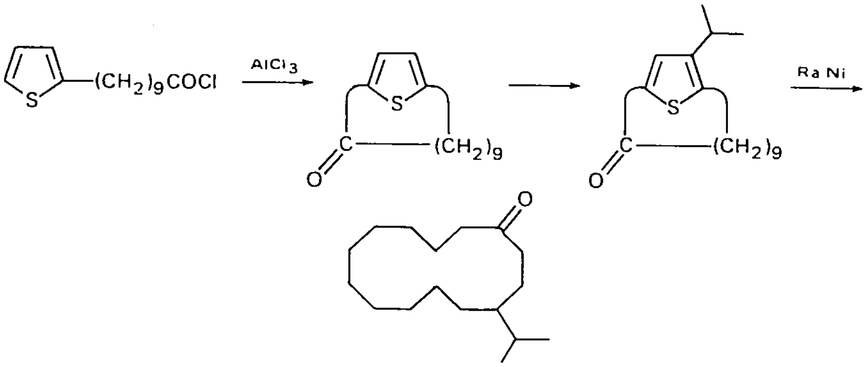
(208)


2 Ac2O
H3PO4
MeC(O)
C(O)Me
1.NaOCl
2. RaNi
HO2C
CO2H

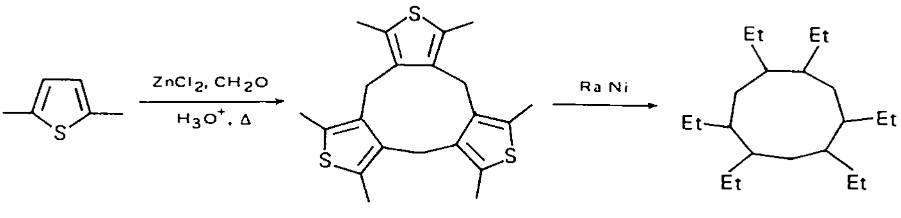
(209)


Et
Pr
Ra Ni
C6H13
Bu

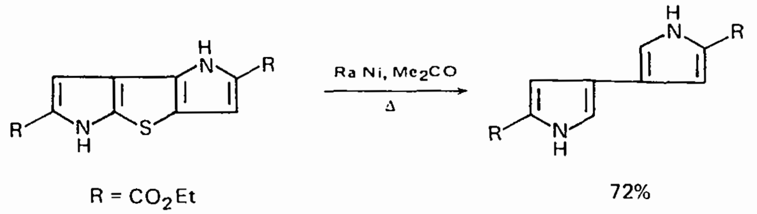
(210)


(CH2)9COCl
AlCl3
(CH2)9
Ra Ni
O

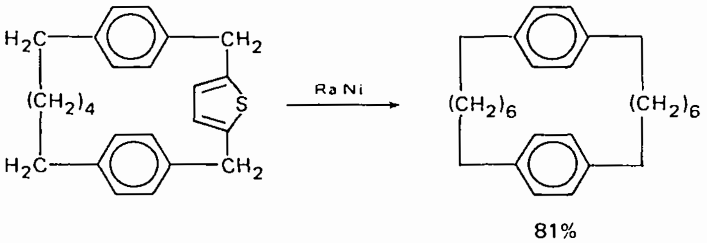
(211)


ZnCl2, CH2O
H3O+, Δ
Ra Ni
Et
42%
100%

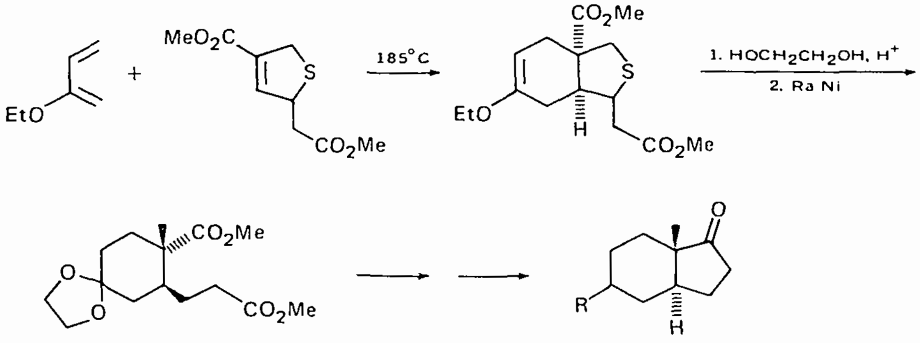
(212)



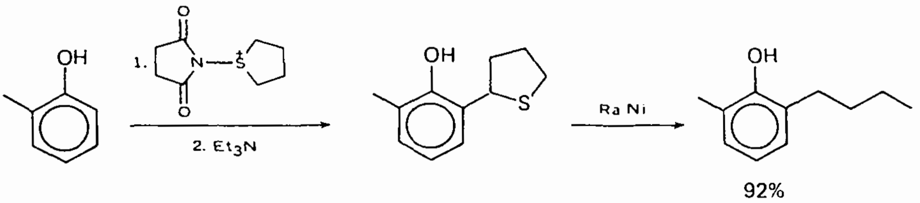
(213)



(214)



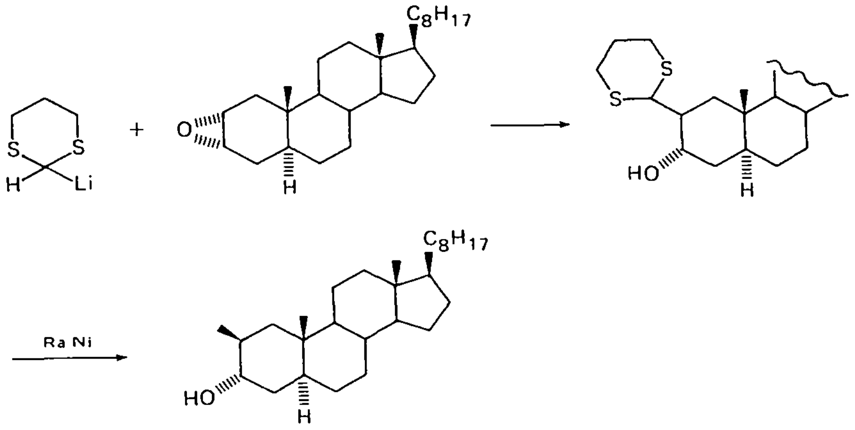
(215)



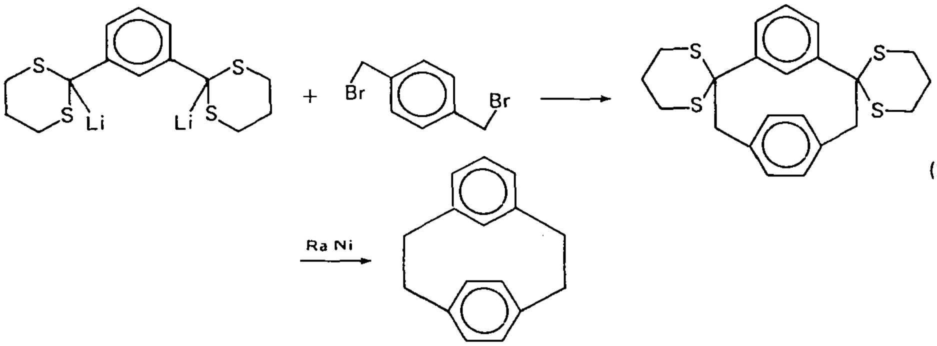
(216)

cyclic dithioacetals have been developed based on the use of 1,3-dithiane anions (equations (217)[291] and (218)[292]) or optically active 1,2-dithiols (equations 219)[293].

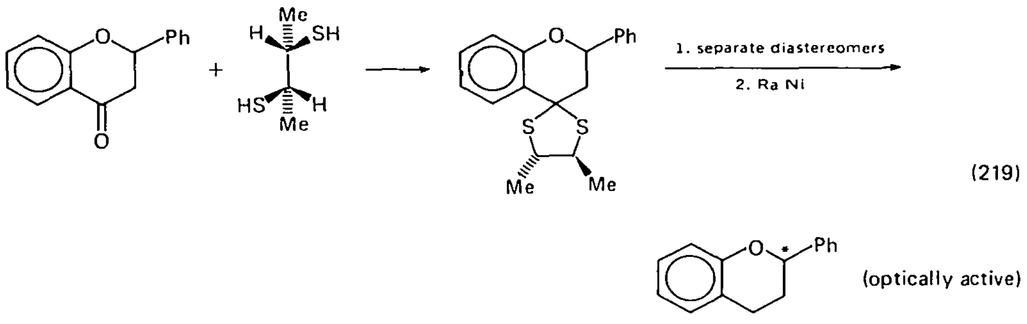
Under the usual conditions of desulphurization, olefinic double bonds, carbonyl and nitro groups are reduced, azoxybenzene and hydrazobenzene suffer reductive cleavage of the N–N bond and benzyl alcohol yields toluene[294]. Raney nickel can be deactivated by refluxing with acetone but this does not always prevent undesired side-reactions (see equation 220[295]). Other examples of undesired reactions occurring with Raney nickel are shown in equations (221)[296] and (222)[268]. In the synthesis of the Cecropia juvenile hormone via the thiacyclohexene route (equation 223)[297] direct Raney nickel treatment gave poor results so that it was necessary to first employ a lithium/ethylamine reduction to give the lithium thiolates which are then cleanly desulphurized by deactivated Raney nickel. In the Raney nickel desulphurization of α-thio ketone **41**, equation (201) above, it was necessary to follow desulphurization with Jones oxidation in order to reoxidize the alcohol which was formed[267].


C8H17
Ra Ni
HO
H

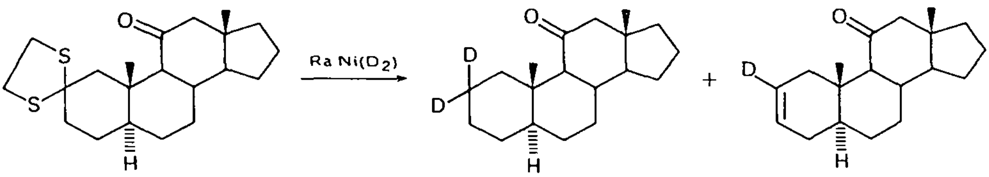
(217)



(218)

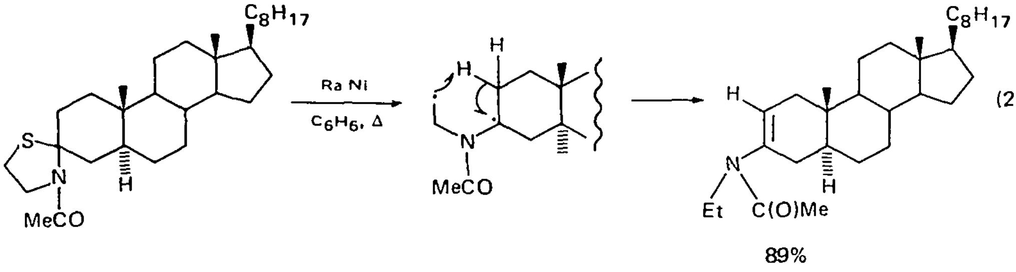

Ph
Me
SH
HS
1. separate diastereomers
2. Ra Ni
(optically active)

(219)

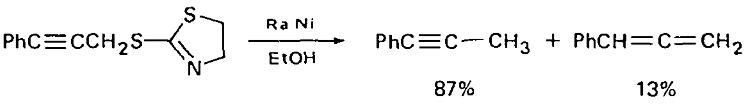


(220)

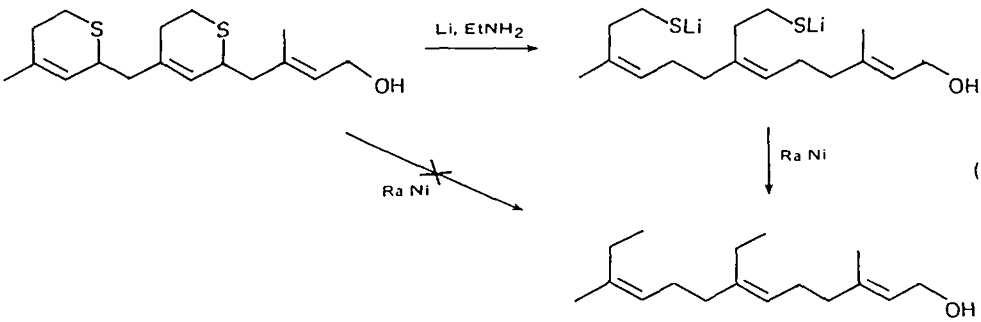
Truce has indicated that nickel boride (Ni_2B), prepared through reaction of sodium borohydride with nickel (II) salts, possesses certain advantages over Raney nickel as a desulphurization agent[298]. These advantages include ease of preparation and handling (nonpyrophoric) and the fact that it can be used to selectively remove


C8H17
Ra Ni
C6H6, Δ
MeCO
H
Et C(O)Me
89%

(221)


PhC≡CCH2S
Ra Ni
EtOH
PhC≡C—CH3 + PhCH=C=CH2
87%
13%

(222)

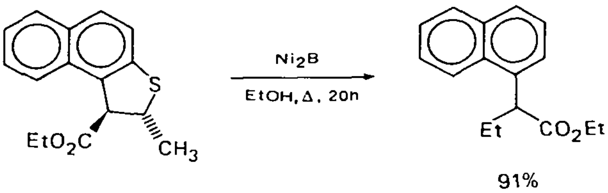

Li, EtNH2
SLi
OH
Ra Ni
Ra Ni

(223)

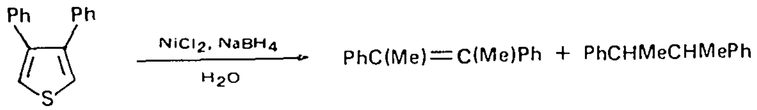
mercapto, sulphide and sulphoxide groups without disturbing sulphone groups which may be present or to selectively remove one of the sulphur atoms of a dithioacetal function (equation 224[299]; it should be noted that this same type of partial desulphurization can be effected in related systems with 'aged' Raney nickel[300]). Some examples of nickel boride desulphurizations are shown in equations (225)[267], (226)[301] and (227)[302].

Raney cobalt, prepared in a manner analogous to Raney nickel, is said to be less reactive than Raney nickel in desulphurizations[303]. However, certain complex cobalt-containing catalysts are of considerable utility in the commercial process of hydrodesulphurization, a process for the removal of organically-bound sulphur from coal and crude oils. In this process a $CoO-MoO_3-Al_2O_3$ (CMA) catalyst

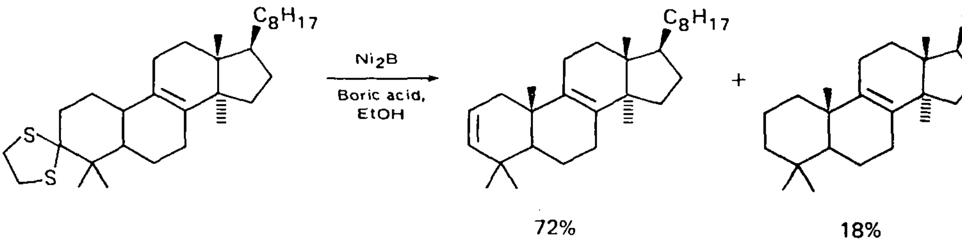
$$\mathrm{PhC(SPh)_2C(O)Ph} \xrightarrow{\mathrm{Ni_2B}} \mathrm{PhCH(SPh)C(O)Ph} \qquad (224)$$


S
EtO2C
CH3
Ni2B
EtOH, Δ, 20h
Et CO2Et
91%

(225)


Ph Ph
S
NiCl2, NaBH4
H2O
PhC(Me)=C(Me)Ph + PhCHMeCHMePh

(226)

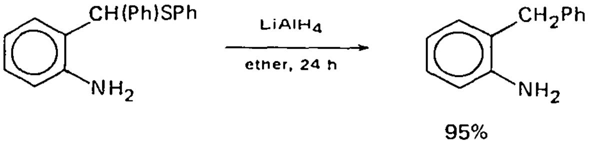

C8H17
Ni2B
Boric acid,
EtOH
C8H17
+
C8H17
72%
18%

(227)

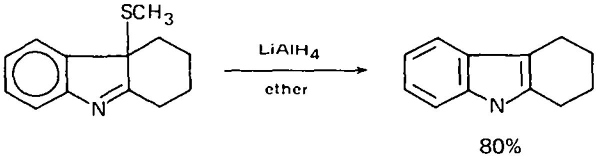
'presulphided' with H_2S/H_2 is employed in a flow system at 250–400°C with H_2 gas at 10–300 atm or alternatively with methanol in place of hydrogen[240,304,305].

C. Lithium Aluminium Hydride and Related Reagents

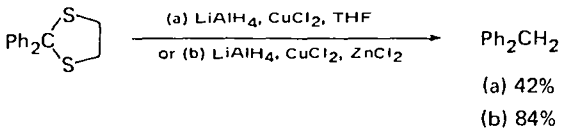
While simple sulphides such as phenyl *n*-propyl sulphide are inert to the action of $LiAlH_4$ even for prolonged periods[306], activated sulphides such as those shown in equations (228)[307] and (229)[308] can be readily reduced. Even sodium borohydride can be used for the reduction in equation (229) (64% yield). Less activated sulphides and dithioacetals undergo reductive desulphurization with $LiAlH_4$ in the presence of certain metallic salts including copper (II) (equations 230 and 231[309]), copper (II) plus zinc (II) (equations 230[309,310] and 232[311]), copper (II) plus lithium


CH(Ph)SPh
NH2
LiAlH4
ether, 24 h
CH2Ph
NH2
95%

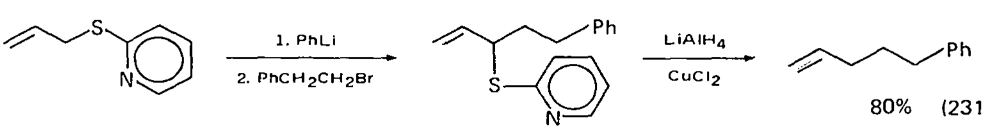
(228)


SCH3
N
LiAlH4
ether
N
80%

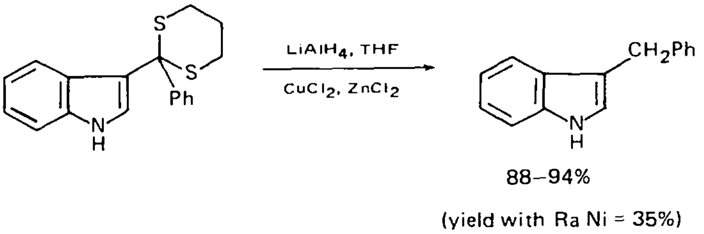
(229)


Ph2C
S
S
(a) LiAlH4, CuCl2, THF
or (b) LiAlH4, CuCl2, ZnCl2
Ph2CH2
(a) 42%
(b) 84%

(230)

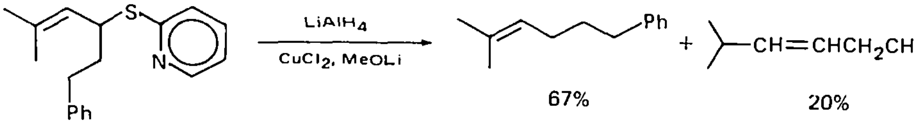

S
N
1. PhLi
2. PhCH2CH2Br
Ph
S
N
LiAlH4
CuCl2
Ph
80%

(231)

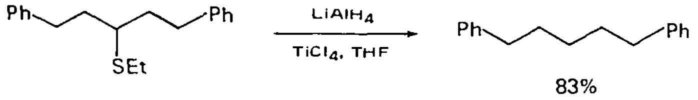

S
S
Ph
N
H
LiAlH4, THF
CuCl2, ZnCl2
CH2Ph
N
H
88–94%
(yield with Ra Ni = 35%)

(232)

methoxide (equation 233[312]), and titanium (IV) (equation 234[8]; see also equation 5).


S
N
Ph
LiAlH$_4$
CuCl$_2$, MeOLi
Ph
+
CH=CHCH$_2$CH$_2$Ph
67%
20%

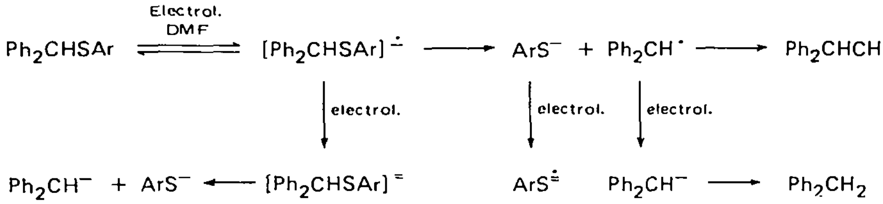
(233)


Ph
Ph
SEt
LiAlH$_4$
TiCl$_4$, THF
Ph
Ph
83%

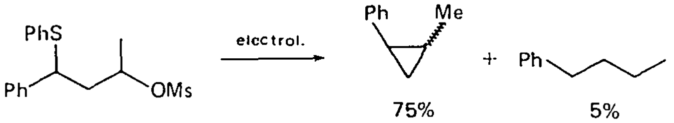
(234)

D. Electrochemical and Photochemical Methods

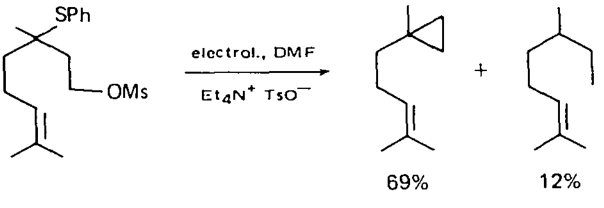
Aryl sulphides undergo reductive C—S cleavage on electrolysis. The overall electrochemical reaction is similar to reductive cleavage by alkali metals, discussed above. Thus initial formation of a sulphide radical anion is followed by collapse of this species to a thiolate anion and a carbon radical which latter species is reduced to a carbanion. Other likely processes include further reduction of the sulphide radical anion to a dianion which fragments to two anions, and reduction of the thiolate anion to a radical dianion (see equation 235[313]). Rather negative potentials ($-E_{1/2}$ ca. 2.7 V) must be employed to reduce aryl alkyl sulphides[314]. Electrolysis in liquid ammonia of *S*-benzylcysteine effects removal of the benzyl groups[315] while electrolysis in DMF of certain γ-mesyl sulphides provides a novel cyclopropane synthesis (equations 236 and 237[316]). The lower reduction potential of these γ-mesyl sulphides ($E_p = -1.60$ V) compared to thioanisole ($E_p < -2.20$ V) and *n*-butyl methanesulphonate ($E_p < -2.20$ V) suggests interaction between the phenylthio and methanesulphonate group in the electron transfer step[316].


Electrol.
DMF
Ph$_2$CHSAr
[Ph$_2$CHSAr]$^{\dot{-}}$
ArS$^-$ + Ph$_2$CH$^\cdot$
Ph$_2$CHCHPh$_2$
electrol.
electrol.
electrol.
Ph$_2$CH$^-$ + ArS$^-$
[Ph$_2$CHSAr]$^=$
ArS$^{\dot{=}}$
Ph$_2$CH$^-$
Ph$_2$CH$_2$

(235)

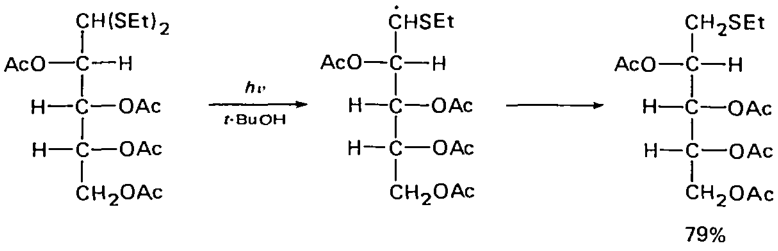

PhS
Ph
OMs
electrol.
Ph
Me
+
Ph
75%
5%

(236)


SPh
OMs
electrol., DMF
Et$_4$N$^+$ TsO$^-$
+
69%
12%

(237)

Dithioacetals on irradiation in alcohols undergo partial desulphurization affording sulphides (equation 238[317,318]). The same reaction can be achieved with aged Raney nickel as well[318].


(238)

E. Other Reducing Agents

Chromous chloride has been found to effect selective reduction of tris(phenylthio)methyl compounds to bis(phenylthio)methyl derivatives in good yields[319].

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 14

Oxiranes

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Abbreviations

AcAc	Acetylacetone
DATMP	Diethylaluminium 2,2,6,6-tetramethylpiperidide
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
LAH	Lithium aluminium hydride
MCPBA	*m*-Chloroperoxybenzoic acid
NBA	*N*-Bromoacetamide
NBS	*N*-Bromosuccinimide
PAA	Peroxyacetic acid
PBA	Peroxybenzoic acid
PNPBA	*p*-Nitroperoxybenzoic acid
TDAP	Tris(dimethylamino)phosphine
TMC	Tetramethyl carbamide
Ts	*p*-Toluenesulphonyl

I. INTRODUCTION

The earlier literature data on the synthesis and chemistry of oxiranes were reviewed by Dittus[1] in 1965 and by Gritter[2] in 1967. Since then, the work relating to the synthesis and chemical transformations of the oxiranes has been surveyed by numerous authors[3-19]. Only a few of these surveys are of a general nature, the majority dealing with some special area. Some of them discuss experimental results that were published five to six years ago. Accordingly, the present review is based mainly on the conclusions drawn from the experimental data of the most recent period (up to the end of 1977). Of the other results since 1965, only those are mentioned that are of general validity, or which were not dealt with in the previous reviews.

II. SYNTHESIS OF OXIRANES

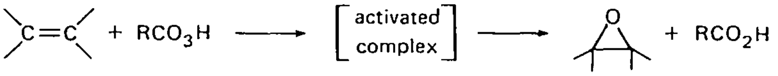
A. By Oxidation of Alkenes

Direct oxidation of alkenes continues to be the main method of preparing oxiranes both in the laboratory and in industry. Significant new results have been achieved in the development of the procedures of liquid-phase oxidation of alkenes. Efforts have been made to perform this oxidation under the mildest possible experimental conditions, which allows an increase in the selectivity of oxirane formation and also the selective oxidation of more sensitive compounds.

1. Oxidation with peroxy acids

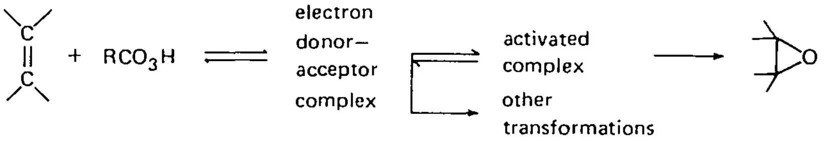
Details on the peroxy acid oxidation of alkenes, the Prilezhaev reaction[18], are to be found in some very good reviews, which deal with the mechanism and stereochemistry of the reaction and its practical modifications[3,6,7,10,11,13,17,18].

The accepted mechanism of alkene oxidation with peroxy acids is that outlined in equation (1). The process involves an addition reaction, where the alkene is the nucleophile and the peroxy acid the electrophile, but binding of the electrophilic species is not followed by binding of an external nucleophilic species.



(1)

The fine mechanism of the reaction is still not known in every respect, for it depends on the electrophilic and nucleophilic characters of the two reactants, their stereostructures and reaction conditions such as temperature, solvent, catalyst, etc. All these factors have a considerable influence on the structure and stability of the transition complex, and on the process determining the reaction rate. After wide-ranging kinetic investigations, Dryuk[20] gave the reaction mechanism as in equation (2). This mechanism is supported by studies of the stereochemical course,



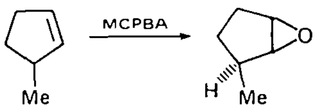
(2)

kinetics and acid catalysis of the reaction, and the side-reactions accompanying it and by the following experimental observations: electron-repelling groups on the alkene increase the reaction rate; the reaction rate is higher for peroxy acids containing electron-attracting substituents; basic solvents decrease the rate of epoxidation. The solvent effect is connected with hydrogen bonds between the peroxy acids and the solvents.

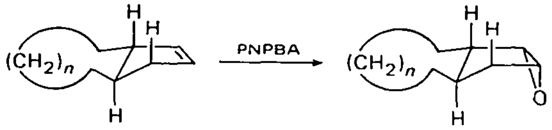
Other investigations[21–28] also deal with the mechanism of the reaction, and with the structure of the transition complex[20,29,30]. Significant conclusions may also be drawn from the results of stereochemical investigations (see below). The 1,3-dipolar cycloaddition mechanism[31–34] has not been confirmed by the recent experimental results.

In contrast with other electrophilic additions, the peroxy acid oxidation is stereochemically *syn*-stereospecific. In the case of cycloalkenes, the C—O bond in the oxirane formed displays axial orientation. With sterically-hindered alkenes, epoxidation occurs from the less-hindered side. The more important stereochemical regularities[13] described earlier for the epoxidation of various types of compounds have been supported by more recent studies; some of these are presented here.

Stereoselectivity to varying degrees has been observed on the peroxy acid epoxidation of some new compound types (equations 3–8)[35–40].

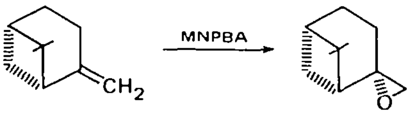


(Ref. 35) (3)

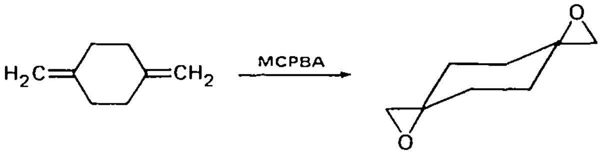

H
H
$(CH_2)_n$
H
PNPBA
H
H
$(CH_2)_n$
O
H

n = 1,2

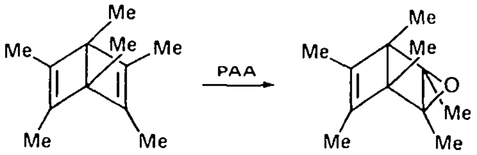
(Ref. 36) (4)



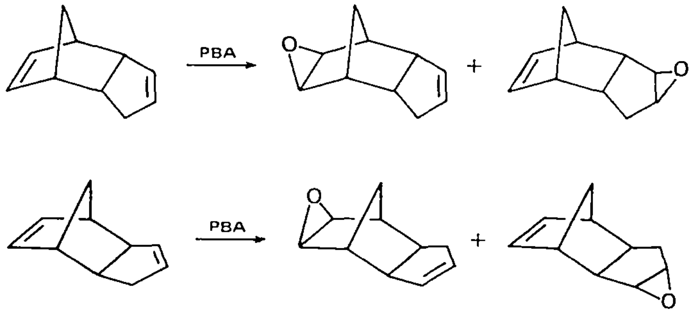
(Ref. 37) (5)


H_2C
CH_2
MCPBA
O
O

(Ref. 38) (6)


Me
Me
Me
Me
Me
Me
PAA
Me
Me
Me
O
Me
Me
Me

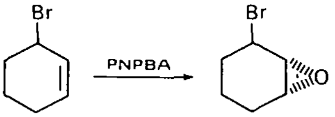
(Ref. 39) (7)


PBA
O
+
O
PBA
O
+
O

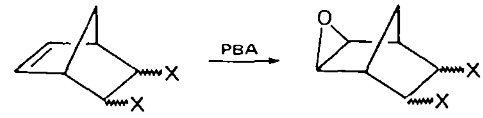
(Ref. 40) (8)

The epoxidation of olefins containing various functional groups is also stereoselective in many cases, as a consequence of steric, electronic and conformational effects. Examples are given in equations (9)–(15)[41–48].

In recent years studies have been made of other compound types and the stereochemical course of their reactions, e.g. for olefins containing a high number

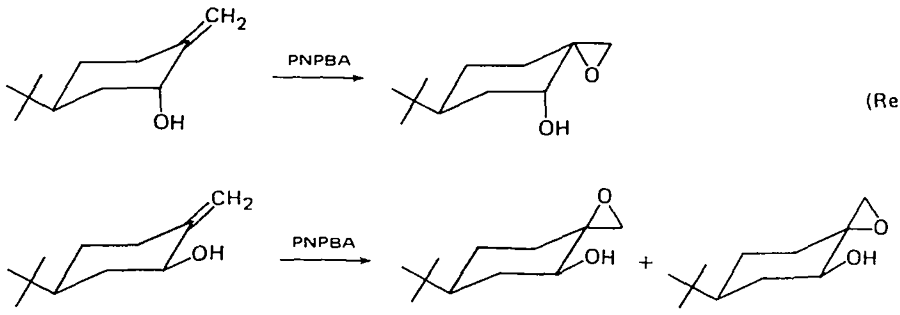

Br
PNPBA
Br
O

(Ref. 41) (9)

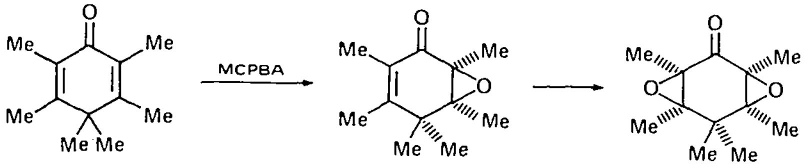


X = Cl,Br,CO_2Me,CN

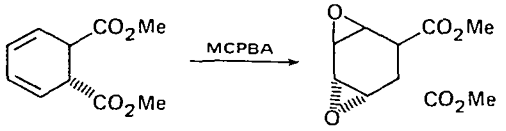
(Ref. 42) (10)


CH2
OH
PNPBA
O
OH
CH2
OH
PNPBA
O
OH
+
O
OH

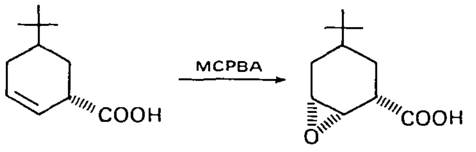
(Ref. 43) (11)


O
Me
Me
Me
Me
Me Me
MCPBA
O
Me
Me
O
Me
Me Me
Me
O
Me
Me
O
O
Me
Me
Me Me

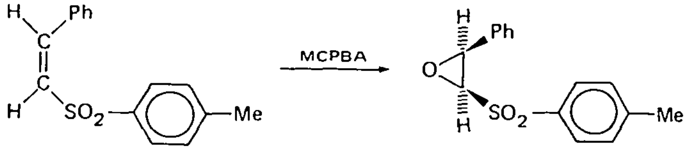
(Ref. 44) (12)


CO2Me
CO2Me
MCPBA
O
CO2Me
CO2Me
O

(Ref. 45) (13)


COOH
MCPBA
COOH
O

(Refs. 46, 47) (14)


H
Ph
C
C
H
SO2
Me
MCPBA
H
Ph
O
H
SO2
Me

(Ref. 48) (15)

of carbon atoms[49], cyclic alkenes and dienes[40,50-55], aromatic systems[56], unsaturated alcohols and their derivatives[57-62], steroids[63-65], unsaturated carboxylic acids and their derivatives[66,67], olefin propellanes[68,69], phosphine oxides[70] and phospholenes[71].

Enantiostereoisomeric oxiranes may be prepared by epoxidation with chiral peroxy acids[72-79]. A method has been elaborated for the separation of racemic oxiranes, using optically active lanthanide complexes[80].

Peroxy acid oxidation is currently the most frequently employed method of epoxidation in the organic preparative laboratory. It gives very good yields, and may also be used for relatively sensitive compounds, such as unsaturated alcohols[81], terpenes[82], acenaphthene[83] and allenes[84-87], or for the preparation of halogenated oxiranes[88-90].

Of the peroxy acids, MCPBA is most favoured, except for procedures elaborated to meet special needs. Alkenes undergoing reaction with difficulty are epoxidized at higher temperature in the presence of radical inhibitors[91]. Peroxy acid stabilizers increase the yield[92]. In the preparation of acid-sensitive oxiranes or the oxidation of acid-sensitive olefins, an alkaline two-phase solvent system is employed at room temperatures[93,94]. Polymer-supported peroxy acids may be used for the oxidation of some olefins[95,96]. In certain cases *in situ* peroxy acid procedures are used[3,97,98].

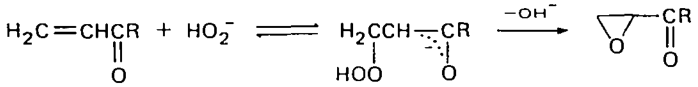
New epoxidizing reagents have recently been introduced, e.g. *o*-sulphoperbenzoic acid[63], *p*-methoxycarbonylperoxybenzoic acid[99], [bis(benzoyldioxy)iodo] benzene[100], *O*-benzylmonoperoxycarbonic acid[101], peroxycarboximidic acids formed from nitriles with hydrogen peroxide[102–107], peroxycarbaminic acids[108,109], peroxyacetyl nitrate[110], disuccinyl peroxide[111] and benzeneperoxyseleninic acid[112].

2. Oxidation with hydrogen peroxide

Hydrogen peroxide may be used for epoxidation in the presence of phenyl isocyanate[113]. Hydrogen peroxide as a direct epoxidizing agent can be employed for the epoxidation of electron-poor olefins. The procedures are of great importance, since compounds may thus be epoxidized even when the peroxy acid procedures have proved ineffective.

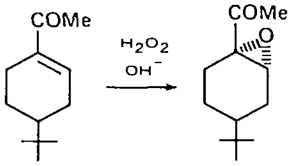
a. Oxidation with alkaline hydrogen peroxide. The earlier literature has been reviewed by Berti[13]. The essence of the method is illustrated in equations (16) and (17). The mechanism of the process depends on the starting compound. No general and completely clear-cut correlations have yet emerged as regards the stereochemistry or stereoselectivity of this epoxidation.

$$H_2O_2 + OH^- \rightleftharpoons HO_2^- + H_2O \qquad (16)$$

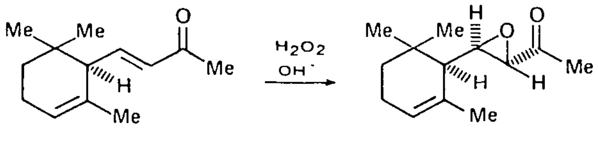


$$H_2C{=}CH\underset{\underset{\displaystyle O}{\|}}{C}R + HO_2^- \rightleftharpoons H_2\underset{\displaystyle HOO}{\overset{}{C}}CH{-}\underset{\displaystyle O^-}{C}R \xrightarrow{-OH^-} \overset{O}{\triangle}{-}\underset{\underset{\displaystyle O}{\|}}{C}R \qquad (17)$$

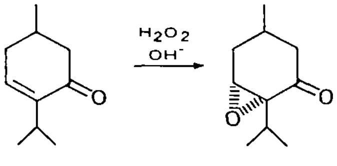
The procedure has been employed effectively for numerous types of compounds: α,β-unsaturated ketones[114–117], nitro olefins[118], α,β-unsaturated nitriles[119,120] *endo*- and *exo*-cyclic enones[121–123] and steroids[124–128]. The epoxidation is often of very high stereoselectivity (equations 18–22):



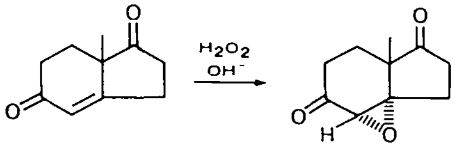
(Ref. 129) (18)



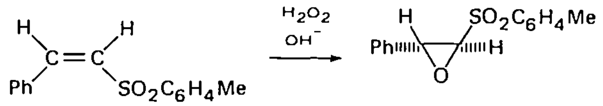
(Ref. 130) (19)



(Ref. 131) (20)

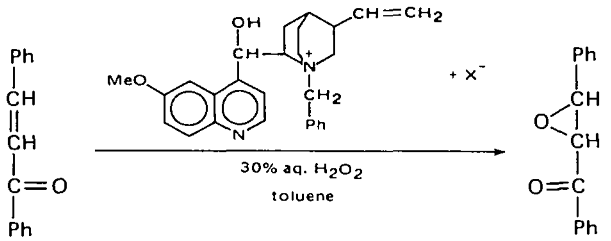


(Ref. 132) (21)



(Refs. 48, 133) (22)

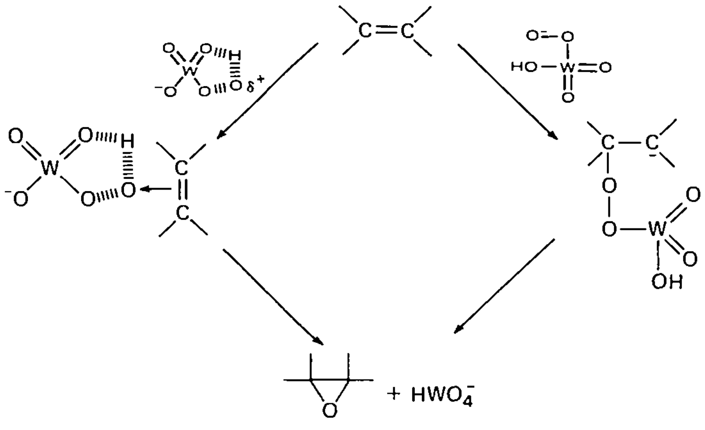
With a chiral phase-transfer catalyst being used as base, optically-active oxiranes may be prepared in excellent yield[134] (equation 23).



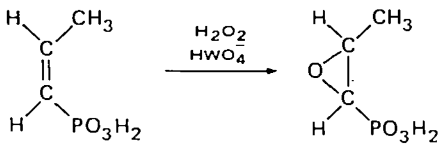
(23)

Hydrogen peroxide is also used in the new procedure of Kametani and co-workers[135].

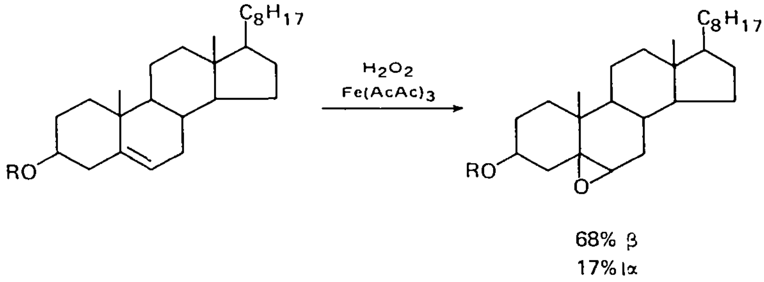
b. Oxidation with hydrogen peroxide and catalyst. Some acids and their various transition metal salts are used as catalysts[10,136–144]. The most frequent catalyst is sodium tungstate ($HWO_4^- + H_2O_2 \rightleftharpoons HWO_5^- + H_2O$), which may behave both as a nucleophilic and an electrophilic reagent, depending on the substrate and the experimental conditions. The epoxidation process is shown in equation (24). Mechanistic studies confirm this reaction path[142,143,145–149], and at the same time provide information on the stereochemical course of the reaction[150–152] (equations 25 and 26).



(24)

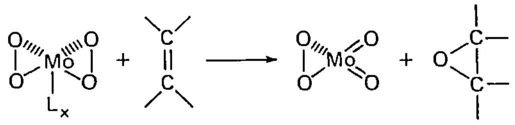


(25)



(26)

Peroxo complexes readily prepared from hydrogen peroxide and MoO_3 can be likewise employed to produce oxiranes[153–156] (equation 27).

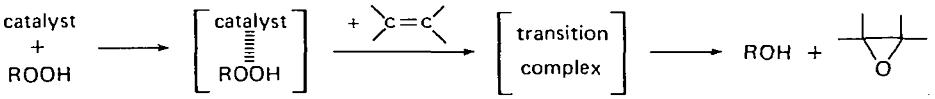


(27)

Useful conclusions have been reached as regards the mechanism[156–159] and stereochemistry[160] of the epoxidation process.

3. *Oxidation with organic hydroperoxides*

Epoxidation of olefins with organic hydroperoxides and metal complex catalysts is both a laboratory method and an industrial procedure. Many reviews[10,161–164] and patents[165–170] deal with this topic. The essence of the procedure is given in equation (28). The following organic hydroperoxides are most frequently used for epoxidation: *t*-butyl hydroperoxide[171,172], cumene hydroperoxide[173,174], ethylbenzene hydroperoxide[175,176] and *t*-amyl hydroperoxide[177]. The effect of the hydroperoxide structure on the epoxidation is discussed by Sheldon and coworkers[178].

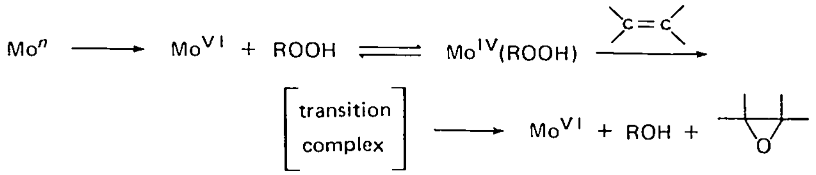


(28)

The catalysts employed fall into two main groups. In the first we have compounds of metals from Groups VIII and IB of the periodic system (mainly Fe, Co and Cu), which initiate processes with free-radical mechanisms via the homolysis of the organic hydroperoxides. The second includes compounds of metals from Groups IVB, VB and VIB (mainly Mo, W, V, Cr and Ti), which exert their catalytic effects by means of heterolysis of the O—O bond. The various Mo and V complexes have found the widest application[179,180]. In the liquid-phase homogeneous catalytic procedure, the metal compounds used (acetylacetonates, naphthenates, carbonyls, oxalates, chlorides, nitrates, etc. and complexes containing different ligands) dissolve well under the given experimental conditions. For heterogeneous catalysis, catalysts supported on Al_2O_3 and SiO_2[181–183] and catalysts bound to synthetic resin[184,185] are mainly used. Various boron compounds have been similarly applied as catalysts or catalyst components[186–189].

The increasing demands relating to the epoxidation procedure are demonstrated not only by the patents, but also by the research aimed at improving the economic efficiency of the method[190,191]. Very recent investigations[192,193] indicate that with chiral metal complex catalysts the method may be employed to prepare enantiomers.

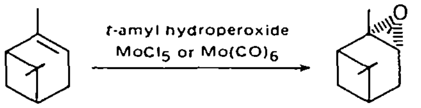
With a view to gaining a deeper understanding of the mechanism of the epoxidation process, wide-ranging examinations of the following have been carried out: reaction kinetics[172,174,194–207], isotope tracing[159,208], intermediates[195,209–213], transition complexes[156,157,174,178,194,214,215], various spectra[212,216,217], stereochemistry (see later) and solvent effects[179,218]. These indicate that the epoxidation mechanism involves the steps shown in equation (29).



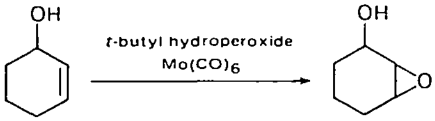
(29)

The mechanism may vary very considerably, depending on the catalyst used, the substrate and the reaction parameters. It is most important to study and understand the coordination of hydroperoxide by the catalyst centre, and the rate-determining oxygen transfer.

Stereochemical examinations have confirmed the stereoselective character of the epoxidation process[164]. From *cis*-olefins *cis*-oxiranes are formed, and from *trans*-olefins *trans*-oxiranes[174]. The epoxidation of cyclic olefins was also shown to be stereoselective[177]. Besides permitting unambiguous conclusions as to the mechanism of the epoxidation, the stereoselective epoxidation of olefins containing various functional groups is also of great preparative importance[57,219–227] (e.g. equations 30 and 31).



(Ref. 177) (30)



(Ref. 222) (31)

4. Oxidation with oxygen

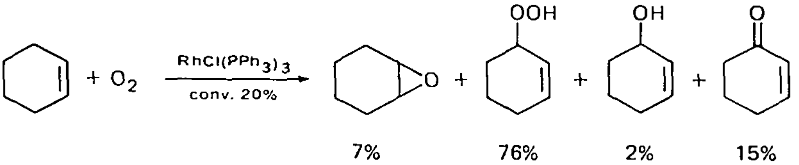
The literature data relating to the procedures are summarized in some monographs and reviews[10,164,228,229]. Direct olefin epoxidation methods with oxygen can be divided into two main groups: oxidation with oxygen without the application of catalysts, and homogeneous and heterogeneous catalytic epoxidation procedures.

Epoxidation procedures not involving catalysts may be classified on the basis of the step-initiating oxidation. Accordingly, they may be thermal procedures[230–232], photocatalytic procedures[233–237] or radical-catalysed procedures[238,239]. Special mention must be made of the cooxidation procedures[10,236,238,240–242], in which the alkenes are oxidized in the presence of substances prone to radical formation.

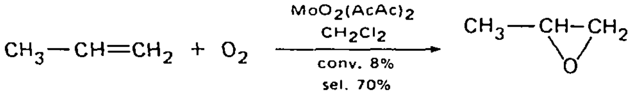
If these methods are compared, from the aspect of application, with the methods described previously and those to be discussed below, the following conclusions may be drawn. The selectivity of these direct oxidation procedures is low; only in certain cases does the yield attain 50%[230,243], although an excellent yield has been described by Shimizu and Bartlett[236]. Thus, they are not very satisfactory as laboratory procedures, but may be of industrial importance in the case of simpler olefins.

A very large number of publications have appeared on studies of the mechanisms[232,236,243-248] and stereochemistry[40,235,236,238,245] of the processes. The epoxidation process is a radical chain-reaction. Depending on the reaction conditions, the chain-propagating radical may be the peroxyacyl radical, the alkenylperoxy radical, etc. In some cases the epoxidation is stereoselective[235].

The procedures based on catalysis by metal complexes are results of research in the past decade. Their great advantages are the considerably lower temperature and the improved selectivity, and hence higher oxirane yields may be attained under milder experimental conditions. It is useful to divide into two main groups the complex catalysts employed in the oxidation of olefins[164]. The first (group A) contains the complexes of the Group VIIB, VIII and IB metals (mainly Co, Ni, Mn, Cu, Ir, Rh, Pt and Ru), and the second (group B) those of the Group IVB, VB and VIB metals (mainly Mo, V, W, Cr and Ti). The oxidizing activity of the group A compounds is higher, but at the same time the selectivity is generally low. Reference may be made to some recent experimental data[249-254], while one reaction is given as illustration[249] in equation (32). Certain metal complexes from group B epoxidize alkenes with lower activity, but with considerably higher selectivity[255-258] (equation 33). Epoxidation by these methods is the subject of several patents[259-262]. Work has also been carried out with mixtures of metal complexes from groups A and B[222,249,263,264].



(32)



(33)

Investigations on the mechanism of epoxidation in the presence of metal complexes have been reported in many papers[257,264-273]. In general, these suggest that the process occurs by a radical chain-reaction, the characters of the key intermediates being fundamentally influenced by the properties of the central metal atom and of the ligands surrounding it, and also by the nature of the substrate.

More recent data on olefins with various heterogeneous catalysts mainly deal with the Ag-catalyst procedure[274-278]. Detailed kinetic studies[279-282] and the stereochemistry of the epoxidation[283] have been reported, as well as the use of new heterogeneous catalysts[261,284-293].

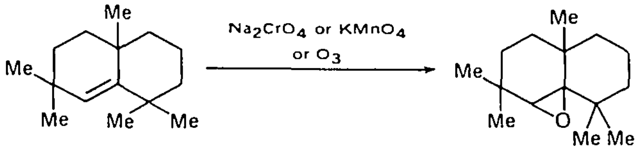
5. *Other methods of oxidation*

Other methods may be employed, mainly when a very hindered double bond is to be epoxidized, or in the event of special needs. Experimental results described for ozone, chromic acid, permanganate and hypochlorite ion are reviewed by Berti[13].

Oxidation with ozone was found to be stereospecific[13]. Ozone has also been used for the epoxidation of propylene in such a way that intermediates suitable for epoxidation were first prepared from it[294,295].

Chromic acid oxidation may be employed only with tri- and tetra-substituted olefins[296-298]. The mechanism of the process seems to involve a carbonium ion type intermediate[298,299].

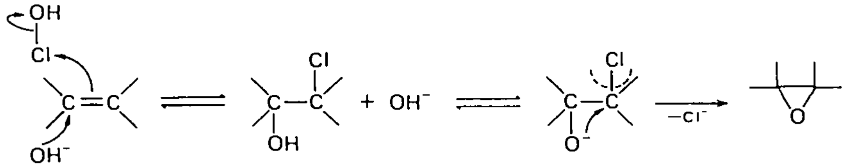
Epoxidation of **1** with peracetic acid is not stereoselective, but with Na_2CrO_4, $KMnO_4$ or O_3 high stereoselectivity is observed[52] (equation 34).



(1)

(34)

Hypochloric acid and its salts can be used primarily for the epoxidation of electron-poor olefins, and very favourably because of the stereospecific nature of the process[48,300]. A *cis*-oxirane is formed from a *cis*-olefin. The mechanism of the process may be explained in accordance with equation (35)[300].



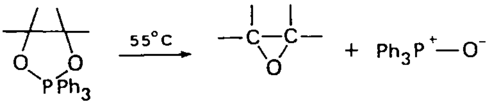
(35)

With this method, 3,4-epoxybutanone-2 can be prepared in very good yield[301], as can phenanthrene 9,10-oxide with a phase-transfer catalyst[302].

Shackelford and coworkers[303] have elaborated a new stereoselective epoxidation method, with an alkaline solution of xenon trioxide. Kruse and coworkers[304] achieved good oxirane yields by applying $NaClO_3$, OsO_4 and $Tl(OAc)_3$ for the epoxidation of C_4 alkenes.

The electrochemical oxidation of olefins has also been used to prepare oxiranes[305].

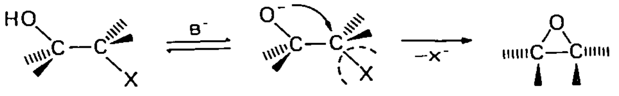
Five-membered cyclic phosphoranes are transformed almost quantitatively to oxiranes[306] (equation 36).



(36)

B. From 1,2-Difunctional Compounds by 1,3-Elimination

2-Substituted alkanols and their esters can be converted to oxiranes by 1,3-elimination via an S_Ni mechanism (equation 37). In the transition state of the



(37)

X = Cl, Br, I, OSO_2R, OCOR, NR_3^+, N_2^+, OH elimination process, the reacting groups are in the antiperiplanar conformation. The oxirane formation is stereospecific. The importance of the individual procedures is very well reflected by the recently published reviews[13,16,17]. Studies on the mechanism[307,308] and stereochemistry of the different reactions have revealed many of their details and the scope of their applicability.

Most papers describe the use of halohydrins, which can be prepared relatively simply and stereospecifically by various procedures: from olefins by the addition of hypohalous acids [usually produced *in situ* e.g. from *t*-butyl hypochlorite[309], *N*-bromosuccinimide (NBS)[35,310,311] or *N*-bromoacetamide (NBA)[36,38,312]], from α-haloketones by reduction[313,314] and from α-halooxo compounds by a Grignard reaction[315]. Epoxycyanides may be obtained from bromoketones by the action of cyanide[316,317]. Iodohydrins may be prepared from olefins in the presence of oxidants[318].

Four chlorohydrin isomers prepared from 3-*t*-butylcyclohexene are transformed stereoselectively to the corresponding *cis*- and *trans*-oxiranes[319]. In conformity with earlier stereochemical studies, variously substituted *trans*(diaxial)-cyclohexanehalohydrins are converted to oxirane derivatives, and the corresponding *cis* compounds to cyclohexanone derivatives in the presence of Ag_2CO_3/celite[320].

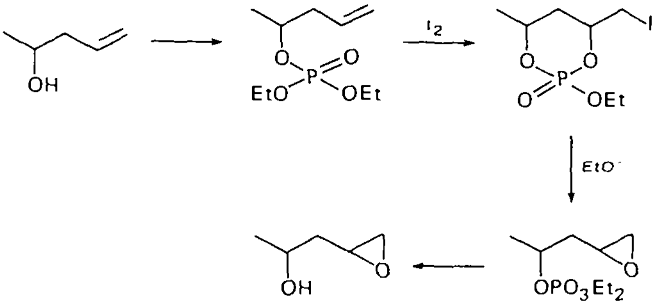
The halohydrin route has been used to prepare good yields of α,β-epoxysulphonamides[321], α-fluorooxiranes[315,322], α-bromooxiranes[314] and optically active oxiranes[323,324].

With NBS, a stereospecific method has been developed for the preparation of vinyloxiranes containing *Z*-configuration double bonds[325]. NBS can also be used in the selective epoxidation of the terminal C=C bond of polyenes[311].

Aromatic oxiranes are mainly prepared by the alkaline reaction of haloacetates[326–329].

By a modification of the halohydrin method, with the use of tributylethoxytin or tributyl-2-halogenalkoxytin, oxiranes may be prepared in excellent yields[330].

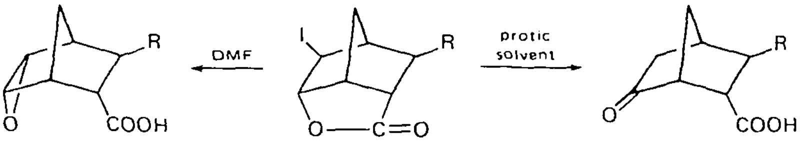
If the iodohydrins can be prepared, high oxirane yields can be achieved[331]. With the modification of the iodohydrin method shown in equation (38), a general



(38)

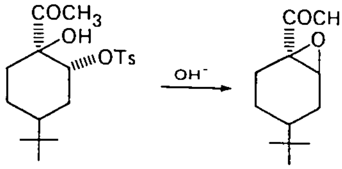
procedure has been elaborated for the stereocontrolled synthesis of acyclic oxiranes[332].

In an aprotic solvent, the bicyclo[2.2.1]heptane iodolactone can be converted to an oxirane derivative[333] (equation 39).

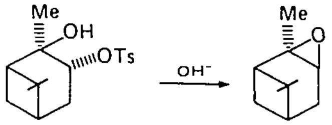


(39)

A widely used method is to prepare sulphonate esters from 1,2-diols by a generally regioselective reaction, and to transform these to oxiranes under basic conditions. This ring-closure method too is stereoselective[129,334-338] (e.g. equations 40 and 41).

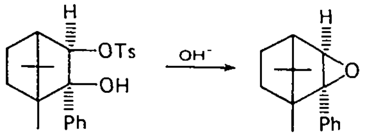

COCH3
OH
OTs
OH⁻
COCH3
O

(Ref. 129) (40)


Me
OH
OTs
OH⁻
Me
O

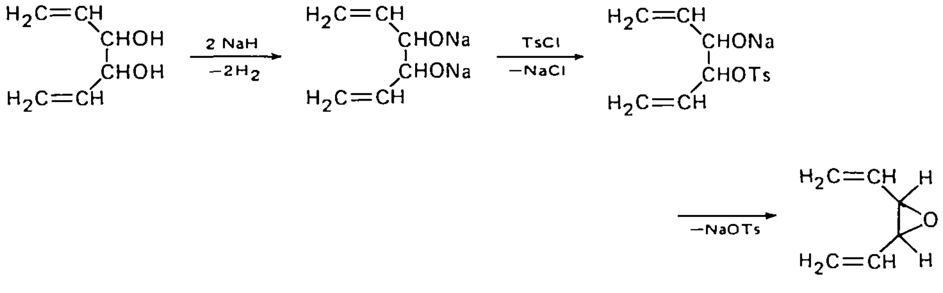
(Ref. 336) (41)

An exception to the *anti* elimination rule was found when the oxirane compound was formed from the *cis*-tosylate[339] (equation 42).


H
OTs
OH
Ph
OH⁻
H
O
Ph

(42)

Cis- and *trans*-2 may be prepared from the corresponding diols (equation 43)[334].


H2C=CH
CHOH
CHOH
H2C=CH
2 NaH
−2H2
H2C=CH
CHONa
CHONa
H2C=CH
TsCl
−NaCl
H2C=CH
CHONa
CHOTs
H2C=CH
−NaOTs
H2C=CH
H
O
H2C=CH
H

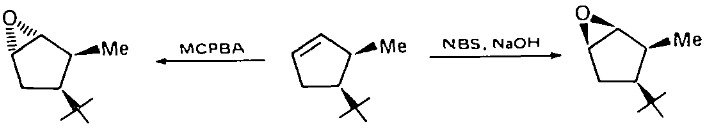
(43)

(2)

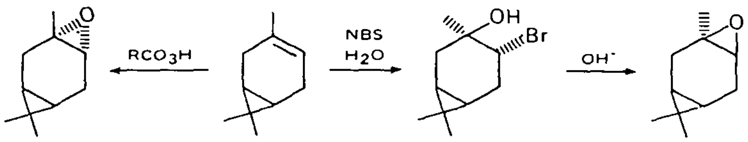
Carboxylate anions[340], trimethylammonium ions[341-343] and diazonium ions[331] have also featured as leaving groups for oxirane synthesis.

In the preparation of alkali-sensitive oxiranes, Ag_2O is used for ring-closure of the halohydrins[344-346].

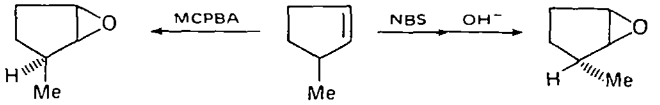
In many cases the 1,3-elimination procedures cannot be replaced by other oxidation methods, due to the sensitivity of the starting substituted olefin[347]. An important application of the halohydrin procedure is for the preparation of oxiranes with configurations opposite to those obtained with the peroxy acid method[35,36,38,312,348-351] (equations 44–46). The method can be similarly employed for the stereoselective preparation of steroid β-oxiranes[346,352]. A new stereospecific chlorooxirane synthesis has been developed with *t*-butyl hypochlorite as epoxidizing


O
Me
MCPBA
Me
NBS, NaOH
O
Me

(Ref. 348) (44)

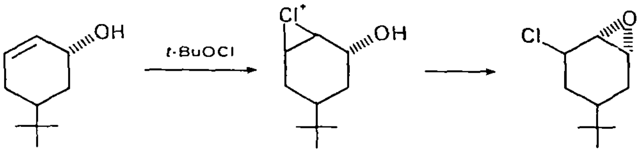

RCO3H
NBS
H2O
OH
Br
OH⁻
O

(Ref. 349) (45)


MCPBA
NBS OH⁻
Me
H
O

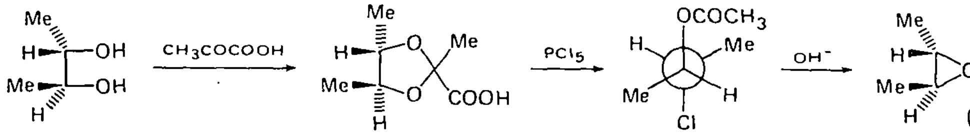
(Ref. 35) (46)

agent[309]. The reaction proceeds with neighbouring-group participation (equation 47). Steroid chlorooxiranes are formed by a similar reaction mechanism[353].

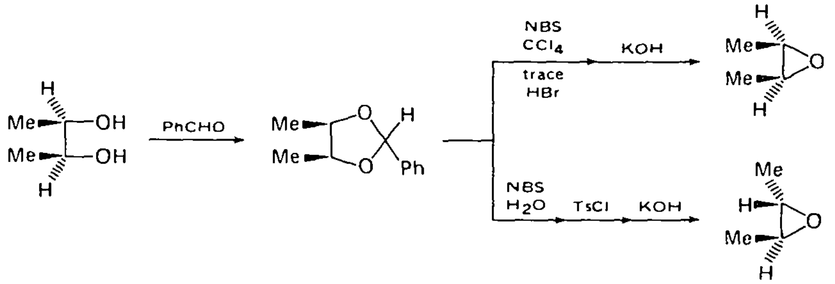

OH
t-BuOCl
Cl⁺
Cl
O

(47)

The 1,3-elimination method can be similarly used for the stereoselective preparation of acyclic oxiranes. Three such methods have been published in recent years; these have the common feature that the synthesis is achieved via cyclic intermediates[332,354,355]. As an example, the synthesis of *R*,*R*-2,3-epoxybutane[354] is shown in equation (48). Double inversion occurs, so that the diol and the oxirane have the same configurations. Both oxirane isomers may be prepared from the same diol[355] (equation 49).

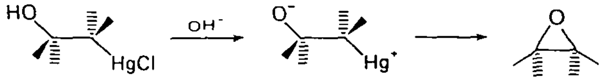

Me
H
OH
CH3COCOOH
COOH
PCl5
OCOCH3
Cl
OH⁻
O

(48)


PhCHO
Ph
NBS
CCl4
trace
HBr
KOH
NBS
H2O
TsCl
KOH
Me
H
OH
O

(49)

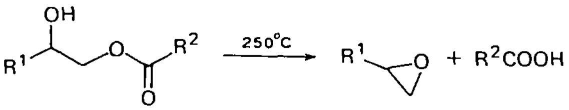
Another 1,3-elimination is the base-catalysed decomposition of β-hydroxyalkylmercurichlorides[356] (equation 50). The reaction is accompanied by the formation of isomeric oxo compounds.


HO
HgCl
OH⁻
O⁻
Hg⁺
O

(50)

Oxiranes have been prepared by the thermolysis of 1,2-diol monoesters[357] (equation 51).

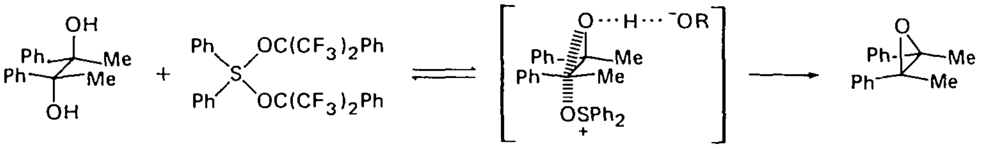
Oxiranes may be formed by the dehydration of 1,2-diols. The presence of oxirane as intermediate has been demonstrated in the pinacoline-type rearrangement of


OH
R1
O
R2
O
250°C
R1
O
+ R2COOH

(51)

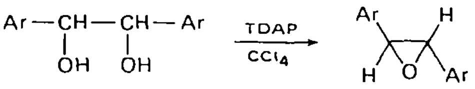
tetraarylethylene glycol[358]. Formation of the oxirane ring has similarly been proved in the case of diols with a steroid skeleton[359], and on the dehydration of diamantyl glycol in the presence of acids[360].

A one-step synthesis of oxiranes has been achieved in the reaction of diaryldialkoxysulphuranes with 1,2-diols[361] (equation 52).


OH
Ph
Me
Ph
Me
OH
+
Ph
OC(CF3)2Ph
S
Ph
OC(CF3)2Ph
O···H···⁻OR
Ph
Me
Ph
Me
OSPh2
+
O
Ph
Me
Ph
Me

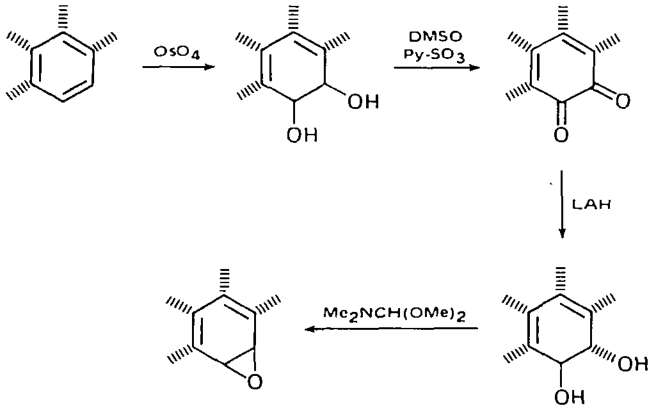
(52)

Oxiranes may also be prepared with TDAP from *meso*-1,2-diols in the presence of CCl$_4$[362,363] (equation 53).


Ar—CH—CH—Ar
OH OH
TDAP
CCl4
Ar
H
H
O
Ar

(53)

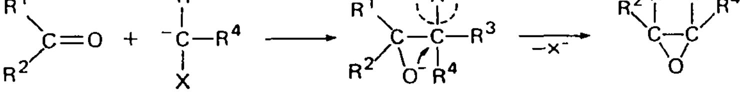
A general method has been developed for the preparation of polycyclic aromatic oxiranes; the final reaction step is the conversion of the corresponding diol to the oxirane by heating with DMF–dimethylacetal[364-366] (equation 54).


OsO4
OH
OH
DMSO
Py-SO3
O
O
LAH
Me2NCH(OMe)2
O
OH
OH

(54)

C. From Carbonyl Compounds

Various nucleophiles react with carbonyl compounds to produce new C–C bonds, and oxiranes are formed. Depending on the nucleophilic reagent, numerous modifications of the procedure outlined in equation (55) have been developed. A number of monographs treat the individual methods from different aspects[1,13,16,17]. Here we shall confine ourselves to a brief survey relating to the procedures, stressing the results of the past few years.

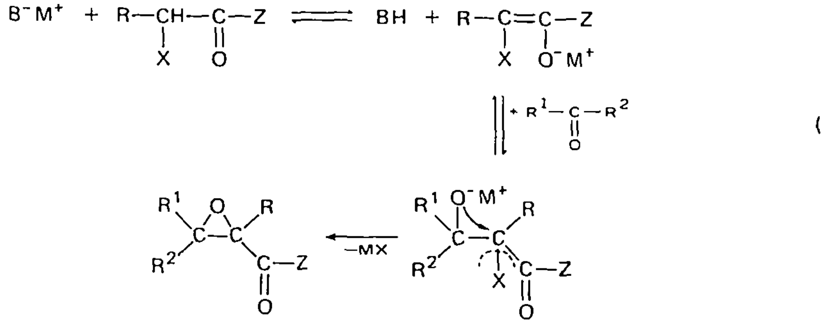

R1
C=O
R2
+
R3
⁻C—R4
X
R1
X
C—C—R3
R2
O⁻
R4
−X⁻
R2
R1
R3
R4
C—C
O

(55)

The most useful method for the preparation of oxiranes containing substituents of an electronegative nature is the Darzens reaction, which proceeds by the above scheme. Besides carbonyl compounds, the following may serve as starting material: α-halocarbonyl compounds[367,368], α-halocarboxylic acid derivatives[369–377], α-halonitriles[378–382], α-halosulphoxides[383,384], α-halosulphones[385,386] and α-halosulphides[387].

The reaction has been studied in detail to establish the effects of various solvents and bases[13]. The phase-transfer catalysis technique has recently been introduced[381,382,386].

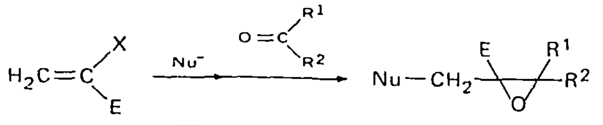
Detailed information on studies of the mechanism of the Darzens reaction is to be found in the literature[13]; it is concluded that[372] the formation of the oxiranes can be interpreted as the result of three reaction steps: proton exchange, aldolization and ring-closure (equation 56).



(56)

In spite of complex investigations[13,378], a uniform picture has not yet emerged as to the steric course of the reaction. The stereochemistry of the process is influenced by the substituents, the base employed and the solvent.

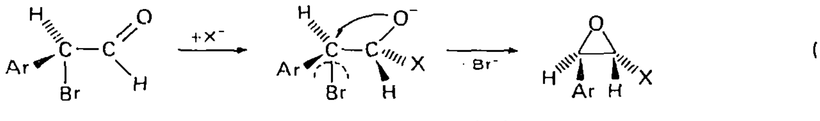
The Darzens reaction was further developed by White[388] (equation 57).



(57)

X = CN, Cl
E = CN, Cl, COOEt
Nu = stabilized carbanion

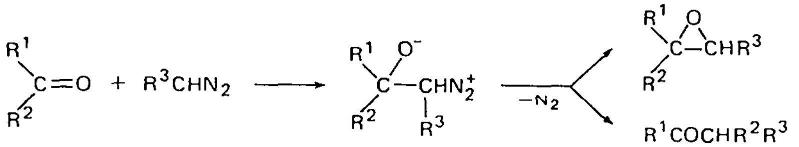
In a manner analogous to the Darzens reaction, 2-methoxyoxiranes and 2-cyanooxiranes can be prepared from carbonyl compounds with methoxide ion[389] or cyanide ion[316,317] (equation 58).



(58)

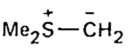
β-Epoxyketones may be prepared in good yield (50–80%) by the dimerization of α-bromoketones in the presence of $Ni(CO)_4$ in DMF[390].

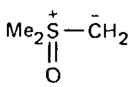
Diazoalkanes with carbonyl compounds give two main products: an oxirane and a carbonyl compound isomeric with this[391] (equation 59). The first step is nucleophilic attack of the diazoalkane. The main conclusions in connection with the reaction are as follows[13]. Of the two parallel reactions, oxirane formation is

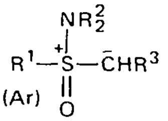

(59)

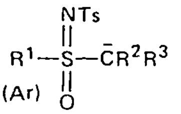
generally of subordinate importance, but may predominate with acyclic carbonyl compounds having electron-attracting substituents in the α-position. Equatorial attack of the diazoalkane is favoured in the case of cyclic ketones. In spite of recent new applications[392–395], the procedure is of minor importance for the preparation of oxiranes.

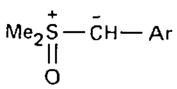
A very good method for the preparation of oxiranes from carbonyl compounds is the Corey synthesis[13,16,17] with sulphonium (3) and oxosulphonium (4) ylides. Recent investigations have led to the proposal of many active methylene transfer reagents, such as 5–9.

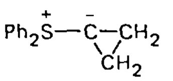

(3)

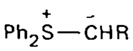

(4)


(5)[396–398]

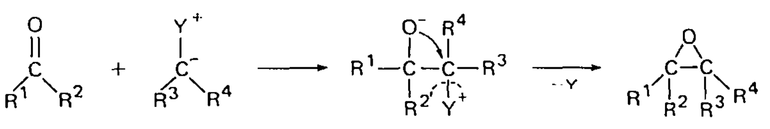

(6)[399, 400]


(7)[401]


(8)[402]

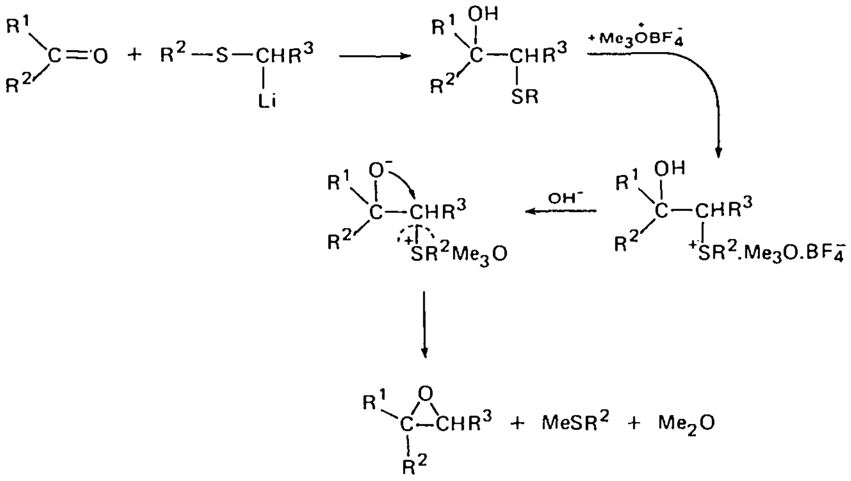

(9)[403]

Yields of more than 80% may be attained. The reagents can in general be easily prepared and stored. Because of all these advantages, different variants of the procedure have become widely used[13,402,404–409]. Introduction of the phase-transfer technique means further advantages of application[410,411]. Asymmetric syntheses too may be carried out with optically-active reagents[412–414]. The currently accepted mechanism of the process is shown in equation (60).


(60)

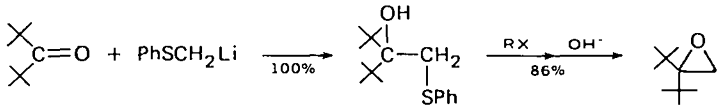
Many authors have dealt with the stereochemistry of the reaction[13,338,396,399,401,415–417]. The reaction is in general stereospecific; the reagent used has a substantial effect on the stereochemical course. Less bulky reagents (e.g. **3**) attack the C=O group from the more sterically hindered side, and the bulkier reagents (e.g. **4**, but also the decisive majority of reagents generally) from the less sterically hindered side[13].

Oxiranes can also be prepared from carbonyl compounds with reagents of type $RSCH_2Li$[401,418–421] (equation 61). As in the Corey reaction, the process



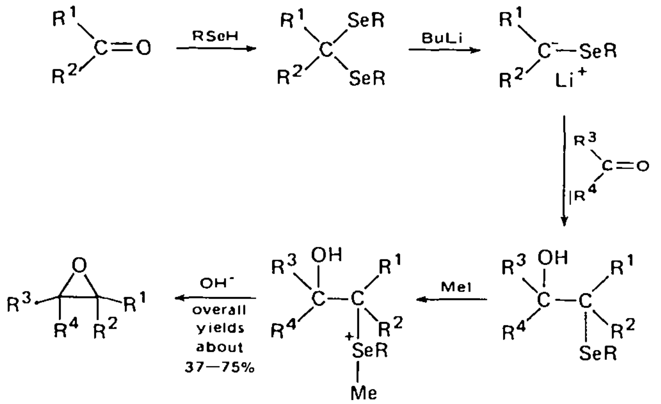
(61)

takes place via a betaine intermediate. Yields vary between 50 and 90%[420] (equation 62).



(62)

A method similar in principle was developed recently[422–427]. The new reagent is the alkylseleno or arylseleno carbanion, comparatively simply prepared from carbonyl compounds (equation 63).

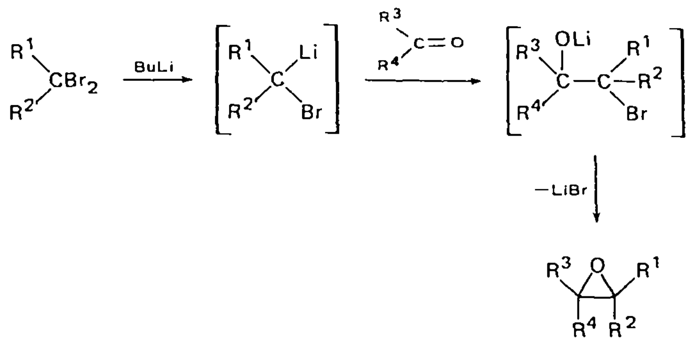


(63)

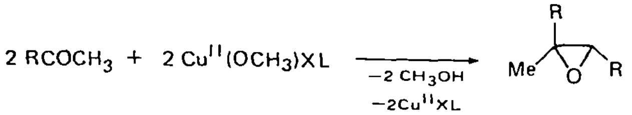
Carbonyl compounds with a geminal bromolithium reagent prepared *in situ* also give oxiranes[428–430] (equation 64). The yield is 60–70%.

Oxiranes are found by the reaction of two moles of an aromatic aldehyde with TDAP[13,431,432].

A new catalytic procedure has been developed for the preparation of α-keto-oxiranes (yield ca. 90%), by the reaction of ketones or keto alcohols with copper(II) methoxides of the type CuX(OMe)L (where X = Cl^-, Br^- or ClO_4^-, and L = pyridine, bipyridyl, etc.)[433,434] (equation 65).



(64)



(65)

III. REACTIONS OF OXIRANES

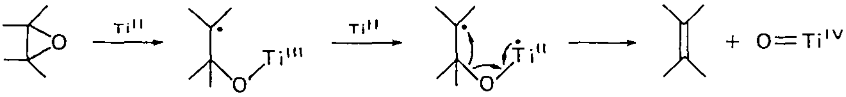
A. Deoxygenation

Deoxygenation may be induced with both electrophilic and nucleophilic reagents. The former attack at the oxygen atom of the oxirane, and the latter at the carbon atom linked to the oxygen. The question of which of the two carbon atoms of the oxirane ring is attacked by the reagent is decided by the substituents on them and by the nucleophilic reagent. In certain cases the deoxygenation is stereospecific, so that, depending on the reagents and reaction conditions employed, retention or inversion may occur. On the basis of the results of the past few years[16], this type of reaction has become suitable for the stereospecific preparation of olefins.

1. Deoxygenation with electrophilic reagents

The metals of the first transition series fall into the following sequence as regards their activities in deoxygenation reactions[435]: V > Cr > Co > Ti > Ni. The metal atom attacks at the oxygen, and isomeric radicals are formed as intermediates[436]. The metal pair Zn–Cu is also used as a reagent[437,438]. This deoxygenation is not stereoselective, as the rate of rotation about the C–C bond in the intermediate radical is almost the same as the rate of formation of the C=C bond.

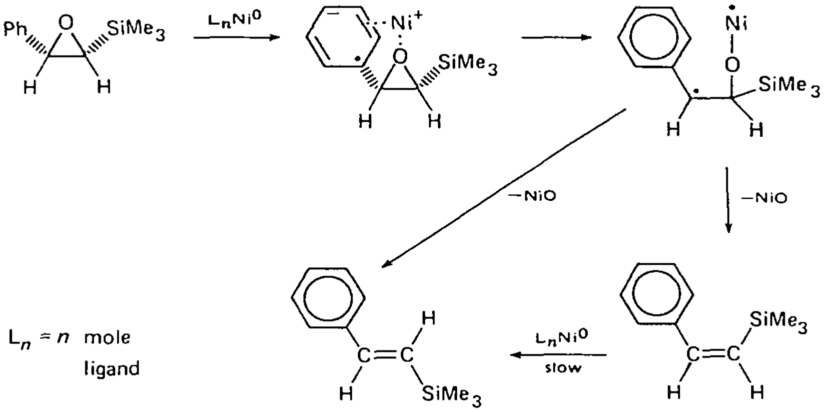
With Ti(II) as reagent, prepared from $TiCl_3$ with $LiAlH_4$, the mechanism of the deoxygenation may be outlined as in equation (66)[439].



(66)

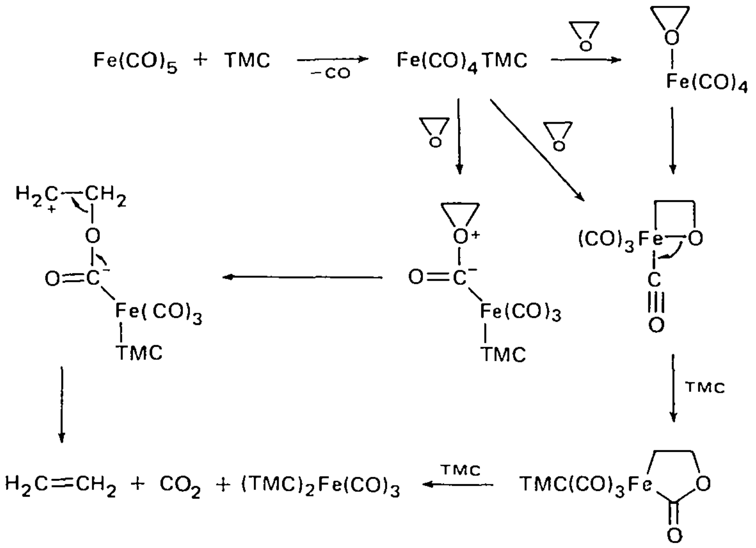
$MgBr_2$ + Mg/Hg may also be used as deoxygenating agents[440]. In deoxygenations with tungsten reagents obtained from WCl_6 with various lithium compounds, stereoselectivity accompanied by retention has been observed in all cases[441]. Metal complexes too may be applied as electrophilic deoxygenating reagents for oxiranes containing electron-attracting substituents[442] (equation 67).

Other electrophilic deoxygenating reagents are cobalt and iron carbonyls[443]. In the case of *cis-* and *trans*-epoxymethyl succinates the deoxygenation is stereo-


Ph
SiMe3
H
H
LnNi0
Ni+
O
SiMe3
H
H
Ni
O
SiMe3
H
H
−NiO
−NiO
Ln = n mole ligand
H
C=C
H
SiMe3
LnNi0
slow
SiMe3
C=C
H
H

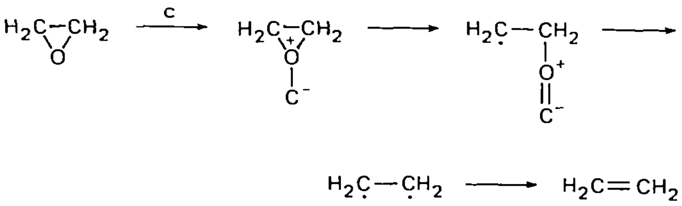
(67)

selective, leading to inversion in both cases. In the presence of iron pentacarbonyl tetramethylcarbamide (TMC), oxirane undergoes deoxygenation in accordance with the mechanism shown in equation 68[444]. It can be seen from this scheme that both the central atom and one of the ligands may act as the electrophilic centre of the reagent.


Fe(CO)5 + TMC
−CO
Fe(CO)4TMC
O
Fe(CO)4
H2C−CH2
O
O=C−
Fe(CO)3
TMC
O+
O=C−
Fe(CO)3
TMC
(CO)3Fe
O
C
O
TMC
H2C=CH2 + CO2 + (TMC)2Fe(CO)3
TMC
TMC(CO)3Fe
O
O

(68)

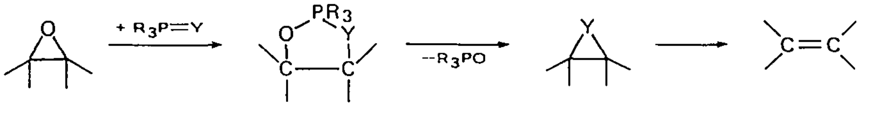
Chemically produced carbon atoms may also be utilized for deoxygenation[445–447] (equation 69). A high degree of stereoselectivity with retention of the configuration has been observed on the deoxygenation of *cis*- and *trans*-2,3-dimethyloxiranes with carbon atoms[447].


H2C−CH2
O
C
H2C−CH2
O
C−
H2C−CH2
O+
C−
H2C−CH2
H2C=CH2

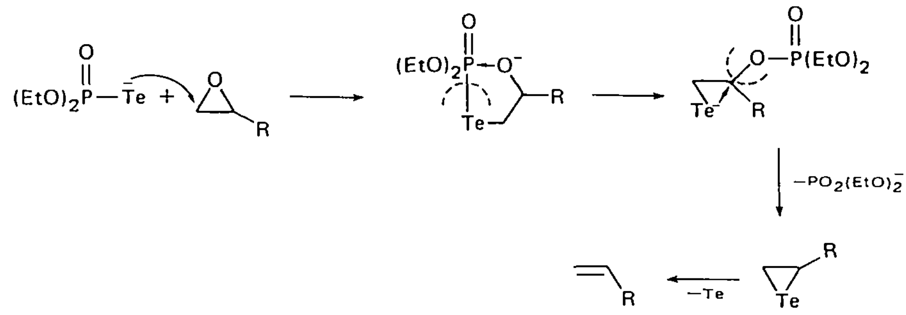
(69)

2. Deoxygenation with nucleophilic reagents

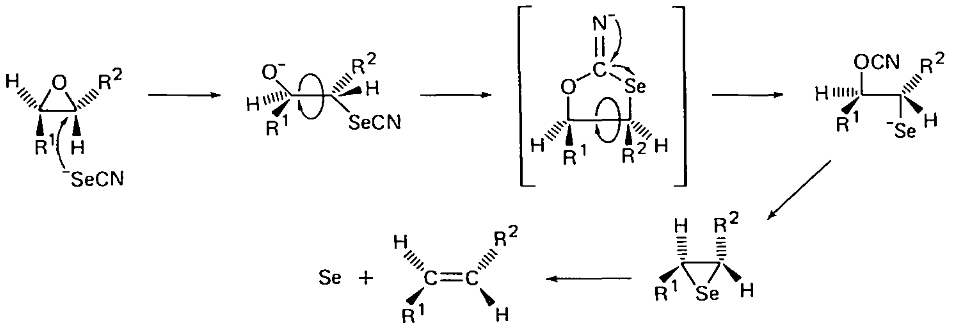
One of the most important representatives of this type is the deoxygenation of oxiranes with compounds $R_3P{=}Y$[448] (where Y may be S[449], Se[450] or Te[451]). In such reactions, first heteroatom exchange occurs, and then the olefins are formed by elimination of the heteroatom of the resulting episulphide, episelenide or epitelluride[448] (equation 70). These deoxygenation methods are stereospecific, with retention of configuration. With sodium *O*,*O*-diethyl phosphorotelluroate as reagent, the reaction is explained as in equation (71)[451]. Deoxygenation via heteroatom exchange can also be achieved with KSeCN[452] (equation 72).


+ R3P=Y
PR3
O
Y
C
C
−R3PO
Y
C=C

(70)

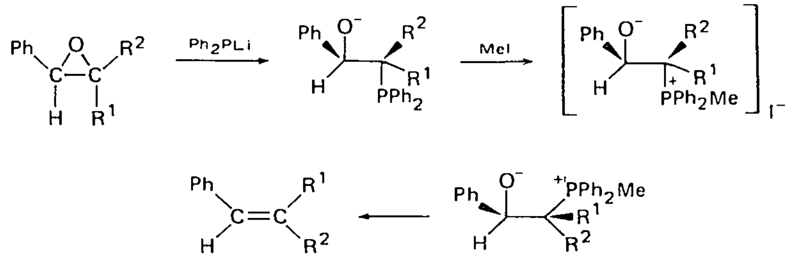

(EtO)2P—Te
O
R
(EtO)2P—O−
Te
R
O—P(EtO)2
Te
R
−PO2(EtO)2−
R
Te
R
−Te

(71)


H
O
R2
R1
H
−SeCN
O−
R2
H
H
R1
SeCN
N−
C
O
Se
H
R1
R2
H
OCN
R2
H
R1
−Se
H
H
R2
R1
Se
H
Se +
H
R2
C=C
R1
H

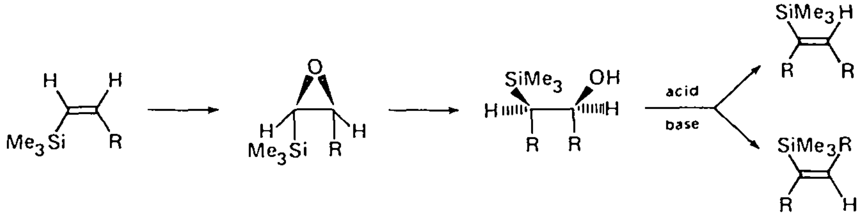
(72)

Ph_2PLi too is suitable for deoxygenation[453,454] (equation 73). Since the nature of the method is stereospecific, it is suitable for the isomerization of olefins via oxiranes.


Ph
O
R2
C—C
H
R1
Ph2PLi
Ph
O−
R2
H
R1
PPh2
MeI
Ph
O−
R2
H
R1
PPh2Me
I−
Ph
R1
C=C
H
R2
Ph
O−
+PPh2Me
R1
H
R2

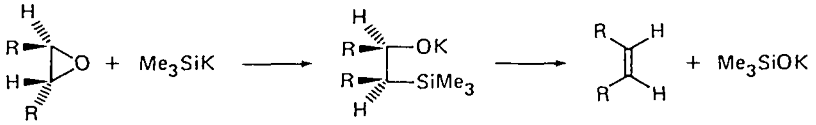
(73)

α,β-Epoxysilanes can be subjected to stereospecific deoxygenation by various methods[455,456]. This procedure is also suitable for the isomerization of olefins, and for the preparation of heteroatom-substituted olefins with epoxysilanes[456]. Inversion occurs if the silyl alcohol formed in the first step is reacted with acid, whereas reaction with base results in retention (equation 74).



(74)

Deoxygenation with trimethylsilylpotassium[457] is stereospecific and is accompanied by inversion (equation 75).



(75)

If oxiranes are reacted with organolithium compounds, in addition to deoxygenation substituted olefins are formed[458].

The complexes $K_2Fe(CO)_4$, $KHFe(CO)_4$[459] and $C_5H_5Fe(CO)_2Na$[460,461] may serve as nucleophilic deoxygenating reagents. In the latter case the process is accompanied by retention of configuration.

3. *Other deoxygenations*

Complex oxiranes undergo enzymatic biodeoxygenation[462].

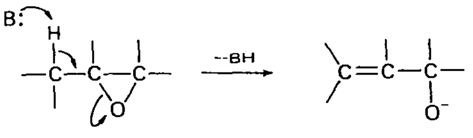
A study has been made of the transformation of cyclohexene oxide on metal complexes of type MY (M = Na, Co, Ni, Cu; Y = ethylenediamine) incorporated into the skeleton of synthetic zeolites[463]. Cyclohexadiene and benzene are formed, as the deoxygenation is followed by dehydrogenation and aromatization. Deoxygenation has also been observed in the catalytic hydrogenolysis of phenyloxiranes[464].

B. Rearrangements

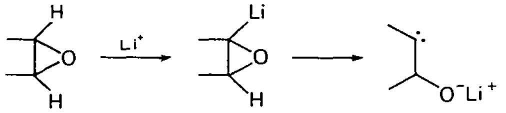
Because of the strained ring, the oxiranes are very reactive compounds, and are capable of many types of rearrangements, discussed in several recent reviews[5,9,12,16,17,465,466]. The main products of the rearrangement of oxiranes are carbonyl compounds and α,β-unsaturated alcohols.

1. *Base-catalysed rearrangements*

The base-catalysed rearrangements involve either α- or β-elimination. The latter is of great synthetic importance, since it gives allyl alcohol derivatives with good stereo- and regio-selectivity (equation 76). α-Elimination is illustrated in equation (77). The carbenoid intermediate[467,468] is stabilized by transannular C—H insertion. If there is no possibility for this, ketones may be formed. Examples are also to be found of γ,δ and ω-eliminations[12].

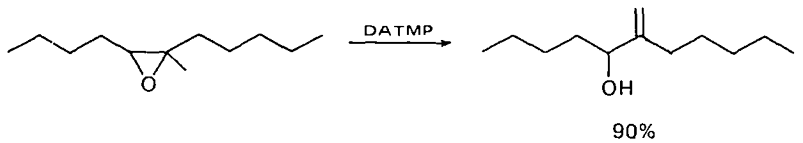


(76)



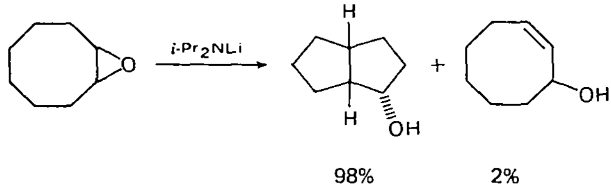
(77)

In the case of aliphatic and alicyclic oxiranes, regioselective hydrogen elimination occurs from the least-substituted carbon atom[469,470,470a], with stereoselective formation of the *trans*-olefin[469,471] and in certain instances the occurrence of *cis* elimination[472]. Equation (78) shows a characteristic example of regio- and stereoselective isomerization[473].

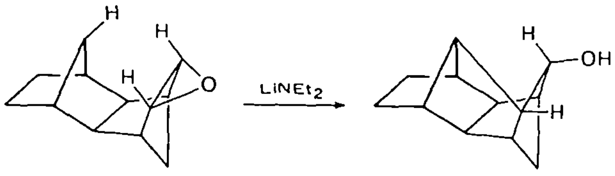


(78)

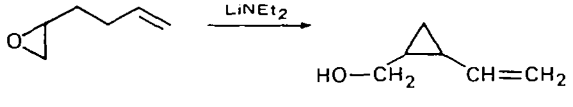
For epoxycyclohexanes the rearrangement to allyl alcohols is maximum with $LiNR_2$ (R = primary alkyl) as reagent; with bulkier bases isomerization occurs to the cyclohexanone[474]. Newer investigations[475] show that at higher temperatures β-elimination and formation of the allyl alcohol is favoured, whereas α-elimination is predominant at lower temperatures. Hence the latter may be suitable for the preparation of bicyclic alcohols. If appropriate reaction conditions are employed, β-elimination can be suppressed[476] (equation 79). Transannular insertion may also be a convenient preparative tool in the case of compounds that are otherwise difficult to prepare[477] (equation 80). Elimination with ketone formation generally occurs if the β-elimination is excluded and no transannular hydrogen is available[478]. With $LiNEt_2$, γ,δ-unsaturated oxiranes are transformed to cyclopropane derivatives[479] (equation 81). Aryl-substituted oxiranes rearrange to carbonyl compounds on the action of $LiNEt_2$[480] (equation 82). In the case of benzyloxirane, however, very rapid β-elimination takes place[481] (equation 83).



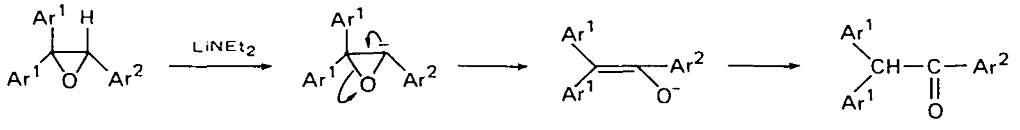
(79)



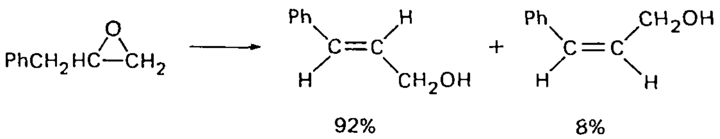
(80)



(81)

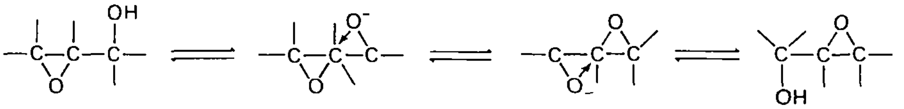


(82)



(83)

Under basic conditions compounds containing a *trans*-hydroxy group in the position α to the oxirane ring tend to be converted to the isomeric α-hydroxyoxirane via intramolecular nucleophilic substitution[9,482,483] (equation 84). The process is known as oxirane migration.



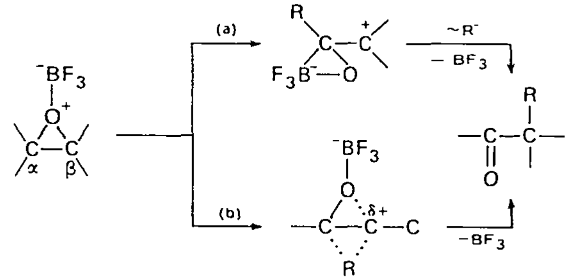
(84)

The rearrangements of α-epoxyketones have been widely studied[64,484–486]. Compounds in which a methylene or methyne group is bonded to the carbon atom adjacent to the carbonyl group, undergo the Favorskii rearrangement (γ-elimination) under nonpolar conditions, and allyl rearrangement under polar conditions. A different rearrangement yields diketones, which undergo benzylic acid rearrangement.

Rearrangements of other oxirane types, on the action of various basic reagents, have also been studied in detail[82,487–494].

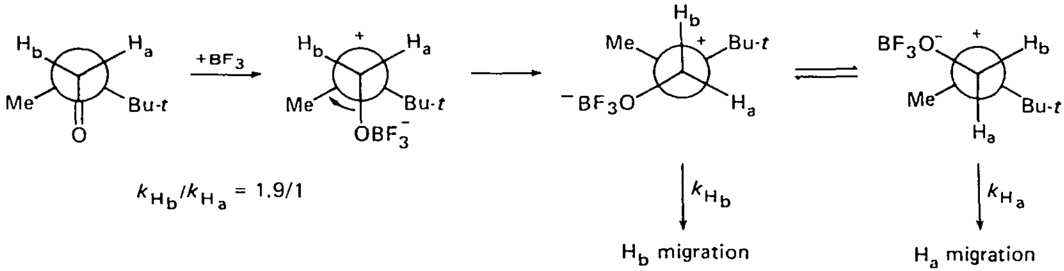
2. *Acid-catalysed rearrangements*

Oxiranes give carbonyl compounds with both Brönsted and Lewis acids. The initial step is the binding of the electrophilic agent, followed by splitting of the C–O bond; this either leads to the formation of a classical carbonium ion, or the bond-splitting and migration of group R occur in a concerted manner (equation 85).



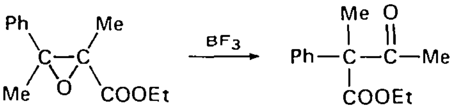
(85)

The nature and rate of the reaction are influenced by the electrophile and also by the substituents. The stereoselective character of the process is generally not too high. From stereochemical data obtained for oxiranes containing a tertiary carbon atom, the formation of a discrete carbonium ion intermediate has been assumed[495–500] (equation 86). To clarify the mechanism of transformation of oxiranes not containing a tertiary carbon atom, the rearrangements of deuterated derivatives of *n*-hexyloxirane have been investigated[501].



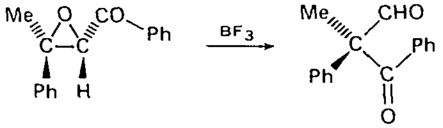
(86)

Many publications have appeared on the isomerizations of alkyl- and aryl-substituted oxiranes also containing various functional groups[500,502–513]. In the rearrangement of oxiranes containing a carbonyl group on the action of Lewis acids, the migration of the functional group may be observed as well[514] (equation 87). In



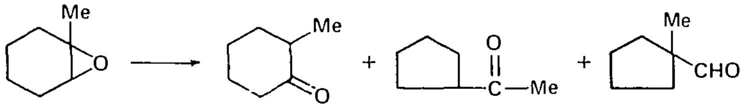
(87)

a study of the Lewis acid-catalysed acyl migration reaction[515], a concerted mechanism was confirmed (equation 88).



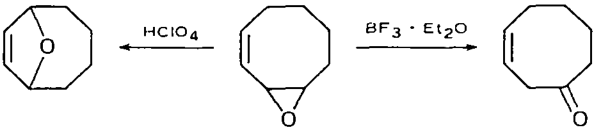
(88)

The isomerizations of the cyclic oxiranes have been examined in detail because of their great variety[345,505,516–524] (e.g. equation 89)[525].

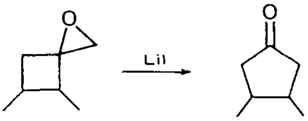


(89)

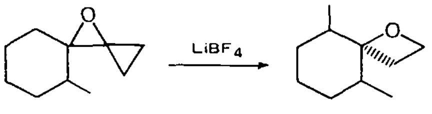
The individual reaction directions are strongly influenced by the reagent employed, the experimental conditions and by electronic and stereochemical factors[526–532] (equations 90–93).



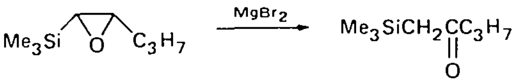
(Ref. 524) (90)



(Ref. 528) (91)

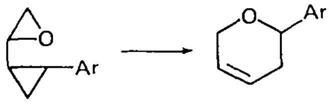


(Ref. 530) (92)

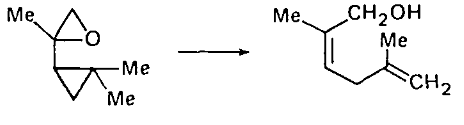


(Ref. 531) (93)

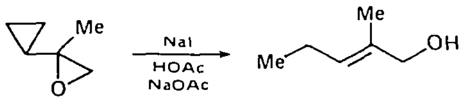
The acid-catalysed isomerization of cyclopropyloxiranes has been studied in some detail[533–537]. The direction of the isomerization depends on the reactant and the experimental conditions (equations 94–96).



(Ref. 535) (94)

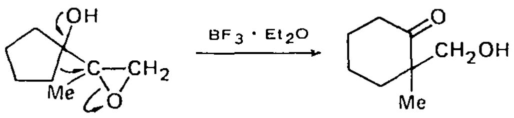


(Ref. 536) (95)



(Ref. 537) (96)

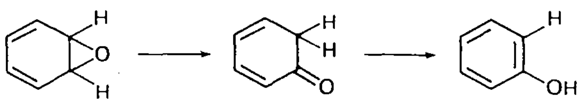
An interesting ring-expansion reaction has been observed for cyclopentanol-oxiranes[538,539] (equation 97).



(97)

Detailed studies have also been made of the isomerizations of various steroid oxiranes[517,540–545]. On the action of $BF_3 \cdot Et_2O$ the oxirane ring linked to the steroid skeleton is isomerized to an oxolane[540]. The ring-expansion is attributed to the overcrowding of the oxirane ring. In the BF_3-catalysed rearrangement of 5,6-epoxy steroids, a long-range substituent effect has been observed[544].

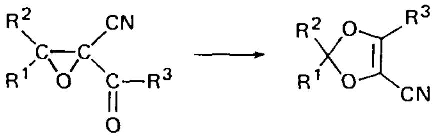
Because of their biochemical interest, arene oxides have recently been subjected to very detailed investigation[546]. These compounds isomerize on the action of acids (equation 98). It was proposed[547–549] that the concerted ring-opening and hydrogen transfer are followed by the dienone–phenol rearrangement. More detailed studies strongly suggest the involvement of a carbonium cation[550].



(98)

3. *Thermal and photochemical rearrangements*

Thermal and photochemical rearrangements of oxiranes involve homolysis of a C–C bond. From a theoretical investigation of the thermal splitting of the C–C bond in the oxirane[551], and on the basis of other studies[552,553], it has been concluded that a biradical structure is more probable than a carbonyl ylide. However, some workers justify the existence of ylide intermediates[554–558]. The formation of the latter was also assumed in the pyrolysis of α-keto-α-cyanooxiranes[559] (equation 99).



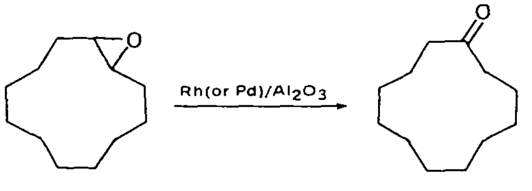
(99)

Various oxiranes have been studied in detail as regards their thermal and photochemical rearrangements in recent years[44,89,390,534,536,560–564a].

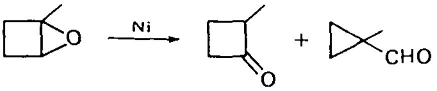
4. *Rearrangement on the action of heterogeneous catalysts and metal complexes*

Most studies deal with the catalytic activities of various metals, metal oxides, phosphates and zeolites.

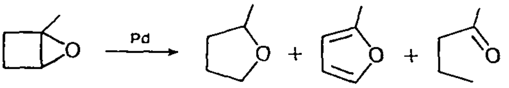
The isomerizing activities of the transition metals have been examined on some model compounds[565–570] (e.g. equations 100–102). The formation of carbonyl compounds is a characteristic transformation.



(Ref. 567) (100)



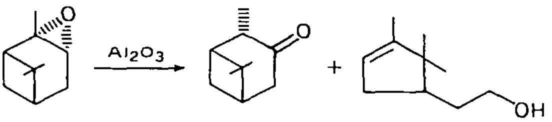
(Ref. 568) (101)



(Ref. 569) (102)

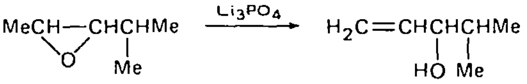
Wide-ranging examinations have been carried out in an attempt to establish the mechanism of the catalytic reaction[565,568,569,571,572].

On oxide catalysts (Al_2O_3, SiO_2, MgO, TiO_2 and ZnO) oxiranes are isomerized to carbonyl compounds and unsaturated alcohols[573–578,526] (e.g. equation 103).



(Ref. 578) (103)

Investigations relating to the isomerizing effect of phosphates[526,579–583] have extended to the catalyst Li_3PO_4. Using the latter, a general method has been elaborated for the preparation of unsaturated alcohols from oxiranes (equation 104).



$$\underset{\text{O}}{\text{MeCH—CH}}\underset{\text{Me}}{\text{CH}}\text{Me} \xrightarrow{Li_3PO_4} H_2C{=}CH\underset{\text{HO}}{\text{CH}}\underset{\text{Me}}{\text{CH}}\text{Me}$$

(Ref. 580) (104)

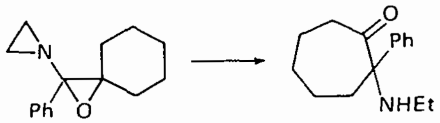
Modified zeolite types catalyse the isomerization of oxiranes to carbonyl compounds also[567,576,584–586].

Recent studies indicate that certain metal complexes also catalyse the isomerization to carbonyl compounds of oxiranes containing a π-electron system[583–593]. The experimental data obtained so far on the isomerization of aliphatic and alicyclic oxiranes have proved that only pentacyanocobalt complexes are active[594].

5. *Other rearrangements*

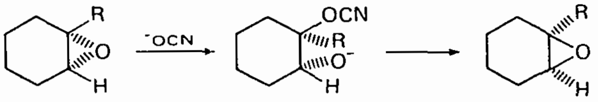
Homoallyl rearrangement occurs with α- and β-pineneoxiranes in the presence of $Et_3N{-}HF$[595]. Phenyloxirane is isomerized to phenylacetaldehyde on natural graphites[596].

Spirooxiranes containing an amine function undergo isomerization accompanied by ring-expansion[597] (equation 105).


N
Ph
O
Ph
NHEt

(105)

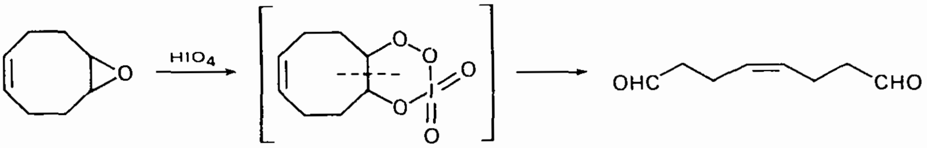
The isomerization presented in equation (106) may be used for the synthesis of oxiranes that are otherwise difficult to prepare (e.g. certain steroid oxiranes)[598,599].


R
O
H
⁻OCN
OCN
R
O⁻
H
R
O
H

(106)

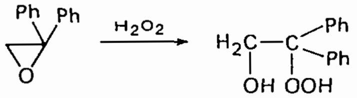
C. Oxidation

Oxidations will be emphasized that are also of preparative importance: On the action of HIO_4, oxiranes containing an olefin bond can be transformed in good yield to dialdehydes, the double bond remaining unaffected[600] (equation 107). Phase-transfer agents can also be used for this oxidation[601].

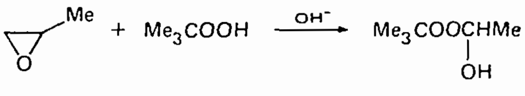

O
HIO4
O
O
I
O
O
O
OHC
CHO

(107)

Dialdehydes may also be prepared using H_2O_2[602], but oxiranes undergo perhydrolysis also with H_2O_2[603a,b] (equation 108). In the base-catalysed addition of hydroperoxides to oxiranes[604] β-hydroxyperoxides are formed (equation 109).

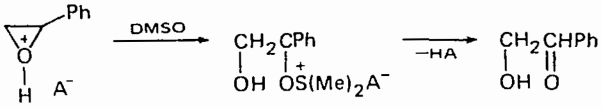

Ph
Ph
O
H2O2
H2C
C
Ph
Ph
OH
OOH

(Ref. 603a) (108)


Me
O
+ Me3COOH
OH⁻
Me3COOCHMe
OH

(109)

On the action of DMSO, α-ketols may be produced[605,606] (equation 110).


Ph
O
H
A⁻
DMSO
CH2CPh
OH OS(Me)2A⁻
−HA
CH2CHPh
OH O

(110)

Oxiranes containing low numbers of carbon atoms may be oxidized to oxalic acid with HNO_3[607].

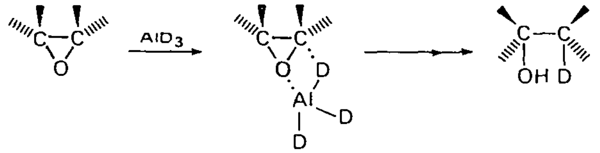
D. Reduction

The reduction of oxiranes with various reagents leads to the formation of alcohols. The development in this area is well reflected by the reviews[5,9,17] that have appeared since 1967[2].

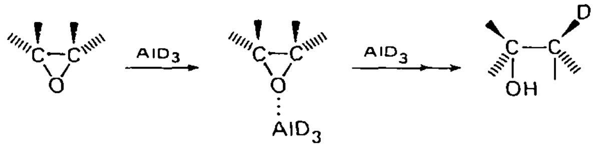
1. Reduction with complex metal hydrides

Most of the publications deal with reduction with $LiAlH_4$. Other reagents used are AlH_3, $LiAlH_4$ + $AlCl_3$, $LiBH_4$, $NaBH_4$, $Zn(BH_4)_2$, and their deuterated analogues.

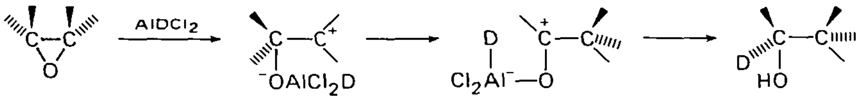
The regioselectivity, stereoselectivity and mechanism of the reaction were studied by Villa and coworkers[505,608-611] who conclude[611] that reduction with a complex metal hydride may proceed either by an intramolecular or an intermolecular mechanism, and that the reduction may also be accompanied by rearrangement (equations 111–113). Whether or not the different individual mechanisms occur is determined by the steric and electric properties of the oxiranes and by the experimental conditions. Other investigations too[327,612,613] support the following findings. On the reduction of oxiranes with $LiAlH_4$, the H^- ion attacks predominantly on the side opposite to the O; that is, the reduction is accompanied by Walden inversion on the carbon atom which took part in the cleavage. In contrast, the carbon atom not participating in the cleavage retains its original configuration. The extent of the inversion depends on the nature of the transition state. If the lifetime of the carbonium ion formed is relatively long, the product is obtained with retention of configuration.



(111)



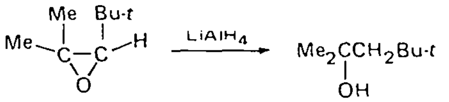
(112)



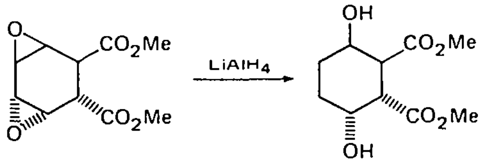
(113)

In the course of the $LiAlH_4$ reduction of oxiranes the H^- ion generally attacks at the least-hindered carbon atom; that is, that carbon atom takes part in the cleavage which has the lowest number of substituents.

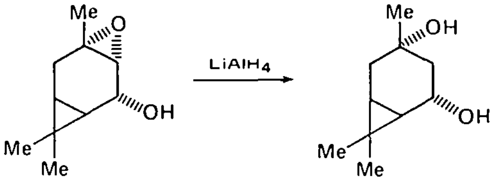
Equations (114)–(117) illustrate some of the regio- and stereo-selective reductions of open-chain and alicyclic oxiranes[37,45,51,219,614-616].



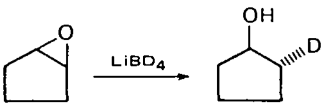
(Ref. 614) (114)



(Ref. 45) (115)



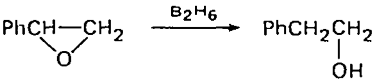
(Ref. 615) (116)



(Ref. 616) (117)

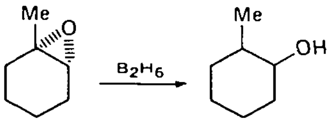
Studies have also been made of the reductions of oxiranes containing other functional groups[87,115,116,470a,617–624].

Oxiranes react with diborane more slowly than with the metal hydrides discussed so far. The oxirane ring is generally opened in the opposite manner to that suggested by the Markownikoff rule[625–627] (e.g. equations 118 and 119). Depending on the reactant and the experimental conditions, however, the ring-opening may also proceed in accordance with the Markownikoff rule[626,628].



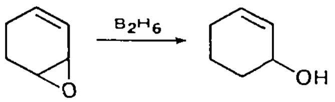
$$\mathrm{PhCH{-}CH_2\ (O)} \xrightarrow{B_2H_6} \mathrm{PhCH_2CH_2OH}$$

(Ref. 625, 626) (118)



(Ref. 627) (119)

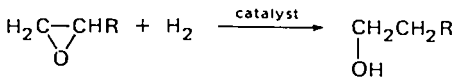
The diborane reduction of α,β-unsaturated oxiranes displays the regioselectivity depicted in equation (120)[629].



(120)

2. *Catalytic hydrogenolysis*

Catalytic hydrogenolysis of oxiranes yields alcohols, and many studies deal with the preparation of primary alcohols from olefins, via oxirane intermediates[630–636], and the stereochemistry[222,568,569,637,638] and mechanism[568,569,636] of the hydrogenolysis (equation 121). Among good catalysts are various supported and support-free metal catalysts[222,630–632], metal borates[633], phosphorus-containing

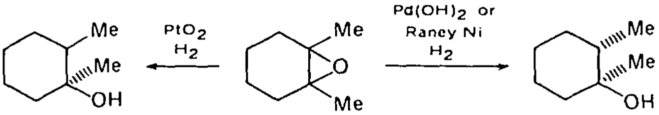


$$\mathrm{H_2C{-}CHR\ (O)} + \mathrm{H_2} \xrightarrow{\text{catalyst}} \mathrm{CH_2CH_2R\ (OH)}$$

(121)

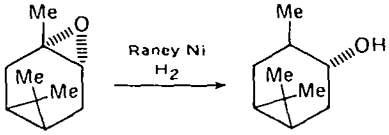
metal catalysts[634] and metal-containing zeolites[635]. The configuration of the alcohol formed is strongly influenced by the catalyst, the reactant and the experimental conditions[631,639].

The review by Akhrem and coworkers[5] deals with ring-openings accompanied by retention of configuration. With 1,2-dimethylcyclohexene oxide[638] hydrogenolysis on Raney nickel and $Pd(OH)_2$ results in retention, while on PtO_2 it results in inversion (equation 122).


Me
Me
OH
PtO2
H2
Me
O
Me
Pd(OH)2 or
Raney Ni
H2
Me
Me
OH

(122)

Extensive stereo- and regio-selectivities have also been observed in the hydrogenolysis of bicyclic monoterpene oxiranes on a Raney nickel catalyst[637] (e.g. equation 123).

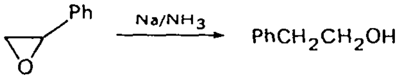

Me
O
Me
Me
Raney Ni
H2
Me
OH
Me
Me

(123)

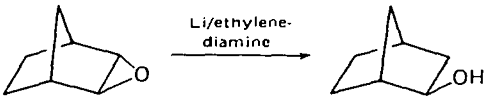
Nickel opens the ring on the more sterically hindered, and palladium on the less sterically hindered side[568,569,640]. The selectivities of Raney nickel and Raney copper are likewise not identical[636].

3. *Other reductions*

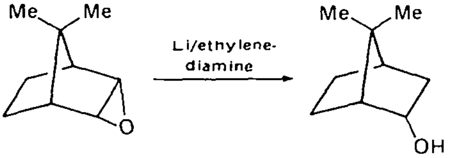
Much work has dealt with the application of alkali metals, and mainly lithium, to the reduction of oxiranes to alcohols[39,121,618,641-647]. Liquid ammonia and ethylenediamine are generally used as solvents. These processes (equations 124–127) are usually regio- and stereo-selective.


Ph
O
Na/NH3
PhCH2CH2OH

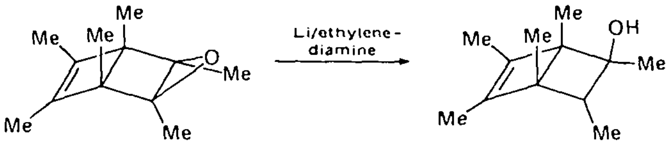
(Ref. 641) (124)


O
Li/ethylene-
diamine
OH

(Ref. 646) (125)


Me
Me
O
Li/ethylene-
diamine
Me
Me
OH

(Ref . 647) (126)

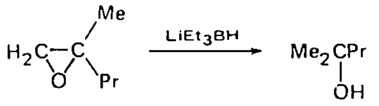

Me
Me
Me
O
Me
Me
Me
Li/ethylene-
diamine
Me
Me
Me
OH
Me
Me
Me

(Ref. 39) (127)

The reagents open the oxirane ring on the more sterically hindered side, with retention of configuration. The alkali metal procedures are simple and clean methods for the reduction of sterically hindered oxiranes. A general synthesis has been elaborated for the preparation of 2-ethynylcycloalkanols with this procedure[644].

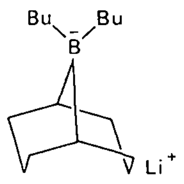
The regioselectivity is the opposite if the reduction is performed in alcoholic medium, when isopropanol is formed from methyloxirane[643]. (The oxirane ring is similarly cleaved on the less sterically-hindered side in the reduction of steroid oxiranes with Cr^{2+} [648].)

Lithium triethyl borohydride has proved an excellent reagent for the reduction of sterically hindered oxiranes prone to rearrangement[649,650]. The reaction results in 'Markownikoff alcohols' (equation 128).

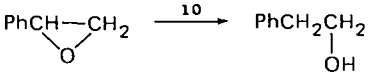

Me
H₂C—C
O
Pr
LiEt₃BH
Me₂CPr
OH

(128)

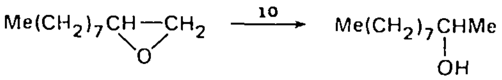
Aliphatic and aromatic oxiranes are reduced with opposite regioselectivities by **10**[651] (equations 129 and 130).



(10)


PhCH—CH₂
O
10
PhCH₂CH₂
OH

(129)


Me(CH₂)₇CH—CH₂
O
10
Me(CH₂)₇CHMe
OH

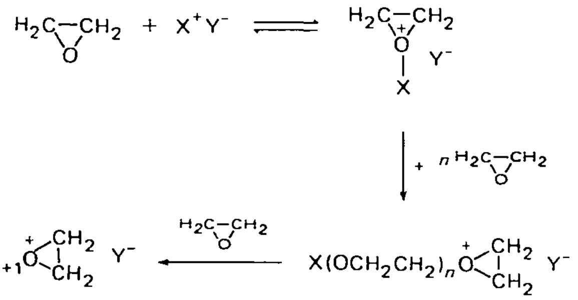
(130)

The regioselectivities are opposite in the reductions of α,β-unsaturated oxiranes with i-Bu_2AlH and with Ca/NH_3[642].

Oxiranes may also be reduced to alcohols with alkoxyaluminium hydrides[620,652] and with aluminium trialkyls[653].

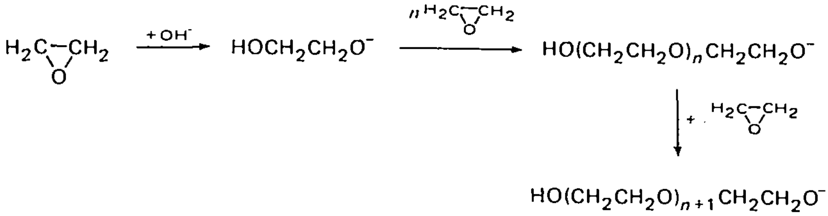
E. Polymerization

Since the monograph by Furukawa and Saegusa[654], the state of development of the various polymerization methods has been well surveyed by a number of reviews up to 1976[655-662]. Hence we shall mention only a few recent characteristic researches[663-668].


H₂C—CH₂
O
+ X⁺Y⁻
H₂C—CH₂
O
+
X
Y⁻
+ n H₂C—CH₂
O
X(OCH₂CH₂)ₙ₊₁O
+
CH₂
CH₂
Y⁻
H₂C—CH₂
O
X(OCH₂CH₂)ₙO
+
CH₂
CH₂
Y⁻

(131)

Lewis acid-catalysed cationic polymerization is outlined in equation (131), and the anionic polymerization induced by basic catalysts in equation (132).



+OH⁻
H_2C-CH_2 O
$HOCH_2CH_2O^-$
$n\ H_2C-CH_2$ O
$HO(CH_2CH_2O)_nCH_2CH_2O^-$
$+\ H_2C-CH_2$ O
$HO(CH_2CH_2O)_{n+1}CH_2CH_2O^-$

(132)

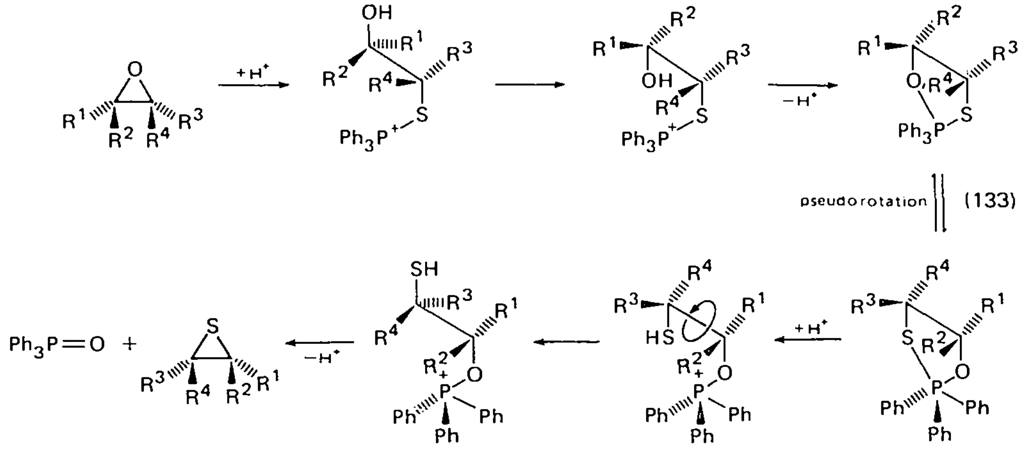
Numerous variants exist within the two main groups, and the literature already referred to also deals with radical polymerizations.

F. Formation of Heterocyclic Compounds

Attention is drawn to three reviews connected with this topic[8,17,19].

1. *Ring-transformation of three-membered heterocyclic compounds into other three-membered heterocyclic compounds*

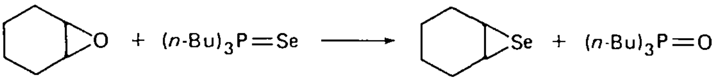
Most experimental data deal with the transformation of oxiranes to thiiranes. Equation (133) presents an example of the stereospecific reaction[669].



+H⁺
−H⁺
pseudorotation
+H⁺
−H⁺
$Ph_3P{=}O$ +
Ph_3P^+
OH
SH
HS

(133)

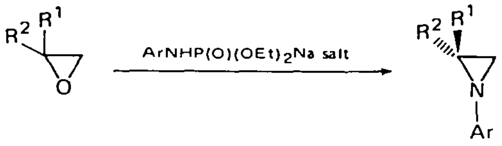
Heteroatom exchange occurs with CS_2[670], with 3-methylbenzenethiazole-2-thione in the presence of trifluoroacetic acid[671], and with 1-phenyl-5-mercaptotetrazole[672]. The yields are high. Oxiranes also react with phosphine selenides in the presence of trifluoroacetic acid[673] (equation 134). The reaction is again stereospecific.



+ $(n\text{-Bu})_3P{=}Se$
+ $(n\text{-Bu})_3P{=}O$

(134)

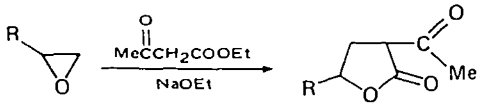
A single-step aziridine synthesis has also been developed[674]; the transformation of oxirane to aziridine occurs by nucleophilic attack of the amidophosphate ester anion on the less-substituted carbon atom, with ring-closure by phosphate elimination (equation 135).


R²
R¹
O
ArNHP(O)(OEt)₂Na salt
R²
R¹
N
Ar

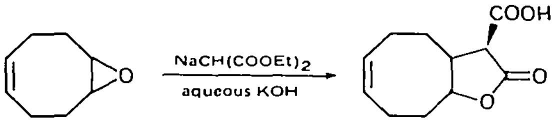
(135)

2. *Ring-expansion to one-heteroatom heterocycles*

In the presence of a copper salt, vinyloxirane reacts with diazomethane to give 3-vinyloxetane[675]. Oxocarboxylic acid derivatives[676] and dicarboxylic acid derivatives[677–680] yield γ-lactones with oxiranes (equations 136 and 137).


R
O
O
MeCCH₂COOEt
NaOEt
R
O
O
C
O
Me

(136)


O
NaCH(COOEt)₂
aqueous KOH
COOH
O
O

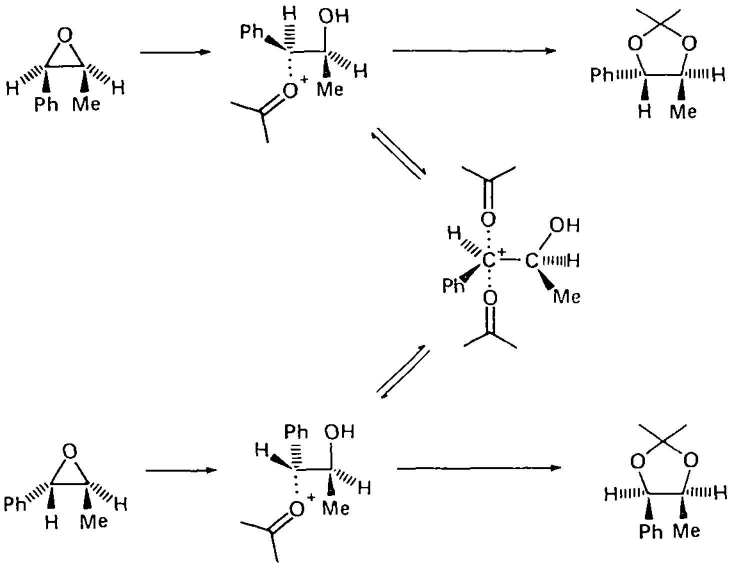
(137)

On the action of BF_3, certain steroid oxiranes undergo isomerization with ring-expansion to yield oxolanes[540].

By acid catalysis, cyclopropyloxiranes can be isomerized to dihydropyrans (see equation 94).

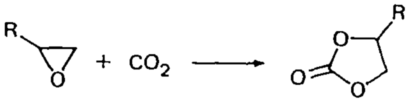
3. *Transformation to two-heteroatom heterocycles*

Carbonyl compounds react with oxiranes via acid- or base-catalysed ring-opening to give 1,3-dioxolanes in very good yield[681–689]. For example, (*E*)- and (*Z*)-2,3-octene oxides are converted with total stereoselectivity to the corresponding *erythro*- and *threo*-acetonide on the action of anhydrous $CuSO_4$, the (*Z*)-oxide reacting three times more quickly[683]. The (*E*)- and (*Z*)-2-methyl-3-phenyloxiranes give the same *erythro*- (66%) and *threo*-acetonide (34%) mixture (equation 138).


O
H
H
Ph
Me
H
OH
Ph
H
O⁺
Me
O
O
Ph
H
H
Me
H
O
OH
C⁺
C
H
Ph
O
Me
O
Ph
H
H
Me
Ph
OH
H
H
O⁺
Me
O
O
H
H
Ph
Me

(138)

In the presence of various catalysts (bases, transition-metal complexes), oxiranes react with CO_2 to form 1,3-dioxolanones[682,688,689] (equation 139).

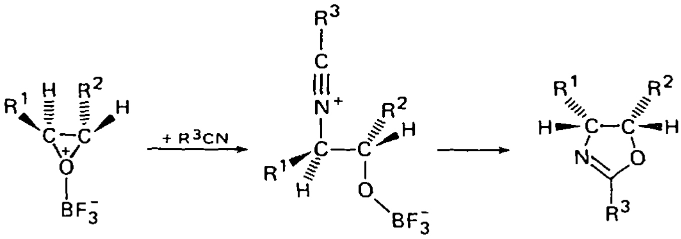


(139)

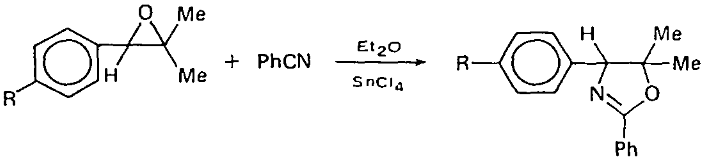
Equations (140)–(147) illustrate the preparation from oxiranes of compounds with oxazoline[690–695], oxathiolane[696], oxaphospholane[697] and oxathiaphospholane[698] skeletons.

The transformations presented in equations (140) and (143) are stereospecific. Oxiranes can also be converted in good yield to trithiocarbonates with NaS_2COEt (sodium *O*-ethyl xanthate)[699], and to oxazolidines with carbodiimide[700] (equations 148 and 149).

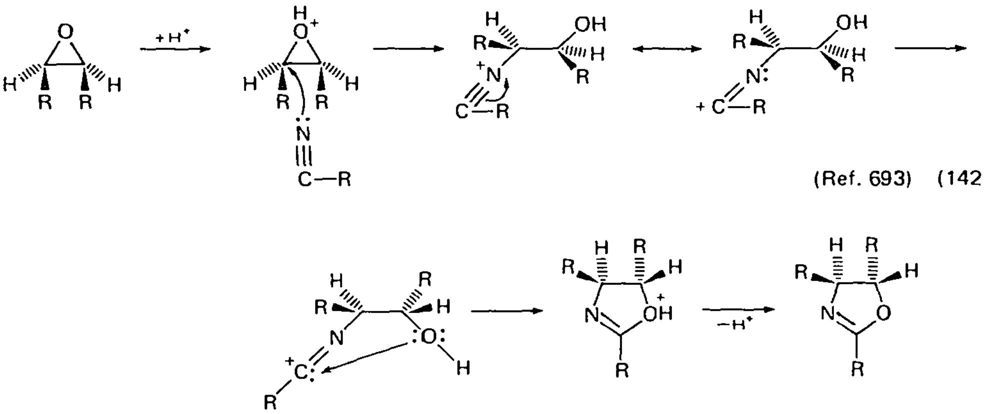
Compounds with 1,3-oxazine[701] and 1,4-oxazine[702,703] skeletons can be prepared from oxiranes with various reactants. An example is presented in equation (150). A trioxan ring is formed in equation (151)[704].


R¹
H
R²
H
C
C
O
BF₃⁻
+ R³CN
R³
C
N⁺
R²
H
R¹
H
O
BF₃⁻
R¹
R²
H
C
C
H
N
O
R³

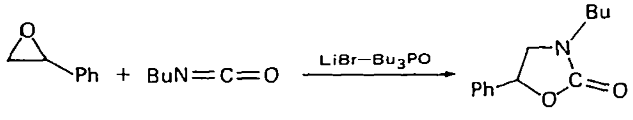
(Ref. 690) (140)


O
Me
H
Me
R
+ PhCN
Et₂O
SnCl₄
R
H
Me
Me
N
O
Ph

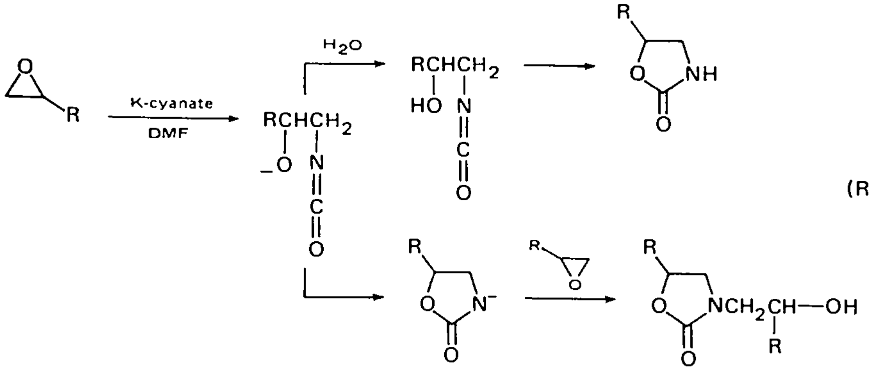
(Ref. 692) (141)


O
H
H
R
R
+H⁺
H
O⁺
H
H
R
R
N
C—R
H
OH
R
H
⁺N
C—R
R
H
OH
R
H
N:
+C—R
R
H
R
R
H
N
C⁺
:O:
H
R
H
R
R
H
N
OH
R
H
R
R
H
N
O
R
−H⁺

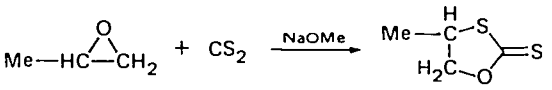
(Ref. 693) (142)


O
Ph
+ BuN=C=O
LiBr—Bu₃PO
Bu
N
C
O
Ph
O

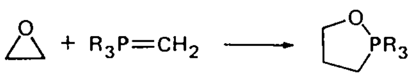
(Ref. 694) (143)


K-cyanate
DMF
H2O

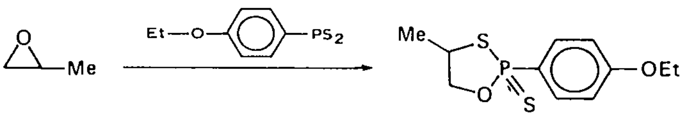
(Ref. 695) (144)



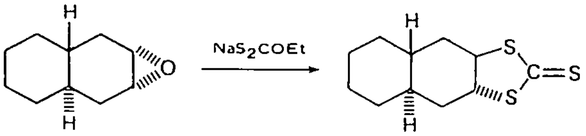
(Ref. 696) (145)



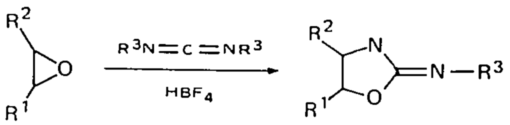
(Ref. 697) (146)



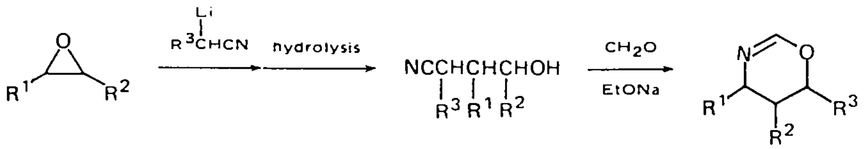
(Ref. 698) (147)



(148)

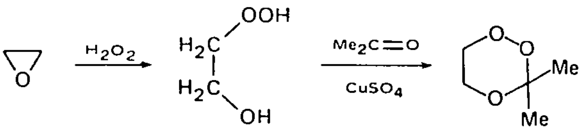


(149)


hydrolysis
CH2O
EtONa

(Ref. 701)

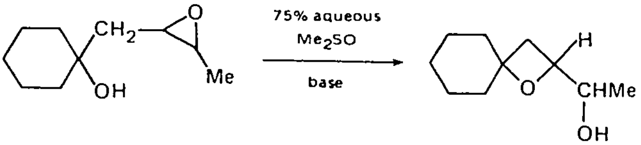
(150)


H2O2
Me2C=O
CuSO4

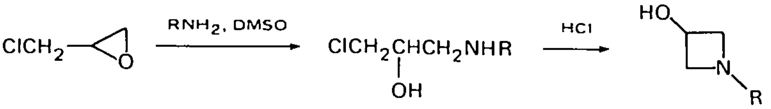
(151)

4. Transformation of oxiranes containing a functional group, by ring-expansion

The ring-expansion of oxiranes to four-membered heterocyclic compounds can be seen in equations (152) and (153).

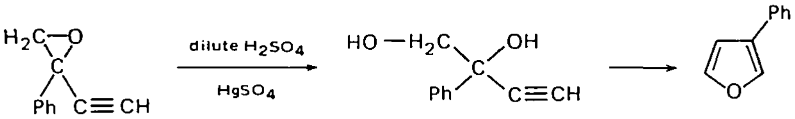

75% aqueous
Me_2SO
base

(Refs. 705, 706) (152)

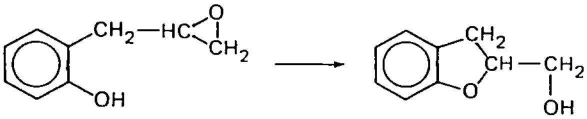

RNH_2, DMSO
$ClCH_2CHCH_2NHR$
OH
HCl

(Ref. 707) (153)

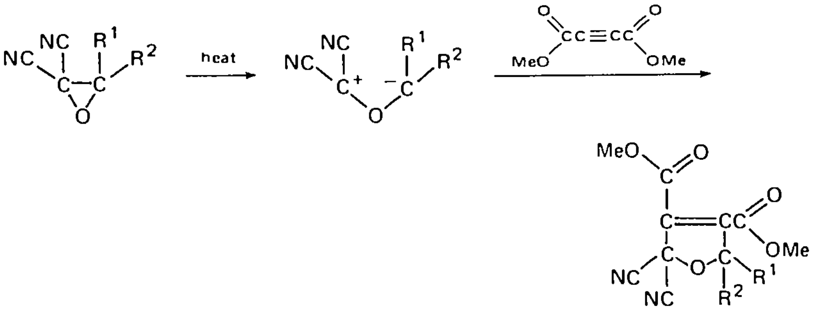
Equations (154)–(168) show the ring-transformations of oxiranes to five-membered heterocyclic compounds. Phenolate neighbouring-group participation has been found in the opening of the oxirane ring[709] (equation 155). By means of 1,3-dipolar cycloaddition[710], dihydrofuran derivatives are formed (equation 156).


dilute H_2SO_4
$HgSO_4$

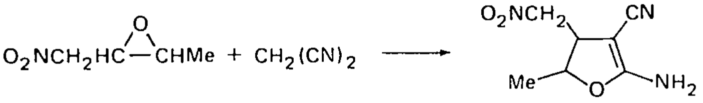
(Ref. 708) (154)



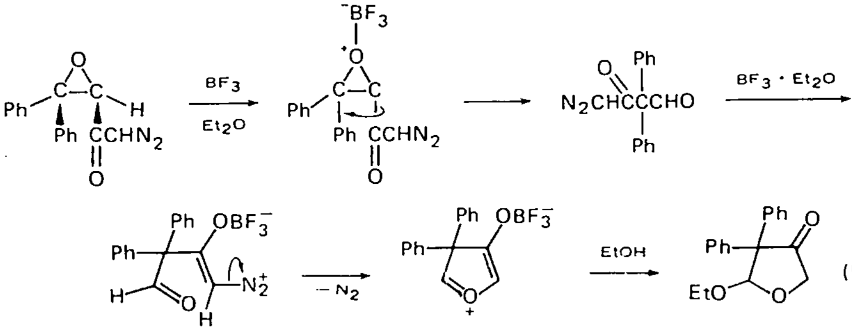
(Ref. 709) (155)



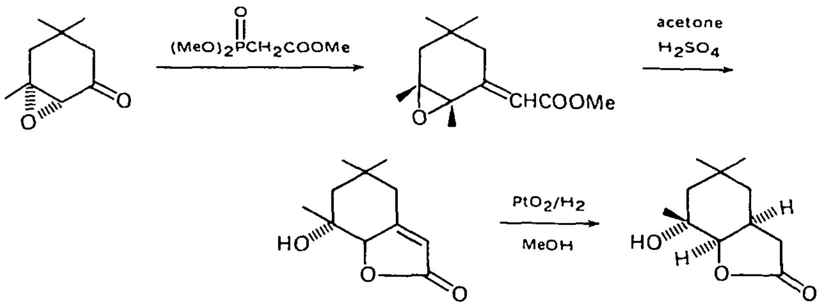
(Ref. 710) (156)


$O_2NCH_2HC—CHMe + CH_2(CN)_2$

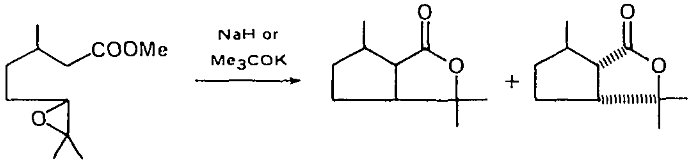
(Ref. 711) (157)


BF_3
Et_2O
$BF_3 \cdot Et_2O$
$-N_2$
EtOH

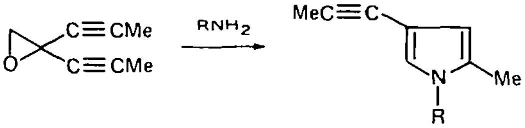
(Ref. 512) (158)


(MeO)2P(O)CH2COOMe
CHCOOMe
acetone
H2SO4
HO
PtO2/H2
MeOH
H

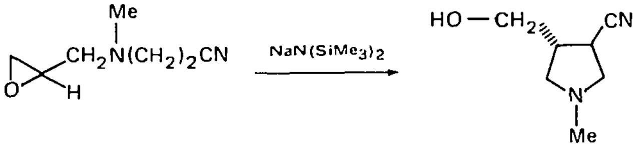
(Ref. 712) (159)


COOMe
NaH or
Me3COK

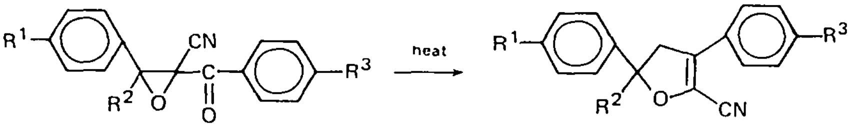
(Ref. 713) (160)


C≡CMe
C≡CMe
RNH2
MeC≡C
Me
N
R

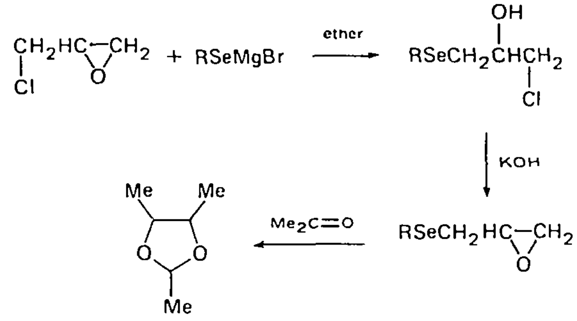
(Ref. 714) (161)


Me
CH2N(CH2)2CN
NaN(SiMe3)2
HO—CH2
CN
N
Me

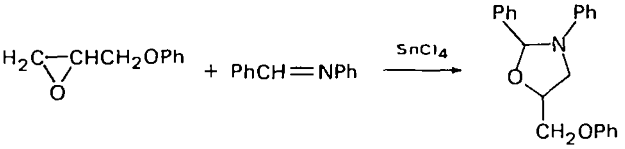
(Ref. 715) (162)


R1
CN
R3
R2
heat
CN

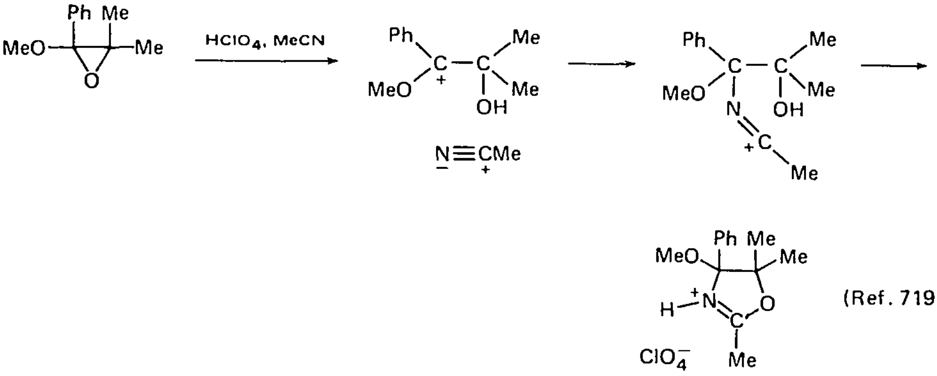
(Ref. 716)
(163)


CH2HC—CH2
Cl
+ RSeMgBr
ether
RSeCH2CHCH2
OH
Cl
KOH
RSeCH2HC—CH2
Me2C=O
Me
Me
Me

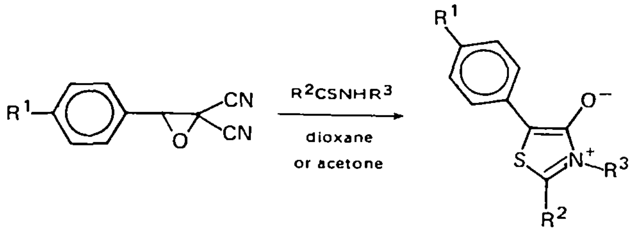
(Ref. 717) (164)


H2C—CHCH2OPh
+ PhCH=NPh
SnCl4
Ph
Ph
N
CH2OPh

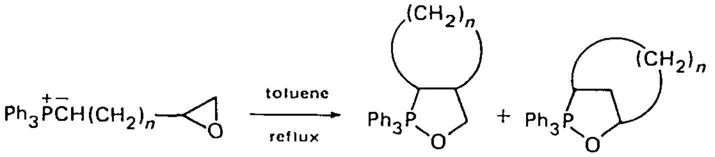
(Ref. 718) (165)



(Ref. 719) (166)



(Ref. 720) (167)



(Ref. 721) (168)

The syntheses presented above generally display very good yields. Additional studies yielded other five-membered[722-730] and six-membered heterocyclic compounds[731-733].

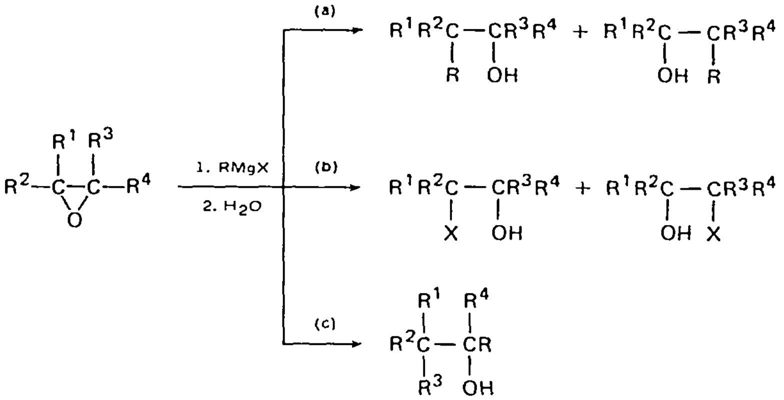
G. Reaction with Organometallic Compounds

In the past ten years, numerous publications have dealt with the reactions of oxiranes with organometallic compounds. The Grignard compounds, dialkylmagnesiums, trialkylaluminiums and lithium dialkylcuprates are the most important organometallic reagents.

1. Reaction with Grignard compounds

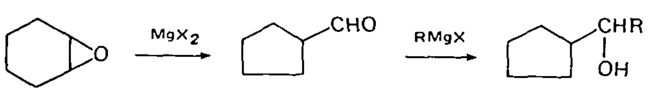
Organomagnesium compounds were the earliest used organometallic compounds for the transformation of oxiranes to alcohols[1,734-736]. In the case of substituted oxiranes, the reaction generally gives an alcohol mixture (equation 169).

Route (a) shows the normal addition, route (b) occurs on the action of the magnesium halide ($2\,RMgX \rightleftharpoons MgX_2 + MgR_2$), and route (c) is due to metal halide-catalysed isomerization of the oxiranes to carbonyl compounds. The latter two reactions do not take place in the case of MgR_2. Via route (a), cyclopentene oxides yield 2-substituted cyclopentanols. Higher cycloalkene oxides give ring-contraction



(169)

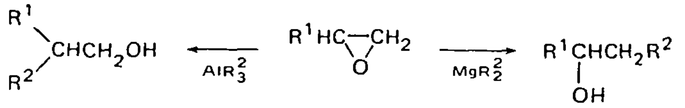
and rearrange to aldehydes, which in turn react with the reagent in the usual manner[737] (equation 170).



(170)

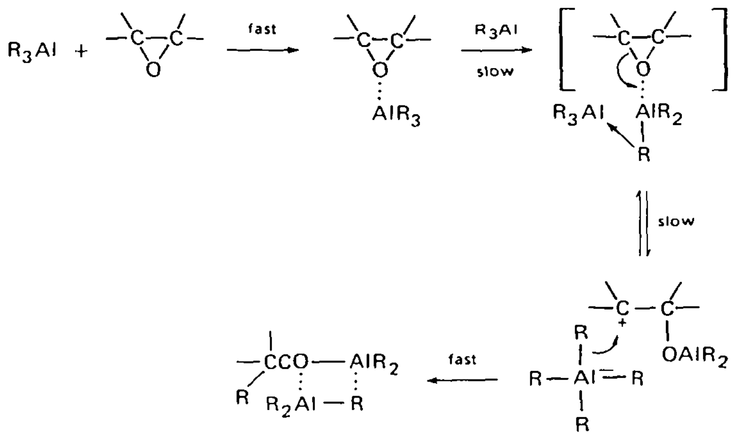
2. *Reaction with magnesium alkyls and aluminium alkyls*

Both types of organometallic compound react with oxiranes to give alcohols[734,738–742]. Comprehensive work has been carried out on the comparison of the reactivities of the two types of compound and the mechanism of the reactions[743]. With a given oxirane, the two organometallic compounds give alcohols with different structures (equation 171). The stereostructure of the

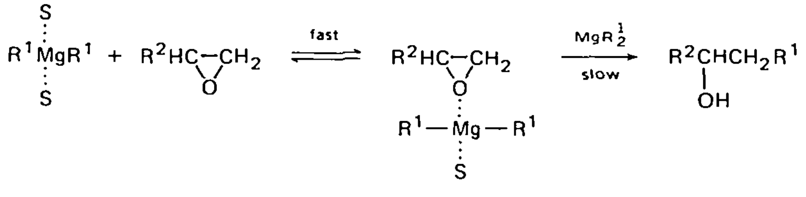


(171)

alcohol formed is also determined by the type of organometallic reagent: in the case of dialkylmagnesium, inversion always occurs at the reacting carbon atom. In both cases a two-step process is assumed (equations 172 and 173).



(172)

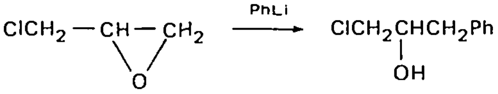

S
R¹MgR¹
S
R²HC—CH₂
O
fast
R²HC—CH₂
O
R¹—Mg—R¹
S
MgR¹₂
slow
R²CHCH₂R¹
OH

(173)

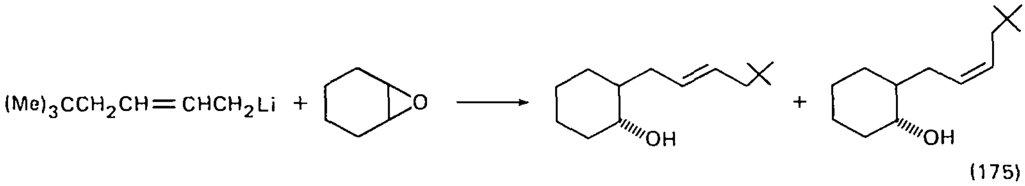
S = solvent molecule

3. *Reaction with lithium dialkylcuprates*

Organolithium compounds generally react at the less-substituted carbon atom with asymmetrically substituted oxiranes[744–746] (equation 174). Similarly, cyclohexene oxide or 2,3-dimethyloxirane react with neopentylallyllithium to give the regular addition products[747] (e.g. equation 175).

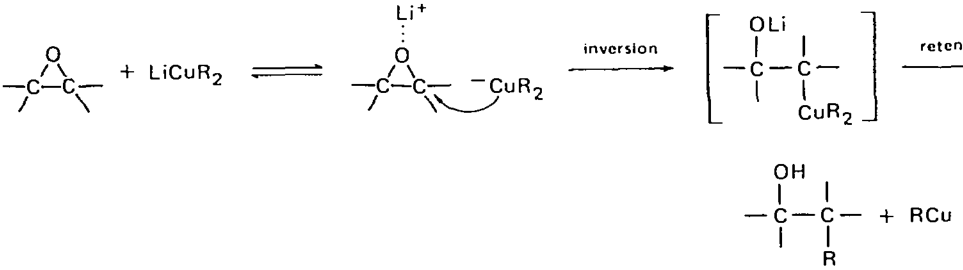


$$ClCH_2-\underset{O}{CH-CH_2} \xrightarrow{PhLi} ClCH_2\underset{OH}{CH}CH_2Ph \qquad (174)$$

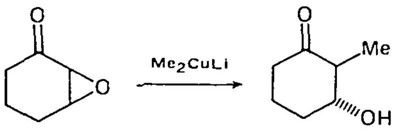

(Me)₃CCH₂CH=CHCH₂Li +
O
OH
+
OH

(175)

Lithium organocuprates are much more effective in their reactions with oxiranes than methyllithium or phenyllithium, and good regioselectivity has been observed[748–750]. The reaction requires much milder conditions than in the case of other organometallic compounds (equation 176). Lithium dimethylcuprate does not react with tetrasubstituted oxiranes[751]. Oxiranes containing unprotected carbonyl groups react only via their oxirane function. Accordingly, the reaction may be utilized for the α-alkylation of α,β-epoxyketones (α,β-unsaturated ketones)[752,753] (equation 177). In general a large excess of the reagent must be taken, and only one of the alkyl groups is incorporated. If the stoichiometric


O
+ LiCuR₂
Li⁺
O
⁻CuR₂
inversion
OLi
CuR₂
retention
OH
R
+ RCu

(176)

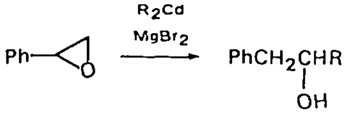

O
O
Me₂CuLi
O
Me
OH

(177)

quantity of R(CN)CuLi is used, the desired alcohol may be obtained in high yield (>90%)[754].

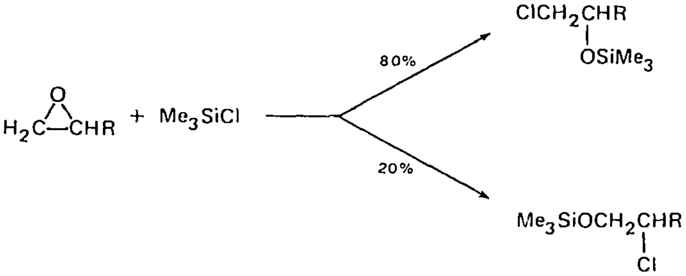
4. *Reaction with other organometallic compounds*

Dialkylcadmium and dialkylzinc do not react with oxiranes. In the presence of $MgBr_2$, however, dialkylcadmium transforms phenyloxirane to a benzyl alkyl carbinol[755] (equation 178).



(178)

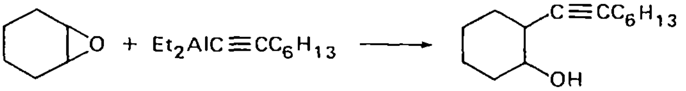
Trimethylchlorosilane reacts with oxiranes to give 1,2-chlorohydrin trimethylsilyl ethers[756] (equation 179). In the presence of magnesium, bistrimethylsilyloxy derivatives are formed[757]. Trimethylisothiocyanatosilane[758] and trimethylsilyl cyanide[759] react in a similar manner.



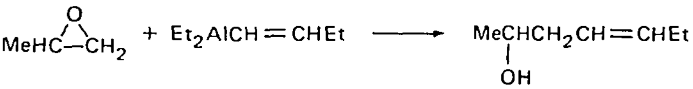
(179)

Oxiranes give olefins in stereospecific transformations with lithiumtrialkylsilane and stannate[453,760–762].

Certain organoaluminium compounds react with oxiranes to yield β-hydroxy acetylenes or β-hydroxy olefins[763–768] (e.g. equations 180 and 181).



(180)

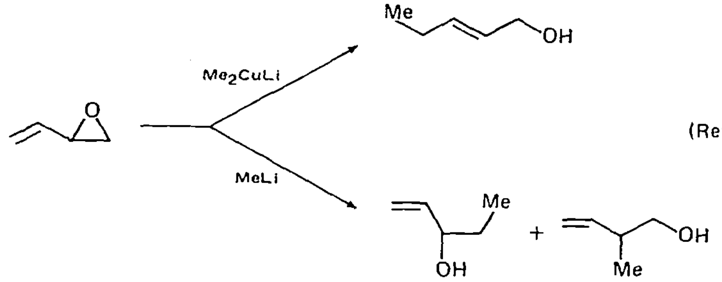


(181)

The mircene–magnesium complex[769], metal salts of imines[770,771], polychloroaryllithium[772], 2-lithium-1,3-dithianes[773,774] and the lithium salts of 2-substituted 4,4-dimethyl-2-oxazolines[775] similarly give alcohols on reaction with oxiranes. With organoselenium compounds the oxiranes are converted to allyl alcohols[491]. The oxirane ring is likewise opened by 3-cyclohexenylpotassium[776].

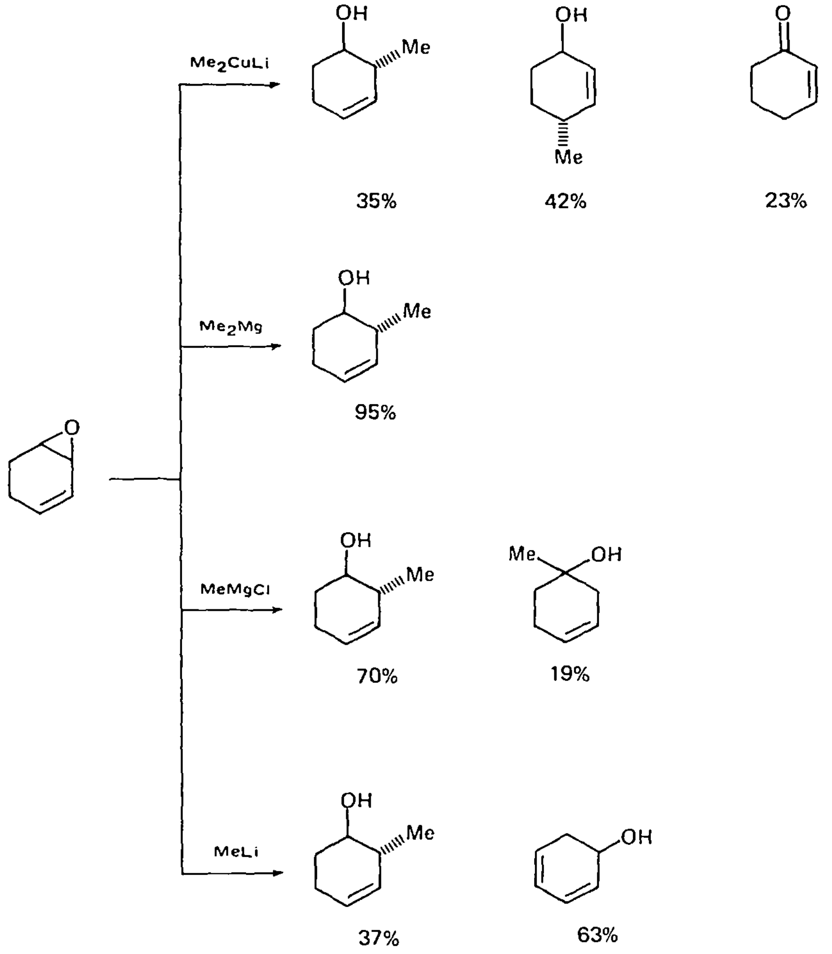
5. *Reaction of oxiranes with unsaturated substituents*

With organometallic compounds, and particularly lithium alkylcuprates, vinyloxiranes mainly participate in a 1,4-addition, which displays extensive stereoselectivity$^{494,777-779}$ (equation 182). The reactions of lithium alkenylcuprates and vinyloxiranes lead to 2,5-dienol systems^{780}.


Me2CuLi
MeLi
Me
OH
O
Me
OH
+
OH
Me

(Ref. 777) (182)

Comparative investigations have been carried out on the transformations of 1,3- and 1,4-cyclohexadiene monoxides and vinyloxirane with certain types of organometallic compounds^{781,782} (e.g. equations 183–186). Cyclopentadiene monoxide gives different products with diethylhexynylaluminium in ether and in toluene^{783}


Me2CuLi
OH
Me
OH
Me
O
35%
42%
23%
Me2Mg
OH
Me
95%
O
MeMgCl
OH
Me
Me
OH
70%
19%
MeLi
OH
Me
OH
37%
63%

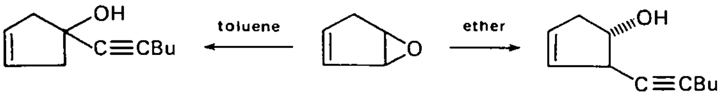
(183)

(184)

(185)

(186)

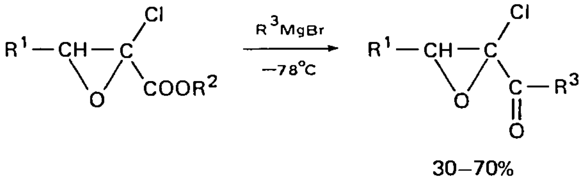
(equation 187). Cyclooctatetraene monoxide reacts with an alkynyl Grignard compound to give a cycloheptatriene derivative via ring-contraction[784].



(187)

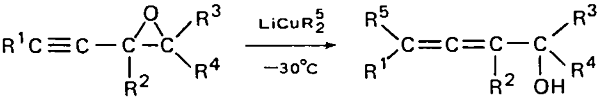
6. *Reaction of oxiranes containing functional groups*

With $LiCuR_2$ at low temperature, α-acetoxyoxiranes give α-alkylketones in moderate yield[785], while α,β-epoxysilanes give a β-hydroxysilane[455,786]. α-Chloroepoxycarboxylic acid esters give rise to a chlorocarbonyloxirane with Grignard reagents[787] (equation 188). α,β-Epoxyketones or open-chain aldehydes can be



(188)

prepared with Grignard compounds and dialkylmagnesium from cyanooxiranes, depending on their structures[788]. The transformations of cyanooxiranes have been studied with lithium dialkylcuprates[789], alkyllithium[790] and trialkylaluminium[791]. At low temperatures, α-heterosubstituted oxiranes react with organolithium compounds, and the 1,2-epoxyalkyllithium compounds obtained serve as an important nucleophilic oxirane source in organic syntheses[792]. With $LiCuR_2$, with a Grignard compound in the presence of a Cu^+ salt, or with trialkylborane[793], alkynyloxiranes can be converted to allene alcohols in good yield[794,795] (equation 189). Studies have also been made of the reactions of chloroxiranes with organomagnesium[796] and organolithium compounds[797–799].



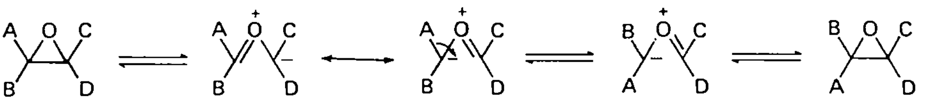
(189)

H. Photochemistry

Photochemical transformations of oxiranes are treated in a number of reviews and monographs[16,17,800–803].

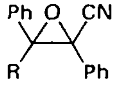
The photochemical transformations include rearrangements, the formation of carbenes, and other reactions, all involving homolysis of a C—C or C—O bond of the oxirane ring.

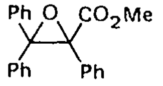
Rearrangements are generally accompanied by isomerization (equation 190); this frequently plays only a subordinate role, but it nevertheless occurs with noteworthy stereoselectivity[804,805]. The intermediate carbonyl ylide is formed by disrotational ring-opening[806–809], and is then converted to the isomeric oxirane by ring-closure after rotation about the C—O bond.

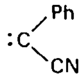


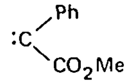
(190)

Oxiranes containing strongly electron-attracting substituents (e.g. CN, COOEt) yield carbenes[810-813]. For example, on the photolysis of **11** and **12**, **13** and **14**,

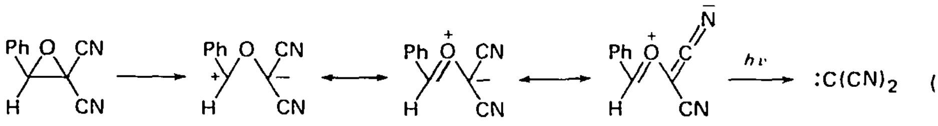

(11)


(12)


(13)

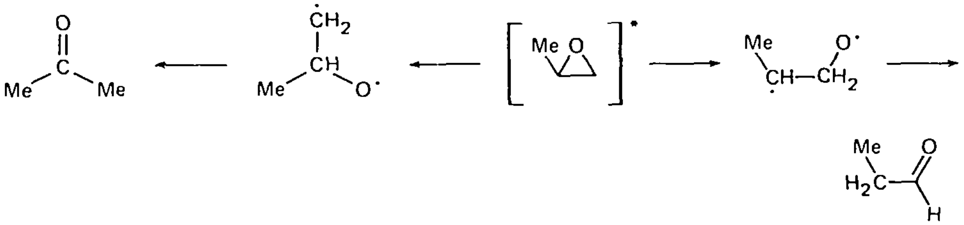

(14)

respectively, are formed. The mechanism of carbene formation was studied by Griffin and coworkers[814], who suggested that it takes place via an ionic mechanism. On the double photolysis of **15** at low temperature, both ylide and carbene formation were demonstrated. On this basis, the mechanism of equation (191) was assumed, with the note that the photochemical reaction of **16** may be followed by concerted or other processes which give rise finally to **17**.


(15) (16) (17) (191)

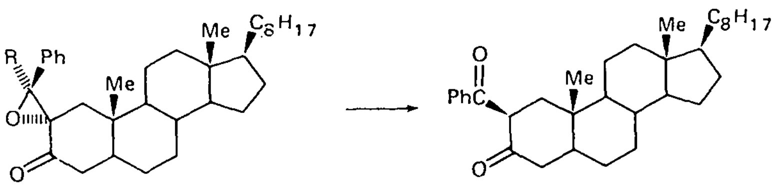
Although the intermediate may also be an ylide[806,815], the first step in most photochemical reactions is the homolytic splitting of one of the C—O bonds[815].

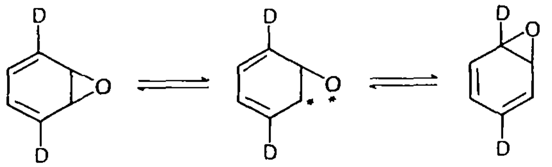
On the low-pressure photolysis of propylene oxide, propionaldehyde and acetone are formed[816] (equation 192). If the pressure is raised, the amount of acetone


(192)

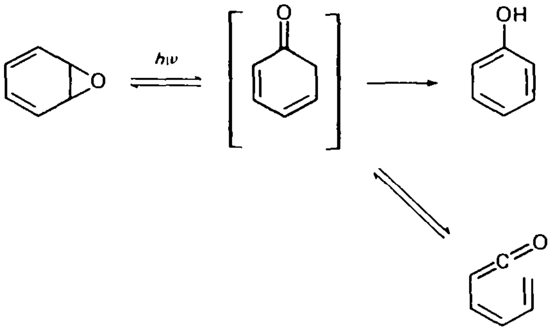
increases, and it emerges from the quenching effect that, under these conditions, the propionaldehyde and acetone cannot be formed from a common intermediate.

Among photocatalytic transformations of oxiranes containing various functional groups[552,553,817-837], some characteristic examples are presented in equations (193)–(198).

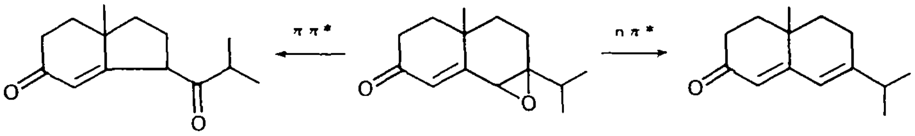

(Ref. 821) (193)


(194)

Spiro-α-carbonyloxiranes are converted to dicarbonyl compounds[820,821] (equation 193). At room temperature benzene oxide is transformed to phenol, while at low temperature oxygen migration around the aromatic ring and ketene formation can also be detected[822] (equations 194 and 195). Equation (196) shows that the direction of the rearrangement also depends on the mode of excitation[825].

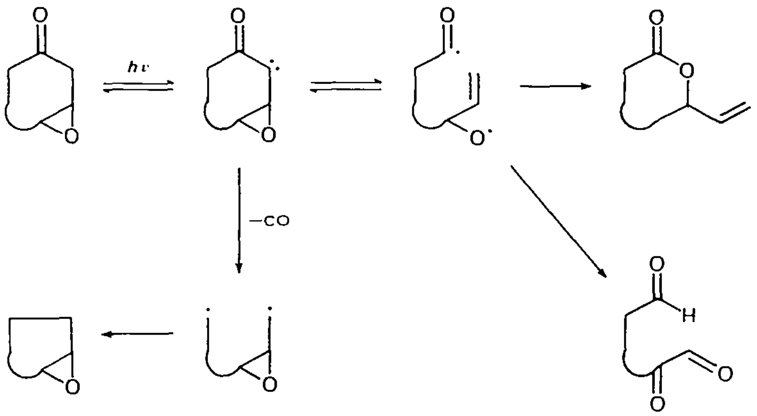


(195)



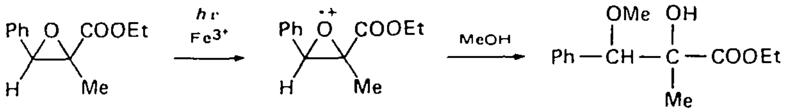
(196)

Murray and coworkers[829] proposed a general scheme for the photochemical transformations of β,γ-epoxycycloketones (equation 197).



(197)

The photolysis of α,β-epoxycarboxylic acid esters in alcoholic solution[833,834] gives addition of the alcohol to the oxirane ring only in the presence of Fe^{3+} ions (equation 198). The photocatalytic solvolysis of certain oxiranes[835], and their photoreduction on the action of alcohols[836], have also been examined. With NBS or other brominating reagents, α-bromooxiranes and α-bromoketones may be prepared by photochemical means[837].



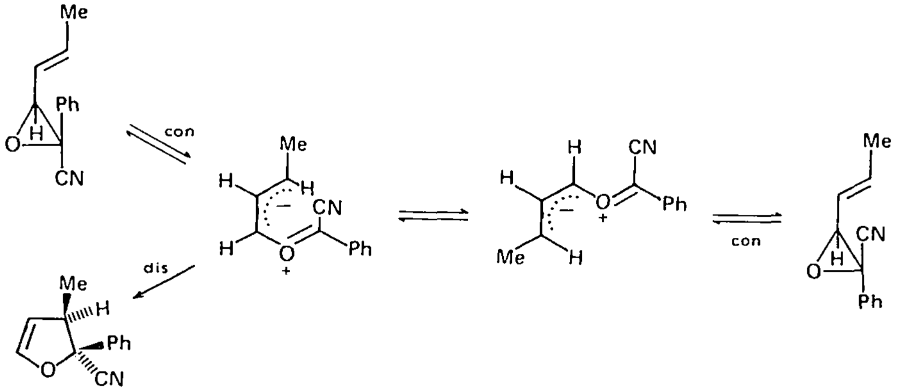
(198)

I. Thermally induced Reactions

Thermally-induced reactions of oxiranes yield rearrangements to carbonyl compounds and unsaturated alcohols, as well as other rearrangements[555–557,838–841].

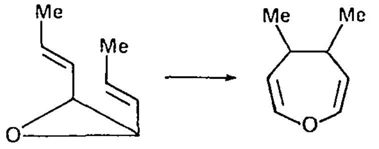
The kinetics of rearrangement of oxiranes to carbonyl compounds and unsaturated alcohols[843–846] indicate that these are monomolecular homogeneous processes; the intermediate biradicals are converted to end-products via intramolecular rearrangement. The radicals playing the key roles in most of the thermal and photochemical reactions of oxiranes can be detected by ESR and their structures studied[842].

The mechanism of the electrocyclization and isomerization processes is outlined in equation (199). Investigation of the stereochemistry of electrocyclization[334,556,840,841] has shown that only *cis*-dihydrofurans are formed. The first step is cleavage of a C—C bond, showing that the biradical structure is favoured[551]. The ring-opening is conrotational[554,840,847].



(199)

Stereospecific formation of dihydrofurans proceeds via disrotational ring-closure of the ylide[557,840]. The isomerization can similarly be explained in accordance with equation (199). The formation of dihydrooxepines from the *cis*-oxirane is a concerted [3,3]sigmatropic rearrangement, the transition state having a boat conformation[554,847] (equation 200).



(200)

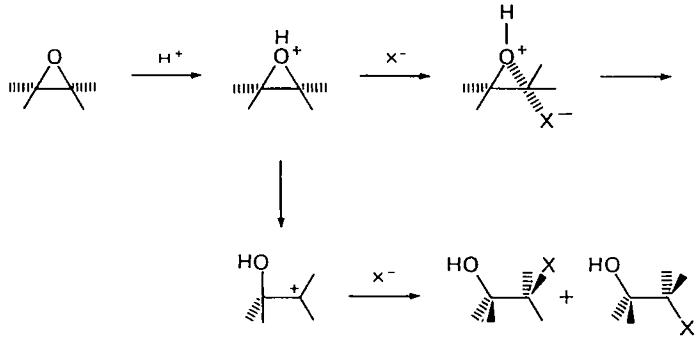
Ylides formed from oxiranes containing electron-attracting substituents have given a possibility for a new type of dioxolane syntheses too[716] (equation 163).

Much new information has been acquired in connection with the pyrolysis of oxiranes linked to large unsaturated rings[848–850]. Additionally, the radical-induced transformations of oxiranes have been investigated[803,848,851–853]. In conclusion, attention is drawn to the review by Huisgen[854] on the electrocyclic ring-opening reactions of the oxiranes.

J. Ring-opening with Nucleophilic Reagents

The most frequent reactions of oxiranes are those involving opening of a C—O bond, in the course of which 1,2-difunctional compounds may be obtained. The

C—O bond may be opened by direct nucleophilic attack on one of the carbon atoms, or first the oxygen is protonated (or a complex is formed with the electrophilic centre of the reagent) and this is followed by nucleophilic attack on the carbon (equations 201 and 202). The equations also illustrate the stereochemical consequences of the two mechanisms. The mechanism and stereochemistry depend on the structure of the starting compound and on the experimental conditions.



(201)

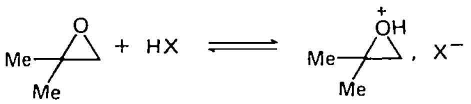
(202)

X = OH, SH, F, Cl, Br, I, CN, OR, OAr, SR, SAr, O_2R, RCO_2, etc.

In general, reactions in basic and neutral media occur by an A2 mechanism, and involve stereospecifically *trans* stereochemistry. There is a particularly abundant literature on the acid-catalysed reactions of the oxiranes.

Most of the publications referred to in recent reviews[9,16,17] or published since deal with factors of a steric, stereoelectronic, polar or conjugative nature, resulting in the regioselectivity and stereoselectivity of the ring-opening. A much-discussed subject is the mechanism of acid-catalysed reactions. The experimental results have been interpreted on the basis of the A2, the A1 or the borderline mechanism.

Comprehensive kinetic studies[855] on the acid catalysis of alkyl-substituted oxiranes in aqueous and non-aqueous media pointed to a competition between the A2 and A1 mechanisms, with the predominance of the former. Anhydrous conditions favour the A1 mechanism, since the halide ion does not play a role in the formation of the transition state. For resolution of the contradictions, a new mechanistic concept is proposed, in which the conjugate acid of the substrate forms a close ion pair (equation 203).

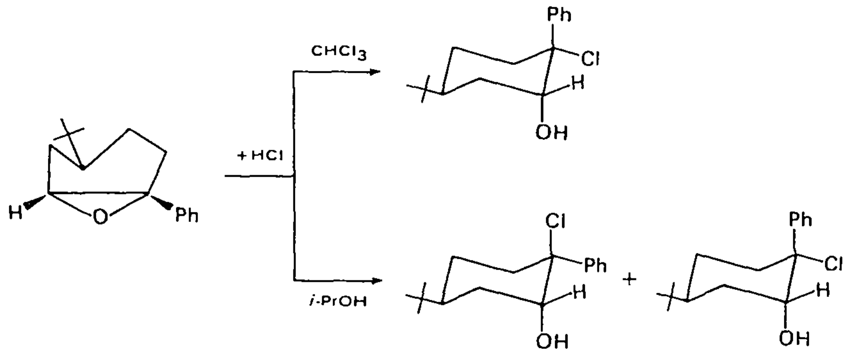


(203)

In another study of the acid-catalysed ring-opening[856] it was concluded that primary and secondary aliphatic oxiranes react by the A2 mechanism, but further investigations are necessary for tertiary and monoaryl-substituted oxiranes.

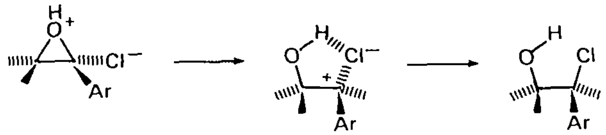
The stereochemistry of the base-catalysed hydrolysis of aryl-substituted oxiranes points to a concerted S_N2 mechanism. With acid hydrolysis, and S_N1 mechanism is suggested for the *trans*-oxirane, and an S_N2 mechanism for the *cis* isomer[857-859].

Many investigations have recently been carried out on the acid hydrolysis of oxiranes[860-869]. The reaction rate and steric course[860] depend to a large extent not only on the configuration of the substrate, but also on the solvent type (equation 204). In a solvent with a low dielectric constant, mainly *cis* opening



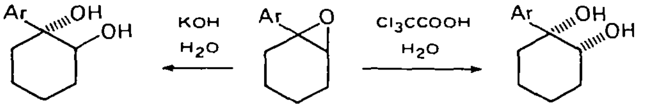
(204)

occurs, with configuration retention. In water or in alcohols, the stereospecificity is lower. The retention can be ascribed in part to the formation of a solvent-protected ion pair, in which the attack by the anion proceeds internally on the electron-deficient benzyl carbon atom (equation 205).

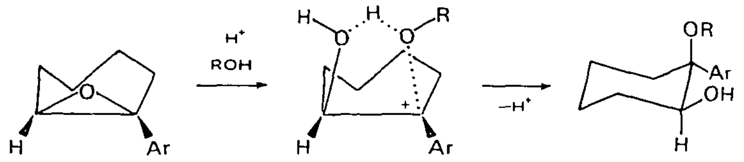


(205)

In the course of stereochemical studies (equations 206 and 207), it has also been proved that the transition state leading to the *cis* products has a high degree of carbocationic character; the tendency towards the retention product is explained



(Ref. 863) (206)

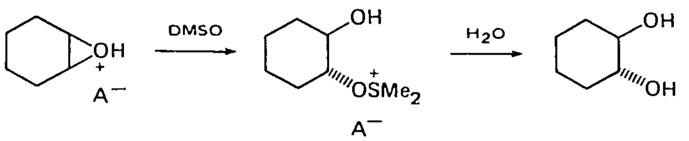


(Ref. 865) (207)

by the favourable entropy content of the transition state of *cis* addition and by the relatively low enthalpic barrier to the breaking of the benzylic C—O bond. At the same time, almost total antistereoselectivity can be observed in aliphatic and cyclo aliphatic oxiranes[348,866]. The importance of the activation parameters in mechanistic studies is confirmed by recent results on the solvolysis of 1-arylcyclohexene oxides[865,867]. Attempts have been made to separate the inductive, conformational and stereoelectronic effects[868]; the conclusion was reached that the inductive effect on the regioselectivity of the reaction plays the determining role, but the other factors are not negligible.

In agreement with the regularities mentioned above, *cis* ring-opening has also been observed with other types of compounds on the action of various electrophilic reagents[5,432]. Neighbouring-group participation is manifested most often in *cis* ring-opening[5,869–872].

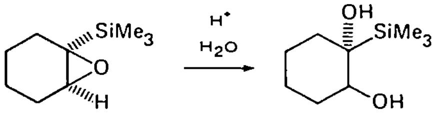
The nucleophilic participation of TDAP and DMSO has been demonstrated in acid-promoted ring-opening reactions of oxiranes. Stable phosphonium and sulphonium salts are formed[873-875] (equation 208).


OH
+
A⁻
DMSO
OH
+
OSMe2
A⁻
H2O
OH
OH

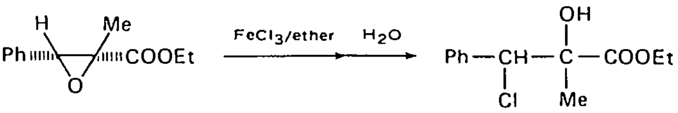
(208)

In recent years, interest has grown in polycyclic aromatic oxides, which are regarded as mediators in polycyclic aromatic carcinogenesis. A number of teams have dealt with the various ring-opening reactions of K-region and non-K-region aromatic oxiranes, and with the kinetics of their hydrolyses[546,876-880].

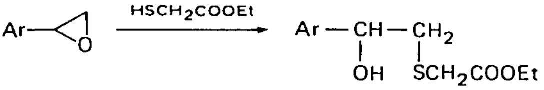
Many studies deal with the stereochemistry[332,881-883] and mechanisms[881,884-895] of the ring-opening. Others deal with the acid-catalysed[129,680,834,896-898] or base-catalysed[322,491,899-904] ring-openings of various oxiranes, and with their utilization in synthetic organic chemistry[491,693,834,905-909], including ring-opening reactions with carbanions[680,776,908,910]. A number of new examples are illustrated in equations (209)–(213).


SiMe3
O
H
H⁺
H2O
OH
SiMe3
OH

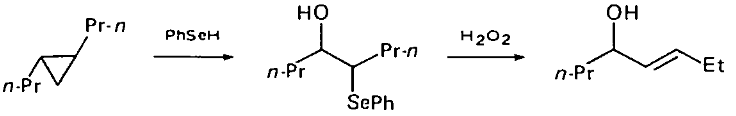
(Ref. 911) (209)


H
Me
Ph
COOEt
O
FeCl3/ether H2O
OH
Ph—CH—C—COOEt
Cl
Me

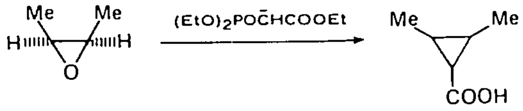
(Ref. 834) (210)


Ar
O
HSCH2COOEt
Ar—CH—CH2
OH
SCH2COOEt

(Ref. 912) (211)


Pr-n
n-Pr
PhSeH
HO
Pr-n
n-Pr
SePh
H2O2
OH
n-Pr
Et

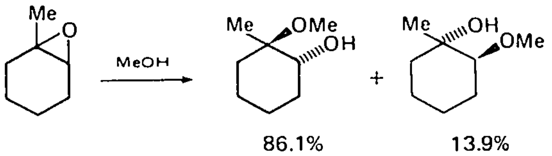
(Ref. 491) (212)


Me
Me
H
H
O
(EtO)2POCHCOOEt
Me
Me
COOH

(Ref. 908) (213)

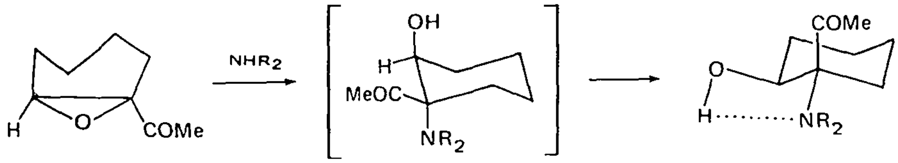
The solvolysis of oxiranes has also been investigated on synthetic ion-exchange resins[913], alumina[914-916] and silica gel[917], and extensive stereoselectivity has been observed in certain cases[915,916].

An interesting ring-opening occurs on the alcoholysis of oxiranes in the dark in the absence of catalysts[918] (equation 214).


Me
O
MeOH
Me
OMe
OH
+
Me
OH
OMe
86.1%
13.9%

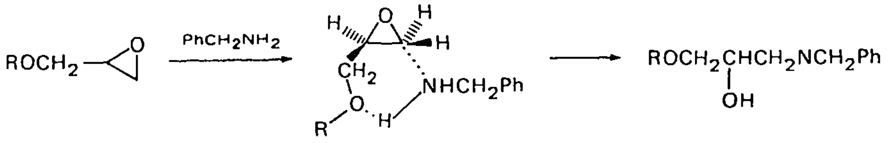
(214)

New investigations have been carried out on the transformations of various oxiranes to yield 1,2-amino alcohols[341,919–929] leading to a deeper understanding of the stereochemistry and the S_N2-type mechanism of the transformation, and to broad synthetic applications. Two examples are presented in equations (215) and (216). Similar studies have led to the recognition of two further modes of anchimeric assistance[931,932].



(Ref. 930)

(215)



(Ref. 931)

(216)

K. Other Reactions

Because of the exceptional reactivity of oxiranes (there is perhaps no reactant towards which oxiranes are immune), it has not been possible to describe a number of special transformations. Of these, some may be listed that are employed in synthetic organic chemistry or in the chemical industry. Recent results confirm that oxiranes may be used effectively for Friedel–Crafts-type syntheses[933,934]; many reactions are known with various organic[935–941] and inorganic[942–950] halogen compounds, organic sulphur compounds[951,952] and organic phosphorus compounds[950,953,954]. The reactions of oxiranes with CO_2[955,956] are also of industrial importance.

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 15

Cyclic ethers

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I. INTRODUCTION

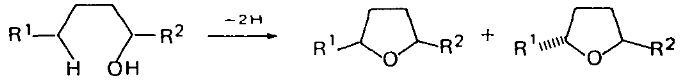
The syntheses and reactions of the cyclic ethers (oxacycloalkanes) have been studied most extensively for the compounds with low numbers (3–6) of ring atoms. It is mainly these oxacycloalkanes that have acquired economic importance. Naturally, the oxiranes are of outstanding significance, and this has justified their review in a separate chapter[1].

The present chapter surveys cyclic ethers with 4–6 ring atoms, i.e. oxetanes, oxolanes and oxanes. The nature of this task and the limited space available preclude the treatment of the synthesis and reactions of compounds of these types also containing other functional groups. The most detailed reviews of the theme outlined above are those of Dittus[2-4] and Kröper[5]. Since the survey by Gritter[6], more recent reviews of certain aspects of the chemistry of cyclic ethers have also been published[7-9].

II. SYNTHESIS OF CYCLIC ETHERS

A. From Monofunctional Hydrocarbon Derivatives

As a result of wide-ranging investigations, a rational procedure has been developed for the synthesis of 2,5-dialkyloxolanes by means of the oxidative intramolecular cyclization of secondary alcohols[10] (equation 1). The yield is 35–95%, depending on the structural features and the experimental conditions. The following have been used as reagents: $Pb(OAc)_4$; $Pb(OAc)_4 + I_2$; HgO or $Hg(OAc)_2 + I_2$ or Br_2; Ag_2O, AgOAc or $Ag_2CO_3 + I_2$ or Br_2. The procedures involving the halogens are known as hypohalite reactions.

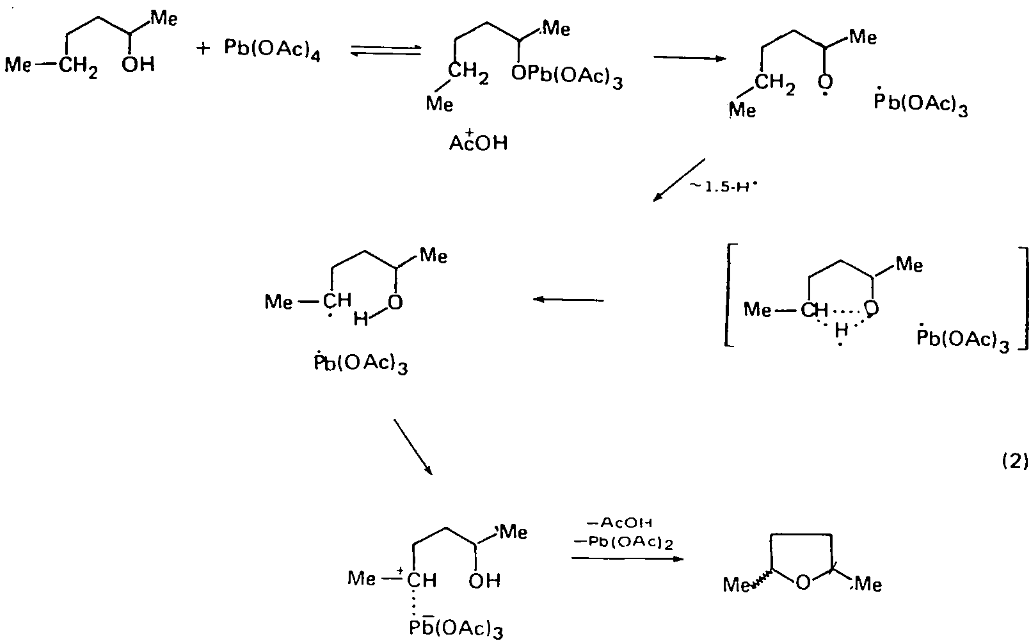


(1)

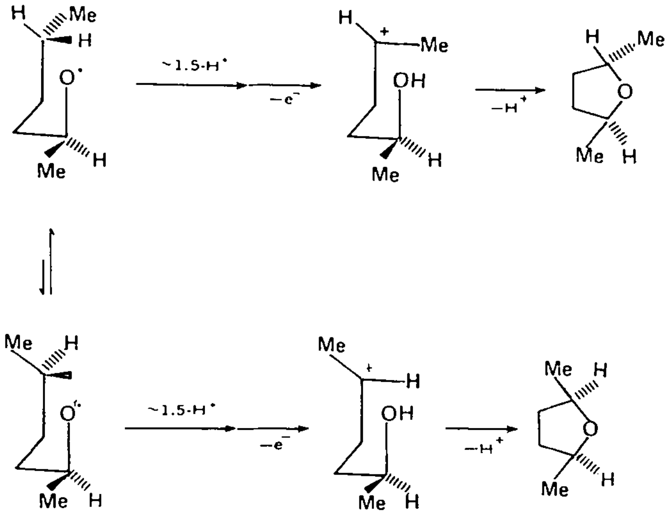
Extensive studies have been carried out on the mechanism and stereochemistry of the cyclization[10,11], which were found to depend both on the configuration and conformation of the alcohol, and on the oxidizing agent employed. The mechanism of the $Pb(OAc)_4$ reaction is illustrated in equation (2), and its stereochemistry in equation (3).

The mechanism and stereochemistry of the hypohalite reaction (the course of which is similar to the previous one) are also treated in detail in the review by Mihailović[10], on the basis of his own results and those of Green and coworkers[11,12].

In spite of the fact that the reactions are not stereoselective, they may be used to advantage for the synthesis of optically active oxolanes: the configuration of the carbon atom bearing the OH group does not change in the course of the transformation, and thus, if the starting alcohol is an optically active one, optically


Me—CH2 OH Me
+ Pb(OAc)4
CH2 OPb(OAc)3 Me
AcOH
Pb(OAc)3
~1.5-H•
Me—CH H O
Pb(OAc)3
Me—+CH OH
Pb(OAc)3
−AcOH
−Pb(OAc)2
Me O Me

(2)


~1.5-H•
−e⁻
−H⁺
OH
Me
H

(3)

active *trans*-2,5-dialkyloxolane may be prepared from the diastereoisomer mixture (obtained in a ratio of nearly 1:1) after chromatographic separation.

B. From Difunctional Hydrocarbon Derivatives

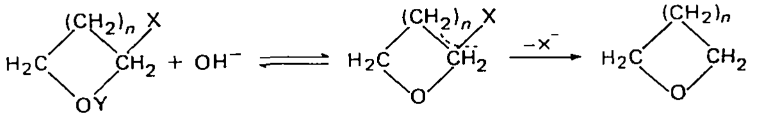
The most general and most frequent procedures for the synthesis of oxacycloalkanes are the transformations under various experimental conditions of the 1,3-, 1,4- and 1,5-diols, and of difunctional compounds prepared from them, to oxetanes, oxolanes or oxanes.

1. Dehydration of diols

Using this method, oxolanes and oxanes can be prepared in very good yield. The results connected with the mechanism and stereochemistry of the dehydration of diols to cyclic ethers, and with the possibilities of application of the method, were surveyed in the chapter 'Dehydration of diols'[13].

2. Basic cyclization of difunctional compounds

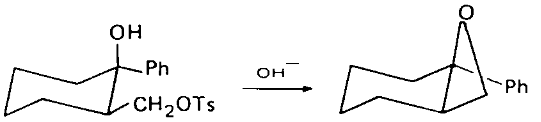
The reaction scheme for this procedure is shown in equation (4). X is most frequently Cl, Br or OTs, while Y is H or Ac. The method may serve for the preparation of oxetanes, oxolanes and oxanes, but it is mainly used in the synthesis of oxetanes. The results of the past 10 years indicate that this procedure has been employed to prepare 2-aryl-[14], 2,2-dialkyl-[15], 3-alkyl- and 3-aryl-[16], 3,3-dialkyl-[17], 2,3-dialkyl-[18,19], 2-aryl-3-alkyl-[18], 2,4-dialkyl-[19] and 2,2,3,3-tetraalkyl-oxetanes[20], C≡C-substituted oxetanes[21–23], and various condensed polycyclic[24,25] and steroid[26,27] oxetanes. A number of publications deal with the preparation of the starting 1,3-chlorohydrins[28] and 1,3-chloroacetates[29,30], and also with the study of the mechanisms of the diol + acetyl chloride reactions[31,32]. Asymmetric induction occurs in the Grignard-type addition reaction of β-chlorobutyraldehyde[28].



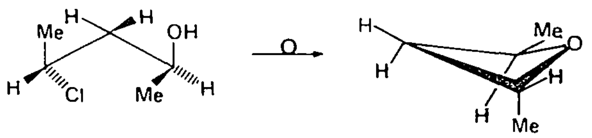
(4)

The earlier finding that, in accordance with the method outlined in equation (4), oxetanes can be prepared in good yield only from compounds containing X in a primary position has been confirmed by additional experimental data[20,33,34], and has been convincingly justified by reaction kinetic and other examinations[19,20,35–37].

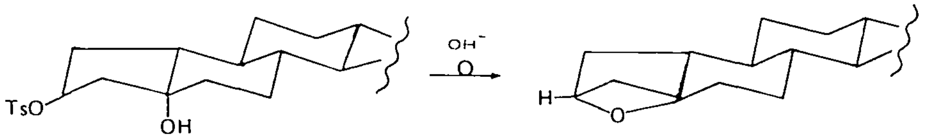
Investigations relating to the mechanism of the reaction, which have extended to the transition states of the molecules, confirm the reaction route of equation (4)[19,35–42]. Studies on the stereochemical course of the process[18,19,24–27,30], according to which the cyclization is stereospecific, similarly support the above mechanism (equations 5–7).



(Ref. 25) (5)



(Ref. 19) (6)

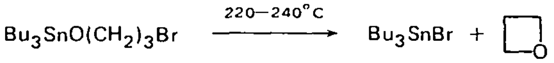


(Ref. 26)

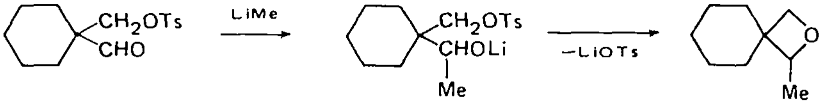
(7)

The basic cyclization of the quaternary salts of 1,3-amino alcohols[43,44] and 1,4-amino alcohols[45] can be employed for the preparation of oxacycloalkanes only in the latter case.

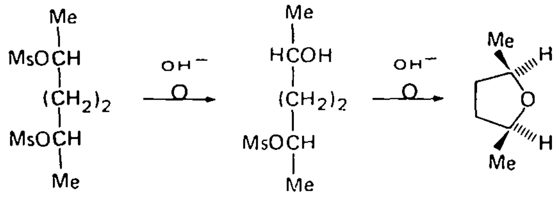
Since new procedures have been elaborated for preparation of the starting compound, the method of equation (8) has been proposed for the synthesis of base-sensitive oxetanes[46].


(8)

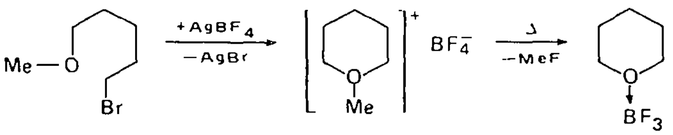
Oxetanes may be prepared too by the reaction of β-tosyloxycarbonyl compounds with organomagnesium or organolithium compounds (similarly by an S_Ni mechanism)[47] (e.g. equation 9).


(9)

The basic cyclization of 1,4-diol dimesylates also occurs via an S_Ni mechanism[48] (equation 10). Since both reactions are accompanied by configuration changes, *cis*-oxolanes may be prepared from *erythro*-diols, and *trans*-oxolanes from *threo*-diols.

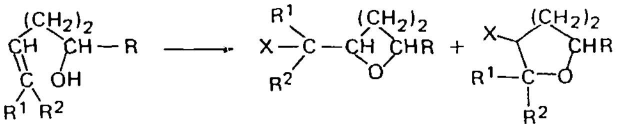

(10)

The presence of the corresponding oxonium salt intermediate has been proved experimentally in the cyclization of γ- and δ-methoxyalkyl halides in the presence of Lewis acids (e.g. equation 11)[49].


(11)

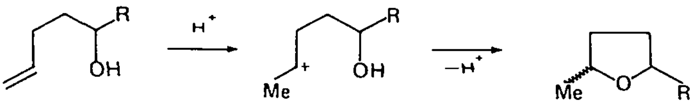
3. *Transformation of unsaturated alcohols*

Oxolanes and oxanes containing functional groups may be prepared in good yield from unsaturated alcohols under very varied experimental conditions and with various reagents (equation 12). The most recent literature data connected with the procedures are to be found in the review by Mihailović[10].

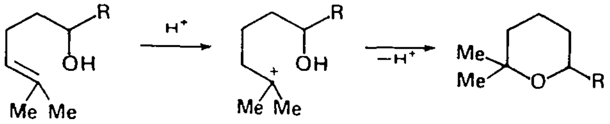

(12)

X = H, OH, OAc, Br, I, NO

Routes to oxolanes and oxanes not containing functional groups are shown in equations (13a) and (13b).

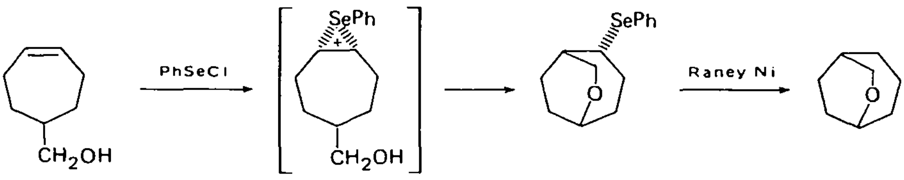


(13a)

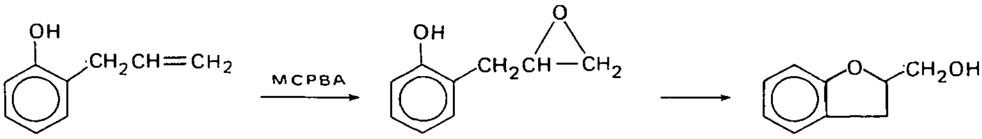


(13b)

PhSeCl can be employed in the synthesis of oxacycloalkanes[50] (equation 14). 2-Allylphenol undergoes cyclization in the manner outlined in equation (15), with neighbouring-group participation[51].



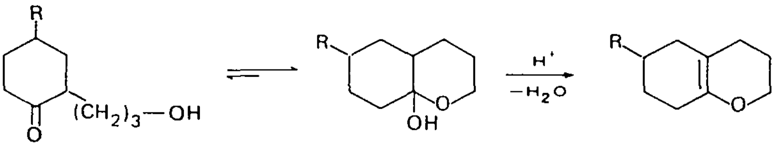
(14)



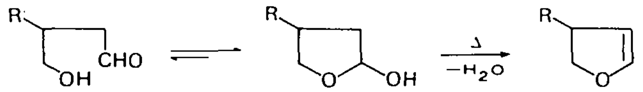
(15)

4. Cyclization of hydroxycarbonyl compounds

Although the intramolecular cyclizations of 1,4- and 1,5-hydroxycarbonyl compounds[52–55] to 2-hydroxy-oxolanes and -oxanes are reversible, subsequent dehydration makes these processes irreversible (equations 16 and 17). By catalytic reduction the cyclic compounds may be saturated, and since the chiral centre is not affected by this process, the method may also be utilized for the preparation of optically active oxolanes and oxanes.



(Ref. 54) (16)



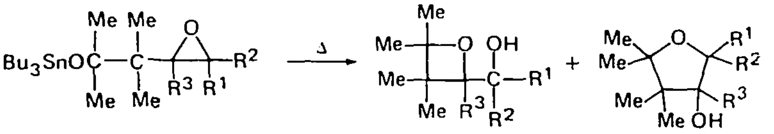
(Ref. 55) (17)

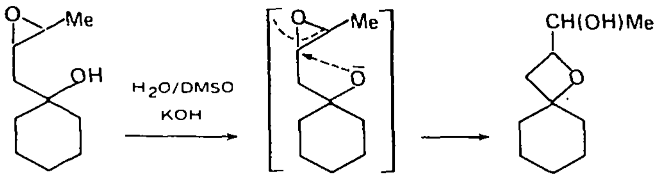
C. From Heterocyclic Compounds

1. *Formation from oxiranes*

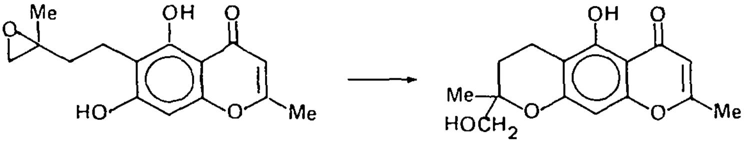
Oxiranes containing various functional groups can be transformed to oxetanes, oxolanes and oxanes.

By means of thermal rearrangement via alkoxytin intermediates, β-hydroxyoxiranes may be converted to oxetane or oxolane derivatives, depending on the substituents on the carbon atoms of the oxirane ring[56] (equation 18). In the presence of bases, certain β-hydroxyoxiranes can be transformed to oxetanes directly in aqueous medium, by intramolecular cyclization[57,58] (e.g. equation 19).

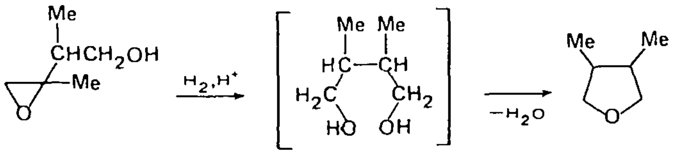

(18)


(19)

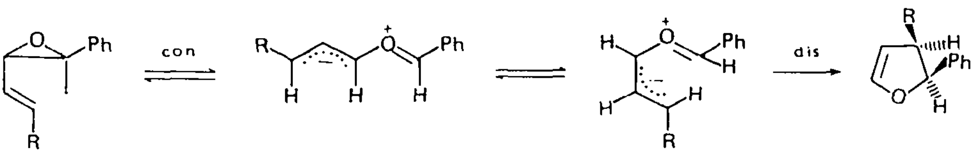
Oxolanes and oxanes may also be prepared from hydroxyoxiranes by either acid- or base-catalysed cyclization[59,60] (e.g. equation 20).


(Ref. 59) (20)

β-Hydroxyoxiranes can be transformed to oxolanes by catalytic hydrogenolysis in the presence of acids, presumably via 1,4-diol intermediates[61] (equation 21).


(21)

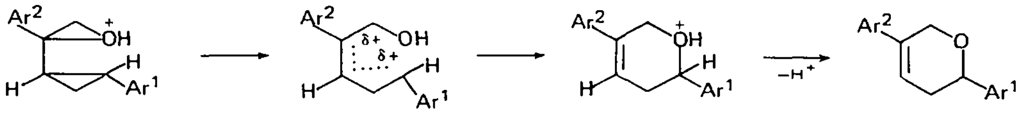
The vinyloxiranes undergo thermal rearrangement to dihydrofurans[62-65]. Equation (22) illustrates the mechanism of the much-examined rearrangement.


(22)

The formation of oxolanes or furans can similarly be observed in certain reactions of steroid oxiranes[66] or methoxyallenеoxiranes[67].

A comparatively simple method has been developed for the preparation of

2-aryl-3,6-dihydro-2*H*-pyrans, by means of the acid-catalysed rearrangement of cyclopropyloxiranes (equation 23)[68,69].

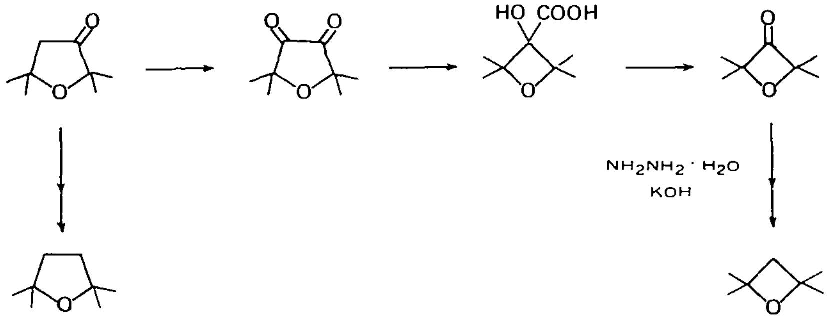

Ar²
OH
H
Ar¹
δ+
−H⁺
O

(23)

2. Reduction of oxacycloalkanones

Lactones can be converted to oxacycloalkanes with $LiAlH_4$, through the Grignard reaction or by catalytic reduction. Detailed studies have been carried out on various hydride-type reagents in the case of steroid lactones[70,71]. In the catalytic hydrogenation of maleic anhydride to oxolane, the effect of the composition of the bimetallic (Re–Ni) catalyst on the oxolane yield has been investigated[72].

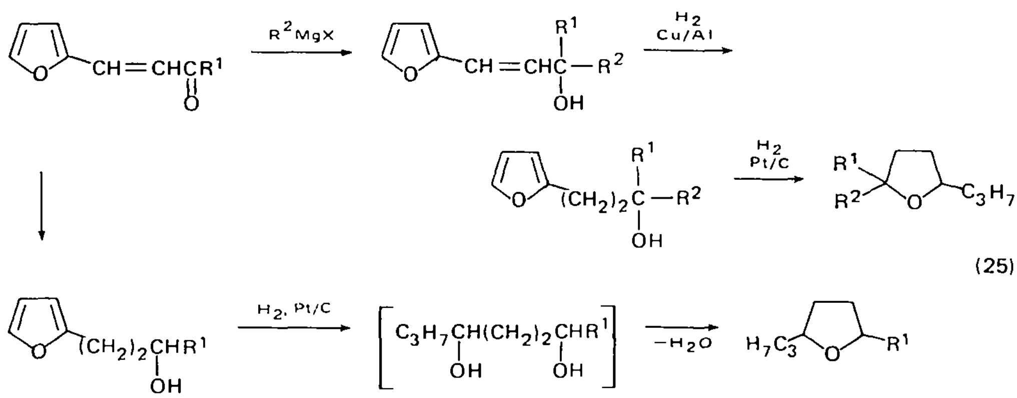
Substituted oxolane-3-one can be utilized for the synthesis of 2,3-dihydrofurans[73], oxetanes[74] and oxolanes[74] (equation 24).


HO COOH
$NH_2NH_2 \cdot H_2O$
KOH

(Ref. 74) (24)

3. Reduction of dihydrofurans and furans

The reductions of furans have been reviewed by Armarego[8] and heterogeneous catalytic reductions (equation 25) by Bel'skii and Shostakovskii[7].

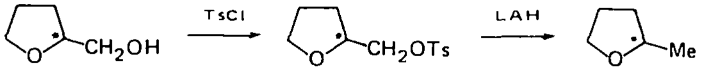

CH=CHCR¹
R²MgX
CH=CHC—R²
OH
H₂ Cu/Al
(CH₂)₂C—R²
H₂ Pt/C
C₃H₇
(CH₂)₂CHR¹
H₂, Pt/C
C₃H₇CH(CH₂)₂CHR¹
−H₂O
H₇C₃
R¹

(25)

A new catalyst has been developed for the reduction of furan and alkylfurans[75].

The application of various zeolites as catalysts for the hydrogenation of alkylfurans has not proved satisfactory[76].

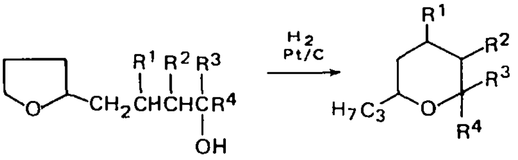
Optically active 2-methyloxolane can be prepared easily and in good yield as in equation (26)[77].


CH2OH
TsCl
CH2OTs
LAH
Me

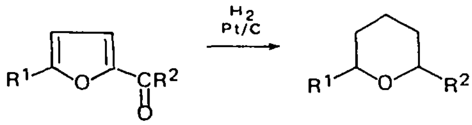
(26)

4. *Preparation of oxanes from oxolanes*

The procedures of Bel'skii[7,78] are also suitable for the preparation of oxanes (equations 27 and 28).


R1 R2 R3
CH2CHCHCR4
OH
H2
Pt/C
R1
R2
R3
H7C3
R4

(27)

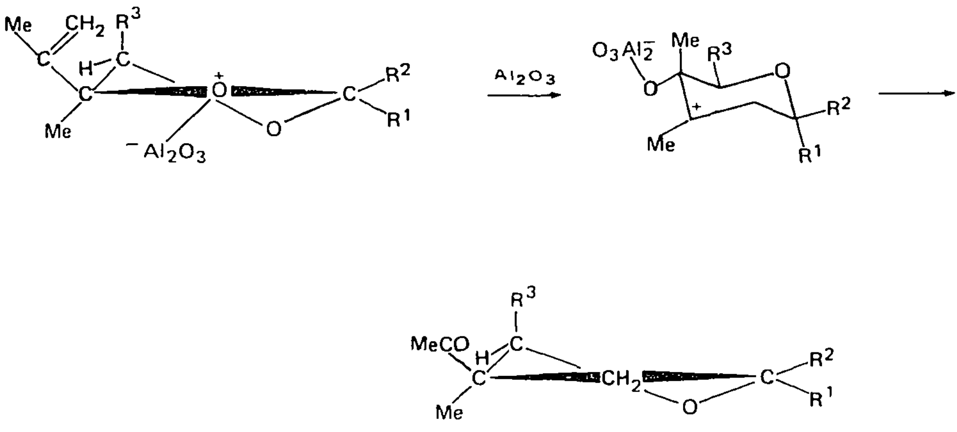

R1
CR2
O
H2
Pt/C
R1
R2

(28)

The mechanism of dehydration of 2-hydroxymethyloxolanes to yield dihydropyrans was studied[79,80]. The application of 2,3-dihydro-4*H*-pyrans as base-stable, acid-labile protective groups has been surveyed by Armarego[8].

5. *Rearrangement of dioxacycloalkanes*

A new procedure has been elaborated by Mousset and coworkers for the preparation of 3-acyloxolanes by means of the rearrangement of 5-vinyl-1,3-dioxolanes in the presence of electrophilic catalysts[81-84]. The stereoselective rearrangement is shown in equation (29). Alkyldimethyl-1,3-dioxanes undergo rearrangement to hydroxyoxanes in the presence of acids[85].


Me
CH2
R3
H
C
O
R2
R1
Me
−Al2O3
Al2O3
O3Al2−
Me
R3
O
+
R2
R1
Me
R3
MeCO
H
C
CH2
R2
R1
Me
O

(29)

D. Via Cycloaddition Reactions

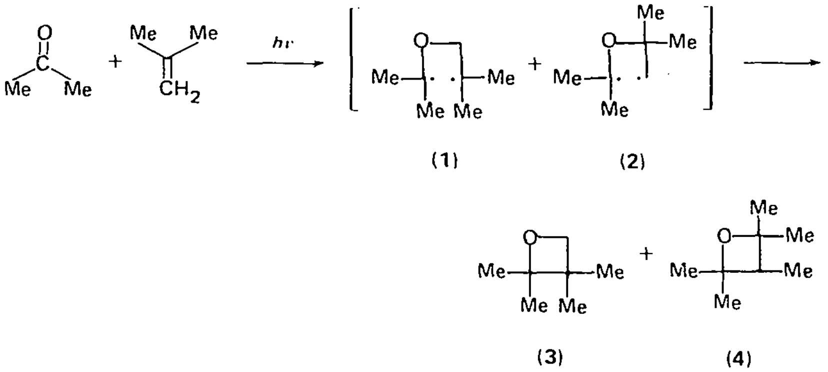
Cycloaddition can be employed for the preparation of oxetanes, oxolanes and oxanes. Many reviews of this topic[8,86-89] have appeared and we shall deal here mainly with the results published since 1974.

1. Synthesis of oxetanes

Oxetanes may be synthesized by the photocatalytic 1,2-cycloaddition of olefins and carbonyl compounds (Paterno–Büchi reaction). The carbonyl compounds used so far include aldehydes, ketones, diketones, quinones, carboxylic acid fluorides, urethanes, acyl nitriles, alkoxycarbonyl nitriles, thiocarbonyls and certain esters, while among the unsaturated compounds used are olefins, allenes, acetylenes, enones, ketene imines and ketene acetals[89].

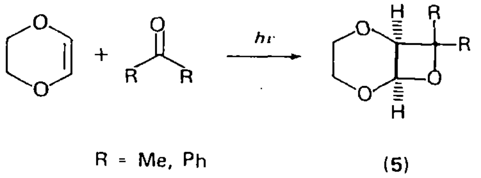
The Paterno–Büchi reaction may occur either intermolecularly or intramolecularly. Meier[89] has tabulated the preparations of more than 200 oxetane derivatives. The yield varies from a few per cent to 80%. More recent papers deal with the regioselectivity, stereochemistry and mechanism of the cycloaddition.

Studies have been made of the cycloadditions of olefins and aldehydes[90,91], olefins and ketones[92-95], and reactants containing various functional groups[96-107] (e.g. equations 30–33). Reaction (30) is fairly regioselective (3:4 = 9:1). The orientation of the cycloaddition is governed by the relative stabilities of the radicals 1 and 2. In general, a mixture of the (*Z*)- and (*E*)-isomers is formed in the addition[96]. However, only the *cis*-anellation (*cis*-fused) product, 5, is obtained in the course of the photocycloadditions of 1,4-dioxene and benzophenone (82%), or acetone (66%)[100] (equation 31). Particularly for rather complex molecules, the biradical formed during the photoreaction may have various structures and, depending on the relative stabilities of the individual radicals, many other products, including oxolanes, may be produced in addition to oxetane[109,110].



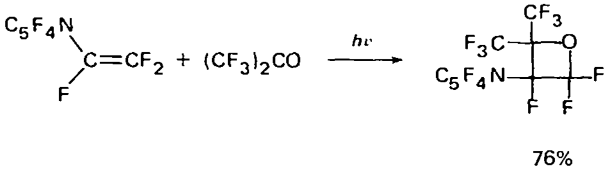
(Ref. 108) (30)

In the case of intramolecular photocycloaddition, the oxetanes formed may be 2,3- and/or 2,4-linked (equation 34). The course of the reaction may be strongly

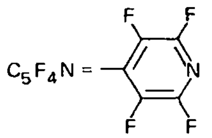


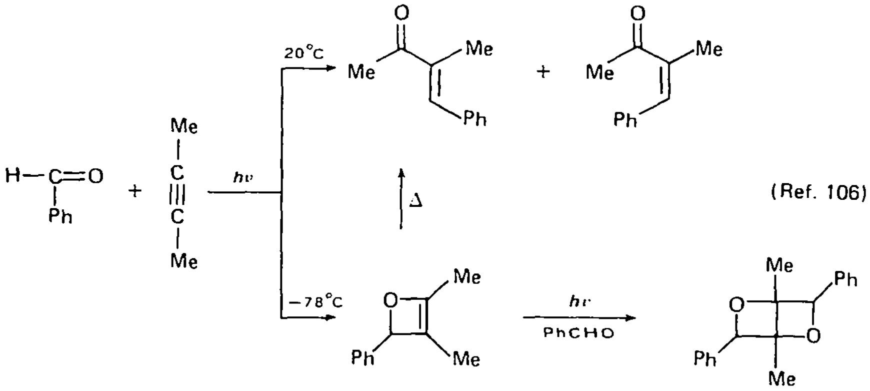
R = Me, Ph (5)

(Ref. 100) (31)

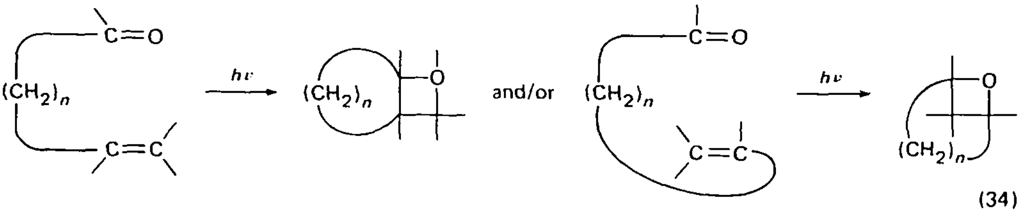

C5F4N
C=CF2 + (CF3)2CO
F
hν
CF3
F3C
O
C5F4N
F
F F
76%

(Ref. 99) (32)


C5F4N =
F F
N
F F


H—C=O
Ph
+
Me
C
C
Me
hν
20°C
O
Me
Me
Ph
+
O
Me
Me
Ph
Δ
−78°C
O
Me
Ph
Me
hν
PhCHO
Me
Ph
O
O
Ph
Me

(Ref. 106) (33)


C=O
(CH2)n
C=C
hν
(CH2)n
O
and/or
C=O
(CH2)n
C=C
hν
O
(CH2)n

(34)

influenced by steric factors. Most reactions have been described for $n = 2$ and $n = 3$[111–113], but 2,2,3,4-tetramethyloxetane has also been prepared in good yield (70%) from a conjugated enone ($n = 0$)[114,115].

Many polycyclic oxetanes have been prepared from systems with rigid skeletons[116], and particularly by the photocycloaddition of 5-acylnorbornenes and their halogen and methoxy derivatives, in yields of 20–90%[117,118].

The Paterno–Büchi reaction is frequently used in more complex syntheses[119,120], and may, for example, yield intermediates in the syntheses of insect pheromones[121] or prostaglandin analogues[122].

Many hypotheses have been put forward for the mechanisms of the Paterno–Büchi reactions. A number of possibilities may be conceived for the radical formation itself, and for the reactions following this[92,93]. Moreover, if the triplet energy of the olefin is lower than that of the carbonyl, energy transfer may take place and olefin dimerization may become predominant.

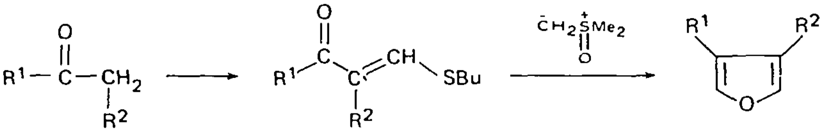
As to the mechanism of the photochemical oxetane formation itself, no general theory exists that is valid for the overwhelming majority of the reactions. In principle, the reaction may be started by the excited (singlet or triplet) carbonyl, or by the olefin. In most cases, however, the initial step is the electrophilic attack of the excited carbonyl. In the first step of the excitation, singlet (^{1}n,π*) carbonyl is produced, which may pass over into a triplet (^{3}n, π*) state in a transition not involving radiation (intersystem crossing). Both states may be reactive (perhaps comparably so)[117], but in general one or other plays a predominant role. Transitions between the triplet and single states are possible by means of vibrational and spin-orbit couplings and other interactions[123]. A triplet state is often assumed in the reactions of aromatic ketones[94,95], while aldehydes and aliphatic ketones primarily react with a singlet carbonyl state[91,97,107,112,123].

As a result of the attack of the excited carbonyl, an excited transition complex (exciplex) is produced, which is converted to a 1,4-biradical, although the oxetane may also be formed from the exciplex via concerted development of two new σ-bonds[97]. The stereospecificity of the reaction in the singlet case is ensured by the higher rotational energy compared to that of the triplet state[124], and by the fact that (*Z*)–(*E*) isomerization at the radical site does not occur in general in a singlet biradical[125]. On the other hand, the regiospecificity is controlled by the relative stabilities of the radicals produced[108]. (A triplet 1,4-biradical may also be stabilized by cyclopropyl conjugation[126].) The biradicals may then be stabilized by ring-closure.

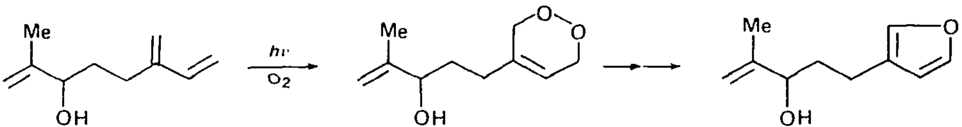
Meier gave a general scheme[89] for the possible reaction pathways of olefins and carbonyl compounds, though the transformations are not always reversible[95].

2. *Synthesis of oxolanes and oxanes*

The 2,3- and 2,5-cycloaddition reactions of furan and its derivatives, which can be used in many cases for the synthesis of condensed polycyclic oxolanes, have been reviewed by Armarego[8] (including the most recent literature data). Here, therefore, attention is merely drawn to the procedures outlined in equations (35)–(37), which show the general methods of synthesis of certain types of oxolanes by means of hydrogenation of the furans formed.

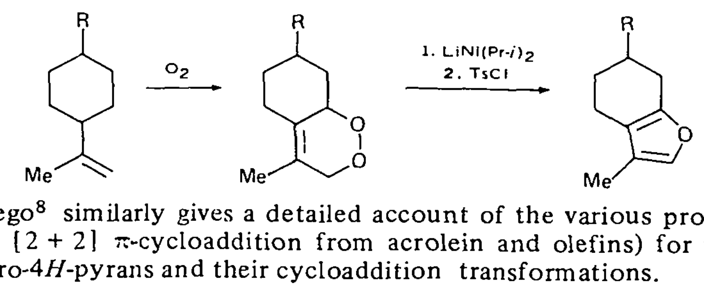


(Ref. 127) (35)



(36)

(Ref. 128)



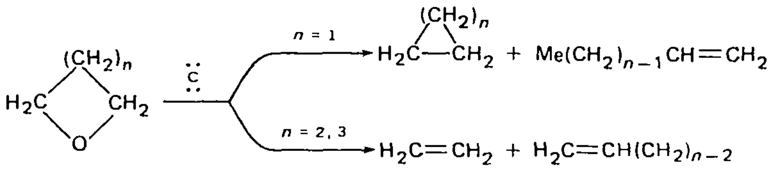
(Ref. 129) (37)

Armarego[8] similarly gives a detailed account of the various procedures (among others by [2 + 2] π-cycloaddition from acrolein and olefins) for the synthesis of 2,3-dihydro-4*H*-pyrans and their cycloaddition transformations.

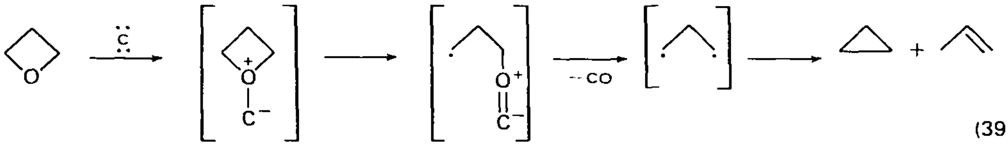
III. REACTIONS OF CYCLIC ETHERS

A. Deoxygenation

Cyclic ethers undergo deoxygenation on reaction with atomic carbon, to give the products outlined in equation (38)[130]. The mechanism of the deoxygenation is shown in equation (39) for the case of oxetane[130].



(38)

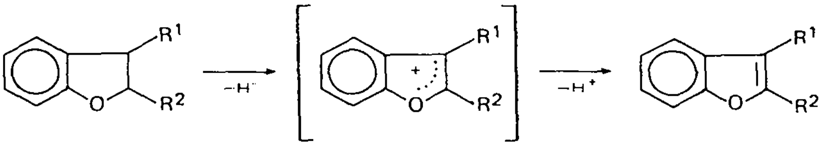


(39)

B. Dehydrogenation

Experimental observations are available only as regards the dehydrogenation of the dihydrofurans and the oxolanes[131-137]. The driving force of the dehydrogenation process is the striving towards aromatization, which is not possible for the oxetanes and the oxanes.

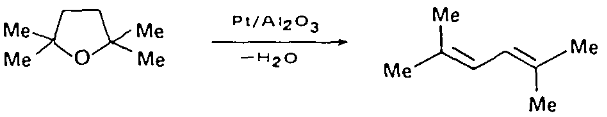
On a Pd/C catalyst, oxolane and the 2-alkyloxolanes are dehydrogenated to the corresponding furans (yield ~80%)[131]. If oxolane and 2,5-dihydrofuran are reacted with hydrogen acceptors transfer–hydrogenation reactions take place[132-134]. Oxolane does not disproportionate on Al_2O_3[135]. 2,3-Dihydrobenzofuran and its derivatives are dehydrogenated to the corresponding benzofurans via an ionic mechanism[136,137] (equation 40).



(40)

C. Dehydration

In connection with the cyclic ethers, work has mainly centred on the dehydration of oxolane to butadiene, and of 2-methyloxolane to piperylene and cyclopentadiene[7]. The dehydration is catalysed by various acidic heterogeneous catalysts. Under similar conditions the oxanes and oxepanes can also be transformed to dienes[138]. 2,5-Dimethyl-2,4-hexadiene can be prepared in good yield from 2,2,5,5-tetramethyloxolane[139] (equation 41).



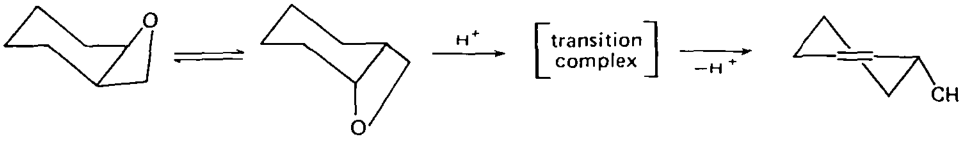
(41)

D. Rearrangements

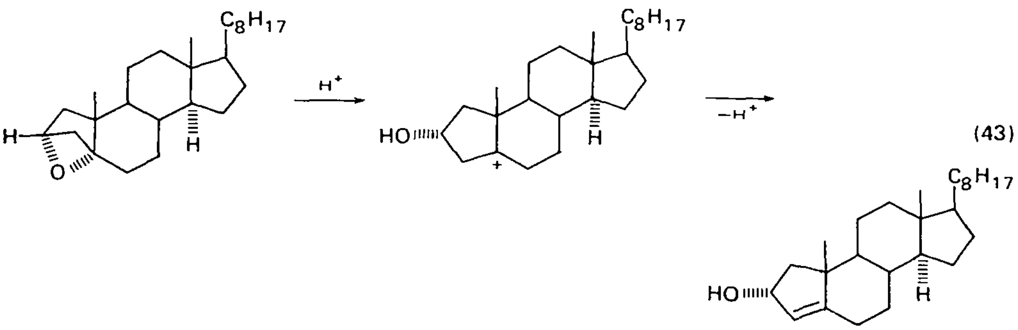
Two reviews have recently appeared on the rearrangements of cyclic ethers[7,8]. Because of the strained ring, the oxetanes (and the oxiranes) exhibit the highest reactivity of the cyclic ethers in rearrangement reactions.

1. Rearrangement of oxetanes

Comparatively few examinations have been made of the acid isomerizations of oxetanes[26,140–145]. By means of acid catalysis the oxetanes are mainly isomerized to unsaturated alcohols[26,143,145]. The isomerization depicted in equation (42)[145] proceeds with high selectivity on a g.l.c. column of acidic character to yield a β,γ-unsaturated alcohol. Another example is presented in equation (43)[26].

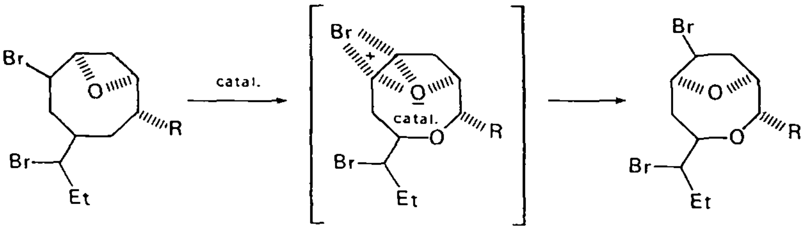

O
H+
transition complex
−H+
O
CH2OH

(42)

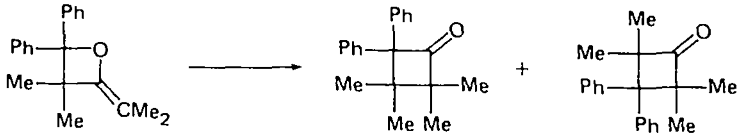

C8H17
H
H
O
H+
C8H17
HO
+
H
−H+
C8H17
HO
H

(43)

Equation (44) shows an acid-catalysed rearrangement of oxetane to oxolane[146]. On the action of neutral Al_2O_3, α-isopropylideneoxetanes are converted to the corresponding cyclobutanones in the course of rearrangement[147] (equation 45).

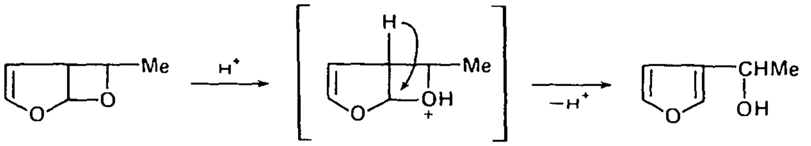

Br
O
R
Br
Et
catal.
Br
+
O
catal.
O
R
Br
Et
Br
O
O
R
Br
Et

(44)


Ph
Ph
O
Me
Me
CMe2
Ph
O
Ph
Me
Me
Me Me
+
Me
O
Me
Ph
Me
Ph Me

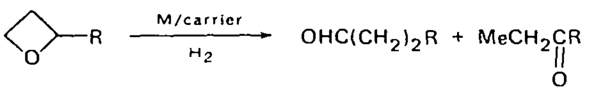
(45)

On Al_2O_3 and $Ca_3(PO_4)_2$ catalysts, isomeric carbonyl compounds are also formed in addition to the corresponding unsaturated alcohols in the rearrangement reactions[144]. The synthesis of 3-substituted furans is made possible by the rearrangement reaction shown in equation (46)[148]. In the presence of hydrogen



(46)

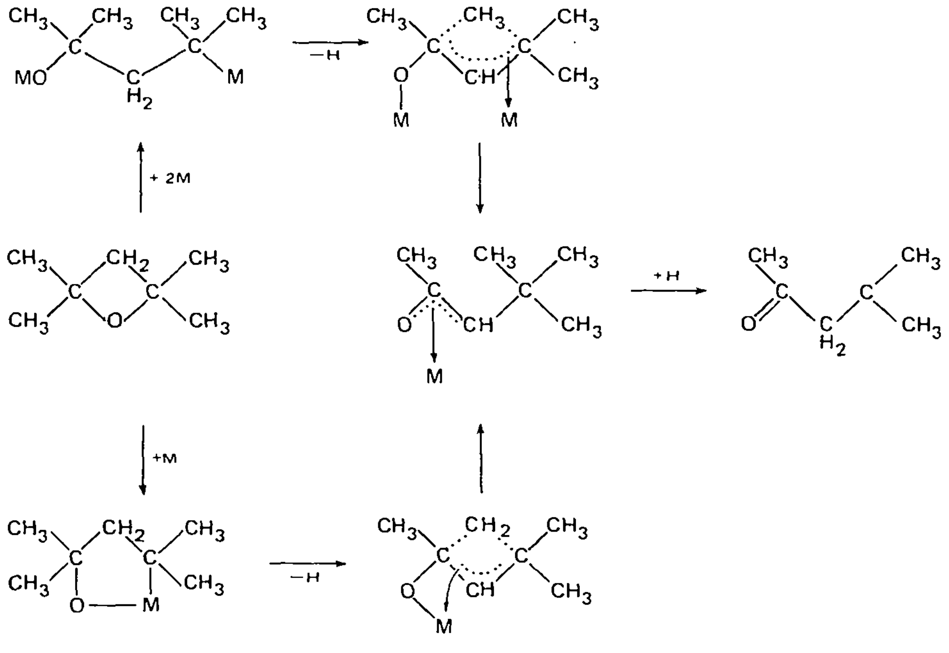
on supported metal catalysts, oxetanes undergo rearrangement to carbonyl compounds[140,149–153b] (equation 47). The mechanism of the reaction is very



$$\text{OHC(CH}_2)_2\text{R} + \text{MeCH}_2\underset{\underset{\text{O}}{\|}}{\text{C}}\text{R} \qquad (47)$$

complex, and depends to a great extent on the reaction conditions. From the examinations to date it is concluded[153b] that the formation of aldehydes can be explained by the participation of the electrophilic centres of the catalyst, while the presence of chemisorbed hydrogen is necessary for the formation of ketones.

On platinum metals, 2,2,4,4-tetramethyloxetane is rearranged to the corresponding ketone via a 1,3-bond shift mechanism[154] (equation 48).

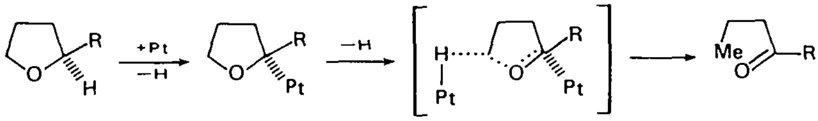


(48)

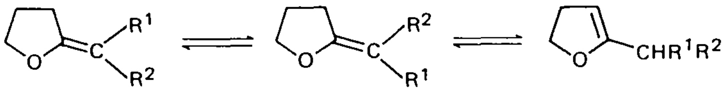
M = Pt, Pd, Rh

2. *Rearrangement of oxolanes and oxanes*

Oxolanes and oxanes are converted to ketones with very high regioselectivity on platinum metals[7]. In mechanistic studies[153b,155,156] it has been established that the presence of hydrogen is indispensable for the process to occur[157], while in all probability the reaction takes place according to a hydroisomerization mechanism[158] (equation 49). Some new results have also been reported on the rearrangement reactions of dihydrofurans and certain furan compounds. Studies have been made of the thermodynamics of isomerizations according to equation (50)[159].

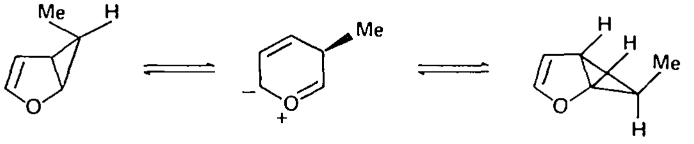


(49)



(50)

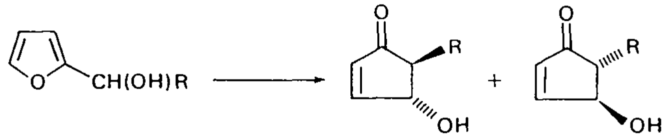
Examples of thermal isomerizations are the interconversions of 6 and 7[160] (equation 51).



(51)

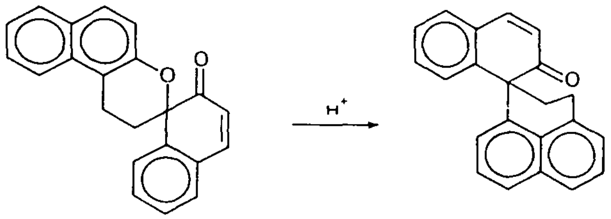
(6) (7)

The acid-catalysed rearrangements of 2-furylcarbinols are electrocyclic reactions occurring with controtation[161] (equation 52). The process is stereospecific, only

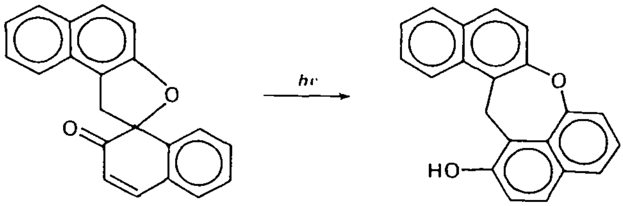


(52)

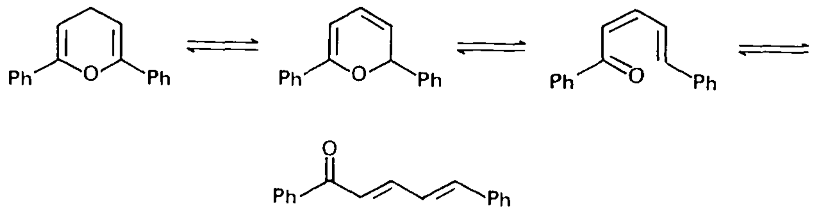
one of the enantiomer pairs being formed. Interesting rearrangements are to be seen in equations (53), (54)[162] and (55)[163].



(53)



(54)



(55)

E. Oxidation

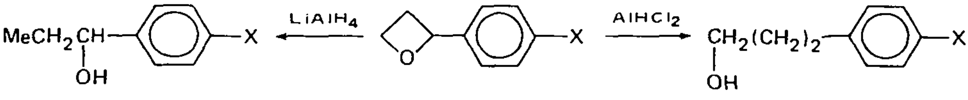
Much interest has been manifested recently in the reaction oxolane → γ-butyrolactone. This process is of industrial importance; it can be carried out in the presence of catalysts[164,165], or electrochemically[166]. A procedure has been developed for the joint preparation of 2-hydroxyoxolane and γ-butyrolactone[164]. Investigations have been carried out on the kinetics and mechanism of the oxidation of oxolane with peroxydisulphate[167].

F. Reduction and Hydrogenolysis

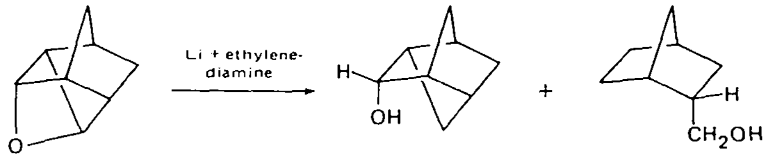
Only a single review has appeared on the reduction and hydrogenolysis of 4-, 5- and 6-membered cyclic ethers[7]; this deals mainly with the hydrogenolysis of oxolanes and the reduction of furans and dihydrofurans. Since the reactivity decreases with the increase of the number of ring atoms, and only the oxetane ring can be opened with metal hydrides, the C–O bonds of oxolanes and oxanes can be cleaved by catalytic hydrogenolysis only.

1. Reduction with complex metal hydrides

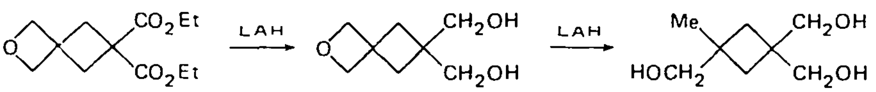
With minor corrections, the regularities discovered for the oxiranes hold for the regioselectivity and mechanism of the reduction of oxetanes with $LiAlH_4$[1]. The regioselectivity is influenced by electronic and steric effects, and also by the nature of the reagent[168,169] (e.g. equation 56). The kinetics of the $LiAlH_4$ reduction of 2-aryloxetanes can be well explained by an S_N2-type mechanism[170]. Studies have also been made of the reductions of certain 2-alkoxyoxetanes[171], polycyclic oxetanes[172] and spirooxetanes containing carbethoxy substituents[58,141] (equations 57–59).



(56)



(57)



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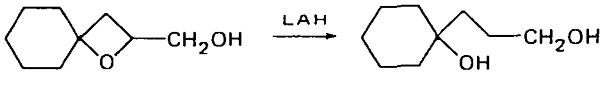
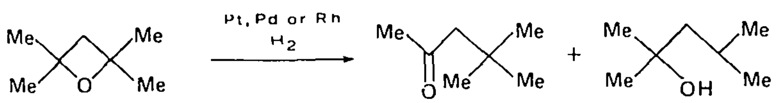

(59)

2. *Catalytic hydrogenolysis*

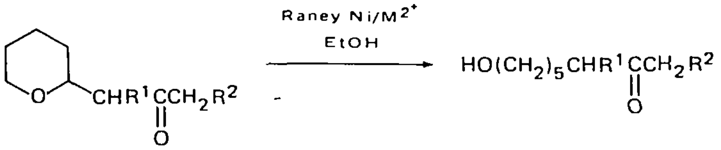
The hydrogenolysis of cyclic ethers on Group VIII metals and on copper has long been known. Recently, in order to elucidate the mechanism, use has been made of the pulse-microreactor technique[153a,b], selective catalyst poisoning[153b], isotope exchange[173], IR techniques[155], calculations of a thermodynamic and thermochemical nature[156] and other investigations relating to the end-products and intermediates[174].

The catalytic hydrogenolysis of oxetanes on various metal catalysts has been employed in syntheses and also in structure confirmations[22,172,175]. The isomerization of 2,2,4,4-tetramethyloxetane on platinum metals is accompanied by hydrogenolysis[154] (equation 60).


(60)

The variation in the regioselectivity of the hydrogenolysis of the oxacycloalkanes under pressure has been interpreted by its dependence on the number of ring atoms and on the catalyst (Raney Cu and Raney Ni)[176].

7-Hydroxyketones may be prepared by hydrogenolysis of the oxane ring[177] (equation 61):


(61)

By hydrogenation on a Pt/C catalyst and subsequent hydrogenolysis, 2-alkyl-2-methyl-2,5-dihydrofurans may be converted to the corresponding isoalkanes[53].

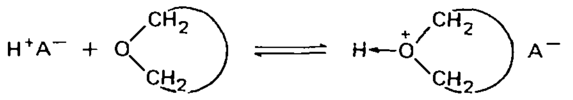
By selective hydrogenation of furfurol, various furan skeleton compounds can be synthetized; the hydrogenation may occur with[178–180] or without[181–186] ring-cleavage. Some of these reactions are of synthetic or industrial importance.

G. Polymerization

The polymerization and copolymerization of cyclic ethers is important from an industrial aspect; this is best demonstrated by the large number of reviews that have appeared in the past decade[187–205].

As with oxiranes, the polymerization may take place by a cationic or an anionic mechanism, depending on the initiator employed. The view has recently begun to become widespread that anionic polymerization of cyclic ethers can proceed only in accordance with the coordination mechanism. The cationic mechanism[206,207] is illustrated in equations (62)–(65). The propagation steps may have either S_N1 or S_N2 mechanisms. The coordination anionic mechanism[208] is outlined in equations (66) and (67) with $Al(OR)_3$ as initiator.

$$BF_3 + H_2O \longrightarrow H^+[BF_3OH]^- = H^+A^- \qquad (62)$$



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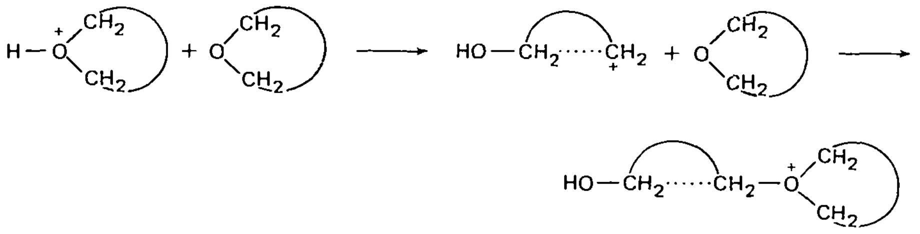

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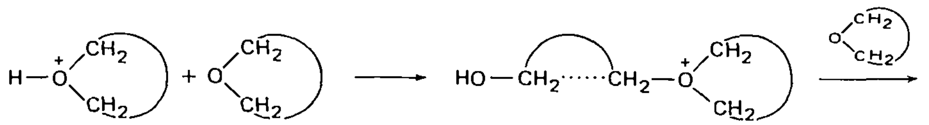

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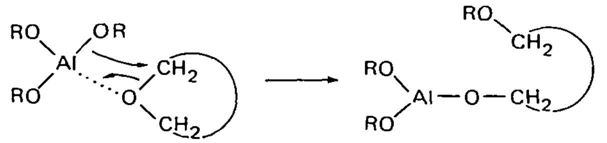

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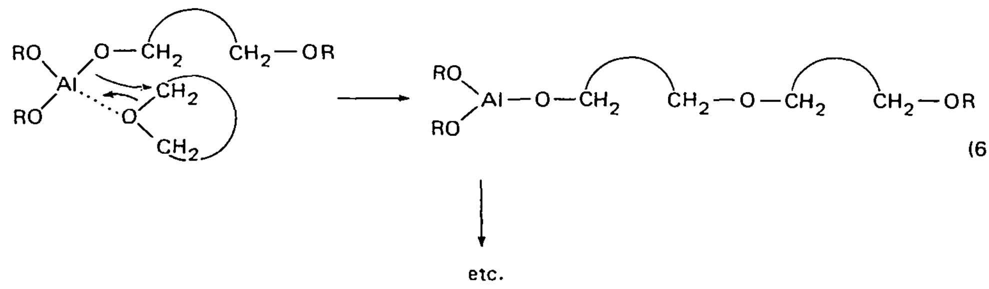
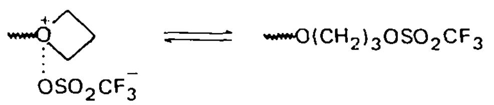


(67)

1. Polymerization of oxetane

According to recent investigations, the following initiators can be used for polymerization of oxetanes via the cationic mechanism: triethyloxonium salts[209], hexafluorophosphate salts[210] (e.g. Et_3O^+ PF_6^-, Ph_3C^+ PF_6^-) and ethyl trifluoromethanesulphonate[211]. It is assumed[211,212] that both the oxonium ion produced in the initiation step, and the ester formed from it, are present in equilibrium (equation 68). With triethyloxonium salt initiators, oligomerization occurs in competition with the polymerization and cyclic trimers and tetramers are formed[209].



(68)

Cyclic ethers often undergo copolymerization on the action of CO_2. If triethylaluminium is used as initiator, the mechanism is anionic[213].

2. *Polymerization of oxolane*

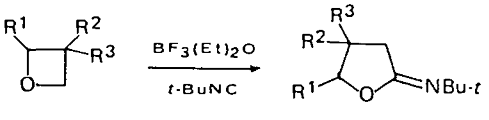
The following initiators are employed in the polymerization of oxolane by the cationic mechanism: ethyl 2,4,6-trinitrobenzenesulphonate[214], the propylene oxide—BF_3 system[215], chlorosulphonic acid[216] and the trityl cation[217]. Esters of superacids have recently been frequently used as initiators[218-222].

The copolymerization of oxolane and methyloxirane has been comprehensively studied by Blanchard and coworkers[223-226]. An examination has been made of the effects of the polymerization of changes in the reaction parameters (temperature, catalyst, cocatalyst, solvent, oxolane—methyloxirane ratio, quantity of water in the reaction mixture). Dicarboxylic acid anhydrides may also be used as partners for oxolane in copolymerization[227]. Like other cyclic ethers, oxolane may also form oligomers[228]. The kinetics of polymerization of oxolane at high pressure in the presence of $Et_3O^+ BF_4^-$ as initiator have been subjected to systematic study[229]. The cationic polymerization of oxepane has also been investigated[230]. Modern methods (e.g. ^{13}C-NMR[212,231]) are being ever more frequently utilized for the study of the polymerization of cyclic ethers. By measurement of the ^{13}C-isotope effect, the pathway of formation of active centres can be followed throughout the course of the cationic polymerization of oxolane[232].

H. Formation of Heterocyclic Compounds

1. *Ring-transformation of oxetanes to five- and six-membered heterocyclic compounds*

With *t*-butyl isocyanide in the presence of boron trifluoride etherate, oxetane is converted to iminooxolane[233] (equation 69). With carbonyl compounds, substituted oxetanes may be transformed to 1,3-dioxanes[234a,b] (equations 70a and b).



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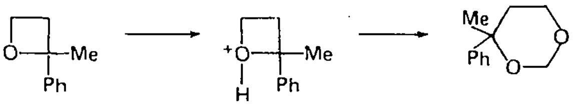
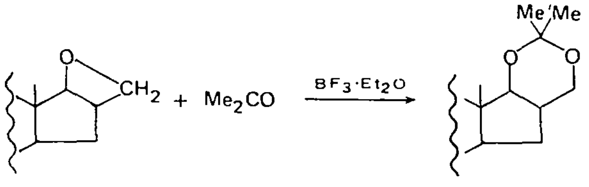


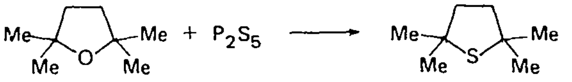
(70a)



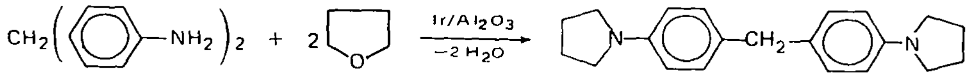
(70b)

2. *Ring-transformation of oxolanes, furans and oxanes*

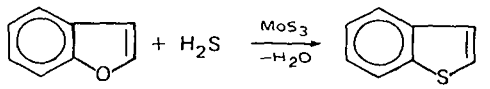
The Yur'ev reaction[234c] is suitable for the preparation of five-membered heterocyclic compounds containing one heteroatom, and their perhydrogenated analogues, from furans and oxolanes. The publications and patents of the past decade have mainly described the application of new catalysts, and the use of new compound types. The importance of the Yur'ev reaction in the chemical industry is demonstrated by the numerous patents[235–240]. The literature provides information on the use of the following catalysts: Cr_2O_3[238], $CuO{\cdot}Cr_2O_3$[238], MoS_3[238], $CoCl_2/Al_2O_3$[240], HF/Al_2O_3[240], potassium phosphotungstate/Al_2O_3[237] and various zeolites[241–251]. Catalyst systems of complex composition are also used (e.g. metal/support + halo acid + sulphonated styrene–divinylbenzene copolymer[236], etc.). Some examples are given in equations (71)–(73).



(Ref. 252) (71)



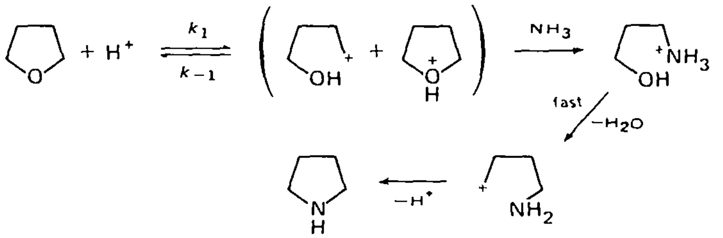
(Ref. 235) (72)



(Ref. 238) (73)

Synthetic zeolites* are effective catalysts of heteroatom exchange. On zeolites of moderate acidity (BaY), the transformation of furan to pyrrole with NH_3 proceeds with a selectivity of ~ 100%[241,242]. With the use of an HL zeolite, oxolane can be converted to pyrrolidine with NH_3 with a selectivity of ~ 90%[244].

It has been established that the active centres are the Brönsted sites formed in the zeolite lattice. The mechanism of the reaction is presented in equation (74)[244].



(74)

1-Propylpyrrolidine can be obtained from oxolane with propylamine on an AlY zeolite catalyst[248]. The transformation of γ-butyrolactone to 2-pyrrolidone is catalised with the greatest selectivity by the CuY zeolite[242,245]. The reaction of γ-butyrolactone and propylamine to give 1-propyl-2-pyrrolidone takes place with the highest yield in the presence of CaY, and with the best selectivity in the presence of CuY[247]. The product depends on the structure of the amine. The yield is lower with NH_3 than with primary amines. The reason for this is to be found in the different basicities, but it is very important that the steric effect too be taken into account.

The preparation of thiophen from furan with H_2S proceeds on Li^+ and Na^+ ion-exchange zeolites[246]. The activities of these catalysts increase with the decrease of the Si/Al ratio, and with the increase of the polarizing power of the cation. Alkali metal ion-exchange zeolites similarly catalyse the transformation of oxolane to thiolane[249]. It has been found that the X zeolites are more active than the corresponding Y zeolites. On CsY zeolite, γ-butyrolactone reacts with H_2S to give γ-thiobutyrolactone in a yield of 99%[250]. The catalytic activity is enhanced in the presence of pyridine, but disappears on the action of HCl; hence, basic sites play a very important role in the ring-transformation. The earlier results on the application of the zeolites in the Yur'ev reaction are reviewed by Venuto and Landis[253].

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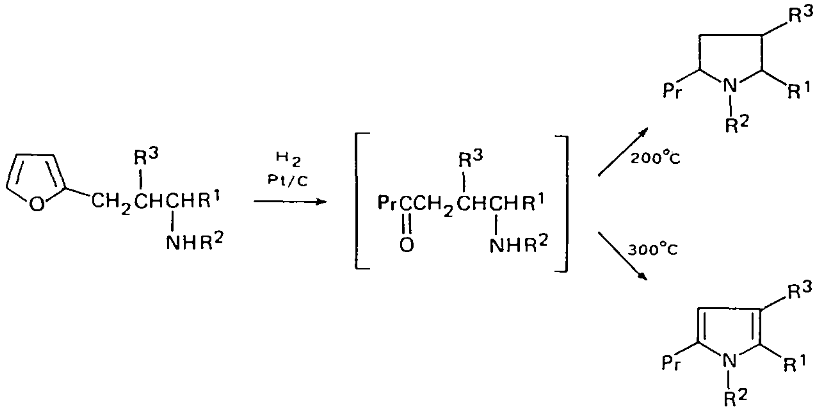
*X and Y zeolites are sodium aluminosilicates of faujasite type with different SiO_2/Al_2O_3 ratios; zeolite is potassium aluminosilicate.

Oxane can be converted with NH_3 to piperidine on synthetic zeolite catalysts[244,251]. The hydrogen-form L zeolites display a higher selectivity than the Y zeolites; dealumination of the L zeolites enhances the catalytic activity and the selectivity[251].

3. Transformation of cyclic ethers containing functional groups to other heterocyclic compounds

This subsection deals with various types of furan-skeleton compounds that can be synthesized from furfurol, and outlines the methods for their transformation to other oxygen- and nitrogen-containing heterocycles. These new methods, using various supported metal catalysts, were developed by Bel'skii and coworkers[7]. Two methods for the preparation of oxanes have already been discussed in Section II. C. 3. Equations (75)–(80) depict the methods whereby it is possible to prepare pyrroles and pyrrolidines[7,254–258], pyrrolines[257], pyridines[7], azepans[259], pyrazines[7] and 1,4-dioxanes[260,261]. All starting compounds may be obtained in good yields by classical syntheses from furfurol. The Yur'ev reaction has been utilized to develop a procedure for the formation of pyrrole from furfurol without isolation of



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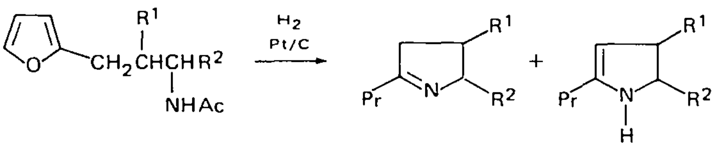

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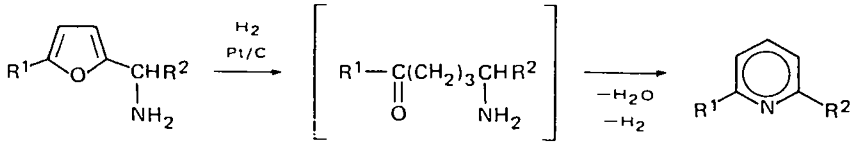

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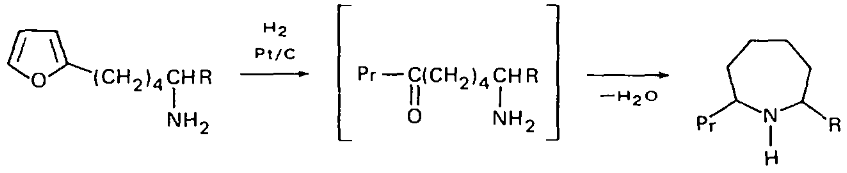

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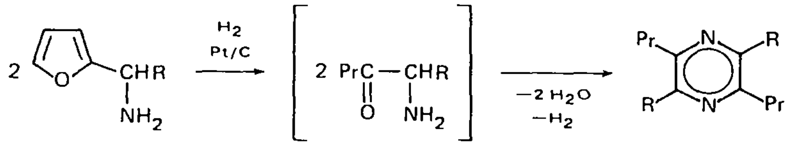

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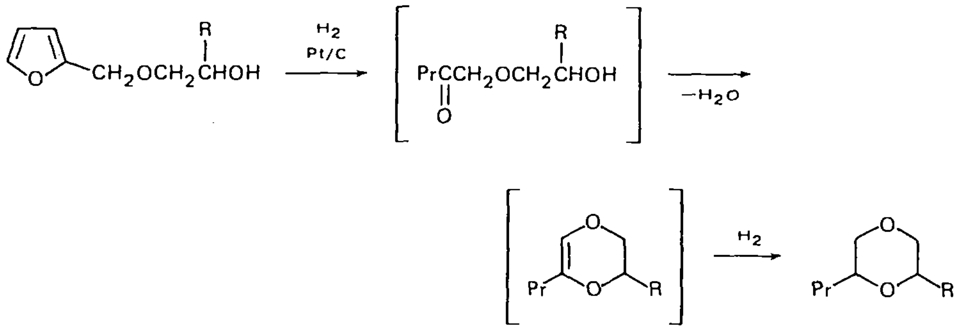
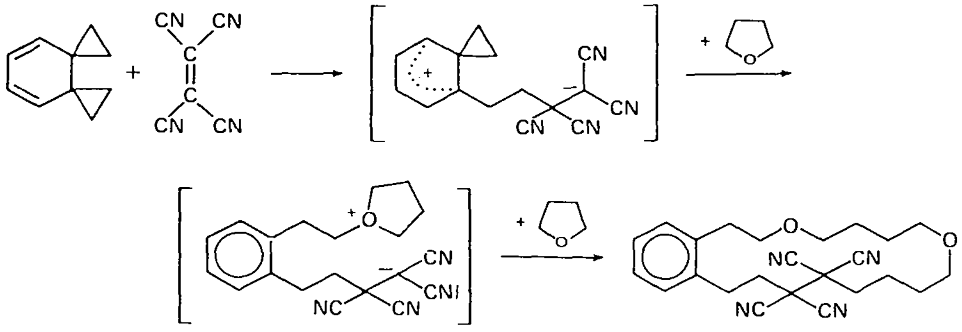


(80)

furan[262]. Finally, equation (81) illustrates a ring-expansion reaction in which two oxolane molecules take part[263].



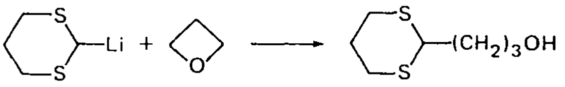
(81)

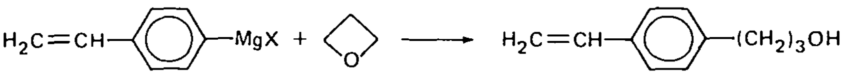
I. Reaction with Organometallic Compounds

Compared to oxiranes[1], the ring-opening of cyclic ethers occurs less readily, since the reactivity decreases with increase in the number of ring atoms. Three reviews on these reactions have appeared in recent years[264-266].

1. Reaction of oxetanes

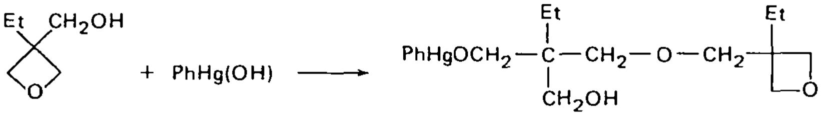
This reaction is generally used for incorporation of the 3-hydroxypropyl group, with the involvement of either an organolithium[267-269] or a Grignard compound[171,270-273] (e.g. equations 82 and 83). In certain cases the reactions of


(Ref. 269) (82)


(Ref. 273) (83)

organolithium compounds are carried out in the presence of cuprous salts[274]. The reaction of 2-methyleneoxetane with phenyllithium results in methyl phenetyl ketone[275]. Whereas oxiranes containing a carbonyl function react regioselectively (via their oxirane function) with certain organometallic compounds[1], oxetan-3-one reacts with a Grignard compound either via its oxo function, or via both functional groups[276].

With trimethylchlorosilane, 2-alkyloxetanes yield the corresponding 1,3-chlorohydrinsilyl ether isomers[277]. On the action of triethylaluminium, pentanol is formed to only a very slight extent[278]. 3-Ethyl-3-hydroxymethyloxetane reacts according to equation (84) with phenylmercurihydroxide, while 3,3-bis(hydroxymethyl)oxetane gives 3,3-bis(phenylmercurioxymethyl)oxetane[279]. An interesting reaction is shown in equation (85)[280].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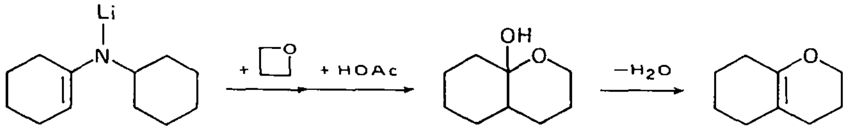
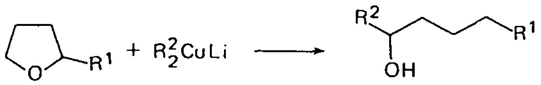
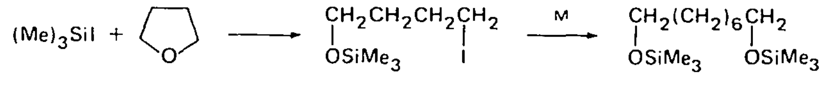

(85)

2. *Reaction of oxolanes*

On the action of alkyllithiums (e.g. *n*-BuLi), the oxolanes decompose to alkene and aldehyde enolate[281-284] after the splitting-off of an α-hydrogen. Alkyllithium and cuprous salt, or lithium dialkylcuprate, causes the ring of the 2-alkyloxolanes to open[274] (equation 86).

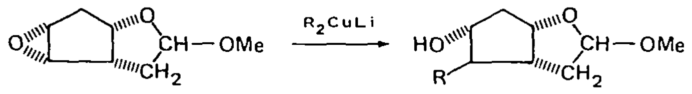

(86)

In the presence of tungsten hexachloride, oxolane undergoes α-phenylation with phenyllithium[285]. On the action of tri- and di-phenylmethyllithium, the corresponding butanol derivatives are obtained[286,287]. Lithium trialkylsilane converts oxolane to 4-trialkylsilanebutanol[288]. Trimethyliodosilane[289,290] and dimethyldichlorosilane[291] yield the corresponding 4-tri- and di-alkylsilyloxybutyl halides. In the presence of metals, trimethyliodosilane reacts with oxolane to give 1,8-bistrimethylsilyloxyoctane[292].


(87)

With a Grignard compound, 2-dialkylaminooxolane forms a 1,4-amino alcohol[293].

3-Oxolanone hydrazone can be opened with alkyllithium to give allene alcohol[294]. 2-Alkoxyoxolane, which also contains an oxirane function, reacts regioselectively with lithium dialkylcuprate via the oxirane function [295] (equation 88).



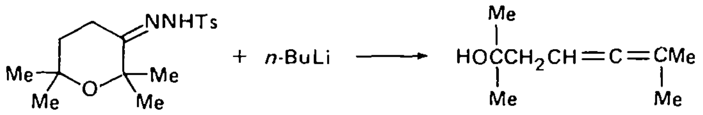
(88)

Oxolane forms various complexes and adducts with transition metal halides[296], rare-earth metal salts[297] and metal complexes[298,299].

2-Hydroxymethyloxolane interacts via the hydroxy function with diphenylzinc and phenylmercurihydroxide[279].

3. *Reaction of oxanes*

The six-membered oxacycloalkanes display a considerably lower reactivity towards organometallic compounds. On the action of *n*-BuLi, only a minimal amount of 1-nonanol is obtained from oxane[274]. The 3-hydrazone derivative gives an allene alcohol on reaction with *n*-BuLi[294] (equation 89).

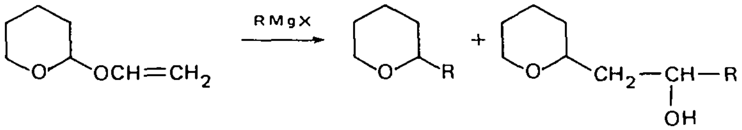


(89)

With trimethyliodosilane, oxane may be opened to 1,5-iodohydrintrimethylsilyl ether, while in the presence of metals (Li, Na, K, Mg) 1,10-decanediolbissilyl ether may be obtained[292,300]. 2-Aminoalkyloxanes react with Grignard compounds to give 1,5-amino alcohols[301].

New experimental data have been reported on the exchange of the 2-chloro atom in 2-chlorooxanes[302] and 2,3-dichlorooxanes[303-308] for alkyl or aryl groups.

Equation (90) shows the double reactivity of 2-vinyloxyoxane[309]. With a Grignard compound, 2-ethynyloxane gives an allene alcohol[308] (equation 91).



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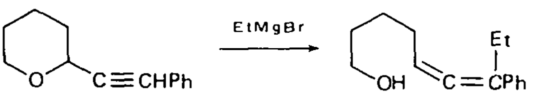


(91)

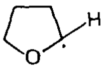
J. Free-radical Chemistry

Reactions of cyclic ethers that take place via a free-radical mechanism may be induced thermally, with a free-radical initiator, photochemically in the presence or the absence of an appropriate sensitizer, and by radiolysis.

In the pyrolysis of oxetanes, fission of the four-membered ring into two parts proceeds with high selectivity. This reaction can be studied readily and permits the understanding of the mechanism of the radical processes. These investigations have extended to oxetane[310,311] and also to 2-alkyl- and 2-aryl- [312-314], 3-alkyl- and 3-aryl- [315,316], 2,2-di- [316], 3,3-di- [317-319], 2,3-di- [314,320,321] and 2,4-disubstituted[322] oxetanes, and to polysubstituted and functional derivatives of oxetane[90,121,316,323-326]. The decomposition of oxetanes has also been studied in the presence of rhodium complexes[327,328]. The publications referred to above include investigations of the kinetics, the regioselectivity and the stereoselectivity of the transformation.

The stereochemical course of the thermolysis has been reported in many papers[90,314,316,320,321,323,328,329]. While not leading to totally uniform conclusions, the results of the investigations may be summarized briefly as follows. The gas-phase thermolysis of oxetanes to olefins and carbonyl compounds is a homogeneous, unimolecular process occurring via a biradical intermediate. The transformation is not completely stereoselective; *cis–trans* isomerization too may be observed during thermolysis.

The tendency of cyclic ethers to undergo radical reactions is due to the comparative weakness of the C–H bonds in the α-position. ESR studies have revealed the formation of the radicals **8** or **9** and **10** in the radiolysis of oxolane and 2-methyloxolane, respectively[330]. α-Radicals are also formed in the case of six-membered cyclic ethers[331,332]. The chemical evidence indicates that the tendencies of oxolane and oxane to form radicals are approximately 10 times higher than those of oxetane and oxiranes, which corresponds with the fact that the C–H bond is stronger than the C–O bond in the latter.



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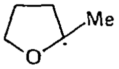

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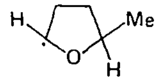
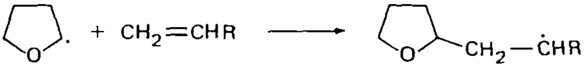
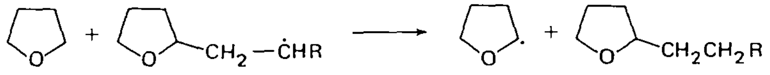


(10)

Radical alkylations of cyclic ethers with olefins[333-336] are initiated by the radicals formed on the thermal decomposition of di-*t*-butyl peroxide. The reaction is suitable for the preparation of 2-alkyloxacycloalkanes from oxolane and oxane by utilization of the appropriate terminal olefin. The yield increases together with the molecular weight of the olefin, and in favourable cases attains 70–80%. The alkylation is a chain-reaction; the chain-propagating steps in the case of oxolane[334] are shown in equations (92) and (93). Chain-termination may be either disproportionation or combination of the radicals[337,338].



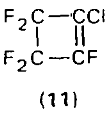
(92)



(93)

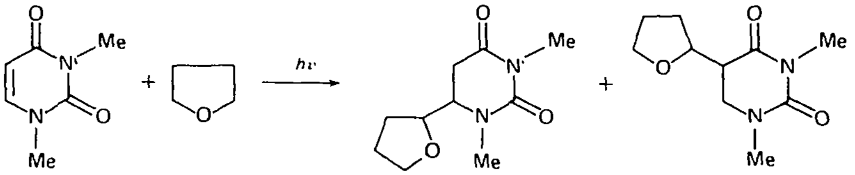
Since both alkenes and ethers are difficult to excite, their photochemical reaction is achieved only in the presence of a sensitizer (e.g. acetone). Triplet-state acetone splits off an α-H atom from the ether, and the reaction proceeds by the same route as the radical-induced one[338]. Cyclic acetals too display an analogous reaction[337].

Similar reaction are also observed in the case of cumulated dienes[340,341]. Depending on the conditions, the reaction of oxacycloalkyl radicals with acetylenes produces either alkylation[342] or ring-opening[343]. By direct photochemical reaction with oxolane, a suitably excitable unsaturated compound such as **11**, for



(11)

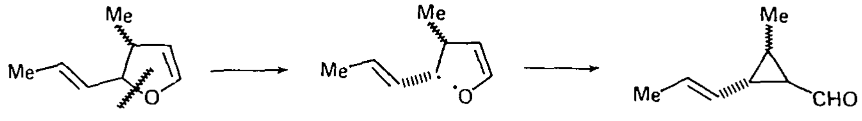
example, gives the corresponding 2-oxolane derivative[344]. Oxolane similarly undergoes direct photochemical addition to maleic anhydride[345,346] and diethyl maleate[338,346]. The reaction may also be induced by radicals[346]. Oxolane may participate in a photoaddition reaction with 1,3-dimethyluracil (equation 94)[347],



(94)

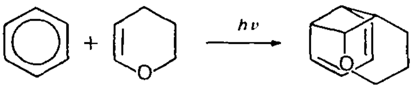
adenine, guanine and caffeine[337]. Excited purine and pyrimidine bases split off hydrogen from $C_{(2)}$ of oxolane, and the radical formed reacts as indicated.

In some reactions of cyclic ethers, ring-contraction occurs[348–350]. On the action of light, tetramethyloxetanone is converted to acetone and dimethylketene in an apolar solvent, and to tetramethyloxirane in a polar solvent[348]. 13 is formed selectively from 12 in a photochemical reaction[350] (equation 95). 2,3-Dihydropyran undergoes addition to benzene with very high stereoselectivity[351] (equation 96).



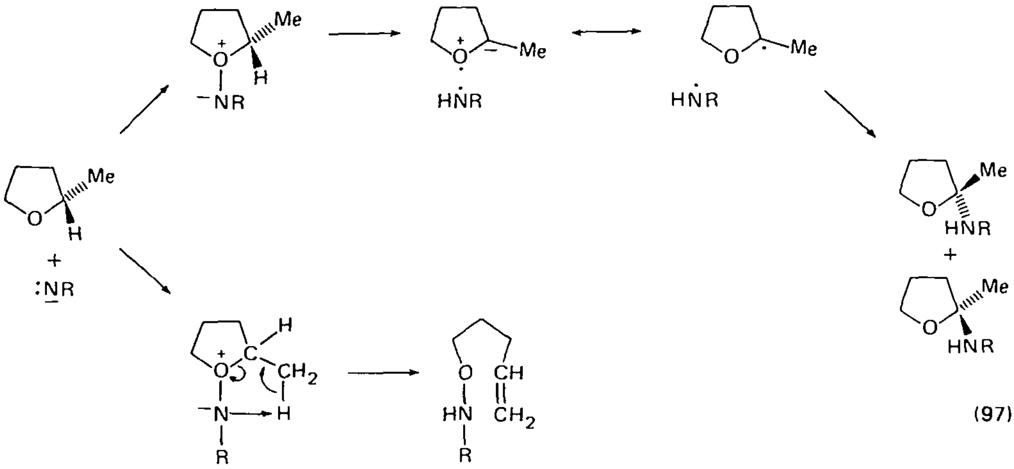
(12) (13)

(95)



(96)

Nitrenes[352,353] and carbenes[354,355] are capable of insertion into the C—H bond. Studies have been made of the reactions of various cyclic ethers and carbethoxynitrene[353]. The mechanism of equation (97) has been proposed for the



(97)

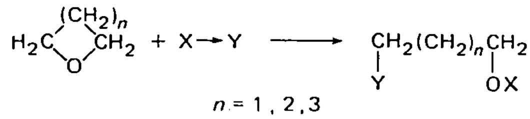
insertion, and for the ring-opening side-reaction. In agreement with earlier observations[352], the attack of singlet nitrene is assumed.

Dichlorocarbene is likewise inserted into the α-C–H bond. α-Dichloromethyloxacycloalkane can be prepared in good yield (80%) via this reaction[354].

Numerous publications have appeared on the fragmentation occurring during the mass-spectroscopic determination of oxetanes[356-358] and cyclic ethers with larger rings[359].

K. Ring-opening with Nucleophilic Reagents

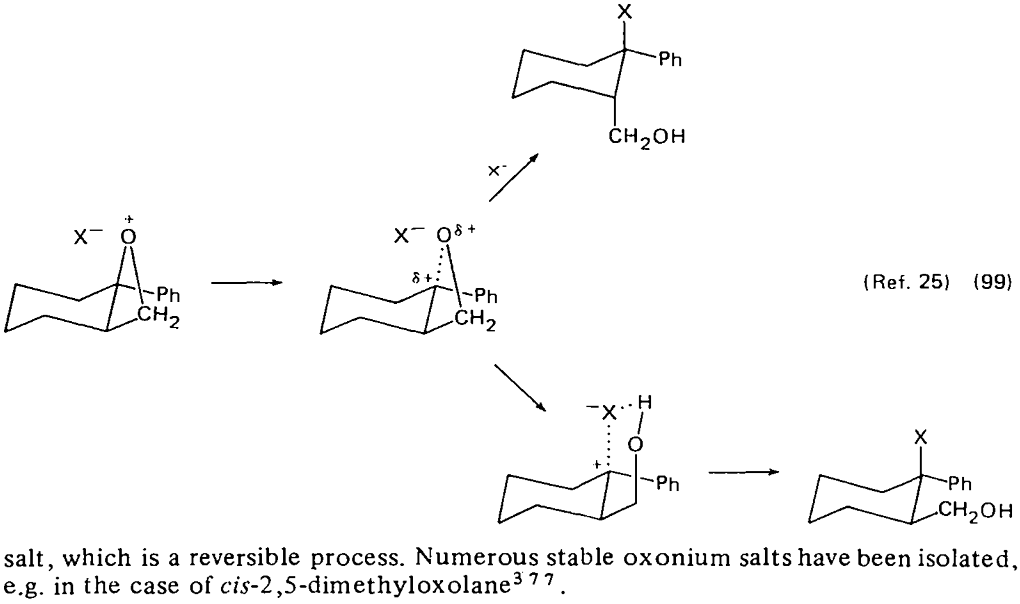
Most of the experimental data in the literature relate to the acid-catalysed hydrolysis[24,26,141,360,361] of cyclic ethers (mainly oxetanes), their alcoholysis[25,362-366] and their transformations with hydrogen halides[362-370], carboxylic acids[25,371,372] and their derivatives[25,373-376]. These reactions are depicted in equation (98).



(98)

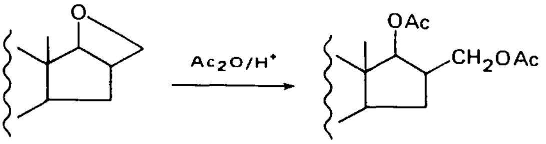
X,Y = H_2O, hydrogen halides, ROH, RCOOH, RCOZ, etc.

Some investigations have been directed towards preparative uses, but the majority deal with regioselectivity, stereochemistry and mechanism. The overwhelming majority of the reactions take place via an S_N2 mechanism. However, some observations (mainly on oxetanes) can only be interpreted by an S_N1 mechanism. The mechanism of the reaction is greatly influenced by the number and type of the ring-atoms, the nature of the reagent and the experimental conditions. Some examples in support of this are presented in equations (99)–(102). In the acid-catalysed ring-opening of cyclic ethers, the first step is the formation of an oxonium salt, which is a reversible process. Numerous stable oxonium salts have been isolated, e.g. in the case of *cis*-2,5-dimethyloxolane[377].



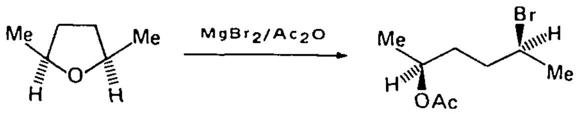
(Ref. 25) (99)

With steroid oxetanes, acid-catalysed *cis* ring-opening has been observed to occur with surprisingly high stereoselectivity[375] (equation 100).

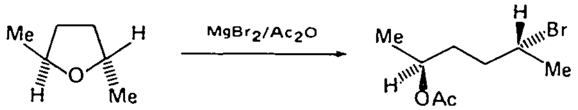


(100)

The ring-openings of *cis*- and *trans*-2,5-dimethyloxolanes take place by an S_N2 mechanism[372] (equations 101 and 102).

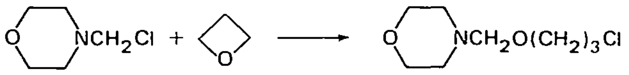


(101)

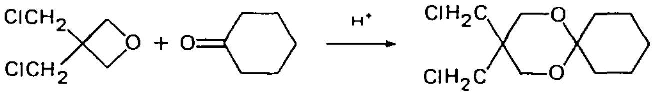


(102)

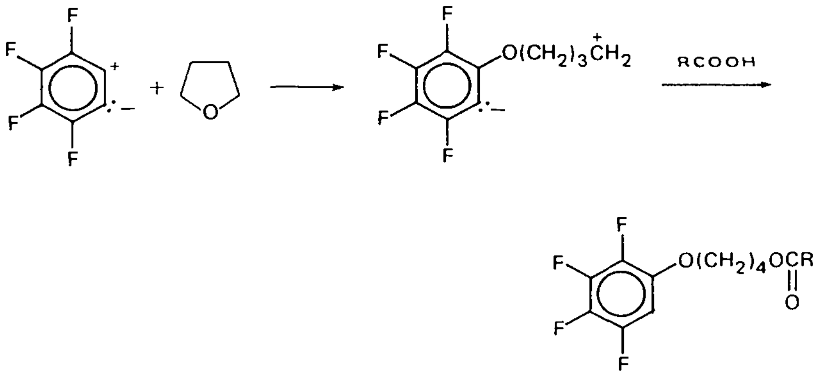
Other ring-openings reactions, mainly of oxetanes, occur, e.g. with phosphorus halides[378-380] or carbonic acid derivatives[373,381]. Some other unusual ring-openings of oxolanes take place with alkyl halides in the presence of mercuric salts[382,383], tetrafluorobenzene[384], alkyl chlorosulphonate[385] and phosgene[373] (equations 103–106):



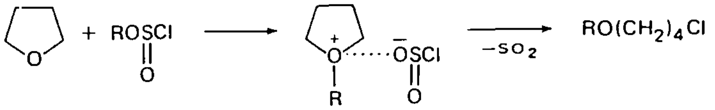
(Ref. 386) (103)



(Ref. 387) (104)



(Ref. 384) (105)



(Ref. 385) (106)

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 16

Dehydration of diols

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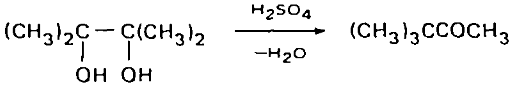
I. DEHYDRATION OF 1,2-DIOLS

The transformations of 1,2-diols accompanied by elimination of water can be summarized in three reactions:

(*i*) The classical process of pinacol rearrangement, first described by Fittig[1], and later studied by Butlerov[2]. Pinacol (**1**) is treated with cold concentrated sulphuric acid and thereby converted to methyl *t*-butyl ketone (pinacone) (**2**) (equation 1).



$$(CH_3)_2\underset{OH}{C}-\underset{OH}{C}(CH_3)_2 \xrightarrow[-H_2O]{H_2SO_4} (CH_3)_3CCOCH_3 \quad (1)$$

(1) (2)

(*ii*) The formation of epoxides, which is observed mainly from tetrasubstituted and certain hindered trisubstituted diols.

(*iii*) The formation of unsaturated compounds, primarily dienes.

The pinacol rearrangement has been studied in great detail, particularly for the secondary–tertiary and ditertiary 1,2-diols. Transformations of other 1,2-diols, and the use of nonacidic reaction conditions differing from the classical ones, have received less attention.

A. Dehydration in the Solution Phase by the Action of Acids

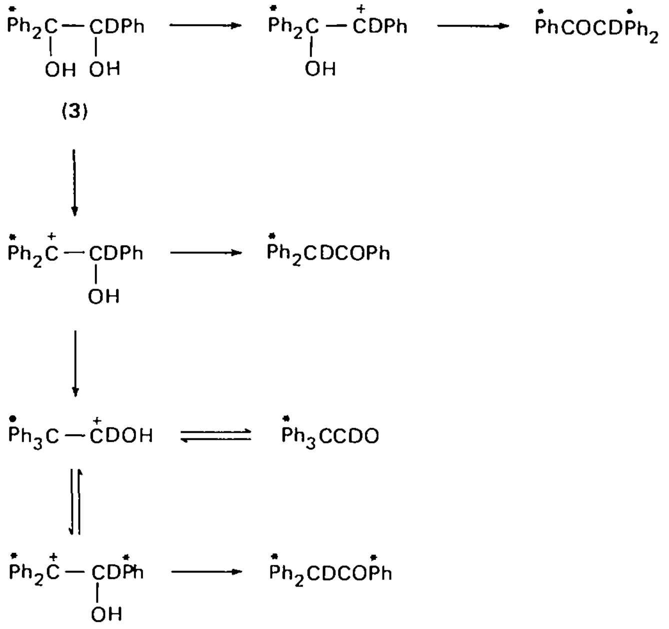
1. *Pinacol rearrangement*

Rearrangement of pinacol with water elimination can be achieved in the presence of mineral acids. Sulphuric acid is used mainly, but use is frequently made of perchloric acid, aromatic sulphonic acids, organic acids (formic acid, oxalic acid) and acetic acid together with iodine, acetyl chloride or acetic anhydride.

Because of the very large volume of literature data we cannot give a full review of all the publications and shall restrict ourselves therefore to a brief survey of the still continuing research that has led to the currently accepted interpretation of the pinacol rearrangement. Using the earlier reviews[3–5] as a starting point, we shall mainly discuss the results of the past 15 years. In 1963, Bunton and Carr[6] came to the conclusion, still generally accepted, that there is no unique mechanism for the pinacol–pinacone rearrangement: depending on the structure of the diol and the reaction conditions, one or other mechanism predominates, or the rearrangement may occur via simultaneous processes.

In principle there are four fundamental routes for the pinacol rearrangement: via a carbonium cation, by a concerted mechanism, via an epoxide intermediate and via vinyl dehydration. Most reactions can be interpreted by means of the first two of these reaction paths, while the data so far obtained suggest that the final possibility may be excluded.

a. Rearrangement via a carbonium cation. This route for the rearrangement has been discussed in detail by Collins[3,7–9]. The reactions of the labelled diol (3) were studied in the presence of five different catalysts (concentrated H_2SO_4, formic acid, dilute H_2SO_4, oxalic acid, dioxan–H_2O–HCl). It was found that the process shown in equation (2) does not play a role in the rearrangement, while the three remaining possibilities (equations 3–5) depend to a large extent on the reaction conditions. The carbonium cation is formed reversibly (neighbouring-group par-



$$\overset{\bullet}{\mathrm{Ph_2C}}(\mathrm{OH})-\mathrm{C}(\mathrm{OH})\mathrm{DPh} \longrightarrow \overset{\bullet}{\mathrm{Ph_2C}}(\mathrm{OH})-\overset{+}{\mathrm{C}}\mathrm{DPh} \longrightarrow \overset{\bullet}{\mathrm{Ph}}\mathrm{COC}\overset{\bullet}{\mathrm{D}}\mathrm{Ph_2} \qquad (2)$$

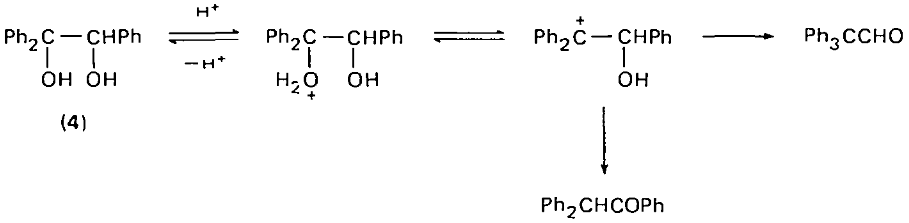
(3)

$$\overset{\bullet}{\mathrm{Ph_2}}\overset{+}{\mathrm{C}}-\mathrm{C}(\mathrm{OH})\mathrm{DPh} \longrightarrow \overset{\bullet}{\mathrm{Ph_2}}\mathrm{CDCOPh} \qquad (3)$$

$$\overset{\bullet}{\mathrm{Ph_3}}\mathrm{C}-\overset{+}{\mathrm{C}}\mathrm{DOH} \rightleftharpoons \overset{\bullet}{\mathrm{Ph_3}}\mathrm{CCDO} \qquad (4)$$

$$\overset{\bullet}{\mathrm{Ph_2}}\overset{+}{\mathrm{C}}-\mathrm{C}(\mathrm{OH})\mathrm{D}\overset{\bullet}{\mathrm{Ph}} \longrightarrow \overset{\bullet}{\mathrm{Ph_2}}\mathrm{CDCO}\overset{\bullet}{\mathrm{Ph}} \qquad (5)$$

ticipation cannot be observed); this is followed by irreversible hydrogen or aryl migration (equation 6).

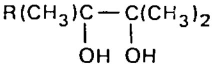


$$\underset{(4)}{\mathrm{Ph_2C(OH)-CH(OH)Ph}} \underset{-\mathrm{H^+}}{\overset{\mathrm{H^+}}{\rightleftharpoons}} \mathrm{Ph_2C(\overset{+}{O}H_2)-CH(OH)Ph} \rightleftharpoons \mathrm{Ph_2\overset{+}{C}-CH(OH)Ph} \longrightarrow \mathrm{Ph_3CCHO} \qquad (6)$$

$$\mathrm{Ph_2\overset{+}{C}-CH(OH)Ph} \longrightarrow \mathrm{Ph_2CHCOPh}$$

At the same time, the presence of the carbonium cation was proved by rate measurements in D_2O[10-12] and by ^{18}O-studies. Since the results reviewed earlier[3], many authors have confirmed the above observations under very varied experimental conditions and with diols of different structures[6,13-21]. Many of the most recent investigations[22-27] support the carbonium cation mechanism. Nevertheless, the results of a number of research groups are in agreement with the existence of a nonclassical bridged carbonium ion[28-37].

b. Concerted mechanism. From a study of the rearrangements of the diols **1**, **5** and **6** in 50% H_2SO_4, Stiles and Mayer[38] found that bond formation by the



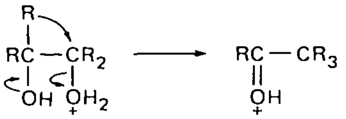
$$\mathrm{R(CH_3)C(OH)-C(OH)(CH_3)_2}$$

(1) R = Me

(5) R = Et

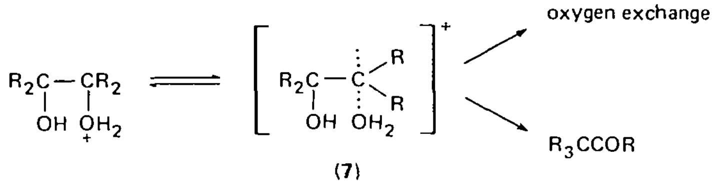
(6) R = *t*-Bu

migrating group occurs in a slow step, which excludes the carbonium ion mechanism. They recommend a concerted reaction pathway (equation 7), in which water is



(7)

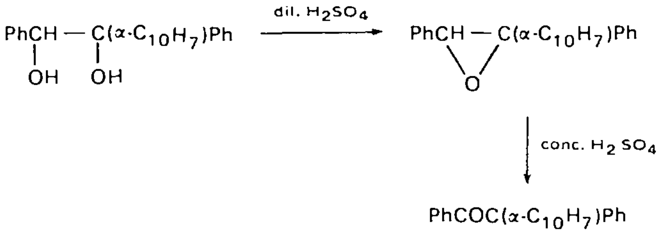
eliminated from the protonated pinacol with the anchimeric assistance of the migrating group. Since oxygen exchange takes place between the pinacol and the solvent during the rearrangement[12], formation of the carbonium hydrate (7) is probable in the first step. This formation is responsible for both the rearrangement and the oxygen exchange (equation 8). The rearrangement involves a backside displacement



(8)

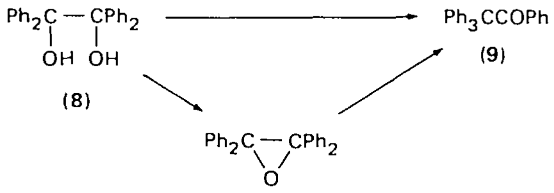
of water by the neighbouring group R. Because of the geometry and hybridization of the carbon atom, this process should occur much more easily than the one shown in equation (7). The rates measured in the cases of the different substituents suggest that for **1** both the carbonium ion route and the concerted mechanism are involved in the rearrangement, while for **5** and **6** the latter pathway predominates. The role of the concerted mechanism is supported by the results of other investigations[39-41].

c. Role of the epoxide intermediate. It has long been known[42-44] that epoxides are formed during the loss of water from certain tetrasubstituted and, hindered trisubstituted 1,2-diols (equation 9). More recently, in a kinetic investigation of the



(9)

reaction of tetraphenylethylene glycol (**8**) in perchloric acid–acetic anhydride, it was found[45] that, besides the direct rearrangement, the transformation also takes place via the epoxide (equation 10) (~80% at 75°C). The ratio of the two processes

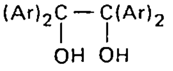


(10)

is determined by the stereostructure of the diol: the *trans*-diol has a favourable conformation for epoxide formation, whereas the *cis*-diol, present in lower amount, leads directly to the ketone (**9**).

In studies of the various methods of rearrangement of *cis*- and *trans*-1,2-dimethylcyclopentanediol[6], pinacol[32,33] and other tetraaryl glycols[46,47] it has been similarly proved that the corresponding epoxides may act as intermediates under certain conditions.

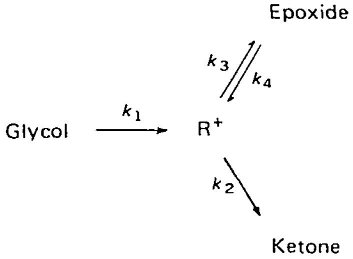
In their study of the rearrangement of the tetraaryl glycols **10**, Pocker and Ronald[46,47] described the transformation with the proved kinetic scheme of equation 11.



$(Ar)_2\underset{OH}{C}-\underset{OH}{C}(Ar)_2$

(10)

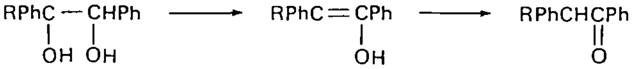
Ar = Ph, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$



(11)

Compared to the previously discussed mechanisms, rearrangement via the epoxide is less general; this path is a rarely-occurring, special case of the rearrangement.

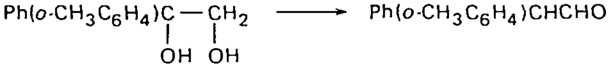
d. Vinyl dehydration. This possibility (equation 12) was first suggested in the



$$RPh\underset{OH}{C}-\underset{OH}{C}HPh \longrightarrow RPhC{=}\underset{OH}{C}Ph \longrightarrow RPhCH\underset{O}{\underset{\|}{C}}Ph \qquad (12)$$

1920s[43,48,49]. As a theoretical possibility, this mechanism was still mentioned by Kleinfelter and Schleyer in 1961[50].

The first evidence against vinyl dehydration was due to Mislow and Siegel[51]. In aqueous H_2SO_4 the dextrorotatory 1-phenyl-1-*o*-tolylethylene glycol (**11**) is converted to the optically active **12** (equation 13), which is incompatible with the formation of an enol intermediate.

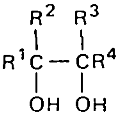


$$Ph(o\text{-}CH_3C_6H_4)\underset{OH}{C}-\underset{OH}{C}H_2 \longrightarrow Ph(o\text{-}CH_3C_6H_4)CHCHO \qquad (13)$$

(+)-(11) (+)-(12)

On the basis of other facts in the relevant literature reports[9,11,28-30], it may be stated that vinyl dehydration does not play a role in the rearrangement of the 1,2-diols in the cases examined.

e. Stereochemistry of the rearrangement. According to an older observation relating to open-chain 1,2-diols[52,53], under identical reaction conditions (in CH_3COOH/I_2 or in CH_3COCl) the *meso* and racemic forms of 1,2-diphenyl-1,2-di-α-naphthylethylene glycol give different products: the higher melting isomer is converted to the phenyl ketone, and the other isomer to the α-naphthyl ketone. Studies with the geometrical isomers of other 1,2-diols[45,54] clearly demonstrated the role of stereochemical factors in the pinacol rearrangement for the open-chain 1,2-diols too. The transformations of various ditertiary diols (**13**) with similar structures have been investigated, in an attempt to obtain a quantitative correlation



$R^1\overset{R^2}{\underset{OH}{C}}-\overset{R^3}{\underset{OH}{C}}R^4$

R^1, R^2, R^3 = Me, Et

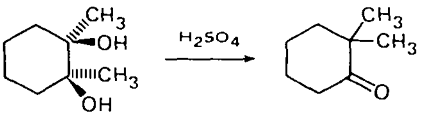
R^4 = t-Bu, t-Am, t-Hex, Et_3C

(13)

for the structure–migrating group interactions[23,24]. The number of carbon atoms in the substituents on the tertiary carbon atoms has an inverse effect on the rate of migration: if the number of carbon atoms on the carbon atom bearing the migrating group is increased, the reaction rate too increases. This may be explained by a relief in the steric strain caused by a change in the hydridization of this carbon atom: $sp^3 \rightarrow sp^2$. If the number of carbon atoms in the substituents on the carbonium ion is increased, the rate of rearrangement is influenced in the inverse way by the hybridization in the opposite direction. The experimental data also showed that another effect too is manifested: this originates from the conformational conditions of the molecule, is independent of the migrating group, and acts against migration. The effect may arise from the substituents of the two tertiary carbon atoms interacting in such a way as to destabilize the conformers favouring migration. Further studies are required, however, for the effect to be given in a quantitative form.

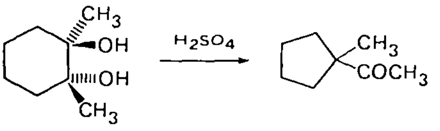
A very large number of publications deal with the stereochemistry of the pinacol rearrangements of alicyclic 1,2-diols with different ring sizes[6,20,25,34,55–66].

In the case of the cyclohexanediols **14** and **15**, even the first investigations[59,66] drew attention to the very characteristic transformations (equations 14 and 15).



(14)

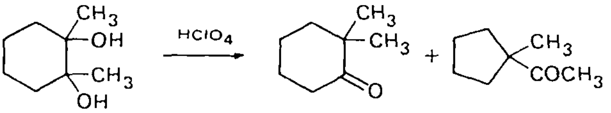
(14)



(15)

(15)

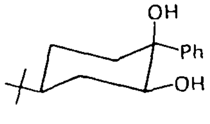
Later, different results were obtained[20,60], for it was found that transformation of the isomers led to the formation of the same product mixture[20] (equation 16).



(16)

(14) or (15) 2–9% 91–98%

The stereochemistry of the process was studied in connection with the transformations of the four isomeric 1-phenyl-4-*t*-butyl-1,2-cyclohexanediols (**16**–**19**) in the BF_3–Et_2O complex[25]. The reaction always begins with the splitting of the benzyl C—O bond, which leads to the formation of the open carbonium ions **20** and **21**. The original configuration of $C_{(1)}$ no longer plays a role in the further reactions of these ions, the subsequent reactions being determined by the position



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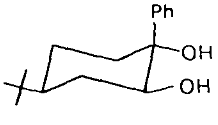

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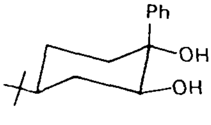

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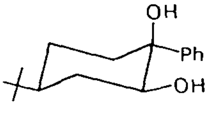
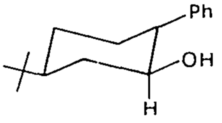


(19)



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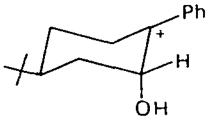
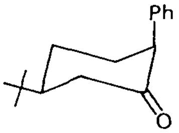


(21)

of the $C_{(2)}$ hydroxy group. In the carbonium ion (**20**) formed from **16** and **17**, the axial hydrogen is readily able to migrate as a hydride anion, and thus the ketone **22** is obtained as product. In the ion **21** which may form from the diols **18** and **19**, hydride anion migration is less favoured in the case of the equatorial hydrogen on $C_{(2)}$; here, therefore, in addition to ketone **23**, a significant amount of aldehyde **24** is formed.



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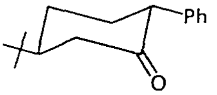

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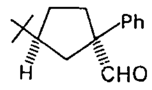
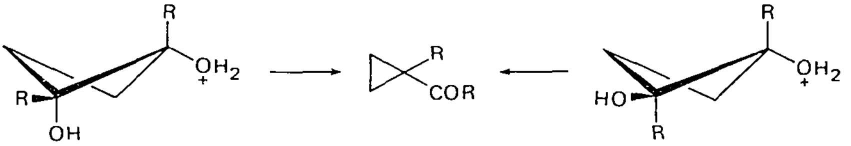


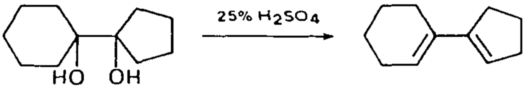
(24)

The study of some isomeric 1,2-cyclobutanediols revealed[34] that the isomers undergo transformation in the same way: in agreement with the stereochemical regularities, a single product, formed by ring contraction, is obtained (equation 17).



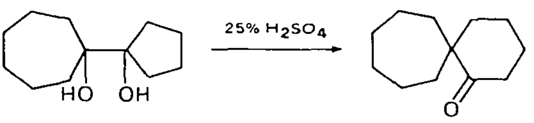
(17)

An investigation of the stereochemistry of the transformations of the diols **25** and **27** in 25% H_2SO_4 showed[13,14] that the diene **26** is formed as the main product from **25**, while the spiroketone **28** is obtained from **27** via pinacol rearrangement (equations 18 and 19). The transformation can be well interpreted in terms of the role of the stereochemical factors. Otherwise, for compounds containing rings of the same size, spiroketone formation occurs primarily in the case of small (C_4 or C_5) rings[13,14,18,67-72], whereas larger rings are characterized by diene formation[13,14,18,73,74]. This is because, for small rings, ring expansion is a possibility for the relief of the ring strain; this factor is not of importance with larger rings, where diene formation will accordingly predominate[14].



(25) (26)

(18)



(27) (28)

(19)

The data relating to the stereochemistry of the rearrangements of cyclic diols are in part contradictory, and numerous factors hamper their interpretation[75]. In many cases, for instance, *cis–trans* isomerization can be observed during the transformations; the products formed are frequently not stable, and undergo interconversion; and different results may be obtained by the application of different reaction conditions. These factors lead to uncertainty in the conclusions drawn.

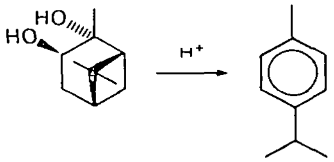
2. *Formation of unsaturated compounds*

In certain cases the pinacol rearrangement is accompanied by diene formation. This has been observed with ditertiary glycols, sometimes on the use of reaction conditions differing from the classical ones.

By applying various reagents (HBr, HI, Cl_3COOH, aniline hydrobromide, $FeCl_3$), Kyriakides[76] prepared 2,3-dimethyl-1,3-butadiene from pinacol, in some cases with good yields. The HBr method has also been employed as a preparative procedure[77]. In the presence of phthalic anhydride[78], dienes are formed as well as ketones from 2,3-butanediol and pinacol. Diene formation has been studied in detail in the course of the dehydration of 3,4-dimethyl-3,4-hexanediol on various catalysts[79]. Catalysts of complex composition, containing WO_3, have also been used in the conversion of various 1,2-diols to dienes[80,81].

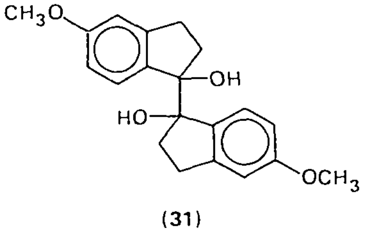
Dienes can be obtained in good yield from bicyclic, ditertiary diols (e.g. **25** and **27**), mainly in the case of larger (C_6 or C_7) rings. Various concentrations of dilute H_2SO_4[13,14,18,73,82], oxalic acid[18,74] or $(CH_3CO)_2O$[70] are suitable agents for the preferential formation of the diene rather than the spiroketone. With certain compounds, nonproton-donor catalysts [$HCl–(CH_3CO)_2O$, $CH_3COCl–(CH_3CO)_2O$] are similarly well suited for the preparation of dienes[83].

With acid catalysis, *p*-cymene (**30**) may be isolated from (–)-*cis*-pinane-*trans*-2,3-diol (**29**) (equation 20)[27], and isomeric dienes are also formed from **31**[84]. Similarly, the transformation of **32** may also lead to aromatic products[22]. The ratio oxo compound/aromatic product depends on R and on the reaction conditions, but it is independent of the configuration of the diol. Transformation as in equation (21), leading to diene formation, proceeds at 100°C in the presence of 50% H_2SO_4[85].



(20)

(29) (30)



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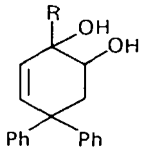
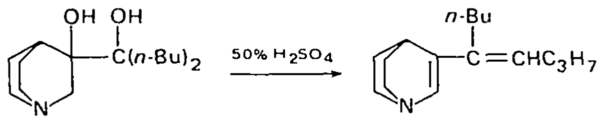


(32)

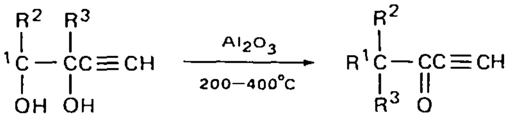
R = Me, Et, *n*-Pr, Ph



(21)

B. Transformations on Alumina

In the presence of alumina, the 1,2-diols are transformed to either a carbonyl compound or a diene. Pinacol yields 2,3-dimethyl-1,3-butadiene[77,86], while other publications[79,87–90] have dealt with the possibilities of ketone and diene formation. The diols 33 are converted to carbonyl compounds of type 34 (equation 22)[91], while 1,2-pentanediol yields pentanal[92].

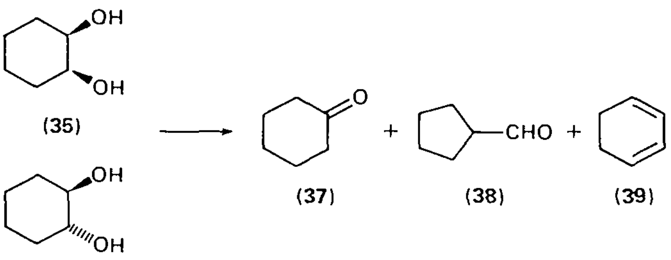


$$\mathrm{R^1}\underset{\mathrm{OH}}{\overset{\mathrm{R^2}}{\mathrm{C}}}-\underset{\mathrm{OH}}{\overset{\mathrm{R^3}}{\mathrm{C}}}\mathrm{C{\equiv}CH} \xrightarrow[200-400^{\circ}\mathrm{C}]{\mathrm{Al_2O_3}} \mathrm{R^1}\underset{\mathrm{R^3}}{\overset{\mathrm{R^2}}{\mathrm{C}}}-\underset{\mathrm{O}}{\overset{}{\mathrm{C}}}\mathrm{C{\equiv}CH} \qquad (22)$$

(33) (34)

$R^1, R^2, R^3 = C_1-C_6$

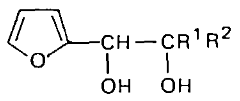
A series of studies on *cis*- and *trans*-1,2-cyclohexanediol (35 and 36)[62,65,88] showed that mainly cyclohexanone (37) is formed from the *cis* isomer, and primarily cyclopentaneformaldehyde (38) from the *trans* compound, together with the 1,3-cyclohexadiene (39) generally accompanying the transformation (equation 23).



(35) (36) (37) (38) (39) (23)

The isomeric 1-methyl-1,2-cyclohexanediols[63] gave a similar result. The transformations can be interpreted by analogy to the processes occurring in acidic medium. For the carbonyl product formation from the diols 40[93], a carbonium cation mechanism was proposed, as shown in equation (24).

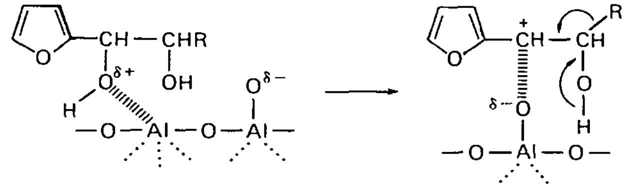
The stereochemistry of the heterogeneous catalytic reaction was studied with



(40)

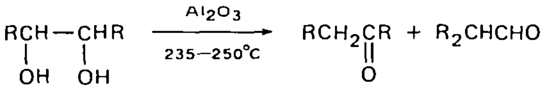
R^1 = H, Me

R^2 = Et, *n*-Pr, *i*-Pr, vinyl, isopropenyl



(24)

the *meso* and racemic forms of 2,3-butanediol (41) and 1,2-diphenylethylene glycol (42) in the vapour phase on alumina (equation 25)[94].



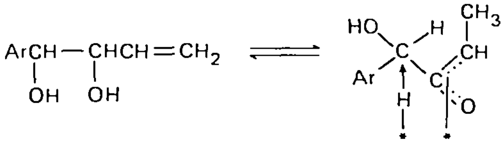
$$\underset{\mathrm{OH}}{\mathrm{RCH}}-\underset{\mathrm{OH}}{\mathrm{CHR}} \xrightarrow[235-250\,^{\circ}\mathrm{C}]{\mathrm{Al_2O_3}} \mathrm{RCH_2}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{R} + \mathrm{R_2CHCHO} \qquad (25)$$

(41) R = Me	(*dl*-41)	92%	6%
	(*meso*-41)	84%	11%
(42) R = Ph	(*dl*-42)	77%	23%
	(*meso*-42)	38%	62%

In the case of the methyl- and phenyl-substituted *meso*-diols, the same conformation leads to the formation of both aldehyde and ketone. The formation of the aldehyde in the case of *meso*-42 is explained by the large eclipsing interaction of the phenyl substituents, and by the high migratory aptitude of the phenyl group. In the case of the *meso*-butanediol, the eclipsing effect is much less, while at the same time the migratory aptitude of the hydrogen exceeds that of the methyl group, and hence the ketone may be obtained as main product. For the *dl* isomers, the ketone and aldehyde are formed from different conformations, but there is no essential eclipsing effect in either case. Overall, therefore, the ketone is the main product from the *dl*-diols, in accordance with the fact that the methyl and phenyl groups are to be found in *anti* positions with regard to each other.

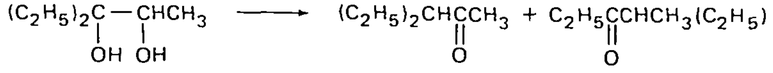
C. Dehydration on the Action of Metals

Metal, (especially copper) catalysts, catalyse the conversion of 1,2-diols to carbonyl compounds[95–104]. In the transformation of vinyl-substituted diols on supported copper catalysts, the vinyl group plays an essential role in the development of the carbonyl group[97,98], as its presence enables the diol to bind on the active centres of the catalyst in accordance with equation (26), with the formation of the π-allyl system.



(26)

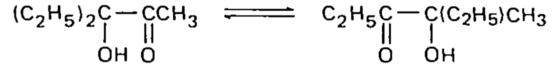
The product ratios obtained[103] with 2-ethyl-2,3-pentanediol (43) on copper catalysts with various properties and on Pt/C (equation 27) provide a possible



$$(\mathrm{C_2H_5})_2\underset{\mathrm{OH}}{\mathrm{C}}-\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{HCH_3} \longrightarrow (\mathrm{C_2H_5})_2\mathrm{CH}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{CH_3} + \mathrm{C_2H_5}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{CHCH_3(C_2H_5)} \qquad (27)$$

(43)

explanation of the reaction path of the rearrangement. Depending on the temperature and the catalyst the products are formed either directly by pinacol rearrangement, or via the α-hydroxyketone (**44**) which is formed by dehydrogenation and which then undergoes rearrangement to the isomeric **45** (equation 28), followed by dehydration and hydrogenation.



$$(C_2H_5)_2\underset{OH}{C}-\underset{O}{\overset{}{C}}CH_3 \rightleftharpoons C_2H_5\underset{O}{C}-\underset{OH}{C}(C_2H_5)CH_3 \qquad (28)$$

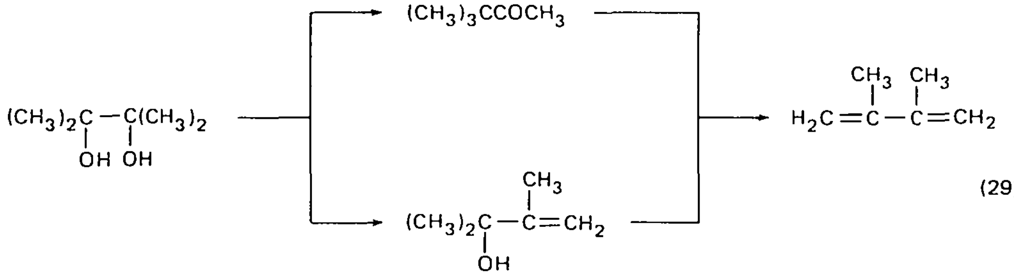
(**44**) (**45**)

On Pd/C catalysts[99,100] and in the presence of palladium-containing two-component alloys[101], 1,2-cyclohexanediol gives cyclohexanone as the main product, together with phenol, resulting from aromatization[99,100]. In the presence of Cu/Al and Cu catalysts[104], *cis*- and *trans*-1,2-cyclohexanediol yield (in addition to other products not formed by dehydration) cyclohexanone, and smaller amounts of formylcyclopentane, cyclohexanol and 2-cyclohexen-1-one. No essential differences were observed in the distributions of the products from these isomers.

D. Dehydration Under Other Conditions

On SiO_2, Na_2HPO_4 or a mixture of the two as catalysts, 1,2-propanediol gives propionaldehyde in good yield[105]. On phosphate catalysts[89,106,107], the transformation leads mainly to diene formation. On $Ca_3(PO_4)_2$[89] and $AlPO_4$[108], pinacol yields pinacone and 2,3-dimethyl-1,3-butadiene, whereas tetraphenylethylene glycol gives only triphenylmethyl phenyl ketone[108]. 2-Methyl-1,3-butadiene forms from 2-methyl-2,3-butanediol with Li_3PO_4 or Li_2HPO_4 catalysts on various supports[106].

The transformations of pinacol (**1**) leading to the diene **47** are as outlined in equation (29)[89]. Aluminium silicate, boron phosphate and silica gel primarily catalyse the rearrangement. On $Ca_3(PO_4)_2$ and Al_2O_3 the main product is the diene, formed via the unsaturated alcohol **46** on the former, and via both routes on the latter, catalyst.


$(CH_3)_2C(OH)-C(OH)(CH_3)_2$
$(CH_3)_3CCOCH_3$
$(CH_3)_2C(OH)-C(CH_3)=CH_2$
$H_2C=C(CH_3)-C(CH_3)=CH_2$

(29)

(**1**) (**46**) (**47**)

Transformations yielding the carbonyl compound and the diene can also be observed with the use of dimethylsulphoxide[82].

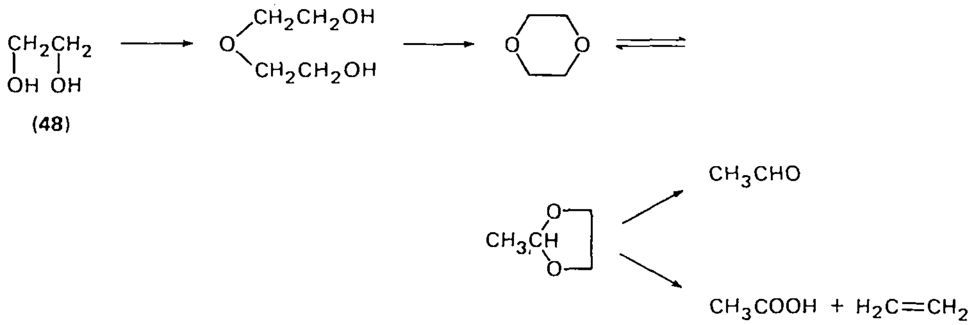
With Friedel–Crafts catalysts (e.g. $AlBr_3$, BBr_3, $TiBr_4$, etc.)[109], **47** is formed in good yield from pinacol, while 1,3-butadiene may be obtained from 2,3-butanediol in the presence of ThO_2[110,111] or under thermal conditions[112].

In the thermal dehydration of ethylene glycol at 700–1000°C, microwave spectroscopy revealed vinyl alcohol, together with a little acetaldehyde and ethylene oxide[113].

The transformation of the derivatives of certain 1,2-diols to carbonyl compounds has also been achieved under photocatalytic conditions[114–116].

E. Intermolecular Water Elimination

In the presence of aluminium silicate catalyst at 200–400°C, ethylene glycol (48) is converted to diethylene glycol[117], but under the given experimental conditions this is not stable and takes part in further reactions (equation 30).

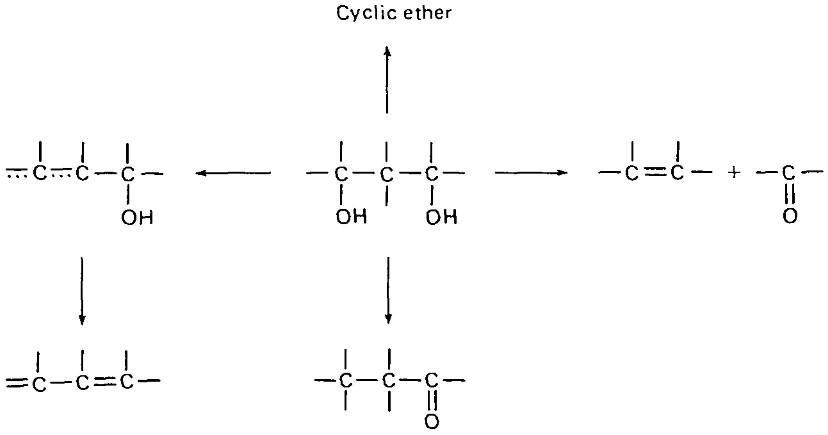


(30)

On the action of ion-exchange resins, the corresponding 1,4-dioxans (2,5-dimethyl- and 2,3,5,6-tetramethyl-1,4-dioxan, respectively) are formed from 1,2-propanediol and from 2,3-butanediol[118].

II. DEHYDRATION OF 1,3-DIOLS

A survey of the literature data relating to the transformations of the 1,3-diols indicates that the dehydration routes shown in equation (31) are characteristic.



(31)

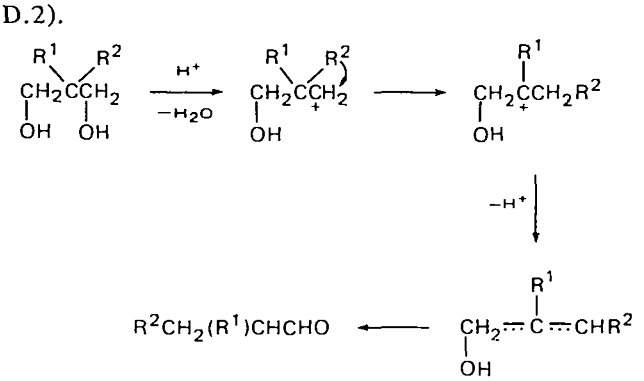
To illustrate these main transformations, some (mainly recent) literature data are listed in Table 1. The tendency in the case of unsubstituted or slightly substituted compounds (diprimary, primary–secondary, disecondary diols) is mainly the formation of carbonyl compounds; with the increase of the number of substituents, the formation of unsaturated alcohols and dienes or dehydration accompanied by fragmentation assume ever greater importance. However, the direction of the reaction depends on the catalyst too.

A. Formation of Carbonyl Compounds with the Same Number of Carbon Atoms as the Starting Diol

This process occurs for diprimary and primary – secondary diols on the action of H_2SO_4 or metal catalysts (primarily various copper catalysts). However, the selectivity of the reaction decreases as the number of substituents rises.

1. Dehydration on the action of sulphuric acid

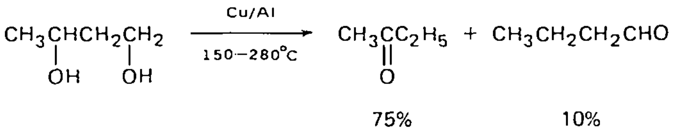
The transformations of simple aliphatic 1,3-diols were studied at the beginning of this century[119–125] and the formation of carbonyl compounds was described. In the course of the dehydration of 2,2-disubstituted 1,3-propanediols and 1,3-butanediols, the reaction leading to the corresponding aldehyde is accompanied by the migration of the substituents on $C_{(2)}$[126–130]. A carbonium cation mechanism has been assumed (equation 32)[129]. In the case of the 2,2-disubstituted 1,3-butanediols, tetrahydrofuran derivatives are formed in parallel with the carbonyl compounds (see Section II.D.2).



(32)

2. Formation of carbonyl compounds on the action of metals

Initial results on metal-catalysed transformations of 1,3-diols are reported in patents[131–133]. Systematic investigations began later[95,96,134]. The role of the catalyst Cu/Al in the transformation of 1,3-butanediol (49) (equation 33) was



$$\underset{\substack{| \quad\quad |\\ OH \quad OH}}{CH_3CHCH_2CH_2} \xrightarrow[150-280^{\circ}C]{Cu/Al} \underset{\substack{\| \\ O \\ 75\%}}{CH_3CC_2H_5} + \underset{10\%}{CH_3CH_2CH_2CHO} \tag{33}$$

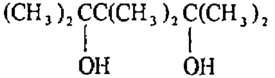
(49)

studied[135], and results were later reported on the transformations of 1,3-propanediol[136] and 1,3-butanediol[137] on various Raney-type catalysts, and on the effects of different supported copper catalysts[138]. It subsequently became possible to generalize the observations on the basis of extensive studies with different types of open-chain[103,139–141] and alicyclic[104,142] diols. It was found that on various copper catalysts certain types of 1,3-diols are converted to carbonyl compounds, and the ditertiary diols to an unsaturated alcohol and a diene[140,143] (see Section II.B.2).

The comprehensive study of dehydration to the carbonyl compound (among others by the use of deuterium-labelled compounds) provides a possibility for the

TABLE 1. Selectivity of dehydration transformations of 1,3-diols

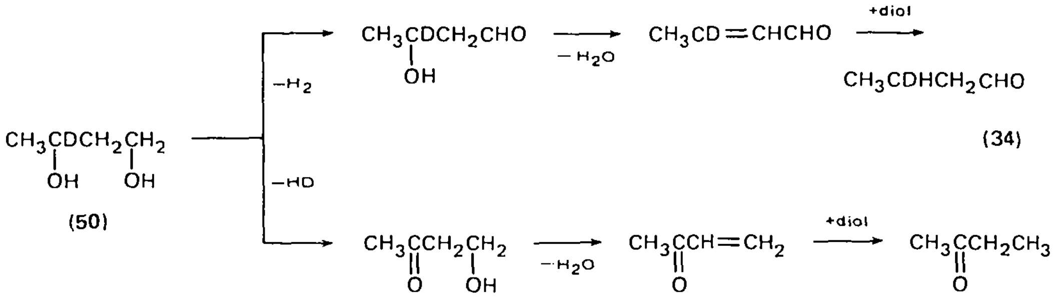
Compound	Catalyst	Selectivity (%)[a]				References
		Oxo compounds	Unsaturated alcohols + dienes	Fragmentation	Cyclic ethers	
$HOCH_2CH_2CH_2OH$	H_2SO_4	?				122
	$Ca_3(PO_4)_2$, 275°C	20	48	32		179
	Al_2O_3, 275°C	34	42	24		
	Cu/Al, Pd/Al, Ni/Al, Co/Al, Zn/Al	max. 75		min. 25		136
	$FSO_3H/SbF_5/SO_2$	100				16
$HOCH_2CH(i\text{-}Pr)CH_2OH$	Cu/Al	60		40		140,143
$HOCH_2CH(n\text{-}Bu)CH_2OH$	$Ca_3(PO_4)_2$		20	80		179
$HOCH_2C(CH_3)_2CH_2OH$	20% H_2SO_4	98				127
$HOCH_2CR^1R^2CH_2OH$	10 N HCl	70–100				128
(R^1, R^2 = alkyl, benzyl, phenyl)	30% H_2SO_4	100				129,130
$HOCH_2C(C_2H_5)_2CH_2OH$	$Ca_3(PO_4)_2$, 300°C		18	71	11	179
$HOCH_2CH$(4-pyridyl)CH_2OH	HCl/HCHO				90	215
$CH_3CH(OH)CH_2CH_2OH$	Benzenesulphonic acid		47			78
	p-TsOH		> 23			167
	$(CH_3)_2SO$	26	54			82
	$Ca_3(PO_4)_2$, 300°C	31	39	21	9	179
	γ-Al_2O_3	40		50		137
	Ni, Cu	50				95,96
	Cu/Al	85				135
	Pd/Al, Co/Al, Ni/Al, Zn/Al, Cu/Zn/Al	max. 55		5–65		137
	$PdCl_2/CuCl_2$	33				150
$RCH(OH)CH_2CH_2OH$ (R = alkyl)	$RhCl_3/PPh_3$	33–89				145
$PhCH(OH)CH_2CH_2OH$	Cu/Al	60		30		140,143
1-Hydroxymethylcyclohexanol-2	Cu/Al	90		10		142,143
$PhCH(OH)CHPhCH_2OH$	28% H_2SO_4			71		205

$RCH(OH)C(CH_3)_2CH_2OH$ (R = alkyl)	20% H_2SO_4	19–69		1–8	18–80	208
	Triethylphosphate	52			32	223
	Wofafit KPS-200 ion exchange resin	27	8		34	225
$PhCH(OH)C(CH_3)_2CH_2OH$	20% H_2SO_4			100		208
$(CH_3)_2C(OH)CH_2CH_2OH$	H_2SO_4		85			160
	$NaHSO_4/Na_2SO_4$		85			
	$Ca_3(PO_4)_2$		100			175
	Cu/Al	15		75		140,143
$CH_3CH(OH)CH_2CH(OH)CH_3$	*p*-TsOH		70	22		168
	$Ca_3(PO_4)_2$, 300°C		55	45		181
	$FSO_3H/SbF_5/SO_2$		100			16
	Cu/Al	85		15		143
	$RhCl_3/PPh_3$	97				145
$PhCH(OH)CH_2CH(OH)Ph$	$KHSO_4$			35		206
i-$PrCH(OH)CH_2CH(OH)CH_3$	*p*-TsOH		14	1	56	224
1,3-Cyclohexanediol	Cu, Ni	95				95,96
	Cu/Al, Cu	100				104
5,5-Dimethyl-1,3-cyclohexanediol	Phthalic anhydride		84			169
$(CH_3)_2C(OH)CH_2CH(OH)CH_3$	H_2SO_4		50			185
	$(CH_3)_2SO$		74			82
	$Ca_3(PO_4)_2$, 275°C		8	92		181
	Al_2O_3, 190°C		77	23		
	$CuSO_4$		98.5	1		184
	$FeCl_3 \cdot 6H_2O$		92			183
	$RhCl_3/PPh_3$	85				146
	Cu/Al	20		75		140
$Ph_2C(OH)CH(CH_3)CH(OH)Ph$	H_2SO_4			65–89		207
$(CH_3)_2C(OH)CH_2(CH_3)_2COH$	$RhCl_3/PPh_3$		100			146
	Cu/Al		100			140,143
 $(CH_3)_2\underset{OH}{C}C(CH_3)_2\underset{OH}{C}(CH_3)_2$	H_2SO_4			100		199
	$FSO_3H/SbF_5/SO_2$			100		16
$R_2C(OH)CH_2CR_2OH$ (R = alkyl, phenyl)	$KHSO_4$, H_2SO_4			15–97		204

---

[a] Selectivity is based on 100 mole of the compound reacted.

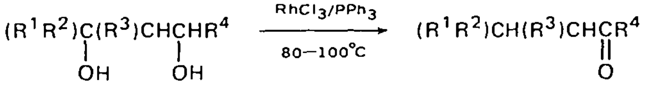
elucidation of the mechanism[143,144]. As seen in the example of 1,3-butanediol-[3-^{2}H] (**50**), the process consists of three steps (equation 34).



(34)

3. *Formation of carbonyl compounds on the action of other agents*

The formation of carbonyl compounds similarly proceeds in the presence of homogeneous catalysts, such as $RhCl_3/PPh_3$[145,146]. Apart from primary – secondary diols, disecondary and even secondary – tertiary diols[146] are transformed to the corresponding ketones (equation 35). On the action of $RhCl_3$ and chiral phosphines[147], it is also possible to achieve the enantioselective dehydration of 1,3-butanediol.



$$(R^1R^2)\underset{OH}{C}(R^3)CH\underset{OH}{C}HR^4 \xrightarrow[80-100°C]{RhCl_3/PPh_3} (R^1R^2)CH(R^3)CH\underset{O}{\overset{\|}{C}}R^4 \qquad (35)$$

With other agents too, carbonyl compounds[16] and unsaturated carbonyl compounds[82,148-150] may be formed.

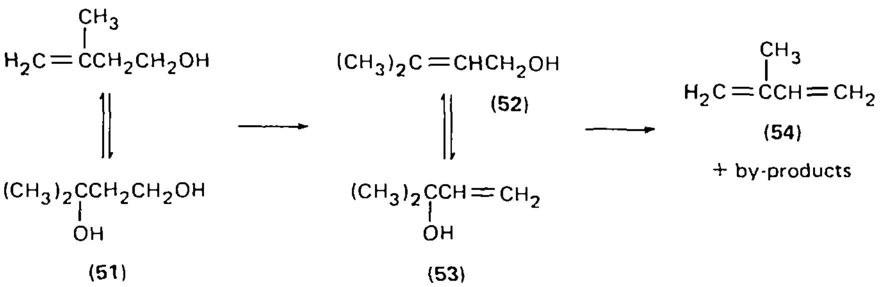
B. Formation of Unsaturated Alcohols and Dienes

The formation of these compounds via 1,2-elimination is a characteristic reaction of polysubstituted diols on the action of various organic and inorganic acids and organic acid anhydrides. The diols may be induced to undergo similar processes by other reactants too [$(CH_3)_2SO$, bromine, iodine, Al_2O_3]. Investigations in connection with the preparation of 1,3-butadiene and isoprene are of importance from an industrial point of view.

1. *Dehydration on the action of acids*

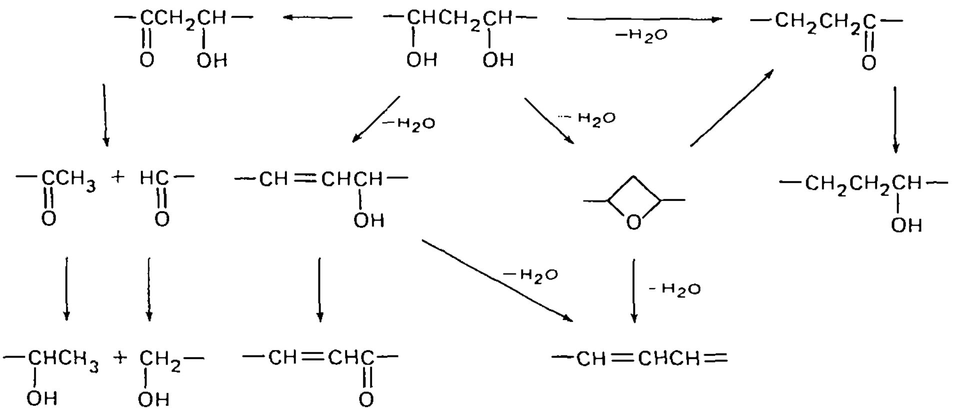
Sulphuric acid[151-161] and hydrogen bromide[75,162,163] are used most frequently with 1,3-diols. References may also be found to molybdic acid[164], HCl/CH_3COOH[165], organic acids (oxalic[157,166], benzenesulphonic[78], *p*-toluenesulphonic[167,168]), and acid anhydrides (phthalic[78,169], acetic[170,171]). Diene is likewise formed in $FSO_3H/SbF_5/SO_2$[16]. Similar agents may be employed for the dehydration of alicyclic compounds[169,172,173].

It is worthwhile to emphasize the results connected with 3-methyl-1,3-butanediol (**51**)[152-156,160,161,174-176]. Kinetic studies[157-159,177] have led to the scheme shown in equation (36). The fastest process in the system is the isomerization of dimethylallyl alcohol (**52**) to dimethylvinyl carbinol (**53**) and isoprene (**54**) and the side-products are formed from the equilibrium mixture of these two compounds.



(36)

The dehydration of some 1,3-diols (1,3-propanediol[178,179], 1,3-butanediol[179], 2-methyl-1,3-butanediol[180], 2,2-diethyl-1,3-propanediol[179], 2-*n*-butyl-1,3-propanediol[179], 2,4-pentanediol[181] and 2-methyl-2,4-pentanediol[181]) have been studied on Al_2O_3 and $Ca_3(PO_4)_2$ catalysts, using heterogeneous catalysts with an acidic character. Equation (37) shows the reactions observed, and shows three dehydration

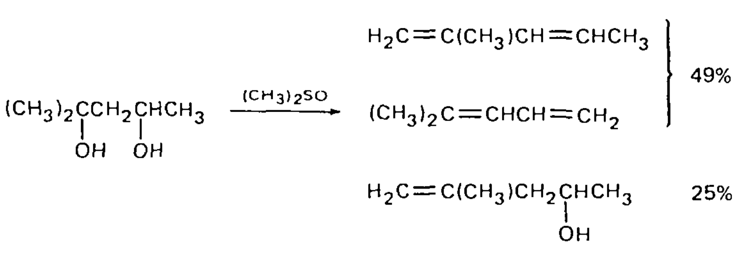


(37)

routes, and various types of fragmentation and hydrogen-transfer processes. The selectivity and the transformation mechanism[182] depend on both the reaction conditions (temperature, space-velocity) and the substrate. Dehydration accompanied by diene formation proceeds with high stereoselectivity[181].

2. *Dehydration on the action of other agents*

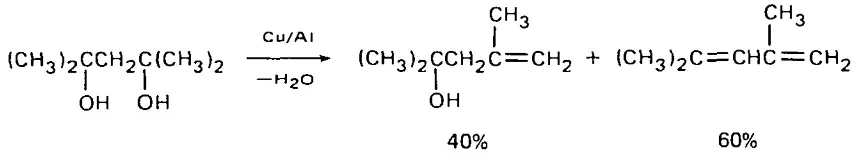
Unsaturated compounds can also be obtained on the action of various metal salts ($FeCl_3$, $CuSO_4$, Na_2SO_4)[170,183,184]. Dienes are obtained in good yield from 2-methyl-2,4-pentanediol on the action of iodine[183-185]. Dienes and an unsaturated alcohol are similarly formed in the presence of $(CH_3)_2SO$ (equation 38)[82].



(38)

Bromine[186] and Al_2O_3[187] convert 1,3-cyclohexanediol to an unsaturated alcohol, while zeolite of NaX-type[188] gives dienes.

In the case of ditertiary diols, which undergo fragmentation on exposure to acids (see Section II.C), unsaturated alcohols and dienes are formed (equation 39) on the action of metal catalysts (Cu/Al, Cu, Pt/C)[140,143] or $RhCl_3/PPh_3$[146].



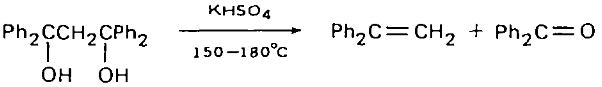
$$(CH_3)_2C(OH)CH_2C(OH)(CH_3)_2 \xrightarrow[-H_2O]{Cu/Al} \underset{40\%}{(CH_3)_2C(OH)CH_2C(CH_3)=CH_2} + \underset{60\%}{(CH_3)_2C=CHC(CH_3)=CH_2} \qquad (39)$$

3. *Preparation of butadiene*

The preparation of butadiene is dealt with in a great number of publications, mainly patents. These describe reaction conditions and catalysts which tend to favour diene formation, such as supported and support-free acidic and neutral phosphates[175,189-192], heterogeneous catalysts containing phosphoric acid[193,194], and other complex heterogeneous catalysts[195-197]. Butadiene may be obtained in a yield better than 90% with a catalyst of involved composition (carborundum – Al – Mg containing SiO_2 and WO_3)[81].

C. Dehydration Accompanied by Fragmentation

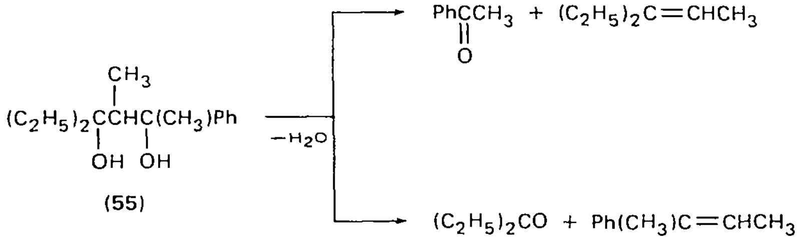
With ditertiary 1,3-diols on the action of H_2SO_4[198-201], $KHSO_4$[202-204] and $FSO_3H/SbF_5/SO_2$[16], water is eliminated, fragmentation occurs, and a carbonyl compound and an olefin are formed (equation 40). The process can also be observed for diols of lower order if the molecule contains a phenyl substituent[205-208], or if a substituent is found on the carbon atom enclosed between the carbon atoms bearing the hydroxy groups[200,205,207,209]. Similar findings hold for the cyclic diols too.



$$Ph_2C(OH)CH_2C(OH)Ph_2 \xrightarrow[150-180°C]{KHSO_4} Ph_2C=CH_2 + Ph_2C=O \qquad (40)$$

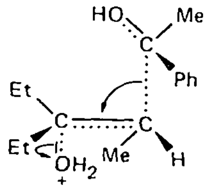
Studies with open-chain diols[200,203,204,206,207] indicate that the transformations take place via a concerted mechanism[200,206,207].

For asymmetrically-substituted compounds (e.g. 55), the possibility exists for two reactions, leading to different products (equation 41), and the direction depends on the stereostructure of the diol[200,210]. In the case of the α- and β-isomers, 56 and 57, respectively, the conformations favour *trans* elimination.

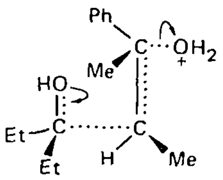


$$\underset{(55)}{(C_2H_5)_2C(OH)CH(CH_3)C(OH)(CH_3)Ph} \xrightarrow{-H_2O} \begin{cases} PhC(=O)CH_3 + (C_2H_5)_2C=CHCH_3 \\ (C_2H_5)_2CO + Ph(CH_3)C=CHCH_3 \end{cases} \qquad (41)$$

An interesting example of the correlation between the structure and the reaction


HO
Me
Ph
Et
Et
OH2
Me
H

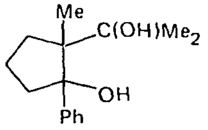
(56)


Ph
OH2
Me
HO
Et
Et
H
Me

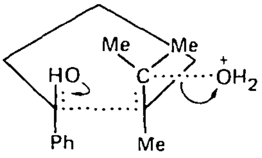
(57)

direction[208] is the difference between the transformations of 2,2-dimethyl-1,3-butanediol and 1-phenyl-2,2-dimethyl-1,3-propanediol: fragmentation occurs only for the latter compound.

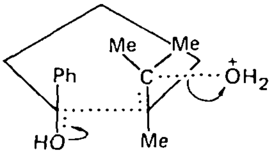
With cyclic 1,3-diols of type 58[210], ring-splitting is the predominant process for the *cis*-diol, whereas ring-splitting and fragmentation of the side-chain are comparable for the *trans* derivative. With the *cis* compound, *trans* elimination occurs in the case of the formation of the ring-splitting product, (59), while with the *trans* compound both splitting products, **60** and **61**, may be obtained by *trans* elimination.


Me
C(OH)Me2
OH
Ph

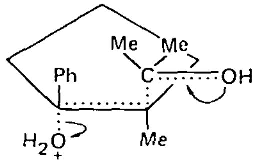
(58)


Me
Me
HO
OH2
Ph
Me

(59)

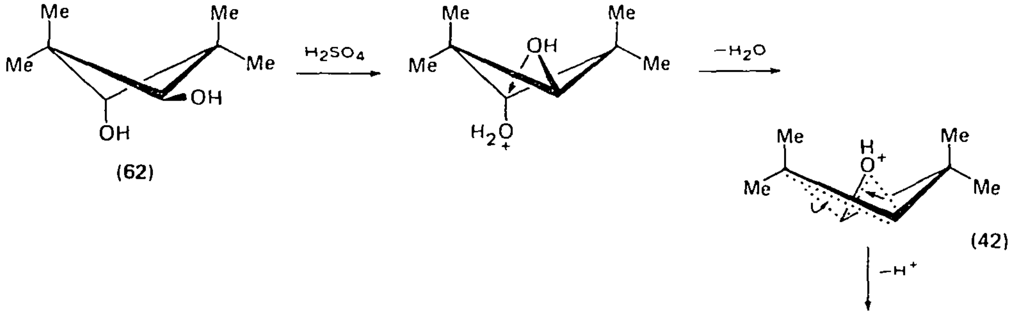

Me
Me
Ph
OH2
HO
Me

(60)


Me
Me
Ph
OH
H2O
Me

(61)

A similar interesting ring-splitting has been described for 2,2,4,4-tetramethyl-1,3-cyclobutanediol (62)[211] (equation 42). The *trans*-diol is converted to the un-


Me
Me
Me
Me
OH
OH
H2SO4
Me
Me
Me
Me
OH
H2O
−H2O
Me
Me
Me
Me
H
O+
−H+

(62)

(42)

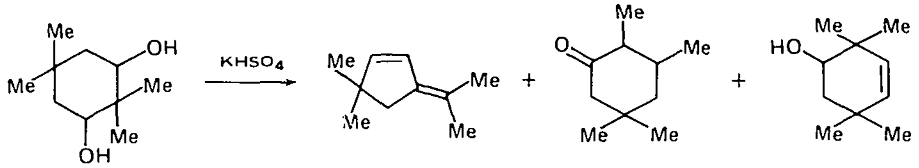
$(CH_3)_2C{=}CH(CH_3)_2CCHO$

(63)

saturated aldehyde **63** via the indicated intermediate, while the *cis* isomer can be recovered unchanged from the reaction mixture.

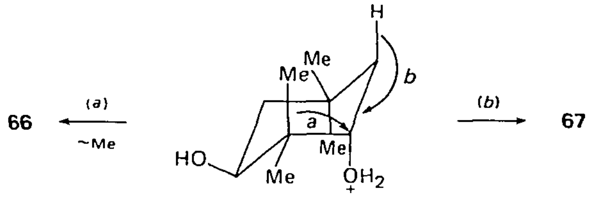
Similar processes accompanied by ring-opening or fragmentation of the side-chain can be observed for other cyclic 1,3-diols[212].

Stereochemically interesting processes have been observed for the transformation of 2,2,5,5-tetramethyl-1,3-cyclohexanediol (**64**) in the presence of $KHSO_4$ (equation 43)[213,214]. Besides the product formed by rearrangement (**65**), a ketone **66** and an unsaturated alcohol **67** were detected. The formation of **65** is justified by the steric arrangements of the system. Additionally, in the case of the *trans*-diol, the formation of **66** or **67** is possible, because the methyl group and hydrogen are in *trans* axial positions to the departing axial hydroxy group (equation 44). For the *cis*-diol, these latter transformations are not favoured as the equatorial hydroxy groups do not give rise to the above steric situation.


Me
OH
Me
Me
Me
OH
KHSO4
Me
Me
Me
Me
+
Me
O
Me
Me
Me
+
HO
Me
Me
Me
Me

(43)

	(64)	(65)	(66)	(67)
cis		88%	12%	
trans		53%	30%	17%


66
(a)
~Me
H
Me
Me
b
a
Me
HO
Me
OH2
+
(b)
67

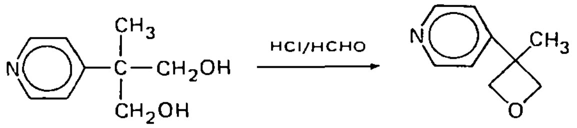
(44)

D. Formation of Cyclic Ethers

1. *Formation of oxetanes*

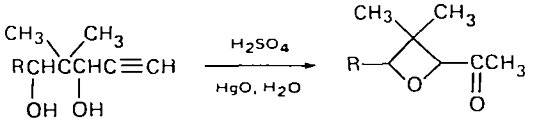
Oxetanes cannot usually be prepared from 1,3-diols by direct water elimination. Nevertheless, the process can be carried out with excellent yield from **68** in the presence of HCl and HCHO (equation 45)[215], and oxetanes were also obtained from some acetylene-1,3-diols (equation 46)[216].

In addition to the above, the presence of 2-methyloxetane and 3,3-diethyloxetane


N
CH3
C—CH2OH
CH2OH
HCl/HCHO
N
CH3
O

(45)

(68) 90%


CH3
CH3
RCHCCHC≡CH
OH OH
H2SO4
HgO, H2O
CH3
CH3
R
O
CCH3
O

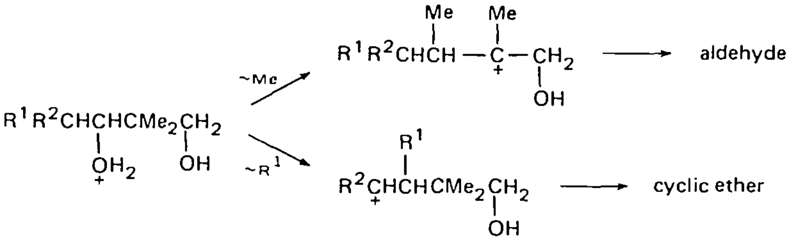
(46)

R = H, CH_3

was demonstrated in the dehydrations of 1,3-butanediol and 2,2-diethyl-1,3-propanediol on $Ca_3(PO_4)_2$ and Al_2O_3[179]. The other literature data[217-220] proved that the procedure is not reproducible.

2. *Formation of oxolanes*

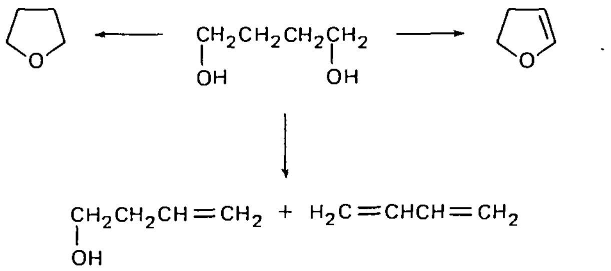
Various 1,3-diols are dehydrated to yield oxolanes on the action of H_2SO_4[121,208,221], H_3PO_4[222], Et_3PO_4[222,223], *p*-toluenesulphonic acid[224] and ion-exchange resin[225]. In certain cases, isomeric aldehydes are formed together with the oxolanes (equation 47). Both products indicated result from rearrangement (alkyl migration). The driving force of the process is the possibility of formation of more stable carbonium ions.



(47)

III. DEHYDRATION OF HIGHER DIOL HOMOLOGUES

The main reactions of this group of diols are summarized in equation (48). The most characteristic process is the transformation to the cyclic ether. Table 2 shows that the process is almost independent of the structure and degree of substitution of the starting diol.



(48)

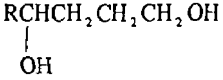
The formation of unsaturated cyclic ethers can be observed on metal catalysts. Unsaturated alcohols and dienes are formed from primary – tertiary and ditertiary diols on the action of various acids, and the same processes are also induced by various oxides and by $Ca_3(PO_4)_2$ at high temperature, independently of the structures of the diols. Other special transformations may be observed also, but these only occur for individual diols.

A. Preparation of Oxacycloalkanes

1. *Cyclodehydration on the action of various agents*

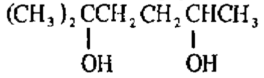
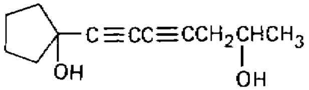
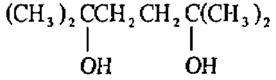
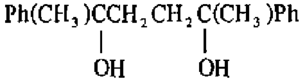
The most general means of carrying our cyclodehydration is to perform the transformation in the presence of mineral acids (H_2SO_4[120,226-249], HCl[249-255],

TABLE 2. Selectivity of dehydration transformations of higher diol homologues

Compound	Catalyst	Selectivity (%)[a]			References
		Cyclic ethers	Unsaturated cyclic ethers	Unsaturated alcohols and dienes	
$HOCH_2CH_2CH_2CH_2OH$	80% H_3PO_4	100			249
	p-TsOH	90			
	Cr oxide	100			
	Na phosphate + Bu phosphate + graphite			95–98	
	$Ca_3(PO_4)_2$, 320°C	99			291
	426°C	27		47	
	Morden bentonite	100			296
	Ion-exchange resin	98			249
	$PdCl_2/CuCl_2$	95			150
	$PdCl_2/CuCl_2/Cu(NO_3)_2$	98			
	Ni/kieselgur	56			303
	Cu/Al	100			305
	Cu or Co/kieselgur		81		330
$HOCH_2CH{=}CHCH_2OH$	Pyridine·HCl	73			318
$HOCH_2CHMeCHMeCH_2OH$	Aluminium silicate	78			299
1, 2-Bis(hydroxymethyl)cyclohexane	H_2SO_4	94			281
$HOCH_2(R)CH(CH_2)_2CH_2OH$ (R = alkyl)	Aluminium silicate	69–76			300
$HOCH_2(CH_2)_4CH_2OH$	57% H_2SO_4	100			325
$CH_3CH(OH)CH_2CH_2CH_2OH$	Cu/Al, Pd/Al	80–90			304
$ArCH(OH)CH_2CH_2CH_2OH$ (Ar = Ph, *p*-$CH_3C_6H_4$)	50% H_3PO_4	70–75			259
$ArCH(OH)CHRCHRCH_2OH$ (R = H, CH_3; Ar = *p*-$CH_3C_6H_4$, Ph, *p*-$CH_3OC_6H_4$, 2-furyl)	*p*-TsOH	70–95			275
 $RCH(OH)CH_2CH_2CH_2OH$ (R = alkyl, Ph, thienyl, cyclohexyl)	60% H_2SO_4	57–72			242

$CH_3CH(OH)(CH_2)_3CH_2OH$	Cu		25		305
$CH_3\underset{OH}{C}HRCH(CH_2)_2CH_2OH$ (R = alkyl)	Aluminium silicate	72–74			301
$CH_3(C_2H_5)C(OH)(CH_2)_2CH_2OH$	$(CH_3)_2SO$	67			310
$Ph(CH_3)C(OH)(CH_2)_2CH_2OH$	H_2SO_4	22–80			335
$(CH_3)_2\underset{OH}{C}(CH_2)_3\underset{OH}{CH_2}$	H_3PO_4	80			260
$(CH_3)_2\underset{OH}{C}(CH_2)_3\underset{CH_3}{CH}CH_2\underset{OH}{CH_2}$	$Ca_3(PO_4)_2$			90	292
$CH_3\underset{OH}{C}HCH_2CH_2\underset{OH}{C}HCH_3$	Al_2O_3, 250°C	70		10	290
	400°C			80	
	$Ca_3(PO_4)_2$, 325°C	63.5		20	
	400°C	30		70	
	Aluminium silicate 200°C	70		15	
	350°C	5		50	
	Al_2O_3	35		25	248
	$PdCl_2/CuCl_2$	67			150
	$PdCl_2/CuCl_2/Cu(NO_3)_2$	85–95			
	$PdCl_2/Cu(NO_3)_2$	97			
	$PdCl_2/NaCl$	94			
	$(CH_3)_2SO$	68			309
	Cu/Al, Pd/Al	80–90			304
	Cu/Al	96			305
	Cu		55		
	Cu/SiO_2	29	19		
$CH_3\underset{OH}{C}HCH_2CH_2CH_2\underset{OH}{C}HCH_3$	Cu/Al	92			305
	Cu	3	61		
	Cu/SiO_2	4	73		
$ArCH(OH)(CH_2)_2CH(OH)CH_3$ (Ar = Ph, 2-furyl)	*p*-TsOH	70–95			275
$Ph\underset{OH}{C}H(CH_2)_2\underset{OH}{C}HPh$	*p*-TsOH	74		8	311
	p-TsOH/benzene	20		>50	
	85% H_3PO_4			90	

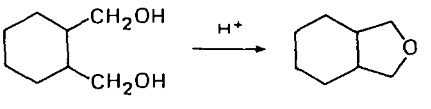
TABLE 2 (continued)

Compound	Catalyst	Selectivity (%)[a] Cyclic ethers	Selectivity (%)[a] Unsaturated cyclic ethers	Selectivity (%)[a] Unsaturated alcohols and dienes	References
$PhCH(OH)(CH_2)_3CH(OH)Ph$	*p*-TsOH	45		25	311
 $(CH_3)_2\underset{OH}{C}CH_2CH_2\underset{OH}{C}HCH_3$	*p*-TsOH	60			224
	$KHSO_4$			62	346
 $(CH_3)_2\underset{OH}{C}CH_2CH_2\underset{OH}{C}(CH_3)_2$	H_2SO_4			42	238
	H_3PO_4	47		26	264
	Al_2O_3			77	349
	$PdCl_2/CuCl_2$	78			150
	Cu/Al, Pd/Al	60–70		30–40	304
	Cu/Al, Cu, Pt/C	65–83		13–17	103
 $Ph(CH_3)\underset{OH}{C}CH_2CH_2\underset{OH}{C}(CH_3)Ph$	$20\% H_2SO_4$	80			247
	HCl/benzene	59		23	
	Formic acid	60			

[a] Selectivity is based on 100 mole of the compound reacted.

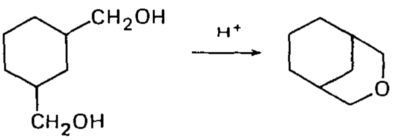
H_3PO_4[248,249,256–265]), or in certain cases acidic salts[266–270]. Organic acids too (benzenesulphonic[271], *p*-toluenesulphonic[224,249,272–276], formic[247,250,277], acetic[278,279], oxalic[249,280]) may be used in the same way. In most cases the cyclic ether formation is selective, and sometimes quantitative. These methods are primarily employed with aliphatic diols.

It is interesting to compare the transformations of 1,2-bis(hydroxymethyl)cyclohexane (**69**) and 1,3-bis(hydroxymethyl)cyclohexane (**70**). On the action of H_2SO_4 or H_3PO_4, the former gives a cyclic ether in excellent yield (equation 49)[268,281], while **70** yields scarcely any **71** (equation 50)[282]. The transformation may likewise occur for cyclic compounds with smaller rings[267,269].



(49)

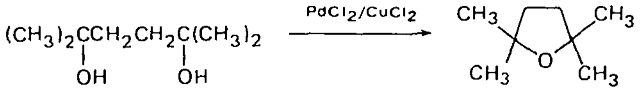
(69) 90–94%



(50)

(70) (71)

Various metal salts (e.g. $MgCl_2$, $CaCl_2$, $ZnCl_2$, $AlCl_3$, $CuSO_4$) similarly catalyse the formation of tetrahydrofuran[235,254,270,283]. Cyclic ethers are also formed from 1,4- and 1,5-diols on the action of $RhCl_3/PPh_3$[145]. The use of $PdCl_2$ together with other salts [$CuCl_2$, $Cu(NO_3)_2$, NaCl] leads to the formation of five- and six-membered cyclic ethers in various yields[150]. The yield is good in the case of the ditertiary 1,4-diol 72 (equation 51).



$$(CH_3)_2\underset{OH}{C}CH_2CH_2\underset{OH}{C}(CH_3)_2 \xrightarrow{PdCl_2/CuCl_2}$$

(51)

(72) 70%

Oxides[249,270,280,283–286], and particularly alumina[92,245,249,270,280,283–285,287–290], are also frequently used for the preparation of cyclic ethers. Acidic and neutral phosphates of various mono- and tri-valent metals can similarly be employed[178,266,270,283,284,290–292]. For example, oxolane is formed quantitatively from 1,4-butanediol in the vapour phase on the action of chromium oxide[249,270], alumina[270,285] and calcium phosphate[178,270,291]. Where $Ca_3(PO_4)_2$ is used as catalyst, however, the transformation is selective only at 250–320°C; at higher temperatures the cyclic ether formation becomes less important than the formation of unsaturated alcohols and dienes (see Section III.C.2).

The corresponding oxacycloalkanes can be obtained from the alicyclic compounds, in yields depending on the structure of the diol[287–289]. From *trans*-1,4-cyclohexanediol the main product is 1,4-epoxycyclohexane[293–295], whereas the *cis* isomer gives primarily 2-cyclohexen-1-ol (see Section III.C.3).

The effect of aluminium silicates has mainly been studied with simple diols. Nearly quantitative yields of oxolane are reported[285,296,297]. With diprimary, primary – secondary and disecondary 1,4- and 1,5-diols too, good yields can be attained[290,298–301]. In the case of zeolites, it has been established[297] that the

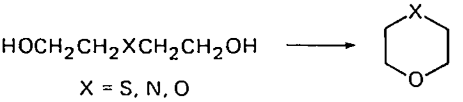
HNaX form and the decationized X form, at temperatures of 240–260°C, are optimal for oxolane formation.

Dehydrations of both 1,4- and 1,5-diols on supported Ni[302,303], Cu and Pd[139,304,305] and Pt[141] catalysts gave generally high yields. Because of the occurrence of other reactions, little 1,4-epoxycyclohexane is formed from the isomeric 1,4-cyclohexanediols, but the yield is always higher from the *trans* than from the *cis* compound[104,306]. The epimerization demonstrated by Pines and Kobylinski[306] (which has also been observed on Cu and Cu/Al catalysts[307]) strongly suggests that in the case of the *cis* compound too the 1,4-epoxycyclohexane is formed from the *trans*-diol, produced by epimerization.

With the diprimary diols, ion-exchange resins lead to cyclic ethers in excellent yields[118,249,308].

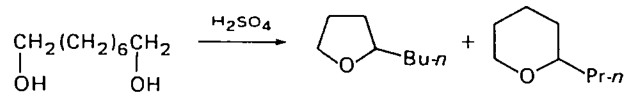
In some cases Me_2SO has also been employed to induce ring-closure. For the open-chain diprimary diols the reaction proceeds with a diol : Me_2SO molar ratio of 2:1, the yield of the cyclic ether decreasing with the distance between the hydroxy groups (oxolane: 70%, oxane: 47%, oxepane: 24%)[82]. The reagent is often used in a very great excess (diol : Me_2SO = 1:12)[248,309-311] without an appreciable change in the yield.

Ring-closure can also be achieved with diols containing a heteroatom. The dehydration has been carried out in the presence of $KHSO_4$[312-314], aluminium silicate[102] and ion-exchange resin[118] (equation 52). Cyclic ethers are likewise formed from diols containing other groups too (trihydroxy compounds[249,315,316], epoxytriols[317], unsaturated diols[249,254,255,264,284,318]).



(52)

α, ω-Diols, with carbon chains consisting of six or more atoms, yield α-substituted oxolane and oxane derivatives, on the action of H_2SO_4 and H_3PO_4, independently of the number of carbon atoms (equation 53)[319-324]. In the reaction of 1,6-hexanediol, a small amount (1.5%) of oxepane too has been detected[325]. Similarly, all three cyclic ethers are also formed in the presence of Al_2O_3 and $Ca_3(PO_4)_2$[178,326].



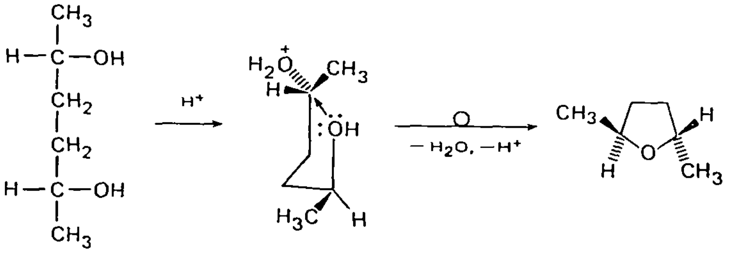
(53)

The formation of cyclic ethers with rings of unexpected size may be promoted by the special electronic structure of the starting compound (as a consequence of electron shifts resulting from the presence of unsaturated bonds)[327,328].

2. *Mechanism of oxacycloalkane formation*

Mihailović and coworkers[248,329] have made a detailed study of the ring-closure of 2,5-hexanediol (73) under various conditions (H_3PO_4, H_2SO_4, Me_2SO, Al_2O_3) and have found that the process is stereoselective in every case: the *meso*-diol is selectively converted to *trans*-2,5-dimethyloxolane (equation 54) and the (±)-diol to *cis*-2,5-dimethyloxolane. It follows from this that the ring-closure takes place by intramolecular substitution of S_N2 type, inversion occurring on the chiral carbon atom bearing the departing protonated hydroxy group.

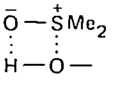
In the presence of Me_2SO, one of the hydroxy groups interacts with the reagent



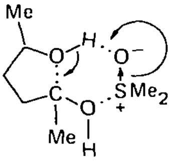
(*meso*-73)

(54)

(74), thereby increasing the polarization of the C—O bond and facilitating cleavage of the bond. The results of Mihailović disprove the conception of Gillis and Beck[309], in whose view the cyclic transition state (75) is produced with the



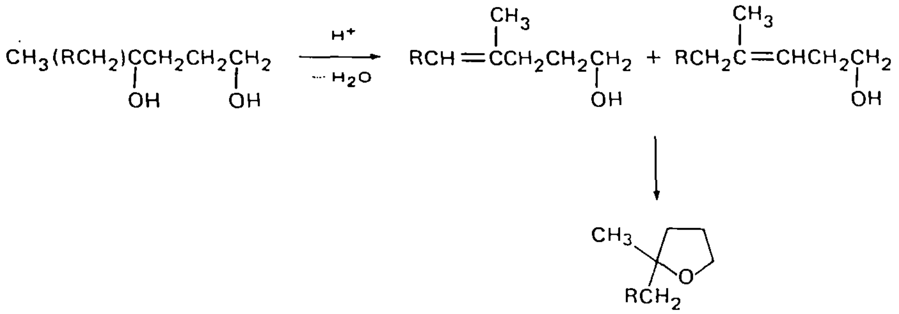
(74)



(75)

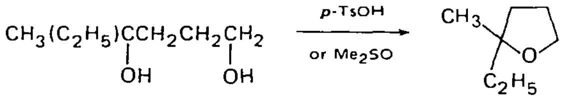
participation of both hydroxy groups of the diol, 75 then being convertible to the cyclic ether without inversion. The intramolecular S_N2 mechanism is supported by other investigations[244,275].

Primary – tertiary diols[238,239,260] yield isomeric unsaturated alcohols by elimination of the tertiary hydroxy group on the action of acids; they then undergo isomerization to give the cyclic ether (equation 55).



(55)

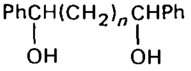
On the reaction of (−)-4-methyl-1,4-hexanediol (76) in the presence of *p*-TsOH or Me_2SO, a racemic cyclic ether (77) is obtained[310]; this is a consequence of the fact that a carbonium ion is formed on the departure of the tertiary hydroxy group, a possibility thus arising for the cessation of the chirality of $C_{(4)}$ (equation 56). The



(−)-(76) racemic (77)

(56)

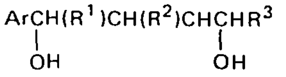
ring-closure proceeds via a carbonium cation in a similar way for diols not containing a tertiary hydroxy group (78, 79, 80), when the molecular structure promotes the formation of the carbonium ion and stabilizes it[275,311].



$\mathrm{Ph\underset{OH}{CH}(CH_2)_n\underset{OH}{CH}Ph}$

$n = 2$ (78)

$n = 3$ (79)



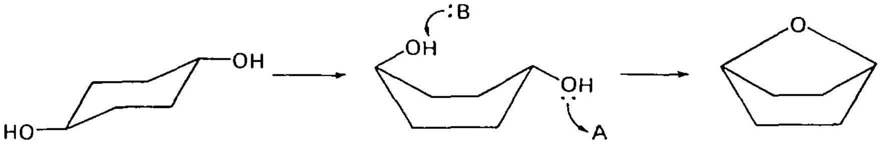
$\mathrm{Ar\underset{OH}{CH}(R^1)CH(R^2)CH\underset{OH}{CH}R^3}$

(80)

Ar = Ph, p-$\mathrm{CH_3C_6H_4}$, p-$\mathrm{CH_3OC_6H_4}$, 2-furyl

On the other hand, the transformation of (–)-**76** on Al_2O_3 catalyst is to a slight extent stereospecific. This can be interpreted[310] by assuming that the $C_{(1)}$ hydroxy group first undergoes selective adsorption, followed by nucleophilic substitution of the $C_{(4)}$ hydroxy group. The low degree of stereoselectivity can be ascribed to the fact that the reaction takes place by another mechanism in addition to the above. Stereospecific dehydration has also been reported in the reactions of various di-secondary diols under similar conditions[245,248,329].

In the study of the Al_2O_3-catalysed transformation of *trans*-1,4-cyclohexanediol (**81**), it was found[294] that the ring-formation involves an S_N2 reaction even under these experimental conditions (equation 57).



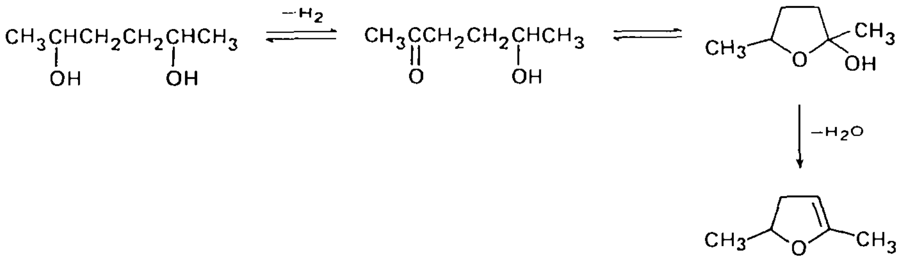
(81)

(57)

Cyclic ethers are formed in an essentially similar manner on metal catalysts of Raney type (Cu/Al, Pd/Al). Cyclodehydration is promoted by the aluminium oxide hydroxides formed during the preparation and remaining on the surface of the catalyst. The intramolecular ring-closure has been proved in studies with 1,4-pentanediol-[4-^{2}H], and the results have been supported by data from measurements on the active centres of the catalysts[143,144,305].

B. Preparation of Unsaturated Cyclic Ethers

Certain metal catalysts may be used to prepare unsaturated oxacycloalkanes. Most of the data refer to supported[305,330–332] and support-free Cu[305] catalysts, but supported Co[330,333] and Ag[331] catalysts may also be employed. The transformation may be interpreted as a dehydration of the hemiacetal formed by dehydrogenation of the diol (equation 58)[305]. The process is explained in a similar way in investigations relating to nonmetallic catalysts[334].



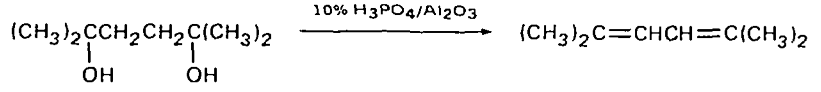
(58)

C. Preparation of Unsaturated Alcohols and Dienes

1. *Dehydration on the action of acids*

The dehydration can be induced with primary – tertiary and ditertiary diols, and is frequently accompanied by the formation of cyclic ethers. The proportions of the two reactions depend on the structure of the diol and on the reaction conditions. For example, with 5-phenyl-1,4-pentanediol[335], only a cyclic ether is formed on the action of H_2SO_4, whereas in the presence of other acids (H_3PO_4, formic acid, acetic acid/NaOAc) an unsaturated alcohol also appears in the product. On the action of *p*-TsOH/benzene and H_3PO_4, 1,4-diphenyl-1,4-butanediol (78) gives a diene, while under different reaction conditions (H_2SO_4, *p*-TsOH, Me_2SO) the main product is a cyclic ether[311].

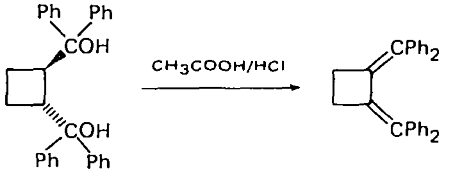
Likewise, H_3PO_4/Al_2O_3 primarily catalyses diene formation from 2,5-dimethyl-2,5-hexanediol (82) (equation 59)[336], while with other ditertiary diols on different



$$\underset{\text{OH}}{(CH_3)_2\overset{}{C}}CH_2CH_2\underset{\text{OH}}{C}(CH_3)_2 \xrightarrow{10\%\ H_3PO_4/Al_2O_3} (CH_3)_2C{=}CHCH{=}C(CH_3)_2 \qquad (59)$$

(82) 83%

catalysts the two main processes run in parallel[232,247,264,337], or the cyclic ether may become the main product[95,261]. For example, the diene **84** is formed in excellent yield from **83** (equation 60), whereas the diene cannot be prepared from the corresponding tetramethyl derivative[267].



(60)

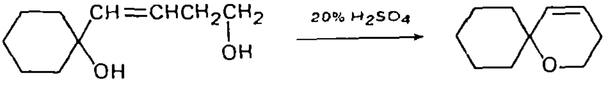
(83) (84)

70%

Diene and unsaturated alcohol are formed from the isomeric 1,4-cyclohexanediols on the action of $KHSO_4$[295,338], $MgSO_4$[338], H_2SO_4[172,339,340] or oxalic acid[339].

1,4-, 1,5- and 1,6-diols have been studied in $FSO_3H/SbF_5/SO_2$[16]. The diprimary compounds do not react at all. 2,5-Hexanediol gives protonated 2,5-dimethyltetrahydrofuran, while **82** is converted to a diene.

Many authors have studied diols containing unsaturated bonds[341-346], a cyclic substituent often being present[344-347]. Here again the reaction direction is influenced by the structure of the diol. In the presence of 20% H_2SO_4 and $HgSO_4$, for instance, **85** gives the dihydropyran derivative **86** (equation 61)[345]; while the

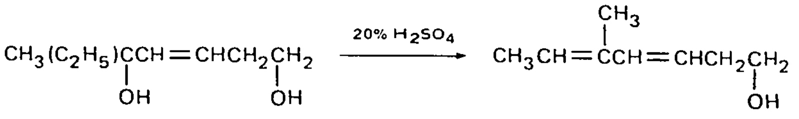


(61)

(85) (86)

44%

dialkyl-substituted compound with similar structure (87) yields the unsaturated alcohol under the same reaction conditions (equation 62).



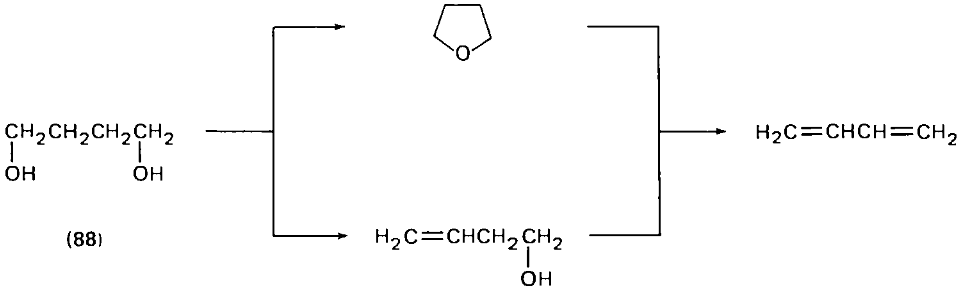
$$\mathrm{CH_3(C_2H_5)\underset{OH}{C}CH{=}CHCH_2\underset{OH}{CH_2}} \xrightarrow{20\%\ \mathrm{H_2SO_4}} \mathrm{CH_3CH{=}\overset{CH_3}{C}CH{=}CHCH_2\underset{OH}{CH_2}} \qquad (62)$$

(87) 49%

2. *Dehydration on phosphate catalysts*

With $Ca_3(PO_4)_2$, detailed investigations present illustrative examples of how the reaction conditions can affect the pathways and hence the product composition. At low temperature, cyclic ether formation is dominant (see Section III.A.1). With the increase of the temperature, the product also includes unsaturated alcohols, and then dienes, and if the temperature is further elevated these become the main products[178,290–292,348].

Dienes may be formed from both the cyclic ether and the unsaturated alcohol, although the process occurs primarily via the unsaturated alcohol. The reaction scheme for general electrophilic catalysts is presented using the example of 1,4-butanediol (88) (equation 63)[178,182,290–292,348].



(88) (63)

Reppe[249] studied the possibilities of diene formation on other, special phosphate catalysts.

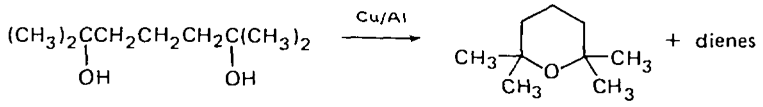
3. *Dehydration on oxide catalysts*

Most of the data refer to *cis*- and *trans*-1,4-cyclohexanediol on the action of Al_2O_3[293–295]. The *cis*-diol yields an unsaturated alcohol, while the *trans* compound possesses a favourable conformation for ring-closure[294] (see Section III.A.2). Detailed studies have been carried out[295] to clarify the dependence of the formation of the three possible products (1,4-epoxycyclohexane, 3-cyclohexen-1-ol, 1,3-cyclohexadiene) on the structure of the starting diol and on the reaction

In the case of open-chain diols, studies have been made with Al_2O_3[248,310,349,350], and also with other oxide catalysts[81,266,350], the latter primarily from the aspect of diene formation.

4. *Dehydration on metal catalysts*

Observations with Cu/Al, Cu and Pt/C catalysts[103] indicate that 2,6-dimethyl-2,6-heptanediol (89) is converted mainly to dienes (equation 64), in contrast with 2,5-dimethyl-2,5-hexanediol (82), yielding mainly the cyclic ether. This phenomenon can be explained by the rapid further reaction of the **90** formed.


(CH3)2CCH2CH2CH2C(CH3)2
OH
OH
Cu/Al
CH3
O
CH3
CH3
CH3
+ dienes

(89) (90)

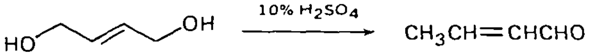
28% 72%

(64)

The isomeric 1,4-cyclohexanediols have been investigated on Ni/SiO_2[306] as well as on Cu/Al and Cu[104] catalysts. On Ni/SiO_2 the transformation was carried out in the presence of hydrogen, and hence the unsaturated compounds could not be detected. On Cu/Al, 3-cyclohexenone and dienes are formed in addition to other products.

D. Other Transformations

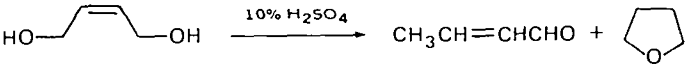
Numerous observations[178,231,249,351-357] show that variously substituted 2-butene-1,4-diols are dehydrated to unsaturated oxo compounds in the presence of acids, $Ca_3(PO_4)_2$, Al_2O_3 and ThO_2 (in the case of the parent compound, 2-butene-1,4-diol, formation of 2,5-dihydrofuran is also found). By study of the isomers, it has been established[353,354] that the *trans* compound (**91**) is converted to crotonaldehyde (**93**), while both products are formed from the *cis*-diol (**92**) (equations 65 and 66). On the basis of the stereostructure, the ring-closure process should predominate for **92**, but here too crotonaldehyde is formed because of the *cis–trans* isomerization.


HO
OH
10% H2SO4
CH3CH=CHCHO

(91) (93)

80%

(65)


HO
OH
10% H2SO4
CH3CH=CHCHO +
O

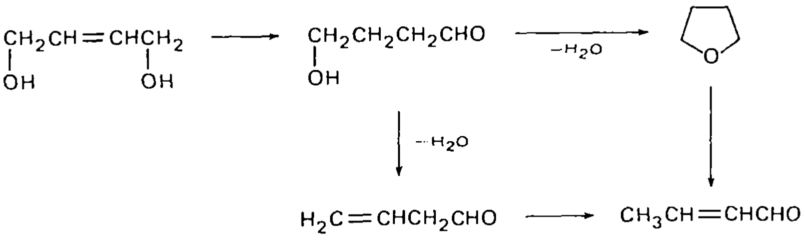
(92) (93)

65% 35%

(66)

In the transformations of the isomers of 1,1,4,4-tetraphenyl-2-butene-1,4-diol in acetic acid, on the other hand, only unidirectional processes can be observed[358].

In the presence of Al_2O_3, $Ca_3(PO_4)_2$ and $Al_2O_3/Ca_3(PO_4)_2$[178,355,356], crotonaldehyde (**93**) is formed from both diol isomers via the two-route dehydration of 4-hydroxybutyraldehyde produced as a result of isomerization (equation 67).

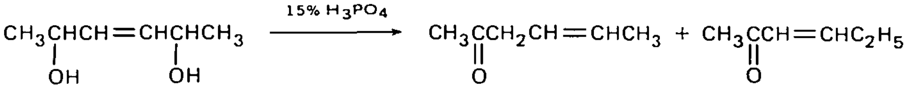

CH2CH=CHCH2
OH
OH
CH2CH2CH2CHO
OH
−H2O
O
−H2O
H2C=CHCH2CHO
CH3CH=CHCHO

(93)

(67)

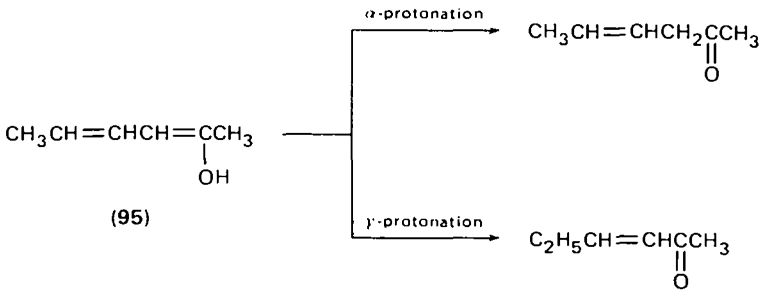
The two processes (isomerization of the diol, and dehydration) occur on different active centres.

3-Hexene-2,5-diol (**94**) in H_3PO_4 gives two isomeric ketones (equation 68)[357]. In an investigation of the mechanism with D_3PO_4/D_2O, it was proved that the product ratio is governed by the protonation of the dienol **95** formed by dehydration and subsequent rearrangement (equation 69). The stabilization is due almost exclusively to α-protonation.



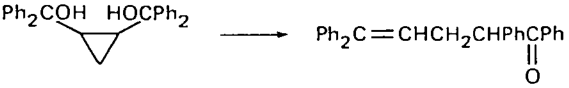
$$\mathrm{CH_3\underset{OH}{\underset{|}{C}}HCH{=}CH\underset{OH}{\underset{|}{C}}HCH_3 \xrightarrow{15\%\ H_3PO_4} CH_3\underset{O}{\underset{\|}{C}}CH_2CH{=}CHCH_3 + CH_3\underset{O}{\underset{\|}{C}}CH{=}CHC_2H_5} \qquad (68)$$

(**94**) 90–95% 5–10%



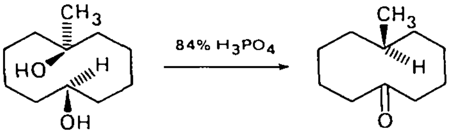
(**95**) (69)

The diol **96** in acetic acid[359], $SOCl_2$[359] and $KHSO_4$[269] forms an unsaturated ketone by ring-opening and phenyl migration (equation 70).



(**96**) (70)

In the reaction of 1-methyl-1,6-cyclohexanediol (**97**), Prelog and Küng[360] isolated the ketone **98** (equation 71). By means of the reaction of the compound



(**97**) (**98**) (71)

labelled with deuterium on $C_{(6)}$, it was proved that 1,6-hydride anion migration takes place in the course of the transformation.

IV. REFERENCES

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 17

Enol ethers—structure, synthesis and reactions

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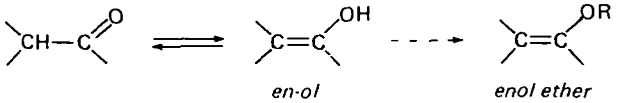
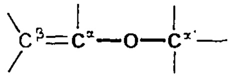
I. INTRODUCTION

The terms *enol ether* and *vinyl ether* are both generally used to designate *O*-alkyl derivatives of the enolized form of carbonyl compounds, specifically of aldehydes and ketones (equation 1). The proposed further differentiation into *enol* ethers[1], as

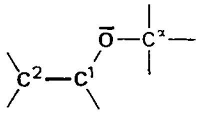


(1)

derived from parent compounds which are enolized extensively (for instance 1,3-diketones etc.), and *vinyl* ethers – derivatives of normal aldehydes and ketones where this is not the case – does not seem practical except for classifying the individual synthetic procedures[2]. However, there is a dual way of approaching the chemistry of the enol ethers: their *prima facie* structure allows them to be characterized either simply as α,β-unsaturated ethers (**1**) or, on the other hand, as +*M*-substituted, i.e. activated alkenes (**2**). Since organic chemistry utilizes enol



(1)



(2)

ethers as functional derivatives for the more facile chemical modification of the parent C=O compound, we shall consider almost exclusively the second aspect, as Effenberger has done in his review on the subject[3]. A note is still necessary on the naming of the enol ethers: they used to be designated according to the generic principle, alkyl alkenyl ether, until, with the latest collective index, *Chemical Abstracts* introduced systematic nomenclature for the enol ethers. However, we shall retain the ether nomenclature, where convenience and lucidity demand it; a concordance of systematic and established names is presented in Table 1 for some of the more common members.

Four basic types of enol ether reactions are outlined in Scheme 1; three of these (halogenation, hydrolysis and polymerization) had already been found by Wislicenus who first synthesized ethyl vinyl ether in 1878:[4]

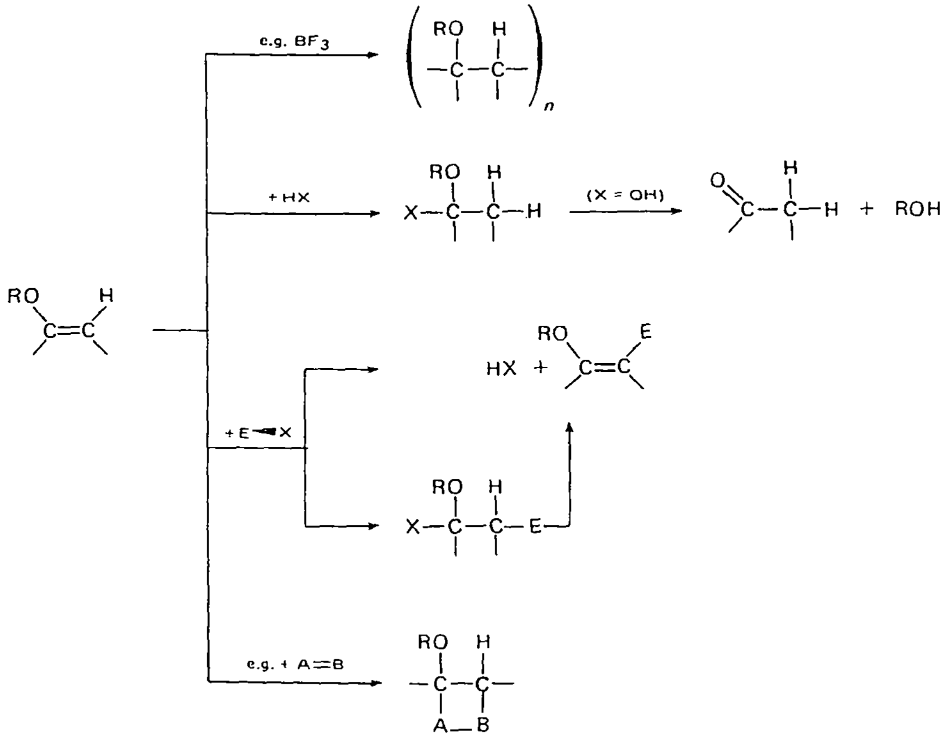
(1) Polymerization in the presence of Lewis acids.
(2) Reaction with protonic species HX, leading either to restitution of the parent carbonyl compound (hydrolysis) or to derivatives such as acetals (addition of ROH).
(3) Electrophilic attack by reagents $E \leftarrow X$; thus, addition and/or substitution products may be formed, the latter either directly via a σ-complex mechanism or in the course of an addition–elimination process.
(4) Cycloaddition, with the regiochemistry determined by the polarization of the enol ether π-system.

With the exception of truly concerted cycloadditions, the initial step in each case is the attack of an electrophile (Lewis acid, H^+, E^+) at the β-carbon of the enol ethers. Their chemistry is thus characterized by a close analogy to the chemistry of enamines which in the past 25 years have gained increasing preparative importance[5,6]. In both classes of compounds, excess π-electron density facilitates an electrophilic attack at the β-carbon, the higher relative nucleophilic potential of the enamines being due to the greater weight of the ammonium as compared with the oxonium resonance structure, **3b** vs. **4b**. This higher reactivity, i.e. the better

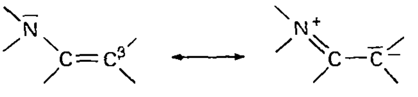
TABLE 1. Established *alkyl alkenyl ether* designation and systematic name for some of the more common enol ethers

Common name	Formula	Systematic nomenclature
Methyl vinyl ether	$CH_3-O-CH=CH_2$	Methoxyethene
Ethyl vinyl ether	$C_2H_5-O-CH=CH_2$	Ethoxyethene
Propyl vinyl ether	$C_3H_7-O-CH=CH_2$	1-(Ethenyloxy)propane
Isopropyl vinyl ether	$(CH_3)_2CH-O-CH=CH_2$	2-(Ethenyloxy)propane
Butyl vinyl ether	$C_4H_9-O-CH=CH_2$	1-(Ethenyloxy)butane
Isobutyl vinyl ether	$(CH_3)_2CHCH_2-O-CH=CH_2$	1-(Ethenyloxy)-2-methylpropane
t-Butyl vinyl ether	$(CH_3)_3C-O-CH=CH_2$	2-(Ethenyloxy)-2-methylpropane
Benzyl vinyl ether	$C_6H_5CH_2-O-CH=CH_2$	[(Ethenyloxy)methyl] benzene
Divinyl ether	$H_2C=CH-O-CH=CH_2$	1,1'-Oxybisethene
Propenyl ethyl ether	$C_2H_5-O-CH=CHCH_3$	1-Ethoxy-1-propene (E/Z)[a]
Propenyl isopropyl ether	$(CH_3)_2CH-O-CH=CHCH_3$	1-(1-Methylethoxy)-1-propene (E/Z)[a]
Isopropenyl ethyl ether	$C_2H_5-O-C(CH_3)=CH_2$	2-Ethoxy-1-propene (*E*/*Z*)[a]
Butenyl ethyl ether	$C_2H_5-O-CH=CHC_2H_5$	1-Ethoxy-1-butene (*E*/*Z*)[a]
Isobutenyl ethyl ether	$C_2H_5-O-CH=C(CH_3)_2$	1–Ethoxy-2-methyl-1-propene (*E*/*Z*)[a]

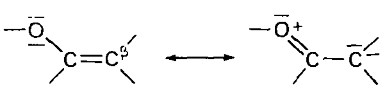
[a] The *E*/*Z* designation replaces the usual *cis*/*trans* nomenclature.



SCHEME 1.



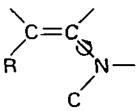
(3a) (3b)



(4a) (4b)

availability of the highest occupied MO for an electrophile, is tantamount, though, to a much lower oxidation potential. Since most electrophiles are at the same time oxidants, enamines are far more susceptible to radical side-reactions, e.g. in halogenation, than enol ethers. Actually, both classes of functional derivatives of carbonyl compounds complement each other rather well. *C*-Acylation with phosgene, oxalylchloride, or sulphonyl isocyanates, for instance, proceeds smoothly with enol ethers, while with enamines stable *N*-acyl products are formed which, as highly deactivated olefins, no longer undergo β-C reaction. On the other hand, it is sometimes rather difficult to find reagents with sufficient electrophilic potential to react with the enol ethers without at the same time inducing cationic polymerization (Friedel–Crafts-type activation is of course self-prohibitive).

In derivatizing the parent carbonyl compound, one is free as a rule to choose the ethereal component; the influence of a specific OR moiety on the reaction behaviour of the double bond is therefore an important aspect of enol ether chemistry. The dependence of enamine reactivity upon the nature of the nitrogen substituents is a well-established fact[7,8]. Towards an uncharged π-system in the ground state, the donor potential of the NR_2 groups decreases in the order, $N(C_2H_5)_2 \gtrsim$ pyrrolidino $> N(CH_3)_2 >$ piperidino $>$ morpholino[8,9]. This gradation is especially manifest from the C^{β} chemical shifts of the *N*-vinyl dialkylamines[9] (even though extreme care has to be taken if ground-state properties such as ^1H- or ^{13}C-NMR data are used for interpretation or prognostication of relative reactivities[8,9]). In *cis*-enamines, steric interaction forces the NR_2 group out of the olefinic plane, sacrificing $N(2p_z)/C{=}C(\pi)$ overlap (5); in *Z*-1-dialkylamino-1-propenes, the charge transfer from the amino moiety to the π-system is thus reduced to half its value in the corresponding vinyl- and *trans*-propenyl-amines[9]. For *cis* enol ethers, 180° rotation about the C^1–X bond relieves the steric strain and at the same time restores optimum C^1—O overlap conditions (6). This double rotational minimum for highest resonance interaction is one of the most significant features of enol ethers.



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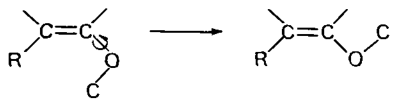
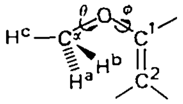


s-cis (6) *s-trans*

II. PHYSICAL PROPERTIES

A. Conformation

Methyl vinyl ether (7, Scheme 2) has been shown by infrared[10] and microwave[11] spectroscopy as well as by electron diffraction[12] to be most stable in a *cisoid* (*syn*, *s-cis*) form, with a planar heavy atom skeleton C=C—O—C. However, there is unequivocal evidence for the presence of a second conformer[10,12]; from the temperature dependence of the relative intensity of distinctive IR bands, it was shown to be less stable by 4.8 kJ mol^{-1} in the gas phase[10]. This second conformer was suggested to be a *gauche* form with a nonplanar skeleton[10], a result seemingly confirmed by electron diffraction (torsional angle $\phi = 80$–$110°$)[12]. When, however,



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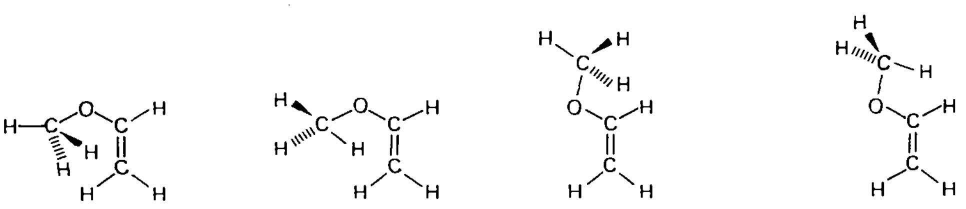


cisoid-staggered (CS) $\phi = 0°$, $\theta = 60°$

cisoid-eclipsed (CE) $\phi = 0°$, $\theta = 0°$

transoid-staggered (TS) $\phi = 180°$, $\theta = 60°$

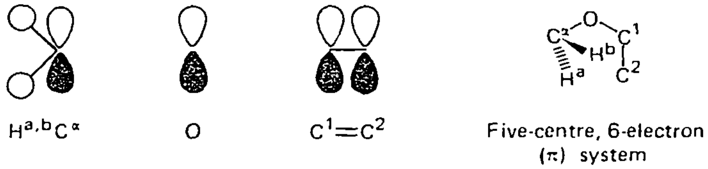
transoid-eclipsed (TE) $\phi = 180°$, $\theta = 0°$

SCHEME 2.

ab initio calculations indicated the second conformer to be the planar *s-trans* form[13], the electron diffraction data were reevaluated[14] by including additional spectroscopic information. On this basis, a torsional angle $\phi \geqslant 150°$ was derived for the minor conformer.

In a detailed *ab initio* calculation of methyl vinyl ether by Epiotis and coworkers[15], the relative orientation of the methyl rotor (θ, see 7) was also taken into account. Once again, on both the STO-3G and the 4-31G level (minimal and extended basis set), the *cisoid* conformation (CS) constitutes the minimum potential for rotation of the vinyl relative to the CH_3O moiety. A second minimum is obtained for $\phi = 180°$ (TS), 4.2 (STO-3G) or 10.5 kJ mol^{-1} (4-31G) higher than that for the CS orientation. The barrier of rotation (CS → TS) is calculated at about 20 kJ mol^{-1}, with a torsional angle $\phi \sim 70°$ in the transition state. The activation energy for the reverse process, TS → CS, has been determined at 15.5 kJ mol^{-1} by ultrasonic absorption[16]; since one has to add the 2.8 kJ mol^{-1} enthalpy difference in solution, the validity of the *ab initio* calculations appears experimentally well substantiated.

The authors[15] also present a descriptive rationale for understanding the conformational preference of methyl vinyl ether, utilizing Epiotis' concept of nonbonded attraction[17]. For this qualitative MO approach, a π-type CH_3-MO is included, incorporating the 1s AOs of the two methyl hydrogens $H^{a,b}$ in staggered position. (The procedure goes back to an idea of Hehre and Pople[18], and has, in a more general context, been pointed out also by Lister and Palmieri[19].) Since of course finite overlap between the $H^{a,b}$ (1s) and $C^2(2p_z)$ orbitals is practical only in the CS orientation, the positive (π) bond order between these two nonbonded centres can exert a stabilizing influence only in the *cisoid* conformation. As a qualitative estimate of interaction energies for both the CS and TS form shows, it is this nonbonded stabilization which accounts for the predominance of the sterically more crowded form. The orbital symmetry approach likewise predicts relative π-bond orders and π-overlap populations in good agreement with the *ab initio* calculations.



The nonbonded attraction argument, as outlined above for methyl vinyl ether, may also be directly applied to the problem of conformational control of the relative stabilities of *geometric* (*E,Z*) isomers[15]. In a fastidious study of the mercuric acetate-catalysed *cis/trans* equilibration of various alkenyl alkyl ethers, Okuyama and collaborators[20] have determined relative thermodynamic stabilities for two homologous series of enol ether *E/Z* pairs (Table 2). In the case of the propenyl ethers (Nos. 1–5, Table 2), when R^2 is a bulky group (isopropyl or *t*-butyl), it is the *Z*-isomer which surprisingly proves to be more stable; for the primary alkyl substituents [$R^2 = CH_3$, C_2H_5, $CH_2CH(CH_3)_2$], on the other hand, the expected order holds ($E > Z$).

For an $H^{\alpha}_{a,b}(1s)$—$C^2(2p_z)$ attractive nonbonded interaction – which provides the additional stabilization for the *cisoid* conformer of methoxyethene – to be operative in other enol ethers also, two α-hydrogen atoms in a *cisoid* staggered position are clearly prerequisite (8). This structural condition can be met only in

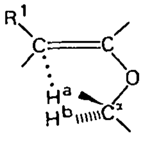
TABLE 2. Relative *E*/*Z* isomer stabilities for alkenyl alkyl ethers (alkoxyalkenes), R^1—CH=CH—OR^2[a] (equilibrium constants *K* and enthalpy and entropy changes for *cis* → *trans* isomerization, in bulk, mercuric acetate-catalysed[20])

No.	R^1	R^2	$K_{cis/trans}$ (25°C)	ΔH^0 (kJ mol^{-1})[b]	ΔS^0 (J K^{-1} mol^{-1})
1	CH_3	CH_3	0.968	3.82	6.2
2		C_2H_5	1.385	1.56	7.9
3		$CH_2CH(CH_3)_2$	1.431	1.80	9.0
4		$CH(CH_3)_2$	2.721	−2.38	0.4
5		$C(CH_3)_3$	3.378	−2.86	0.6
2	CH_3	C_2H_5	1.385	1.56	7.9
6	C_2H_5		0.874	2.37	6.8
7	C_5H_{11}		0.880	3.85	11.8
8	$CH_2CH(CH_3)_2$		0.901	2.74	8.3
9	$CH(CH_3)_2$		0.583	3.28	6.5
10	$C(CH_3)_3$		0.126	7.00	6.2
11	CH_2=CH	C_2H_5	0.450	3.87	6.2
12	C_6H_5		0.728	1.60	2.7
13	Cl		4.522	−2.77	3.3

[a] For thermodynamic data (*K*, ΔH^0, ΔS^0) of 2- and 3-alkoxy-2-alkenes and even higher substituted enol ethers, see the work of Taskinen and coworkers[21-25].

[b] Error limit in the last digit ±0.01–0.02.

E-methoxy- and -ethoxy-1-alkenes, but not in the corresponding isopropoxy and *t*-butoxy derivatives; in their *E*-form, these enol ethers are restricted to the *transoid* conformation, and thus lack nonbonded stabilization. For *Z*-propenyl ethers, *cisoid* orientation of the alkoxy group OR^2 is *a priori* impossible. However, via $C^3H_2^{a,b}$ (1s)—O(2p$_z$) interaction (**9**), a five centre, 6π-electron nonbonded stabilization,



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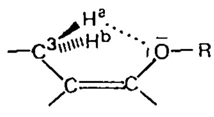
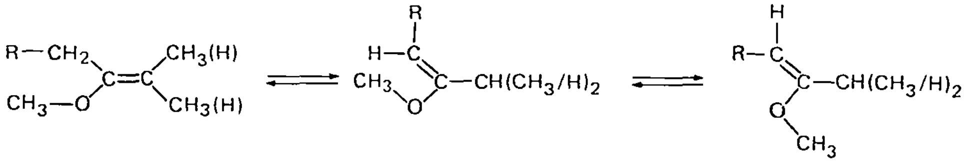


(9)

analogous to that for the *E*-isomers, may likewise be achieved for the *Z*-compounds. Though less effective than in **8**, this nonbonded attraction (**9**) quite obviously suffices to swing the balance in favour of the *Z*-isomer for enol ethers with *s*- and *t*-alkoxy groups (see Table 2).

Additional experimental substantiation for this striking argument[15] has come forth recently[21]. Taskinen and his group have in a series of papers reported on the thermodynamics of vinyl ethers, determined from isomerization equilibria such as **10** ⇄ **11** ⇄ **12** in an inert medium (hexane or cyclohexane, I_2-catalysed)[21]. From



(10) (11-*E*) (12-*Z*)

the respective thermodynamic data for the isomerization of various substituted enol ethers[22,23], Taskinen and Anttila have evaluated interaction energies, $S[R^1 \leftrightarrow R^2]$, between two *Z*-substituents across the C=C double bond of enol ethers (Table 3)[21]. As the negative $S[O \leftrightarrow R^2]$ values reveal, *cis* interaction between CH_3O and alkyl groups is indeed stabilizing. This stabilizing effect decreases sharply, though, from CH_3 to $CH(CH_3)_2$; for $[CH_3O \leftrightarrow C(CH_3)_3]$, *Z*-interaction is destabilizing already.

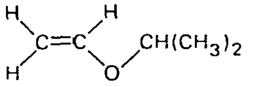
TABLE 3. Steric interaction energies for two *Z*-substituents R^1, R^2 across the C=C bond of enol ethers[21]

R^1	R^2	$S[R^1 \longleftrightarrow R^2]$ (kJ mol^{-1})
$C(CH_3)_3$	CH_3	18.2 ± 1.0
$CH(CH_3)_2$	C_6H_5	11 ± 2
	C_2H_5	6.1 ± 0.6
	$CH(CH_3)_2$	6.0 ± 0.6
OCH_3	$C(CH_3)_3$	2.9 ± 0.5
	$CH(CH_3)_2$	− 0.7 ± 0.5
	C_2H_5	− 1.5 ± 0.5
	C_6H_5	− 2.1 ± 0.6
	CH_3	− 2.9 ± 0.2

B. Spectral Properties

In photoelectron (PE) spectroscopy, unsaturated ethers are characterized by two low ionization potentials (IP), originated from π-type MOs[26]. The uppermost occupied orbital, as shown by the vibrational fine structure of the first PE band[26,27], is highly populated in the C=C bond, with partial charge transfer from the heteroatom[26,28] ($\pi_{C=C}$); the second MO corresponds mainly to the oxygen lone pair (n_O). By resonance interaction, π_{CC} and n_O, which *per se* have rather similar energies, are split 2–3 eV[29] (the effective mesomeric stabilization for, for example, 3,4-dihydropyran[30] is 1.2 eV). The separation between the first two ionization potentials $IP_{1,2}$ of enol ethers thus provides a sensitive probe for $C{=}C(\pi)/O(2p_z)$ collinearity[31].

For the *cisoid* conformers of *n*-alkoxyethenes and pyrans, $\Delta IP_{1,2}$ is generally 2.5–3.0 eV[26–31]. At elevated temperatures (510 K), bands of a second conformer emerge in the PE spectrum of methyl vinyl ether[31]; since $\Delta IP_{1,2}$ is even larger for this minor form, it likewise must have planar, i.e. *s-trans* conformation. Large ΔIP values argue a highly resonance-stabilized conformation also for the dominant form of isopropyl vinyl ether and of 2-methoxy-2-butene (**14**); for sterical reasons, this once again must be the *s-trans* orientation. The lesser conformer of **13** and **14**, observed at 510 K, is characterized by a $\Delta IP_{1,2} < 0.5$ eV[31], clearly indicative of *gauche* orientation.



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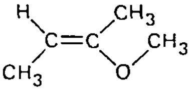
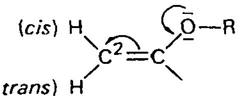


(14)

Even though conformational isomerism of vinyl ethers was first discovered from vibrational evidence[32,33], IR spectroscopy has proven a rather fickle tool for more detailed structural elucidation. Trofimov and collaborators[34] have ruled out a planar, resonance-stabilized conformation for alkoxyethenes with bulkier OR groups from the analysis of two bands each in the $\nu_{C=C}$, $\nu_{C=O}$ and $\omega_{=CH_2}$ region. They have completely neglected, however, the possibility of *two* planar conformations (CS, TS), considering only a 'planar' and 'nonplanar' form (without C=C/O resonance). In fact, a closer inspection of their published vibrational data reveals that the critical IR absorptions show coalescence rather than true alternate behaviour with increasing bulkiness of OR. For the sterically crowded *Z*-propenyl ethers, IR spectra clearly indicate the presence of only one, probably *gauche*, conformer[35].

In a recent extensive vibrational study of *n*-alkyl vinyl ethers in the gaseous, liquid and solid state[36], the enthalpy differences between major (*cisoid*) and minor conformers were determined from relative Raman intensities in good agreement with the results cited above[10,12,31]. However, the band assignment in this work[36] relies mainly on the – meanwhile revised[14] – electron diffraction results ($\phi = 80–110°$)[12]. Furthermore, a frequency decrease from 586 to 504 cm^{-1} is calculated for the C=C–O bending mode between the *cisoid* and *transoid* forms ($\phi = 0°/180°$); since the actual absorption comes at 526 cm^{-1}, the second conformer is definitely assigned the *skew* orientation ($\phi \sim 120°$). Owen and co-workers[37], in a painstaking comparative analysis of *E*/*Z*-methyl and -ethyl propenyl ether, likewise found evidence for nonplanarity; using mainly the observed band contours, they favour but slight deviation from the (planar) *s-trans* form. Ford, Katritzky and Topsom[38] also interpret their IR data in terms of a more or less coplanar second conformer for the *n*-alkyl vinyl ethers.

Both ^{13}C- and ^{1}H-NMR respond with a large upfield shift of C-2 and the β-vinyl protons to the increased C-2 π-charge density in the vinyl ethers (15), but detailed



(15)

analysis once more presents a rather confusing picture. In the first ^{1}H-NMR investigations on vinyl ethers[39,40], the chemical shift difference between *cis* and *trans* C-2 protons (15), which depends strongly on the nature of the alkoxy group, was taken as indicative of the relative contribution of the oxonium resonance structure[40]. In fact, however, only the *cis* proton moves downfield, from δ 4.23 (OCH_3) to 4.76 p.p.m. [$OC(CH)_3)_3$], while $\delta_{H\text{-}trans}$ remains largely unaffected (the same behaviour was found for vinyl amines[9,41]). Actually, the authors[40] were interpreting the (anisotropic) shift differences[8] between the *s-cis* and *s-trans* form and not the graduation in resonance interaction: variations in π-charge density should affect both protons identically. We ourselves found[42] that the α-OR protons (OCH_2—, OCH_3) of propenyl and butenyl methyl and ethyl ether appear consistently 0.1 p.p.m. better shielded in the *trans*- than in the respective *cis*-ethers. In the CS conformation[15] (7), the two *cisoid* α-protons ($H^{a,b}$) come to lie well within the shielding region of the C=C anisotropy field[42]; the identical *E*/*Z* shift difference for methyl and ethyl ethers are a good argument for both *trans* compounds adopting the same (CS) conformation.

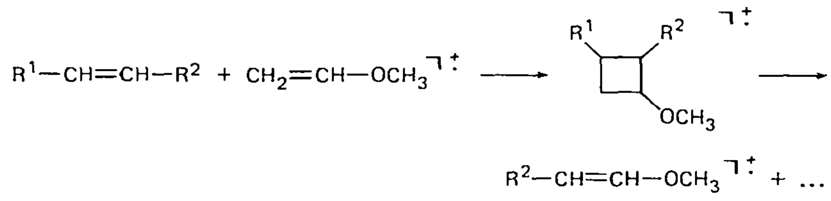
The groups of Hatada[43] and of Trofimov[44] also report a linear correlation between δ(C-2) and Taft's E_s constants for vinyl ethers with various OR groups. Their conclusion that with increasing bulkiness of R the *gauche* conformer becomes more and more favoured over the *s-cis* and *s-trans* forms is not valid, though, as a downfield shift of comparable magnitude is found for the structurally analogous alkenes[45] (with the ethereal O replaced by CH_2). Rojas and Crandall[46] have systematically investigated a series of alkenyl methyl ethers by ^{13}C-NMR: they report both the C-2 and the OCH_3 resonances at consistently higher field for the *trans* compounds, indicating the well-known *cisoid* γ-interaction [$C^2 \leftrightarrow OCH_3$] (Table 4). The pronounced downfield shift of C-2 in the *cis* compounds is probably due largely to the spatial interaction [$O \leftrightarrow C^3$] and not to steric inhibition of resonance; it is practically independent of the size of both alkyl and alkoxy groups[46]. In the propenyl *amine* series, on the other hand, where sterical hindrance indeed causes torsion of the NR_2 group[41], thus effectively reducing N(2p$_z$)/C=C resonance, we have found large downfield shifts for C-2 between *trans*- and *cis*-enamine (e.g. 18 p.p.m. between *E*- and *Z*-1-diethylamino-1-propene)[9].

TABLE 4.

		δ(p.p.m.)			
		cis	*trans*	Δδ	Ref.
CH_3—C^2H=CH—OCH_3	C-2	100.2	96.0	4.2	46
	OCH_3	58.5	54.9	3.6	
n-C_4H_9—C^2H=CH—OCH_3	C-2	106.6	101.8	4.8	46
	OCH_3	58.4	54.6	3.8	
C_2H_5—C^2H=CH—OC_2H_5				4.0	41

Steiger and coworkers[47] have calculated $^{1}H/^{1}H$ and $^{1}H/^{13}C$ coupling constants for vinyl compounds, and discussed the CNDO/2-derived values in terms of configuration and conformation about the double bond.

The fragmentation of alkyl vinyl ethers in electron impact mass spectrometry (EI-MS) is triggered by H-migration[48]; it proceeds by multiple H-transfer, via 2-methyl-substituted cyclic ether cations[48,49], the most prominent fragment being ionized vinyl alcohol, $CH_2{=}CH{-}OH]^{+\cdot}$ (m/e 44)[48,50]. In ion cyclotron MS, unsaturated compounds undergo [2 + 2]cycloaddition with the molecular ion of methyl vinyl ether[51]. The cycloadducts are then cleaved orthogonally to the original cycloaddition orientation (equation 2), with the major radical cation **16** indicating the position of the double bond in the substrate.



(2)

(16)

For a series of alkyl and aryl vinyl ethers, dipole moments were correlated with electronic and steric substituent constants[52], and also with relative basicities[53] (determined from ν_{O-H} shifts due to enol ether/phenol hydrogen bonding). From the temperature dependence of the dipole moment of methyl vinyl ether, an attempt was made to estimate μ for the different ethoxyethene conformations[54].

C. Summary: Conformation and Reactivity

The evidence of the reported physical investigations, probing for the molecular ground state of the enol ethers, may be summed up as follows:

> For *trans*(*E*)-alkenyl ethers with primary alkoxy substituents, the *cisoid* conformation is always predominant; the second conformer of methyl vinyl ether – at least in the gas state – is either the *s-trans* form or a conformation with ϕ close to 180°.
>
> The corresponding *cis*(*Z*)-alkenyl ethers, as well as vinyl and *E*-alkenyl ethers with bulkier OR groups, adopt the *s-trans* conformation; here, the less stable conformer has *gauche* orientation.
>
> For sterically highly hindered enol ethers (with bulky substitution in geminal and/or *Z*-position at C-2), co-planar orientation is no longer feasible.

However, the electronic stabilization by $O(2p_z)/C{=}C(\pi)$ resonance in the neutral molecule is limited to interaction with unfilled antibonding MOs. Only in the more or less charged transition state of an electrophilic attack on enol ethers or of cycloaddition reactions, the full mesomeric potential of the $+M$-substituents (OR or NR_2) is challenged, and resonance stabilization may easily overcome steric barriers which are prohibitive in the ground state.

In contrast to the *prima facie* controversial interpretation of C=C/OR interaction in the ground state, the evidence on how the nature of the alkoxy group influences the *relative reactivity* of the enol ethers is unequivocal. For the hydrolysis, in charge-transfer complex spectra, towards electrophiles, and in cycloadditions, the inductive hierarchy is strictly observed: $OC(CH_3)_3 > OCH(CH_3)_2 >$

$OC_2H_5 > OCH_3$[55]. The reactivity of alkoxyethene monomers in cationic polymerization likewise follows this order, correlating with Taft's σ_I- or σ^*-constants[56,57].

III. PREPARATION

The various synthetic routes to enol ethers have been comprehensively summarized in a new volume of Houben–Weyl[1,2]. In the approved manner of this handbook, both scope and limitations are outlined for each procedure, and full experimental details given for one exemplary case. We shall therefore confine ourselves to a brief sketch of the most important synthetic pathways, emphasizing mainly recent developments.

The *vinylation of alcohols* by acetylene (equation 3) can be achieved under alkali catalysis (Favorskii[58] and Reppe[59]). For various substituted phenols, Zn, Cd

$$H{-}C{\equiv}C{-}H + ROH \xrightarrow[180\text{–}200^{\circ}C/20\text{–}50\ \text{bar}]{KOH} RO{-}CH{=}CH_2 \qquad (3)$$

and Hg(II) acetate and like catalysts have also been employed successfully[60]. Substantially lower temperatures are required in the case of activated alcohols[61]. With methyl- and *t*-butyl-acetylene, nucleophilic addition of aliphatic alcohols ROH $[R = CH_3 \ldots C(CH_3)_3]$ usually affords α-substituted ethenyl ethers, $RO{-}\overset{|}{C}{=}CH_2$[62]; in the case of severe steric crowding, however, *cis*-propenyl ethers are obtained. An alternative, convenient laboratory procedure starts from the diphosphonium salt **17**. Alcoholysis of one of the Ph_3P groups yields the intermediate **18** from which the vinyl ether is obtained by alkaline hydrolysis (equation 4)[63]. By using $NaOD/D_2O$ in the last step, β,β-dideuterated ethenyl ethers may be prepared.

$$\underset{(17)}{[Ph_3P^+{-}CH{=}CH{-}^+PPh_3]\ 2\,Br^-} \xrightarrow[NEt_3]{ROH} \underset{(18)}{[RO{-}CH{=}CH{-}^+PPh_3]\ Br^-} \xrightarrow[H_2O]{NaOH} RO{-}CH{=}CH_2 \qquad (4)$$

Transvinylation (equation 5) is catalysed by Hg(II) salts of weak acids; the process is reversible[64]. Therefore, if the donating enol ether does not boil higher than the alcohol to be vinylated, or if **19** cannot be distilled off, ethyl vinyl ether

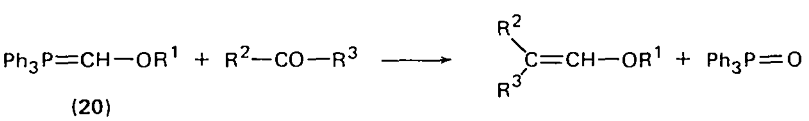
$$R^1O{-}CH{=}CH_2 + R^2OH \xrightleftharpoons{Hg(II)} R^1OH + \underset{(19)}{R^2O{-}CH{=}CH_2} \qquad (5)$$

has to be used in large excess, and the catalyst destroyed before work-up. Vinyl interchange under Pd(II) catalysis proceeds stereospecifically[65], with inversion of the configuration about the C=C double bond; thus, from *E*-propenyl ethyl ether and propanol, *Z*-propenyl propyl ether is formed. The drawback of the method – acetal formation above −25°C – has been overcome with special bidentate Pd(II) complexes[66]. If optically active alcohols are converted to vinyl ethers by Hg(II)-catalysed transvinylation, and then recovered by acid hydrolysis (see below), their optical rotation is retained unimpaired[67] – unequivocal evidence that the vinylic (and not the alkylic) C—O bond is broken in vinyl interchange.

By far the most important laboratory synthesis for enol ethers is the elimination of alcohol from acetals[2] (acid-catalysed: $KHSO_4$, *p*-toluenesulphonic acid, $Ca_3(PO_4)_2$[68] etc.). For high preparative yields, careful separation of the alcohol formed is mandatory[69] since the overall sequence, $>C{=}O \rightleftarrows$ acetal/ketal $\rightleftarrows$ vinyl ether, is fully reversible, and the enol ether equilibrium concentration is only ~50 p.p.m.[70]. (For acetaldehyde and its mono- and di-chloro derivative, the thermodynamics of this sequence have been carefully studied by ^{14}C- and ^{3}H-labelling[71].) If one or more isomeric enol ethers can be formed, thermodynamic equilibration of the product mixture may be achieved by traces of acid or, specifically, with iodine[72]. Acetals of acid-labile substrates can be decomposed thermally; especially for steroids, a number of special modifications has been devised[2] (e.g. reaction with 2,2-dimethoxypropane, which is not supposed to proceed via transacetalization). By the method of acid-catalysed pyrolysis (~150°C/≤0.1 Torr)[73], several nitroalkyl vinyl ethers could be prepared in excellent yield[74].

If the acet(ket)alization is carried out with orthoformates[75], the acetals/ketals, especially of cyclanones[69], need not be isolated; with *Amberlyst-15*® and ethyl orthoformate, the procedure can be run in one step (0°C, N_2 atmosphere), the enol ethers being formed either directly, or by work-up distillation with a trace of *p*-toluenesulphonic acid[76]. The enols or enolate salts of 1,3-diketo compounds can be alkylated directly at one oxo function (in dipolar aprotic solvents, employing highly reactive alkylating agents with low S_N2 potential and *hard* leaving groups)[77].

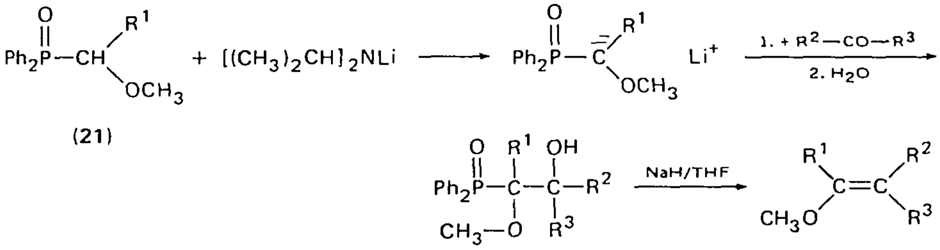
The *Horner–Wittig reaction* (equation 6) of triaryl(oxymethylidene)phosphoranes (**20**) with carbonyl compounds provides a versatile access to variously substituted enol ethers[78]; the yields are generally better for R = aryl than for the



$$Ph_3P{=}CH{-}OR^1 + R^2{-}CO{-}R^3 \longrightarrow (R^2)(R^3)C{=}CH{-}OR^1 + Ph_3P{=}O \qquad (6)$$

(20)

alkoxymethylidene derivatives. A modified procedure (equation 7)[79], using phosphine oxides (**21**), is far superior to the process via the ylides in scope, yield, use of stable crystalline reagents and ease of product separation. Since the two diastereomeric adducts **22** can be separated chromatographically, sterically pure *E*- and *Z*-isomers of the vinyl ethers may thus be conveniently prepared[79].

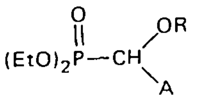


(7)

(21)

(22)

Symmetrical divinyl ethers have become easily available from the reaction of bis(phosphonium) salts, $Ph_3P^+{-}CH{=}CH{-}^+PPh_3$, alkoxides and carbonyl compounds[80]. From (alkoxymethane)phosphonic esters with –*M*-substituents in the α-position (**23**), various enol ethers with -acyl functions can be prepared[81]. The C^1–OR element of the enol ether need not be supplied from the phosphorane



$$(EtO)_2P(O){-}CH(OR)(A)$$

A = COOR, CONH$_2$, COR, Ph

(23)

component: examples for this 'reversal of polarity' are the reactions of triphenyl(alkylidene)phosphoranes with ethyl fluoroacetates[82] or with (alkyl/arylmethoxycarbene)pentacarbonyltungsten, $(OC)_5W{:}CROCH_3$[83].

Rearrangement of allyl alkyl ethers with alkoxides in DMSO leads, stereospecifically, to the corresponding *cis*-propenyl ethers[84]; the analogous procedure has been employed for the synthesis of *cis*-1-dialkylamino-1-propenes[85,41]. In carbohydrate chemistry, this reaction is utilized as the first step in cleaving off allylic protecting groups, followed by hydrolysis of the propenyl ethers[86,87]. Alkoxy-substituted arenes (benzenes, naphthalenes etc.) are transformed to cyclohexenyl enol ethers (1-alkoxy-1,4-cyclohexadienes) by either Birch or electrolytic reduction[2].

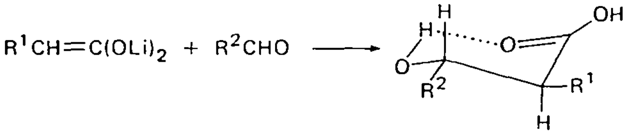
Further *special procedures* include: dehydrohalogenation of halo ethers and acetals[88,89]; decomposition of β'-alkoxy-tosylhydrazones (NaOR, 160°C), yielding, via β-alkoxycarbenes, preferentially *cis*-enol ethers[90,91]; reaction of methoxyallene with organocopper(I) compounds[92]; CuBr-catalysed reaction of Grignard compounds with α,β-unsaturated acetals (equation 8)[93]; β-alkylation of β-bromovinyl ethyl ether with RMgBr, in the presence of catalytic amounts of nickel phosphine complexes[94]. Dehydrative decarboxylation of *threo*-3-hydroxycarbonic acids (24), which are formed with high stereoselectivity[95] from dilithiated carbonic acids and ketones[96] or aldehydes, provides another stereoselective access to enol ethers; reaction of 24 with tosylchloride leads, via the β-lactone, to the *E*-form, while reaction with the azodicarboxylate/Ph$_3$P adduct leads to the *Z*-form[95].

$$R^1MgX + R^2CH{=}C(R^3){-}CH(OEt_2) \xrightarrow{CuBr} R^1R^2CH{-}CR^3{=}CH{-}OEt \qquad (8)$$

$R^1 = CH_3 \ldots C(CH_3)_3$

$R^2, R^3 = H, CH_3$

$X = Cl, Br$



(9)

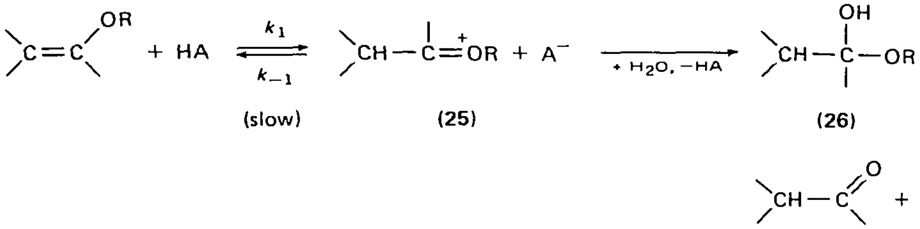
(24)

IV. ELECTROPHILIC REACTIONS

In this section, reactions of the enol ethers with electrophilic reagents, $E \rightarrow X$ or E^+X^-, shall be discussed, regardless of whether addition or substitution products are formed. Cycloadditions, on the other hand, will be dealt with separately.

A. Hydrolysis[97,98]

It is now well established that for the hydrolysis of simple vinyl ethers, proton transfer from the catalysing acid to the substrate is rate-determining (equation 10). Subsequently, the cationic intermediate (25) is rapidly hydrated to the hemiacetal/ketal (26) which in a last, fast step decomposes to the parent carbonyl compound and alcohol. Addition of H$_2$O to 25 has proven decidedly faster than retrodeprotonation in all cases investigated so far[99,100], with but one special exception[101].

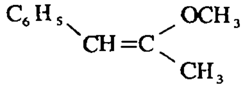
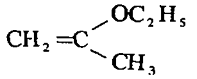
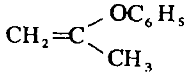
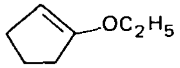
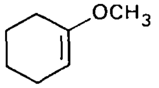
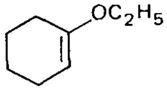
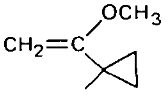


(10)

Even for the most reactive member, α-cyclopropylvinyl methyl ether (see Table 5), this mechanism still holds[100], although the margin for the limiting condition, $k_{-1}[A^-] < k_2[H_2O]$, cannot be very large; enamine protonation, for example, is rapidly reversible.

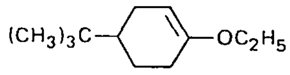
There is a linear relationship between the two sets of log *k* values for acid-catalysed hydrolysis of a series of vinyl ethers and of the corresponding formaldehyde acetals, $CH_2(OR)_2$[102]; this definitely excludes a nucleophilic function of

TABLE 5. Rates of H_3O^+-catalysed hydrolysis of various enol ethers in aqueous solution (25°C)

Enol ether	$k_{H_3O^+}$ (M^{-1} s^{-1})	Reference
$CH_2{=}CHOC_2H_5$	1.87	102[a]
$CH_2{=}CHOC_4H_9$-*n*	2.00	102[a]
$CH_2{=}CHOCH_2CH(CH_3)_2$	2.25	102[a]
$CH_2{=}CHOCH(CH_3)_2$	4.45	102[a]
$CH_2{=}CHOCH_2CH_2Cl$	0.165	102[a]
$CH_2{=}CHOC_2H_5$	2.13 ± 0.01	113[b]
 $C_6H_5CH{=}C(OCH_3)CH_3$	1.66 ± 0.02	108[b]
 $CH_2{=}C(OC_2H_5)CH_3$	(5.79 ± 0.11) 10^2	103[b]
$CH_2{=}CHOC_6H_5$	(3.28 ± 0.02)10^{-3}	103[b]
 $CH_2{=}C(OC_6H_5)CH_3$	5.98 ± 0.04	103[b]
	(4.54 ± 0.17)10^2	103[b]
	(4.23 ± 0.04)10^1	103[b]
	(8.00 ± 0.12)10^1	103[b]
	(7.49)10^3	100[b]

[a] Determined with HCl-catalysis in H_2O.
[b] Determined in aqueous $HClO_4$ solution.

the conjugate base of the catalyst, A^-, in the transition state of vinyl ether hydrolysis. The reaction is subject to general acid catalysis[102,103] for which H_3PO_4 has proven an unusually active catalyst[104]. A Brønsted factor, $\alpha = 0.63$, was determined[103] for the hydrolysis of cyclopentenyl and isopropenyl ethers with carboxylic acid catalysis. This can be interpreted in terms of a significant degree of proton transfer to the enol ether in the transition state[103]. A salt effect was not detected[105]. The unexpected small primary isotope effect, $k_H/k_D = 3.3 - 3.5$, for vinyl ether hydrolysis with HF/H_2O and DF/D_2O was attributed to strong hydrogenic bending vibrations in the transition state[99] (which are absent, of course, in the diatomic H/D donor).



(27)

All this evidence goes to show that the proton transfer is characterized by a rather late transition state, resembling the cationic species; the enol ether 27, for instance, incorporates D mainly in the axial position in deuteriolysis[106]. Consequently, the individual rates of hydrolysis (see Table 5) can be correlated with the stabilities of the intermediate carbenium ions (25), relative to that of the free vinyl ethers. (This is also important for understanding the mechanism of the reaction with electrophiles and of the stereospecific polymerization of enol ethers in homogeneous media[107].) The large rate increase upon α-alkyl substitution ($10^2 - 10^4$) thus becomes easily understandable. The slower hydrolysis of β-styryl ethers $C_6H_5{-}CH{=}C(CH_3){-}OR$ (equivalent to an increase in $\Delta G^{\neq}$ of ~12 kJ mol^{-1}) is attributed to additional (resonance) stabilization of the ground state[108]; β-alkyl substituents likewise retard the rate of hydrolysis. The higher reactivity of *cis*-1-alkenyl ethers, on the other hand, which generally are hydrolysed four times faster than the corresponding *trans* isomers[107] – irrespective of the relative *cis*/*trans* ground-state stability[109] – therefore cannot be due solely to their lesser thermodynamic stability[20]. Within the ethenyl ether series, $CH_2{=}CH{-}OR$, dependence of reactivity on the nature of OR follows the inductive order[110] [0.05 M HCl in acetone/water (80 : 20), 25°C]:

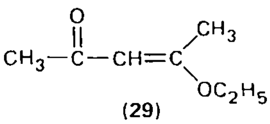
R	CH_3	C_2H_5	$CH_2CH(CH_3)_2$	$CH(CH_3)_2$	$C(CH_3)_3$	CH_2CH_2Cl
Relative rate of hydrolysis[110]	1.0	2.0	1.6	7.3	16.6	0.18

The relative rates are strongly dependent on medium polarity and the acid catalyst[110]; only two sets of vinyl ether hydrolysis data, each obtained for pure H_3O^+ catalysis under identical conditions, are therefore presented in Table 5.

Butadienyl ethers (28) are protonated exclusively at the terminal carbon, C-4[111]; for 29, hydrolysis proceeds via both the normal pathway (rate-limiting C-3 protonation) *and* protonation at the carbonyl group[112].

$C^4H_2{=}CH{-}CH{=}CH{-}OR$

(28)



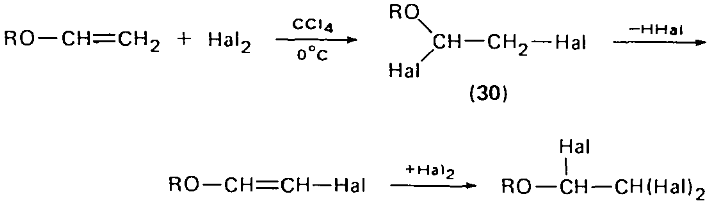
$CH_3{-}\overset{\overset{\large O}{\|}}{C}{-}CH{=}C(CH_3)(OC_2H_5)$

(29)

The reaction of vinyl ethers with protic agents other than H_2O[114] (alcohols, mercaptans, acids etc.) follows the same mechanistic course as hydrolysis, with rate-limiting H^+-transfer to the olefinic C-2[113]; true electrophilic addition is therefore always in the Markownikoff direction. Within structurally related series of X—H compounds, reactivities towards alkoxyalkenes have been correlated with a variety of σ-constants (see for example Reference 115).

B. Halogenation

The addition of Cl_2 and Br_2 to vinyl ethers has been studied extensively by Shostakovskii and coworkers[116]. The reaction is highly exothermic, often leading to substantial amounts of by-products; by HHal elimination, for instance, and subsequent addition of a second Hal_2 molecule, trihalo ethers are formed (equation 11)[117]. If carried out at −20°C in the dark, however, the reaction of

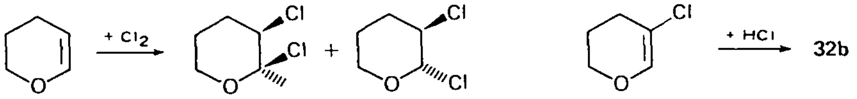


(30)

(11)

Cl_2, Br_2 and ICl even with the more reactive aliphatic enol ethers can be held at the stage of the primary addition compounds (30)[118]. Direct iodination gives only polymers[119]. Fluorination of enol ethers has gained importance in the steroid field; with $FClO_3$ in pyridine, fluorine can be introduced into steroids with excellent yields under mild conditions[120].

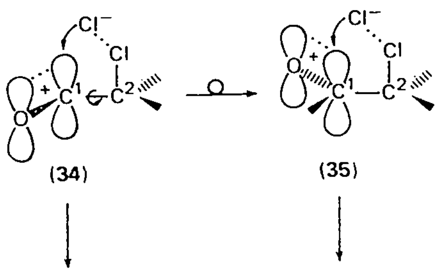
The stereochemistry of the reaction with electrophilic halogen is controlled by several factors. Addition of Cl_2 to the dihydropyran 31 in pentane gives stereoselectively the *cis*-dichloro derivative (80% 32a), while in CH_2Cl_2 the stereochemistry is inverted (66% 32b)[121]; this solvent dependence has been confirmed repeatedly[122]. (HCl addition to 33, on the other hand, is exclusively *syn*.)



(31) (32a) (32b) (33)

(12)

Primarily, a '*syn*' ion pair is supposed to be formed (34) which in nonpolar solvents rapidly collapses to the *cis*-dichloro product[121]. The *trans* reaction can be triggered in three different ways: (1) dissociation of the Cl^-, (2) attack of a protic solvent molecule at C-1 from the backside or (3), for acyclic substrates, rotation of the $RO^+{=}C^1$ moiety about the C^1—C^2 bond (34 → 35)[121]; this results in *trans* addition from the collapse of the '*anti*' Cl · · · Cl ion pair (35).



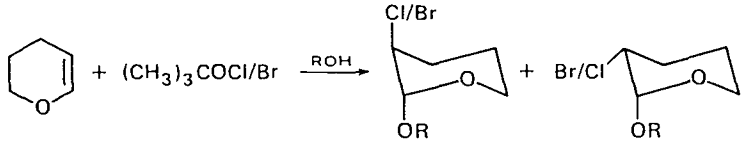
(34) (35)

(13)

cis-Dichloro product *trans*-Dichloro product

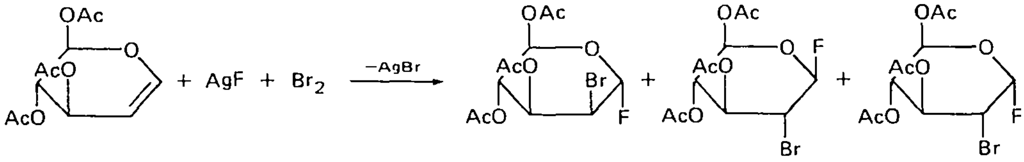
The percentage of *anti* addition increases in the order $Cl_2 < Br_2 < ICl$ and likewise from *p*-methoxy- to *p*-chlorophenyl enol ethers[118] (i.e. with decreasing availability of the ether oxygen lone pair); apparently, halonium stabilization competes more and more with the RO resonance interaction which is the decisive factor in chlorination[121]. This argument has been confirmed by kinetic investigations of iodination and bromination in water: they demonstrate that much less charge is localized at C-1 in the transition state of electrophilic I_2 attack than in protonation[123] (see above); this must be due to iodine participation. For the reaction with Br_2, such halonium stabilization is much less effective[124]. The bromination of acetone in methanol, by the way, proceeds almost exclusively via the enol ether present in the equilibrium, $CH_3{-}C(OH){=}CH_2 \rightleftarrows (CH_3)_2CO \rightleftarrows (CH_3)_2C(OR)_2 \rightleftarrows CH_3{-}C(OR){=}CH_2$[125].

With *N*-bromophthalimide in alcohol or carboxylic acids, cyclic and acyclic enol ethers are transformed into α-bromoacetals in excellent yield[126]; the reaction is definitely ionic and not radical. From the reaction in CCl_4, the addition product of Br^+ and phthalimide can be isolated (65%)[127]; *N*-chloro-, -bromo- and -iodosuccinimide have also been employed successfully[128]. With *t*-butyl hypochlorite in ROH (equation 14), *trans* addition predominates (85%)[129]; in benzyl alcohol or carboxylic acids, and likewise with hypobromite, the percentage of *anti* reaction is even higher. Chlorination of aliphatic enol ethers and dihydropyrans with iodosobenzenedichloride, $C_6H_5ICl_2$, is >95% *trans*[130]; it has been described as a radical chain reaction, with short chain-length.



(14)

Halogenation of intermediates with an enol ether partial structure has gained increasing importance in carbohydrate chemistry. Reaction of Cl_2 with D-glucal triacetate (36) in non-polar solvents gives exclusively *cis* and in polar medium predominantly *trans* addition[131]. 36 has also been bromofluorinated in good yield with AgF/Br_2 in CH_3CN (equation 15)[132]; although the reaction is mainly *trans* (37, 38), 20% *cis* product (39) is still formed. This addition likewise works with AgF/I_2 or with *N*-bromo(iodo) succinimide and HF[132].



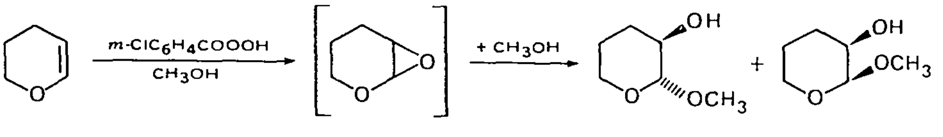
(36) (37) (38) (39)

(15)

If the halogenation of the enol ethers is not used solely for the specific introduction of an α-halogen into the parent carbonyl compound, the halo ethers are usually transformed further by HHal elimination and/or nucleophilic substitution. Among these follow-up reactions, a specific synthesis for mixed ketene acetals should be mentioned[133]: bromination of $EtO{-}CH{=}CH_2$ with Br_2 (in Et_2O at −30°C), followed by substitution of the α-Br with RO^-, and then by dehydrohalogenation, yields the mixed ketene acetal.

C. Reactions with Electrophilic O, S, N and P

Enol ethers are fairly stable against O_2 and react only with stronger oxidants (O_3, peracids etc.). The epoxides formed from peracids and enol ethers are usually hydrolysed immediately in the acidic reaction medium[134]. If the epoxidation is carried out in alcohol (equation 16), α-hydroxyacetals can be isolated in excellent yield, with the addition of ROH preferentially *trans*[135]. The procedure works equally well with 1-methoxycyclohexene, affording 1,1-dimethoxy-2-hydroxycyclohexane, and allows the facile synthesis of mixed α-hydroxyacetals if the enol ether bears an OR function different from that of the epoxidation medium[135]. With enol esters[136] and with some special enol ethers (equation 17)[137], the epoxides can be isolated.



(16)

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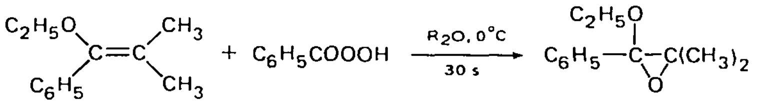
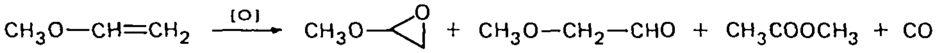


(17)

90%

With ground-state (^3P) oxygen atoms (generated by Hg-sensitized photodecomposition of nitrous oxide), methyl vinyl ether is transformed into the oxirane **40** with 45% yield[138] (total yield of oxygenation products 86%, equation 18). **40**



(18)

45% 26% 2% 13%

(40)

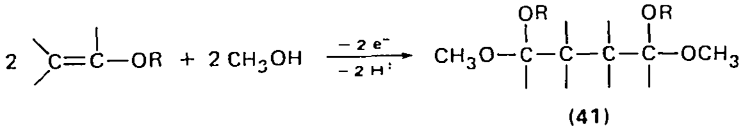
is stable in $CDCl_3$ solution at 25°C for several hours, but attempts at isolation or purification failed. With the exception of 2,3-dihydrofuran, 2-alkoxyoxiranes could be obtained from various enol ethers in 40% yield[138] (though not yet on a larger preparative scale).

The ozonization of enol ethers (equation 19) is of analytical value since it allows the definite cleavage of an α-C—C bond in the parent carbonyl compound[139]; from enol ethers of cyclic ketones, ω-formylcarboxylic acids thus become readily available[140].

$$R^2CH{=}CR^1{-}OR^3 \xrightarrow[2.\ H_2/Pd]{1.\ O_3} R^1COOR^3 + R^2CHO \tag{19}$$

Anodic oxidation of 1-alkenyl alkyl ethers[141,142] in methanol (equation 20) yields 50% 1,4-dialkoxy-1,4-dimethoxybutanes (**41**)[142] (acetals of 1,4-dicarbonyl compounds); analogous β,β'-dimerization of 1-alkoxycycloalkenes affords, after hydrolysis, 2,2'-bis(cycloalkanones) with 30–50% current yield[142].

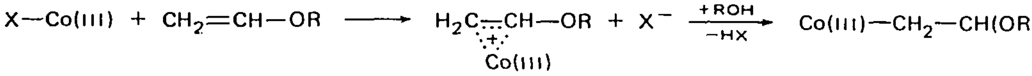
Two *O*-functions (e.g. $OCOCH_3$) are usually incorporated into enol ethers upon



$$2\ \rangle C{=}\overset{|}{C}{-}OR + 2\,CH_3OH \xrightarrow[-2\,H^+]{-2\,e^-} CH_3O{-}\overset{OR}{\underset{|}{C}}{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{\overset{|}{C}}{-}\overset{OR}{\underset{|}{C}}{-}OCH_3 \tag{20}$$

(41)

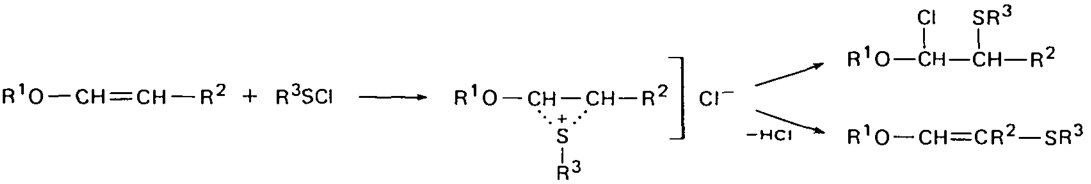
oxidation with Pb(IV)[143] or Tl(III) acetate[144], with benzoyl peroxide[145], and with HO• radicals[146]. Reaction of Co(III) derivatives (cobalamines, cobaloximes) with vinyl ethers gives, very probably via the π-bonded complexes **42**, the corresponding σ-bonded α-Co acetals (equation 21)[147].



$$\text{X—Co(III)} + \text{CH}_2\text{=CH—OR} \longrightarrow \text{H}_2\text{C}\overset{}{\underset{\text{Co(III)}}{\overset{+}{=}}}\text{CH—OR} + \text{X}^- \xrightarrow[-\text{HX}]{+\text{ROH}} \text{Co(III)—CH}_2\text{—CH(OR)}_2$$

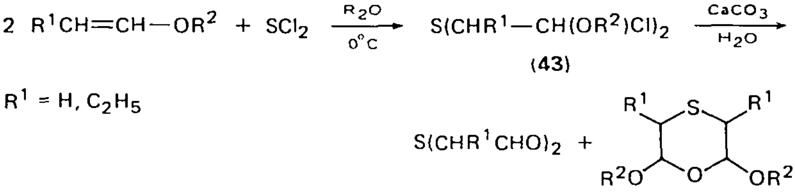
(42) (21)

Thiols RSH add to enol ethers at lower temperatures (e.g. −20°C in SO_2) to yield the respective mixed *O,S*-acetals[148]; reaction at elevated temperature with either azoisobutyronitrile[149,150] or UV irradiation[151], on the other hand, gives the anti-Markownikoff adducts (1-alkoxy-2-alkylthio-) in high yield. With sulphenyl chlorides, both addition and substitution products are formed[152–154] (equation 22), depending on the reaction conditions and the nature of the substituents. The addition is exclusively *trans*, with the RS moiety always at C-2, owing probably to the intermediacy of a thiirenium structure[154].



(22)

The 1 : 2 adducts of SCl_2 with vinyl ethers (**43**) are stable in solution but cannot be isolated[155]; hydrolytic work-up yields both the expected dialdehydes **44** and the oxathianes **45** in comparable amounts (equation 23). The primary addition products of enol ethers with dichlorodisulphane, S_2Cl_2, are even less stable; the dithianes can be isolated, though, after nucleophilic Cl/OR exchange[156] or alkaline hydrolysis[157].

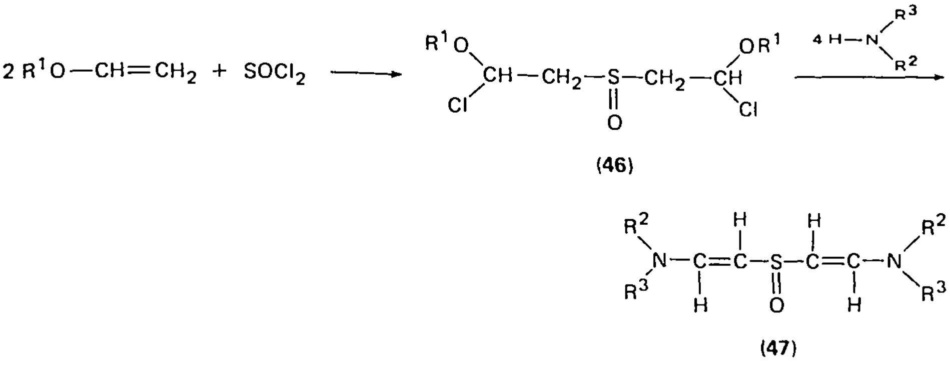


(23)

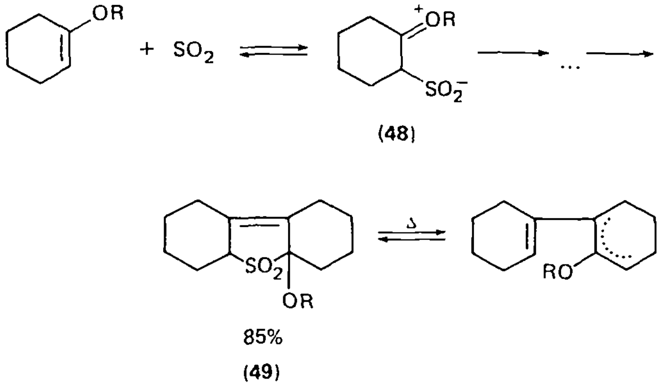
(44) (45)

Thionyl chloride, too, reacts with two molecules of ethenyl ethers (equation 24)[158]. The bis(β-alkoxy-β-chloroethyl)sulphoxides **46** can be transformed to the dienamines **47**; tertiary amines give double HCl elimination, partially accompanied by rearrangement[158]. Only one-sided 1:1-addition is observed with the higher 1-alkenyl ethers. 1-Alkoxycyclohexenes react with SO_2 (equation 25), reversibly forming a 1,3-dipole (**48**) not stabilized by conjugation[159]; **48** can also be reached directly from the acetal in SO_2. [2 + 3]Cycloaddition of **48** to another cyclohexenyl ether molecule, followed by ROH elimination, yields the tricyclic **49**[159]. β-Sulphonylation of vinyl ethers is also possible with the pyridine–SO_3 adduct[160].

Nitrosyl halides smoothly add to enol ethers with the expected regiochemistry ($ON^{\delta+}$—$Cl^{\delta-}$), but the (probably dimeric) α-halo-β-nitroso ethers so formed (e.g.

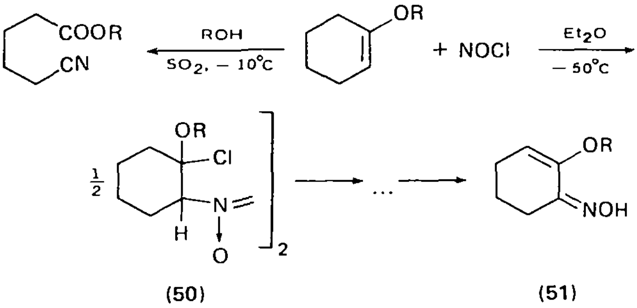


(24)



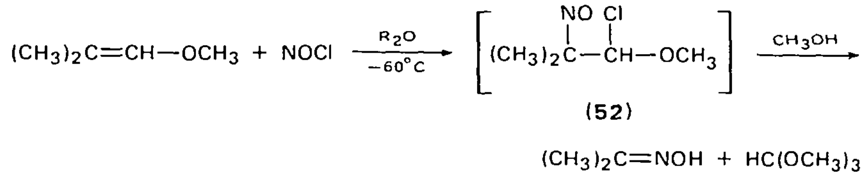
(25)

50) are very labile^{161}. Alcoholysis in basic medium yields the corresponding nitroso acetals which are generated directly from enol ethers and alkyl nitrites^{161}. Nitrosation in the presence of alcohol, or work-up without a HCl scavenger, affords oximes^{162}; thus, cyclohexenoneoximes (**51**) are obtained from 1-alkoxycyclohexenes (equation 26)^{162}. If the nitrosation leads to tertiary nitrosyl compounds



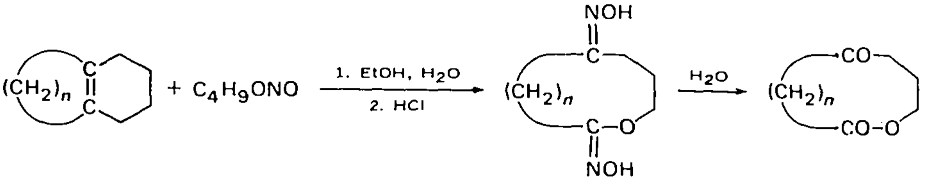
(26)

(52) where tautomerization to the oxime is impossible, the original enol ether C=C bond is broken upon alcoholysis (equation 27)^{163}. Under proper reaction conditions, '*nitrosolytic*' C—C cleavage can also be achieved for less substituted enol ethers (see equation 26)^{162}. This reaction has been put to elegant use in makrolide synthesis^{164}. Nitrosation of **53** in the presence of stoichiometric quantities of ROH and H_2O (equation 28) results in cleavage of the central C=C bond, yielding the dioximes **54** and, upon hydrolysis, the ketolactones **55**.



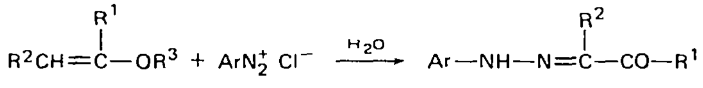
$$(CH_3)_2C{=}CH{-}OCH_3 + NOCl \xrightarrow[-60^\circ C]{R_2O} \left[(CH_3)_2\overset{NO}{\overset{|}{C}}{-}\overset{Cl}{\overset{|}{C}}H{-}OCH_3\right] \xrightarrow{CH_3OH} (CH_3)_2C{=}NOH + HC(OCH_3)_3 \qquad (27)$$

(52)



(53) (54) (55) (28)

Diazonium salts couple readily with α- and β-substituted vinyl ethers in the β-position (equation 29), but only the hydrolysed glyoxalhydrazones 56 can be



$$R^2CH{=}\overset{R^1}{\overset{|}{C}}{-}OR^3 + ArN_2^+\ Cl^- \xrightarrow{H_2O} Ar{-}NH{-}N{=}\overset{R^2}{\overset{|}{C}}{-}CO{-}R^1 \qquad (29)$$

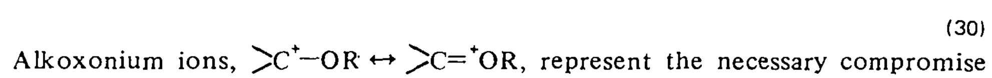
R^1, R^2 = H, alkyl (56)

isolated[165,166]. The analogous reaction of α-ethoxystyrene with azo esters gives – apart from Diels–Alder cycloaddition – the β-hydrazino-substituted styrene[167] (probably via a dipolar intermediate).

In the presence of, for example, azoisobutyronitrile, H—PO(OR)$_2$ and other P(III) derivatives are smoothly added to vinyl ethers (of course with anti-Markownikoff orientation)[168]; phosphine itself gives mono, bis- and tris-(β-alkoxyalkyl)phosphines[169]. With PCl_5 and tetrahalophosphoranes, β-*substitution* products are formed via an ionic mechanism[170].

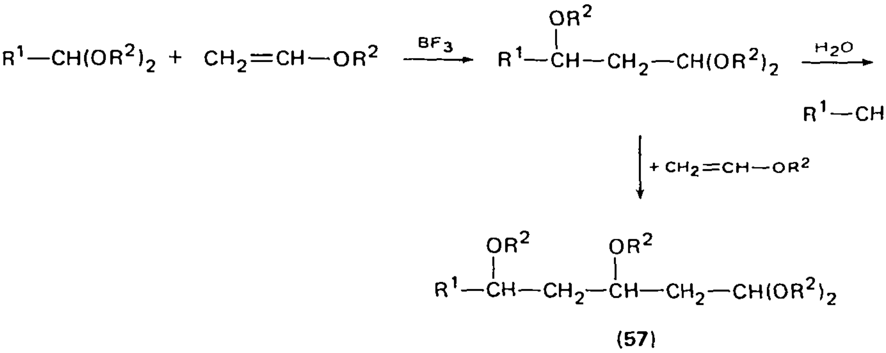
D. Reactions with Carbon Electrophiles

While β-alkylation of enamines is a facile process with a variety of alkylating agents RX[5,7,171], the nucleophilicity of the C-2 in enol ethers is not sufficient for uncatalysed reactions[172]. Activation of the alkylating agents with Friedel–Crafts catalysts as a rule is self-prohibitive with the polymerization-prone enol ethers. Vol'pin and collaborators[173] report the addition of tropylium bromide to alkenyl ethers which leads to cycloheptatrienyl acetaldehydes (equation 30); the reaction conditions have to be carefully adjusted since usually the action of tropylium salts results in polymerization of vinyl ethers[174].



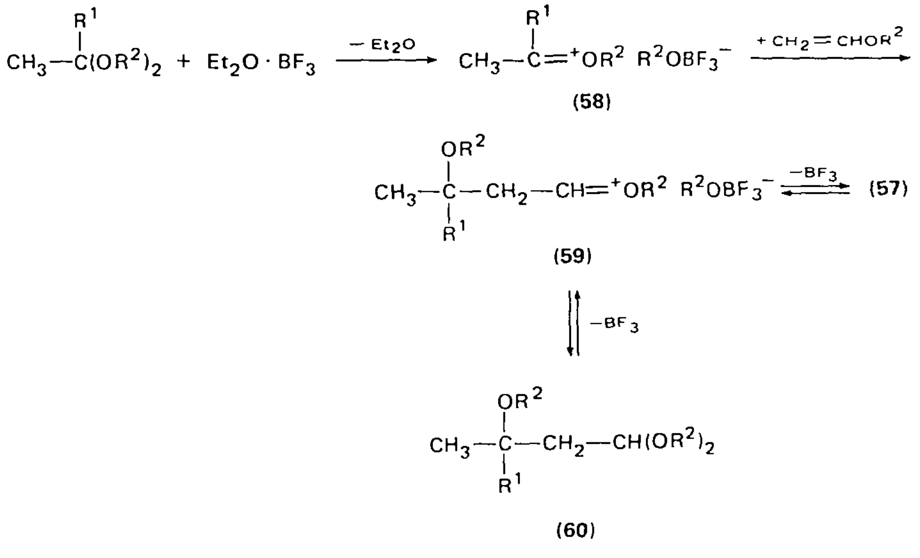
(30)

Alkoxonium ions, $>\!\overset{+}{C}{-}OR \leftrightarrow\ >\!C{=}\overset{+}{O}R$, represent the necessary compromise between sufficient activation of the electrophilic carbon centre and suppression of enol ether polymerization, and the polar C—C linkage of aldehydes or ketones and their derivatives with enol ethers has found widespread application[175,176]. The BF_3-catalysed reaction of enol ethers with acetals[177], for instance, constitutes a valuable alternative to the classic aldol condensation, the main preparative advantage lying in the unequivocal course of the reaction[178] since enol ether and acetal can each act only as electrophilic and nucleophilic (methylene and carbonyl) component, respectively[179]. Depending on the nature of the reactants and reaction conditions, either β-alkoxyacetals or α,β-unsaturated aldehydes are formed (equation 31); at the acetal stage, addition of a second vinyl ether molecule is possible.



(31)

Hoaglin and Hirsh have proposed a carbenium ion mechanism (equation 32) for the overall reaction[178], analogous to that for the acid-catalysed aldol reaction. The first step in this sequence is the dissociation of the primary $>O \rightarrow BF_3$ complexation product to the alkoxonium species **58** (probably in the form of an ion pair). Electrophilic attack of **58** upon a vinyl ether molecule leads to a new alkoxonium ion (**59**) which then either adds an alkoxy moiety, forming the β-alkoxyacetal **60**, or another $CH_2{=}CH{-}OR^2$ to the 1 : 2-adducts **57**. The partitioning between these two pathways is governed, of course, through the relative electrophilicity of **58** and **59**. Yet even with the least reactive saturated aliphatic acetals, the reaction can be held at the 1 : 1-addition stage (**60**) with at least 80% yield if a large (5:1 or

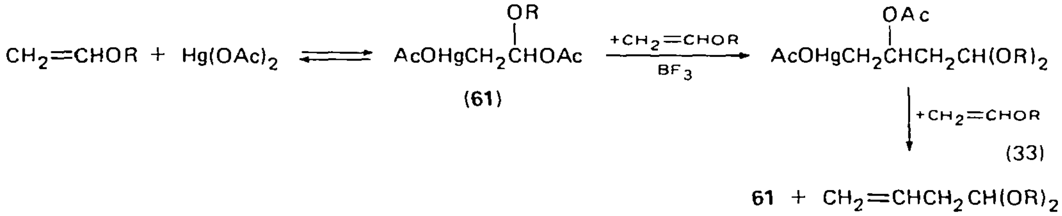


(32)

more) excess of acetal is used[178]. From ketals (R^1 = alkyl), on the other hand, practically no 1:1-product is obtained since in this case 59 is so much more reactive than 58.

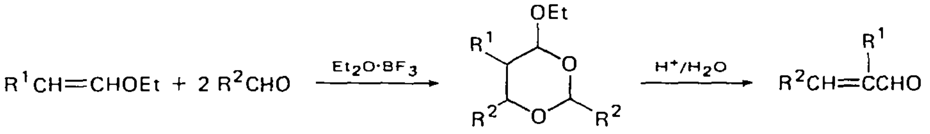
Mainly 1:1-products are formed even from the equimolar reaction of aromatic aldehyde acetals[180]; with α,β-unsaturated acetals, which show the highest reactivity towards enol ethers, the aspect is still more propitious. Because of its well-defined (1:1) stoichiometry and definite regiochemistry, the condensation of unsaturated aldehyde acetals with vinyl ethers could thus be successfully employed in the synthesis of polyene aldehydes[181] (with $ZnCl_2$ catalysis) and of carotinoids[182]. If 1-alkoxy-1,3-dienes are used as the enol ether component, the electrophilic alkoxonium centre of the acetal adds exclusively at C-4[183]. Alkoxydienes and 1-substituted enol ethers (ketone derivatives) which have a much higher polymerization tendency than the enol ethers of saturated aldehydes[180], can be coupled only with the more reactive (aromatic and unsaturated) acetals since the Lewis-acid catalysts, used in the acetal condensation, at the same time promote polymerization.

Dioxolanes and other cyclic acetals have also been employed in enol ether condensations[184]; with the much less reactive thioacetals, the reaction is limited to phenyl vinyl and divinyl ethers[185] which do not polymerize so easily. The enhanced electrophilicity of the carbenium ions generated from α-halo ethers[186] and Schiff bases in HOAc[187], on the other hand, makes for especially smooth addition to enol ethers. Mechanistically, the dimerization of vinyl ethers with BF_3 in the presence of Hg(II) salts (equation 33)[188] must also be classified among the condensation reactions with activated acetals.



$$CH_2{=}CHOR + Hg(OAc)_2 \rightleftharpoons \underset{(61)}{AcOHgCH_2\overset{OR}{\overset{|}{C}}HOAc} \xrightarrow[BF_3]{+CH_2=CHOR} AcOHgCH_2\overset{OAc}{\overset{|}{C}}HCH_2CH(OR)_2 \xrightarrow{+CH_2=CHOR} 61 + CH_2{=}CHCH_2CH(OR)_2 \qquad (33)$$

Hoaglin and Hirsh also report the BF_3-catalysed *direct* condensation of aliphatic aldehydes with enol ethers[189] leading, via 1,3-dioxanes, to α,β-unsaturated aldehydes (equation 34). Their findings have been confirmed by a Japanese group[190];

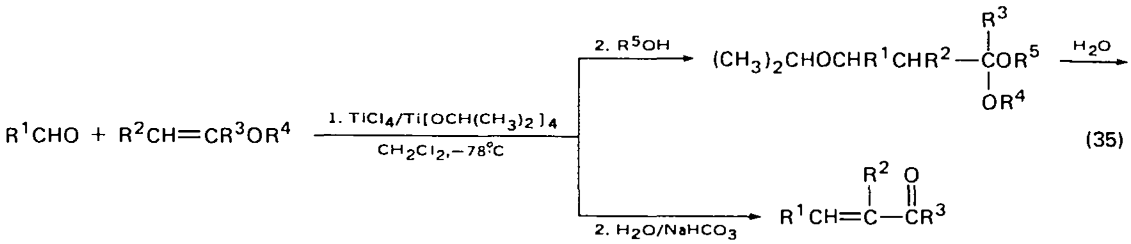


(34)

(62)

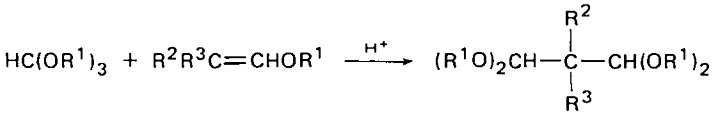
if the catalyst is neutralized before hydrolysis, the dioxanes 62 can be isolated and cleaved independently. These authors[190] have also extended the vinyl ether condensation to acetone and to methyl ethyl ketone. The rather poor yields are due to the lesser carbonyl activity of the ketones and the concomitant increase in side-reactions; among these, *trans*-enoletherification between vinyl ether and ketone is most important[191] (thus, the regiospecificity of the reaction is lost). But even if ketones are subjected to BF_3-catalysed condensation with their own enol ethers (to avoid the product mixture due to *trans*-enoletherification), the yields of definite 1:1-products are unsatisfactory (20–50%)[192].

Excellent yields are reported for cross aldol condensation via enol ethers with titanium catalysts (equation 35)[193]; essential for the success of the reaction is that both components are present in equimolar quantities, and that $TiCl_4$ *and* $Ti(OR)_4$ are applied together.

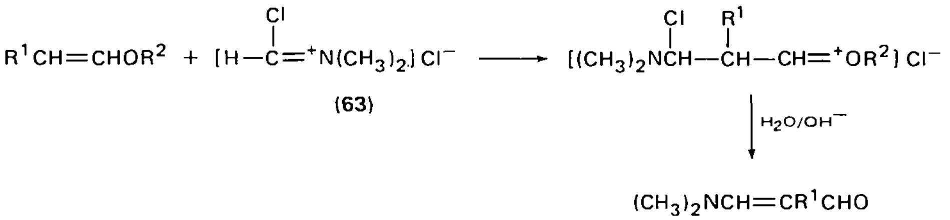


$$R^1CHO + R^2CH{=}CR^3OR^4 \xrightarrow[CH_2Cl_2,\,-78^\circ C]{1.\ TiCl_4/Ti[OCH(CH_3)_2]_4} \begin{cases} \xrightarrow{2.\ R^5OH} (CH_3)_2CHOCHR^1CHR^2{-}\overset{\displaystyle R^3}{\underset{\displaystyle OR^4}{C}}OR^5 \xrightarrow{H_2O} \\ \xrightarrow[2.\ H_2O/NaHCO_3]{} R^1CH{=}\overset{\displaystyle R^2}{C}{-}\overset{\displaystyle O}{\overset{\|}{C}}R^3 \end{cases} \tag{35}$$

The *formylation* of enol ethers with orthoformates[176,194] (equation 36) follows the same mechanistic course as the acetal condensations; the malonaldehyde derivatives thus formed constitute valuable building blocks for heterocyclic syntheses[195]. Among the Vilsmeier–Haack reagents, **63** (derived from DMF and phosgene) has the least Lewis-acid properties, and so has been employed most successfully for the formylation of vinyl ethers[196,197] (equation 37).



$$HC(OR^1)_3 + R^2R^3C{=}CHOR^1 \xrightarrow{H^+} (R^1O)_2CH{-}\overset{\displaystyle R^2}{\underset{\displaystyle R^3}{C}}{-}CH(OR^1)_2 \tag{36}$$

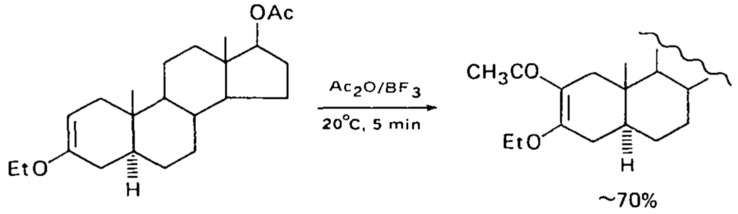


$$R^1CH{=}CHOR^2 + [H{-}\overset{\displaystyle Cl}{C}{=}{}^+N(CH_3)_2]Cl^- \longrightarrow [(CH_3)_2N\overset{\displaystyle Cl}{C}H{-}\overset{\displaystyle R^1}{C}H{-}CH{=}{}^+OR^2]Cl^- \xrightarrow{H_2O/OH^-} (CH_3)_2NCH{=}CR^1CHO \tag{37}$$

(63)

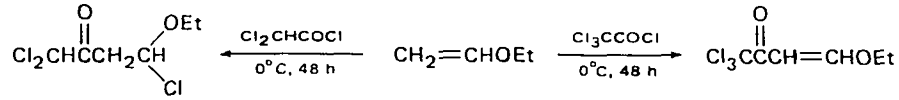
The decreasing reactivity of the higher ortho esters bars enol ether acylation beyond the orthoacetate stage, and has not been used much even there[198]. Tetramethoxymethane (methyl orthocarbonate), on the other hand, can be added smoothly to vinyl ethers under $SnCl_4$ catalysis[199].

The *acylation* of vinyl ethers requires strong activation of the acylating agents. Employment of Friedel–Crafts catalysts is naturally limited to enol ethers with negligible polymerization tendency, a prerequisite met fully by steroid enol ethers (equation 38)[200]. Electronegative substituents likewise raise the carbonyl activity



(38)

of the acyl component; with trifluoro(chloro)acetic anhydride, or the mixed trihaloacetic acetic anhydrides, vinyl ethers are β-trihaloacyl-substituted in quantitative yield[201]. Effenberger and Maier have demonstrated strikingly how the course of the reaction depends on the electrophilic potential of the acyl function[202]: while acetyl chloride does not react at all with ethyl vinyl ether, and chloroacetyl chloride causes polymerization, dichloroacetyl chloride gives the addition, trichloroacetyl chloride the substitution product (equation 39).



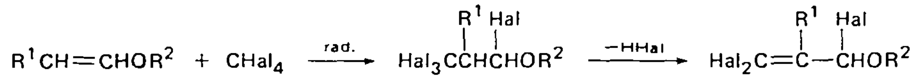
$$\mathrm{Cl_2CH\overset{O}{\overset{\|}{C}}CH_2\underset{Cl}{\overset{OEt}{CH}}} \xleftarrow[0^\circ\mathrm{C},\ 48\ \mathrm{h}]{\mathrm{Cl_2CHCOCl}} \mathrm{CH_2{=}CHOEt} \xrightarrow[0^\circ\mathrm{C},\ 48\ \mathrm{h}]{\mathrm{Cl_3CCOCl}} \mathrm{Cl_3C\overset{O}{\overset{\|}{C}}CH{=}CHOEt} \qquad (39)$$

Oxalyl chloride, with similarly enhanced electrophilicity, readily adds two moles of enol ether at room temperature[203]; the resulting double α-halo ethers can be dehydrohalogenated facilely with tertiary amines. In the case of 3,4-dihydro-2*H*-pyran, the addition of $(\mathrm{COCl})_2$ is exclusively *cis*[204]. Substitution of vinyl ethers with phosgene at 0°C yields β-alkoxyacryl chlorides (equation 40)[205]

$$\mathrm{ROCH{=}CH_2 + COCl_2 \xrightarrow{-HCl} ROCH{=}CHCOCl} \qquad (40)$$

which represent valuable reagents in heterocyclic syntheses[206]; β-CO—NCO substitution is found in the reaction of vinyl ethers with isocyanatocarbonyl chloride[207]. β-Carboxamidation of enol ethers with isocyanates[208], though likewise a substitution reaction, proceeds via cycloaddition, and will be dealt with in Section V.B.

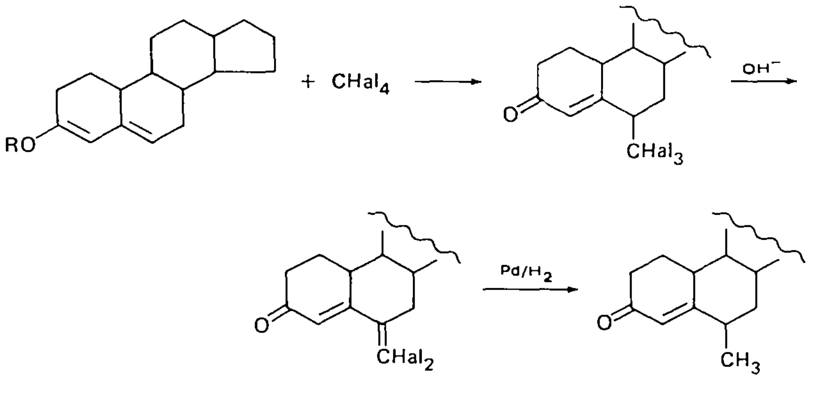
In the presence of radical initiators or with UV irradiation, tetrahalomethanes can be added to the enol ether double bond (equation 41)[209]; if mixed tetrahalomethanes are used, the halogen which is easiest cleaved off radically (Br•) is found in the α-position of the halo ether **64**[210]. These primary adducts (**64**) are thermally



$$\mathrm{R^1CH{=}CHOR^2 + CHal_4 \xrightarrow{rad.} Hal_3C\overset{R^1}{\overset{|}{C}}H\overset{Hal}{\overset{|}{C}}HOR^2 \xrightarrow{-HHal} Hal_2C{=}\overset{R^1}{\overset{|}{C}}{-}\overset{Hal}{\overset{|}{C}}HOR^2} \qquad (41)$$

(64)

extremely labile, and give off HHal on distillation[209]. From the reaction of glycol divinyl ethers with $\mathrm{CCl_4}$ and azoisobutyronitrile, up to 50% bis(trichloroallyl) ethers, $(\mathrm{-CH_2OCHClCH{=}CCl_2})_2$, could be isolated[211]. The reaction has been utilized for the introduction of a $\mathrm{CH_3}$ group into the 6-position of steroids[212] (equation 42). Tetranitromethane has likewise been added radically to enol ethers, forming isoxazolidines[212a].



(42)

V. CYCLOADDITIONS

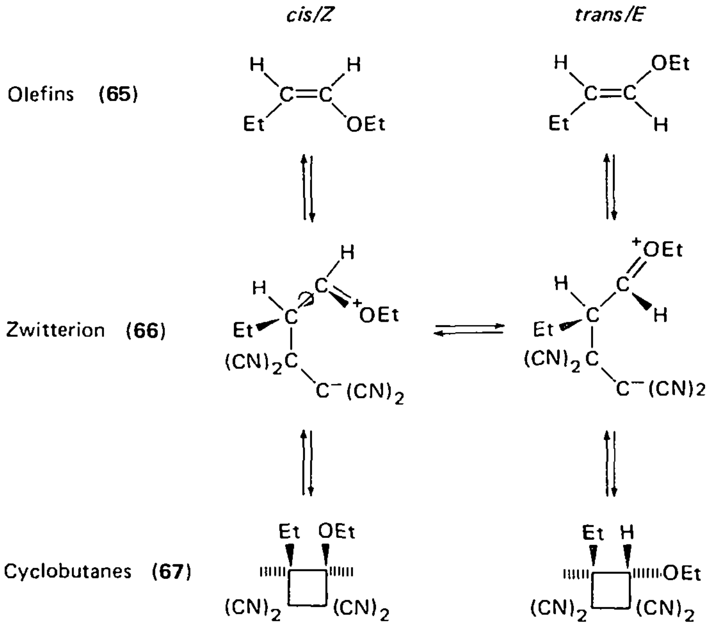
Between enamines and nonhetero-substituted alkenes, enol ethers hold a midway position in overall reactivity as electron-rich olefins, as well as in the polarization of the C=C π-bond. In thermal [2 + 2] cycloadditions (for definitions, see Reference 213), that asymmetry in the π-electron system is of paramount importance since the principle of orbital symmetry conservation[214] forbids a concerted course, with parallel approach of the two π-systems, for this reaction[214,215]. (The orthogonal ($_{\pi}2_s + _{\pi}2_a$) mode[216,217], which allows synchronous bond closure, is definitely operative only with ketenes[217], and perhaps with heterocumulenes.) Consequently, [2 + 2] cycloadditions with alkenes proceed via (singlet) biradicalic intermediates[218] while the highly polarized π-system of enamines tends towards a polar, two-step mechanism[219,220], with a concomitant shift in the product spectrum from addition to substitution derivatives. For electrophilic additions to enol ethers (e.g. acylation), a similar predominance of substitution over addition with increasing reactivity, i.e. higher polarization of the attacking electrophile, has been noted above.

The moderate activation of alkoxy-substituted alkenes designates them as mechanistic borderline cases. Also, the free choice of the OR moiety, with definite gradation in electron release, and the possibility of selective synthesis of geometric isomers (or, alternatively, the ease of their separation) allows the construction of substrates specifically adapted to individual mechanistic problems. Enol ethers have thus become favourite subjects for studying the mechanism of [2 + 2] cycloaddition; in particular, the query '*concerted* or *not concerted*' has instigated some highly sophisticated work.

A. [2 + 2] Cycloadditions with Tetracyanoethylene

The cycloaddition reaction of enol ethers with tetracyanoethylene (TCNE) can now be considered as definitely cleared up in almost every mechanistic detail[221,222]. Even though reaction mechanisms are more or less based on circumstantial evidence, 'the network of mechanistic criteria and experimental findings'[221] which Huisgen and his coworkers have accumulated in this case, must be regarded as extremely tight, and their ratiocination as very compelling indeed: The cycloaddition is *not stereospecific* with respect to the electron-rich double bond, and proceeds via a zwitterionic intermediate (**66** in Scheme 3).

Vinyl ethers, and even the phenylogous *p*-alkoxystyrenes, are sufficiently electron-rich to form cyclobutanes with TCNE at room temperature[223] (TCNE is characterized by a highly electron-deficient C=C bond with low-lying MOs). The reaction of either *E*- or *Z*-butenyl ethyl ether with TCNE, for instance, is completed within a few seconds and yields, quantitatively, *two* cyclobutane derivatives (Scheme 3): in the major product, the configuration of the alkenyl ether is retained, in the minor one, inverted (^{1}H-NMR evidence). This stereochemical leakage increases with solvent polarity (Table 6) since rotation about the C-1/C-2 bond in the zwitterionic intermediate **66** becomes more and more favoured relative to ring-closure by better solvation and reduced Coulomb attraction. But even in acetonitrile, ring-closure is still five times faster than this rotation for both *cis*- and *trans*-**66**[224]. In contrast, rotation is much faster than cyclobutane formation for the biradical from tetrafluoroethene and (*Z*)-2-butene[225]; the [2 + 2] cycloaddition of benzyne to (*E*)- and (*Z*)-1-propenyl ethyl ether, supposedly proceeding via a biradical, likewise shows substantial nonstereospecific portions[226]. The addition of fumaro- and maleo-nitrile to tetramethoxyethene, on the other hand, though very probably still proceeding via zwitterionic intermediates, gives sterically



SCHEME 3.

pure E- and Z-dicyanocyclobutanes, respectively[227]. Thus, TCNE/enol ether cycloadditions appear to rank at the lower end of the stereoselectivity scale among [2 + 2] cycloadditions via zwitterions. The nevertheless fairly high stereochemical fidelity (Table 6), compared with the biradicals, can easily be rationalized in terms of Coulomb attraction of the charge centres (see below); however, 'through-bond coupling' seems to contribute significantly to the height of the rotational barrier around the C-1/C-2 bond[221,228].

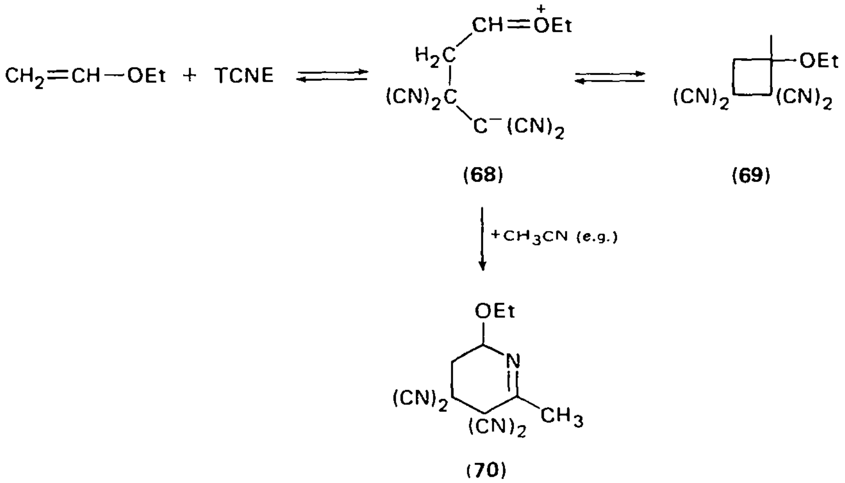
If TCNE is reacted in CH_3CN with 1.1 equivalents of (Z)-1-butenyl ethyl ether of $\geqslant$99.5% configurational purity, the 0.1 equivalents of enol ether recovered turn out to be 18% $Z \rightarrow E$-isomerized[224]. For this, the simplest mechanism is formation of Z-**66**, rotation to E-**66**, and dissociation into the starting materials (see Scheme 3). The zwitterion thus enters into three competitive processes: ring-closure, rotation about the former enol ether double bond, and redissociation[221]. But the mechanistic picture is still more complex. If a $CHCl_3$ solution of the

TABLE 6. % Cyclobutane (67) with inverted configuration (see text), starting from (Z)- and (E)-1-butenyl ethyl ether

Solvent	(Z)	(E)
Benzene	2	2
CH_2Cl_2	7	3
Ethyl acetate	10	5
Acetonitrile	18	16

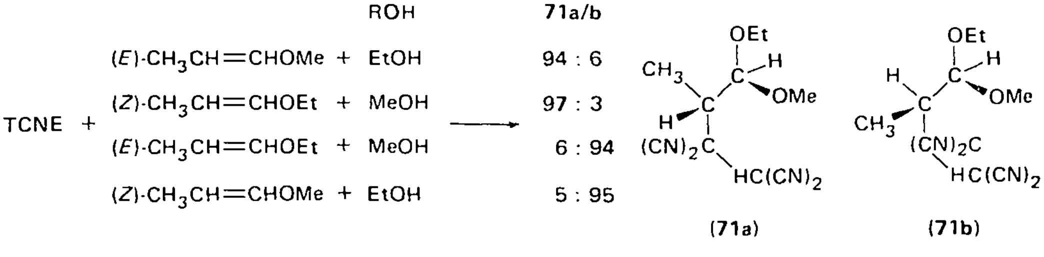
TCNE/α-methoxystyrene cycloadduct is heated to 50°C, the red–violet colouring of the CT complex between TCNE and enol ether develops reversibly. The TCNE present in the equilibrium, although not measurable directly, can be intercepted with the more reactive ethyl vinyl ether, and so be transferred quantitatively from the 1-methoxy-1-phenyl- to the 1-ethoxy-2,2,3,3-tetracyanocyclobutane. (In a similar situation, we have found ⩾30% cycloreversion for ketene acetal/isocyanate cycloadducts at 65°C; in this case, both constituents are easily identified by ^{1}H-NMR[229].) In view of these results, it is not surprising that the stereoisomeric cyclobutanes (**67**), which are stable in nonpolar solvents, slowly isomerize in CH_3CN solution[224].

The zwitterion thus turns out to be the pivot around which the whole cycloaddition scene revolves[221], yet so far its intermediacy has been *inferred* from kinetic and mechanistic evidence only. If the cycloadduct from TCNE and ethyl vinyl ether (**69**) is incubated with $CH_3C{\equiv}N$, $(CH_3)_2C{=}O$, or $C_6H_5CH{=}NCH_3$, though, the 1,4-dipole of the zwitterion **68** is *intercepted*, and **69** converted quantitatively into six-membered ring-products (equation 43)[230]. Since addition of these dipolarophiles to **68** is rather slow, only 4–6% of **70** can be isolated directly from the cycloaddition in acetonitrile or acetone.


CH2=CH—OEt + TCNE
CH=ŌEt
H2C
(CN)2C
C⁻(CN)2
OEt
(CN)2
(CN)2
(68)
(69)
+CH3CN (e.g.)
OEt
N
(CN)2
(CN)2
CH3
(70)

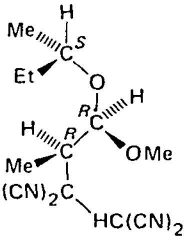
(43)

Interception with ROH at 0°C is much more effective; 60–90%, depending on R, of the acetals **71** are formed under kinetic control[231] (alcoholysis of the cyclobutanes, also via the zwitterion, is much slower). The addition of alcohol to the zwitterion is a highly stereoselective process as the extreme partitioning between the two diastereomeric acetals (**71a/b**) for the reactions in Scheme 4 manifests


ROH
71a/b
TCNE +
(E)-CH3CH=CHOMe + EtOH 94 : 6
(Z)-CH3CH=CHOEt + MeOH 97 : 3
(E)-CH3CH=CHOEt + MeOH 6 : 94
(Z)-CH3CH=CHOMe + EtOH 5 : 95
OEt
H
OMe
CH3
H
(CN)2C
HC(CN)2
(71a)
OEt
H
OMe
H
CH3
(CN)2C
HC(CN)2
(71b)

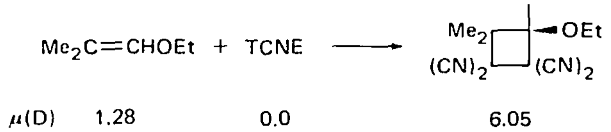
SCHEME 4.

In the *gauche* or *cis* conformation of the zwitterion, tacitly assumed in Scheme 3, the $(CN)_2C|^-$ group offers 'built-in solvation'[232] from the inner side to the carboxonium pole; in fact, **66** represents an intramolecular ion pair with substantial charge transfer. Nucleophilic attack of ROH should thus be from the outside. This could be verified by intercepting the 1,4-dipole from (*Z*)-1-propenyl methyl ether and TCNE with (*S*)-2-butanol. One of the two diastereomeric acetals, formed in comparable amounts, was isolated by crystallization from (*S*)-2-butanol, and demonstrated by X-ray analysis to have *RRS*-structure (72)[233], that is, indeed the result of outside attack of ROH.



(72)

The rate of TCNE/enol ether cycloaddition strongly depends on the polarity of the reaction medium[230]; the immense acceleration, $\sim 10^4$ from cyclohexane to acetonitrile, is unique among cycloadditions. A plot of log k vs. E_T for the reaction of four different enol ethers in ten solvents displays very good linearity over practically the whole polarity range[234,235]. Since TCNE cycloadditions, for example equation (44), are accompanied by a considerable increase in substrate polarity, these rate enhancements do not represent *prima facie* evidence of (di)polar intermediates. From the experimental solvent dependency, dipole moments of 10–14 D were calculated for the transition state; these values, representing about 2/3 of the fully developed charge in the zwitterion, are definitely larger than expected for a concerted pathway[221]. The large negative value for the volume of activation $\Delta V^{\neq}_{\mathrm{exp}}$ (–36 ml/mol, constant for a series of enol ethers)[235] and the solvent dependence of $\Delta V^{\neq}$ [236] can be explained only in terms of a two-step process via zwitterionic intermediates. The CT complex between TCNE and the enol ethers is a dead-end (side) equilibrium[235]; it is *not* traversed in the course of the cycloaddition as usually formulated[237].



(44)

Acrylo- and fumaro-nitrile do not react with enol ethers, owing to insufficient stabilization of the zwitterion by only one CN group. Between 1,1-di-, tri- and tetra-cyanoethene, on the other hand, no great difference in cycloaddition reactivity is found[238] (Table 7); in fact, TCNE reacts slowest. In Diels–Alder cycloadditions, these cyanoethenes exhibit a gradation of $10^7 - 10^9$ in relative reactivity[239] (Table 7); the comparison once again demonstrates the fundamental disparity between these established concerted processes and the [2 + 2] cycloaddition of TCNE.

As expected for the zwitterionic mechanism, the TCNE cycloaddition rate is enhanced tremendously by a second α-substituent in the vinyl ether (R, Ar, OR);

TABLE 7. Relative rates for [2 + 2] cycloadditions of polycyanoethenes[238,239]

	[2 + 2] (benzene, 25°C)	Diels–Alder (dioxane, 20°C)	
	Isobutenyl methyl ether	Cyclopentadiene	Dimethyl-anthracene
Acrylonitrile	0	0.52	0.45
Fumaronitrile	0	4.1×10^1	7.0×10^1
1, 1-Dicyanoethene	16.0	2.3×10^4	6.4×10^4
Tricyanoethene	1.2	2.4×10^5	3.0×10^6
Tetracyanoethene	1.0^a	2.2×10^7	6.5×10^9

$^a k_2 = 3.97 \times 10^{-5}\,M^{-1}\,s^{-1}$; this value has to be divided by a statistical factor of 2 for the relative rate.

TABLE 8. Experimental rate constants k_2 [$10^{-3}\,M^{-1}\,s^{-1}$] for TCNE cycloaddition to enol ethers (in ethyl acetate, 25°C)[240]

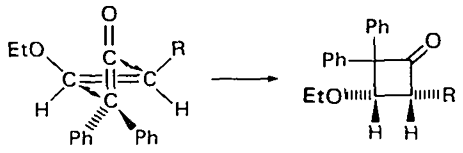
R	CH_2=CHOR	(Z)-C_2H_5CH=CHOR	(E)-C_2H_5CH=CHOR
C_6H_5	0.0043	–	–
CH_3	–	5.5	4.2
C_2H_5	18	15	17
n-C_4H_9	20	–	–
$CH(CH_3)_2$	–	28	57
c-C_6H_{11}	112	–	–
$C(CH_3)_3$	255	80	140

α-methoxystyrene, for instance, reacts 10^5 times faster than β-methoxystyrene[240]. In contrast, the acceleration by β-substituents is moderate, ~50-fold for CH_3, but rapidly dropping again with increasing bulkiness (Table 8)[240]. Between (Z)- and (E)-1-alkenyl ethers, there is but little difference in TCNE cycloaddition reactivity (Table 8) – in striking contrast to ketene cycloadditions[216,241] (see below). The higher relative reactivity of the (Z)-1-butenyl methyl and ethyl ethers is due to the additional ground-state stabilization of the corresponding E-compounds by non-bonded attraction in the s-cis conformation.

These mechanistic findings for the TCNE addition are also pertinent for the reaction of enol ethers with other highly electron-deficient cyano- or (alkoxycarbonyl)-ethenes[242]. Furthermore, since the zwitterion is structurally analogous to the species produced in the initial step of the cationic enol ether polymerization, relative reactivities towards TCNE can be directly correlated with relative polymerization rates for vinyl ethers with various alkoxy moieties and different α- and/or β-substituents (e.g $(CH_3)_3C{-}O > (CH_3)_2CH{-}O > C_2H_5{-}O \sim n$- or i-alkyl)[243,244].

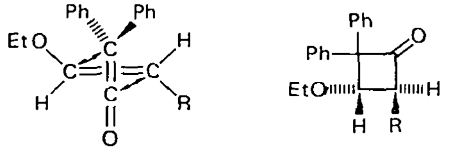
B. Other [$_\pi 2 + _\pi 2$] Cycloadditions

The addition of diphenylketene to enol ethers (discovered as early as in 1920[245]) leads exclusively to 3-alkoxycyclobutanones (75). By now, the concerted nature of this cycloaddition, following the [$_\pi 2_a + _\pi 2_s$] mechanism of Woodward and Hoffman (equations 45 and 46)[215], can be considered as safely estab-



(73) (Z)-(75)

(45)



(74) (E)-(75)

(46)

lished[216,217,246]. The decisive factor in favour of the orthogonal approach is the additional stabilization, provided through the interaction of the *unoccupied C=O orbital in the ketene and the HOMO of the ketenophile*[217]. *This interaction* is also responsible for the regiochemistry of the cycloaddition, i.e. for the addition of the ketene *C=C* bond to the enol ether[217]; bis(trifluoromethyl)ketene adds to enol ethers with the *C=O*[247], bis(trifluoromethyl)ketene imines with the *C=N* double bond[248].

The PMO treatment[217] predicts that successive replacement of the β-hydrogens *in ethyl vinyl ether should accelerate the ketene addition (by raising the enol ether* HOMO energy). (*Z*)-1-Propenyl ethyl ether indeed reacts slightly faster (Table 9), addition to the *E*-isomer, however, is retarded almost 100-fold[241]. This rate enhancement of ~10^2 for *cis*- over the respective *trans*-olefins appears to be a unique feature of ketene $({}_{\pi}2_a + {}_{\pi}2_s)$ cycloadditions[216,249,250], and must be due to the extremely stringent steric requirements for the antarafacial approach. Huisgen and Mayr[241] have advanced cogent arguments for diverse ketene orientation in the transition states of *Z*- and *E*-enol ether addition (since cyclobutane bonding cannot be far progressed in the transition state[241], the orientation complexes 73 and 74 represent appropriate models). The different steric interaction in

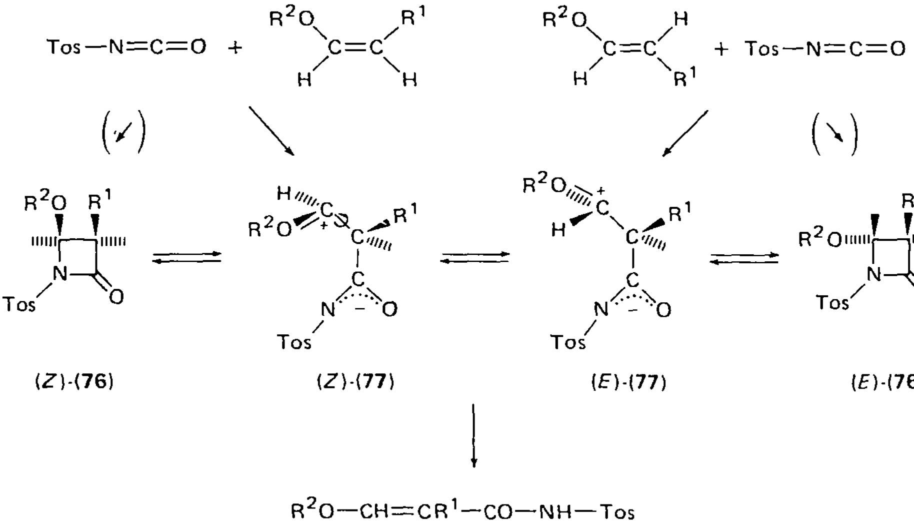
TABLE 9. Cycloaddition rate constants k_2 (10^{-4} M^{-1} s^{-1}) of diphenylketene to *E*/*Z*-isomeric 1-alkenyl ethers

	$(Z)/(E)$-$C_2H_5OCH{=}CHR^1$ (in benzonitrile, 40°C)[241]				
	R^1 = H	CH_3	C_2H_5	$(CH_3)_2CH$	$C(CH_3)_3$
k_{cis} → (*Z*)-(75)	{45}	109	128	117	~ 3.7
k_{trans} → (*E*)-(75)		1.29	1.20	0.742	0.054
k_{cis}/k_{trans}	–	84	107	158	~70
	$(Z)/(E)$-$R^2OCH{=}CHR^1$ (in CCl_4, 23°C)[249]				
k_{cis}/k_{trans} R^2 = C_2H_5	–	120	115	–	–
R^2 = CH_3	–	160	150	–	–

73 and 74 is self-evident. Increasing the bulkiness of the β-vinyl substituent from methyl to isopropyl (Table 9) leaves both the *cis* and *trans* rate and the k_{cis}/k_{trans} ratio nearly unchanged; in the case of the quasi-isotropic *t*-butyl rotor, however, where no special conformation is possible which would minimize steric interaction in the transition state, the rate drops sharply (Table 9), but once more the *cis*/*trans* ratio is hardly affected.

Detailed mechanistic and kinetic investigations have also been reported for dimethylketene[250] and other ketene derivatives. With unsymmetrical ketenes, the large substituent is turned to the outside in the orientation complex[251], and – in cyclobutanone formation with alkyl vinyl ethers – ends up predominantly (though by no means always exclusively) in the *E*-position to OR. The (*Z*/*E*) stereochemistry of the enol ethers which enter the concerted process as the suprafacial component of course always remains unimpaired.

The cycloaddition of *E*- and *Z*-enol ethers to *heterocumulenes* (e.g. isocyanates) likewise proceeds with very high stereoselectivity even in polar solvents such as CH_3CN[42,249] (Scheme 5). For the two azetidinones, (*Z*)-76 and (*E*)-76, obtained from tosyl isocyanate and *cis*- and *trans*-enol ethers, respectively, stereoselectivity can be assessed at ≥95% since the isomers are easily differentiated by ^{1}H-NMR[42,252]. Unlike the cyclobutanones 75, the NCO adducts are thermally unstable: in solution, the sterically pure azetidinones are converted to an equilibrium *E*/*Z* mixture (60–75% *E*) and, finally, into the acrylamides 78. The rate enhancement for the ethoxy over the methoxy derivatives is much more pronounced in epimerization – which must traverse the zwitterion 77 – than in cycloaddition; thence, and from the stereochemistry of the cycloaddition, a concerted ($_{\pi}2_a + {}_{\pi}2_s$) mechanism was advanced also for the $-N{=}C{=}O$ addition[249]. In view of the high stereochemical fidelity of the two-step TCNE addition and its overall kinetics, this view will probably have to be revised. The low k_{cis}/k_{trans} ratios for the tosyl



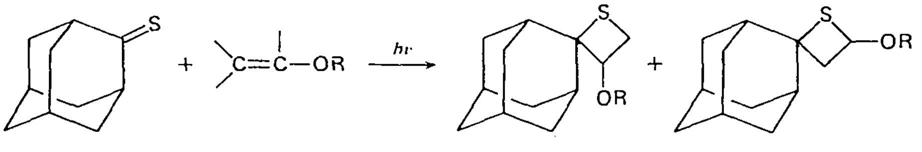
(78)

SCHEME 5.

isocyanate cycloaddition (5–10 in CCl_4 and 3–4 in CD_3CN) likewise argue against the orthogonal π–π approach (see above).

Reaction of reactive *N*-acyl (CCl_3CO) isocyanates with enol ethers affords both [2 + 2]- and [2 + 4]-cycloaddition[253]; both products are unstable and isomerize to the respective β-substitution products. With *N*-thioaroyl isocyanates, only [2 + 4] products are found[254].

The efficiency of electron-rich olefins, e.g. vinyl ethers, in quenching singlet and triplet n,π* ketone fluorescence and/or phosphorescence correlates well with TCNE charge-transfer data and gas-phase ionization potentials[255]. Quenching involves an *exciplex* which partitions either to generate ground states, or to yield biradicals and thence oxetanes[255]. The [2 + 2] photocyloaddition of enol ethers to 2-cyclohexenone, which affords 7-alkoxybicyclo[4.2.0]-2-octanones in good yield, is likewise formulated via a π-complex with the excited ketone[256]. The same regiochemistry is observed for the photoaddition of *t*-butyl vinyl ether to 1,3-dimethyluracil[257]. Irradiation of adamantanethione in the presence of enol ethers yields alkoxyspirothietanes (equation 47)[258], but in extremely low quantum yield. From the n,π* triplet, only **79** is obtained, with the C=C stereochemistry scrambled as becomes a biradical; with the π,π*-excited thione (singlet), on the other hand, both **79** and **80** are formed. Addition in this case is no longer *regio*-, yet fully *stereo-specific*[258]. In photoaddition to benzene, ethyl vinyl ether gives the largest amount of [2 + 2]addition of all olefins; in polar solvents, the [2 + 2]/[2 + 4] ratio is even higher[259].



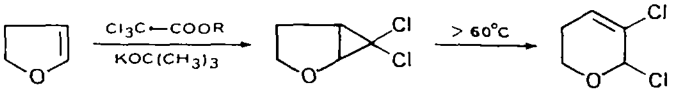
(47)

	(79)	(80)
Excitation: 500 nm (n, π*)	100%	0%
254 nm (π, π*)	67%	33%

C. [1 + 2] Cyloadditions (Carbene Reactions)

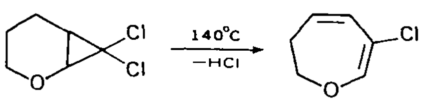
Singlet carbenes and nitrenes react with enol ethers in a straightforward manner: there is practically no insertion, and the cycloaddition is stereospecifically *cis*[260], i.e. in a more or less concerted fashion[261]. Dihalocarbenes (which have found the widest preparative application) as electrophilic agents add faster to enol ethers than to alkenes[262]; within the $CH_2{=}CHOR$ series [$R = CH_3 \ldots C(CH_3)_3$], relative reactivity towards CCl_2 follows the well-known inductive order as in hydrolysis, polymerization etc.[263]. The bicyclic products formed from cyclic enol ethers can undergo thermal cyclopropane ring cleavage (equation 48 and 49); in the dihydrofuran adduct **81** this rearrangement is an extremely facile process[264], in **82** it requires 140°C[265].

Dichlorocarbene addition to enol ethers of cyclic ketones with subsequent ring



(48)

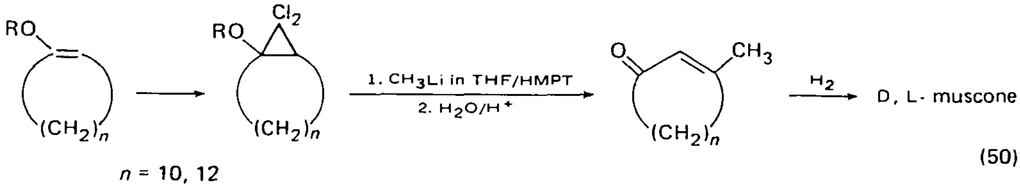
(81)



(82)

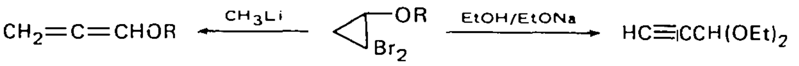
(49)

enlargement has been utilized for an elegant muscone synthesis (equation 50)[266], and also for the preparation of steroids with a tropone structure of the A-ring[267].



(50)

1,1-Dibromo-2-alkoxycyclopropanes, formed in 50% yield by CBr_2 addition to vinyl ethers, offer a convenient access to alkoxyallenes or, alternatively, to propargyl aldehyde acetals (equation 51)[268]. Chlorocarbene likewise adds to vinyl



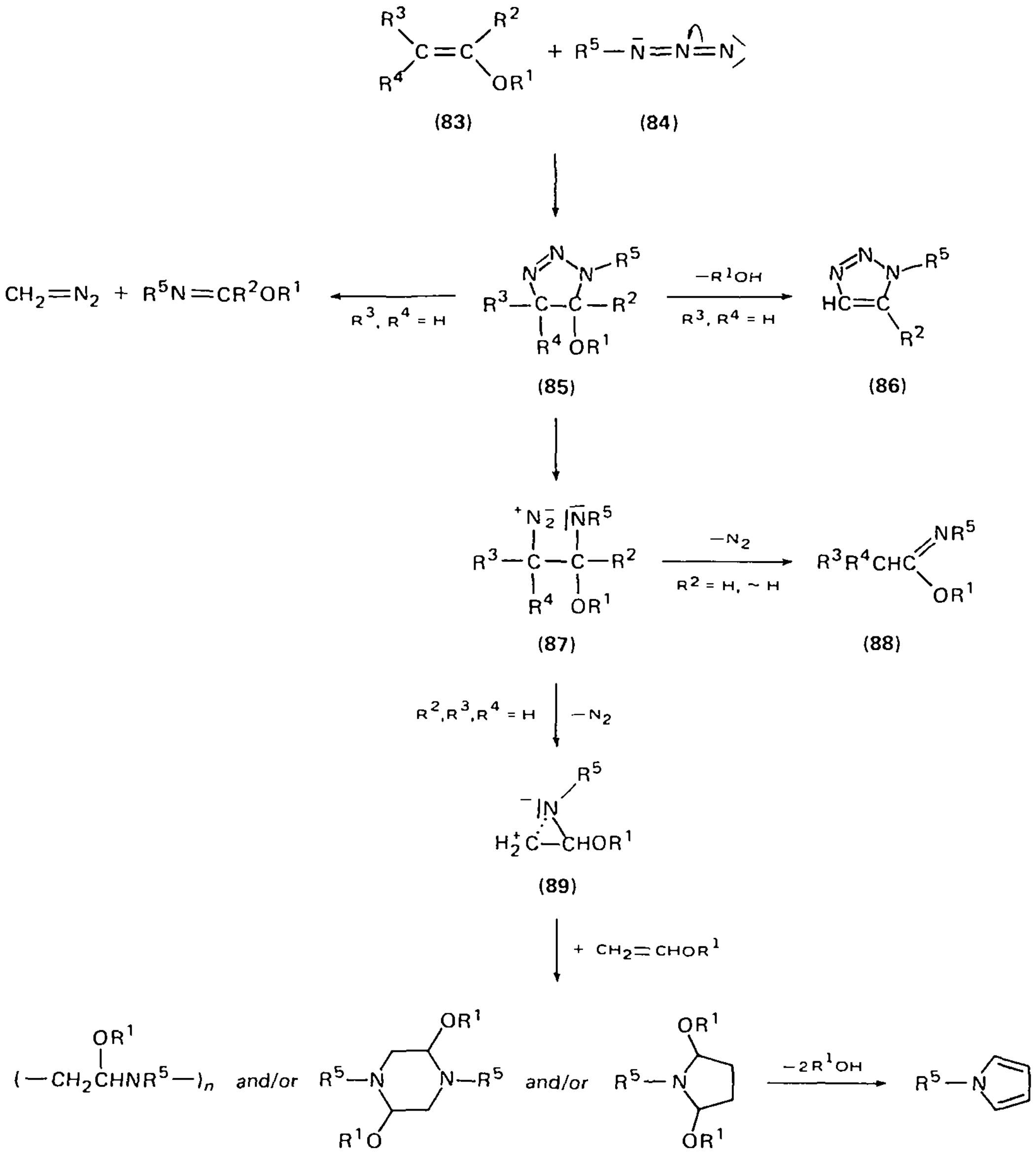
(51)

ethers in fair yield; the alkoxychlorocyclopropanes obtained are predominantly *cis* (*cis/trans* 20 : 1)[269]. *Cis*-Disubstituted cyclopropanes are formed preferentially, too, with alkoxycarbene while phenoxycarbene gives the *trans*-diethers[270,271]. Cyclopropane formation from simple vinyl ethers in moderate to good yields has been reported also for difluoro-[272], fluorobromo-[273] and phenylthiocarbene[274,275]. The addition of cyclohexylidene carbene to *t*-butyl vinyl ether, yielding cyclohexylidenecyclopropane[276], is noteworthy, too.

D. 1,3-Dipolar [2 + 3] Cycloadditions

Among 1,3-dipolar cycloadditions[277] to enol ethers, both mechanistic[278] and preparative studies have been focused on the reaction with aryl, acyl and sulphonyl azides (less activated azides do not react, and some less reactive enol ethers are inert even towards *p*-nitrophenyl azide[279]). The overall reaction (Scheme 6) offers an extreme width in its product spectrum, depending on the number and nature of the substituents in both reactants[278,280].

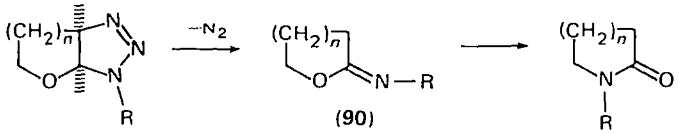
The primary 1,3-addition of the azide has been demonstrated to proceed stereospecifically *cis*[281]; the terminal azido nitrogen always attacks the π-bond at the electron-rich β-position, while the more nucleophilic N-1 bonds to C-1, in the α-position to OR. The addition rate is strongly accelerated with increasing solvent polarity[282] and is, for instance, 5×10^4 times faster with picryl than with phenyl azide[283]; however, a concerted reaction mechanism, though with partial charges in the transition state at N-1 (δ^-) and C-5 (δ^+) of the incipient triazoline structure (85)[282], is now generally accepted[278] (but not by Firestone, see below). The triazolines from *p*-nitrophenyl azide and β,β-unsubstituted vinyl ethers (83) (R^3 = R^4 = H) lose alcohol R^1OH at 130–150°C to form triazoles (86), e.g. 1-nitrophenyltriazole from butyl vinyl ether (Scheme 6)[279]. The triazolines from vinyl ethers and phosphoryl azides (84, $R^5 = R_2P({=}O){-}$), on the other hand, undergo thermal 1,3-dipolar cycloreversion to diazo compounds[284] (more generally observed with enamine/azide cycloadducts[285]). The triazolines from 1-alkenyl and isobutenyl ethers and *p*-nitrophenyl azide are much more labile[280], owing probably


(83)
(84)
(85)
(86)
(87)
(88)
(89)
$-R^1OH$
$R^3, R^4 = H$
$-N_2$
$R^2 = H, \sim H$
$R^2, R^3, R^4 = H$
$+ CH_2{=}CHOR^1$
$-2R^1OH$
and/or

SCHEME 6.

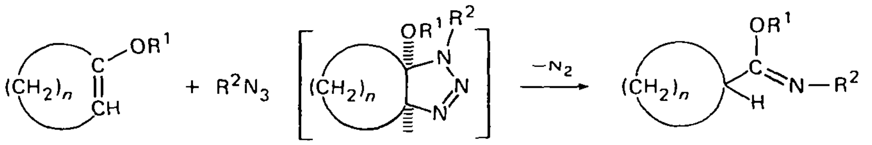
to better stabilization of the incipient carbenium centre in 85; the N_2 expulsion is accompanied by a 1,2-hydrogen shift, with formation of imino ethers (88). Since both cycloaddition to *Z*-alkenyl ethers and N—N bond scission in the respective *cis*-triazolines are much faster than for the corresponding *trans* compounds[281], only *trans*-4-alkyl-5-alkoxytriazolines (85) ($R^2 = R^4 = H$) are obtained besides imino ethers from *E*/*Z* mixtures of 1-propenyl and 1-butenyl ethers[280]; with tosyl azide[280] or trichloroacetyl azide[286] (where the negative charge in **87** is especially well stabilized), only imino ethers (**88**) are isolated (some in quantitative yield[280]). Tosyl azide reaction with unsubstituted vinyl ethers usually produces only polymeric oily material; under special conditions, however, either piperazines or pyrrols can be obtained, some in very good yields[287]. Whether nucleophilic attack of the second enol ether molecule — with either subsequent ring-closure to a 2,5-dialkoxytetrahydropyrrol or further $CH_2{=}CHOR^1$ addition, followed by polymerization — is to the zwitterion **87** or to **89**, cannot be decided[280]. However, acetolysis[279] and alcoholysis[288] of the triazolines **85**, in which the R^5NH group ends up at the β-carbon of the former enol ether, must by necessity proceed via intermediate aziridine structures.

Thermal decomposition of the *N*-aryltriazolines from cyclic enol ethers (equation 52)[279] or direct cycloaddition with tosyl azides[279,289] affords the



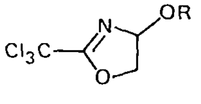
(52)

iminolactones **90** which can then undergo Chapman rearrangement[289]. If no α-hydrogen is present and ROH elimination not feasible, as in the derivatives of alkoxycycloalkenes (equation 53), imino ether formation occurs via Wagner–Meerwein rearrangement[290].

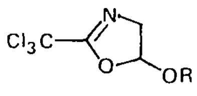


(53)

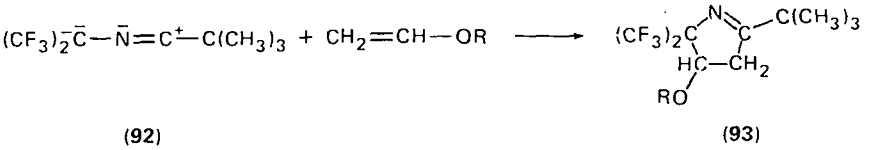
As Huisgen has repeatedly emphasized[278], the directionality in 1,3-dipolar cycloadditions still remains a fairly dark phenomenon. The addition of trichloroacetyl azide to methyl and ethyl vinyl ether, for instance, affords two oxazolines (**91a,b**) after N_2 elimination[291] which can obtain only from two cycloadducts with opposite regiochemistry. The nitrile ylide **92** combines with simple vinyl ethers to form 4-RO-substituted pyrrolines (equation 54); but with phenyl vinyl ether, 12% of the inverted addition product is found besides 88% **93**[292]. The slightly reduced polarity of the phenoxyalkene apparently suffices to overturn the usual addition direction.



(91a)



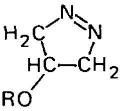
(91b)



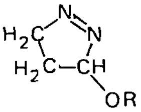
(54)

$R = C_4H_9, CH_2CH(CH_3)_2, C_6H_5$

For the addition of diazomethane to vinyl ethers, formation of 4-alkoxypyrazolines (**94a**) has been reported[278,293], i.e. addition of the CH_2N_2 dipole in the same sense as to ethoxyacetylene. Firestone (who has fought for diradical intermediates in 1,3-dipolar cycloadditions from the beginning[294]) reports, however, the formation of 3-ethoxypyrazoline (**94b**) from a 38-day reaction of CH_2N_2 with ethyl vinyl ether in the dark[295] (the combined $^1H/^{13}C$-NMR evidence is irrefutable). This result could be accommodated by Firestone's biradical theory, but would invalidate the only theoretical 'silver lining' in the dark world of 1,3-dipolar cycloaddition directionality. This rationalization is based upon the frontier orbital concept of Fukui[296], and argues that the direction of 1,3-dipolar cycloaddition is governed by HOMO(1,3-dipole)/LUMO(dipolarophile) interaction[297,298]; for the CH_2N_2/enol ether reaction, addition is predicted between the terminal N atom of CH_2N_2 and the C-2 of the vinyl ether, as in **94a**.



(94a)



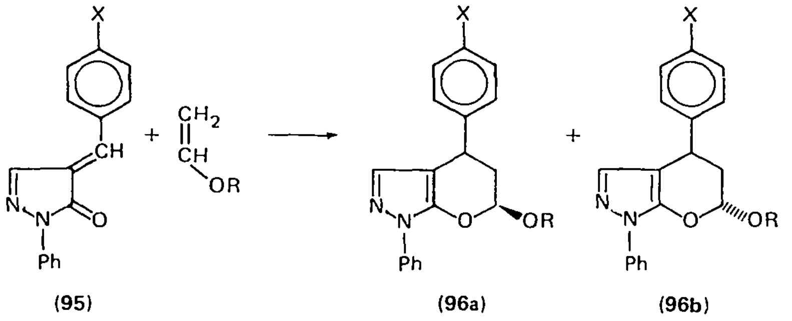
(94b)

Further heterocyclic syntheses via enol ethers include 1,3-cycloadditions of nitrile oxides, generated *in situ*[299], and of phenylsydnone[300].

E. [2 + 4] Cycloadditions

Normal Diels–Alder reactions, with electron-deficient dienophiles[301], are of course facilitated by alkoxy groups in the diene[302]; however, as a rule the entropic term contributes more than half to the free activation energy, so that steric effects frequently override the electronic influence[303] as is often found for truly concerted processes. 1-Alkoxy-1,3-cyclohexadienes, readily accessible by Birch reduction of alkoxyarenes and subsequent KNH_2 rearrangement[2], add twice to *p*-benzoquinone[304]. For Diels–Alder additions with inverse electron demand[301,305], enol ethers (like enamines) are ideally suited substrates; they smoothly react with cyclones, hexachloropentadiene and 1,2,4,5-tetrazines[306–309].

Desimoni and coworkers[310] have extensively studied the mechanism and stereochemistry of the [2 + 4] cycloaddition of vinyl ethers with α,β-unsaturated carbonyl compounds, namely with 4-benzal-5-pyrazolones (equation 55). The reaction is first order in each reactant, stereospecific with respect to the enol ether double bond, as demonstrated for the addition of (*Z*/*E*)-1-propenyl propyl ether to 4-benzal-1,3-diphenyl-5-pyrazolones[311], and the resulting dihydropyran is formed preferentially with the 4-aryl and 6-alkoxy substituents *cis* to each other (**96a**)[312]. The underlying additional stabilization of the *endo* transition state (here via $R\underline{\bar{O}} \leftrightarrow C{=}O$ interaction) is analogous to that found for the regular Diels-Alder reaction[301]. Thus, all kinetic and stereochemical evidence indicates a concerted mechanism[310], with the rate of addition controlled solely by HOMO(vinyl ether)/LUMO-(benzalpyrazolone) interaction[297]. Variation of the *p*-benzal substituent in the diene component (**95**) from NO_2 to $N(CH_3)_2$ leads to a decrease in rate by a factor of ~10^2 while the *cis*/*trans* ratio remains practically unaffected; for both k_{cis} and k_{trans} perfect Hammett plots vs. σ_p^+ are obtained[310]. Variation of the OR moiety in the enol ether has much less effect; although the inductive order basically holds, the influence of steric effects on the addition rate, e.g. in *t*-butyl vinyl ether, is of the same order of magnitude[310]. It would be interesting now to test the kinetics of the benzalpyrazolone cycloaddition to various (*Z*/*E*)-1-alkenyl ethers.

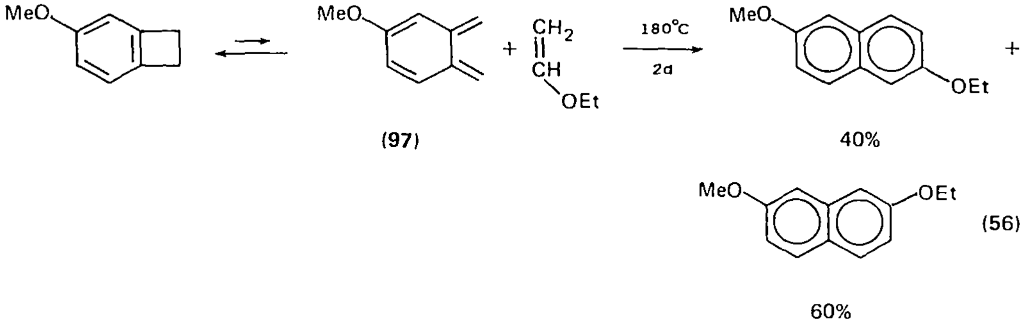


(55)

R = CH(CH$_3$)$_2$ a/b 2.25–2.97 for X = NO$_2$ $\longrightarrow$ N(CH$_3$)$_2$

For the addition to 3,4-dihydro-2*H*-pyran, some *trans* addition to the pyran double bond is found; a small fraction of the reaction thus must proceed via a zwitterionic intermediate[313]. The cycloadditions of 2-alkylidenecycloalkanones with enol ethers require 170°C and show definite acid catalysis[314]; thence, an electrophilic attack on the vinyl ether, with polar intermediates, has been postulated. The BF$_3$ catalysis in the reaction of enol ethers with *N*-aryl Schiff bases[315] likewise argues a polar mechanism.

Diels–Alder additions of electron-rich olefins C=C—$\bar{X}$ to electron-rich dienes (with a +M-substituent, $-\bar{X}$, in the 1- or 2-position) are virtually unknown. In one example, the reaction of the diene **97** (with OCH$_3$ in a vinylogous 2-position) and ethyl vinyl ether (equation 56), two cycloadducts are formed with moderate regioselectivity[316]; the major product, however, is the one expected on the basis of frontier orbital theory while the biradical formalism predicts the opposite polarization.

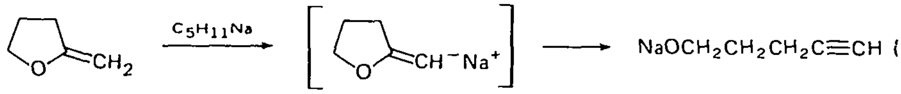


(56)

1,4-Dipolar cycloaddition of the dipolar species, generated from α-chloroaldonitrones and AgBF$_4$, with cyclic enol ethers of varying ring-size offers a further convenient route to medium-ring lactones[317]. In the presence of Lewis acids, 1,5-dipolar addition of 1,3-oxazolidines to cyclic enol ethers leads to 1,4-oxazepines in good yield[318].

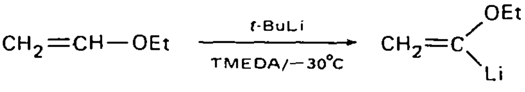
VI. METALATION

Both α- and β-vinylic hydrogen atoms in enol ethers can be substituted with pentylsodium[319]. The α-sodium derivative can be trapped with CO$_2$; β-metalation, on the other hand, results in immediate cleavage into alcohol and acetylene, as in equation (57)[319].


$C_5H_{11}Na$
CH_2
CH^-Na^+
$NaOCH_2CH_2CH_2C{\equiv}CH$

(57)

The first successful metalation with LiR was reported in 1972[320]. Because of their generally much lower reactivity, the most reactive lithio compounds must be employed (equation 58); to avoid fragmentation and effectively halt the reaction at the stage of the lithio derivative (**98**), rather special reaction conditions are needed. With *t*-BuLi in tetramethylethanediamine (TMEDA) at −30°C[320], or in THF at −65°C[321], ethenyl as well as (*Z*/*E*)-propenyl alkyl ethers can be lithiated in the α-position in essentially quantitative yield. Once formed, 1-methoxyvinyllithium (**98b**), for instance, is surprisingly stable up to 0°C[321].

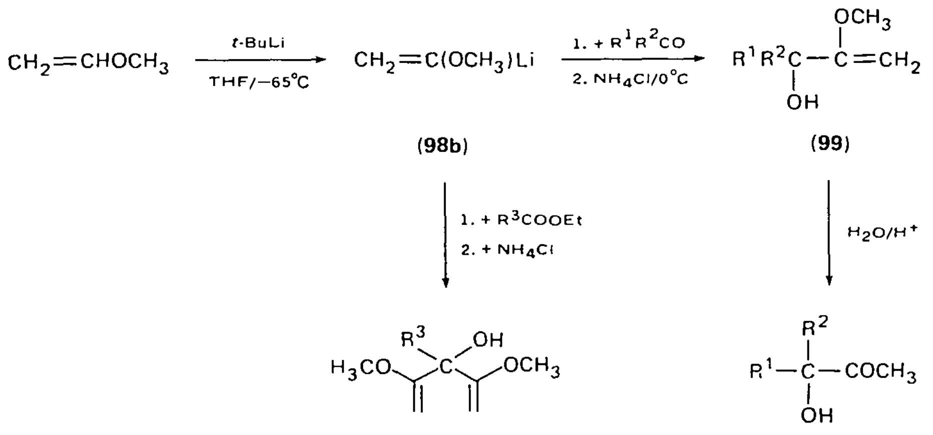

$CH_2{=}CH{-}OEt$
t-BuLi
TMEDA/−30°C
$CH_2{=}C$
OEt
Li

(58)

(**98a**)

$$[CH_2{=}\overset{-}{C}{-}OR] \longrightarrow [CH_3{-}\overset{-}{C}{=}O]$$

The usual enol ether polarity is inverted in **98**, electrophilic substitution now being directed to C-1 ('*Umpolung*'); at the same time, 1-alkoxyvinyllithium represents a masked acetyl anion, i.e. a synthon which allows *nucleophilic* acetylation. It readily adds to aldehyde and ketone C=O functions (equation 59), even in the sterically demanding case of 17-ketosteroids[321], and causes *no* enolization in the carbonyl substrate. If the addition reaction is quenched with NH_4Cl at 0°C, the enol ether (**99**) is recovered and can be further modified electrophilically at C-2; work-up with H_2O/H^+ directly gives the α-hydroxylacyl product (**100**). Reaction of **98b** with ethyl carboxylates results in double $CH_2{=}C{-}OCH_3$ substitution (**101**)[320].


$CH_2{=}CHOCH_3$
t-BuLi
THF/−65°C
$CH_2{=}C(OCH_3)Li$
1. + R^1R^2CO
2. NH_4Cl/0°C
OCH_3
$R^1R^2C{-}C{=}CH_2$
OH
1. + R^3COOEt
2. + NH_4Cl
H_2O/H^+
R^3
OH
H_3CO
C
OCH_3
R^2
$R^1{-}C{-}COCH_3$
OH

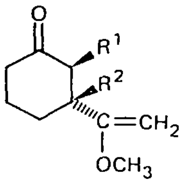
(**98b**) (**99**)

(59)

(**101**) (**100**)

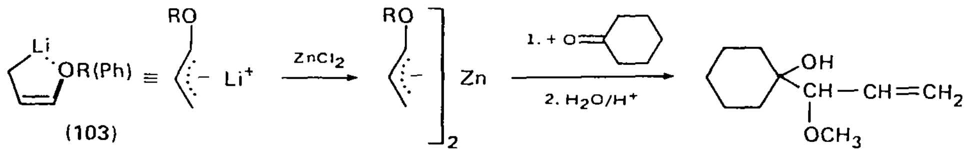
α-Lithiation of cyclic enol ethers (dihydro-furans, -pyrans) likewise requires *t*-BuLi (*n*- or *s*-BuLi are not sufficient)[322]; the solvent THF is best kept at the minimum of 0.5–0.75 equivalents which are necessary for LiR dissociation. (*Z*)-1,2-Dimethoxyethene, in contrast, is smoothly monolithiated with *n*-BuLi (0°C in THF/TMEDA) and added to various carbonyl compounds, e.g. 17-ketosteroids[323].

With specially prepared Cu(I) salts, **98a** can be transformed into bis(α-methoxy-ethenyl)cuprate, $(R_2Cu)Li$; this reagent is highly selective, adding to α,β-unsaturated cyclohexenones exclusively in the 1,4-position[324,325] (**102**), though rather sensitive towards sterical crowding at the electrophilic site.



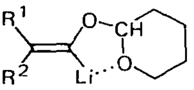
(102)

1-Alkoxy-2-propenyllithium (**103**) is readily accessible by α-metalation of allyl ethers with *n*- or *s*-BuLi(−65°C in THF)[326,327]; both alkylation and C=O addition take place, however, at the terminal C-3 [only after transformation into the corresponding zinc dialkyl (equation 60) can quantitative α-reaction be enforced[326]].



(60)

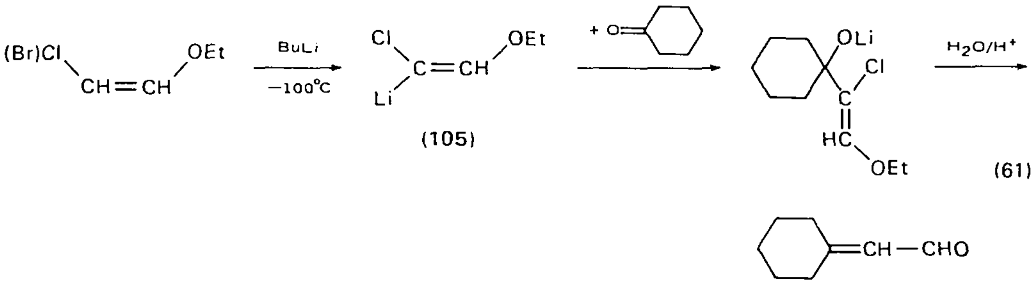
Allylic lithiation, and subsequent γ-alkylation, is likewise observed for (*Z*)-1-propenyl phenyl ether with *n*-BuLi/$(CH_3)_3COK$[327], due probably to cheletropic Li ↔ OR interaction. If, however, the 2-tetrahydropyranyl moiety is employed as ethereal component, the respective vinyl, (*Z*)-1-alkenyl, and also isobutenyl ethers are metalated exclusively in the α-position with *s*-BuLi/*t*-BuOK (−78°C in THF)[328], owing probably once more to cheletropic stabilization (**104**).



(104)

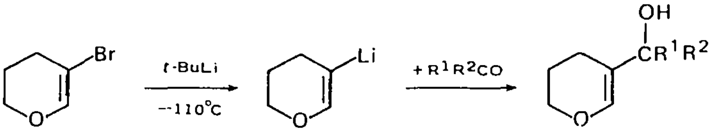
These 2-tetrahydropyranyl enol ethers can thus be readily alkylated, α- or β-hydroxyalkylated, and even formylated in the α-position[328].

In both (*E*)- and (*Z*)-2-halovinyl ethers, the remaining β-hydrogen can be lithiated with BuLi (**105**) (−100°C in hexane/THF)[329]; **105** can either be trapped with CO_2, alkylated with RX, or added to C=O compounds (equation 61). HCl elimination with a second mole of RLi yields alkoxyethinyllithium, Li—C≡C—OR[329]. From the 2-stannyl vinyl ethers, the corresponding nonhalogenated β-lithio-



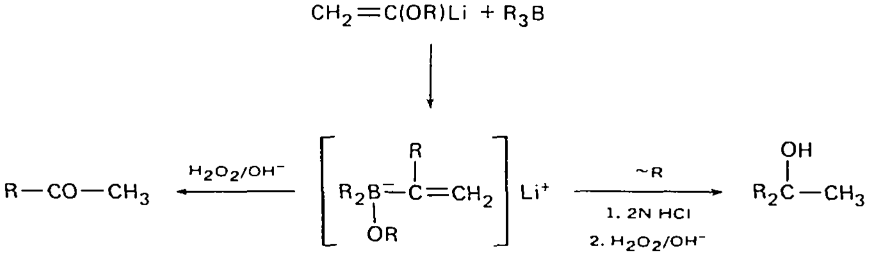
(61)

alkoxyethenes are accessible[330]. Reaction of 5-bromo-3,4-dihydro-2*H*-pyran, on the other hand, with *t*-BuLi at −110°C yields the β-lithio derivative (**106**) via metal–halogen exchange[331]. **106** is significantly less stable than Li—CH=CH—OR, and shows alkyne cleavage already above −90°C. At −110°C, though, it can be added in high yield to ketones (equation 62); after transformation into the corresponding dialkyllithium cuprate, **106** also gives selective 1,4-addition to α,β-unsaturated ketones[331].


Br
t-BuLi
−110°C
Li
+ R¹R²CO
OH
CR¹R²
O

(106) (62)

1-Ethoxyvinyllithium also reacts readily with trialkylboranes (equation 63)[332]. For sterically undemanding *n*-alkyl BR_3 groups, oxidation of the '*ate*' complex (**107**) is faster than a second R transfer, and ketones (**108**) are obtained in good yield. With bulkier alkyl groups, or in the presence of acid, rearrangement is much faster, and the reaction is directed quantitatively towards the dialkyl methyl carbinols (**109**)[332].

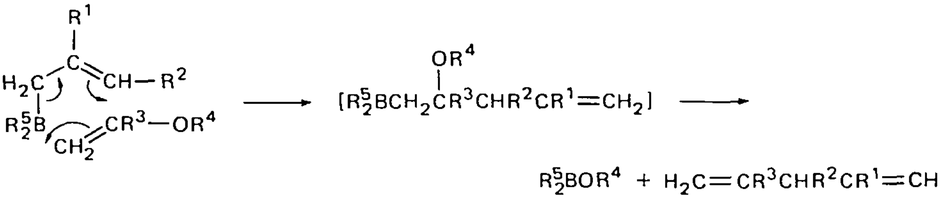

CH₂=C(OR)Li + R₃B
R—CO—CH₃
H₂O₂/OH⁻
R
R₂B⁻—C=CH₂
OR
Li⁺
~R
1. 2N HCl
2. H₂O₂/OH⁻
OH
R₂C—CH₃

(63)

(108) (107) (109)

R = *n*-alkyl .... *c*-C_6H_{11}

Silanes can be added in good yield to enol ethers with $H_2[PtCl_6]$ or Pd/C catalysts[333]; in general, though, partitioning between addition and the usually prevailing cleavage of the vinyl ether linkage, =C—OR, by silane or borane reagents depends critically on catalysts and reaction conditions[334,335] (low temperature usually favouring addition). Reaction of triallylboranes with vinyl ethers, proceeding probably via a Claisen-type cyclic rearrangement (equation 64), affords a convenient synthesis of 1,4-dienes[336].


R¹
H₂C
C
CH—R²
R⁵₂B
CR³—OR⁴
CH₂
OR⁴
[R⁵₂BCH₂CR³CHR²CR¹=CH₂]
R⁵₂BOR⁴ + H₂C=CR³CHR²CR¹=CH₂

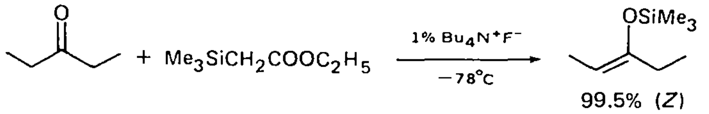
(64)

With Grignard reagents, either the vinyl or the alkyl ether C—O bond is broken, depending largely on the size and nature of the vinyl ether C-1 substituent[337].

VII. SILYL ENOL ETHERS[338,339]

A. Preparation and Reactivity

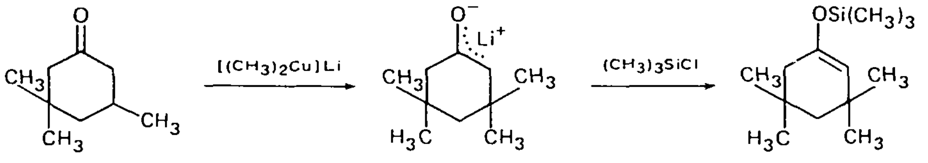
The OR group of alkyl alkenyl ethers as a rule is introduced via nucleophilic reactions (Section III); silyl enol ethers, $R_3Si{-}O{-}C{=}C\langle$, on the other hand, are without exception prepared by *O*-silylation of either the parent carbonyl compound or its enolate, and not by incorporation of a silyloxy moiety[338]. The standard procedure for *O*-silylation is refluxing the carbonyl substrate with chlorotrimethylsilane (Me_3SiCl) and triethylamine or diazabicyclo[2.2.2]octane in DMF[340]. Silylation is much faster and can be effected under far milder conditions with some new reagents such as trimethylsilyl trifluoromethanesulphonate[341], or alternatively, Me_3SiCl in the presence of $C_4F_9SO_3K$ (with NEt_3 in cyclohexane)[342], or trimethylsilyl ethyl acetate[343]. The latter reagent, in the presence of quaternary ammonium fluorides, also allows highly *stereo*selective ($\geqslant$99%) preparation of *Z*-enol ethers (equation 65)[344]. *E*-Enol silyl ethers are best prepared



(65)

with Me_3SiCl and lithium diisopropylamide[345] or lithium 2,2,6,6-tetramethylpiperidide[343].

Enolate ions can be generated *regio*specifically with $(R_2Cu)Li$ from α,α′-dibromo- or α,β-unsaturated ketones (equation 66) or by Li/NH_3 reduction of such



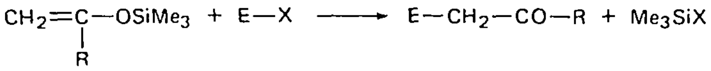
(66)

(110)

alkenones, and then trapped by reaction with Me_3SiCl as silyloxyalkenes (**110**)[338]. Potassium hydride[346] or lithium hexamethyldisilazane[347] have been employed successfully for the metalation (with subsequent silylation) of sterically hindered, e.g. *t*-butyl, ketones.

1,4-Addition of hydrosilanes to α,β-unsaturated aldehydes and ketones is affected with Pt, Ni, and especially Rh catalysts[338]; among these, $(Ph_3P)_3RhCl$ has been found the most effective[348]. Some special catalysts also allow the dehydrogenative silylation of saturated C=O compounds.

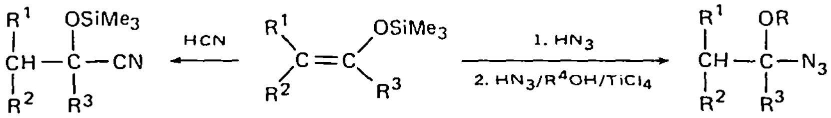
Trimethylsilyl vinyl ether is most stable in the *s-trans* conformation (owing to the larger size of the $SiMe_3$ group and, probably, to the lack of nonbonded attractive stabilization). Relative to Me_3SiOMe, the Si—O force constant in silyl vinyl ethers appears diminished by ~25%[349]; for silyl phenyl ether, $H_3SiOC_6H_5$, an unusually large Si—O distance has been determined[350]. Both findings indicate an especially high mesomeric potential of the silyoxy oxygen – as has indeed been verified by the great reactivity of silyl enol ethers[339]. Conversely, the SiR_3 moiety in silyl vinyl ethers is rather labile; it is often removed directly by the nucleophilic counterion, X^-, of the attacking electrophile, thus regenerating the parent carbonyl compound, now in the α-substituted form (equation 67). Ethenyloxytrimethylsilane has consequently been employed as *silylating* agent for alcohols, thiols, amines and acids[351].



$$CH_2{=}\underset{\displaystyle R}{\underset{|}{C}}{-}OSiMe_3 + E{-}X \longrightarrow E{-}CH_2{-}CO{-}R + Me_3SiX \qquad (67)$$

B. Reactions with Heteroelectrophiles

Among the reactions of silyl enol ethers with protic reagents HX, that with liquid anhydrous HCN is noteworthy, affording α-silyloxynitriles (**111**) in ~50% yield (equation 68)[352]. With HN_3, the α-azido silyl ethers **112a**, and with HN_3 and excess alcohol in the presence of $TiCl_4$, the α-azido alkyl ethers **112b** are formed[353].

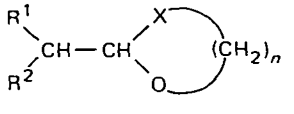


(68)

(111) (112a) R = $SiMe_3$

(112b) R = R^4

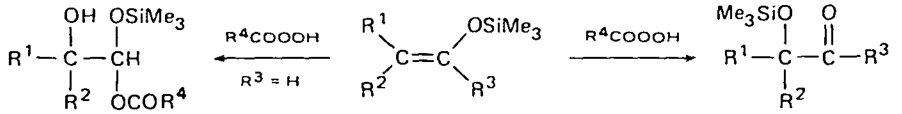
Acid-catalysed addition of α,ω-diols or 2-mercaptoethanol provides a rapid and high-yield synthesis of *O,O*- and *O,S*-acetals (**113**), respectively[354]; with isopropenyl trimethylsilyl ether, *trans*-cyclohexane-1,2-diol has thus successfully been transformed into the corresponding acetonide for the first time.



(113)

X = O, S

Halogenation of silyl enol ethers (with molecular Cl_2, Br_2 or, alternatively, *N*-halosuccinimides) yields not the addition products but rather the desilylated α-halocarbonyl compounds[355], and is especially suited for the preparation of α-halo aldehydes[356]. However, bromination in the presence of triethylamine (in CH_2Cl_2, −60°C) smoothly affords 2-bromo-substituted 1-silyloxy-1-alkenes[357]. Peroxidation of ketone-derived silyl enol ethers with, for example, *m*-perbenzoic acid gives, via an intramolecular Si migration, the α-silyloxyketones **114** in 70–90% yield (equation 69)[358]; from 1-silyloxyalkenes, the α-hydroxyacetals **115** are obtained[359].

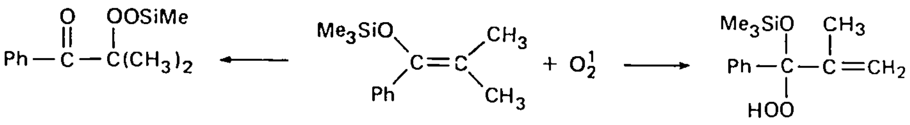


(69)

(115) (114)

$R^4 = m\text{-}ClC_6H_4$

Me_3Si migration (**116**) likewise occurs in the photosensitized addition of singlet oxygen (equation 70), the second peroxide (**117**) being formed via an ene-reaction pathway[360]. $Pb(OCOR)_4$ oxidation[361] and ozonolytic cleavage[362] of the C=C–OSi bond proceed as in the case of alkyl enol ethers; the silyl enol ether of camphor, however, is simply oxidized by ozone (again with a $SiMe_3$ shift) to α-silyloxycamphor.

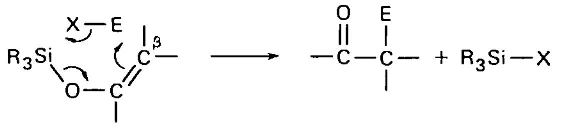


(116) (117) (70)

Oxidation of (ketone-derived) silyl enol ethers with $AgNO_3$ in polar aprotic medium yields (β,β-coupled) 1,4-diketones, and may also be applied for cross-coupling reactions (equation 71)[363]; the high specificity is rationalized in terms of a silver enolate intermediate, generated regiospecifically.

$$2\,R^1R^2C{=}CR^3{-}OSiMe_3 \xrightarrow[60-100^\circ C]{AgNO_3/DMSO} R^3COCR^1R^2CR^1R^2COR^3 \qquad (71)$$

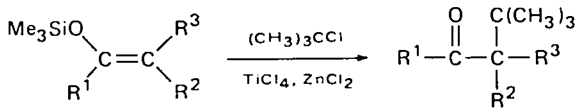
Attack of sulphur or nitrogen electrophiles at the β-carbon of silyl enol ethers always proceeds with concomitant desilylation; for this, a smooth six-centre mechanism can be envisaged (equation 72). Thus, reaction of sulphenyl or sulphonyl halides with silyl enol ethers gives β-keto sulphides[364] and sulphones[365], respectively, in good yield; sulphonation with sulphamoyl chlorides requires metal halide catalysis and is rather troublesome[366]. Nitrosation with NOCl produces, as in the case of the alkoxy analogues, the tautomeric α-oximino derivatives[367]; with nitryl chloride, NO_2Cl, the *α-halo* C=O derivatives are formed[368], due probably to the inverted regiochemistry of the electrophilic attack. β-Nitration of acyclic, cyclic and bicyclic silyl enol ethers can be effected in excellent yields with nitronium tetrafluoroborate (in CH_3CN, −25°C)[369].



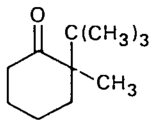
(72)

C. Reactions with Carbon Electrophiles; Metalation

Even with the highly reactive silyl enol ethers, C—C linkage requires strong activation of the carbon electrophile, $TiCl_4$ having proven the most versatile among the various Lewis acids. Thus, Reetz and Maier[370] have developed the first direct and general *t*-alkylation procedure by treating a mixture of silyl enol ether (**118**) and *t*-butyl chloride in CH_2Cl_2 at −45 to −78°C with one equivalent $TiCl_4$ (equation 73). The reaction opens a facile route to compounds with two adjacent quaternary carbon centres (hexasubstituted ethanes) as in **119**, proceeding even then with



(118) (20–90%) (73)

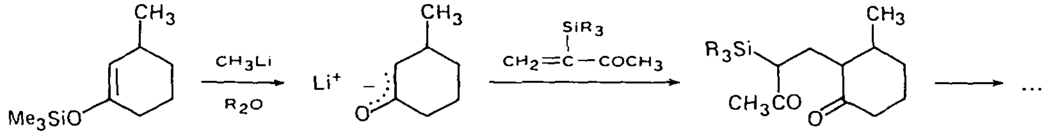


(119)

86%

$\geqslant$95% regioselectivity. It works equally well with α-bromoadamantane as the alkylating agent[371], and is being extended to other alkyl halides[370]. Less heavily substituted silyloxyalkenes require $ZnCl_2$ (in catalytic amount) and give decidely lower yields.

As a rule, however, the directed enolates, regenerated from the silyl enol ethers with CH_3Li (e.g. **120**), are used as substrates for the uncatalysed alkylation with either alkyl or allyl halides[340,372,373]. Dialkylation and insufficient regioselectivity remain problematic, even if the anionic substrates are set free under nonequilibrating conditions by a specific reaction (desilylation with CH_3Li, perhaps again via a six-centre process?). This can be overcome by generating the enolates, with either stoichiometric[374] or catalytic[375] amounts of $NR_4{}^+F^-$, in the form of their quaternary ammonium salts. A new procedure for the annelation of cyclohexanones utilizes the (Michael-type) addition of α-silylated vinyl ketones to cyclohexanone enolates (equation 74)[372,376].



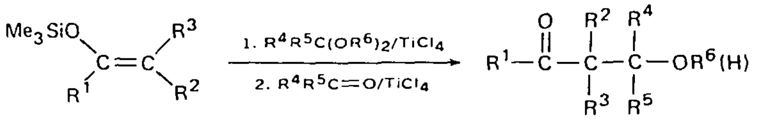
(120)

(74)

Reaction of a silyl enol ether-derived enolate with trifluoromethanesulphonic anhydride represents the most convenient route to primary vinyl triflates and thence vinylidene carbenes (equation 75)[377].

$$R^1R^2C{=}CHOSiMe_3 \xrightarrow[2.\ (CF_3SO_2)O]{1.\ CH_3Li} R^1R^2C{=}CHOSO_2CF_3 \longrightarrow R^1R^2C{=}C| \qquad (75)$$

Enolate substitution with 'functionalized' C-electrophiles is limited to CH_2O[372]. If the carbonyl component is strongly activated by one equivalent of $TiCl_4$, however, both aldehydes and ketones[378] as well as the respective acetals and ketals[379] undergo smooth condensation with the parent silyl enol ethers (equation 76). The

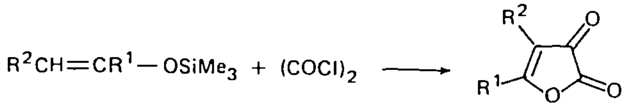


$$\underset{(121)}{(Me_3SiO)R^1C{=}CR^2R^3} \xrightarrow[2.\ R^4R^5C{=}O/TiCl_4]{1.\ R^4R^5C(OR^6)_2/TiCl_4} R^1{-}\overset{O}{\overset{\|}{C}}{-}\underset{R^3}{\overset{R^2}{C}}{-}\underset{R^5}{\overset{R^4}{C}}{-}OR^6(H) \qquad (76)$$

(121)

regioselectivity of these cross-aldol reactions is exceptional, differentiating even between two unlike C=O functionalities in the carbonyl component; at least one substituent (R^{1-3} in **121**), though, must be hydrogen. By using $TiCl_4$ in conjunction with Ti(IV) isopropoxide, the acetal condensation could be extended to 1-trimethylsilyloxy-1,3-butadiene[380]. In the presence of $TiCl_4$ or, better, of $TiCl_4$ *and* $Ti[OCH(CH_3)_2]_4$, the Michael reaction of α,β-unsaturated ketones, the respective acetals and esters with silyl enol ethers affords 1,5-dicarbonyl compounds in good to excellent yield[381]; with the acetals of α,β-unsaturated aldehydes, Ti(IV) *t*-butoxide must be employed.

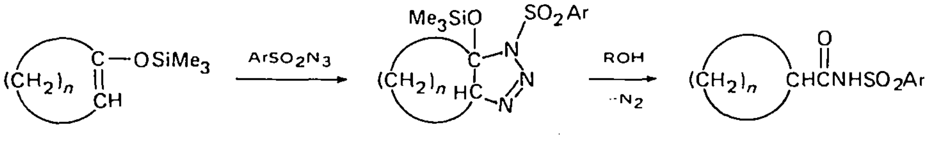
Despite the high nucleophilic potential of silyl enol ethers, their acylation requires di- or tri-haloacyl halides[382] and anhydrides[383], respectively; since the primary addition products immediately lose Me_3SiX, the α-acylated carbonyl derivatives are formed under nonacidic conditions. In the presence of $HgCl_2$[383] or *N*-(4-pyridyl)-pyrrolidine[338], silyl enol ethers are *O*-acylated even with nonactivated acyl halides. Acylation with oxalyl chloride provides the first general route to furandiones (equation 77)[384].


R²CH=CR¹—OSiMe₃ + (COCl)₂
R²
R¹
O
O
O

(77)

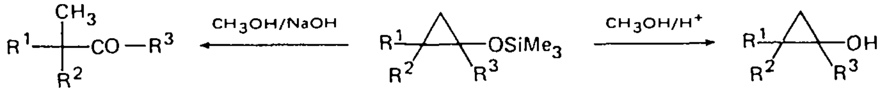
D. Cycloaddition Reactions

The cycloaddition behaviour of silyl enol ethers fully parallels that of alkyl enol ethers. *trans*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene, for instance, has proven a valuable and highly reactive diene component in Diels–Alder additions[385], especially because of the ease with which the C=O function can be regenerated from the C=C—OSi functionality in the [2 + 4]cycloadduct. 1,3-Dipolar cycloaddition of arenesulphonyl azides offers a convenient route to *N*-sulphonyl cycloalkanecarboxamides, (equation 78)[386]. [2 + 2]Cycloadditions, yielding either cyclobutane derivatives or β-substitution products, likewise present no surprising aspects[338].


C—OSiMe₃
(CH₂)ₙ
CH
ArSO₂N₃
Me₃SiO
SO₂Ar
C
N
N
N
HC
(CH₂)ₙ
ROH
–N₂
O
CHCNHSO₂Ar
(CH₂)ₙ

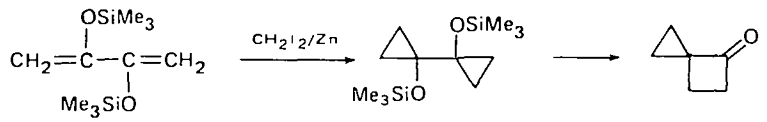
(78)

The Simmons–Smith cyclopropanation of silyloxyalkenes and subsequent transformation of the resultant silyloxycyclopropanes has been developed as a general synthetic procedure by Conia and his group[387]; cyclopropanols (equation 79), α-methyl carbonyl compounds (122), cyclobutanones (equation 80) and cyclopentanones have thus become readily available (average yields ⩾90%). At the same time, equation (80) presents a general route to α-spirocyclobutanones[387].


CH₃
R¹
CO—R³
R²
CH₃OH/NaOH
R¹
OSiMe₃
R²
R³
CH₃OH/H⁺
R¹
OH
R²
R³

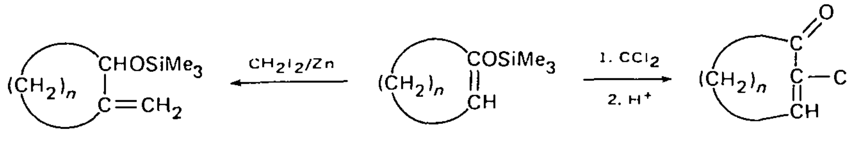
(79)

(122)


OSiMe₃
CH₂=C—C=CH₂
Me₃SiO
CH₂I₂/Zn
OSiMe₃
Me₃SiO
O

(80)

β-Methylidene substitution is observed (123) if the Simmons–Smith reaction is carried out with one third the amount of solvent usually employed[388]. The 1-silyloxy-2,2-dihalocyclopropanes from CCl_2 or CBr_2 addition upon acidic hydrolysis undergo ring enlargement (124), with excellent overall yields[389].


CHOSiMe₃
(CH₂)ₙ
C=CH₂
CH₂I₂/Zn
COSiMe₃
(CH₂)ₙ
CH
1. CCl₂
2. H⁺
O
C
(CH₂)ₙ
C—Cl
CH

(81)

(123) (124)

VIII. THIOENOL ETHERS

A. Physical Properties

For methyl vinyl sulphide, as for methyl vinyl ether (see Section II), a temperature-dependent equilibrium between two conformations, *s-cis* and *gauche*, has been established. From the most recent photoelectron-spectroscopic data, measured in the range 20–600°C[390], the energy difference between the two forms was determined at 9.6 ± 0.8 kJ/mol, with an equilibrium concentration of 94% *cis* at 25–40°C, and of 81% at 200°C. These values are in good accord with earlier PE[27], electron diffraction[391] and IR results[392], but differ sharply from the electron diffraction data interpretation of Samdal and Seip[14] (33–38% *cis* at 200°C). There is general agreement, though, bolstered by *ab initio* calculations[14], that the lesser conformer of methyl vinyl sulphide has a *gauche* orientation ($\phi \sim 105°$)[14].

The first PE ionization potential for *s-cis* methyl vinyl sulphide (8.45 eV)[393,26] is lower than for the *s-cis* conformer of the oxo analogue[31]; nevertheless, the $n_S-\pi$ resonance interaction of SCH_3 is much less pronounced than for OCH_3 as shown, for instance, by the calculated gross atomic populations in the frontier orbital[26]:

$$\underset{0.63}{CH_2}{=}\underset{0.20}{CH}{-}\underset{1.10}{S}{-}CH_3 \qquad \underset{1.03}{CH_2}{=}\underset{0.53}{CH}{-}\underset{0.39}{O}{-}CH_3$$

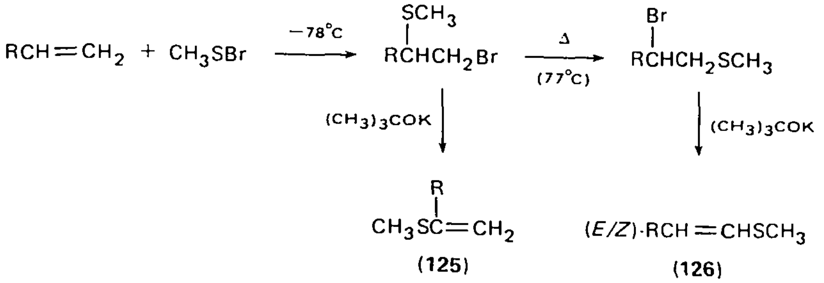
Calculations also demonstrate that C—S hyperconjugation lowers the σ_{C-S} orbital energy in a 90° conformation[390] (in contrast, PE spectroscopy indicates that in allyl methyl sulphide C—S hyperconjugation is unimportant[394]). The barrier of rotation from *gauche* to *s-cis* (8 kJ/mol, as determined by ultrasonic relaxation[16]) is only half that for methyl vinyl ether (*s-trans* → *s-cis*), but rather similar for the reverse process[19,395].

Since the smaller bond angle $=C-S-CH_3$ (~95°)[392] induces significant steric strain in the *cisoid* orientation even for methyl vinyl sulphide, the homologous alkylthioethenes [$R = C_2H_5 \ldots C(CH_3)_3$] probably assume *s-trans* conformation[38,396]. Within the methyl . . . *t*-butyl vinyl sulphide series, both ^{1}H-[397] and ^{13}C-NMR behaviour[44,398] closely parallel that of the corresponding enol ethers, especially in the pronounced downfield shift of the β-vinyl carbon resonance with increasing bulk of the alkyl group. As in the case of the alkoxyethenes, this is most probably not due to steric inhibition of resonance (see Section II.B).

B. Preparation

Thioenol ethers are prepared either by dehydration of β-hydroxyethyl sulphides with KOH[399], or by HX elimination from β-haloethyl sulphides[400]. The latter reaction has recently been extended to the selective synthesis of, alternatively, 1- or 2-alkenyl sulphides (equation 82)[401]; at –78°C, sulphenyl bromide addition and subsequent dehalogenation affords **125** and **126** in 85:15 ratio; at elevated temperature, the product ratio is reversed (5:95).

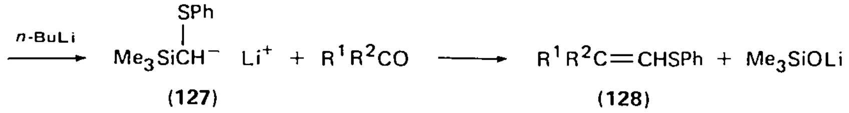
The alkoxide-catalysed rearrangement of allyl sulphides in ethanol yields propenyl sulphides at reflux temperature[402]; under these conditions, the corresponding allyl ethers are recovered unchanged. Wittig–Horner reaction of the ylides, generated from (methylthio)methyl phosphine oxides[403] or from (methylthio)methanephosphonic esters[404], succeeds with alkyl and aryl ketones as well as with aldehydes; usually, though, only the respective phenyl sulphides have been prepared. The most general route to phenyl alkenyl sulphides so far is the elimination of thiophenol from thioketals with Cu(I) ions (equation 83)[405].



(82)

$$R^1R^2CHC(SPh)_2R^3 + Cu^+ \xrightarrow[THF]{C_6H_6} R^1R^2C{=}CR^3SPh + CuSPh + H^+ \qquad (83)$$

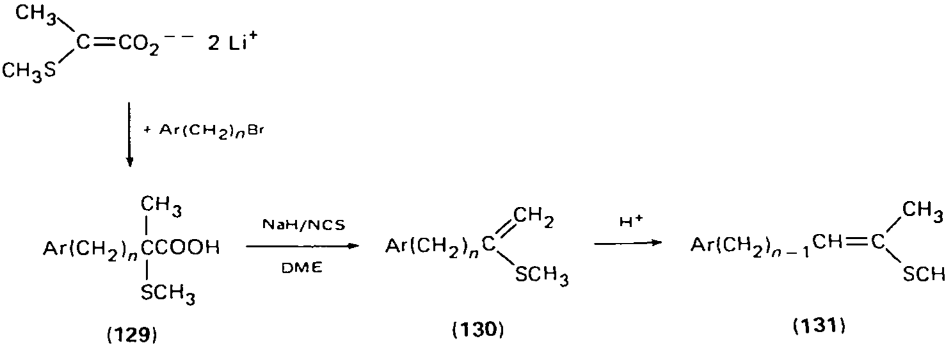
Condensation of a silyl- *and* thienyl-substituted methyllithium (**127**) with ketones (equation 84) yields alkenyl phenyl sulphides (**128**) in good to excellent



$$\xrightarrow{n\text{-BuLi}} \underset{\textbf{(127)}}{Me_3Si\overset{SPh}{\overset{|}{C}}H^- \ Li^+} + R^1R^2CO \longrightarrow \underset{\textbf{(128)}}{R^1R^2C{=}CHSPh} + Me_3SiOLi \qquad (84)$$

yield even in the case of sterically hindered and α,β-unsaturated substrates (e.g. pinacolone, cyclohexenone)[406]. While the oxygen analogues require *t*-BuLi to minimize nucleophilic attack at the oxygen (i.e. ether cleavage), *n*-BuLi is sufficient for thienyl carbanion generation (equation 84).

Terminally unsaturated thioenol ethers (**130**) are formed selectively if metalated 2-methyl-2-methylthiocarboxylic acids (**129**) are treated with *N*-chlorosuccinimide (NCS) (equation 85)[407]. A highly polar aprotic solvent like dimethoxyethane is prerequisite for the practically specific regiochemistry of the elimination (no trace of the alternative thioenol ether **131** is detectable). By treatment with anhydrous acid, **130** is rapidly converted to the thermodynamically more stable isomer **131**.



(85)

C. Reactivity

For the hydrolysis of alkenyl sulphides, too, a mechanism with rate-determining β-carbon protonation has been definitively established (Brønsted factor $\alpha = 0.7$)[398,109]. Thus, hydrolysis can be considered as a model reaction for electrophilic addition/substitution processes. Generally, it proceeds 100–1000 times slower[398] (Table 10) than with the structurally analogous enol ethers (see Section IV.A, Table 5). The gross substituent effects are the same as in the enol ether

TABLE 10. Rates of H_3O^+-catalysed hydrolysis[a] of various alkyl alkenyl sulphides, $k_{H_3O^+}$ (10^{-3} M^{-1} s^{-1})

R =	CH_3	C_2H_5	$CH(CH_3)_2$	$C(CH_3)_3$
CH_2=CHSR	11.7	10.4	8.98	4.17
CH_3CH=CHSR (*Z*)	–	0.49	0.79	0.54
(*E*)	–	0.28	0.45	0.34
CH_2=C(CH_3)SR	–	814	–	–

[a] Determined with aqueous HCl in 10% aqueous CH_3CN solution, ionic strength adjusted to μ = 0.50 by addition of KCl, 25°C.

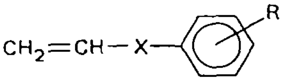
series[107], β-alkyl substituents retarding the rate by a factor of ~100, while α-CH_3 increases the reactivity about hundredfold (Table 10)[398]. The reversed order in the hierarchy of the *S*-alkyl substituents, which is in contrast to that found for CH_2=CHOR, has been rationalized in terms of decreasing hyperconjugative potential [$C(CH_3)_3 \leqslant CH_3$][398]; hyperconjugation of course can operate only via vacant sulphur orbitals. As the interchange of relative reactivity between ethyl and isopropyl vinyl and propenyl sulphides, respectively, indicates, the balance between the various effects is rather delicate in the ground state.

The rates of cycloaddition of thioenol ethers with TCNE, in striking contrast, are much higher than for the corresponding enol ether reactions[408]. This must be due to a specific sulfur effect since the relative gradation between the various alkenyl substrates, as well as the gradation between the individual SR functions within each series (Table 11)[408], are practically identical with that found for the alkoxyalkenes

TABLE 11. Experimental rate constants, k_2 (10^{-3} M^{-1} s^{-1}), for TCNE cycloaddition to alkyl alkenyl sulphides (in CH_2Cl_2, 25°C)[408]

R =	CH_3	C_2H_5	$CH(CH_3)_2$	$C(CH_3)_3$
CH_2=CHSR	21.0	34.2	85.4	252.0
CH_3CH=CHSR (*Z*)	–	7.69	14.3	51.3
(*E*)	–	25.6	52.7	93.1
CH_2=C(CH_3)SR	–	2150	–	–
CH_2=C(CH_3)OR	–	19.9	–	–

TABLE 12. Experimental rate constants, k_2 (10^{-5} M^{-1} s^{-1}), for TCNE cycloaddition to vinyl phenyl ethers and sulphides:



R	X = O	X = S
p-OCH_3	2.4	4470
p-CH_3	0.98	719
m-CH_3	0.65	215
H	0.35	102

(see Section V.A, Table 8). The higher cycloaddition reactivity of (*E*)- compared to (*Z*)-propenyl compounds is even more pronounced in the alkylthio series[408]. The same authors have also demonstrated that, in the cycloaddition of TCNE to vinyl phenyl ethers and vinyl phenyl sulphides, the effect of a *m*- or *p*-aryl substituent is transmitted far better through the S than the O linkage[408] (Table 12), an effect predicted by CNDO/2 calculations[409].

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 18

Oxathiacyclanes: preparation, structure and reactions

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I. INTRODUCTION

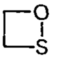
The purpose of this chapter is to discuss the chemistry of different oxathiacyclanes emphasizing their distinctive features in relation to their oxygen or sulphur counterparts. We have also included compounds containing O—S, S—S or S=O bonds. Sultones are excluded since they are mainly synthetic intermediates and can be prepared from sultines by oxidation or even directly without an attack on the hydroxyl or mercapto group.

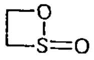
The material in this chapter has not been extensively reviewed earlier, although it has been touched on lightly[1,2].

II. FOUR-MEMBERED RINGS

A. 1,2-Oxathietane

The geometry of 1,2-oxathietane (1), which is known only as its 2-oxide (2), has been optimized using the CNDO/B parametrization[3].

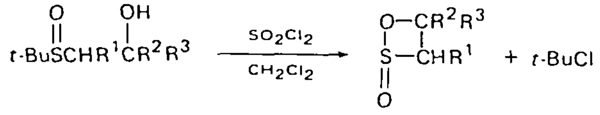

(1)


(2)

If capable of existence, 1 can be expected to exhibit equilibrium behaviour similar to that of oxetane[2–5] and thietane[6–8].

B. 2-Oxo-1,2-oxathietane

Durst and coworkers[9] found that β-hydroxysulphoxides (3) react with *N*-bromosuccinimide, *N*-chlorosuccinimide or SO_2Cl_2 to give initially 2-oxo-1,2-oxathietanes (4), which are probably formed via intramolecular cyclization of the initially formed β-hydroxychlorosulphonium chloride to an alkoxyoxosulphonium salt which fragments to 4 and *t*-butyl chloride (equation 1). They were, however, able to

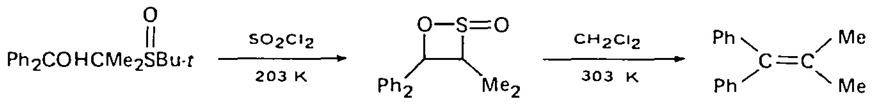


$$t\text{-BuS(O)CHR}^1\text{CR}^2\text{R}^3\text{OH} \xrightarrow[CH_2Cl_2]{SO_2Cl_2} \text{cyclo-[O—CR}^2\text{R}^3\text{—CHR}^1\text{—S(=O)]} + t\text{-BuCl} \qquad (1)$$

(3) (4)

characterize only the 4-phenyl derivative of **4** with its ^{1}H-NMR spectrum from a crude product since 2-oxo-1,2-oxathietanes exhibit only limited thermal stability.

Later on, a crystalline derivative (**6**) was isolated in a 45% yield from the reaction of **5** with SO_2Cl_2 at 203 K (equation 2)[10]. **6** decomposed quantitatively into



(**5**) (**6**) (2)

1,1-diphenyl-2,2-dimethylethylene when warmed in CH_2Cl_2 at 303 K for 24 h. The authors[10] suggest that the conformation of **6** is nonplanar with the substituents on $C_{(3)}$ and $C_{(4)}$ as far apart as possible. On these grounds increasing substitution decreases the stability of the transition state for decomposition which in turn increases the relative stability of **6**.

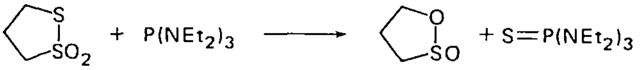
The geometry of **2** has been optimized by CNDO/B parametrization[11] and the *exo*-oxygen is predicted to lie 62° out of the average plane of the ring[12]. The potential energy surface for the [2 + 2] retrocycloaddition of **2** has also been partially investigated[12].

III. FIVE-MEMBERED RINGS

A. 2-Oxo-1,2-oxathiolanes

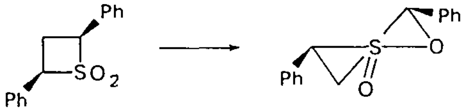
1. Preparation

Since 2-oxo-1,2-oxathiolanes (**7**) are also cyclic sulphinate esters they can be synthesized by a reductive desulphurization of thiosulphonates[13,14] (equation 3).

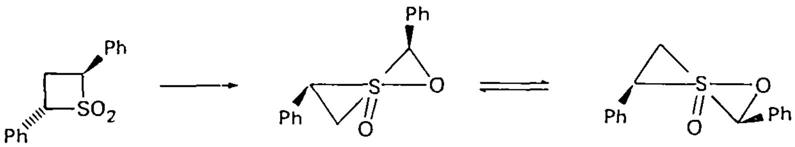


(**7**) (3)

Treatment of *cis*- and *trans*-2,4-diphenylthietane-1,1-dioxides (**8** and **9**) with *t*-butoxymagnesium bromide gave *cis*-3,*cis*-5-diphenyl-*r*-2-oxo- (**10**) and *cis*-3,*trans*-5-diphenyl-*r*-2-oxo-1,2-oxathiolanes (**11**), respectively[15]. The mechanism of this reaction has been discussed and believed to resemble closely that of the Stevens rearrangement[16,17].

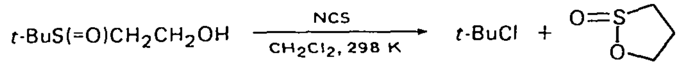


(**8**) (**10**)



(**9**) (**11a**) (**11b**)

The best route to 2-oxo-1,2-oxathiolanes and other related cyclic sulphinate esters is, however, the cyclization of *t*-butyl hydroxyalkylsulphoxides with *N*-chlorosuccinimide or SO_2Cl_2 in CH_2Cl_2[18,19] (equation 4).



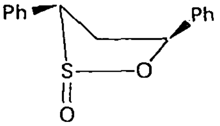
(4)

(7)

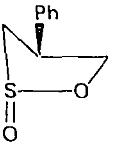
2. Structure

Dodson and colleagues[15] analysed the ^{1}H-NMR spectra of **10** and **11** and found that the observed parameters are best explained by assuming that the sultines exist in half-chair conformations where the bond connecting $C_{(4)}$ and $C_{(5)}$ bisects the plane including $C_{(3)}$, $S_{(2)}$ and $O_{(1)}$.

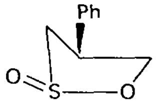
The *cis*-sultine (**10**) is practically anancomeric whereas the *trans* isomer behaves like a 9 : 1 mixture of **11a** and **11b**, although calculation of dihedral angles suggests that the conformation of **11** resembles an envelope (**11c**) more closely than the half-chair forms (**11a** and **11b**). The latter conclusion is in good accord with the structural properties of 2-oxo-1,3,2-dioxathiolanes (see Section III.F.2) and the conclusion based on ^{1}H- and ^{13}C-NMR spectra[19] that *cis*- (**12**) and *trans*-4-phenyl-2-oxo-1,2-oxathiolanes (**13**) prefer $C_{(3)}$ envelope conformations. Despite the preparation of various substituted 2-oxo-1,2-oxathiolanes[18,19] their detailed structural features are still largely unknown.



(11c)

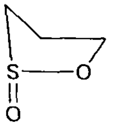


(13)



(12)

Exner and coworkers[20] tried to correlate the magnitude of the dipole moments with the postulate that the strong preference for an axial S=O configuration in 2-oxo-1,3,2-dioxathiolanes, 2-oxo-1,2-oxathiolanes, and in the corresponding six-membered rings[14] results from a dipolar interaction analogous to the anomeric effect[21]. Their attempts to estimate the dipole moment of **7** failed, however, although they were able to evaluate the dipole moment of **14** by assuming that 2-oxo-1,2-oxathiane exists predominantly in the S=O axial chair form (**14**).



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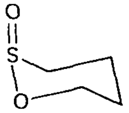


(14)

3. *Reactions*

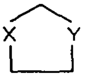
Najam and Tillett[22] studied the alkaline hydrolysis of 7 and **14** and determined their enthalpies and entropies of activation. The close similarity in the rates of hydrolysis is surprising and also the order of magnitude (7 > **14**) opposite to that observed for the hydrolysis of other cyclic esters of sulphur or for the hydrolysis of cyclic carbonates and lactones[23–26]. The authors[22] were not, however, able to make any definite conclusions as to the detailed mechanism of the decomposition except that 2-oxo-1,2-oxathiolane (7) does not undergo ^{18}O-exchange with the solvent during the hydrolytic reaction.

Preparation of chiral sulphoxides from 7 and **14** with various Grignard and/or organocopper lithium reagents has also been studied. The latter reagents were found to give better yields[27].

B. 1,3-Oxathiolanes

1. *Introduction*

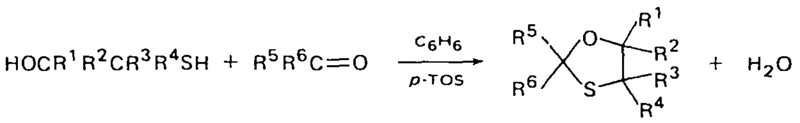
1,3-Oxathiolane (15) and its substituted derivatives are the most widely studied five-membered oxathiacyclanes. This is due to several factors. Firstly, they can be easily prepared, and secondly (see Section III.B.2), they are interesting intermediates between their symmetric counterparts, 1,3-dioxolanes (16) and 1,3-dithiolanes (17), and hence offer a simple opportunity to make a thorough study of the kind of similarities and differences existing in 15–17. Moreover, epimeric 1,3-oxathiolanes can be equilibrated to obtain energetic information from the structural properties and their ^{1}H-NMR spectra are normally reasonably well resolved at least at 220 MHz.



(15) X = O; Y = S
(16) X = Y = O
(17) X = Y = S

2. *Preparation*

In most cases 1,3-oxathiolanes have been synthesized conventionally (equation 5) by the *p*-toluenesulphonic acid–benzene (or CH_2Cl_2) azeotrope method[28–39]. Wilson and coworkers[38] obtained somewhat higher yields by using BF_3–Et_2O instead of *p*-TOS–benzene.

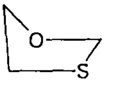


(18) (5)

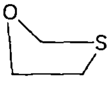
The preparation of some 2-alkylimino- and 2-acylimino-1,3-oxathiolanes has also been reported[40–42].

3. *Structure*

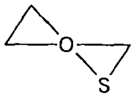
Cooper and Norton[43] have determined the crystal structure of the 1,3-oxathiolane ring in cholestan-4-one-3-spiro(2,5-oxathiolane) and found that it has an envelope conformation where the methylene group next to the ring oxygen lays 51 pm out of the plane of the remainder of the oxathiolane ring ($C_{(5)}$-envelope, 15a). Pasto and coworkers[44] analysed the ^1H-NMR spectra of some 2-substituted derivatives and concluded from the chemical shift data that the $O_{(1)}$-envelope (**15b**) is most compatible with their NMR results. Their approach was, however, rather complicated and based on the postulation that the 2-*t*-butyl derivative is conformationally homogeneous, an assumption which is valid only if there is no other strongly interacting substituent[45]. Nevertheless they were able to estimate conformational energies for the 2-methyl and 2-ethyl groups fairly accurately[30,46] but greatly overestimated that for 2-isopropyl. Wilson and colleagues[47] concluded from the $^3J_{HH}$ coupling constants for a set of 2-substituted 1,3-oxathiolanes that the $C_{(5)}$-envelope (**15a**) is the preferred conformation, although they could not altogether exclude the existence of the $O_{(1)}$-envelope (**15b**) which they regarded as the next stable ring conformation. Later on Wilson[48] carried out conformational energy calculations on 1,3-oxathiolane (**15**) and 2-methyl-1,3-oxathiolane (**19**) and pointed out that the conformational energy minima for both compounds are quite shallow and the lowest energy transition states for pseudorotation are of the order of 13 kJ mol^{-1}. In both cases the minimum exists at the $C_{(5)}$-envelope (**15a**) where in the case of **19** the methyl group is *anti* to $C_{(5)}$ with respect to the ring plane.



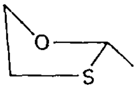
(15a)



(15b)



(15c)



(19)

A systematic study of the ^1H-NMR spectra of several diastereomeric alkyl-substituted 1,3-oxathiolanes[28–31,45,49,50] in conjunction with the chemical equilibration of epimeric derivatives[29–31,45,46] has been proved to be very fruitful. Table 1 lists the results of chemical equilibration of several epimeric 1,3-oxathiolanes together with some comparable data for 1,3-dioxolanes (**16**)[51] and 1,3-dithiolanes (**17**)[52].

Together with the values of vicinal coupling constants ($^3J_{45}$), these results confirmed that the most favoured ring conformation is the $C_{(5)}$-envelope (**15a**), although in some cases the $O_{(1)}$-envelope or the half-chair form where $C_{(4)}$ is above and $S_{(3)}$ below the plane defined by the remaining three atoms (**15c**) may appear to be favoured[31,53].

Conformational energies[31,53] increase in the order Me-4 $\leqslant$ Me-2 $<$ Et-2 $<$ Me-5 $<$ *i*-Pr-2 $\leqslant$ *t*-Bu-2 in such a way that $-\Delta G^{\ominus}$(4-Me) ~ 0 and $-\Delta G^{\ominus}$(2-*t*-Bu) = 8.6 kJ mol^{-1} whereas the rest of the values are between 4.6 and 5.7 kJ mol^{-1}.

It is interesting to note that all of the available evidence is in accordance with the observation that a sulphur atom tends to increase the puckering of a five-membered ring[52,54] whereas an oxygen atom appears to do the opposite[51]. Furthermore, the distortion due to the greatly different bond lengths[43] in **15** is responsible for the special features of this ring system, at least to the extent that 1,3-oxathiolane can almost better be compared with 1,3-oxathianes than with its symmetric counterparts, **16** and **17**.

Eliel and coworkers[51] pointed out that the steric requirements of the 1,3-dioxolane ring are very small and only the most bulky substituents may raise

TABLE 1. Thermodynamic parameters for the chemical equilibration of various 1,3-oxathiolanes. Some data for 1,3-dioxolanes and 1,3-dithiolanes have been included for comparison

Compound	$-\Delta H^\ominus$ (kJ mol^{-1})	$-\Delta S^\ominus$ (J mol^{-1} K^{-1})	$-\Delta G^\ominus$ (kJ mol^{-1})	Reference
2,5-Me_2[a]	4.7 ± 0.3	5.6 ± 1.0	3.0	29
2-Et-5-Me[a]	4.87 ± 0.07	7.6 ± 0.25	2.6	29
2-*i*-Pr-5-Me[a]	3.2 ± 0.1	3.1 ± 0.4	2.3	29
2-*t*-Bu-5-Me[a]	4.60 ± 0.05	2.9 ± 0.2	3.7	43
2-Et-2,5-Me_2[b]	1.11 ± 0.08	0.2 ± 0.25	1.05	29
2-*t*-Bu-2,5-Me_2[b]	–	–	4.0	29
2,4-Me_2[a]	−0.18 ± 0.02	−0.1 ± 0.06	−0.15	30
2-Et-2,4-Me_2[b]	−0.41 ± 0.01	−1.95 ± 0.02	0.17	30
2-*i*-Pr-2,4-Me_2[b]	−0.29 ± 0.04	−5.5 ± 0.1	1.1	30
2,4,5-Me_3[c]	4.57 ± 0.08	4.9 ± 0.2	3.1	31
2,4,5-Me_3[d]	5.2 ± 0.2	7.2 ± 0.65	3.0	31
2,4,4,5-Me_4[a]	4.44 ± 0.03	3.4 ± 0.1	3.4	31
2,4-Me_2-1,3-dithiolane[a]	−0.01 ± 0.06	−1.0 ± 0.2	−0.3	1,52
2-*t*-Bu-4-Me-1,3-diothiolane[a]	–	–	0.5	49
2-Et-2,4-Me_2-1,3-dithiolane[b]	–	–	0.7	49
2,4-Me_2-1,3-dioxolane[a]	0.8	1.1 ± 0.2	1.15	1,51
2,4,5-Me_3-1,3-dioxolane[c,e]	3.1 ± 0.2	1.2 ± 0.6	2.8	51

[a] K = *cis*/*trans*.

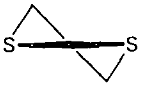
[b] K = (*r*-2-alkyl-*t*-2, *t*-5-Me_2)/(*r*-2-alkyl-*t*-2, *c*-5-Me_2) or K = (*r*-2-alkyl-*t*-2, *c*-4-Me_2)/(*r*-2-alkyl-*t*-2, *t*-4-Me_2).

[c] K = (*r*-2, *t*-4, *t*-5-Me_3)/(*r*-2, *c*-4, *c*-5-Me_3).

[d] K = (*r*-2, *c*-4, *t*-5-Me_3)/(*r*-2, *t*-4, *c*-5-Me_3).

[e] Recalculated from the equilibration data in Reference 51.

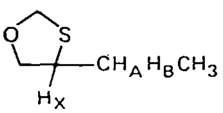
the barriers for the otherwise fairly free pseudorotation. This is understandable since the deviation of the ring atoms from the average plane of the molecule is fairly small. The importance of the ring atoms as structure-forming factors is seen when comparing 1,3-dithiolanes and 1,3-oxathiolanes with 1,3-dioxolanes. The former has relatively great preference towards the half-chair form where $C_{(2)}$ is at the isoclinal position (17c)[52,54]. Due to the long C–S bonds, isomeric 2,4-dimethyl-1,3-dithiolanes (Table 1) are almost equally stable. The same situation



(17c)

also prevails in the case of 2,4-dialkyl-1,3-oxathiolanes. A comparison of the equilibria shown in Table 1 demonstrates the similarities and differences in **15**, **16** and **17** quite well. Recent ^{13}C-NMR chemical-shift correlations[55] for alkyl-substituted 1,3-oxathiolanes lend further support to the above structural views.

The relative stabilities of the ethyl rotamers[56] of 4-ethyl-1,3-oxathiolane (**20**) and its 2- and 5-alkyl-substituted derivatives have been determined[50] using the Karplus equation and the values of J_{AX} and J_{BX} from the methylene protons of the ethyl group to $H_{(4)}$. In general **21a** is 1.7 ± 0.2 kJ mol^{-1} more stable than **21b** and 3.0 ± 0.4 kJ mol^{-1} more stable than **21c**, although their relative amounts



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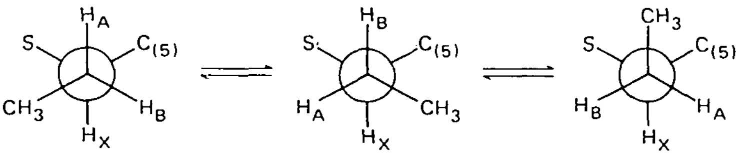
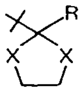
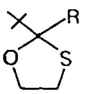


(21a) (21b) (21c)

depend also on the accessible ring conformations. Bushweller and colleagues[57,58] investigated the rate of the *t*-butyl rotation in **22**–**26** with the aid of the ^{1}H-DNMR spectra and determined their activation parameters. In going from **22** to **23** and from **24** to **25** the barrier increases by about 12 kJ mol^{-1} indicating that methyl is substantially more hindering to *t*-butyl rotation than hydrogen as expected. Replacement of O by S in **26** increases $\Delta G^{\neq}$ by about 10 (**25**) and 13 kJ mol^{-1} (**23**); in other words the second step enhances the barrier much less than the first as expected in the light of the structural differences (see above).

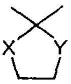


(22) X = S, R = H
(23) X = S, R = Me
(26) X = O, R = Me

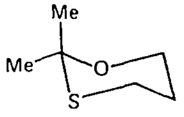


(24) R = H
(25) R = Me

Aromatic solvent-induced shifts in the ^{1}H-NMR spectra (C_6H_6 or $C_6H_5CH_3$ vs. CCl_4) of the methylene protons in the 4,5-position of 2,2-dimethyl-1,3-dioxolane (27)[59], -dithiolane (28)[59] and -oxathiolane (29)[60] are close to each other (0.3–0.4 p.p.m.) and 29 has been shown to solvate with toluene similarly to 2,2-dimethyl-1,3-oxathiane (30).



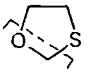
(27) X = Y = O
(28) X = Y = S
(29) X = O, Y = S



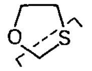
(30)

Optical rotatory dispersion, circular dichroism and IR data for a series of 3-spiro-1,3-dioxolane, -1,3-oxathiolane and -1,3-dithiolane derivatives of 4-oxosteroids have been discussed and an axial sulphur substituent α to the carbonyl found to greatly enhance the carbonyl Cotton effect[61].

Mass spectrometric fragmentation pathways of 1,3-oxathiolane (15) and its alkyl derivatives have been well documentated[62-64]. Types I and II are the main fragmentation routes, although the parent compound (15) decomposes also by type V[63] and 19 by type III[64]. The various modes of fragmentation of 1,3-dithiolanes and 1,3-oxathiolanes resemble each other closely but differ considerably from those of 1,3-dioxolanes[63,64] (Table 2). This is in agreement with the general observation that sulphur increases the relative stability of the parent and large fragment ions. The intensity of the parent-less-methyl ion of 2-substituted 1,3-oxathiolanes (Table 2) is less than that of the corresponding 1,3-dithiolanes or 1,3-dioxolanes which is probably due to a weaker resonance stabilization in the former.



(I)



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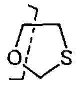

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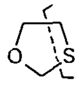

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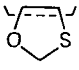


(V)

4. *Reactions*

a. Acid-catalysed hydrolysis. De and Fedor[32] studied the acid-catalysed hydrolysis of 2-(substituted phenyl)-1,3-oxathiolanes (31) and concluded that protonation occurs predominantly on the oxygen atom which actually means that the ring

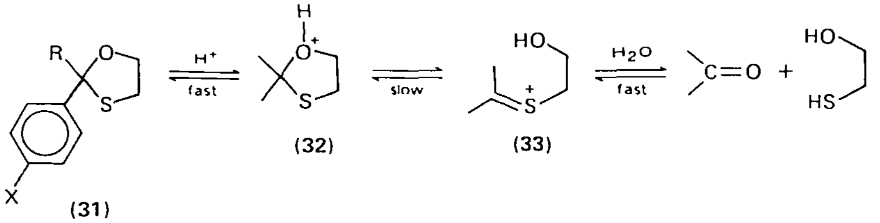
TABLE 2. The relative intensities of the $[M]^+$ and $[M - Me]^+$ ions of some 1,3-diheterocyclopentanes at 70 eV[64]

Compound	$[M]^+$ (%)	$[M - Me]^+$ (%)
2-Methyl-1,3-dioxolane	11	100
2-Methyl-1,3-oxathiolane	51	16
2-Methyl-1,3-dithiolane	100	91
2,2-Dimethyl-1,3-dioxolane	–	53
2,2-Dimethyl-1,3-oxathiolane	21	6
2,2-Dimethyl-1,3-dithiolane	49	53

cleavage should principally involve the acetal carbon—oxygen bond. Furthermore, these authors have proposed the A2 mechanism for the hydrolytic decomposition.

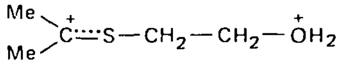
Fife and Jao[33] came to the conclusion that the ring rupture proceeds via the sulphur-protonated conjugate acid which would require breaking of the acetal carbon—sulphur bond in the critical transition state. Moreover, they proposed A1 mechanism for the hydrolysis reaction.

Pihlaja[65] has shown that the data for the hydrolytic decomposition of **15**, **19** and **29** are, however, best consistent with an A1 mechanism in which the ring cleavage occurs at the acetal carbon—oxygen bond (equation 6). A peculiar feature of the acid-catalysed hydrolysis of 1,3-oxathiolanes is the specific solvent deuterium isotope effect since the rate is much higher when the deuterium atom fraction approaches unity than one would expect. This is best understood by assuming that a carbonium—sulphonium ion intermediate is formed, in which the hybridized p- and d-orbitals of sulphur have a significant contribution[65]. Another explanation is that the reaction involves parallel routes[66]. There is, however, very little support for this view and all the available evidence seems to point to the mechanism involving **32** and **33**[32,33,67,68].



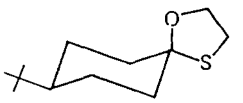
(31) (32) (33) (6)

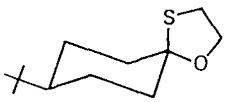
Guinot and Lamaty[67,68] found that the protonation of 2,2-dimethyl-1,3-oxathiolane (**29**) in $FSO_3H–SbF_5$ led exclusively to the formation of the carbonium—sulfonium cation (**34**) which despite the extreme conditions[67] accords with the results for the hydrolytic decomposition[65]. They also concluded[68] from the magnitude of the kinetic deuterium isotope effects of **35** and **36** that the acid-catalysed hydrolysis proceeds through the C—O bond rupture since in the case of the C—S bond cleavage k_H/k_D should have been greater for **36** and not for **35** as observed:



$$\mathrm{Me_2}\overset{+}{\mathrm{C}}\!\!\;{\cdots}\!\!\;\mathrm{S{-}CH_2{-}CH_2{-}}\overset{+}{\mathrm{O}}\mathrm{H_2}$$

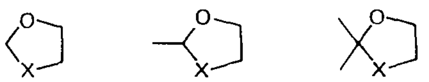
(34)





k_H/k_D	1.32	1.11
	(35)	(36)

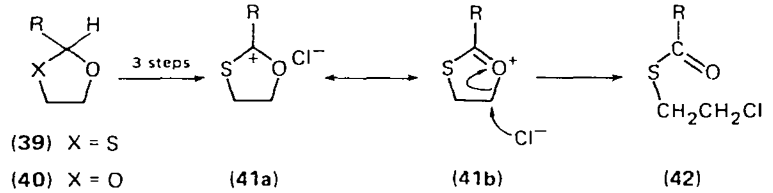
The relative rates in the oxathiolane series **38** are very similar to those in the corresponding 1,3-dioxolane series (**37**)



(37) X = O;	k_{rel}	1	4300	43,000
(38) X = S;	k_{rel}	1	2250	114,000

whereas 1,3-dithiolanes are practically inert under the same conditions[65]. The rate increase due to the second methyl substituent is 57-fold in **38** but only 10-fold in **37**[69]. In both cases, however, one of the groups bound by the bonds attached to the acetal carbon is forced to bend inward and the other outward in relation to the ring. This steric retardation is different in 2,2-dimethyl-1,3-dioxolane[65,69] and 2,2-dimethyl-1,3-oxathiolane[65] since in the latter the interaction between a bending 2-methyl and a 4-hydrogen is at least initially very small (Table 2) whereas that between the bending 2-methyl and a 5-hydrogen is even initially around 4 kJ mol^{-1}.

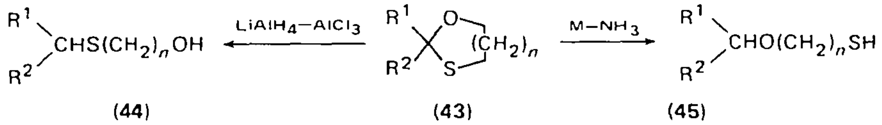
b. Photochemically initiated reactions. These reactions have been studied in $CFCl_3$ at 273 K[35]. In the presence of benzophenone 2-alkyl-1,3-oxathiolanes (**39**) are photolysed considerably more slowly than the corresponding 2-alkyl-1,3-dioxolanes (**40**) under similar conditions and furthermore the former react very selectively (equation 7). Only the *S*-2-chloroethyl thio ester (**42**) is formed with no trace of the *O*-2-chloroethyl thio ester. Assuming a similar mechanism as for the photolyses of 2-substituted 1,3-dioxolanes the observed reaction products can be explained by the resonance structure **41b**. The higher stability of **42** as compared with *O*-alkyl thio esters[35] may also contribute to the occurrence of the specific ring-opening.



(7)

c. Reduction. The reduction of **43** with $LiAlH_4$-$AlCl_3$ (equation 8) leads to the corresponding β-hydroxyethyl and γ-hydroxypropyl sulphides (**44**)[36] whereas the reduction with metal–liquid ammonia combinations (equation 9) gives rise to β- and γ-alkoxythiols (**45**)[34,70]. The hydrogenolysis by the 'mixed hydride'[71] in ether solution involves selective cleavage of the C–O bond but the M–NH_3 reduction occurs principally through a C–S bond rupture, although in some cases the yields remain low[34].

(8)



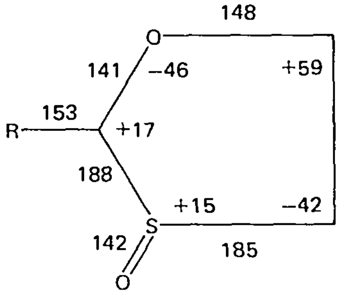
(9)

d. Miscellaneous reactions. Wilson and Huang[72] used halogenation of 1,3-oxathiolanes derived from benzophenone, diisopropyl ketone and cycloheptanone for regeneration of the ketone.

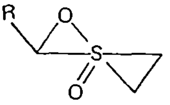
Emerson and Wynberg[73] reported good to excellent yields of the corresponding aldehydes and ketones in the treatment of 1,3-oxathiolanes with a solution of sodium *N*-chloro-*p*-toluenesulphonamide in water, ethanol or methanol under mild conditions. This method is a useful addition to the older more tedious methods[72] in protecting carbonyl groups during synthesis.

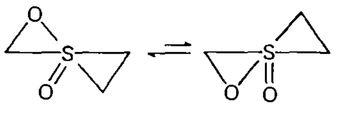
C. 3-Oxo-1,3-oxathiolanes

Very little is known about 3-oxo-1,3-oxathiolane (**46**) and its derivatives, although Hoge and Fischer determined the crystal structure (bond lengths in pm and torsion angles) of 2-*p*-nitrophenyl-3-oxo-1,3-oxathiolane (**47**)[74]. The purpose of this analysis was to solve the configuration of the single product obtained in the oxidation of 2-*p*-nitrophenyl-1,3-oxathiolane instead of two diastereoisomeric sulphoxides. The results showed that the oxygen was introduced in the *trans* position (**47**) and torsion angles show the ring to be in the half-chair form with $O_{(1)}$ and $C_{(5)}$ above and below the plane of the other three atoms of the ring. This observation is in accordance with the conclusions reached from the 300 MHz ^1H spectra which also suggest that **46** greatly favours the half-chair form where the oxo group is *anti* to the ring oxygen (**46a**). From $^3J_{45}$ values it has been estimated that **46a** is about 4.6 kJ mol^{-1} more stable than **46b**[75]. The above conclusion is also in accordance with the observations of Harpp and Gleason[14].



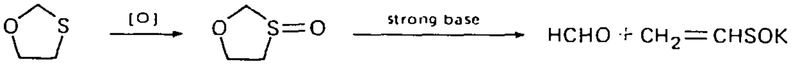
(47)





(46a) (46b)

Schank and coworkers report a cyclofragmentation of 3-oxo-1,3-oxathiolanes (equation 10) to vinyl sulphenates (**48**)[76]. Kellogg[77] mentioned the oxidative formation of substituted 3-oxo-1,3-oxathiolanes from the corresponding *trans*-2,4-disubstituted 5-diphenylmethylene-1,3-oxathiolanes but did not characterize them very well.



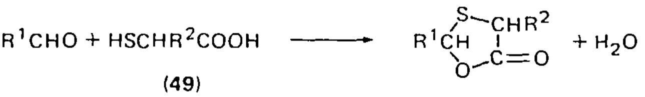
(10)

(48)

D. 5-Oxo-1,3-oxathiolanes

1. *Preparation*

The title compounds are both thioacetals and esters and can be prepared by various methods from aldehydes or ketones and α-mercaptocarboxylic acids (**49**)[78]. Satsumabayashi and colleagues[79] used three different modifications to obtain **50** (equation 11). In method A the reactions were carried out in refluxing benzene with azeotropic removal of the water eliminated. Method B produced **50** by stirring equimolar amounts of the reactants without any solvent or dehydrating agent, followed by direct distillation. Method C also required boiling benzene but with *p*-toluenesulphonic acid catalyst and without azeotropic removal of the water



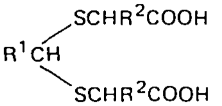
$$R^1CHO + HSCHR^2COOH \longrightarrow R^1CH\langle{}^{S-CHR^2}_{O-C=O} + H_2O \qquad (11)$$

(49) (50)

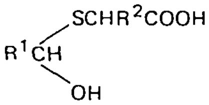
R^1 = Me, Et, Pr, Ph, p-$NO_2C_6H_4$, p-$CH_3C_6H_4$

R^2 = H, Me

formed in the reaction. Yields are not high (14–56%), partly because of the formation of side-products (51) and/or intermediates (52).

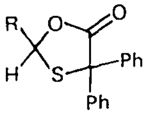


(51)



(52)

Pailer and coworkers[80] prepared several 2-substituted 4,4-diphenyl-5-oxo-1,3-oxathiolanes (53) by transacetalization and purified them as their hydrochlorides. Some authors[81–83] have used $BF_3.Et_2O$ as catalyst to enhance the yield of some 5-oxo-1,3-oxathiolanes.

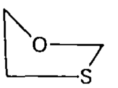


(53)

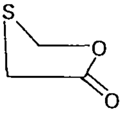
R = Me_2NCH_2, Et_2NCH_2, $Me_2NCH_2CH_2$, p-$Me_2NC_6H_4$, etc.

2. Structure

Due to the lactone grouping –C–C(=O)–O–C–, the conformational situation in 54 is clearly different from that in 1,3-oxathiolane (15) which has been shown to favour the $C_{(5)}$ envelope form (Section III.B.3). The only significant conformation of 5-oxo-1,3-oxathiolane (54) is an envelope where $S_{(3)}$ is the flap atom[83]. Chemical equilibration of epimeric 2,4-dimethyl and 2-t-butyl-4-methyl derivatives have shown that 2-Me, 2-t-Bu and 4-Me favour equatorial positions by 7.6, 9.8 and 1.2 kJ mol^{-1}, respectively[83]. The enhanced magnitude of the conformational energies is in accordance with the structural difference between 54 and 15.

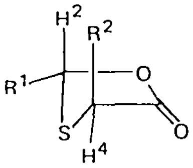


(15)

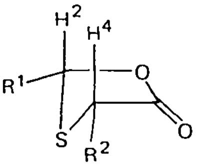


(54)

^{1}H-NMR spectra have shown that $trans$-2,4-dialkyl-5-oxo,1,3-oxathiolanes (55) exhibit larger $^4J_{24}$ values than the cis forms (56) in good agreement with the relative magnitude of the $^4J_{2,5}$ values in correspondingly substituted 1,3-dioxolanes[84].

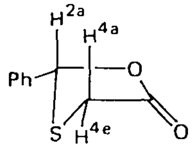


(55) $^4J_{24}$ = 0.7 Hz

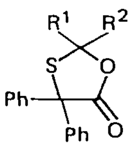


(56) $^4J_{24}$ = 0.4 Hz

Accordingly, 2-phenyl-5-oxo-1,3-oxathiolane (57) is mainly in the equatorial envelope form and $^4J_{2a4e}$ is about 0.6 Hz and $^4J_{2a4a}$ about 0.4 Hz as reported by Brink, although he was not able to assign the relative orientation of the protons in 57[85]. The characteristic IR bands of several alkyl-substituted 5-oxo-1,3-oxathiolanes have also been reported[83].

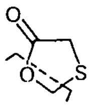


(57)

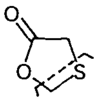


(58)

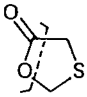
Møller and Pedersen[81] studied the electron impact mass spectra of some 2-mono- and 2,2-dialkyl-substituted 4,4-diphenyl-5-oxo-1,3-oxathiolanes (58) and came to the naïve conclusion that the ester function appreciably changes the balance between the different fragmentation modes from that of 1,3-oxathiolane (15) and its alkyl derivatives[62] for which types I and II predominate (Section III.B.3). The main fragmentation mode of 2,2-dialkyl-substituted derivatives[81] (58: $R^1 = R^2 =$ alkyl) is III followed by types V and II whereas for 2-monoalkyl derivatives[80,81] (58: $R^1 = H$, $R^2 =$ alkyl) the most important mode is IV, followed by III, I, II and V.



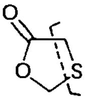
(I)



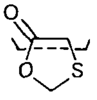
(II)



(III)



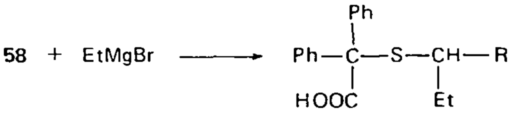
(IV)



(V)

3. *Reactions*

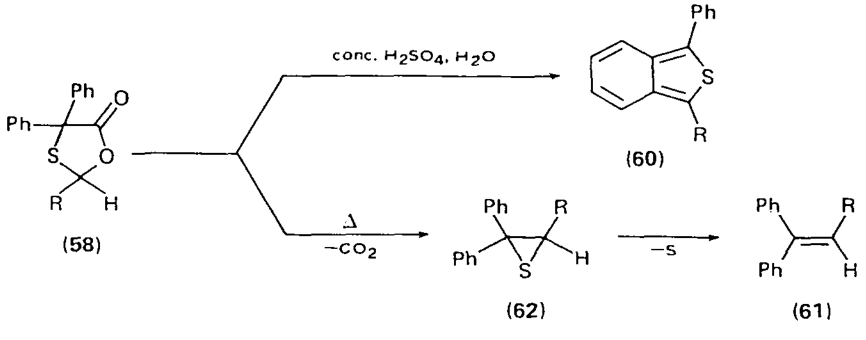
The reaction of 2-aryl-4,4-diphenyl-5-oxo-1,3-oxathiolane (58) with ethylmagnesium bromide[86] (equation 12) gives the acid 59 when R = Ph or p-$CH_3OC_6H_4$, whereas no 59 is formed when R = p-$NO_2C_6H_4$. The acids are the result of an attack on $C_{(2)}$ and a subsequent cleavage of the carbon–oxygen bond[86,87].



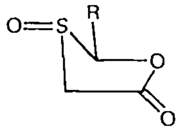
$$58 + \mathrm{EtMgBr} \longrightarrow \mathrm{Ph{-}\underset{HOOC}{\overset{Ph}{C}}{-}S{-}\underset{Et}{CH}{-}R} \qquad (12)$$

(59)

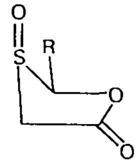
On treatment with concentrated sulphuric acid and dilution with water (equation 13), 58 gives isobenzothiophenes (60) as primary products[88,89]. Pyrolysis of 58 (equation 14) gives rise to 1,1,2-triarylethylenes (61) via thiirane intermediates (62)[90].



Oxidation of **58** with either peroxysebacic acid or H_2O_2 gives both diastereoisomeric forms of **63**, the relative configurations of which are assigned on the basis of their ^{1}H-NMR spectra[91]. The assignment has been carried out by postulating the signal of $\underline{H}_{(2)}$ of the *trans* form (**63a**) at higher field. In most cases this isomer was also the main product of oxidation[91] in agreement with the orientation of the S=O group in **63** (Section III.C)[74,75].

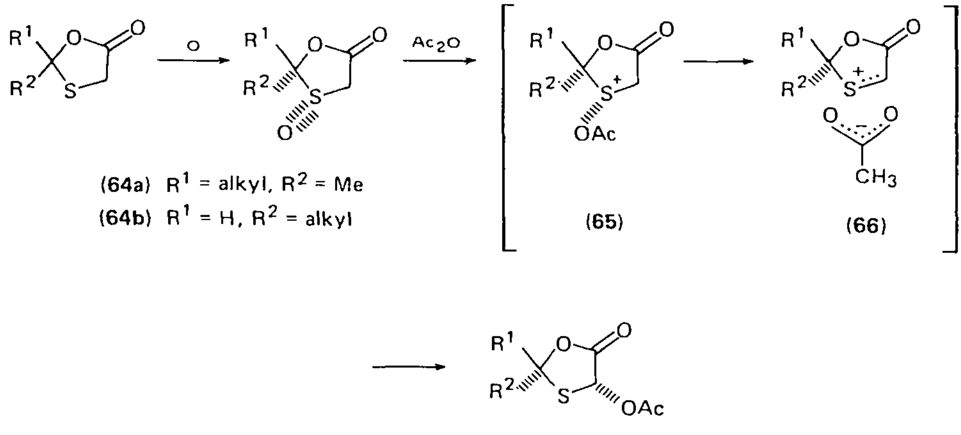


(63a)



(63b)

Glue and colleagues[92] prepared some 2,2-dialkyl-substituted 3,5-dioxo-1,3-oxathiolanes (**64**) by smooth oxidation (H_2O_2, glacial AcOH, 298 K) and studied their reactions with acetic anhydride (equation 15). A highly stereoselective process (Pummerer rearrangement) gives the corresponding 4-acetoxy-2,2-dialkyl-5-oxo-1,3-oxathiolanes (**67**), in which the acetoxy group stereochemically retains the orientation of the S=O bond in **64**. The stereoselectivity has been explained by an intramolecular process, possibly proceeding via the acetoxysulphonium ion **65** and the ion pair **66** to **67**[92].



(64a) R¹ = alkyl, R² = Me
(64b) R¹ = H, R² = alkyl

(65)

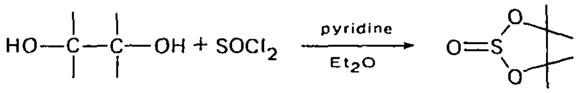
(66)

(15)

(67a) R¹ = alkyl, R² = Me
(67b) R¹ = Me, R² = alkyl

E. 2-Oxo-1,3,2-dioxathiolanes

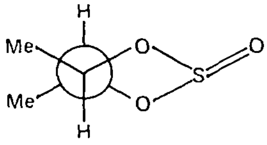
Of the various methods of preparation[93,94] of cyclic sulphites the best yields have been obtained by the condensation of 1,2-diols with thionyl chloride in the presence of pyridine[95] (equation 16). The ring geometry of **68** and its alkyl and phenyl derivatives have been extensively studied by electron diffraction[96,97], IR[98] ^{1}H-NMR[95,98,99], CD techniques[100] and ^{13}C-NMR[101]; these reports review the older literature fairly thoroughly. Although the electron diffraction study of 2-oxo-1,3,2-dioxathiolane (**68**) itself postulates an essentially planar structure for


HO—C—C—OH + SOCl2
pyridine
Et2O
O=S
O
O

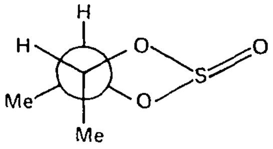
(16)

(68)

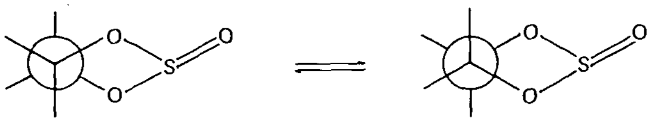
the ring, a later report[97] shows that the experimental findings for *cis*-4, *trans*-5, *r*-2-oxo- (69) and *trans*-4, *trans*-5, *r*-2-oxo-1,3,2-dioxathiolanes (70) can be best explained by the existence of the twist-envelope forms in agreement with the CD[100], IR[98] and the most recent NMR work[98,101]. These twist-envelope forms are interconverted by rapid pseudorotatory (68a and 68b) paths not involving


H
Me
Me
H
O
O
S
O

(69)


H
H
Me
Me
O
O
S
O

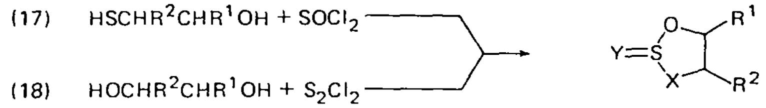
(70)



(68a) (68b)

inversion at sulphur. The existence of the twist-envelope conformations gains indirect support from the great preference of the axial S=O group in the corresponding six-membered sulphites (see Section IV.G).

In this context it is worth noting that 2-oxo-1,2,3-oxadithiolane (71) and its 5-methyl derivative (72) have also been prepared[102] (equation 17). Thompson and coworkers[103] have obtained 2-thioxo-1,3,2-dioxathiolanes 73–75 from the reaction of sulphur monochloride with 1,2-ethanediol, 1,2-propanediol and 2,3-butanediols (equation 18), and found by spectroscopic means that they resemble structurally 68 and its methyl derivatives.


(17) HSCHR2CHR1OH + SOCl2
(18) HOCHR2CHR1OH + S2Cl2
Y=S
O
X
R1
R2

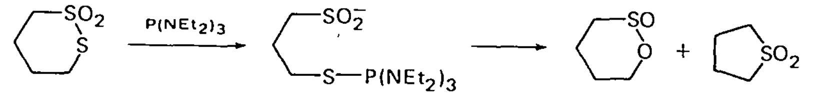
	X	Y	R¹	R¹
(71)	S	O	H	H
(72)	S	O	Me	H
(73)	O	S	H	H
(74)	O	S	H	Me
(75)	O	S	Me	Me

IV. SIX-MEMBERED RINGS

A. 2-Oxo-1,2-Oxathianes

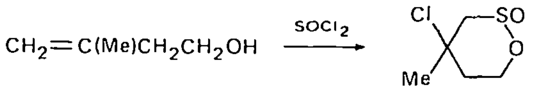
1. *Preparation*

The 1,2-oxathiane system is unknown and apparently unstable, but the 2-oxides are fairly well described in the literature. As sulphinate esters, the title compounds, e.g. the nonsubstituted molecule (**76**), can be prepared via the reductive desulphurization coupled with rearrangement of the six-membered thiosulphonate (**77**) in the presence of tris(diethylamino)phosphine (equation 19)[13a,14]. The conformation of **76** (90%) and **78** (10%) was attributed to the ambivalent nature of the intermediate sulphinate anion (**79**) capable of cyclizing through either the sulphur or oxygen atom[13a].



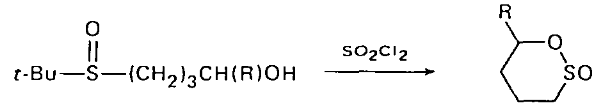
(**77**) (**79**) (**76**) (**78**) (19)

Certain 4-chloro derivatives (**80**) are obtained by treatment of 3-butenols with $SOCl_2$ (equation 20)[104,105].



(**80**) (20)

The most general route to cyclic sultines developed by Sharma and coworkers[19] utilizes cleavage of *t*-butyl (δ-hydroxyalkyl)sulfoxides (**81**) by SO_2Cl_2, and enables preparation of several specifically substituted derivatives such as **82** from relatively simple precursors in isolated yields of ca. 75% (equation 21). Although this method reduced the problem of preparing various alkylated 2-oxo-1,2-oxathianes mainly to the synthesis of properly substituted derivatives of **81**, it was unsuccessful in a few cases, e.g. in the production of sultines with a phenyl or two methyl groups α to the sulphur atom[19]. Furthermore, the products obtained showed high diastereomeric purity, which was reasoned to follow from great stability differences between isomers and/or their facile epimerization under the reaction or isolation conditions[19].

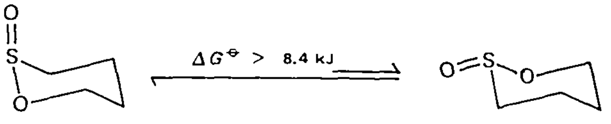


(**81**) (**82**) (21)

2. *Structure*

The main interest in the structural study of 2-oxo-1,2-oxathianes is concerned with the steric disposition and different interactions of the S=O group, and hence, with the more general question of the conformational behaviour of molecules possessing polar groups or atoms.

The 100 MHz ^{1}H-NMR spectrum of **76**, as temperature-independent from −90 to +150°C, is best interpreted in terms of a rigid chair conformation with a strong preference for the axial structure (**76a**) over the equatorial one (**76b**)[14]. The energy

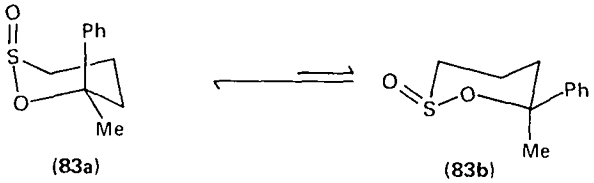


(76a) (76b)

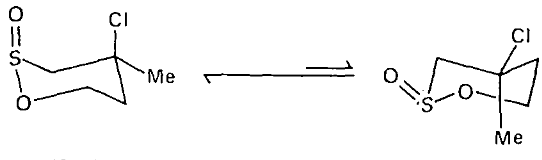
difference, ca. 8.4 kJ mol^{-1}, estimated indirectly from the ^{1}H-NMR spectrum, is well in line with those presented for the sulphoxide group in thiane oxides (0.8–2 kJ)[107], and in 2-oxo-1,3,2-dioxathianes (12–20 kJ)[108], if the reasoning based on dipole–dipole interactions between the exocyclic and ring heteroatoms[14,21] is relevant.

This concept is qualitatively supported by the dipole moment measurements of Exner and coworkers[20], who found that the experimental value for **76** is consistent with the estimated one only if a chair form with the axial S=O group (**76a**) is assumed to predominate.

By ^{1}H-NMR and ^{13}C-NMR measurements as complementary tools Buchanan and his colleagues[106] came to the conclusion that even molecules like **83** with an axial substituent in their 6-position still exist in a chair–chair equilibrium which prefers the *syn*-axial alternative (**83a**). Possible reasons for this somewhat conflicting behaviour[94,109,110] are not discussed[106], but it finds some resemblance in the results of the combined ^{1}H-NMR and IR study by Dhami[104,105], who noted that *cis*-4-chloro-, *trans*-4-methyl, *r*-2-oxo-1,2-oxathiane (**84**) exists in a single chair form (**84a**) where both the Cl and S=O groupings are axially orientated (see also Sections IV.C. and IV.G).



(83a) (83b)



(84a) (84b)

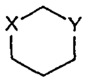
3. *Reactions*

The kinetics of the alkaline hydrolysis of **76** was studied by Najam and Tilett[22], who reported some anomalous features in the relative reactivity along the series from five- to six-membered and open-chain analogues (see Section III.A.3). The facile oxidation of 2-oxo-1,2-oxathianes has served as a proof of their structure[13a], and also as a means of preparing cyclic sultones[19] which are difficult to synthesize by direct methods.

B. 1,3-Oxathianes

1. *General remarks*

The 1,3-oxathiane system (85), as structurally intermediate between 1,3-dioxane (86) and 1,3-dithiane (87), offers an interesting opportunity to compare

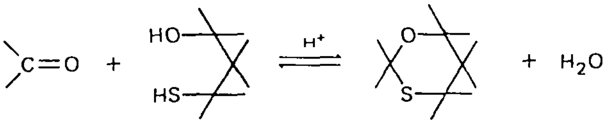


(85) X = O, Y = S
(86) X = Y = O
(87) X = Y = S

conformational and other structural properties and to test the degree of additivity of such effects. A strict parallelism in the features of these three analogues is not expected, since structural parameters such as bond lengths and angles may undergo different compromizing alterations in each case to optimize the ring geometry.

2. *Preparation*

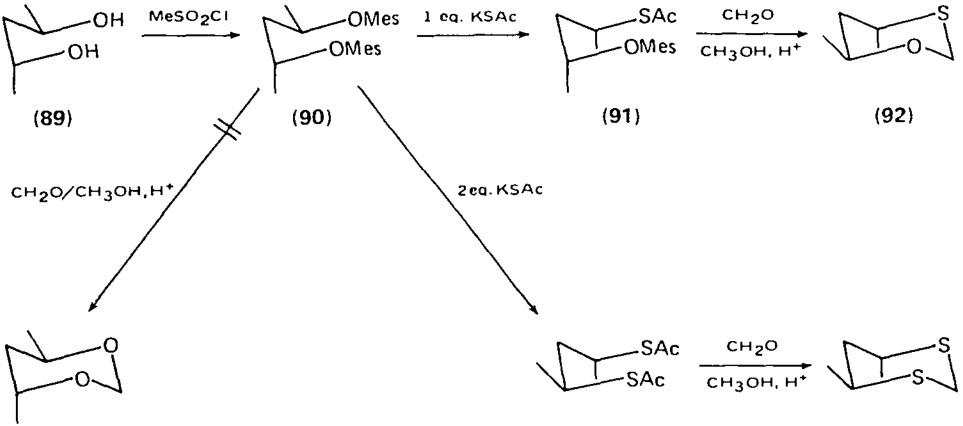
Most alkyl-substituted 1,3-oxathianes (88) can be synthesized by conventional acid-catalysed condensation of a suitable mercaptoalkanol and a carbonyl compound or its acetal in the case of sterically constrained molecules (equation 22)[111–119].



(88)

(22)

Certain derivatives are obtained in 90% yields by the ring-closure of mixed diesters (equation 23)[119,120]. Due to the stereospecifity of the whole reaction sequence from 1,3-diol (89) via the dimesylate (90) and the 2-mesyloxy-4-thiolacetoxypentane (91), optically active forms of 1,3-oxathianes (92) may be obtained if enantiomers of 89 are available in reasonable purity[120]. While the 1,3-dioxane (93) is not formed from 90, the disubstitution product (94) leads to 1,3-dithiane (95),



(23)

with the same configuration as **92**, indicating that the mechanism of the ring-closure does not involve hydrolysis of the OMes group, but rather that of the SAc function, followed by internal S_N2 displacement of the sulphonate grouping[120].

Some synthetic utility may be derived also from the reaction of **85** with *s*-butyllithium to give 1,3-oxathianyl-2-lithium, which on subsequent treatment with alkyl halides yields a variety of 2-alkylated 1,3-oxathianes[121]. Similarly, the acid-catalysed equilibration of **85** with 2-*R*-substituted 1,3-dioxanes leads to 2-*R*-1,3-oxathianes[122,123] in 79–95% yields.

3. *Structure*

There are no exact studies on the ring geometry of **85**, but ^{1}H-NMR data[111,114–116,118,119,124–135] for variously substituted derivates show that its fundamental conformation is a chair form with some special features due to the coexistence of oxygen and sulphur atoms in the same ring.

Although Gelan and Anteunis[128] tried to construct two deformed models for the chair form of **85**, this has later been shown to be a misinterpretation of the dissymmetric character of the 1,3-oxathiane ring itself[115,130–132,136].

Table 3 presents a collection of Buys–Lambert *R*-values $[R = {}^3J_{trans}/{}^3J_{cis}]$[130–133] and torsional angles $[\cos^2\psi = 3/(2 + 4R)]$[130–133] determined recently for some 1,3-oxathianes as well as those for certain 1,3-dioxanes and 1,3-dithianes. These values clearly demonstrate that oxygen-containing rings have an inherent tendency to flatten the $C_{(4)}-C_{(5)}-C_{(6)}$ moiety (in **86** and **97** $\psi_{4,5} = \psi_{5,6} = 55^\circ$), while their sulphur analogues favour a somewhat puckered shape (in **87** and **98** $\psi_{4,5} = \psi_{5,6} = 63^\circ$)[131–133]. Interestingly, **85** can still adopt a normally staggered arrangement, and contrary to a previous conclusion[126] the type of substitution does not seem to engender any profound effect ($\psi_{4,5} = \psi_{5,6} \sim 60^\circ$ in **85**, **96**, **100** and **101**), with the exception of derivatives with severe steric crowding in their

TABLE 3. *R*-values and torsional angles (ψ) in some 1,3-oxathianes, 1,3-dioxanes and 1,3-dithianes

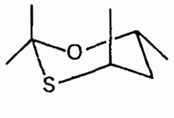
Compound		Side	*R*	ψ	Reference
(85)	1,3-Oxathiane	S	2.97	61	130
		O	2.29	59	130
(86)	1,3-Dioxane	O	1.76	55	131,132
(87)	1,3-Dithiane	S	3.23	63	131,132
(96)	2-Me-1,3-Oxathiane	S	2.38	59	115
		O	2.44	60	115
(97)	2-R-1,3-Dioxane[a]	O	1.81	55	132, 133
(98)	2-R-1,3-Dithiane[b]	S	3.23	63	132,133
(99)	2,2-Me_2-1,3-Oxathiane	S	2.47	60	130
		O	1.94	56	130
(100)	4,4-Me_2-1,3-Oxathiane	O	2.40	59	115
(101)	6,6-Me_2-1,3-Oxathiane	S	2.50	60	115
(102)	2,2-*trans*-4,6-Me_4-1,3-Oxathiane	O,S	1.65[c]	<54[c]	115

[a] R = *p*-chlorophenyl[132] or *t*-butyl[133].

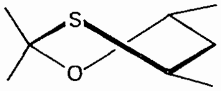
[b] R = phenyl[132].

[c] Average value for the $C_{(4)}-C_{(5)}-C_{(6)}$ moiety.

chair forms, e.g. **99** and **102**[115]. In fact, the average torsional angle (~ 54°) determined for 2,2-*trans*-4,6-tetramethyl-1,3-oxathiane (**102**) is characteristic of a 2,5-twist–boat (**102b**). In general, 1,3-oxathianes having various *syn*-axial 2,4- or 2,6-methyl–methyl interactions in their chair conformations favour some of the three conceivable (1,4-, 3,6-, or 2,5-) twist forms[114,115,137,138]. The basic geometry of the 1,3-oxathiane ring is also consistent with aromatic solvent-induced ^{1}H-NMR shifts of the ring protons[60] (see Section III.B).

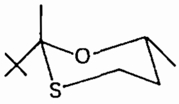


(102a)

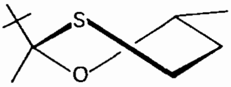


(102b)

As to the quantitative evaluation of different stereochemical preferences, most information apart from ^{1}H-NMR data has been provided by chemical equilibration[114,116,138–140] of proper epimeric 1,3-oxathianes. For instance, the chair–twist energy parameters for **85** were estimated[138] and recently recalculated[115] from equilibrium data for *r*-2-*t*-butyl-2,*cis*-6- (**103**), and *r*-2-*t*-butyl-2,*trans*-6-dimethyl-1,3-oxathianes (**104**) by making some relevant assumptions about the plausibility of contributing twist forms[115,137]. The values thus obtained for the chair–2,5-twist equilibrium (equation 24) are roughly intermediate to those evaluated for **86** and **87**[1,129] (Table 4), and indicate a fair additivity of the opposite trends. Conformational energies of methyl groups at different positions of the 1,3-oxathiane ring derived from equilibration data[138–140] are presented in Table 5 together with the corresponding values for the symmetric analogues **86** and **87**[1,129].



(103)



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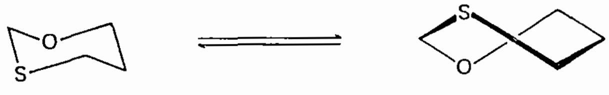


Chair 2,5-Twist (24)

As expected, steric demands are greatest around the 2-carbon atom as suggested also by the enhanced rate for ring-reversal[111] and the relatively short spin-lattice relaxation time of $C_{(2)}$[141] in 2,2-dimethyl-1,3-oxathiane. Due to the constrained nature of the dissymmetric ring (**85**), its $\Delta G^{\ominus}$(2-Me) is clearly higher than the mean value of the same interactions in **86** and **87**[1,111,129–139]. Positions 6 in **85** and **86** are energetically comparable whereas $\Delta G^{\ominus}$(4-Me) is enhanced in going from **87** to

TABLE 4. Chair–twist free energy, enthalpy and entropy differences for 1,3-oxathiane, 1,3-dioxane and 1,3-dithiane

Compound	$\Delta G^{\ominus}_{\mathrm{CT}}$ (kJ mol^{-1})	$\Delta H^{\ominus}_{\mathrm{CT}}$ (kJ mol^{-1})	$\Delta S^{\ominus}_{\mathrm{CT}}$ (J mol^{-1} K^{-1})	Reference
(85) 1,3-Oxathiane	23.5	27.0	11.6	115,138
(86) 1,3-Dioxane	33.5	35.8	9.1	1,129
(87) 1,3-Dithiane	11.0	16.7	19.0	1,129

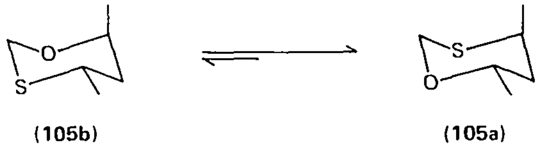
TABLE 5. Conformational preferences of the methyl groups at different positions in 1,3-oxathianes, 1,3-dioxanes and 1,3-dithianes

Parent compound	Conformational energy (kJ mol^{-1}) for different locations 2a	4a	5a	6a	References
(85) 1,3-Oxathiane	13.6	7.4	2.9–3.7	12.3	115,116,139,140
(86) 1,3-Dioxane	16.7	12.2	ca. 4	12.2	1,129
(87) 1,3-Dithiane	8.0	6.5	4.9	6.5	1,129

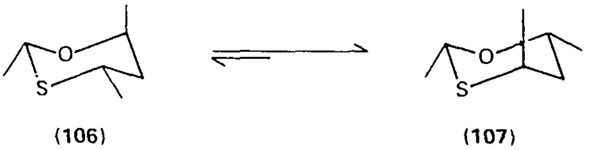
85 (6.5 vs. 7.4 kJ mol^{-1}) at the expense of some loss in torsional strain [111,115,129]. The relatively low ΔG° (5-Me) of 85 is, apart from the small steric requirements of the heteroatoms[111,129], a manifestation of the fundamental deformation of the ring, whereas the slightly higher estimate for 87 is attributed to the enhanced puckering of its $C_{(4)}-C_{(5)}-C_{(6)}$ region and/or to the large van der Waals' radius of sulphur as compared to oxygen[111,114,129].

From ^{1}H-NMR[126,134,135] and equilibration[126,135,138-140] studies it appears that the acceptance of the additivity principle is justified or at least of value in the semiquantitative evaluation of steric effects in simple 1,3-oxathianes. For instance, *trans*-4,6-dimethyl-1,3-oxathiane (**105**) involves the 4- (**105a**) and 6-axial (**105b**) conformations in a ratio of 87 : 13 as concluded from the vicinal ^{1}H–^{1}H coupling constants[126,134], in fair agreement with the energy difference obtained directly from the respective interactions in 1,3-dioxanes and 1,3-dithianes (12.2–6.5 = 5.7 kJ mol^{-1}) (Table 5).

Later on, however, the above result was argued in a study based on a chemical-shift method[119], which led to controversial thermodynamic parameters. The results of a chemical equilibration of suitable anancomeric model compounds, *r*-2-*cis*-4-*trans*-6- (**106**) and *r*-2-*trans*-4-*cis*-6-trimethyl-1,3-oxathianes (**107**) at various temperatures[139,140] firmly confirmed the original estimates[126,134] and made the chemical-shift method questionable.

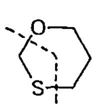


(105b) (105a)

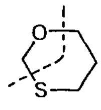


(106) (107)

Additional structural knowledge about the title compounds comes from electron impact mass spectrometric studies[142-145]. The main features in the positive-ion mass spectra of 1,3-oxathianes[142] are the relatively high intensity of molecular and large fragment ions, the abundance of metastable transitions and the preferential charge retention on sulphur-containing fragments over the oxygen analogues, probably due to the ability of sulphur to stabilize the electron deficiency with the aid of its d-shell electrons. The course of fragmentation depends somewhat on the substitution pattern but only two principal modes of ring cleavage (I and II) are found[142], which is different from the behaviour of 1,3-dioxanes but comparable rather to that of 1,3-oxathiolanes (see Section III.B.3)[62-64].



(I)



(II)

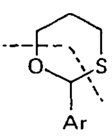
Measurement of the ionization and appearance potentials for a series of stereoisomeric 1,3-oxathianes has yielded information about their conformational energies in the gas phase[143]. According to the principles derived originally by Pihlaja and Jalonen[146] it was found that in the formation of the M^+ or $[M-Me]^+$ ions the nonbonding interactions are mainly released, so that differences in the ground-state enthalpies of isomeric structures can be evaluated from equations (25) and (26)[143,146,147], where AP is the appearance potential of the primary fragment

$$\mathrm{IP}([M]^+) - \mathrm{IP}([M_1]^+) = \Delta H_f^{\ominus}(M_1) - \Delta H_f^{\ominus}(M) \tag{25}$$

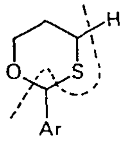
$$\mathrm{AP}([M-R]^+) - \mathrm{AP}([M_1-R]^+) = \Delta H_f^{\ominus}(M_1) - \Delta H_f^{\ominus}(M) \tag{26}$$

ion, IP the ionization potential and $\Delta H_f^{\ominus}$ the standard enthalpy of formation of the compound in question. The most interesting point was the observation[143] that $\Delta H_{CT}^{\ominus}$ for the 1,3-oxathiane family in the gaseous state (25 kJ mol^{-1}) is not far from the result obtained by chemical equilibration (ca. 27 kJ mol^{-1})[115,138]. Also the values of other conformational energies from appearance and/or ionization potentials are in fair agreement with the liquid-phase values[115,139].

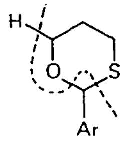
Bowie and Ho[144] studied negative-ion mass spectra of 2-aryl-1,3-oxathianes (2-aryl = *o*-, *m*- or *p*-nitrophenyl). The spectra were characterized by intense molecular anions and large fragment ions produced by simple (I–III) or complex modes of cleavage. With the aid of deuterated derivatives the authors[144] were able



(I)



(II)

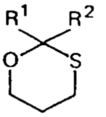


(III)

to show that the extent of hydrogen randomization between the 2-, 4- and 6-positions depends in a specific way upon the isomer in question, the behaviour of which parallels that noted for corresponding 1,3-dithianes[145] but is in marked contrast to isomeric 2-nitrophenyl-1,3-dioxanes[144] which display mutually very similar spectra and exhibit no hydrogen scrambling.

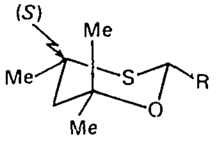
4. Reactions

Pihlaja and coworkers[148] determined the relative rates for the acid-catalysed hydrolysis of 1,3-oxathiane (**85**), 2-methyl-1,3-oxathiane (**108**) and 2,2-dimethyl-1,3-oxathiane (**109**) and found that the acceleration effect for **108** is exceptionally low in comparison with 1,3-oxathiolanes[65]. A possible explanation is the acidic character of the protons at position 2 in **85** and **108**, but the exact mechanism for the hydrolytic decomposition of 85, 108 and related molecules is not clear and requires further study[149].

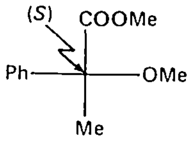


(85) $R^1 = R^2 = H$
(108) $R^1 = H, R^2 = Me$
(109) $R^1 = R^2 = Me$

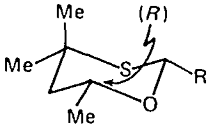
Eliel and his colleagues[150] described an asymmetric synthesis of (*S*)-(+)-atrolactic acid methyl ether (110) proceeding either from (*S*)-(–)-4,6,6-trimethyl-1,3-oxathiane (111, R = H) with about 100% optical yield, or from (*R*)-(+)-4,4,6-trimethyl-1,3-oxathiane (112, R = H) with ca. 92% optical yield. The reaction sequence involves a stereoselective electrophilic attack on a biased 2-lithio-1,3-oxathiane leading exclusively to equatorial substitution, where the original chirality at $C_{(4)}$ or $C_{(6)}$ is transferred to $C_{(2)}$, and an asymmetric reaction of a Grignard reagent to yield 111 (R = (*S*)-C(OH)MePh) with an exocyclic asymmetric centre which after methylation, ring-cleavage and oxidation produces 110[150].



(111)



(110)

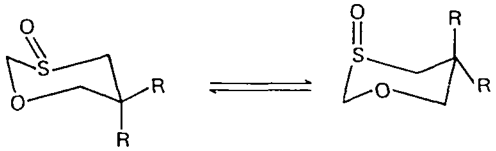


(112)

For the reduction of cyclic monothio-acetals and -ketals, see Section III.B.4.

C. 3-Oxo-1,3-oxathianes

Only a few reports[151–153] have appeared on the properties of the title compounds, although they offer an easily preparable model to study the often unexpected interactions between polar functions. For instance, 113 was obtained in high yield (94%) by treatment of 1,3-oxathiane (85, see Section IV.B.2) with sodium metaperiodate in water–methanol solution[151].



(a) (b)

(113) R = H
(114) R = Me

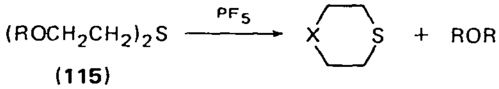
Conformational preferences in 113[152,153] and 114[153] were examined by ^{1}H-NMR spectra. Interestingly, at ambient temperatures 113a and 113b are nearly equally populated, whereas at –95°C 113b is reported to predominate in a ratio of 8 : 1[152] which is approximately in agreement with the result of 84 : 16 at –98°C ($-\Delta G^\circ = 2.4$ kJ mol^{-1})[153]. In 114 with *gem*-dimethyl grouping at the 5-position, the proportion of 114b is drastically lowered (114b/114a ~ 1 : 9 and $-\Delta G^\circ \sim 3.0$ kJ mol^{-1})[153]. Consequently, the disfavouring effect caused by *syn*-axial S=O and methyl groups would amount to 5.4 kJ mol^{-1}.

These results are pronouncedly different from those observed for thiane-1-oxides ($-\Delta G^{\circ} = 0.73$ kJ mol^{-1} in favour of the axial S=O form)[154], and for 1,3-dithiane-3-oxides (equatorial preference of S=O at and below ambient temperatures)[152,153], emphasizing the difficulties in evaluating interactions between polar groups and lone-pair electrons.

D. 1,4-Oxathianes

1. Preparation

1,4-Oxathianes have been synthesized with a variety of different methods of which the most recent ones will be described in the following. Karabinos and Hazdra[155] obtained 1,4-oxathiane (**116**) and 1,4-dithiane (**117**) in a 7 : 1 ratio from the cyclization of thiodiethyleneglycol (**115**) upon treatment with PF_5 (equation 27).



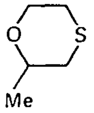
(27)

(**115**)

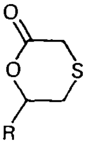
(**116**) X = O

(**117**) X = S

Black prepared 2-methyl-1,4-oxathiane (**118**) from 1-(2-hydroxyethylthio)-2-propanol by dehydration with orthophosphoric acid and some 2-oxo-1,4-oxathianes (**119**) from the reactions of thioglycolic acid with oxiranes[156].

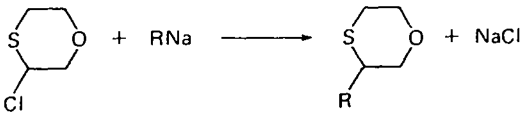


(**118**)



(**119**) R = H, Me, Ph

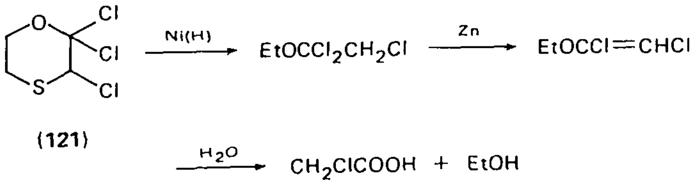
3-Chloro-1,4-oxathiane (**120**) has been prepared by chlorinating the parent compound with *N*-chlorosuccinimide[157] or with Cl_2 in CCl_4 at ca. 260 K[158]. In a reaction with RNa **120** gave different 3-substituted 1,4-oxathianes (equation 28)[158].



(28)

(**120**)

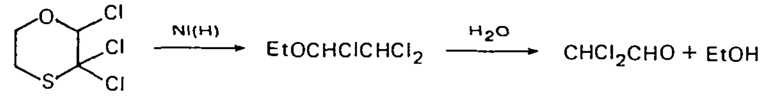
Evans and Mason[159] used a modification of the Haubein method[160] to synthesize 2,2,3- (**121**) and 2,3,3-trichloro-1,4-oxathianes (**122**), both of which were shown with the aid of the hydrolysis products to be substituted on the same side. The structure of **121** was confirmed by desulphurization (equation 29) which



(**121**)

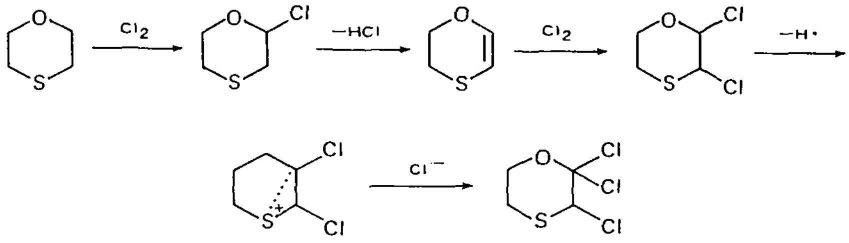
(29)

resulted in the formation of monochloroacetic acid and ethanol. Similarly, **122** gave dichloroacetaldehyde and ethanol (equation 30). The formation of **122** is consistent with the chlorination and thermal dehydrohalogenation of diethyl ether[161] whereas for that of **121** at 353 K an entirely different mechanism must be postulated (equation 31)[159,162].



(122)

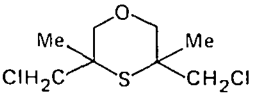
(30)



(121)

(31)

Hydrogenolysis of the acetal function of 2,8-dioxa-6-thiabicyclo[3.2.1]octanes also affords 1,4-oxathianes[163]. Reaction of $(CH_2{=}CCH_3CH_2)_2O$ with SCl_2 gives 3,3-dichloromethyl-3,3-dimethyl-1,4-oxathiane (**123**)[164] and hydrolysis of $(ROCHClCH_2)_2S$ yields 2,6-dialkoxy-1,4-oxathianes (**124**)[165].



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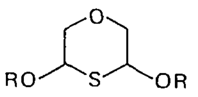

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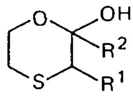
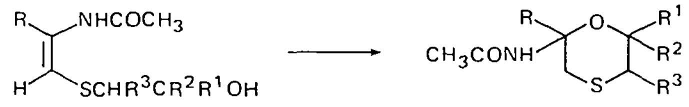


(126)

Blagoveschchenskii and colleagues[166] prepared several 2- and 3-substituted 1,4-oxathianes by treatment of 1,4-oxathiene and 3-chloro-1,4-oxathiane with RH (R = Me_3CO, PrS, Me_3CS, Me_2EtCS, $PhCH_2S$, PhS, $(MeO)_2P(S)S$ and $(EtO)_2P(S)S$), respectively. Acetamido-substituted 1,4-oxathianes (**125**) can be obtained through the base- or acid-catalysed intramolecular cyclization of *S*-hydroxyalkylated 2-acetamidopropenethiolates (equation 32)[167].



(125)

(32)

1,4-Oxathianes have also been prepared by mercuric salt ring-closure from diallyl sulphide[168] and by cyclization upon electrochemical fluorination of **115** (R = H)[169]. The reaction of 2-mercaptoethanol with $R^1CHXCOR^2$ (X = halogen) in C_6H_6 containing KOAc gives substituted 1,4-oxathianes (**126**) in good yields[170].

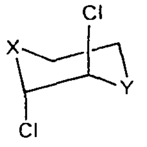
Some 2-oxo-1,4-oxathianes have been prepared by heating mercaptoacetic acid with oxirane or substituted oxiranes[171] as well as by intramolecular dehydration of $HOCH_2CHRSCH_2CO_2H$(R = H, Me)[172]. These methods have been used to synthesize the corresponding seven-membered compounds, 2-oxo-1,4-oxathiepanes (see Section V.A.).

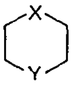
2. *Structure*

The conformation and structural characteristics of 1,4-oxathiane and many of its derivatives[155,173,174] have been extensively studied. Jensen and Neese[175] determined the activation parameters for the ring-reversal process (chair to twist) of 1,4-oxathiane and found them to be $\Delta H^{\neq}$ 37 ± 3 kJ mol^{-1}, $\Delta S^{\neq}$ 2 ± 1 J mol^{-1} K^{-1} and $\Delta G^{\neq}$ 36 ± 1 kJ mol^{-1}. The free energies of activation measured for the ring-reversal of 2-oxo-1,4-oxathiane and its 6-methyl, 5-phenyl and 6-phenyl derivatives are 41, 73, 79 and 79 kJ mol^{-1}, respectively[176].

The microwave[177], IR and Raman[178], and electron diffraction[179,180] results for 1,4-oxathiane are all in accord with a chair form. The crystal structure of *trans*-2,3-dichloro-1,4-oxathiane (**127**) shows that the molecule has a chair conformation with the chlorine atoms in axial positions[181]. The overall geometry of **127** is halfway between the conformations of the corresponding *trans*-2,3-dichloro derivatives of 1,4-dioxane (**128**) and 1,4-dithiane (**129**)[182–185]. The torsional angle in **127** is 60° from the values of the vicinal ^{1}H-coupling constants using the Buys–Lambert approach[132,186] in good agreement with the diffraction results[181]. **128** is somewhat less puckered since its torsion angle is only 57°.

Crossley and coworkers tried to apply an improved microwave procedure to the detailed conformational study of 1,4-diheterocyclohexanes (**116**, **117** and **130**) but with a relatively small amount of new information[187]. In a number of papers Zefirov and colleagues[188,189] have studied the conformational properties of 2-substituted 1,4-oxathianes and heteroanalogues of bicyclo[3.3.1]nonane[189,190]. The results of these investigations have been already reviewed[2].





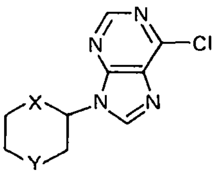
(**127**) X = O, Y = S
(**128**) X = O, Y = O
(**129**) X = S, Y = S

(**116**) X = O, Y = S
(**117**) X = S, Y = S
(**130**) X = O, Y = O

Burdon and Parsons synthesized different highly fluorinated 1,4-oxathianes[191] and deduced their structures from the ^{19}F-NMR spectra by a chemical-shift parameter scheme[192]. The majority of the compounds exist in chair conformations, with a strong anomeric effect or its equivalent operating both α to oxygen and α to sulphur[192]. A comparison with a similar set of polyfluorinated 1,4-dioxanes has also been made. Phillips and Wray[193] evaluated an additive method of calculating $^2J_{HF}$ in polyfluoro-1,4-dioxanes and -oxathianes and stated that the approach may be useful in stereochemical and conformational studies of related molecules.

Szarek and colleagues[194] studied the ^{13}C-NMR spectra of a number of 1,4-oxathianes including 4-oxo and 4,4-dioxo derivatives and applied the results to carrying out a structural differentiation of the two nucleotides **131** and **132**.

Condé-Caprace and Collin[195] discussed the various modes of fragmentation of **116** and **117** and found that they are qualitatively very similar but differ considerably from those of 1,4-dioxane (**130**)[196] (see also Sections III.B.3 and IV.B.3).



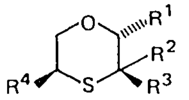
(131) X = O, Y = S
(132) X = S, Y = O

Obviously the influence of the sulphur atom predominates in the case of oxathiacyclanes[62-64,142,195].

Sweigart and Turner[197] studied the photoelectron spectra and lone-pair ionization potentials in some oxygen and sulphur heterocycles including **116** and interpreted the lone-pair interactions in terms of through-space and through-bond mechanisms; the latter is favoured in **116**, **117** and **130**, whereas 1,3-diheterocyclanes prefer the former.

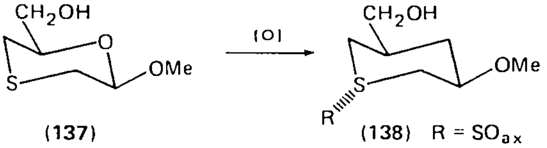
3. Reactions and 4-oxo-1,4-oxathiane

Havinga and coworkers[198] studied the chlorination of **116** under different conditions and prepared 3-chloro- (**133**), *trans*-2,3-dichloro- (**127**), 3,3-dichloro- (**134**), 2,3,3-trichloro- (**121**), *cis*-3,5-dichloro- (**135**) and *trans*-2,3,3,5-tetrachloro-1,4-oxathianes (**136**). The substitution takes place preferentially at $C_{(3)}$ and, up to three chlorine atoms, in the same half of the ring. The use of peroxides favours substitution at $C_{(2)}$.



	R^1	R^2	R^3	R^4
(133)	H	H	Cl	H
(134)	H	Cl	Cl	H
(135)	H	H	Cl	Cl
(136)	Cl	Cl	Cl	Cl

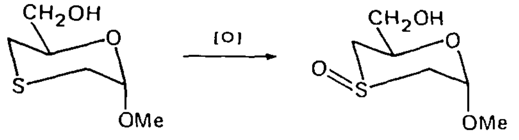
The oxidation of **116** by H_2O_2 in several solvents and mixed-solvent systems and the influence of solvent on the mechanistically related *t*-butyl hydroperoxide oxidation have also been studied[199]. Foster and colleagues[200,201] treated **137** with $NaIO_4$ and obtained a 10 : 1 mixture of the axial (**138**) and equatorial (**139**) sulphoxides. With O_3 the sulphoxides were obtained in about equimolar yields. In general, the control of *S*-oxidation was best achieved by variation of the configuration at the anomeric centre, $C_{(2)}$; an axial substituent engenders equatorial *S*-oxygenation whereas an equatorial substituent leads to an axial *S*-oxide.



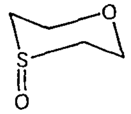
(137)

(138) R = SO_{ax}
(139) R = SO_{eq}

Foster and coworkers[202] also used ^{1}H-NMR spectra to assign sulphoxide configuration using the significantly different shielding effects of axial and equatorial S=O groups[203]. A crystal structure determination[204] established that the major sulphoxide obtained by $NaIO_4$ oxidation of *trans*-2-methoxy-6-hydroxymethyl-1,4-oxathiane (**140**) has the *trans*-4-methoxy, *cis*-6-hydroxymethyl, *r*-4-oxo configuration (**141**) in agreement with ^1H-NMR results[205].



(140) (141)



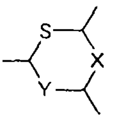
(142)

^{13}C-NMR data[203,206] for 4-oxo-1,4-oxathiane (**142**) indicate that the sulphinyl oxygen prefers the axial position by 2.8 kJ mol^{-1} at 205 K. This is at least in qualitative agreement with the report[207] which on the basis of IR and Raman spectra (solid and liquid samples) considers the oxide to have the C_s chair-axial conformation (**142**).

1,4-Oxathiane (**116**), like 1,4-dioxane (**130**), easily forms complexes with iodine[208], $ZnMe_2$[209] and many metal halogenides[210–213], but this topic will not be considered here.

E. 1,3,5-Oxadithianes and -Dioxathianes

The title triheterocyclohexanes are not well characterized. The reaction of saturated aldehydes with gaseous H_2S has been reported[214] to give **143**–**145**. Some 4-alkoxy-4-alkyl derivatives of **144** can be obtained in 40–50% yield by treating sodium oxydimethylenedithiosulphate with CH_3COOR in absolute propanol in the presence of HCl for 7–8 h[215]. Dipole moment and ^1H-NMR studies show that at least the most stable isomer of **143** exists in a chair conformation with three equatorial substituents[216].

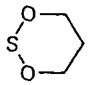


(143) X = O, Y = O
(144) X = S, Y = O
(145) X = S, Y = S

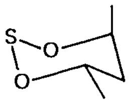
Oxidation of **144** with perhydrol for 2.5 h at 333–338 K gives the 3,3,5,5-tetroxide in nearly quantitative yield[215]. The H–D exchange at $C_{(2)}$ of **145** accelerates when $S_{(5)}$ is converted to a sulphinyl or sulphonyl group. The remote participation of the sulphur atom is also seen in the slow H–D exchange at $C_{(6)}$ of **143**[217].

F. 1,3,2-Dioxathianes

Very little attention has been paid to 1,3,2-dioxathianes, although their 2-oxides have been widely studied (see Section IV.G). Since the early attempts[103] [see also Section III.E] to prepare 1,3,2-dioxathiane (**146**) and some of its alkyl derivatives Wood and coworkers[218,219] have reported the synthesis of a number of methyl-substituted 1,3,2-dioxathianes. The barrier ($\Delta G^{\neq}$) to the ring-reversal of **146** is somewhat higher than that for cyclohexane or 1,3-dioxane but lower than that for 1,2,3-trithiane[219]. ^{13}C-chemical shifts for *trans*-4,6-dimethyl-1,3,2-dioxathiane (**147**) have also been reported[110]. The above results are still in some doubt since one of the present authors[220] has not been able to repeat the preparation of the materials.



(146)

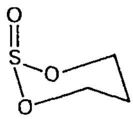


(147)

	δ (p.p.m.)
$C_{(4,6)}$	74.8
$C_{(5)}$	39.4
$\underline{C}H_{3(4,6)}$	19.7

G. 2-Oxo-1,3,2-dioxathianes

These compounds are cyclic sulphites and can be easily prepared from $SOCl_2$ and 1,3-diols[94,221–224]. Despite the fact that during the last 10–15 years some 40 papers have been published on the structure of **148** and its alkyl and halo derivatives a considerable extent of controversy has been left in the detailed explanation of the results. Very recently it was pointed out that both ^{1}H-NMR spectra and dipole moments can be interpreted consistently only if **148** and its alkyl derivatives greatly prefer chair forms (usually with an axial S=O group)[224]. In the same context the chair form of **146** is estimated to be ca. 31 kJ mol^{-1} more stable than the twist form[224]. Two other recent reports[225,226] confirm the conclusions made by Pihlaja and coworkers[224] as to the high preference of the chair form and withdraw, together with the latter and some other consistent publications[131,227–241], the significance of the discussion based on the existence of simple alkyl-substituted derivatives in the twist form[94,109,110,222,242–253]. In a forthcoming report[230] a correct assignment of the IR bands in the 1180–1250 cm^{-1} region also disproves the necessity of twist forms in contrast to opposite claims[247,252,253]. The only substituted 2-oxo-1,3,2-dioxathiane which has been proved to attain a twist conformation is *trans*-5-chloro, *cis*-4, *trans*-6-di-*t*-butyl, *r*-2-oxo-1,3,2-dioxathiane (**149**)[227]. A complete discussion as to the detailed structure and properties of **148** and its derivatives will be published in a separate review[230] and in some future reports[228–230].



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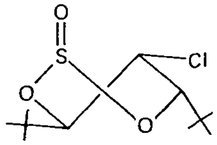
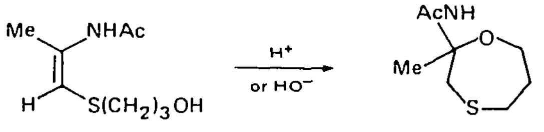


(149)

V. SEVEN-MEMBERED AND LARGER RINGS

A. 1,4-Oxathiepanes

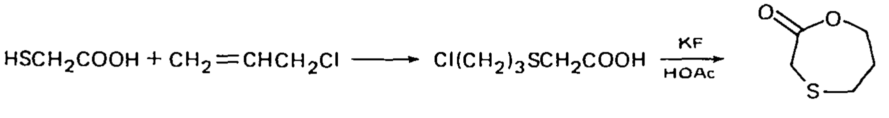
Acetamido substituted 1,4-oxathiepane (**150**) can be prepared via acid- (or base-) catalysed intramolecular cyclization of the *Z*-isomer of *S*-hydroxyalkylated 2-acetamidopropenethiol (**151**) (equation 33)[254]. The structure of **150** was stated to be confirmed by conventional means but no data were reported[254]. Attempts to synthesize eight-membered rings by lengthening the hydroxyalkyl chain failed[254].


Me
NHAc
H
S(CH2)3OH
H+
or HO−
AcNH
O
Me
S

(33)

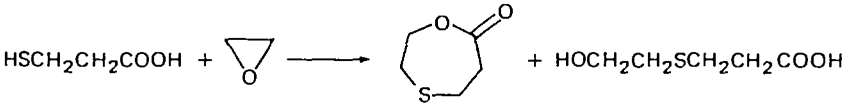
(151) (150)

Preparations of 2-oxo-1,4-oxathiepane (152) (equation 34)[172], and 7-oxo-1,4-oxathiepane (153) (equation 35)[171] have also been reported. The latter synthesis utilizing the ring-cleavage of oxiranes by β-mercaptopropionic acid (154) leads to appreciable amounts of 155 as a by-product[171].


HSCH2COOH + CH2=CHCH2Cl
Cl(CH2)3SCH2COOH
KF
HOAc
O
O
S

(34)

(152)

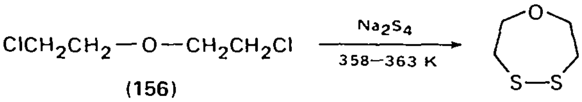

HSCH2CH2COOH +
O
O
O
S
+ HOCH2CH2SCH2CH2COOH

(35)

(154) (153) (155)

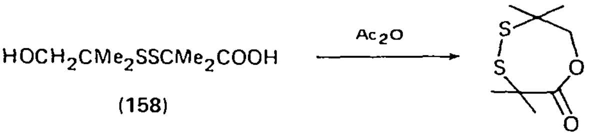
B. 1,4,5-Oxadithiepanes

1,4,5-Oxadithiepane (157) is obtained by treating 156 with Na_2S_4 at 358–363 K in aqueous solution in the presence of sodium alkylnaphthalenesulphonate, NaOH and $MgCl_2$ (equation 36)[255]. Cannizzaro reaction of 2,2′-dithiobis(2-methylpropanal) in aqueous NaOH yields 158 which is readily cyclized in the presence of Ac_2O to 2-oxo-1,4,5-oxadithiepane (159) (equation 37)[256]. Both 157[255,257] and 159[256] are readily polymerized by alkoxide, alkylaluminium and metal hydride catalysis.


ClCH2CH2—O—CH2CH2Cl
Na2S4
358–363 K
O
S—S

(36)

(156) (157)


HOCH2CMe2SSCMe2COOH
Ac2O
S
S
O
O

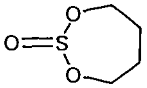
(37)

(158) (159)

Heats of polymerization for 157 in bulk, C_6H_6 and 1,4-dioxane solutions were measured by Dainton and coworkers[257] who suggested an anionic mechanism for iodine-catalysed reaction in which I^- is assumed to be the initiator.

C. 2-Oxo-1,3,2-dioxathiepanes

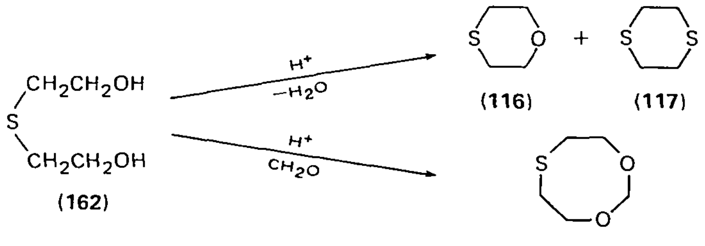
Seven-membered cyclic sulphites (160) can be similarly synthesized, though in lower yields than their six-membered homologues (see Section IV.G.), e.g. by treatment of the corresponding diol with $SOCl_2$[258-261]. Structural information about **160** is very limited. According to ^1H-NMR and IR measurements by Faucher and Guimaraes[262] the most favoured form at room temperature is a chair, but the detailed conformational behaviour remains an open question. Hydrolysis of **160** under acidic or alkaline conditions was found to occur by a bimolecular (A2) mechanism[259,263] which is also normal for lower homologues and acyclic sulphites[263].



(160)

D. 1,3,6-Dioxathiocanes

1,3,6-Dioxathiocane (**161**) is a true acetal, and can be smoothly prepared via condensation of thiodiethylene glycol (**162**) and formaldehyde (equation 38)[264,265].



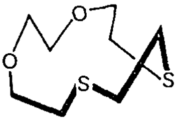
(38)

Direct cyclization of **162** gives 1,4-oxathiane (**116**), or after disproportionation, 1,4-dithiane (**117**)[264] (see also Section IV.D.1). In an IR study of **161** and related heterocycles Tarte and Laurent[266] discovered that the oxygen atom has little effect on the CH_2 deformation frequency whereas sulphur lowers that of adjacent CH_2 groups by ca. 40 cm^{-1}.

Mass spectrometric fragmentation of **161**[267] includes the loss of CH_2O and the formation of the 1,4-oxathiane molecular ion in the primary stage, and secondary transitions lead to the same fragment ions with similar relative abundances as observed for **116** which is a common mode for seven- and six-membered oxygen heterocycles[268].

E. Macrocyclic Rings

Several polyether sulphides containing 9–21 ring atoms have been prepared[269] by treatment of an oligoethylene glycol with a suitable dithiol or Na_2S in ethanol solution. The crystal structure of the molecules exhibits certain nonplanar regular arrangements of the ethylene 1,4-dithia, 1,4-oxathia and 1,4-dioxa fragments as evidenced by X-ray analysis. Also ^1H-NMR spectra recorded for some members



(163)

such as 1,4-dithia(12-crown-4) (**163**) are reported to be consistent with the assumed stereostructures[269].

VI. REFERENCES

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 19

Allene oxides and related species

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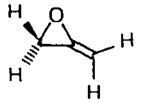
I. INTRODUCTION

Allene oxide (1) is a member of the family of strained small-ring compounds. The parent compound itself is part of the C_3H_4O energy surface that besides **1** includes cyclopropanone (2), oxyallyl (3) and 4, all of which are valence tautomers. Allene oxides contain within their framework the structural elements of an enol ether, a double bond and an epoxide, elements that cause them to be of considerable intrinsic interest.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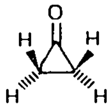
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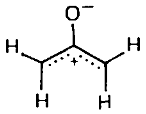
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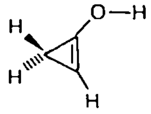
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Despite their intrinsic interest as well as their close relationship to the well-known and extensively investigated epoxides, little was known about allene oxides until recently. This surprising lack of investigation is due to their considerable instability and high reactivity, particularly in comparison to normal epoxides. However, within the last dozen years, allene oxides have been the subject of both theoretical and experimental attention. This chapter will provide an account and summary of the available data through late 1978. Separate sections will deal with theoretical calculations, preparation and chemistry of allene oxides. A final section will briefly cover the little that is known about related species such as allene episulphides, oxaspiropentanes, etc.

II. THEORETICAL CALCULATIONS

A number of quantum-mechanical calculations dealing with the C_3H_4O energy surface have appeared. The majority of these calculations deal with the interconversions between cyclopropanone (2) and oxyallyl (3) but several also treat allene oxide (1). The results of these calculations are summarized in Table 1.

It is evident from the data in Table 1 that with the exception of EHMO, calculations predict 2 to be more stable than either 1 or 3. In fact, 1 is predicted to be some 6–21 kcal/mol less stable than 2. All calculations except EHMO also predict that singlet oxyallyl (3) resulting from the disrotatory ring-opening[8] of 2 is a high-energy species with some 36–232 kcal/mol above 2 and therefore higher in energy than even 1.

Besides disagreement on the relative stabilities of these species as determined by the various calculational methods, there is the question of the exact mechanism of interconversion or isomerization between 1, 2 and 3. Liberles and coworkers[4,5] consider 3 to be an intermediate (or at least a transition state) in the known (see below) isomerization of 1 to 2. Although substituted oxyallyls have been postulated as intermediates[9] and even as stable entities[10], the actual evidence for their existence is rather scant.

A novel pathway, shown in Figure 1 and Scheme 1, for the isomerization of allene oxide (1) to cyclopropanone (2) was proposed by Zandler and coworkers[6]

TABLE 1. Theoretical calculations of the C_3H_4O energy surface

	Relative energies (kcal/mol)[b]			
Calculation[a]	1	2	3	Reference
EHMO	–21	0.0	–23	1
MINDO/2	*c*	0.0	78	2
INDO	*c*	0.0	220	3
INDO	6	0.0	232	4
ab initio SCF	21	0.0	83	4
MINDO	*c*	0.0	36	5
CNDO/2	*c*	0.0	110	6
MINDO/3	*c*	0.0	66	7

[a] See original reference for definition and details.
[b] Relative to cyclopropanone (2): negative energy indicates greater stability than 2, positive energy indicates lower stability than 2.
[c] Not given.

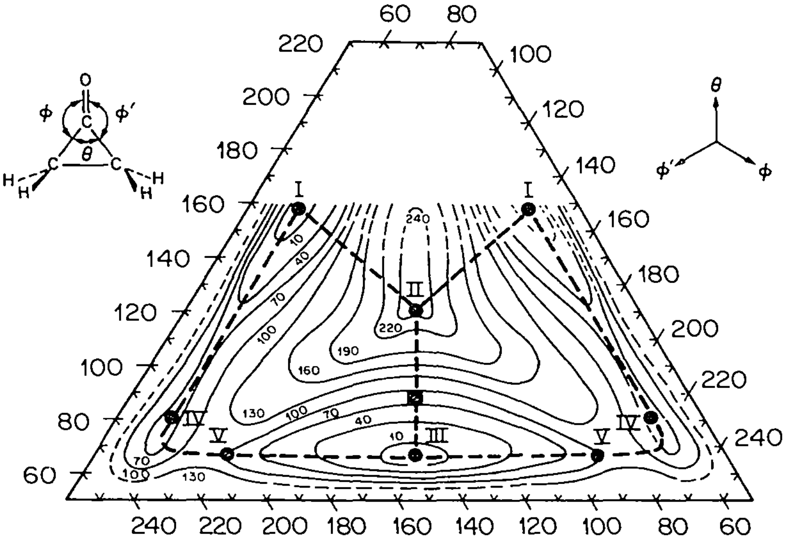
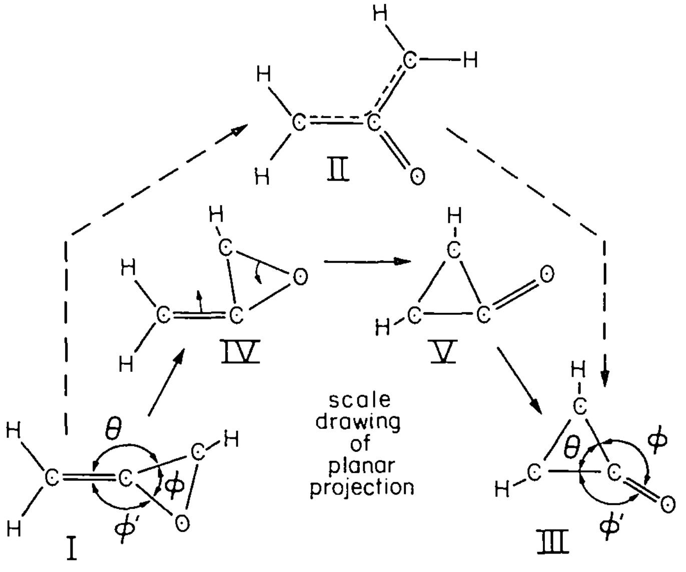


FIGURE 1. Contour diagram of the CNDO/2 energy surface for the allene oxide–oxallyl–cyclopropanone system. The contour spacing is 30 kcal/mol. Reprinted with permission from M. E. Zandler, C. E. Choc and C. K. Johnson, *J. Amer. Chem. Soc.*, **96**, 3317 (1974). Copyright by the American Chemical Society.

The Zandler pathway primarily involves bending motions via I → IV → V → III of Scheme 1 for the allene oxide–cyclopropanone isomerization. Such a pathway has only one half the energy barrier of the pathway via II. The lower barrier was suggested[6] to be the result of the lower energy requirements of bond bending compared to bond stretching. Stabilization due to delocalization in II is apparently insufficient to compensate for destabilization due to bond breakage[6]. On the



SCHEME 1. Reprinted with permission from M. E. Zandler, C. E. Choc and C. K. Johnson, *J. Amer. Chem. Soc.*, **96**, 3317 (1974). Copyright by the American Chemical Society.

CNDO/2 energy surface, the three-membered ring is preserved intact until bending allows another ring to form with minimal bond stretch (Figure 1). However, as the authors point out[6], the reliability of this novel isomerization mechanism is hard to assess since CNDO/2 is known to overestimate bond force constants causing excess resistance in bond stretching. Ring strain may be improperly estimated as well. It will be interesting to see if these results hold up under more sophisticated *ab initio* calculations or if the pathway via oxyallyl (II) is the true theoretically predicted one for the allene oxide–cyclopropanone interconversion. The Zandler mechanism versus the oxyallyl pathway may be subject to experimental verification. Rearrangement of an optically active allene oxide should result in an optically active cyclopropanone via the Zandler pathway, whereas it should give racemic cyclopropanone via the intermediacy (or transition state) of the planar symmetrical oxyallyl. No such experimental data are available to date.

A semiempirical calculation has also been done on the ring-opening of substituted cyclopropanones to the corresponding oxyallyls[5]. Unfortunately, the corresponding substituted allene oxides were not considered. This calculation shows that methyl-, methoxy- and fluorine-substituted cyclopropanones undergo ring-opening to oxyallyl more readily than the parent compound but the exact magnitudes of the energy differences between the appropriate isomeric cyclopropanone and oxyallyl are unreliable[5].

Recently, an estimate of the thermodynamic energy difference between allene oxide (1) and cyclopropanone (2) has been made[11] by means of the appropriate bond dissociation energies[12]. This estimate showed 2 to be 22 kcal/mol more stable than the isomeric 1. This 'thermodynamic' value of 22 kcal/mol is remarkably close to the 21 kcal/mol difference between 1 and 2 predicted by *ab initio* calculations[4] (see Table 1). Although this agreement is likely to be fortuitous, other indirect data from microwave[13] and photoelectron spectroscopy[14] studies on 2 also suggest 2 to be the most stable isomer on the C_3H_4O energy surface.

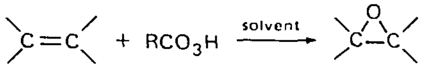
III. PREPARATION

Allene oxides have been proposed as intermediates, along with cyclopropanones, in the Favorskii reaction[15,16]. As yet, no allene oxides and only a few cyclopropanones have been trapped in the Favorskii reaction[17]. Indeed very few allene oxides at all have been isolated as stable compounds at room temperature.

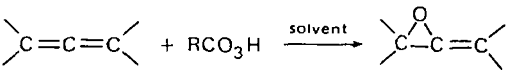
There are two main approaches to the synthesis of allene oxides: peracid oxidation of allenes and exocyclic β-elimination of an epoxide. Each of these will be discussed in turn together with some miscellaneous methods.

A. Peracid Oxidation of Allenes

Analogously to normal epoxidation of olefins via peracids, peracid oxidation would seem the logical and simplest entry into allene oxides (equations 1 and 2).



(1)

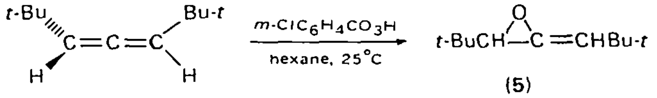


(2)

As part of an extensive investigation of epoxidation reactions, Boeseken[18] investigated the reaction of peracetic acid with 1,1-dimethylallene and reported 3-acetoxy-

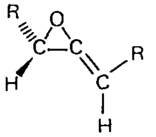
3-methyl-2-butanone but no allene oxide as part of the products. Early Russian work[19] reported dioxidation products, albeit with meagre evidence, in the peracid reaction of several substituted allenes. More recently, an extensive investigation of peracid oxidation of various allenes has been carried out by Crandall and coworkers[20-25]. As will be shown in Section IV there is little doubt that allene oxides are involved in many of these peracid oxidations of allenes. However, except in two instances they could not be isolated as stable compounds owing to their great propensity to react with nucleophiles, undergo further epoxidation to the allene dioxide and in some instances isomerize to the corresponding cyclopropanone.

The first stable allene oxide was prepared and isolated by Camp and Greene[26] by the reaction of *m*-chloroperbenzoic acid with excess 1,3-di-*t*-butylallene in hexane (equation 3). The allene oxide 5 is a colourless liquid, stable for long

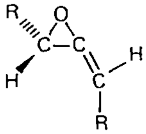


(5) (3)

periods at room temperature, with spectral properties fully consistent with its structure[26]. There are two geometric isomers possible for any 1,3-disubstituted allene oxide, **6a** and **6b**. The simplicity of the NMR spectrum of **5** (CCl_4), δ0.98 (s, 9H), 1.08 (s, 9H), 3.25 (s, 1H), 4.82 (s, 1H) suggests that it is a single species but of unknown geometry.

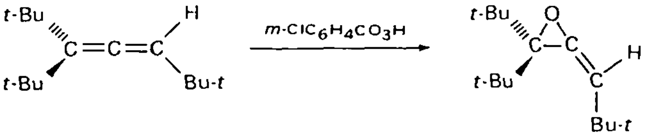


(6a)



(6b)

Reaction of 1,1,3-tri-*t*-butylallene (**7**) with *m*-chloroperbenzoic acid gave the stable tri-*t*-butylallene oxide (**8**)[24] (equation 4).

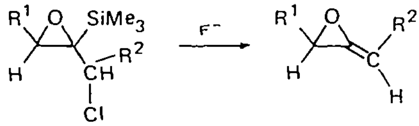


(7) (8) (4)

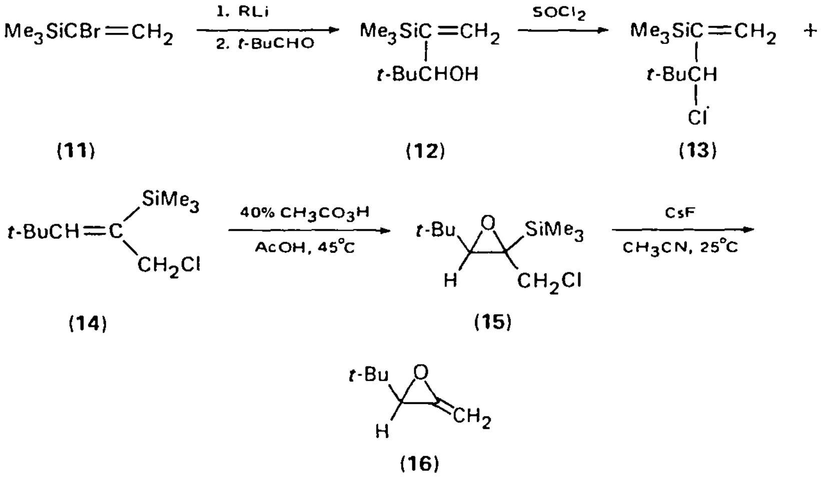
Allene oxides **5** and **8** undoubtedly owe their considerable stability to the bulky *t*-butyl substituents that provide steric stabilization by preventing the usual (see below) interaction with nucleophiles.

B. Exocyclic β-Elimination of Epoxides

An elegant synthesis of allene oxides has been developed by Chan and coworkers[27-30] via dehalosilylation[31] of epoxides (**9**) (equation 5). This approach



(9) (10) (5)

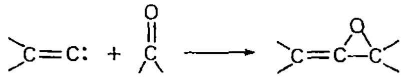


SCHEME 2.

has the advantage that the epoxide ring is preformed by standard techniques with a subsequent elimination under very mild conditions to generate the double bond and hence the final allene oxides (10). This approach has been successfully applied to the preparation and isolation of 1-*t*-butylallene oxide (16) as shown in Scheme 2. Reaction of vinylsilane (11) with alkyllithium followed by pivaldehyde gave alcohol (12) which gave a mixture of chlorides 13 and 14 upon treatment with $SOCl_2$[32]. Epoxidation of 14 gave epoxide 15 which upon fluoride-initiated dehalosilylation gave the product 16[30]. Allene oxide (16) was formed, in 55% yield from 15, as a colourless liquid which is stable in dilute solutions at room temperature for 1–2 h followed by polymerization[30]. Numerous other allene oxides were prepared *in situ* via this technique and reacted with various nucleophiles as will be discussed in Section IV.

C. Miscellaneous Methods

An interesting approach to allene oxides consists of the addition of an unsaturated carbene[33] (17) to a carbonyl group (equation 6). Such a reaction has been

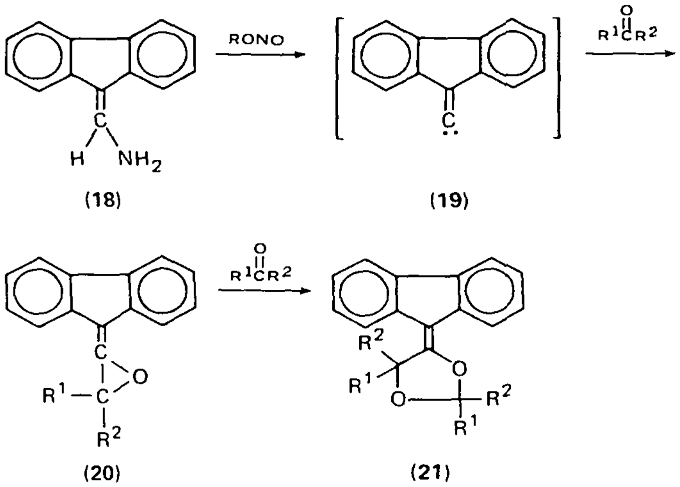


(17)

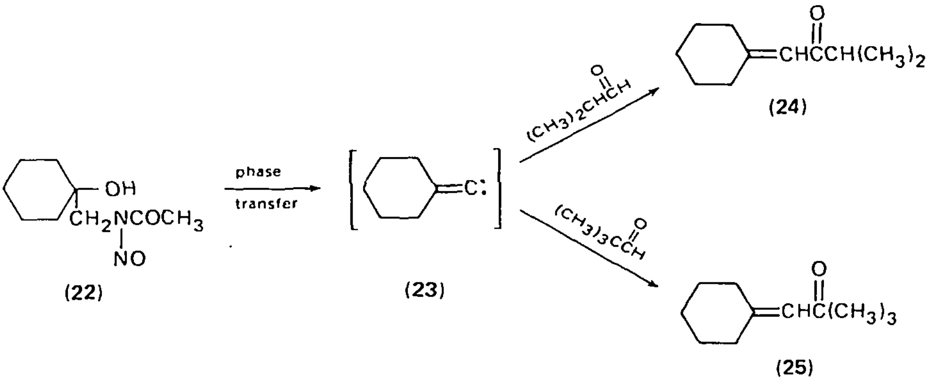
(6)

investigated by Kuo and Nye[34] as well as Newman and Liang[35]. Kuo and Nye[34] investigated the addition of carbene (19), obtained via deamination of the precursor 18, to a variety of carbonyl groups resulting in diadducts (21) as shown in Scheme 3. The diadducts (21) were postulated to arise via the addition of a second carbonyl group to allene oxides (20) although no direct evidence was provided for the actual intermediacy of 20. Both aldehydes such as pivaldehyde and *p*-tolualdehyde as well as ketones such as acetone and acetophenone were employed as substrates in Scheme 3[34].

Completely different results were obtained by Newman and Liang[35]. Under phase-transfer conditions, the carbene precursor 22 gave adducts 24 and 25 with isobutyraldehyde and pivaldehyde, respectively, as shown in Scheme 4. These



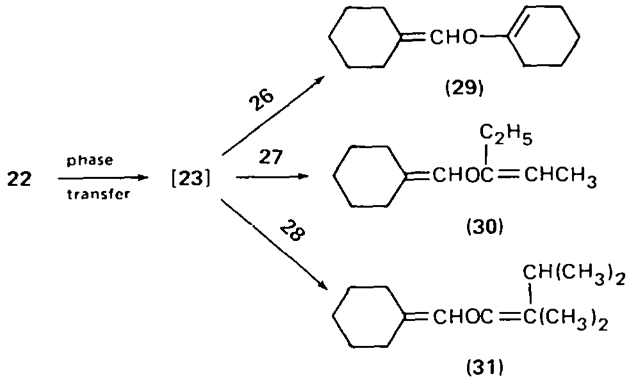
SCHEME 3.



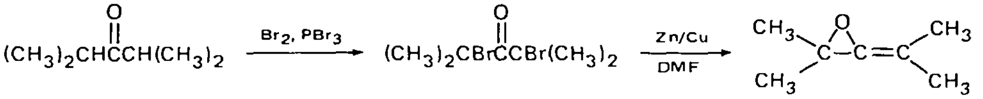
SCHEME 4.

products imply insertion of the possible intermediate carbene (23) into the aldehyde C—H bond. Yet a different set of products was observed by interaction of 22, again under phase-transfer conditions, with ketones such as cyclohexanone (26), diethyl ketone (27) and diisopropyl ketone (28) as shown in Scheme 5. Products 29—31 imply insertion of 23 into the enol forms of the respective carbonyl derivatives. No allene oxide or allene oxide derived products were observed by Newman and Liang[35]. The reasons for the discrepancy of the results of Kuo and Nye and Newman and Liang is not clear. It may be the result of the differing modes of carbene generation or the different reaction conditions. It is possible that unsaturated carbenes may not be involved in the reactions of Newman and Liang[35].

There has been a claim made[36] that tetramethylallene oxide (33) was obtained by the zinc—copper debromination of ketone 32 in dimethylformamide (equation 7). However, subsequent results have shown that the actual product was 4-isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane (34) rather than 33[37].

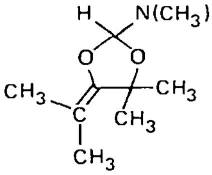


SCHEME 5.



(32) (33) (7)

Formally, 34 may be looked upon as a 1,3-dipolar adduct between tetramethyloxyallyl (3 : CH_3 instead of H) and dimethylformamide. Whether an allene oxide is involved in the above reactions is at present unclear.



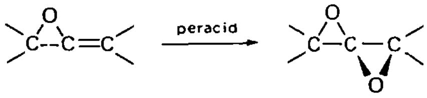
(34)

IV. REACTIONS

The reactions of allene oxides generally fall in three categories: (a) further oxidation and formation of spiro dioxides; (b) isomerization to cyclopropanones and (c) interaction with nucleophiles. The exact mode of reaction of specific allene oxides is highly dependent upon the substituents as well as the reaction conditions. Spiro dioxide formation can of course only occur under peracid or other oxidizing conditions. Monosubstituted allene oxides as well as the parent compound, **1**, generally react with nucleophiles or undergo polymerization rather than isomerization to the corresponding cyclopropanones[32]. Bulky substituents such as *t*-butyl that provide steric *hindrance* to interaction with nucleophiles allow isomerization to cyclopropanone. For aryl- or di-substituted allene oxides the rate of isomerization to cyclopropanone is generally faster than nucleophilic attack[32]. Each of these reactions will now be discussed in more detail.

A. Further Oxidation

In the presence of peracids used to form the allene oxides from the precursor allenes, the former generally undergo further oxidation. The initial intermediate is believed to be a 1,4-dioxaspiro[2,2]pentane (35) that itself undergoes further reaction (equation 8).

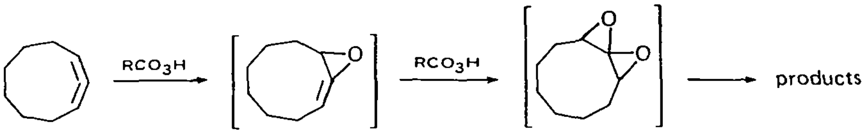


(35)

(8)

Epoxidation of tetramethylallene[21] with peracetic acid gave 52% of 2-acetoxy-2,4-dimethyl-3-pentanone (see below), 39% of 2-acetoxy-4-hydroxy-2,4-dimethyl-3-pentanone (37), 4% of 4-hydroxy-2,4-dimethylpent-1-en-3-one (38), 3% tetramethyl-3-oxetanone (39) and 2% of lactone (40) as shown in Scheme 6. These products were rationalized via the intermediacy of the spiro dioxide 36. Protonation followed by isomerization of 36 results in 37 and 38. Acid-catalysed or thermal isomerization of 36 results in 39 which upon Baeyer–Villiger oxidation gives lactone 40.

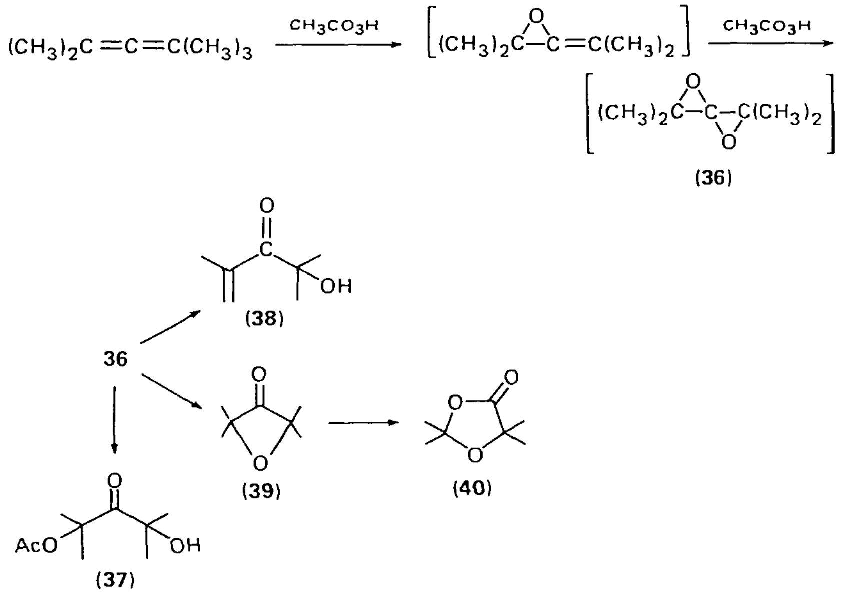
Similarly the spiro dioxide 43 has been invoked to account for the observed products in the peracid oxidation[25,38] of 1,2-cyclononadiene (41) as shown in equation (9). In the peracid oxidation of 2,5,5-trimethyl-2,3-hexadiene (44), the



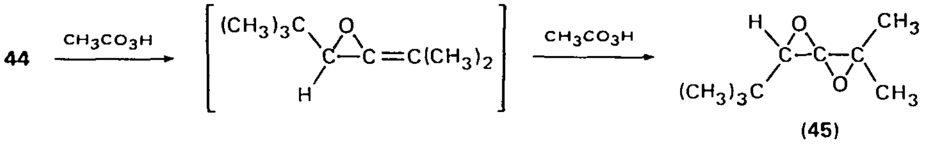
(41) (42) (43)

(9)

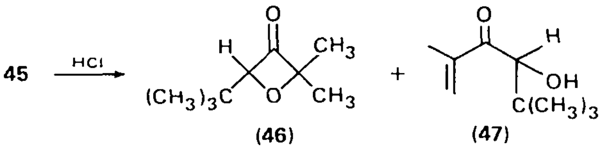
spiro dioxide 45 could be isolated as a stable compound and spectrally characterized (equation 10)[22]. Reaction of 45 with HCl was shown[22] to give oxetanone (46) and an unsaturated ketone (47) (equation 11). The products 46 and 47 are



SCHEME 6.



(10)

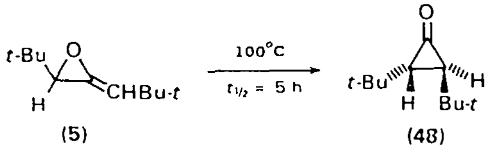


(11)

analogous to products observed in the peracid oxidation of tetramethylallene where the intermediate spiro dioxide could not be isolated. Hence, there is little doubt that spiro oxides or diepoxides are viable reaction intermediaries or products in the further reaction of the intermediate allene oxides resulting from the peracid treatment of certain allenes.

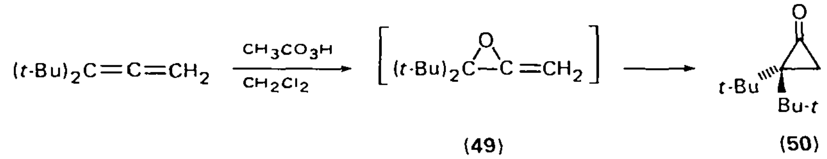
B. Isomerization to Cyclopropanones

As indicated in Section I, the allene oxide–cyclopropanone isomerization has attracted considerable theoretical as well as experimental[8,17] interest. It represents the interconversion of two highly strained small-ring systems[39]. Numerous such isomerizations have been observed. Perhaps the most clear-cut example is the isomerization of 1,3-di-*t*-butylallene oxide (5) to *trans*-2,3-di-*t*-butylcyclopropanone (48) with a $t_{1/2}$ of five hours at 100°C (equation 12). Similarly, peracid



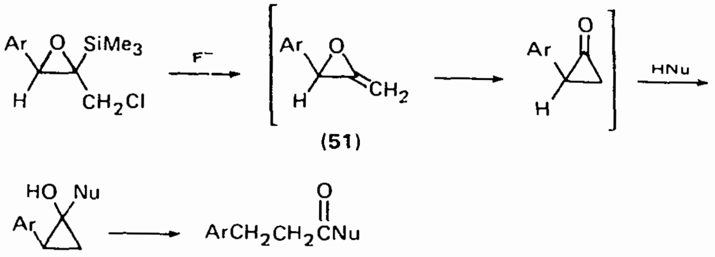
(12)

oxidation of 1,1-di-*t*-butylallene in methylene chloride gave 2,2-di-*t*-butylcyclopropanone (50) as the sole product presumably via the intermediacy of the isomeric allene oxide 49, which could not be isolated (equation 13)[23].



(13)

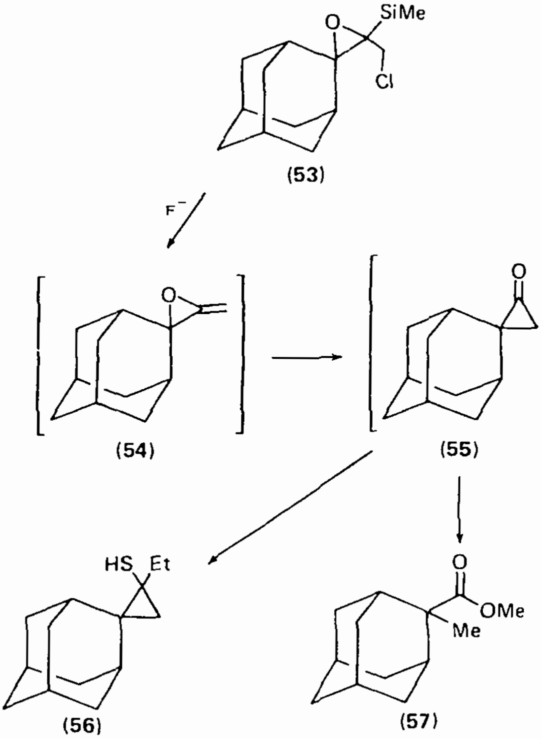
Other instances of allene oxide–cyclopropanone isomerization involve cases where neither the allene oxide nor the cyclopropanone could be isolated under the reaction conditions employed, but the isomerization could nevertheless be clearly inferred from the isolated products and the known[8,17] solution chemistry of cyclopropanones. The reaction of tetramethylallene with peracetic acid in methanol leads to, besides other products already mentioned in the previous section, 37% of tetramethylethylene oxide and other products that were rationalized via the isomerization of the allene oxide to tetramethylcyclopropanone and the subsequent reactions of the latter[25]. Cyclooctene epoxide obtained in the peracid oxidation of 1,2-cyclononadiene was similarly rationalized[25,38]. Cyclopropane-derived products



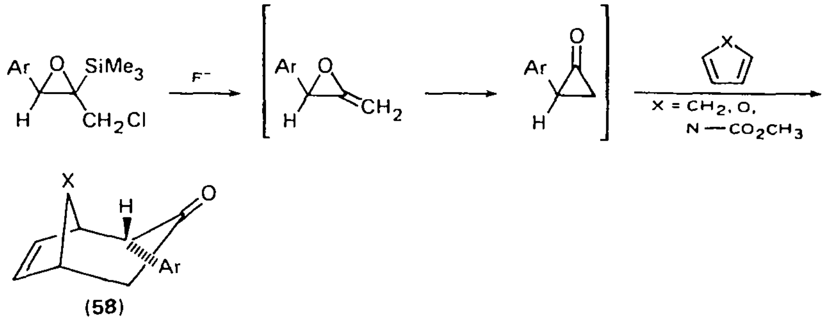
(52) Ar = Ph, p-$CH_3C_6H_4$
Nu = OMe, EtS, PhNH

SCHEME 7.

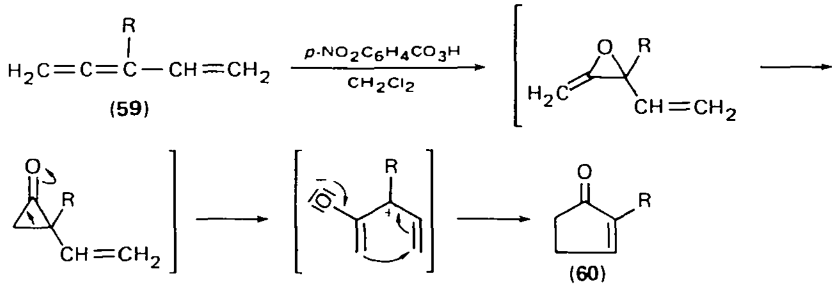
(52) were also observed[30] in the reaction of 1-arylallene oxides (51) with various nucleophiles as shown in Scheme 7. The 1-aryl substituents in the reactions of Scheme 7 are essential for isomerization to occur. In the case of 1-alkyl- or 3-aryl-allene oxides the allene oxide itself was intercepted by the nucleophiles (see below) prior to rearrangement to the corresponding cyclopropanone[30]. Similar results were obtained[30] in the reaction of spiroadamantylallene oxide (54) obtained via desilylation of 53 as shown in Scheme 8. In this case the rearranged cyclopropanone intermediate (55) could be trapped as the hemithioketal (56) by reaction with ethanethiol[30]. The rearrangement of 51 and 54 were interpreted[30] as



SCHEME 8.

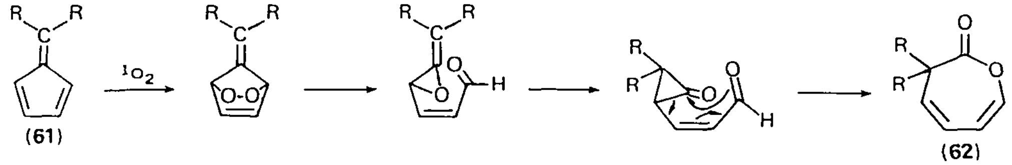


SCHEME 9.



R = Me, *n*-Pr

SCHEME 10.



R = Me, Ph

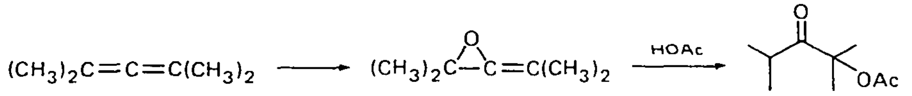
SCHEME 11.

evidence for an oxyallyl intermediate in the allene oxide–cyclopropanone isomerization. In the case of 51 the isomeric cyclopropanones were also trapped[40] as Diels–Alder adducts (58) as shown in Scheme 9.

Allene oxide–cyclopropanone isomerization was also invoked[41] to account for the observed cyclopentenone products (60) in the peracid oxidation of vinylallenes (59) as shown in Scheme 10. Similarly, the allene oxide–cyclopropanone isomerization was used to explain[42] the formation of 3,3-disubstituted-2-(3*H*)-oxepinones (62) in the dye-sensitized photooxygenation via singlet oxygen of 6,6-disubstituted fulvenes (61) as shown in Scheme 11.

C. Reaction with Nucleophiles

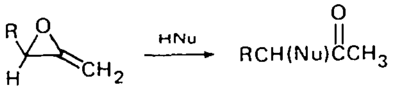
Allene oxides monosubstituted by a 1- or 3-alkyl group and other sterically unhindered allene oxides readily undergo nucleophilic substitution with a variety of nucleophiles. The major product (53%) in the peracetic acid oxidation of tetramethylallene is the acetoxyketones (**63**) resulting from interaction of the intermediate allene oxide with HOAc[21] (equation 14). Similarly, a wide variety of


$(CH_3)_2C{=}C{=}C(CH_3)_2$
$(CH_3)_2C$—$C{=}C(CH_3)_2$
O
HOAc
O
OAc

(63)

(14)

1-monoalkyl-substituted allene oxides (**64**) gave[32] ketone products (**65**) as shown in equation (15). The reactions of **64** with the nucleophiles (HNu) were found to be


R
O
H
CH_2
HNu
O
$RCH(Nu)CCH_3$

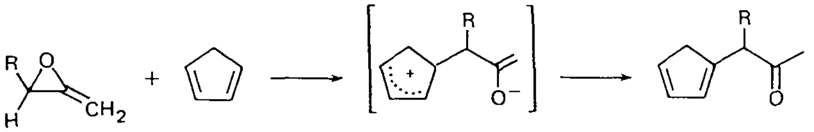
(64) (65)

(15)

R = H, Me, *i*-Pr, *t*-Bu, *c*-C_6H_{11}, *n*-$C_{10}H_{21}$
Nu = OH, OMe, EtS, Cl, PhO, PhS, PhNH

regiospecific as demonstrated by the behaviour of isomeric allene oxides (**66**) shown in Scheme 12. Isomer **66a** upon reaction with methanol gave exclusively the methoxyketone (**67a**) with none of **67b** as product, whereas isomer **66b** gave only the methoxyketone (**67b**) under identical conditions[32]. This regiospecificity indicates exclusive nucleophilic attack upon the 'tetrahedral carbon' of the isomeric epoxides (**66**) and also rules out a common species such as an oxyallyl or cyclopropanone as the intermediate in these reactions.

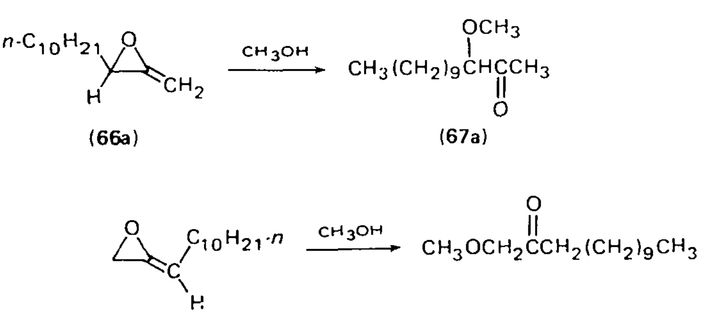
Allene oxides (**64**) have also been trapped by cyclopentadiene to give ketones (**69**) presumably via the intermediacy of zwitterions (**68**)[40] (equation 16). This reaction further demonstrates the electrophilic nature of allene oxides.


R
O
H
CH_2
+
R
+
O^-
R
O

(64) (68) (69)

(16)

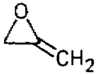
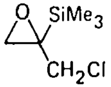
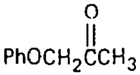
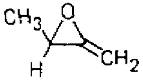
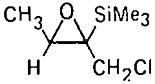
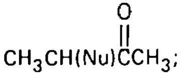
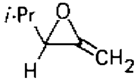
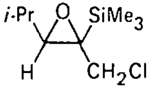
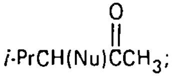
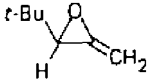
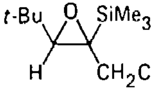
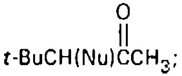
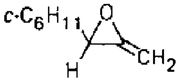
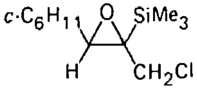
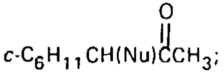
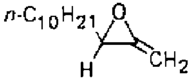
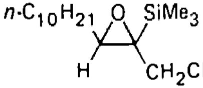
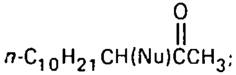
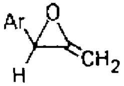
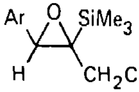
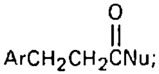
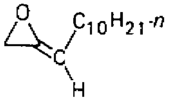
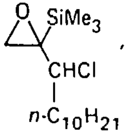
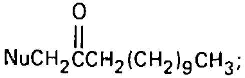
A summary of known allene oxides, their mode of generation and major reaction products are given in Table 2.


n-$C_{10}H_{21}$
O
H
CH_2
CH_3OH
OCH_3
$CH_3(CH_2)_9CHCCH_3$
O
(66a)
(67a)
O
$C_{10}H_{21}$-*n*
C
H
CH_3OH
O
$CH_3OCH_2CCH_2(CH_2)_9CH_3$

(66b) (67b)

SCHEME 12.

TABLE 2. Summary of the preparation and reactions of allene oxides

Allene oxide	Reaction conditions	Products	Reference
	 , CsF, CH$_3$CN, PhOH, 25°C	 $\mathrm{PhOCH_2\overset{O}{\overset{\parallel}{C}}CH_3}$	32
	 , CsF, CH$_3$CN, HNu, 25°C	 $\mathrm{CH_3CH(Nu)\overset{O}{\overset{\parallel}{C}}CH_3}$; Nu = Cl, PhO, (*i*-Pr)$_2$N	32
	 , CsF, CH$_3$CN, HNu, 25°C	 $i\text{-}\mathrm{PrCH(Nu)\overset{O}{\overset{\parallel}{C}}CH_3}$; Nu = Cl, PhO, EtS, PhS	32
	 , CsF, CH$_3$CN, HNu, 25°C	 $t\text{-}\mathrm{BuCH(Nu)\overset{O}{\overset{\parallel}{C}}CH_3}$; Nu = OH, EtS, CCl$_3CO_2$	32
	 , CsF, CH$_3$CN, HNu, 25°C	 $c\text{-}\mathrm{C_6H_{11}CH(Nu)\overset{O}{\overset{\parallel}{C}}CH_3}$; Nu = Cl	32
	 , CsF, CH$_3$CN, HNu, 25°C	 $n\text{-}\mathrm{C_{10}H_{21}CH(Nu)\overset{O}{\overset{\parallel}{C}}CH_3}$; Nu = Cl, MeO	32
 Ar = Ph, *p*-CH$_3$C$_6$H$_4$	 , CsF, CH$_3$CN, HNu, 25°C	 $\mathrm{ArCH_2CH_2\overset{O}{\overset{\parallel}{C}}Nu}$; Nu = MeO, EtS, PhNH, PhO; Ar = Ph, *p*-CH$_3$C$_6$H$_4$	32
	 , CsF, CH$_3$CN, HNu, 25°C	 $\mathrm{NuCH_2\overset{O}{\overset{\parallel}{C}}CH_2(CH_2)_9CH_3}$; Nu = MeO, PhO	32

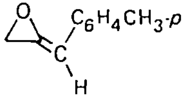
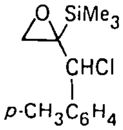
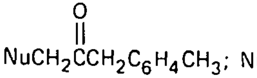
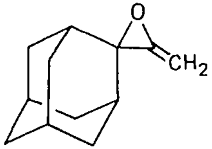
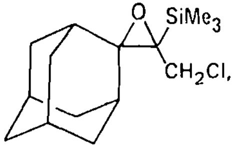
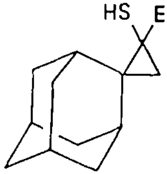
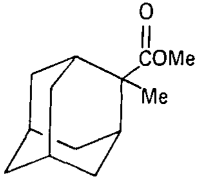
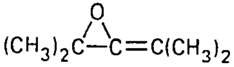
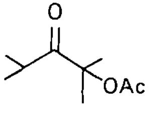
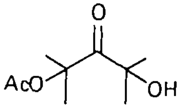
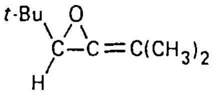
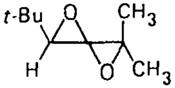
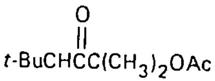
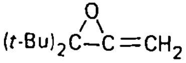
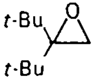
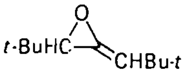
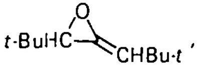
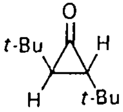
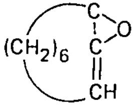
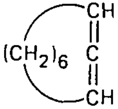
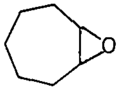
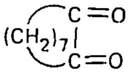
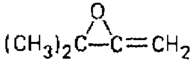
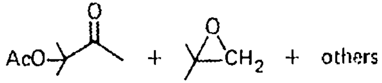
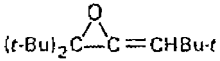
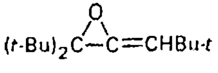
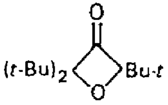
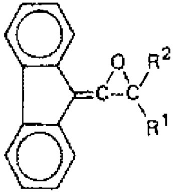
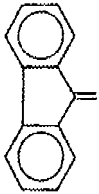
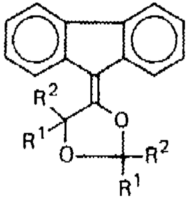
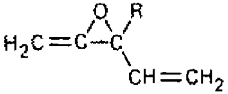
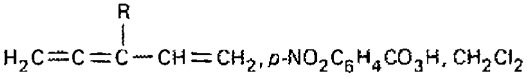
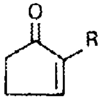
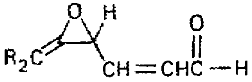
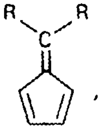
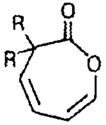
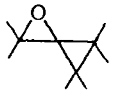
	 CsF, CH_3CN, HNu, 25°C	 $\mathrm{NuCH_2\overset{\overset{O}{\|}}{C}CH_2C_6H_4CH_3}$; Nu = EtS, PhO	32
	 Et_4NF, CH_3CN, HNu, 25°C	 Nu = EtS  Nu = MeO	32
 $(CH_3)_2\overset{O}{C{-}C}{=}C(CH_3)_2$	$(CH_3)_2C{=}C{=}C(CH_3)_2$, 40% CH_3CO_3H, Na_2CO_3, CH_2Cl_2, 0°C	 52% +  39% + others	21
	$t\text{-}BuCH{=}C{=}C(CH_3)_2$, CH_3CO_3H, Na_2CO_3, CH_2Cl_2, 0°C	 +  $t\text{-}BuCH\overset{\overset{O}{\|}}{C}C(CH_3)_2OAc$	22
 $(t\text{-}Bu)_2\overset{O}{C{-}C}{=}CH_2$	$(t\text{-}Bu)_2C{=}C{=}CH_2$, CH_3CO_3H		23
	$t\text{-}BuCH{=}C{=}CHBu\text{-}t$, $m\text{-}ClC_6H_4CO_3H$, hexane, 25°C	 , at 25°C  at 100°C	26
	 , RCO_3H, $NaNO_3$, CH_2Cl_2, 0°C	 +  + others	25,38

TABLE 2. (*continued*)

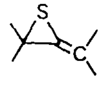
Allene oxide	Reaction conditions	Products	Reference
	$(CH_3)_2C{=}C{=}CH_2$, CH_3CO_3H, $NaNO_3$, CH_2Cl_2, 0°C		25
	$(t\text{-}Bu)_2C{=}C{=}CHBu\text{-}t$, $m\text{-}ClC_6H_4CO_3H$,	 10  1	24
	 $=CHNH_2$, RONO, C_6H_6, $R^1\overset{O}{\overset{\|}{C}}R^2$, reflux		34
	 $H_2C{=}C{=}\overset{R}{\overset{\vert}{C}}{-}CH{=}CH_2$, $p\text{-}NO_2C_6H_4CO_3H$, CH_2Cl_2		41
	 , $^1O_2$		42

V. RELATED SPECIES

To the best of our knowledge, from a limited literature search, cumulene oxides are not known. Since most cumulenes are relatively thermally unstable or unstable towards oxygen, their oxides presumably would be too unstable to isolate. In this section we will discuss two species related to allene oxides namely oxaspiropentanes (70) and allene episulphides (71).



(70)

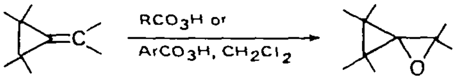


(71)

A. Oxaspiropentanes

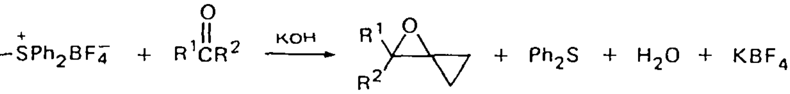
To the extent that one normally considers the electron-rich bonds of a cyclopropane as being analogous to the π-system of a double bond, oxaspiropentanes (70) are related to allene oxides. Furthermore oxaspiropentanes like allene oxides are highly strained small-ring molecules. The strain energy of cyclopropane and its oxygen analogue ethylene oxide are within one kcal/mol the same at 28 kcal/mol[43]. Therefore the strain energy of oxaspiropentane is likely to be close to the 65 kcal/mol of strain energy in spiropentane[44].

Oxaspiropentanes with different alkyl and aryl substituents, as well as the parent compound, are readily available by the peracid oxidation of alkylidene cyclopropanes developed by Crandall and coworkers[45] (equation 17) and subsequently applied to a large number of systems[46-48].



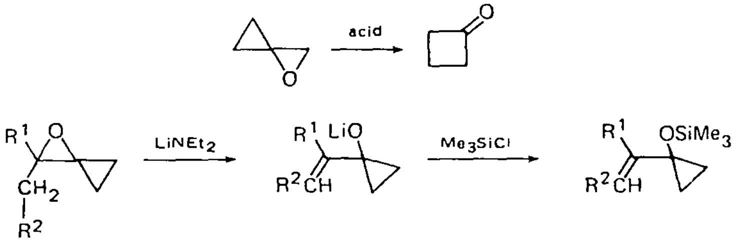
(17)

A second major route to oxaspiropentanes is the reaction of sulphur ylides with carbonyl compounds as developed by Trost and coworkers[49-51]. In particular, reaction of diphenylsulphonium cyclopropylylide with carbonyl compounds gave high yields of oxaspiropentanes (equation 18).

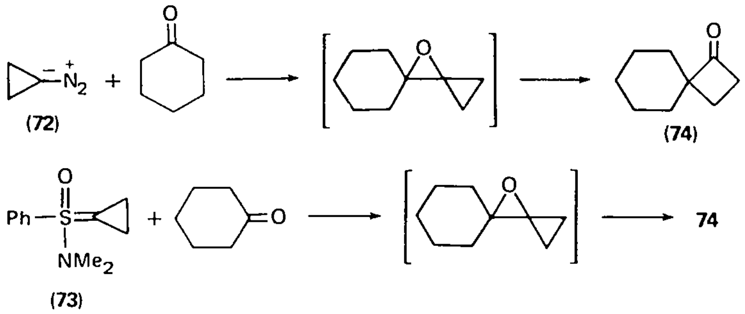


(18)

There are two major modes of reaction of oxaspiropentanes: Lewis or Brønsted acid catalysed rearrangement to cyclobutanones[45-49] and base-catalysed rearrangement to vinyl cyclopropanols[51] isolated as the silyl ether as shown in Scheme 13. The oxaspiropentane–cyclobutanone rearrangement has been invoked to explain



SCHEME 13.


(72)
(73)
(74)
Ph
NMe2
74

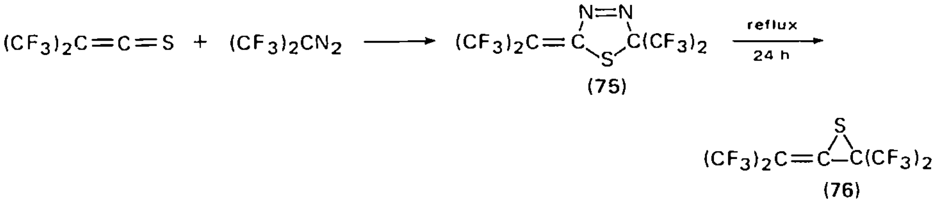
SCHEME 14.

the formation of the spiroketone **74** in the reaction of the diazocyclopropane **72**[52] as well as the ylide **73**[53] to cyclohexanone as shown in Scheme 14.

Finally, oxaspiropentanes, virtually unknown ten years ago, have proven to be versatile synthetic intermediates[50,51].

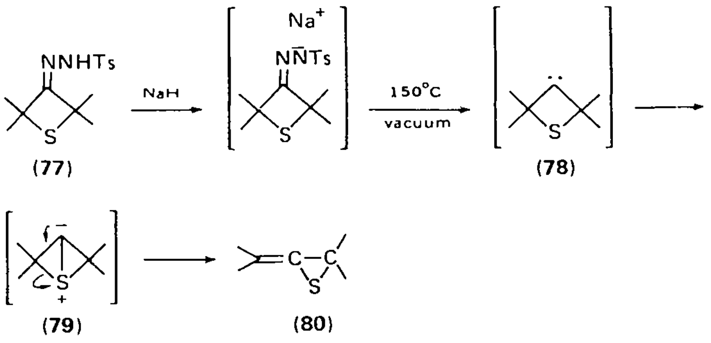
B. Allene Episulphides

Allene episulfides (71) are the sulphur analogues of allene oxides. To date, only three examples of allene episulphides are known. The first synthesis by Middleton[54] involved the reaction of bistrifluoromethyl thioketene with bistrifluoromethyl diazomethane to give thiadiazoline (75) as a stable compound. Heating of 75 at reflux for 24 hours gave the tetratrifluoromethylallene episulphide 76 as a stable colourless liquid as shown in equation (19).

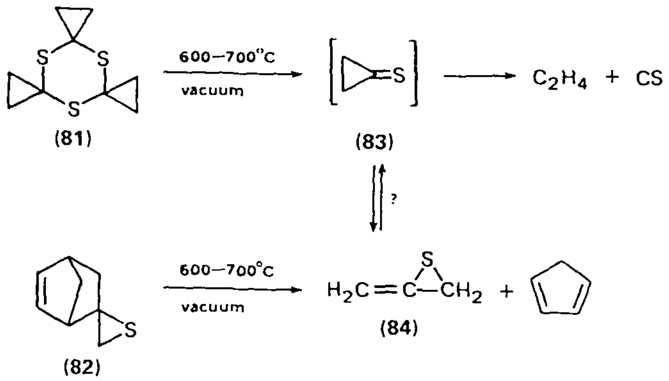

$(CF_3)_2C{=}C{=}S$ + $(CF_3)_2CN_2$
$(CF_3)_2C{=}C$ $C(CF_3)_2$
N=N
S
(75)
reflux
24 h
$(CF_3)_2C{=}C{-}C(CF_3)_2$
S
(76)

(19)

The tetramethylallene episulphide **80** was prepared by vacuum pyrolysis of **77** as shown in Scheme 15. The carbene **78** and the ylide **79** were proposed[55] as possible intermediates in the pyrolysis of **77** to give **80** as a colourless stable liquid.


NNHTs
NaH
Na+
NNTs
150°C
vacuum
(77)
(78)
(79)
(80)

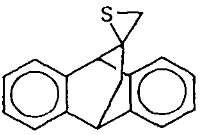
SCHEME 15.


600–700°C
vacuum
C_2H_4 + CS
(81)
(83)
?
600–700°C
vacuum
$H_2C{=}C{-}CH_2$
(84)
(82)

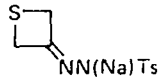
SCHEME 16.

Recently, the parent allene episulphide 84 has been prepared and characterized by flask vacuum pyrolysis of either 81 or 82 as shown in Scheme 16, Decomposition of 81 is proposed to proceed through 83 as evidenced by the formation of ethylene and CS besides 84, whereas precursor 82 is proposed to give the episulfide directly via a retro-Diels–Alder loss of cyclopentadiene. A microwave determination confirms the structure of 84 with an unsually long C(sp^3)–S bond of 1.849 Å. The dipole moment of 84 was found to be 1.36 D[56]. Allene episulphide was found to have a gas-phase lifetime of about 3 min at room temperature and 20 min at dry-ice temperature at 0.05 Torr[56].

Episulphide 84 can also be prepared by the pyrolyisis of 85 and 86 at 520°C.

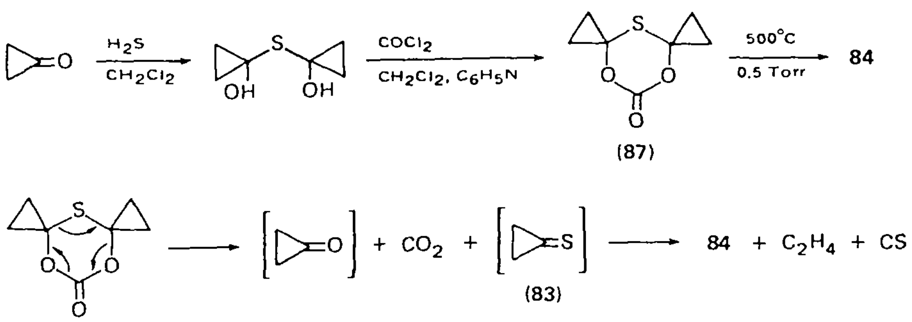


(85)



(86)

The formation of 84 has been independently reported[57] via pyrolysis of 87 at 500°C and 0.5 Torr as shown in Scheme 17. The formation of 84 from 87 was explained via a $2\pi_s + 2\pi_s + 2\pi_s$ cycloreversion and the intermediacy of 83. The observation of C_2H_4 and CS in the decomposition of both 81 and 87 seems consistent with the involvement of 83.


H_2S
CH_2Cl_2
OH
OH
$COCl_2$
CH_2Cl_2, C_6H_5N
500°C
0.5 Torr
84
(87)
+ CO_2 +
84 + C_2H_4 + CS
(83)

SCHEME 17.

Both experimental observations as well as thermodynamic considerations[56] indicate that the more stable isomer is **84** rather than **83**. Using appropriate bond energies **84** is predicted to be some 7 kcal/mol more stable than **83**[56]. This, of course, is in contrast to the greater stability of the cyclopropanone rather than the allene oxide in the case of the oxygen analogue. The greater stability of cyclopropanone compared to allene oxide is probably partially due to the strong 172 kcal/mol bond strength of a carbonyl, whereas the analogous C=S bond is only 129 kcal/mol thus providing less of a thermodynamic stability to the thiocyclopropanone compared to its isomeric allene episulphide.

VI. ACKNOWLEDGEMENT

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 20

Advances in the chemistry of acetals, ketals and ortho esters

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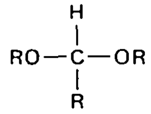
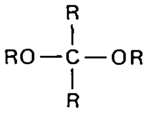
I. INTRODUCTION

Acetals and ketals are characterized by the presence of two alkoxy groups (—OR) attached to a carbon atom. Acetals (1) differ from ketals (2) in that they always have at least one hydrogen atom attached to the central carbon atom involved in C—O bond formation. Ketals are obtained by replacing the hydrogen atom of the acetal with an alkyl group (—R). Because of the similarity of acetals and ketals, it is common to find both categorized as acetals. Replacement of the alkyl group of 2 with an alkoxy group leads to an ortho ester (3).



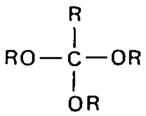
$$\begin{array}{c} \mathrm{H} \\ | \\ \mathrm{RO{-}C{-}OR} \\ | \\ \mathrm{R} \end{array}$$

(1)



$$\begin{array}{c} \mathrm{R} \\ | \\ \mathrm{RO{-}C{-}OR} \\ | \\ \mathrm{R} \end{array}$$

(2)



$$\begin{array}{c} \mathrm{R} \\ | \\ \mathrm{RO{-}C{-}OR} \\ | \\ \mathrm{OR} \end{array}$$

(3)

The corresponding sulphur compounds are known as thioacetals, thioketals (mercaptals) and orthothio esters. They are formed by substitution of the alkoxy groups in 1, 2 or 3 with mercapto groups (—SR). Mixed *O, S*-acetals are also well known.

Previous reviews of the preparation and chemistry of acetals, ketals and ortho esters have appeared. In two earlier volumes of this series Schmitz and Eichhorn[1] have written a chapter on the chemistry of acetals and ketals, and Cordes[2] has contributed a chapter on ortho esters. Ortho esters have also been reviewed by DeWolfe[3] in his monograph on ortho acid derivatives. The mechanism of hydrolysis of acetals and related substances has been the subject of several reviews[4–7] since 1970, the most comprehensive by Cordes[8] appearing in 1974. Since these reviews are so recent and readily accessible, this chapter will deal primarily with material published since 1973.

We begin this review with a discussion of some recent developments in the synthesis of acetals, ortho esters and related substances. Mechanistic considerations are also included whenever they may serve to clarify conditions conducive to the formation of the compounds. It should be noted that during the last few years a good deal of important work on the hydrolysis of acetals has been carried out in a number of laboratories. Consequently, in order to bring the subject up to date, we shall devote a substantial portion of this chapter to the hydrolysis mechanism and its useful implications.

II. FORMATION OF ACETALS, KETALS AND ORTHO ESTERS

A. Introduction

The chief methods for preparing acetals, ketals, ortho esters and their thio analogues have been treated adequately in the forementioned reviews[1–3] and it will suffice in this chapter to give a perfunctory survey of these methods, in particular giving references to more recent work.

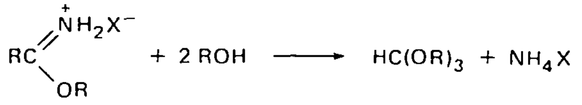
The main methods of formation of acetals and ortho esters involve addition and substitution reactions. Simple acid-catalysed additions of alcohols and thiols to aldehydes and ketones are of primary importance due to the wide use of this reaction as a method of protecting the carbonyl group by conversion to an acetal or related compound. Alcohols and thiols also add readily to oxocarbonium ions[9], alkynes[1] and α,β-unsaturated ethers[1] to yield acetals and thioacetals. Ortho esters are products of alcohol additions to ketene acetals[2].

The second type of reaction involves nucleophilic substitution by an alcohol or thiol for a suitable leaving group attached to the central carbon of the substrate (equation 1). For example, addition of excess alcohol to imidate salts (4) gives

$$\mathrm{ROCR_2Y + RXH \longrightarrow ROCR_2XR + YH} \qquad (1)$$

$$\mathrm{X = O, S}$$

simple[10] or mixed[11,12] ortho esters (equation 2). This reaction, known as the Pinner synthesis, is restricted to substitution by primary and secondary alcohols.



(4)

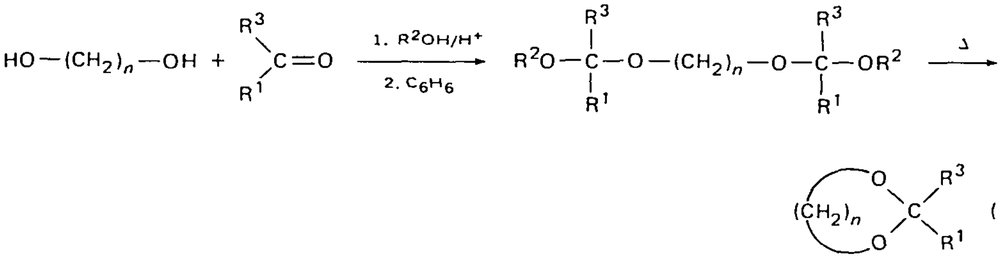
(2)

Ortho esters may also be obtained from the action of sodium alkoxides on polyhalides[2], as shown in equation (3).

$$R^1CX_3 + 3\,NaOR^2 \longrightarrow R^1C(OR^2)_3 + 3\,NaX \qquad (3)$$

B. Some Recent Methods

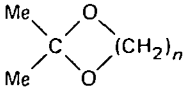
Direct acetalization (or ketalization) of an aldehyde (or ketone) is not generally an obstacle in synthetic sequences. Sometimes, however, conventional methods fail completely or give low yields when the product is a strained cyclic acetal or an acetal of unusually low stability. Recently, successful syntheses of strained 1,3-dioxacyclanes (5) have been reported involving mixed acetal precursors[13] (equation 4). After initial formation of the mixed acetal, benzene it added and exess alcohol and water are removed by azeotropic entrainment. Thermal decomposition of the mixed acetal gives rise to the final cyclic acetal.



(5)

(4)

Monomeric (6) and dimeric (7) 2,2-dimethyl-1,3-dioxacyclanes are formed by the reaction of a diol with 2,2-dimethoxypropane under the influence of an acid catalyst[14]. Dimeric cyclic ketals of ring-size 12–22 form readily by this method; however only monomeric cyclic ketals were isolated from 1,3-propane- and 1,4-butane-diol. The dimeric cyclic ketal of butanediol could be prepared from but-2-yn-1,4-diol using this same method and by the oligomerization of 2,2-dimethyl-1,3-dioxopan[15].



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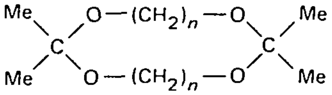
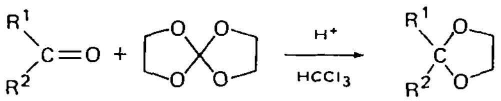


(7)

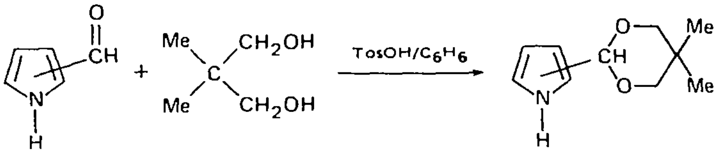
Barton, Dawes and Magnus[16] have recently shown that diethylene orthocarbonate (8) is a useful reagent for the conversion of ketones into their corresponding dioxolanes in good yield at room temperature (equation 5). Pyrrole-2- (9a) and



(8)

(5)

pyrrole-3-carbaldehydes (**9b**) yield interesting acetals on treatment with 2,2-dimethyl-1,3-propanediol in the presence of *p*-toluenesulphonic acid catalyst and dry benzene[17] (equation 6).

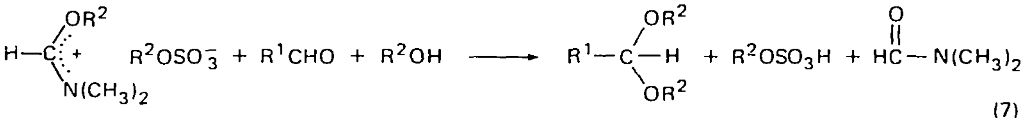


(6)

(9) (a) 2-substituted

(b) 3-substituted

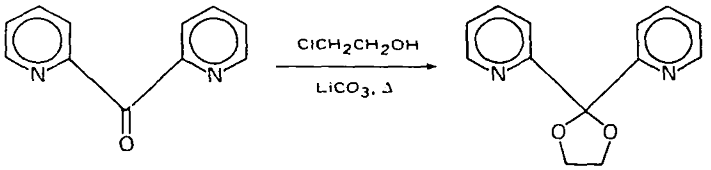
Dimethylformamide–dialkyl sulphate adducts (**10**) react rapidly with aldehydes and alcohols to give acetals as products in excellent yield[18] (equation 7).



$$H{-}\overset{OR^2}{\underset{N(CH_3)_2}{C}}{+}\ R^2OSO_3^- + R^1CHO + R^2OH \longrightarrow R^1{-}\overset{OR^2}{\underset{OR^2}{C}}{-}H + R^2OSO_3H + HC(=O){-}N(CH_3)_2 \quad (7)$$

(10)

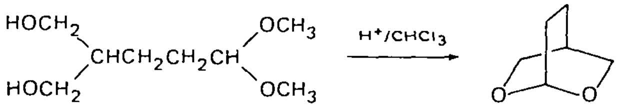
Base-catalysed ketalization has also been observed. Newkome, Sauer and McClure[19] showed that di-2-pyridyl ketone (**11**) could be converted to 2,2-di(2-pyridyl)1,3-dioxolane (**12**) in 45% yield in refluxing 2-chloroethanol with anhydrous lithium carbonate added (equation 8). The reaction is believed to proceed through initial quaternization of **11** by 2-chloroethanol.



(11) (12)

(8)

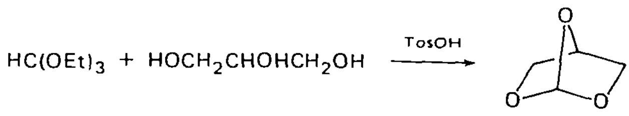
Hall and coworkers[20-23] have recently developed methods of preparing highly reactive bicyclic acetals. The syntheses require diol acetals (**13**) as intermediates, which undergo intramolecular acid-catalysed acetal exchange to yield bicyclic acetals, as illustrated in the synthesis of 2,6-dioxabicyclo[2.2.2] octane (**14**) (equation 9).



(13) (14)

(9)

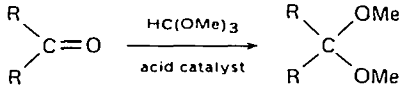
In a similar reaction, ethyl orthoformate (**15**) reacts with triols (e.g. glycerol) in the presence of *p*-toluenesulphonic acid as catalyst to give the corresponding bicyclic ortho esters in good yield[24] (equation 10).



(15) (16)

(10)

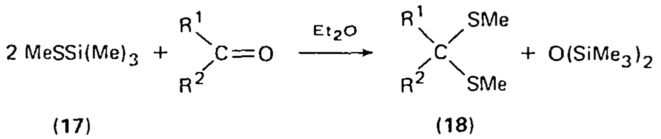
Acetals and ketals have also been recorded as products from the reaction of methyl orthoformate and aldehydes or ketones in the presence of acid catalysts such as sulphuric acid[24–26] ethanolic hydrogen chloride[27,28], *p*-toluenesulphonic acid[29–31], ferric chloride[32,33], ammonium nitrate[34,35], ammonium chloride[36] or amberlyst-15[37], an acidic ion exchange resin (equation 11).



(11)

More recently, Taylor and Chiang[38] found that the reaction proceeds most readily and with highest yields (> 90% for all cases reported) when acidic montmorillonite clay K-10 is used as the catalyst.

Evans and coworkers[39] examined a new method for the formation of thioketals: an aldehyde or ketone reacts spontaneously with methylthiotrimethylsilane (**17**) to give the thioketal (**18**) in excellent yield in the absence of an acid catalyst (equation 12).



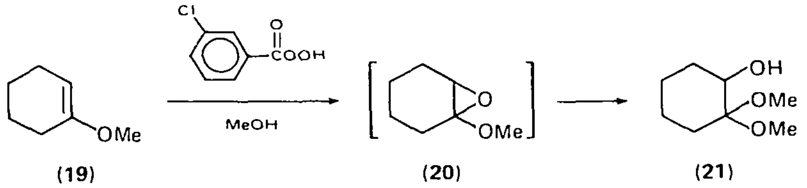
(12)

C. Miscellaneous Preparations

The following methods are less general, and starting materials may contain functional groups other than carbonyl groups.

1. *From olefins*

According to Frimer[40], α-hydroxyacetals (**21**) can be conveniently prepared by the action of a peracid on the corresponding vinyl ether (**19**) in alcoholic solvents. The proposed mechanism represents formation of an epoxy ether intermediate (**20**) followed by its rapid solvolysis. The ether oxygen may be either exo- or endo-cyclic as shown in equations (13) and (14). Yields are high and the reaction can be used with acid- and base-sensitive compounds. It is also possible to obtain hydroxy spiroacetals **22** by the reaction of enol acetals with hydroxyketones in the presence of ultraviolet light[41] (equation 15).



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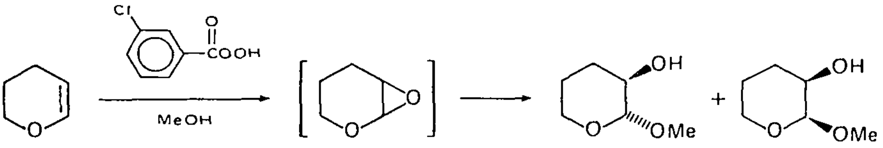

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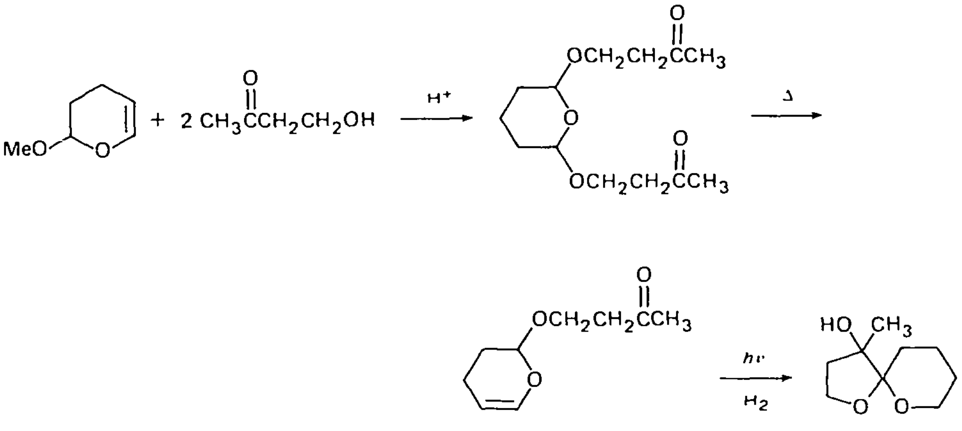
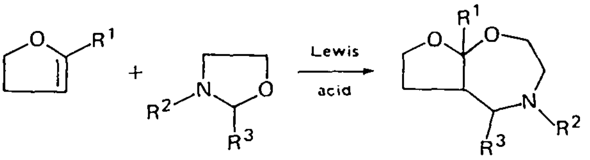


(22)

(15)

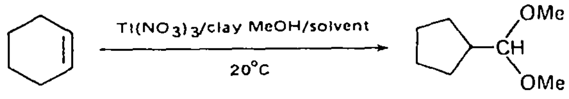
Griengl and Bleikolm[42,43] report that 5-alkyl-2,3-dihydrofurans (23) react with 1,3-oxazolidines (24) in dimethyl sulphoxide in the presence of Lewis acids to give cyclic acetals (equation 16).



(23) (24)

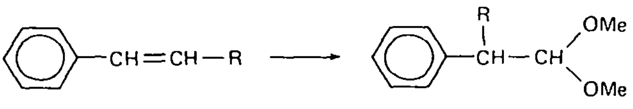
(16)

Simple alkenes such as cyclohexene, styrene and 1-phenyl-1-propene (26, R = Me) undergo extremely rapid oxidative rearrangement to give the corresponding dimethyl acetals (25) and (27) by interaction with thallium (III) nitrate absorbed on K-10, a readily available and inexpensive acidic montmorillonite clay, in an inert solvent (heptane, methylene chloride, carbon tetrachloride, toluene, dioxane)[44] (equations 17 and 18).



(25)

(17)

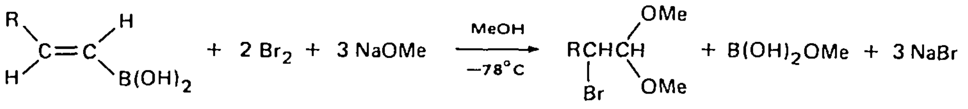


(26) (27)

(18)

2. *From organoborane derivatives*

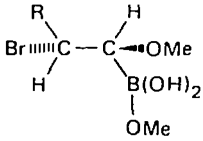
Several preparations of acetals involving boron intermediates have been reported. For example, alkenylboronic acids (28) react with bromine[45] in the presence of sodium methoxide and methanol to form the corresponding α-bromo dimethyl acetals (29) in good yield (equation 19). The reaction apparently proceeds through



(19)

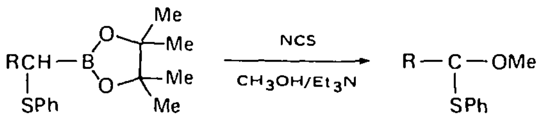
(28) (29)

a methyl vinyl ether intermediate formed by the *trans* elimination of boron and bromine from **30**.



(30)

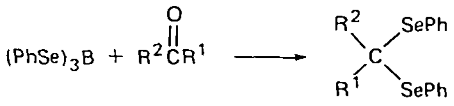
α-(Phenylthio)alkylboron compounds of the type **31** are efficiently and selectively cleaved by *N*-chlorosuccinimide (NCS) in basic methanol to give the corresponding monothioacetal (**32**) or, in the presence of excess NCS, the acetal[46] (equation 20). The reaction is reported to be compatible with an alkene or acetal function elsewhere in the molecule and is useful in that it converts an organoborane directly into a thioacetal under mild basic conditions.



(20)

(31) (32)

In an isolated example, Clive and Menchen[47] have shown that tris-(phenylseleno)borane (**33**) converts aldehydes and ketones into selenoacetals (**34**) in good yield (equation 21).

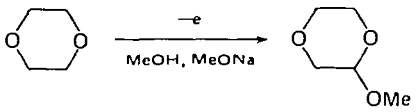


(21)

(33) (34)

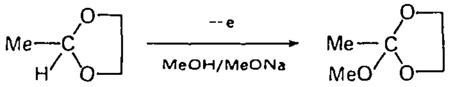
3. *From oxidations*

Shono and Matsumura[48] have shown that certain aliphatic saturated ethers can be converted to acetals by electrochemical anodic substitution of hydrogen atoms by methoxy groups (equation 22). It was suggested that the reaction involves hydrogen atom abstraction from the α-position of the ether by an anodically generated radical. Consequently acetal yields are observed to be dependent on the reactivity–selectivity of the α-hydrogen abstraction step.



(22)

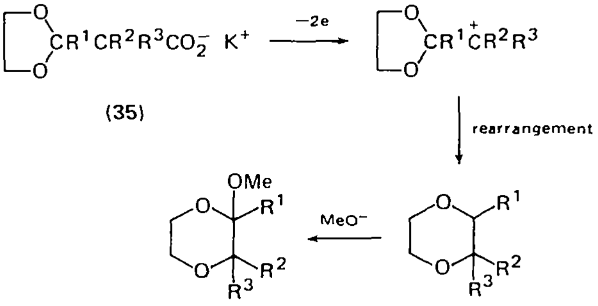
Extending the foregoing procedure, Scheeren and coworkers[49] showed that acetals can be converted electrochemically into ortho esters (equation 23). Again



(23)

the reaction was shown to be dependent on the accessibility of the hydrogen, since acetals with bulky groups at the carbon atom gave low yields.

In addition, 2-methoxy-1,4-dioxanes (36) have been obtained electrochemically[50] by anodic oxidation of β-oxocarboxylate ethylene acetals (35) (equation 24).

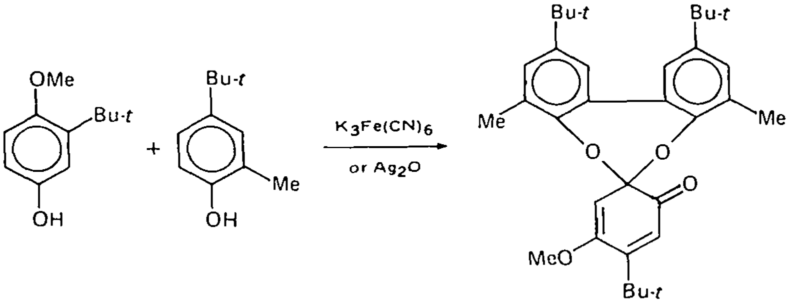


(35)

(24)

(36)

Hewgill and coworkers[51,52] have recently shown that mixtures of phenols with alkoxyphenols can be oxidized by silver oxide or potassium ferricyanide to yield interesting and novel trimeric spiroacetals such as 37 (equation 25). Since one pair of phenols can yield up to six trimers, separation of the products can be a formidable task.



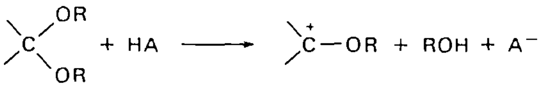
(25)

(37)

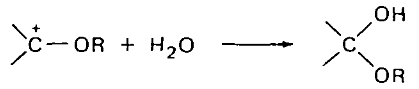
III. HYDROLYSIS OF ACETALS, KETALS AND ORTHO ESTERS

A. Introduction

The hydrolysis of acetals, ketals and ortho esters may be generally understood in terms of three basic reaction stages: (1) protonation of the acetal to generate an oxocarbonium ion, (2) hydrolysis of the oxocarbonium ion to a hemiacetal and (3) breakdown of the latter to an alcohol and an aldehyde or ketone (equations 26–28[2,4,8].



$$>C(OR)_2 + HA \longrightarrow >\overset{+}{C}-OR + ROH + A^- \qquad (26)$$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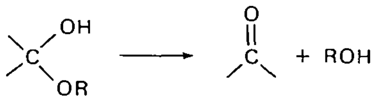

(28)

Some mechanistic studies have addressed the problem of ascertaining which stage in the mechanism is rate-determining, while others have investigated the degree to which proton transfer from the catalyst to an ether oxygen of the acetal (equation 26) is sychronous with C—O bond cleavage between this oxygen and the central carbon atom. Investigators have relied primarily on kinetics to elucidate the mechanistic details and for most of the substrates studied the rate-determining step involved C—O bond cleavage[2,4,8] (equation 26). Usually preequilibrium protonation of the acetal occurs much more rapidly than C—O bond cleavage, the hydrolysis being subject to specific acid catalysis. However, general acid catalysis has been observed in a number of acetals, ketals and ortho esters in which either a resonably stable oxocarbonium ion is formed (e.g. tropone diethyl ketal[53,54]) or oxygen basicity is suppressed (e.g. 2-(4-nitrophenoxy)tetrahydropyran[55,56]).

The detection of general acid catalysis implies that proton transfer must be involved in the rate-determining step. The nature of this involvement has presented interesting and challenging mechanistic questions which bear directly on the validity of the currently accepted general mechanism[8] and are of general interest in physical organic chemistry.

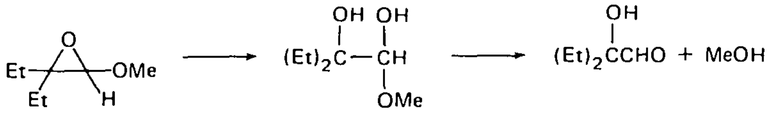
Until recently, essentially all kinetic studies inferred that the reaction stage involving formation of the oxocarbonium ion intermediate is the rate-determining step in the hydrolysis[8]. Consequently, direct kinetic studies of the latter stages of the reaction were not possible, although some indirect kinetic investigations have been reported[57-60]. In the remainder of this section, we shall discuss some of the more recent studies which have been carried out on acetal hydrolysis, including those where direct detection and study of the oxocarbonium ion and the hemiacetal intermediates formed in these reactions has been possible.

B. Rate-determining Step

Without apparent exception experimental investigations have shown that acetals, ketals and ortho esters hydrolyse by similar mechanisms at high pH[2,4,8], i.e. rate-limiting formation of the oxocarbonium ion (equation 26). On the other hand, in the pH region near neutrality or below, this conclusion may not be justified. In some recent studies of acetal hydrolysis it has been possible to detect a change in the rate-determining step under certain conditions. The key to the understanding of the changes in the rate-determining step comes from a consideration of the nature of acid catalysis on each step in the hydrolysis mechanism. Discussion of this important aspect of the mechanism will be postponed until the end of this section.

1. Detection of hemiacetal intermediates

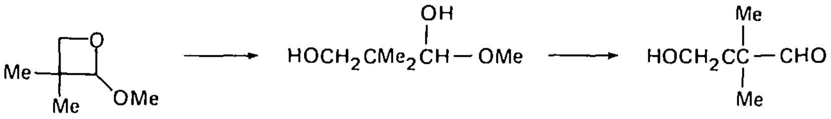
Schaleger and coworkers[61,62] thoroughly investigated the kinetics of hydrolysis of 1-methoxy-2-ethyl-1,2-epoxybutane (38) to form methanol and 2-ethyl-2-hydroxybutanal (40) (equation 29). They found that the pH-dependence of the rates of hydrolysis for 38 displayed a maximum at about pH 8, indicative of a



(38) (39) (40) (29)

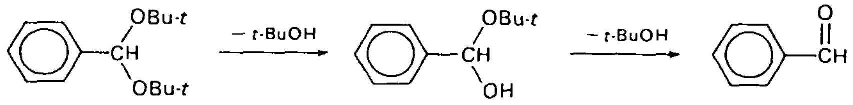
change in the rate-determining step. In the region of the rate maximum the reaction exhibited an induction period which could be accounted for by using the standard rate expression for two consecutive reactions and the rate constants obtained in the high and low acidity regions. The authors argued that these observations lend support to a mechanism in which oxocarbonium ion formation is rate-determining at pH values greater than 8.0, and hydrolysis of a hemiacetal intermediate (39) becomes rate-limiting at low pH values. An alternative explanation for the change in rate-determining step would involve a mechanism where hydrolysis of the oxocarbonium ion has become the slow step at high acidity. However, theoretical and experimental evidence to be discussed below preclude this possibility.

Atkinson and Bruice[63] have similarly observed that during general acid-catalysed hydrolysis of 2-methoxy-3,3-dimethyloxetane (41) (equation 30) an induction period occurs in the pH region 6.1–7.9. As in the preceding example, the authors postulated that the induction period was due to the build-up of hemiacetal.



(41) (42) (30)

The exceptional behaviour of these two cyclic acetals, 38 and 41, can be attributed to relief of steric strain in the ground state[63] which facilitates bond breaking and promotes general acid catalysis. Thus one might also expect to detect hemiacetal intermediates during hydrolysis of other acetals in which both alkoxy groups are unusually bulky. In search of such an acetal, Capon[64] reinvestigated the hydrolysis reaction of benzaldehyde di-*t*-butyl acetal (43) (equation 31), originally

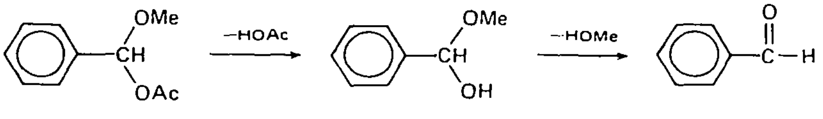


(43) (31)

studied by Anderson and Fife[65] and found to be subject to general acid catalysis. He discovered that under the conditions of aqueous buffer concentrations less than 0.025M and in the pH range 4.6–7.0 the reaction of 43 showed an induction period. On the basis of this observation the reaction was postulated to involve hemiacetal intermediates.

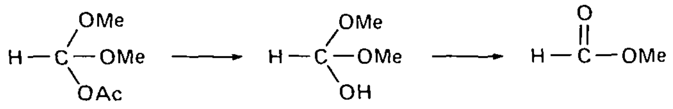
Very soon thereafter, Jensen and Lenz[66] showed that hemiacetals could equally well be detected in a number of substituted benzaldehyde diethyl acetals. By means of rapid quenching experiments which utilized the fact that hemiacetal decomposition is acid- and base-catalysed, whereas its formation is only acid-catalysed, these authors were able to determine [hemiacetal]/[acetal] ratios at various reaction times. They concluded that the concentration of hemiacetal can be quite substantial, approaching 40% of the total substrate concentration (for *p*-methoxybenzaldehyde) at optimum times.

Further important evidence for the existence of hemiacetal intermediates in acetal hydrolysis has been gained by means of studies of analogous acylal hydrolysis. Capon and coworkers[67] selected α-acetoxy-α-methoxytoluene (44), an acylal, as a model compound. In **44**, the acetoxy function is a much better leaving group than the corresponding alkoxy group in an acetal and consequently its expulsion does not require acid catalysis. Since the authors found that the reaction (equation 32)



(44) (45) (32)

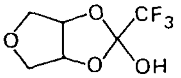
showed general acid and general base catalysis, they postulated that the rate-determining step in the hydrolysis was decomposition of the hemiacetal (45). This conclusion was further substantiated by the fact that the rate constants for **44** and the α-chloroacetoxy derivative were identical. In a related investigation, Capon and coworkers[68] were able to record the nuclear magnetic resonance spectrum of dimethyl hemiorthoformate (47) derived from the hydrolysis of acetoxydimethoxy methane (46) (equation 33), thus supplying direct spectroscopic evidence for the existence of the hydrogen ortho ester.



$$H{-}C(OMe)_2(OAc) \longrightarrow H{-}C(OMe)_2(OH) \longrightarrow H{-}C({=}O){-}OMe \qquad (33)$$

(46) (47)

In an earlier investigation Bladon and Forrest[69] treated *cis*-3,4-dihydroxytetrahydrofuran with excess trifluoracetic anhydride and obtained a crystalline compound. The cyclic hydrogen ortho ester structure (48), was suggested, since the



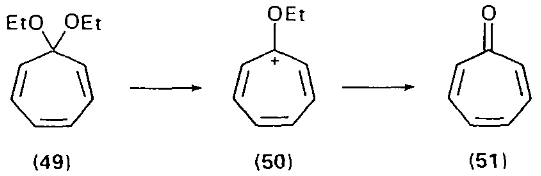
(48)

compound lacked a carbonyl stretching band in the solid infrared spectrum and displayed a proton NMR spectrum characteristic of a cyclic structure.

2. *Detection of oxocarbonium ion intermediates*

As we have seen in the examples quoted in our preceding discussion, a changeover of the rate-determining step in the overall hydrolysis has allowed the detection and direct measurement of the rate constant for decomposition of the hemiacetal intermediate. In some cases it has also been possible to detect oxocarbonium ions as transient intermediates, again by arranging conditions such that the oxocarbonium ion forms more rapidly than it decays.

Recently, McClelland and Ahmad[70,71] studied the kinetics of hydrolysis of certain ketals and ortho esters, and reported that oxocarbonium ion intermediates could be detected spectroscopically during the reaction. These authors selected as model compounds for the hydrolysis studies ketals known to produce very stable oxocarbonium ions such as tropone diethyl ketal (49)[53,54] trimethyl orthomesitoate (52)[54] and dialkyl ketals of 2,3-diphenylcyclopropenone (55)[54] (equations 34–36).



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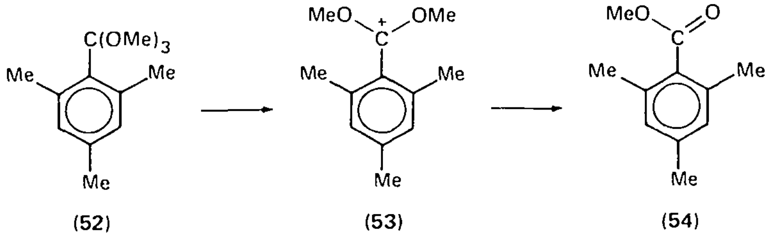

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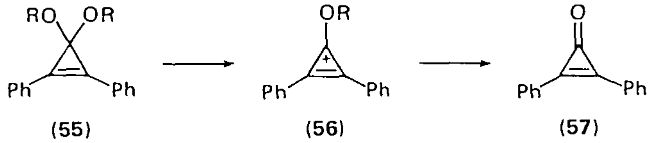


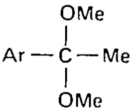
(36)

Below pH 5, the initial ultraviolet spectra of aqueous solutions of **49** are identical to the ultraviolet spectrum obtained on dissolving in water the borofluorate salt of the ethoxytropylium ion (**50**). In both cases the spectrum slowly changes to that of tropone (**51**) as the hydrolysis product is formed. The rate constants obtained following this change were identical within experimental error starting with either **49** or the salt **50**. These spectral and kinetic observations were found to be concordant with a mechanism in this pH region involving rapid conversion of the ketal **49** to the oxocarbonium ion **50** and subsequent rate-limiting hydrolysis of **50** to tropone (**51**). Above pH 8.5, formation of the ion, **50**, becomes rate-limiting.

The experimental results for **52** and **55** were analogous to that of **49** and support a similar mechanism for hydrolysis in acidic solutions. Since ions **53** and **56** are much less stabilized than **50**, their rates of decay were found to be significantly faster than that of **50** requiring stopped-flow techniques to obtain rate constants and spectra of the transient oxocarbonium ion intermediates.

For oxocarbonium ions which have very high reactivity in water, i.e. very short life-times, their existence cannot be demonstrated by the direct methods outlined above. One approach to studying these ions has been to follow the hydrolysis in aqueous sulphuric acid solutions where the activity of water is substantially reduced and consequently the reactivity of the ion is decreased[71]. The results obtained in strong acid media are then extrapolated to water.

Recently Young and Jencks[60] have described a different approach for demonstrating the existence of oxocarbonium ions as intermediates in ketal hydrolysis and to estimate the life-time of the free ions. These authors examined the hydrolysis of acetophenone dimethyl ketals (**58**) in the presence of sulphite ion, which acts as a

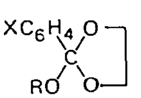


$$\mathrm{Ar{-}C(OMe)_2{-}Me}$$

(58)

trap for the intermediate oxocarbonium ion derived from 58. A detailed study of the trapping and partitioning of products obtained from the acid-catalysed cleavage of 58 revealed that the reaction proceeds through a free solvent-equilibriated oxocarbonium ion intermediate. Addition of the sulphite trap did not affect the kinetics of the hydrolysis; therefore, trapping must occur after the rate-determining step. In addition the intermediate was found to have a sufficiently long life-time to react with either sulphite ion or water. This was reflected in the ratios of the rate constants for reaction of the oxocarbonium with 1M sulphite ion (k_S) and with water (k_{H_2O}), which were found to be in the range 1.3×10^{-1} to 7×10^{2}. The ρ^+ value for the ratio k_{H_2O}/k_S of a series of *m*- and *p*-substituted acetophenone dimethyl ketals is 1.6. This suggested that both k_{H_2O} and k_S cannot represent activation-controlled rate constants since the substituent effects on the ratio of rate constants should approximately cancel ($\rho^+ \simeq 0$). This lack of insensitivity of the product ratio to substituent effects taken with the absolute magnitude of the rate ratios, indicated that rate the constant k_S must represent a diffusion-controlled reaction of sulphite ion with the oxocarbonium ion.

Kresge and coworkers[72–74] studied the kinetics of hydrolysis of a series of 2-aryl-(and 2-cyclopropyl-)2-alkoxy-1,3-dioxolanes (**59** and **60**). These compounds



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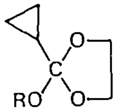
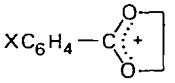


(60)

are of interest because they represent the only known examples where both oxocarbonium ion and hydrogen ortho ester intermediates can be detected together in the same reacting system.

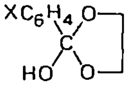
In dilute acid solutions (pH 4.5–7.5), the first stage of the three-stage mechanism of equations (26)–(28), formation of the dioxolenium ion (**61**), is rate-limiting. Direct evidence for the existence of **61** was provided by the detection of



(61)

N-hydroxybenzimidate ester products[75] upon addition of hydroxylamine as an oxocarbonium ion trapping agent[76,77]. Further evidence for rate-limiting expulsion of the exocyclic alkoxy group was provided by monitoring the reaction using a radiochemical tracer (tritium) in the exocyclic alkoxy group of 2-(2,2-dichloroethoxy)-2-phenyl-1,3-dioxolane. The authors found that the rate of expulsion of the exocyclic group was identical to the rate of formation of the carboxylic ester. When a comparison is made of the rates of acid-catalysed hydrolysis of the substrates containing various exocyclic groups, one finds that the rates depend on the nature of the leaving group. For the series of 2-alkoxy-2-phenyl-1,3-dioxolanes the following relative rates were reported: R = OCH_2CHCl_2 : 1; $OCH_2{\equiv}CH$: 1.34; OCH_2CH_2Cl : 1.48; OCH_2CH_2OMe : 2.11; OMe : 4.36; OEt : 6.60. These data clearly show that loss of the exocyclic group and consequently formation of the dioxolenium ion is involved in the rate-determining steps.

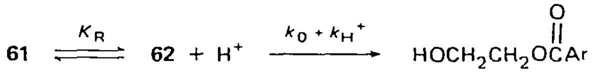
As might be expected from the foregoing discussions, the authors observed that the kinetics for the hydrolysis reaction of **59** underwent a change as the pH of the solution was lowered, and in regions of intermediate acidity a pronounced induction period was observed. In hydrochloric acid solutions of low pH (<3.0), it turns out that the hydronium ion catalytic coefficients (k_{H^+}) become independent of the nature of the exocyclic group. For the series of six substrates which in solutions of high pH gave a sevenfold variation in k_{H^+}, at low pH all give carboxylic acid ester at the same rate ($k_{\mathrm{H}^+} = 3.0 \pm 0.13 \times 10^2\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$). Evidently at low pH the decomposition of the hydrogen ortho ester (62) has become the slow step.



(62)

Dialkoxycarbonium ions have characteristic ultraviolet spectra with absorption maxima near 300 nm. By using a stopped-flow apparatus as a transient spectrometer, Kresge and coworkers[73] were able to detect dioxolenium ions during the hydrolysis of some cyclic ortho esters. The absorbance of the transient dioxolenium ion present during hydrolysis of 2-methoxy-2-(*p*-methoxyphenyl)1,3-dioxolane (59; R = Me, X = *p*-OMe) in 0.5M $HClO_4$ decayed according to first-order kinetics. The data yielded rate constants identical to those obtained by monitoring the formation of carboxylic acid ester product under the same conditions. At lower acidity the decay of the transient dioxolenium ion (generated from either 59 (R = Me, X = *p*-OMe) in 0.02M $HClO_4$ or from the corresponding amide acetal, 2-(*N,N*-dimethylamine)-2-(*p*-methoxyphenyl)-1,3-dioxolane), was observed to be biphasic. The initial fast portion of the decay curve could be attributed to reaction between water and the dioxolenium ion since the first-order rate constants which were obtained from the data were of the magnitude expected for reaction of **61** with water[71] ($k = 1.0 \times 10^3\ \mathrm{s}^{-1}$).

The second slower portion of the biphasic dioxolenium ion decay also yielded first-order rate constants which were identical to those obtained by monitoring the carboxylic acid ester product. This portion of the decay reaction was found to be acid-catalysed, but the relationship between the observed rate constant and the acid concentration was not linear. It was suggested that these experimental results are understandable in terms of a reaction scheme (equation 37) where the dioxolenium ion (61) is in equilibrium with the hydrogen ortho ester (62) plus a proton.



$$61 \xrightleftharpoons{K_R} 62 + \mathrm{H}^+ \xrightarrow{k_0 + k_{\mathrm{H}^+}} \mathrm{HOCH_2CH_2O}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\mathrm{Ar} \tag{37}$$

The rate law required by this mechanism is:

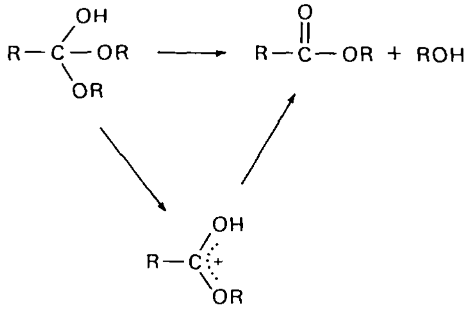
$$k_{\mathrm{obs}} = \frac{k_0 + k_{\mathrm{H}^+}[\mathrm{H}^+]}{1 + [\mathrm{H}^+]/K_{\mathrm{R}}}$$

The best values of the three parameters, $k_0 = 1.4\ \mathrm{s}^{-1}$, $k_{\mathrm{H}^+} = 7.5 \times 10^2\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ and $\mathrm{p}K_{\mathrm{R}} = 1.1$ for **61** (R = Me, X = *p*-OMe), were obtained by fitting the observed first-order rate constants to this equation.

Dioxolenium ion intermediates could also be detected during hydrolysis of the cyclopropyl derivative **60**; however, only the second phase of the decay curve could be discerned. For the other substituted phenyldioxolanes studied[73] (59; R = OMe; X = *p*-tolyl, H, *p*-F, *p*-Cl, *p*-Br, *m*-Cl and *p*-NO_2) only weak transient dioxolenium ion absorbances could be detected and therefore calculation of $\mathrm{p}K_{\mathrm{R}}$ values was not possible.

3. Origin of the change in the rate-determining step

In the preceding discussion we have encountered a number of examples of acetals and ortho esters which undergo a change in rate-determining step during hydrolysis as the acidity of the media is varied. However, in general most acetals, ketals and ortho esters are not found to undergo a change in rate-determining step, C–O bond cleavage (equation 26) remaining as the slow step at all pH values. Kresge and coworkers[73] have pointed out that normally, the third stage of the hydrolysis mechanism (equation 28) should always be somewhat faster than the first stage (equation 26), since unstable cationic intermediates (**63**) like those formed in stage 1, can be avoided in stage 3 (equation 38). Therefore, as the acidity of the media is decreased a change in rate-determining step from stage 3 to stage 1 should not occur. This prediction appears to be fully corroborated in the case of acetals, ketals and ortho esters derived from aliphatic substrates. Among the examples which do exhibit a change, various perturbations in the substrates can be recognized that make the first stage of the hydrolysis more rapid than the third stage, and by virtue of the base catalysis of stage 3 allow a change as acidity is decreased. Some of these structural features which can cause an increase in stage 1 have been previously noted: e.g. the highly strained cyclic[61–63] and *t*-butyl acetals[64,66] and acyloxy ortho esters[68] and acylals[67] which contain very good leaving groups. In the case of aromatic dioxolanes the change in rate-determining step has been ascribed to the phenyl group effect[78].


(63)

(38)

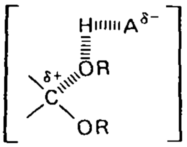
C. General Acid Catalysis

As we have detailed in the preceding discussion, several examples of acetals, ketals and ortho esters are now known which undergo a change in rate-determining step, providing strong direct evidence for a three-stage mechanism for hydrolysis. We now direct our attention to the first stage of this acid-catalysed reaction – generation of the oxocarbonium ion by loss of an OR group from the substrate.

1. Evidence for concerted C–O bond cleavage

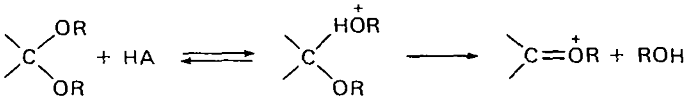
For most substrates studied stage 1 involves rate-determining C–O bond cleavage without accompanying buffer catalysis (A1 mechanism)[4]. The factors which promote general acid catalysis in the hydrolysis of these substrates as well as much of the previous work in this area have recently been reviewed in detail[4,8].

In cases where general acid catalysis has been established unambiguously, the expulsion of the alkoxide ion from the substrate is consistent with a concerted process involving a transition state like **64**.



(64)

Alternative mechanisms for general acid catalysis are unattractive. For instance, a stepwise mechanism (equation 39) of general catalysis can be excluded on the



(39)

basis of several arguments[79]. For this mechanism to satisfactorily account for the observed general acid catalysis, simple proton transfer must be rate-limiting. Acetals, ketals and ortho esters are only weakly basic, the pK_a values of the conjugate acids varying over a range of -3.70 to -8.5[8]. Thus, protonation of these compounds in aqueous solution is thermodynamically very unfavourable and the processes should have very late transition states. Assuming that Brønsted exponents, α and β, can be used as a measure of transition state structure[80], it follows that Brønsted plots for the hydrolysis would be expected to yield α-values close to one[81]. However, α-values which have been determined for acetal and ortho ester hydrolysis are generally found to be around 0.5[8].

Secondly, the magnitude of the calculated rate constants for protonation of the substrate is insufficient to account for the observed overall rate constant for hydrolysis. Assuming the rate of deprotonation of the conjugate acid to be diffusion-controlled, 10^{10} M^{-1} s^{-1}, and using known pK_a values of the substrates, the calculated rate constants for protonation are as much as 10^5 times smaller than the observed rate constants.

2. *Structure–reactivity relationships*

The general problem of concerted versus stepwise reaction pathways, such as the hydrolysis of acetals, ketals and ortho esters considered here, has received considerable attention recently and is still a matter of controversy[82-87]. For reactions which can occur by either a stepwise route or by a concerted route one must analyse reaction paths in terms of motion along more than one dimension of a potential energy surface. This approach, recently popularized by More O'Ferrall[88] and Jencks[82], was first used by Ingold, Hughes and Shapiro[89], recognized by Bunnett[90,91] in his formulation of the theory of the variable E2 transition state and later applied to proton transfer reactions by Albery[92]. Thornton has summarized these arguments as the reacting bond rules[93] which consider the effect of change in structure along the reaction coordinate (parallel effects) and effects perpendicular to it (perpendicular effects). Parallel effects correspond closely to the predictions based on the Leffler–Hammond[94,95] postulate while perpendicular effects lead to conclusions opposite of these predictions.

It is useful to illustrate these structure–reactivity relationships on a three-dimensional potential energy contour diagram. Such a diagram (referred to as a

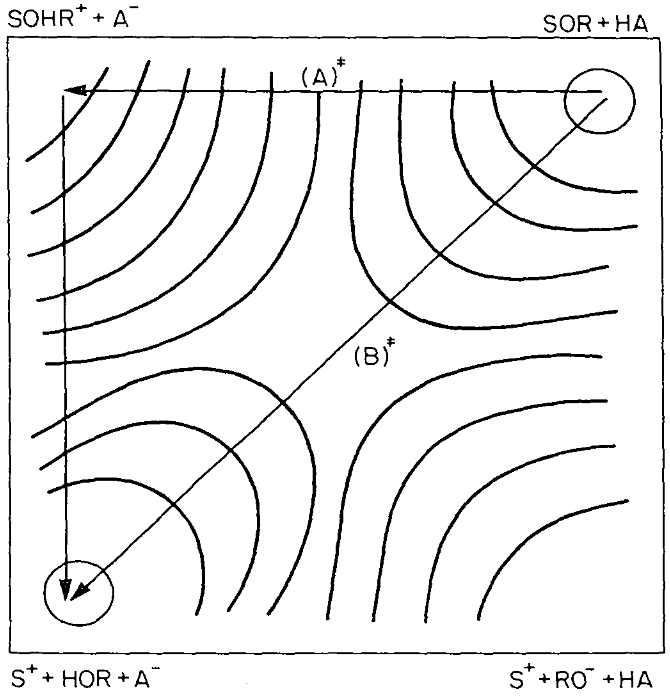


FIGURE 1. A contour map representing the potential energy surface for the first stage of acetal hydrolysis (equation 26). Path (A) represents the stepwise reaction route, while path (B) represents the concerted reaction route.

More O'Ferrall–Jencks plot) for the first stage of hydrolysis of an acetal or related substance is shown in Figure 1. The horizontal axis represents the progress of proton transfer and the vertical axis denotes the progress of C—O bond cleavage. Potential energy is the third dimension, and is represented by the contour lines in the figure. The starting materials, acetal (SOR) and the acid (HA), are in the upper right-hand corner of the diagram, and the products, oxocarbonium ion (S^+), alcohol (ROH) and conjugate base of the catalyst (A^-), are in the lower left-hand corner. Starting in the upper right-hand corner the reaction can proceed via a stepwise reaction mechanism along the edges of the diagram from SOR to $SOHR^+$ through transition state (A), followed by C—O bond cleavage to products S^+. The reaction coordinate for the concerted route would lie near the diagonal from SOR to S^+, avoiding the high-energy intermediates at the corners, and involves passage through transition state (B).

With reference to the two possible pathways for hydrolysis of an acetal presented in Figure 1, we now consider the effect on the system of changing the R group of the substrate. Introduction of an electron-withdrawing substituent into R will stabilize RO^- and destabilize $SOHR^+$. Consequently, the upper left-hand corner of Figure 1 will be raised relative to the lower right-hand corner. This will induce a parallel shift of transition state (A) for the stepwise process toward the destabilized corner (a Hammond effect). The result will be a transition state involving more proton transfer and more positive charge development on the oxygen atom in SOR, corresponding to an increase in the Brønsted exponent α. On the other hand, this same change in R will cause transition state (B) for the concerted pathway to move toward the stabilized corner (anti-Hammond, perpendicular effect). This will result in measurement of lower Brønsted α-values as the electron-withdrawing power of R increases.

It is convenient to express the relationship between the extent of proton transfer (α) and the basicity of the proton accepting site of the leaving group (pK_{lg}) in terms of the interaction coefficient $p_{xy'}$[96] of equation (40). Since hydrolysis via a

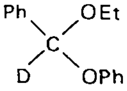
$$p_{xy'} = \frac{\partial \alpha}{\partial pK_{lg}} \tag{40}$$

concerted mechanism predicts an increase in α with increasing basicity of the leaving alcohol, this corresponds to a positive $p_{xy'}$ coefficient. A look into the experimental picture clearly shows that anti-Hammond behaviour has been observed in the hydrolysis of acetals and ortho esters and in a number of other systems in which alcohol or water is expelled from a substrate by a concerted acid-catalysed pathway. For instance, Capon and Nimmo[97] obtained an interaction coefficient $p_{xy'} = 0.2$ for the aryl oxide ion expulsion from benzaldehyde aryl methyl acetals, and Kresge and coworkers[74] in a similar study of alcohol expulsion from 2-alkoxy-2-phenyl-1,3-dioxolanes obtained a value of $p_{xy'} = 0.08$. Other studies include alkoxide ion expulsion from addition compounds of phthalimidium ion[79] ($p_{xy'} = 0.07$), from formaldehyde[98] ($p_{xy'} = 0.09$), from tosylhydrazone addition compounds[99] ($p_{xy'} = 0.05$) and from Meisenheimer complexes of the 1,1-dialkoxy-2,6-dinitro-4-*X*-cyclohexadianate type[100] ($p_{xy'} = 0.12$).

3. Secondary deuterium isotope effects

It is generally believed that the magnitude of secondary deuterium kinetic isotope effects can be used as a probe of transition-state structure. The secondary effects depend on the strengthening or loosening of C—H bonds which are not broken in the rate-determining step. In the hydrolysis of acetals, ketals and ortho esters, the hybridization of the central carbon changes from sp^3 to sp^2 with a concomitant change of the C—H bond force constants. Thus k_H/k_D should reveal the 'product-like' or 'reactant-like' nature of the transition state. Earlier investigations of secondary deuterium isotope effects in acid-catalysed hydrolysis of acetals, ketals and ortho esters have been surveyed in detail by Cordes[8].

Recently, Lamaty and Nguyen[101] determined the α-secondary isotope effect for the hydrolysis of benzaldehyde ethyl phenyl acetal (65) catalysed by a series of



(65)

acetic and cacodylic acid buffers. The reaction was found to exhibit an α-secondary isotope effect which depended on the strength of the acid catalyst. At 25°C, k_H/k_D are: for H_3O^+, 1.045; acetic acid, 1.175; cacodylic acid, 1.190; H_2O, 1.243. Thus these data indicate that as the strength of the catalysing acid decreases there is a shift toward a transition state that more closely resembles the carbonium ion.

It is interesting to consider this trend in the α-deuterium isotope effect with reference to a More O'Ferrall—Jencks diagram (Figure 1). If the strength of the acid catalyst is increased, the right-hand side of the diagram will be raised relative to the left-hand side of the diagram. If the reaction coordinate is diagonal this will have the effect of moving the position of the transition state toward the upper right-hand corner (Leffler–Hammond effect[94,95]) and at the same time toward the upper left-hand corner (Thornton effect[93]). The resultant of the vectors for the movements will cause the reaction coordinate to move closer to the top edge of the diagram and in the direction of less C—O bond cleavage, in agreement with the observed isotope effects.

D. Medium Effects

1. *Kinetic solvent isotope effects*

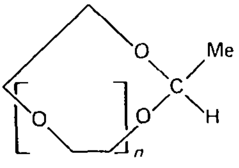
The kinetic solvent isotope effects resulting from a change in solvent from H_2O to D_2O in the hydrolysis of various acetals and ortho esters can be useful in studying the reaction mechanism. For the A1 mechanism, preequilibrium proton transfer followed by a rate-determining reaction of the protonated substrate, the calculations of Schowen[102] predict, and it is observed experimentally[8], that k_{H_2O}/k_{D_2O} should fall in the range 0.29–0.43. On the other hand, if the first step involves rate-determining proton transfer (A-S_E2) the reaction will be influenced by both primary and secondary isotope effects. In a rate-determining proton transfer from hydronium ion to an acetal or ortho ester the maximum value of k_{H_2O}/k_{D_2O} will be around 3 since both primary and secondary effects contribute[103]. Only primary effects are important when the proton transfer is from a molecular acid and values of k_{H_2O}/k_{D_2O} in the neighbourhood of 7 are expected[103]. In cases where general catalysis can be detected in the hydrolysis of acetals and ortho esters, the observed isotope effects fall in the range $k_{H_2O}/k_{D_2O} = 1.4–3.4$[8,104]. Consequently, these results do not support the A1 mechanism, nor are they large enough to be in complete agreement with a true A-S_E2 mechanism. These results might be interpreted as supporting evidence for the concerted process involving proton transfer and C–O bond breakage occurring in the same step. This view, however, is in opposition to the rule of Swain, Kuhn and Schowen[105], which states that, for proton transfers between electronegative atoms in a reaction which requires heavy atom reorganization, the proton lies in a completely bonded potential well and should not give rise to primary hydrogen isotope effects. In other words, the hydrogenic motion must take place in a rapid step before or after C–O bond breakage. It follows then, that a Brønsted plot should have a slope α equal to zero or one, contrary to what is observed experimentally (α generally has a value around 0.5).

Recently, Eliason and Kreevoy[106] attempted to resolve the question of the apparent failure of the Swain–Schown rule. They have shown that application of a hydrogenic potential function model that has a double minium and a shallow central maximum leads to the correct prediction of the experimental results. In this model the transferring proton is always in a bound state, retaining zero point energy, while the reaction coordinate consists almost entirely of heavy atom motion. A similar model also has been proposed by Young and Jencks[60].

2. *Salt effects*

Kubler and coworkers examined kinetic salt effects on the hydrolysis of benzaldehyde dimethyl acetal in water[107] and in 95% methanol–5% water[108]. Neutral salts such as alkali metal and ammonium perchlorates and halides increase the rate of acid hydrolysis. The rate enhancement showed specific cation effects in the order $Li^+ < Na^+ < K^+ < NH_4^+$. According to the authors the observed kinetic salt effects could not be rationalized in terms of the Debye–Huckel–Brønsted approach, indicating that factors other than activity coefficient changes (for example steric effects) are important when considering salt effects on acetal hydrolysis reactions.

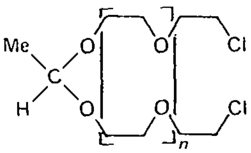
Gold and Sghibartz[109] examined the kinetic salt effects on the acid-catalysed hydrolysis of some crown ether acetals (66) in dioxane–water (60 : 40 by volume) at 25°C.



(66)

For the series of compounds (66) with $n = 0–3$, corresponding to acetals containing 5-, 8-, 11- and 14-membered rings and 2,3,4 and 5 oxygen atoms in the ring, respectively, they found that in the presence of 0.25M alkali metal salts only a small increase in the hydrolysis rate was observed. On the other hand, alkali metal salts produced marked rate retardation in acetals of ring-size 17 and 20 ($n = 4–5$). They explained these results by pointing out that these latter acetals have very similar ring-sizes to 18-crown-6 and other cyclic polyethers which are known to be strong chelating agents of alkali metals. It is reasonable then to suppose that cation binding reduces the rate of hydrolysis and accounts for the observed salt effects.

Unlike the crown ether acetals, only small salt effects on the rate of hydrolysis of acyclic ether acetals 67 were found.



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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 21

The photochemistry of saturated alcohols, ethers and acetals

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I. INTRODUCTION

In this review we intend to consider the photochemistry of only those title compounds where the alcohol, ether or acetal function supplies the chromophore. The oxygen lone-pair electrons undergo an n → 3s Rydberg-type transition[1] around 185 nm. The photochemistry of compounds with additional chromophores that are excited at longer wavelengths, such as carbonyl or aryl substituents, is dominated by these chromophores. The 'real' photochemistry of alcohols, ethers and acetals can, strictly speaking, only be studied with the saturated compounds. A less restrictive approach has been taken in two reviews[2,3] in this series.

Since the topic has been reviewed by us recently[4] in some detail, we shall give a briefer and more general account here. Material that has become available in the meantime has been included.

Although the carbonyl-sensitized photolysis[2,3] of the title compounds is not discussed in the present review, we are reporting briefly on the present knowledge of the Hg-sensitized photolysis and the photolysis of O_2-charge-transfer complexes. In both kinds of systems, the alcohol and ether oxygen may be involved as the fulcrum of the interaction.

II. ABSORPTION SPECTRA. ACTINOMETRY AT 185 nm

Saturated alcohols, ethers, and acetals start to absorb noticeably around 200 nm. The maximum of the first absorption band which has been attributed to an $n \rightarrow \sigma^*$[5] or Rydberg-type[1] transition lies near 185 nm. In the gas phase this first absorption band of alcohols is structureless whereas with ethers it usually shows pronounced fine structure[1]. The absorption coefficients of some selected compounds are compiled in Table 1. Formaldehyde dimethyl acetal[16] has a rather low extinction coefficient at 185 nm. Possibly its first absorption maximum lies well below 185 nm. This would correlate with its comparatively high ionization potential[19]. With the remarkable exception of 1,4-dioxane[15], the liquid-phase absorption coefficients of ethers and acetals match those of the gas phase, at least over the range where both can be measured.

With alcohols there is no such matching. Their absorbance at 185 nm is much lower in the neat liquid (e.g. $\epsilon(\text{MeOH}) \approx 7$[20,21], $\epsilon(\text{i-PrOH}) = 32$[22], $\epsilon(t\text{-BuOH}) = 90$[22]) than in the gas phase (see Table 1). This is most likely due to hydrogen bonding in the liquid which causes a blue shift of the absorption band, as is also observed with water[1]. In agreement with this interpretation the extinction coefficient of *t*-butanol at 185 nm increases on dilution with saturated hydrocarbons[23-25]. At shorter wavelengths other chromophores ($\sigma \rightarrow \sigma^*$) are excited. In this wavelength region, fine structure of the absorption bands is observed with alcohols as well[26].

TABLE 1. Molar extinction coefficients (base ten, averaged) of some saturated alcohols, ethers, and acetals at 185 nm in the gas phase

Compound	ϵ_{185} (M^{-1} cm^{-1})	Reference
Methanol	~ 160	6–8
Isopropanol	~ 240	6–8
t-Butanol	1150	7
Diethyl ether	~2000	7, 9–11
Diisopropyl ether	500	7
Di-*t*-butyl ether	2200	12
t-Butyl methyl ether	200	9
Tetrahydrofuran	~ 650	13, 14
1,4-Dioxane	3000	14,15
Formaldehyde dimethyl acetal	50	16
Pivalaldehyde dimethyl acetal	400	17
1,3-Dioxolane	480	18

In the saturated systems considered here, the alcohol or ether chromophore is selectively excited at 185 nm, a major spectral line of the Hg low-pressure arc lamp. The other major spectral line of this lamp, 254 nm, is not absorbed by these systems, or does not contribute significantly to their photolysis. At 185 nm the actinometry of liquid systems is most easily accomplished using the Farkas actinometer, a 5M aqueous ethanol solution which gives H_2 with a quantum yield of 0.4. The Farkas actinometer has been discussed in detail elsewhere[4].

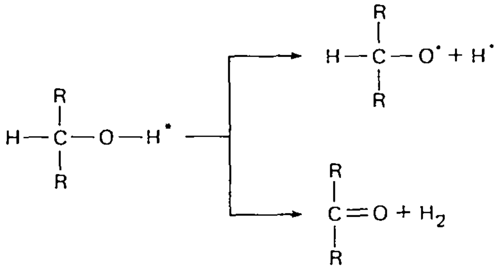
III. PHOTOLYSIS OF ALCOHOLS

Studies have been made of the photochemistry of methanol[26-33], ethanol[27,29,34], isopropanol[27,35-39], *t*-butanol[24,25,38,40-42] and ethylene glycol[43]. In these systems the quantum yields of the sum of the primary processes leading to products approaches unity. Judging from the work on methanol it appears to make little difference, with respect to the importance of the various primary processes (see Scheme 1), whether the photolysis is carried out in the gas phase[30-33] or in the neat liquid[27-29]. However, considering the strong influence that nonabsorbing solvents exert on the primary processes of *t*-butanol[24,25] this may not be generally true. Extensive gas-phase studies on the direct photolysis of alcohols other than methanol are lacking.

Primary and secondary alcohols appear to show a similar photolytic behaviour which differs strongly from that of tertiary alcohols if *t*-butanol is taken as an example which can be generalized.

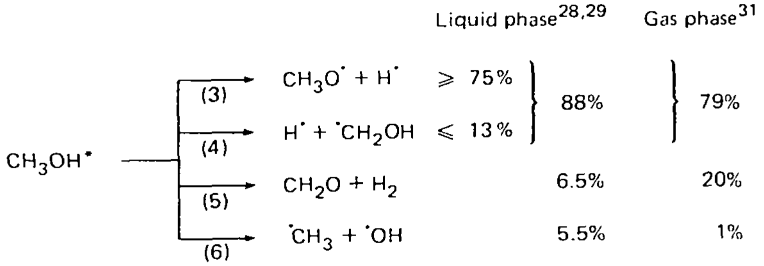
A. Primary and Secondary Alcohols

The most important process in the photolysis of primary and secondary alcohols is the scission of the O—H bond, a bond which is the strongest in the ground state of these molecules. Two processes are conceivable: (*i*) the homolytic scission of the O—H bond (reaction 1) or (*ii*) the elimination of molecular hydrogen (reaction 2).



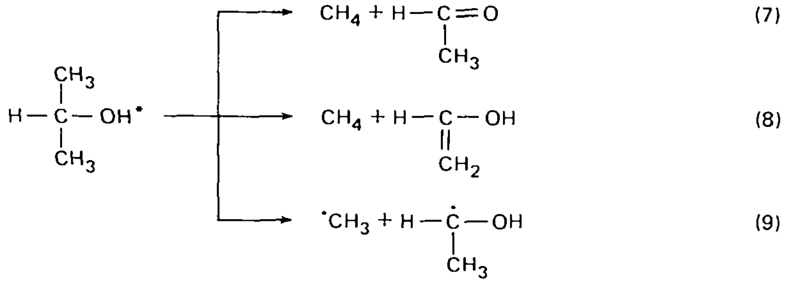
(1)

(2)



SCHEME 1. 185 nm photolysis of neat methanol.

In methanol process (1) (reaction 3 in Scheme 1) is predominant and process (2) (reaction 5 in Scheme 1) is almost negligible. With increasing methyl substitution process (2) appears to gain at the cost of process (1) (in methanol, $\phi(2)/\phi(1) \approx 0.09$; in ethanol, $\phi(2)/\phi(1) \approx 1$; in isopropanol, $\phi(2)/\phi(1) \approx 3$). The scission of the C—O bond is of minor importance (<10%) as is the scission of the C—C bond in ethanol (<2%) and isopropanol (5.5%). It has been shown[37] that in isopropanol the C—C bond is preferentially broken via elimination of molecular methane, as depicted in reactions (7) and (8), and that methyl radicals (reaction 9) play only a very minor role. Also of little importance is the homolytic scission of a C—H bond.

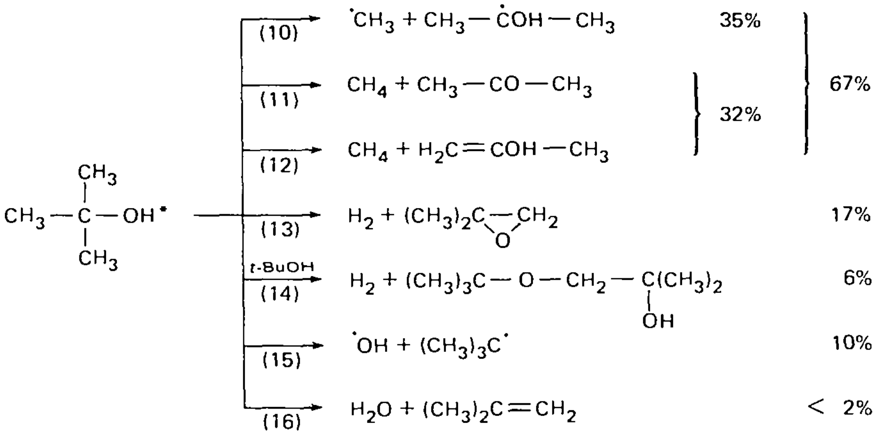


Such a process does not contribute to more than about 15%, mostly less, of all primary processes in the lower alcohols investigated.

Excitation at wavelengths shorter than 185 nm does not bring about a drastic change in the gas-phase photolysis of methanol[26]. Below a threshold of 130 nm for methanol and 145 nm for C_2–C_4 alcohols the formation of electronically excited OH radicals was observed[44].

B. Tertiary Butanol

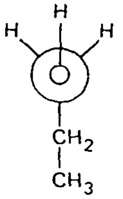
It appears that with the primary and secondary alcohols the excitation of the oxygen lone pair activates above all the oxygen–hydrogen bond. However, this is no longer true in neat *t*-butanol (Scheme 2). Homolytic scission of the O—H bond appears not to occur. Instead O—H bond scission occurs via two molecular modes:



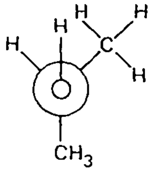
SCHEME 2. 185 nm photolysis of neat *t*-butanol[41].

(*i*) intramolecular epoxide formation (reaction 13), and (*ii*) intermolecular ether formation (reaction 14)[40,41].

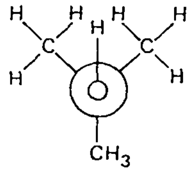
A process similar to reaction (13) has also been observed[38] with isopropanol and *s*-butanol but not with ethanol, *n*-propanol, *n*-butanol and isobutanol. The most likely ground-state conformation in the primary alcohols does not favour epoxide formation, whereas the Newman projections show that there is a likelihood of such an interaction in isopropanol and in *t*-butanol. The primary and secondary alcohols could also, in principle, undergo a reaction similar to that depicted in reaction (14). The corresponding products, however, were not observed. If the connection happens to be made to the hydroxyl-bearing carbon atom, one expects not to see the product, which as a hemiacetal is unstable, and the process therefore would be indistinguishable from reaction (6).



n-Propanol



Isopropanol



t-Butanol

In the case of *t*-butanol the scission of a C—C bond is dominant (67%). This is strictly true only for the neat liquid. On dilution with a hydrocarbon such as cyclohexane the importance of C—C bond breakage drops and that of O—H scission rises drastically. An attempt to correlate this effect with changes in the degree of association has been only partially successful[25]. The present state of knowledge is insufficient to theoretically predict the photolytic behaviour of these simple molecules, even when they exist isolated in the gas phase, and there is a still lesser chance to explain such strong solvent effects, considering that the quantum energy is about 200 kJ mol^{-1} above the dissociation energy of any of the bonds involved, and that the energy changes due to hydrogen bonding are only a few kJ. All these strong effects must result from minute alterations in the structure of the excited state.

C. Alkoxide Ions

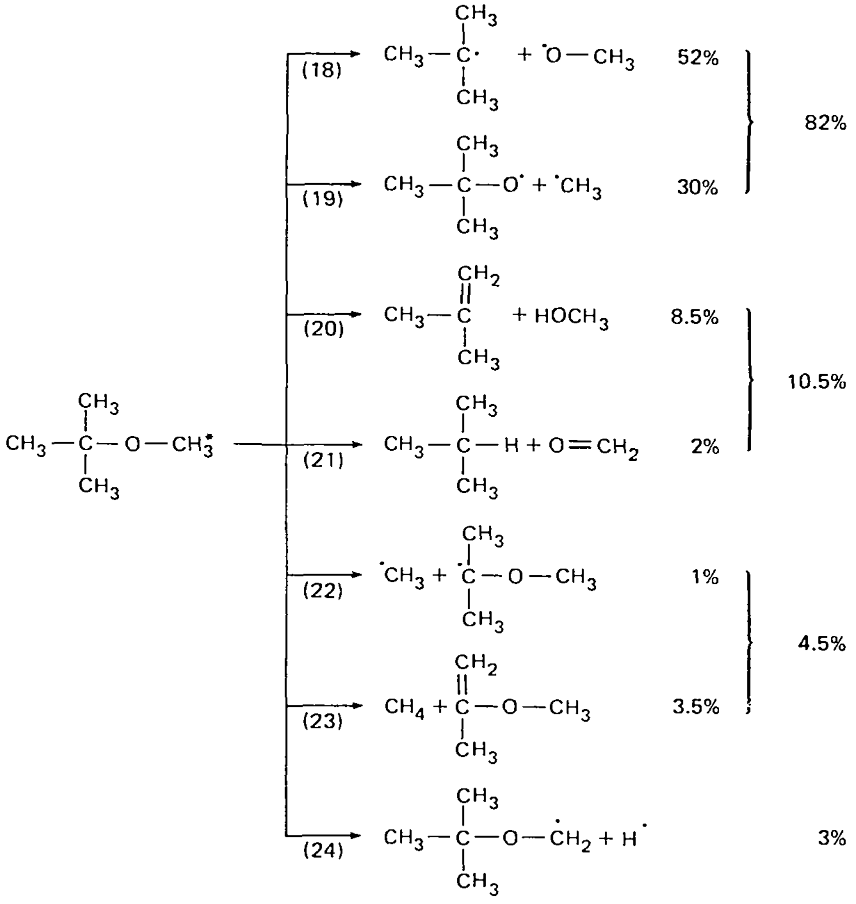
Alkoxide ions absorb light at longer wavelengths than do the alcohols themselves, and in liquid ammonia electrons are ejected at 254 as well as 316 nm with quantum yields of unity[45] (reaction 17). In liquid ammonia the electrons become solvated and are detected by their blue colour.

$$\mathrm{EtO^-} \xrightarrow{h\nu} \mathrm{EtO^\bullet} + e^-_{\mathrm{solv}} \tag{17}$$

IV. PHOTOLYSIS OF ETHERS

A. Acyclic Ethers

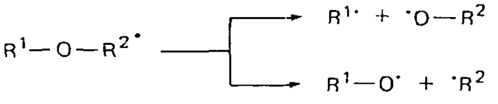
In the photolysis of saturated acyclic ethers at 185 nm in the liquid phase[9,12,46-49] the major process is the scission of a C—O bond. This scission can proceed by homolysis or via a molecular process, the latter being indistinguishable



SCHEME 3. 185 nm photolysis of *t*-butyl methyl ether[9].

from cage disproportionation reactions. A typical example is the photolysis of *t*-butyl methyl ether. Its primary processes are depicted in Scheme 3. In general, the homolytic scissions predominate over the molecular processes (cf. *t*-butyl methyl ether[9], diethyl ether[46] and methyl *n*-propyl ether[47]). The reverse is the case with di-*t*-butyl ether[12]. Other reactions than those involving the oxygen in one way or other are negligible by comparison (see Scheme 3 and cf. Reference 4).

Asymmetrically substituted ethers split the C—O bonds with different probabilities (reactions 25 and 26). Because of the high hydrogen-abstracting power of the alkoxyl radicals ($R^1O^\bullet$ and $R^2O^\bullet$) these radicals are rapidly converted into the corresponding alcohols (R^1OH and R^2OH). The quantum yields of the alcohols are an approximate measure of the primary processes (25) and (26), approximate only in so far as molecular processes such as reaction (20) in Scheme 3 also contribute to the formation of alcohols. Table 2 gives a compilation of data presently available.



$$R^1{-}O{-}R^{2*} \longrightarrow R^{1\bullet} + {}^\bullet O{-}R^2 \qquad (25)$$

$$R^1{-}O{-}R^{2*} \longrightarrow R^1{-}O^\bullet + {}^\bullet R^2 \qquad (26)$$

TABLE 2. UV photolysis (λ = 185 nm) of liquid ethers (R^1–O–R^2). Quantum yields of alcohols

<table>
<tr><th>R^1–O–R^2</th><th>$\phi(R^1$–OH)</th><th>$\phi(R^2$–OH)</th><th>Reference</th></tr>
<tr><td>Et–O–Et</td><td colspan="2">0.46</td><td>46</td></tr>
<tr><td>Me–O–Pr-<i>n</i></td><td>0.16</td><td>0.70</td><td>47</td></tr>
<tr><td>Me–O–Pr-<i>i</i></td><td>0.16</td><td>0.40</td><td>4</td></tr>
<tr><td>Me–O–Bu-<i>n</i></td><td>0.08</td><td>0.44</td><td>4</td></tr>
<tr><td>Me–O–Bu-<i>t</i></td><td>0.41</td><td>0.20</td><td>9</td></tr>
<tr><td><i>t</i>-Bu–O–Bu-<i>t</i></td><td colspan="2">0.84</td><td>12</td></tr>
<tr><td>Et–O–Pr-<i>n</i></td><td>0.31</td><td>0.28</td><td>4</td></tr>
<tr><td>Et–O–Pr-<i>i</i></td><td>0.26</td><td>0.25</td><td>4</td></tr>
</table>

These data suggest that in the competition between reactions (25) and (26) the smaller alkyl group is split off preferentially, though *t*-butyl methyl ether presents an exception to the rule. This behaviour of the ether chromophore is in contrast[47] to that of the carbonyl chromophore in aliphatic ketones, where the large alkyl group is preferentially eliminated in the α-cleavage process. No theoretical studies are yet available that could interpret the photolytical behaviour of the ethers.

The photolysis of acyclic ethers in the gas phase[50–52] is probably[4] mechanistically similar to that in the liquid phase. The elucidation of the primary processes on the basis of the products formed is more difficult because of the formation of thermally excited radicals which break down into smaller fragments.

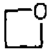
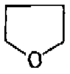
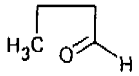
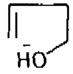
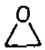
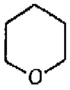
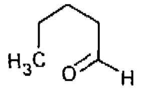
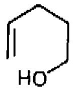
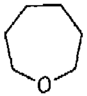
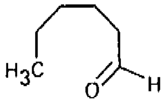
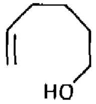
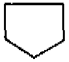
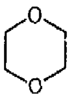
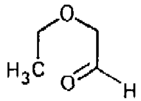
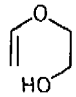
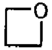
B. Cyclic Ethers

The photolysis of cyclic ethers presents a more complicated picture. Here as well, it is the C—O bond that is mostly cleaved. The intermediacy of a biradical has been suggested in the photolysis of 2,5-dimethyltetrahydrofuran[53] where the *cis* (*trans*) form is converted into the *trans* (*cis*) form (reaction 39, see below). Similar to the acyclic ethers where true molecular processes could not be distinguished from cage disproportionation reactions, the reactive intermediate biradical may undergo disproportionation reactions as well (e.g. reactions 42 and 43, see below). In competition the biradical may, especially in the gas phase at low pressures, undergo a fragmentation by elimination of an unsaturated molecule (e.g. reaction 40, see below) resulting in a smaller biradical. Evidence obtained with tetrahydrofuran[53] indicates that molecular processes also lead to such fragment products.

Table 3 comprises a selection of data obtained in the photolysis of some cyclic ethers in the liquid phase. These data reflect the great differences in the photolytic behaviour of these ethers. For oxiranes no liquid-phase data are available. In oxetanes only breakdown into unsaturated molecules has been observed[54]. In tetrahydrofuran[53], reclosure of the biradical and molecular breakdown into cyclopropane and formaldehyde predominates, whereas in tetrahydropyran[55] mainly the disproportionation products are observed, and breakdown into smaller fragments is negligible (on a further reaction see below). In the oxepane[56] system there is no fragmentation. In 1,4-dioxane[15] only one disproportionation route (or molecular process?), i.e. that leading to the unsaturated alcohol, is observed. Fragmentation, either via the biradical or a molecular process does not halt at the first step (cyclobutane and formaldehyde) but efficiently proceeds to ethylene and further formaldehyde.

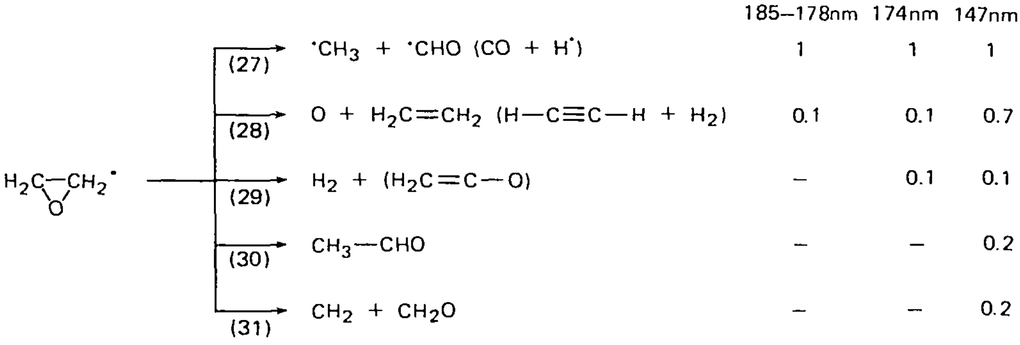
The photolysis of the various cyclic ethers is discussed below in more detail.

TABLE 3. Some characteristic products in the photolysis of cyclic ethers in the liquid phase

Ether	Aldehyde	Olefin-alcohol	Simple fragmentation	Double fragmentation	Reference
 In solution	CH_3CH_2CHO Absent	$H_2C{=}CHCH_2OH$ Not observed	$CH_2O + H_2C{=}CH_2$ ⩾ 95% of products	$CO + H_2 + H_2C{=}CH_2$ Little if any	54
 Neat	 $\phi = 0.06$	 $\phi = 0.02$	$+ CH_2O$ $\phi = 0.19$ $H_2C{=}CH_2 +$ $,CH_3CHO$ $\phi = 0.025$	None	53
 Neat	 $\phi = 0.13$	 $\phi = 0.4$	$+ CH_2O$ $\phi = 0.002$	$2\,H_2C{=}CH_2 + CH_2O$ $\phi = 0.005$	55
 Neat	 $\phi = 0.09$	 $\phi = 0.2$	 $+ CH_2O$ Absent	None	56
 Neat	 Absent	 $\phi = 0.17$	 $+ CH_2O$ $\phi = 0.04$	$H_2C{=}CH_2 + 2\,CH_2O$ $\phi = 0.15$	15

1. *Oxiranes*

The photolysis of oxirane has been studied in the gas phase[57–60] only. It may be conjectured that the main primary photochemical event is C—O bond scission, which is followed by extensive breakdown into smaller fragments (reaction 27). There is a strong wavelength dependence in the pattern of primary processes[60]. Whereas reaction (28), the extrusion of an oxygen atom and the inverse to epoxide formation[61], is of little importance above 174 nm, it plays a considerable role at 147 nm. At this wavelength two further primary processes (reaction 30 and 31) are believed[60] to set in. Much of the excess energy of reaction (28) is carried off by the ethylene molecule which can break down further into acetylene and hydrogen.


185–178nm 174nm 147nm
(27) ·CH3 + ·CHO (CO + H·) 1 1 1
(28) O + H2C=CH2 (H—C≡C—H + H2) 0.1 0.1 0.7
(29) H2 + (H2C=C—O) – 0.1 0.1
(30) CH3—CHO – – 0.2
(31) CH2 + CH2O – – 0.2
H2C—CH2*
O

SCHEME 4. Photolysis of ethylene oxide in the gas phase. Relative importance of primary processes at different wavelengths[60].

The fate of the oxygen atom and the CH_2 remains unclear. If oxygen atoms are generated in the singlet state they might give rise to formaldehyde via insertion into an epoxide C—H bond and subsequent fragmentation. Formaldehyde is the main product at 147 nm and half of it has been ascribed[60] to reaction (32) even at the comparatively low pressures (13 torr) that were employed.

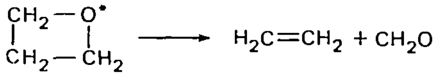
$$\cdot CHO + \cdot H + M \longrightarrow CH_2O + M \qquad (32)$$

Another open question is that of the fate of the oxiranyl radicals which one expects in this system where hydrogen atoms and methyl radicals, possibly hot, are formed with a substantial quantum yield. It is known that such radicals readily undergo fragmentation because of ring strain[62,63].

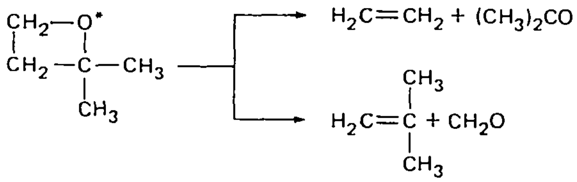
The 185 nm photolysis of 2-methyloxirane vapour[64] apparently leads to considerable primary rearrangement into propanal. Some acetone and propanal were thought to be produced via rearrangement of the 2- and 3-oxiranyl radicals. It is not known whether there were any hydrogen and hydrocarbons produced.

2. *Oxetanes*

The photolysis of oxetanes has been studied in the gas phase as well as in isooctane and aqueous solutions[54]. Oxetane has been reported to give exclusively formaldehyde and ethylene (reaction 33) whereas 2,2-dimethyloxetane gives acetone and ethylene (reaction 34) as well as formaldehyde and isobutylene (reaction 35), $\phi(34)/\phi(35)$ being 1.2. The conceivable ring-opened products (see



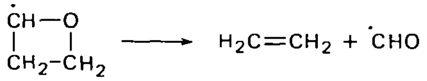
(33)



(34)

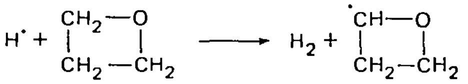
(35)

Table 3) were not observed (propionaldehyde) or not looked for (allyl alcohol). At photolysis temperatures above 100°C a chain-reaction sets in (reactions 36–38).



(36)

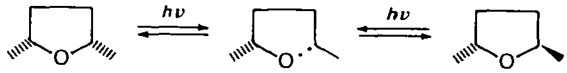
$$\dot{C}HO \longrightarrow CO + H^{\bullet} \tag{37}$$



(38)

3. Tetrahydrofurans

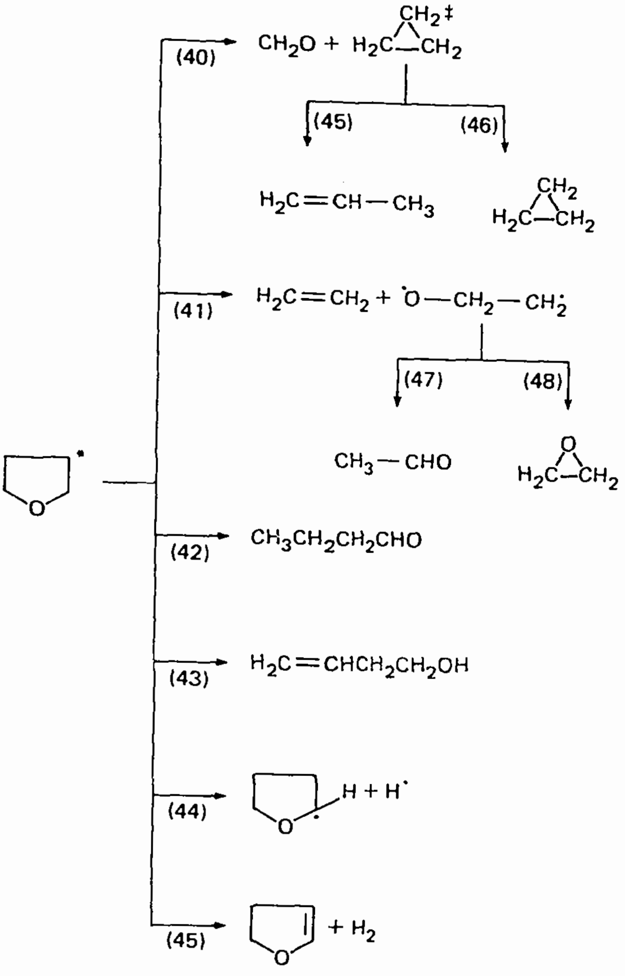
The photolysis (λ = 185 nm) of tetrahydrofuran and some of its methyl derivatives has been studied in the liquid phase[53]. The fact that *cis*(*trans*)-2,5-dimethyltetrahydrofuran gives the *trans*(*cis*) compound with a quantum yield of 0.2 is good evidence that formation of a biradical by C—O bond scission must play a considerable role (reaction 39). The same biradical may also be considered the



(39)

precursor of some other products (see reactions 42 and 43, Scheme 5). Substitution of hydrogen by methyl has a strong but as yet unexplained effect on the primary photochemical and some of the subsequent processes. The most noticeable influence is on $\phi(H_2)$ which rises from below 10^{-4} in 2,2,5,5-tetramethyltetrahydrofuran to 0.07 in tetrahydrofuran, 0.17 in 2-methyltetrahydrofuran and ultimately to the high value of 0.29 (0.27) in the case of *trans*(*cis*)-2,5-dimethyltetrahydrofuran. Although H atoms may be involved (reaction 44) it is not unlikely that in the cases where $\phi(H_2)$ is very high, hydrogen results from a molecular process (reaction 45). A molecular process has also been postulated for the formation of hydrogen in the photolysis of liquid diethyl ether[46].

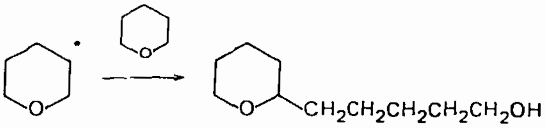
In the gas-phase photolysis of tetrahydrofuran[65,66] fragmentation dominates the other processes, and the products are not yet thermalized, e.g. the hot cyclopropane from reaction (40) gives largely propene. In the liquid-phase photolysis, however, the cyclopropane: propene ration is 97 : 3[53]. In a recent gas-phase study[67] where some deuterium-labelled tetrahydrofurans were investigated, evidence is presented that not only the hydrocarbon radicals methyl and/or methylene, but also vinyl and allyl are produced in primary processes.


(40)
$CH_2O + H_2C\!-\!CH_2$ $CH_2^{\ddagger}$
(45)
(46)
$H_2C{=}CH{-}CH_3$
(41)
$H_2C{=}CH_2 + \dot{O}{-}CH_2{-}\dot{C}H_2$
(47)
(48)
$CH_3{-}CHO$
(42)
$CH_3CH_2CH_2CHO$
(43)
$H_2C{=}CHCH_2CH_2OH$
(44)
H + H˙
(45)
$+ H_2$

SCHEME 5. 185 nm photolysis of liquid tetrahydrofuran[53].

4. *Tetrahydropyran and oxepane*

The photolysis of liquid tetrahydropyran[55] at 185 nm resembles that of tetrahydrofuran. Typical products are listed in Table 3. However, there is a major product, 2-(5-hydroxypentyl)tetrahydropyran ($\phi = 0.21$) which appears to be formed without free radicals as intermediates (reaction 46). The mechanism of this


$CH_2CH_2CH_2CH_2CH_2OH$

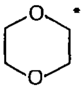
(46)

reaction is not known. Similar compounds also appear to be formed in the photolysis of tetrahydrofuran[53] and oxepane[56], albeit with lower quantum yields.

There is only very little fragmentation of the presumed biradical in the tetrahydropyran system, and none has been observed in the case of oxepane[56] (see Table 3).

5. *1,4-Dioxane*

1,4-Dioxane presents in its photochemistry some interesting features compared to the cyclic ethers discussed hitherto. In the gas phase[68a] it shows a fairly clean decomposition into formaldehyde and ethylene in a ratio of about 2 : 1 (reaction 47), with a quantum yield of ethylene near 0.9. This is also one of the main primary processes in the liquid phase[15] (see Table 3). Similarly, the related compound 1,4,6,9-tetraoxabicyclo[4,4,0]decane photolysed in cyclohexane gives ethylene ($\phi = 0.56$) and ethylene glycol diformate ($\phi = 0.5$) as the only major products[68b].



$$\longrightarrow 2\,CH_2O + C_2H_4 \qquad (47)$$

It has been shown[69,70] to fluoresce in the liquid phase with a quantum yield of 0.03. The fluorescence is blue-shifted on addition of saturated hydrocarbons and red-shifted on addition of water. In both cases the additives decrease the fluorescence quantum yield. N_2O[71,72] also quenches the fluorescence, more strongly than it quenches the formation of the products described above (~85% vs. ~35%). At the same time, nitrogen [$\phi(N_2) \approx 0.6$] and 2-hydroxy-1,4-dioxane are formed[15]. These results have been explained by assuming an excimer state for the fluorescence which is more strongly quenched by N_2O than is the product-forming state[15]. In both cases energy is transferred to N_2O, giving rise to oxygen atoms and nitrogen. The former insert into the C—H bond of 1,4-dioxane giving 2-hydroxy-1,4-dioxane (reactions 48–51).

$$\text{1,4-dioxane} \xrightarrow{h\nu} \text{1,4-dioxane}^{*} \qquad (48)$$

$$\text{1,4-dioxane}^{*} + N_2O \longrightarrow \text{1,4-dioxane} + N_2O^{*} \qquad (49)$$

$$N_2O^{*} \longrightarrow N_2 + O \qquad (50)$$

$$O + \text{1,4-dioxane} \longrightarrow \text{2-hydroxy-1,4-dioxane} \qquad (51)$$

The photolysis of 1,4-dioxane in water appears to be quite different, with hydrogen being a major product. N_2O suppresses the formation of hydrogen, and nitrogen is formed instead with a quantum yield near unity. The corresponding product is bidioxanyl. There are negligible amounts of 2-hydroxy-1,4-dioxane[15]. The proposed mechanism involves the formation of a solvated electron in the first step (reaction 52)[15,71]. The radical cation is considered to rapidly lose a proton (reaction 53). The solvated electron reacts with the proton to give a hydrogen atom (reaction 54), or with N_2O to give a hydroxyl radical (reaction 55). Both will abstract a hydrogen atom from 1,4-dioxane (reaction 56). The resulting dioxanyl

$$\text{1,4-dioxane}^{*} \longrightarrow (\text{1,4-dioxane})^{\cdot +} + e^-_{aq} \qquad (52)$$

$$(\text{1,4-dioxane})^{\cdot +} \longrightarrow (\text{1,4-dioxane—H})^{\cdot} + H^+ \qquad (53)$$

$$e^-_{aq} + H^+ \longrightarrow H^{\cdot} \qquad (54)$$

$$e^-_{aq} + N_2O \longrightarrow {}^{\cdot}OH + N_2 + OH^- \qquad (55)$$

$$\mathrm{H^{\cdot}(^{\cdot}OH) + 1{,}4\text{-dioxane} \longrightarrow H_2(H_2O) + (1{,}4\text{-dioxane}-H)^{\cdot}} \qquad (56)$$

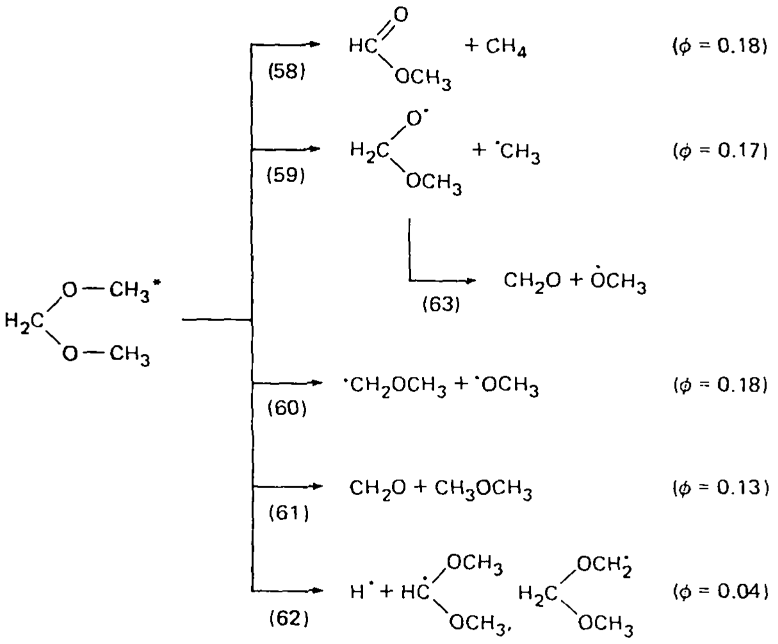
$$\mathrm{2(1{,}4\text{-dioxane}-H)^{\cdot} \longrightarrow bidioxanyl} \qquad (57)$$

radicals combine to bidioxanyl (reaction 57). Support for the hypothesis of the solvated electron as an intermediate had been drawn from the fact that N_2O and H^+ compete for the same species[71]. However, it has been pointed out[15,71] that the results could also be explained by the assumption that the excited 1,4-dioxane transfers an electron to the proton and to N_2O such that the ratio of the rates of these reactions is the same as the ratio of the rates of the reactions (54) and (55).

A variety of products was found when 1,4-dioxane was irradiated at 254 nm[73,74]. Since 1,4-dioxane is frequently used as a solvent for photochemical reactions in this wavelength region the finding is clearly important. It seems possible, though, that one is dealing here with a decomposition sensitized by traces of carbonyl impurities and oxygen. The latter causes charge-transfer absorptions in ethers (see below). As some of its products are carbonyl compounds the decomposition is self-enhancing.

V. PHOTOLYSIS OF ACETALS

The photolytic behaviour of acyclic saturated acetals resembles that of the ethers. Again, C—O bond cleavage is the major process. Scheme 6 presents the reactions of the simplest compound in this series, formaldehyde dimethyl acetal[16]. Data on acetaldehyde dimethyl acetal[75] and pivalaldehyde dimethyl acetal[17] are also available. Acetaldehyde dimethyl acetal varies in that, to a considerable extent, reaction (64) seems to take place, to the possible exclusion of the molecular route (65), the analogue of which is thought to play a major role in the photolysis of

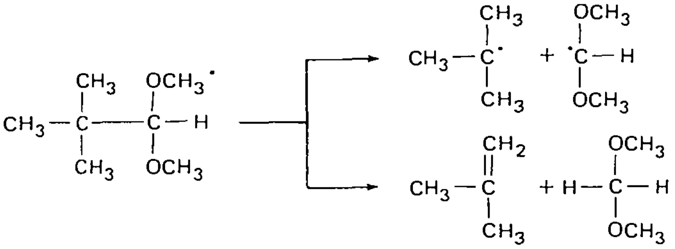


SCHEME 6. Primary processes and their quantum yields in the 185 nm photolysis of liquid formaldehyde dimethyl acetal[16].

$$CH_3-CH(OCH_3)_2^{\bullet} \longrightarrow H_2C{=}CHOCH_3 + CH_3OH \quad (64)$$

$$CH_3-CH(OCH_3)_2^{\bullet} \longrightarrow CH_3-COOCH_3 + CH_4 \quad (65)$$

formaldehyde dimethyl acetal (reaction 58 in Scheme 6). In acetaldehyde dimethyl acetal[75] the scission of the C—C bond in a primary process is only of small importance ($\phi < 0.02$). However, this process appears quite important in pivalaldehyde dimethyl acetal where the processes (66) and (67) together have a quantum yield of 0.16.

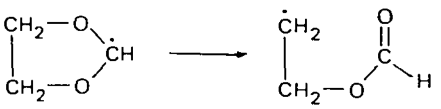

(66)

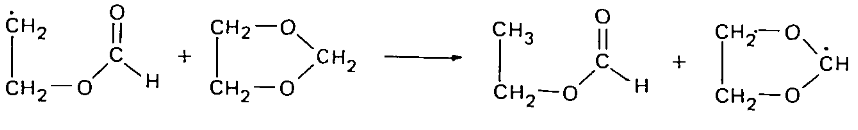
(67)

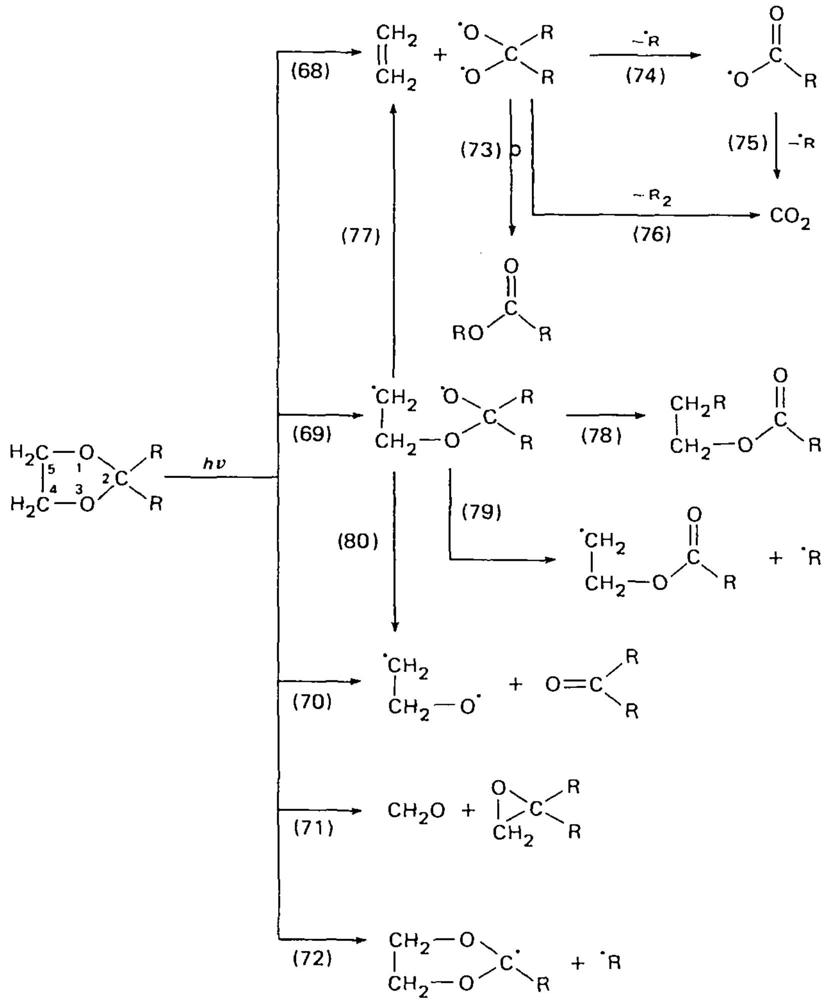
Among the cyclic acetals, 1,3-dioxolane[76,18] and 2,2-dimethyl-1,3-dioxolane[18] have been studied, the former in both the gas phase[76] and the liquid phase[18]. The gas-phase photolysis leads to a nearly complete breakdown into small fragments whereas in the liquid phase some of the intermediates are thermally stabilized so that the reaction paths can be traced with more confidence. The scission of a C—O bond predominates. A mechanism is proposed in Scheme 7. As in the cyclic ethers the intermediacy of biradicals leads to various fragments. CO_2 ($\phi \approx 0.1$), and acetaldehyde and ethylene oxide (together $\phi \approx 0.3$) are important products. The CO_2 may be formed via the dioxirane intermediate or its biradical equivalent (from reaction 68, see Scheme 7). Dioxirane has been detected as a highly unstable product in the ozonization of ethylene, and found to decompose into formic acid, CO and H_2O as well as CO_2, H_2 and 2 $H^{\bullet}$[77,78]. The precursor of acetaldehyde and ethylene oxide is considered to be the biradical $^{\bullet}CH_2-CH_2-O^{\bullet}$. In 1,3-dioxolane the yield of ethylene oxide is somewhat higher ($\phi = 0.18$) than that of acetaldehyde ($\phi = 0.16$) because reaction (71) can also give ethylene oxide. In 2,3-dimethyl-1,3-dioxolane, ϕ(acetaldehyde) = 0.14 and ϕ(ethylene oxide) = 0.12 has been found, possibly indicating that the biradical $^{\bullet}CH_2-CH_2-O^{\bullet}$ rearranges to acetaldehyde with a slight preference compared to ring-closure.

In 1,3-dioxolane a free radical-induced chain-reaction sets in (reaction 81 and 82) which gives rise to ethyl formate. The radical-induced rearrangement of 1,3-dioxolanes and other 1,3-dioxacyclanes into esters is well known (cf. References 79–81).

Whereas the quantum yields of primary processes in the 185 nm photolysis of the above aliphatic acetals range from about 0.6 to near unity no products were


(81)


(82)



SCHEME 7. Primary processes in the photolysis (λ = 185 nm) of liquid 1,3-dioxolane (R = H) and 2,2-dimethyl-1,3-dioxolane (R = CH_3)[18].

found in the photolysis of 2-phenyl-1,3-dioxolane[82] at 254 nm, where it absorbs strongly. This indicates that primary processes leading to products must have a quantum yield of much less than 10^{-2}, considering that this compound also undergoes radical-induced rearrangement to ethyl benzoate via a chain reaction[83]. Likewise, the photodegradation of polyoxymethylene around 300 nm has been shown[84] to proceed only through sensitization, e.g. if carbonyl groups are present.

VI. Hg-SENSITIZED PHOTOLYSIS OF ALCOHOLS AND ETHERS

The Hg-photosensitized decomposition (λ = 254 nm) of alcohols[85-100] and ethers[88,101-111] has found considerable attention. Two possible primary processes have been envisioned: (*i*) abstraction of hydrogen by Hg*, and (*ii*) energy transfer from Hg* to the substrate, with ensuing decomposition. Whereas alcohols (except perhaps *t*-butanol[94]), acyclic saturated ethers[88,101,103,105,108–110] and alkanes (cf. Reference 112) fit the first hypothesis, the behaviour of vinyl ethers[113–115], epoxides[104,106,107,111], thiols[116] and sulphides (cf. Reference 11) agree more with the second, in that bonds other than those to hydrogen are cleaved, often to the virtual exclusion of hydrogen production. Alcohols suffer O—H bond cleavage, acyclic ethers and alkanes lose a carbon-bound hydrogen. It seems that a complex (Hg·RH)* might be the intermediate for both paths (equations 83—85). Evidence

$$\mathrm{Hg^{*} + RH \longrightarrow (Hg\cdot RH)^{*}} \tag{83}$$

$$\mathrm{(Hg\cdot RH)^{*}} \longrightarrow \mathrm{R^{\bullet} + {}^{\bullet}HgH} \tag{84}$$

$$\mathrm{(Hg\cdot RH)^{*}} \longrightarrow \mathrm{Hg + fragments} \tag{85}$$

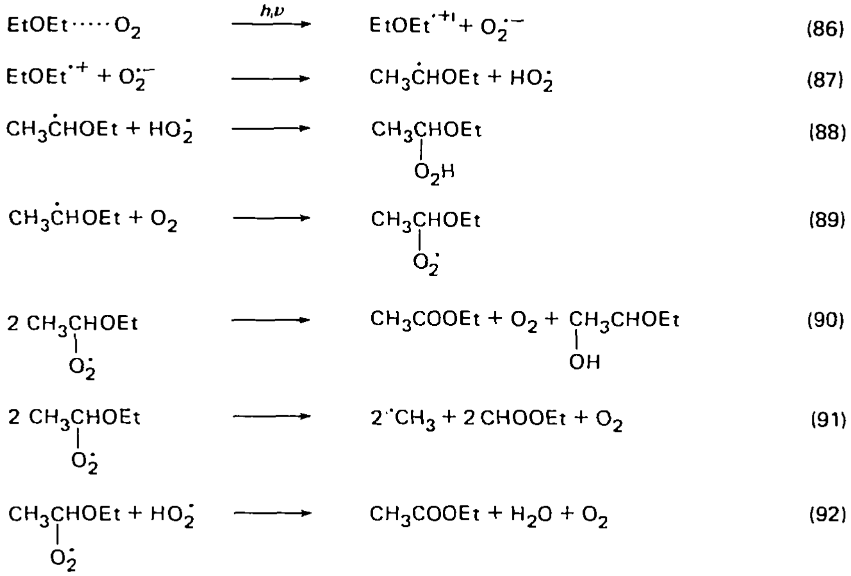
in favour of such complexes has been obtained[99,112,118–120]. In particular, the lifetime of (Hg·CH_3OH)* has been determined[99] at 14 ns. (A similar complex (Cd·CH_3OH)* has been observed. The Cd-photosensitized decomposition (λ = 326 nm) apparently also proceeds via O—H bond fission[121]. The transient species HgH has also been observed[97,122]. Depending on whether the substrate was CH_3OH or CH_3OD HgH or HgD was seen[97], supporting conclusions drawn from earlier work that the simple alcohols lose hydrogen from the hydroxyl group in the primary process.

A recent study[100] of the Hg-photosensitized decomposition of liquid methanol and of its aqueous solutions indicated, on the basis of isotopic labelling, that both oxygen- and carbon-bound hydrogen atoms are initially removed. It must be noted that this is a complicated system because Hg* forms complexes with, and decomposes, water as well, even though with a comparatively small quantum yield[100]. In the gas phase, the hydrogen quantum yield of methanol is 30—40 times higher than that of water (cf. Reference 5). One expects, therefore, some decomposition of methanol induced by active species generated from the water.

In acyclic ethers, the case for attack at the C—H bond has been convincingly presented (cf. Reference 101). Epoxides show a more complex behaviour. For instance, in the Hg-sensitized photolysis of *trans*-2,3-epoxybutane[107], methyl radicals play a major role, and some *cis* isomer was also found. The latter points toward a biradical intermediate. Recently it has been suggested that there maybe at least one biphotonic process involved in the Hg-sensitized photolysis of ethylene oxide[111]. A further cause for complexity of the mechanism is the fact that owing to ring strain oxiranyl radicals are prone to ring-opening rearrangement[62,63].

VII. PHOTOLYSIS OF O_2—CHARGE-TRANSFER COMPLEXES

Like many other compounds, ethers[123–130] and alcohols[123,131] on saturation with oxygen show a new absorption in the UV which disappears again when the liquid is purged with an inert gas. This absorption has been attributed to a substrate—oxygen charge-transfer complex[132]. In diethyl ether[127] the maximum of this absorption is at 215 nm. This CT complex is very photoactive [ϕ(primary processes leading to products) $\approx$ 0.5 at 254 nm]. The formation of all products can be accounted for if the primary process is assumed to be the transfer of an electron from the ether to O_2 (reaction 86) followed by a number of subsequent reactions (87—92). The ether—O_2 CT complexes show a considerable absorbance even above 260 nm, and part of the light-induced autoxidation that is observed in ethers may



$$\mathrm{EtOEt\cdots O_2} \xrightarrow{h\nu} \mathrm{EtOEt^{\cdot+} + O_2^{\cdot-}} \qquad (86)$$

$$\mathrm{EtOEt^{\cdot+} + O_2^{\cdot-}} \longrightarrow \mathrm{CH_3\dot{C}HOEt + HO_2^{\cdot}} \qquad (87)$$

$$\mathrm{CH_3\dot{C}HOEt + HO_2^{\cdot}} \longrightarrow \mathrm{CH_3\underset{\underset{O_2H}{|}}{C}HOEt} \qquad (88)$$

$$\mathrm{CH_3\dot{C}HOEt + O_2} \longrightarrow \mathrm{CH_3\underset{\underset{O_2^{\cdot}}{|}}{C}HOEt} \qquad (89)$$

$$\mathrm{2\,CH_3\underset{\underset{O_2^{\cdot}}{|}}{C}HOEt} \longrightarrow \mathrm{CH_3COOEt + O_2 + \underset{\underset{OH}{|}}{C}H_3CHOEt} \qquad (90)$$

$$\mathrm{2\,CH_3\underset{\underset{O_2^{\cdot}}{|}}{C}HOEt} \longrightarrow \mathrm{2\,{}^{\cdot}CH_3 + 2\,CHOOEt + O_2} \qquad (91)$$

$$\mathrm{CH_3\underset{\underset{O_2^{\cdot}}{|}}{C}HOEt + HO_2^{\cdot}} \longrightarrow \mathrm{CH_3COOEt + H_2O + O_2} \qquad (92)$$

occur by way of such reactions. Since their products are hydroperoxides and carbonyl compounds which are also photoactive, the system is self-enhancing Alcohol–O_2 CT complexes begin to absorb appreciably at shorter wavelengths[123,131] than do the ether–O_2 CT complexes, and are therefore perhaps less likely to interfere with photochemical studies at wavelengths usually employed. It has been pointed out[133] that in cases where ethanol is used as a solvent in dye lasers the products of the reaction, among them acetic acid, acetaldehyde and hydrogen peroxide[131], can impair the functioning of the laser system.

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 22

The photolysis of saturated thiols, sulphides and disulphides

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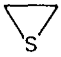
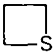
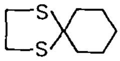
I. INTRODUCTION

This chapter deals with the photochemistry of saturated organic divalent sulphur compounds. In a preceding volume of this series, the photochemistry of thiols has been reviewed[1], and in this respect the present chapter is supplementary. Other reviews touching on the subject have appeared[2-7].

The title compounds start to absorb at considerably longer wavelengths than their oxygen analogues. Their first absorption band is assigned to a transition which has more or less $n-\sigma^*$ nature while at shorter wavelengths Ryberg-type transitions come into play[8]. Spectral data of some compounds of interest are presented in Table 1.

TABLE 1. Molar extinction coefficients (base ten) of some organic divalent sulphur compounds near 254 nm, and some λ_{max} values

Compound	Medium	ϵ, M^{-1} cm^{-1} (λ, nm)	λ_{max}[a]	λ_{max}[b]
MeSH	Vapour	~60 (254)[9]	~230[10]	204[10]
EtSH	Vapour	~80 (254)[10]	~230[10]	202[10]
	n-Heptane	40 (254)[11]	~230[11]	196[11]
Me_2S	Vapour	~10 (240)[9]	~220[10]	205[10]
Et_2S	Vapour	~30 (240)[9]	~220[10]	205[10]
	Vapour	17 (254)[10]	~260[10]	209[10] [c]
	Vapour	12 (254)[10]	~260[10]	205[10] [c]
	Ethanol	833 (248)[12]	248[12]	
Me_2S_2	Vapour	~300 (254)[9]	250[9]	
	Liquid	316 (254)[13]		
Et_2S_2	Vapour	~310 (254)[9]	255[9]	

[a] First absorption band.
[b] Second absorption band.
[c] Band shows structure.

II. PHOTOLYSIS OF THIOLS

A. The General Reactions

The photolysis of saturated thiols[1,13-25] can be generally described by the primary reactions (1) and (2). The subsequent reactions (3)–(6) explain the major products: hydrogen, disulphides, alkanes and hydrogen sulphide. Although reactions (1)–(6) account well for the general picture there are some variations in detail, depending on the nature of the substrate, the excitation wavelength and the medium in which the photolysis takes place. Hg photosensitization also leads to both S–H and C–S cleavage[26].

$$RSH \xrightarrow{h\nu} RS^{\bullet} + H^{\bullet} \quad (1)$$

$$RSH \xrightarrow{h\nu} R^{\bullet} + {}^{\bullet}SH \quad (2)$$

$$H^{\bullet} + RSH \longrightarrow H_2 + RS^{\bullet} \quad (3)$$

$$RS^{\bullet} + RS^{\bullet} \longrightarrow RSSR \quad (4)$$

$${}^{\bullet}R + RSH \longrightarrow RH + RS^{\bullet} \quad (5)$$

$${}^{\bullet}SH + RSH \longrightarrow H_2S + RS^{\bullet} \quad (6)$$

B. Factors Changing the Relative Importance of the Primary Processes

In the gas-phase photolysis of methanethiol[14] and ethanethiol[15] the sum of the quantum yields of reactions (1) and (2) is essentially unity. With increasing quantum energy the contribution of reaction (2) grows. For methanethiol, the ratio $\phi(1)/\phi(2)$ drops from 13 at 254 nm to 3 at 214 nm[14]. At 195 nm it is 1.7[18]. Ethanethiol is similar[15]. In assessing these ratios, the possibility of hot hydrogen atoms $\mathrm{H}^{\cdot *}$ being present (from reaction 1) has been taken into account[14,15]. $\mathrm{H}^{\cdot *}$ can mimic reaction (2) through the displacement reaction (7) (see also below).

$$\mathrm{H}^{\cdot *} + \mathrm{RSH} \longrightarrow \mathrm{R}^{\cdot} + \mathrm{H_2S} \qquad (7)$$

There is evidence that even thermalized H atoms can bring about such a displacement[23,27]. The substitution of the sulphur-bound hydrogen by deuterium considerably enhances $\phi(2)$ at the cost of $\phi(1)$[17].

A suppression of reaction (2) has been noted in liquid ethanethiol photolysed at 254 nm where $\phi(1)$ was found to be 0.25, which value apparently represents the total quantum yield of primary processes since other products were not detected[13].

C. The Secondary Processes

Reactions (3)–(6) represent the obvious subsequent reactions of thermally equilibrated radicals in the thiol system where the thiol group constitutes an excellent hydrogen donor. However, in reaction (1) hot H atoms and hot $\mathrm{RS}^{\cdot}$ radicals are initially formed[14–17,20], and there is evidence that reaction (7) is far from negligible[14–17,28]. Such a displacement has also been postulated[23] to occur in the liquid phase where it is thought to involve thermal H atoms[23,27]. The photolysis of liquid thiols yields $\mathrm{H_2}$ and $\mathrm{H_2S}$, their ratio depending on the nature of the thiol. In liquid *t*-butanethiol the ratio $\phi(\mathrm{H_2S})/\phi(\mathrm{H_2}) \approx 1$, in the (secondary) cyclohexanethiol it drops to ~0.25[23], and in the (primary) ethanethiol no $\mathrm{H_2S}$ appears to be formed at all[13]. Addition of hydrogen donors led to a decrease in this ratio with increasing donor concentration[23]. The donor (QH) is considered to compete for hydrogen atoms (reactions 8 and 9) thus reducing the $\mathrm{H_2S}$ and

$$\mathrm{H}^{\cdot} + \mathrm{RSH} \longrightarrow \mathrm{R}^{\cdot} + \mathrm{H_2S} \qquad (8)$$

$$\mathrm{H}^{\cdot} + \mathrm{QH} \longrightarrow \mathrm{H_2} + \mathrm{Q}^{\cdot} \qquad (9)$$

enhancing the $\mathrm{H_2}$ yield. It is reasonable to assume that reaction (8) involves the intermediate $\mathrm{R\underset{\cdot}{S}H_2}$. Similar complex radicals are formed from sulphides with hydroxyl $(\mathrm{R_2S\dot{O}H})$[29], phenyl, hydrogen and $^{\cdot}\mathrm{SH}$[30b]. The formation of these complexes is subject to conformational constraints[30a].

Hot H atoms should be able to abstract carbon-bound hydrogen in competition to reactions (3) and (7). However, no HD has been found in the gas-phase photolysis of $\mathrm{CH_3SD}$[24]. In contrast, there is e.s.r. spectroscopic evidence that carbon-centred radicals are formed when thiols are irradiated in a rare-gas matrix at 77 K[20]. There seems to be a contradiction between these two facts which is not resolved by the report of the absence of dithiol from the gas-phase photolysis products of thiols[14,15] because it can be argued that the thiol radicals are converted into thiyl radicals in reaction (10).

$$\mathrm{R\dot{C}HSH} + \mathrm{RCH_2SH} \longrightarrow \mathrm{RCH_2SH} + \mathrm{RCH_2S}^{\cdot} \qquad (10)$$

There is also evidence for hot thiyl radicals. Ethylthiyl radicals obtained in the 195 nm photolysis of ethanethiol decompose into methyl radicals and thioformaldehyde. If thiols are photolysed at 254 nm in an organic matrix at 77 K, hot $\mathrm{RS}^{\cdot}$ radicals as well as hot H atoms are produced[20]. Both mostly generate solvent radicals by hydrogen abstraction, rather than being thermalized. The hotness of the $\mathrm{RS}^{\cdot}$ is conclusively proved by the fact that at 77 K only a fraction of all radicals in the system are $\mathrm{RS}^{\cdot}$, most being solvent radicals. On warming the solvent radicals disappear and regenerate RS$^•$ radicals. The RS$^•$ radicals are stable until the matrix is melted[20]. Even though thermal thiyl radicals at room temperature are practically inert with respect to abstraction of aliphatic carbon-bound hydrogen atoms, they are known to abstract more weakly bound hydrogen[31,32].

The usual fate of the RS$^•$ radicals is their dimerization (reaction 4) as the disproportionation/combination ratio for RS$^•$ radicals is small (~0.04 for MeS$^•$[33] and ~0.13 for EtS$^•$[34] in the gas phase and near zero for EtS$^•$ in the liquid phase[13]). Thioformaldehyde, a conceivable disproportionation product of MeS$^•$, is produced in the photolysis of methanethiol in an argon matrix, most likely from photolysis of the primarily generated MeS$^•$[19].

When thiyl radicals are produced in the presence of trivalent organophosphorus compounds, they are desulphurized to the alkyl radicals (reaction 11)[35]. Thiyl radicals add reversibly to olefins as shown by *cis–trans* isomerization

$$R^1S^• + PR^2_3 \longrightarrow R^{1•} + S{=}PR^2_3 \qquad (11)$$

that occurs in the presence of thiyl[36,37] (e.g. reaction 12), and induce a chain-reaction (reactions 12 and 13) which can be of preparative value (cf. Reference 6). Further examples of reactions undergone by thiyl radicals can be found in Chapter 24.

$$RS^• + H_2C{=}CH_2 \rightleftharpoons RSCH_2{-}CH_2^• \qquad (12)$$

$$RS{-}CH_2{-}CH_2^• + RSH \longrightarrow RSCH_2CH_3 + RS^• \qquad (13)$$

There are conflicting statements in the literature as to the affinity of thiyl radicals towards oxygen (reaction 14). The gas-phase photolysis of methanethiol

$$RS^• + O_2 \longrightarrow RSO_2^• \qquad (14)$$

near 230 and 260 nm in the presence of oxygen[25] leads to dimethyl disulphide and a peroxidic compound as the major products. The latter compound was believed to be hydrogen peroxide. These findings were taken to indicate that reaction (14) does not effectively compete with disulphide formation (reaction 4). However MeS$^•$ generated at shorter wavelengths has been found to react rapidly with oxygen[18]. Also, the radiolysis of mercaptoethanol[27] and cysteine[38] in oxygenated aqueous solution has shown that reaction (14) is fast, almost diffusion-controlled in these systems[39], where it is in part followed by reaction (15).

$$RSO_2^• + RSH \longrightarrow RSOOH + RS^• \qquad (15)$$

D. Photolysis of Thiols in Aqueous Solutions

In aqueous solutions the thiols are in equilibrium with their anions [e.g. pK(SH of cysteine) = 8.5[40]]. On photoexcitation the thiolates eject an electron (reaction 16). The electrons become solvated (see Chapter 23) and rapidly react with the thiols to give R$^•$ radicals (reaction 17, see Chapter 24). RS$^•$ radicals and thiolates

$$RS^- \xrightarrow{h\nu} RS^• + e^-_{aq} \qquad (16)$$

$$e^-_{aq} + RSH \longrightarrow HS^- + R^• \qquad (17)$$

$$RS^• + RS^- \rightleftharpoons (RSSR)^{•-} \qquad (18)$$

form complexes[41] (reaction 18, for details see Chapter 24), which can be easily monitored by their strong optical absorption near 420 nm[42].

III. PHOTOLYSIS OF SULPHIDES

A. Acyclic Alkyl Sulphides

In the photolysis of acyclic alkyl sulphides[18,34,43-49] the main if not the only process is the scission of a carbon–sulphur bond (reactions 19a and 19b). In the competition between methyl and larger alkyl groups it is the methyl radical which is preferentially eliminated[43]. In the gas-phase photolysis (λ = 229 nm) of $CH_3-S-C_2H_5$, $\phi(19a)/\phi(19b) = 1.3$ is observed[47]. This preference appears to parallel the photolytic behaviour of ethers. Whereas in the gas-phase photolysis of thiols the sum of the quantum yields of primary decomposition is essentially unity (see above), this seems to be no longer true with dialkyl sulphides, e.g. with dimethyl, ethyl methyl and diethyl sulphide a value of only about 0.5 has been found[34]. The absence of hydrogen cannot entirely rule out C—H bond rupture in view of the possible displacement reaction[30b] analogous to reaction (8). The absence of methane in the photolysis of diethyl sulphide[48] indicates that C–C bond rupture does not occur.

$$R^1-S-R^2 \xrightarrow{h\nu} \left[\begin{array}{ll} \longrightarrow R^{1\cdot} + {}^{\cdot}SR^2 & (19a) \\ \longrightarrow R^1S^{\cdot} + {}^{\cdot}R^2 & (19b) \end{array}\right.$$

Minor contributions of molecular processes (reactions 20 and 21) in the diethyl sulphide photolysis are possible but not established since the same products could also arise from disproportionation reactions of the radicals formed in reaction (19).

$$CH_3-CH_2-S-C_2H_5 \xrightarrow{h\nu} H_2C{=}CH_2 + C_2H_5SH \qquad (20)$$

$$CH_3-CH_2-S-C_2H_5 \xrightarrow{h\nu} CH_3-CH_3 + S{=}CH-CH_3 \qquad (21)$$

The radicals generated in reaction (19) retain a certain amount of excess energy depending on the wavelength of the exciting light. Particularly in the case of $MeS^{\cdot}$ generated from dimethyl sulphide[46] this excess energy manifests itself by permitting hydrogen abstraction reactions to occur (reaction 22). Because the excess energy is spread over more degrees of freedom the radicals formed in the photolysis of diethyl sulphide[48] are less hot. Similar reactions are observed in organic matrices at 77 K[49], their behaviour resembling that of the thiol-containing glasses[20].

$$MeS^{\cdot *} + RH \longrightarrow MeSH + R^{\cdot} \qquad (22)$$

The Hg-photosensitized decomposition of acyclic sulphides[33,34,50] leads to the same products that are obtained in the direct photolysis. In contrast with the ethers and hydrocarbons, no hydrogen is observed, and the main primary process is apparently reaction (23). However, one might keep in mind that alkyl displacement by H atoms[30b] can mask C—H bond cleavage. In diethyl sulphide there may be a side-reaction which could amount to at most 20% (reaction 24)[34].

$$R-S-R + Hg^{*} \longrightarrow RS^{\cdot} + R^{\cdot} + Hg \qquad (23)$$

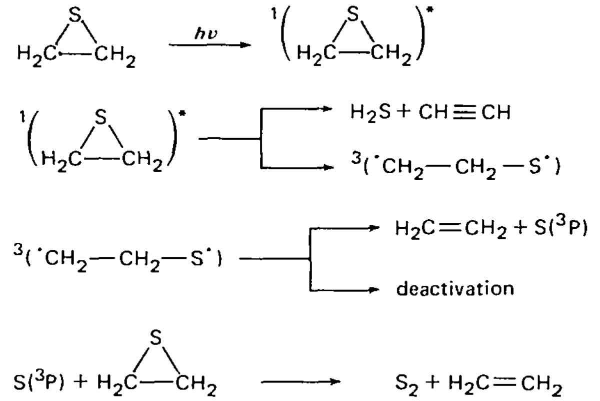
$$(C_2H_5)_2S + Hg^{*} \longrightarrow C_2H_5SH + C_2H_4 + Hg \qquad (24)$$

B. Cyclic Sulphides

The photolysis mechanisms of cyclic sulphides (for reviews see also References 3, 5 and 7) strongly differ from their acyclic analogues. Major differences are also observed between thiiranes and thietanes, which will be separately dealt with.

1. Thiiranes

The essential mechanism of the thiirane photolysis is represented[3,51] by the reactions (25)–(30). Direct excitation leads to the singlet excited state (reaction 25) which either decomposes into minor products hydrogen sulphide and acetylene (reaction 26) or mainly crosses over to the triplet state (reaction 27). The triplet species can decompose into ethylene and $S(^3P)$ (reaction 28), or be deactivated (reaction 29). The excited sulphur atoms appear to react efficiently with thiirane, extracting a sulphur atom (reaction 30). The importance of reaction (28) followed by reaction (30) is shown by the high quantum yield of ethylene $[\phi(C_2H_4) = 1.9]$. The existence of sulphur atoms was proved through the formation of thiiranes from added olefins[51]. This reaction is given by both singlet and triplet sulphur atoms[52,53], but thiols which are produced from paraffins and excited singlet sulphur atoms were not detected[51]. Therefore the S atoms must be in the triplet state, which implies the triplet state precursor (reaction 28). This intermediate may have biradical character, since tetrahydrothiophene was found when ethylene had been added[53] (reaction 31). It has been shown in a different system that $S(^3P)$ rapidly reacts with thiirane[54] (reaction 30). Other reactive species such as hydrogen atoms, carbon atoms, and methyl radicals do the same (cf. Reference 55). The S_2 formed in reaction (30) can be identified by its UV absorption spectrum. A further reaction leading to ethylene is possible (reaction 32). Such a reaction operates in the pyrolysis of thiirane[56a]. The system may be even more complex since thermally excited thiirane generated by the addition of $S(^1D_2)$ to ethylene rearranges into vinylthiol with high efficiency[56b].



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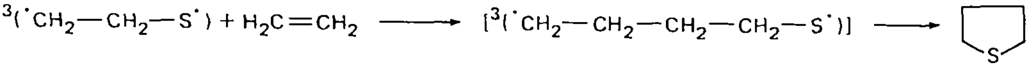

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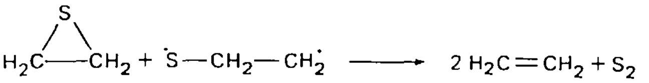


(32)

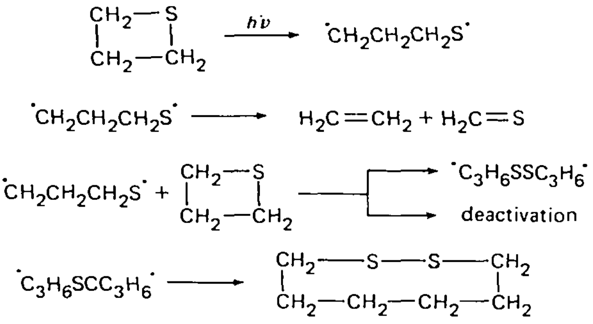
The photolysis of thiirane in the liquid state, neat and in hydrocarbon solutions, is explained similarly[57]. $\phi(C_2H_4)$ increases with increasing thiirane concentration. This could be due to a competition between reactions (29) and (32). The maximum value of 0.8 for $\phi(C_2H_4)$ is reached in neat thiirane. Considerable formation of polymeric products was observed in the photolysis of liquid methylthiirane[58].

The photolysis of tetrafluorothiirane has been reported to show very little conversion even after prolonged irradiation[59]. The reason for this might be that the spectrum of the irradiating light and the absorption spectrum did not match sufficiently well. It is known that the UV absorption spectra of perfluorinated compounds often exhibit a marked blue-shift compared to their prototypes (cf. References 8 and 60).

2. *Thietanes*

The photochemistry of thietane[61-64] (including some alkyl-substituted thietanes[64,65]) has been studied over a wide wavelength range, between 214 and 313 nm. This range straddles two absorption bands. The maximum of the first is near 260 nm, that of the second more structured one is near 206 nm[10]. These two bands lead to remarkably different photochemistries.

The results obtained using 254 and 313 nm light (first absorption band) lend themselves to interpretation more readily. The essential features of the mechanism[64] consist of reactions (33)–(37). The main product is ethylene. Its quantum yield rises with the temperature. At elevated temperatures where the deactivation step (36) is disfavoured the sum of $\phi(34)$ and $\phi(37)$ attains unity[64]. Their ratio is larger than 10 : 1 in all cases[64].



(33)

(34)

(35)

(36)

(37)

The biradical hypothesis is strongly supported by the finding that suitably substituted thietanes on photolysis undergo *cis–trans* isomerization[64,65] and that in solution propyl disulphide is produced (reactions 38 and 39). As is to be expected,

$$\dot{C}H_2{-}CH_2{-}CH_2{-}\dot{S} + RH \longrightarrow CH_3{-}CH_2{-}CH_2{-}\dot{S} + \dot{R} \qquad (38)$$

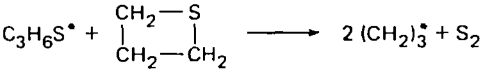
$$2\ C_3H_7\dot{S} \longrightarrow C_3H_7SSC_3H_7 \qquad (39)$$

1,6-hexanedithiol is not formed because the biradical with its alkyl end preferentially abstracts a hydrogen atom from the substrate (reaction 38) and the propanethiyl radicals so formed then combine (reaction 39)[64].

Propylene[61,62,64] and cyclopropane[61] have been found in small amounts and evidence has been presented[62,64] that propylene is formed in a secondary reaction.

The mechanism of the photolysis in the second absorption band appears to be more complex[61]. Irradiation at 214 and 229 nm produces much cyclopropane and propylene beside ethylene. The ratio $\phi(C_2H_4)/\phi(c\text{-}C_3H_6 + C_3H_6)$ is near 0.7 at 214 nm, and near 1.2 at 229 nm[61]. In agreement with the assumption of a trimethylene intermediate species, the cyclopropane to propylene ratio increases with increasing pressure. It appears extremely unlikely that the C_3H_6 hydrocarbon products are secondary here. The conversions reached[61] were less than 1% in the experiments with the higher substrate pressures, and it is there that the C_3H_6

products are relatively most important. The essential process that has been postulated[61] to explain the formation of C_3H_6 is reaction (40). A similar process


(40)

(reaction 32) may occur in the photolysis of thiirane[3,51]. The postulate of reaction (40) is in accordance with the observation that the sum of $\phi(C_2H_4)$, $\phi(c\text{-}C_3H_6)$ and $\phi(C_3H_6)$ under some conditions exceeds unity, reaching a value near 1.4[61] at a substrate pressure of about 1 torr and a temperature of 236°C.

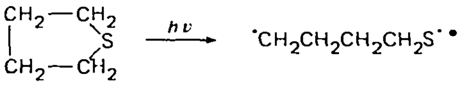
The Hg-photosensitized decomposition of thietanes has also been studied[61,66,67]. Its results are similar to those of the direct photolysis in the first UV absorption band. The C–S bond is cleaved to the biradical which then undergoes fragmentation, or *cis–trans* rearrangement and reclosure. There is some evidence[67] for a small contribution by reaction (41). The alternative possibility of process (42) is not excluded.

$$^{\bullet}CH_2CH_2CH_2S^{\bullet} \longrightarrow {}^{\bullet}CH_2{-}CH{=}CH_2 + HS^{\bullet} \qquad (41)$$

$$Hg^{*} + C_3H_6S \longrightarrow {}^{\bullet}HgSH + {}^{\bullet}C_3H_5 \qquad (42)$$

3. *Thiolane and higher cyclic sulphides*

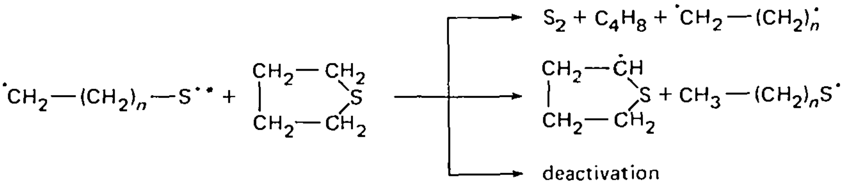
The photolysis of thiolane resembles that of thietane in that here also there is a strong variation in photolytic behaviour depending on whether the compound is photolysed at 254 nm[3] or at 214 nm[68] and that the biradical (here $^{\bullet}CH_2-CH_2-CH_2-CH_2-S^{\bullet}$) plays a major role as an intermediate at both wavelengths. The intermediacy of the thiapentamethylene biradical was proved through addition reactions with olefins[3]. The wavelength dependence is largely expressed in the change of relative abundance of products. Reactions (43) to (51) constitute a plausible mechanism with features similar to those postulated for thiirane and thietane.


(43)

$$^{\bullet}CH_2CH_2CH_2CH_2S^{\bullet\,\bullet} \longrightarrow H_2C{=}CH_2 + {}^{\bullet}CH_2CH_2S^{\bullet} \qquad (44)$$

$$^{\bullet}CH_2CH_2CH_2CH_2S^{\bullet\,\bullet} \longrightarrow {}^{\bullet}CH_2CH_2CH_2^{\bullet} + CH_2S \qquad (45)$$

$$^{\bullet}CH_2{-}(CH_2)_m{-}S^{\bullet} + {}^{\bullet}CH_2{-}(CH_2)_n{-}S^{\bullet} \longrightarrow S_2 + {}^{\bullet}CH_2{-}(CH_2)_m^{\bullet} + {}^{\bullet}CH_2{-}(CH_2)_n^{\bullet} \qquad (46)$$



(47)
(48)
(49)

$$^{\bullet}CH_2CH_2CH_2CH_2^{\bullet} \longrightarrow 2\,H_2C{=}CH_2,\, c\text{-}C_4H_8 \qquad (50)$$

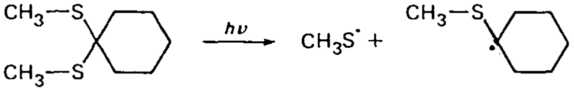
$$^{\bullet}R^1 + {}^{\bullet}R^2 \longrightarrow \text{products} \qquad (51)$$

($^{\bullet}R^1, {}^{\bullet}R^2$ = any radical; m, n = 1 or 3)

Ethylene has also been observed as a product in the liquid-phase photolysis of thiacyclopentane and thiacyclohexane[43], and ESR experiments at 77 K have given evidence for $^\bullet(CH_2)_nS^\bullet$ biradicals from these compounds[69,70].

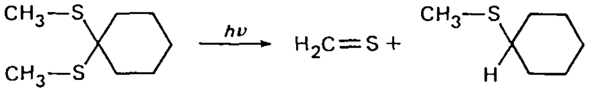
IV. PHOTOLYSIS OF DITHIAACETALS

The photolysis of a few dithiaacetals[12,71-73] has been studied and is similar to that of the sulphides in so far as here too, an S—C bond is cleaved in the primary process. The products observed in the photolysis of 1,1-bis(methylthio) cyclohexane [71] are cyclohexyl methyl sulphide and dimethyl disulphide. The formation of the latter indicates that the scission of a C—S bond (reaction 52) in an important primary process. The formation of cyclohexyl methyl sulphide is not as straightforward as the route to dimethyl disulphide (reaction 53). One might consider disproportionation reactions but also a molecular process such as reaction (54). A similar process has been invoked[12] to explain the formation of cyclohexanethion which appears to be the precursor of its dimer, the major identified product in the photolysis of 1,3-dithiacyclopentane-2-spiro-1′-cyclohexane (reactions 55 and 56). Possibly by a process similar to reaction (54), the photolysis of D-galactose diethyl dithioacetal[72] yields 1-*S*-ethyl-1-thio-D-galactitol in 60% yield (reaction 57).

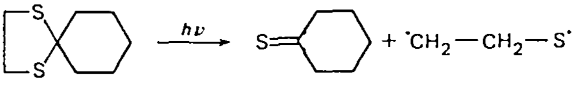


(52)

$$2\,CH_3{-}S^\bullet \longrightarrow CH_3{-}S{-}S{-}CH_3 \qquad (53)$$



(54)



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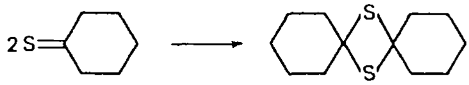
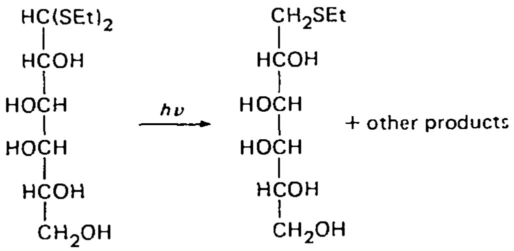


(56)

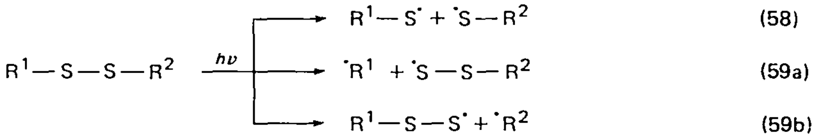


$$\begin{array}{c} HC(SEt)_2 \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ CH_2OH \end{array} \xrightarrow{h\nu} \begin{array}{c} CH_2SEt \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ CH_2OH \end{array} + \text{other products} \qquad (57)$$

V. PHOTOLYSIS OF DISULPHIDES

The photolysis of disulphides found considerable attention[13,18,23,45,49,69,74-89] and has been the subject of a number of reviews[2-4].

The scission of the S–S bond (reaction 58) and of a C–S bond (reaction 59) are the two major primary processes. There are many investigations reporting that on



$$R^1{-}S{-}S{-}R^2 \xrightarrow{h\nu} \begin{cases} R^1{-}S^\bullet + {}^\bullet S{-}R^2 & (58) \\ {}^\bullet R^1 + {}^\bullet S{-}S{-}R^2 & (59a) \\ R^1{-}S{-}S^\bullet + {}^\bullet R^2 & (59b) \end{cases}$$

excitation at wavelengths above 230 nm only reaction (58) occurs (cf. References 13 and 80–82). However, it has also been reported that under such conditions methane was a product in the photolysis of dimethyl disulphide[86], polarized isobutane and isobutene were detected in a photo-CIDNP study of di-*t*-butyl disulphide[85], and RSS$^\bullet$ radicals were detected by ESR spectroscopy in the 254 nm photolysis of disulphides in an organic matrix at low temperature[49].

The rate ratio of reaction (58) over reaction (59) strongly varies with the wavelength of the exciting light, C–S splitting (reaction 59) becoming increasingly important at shorter wavelengths. In the dimethyl disulphide gas-phase system where $\phi(59)/\phi(58)$ has been reported to be practically nil at 254 nm[80], $\phi(59)/\phi(58)$ is around 0.7 at 185 nm[18], whereas in its Hg-photosensitized decomposition[50] this ratio is 0.25. Equally, C—S cleavage is induced by other photosensitizers[90]. The RS$^\bullet$ radicals formed in reaction (58) can undergo the transposition reaction (60) which is part of a chain-reaction. ϕ(Me-S-S-Et) = 330 was found in the

$$R^1S^\bullet + R^1{-}S{-}S{-}R^2 \longrightarrow R^1{-}S{-}S{-}R^1 + R^2{-}S^\bullet \qquad (60)$$

cophotolysis ($\lambda \sim 260$ nm) of dimethyl disulphide and diethyl disulphide in the liquid phase[81]. Since any other process is insignificant compared to the transposition reaction a photostationary state can be established (reaction 61). For

$$2\,R^1{-}S{-}S{-}R^2 \underset{h\nu}{\overset{h\nu}{\rightleftharpoons}} R^1{-}S{-}S{-}R^1 + R^2{-}S{-}S{-}R^2 \qquad (61)$$

R^1 = Me and R^2 = Et the value of the equilibrium constant K = [MeSSEt]^2/[MeSSMe][EtSSEt] has been found to be ~5 in the liquid phase[76,81]. The efficiency of the transposition diminishes rapidly as the alkyls get larger[13,77].

A similar transposition takes place in the presence of thiols[23] (reactions 62–64).

$$R^1{-}S{-}S{-}R^1 \xrightarrow{h\nu} 2\,R^1{-}S^\bullet \qquad (62)$$

$$R^1{-}S^\bullet + R^2{-}SH \longrightarrow R^1{-}SH + R^2{-}S^\bullet \qquad (63)$$

$$R^2{-}S^\bullet + R^1{-}S{-}S{-}R^1 \longrightarrow R^2{-}S{-}S{-}R^1 + R^1S^\bullet \qquad (64)$$

Cleavage of the disulphide bond by radicals other than thiyl (cf. Reference 2) e.g. OH radicals[91], has also been observed.

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 23

Radiation chemistry of alcohols and ethers

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I. INTRODUCTION

The great interest in the radiation chemistry of alcohols is reflected in the number of reviews that deal with this topic (cf. References 1–5). Alcohols are among the most polar organic compounds. In so far as alcohols as a class are especially closely related to water, which has served as the main substrate for investigating the effect of ionizing radiation on condensed matter in the beginning stages of radiation chemistry, the scope of this interest is easily understandable. In comparison with this, ethers have found little attention[1]. The material on the radiolysis of alcohols and ethers in aqueous solution[6] is at least as extensive as that devoted to these compounds in the neat state, and has contributed much to the present knowledge of their free-radical chemistry.

Most of the kinetic data are obtained using the pulse radiolysis technique[7], where a short pulse of high-energy (>1 MeV) electrons is made to penetrate a cell filled with the material to be investigated. Pulse durations of about one microsecond are standard conditions, but equipment delivering pulses on the nanosecond and picosecond time-scale is becoming increasingly widespread. The short pulses of ionizing radiation produce radical and ionic intermediates. Their fate can be monitored by following the change of the optical absorption, or of the conductivity, to the extent that in the course of the reaction charged species are formed or destroyed. It is recalled that a radical $^{\cdot}QH$ may be involved in hydrolytic equilibria (1) and (2), and that the differently protonated forms of a radical behave as

$$(1) \qquad Q^{\cdot -} \overset{H^+}{\rightleftharpoons} QH^{\cdot} \overset{H^+}{\rightleftharpoons} QH_2^{\cdot +} \qquad (2)$$

chemically distinct species. The conductivity technique has been increasingly used in the recent past and has yielded most interesting results. The accelerator may also be coupled with an ESR spectrometer. This *in situ* technique[8] is usually run under steady-state conditions to identify the radicals but can also be used under pulsed conditions for kinetic measurements. CIDNP studies of the radiolysis of alcohols in aqueous solution have been reported[9], and the combination of pulse radiolysis and polarography has been reviewed[10]. For the investigation of polymer degradation a light-scattering method has been used together with pulse radiolysis[11].

The present review is divided into two sections. The first one deals with the results obtained in the radiolysis of the neat compounds. It consists mainly of material on alcohols, and supplements the picture given by Basson[5] in a previous volume of this series. In the second section some emphasis is placed on the radiation chemistry of aqueous solutions as it is felt that its results might perhaps be of a more general interest.

II. NEAT ALCOHOLS IN THE LIQUID AND SOLID STATE

A. Energy Absorption and Primary Processes

Ionizing radiation absorbed by matter is dissipated by ionization (reaction 3) and excitation processes (reaction 4). The energy is deposited at random along the

$$M \xrightarrow{\gamma} M^{\cdot +} + e^- \qquad (3)$$

$$M \xrightarrow{\gamma} M^* \qquad (4)$$

tracks of the energetic charged particles (in γ-radiolysis these are electrons produced mostly through the Compton effect) in small packages called spurs. In these spurs, one or more ion pairs or radical fragment pairs (from reaction 5) are

$$M^* \longrightarrow {}^{\cdot}R^1 + {}^{\cdot}R^2 \qquad (5)$$

generated from the substrate molecules, with these reactive species existing at first in close proximity so that their concentration within the spurs is much greater than in the bulk of the medium. In this respect, as well as because the spurs are strung along the linear tracks, the concentration of the reactive intermediates is inhomogeneous (for details see References 12–16). Part of the species will react with each other before they can escape into the bulk of the solution. Excitation energy that does not lead to chemical change within the spur may be transferred between substrate molecules under certain conditions and so leave the spur. Quanta of mobile energy of this kind have been termed excitons (cf. Reference 17).

A complete radiolysis mechanism would require that the yields be known of reactions (3) and (4) which precede all the other processes of chemical change. This information is usually not available because part of the excited substrate molecules are superexcited and therefore able to undergo reaction (6). In the gas phase,

$$M^{*} \longrightarrow M^{\cdot +} + e^{-} \qquad (6)$$

G(ionization)† ≈ 4 has been found for alcohols[18]. Because of a lowering of the ionization potential in the liquid compared to the gaseous state[19], G(ionization) might be somewhat higher in the liquid. As it cannot be determined directly in liquid alcohols, attempts have been made to establish it indirectly by using high concentrations of electron scavengers such as N_2O where $G(N_2)$ has been considered[20] to reflect G(scavenged electrons) (reaction 7). The results[20] are in agreement with the above reasoning. One has to keep in mind, however, that excited states may transfer their energy to N_2O and thus also yield N_2 (reaction 8)[21,22]. As the

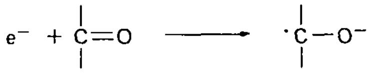
$$e^{-} + N_2O \longrightarrow N_2 + O^{\cdot -} \qquad (7)$$

$$M^{*} + N_2O \longrightarrow M + N_2 + O \qquad (8)$$

excited states of alcohols appear to be either very short-lived, or inefficiently to transfer energy to N_2O dissolved therein at atmospheric pressure ($\leqslant 4\%$ transfer from the lowest excited state of *t*-butanol[23]), $G(N_2)$ might begin to be driven beyond G(reaction 7) at elevated N_2O pressure. On the other hand, sufficiently high electron scavenger concentrations are desirable and necessary to compete successfully against the spur reactions of the electron such as reactions (9)–(11).

$$e^{-} + ROH_2^{+} \longrightarrow ROH + H^{\cdot} \qquad (9)$$

$$e^{-} + RO^{\cdot} \longrightarrow RO^{-} \qquad (10)$$



$$e^{-} + \geq C{=}O \longrightarrow {}^{\cdot}\!\geq C{-}O^{-} \qquad (11)$$

(The carbonyl compound in reaction 11 is formed as a molecular product; see below). The radiation-induced chain-reaction of N_2O with alcohols has been shown to occur only at elevated temperatures[24,25].

The G-value of excitation is more difficult to assess. If the theory of the optical approximation[26,27] holds, higher excited states play a larger role than does the lowest one. Unfortunately, in liquid alcohols only information on the breakdown of the lowest excited state is available[28] (see Chapter 21). Besides straightforward ionization (reaction 3), ionization accompanied by a fragmentation of the radical cation (reaction 12) has often been considered to account for some products, and

$$M \xrightarrow{\gamma} N^{+} + R^{\cdot} + e^{-} \qquad (12)$$

attempts have been made to correlate product formation in the liquid phase with mass spectra[29-31]. In that approach data obtained at pressures below 10^{-5} bar must be extrapolated to the conditions of the liquid state, where, however, rapid thermalization of a vibrationally excited radical cation can occur. Electronically excited radical cations may behave differently, though.

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†The radiation-chemical yield G, 'G-value', is defined by the equation $G = N/E$; unit: $(100\ \mathrm{eV})^{-1}$; N = number of species or events of whatever kind, E = radiation energy absorbed causing these events.

B. Solvation of the Electron

The electron ejected in the ionization process (reaction 3) can, after thermalization, become solvated (reaction 13). (Negative solvation clusters in the gas phase

$$e^- + n\,\text{ROH} \longrightarrow e^-_{\text{solv}} \tag{13}$$

are also known[31b]). If the electrons are solvated outside the so-called Onsager radius where its potential energy in the field of the geminate positive ion ($e^2/\epsilon r$) equals its thermal energy (kT) (cf. Reference 32), they are called free electrons. Considerable effort has been spent to determine the yield of free electrons in alcohols (cf. References 33 and 34). Because the Onsager radius depends inversely on the dielectic constant of the medium, the free-ion yield is also a function of the dielectric constant (note that in condensed states the free ion yield is necessarily smaller than the ionization yield). For the lower alcohols G-values between 1 and 2 have been found (for a compilation see References 4 and 35).

It would exceed the scope of this article to extensively review the present knowledge about the properties of the solvated electron in alcohols (for reviews see References 3, 4, 36–43), but a brief account seems in order. In alcohols the solvated electron can be readily detected by its strong optical absorption peaking between 600 and 800 nm, and also by its ESR signal in the glassy state at low temperatures, where one speaks of the trapped electron[3,44–48]. Making use of the picosecond pulse radiolysis technique at room temperature[49–53] or by slowing down the solvation process through lowering the temperature and working at the nanosecond or microsecond time-scale[54–63], the solvation of the electron can be followed spectroscopically. The photodisentrapment of the partially or fully solvated electrons, called photobleaching, has been used to obtain information on the different kinds of electron trap that may exist in a polar medium[63b,64–68]. During photobleaching alcohol radicals are formed[69] via reaction (14) and subsequent

$$e^-_{\text{solv}} + \text{ROH} \longrightarrow \text{RO}^- + \text{H}^{\bullet} \tag{14}$$

hydrogen abstraction by $\text{H}^{\bullet}$ (see below). At the early stages where the electron trap is not yet fully established (shallow) a strong absorption in the infrared, due to the 'presolvated' electron, is observed which shifts to the visible as solvation proceeds[64,70–72]. The broadness of the final absorption band of the solvated electron is considered to be due to a distribution of trap depths, or to a superposition of different optical transitions from the same ground state[73–79]. The nature of the solvation shell of the trapped electron in low-temperature glasses has also been studied by ESR spectroscopy[80,81].

The solvated electron is considered to reside within a cavity formed by a shell of polarized solvent molecules. The change of the nature of this cavity with temperature or pressure influences the optical absorption spectrum of the solvated electron, a decrease in temperature[82,83] or an increase in pressure[84,85] causing a blue-shift as the cavity is contracted (cf. References 64 and 86) or compressed[87]. The change with temperature has also been explained on the basis of thermal disorientation of the cavity-forming dipoles[88]. In mixed solvents the electron tends to associate with molecular aggregates of the more polar constituent[89–91] as shown by the fact that its absorption spectrum is essentially the same as in the pure polar compound at concentrations of the latter of 10 mol % or even less[92–95]. As expected, under certain conditions a build-up of the solvation shell has also been observed whereby the less polar neighbour molecules around the electron are progressively replaced by molecules of the more polar compound[82,96–98].

It is thought that in low-temperature glasses the trapped electron reacts with acceptors mostly by tunnelling[99]. The ease of the tunnelling phenomenon seems to depend on the nature of the medium[100]. Presolvated and solvated electrons react at different rates[62,101-108]. The orientation of the acceptor with respect to the tunnelling electron may also influence the reaction rate[109]. If the solid is crystalline instead of glassy, then under otherwise equal conditions the number of electrons becoming trapped is much smaller[110].

In liquid alcohols the reactions of the solvated electron have been monitored by pulse radiolysis, making use of its strong optical absorption[84,85,111-113], and by the salt effect on its reactions with scavengers[114,115]. At room temperature the solvated electron reacts comparatively slowly with alcohols (reaction 14: k_{14}(MeOH, EtOH) $\leqslant 10^5$ M $^{-1}$ s^{-1} (Ref. 113); k_{14}(EtOH) = 7×10^3 M $^{-1}$ s^{-1} (Ref. 116)). Reaction (15) predominates over reaction (14) in benzyl[117] and allyl[118] alcohols where the ensuing radical is resonance-stabilized. It has been suggested[119] that in *t*-butanol the presolvated electron can undergo a reaction similar to (15), but with a higher specific rate. Data on solvated electron reactions in alcohols have been compiled[120-122].

$$e^-_{solv} + ROH \longrightarrow R^{\cdot} + OH^- \qquad (15)$$

C. Ion-molecule Reactions

Knowledge about ion-molecule reactions stems from studies in the gas phase[123-127] where it has been shown that the molecular ions of alcohols efficiently (in principle on every encounter) transfer a proton to an alcohol molecule. Oxygen-bound and α-carbon-bound H atoms are transferred with about equal rates (exemplified by reactions 16 and 17). In the condensed state reaction (16) has been considered to be much favoured over reaction (17) because the oxygen-bound hydrogen is involved in hydrogen bonding, in contrast to the carbon-bound one[128a].

$$CH_3OD^{+\cdot} + CH_3OD \longrightarrow CH_3O^{\cdot} + CH_3OD_2^+ \qquad (16)$$

$$CH_3OD^{+\cdot} + CH_3OD \longrightarrow {}^{\cdot}CH_2OD + CH_3ODH^+ \qquad (17)$$

The direct measurement by ESR spectroscopy of the alkoxyl radical in irradiated crystalline methanol has been reported[128b], but its detection in alcohol glasses[129] is difficult because of line broadening and its presence in irradiated liquid alcohols has only been established using the spin labelling technique[130-135]. The *G*-values obtained by making use of the alkoxyl radical's oxidizing properties reach values between 1.5 and 2.0 for ethanol and methanol[136]. The question as to whether, in methanol, $G(CH_3O^{\cdot})$ and $G(^{\cdot}CH_2OH)$ (from reaction 17) are roughly equal[130,133,135] or whether essentially only the alkoxyl radical is primary[134a,c] is still being debated[128a,134]. The abundance of α-hydroxyalkyl radicals in the radiolysis of primary and secondary alcohols is no indication of the importance of reaction (17) because these radicals have several different precursors, mainly alkoxyl and $H^{\cdot}$.

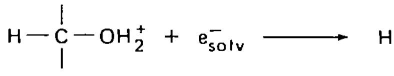
The alkoxyl radicals react rapidly and in primary and secondary alcohols they are converted into α-hydroxyalkyl radicals (reaction 18). By pulse radiolysis k_{18} has been measured[137a] as 2.6×10^5 M $^{-1}$ s^{-1}. An intramolecular rearrangement of the methoxyl into the hydroxymethyl radical has also been invoked[128b], a reaction which might be analogous to the same reaction occurring in aqueous solution where it is mediated by the solvent[137b,c]. Some of the reactions of the hydroxymethyl radical in methanol have been studied by pulse radiolysis[137d].

$$CH_3O^{\cdot} + CH_3OH \longrightarrow CH_3OH + {}^{\cdot}CH_2OH \qquad (18)$$

D. Formation of Hydrogen

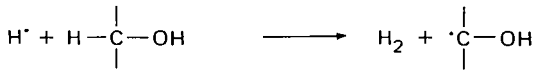
In Table 1 the major products of the radiolysis of some neat alcohols (methanol[122], ethanol[121], propanol[138-139], 2-propanol[31,140-143], *n*-butanol[30], 2-butanol[29], isobutanol[29] and *t*-butanol[29,144,145] in the liquid phase near room temperature are summarized. Where different values exist in the literature the average has been taken, or preference has been given to work where the applied dose was kept low and a reasonable material balance was obtained. It is seen from Table 1 that in all these alcohols, except *t*-butanol, hydrogen is the main product.

The predominant reaction is considered to be the reaction of the electron with the protonated alcohol (from the very fast reactions 16 and 17). Reaction (19)



$$\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}OH_2^+} + e^-_{\mathrm{solv}} \longrightarrow \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}OH} + \mathrm{H}^\bullet \tag{19}$$

produces an H atom which rapidly reacts with the alcohol by abstracting hydrogen preferentially at the position α to the hydroxyl group (reaction 20). Indeed, if the

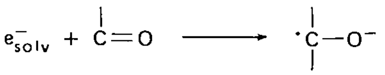


$$\mathrm{H}^\bullet + \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}OH} \longrightarrow \mathrm{H_2} + \mathrm{{}^\bullet\overset{|}{\underset{|}{C}}{-}OH} \tag{20}$$

electrons are removed by electron scavengers $G(\mathrm{H_2})$ is strongly reduced (but not fully suppressed, see below)[142,146,147a]. In competition with this reaction the electron might react with the alkoxyl radicals from reaction (16) (reaction 21: its

$$e^-_{\mathrm{solv}} + \mathrm{RO}^\bullet \longrightarrow \mathrm{RO}^- \tag{21}$$

reaction with the α-hydroxyalkyl radical has also been considered[147b]), or might be scavenged by carbonyl compounds (reaction 22) present as impurities or formed



$$e^-_{\mathrm{solv}} + \mathrm{\overset{|}{C}{=}O} \longrightarrow \mathrm{{}^\bullet\overset{|}{\underset{|}{C}}{-}O^-} \tag{22}$$

during radiolysis. On addition of acid these reactions are suppressed. $G(\mathrm{H_2})$ rises accordingly and in the series of *n*-alcohols reaches a value of about 6[146,148,149]. In Table 2 are shown the effects of the electron scavenger $\mathrm{N_2O}$ and of acid on the relative isotopic composition of the hydrogen evolved in the γ-radiolysis of several deuterated *n*-butanols[150]. Under strongly acidic conditions the major part (about two thirds to three quarters) of the hydrogen evolved from monodeuterated (at oxygen) alcohols is found as HD. The yield of $\mathrm{D_2}$ is negligible.

It has been suggested[151] that the electron might be chemically trapped by $\mathrm{H}^\bullet$ (reaction 23). The hydride is expected to form hydrogen in reaction (24), but the

$$e^- + \mathrm{H}^\bullet \longrightarrow \mathrm{H}^- \tag{23}$$

$$\mathrm{H}^- + \mathrm{ROH} \longrightarrow \mathrm{H_2} + \mathrm{RO}^- \tag{24}$$

smallness of the $\mathrm{D_2}$ yield from *O*-deuterated alcohols where considerable formation of $\mathrm{D}^\bullet$ is expected means that reaction (23) should be rather minor.

The foregoing facts are in agreement with the electron being an important hydrogen precursor, and with a good likelihood of reaction (19) followed by (20). However, the remainder ($G \approx 1.5$; about a quarter) of the hydrogen evolved (consisting of $\mathrm{H_2}$ in the mono(-oxygen-)deuterated alcohols) must have other sources which are not yet fully understood. The fragmentation of the primary ion has been proposed as a possibility (e.g. reaction 27). On the basis of the fact that formyl radical is produced in the radiolysis of methanol at 4 K even after low

TABLE 1. *G*-values of the major products in the radiolysis of liquid alcohols

Alcohol	H_2	Carbonyl compound	Dehydrodimer	α-Fragmentation products (*G*-values)
Methanol	5.4	1.95	3.5	–
Ethanol	5.0	3.2	1.7	Methane (0.6)
Propanol	4.4	2.9	1.5	Ethane (2.0), formaldehyde (1.9)
2-Propanol	4.5	4.0	0.6	Methane (1.55), acetaldehyde (0.9)
n-Butanol	4.45	3.15	1.55	Propane (1.9), formaldehyde (1.9)
2-Butanol	3.7	3.6	Not measured	Methane (1.2), propionaldehyde (0.8), ethane (3.5), acetaldehyde (3.4)
Isobutanol	Not measured	Not measured	Not measured	Propane (2.5), propene (1.2), formaldehyde (2.5)
t-Butanol	0.8	–	0.9	Methane (3.7), acetone (3.5)

TABLE 2. H_2, HD, D_2 distribution in the γ-radiolysis of some deuterated *n*-butanols[150]. Additives: (*a*) 0.1 M H_2SO_4 (D_2SO_4), (*b*) ~0.1 M N_2O. Average absolute total hydrogen *G*-values: (*a*) 5.8, (*b*) 1.6

	H_2 (%)		HD (%)		D_2 (%)	
Alcohol	Acid[a]	N_2O[b]	Acid[a]	N_2O[b]	Acid[a]	N_2O[b]
(A) $CH_3CH_2CH_2CH_2OD$	30	82	69	18	1	0
(B) $CH_3CH_2CH_2CD_2OD$	12	63	56	29	32	8
(C) $CH_3CH_2CD_2CH_2OH$	95	–	5	–	0	–
(D) $CD_3CD_2CD_2CH_2OH$	86	59	12	34	2	7
(E) $CD_3CH_2CH_2CH_2OH$	97	94	3	6	0	0

exposures, reactions (25) and (26) have been considered[128]. It is certain that hydrogen atoms are formed in the dissociation of excited alcohol molecules (see

$$CH_3O^{\cdot *} \longrightarrow H_2 + H\dot{C}O \qquad (25)$$

$$^{\cdot}CH_2OD^{*} \longrightarrow HD + H\dot{C}O \qquad (26)$$

$$CH_3OH^{\cdot +} \xrightarrow{\gamma} CH_2OH^{+} + H^{\cdot} \qquad (27)$$

Chapter 21). No material is available on the behaviour of liquid alcohols excited at wavelengths below 185 nm. In the 185 nm photolysis of methanol (see Chapter 22) reaction (28) strongly predominates over reaction (29).

In the radiolysis of *O*-deuterated alcohols some of the HD is expected from reactions such as (28) and (30), whereas reactions such as (29) followed by (20) will lead to the formation of some H_2.

$$CH_3OD^{*} \longrightarrow CH_3O^{\cdot} + D^{\cdot} \qquad (28)$$

$$CH_3OD^{*} \longrightarrow {}^{\cdot}CH_2OD + H^{\cdot} \qquad (29)$$

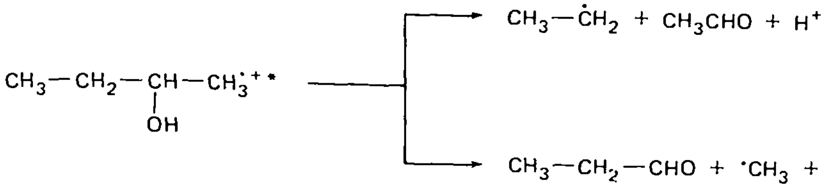
$$CH_3OD^{*} \longrightarrow CH_2O + HD \qquad (30)$$

The results listed in Table 2 indicate that there is also some primary carbon—hydrogen cleavage from carbons other than $C_{(1)}$, possibly through formation of hydrogen atoms. Molecular hydrogen elimination from vicinal hydrogen-bearing carbon atoms cannot be excluded whereas carbene formation appears unlikely noting the absence of D_2 from the hydrogen produced by the butanols C and E (Table 2), which is in line with expectations based on saturated hydrocarbon radiolysis where carbene formation through geminal molecular hydrogen elimination is considered a minor process[152].

A further uncertainty with respect to the interpretation of the mechanism of hydrogen formation comes from the very low $G(H_2)$ in the case of *t*-butanol (Table 1). This may be partially due to the low reactivity of hydrogen atoms with *t*-butanol (cf. Table 5) which could lead to a reaction of the hydrogen atom with another radical in the same spur, whereas the chance that it meets a radical from another spur (randomized radical) is minute (1 : 10,000) at the dose rates commonly used. Fully one third of $G(H_2)$ finds its equivalent in the sum of G(isobutene oxide) and G(*t*-butoxy-2-hydroxy-2-methylpropane)[145]. These two products are also formed in the photolysis of *t*-butanol at 185 nm[153] where they balance all the H_2 formed (see Chapter 21). A more detailed study on the radiolysis of *t*-butanol would certainly also help to better understand the radiolysis of primary and secondary alcohols.

E. Fragmentation of the Carbon—Oxygen Skeleton

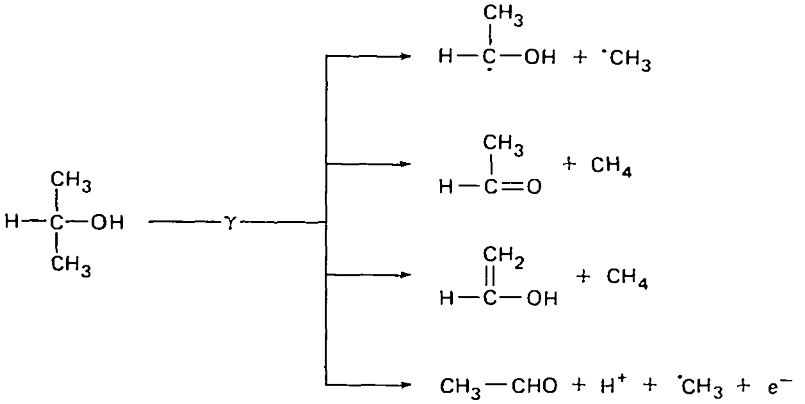
It is seen from Table 1 that the higher alcohols show considerable C—C bond fragmentation. It is not clear whether the apparent decrease of $G(H_2)$ in the neat higher alcohols perhaps reflects a real decrease of the contribution to the hydrogen yield from nonionic fragmentation, or is due to considerable electron scavenging by impurities or accumulated radiolysis products. On acidification $G(H_2)$ 6 is found[148], at least for all *n*-alcohols shown in Table 1. It has been proposed (cf. References 29 and 154) that C—C bond rupture may result from the fragmentation of the primary radical cation, e.g. reactions (31) and (32).



$$CH_3-CH_2-CH(OH)-CH_3^{+*} \longrightarrow CH_3-\dot{C}H_2 + CH_3CHO + H^+ \quad (31)$$

$$\longrightarrow CH_3-CH_2-CHO + {}^{\cdot}CH_3 + H^+ \quad (32)$$

There is some more detailed material on the C–C bond fragmentation in isopropanol[155,156]. Using deuterated isopropanols and radical scavengers it has been shown that electron scavengers do not influence methane formation, that the major part of the methane has methyl radicals (95%) as precursors (70% scavengable and 25% 'hot'), and only ~5% is formed *via* the molecular processes (34) and (35). In reaction (33) a hydroxyethyl radical is formed together with the methyl

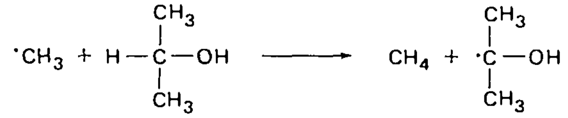


$$(CH_3)_2CHOH \xrightarrow{\gamma} H-\dot{C}(CH_3)-OH + {}^{\cdot}CH_3 \quad (33)$$

$$\longrightarrow H-C(CH_3){=}O + CH_4 \quad (34)$$

$$\longrightarrow H-C(=CH_2)-OH + CH_4 \quad (35)$$

$$\longrightarrow CH_3-CHO + H^+ + {}^{\cdot}CH_3 + e^- \quad (36)$$



$$ {}^{\cdot}CH_3 + H-C(CH_3)_2-OH \longrightarrow CH_4 + {}^{\cdot}C(CH_3)_2-OH \quad (37)$$

radical. The former may be scavenged by naphthalene and oxidized by benzophenone to acetaldehyde, leaving the methyl radical reactions (methane formation by H abstraction from isopropanol, reaction 37) unaffected. The acetaldehyde results indicate that only about 40% of the acetaldehyde is formed directly (reactions 34–36). There appears to be a major (60%) contribution from reaction (33) with an excited state as the precursor. This excited state must be an upper excited state because the lowest excited state which is reached in the 185 nm photolysis shows, as far as C–C bond cleavage is concerned, essentially merely reactions (34) and (35), and these with only a low quantum yield[157,158].

It has been suggested that, apart from in reaction (15), the 'parent' alkyl radical may be formed from alcohols by the dissociative electron capture of the protonated alcohol[159,160] (reaction 38). However, this reaction does not appear to play a role

$$R-OH_2^+ + e^-_{solv} \longrightarrow R^{\cdot} + H_2O \quad (38)$$

in methane formation from methanol where it has been shown[161] that $G(CH_4)$ is unaffected by addition of either H^+ or N_2O.

In the radiolysis of alcohols at room temperature or below, ethers are formed with low G-values[162]. Besides the trivial reaction (39), reaction (40) has been considered[162]. One would also envisage reaction (41), a reaction which has been shown to be implicated in the formation of ethers in the gas-phase radiolysis of alcohols (see below).

$$R^1O^{\cdot} + {}^{\cdot}R^2 \longrightarrow R^1OR^2 \qquad (39)$$

$$R^1OH + {}^{+}R^2 \longrightarrow R^1OR^2 + H^+ \qquad (40)$$

$$R^1OH_2^+ + R^1OH \longrightarrow R^1OR^1 + H_2O + H^+ \qquad (41)$$

III. ALCOHOLS IN THE GAS PHASE

In the gas phase the *G*-values of products (Table 3) are much higher than in the liquid phase (Table 1). This may result from the breakdown of excited molecules, radical cations and radicals which in the liquid phase are thermalized. A typical example is the formation of olefins, e.g. reaction (42). Such processes, being

$$CH_3{-}CH_2OH \longrightarrow H_2C{=}CH_2 + H_2O,\ \Delta H = 46\ \text{kJ/mol} \qquad (42)$$

endothermic from the ground state, play a comparatively small role in the liquid-phase radiolysis (about one fifth of the gas-phase yield in ethanol[121] and isopropanol[143,163]). Scission of C–C bonds is also drastically enhanced on going from the liquid to the gas phase (cf. Reference 121).

In the gas phase, ionization of alcohols occurs with a *G*-value of 4[18]. Electron scavengers reduce $G(H_2)$ by the same amount[164,165,166a], and it has therefore been argued[164] that the only reaction of the electron is that with a protonated alcohol (reaction 19). Dissociative electron capture by ROH leading to the formation of RO^- as well as H^- may play a small role[166b].

There are a number of attempts to correlate mass spectral data with the reactions occurring in the gas-phase radiolysis[123,167–170]. Obviously, such an approach is more justifiable here than in the case of liquid-phase data[29–31,139,154]. However, it has been pointed out[168] that there remain many uncertainties with respect to an acceptable theoretical treatment of this problem.

At elevated temperatures (>250°C) chain-reactions set in[163,171–175] (for a review see Reference 176). There are essentially four types of chain-reactions which are depicted by the overall reactions (43)–(46).

The protonated alcohols from reactions (16), (17) and (50) are probably the common precursors in the formation of olefins and ethers (e.g. reactions 47–49). It has been shown[127,177] that extensive clustering (reaction 48) occurs, the number of alcohol molecules within the cluster depending on alcohol pressure.

The chain-reactions leading to hydrogen and carbonyl compound (reaction 45) and to alkane and aldehyde (reaction 46) are considered to be free radical in nature.

TABLE 3. *G*-values of modes of cleavage in the gas-phase radiolysis of some alcohols

	MeOH[167] [a]	EtOH[164] [b]	*i*-PrOH[163]
G(C–H and O–H bond cleavage)	10.4	9.9	7.2
G(C–O bond cleavage)	0.3	1.8	2.9
G(C–C bond cleavage)		3.3	5.3

[a] For other work see compilation[122].
[b] For other work see compilation[121].

$$\text{Alcohol} \longrightarrow \begin{cases} H_2O + \text{olefin} & (43) \\ H_2O + \text{ether} & (44) \\ H_2 + \text{carbonyl} & (45) \\ \text{alkane} + \text{aldehyde} & (46) \end{cases}$$

$$C_2H_5OH_2^+ \longrightarrow H_2C{=}CH_2 + H_3O^+ \tag{47}$$

$$C_2H_5OH_2^+ + C_2H_5OH \longrightarrow (C_2H_5OH)_2H^+ \tag{48}$$

$$(C_2H_5OH)_2H^+ \longrightarrow C_2H_5{-}O{-}C_2H_5 + H_3O^+ \tag{49}$$

$$H_3O^+ + C_2H_5OH \longrightarrow C_2H_5OH_2^+ + H_2O \tag{50}$$

IV. NEAT ETHERS

The most readily apparent difference between the radiolysis of neat ethers and neat alcohols is based on the fact that the dielectric constants of ethers are smaller and their basicity greater than the corresponding properties in alcohols. Because of the smaller dielectric constant the free ion yield is smaller on account of a higher probability of geminate charge recombination [G(free ion) < 1[178]]. Higher basicity means that the positive charge, which is formed and stabilized in reactions (51) and (52), remains somewhat more localized because the proton tends to be less mobile in R_2OH^+ than in ROH_2^+.

$$R_2O \xrightarrow{\gamma} R_2O^{+\cdot} + e^- \tag{51}$$

$$R_2O^{+\cdot} + R_2O \longrightarrow R_2OH^+ + R_2O(-H)^\cdot \tag{52}$$

In contrast, the mobility of the solvated[179] or the trapped[180] electron is higher because of the lower polarity of the ether molecule. Direct evidence of the lesser stabilization of the electron is provided by its optical absorption spectrum. Whereas in alcohols its absorption maximum lies between about 600 to 800 nm, in ethers it absorbs near 2000 nm at room temperature[181-184]. There is a relatively larger blue-shift of the absorption maximum with decreasing temperature[184], presumably because the weaker ether molecular dipoles are more easily depolarized as the temperature rises. At about 77 K the blue-shift reaches its maximum value, with the spectrum peaking near 1200 nm[185,186] (cf. Reference 1). At still lower temperatures the maximum is again found at somewhat longer wavelengths but flattened as the dipoles are frozen in[185,187] (for a review see Reference 188a). In 2-methyltetrahydrofuran glass an inner solvation shell of three equivalent solvent molecules appears to envelop the electron[188b].

An interesting method, not applicable to protic media such as alcohols, to extend (by a factor of five) the lifetime of the solvated electron in 1,4-dioxane consists of exchanging the oxonium ion against the unreactive Li^+ (reaction 53)[189]. In ethers, alkali metal cations and solvated electrons coexist as ion pairs (M^+, e^-_{solv}) which

$$R_2OH^+ + LiAlH_4 \longrightarrow Li^+ + R_2O + AlH_3 + H_2 \tag{53}$$

are characterized by a strong blue-shift of the solvated electron absorption spectrum[190–193]. The other alkali ions are not as stable as Li^+ toward the solvated electron. Na^- and K^- were produced in the radiolysis of tetrahydrofuran solutions of the alkali metals, or their boronates[191,192]. Spectra of e^-_{solv}, Na^- and K^- in various ethers have been obtained[194].

As with the alcohols, the radiolysis of ethers is through ionic as well as through excited states. A G-value near 4.3 for total ionization has been measured in the gas phase for various ethers[195], and similar values have been accepted for the liquid phase[196–198].

Apart from undergoing fragmentation, molecules is excited states may also transfer energy to solutes[189], or show luminescence[199]. The latter behaviour is seen to be of particular importance in 1,4-dioxane, in some contrast to other ethers. Dioxane fluoresces (λ_{max} 247 nm) on excitation with 185 nm light[200,201] and also on radiolysis[199,202]. This fluorescence is quenched by N_2O[22,203] and other quenchers[202,203]. Energy transfer to scintillators yields visible light; this property together with the ability of 1,4-dioxane to accommodate aqueous material in homogeneous distribution have earned it a place among the media employed for low-energy β-radiation counting (cf. References 204 and 205).

Hydrogen is a major radiolysis product (cf. Reference 1) in all ethers investigated, including diethyl[206,207], di-*n*-propyl[196], diisopropyl[208] and dibutyl[208] ethers, tetrahydrofuran[209–211], 2-methyltetrahydrofuran[208,212–215] and 1,4-dioxane[208,216–219]. It is thought that several different modes of hydrogen formation are in operation. Following reactions (51) and (52), the solvated electron neutralizes the oxonium ion (reaction 54). Hydrogen atoms abstract from the ether, predominantly in the α-position (reaction 55). Also, atomic as well as molecular hydrogen is formed from excited molecules (reactions 56 and 57), or in spur reactions irrepressible by electron or radical scavengers.

$$R^1_2OH^+ + e^-_{solv} \longrightarrow R^1_2O + H^\cdot \qquad (54)$$

$$H^\cdot + R^2{-}CH_2{-}O{-}R^1 \longrightarrow R^2{-}\dot{C}H{-}OR^1 + H_2 \qquad (55)$$

$$R^1_2O \xrightarrow{\gamma} R^1_2O(-H)^\cdot + H^\cdot \qquad (56)$$

$$R^3{-}CH_2{-}CH_2{-}OR^1 \xrightarrow{\gamma} R^3{-}HC{=}CH{-}OR^1 + H_2 \qquad (57)$$

In most cases few if any other products have been measured. Especially in the cases of the cyclic ethers the radiolysis mechanism is far from clear. Fragmentation of the carbon–oxygen skeleton probably leads to biradical intermediates which may react in a variety of ways, side by side with the different monoradicals. In the case of 2-methyltetrahydrofuran both the tertiary and the secondary α-radical seem now established[220,221].

Diethyl ether presents a case where an extensive product analysis has been carried out for both gas- and liquid-phase radiolysis[206,207]. The product distribution differs in the two phases although G(ether consumption) is nearly the same, at about 11.3. Similar to photolysis[222] and pyrolysis[223], cleavage of the C–O bond is a major event[206,207,210,216] in radiolysis, probably partly through ionic, and partly through excited states (reactions 58–61). There is some evidence that dissociative electron capture (reaction 62) may also occur[224,225]. Fragments resulting from C–C bond rupture such as methane and successor products of CH_3 are of lesser importance and, as expected, more in evidence among the products from the gas-phase radiolysis[207].

$$R_2OH^+ + e^- \longrightarrow ROH + R^{\cdot} \qquad (58)$$

$$R_2O \begin{cases} \xrightarrow{\gamma} ROH + \text{olefin} & (59) \\ \xrightarrow{\gamma} R'CH{=}O + RH & (60) \\ \xrightarrow{\gamma} RO^{\cdot} + {}^{\cdot}R & (61) \end{cases}$$

$$R_2O + e^- \longrightarrow RO^- + {}^{\cdot}R \qquad (62)$$

V. AQUEOUS SOLUTIONS OF ALCOHOLS AND ETHERS

A. Primary Species in the Radiolysis of Aqueous Solutions

If dilute aqueous solutions are irradiated with ionizing radiation, the radiation energy is largely absorbed by the solvent water leading to OH radicals, hydrated electrons (e^-_{aq}), H atoms, the molecular products H_2O_2 and H_2, as well as the ions H^+ and OH^- (reaction 63).

$$H_2O \xrightarrow{\gamma} {}^{\cdot}OH, e^-_{aq}, H^{\cdot}, H_2O_2, H_2, H^+, OH^- \qquad (63)$$

$$e^-_{aq} + N_2O \longrightarrow {}^{\cdot}OH + N_2 + OH^- \qquad (64)$$

$$e^-_{aq} + H^+ \longrightarrow H^{\cdot} \qquad (65)$$

$$e^-_{aq} + O_2 \longrightarrow O_2^{\cdot -} \qquad (66)$$

$$H^{\cdot} + O_2 \longrightarrow HO_2^{\cdot} \qquad (67)$$

The hydrated electrons (for rate constants see References 226 and 227) can be converted into OH radicals by saturating the solution with N_2O (reaction 64; $[N_2O] = 2.2 \times 10^{-2}$ M at 20°C and atmospheric pressure, $k_{64} = 5.6 \times 10^9$ $M^{-1}\ s^{-1}$). At low pH they are converted into H atoms (reaction 65; $k_{65} = 2.3 \times 10^{10}$ $M^{-1}\ s^{-1}$). In the presence of O_2, hydrated electrons can be converted into $O_2^{\cdot -}$ radicals (reaction 66; $k_{66} = 2 \times 10^{10}$ $M^{-1}\ s^{-1}$). The H atom (for rate constants see Reference 228) does not react with N_2O but reacts readily with O_2 (reaction 67; $k_{67} = 10^{10} M^{-1} s^{-1}$). The resulting $HO_2^{\cdot}$ is in equilibrium with its basic form $O_2^{\cdot -}$ [pK_a ($HO_2^{\cdot}$) = 4.75)[229]. Saturation of an aqueous solution with a mixture of N_2O/O_2 (4/1 v/v) converts hydrated electrons into OH radicals whereas the H atoms are scavenged by O_2. The G-values of the molecular products and of the ions are little

TABLE 4. G-values of radicals generated in the γ-radiolysis of neutral water in the presence of inert gases (e.g. He, Ar, N_2), N_2O and O_2

Saturating gas	$G({}^{\cdot}OH)$	$G(e^-_{aq})$	$G(H^{\cdot})$	$G(O_2^{\cdot -})$
Inert gas	2.7	2.7	0.55	–
N_2O	5.4[a]	–	0.55	–
O_2	2.7	–	–	3.25
N_2O/O_2 (4/1 v/v)	5.4[a]	–	–	0.55

[a] There is evidence[230,231] that under N_2O saturation G(OH) may be as high as 6.

changed by these additives [($G(H_2O_2) = 0.7$, $G(H_2) = 0.45$, $G(H^+) = 3.4$, $G(OH^-) = 0.6$]. The G-values of the radicals at the various conditions are summarized in Table 4. The values for $O_2^{\cdot -}$ given in Table 4 are only valid as long as other additives are used in concentrations which do not interfere with reactions (66) or (67).

B. Deoxygenated Solutions

1. *Saturated alcohols*

Hydrated electrons do not react with saturated alcohols at a measurable rate ($k < 10^6\ M^{-1}s^{-1}$)[226,232]. However, OH radicals and H atoms rapidly react with these substrates by hydrogen abstraction. The OH radical (for rate constants see References 233 and 234) reacts considerably faster than the H atom[228]. The reactivity of the $SO_4^{\cdot -}$ radical is somewhere in between[235] (Table 5). The latter can be generated by reaction of the solvated electron with $S_2O_8^{--}$ (reaction 68). The

$$e^-_{aq} + S_2O_8^{--} \longrightarrow SO_4^{--} + SO_4^{\cdot -} \qquad (68)$$

preferred site of attack of the OH radical is the position α to the hydroxyl group[236,237]. With increasing chain-length of the alcohol the probability of H abstraction at positions other than α to the hydroxyl group increases. There is always a very low probability of H abstraction at the hydroxyl group (Table 6).

TABLE 5. Rate constants ($M^{-1}s^{-1}$) of OH radicals, H atoms and $SO_4^{\cdot -}$ radicals with some alcohols in aqueous solutions (references see text)

Substrate	$^{\cdot}OH$	$H^{\cdot}$	$SO_4^{\cdot -}$
Methanol	9×10^8	2×10^6	3.2×10^6
Methanol-d_3	4.2×10^8	2.5×10^{5a}	1.2×10^6
Ethanol	1.8×10^9	2.6×10^7	1.6×10^7
2-Propanol	2.0×10^9	6.5×10^7	3.2×10^7
2-Methyl-2-propanol	4.5×10^8	8×10^4	4.0×10^5

[a]Value calculated from $k(H^{\cdot}$ + methanol) on the basis of an H/D isotope effect of 7.5[235b].

TABLE 6. Relative yields (%) of H abstraction by OH radicals at different positions from various alcohols[237]

Substrate	α	β,γ,δ etc.	OH
CH_3OH	93.0	–	7.0
C_2H_5OH	84.3	13.2	2.5
$CH_3CH_2CH_2OH$	53.4	46.0	<0.5
$(CH_3)_2CHOH$	85.5	13.3	1.2
$CH_3CH_2CH_2CH_2OH$	41.0	58.5	<0.5
$(CH_3)_3COH$	–	95.7	4.3
$CH_2OH{-}CH_2OH$	100	–	<0.1
$CH_2OH{-}CHOH{-}CH_3$	79.2	20.7	<0.1
$CH_3{-}CHOH{-}CHOH{-}CH_3$	71.0	29.0	<0.1

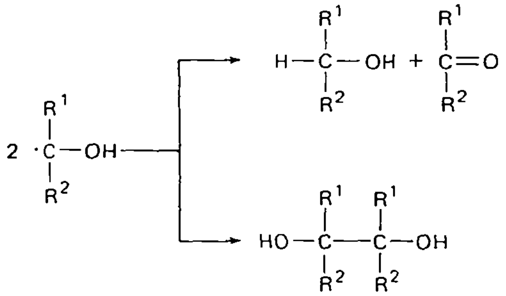
TABLE 7. p*K* values of some α-hydroxyalkyl radicals and their parent alcohols

Radical	p*K*	p*K* of parent alcohol	Δp*K*
$^{\bullet}CH_2OH$	10.71[a] 10.7[b]	15.09[c]	−4.38
$CH_3\dot{C}HOH$	11.51[a] 11.6[b]	15.93[c]	−4.42
$(CH_3)_2\dot{C}OH$	12.03[a] 12.2[b]	17.1[c]	−5.07
$(CF_3)_2\dot{C}OH$	1.70[a]	9.8[a]	−8.1

[a] From Reference 239.
[b] From Reference 238.
[c] From Reference 240.

Using the pulse radiolysis technique it has been shown that the α-hydroxyalkyl radicals are more acidic by about four p*K* units than their parent alcohols[238]. This has been confirmed by *in situ* ESR spectroscopic studies[239] (Table 7).

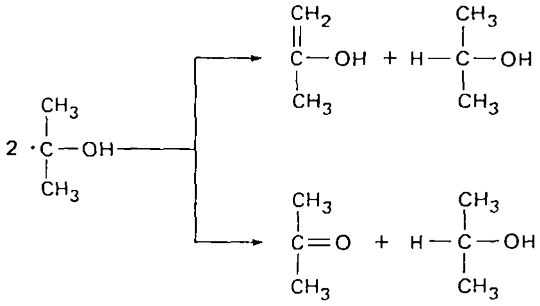
In their self-termination, the α-hydroxyalkyl radicals disproportionate and dimerize (reactions 69 and 70).



$$2\,{}^{\bullet}C(R^1)(R^2)OH \rightarrow H{-}C(R^1)(R^2){-}OH + R^1R^2C{=}O \qquad (69)$$

$$2\,{}^{\bullet}C(R^1)(R^2)OH \rightarrow HO{-}C(R^1)(R^2){-}C(R^1)(R^2){-}OH \qquad (70)$$

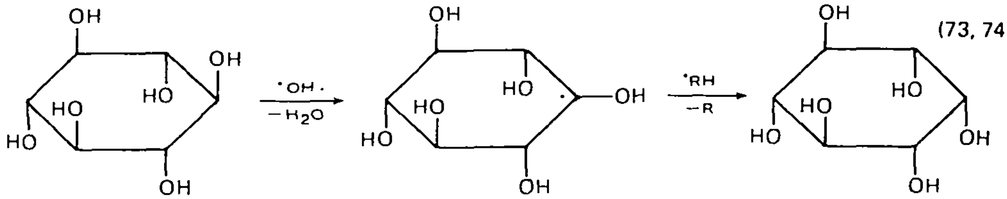
The disproportionation/dimerization ratio increases with increasing methyl substitution ($R^1 = R^2 = H$, $k_{69}/k_{70} < 0.1$; $R^1 = H$, $R^2 = CH_3$, $k_{69}/k_{70} = 0.43$; $R^1 = R^2 = CH_3$, $k_{69}/k_{70} \sim 4$)[28]. In the disproportionation of 2-hydroxypropyl-(2) radicals the transfer of a carbon-bound hydrogen atom (reaction 71) has a higher probability than the transfer of the oxygen-bound hydrogen atom (reaction 72)[241].



$$2\,{}^{\bullet}C(CH_3)_2OH \rightarrow CH_2{=}C(OH)CH_3 + H{-}C(CH_3)_2{-}OH \qquad (71)$$

$$2\,{}^{\bullet}C(CH_3)_2OH \rightarrow (CH_3)_2C{=}O + H{-}C(CH_3)_2{-}OH \qquad (72)$$

An optically active carbon atom which carries an OH group may lose its former optical activity on going from the alcohol through the radical state back to the alcohol. This has been found[242] with *scyllo*-inositol where the major disproportionation product is *myo*-inositol (reactions 73 and 74).



(73, 74)

The α-hydroxyalkyl radicals are rapidly oxidized by $Fe(CN)_6^{3-}$ (reaction 75; $k \approx 4 \times 10^9$ $M^{-1}s^{-1}$), a reaction which has been followed by pulse radiolysis[236].

$$[Fe(CN)_6]^{3-} + R_2\dot{C}OH \longrightarrow [Fe(CN)_6]^{4-} + R_2CO + H^+ \qquad (75)$$

With Fe^{2+} ions these radicals form a complex which can be monitored by its short-lived absorption[243]. However, reduction of these radicals does not take place, and the products are the same as observed in the absence of Fe^{2+} ions. Intermediate complexes of the α-hydroxyalkyl radicals with other metal ions such as Ag^{+}[244], Ag_2^{+}[245], Ni^{+}[246], Cd^{+}[247] and Pb^{+}[248a] were also detected. A compilation of rate constants for the reaction of metal ions in unusual valence states has appeared[248b].

The reaction of α-hydroxyalkyl radicals with hydrogen peroxide is quite rapid (reaction 76; $k \approx 10^5$ $M^{-1}s^{-1}$)[249-251] and leads to the formation of an OH radical which propagates a chain.

$$R_2\dot{C}OH + H_2O_2 \longrightarrow R_2CO + H_2O + {}^{\cdot}OH \qquad (76)$$

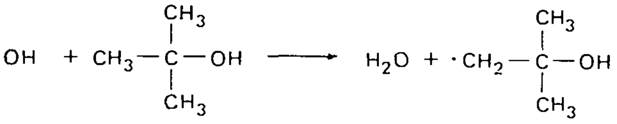
The anions of the α-hydroxyalkyl radicals are better electron donors than the α-hydroxyalkyl radicals themselves (for p*K* values see Table 7). Therefore, electron-transfer reactions are more efficient at high pH where chain-reactions have been observed with alkyl halides and with N_2O[252-256]. Likely propagating steps are the reactions (77) and (78).

$$R^1_2CO^{\cdot -} + R^2Br \longrightarrow R^1_2CO + R^{2\cdot} + Br^- \qquad (77)$$

$$R^1_2CO^{\cdot -} + N_2O \longrightarrow R^1_2CO + N_2 + O^{\cdot -} \qquad (78)$$

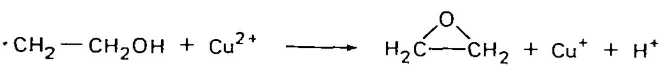
β-Hydroxyalkyl radicals are also formed in the reactions of OH radicals with primary and secondary alcohols, even though with low yields (see Table 6). They can be generated more conveniently by reacting OH radicals with olefins, for example reaction (79). Further, β-hydroxyalkyl radicals are formed in the reaction of OH radicals with tertiary alcohols, e.g. *t*-butanol (reaction 80).

$$^{\cdot}OH + H_2C{=}CH_2 \longrightarrow {}^{\cdot}CH_2{-}CH_2OH \qquad (79)$$



$$^{\cdot}OH + CH_3{-}\underset{CH_3}{\overset{CH_3}{C}}{-}OH \longrightarrow H_2O + {\cdot}CH_2{-}\underset{CH_3}{\overset{CH_3}{C}}{-}OH \qquad (80)$$

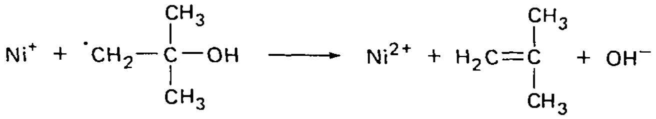
In their reaction with Cu^{2+} they are reported to give epoxides (e.g. reaction 81)[257,258].



(81)

From strongly reducing metal ions such as Ni^+ the β-hydroxyalkyl radicals accept an electron, yielding olefins (e.g. reaction 82)[246].

β-Hydroxyalkyl radicals also abstract hydrogen atoms from their parent alcohol



$$Ni^+ + {}^{\bullet}CH_2-C(CH_3)_2-OH \longrightarrow Ni^{2+} + H_2C{=}C(CH_3)_2 + OH^- \qquad (82)$$

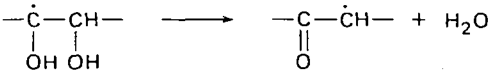
if derived from a primary or secondary alcohol. Thereby the β-hydroxyalkyl radicals are converted into α-hydroxyalkyl radicals (e.g. reaction 83). The rate

$$ {}^{\bullet}CH_2-CH_2OH + CH_3-CH_2OH \longrightarrow CH_3-CH_2OH + CH_3-\dot{C}HOH \qquad (83)$$

constant of this reaction is around $30-50\ M^{-1}s^{-1}$ [249,259,260]. A value higher by one order of magnitude has also been reported[261].

2. *Polyhydric alcohols and carbohydrates*

The radiolysis of polyhydric alcohols and carbohydrates in deoxygenated aqueous solution is characterized by the elimination of water from the original 1,2-dihydroxyalkyl radicals (reaction 84). This reactions has first been observed by



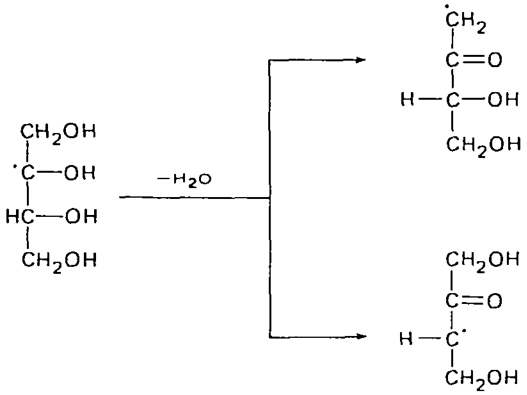
$$-\dot{C}(OH)-CH(OH)- \longrightarrow -C(=O)-\dot{C}H- + H_2O \qquad (84)$$

ESR spectroscopy[262-265] and was later further investigated by product analysis[266-269] and pulse radiolysis[270]. The elimination of water is acid- and base-catalysed. The acylalkyl radicals $(-CO-\dot{C}H-)$ have oxidizing properties[270b] and readily abstract hydrogen atoms from the starting material (e.g. reaction 85), thus inducing chain-reactions. In the case of ethylene glycol as a substrate the rate constant of reaction (85) was found to be $75\ M^{-1}s^{-1}$ [268]. A typical example of the

$$ {}^{\bullet}CH_2-CHO + CH_2OH-CH_2OH \longrightarrow CH_3-CHO + {}^{\bullet}CHOH-CH_2OH \qquad (85)$$

various reactions involved is given in Scheme 1 for the simplest molecule in this series, ethylene glycol.

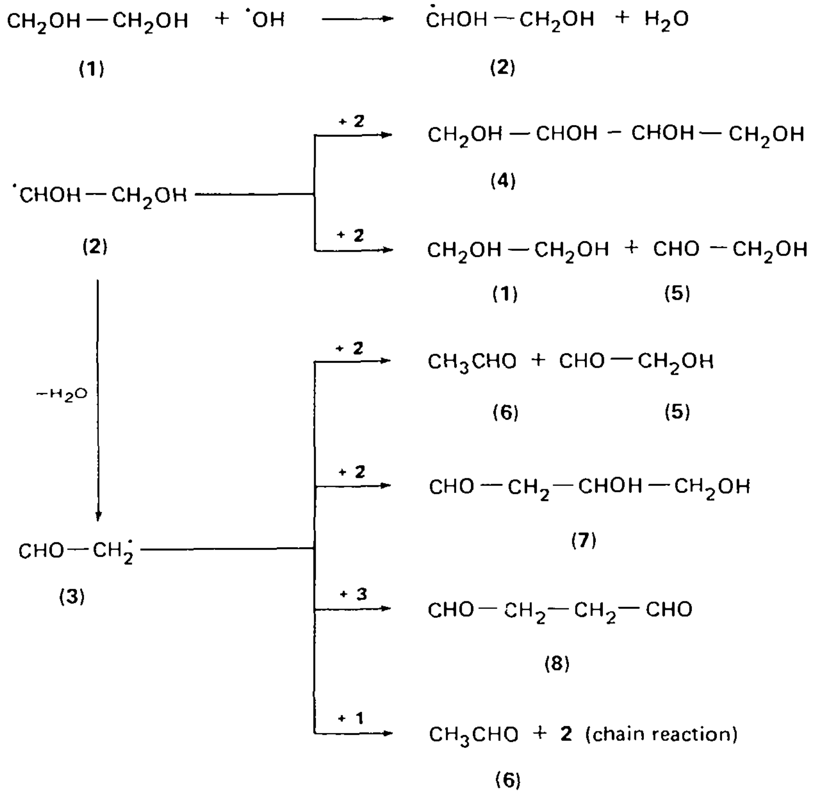
In the case of erythritol the radical at $C_{(2)}$ has two possible ways to eliminate water. It is noted[271,272] that the elimination towards $C_{(1)}$ (reaction 86) is preferred by a factor of seven over that towards $C_{(3)}$ (reaction 87). The reasons for this unexpected preference are not yet known.



(86)

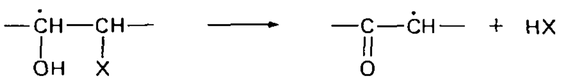
(87)

The same type of reaction can proceed with β-alkoxy-α-hydroxyl radicals (reaction 88, X = OR)[270b,272-276]. Reaction (88) is especially fast if X is a good leaving group, e.g. F, Cl, Br, I, CH_3CO_2 and H_2PO_4[262,265,277-281].



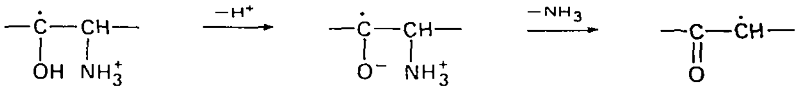
SCHEME 1. Reactions of radicals derived from ethylene glycol[a]

[a]G-values of products (Reference 267) of a N_2O-saturated 0.1 M solution of ethylene glycol at 20°C and at a dose rate of 0.1 W kg^{-1}. G(tetritol, 4) = 0.15, G(glycolaldehyde, 5) = 1.05, G(acetaldehyde, 6) = 1.2, G(2-deoxytetrose, 7) = 0.25 and G(succinaldehyde, 8) = 1.7.



$$-\underset{OH}{\dot{C}H}-\underset{X}{CH}- \longrightarrow -\underset{\underset{O}{\|}}{C}-\dot{C}H- + HX \qquad (88)$$

The radical-induced deamination of amino alcohols and amino sugars has been considered[282,283] to proceed through the radical zwitterion (reactions 89, 90).



$$-\underset{OH}{\dot{C}}-\underset{NH_3^+}{CH}- \xrightarrow{-H^+} -\underset{O^-}{\dot{C}}-\underset{NH_3^+}{CH}- \xrightarrow{-NH_3} -\underset{\underset{O}{\|}}{C}-\dot{C}H- \qquad (89, 90)$$

This pathway may be followed even at pH 5 where deamination is still observed. In the hydrolytic equilibrium, the radical zwitterion might be present at a sufficient concentration. The acidity increase of an OH group that is attached to a carbon atom carrying a free spin is well known (cf. Table 7).

The products which have been identified thus far in the γ-radiolysis of aqueous solutions of D-glucose are listed in Table 8. The importance of the water elimination reaction (reaction 84) and the analogous reaction (reaction 88) is apparent from the number of the deoxy sugars that are formed via these reactions. (About

TABLE 8. Products and their initial *G*-values from the γ-radiolysis of deoxygenated N_2O-saturated[273] or N_2O/O_2 (4 : 1)-saturated[284] aqueous solutions of D-glucose at a dose rate of 0.18 W kg^{-1} at room temperature

	G-values	
Products	N_2O	N_2O/O_2
D-Gluconic acid	0.15	0.90
D-*arabino*-Hexosulose	0.15	0.90
D-*ribo*-Hexos-3-ulose	0.10	0.57
D-*xylo*-Hexos-4-ulose	0.075	0.50
D-*xylo*-Hexos-5-ulose	0.18	0.60
D-*gluco*-Hexodialdose	0.22	1.55
2-Deoxy-D-*arabino*-hexonic acid	0.95	Absent
5-Deoxy-D-*threo*-hexos-4-ulose		Absent
5-Deoxy-D-*xylo*-hexonic acid	0.08	Absent
2-Deoxy-D-*erythro*-hexos-5-ulose		Absent
5-Deoxy-D-*xylo*-hexodialdose		Absent
3-Deoxy-D-*erythro*-hexos-4-ulose		Absent
3-Deoxy-D-*erythro*-hexosulose	0.25	Absent
4-Deoxy-L-*threo*-hexos-5-ulose		Absent
6-Deoxy-D-*xylo*-hexos-5-ulose	0.05	Absent
2-Deoxy-D-*erythro*-hexos-3-ulose	[a]	Absent
4-Deoxy-D-*threo*-hexos-3-ulose	[a]	Absent
D-Arabinose	0.01	0.10
D-Arabinonic acid	Absent	
D-Ribose	<0.005	Absent
D-Xylose	<0.005	0.08
xylo-Pentodialdose	Absent	
2-Deoxy-D-*erythro*-pentose	0.04	Absent
D-Erythrose	0.01	0.02
D-Erythronic acid	Absent	
Threose	<0.003	Absent
L-*threo*-Tetrodialdose	Absent	0.20
3-Deoxytetrulose	0.02	Absent
Dihydroxyacetone	0.03	Absent
D-Glyceraldehyde and glyceric acid	Absent	0.13
Glyoxal	[b]	0.11
Glyoxylic acid and glycolic acid	[b]	0.4
Formaldehyde	[b]	0.12
Formic acid	[b]	0.6
D-Glucose consumption	5.6	5.6

[a] Products identified (no *G*-values given) in Reference 285. They are expected to be included in the *G*-values of the other deoxyhexosulose given in the table.

[b] Not determined, probably absent.

reactions typical for the lactol function see below.) For a detailed discussion of the radiation chemistry of carbohydrates see Reference 286.

3. Saturated ethers and acetals

Solvated electrons do not react with these substrates but OH radicals and H atoms rapidly abstract hydrogen atoms if such are available in the α-position to the ether linkage (reaction 91).

$$R^1CH_2OR^2 + {}^{\bullet}OH \longrightarrow R^1\overset{\bullet}{C}HOR^2 + H_2O \qquad (91)$$

The resulting α-alkoxyalkyl radicals show a number of reactions which resemble those observed with α-hydroxyalkyl radicals. They are readily oxidized by $[Fe(CN)_6]^{3-}$ ($k = 2 \times 10^9$ M^{-1}s^{-1})[236] or hydrogen peroxide ($k = 5.5 \times 10^4$ M^{-1}s^{-1})[287].

In reaction (92), the 1-ethoxyethyl radicals derived from diethyl ether via reaction (91) yield only acetaldhyde and ethanol. A likely intermediate is the carbonium ion (oxonium ion). This must react much more rapidly (>20-fold) with water to give acetaldehyde ethyl hemiacetal (reaction 93) and ultimately acetaldehyde and ethanol (reaction 94) rather than lose a proton to give ethyl vinyl ether (reaction 95)[288]. In the absence of an oxidant the latter is formed as a disproportionation product of two ethoxyethyl radicals. Their dimer, 2,3-diethoxybutane, is

$$CH_3\overset{\bullet}{C}HOC_2H_5 + [Fe(CN)_6]^{-3} \longrightarrow CH_3CH{=}\overset{+}{O}C_2H_5 + [Fe(CN)_6]^{4-} \qquad (92)$$

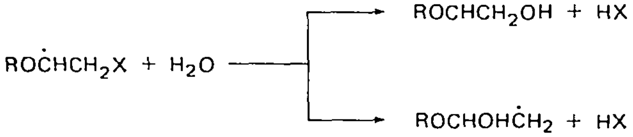
$$CH_3\overset{+}{C}HOC_2H_5 + H_2O \longrightarrow CH_3CHOHOC_2H_5 + H^+ \qquad (93)$$

$$CH_3CHOHOC_2H_5 \longrightarrow CH_3CHO + C_2H_5OH \qquad (94)$$

$$CH_3CH{=}\overset{+}{O}C_2H_5 \longrightarrow CH_2{=}CH_2OC_2H_5 + H^+ \qquad (95)$$

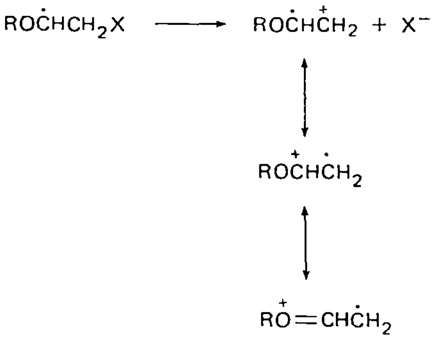
also formed. Because of the high reactivity of H_2O_2 with the ethoxyethyl radicals the radiolytically generated hydrogen peroxide (see above) can only attain very low steady-state concentrations at the usual dose rates of ^{60}Co γ-irradiation. The products of the reaction of the ethoxyethyl radicals with hydrogen peroxide are acetaldehyde and ethanol. A chain-reaction is induced by the OH radical liberated in this reaction[288].

α-Alkoxyalkyl radicals which carry a good leaving group (e.g. X = halogen or phosphate) in the position β to the free spin rapidly eliminate this group and two new radicals are observed[278,289] by ESR spectroscopy, instead of the original radical (reactions 96 and 97). The most likely intermediate is the radical cation formed in reaction 98. Evidence for this, among other indications, is the fact that



$$RO\overset{\bullet}{C}HCH_2X + H_2O \longrightarrow RO\overset{\bullet}{C}HCH_2OH + HX \qquad (96)$$

$$RO\overset{\bullet}{C}HCH_2X + H_2O \longrightarrow ROCHOH\overset{\bullet}{C}H_2 + HX \qquad (97)$$



$$RO\overset{\bullet}{C}HCH_2X \longrightarrow RO\overset{\bullet}{C}H\overset{+}{C}H_2 + X^- \qquad (98)$$

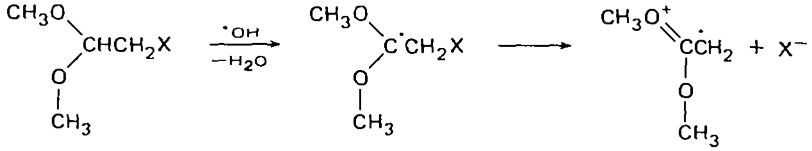
$$\updownarrow$$

$$RO\overset{+}{C}H\overset{\bullet}{C}H_2$$

$$\updownarrow$$

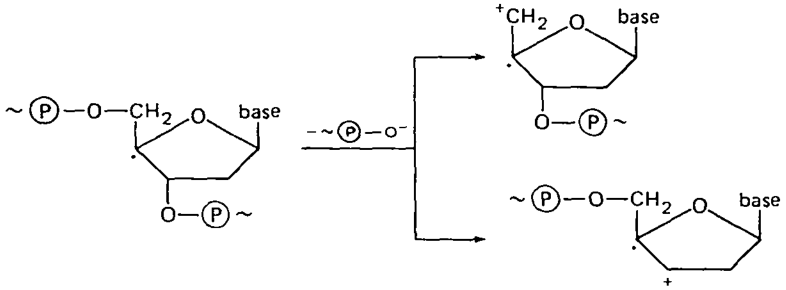
$$R\overset{+}{O}{=}CH\overset{\bullet}{C}H_2$$

the radical cation which one gets from an acetal (reactions 99, 100) is stable against hydrolysis within its life-time with respect to diffusion-controlled second-order decay[290].


(99, 100)

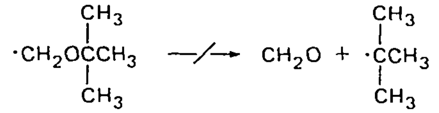
The rate of the elimination of phosphate from such radicals ($R = CH_3$, X = phosphate; reaction 98) strongly depends on the state of protonation of the phosphate group. Going from the dianion to the neutral form, the rate constant of phosphate elimination increases by three to four orders of magnitude with each protonation step ($X = PO_4^{2-}$, $k_{98} \approx 0.1-1\ s^{-1}$; $X = HPO_4^-$, $k_{98} \approx 10^3\ s^{-1}$; $X = H_2PO_4$, $k_{98} \approx 3 \times 10^6$)[289].

The mechanism which has been described here appears also to operate in the formation of OH radical-induced strand breaks of DNA[291-293]. The isolated products are in agreement with the radical at $C_{(4')}$ being their precursor. The DNA strand is broken by the elimination of the phosphate ester group at the 3′ and 5′ positions (reactions 101 and 102).

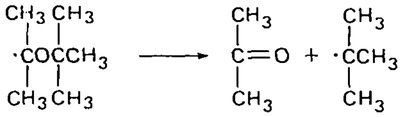

(101)

(102)

The α-alkoxyalkyl radicals undergo fragmentation reactions[294]. If they are suitably substituted the rate of fragmentation can compete successfully with the biomolecular decay processes. For example[295], steady-state conditions can be chosen such that reaction (103) is not observed by ESR spectroscopy, in contrast to reaction (104). The latter appears to be faster by more than two orders of magnitude at room temperature, and only the *t*-butyl radical is seen.


(103)

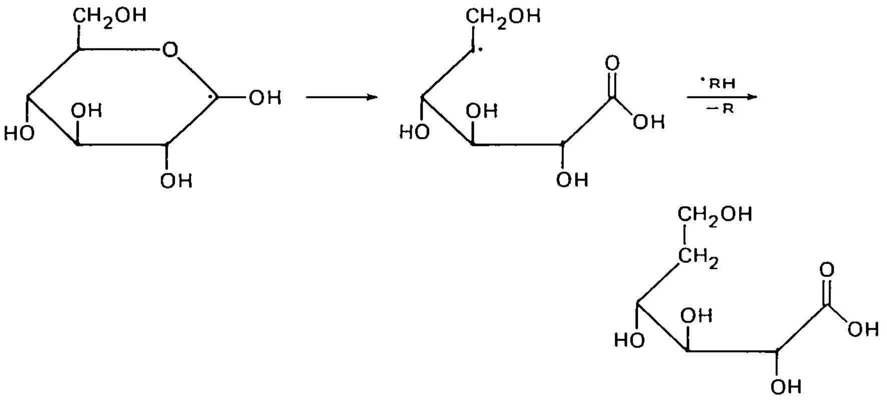
$$\cdot CH_2O\overset{CH_3}{\underset{CH_3}{C}}CH_3 \not\longrightarrow CH_2O + \cdot\overset{CH_3}{\underset{CH_3}{C}}CH_3 \qquad (103)$$


(104)

$$\cdot\overset{CH_3}{\underset{CH_3}{C}}O\overset{CH_3}{\underset{CH_3}{C}}CH_3 \longrightarrow \overset{CH_3}{\underset{CH_3}{C}}{=}O + \cdot\overset{CH_3}{\underset{CH_3}{C}}CH_3 \qquad (104)$$

Similar reactions have been invoked to explain some products in the radiolysis of sugars, e.g. 5-deoxy-D-*xylo*-hexonic acid from D-glucose[273] (cf. Table 8; reactions 105 and 106).

One of the pathways in the radiation-induced scission of the glycosidic linkage of disaccharides[296,297a] and fragmentation of dioxolanes[297b] is also thought to

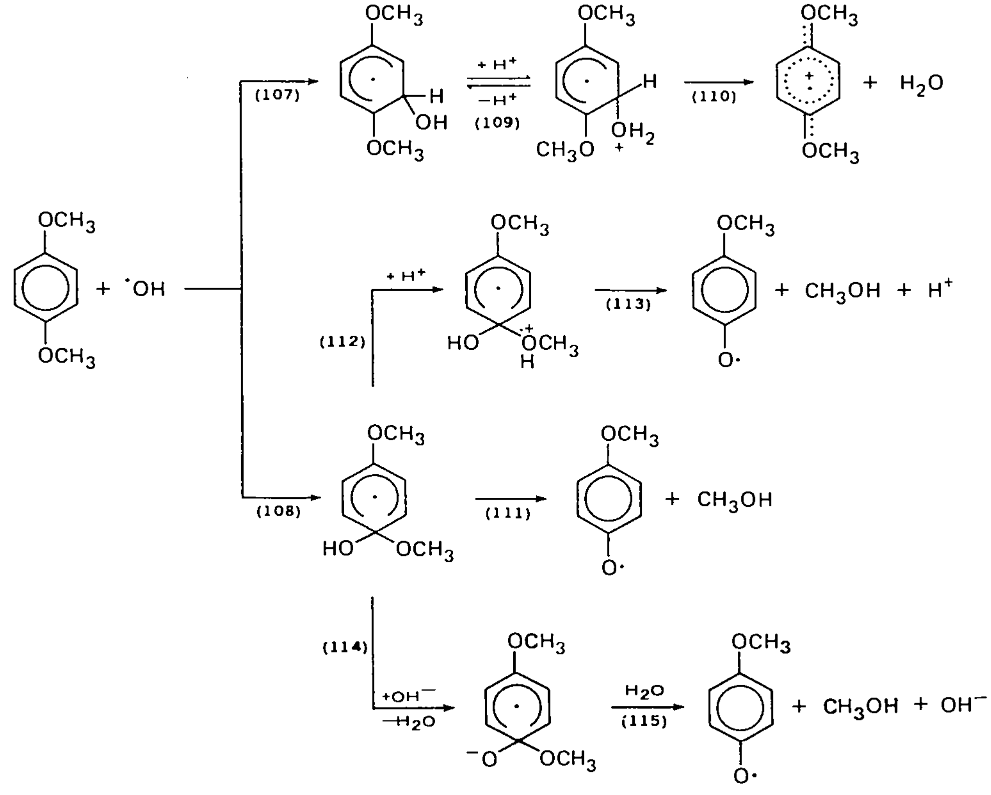


(105, 106)

follow this type of reaction, as do some interesting chain-reactions in crystalline carbohydrates induced by γ-irradiation$^{298-300}$.

4. Phenols and aromatic ethers

The radiation chemistry of phenols$^{301-311}$ and aromatic ethers$^{305,309,310,312-318}$ is different from that of their aliphatic counterparts largely because

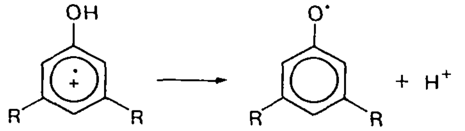

(107)
+H⁺
−H⁺
(109)
(110)
+ H₂O
+ •OH
(112)
+H⁺
(113)
+ CH₃OH + H⁺
(108)
(111)
+ CH₃OH
(114)
+OH⁻
−H₂O
H₂O
(115)
+ CH₃OH + OH⁻

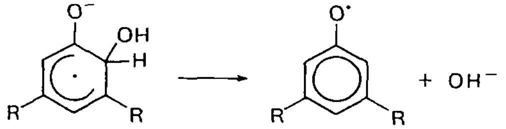
SCHEME 2.

the OH radicals add to the ring but do not abstract hydrogen. Indeed, there appears to be negligible, if any, H abstraction even from the methyl groups of methoxylated benzenes[318]. Because of their electrophilicity the OH radicals add preferentially at positions activated by electron-donating substituents[309-311,317].

Scheme 2 gives an example of the general reaction mechanism. In the chosen case of 1,4-dimethoxybenzene[318] there are two possibilities for OH addition, namely at a free position (reaction 107, see Scheme 2) and at the *ipso* position (reaction 108). The protonation of the OH group and elimination of water leads to the formation of the radical cation (reactions 109 and 110), which is well characterized by its ESR spectrum[318]. The same species is obtained by electron transfer from 1,4-dimethoxybenzene to Tl^{2+}, Ag^{2+} and $SO_4^{\cdot -}$ [316]. The *ipso* OH adduct eliminates methanol in a spontaneous reaction (111) and in an acid- (112 and 113) and base- (114 and 115) catalysed reaction giving a phenoxyl radical. Similar reactions were observed with methoxylated benzoic acids where the formation of the radical cation leads to a zwitterion[315,316].

In the phenol series the radical cations immediately ($t_{1/2} < 1\mu s$)[309] lose a proton and are converted into phenoxyl radicals (reaction 116) which are observed by ESR spectroscopy[308]. Phenoxyl radicals are also formed under basic conditions from the deprotonated dihydroxycyclohexadienyl radicals (reaction 117)[309].


(116)

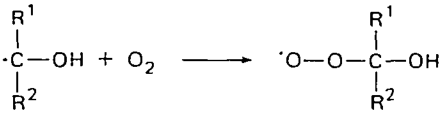

(117)

Among the final products of the reaction of OH radicals with phenols are more highly hydroxylated phenols[301-304,306,311b]. Some of these reactions are also of preparative interest[303]. In the presence of HBr the OH radical can be converted into a Br• atom which also adds to the aromatic ring. Under such conditions 2-bromo-4-nitrophenol, among other products, is formed from 4-nitrophenol[307].

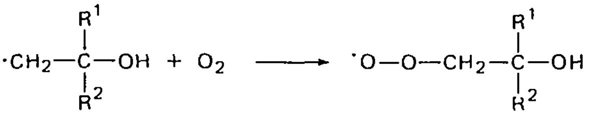
C. Oxygenated Solutions of Saturated Alcohols, Ethers and Carbohydrates

The reactions of peroxyl radicals derived from alcohols can be most conveniently studied using radiation techniques. If N_2O/O_2 (4 : 1 v/v) saturated solutions containing aliphatic alcohols are irradiated with ionizing radiation the majority of the primary radicals are OH radicals (cf. Table 4) which rapidly (cf. Table 5) abstract carbon-bound hydrogen atoms (cf. Table 6). These carbon-centred radicals add molecular oxygen at virtually diffusion-controlled rates (e.g. reactions 118 and 119)[236].

The peroxyl radicals derived from α-hydroxyalkyl radicals and from β-hydroxyalkyl radicals show quite a different behaviour.


(118)

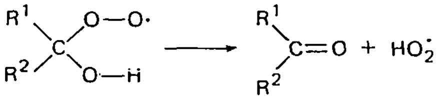
$$\cdot C(R^1)(R^2)-OH + O_2 \longrightarrow \cdot O-O-C(R^1)(R^2)-OH \qquad (118)$$



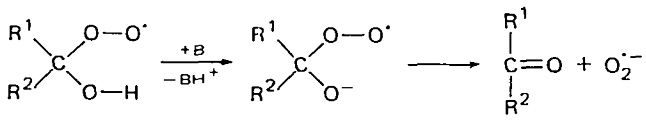
$$\cdot CH_2-\overset{R^1}{\underset{R^2}{C}}-OH + O_2 \longrightarrow {}^{\bullet}O-O-CH_2-\overset{R^1}{\underset{R^2}{C}}-OH$$

(119)

The α-hydroxyalkylperoxyl radicals undergo a unimolecular elimination of $HO_2^{\bullet}$[284,319–324], most likely[321] via a five-membered transition state (reaction 120). The reaction parameters are given in Table 9. There is also a base-catalysed pathway (reactions 121 and 122) which is nearly diffusion-controlled in the case of hydroxide ion acting as the base (Table 9), but is about three orders of magnitude slower with phosphate.

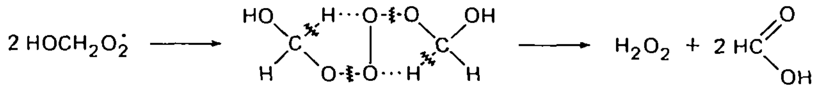


(120)



(121, 122)

In competition to the elimination of $HO_2^{\bullet}$ there is the bimolecular decay of the α-hydroxyalkylperoxyl radicals which is near to diffusion-controlled. Because of the comparatively slow elimination of $HO_2^{\bullet}$ at pH 7 in the case of the $HOCH_2O_2^{\bullet}$ radical (cf. Table 9), the bimolecular decay kinetics and its products can be studied more conveniently than in other cases. It has been shown[325] that the major route (> 80%) leads to formic acid and hydrogen peroxide (reactions 123 and 124). A very short-lived tetroxide and a bicyclic transition state which resembles the monocyclic transition state of the $HO_2^{\bullet}$ elimination has been postulated.

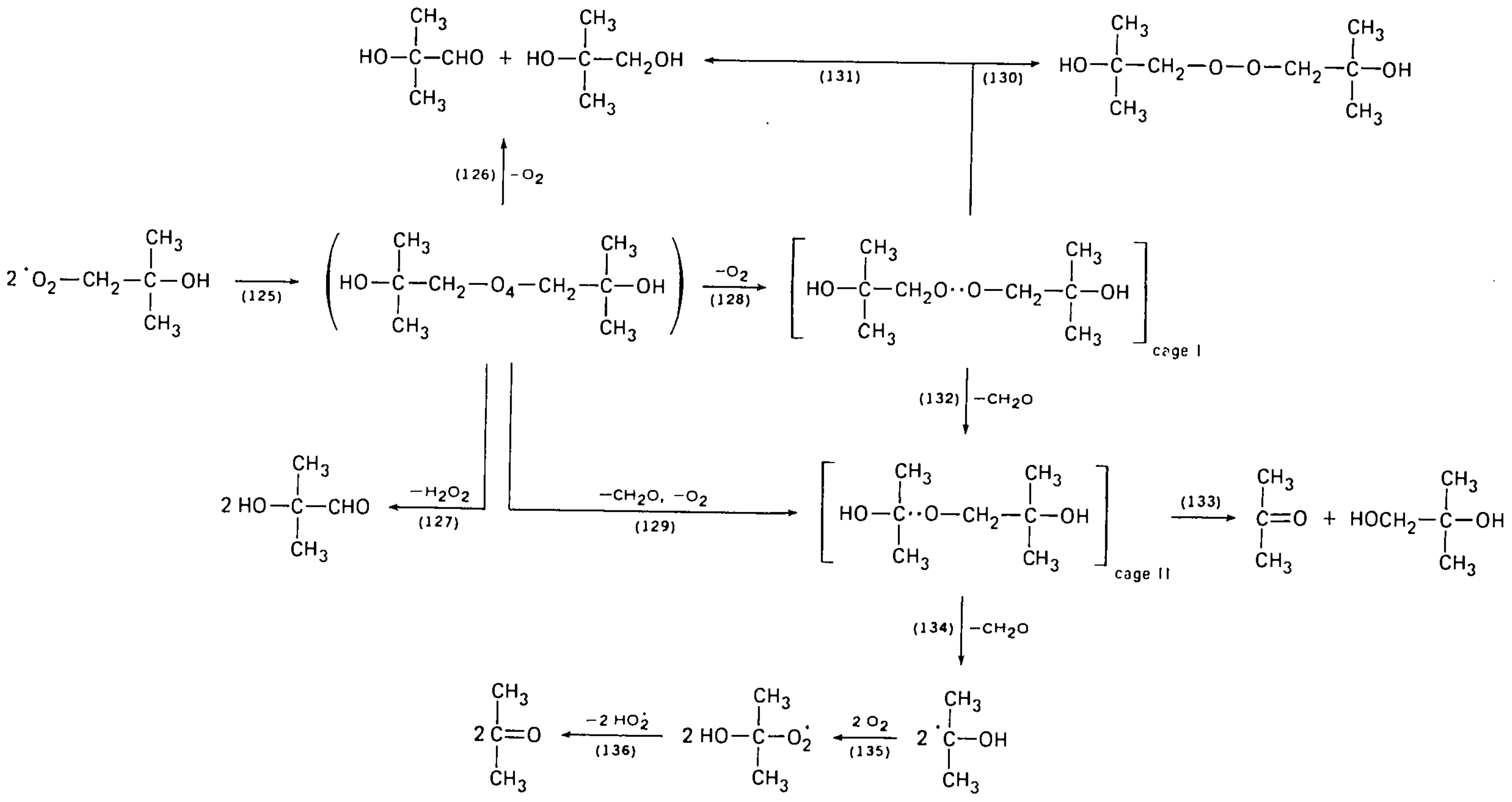


(123, 124)

The β-hydroxyalkylperoxyl radicals decay only by second-order reactions which are also near to diffusion-controlled judging from the data obtained with the peroxyl radical derived from *t*-butanol[326]. A very short-lived tetroxide has been considered to decompose along various pathways as indicated in Scheme 3. Reaction (126) is formulated according to the Russell mechanism (cf. Reference 327), a concerted process with a six-membered transition state. Reaction (128) depicts the elimination of O_2 and the formation of two caged oxyl radicals which either combine to the peroxide (reaction 130) or disproportionate (reaction 131) to give

TABLE 9. Rate constants for the first-order formation of H^+ and $O_2^{\bullet -}$ from $R^1R^2C(OH)OO^{\bullet}$ radicals (k_1) and for the OH^--catalysed reaction (k_2) in aqueous solutions

R^1	R^2	k_1 at 22°C (s^{-1})	Activation energy (kJ mol^{-1})	Preexponential factor (s^{-1})	k_2 at 22°C (M^{-1} s^{-1})
H	H	<10			~15×10^9
H	CH_3	52	60	2×10^{12}	8×10^9
CH_3	CH_3	~670	56	6×10^{12}	5×10^9
OR	OH	>70,000			

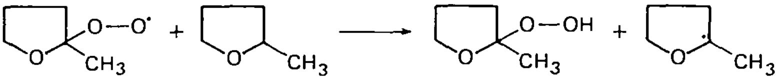

(125)
(126) −O2
(127) −H2O2
(128) −O2
(129) −CH2O, −O2
(130)
(131)
(132) −CH2O
cage I
(133)
cage II
(134) −CH2O
(135) 2 O2
(136) −2 HO2·

SCHEME 3.

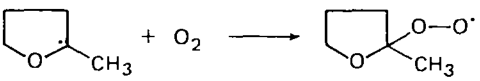
the same products as obtained via the Russell mechanism. The oxyl radicals can also fragment (reactions 132 and 134). Formaldehyde and 2-hydroxypropyl-(2) radicals are the products. Another path to the same products is given by reaction (129). The elimination of H_2O_2 (reaction 127) is similar to the major reaction of two $HOCH_2O_2^{\bullet}$ radicals (reaction 124). The hydroxypropyl-(2) radicals rapidly add oxygen to give the corresponding peroxyl radicals which eliminate $HO_2^{\bullet}$ according to the mechanisms discussed (reactions 120–122). In a pulse radiolysis experiment the kinetics of the overall process have been followed through the change of conductivity caused by the appearance of H^+ and $O_2^{\bullet -}$ [$pK_a(HO_2^{\bullet}) = 4.75$)].

There is very little material on the fate of peroxyl radicals derived from ethers in aqueous solutions as studied by radiation techniques. The decay kinetics of the α-alkoxyalkylperoxyl radicals generated under these conditions are still open to question (cf. References 322 and 328).

The α-alkoxyalkylperoxyl radicals readily undergo a chain autoxidation reaction[324,329] (e.g. reactions 137 and 138). This reaction is apparently not given at neutral pH by the α-hydroxylalkylperoxyl radicals because of their fast $HO_2^{\bullet}$ elimination (reactions 120–122). At neutral pH this leads to $O_2^{\bullet -}$, a species of low H-abstractive power which is incapable of propagating a chain[324,330].



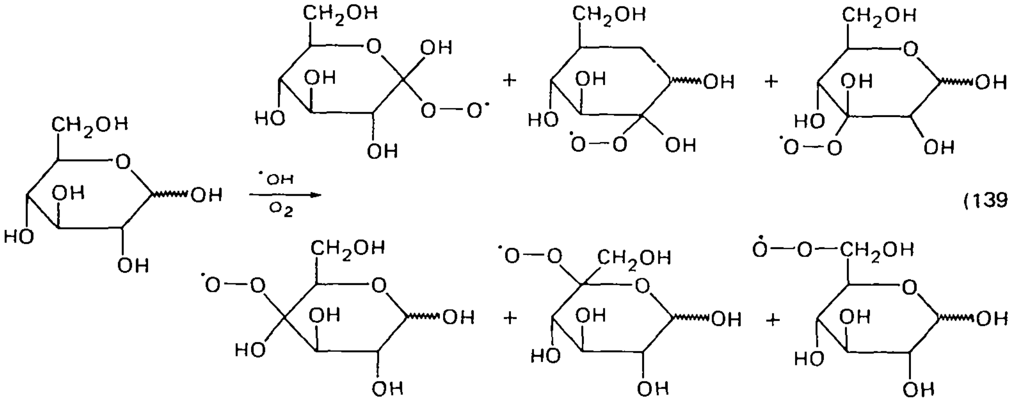
(137)



(138)

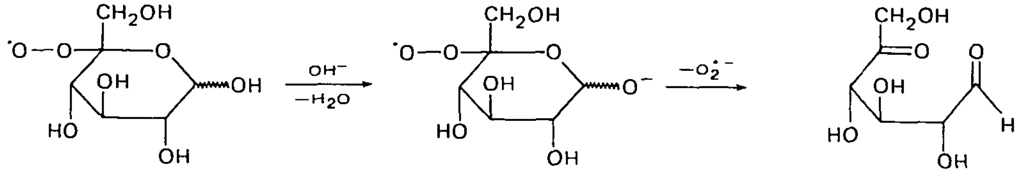
Because of the fast reaction of O_2 with the radicals formed by OH attack on carbohydrates the transformation reactions of the sugar radicals (see above) are fully suppressed in neutral oxygen- or air-saturated solutions. Instead, the reactions of the corresponding peroxyl radicals occur.

As discussed above, the high reactivity of the OH radical leads to an approximately random abstraction of carbon-bound hydrogen atoms from carbohydrates, and the radiolysis of D-glucose in N_2O/O_2-saturated aqueous solutions leads to six different peroxyl radicals with about equal yields (reaction 139)[284].

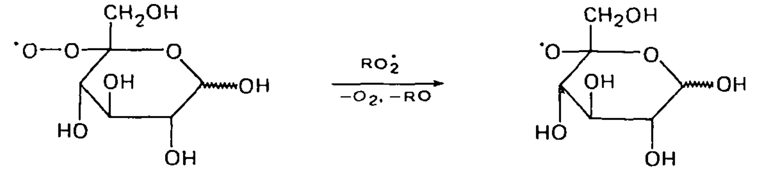


(139)

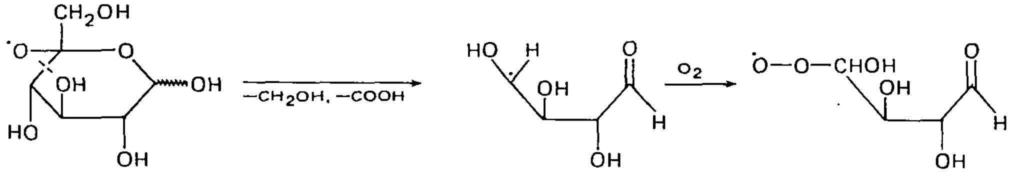
Five of these (those at $C_{(1)}$ to $C_{(4)}$ and $C_{(6)}$) are α-hydroxyalkylperoxyl radicals which readily eliminate $HO_2^{\bullet}$ (reactions 120–122). Especially fast ($k > 7 \times 10^4\ s^{-1}$) is the $HO_2^{\bullet}$ elimination from the peroxyl radical at $C_{(1)}$. But even the peroxyl radical at $C_{(5)}$ may, with base catalysis, eliminate $HO_2^{\bullet}$ (reactions 140 and 141). The corresponding carbonyl compounds are thus the major products (see Table 8). In competition with this $HO_2^{\bullet}$ elimination the sugar peroxyl radicals undergo reactions second order in peroxyl radicals. The longest-lived peroxyl radical, that at $C_{(5)}$, shows most clearly such a reaction (reactions 142–145). The reaction sequence is similar to that discussed above (cf. Scheme 3). The end-product is L-*threo*-tetrodialdose (see Table 8). As expected the *erythro* isomer is formed from the peroxyl radical at $C_{(5)}$ of D-ribose[331]. Similar reaction sequences have been considered for an explanation of some products from the radiolysis of oxygenated solutions of ribose-5-phosphate[332], *N*-acetylglucosamine[333] and thymidine[334]. In DNA the peroxyl radical at $C_{(5')}$ has been considered[335] to give rise to DNA strand breaks via such a mechanism, and that at $C_{(2')}$ to an alkali-labile[336] site (for a review see Reference 293).



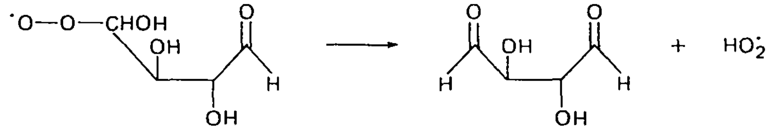
(140, 141)



(142)



(143, 144)



(145)

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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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CHAPTER 24

Radiation chemistry of thiols, sulphides and disulphides

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I. INTRODUCTION

The observation that sulphhydryl compounds can to some extent prevent radiation damage *in vivo*[1,2] has stimulated considerable interest in the radiation chemistry of these compounds. Research in this field has been further motivated by the fact that thiol and disulphide groups, although there are only relatively few of them along the protein chain, are nevertheless crucial to the proper functioning of many enzymes. Thiol and disulphide groups are among the most radiation-sensitive functions in proteins, and it has been suggested that disulphide cleavage can result in enzyme inactivation. In this and other contexts radiation techniques have helped to shed some light on the nature of the active sites[3].

The radiolysis of thiols and disulphides has been reviewed in a previous volume of this series[4a], with an emphasis on aqueous solutions (cf. also Reference 4b). The radiation chemistry of thiols and sulphides has also been studied in nonaqueous systems, neat and in solution, spectroscopically and by product analysis. Some of this work has been discussed in a number of reviews[5–9].

At first glance, the radiation chemistry of thiols may seem deceptively simple. Because the sulphhydryl hydrogen is easily abstracted by most radicals, the alkylthiyl radical is the most frequent radical species in such systems. Their disproportionation/combination ratios tend to be small (cf. Chapter 22), and their main product therefore is the disulphide. However, the scope of thiol radiation chemistry is wide compared to that of alcohols because of several features relating to the sulphur atom. Thiols are more acidic but also seem to undergo protonation more easily than alcohols (at least in the gas phase[10]). With sulphides, this basicity is reflected in the existence of stable trialkylsulphonium compounds such as, for instance, $[SR_3]^+\ SR^-$ and $([SR_3]^+)_2\ S^{2-}$ which are stoichiometrically a complex of several sulphide molecules[11].

In further contrast to alcohols, ethers and peroxides, the divalent sulphur atom in their sulphur analogues manifests a readiness to acquire a tetravalent nature, in that complex radicals $R_3S^{\bullet}$ often appear as intermediates leading in some cases to radical chain reactions. The easy formation and relatively long life-time of radical cations (e.g. $RSR^{\bullet+}$, $RSSR^{\bullet+}$) is another feature of the sulphur compounds not observed with their oxygen analogues. The variety of radical species often present in such systems in fact seems sometimes to have led to the misassignment of ESR signals to the simplest of these radicals, thiyl[12], whose spectrum is often obscured by the spectra of the other species. However, thiyl has been detected by spin trapping[13–17].

It will be shown that radiation techniques have already considerably expanded the knowledge of the chemistry of carbon-bound sulphur in its lower unstable oxidation states, even though all the complexities are far from being fully understood, especially in nonaqueous media. For this reason mechanisms which are suggested in the section on nonaqueous systems have to be taken with more reservations than those proposed in the aqueous systems where far better kinetic data are available.

II. RADIOLYSIS IN NONAQUEOUS MEDIA

A. Thiols

The present section deals with the radiolysis of thiols (neat liquid and solid[15,17–29], nonaqueous solutions[19–22,26,30–38], gas phase[39–44]), and where it seemed appropriate mass-spectrometric data[44–50] (cf. Reference 10) have been used to interpret the results.

Isotopically labelled thiols have been employed in hydrocarbon radiolysis as a probe to distinguish between the contributions of molecular nonionic primary processes such as reaction (1) and free-radical processes (reactions 2 and 3), in the hydrocarbon (R^1H). The main radical processes involving the thiol and its radicals in saturated hydrocarbon solution are given by reactions (4)–(10). Processes (9)

$$\mathrm{R^1H} \xrightarrow{\gamma} \mathrm{H_2} + \text{olefin} \tag{1}$$

$$\mathrm{R^1H} \xrightarrow{\gamma} {}^{\bullet}\mathrm{R^1} + \mathrm{H^{\bullet}} \tag{2}$$

$$\mathrm{R^1H} \xrightarrow{\gamma} \mathrm{R^1H^{+\bullet}} + e^- \tag{3}$$

$${}^{\bullet}\mathrm{R^1} + \mathrm{R^2SH} \longrightarrow \mathrm{R^1H} + \mathrm{R^2S^{\bullet}} \tag{4}$$

$$\mathrm{H^{\bullet} + R^2SH \longrightarrow H_2 + R^2S^{\bullet}} \tag{5}$$

$$\mathrm{H^{\bullet} + R^2SH \longrightarrow {}^{\bullet}R^2 + H_2S} \tag{6}$$

$$\mathrm{R^2S^{\bullet} + R^2S^{\bullet} \longrightarrow R^2SSR^2} \tag{7}$$

$$\mathrm{R^2S^{\bullet} + {}^{\bullet}R^1 \longrightarrow R^2SR^1} \tag{8}$$

$$\mathrm{R^2S^{\bullet} + R^2SH \underset{(10)}{\overset{(9)}{\rightleftharpoons}} R^2SS^{\bullet}(H)R^2} \tag{9, 10}$$

and (10) are an example[17] of the tendency of complex radicals to be formed in the radiolysis of organosulphur systems. The optical absorption spectrum of a species thought to be EtSS(H)Et has been observed[38]; the existence of the homologous species $\mathrm{RSSR_2^{\bullet}}$ would not seem improbable[17]. The homolytic displacement reaction (6) has recently been established in the photolysis of thiols[51] and may have to be taken into consideration in radiolytic systems as well.

In olefinic hydrocarbons chain processes occur such as (11) and (12) which have been shown to lead to *G*-values† of the order of 10^5 for the isomerization of *cis*- into *trans*-2-butene[52]. The reverse reaction is also observed and has a *G*-value three to ten times smaller.

$$\mathrm{RS^{\bullet} + Et{-}CH{=}CH{-}Et \underset{(12)}{\overset{(11)}{\rightleftharpoons}} Et{-}CH(SR){-}\dot{C}H{-}Et} \tag{11,12}$$

In the gaseous thiol/carbon monoxide system[53] a chain-reaction of a different kind appears to be operating at elevated temperatures through the addition of the thiyl radical to carbon monoxide (reaction 13). The resulting radical loses carbon oxide sulphide (reaction 14), and the alkyl radical propagates the chain by hydrogen abstraction from the thiol (reaction 4).

$$\mathrm{RS^{\bullet} + CO \longrightarrow (R{-}S{=}C{=}O)^{\bullet}} \tag{13}$$

$$\mathrm{(R{-}S{=}C{=}O)^{\bullet} \longrightarrow R^{\bullet} + S{=}C{=}O} \tag{14}$$

As discussed so far, the reactions of thiols in the radiolytic systems are the same as in other free-radical generating systems. The formation of charged species (radical cations and electrons) by the absorption of ionizing radiation (cf. Chapter 23) brings about new aspects. Thiols appear to be able to scavenge positive charges (reactions 15 and 16). Their gas-phase ionization potential (*I*) is lower and their

$$\mathrm{R^1H^{+\bullet} + R^2SH \longrightarrow {}^{\bullet}R^1 + R^2RSH_2^+} \tag{15}$$

$$\mathrm{R^1H^{+\bullet} + R^2SH \longrightarrow R^1H + R^2SH^{+\bullet}} \tag{16}$$

gas-phase proton affinity (*P*) is perhaps slightly higher than the corresponding properties of alcohols; $I(\mathrm{EtSH}) = 9.28$ eV, $I(\mathrm{EtOH}) = 10.48$ eV[54]; $P(\mathrm{MeSH}) = 770\ \mathrm{kJ\ mol^{-1}}$, $P(\mathrm{MeOH}) = 760\ \mathrm{kJ\ mol^{-1}}$ [55]. The same holds with respect to saturated hydrocarbons but may not always be the case with unsaturated ones[56].

The scavenging of the positive charge from a hydrocarbon radical cation, $\mathrm{R^1H^{+\bullet}}$ (reactions 15 and 16), may be followed by a proton transfer between thiol radical cation and thiol (reaction 17) or the formation of a complexed radical cation (reaction 18). Complexed radical cations from sulphides, $\mathrm{(RSR)_2^{+\bullet}}$, are well estab-

---

†The quantity *G*, called *G*-value, is defined through $G = N/E$, unit $(100\ \mathrm{eV})^{-1}$, where *N* is the number of radiolytically generated species or events of whatever kind caused by the absorbed radiation energy *E*.

$$R^2SH^{+\bullet} + R^2SH \longrightarrow R^2S^\bullet + R^2SH_2^+ \qquad (17)$$

$$R^2SH^{+\bullet} + R^2SH \longrightarrow (R^2SH)_2^{+\bullet} \qquad (18)$$

lished species[57] (see below). They are the structural analogues of $(RSH)_2^{+\bullet}$. It can be estimated from thermochemical data that reaction (15) tends to be more exothermic than reaction (16) but one might expect that its activation energy be higher. Reaction (17) appears close to thermoneutral (see below). Formation of the complex $(RSH)_2^{+\bullet}$ (reaction 18) is considered[17] as an alternative to proton loss (reaction 17). In fact the latter appears to be unimportant, because in low-temperature glasses the thiyl radical is not seen unless the matrix is bleached or annealed[23,38]. Reaction (17) has also been excluded in the radiolysis of thiophenol[19].

The train of events undergone by the negative charge is not clear. In hydrocarbons containing alcohols it is known that the electron becomes solvated within a solute domain[58]. The smaller polarity of the thiol molecule [dielectric constants: $\epsilon(EtSH) = 6.9$; $\epsilon(EtOH) = 24.3$[59]] would make a similar effect (reaction 19) energetically less rewarding but not impossible. Also, owing to their relatively low polarity thiols have a lower tendency than alcohols to form domains in hydrocarbon solution. Other possibilities could be suggested (reactions 20–22).

$$e^- + n\,RSH \longrightarrow e^-_{solv} \qquad (19)$$

$$e^- + RSH \longrightarrow RS^- + H^\bullet \qquad (20)$$

$$e^- + RSH \longrightarrow R^\bullet + {}^-SH \qquad (21)$$

$$e^- + RSH \longrightarrow RSH^{\bullet -} \qquad (22)$$

Thermochemical argument indicates that reactions (20) and (21) should be endothermic in the gas phase, reaction (21) to a lesser extent than reaction (20)[49,50] However, the appearance potential of reaction (20) is found to be lower than that of (21)[44]. In methanolic and aqueous glasses reaction (21) has been shown to occur[17], but there is no evidence that it occurs in a hydrocarbon matrix[38] or in the neat thiol[17] at 77 K. This would leave $RSH^{-\bullet}$ as the most likely carrier of negative charge in non-aqueous media. In fact the radical anion $RSH^{\bullet -}$ is supposed to have been observed by ESR spectroscopy in the low-temperature radiolysis of thiols[23,28,38,60,61] (but cf. Reference 17) whereas the trapped electron was not seen[38,61].

In view of the foregoing, there are many possible neutralization reactions. In particular, reaction (23) has been discussed to explain the growth in the thiyl ESR

$$RSH^{-\bullet} + RSH^{+\bullet} \longrightarrow RSH + RS^\bullet + H^\bullet \qquad (23)$$

signal during annealing of γ-irradiated thiol glasses while the signals assigned to $RSH^{-\bullet}$ and $RSH^{+\bullet}$ diminish[26,38].

The radiolysis of neat thiols awaits further investigations, and the mechanisms presented here are largely reasonable extrapolations from data obtained with similar systems. Thus, reactions (24)–(31) should be considered together with the above-mentioned ones. Reactions such as (25) and (26) are observed in the photolysis of thiols, the former predominating by roughly an order of magnitude (see Chapter 22). In the radiolysis[19,39] the situation may be not much different considering the similar ratios of disulphide and H_2S formation.

Reaction (27) is an intriguing one. There seems to be ESR spectroscopic evidence that it does not occur in methyl, ethyl, propyl and butyl thiols, but from pentyl

$$\mathrm{RSH} \xrightarrow{\gamma} \mathrm{RSH}^{+\bullet} + e^- \qquad (24)$$

$$\mathrm{RSH} \xrightarrow{\gamma} \mathrm{RS}^{\bullet} + \mathrm{H}^{\bullet} \qquad (25)$$

$$\mathrm{RSH} \xrightarrow{\gamma} \mathrm{R}^{\bullet} + {}^{\bullet}\mathrm{SH} \qquad (26)$$

$$\mathrm{RSH} \xrightarrow{\gamma} {}^{\bullet}\mathrm{R(-H)SH} + \mathrm{H}^{\bullet} \qquad (27)$$

$$\mathrm{RSH}^{+\bullet} + \mathrm{RSH} \longrightarrow {}^{\bullet}\mathrm{R(-H)SH} + \mathrm{RSH}_2^{+} \qquad (28)$$

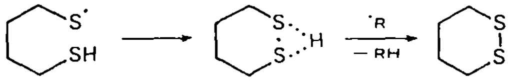
$$\mathrm{HS}^{\bullet} + \mathrm{RSH} \longrightarrow \mathrm{RS}^{\bullet} + \mathrm{H_2S} \qquad (29)$$

$$ {}^{\bullet}\mathrm{R(-H)SH} + \mathrm{RSH} \longrightarrow \mathrm{RSH} + \mathrm{RS}^{\bullet} \qquad (30)$$

$$\mathrm{RS}^{\bullet} + {}^{\bullet}\mathrm{SH} \longrightarrow \mathrm{RSSH} \qquad (31)$$

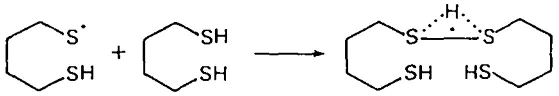
thiol onward an increasing proportion of the radicals observed appear to be alkyl thiol radicals ${}^{\bullet}\mathrm{R(-H)SH}$[24,25,29]. It has been surmised that efficient energy transfer down the alkyl chain to the sulphhydryl or other accepting groups is possible only if the distance to be spanned is less than about five carbon links[24,62,63]. Another implication of the absence of these radicals including the thiol α-radical is that reaction (28) ought to be even less important than reaction (17) (if, indeed, they occur at all in the condensed state). In the gas phase, it has been shown[46] with methanethiol that reactions (17) and (28) occur at a ratio of about 10 : 1; epithermal ions are perhaps involved. This is in contrast to the alcohols where proton transfer is about equally likely from the oxygen and the α-carbon atom[64].

Interesting results have been obtained with 1,4-butanedithiol[21]. In dilute hydrocarbon solutions 1,2-dithiane was formed in high yield (reactions 32 and 33). Its



(32, 33)

yield was shown to decrease with increasing dithiol concentration while that of disulphidic compounds of higher molecular weight increased. One might suggest a cyclization reaction (reaction 32) to occur in competition with bimolecular addition (reaction 34), the latter being favoured at high dithiol concentrations.



(34)

In the presence of oxygen (cf. References[5,6,8,33,65]), initial *G*-values of thiol consumption rise strongly with falling dose rate and increasing thiol concentration, thus suggesting a chain-reaction. A considerable part of the thiol consumed is transformed into the disulphide, but other more highly oxidized products which are certainly formed have not been measured.

B. Disulphides

In studies on the formation and properties of radicals and radical ions from the radiolysis of organic disulphides in low-temperature glasses[28,37,38,66–70] and in the gas-phase[44,71] it has been shown that disulphides are remarkably good acceptors of various charged and radical species in nonaqueous media. In hydrocarbon solution the efficiency of disulphide as electron scavenger[72] is comparable to that of sulphur hexafluoride and other good electron scavengers[73], and as hydrogen atom scavenger, to that of ethylene. There is no doubt that some of the positive charge is trapped as well, probably by disulphide radical cation, and perhaps also by sulphonium ion formation (reactions 35 and 36).

$$R^1H^{\cdot+} + R^2SSR^2 \longrightarrow R^1H + R^2SS\dot{R}^{+2} \qquad (35)$$

$$R^1H^{\cdot+} + R^2SSR^2 \longrightarrow {}^{\cdot}R^1 + R^2SS(H)\overset{+}{R}{}^2 \qquad (36)$$

In dilute cyclohexane solution diethyl and dipropyl disulphides rapidly equilibrate under the influence of ionizing radiation[72], and it may be inferred[74] that thiyl radicals are also present, generated via reactions (37)–(43). Reactions (40) and (41) explain the formation of thiol[72]. The other product, cyclohexyl propyl sulphide RSPr, is formed[17] in reactions (42) and (43). The mixed disulphide is formed[72] via reactions (44)–(46). In the presence of thiols a similar transposition takes place[72] via reactions (47) (cf. Reference 70) and (48).

$$PrSSPr + e^- \longrightarrow PrSSPr^{\cdot -} \qquad (37)$$

$$PrSSPr^{\cdot -} \underset{(39)}{\overset{(38)}{\rightleftharpoons}} PrS^{\cdot} + PrS^- \qquad (38, 39)$$

$$PrSSPr + H^{\cdot} \longrightarrow PrS\dot{S}(H)Pr \qquad (40)$$

$$PrS\dot{S}(H)Pr \longrightarrow PrS^{\cdot} + PrSH \qquad (41)$$

$$PrSSPr + R^{\cdot} \longrightarrow PrS\dot{S}(R)Pr \qquad (42)$$

$$PrS\dot{S}(R)Pr \longrightarrow PrS^{\cdot} + RSPr \qquad (43)$$

$$PrS^{\cdot} + EtSSEt \longrightarrow EtS\dot{S}(SPr)Et \qquad (44)$$

$$PrS^- + EtSSEt^{\cdot+} \longrightarrow EtS\dot{S}(SPr)Et \qquad (45)$$

$$EtS\dot{S}(SPr)Et \longrightarrow EtSSPr + EtS^{\cdot} \qquad (46)$$

$$PrS^{\cdot} + EtSH \longrightarrow PrS\dot{S}(H)Et \qquad (47)$$

$$PrS\dot{S}(H)Et \longrightarrow EtS^{\cdot} + PrSH \qquad (48)$$

There is a strong reduction of cyclohexane consumption, from $G = 7.3$ in the pure solvent to about half this value in a solution 0.005 M in the disulphide[72]. On the other hand, G(disulphide consumption) is about unity at this concentration. The possibility of the formation of undetected sulphur-containing products has been considered. The apparent discrepancy could also imply a protective action, possibly via processes such as (49)–(51). Radical cation complexes of the type $[RSSR]_2^{+\cdot}$ have been observed in the gas phase[71] and in solid media[38].

$$RSSR^{+\cdot} + RSSR^{-\cdot} \longrightarrow 2\,RSSR \qquad (49)$$

$$RSSR^{+\cdot} + RSSR \rightleftharpoons [RSSR]_2^{+\cdot} \qquad (50)$$

$$[RSSR]_2^{+\cdot} + RSSR^{-\cdot} \longrightarrow 3\,RSSR \qquad (51)$$

C. Sulphides

The present information on the radiolysis of sulphides (nonaqueous liquid[75-80] and solid[20,37,38,70,81-86,87a] conditions; mass-spectrometric studies[45,47,51,71,87b]) reveals little about the nature of the final products. Apart from studies on thiophene[75,77] the only product that seems to have been measured is hydrogen[20,81-83]. It is noted that hydrogen formation declines as the atomic fraction of sulphur in the system is increased either intramolecularly by employing lower alkyl homologues [from $G(H_2) = 1.5$ in $(C_{11}H_{23})_2S$ to 0.14 in $(CH_3)_2S$)], or in an alkane/dialkyl sulphide mixture by increasing the sulphide content[20,83]. It is not yet ascertained whether or not the cleavage of the carbon–sulphur bond plays a major role. This reaction has been shown to be the main process in the photolysis of sulphides (see Chapter 22). Carbon-centred radicals have been observed by ESR spectroscopy of glassy radiolysed samples of sulphides where apparently sulphide radicals $^{\bullet}R(-H)SR$ of all possible types are being formed[20,81,82]. 2-Methyltetrahydrothiophene, in contrast to 2-methyltetrahydrofuran, does not physically trap electrons[84]. Instead, anion radicals are formed which seem to be ring-opened forms of the type $R_2\dot{C}{-}S^-$. Dissociative electron capture by dimethyl sulphide[44]

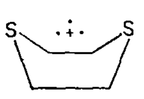
$$CH_3SCH_3 + e^- \longrightarrow CH_3S^- + \dot{C}H_3 \tag{52}$$

$$(CH_3)_2S^{+\cdot} + (CH_3)_2S \longrightarrow (CH_3)_2SH^+ + {}^{\cdot}CH_2SCH_3 \tag{53}$$

(reaction 52) is endothermic in the gas phase but occurs in methanolic glass[70]. Proton transfer (reaction 53) appears to be slightly endothermic in the gas phase[71] which would suggest that, until it is neutralized, the positive charge remains in the

$$R_2S^{+\cdot} + R_2S \rightleftharpoons [R_2SSR_2]^{+\cdot} \tag{54}$$

form of the original radical cation of its complex $(R_2S)_2^{\cdot+}$ (reaction 54). Optical, ESR, mass spectroscopical, and product studies have adduced evidence for such complexes[12,38,57,70,79,80a,88,89]. From 1,4-dithiane an intramolecular cation-radical complex (1) is formed by electron removal that absorbs near 600 nm. An intermolecular complex (2) is formed from 1,3-dithiane in nonpolar media which absorbs at the remarkably long wavelength of 750 nm[79,80a].



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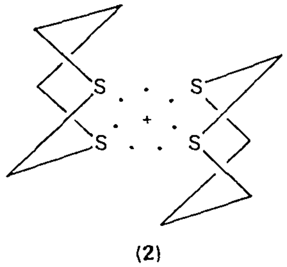

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III. RADIOLYSIS IN AQUEOUS SOLUTIONS

A. Radiolysis of Water

The primary processes in the radiolysis of aqueous solutions have been discussed in some detail in an earlier review[4] and in a preceding chapter of this volume (Chapter 23). In the latter a compilation of the *G*-values of the primary species under various conditions can be found. A brief account is given here.

The primary free radical species formed in the radiolysis of water are OH radicals, solvated electrons (e_{aq}^-) and H atoms. Protons and hydroxide ions as well as some molecular hydrogen and hydrogen peroxide are also formed (reaction 55). The solvated electrons can be converted into OH radicals by N_2O (reaction 56). In acidic solutions the solvated electron is converted into a hydrogen atom (reaction 57). Hydroxyl radicals, e_{aq}^-, and H atoms readily react with the title

$$H_2O \xrightarrow{\gamma} {}^{\cdot}OH, e_{aq}^-, H^{\cdot}, H^+, OH^-, H_2, H_2O_2 \tag{55}$$

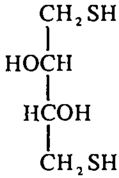
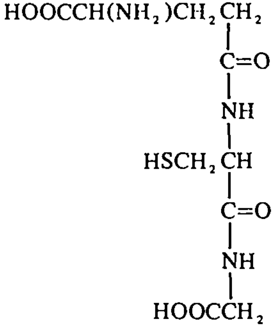
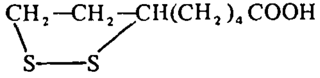
$$e_{aq}^- + N_2O \longrightarrow {}^{\cdot}OH + N_2 + OH^- \tag{56}$$

$$e_{aq}^- + H^+ \longrightarrow H^{\cdot} \tag{57}$$

compounds. There is now a wealth of rate constants available (for compilations see: OH radicals[90,91], solvated electrons[92,93], H atoms[94]). In the following sections the reactions of the three water-derived radicals with the title compounds and the subsequent free-radical reactions are discussed.

In order to aid the reader, the formulae and trivial names of some sulphur-containing compounds of biochemical interest that are mentioned below are listed in Table 1.

TABLE 1. Trivial names and formulae of sulphur-containing compounds mentioned in the text

Name	Formula
Cysteamine	$HSCH_2CH_2NH_2$
Cysteine	$HSCH_2CH(NH_2)COOH$
Cystine	$(SCH_2CH(NH_2)COOH)_2$
1,4-Dithiothreitol	 $HSCH_2CH(OH)CH(OH)CH_2SH$
Gluathione(= glutamylcysteinylglycine)	 $HOOCCH(NH_2)CH_2CH_2C(=O)NHCH(CH_2SH)C(=O)NHCH_2COOH$
Lipoic acid	
Methional	$CH_3SCH_2CH_2CHO$
Methionine	$CH_3SCH_2CH_2CH(NH_2)COOH$
Penicillamine	$HSC(CH_3)_2CH(NH_2)COOH$

B. Deoxygenated Solutions

1. *Thiols*

Thiols rapidly react with the hydrated electron. The rate[95,96] is near to diffusion-controlled if the thiol is neutral or positively charged [$k(e_{aq}^- + RSH) \sim 10^{10}$ M^{-1} s^{-1}]. The rate constant drops if the electron reacts with a negatively charged species. It appears not to make much difference whether an adjacent carboxyl group is dissociated, or the sulphydryl group itself. A further strong reduction in the reaction rate is observed with doubly negatively charged species. Under these conditions the rate constants $k(e_{aq}^- + RSH)$ drop to ~3 x 10^8 M^{-1} s^{-1}. Two processes are conceivable (reactions 58 and 59). Because of the lower dissociation

$$RSH + e_{aq}^- \longrightarrow R^{\cdot} + SH^- \qquad (58)$$

$$RSH + e_{aq}^- \longrightarrow RS^- + H^{\cdot} \qquad (59)$$

energy of the C—S bond compared to that of the S—H bond one might expect reaction (58) to be favoured over reaction (59). Indeed, it has been suggested[95] that only reaction (58) occurs and that reaction (59) can be neglected. However, there is evidence that at least in 2-hydroxyethanethiol[97] and in 2-aminoethanethiol(cysteamine)[98] reaction (59) may play a considerable role. This is seen from the fact that $G(H_2S)$ (from reaction 58) does not reach the expected value of 2.7, but only 1.65 in the case of 2-hydroxyethanethiol and 2.0 with 2-aminoethanethiol. There are some more cases which, however, do not show such a strong effect. It is recalled that dissociative electron capture similar to reaction (59) has been observed in the gas phase (see above).

In acidic solutions the hydrated electron is converted into H atoms (reaction 57). Under these conditions the reaction of the H atoms can conveniently be studied. There are two major processes (reactions 60 and 61). The overall rate constant

$$RSH + H^{\cdot} \longrightarrow H_2 + RS^{\cdot} \qquad (60)$$

$$RSH + H^{\cdot} \longrightarrow R^{\cdot} + H_2S \qquad (61)$$

$k_{(60+61)}$ is around 10^9 M^{-1} s^{-1} for a number of thiols studied. The ratio k_{60}/k_{61} can be derived from the ratio $G(H_2)/G(H_2S)$ if $G(H_2)$ is corrected for the 'molecular H_2' from reaction (55). The k_{60}/k_{61} ratio is near five[99,100] for primary thiols, but decreases for secondary (1.8[101] and 0.55[99], observed for two different thiols) and tertiary thiols (0.82[101] and 0.44[99], observed for two different thiols). It has been reported[102] that $G(H_2S)$ increases with increasing temperature. This effect has been reinvestigated[101] but could not be reproduced with either cysteine or penicillamine. Thus it appears that k_{60}/k_{61} is not much temperature-dependent. Reaction (60) can be interpreted as a hydrogen abstraction reaction whereas reaction (61) constitutes a displacement reaction. However, it might well be that both reactions have a common precursor, a hydrogen atom adduct radical (reaction 62) in which the sulphur exhibits a three-electron bond. It has already been

$$RSH + H^{\cdot} \longrightarrow R\dot{S}H_2 \qquad (62)$$

emphasized (and further examples will be shown below) that there is increasing evidence for organic sulphur compounds to be able to complex radicals before decomposing into other free-radical species.

The hydroxyl radical has been shown[103] to react with thiols (reaction 63) at virtually diffusion-controlled rates [$k_{63} = (1-2) \times 10^{10}$ M^{-1} s^{-1}]. The reaction with thiolates (reaction 64) is generally slower by a factor of two[103]. There is good evidence from ESR spectroscopic studies[104] that carbon-centred radicals are also formed from thiols on OH attack (reaction 65).

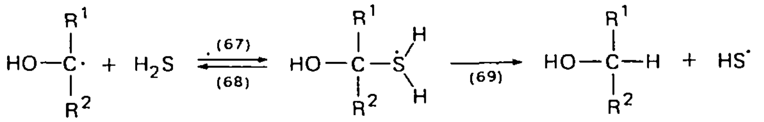
$$^{\cdot}OH + RSH \longrightarrow H_2O + RS^{\cdot} \qquad (63)$$

$$^{\cdot}OH + RS^- \longrightarrow OH^- + RS^{\cdot} \qquad (64)$$

$$^{\cdot}OH + RSH \longrightarrow H_2O + {}^{\cdot}(R{-}H)SH \qquad (65)$$

$$^{\cdot}R + RSH \longrightarrow RH + RS^{\cdot} \qquad (66)$$

Rate constants of the reactions of some radicals with various thiols (reaction 66) are summarized in Table 2. These rate constants mostly cluster around 10^8 M^{-1} s^{-1}. However, there are a number of other radicals which show rate constants smaller than 10^7 M^{-1} s^{-1}, among them the OH adduct radicals of uracil and thymidine[105]. This must be borne in mind when the radiation protection of cellular DNA by sulphhydryl compounds is discussed[106] (for a review see Reference 107). It appears worth noting that the 2-hydroxy-2-propyl radical derived from isopropanol reacts considerably faster than the hydroxymethyl radical derived from methanol. The 1-hydroxyethyl radical (derived from ethanol) lies in between. This finding is somewhat surprising. In fact, one might expect the reverse order, because in general hydrogen is more difficult to abstract from methanol than from isopropanol, and therefore the reduction of the corresponding radical should be easier for hydroxymethyl than for 2-hydroxy-2-propyl. Attempts to detect a short-lived complex such as formed by H_2S[108] (reactions 67–69), have failed with thiols[103]. 2-Hydroxy-2-propyl is electron-richer than the hydroxymethyl radical and therefore it should undergo formation of the tetravalent complex $RR'\dot{S}H$ more readily, which might help to explain the unexpected behaviour of these alkyl radicals. In this context it is perhaps useful to remember that sulphur tetrahalides are known but not the sulphur tetrahydride.



$$HO-\underset{R^2}{\overset{R^1}{C}}\cdot + H_2S \underset{(68)}{\overset{(67)}{\rightleftharpoons}} HO-\underset{R^2}{\overset{R^1}{C}}-\dot{S}\begin{smallmatrix}H\\H\end{smallmatrix} \xrightarrow[(69)]{} HO-\underset{R^2}{\overset{R^1}{C}}-H + HS^{\cdot} \qquad (67-69)$$

The reactions of some inorganic radicals with thiols have also been studied[109,110] (see Table 2). It is interesting[111] that the carboxyl anion radical, $CO_2^{\cdot-}$, can abstract an H atom from thiols (reaction 70), but that the $RS^{\cdot}$ radical also abstracts an H atom from formate (reaction 71). This conclusion has been drawn from the fact that tritium-labelled formate solutions exchange with water large amounts of tritium if irradiated in the presence of cysteine. Formation of oxalic acid, the combination product of two $CO_2^{\cdot-}$ entities, is suppressed and the formation of CO_2 is observed instead. This might result from a reaction of the $RS^{\cdot}$ radicals with $CO_2^{\cdot-}$ (reaction 72).

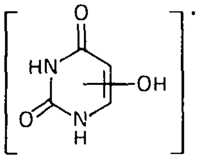
$$CO_2^{\cdot-} + RSH \underset{(71)}{\overset{(70)}{\rightleftharpoons}} HCO_2^- + RS^{\cdot} \qquad (70, 71)$$

$$CO_2^{\cdot-} + RS^{\cdot} \longrightarrow CO_2 + RS^- \qquad (72)$$

A similar equilibrium is observed[112,113] in the phosphite/thiol system (reactions 73 and 74). The equilibrium constant is 800, k_{73} being 3×10^8 and k_{74} 3.8×10^5 M^{-1} s^{-1}.

Thiolate ions readily complex with $RS^{\cdot}$ radicals (reaction 75). The rate constant

TABLE 2. Rate constants for the reaction of some organic and inorganic radicals with various thiols

Radical	Substrate	pH	Rate constant ($M^{-1}\ s^{-1}$)	References
$^{\bullet}CH_3$	CH_3SH	11	7.4×10^7	103
$HOCH_2CH_2^{\bullet}$	$HOCH_2CH_2SH$	10	4.7×10^7	103
$(CH_3)_2C(OH)CH_2^{\bullet}$	$HOCH_2CH_2SH$	10	8.2×10^7	103
	$HSCH_2CHOH{-}CHOH{-}CH_2SH$	7	6.8×10^7	110
	$H_2NCH_2CH_2SH$	7.6	1.8×10^7	105
	$H_2NCH_2CH_2SH$	7.6	$<10^7$	105
$^{\bullet}CH_2OH$	$HOCH_2CH_2SH$	10	1.3×10^8	103
	$HSCH_2CHOH{-}CHOH{-}CH_2SH$	7	6.8×10^7	110
	$H_2NCH_2CH_2SH$	7.6	6.8×10^7	105
$CH_3\dot{C}HOH$	$HOCH_2CH_2SH$	10	2.3×10^8	103
	$H_2NCH_2CH_2SH$	7.6	1.4×10^8	105
$(CH_3)_2\dot{C}OH$	$HOCH_2CH_2SH$	10	5.1×10^8	103
	$HSCH_2CHOH{-}CHOH{-}CH_2SH$	7	2.1×10^8	110
	$H_2NCH_2CH_2SH$	7.6	4.2×10^8	105
$Cl_2^{\bullet -}$	$HSCH_2CHOH{-}CHOH{-}CH_2SH$	2	3.0×10^9	110
$(CNS)_2^{\bullet -}$	$HSCH_2CHOH{-}CHOH{-}CH_2SH$	7	2.1×10^7	110
$I_2^{\bullet -}$	$HSCH_2CHOH{-}CHOH{-}CH_2SH$	7	1.9×10^7	110
$CO_3^{\bullet -}$	$HSCH_2CHOH{-}CHOH{-}CH_2SH$	11	4.1×10^8	110

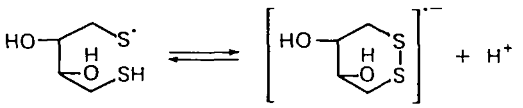
$$PO_3^{\cdot\,2-} + RSH \underset{(74)}{\overset{(73)}{\rightleftharpoons}} HPO_3^{2-} + RS^{\cdot} \qquad (73, 74)$$

k_{75} is of the order of 10^9 M^{-1} s^{-1} for a large number of thiols. This behaviour of the RS$^{\cdot}$ is similar to that of halogen and pseudohalogen radicals which readily complex with halogenide and pseudohalogenide ions. The back-reaction (reaction 76) is usually three orders of magnitude slower (k_{76} ~ 10^6 s^{-1}) and hence the

$$RS^{\cdot} + RS^{-} \underset{(76)}{\overset{(75)}{\rightleftharpoons}} RSSR^{\cdot -} \qquad (75, 76)$$

equilibrium constants are around 10^3 M[95,114]. In the case of dithiothreitol[110,115] the corresponding RS$^{\cdot}$ radical complexes only with the RS^{-} group within the same molecule (equilibrium 77) but not intermolecularly. The resulting complex has a pK of 5.5.

Whereas the linear disulphide radical anions decay by first-order, the cyclic ones[115,116] decay only by second order (e.g. reaction 78). Because on protonation the corresponding thiyl radicals are formed the decay rate will depend on the pH[115].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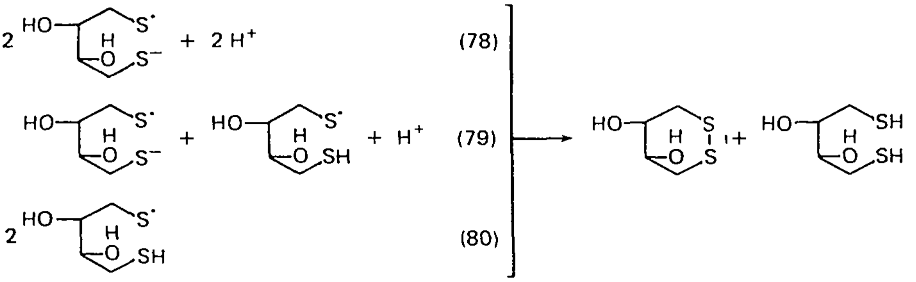
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(79)

(80)

(78–80)

As expected k_{78} is smaller (1.7×10^8 M^{-1} s^{-1}) than k_{80} (1.7×10^9 M^{-1} s^{-1}) whereas the reaction of the anion with the neutral thiyl radical is the fastest ($k_{79} = 2.5 \times 10^9$). A remarkable product from the radiolysis of penicillamine is the trisulphide. It has been proposed[117,118] that it is formed via reactions (81) and (82).

$$RSSR^{-\cdot} + H_2O \longrightarrow RSS^{\cdot} + RH + OH^{-} \qquad (81)$$

$$RSS^{\cdot} + RS^{\cdot} \longrightarrow RSSSR \qquad (82)$$

2. Disulphides

Disulphides react with the solvated electron at virtually diffusion-controlled rates to give radical anions. The latter can dissociate[113] (reaction 75) into thiyl radicals and thiolate ions as discussed above. The disulphide anion radicals are protonated (reaction 83) with rate constants[119,120] between 6×10^8 and 7×10^{10}

$$RSSR^{\cdot -} + H^{+} \longrightarrow RSSRH^{\cdot} \qquad (83)$$

M^{-1} s^{-1}. The resulting H adduct radical is thought[119,120] to decompose rapidly into thiol and a thiyl radical (reaction 84). Thiyl radicals react readily with disulphides (reaction 85) and mixed disulphides are formed via a chain reaction on

$$\mathrm{RSSRH^{\cdot}} \longrightarrow \mathrm{RSH} + \mathrm{RS^{\cdot}} \qquad (84)$$

irradiation of a mixture of two different disulphides[112,113,121], just as in non-aqueous media (see above).

$$\mathrm{R^1SSR^1} + \mathrm{R^2S^{\cdot}} \longrightarrow \mathrm{R^1SSR^2} + \mathrm{R^1S^{\cdot}} \qquad (85)$$

The reaction of OH radicals with disulphides has been shown[122,123] to give rise to about equal yields of radical cations (reaction 86) and OH radical adducts (reaction 87). The formation of these radical cations which had already been

$$\mathrm{RSSR} + {}^{\cdot}\mathrm{OH} \longrightarrow \begin{cases} \mathrm{RSSR^{\cdot +}} + \mathrm{OH^-} & (86) \\ \mathrm{RSSR(OH)^{\cdot}} & (87) \end{cases}$$

postulated earlier[124] has been proven by the appearance of conducting species. The existence of the OH adduct radicals is more indirectly inferred and finds its support by a number of subsequent reactions (see below) that help to explain the data.

The formation of disulphide radical cations is not only brought about by OH radicals but more efficiently (~100%) by other oxidizing radicals such as the radical cations of 1,3,5-trimethoxybenzene and thio ethers, $\mathrm{SO_4^{\cdot -}}$, $\mathrm{Br_2^{\cdot -}}$, and by metal ions in unstable valency states such as $\mathrm{Ag^{2+}}$, $\mathrm{Ag(OH)^+}$ and $\mathrm{Tl^{2+}}$. $\mathrm{Tl(OH)^+}$ reacts with 80% efficiency and the carbonate radical ion, $\mathrm{CO_3^{\cdot -}}$, with only 10% efficiency[125].

In alkaline solutions the cation radicals decay in a first-order reaction[123] (reaction 88). The rate of reaction (88) is not diffusion-controlled. A good correlation of a log k/k_0 plot against the Taft σ-parameters of the R groups was taken as

$$\mathrm{RSSR^{\cdot +}} + \mathrm{OH^-} \longrightarrow \mathrm{RSSR(OH)^{\cdot}} \qquad (88)$$

an indication that the rate of reaction (88) depends on the effective charge at the sulphur bridge. In addition, structural effects may contribute to the observed changes in the rate constants since steric hindrance also increases parallel to the inductive effect[123].

In neutral and slightly acid solution these species decay by second-order kinetics which can be followed using their strong absorption near 420 nm, and it has been shown that the rate is virtually diffusion-controlled. The rate of the disappearance of conductivity is slower than the decay of the optical signal, suggesting that the less-absorbing doubly-charged product of reaction (89) has a certain life-time.

$$2\,\mathrm{RSSR^{\cdot +}} \longrightarrow \mathrm{RSSR^{2+}} + \mathrm{RSSR} \qquad (89)$$

The radical cation $\mathrm{RSSR^{+\cdot}}$ itself is an oxidizing species and readily reacts with $\mathrm{Fe(CN)_6^{4-}}$ at a diffusion-controlled rate, but about four orders of magnitude slower with $\mathrm{Fe_{aq}^{2+}}$. In the latter case the variations in the rate of reaction (90), depending on

$$\mathrm{RSSR^{\cdot +}} + \mathrm{Fe_{aq}^{2+}} \longrightarrow \mathrm{RSSR} + \mathrm{Fe_{aq}^{3+}} \qquad (90)$$

the nature of R in $\mathrm{RSSR^{\cdot +}}$, have been explained to be due to similar effects as in the case of reaction (88).

Pulse radiolysis experiments[123] suggest that at pH > 10 the OH adduct radicals (from reactions 87 and 88) undergo a base-catalysed decomposition (reaction 91). In fact, at pH > 12, $G(\mathrm{EtSH}) = 5.5$ was found in the case of diethyl disulphide[123].

$$\mathrm{RSSR(OH)^{\cdot}} + \mathrm{OH^-} \longrightarrow \mathrm{RS^-} + \mathrm{RS(OH)_2^{\cdot}} \qquad (91)$$

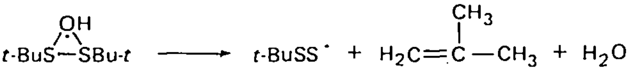
In competition with reaction (91) the OH adduct radical may break up according to reaction (92). Sulphenic acid (RSOH) may also be formed from $\mathrm{RSSR^{2+}}$ (reaction

93) which is generated by reaction (89). Sulphenic acid, which is a fairly unstable, reducing compound[126], and the RSO$^\bullet$ (RS(OH)$_2^\bullet$) radical further undergo a number

$$\mathrm{RSSR(OH)^{\bullet}} \longrightarrow \mathrm{RS^{\bullet} + RSOH} \tag{92}$$

$$\mathrm{RSSR^{2+} + 2\,H_2O} \longrightarrow \mathrm{2\,RSOH + 2\,H^+} \tag{93}$$

of reactions, the products of which have not been fully characterized. In the case of di-*t*-butyl disulphide, isobutylene and trisulphide is produced[123], and it has been suggested that they may be formed via reaction (94) which is reminiscent of reaction (81).



$$t\text{-BuS}\overset{\text{OH}}{\frown}\text{SBu-}t \longrightarrow t\text{-BuSS}^{\bullet} + \mathrm{H_2C{=}\overset{CH_3}{C}{-}CH_3 + H_2O} \tag{94}$$

Attention is drawn to the possibility that complications could arise with some disulphides on account of hydrolysis when they are investigated in alkaline media (reaction 95)[127].

$$\mathrm{RSSR + OH^-} \longrightarrow \mathrm{RSOH + RS^-} \tag{95}$$

3. *Sulphides*

Sulphides appear to react much more slowly ($k_{96} \approx 5 \times 10^7$ M^{-1} s^{-1})[95,128] with hydrated electrons than do thiols and disulphides. In this reaction a C—S bond is cleaved (reaction 96) as has been confirmed by ESR spectroscopic studies

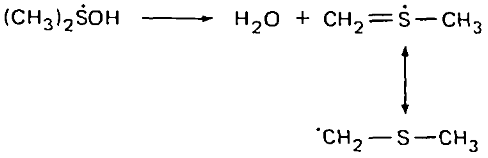
$$\mathrm{R{-}S{-}R} + e^-_{aq} \longrightarrow \mathrm{R{-}S^- + {}^{\bullet}R} \tag{96}$$

and by product analysis[129]. The subsequent reactions have so far not found much attention.

In the case of thiophene[128] the electron adduct appears to become protonated. 2,2′-Bithienyl has been found as the major reaction product. In acidic solutions, the same optical spectra are observed. However, under these conditions the thiophene ring appears to break down and sulphur is liberated while the yield of 2,2′-bithienyl is drastically reduced.

The OH radical reacts with sulphides [$k_{97} \approx (1-2) \times 10^{10}$ M^{-1} s^{-1}][130]. The first step has been suggested[130] to consist of OH addition to the sulphur (reaction 97). At low sulphide concentrations ($<10^{-4}$ M) the $R_2\dot{S}OH$ radicals eliminate H_2O (e.g. reaction 98). At sulphide concentrations above 10^{-4} M it was observed[130a]

$$\mathrm{R{-}S{-}R + OH} \longrightarrow \mathrm{R_2\dot{S}OH} \tag{97}$$



$$\mathrm{(CH_3)_2\dot{S}OH} \longrightarrow \mathrm{H_2O + CH_2{=}\dot{S}{-}CH_3} \longleftrightarrow \mathrm{{}^{\bullet}CH_2{-}S{-}CH_3} \tag{98}$$

that the OH adduct radical $R_2\dot{S}OH$ complexes with another sulphide molecule (reaction 99). The complexed OH-adduct is readily converted into the complexed

$$\mathrm{R_2\dot{S}OH + R_2S} \longrightarrow \mathrm{[(R_2S)_2OH]^{\bullet}} \tag{99}$$

radical cation either directly (reactions 100–102) or via the molecular species ($R_2\dot{S}OH$, $R_2S^{\bullet+}$) reaction (99) being reversible[130b]. Whereas with a number of

$$[(R_2S)_2OH]^\bullet \longrightarrow (R_2S)_2^{\bullet +} + OH^- \qquad (100)$$

$$[(R_2S)_2OH]^\bullet \xrightarrow{H^+} (R_2S)_2^{\bullet +} + H_2O \qquad (101)$$

$$[(R_2S)_2OH]^\bullet \xrightarrow{H_2PO_4^-} (R_2S)_2^{\bullet +} + HPO_4^{2-} + H_2O \qquad (102)$$

simple sulphides the formation of the complexed cation radical proceeds even in solutions at pH 10 (reaction 100), methionine is converted under more acidic conditions only (reactions 101 and 102)[130c]. The radical cation complex $(R_2S)_2^{\bullet +}$ is relatively stable but is in equilibrium with its components (reaction 103). There is

$$(R_2S)_2^{\bullet +} \rightleftharpoons R_2S^{+\bullet} + R_2S \qquad (103)$$

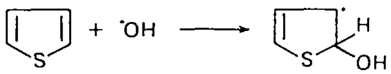
increasing evidence for cation radicals in these systems, both from ESR spectroscopic studies[14,70,88] and pulse radiolytic investigations[57,89a,130–132a,b].

Intermolecular as well as intramolecular complexes are formed with di- and tri-thianes[57,89a,132c]. Stabilization of the oxidized sulphur atom can be effected by heteroatoms other than sulphur[89a,132a,b]. For example $R_2\dot{S}Br$ or $R_2\dot{S}Cl$ are formed in the reaction of a sulphide with a complexed halogen atom, $Br_2^{\bullet -}$ or $Cl_2^{\bullet -}$ (e.g. reaction 104). At low bromide concentrations where primarily $R_2\dot{S}OH$ is formed the same absorption has been observed[89a] suggesting that reaction (105) can also take place.

$$R_2S + Br_2^{\bullet -} \longrightarrow R_2SBr^\bullet + Br^- \qquad (104)$$

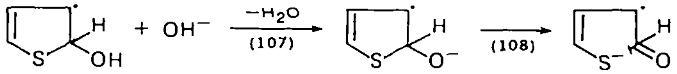
$$R_2\dot{S}OH + Br^- \longrightarrow R_2SBr^\bullet + OH^- \qquad (105)$$

The suggestion[133] that thiophene adds OH radicals predominantly at $C_{(2)}$ (reaction 106) has been confirmed by ESR spectroscopic studies[134]. In alkaline



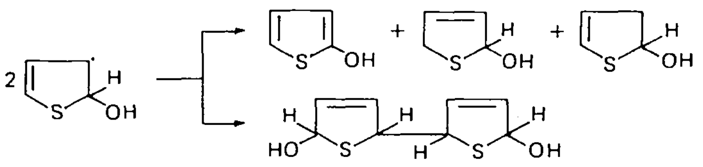
(106)

solutions the OH adduct radical rearranges and opens the ring[133,134] (reactions 107 and 108). Whereas earlier work[133] had indicated that an equilibrium between the



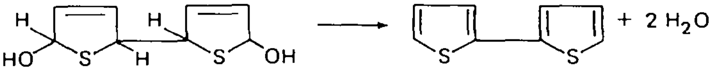
(107, 108)

OH adduct and its ring-closed anion exists, it was later[134] concluded that deprotonation immediately leads to the ring-opened species. Attempts to identify this species by ESR spectroscopy failed, however[134]. Because of the high tendency of polymerization of hydroxylated thiophenes, product analysis was restricted to the identification of the thiolactone (from the disproportionation reaction 109) and of 2,2′-bithienyl, a product which most likely arises by water elimination (reaction 111) of the combination product formed in reaction (110).



(109)

(110)



(111)

C. Oxygenated Solutions

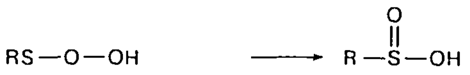
Whereas the free-radical chemistry of deoxygenated solutions of thiols and their derivatives is reasonably well understood, this is not the case with oxygenated solutions. One reason for this may be the relatively low rate of oxygen addition to sulphur-centred radicals (reaction 112). Oxygen adds to carbon-centred radicals at virtually diffusion-controlled rates [$k(R_3C^{\bullet} + O_2) \approx 2 \times 10^9$ M^{-1} s^{-1}] while the rate of reaction of thiyl radicals with oxygen appears to be considerably lower (Table 3). Thus at thiolate concentrations higher than those of oxygen the reaction of the thiyl radical with the thiolate anion to give $RSSR^{\bullet -}$ (reaction 75) might successfully compete with reaction (112). This effect is most prominent in compounds which contain two sulphhydryl groups such as dithiothreitol. As a result of this, O_2 reacts with $RSSR^{\bullet -}$ giving the disulphide and $O_2^{\bullet -}$ (reaction 113). At low pH where reaction (112) predominates, the resulting $RSO_2^{\bullet}$ radicals may undergo a number of reactions. Although the system is not yet fully understood some mechanistic aspects can be discussed here.

$$RS^{\bullet} + O_2 \longrightarrow RSO_2^{\bullet} \tag{112}$$

$$RSSR^{\bullet -} + O_2 \longrightarrow RSSR + O_2^{\bullet -} \tag{113}$$

It is observed that a chain-reaction takes place, the importance of which depends on thiol concentration and on the dose rate. The first step appears to be reaction (114). The resulting hydroperoxide may undergo two competing processes, a rearrangement into sulphinic acid (reaction 115) and hydrolysis (reaction 116). Both reactions may well proceed by proton catalysis, and the substituent R may have an influence on k_{115}/k_{116}. Thus in the case of glutathione[136] both the sulphinic acid

$$RSO_2^{\bullet} + RSH \longrightarrow RS{-}O{-}O{-}H + RS^{\bullet} \tag{114}$$



$$RS{-}O{-}OH \longrightarrow R{-}\overset{\overset{\displaystyle O}{\|}}{S}{-}OH \tag{115}$$

$$RS{-}O{-}OH + H_2O \longrightarrow RSOH + H_2O_2 \tag{116}$$

TABLE 3. Rate constants of the reaction of O_2 with some free-radical species derived from thiols and their derivatives[135]

Radical	k (M^{-1} s^{-1})
$HOOCCH(NH_2)C(CH_3)_2S^{\bullet}$	4×10^7
$C_2H_5S^{\bullet}$	3.4×10^8
t-$BuS^{\bullet}$	7.8×10^8
$HOCH_2CH_2S^{\bullet}$	2.3×10^8
$CH_3SCH_2^{\bullet} \longleftrightarrow CH_3\dot{S}{=}CH_2$	4.4×10^8
$C_2H_5S{-}\dot{C}HCH_3 \longleftrightarrow C_2H_5\dot{S}{=}CHCH_3$	6.2×10^8
$(CH_3)_2CHS{-}\dot{C}(CH_3)_2 \longleftrightarrow (CH_3)_2CH\dot{S}{=}(CH_3)_2$	1.0×10^9
$RSSR^{\bullet +}$	Unreactive[a]
$R_2S^{\bullet +}$	Unreactive[a]
$(R_2S)_2^{\bullet +}$	Unreactive[a]

[a] Time-scale of pulse radiolysis experiments.

$$\mathrm{RS{-}O{-}OH + RSH \longrightarrow RSSR + H_2O_2} \qquad (117)$$

$$\mathrm{RSOH + RSH \longrightarrow RSSR + H_2O} \qquad (118)$$

and the disulphide are formed, whereas in the case of cysteine[137] only the disulphide and H_2O_2 have been reported as products. However, there appears to be a further reaction (reaction 117) which competes with reactions (115) and (116). Reaction (117) depends on the thiol concentration and therefore should only be noticeable at higher thiol concentrations. Its product is the disulphide, and indeed it has been found[136] that the disulphide/sulphinic acid ratio increases with increasing thiol concentration. The termination of the chain is less clear than the propagation and reactions such as (119) have been suggested[137].

$$\mathrm{2\,RSO_2^{\bullet} \longrightarrow RSSR + 2\,O_2} \qquad (119)$$

In neutral and alkaline solutions values are reached[137-140] for $G(-\mathrm{RSH})$ which suggest that a chain-reaction must occur under these conditions as well. Because of the fast establishment of the equilibrium leading to $\mathrm{RSSR}^{\bullet -}$ reaction (113) must take part. The $\mathrm{O_2^{\bullet -}}$ radical must be the chain-carrier as it has been convincingly shown[137] that its conjugated acid $\mathrm{HO_2^{\bullet}}$ is not capable of propagating a chain. It has been argued[137] that the $\mathrm{HO_2^{\bullet}}$ radical cannot abstract an H atom from the thiol,

$$\mathrm{O_2^{\bullet -} + RSH \xrightarrow{H^+} RS^{\bullet} + H_2O_2} \qquad (120)$$

but that $\mathrm{O_2^{\bullet -}}$ does (reaction 120). This reasoning is somewhat surprising as $\mathrm{O_2^{\bullet -}}$ is expected to be a poorer hydrogen abstractor than its conjugated acid $\mathrm{HO_2^{\bullet}}$. Evidence for this is given in experiments where it has been shown that $\mathrm{O_2^{\bullet -}}$ does not react with alcohols but that $\mathrm{HO_2^{\bullet}}$ has sufficient abstractive power to propagate a chain (see Chapter 23). Thus one might have to reformulate the mechanism of this chain-reaction and consider that the thiolate anion could be involved, or that $\mathrm{O_2^{\bullet -}}$ could form a labile complex with the thiol, a reaction which might not be undergone by the $\mathrm{HO_2^{\bullet}}$ radical. In this context it might be mentioned that the question as to whether $\mathrm{O_2^{\bullet -}}$ can react with a sulphide (methional) has been considered[141].

The reaction of oxygen with radicals derived from OH attack on disulphides is far from being understood. Major products are the corresponding sulphonic acids[142-147] The straight disulphides were observed[144] on irradiation of the mixed disulphides, e.g. CySSCy and CyaSSCya from CySSCya.

It has been shown[135] that the radical cations $\mathrm{RSSR}^{\bullet +}$ do not react with O_2, at least not on the time-scale of pulse radiolysis experiments. However, it cannot be excluded that such a reaction takes place under ^{60}Co-γ conditions where the lifetime of the radical cations would be longer because of the usually much lower dose rates of ^{60}Co-γ sources compared to those employed in pulse radiolysis. A similar passivity towards O_2 is also observed with the radical cations derived from sulphides[135].

D. Some Biochemical Aspects

DNA is considered the major target in the radiation-induced deactivation of the living cell[2,148]. It has been found that sulphhydryl compounds can to some extent protect against this damage[2] (cf. Reference 149). In order to rationalize this observation it has been postulated that sulphhydryl compounds can repair radiation-induced DNA radicals. These radicals can be formed by an attack of radicals generated in the neighbourhood of DNA, or by its direct ionization. On hydrogen abstraction in the former case (reaction 121), or proton loss in the latter (reaction 122), a radical is formed which may undergo reactions leading to a damaged site, or may be repaired by sulphhydryl compounds according to reaction (123). The same sort of protection could also be exerted in favour of other vital components of the cell.

$$\mathrm{RH\ (i.e.\ DNA)} + \mathrm{X}^{\bullet} \longrightarrow \mathrm{R}^{\bullet} + \mathrm{XH} \tag{121}$$

$$\mathrm{RH}^{+\bullet} \longrightarrow \mathrm{R}^{\bullet} + \mathrm{H}^{+} \tag{122}$$

$$\mathrm{R}^{\bullet} + \mathrm{R^1SH} \longrightarrow \mathrm{RH} + \mathrm{R^1S}^{\bullet} \tag{123}$$

Another aspect is the radiation-induced deactivation of enzymes, and in the present context this topic is of interest in so far as they contain[150] sulphhydryl, sulphide and disulphide functions. It has been found that in some (e.g. papain[151–154], trypsin[155], ribonuclease[156–158], lactate dehydrogenase[159], yeast alcohol dehydrogenase[160] and glyceraldehyde-3-phosphate dehydrogenase[161]), but not all, enzymes (e.g. α-chymotrypsin[162] and carboxypeptidase A[163]), sulphur-containing functions appear to be critically involved.

Impairment[164,165] of enzymatic activity may be through damage to the active site as well as through disruption of the proper conformation[166]. Inactivation of an enzyme through radiation is complete only after several hits have been scored[167,168] even though transfer of charge and free-radical sites occurs to some extent within the enzyme molecule[169–174]. It has been shown with papain that the degree of inactivation by OH radicals is higher in the presence of oxygen[175].

Other important free-radical targets in proteins are the aromatic amino acids, tyrosine and tryptophane[176]. Even radicals derived from sulphur-containing amino acids bind to proteins through addition to the aromatic constituents[177,178]. The involvement of complexed inorganic [e.g. $\mathrm{Br}_2^{\bullet -}$ or $(\mathrm{SCN})_2^{\bullet -}$] and other radicals in these deactivation processes has been studied[151,179–183]. These radicals have been shown to react with more specificity than the highly reactive OH radical.

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Author Index

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Arends, M. 979 (102), *991*

Arens, J. F. 647 (736), *676*; 808 (400), *820*

Areshidze, Kh. I. 745 (297), *759*

Aresta, M. 710 (370), *720*

Arhart, R. J. 623 (361), *668*

Arigoni, D. 500 (217), 501 (222), *534*

Arimoto, T. 790 (237), *816*

Arison, B. H. 615 (150), *663*

Armarego, W. L. F. 610, 611, 620, 623, 625, 630, 637, 641, 652, 656 (17), *660*; 684, 690–692, 694, 696 (8), *712*; 822, 847 (2), *853*

Armatis, F. J. 120 (163), *152*
Armstrong, D. A. 979 (102), 982 (118), 988 (151, 153, 154, 159, 161, 172, 175, 176, 182), *991–993*
Arnaud-Neu, F. 87 (78), 94, 95, 115 (97), 137 (242), *149*, *150*, *155*
Arndt, H. C. 592 (266), *607*
Arnett, E. M. 92 (87), *149*
Arnold, D. R. 692 (88), *714*
Arnold, H. R. 745 (286), *759*
Arnold, R. T. 736 (171), *756*
Arnold, Z. 484 (87), *530*; 785 (196), *815*
Aronowitz, D. 452 (30), *467*
Arro, J. 363 (72), *376*
Arshinova, R. P. 850 (239, 240), *858*
Arth, G. E. 485 (99), *531*
Arumugam, N. 544 (322), *608*
Arundale, E. 736 (149), *755*
Arvis, M. 946 (214), *967*
Arzoumanian, H. 618 (249, 291), *665*, *666*
Asabe, Y. 833 (84), *854*
Asada, M. 46 (173), *57*; 96 (103c), *150*
Asahara, T. 611 (25), *660*
Asay, R. E. 11, 12 (44), 31 (116, 118–120), 32 (124), *53*, *55*; 60 (9r), 83, 84 (70a,b), 94 (70b), *145*, *148*
Asche, R. 316 (244), *324*
Ash, D. K. 823 (13b), *853*
Ashby, E. C. 637 (614), 638, 640 (620), *673*
Ashley, K. R. 636 (600), *673*
Ashmore, P. G. 450 (4), *466*
Ashworth, M. R. F. 541 (10), *600*
Ashworth, R. W. 635 (593), *673*
Asinger, F. 658 (902), *679*
Asmus, K.-D. 925 (29), 926 (39b), 932 (91), *933*, *934*; 948 (237), 949 (238), *967*; 974 (57), 976 (73), 977 (79, 80a, 89a), 980–982 (113), 983 (113, 122, 123, 125), 984 (123, 130a–c), 985 (57, 89a, 130a–c, 132a,b), 986, 987 (135), *990–992*
Asperger, S. 425 (8), (9), *438*
Asratyan, G. V. 620, 658 (322), *667*
Asthana, M. R. 270, 272 (79), *276*
Astolfi, L. 798 (312), *818*
Astrup, E. E. 178 (8), 180 (24), *212*
Atavin, A. S. 415 (366), 417 (402), 426, 427 (401), *446*, *447*; 769 (34), 786 (211), *812*, *816*
Atkins, T. J. 19, 21 (70), *54*
Atkinson, J. G. 384 (10), *438*
Atkinson, R. F. 890, 895 (63), *902*
Atlani, M. 620, 624 (317), *667*
Atsumi, K. 591 (264), *607*
Attenburrow, J. 492 (154), *532*
Audier, H. E. 306 (75), 307 (75, 89), 308 (106), 325 (292), *320*, *321*, *325*; 656 (857–859), *678*
Audrieth, L. F. 587 (241), *606*
Aue, D. H. 316, 317 (254), 318 (272), *324*; 875 (47), *879*
Auer-Welsbach, C. 707 (297), *718*
Augustin, J. 401 (11), *438*
Augustine, R. L. (12), *438*
Auidini, A. 87 (78), *149*
Aulakh, G. S. 619 (296), *666*
Auret, B. J. 567 (161), *604*
Ausloos, P. 942 (152), *965*
Avetisov, A. K. 618 (280, 281), *666*
Avigad, G. 289 (24), *297*
Avigan, J. 493 (160), *532*
Avirah, T. K. 847 (177), *856*
Avnir, D. 623 (366), *668*
Avondet, A. G. 80–82 (67b), 84 (69), 92 (67b, 69), 93, 94 (69), 101 (67b, 69), *148*
Avots, A. A. 703 (240), *717*
Awasthy, A. K. 476 (46), *529*
Awerbouch, O. 613 (70), *661*
Axenrod, T. 318 (277), *325*
Aya, I. 807 (388), *820*
Aya, T. 807 (388), *820*
Aycard, J. P. 613 (67), *661*
Aylward, D. E. 488, 499 (128), *531*
Ayres, D. C. 527 (391), *538*
Ayrey, G. 392 (15), 393 (14), 398 (13), *438*
Azami, T. 435 (16), *438*
Azerad, R. 396 (337), *446*
Azman, A. 611 (34), *660*
Azrak, R. G. 184, 185 (47), *212*
Azuma, H. 618 (271), *666*

Baake, H. 613 (69), *661*
Baba, H. 846 (169), *856*
Baba, Sh. 650 (763), *676*
Babakhanov, R. A. 659 (945), *680*
Babler, J. H. 486 (109), *531*
Baccouche, M. 618 (291), *666*
Bach, R. D. 611 (23), 633 (515), *660*, *671*
Bachelor, F. W. 624 (369), *668*
Bachhawat, J. M. 613, 614 (63), *661*
Bachman, G. B. 736 (163), *756*
Bachmann, J. P. 519 (330), *537*
Bachmann, W. E. 725 (53), 726 (56–58), *753*
Back, T. G. 390 (144), *441*
Backlin, R. 950 (256), *968*
Bacon, C. C. 555, 567 (115), *603*
Bacon, R. G. R. 736 (162), *756*
Bacquet, C. 888 (50), *901*
Baddeley, G. 242 (21), *275*
Badding, V. G. 425 (101), *440*; 825, 831 (36), *853*

Bade, T. R. 496, 497 (190), *533*
Badea, F. 630 (465), *670*
Bader, R. F. W. (17), *438*
Badev, A. 618 (293), *666*
Badeva, V. 618 (293), *666*
Badger, G. M. 597 (303), *607*
Badiello, R. 987 (140), 988 (160), *992*
Bafus, D. 315 (238), *324*
Bahnemann, D. 925 (29), 926 (39b), *933*; 977 (89a), 984 (130a), 985 (89a, 130a, 132a,b), 986, 987 (135), *990*, *992*
Baijal, M. D. 702 (226), *717*
Baikova, Zh. G. 700 (178), *715*
Bailey, A. S. 795 (283), *817*
Bailey, F. P. 432 (393), *447*
Bailey, P. S. 386 (18), *438*; 556 (121), *603*
Bailey, W. F. 242 (23), 248 (100), 252, 254, 255 (22), 256 (23), *275*, *277*; 511 (292), *536*
Bailey, W. J. 527 (389), *538*
Baizer, M. M. 327 (1), 334 (1, 22), 337 (1), *349*, *350*
Bak, B. (19), *438*
Baker, J. G. 184 (44), *212*
Baker, R. (20), *438*; 473 (19), 488 (129), *529*, *531*; 650 (769), *676*
Baker, R. T. K. 709 (349), *719*
Baker, T. N. 616 (180), 617 (196), *663*, *664*
Baker, T. N. III 616 (169), *663*
Bakhtadze, I. G. 972, 975 (5), *988*
Balandin, A. A. 422 (407b), *448*
Balashova, A. A. 919 (133), *922*
Baldas, J. 306–308 (83), *320*
Baldeschwieler, J. D. 302 (31), *319*
Baldwin, J. E. 590 (258), *606*; 800 (321), 801 (324), *818*; 846, 851 (172), *856*; 862 (13), *878*
Baldwin, M. J. 780 (154), *814*
Balenović, K. 567 (161), 571 (185), *604*, *605*
Bales, B. L. 938 (80), *964*
Balezina, G. G. 774 (89), *813*
Ball, J. S. 463, 464 (96), *468*; 927, 931 (43), *933*
Ball, M. 636 (604), *673*
Ball, S. 490, 492 (140), *532*
Ballantine, J. A. 312 (181), *322*
Ballard, S. A. 735, 737 (184), *756*
Balsamo, A. 656 (862–864), 657 (863), *678*; 686 (18, 25), 710 (25), *712*
Balthazor, T. M. 551 (90), *602*
Baltrusch, E. 839 (117), *855*
Bambenek, M. 947, 948 (226), *967*; 978 (92), *991*
Bamford, C. H. 372 (113), *377*
Bamkole, T. O. 463, 464 (98, 99), *468*
Bandmann, H. 904, 909, 910 (15), 914, 915 (15, 71), *919*, *921*; 937, 946 (22), *962*
Banerjee, A. K. 62 (19e,f), *146*
Banerjee, D. 642 (679, 680), 658 (680), *674*
Banerji, K. B. 499 (210), *533*
Banerji, K. K. 487 (120), 488 (120, 126), *531*
Banerji, S. K. 499 (210), *533*
Banfi, D. 406 (21, 22), *438*
Banko, K. 624 (386), *668*
Banks, D. B. 630 (468), *670*
Banks, H. 394, 395 (350), *446*
Banks, H. D. 243, 249, 252 (63), *276*
Banno, K. 806 (378), *820*
Banoo, F. 483 (85), 488 (130), *530*, *531*
Bansal, K. M. 944 (164, 171, 172, 176), 951 (270a), *966*, *968*
Bansal, R. K. 624 (369), *668*
Barakat, T. M. 436 (23), *438*
Baranenkov, V. I. 9 (28), *53*
Barantsevich, E. N. 620 (307), *667*
Barbadaro, S. 698 (161), *715*
Barbarella, G. 245–247 (24), *275*
Barbier, G. 778 (123, 124), *814*
Barbieri, G. 547, 548, 573 (56), *601*
Barcza, S. 745, (272), *758*
Bargar, T. W. 553 (94), *602*
Barili, B. L. 658 (883), *679*
Barili, P. L. 611 (21, 22), 612 (41), *660*; 723, 726 (25), *753*
Barker, N. T. 938 (93a,b), *964*
Barker, R. 741, 747 (244), *758*
Barker, S. A. 238 (25), *275*
Barkovskaya, L. Ya. 704 (259), *717*
Barltrop, J. A. 692, 694 (97), *714*
Barnard, D. 392 (15), 393 (14), 428 (24), *438*; 542, 543, 546 (11), 556 (119), *600*, *603*
Barnard, J. A. 453 (34), 454 (36, 37), 455 (38, 40), *467*
Barner, R. 414 (139), *441*
Barnes, K. K. 327 (7), *349*
Barnes, R. K. 616 (186), *664*
Barnett, B. L. 120 (162c), *152*
Barnier, J. P. 807 (387), *820*
Barnier, J.-P. 723, 726, 727 (34), *753*
Baron, D. 33 (128), *55*; 363 (75–77), *376*
Barrelle, M. 492 (156), *532*; 631 (479), *670*
Barrett, J. 847 (174), *856*; 904 (21), *920*
Barroeta, N. 413 (25), *438*; 465, 466 (102), *468*
Barron, H. E. 554 (105), *602*
Barrone, G. 621 (346), *667*
Barrucco, J. F. S. 723, 728 (27), *753*
Barry, J. E. 347 (52), *350*

Barsegov, R. G. 972 (23–25), 974 (23), 975 (24, 25), *989*
Barta, M. A. 486 (110), *531*
Bartell, L. S. 179 (12), *212*
Bartels, A. P. 517 (316), *536*
Barter, R. M. 488, 515 (127), *531*
Barthel, J. W. 518 (319), *536*
Bartlett, P. A. 620, 622, 658 (332), *667*
Bartlett, P. D. 617, 618 (236), 619 (306), *665*, *667*; 726 (59, 61), *753*, *754*; 787 (218, 225), *816*
Bartman, B. 33 (128), *55*
Bartók, G. B. 686 (19, 35–37, 41, 42), *712*, *713*
Bartók, M. 635 (566, 571, 572), 638, 639 (636), *672*, *673*; 684 (1), 686 (13, 15–17, 19, 28, 29, 31, 32, 34–37, 41, 42), 687 (43, 44), 690 (74), 696 (140, 144, 145), 697 (140, 144, 149–157), 698 (158), 699 (1), 700 (153–156, 174, 176, 186), 705 (1, 262), 706 (1), 707 (302, 310, 313, 315, 318, 322), *712*, *713*, *715*, *716*, *718*, *719*; 730 (103, 104), 731 (104), 733 (103, 104, 135–143), 734 (135–137, 140, 142, 143, 179), 735 (104, 140, 143, 146), 736 (143, 144, 146), 737 (179, 182), 738 (140, 143, 146), 741 (179), 742, 743 (304, 305), 744 (103, 304), 746 (104, 139, 304, 305, 307), 748 (143, 144, 305), 750 (103, 182), 751 (104), *754–756*, *759*
Barton, D. H. R. 479 (59), 506 (256), 509 (282, 283), 521 (342), *530*, *535*, *537*; 579 (217), 597 (302), *605*, *607*; 632 (486), *670*; 883 (16), *901*
Barton, J. 611 (26), *660*
Barton, J. P. 926 (38, 39a), *933*; 987 (137), *992*
Barton, S. S. 365 (89), *376*
Bartsch, R. A. 168, 172 (46), *173*
Bartsch, W. 741 (236), *757*
Baryshnikov, Yu. N. 419 (26), *438*
Barzynski, H. 939 (110), *964*
Bashkirov, A. N. 618 (292), *666*
Basiladze, Ts. M. 972, 975 (29), *989*
Bass, J. D. 794 (256), *817*
Bass, R. G. 751 (358), *760*
Basselier, J. J. 308 (119), *321*
Basselier, J.-J. 308 (117), *321*
Basson, R. A. 935, 936 (5), 937 (29, 30, 31a), 940 (29, 30, 31a, 139a–c), 942 (29, 154), 944 (29, 30, 31a, 139a–c, 154), *962*, *965*
Bassus, J. 353, 357, 358 (18), 370 (103), 372 (112), *375*, *377*
Bastard, J. 503 (234), *534*
Bastide, J. 798 (298), *818*
Bateman, L. 542, 543, 546 (11), *600*
Bates, G. S. 521 (338), *537*
Bates, R. B. 706 (283), *718*
Batich, C. 769 (29), *811*
Batts, B. D. 431 (27), *438*
Battersby, A. R. 373 (128), *377*
Battistini, C. 656 (836–865, 867), 657 (863), 865, 867), *678*, *679*
Battistuzzi, R. 435 (258), *444*
Batts, B. D. 431 (27), *438*
Batzer, H. 562 (145a), *603*
Baudot, Ph. 119 (155), *152*
Baudoy, R. 518 (323), *537*
Baudy, M. 647 (720), *675*
Bauer, F. 733, 734 (122), *755*
Bauer, P. 723, 726 (23, 24), *753*
Bauer, S. 522 (350), *537*
Bauer, S. H. 183 (41), 185 (49, 52), *212*; 465 (107), *468*
Baukov, Y. I. 806 (383), *820*
Baum, K. 710 (376), *720*
Baumann, A. 526 (382), *538*
Baumann, W. J. 301 (19), *319*
Baumgarten, R. L. 380 (28a), *438*
Baumgartner, P. 618 (286), *666*
Baumstark, A. L. 619 (306), *667*
Baverstock, K. F. 988 (162), *992*
Bavoux, C. 187 (56), *213*
Bawn, C. E. 782 (174), *815*
Baxendale, J. H. 936 (7b), 938 (54, 56, 59, 63a, 90, 91), 939 (104b, 122), 940 (122), 944 (122, 167), 945 (189), 946 (189, 199, 209, 218), *962–964*, *966*, *967*; 974 (58), *990*
Bayanova, N. N. 616 (173), *663*
Bayer, H. O. 518 (325, 326), *537*
Bayer, O. 783, 795 (176), *815*
Bayomi, S. M. 625 (417), *669*
Baywater, S. 120 (160), *152*
Bazant, V. 618 (274), *666*
Bazhenova, T. N. 771 (52), *812*
Bazhin, N. M. 951 (263), *968*
Beach, J. A. 236 (42), *275*
Beagley, B. 181 (29), *212*
Beak, P. 435 (28b), *438*
Beal, D. A. 515 (304), *536*
Beall, H. 231 (26), *275*
Beam, C. F. 511 (292), *536*
Beames, D. J. 649 (750), *676*; 707 (295), *718*
Beard, C. 492 (153), *532*
Beard, C. C. 64 (28b), *147*
Beard, Ch. D. 710 (376), *720*
Beare, S. 706 (284), *718*
Beati, E. 729, 745 (92), *754*
Beattie, T. R. 615 (150), *663*
Beauchamp, J. L. 302 (33), 303 (43), 305 (33), 314 (221), 316, 317 (255), 318 (271), *319*, *323*, *324*

Beaucourt, J. P. 395 (316), *445*
Beaumond, D. 946 (199, 209), *966, 967*
Bebchuk, A. S. 919 (133), *922*
Bebesel, P. I. 390 (29), *439*
Beck, B. H. 236, 249 (96), *277*
Beck, G. 936 (11a,b), 949 (238), *962, 967*; 985 (131), *992*
Beck, P. E. 743, 746, 747 (309), *759*
Becker, E. W. 390 (63), *439*
Becker, H. D. 507 (267), *535*; 653, 654 (820), *677*
Becker, H.-D. 903, 904 (2), *919*
Becker, M. 626 (430), *669*
Becker, R. S. 653 (815), *677*
Becker, W. J. 479 (63), *530*
Beckey, H. D. 302, 310 (30), *319*
Beckford, H. F. 27 (103), *54*; 97 (108), *150*
Beckmann, E. 472 (14), *529*
Becu, C. 883 (13), *901*
Bedekovic, D. 109 (132), *151*
Bedell, S. F. 885 (32), *901*
Bednarski, T. M. 619 (304), *666*
Beecham, A. F. 294, 295 (42), 296 (61), *297, 298*
Beekmann, P. 510 (286), *536*
Beesk, F. 955 (292), *969*
Beg, M. A. 615 (147–149), *663*
Begidov, C. Kh. 745 (273), *758*
Begun, G. M. 437 (303), *445*
Behan, J. M. 629 (452), *670*
Behr, J. M. 62, 91, 107 (16m), *146*
Behr, J. P. 62, 91, 107, 116, 117 (16g), *146*; 201 (94), *213*
Behr, J.-P. 47 (177), *57*
Behrens, G. 911, 918 (62), *920*; 951 (265, 272, 277), 954 (289), 955 (289, 290), 958 (321), *968, 969*
Beisekov, T. 700 (183), *716*
Bekhli, E. Yu. 702 (217), *716*
Bekker, R. A. 620 (322), 625 (395), 658 (322), *667, 668*
Beland, I. A. 658 (877), *679*
Belenkii, L. 593 (285), *607*
Beletskaya, I. P. 169 (58), *174*
Belevskii, V. N. 939 (133b), 943 (160), *965*
Belew, J. S. 507 (269), *535*
Belič, I. 507 (268), *535*
Bell, E. V. 571 (176), *604*
Bell, R. H. 521 (341), *537*
Belleau, B. 779 (141), *814*
Bellido, I. S. 723, 728 (27), *753*
Belloni, J. 907 (45), *920*
Bellucci, G. 611 (21, 22), 612 (41), 656, 657 (866), 658 (883), *660, 678, 679*
Beloslyudova, T. M. 700 (179, 180), *716*
Belousov, V. M. 617 (215), *664*
Belousova, L. I. 772 (60), *812*
Belov, P. S. 711 (387), *720*
Bel'skii, I. F. 684, 690 (7), 691 (7, 78), 695–697, 699 (7), 704 (7, 254–261), 707 (302), *712, 713, 717, 718*
Belyaev, V. A. 616 (165), 617 (217), *663, 664*
Bendazzoli, G. L. 291, 292 (29), *297*
Bender, M. L. 187 (61), *213*
Beneche, M. 614 (124), *662*
Benedek, I. 640 (656), *674*; 700 (192), *716*
Benedict, J. T. 658 (882), *679*
Benesch, R. 926 (40), *933*
Benesch, R. E. 926 (40), *933*
Benett, D. 653 (816), *677*
Bengelmans, R. 167 (40), *173*
Bengsch, E. 422 (30), *439*
Benjamin, B. M. 723 (30, 31), 725 (30, 54), *753*
Benjamin, P. M. 722 (8), *753*
Bennett, C. F. 548 (67), *602*
Bennett, D. 911 (64), *921*
Bennett, G. M. 571 (176), *604*
Bennett, P. 634 (533), *671*
Bennett, R. H. 845 (157), *856*
Benoit, F. M. 309, 310 (136), 317 (259), 318 (136), *321, 324*
Bensel, N. 642 (677), 646 (712), *674, 675*
Bensing, R. L. 365 (90), *376*
Benson, D. 571, 587 (4), 498 (197), *528, 533*
Benson, S. W. 363 (52, 53), 371 (110), *375, 377*; 411 (31), *439*; 462, 464 (95), 465 (95, 101), 466 (101), *468*; 862 (12), *878*
Bente, P. F. III 302 (32a,b), *319*
Bentley, T. W. 300 (8), *319*
Benton, W. H. 60 (9t), *145*
Beranek, J. 618 (274), *666*
Berchtold, G. A. 613 (66), 630 (467), 635 (593), *661, 670, 673*; 924 (12), 931 (12, 71), *933, 934*
Berenblum, A. S. 973 (53), *990*
Beresford, G. D. 34 (130), *55*
Berg, J. 390 (351), *446*
Bergdolt, A. 972 (31, 32), *989*
Bergen, T. J. van 32 (126), 33 (127), *55*; 91 (82b), *149*; 598 (308), *608*
Bergensen, K. 571 (177), *604*; 840 (133), 844, 845 (152), *855, 856*
Bergmann, E. 725 (52), *753*
Bergmann, E. D. 658 (905), *679*; 885 (35), *901*
Bergmann, M. 779 (134), *814*
Bergson, G. 295 (52), *297*

Bergstrom, R. G. 893 (72–74), 894, 895 (73), 898 (74), 899 (104), *902*
Berk, S. 977 (77), *990*
Berke, C. 776 (105), *813*
Berkovich, E. G. 431 (368), *447*
Berkowitz, L. M. 494, 513 (168), *532*
Berlin, K. D. 795 (284), *818*
Berman, E. L. 702 (232), *717*
Bernardi, F. 766, 768, 770 (15), *811*
Bernas, A. 937 (19), *962*
Bernasconi, C. F. 421 (32), *439*; 898 (100), *902*
Bernasek, S. L. 304 (45), *319*
Bernat, J. 401 (11), *438*
Bernáth, G. 659 (927), *680*
Beroza, M. 307 (86), *320*
Berse, C. 643 (702), 658 (912), *675*, *680*; 846, 851 (171), *856*
Bertholon, G. 187 (56), *213*; 353 (17, 18), 355 (21, 22), 357, 358 (17, 18), 362 (59), 363 (73), 367 (95), 370 (101–104), 372 (112), 373 (127, 129), *375–377*
Berti, G. 610 (13), 611 (13, 22), 614, 618 (13), 620 (13, 313), 621 (340, 341), 623–626 (13), 634, 642 (540), 656 (860, 864, 866–868), 657 (866–868), 658 (873), 659 (341), *659*, *660*, *667*, *671*, *678*, *679*; 689 (66); *713*; 723, 726 (25), *753*
Bertie, J. E. 436 (33), *439*
Bertinchamps, A. J. 987 (148), *992*
Bertini, F. 626 (428), 627 (440), *669*
Bertoniere, N. R. 652 (802), 653 (812, 815), *677*
Bertran, J. 356 (30), *375*
Bertrand, M. 309 (123, 124), 311 (124), *321*; 613 (86, 87), 638 (87), 649 (746), *661*, *676*; 870, 874 (41), *879*; 917, 918 (101), *921*
Bertucci, C. 298 (65), *298*
Bertz, S. H. 774 (83), *813*
Besemer, A. C. 390 (351), *446*
Bessière, Y. 611, 612, 637 (37), *660*
Bessière-Chrétien, Y. 647 (724), *675*
Bessonov, V. A. 432 (356), *446*
Bestmann, H. J. 613 (49), *660*; 705 (272), *718*; 774 (82), *813*
Bethall, D. 635 (564), *672*
Bethke, H. 520 (334), *537*
Beugelmans, R. 486 (114), *531*
Beveridge, D. L. 353 (9), *374*
Bewley, T. A. 296 (58, 63, 64), *298*
Beychok, S. 295 (48), 296 (48, 55), *297*
Beyler, R. E. 485 (99), *531*
Beynon, J. H. 300 (11), 309 (123, 124), 311 (124), *319*, *321*
Beynon, P. J. 494 (166, 170), *532*
Bezmenova, T. E. 416 (34), *439*
Bhacca, N. S. 652 (807), *677*
Bhagwat, V. W. 123 (175), *153*
Bhat, G. 224 (158), 265–267 (43), *275*, *278*; 828 (58), *854*
Bhattacharjya, A. 708 (326), *719*; 876 (55), *879*
Bhattacharyya, S. C. 512 (295), *536*
Bianchi, R. 626 (434), *669*
Bibby, C. 708 (327), *719*
Bichiashvili, A. D. 972 (7, 22-25, 29, 35), 974 (23, 61), 975 (24, 25, 62, 63), *988–990*
Bickel, A. F. 511 (291), *536*
Bickham, D. 693 (119), *714*
Biddiscombe, D. P. 363, 367 (69, 70), *376*
Bielefeld, M. A. 522 (344), *537*
Bielski, B. H. 947 (229), *967*
Bielski, B. H. J. 982 (115), *991*
Biemann, K. 311 (172), *322*
Bien, J. M. 808 (391), *820*
Bierenbaum, R. 693 (118), *714*
Bierl, B. A. 307 (86), *320*
Bierman, M. H. 497 (194), *533*
Bigeleisen, J. (35), *439*
Biggi, G. 167 (43), *173*
Biggs, J. 687 (46), *713*
Bijen, J. M. J. M. 177 (6), 181, 182 (31), 185 (50), *212*
Bikeev, Sh. S. 613 (50, 51), 637 (51), *660*
Bild, N. 308 (111), *321*
Billig, F. 587 (244), *606*
Billups, W. E. 526 (384), *538*
Bilofsky, H. S. 230 (47), 265–267 (43), *275*, *276*
Biloski, A. J. 542 (320), *608*
Bingham, K. D. 611 (32), *660*
Bingham, R. C. 860 (7), *878*
Binkley, J. S. 766 (18), *811*
Bin Othman, A. H. 36 (142), 37 (143), *56*
Binsch, G. 270 (173), *278*; 572 (186), *605*; 787, 791, 792 (216), *816*; 826, 827 (51), *854*
Bioul, J. P. 700 (196), *716*
Birch, A. J. 517 (313), *536*; 795 (267), 798 (304), *817*, *818*; 885 (27), *901*
Birch, S. F. 734, 736 (167), 742, 745 (281), *756*, *758*; 931, 932 (77), *934*
Birchall, M. 709, 710 (354), *719*
Bird, C. W. 633 (523), *671*
Birkhäuser, A. 503 (239), *534*
Birkhofer, L. 658 (900), *679*
Birner, P. 355 (27), *375*
Biros, F. J. 479 (62), *530*
Bisby, R. H. 980 (108), 988 (167, 179, 180), *991*, *993*
Bishop, C. A. (89), *440*
Bishop, C. T. 31 (116, 117), *55*

Bishop, D. J. 925 (30a), *933*
Bissett, F. H. 236 (49), *276*
Bissig, P. 647 (731), *676*
Bissig, R. 92 (83, 84), 106 (119), 115 (141), *149–151*
Bist, H. D. 362 (49), *375*
Bistrzycki, A. 832 (78), *854*
Bjellqvist, B. 972 (40), *989*
Bjorkquist, D. 766 (17), *811*
Bjorkquist, L. 766 (17), *811*
Black, D. K. 845 (156), *856*
Black, D. St. C. 4 (14), 20, 22 (76), 23, 24 (85), 36 (137), *52*, *54*, *55*; 60, 101 (8a), *145*
Black, P. E. 701 (210), *716*
Blackborow, J. R. 94 (96), *149*
Blackborrow, J. R. 25 (94), *54*
Blackburn, C. E. 404 (36), *439*
Blackett, B. N. 437 (37), *439*; 632 (496, 498–500), 633 (500), *670*, *671*
Blackwell, L. F. 394 (38, 39), *439*
Bladon, P. 891 (69), *902*
Blagodatskikh, S. A. 614 (103), *662*
Blagoveschchenskii, V. S. 845 (158), 846 (166), 847 (188), *856*
Blain, M. 776 (111), *813*
Blais, J. 937 (19), *962*
Blakis, U. 217 (27), *275*
Blanc, A. 618 (249), *665*
Blanchard, K. R. 875 (44), *879*
Blanchard, L. P. 640 (664, 665), *674*; 702 (223–226), *717*
Blanco, L. 804 (355), 807 (389), *819*, *820*
Blandina, L. A. 638, 639 (635), *673*
Blank, B. 513 (299), *536*; 949 (241), *967*
Blanzat, J. 40 (150), *56*; 62, 135 (12b), *145*
Blasius, E. 60 (5a), 110 (133c), 143 (5a), *144*, *151*
Blatcher, P. 571 (179b), *604*
Blatz, H. 735, 741 (225), *757*
Blazhin, Yu. M. 736 (157, 166, 177), *756*
Bledsoe, J. O. 635 (574), *672*
Bleger, J. 738 (186), *756*
Bleikolm, A. 799 (318), *818*; 886 (42, 43), *901*
Blezard, M. 624 (383), *668*
Blicke, F. F. 741 (253), *758*
Blinov, B. B. 691 (76), *713*
Bloch, M. 769 (30), *811*
Block, B. 267 (110), *277*
Block, E. 544 (33), 546 (45), 547 (52), 556 (123), 558 (123, 132), 564, 566 (149), 571 (183), 572 (183, 187), 577 (33), 585, 587 (149), *601*, *603–605*; 862 (11), 877, 878 (56), *878*, *879*; 923 (4), 926 (35), 931 (4), *932*, *933*
Blocki, D. 264 (28), *275*
Blok, A. P. 846 (167), 850 (254), *856*, *858*
Blokhina, A. N. 802 (334), *819*
Blokhina, O. G. 706 (291), *718*
Blomquist, A. T. 741 (252), *758*
Blood, A. E. 748 (331), *760*
Bloor, J. E. 355, 360 (23), *375*
Blount, J. F. 207 (103), *214*
Blout, E. R. 33 (128), *55*; 295 (47), *297*
Blukis, U. 177 (3), *211*
Blum, J. 520 (333), *537*; 623 (366), 635 (589–591), 641 (674), *668*, *672*, *674*
Bly, R. K. 520 (334), *537*; 625 (392), *668*
Bly, R. S. 625 (392), *668*
Blyumberg, E. A. 618 (244, 246), *665*
Blyumenfel'd, A. L. 708 (332), *719*
Boar, R. B. 597 (302), *607*
Boberg, F. 399 (40), 427 (349), *439*, *446*
Bobik, A. 408 (41), *439*
Bobolev, A. V. 618 (261, 288), *665*, *666*
Bobylev, B. N. 616 (191), 617 (206, 207), 635 (579), *664*, *672*
Bobyleva, L. I. 617 (206, 207), *664*
Bocard, C. 618 (259, 286), *665*, *666*
Boche, G. 795 (274), *817*
Bochkarev, V. N. 307 (102, 103), *321*
Bocian, D. F. 268–270 (29, 30), *275*
Bock, H. 544, 577 (33), *601*; 769 (27), 808 (27, 393), *811*, *820*
Bockrath, B. 946 (190), *966*
Boden, R. 165 (25), *173*
Boden, R. M. 171 (68), *174*
Bodor, N. 860 (2), *878*
Bodot, H. 613 (67), *661*
Bodwell, C. E. 553 (96), *602*
Boeckman, R. K. 800 (322), 801 (324), *818*
Boeckman, R. K. Jr. 631 (475), *670*
Boekelheide, V. 595 (292), *607*
Boelema, E. 623 (360), *668*
Boelens, M. 849 (214), *857*
Boelsma, G. H. 633 (520), *671*
Boer, Th. J. de 825, 831 (35), *853*
Boeseken, J. 862 (18), *878*
Boëtius, M. 399 (375), *447*
Bogajian, C. 633 (514), *671*
Bogatskaya, L. G. 700 (186), *716*
Bogatskii, A. V. 686 (19, 28, 30), *712*; 839 (117), *855*
Bogatyreva, T. A. 795 (273), *817*
Bogdanova, A. V. 798 (307), *818*
Bogdanowicz, M. J. 625 (402, 407), *668*, *669*; 875 (49–51), 876 (50, 51), *879*
Bogentoft, C. 518 (323), *537*
Boger, D. L. 486 (111), *531*

Bogolyubov, G. M. 306 (80, 82), *320*
Bohlmann, F. 310 (145), 314 (145, 228), *322*, *324*; 520 (334, 336), 521 (336), *537*
Bohm, B. A. 452 (16), *466*
Böhm, R. 308 (111), *321*; 825 (39), *853*
Böhme, H. 544 (29), 554 (106), 555 (110), *601–603*; 711 (386), *720*
Bohn, R. K. 179 (15), *212*
Boigegrian, R. 623 (362, 363), *668*
Boiko, Yu. A. 306 (80), *320*
Boileau, S. 120 (159, 160), *152*
Boireau, G. 648 (743), *676*
Boison, J. K. O. 459 (61), *467*
Boivin, J. L. 462, 463 (93), *468*
Bolman, P. S. H. 931 (69), *934*
Bologa, M. 400 (42), *439*
Bol'shakov, B. V. 977 (83), *990*
Bolton, G. L. 939 (104a, 105, 111, 112, 113a), *964*
Bolton, P. D. 363 (78), *376*
Bombieri, G. 132 (223a,b), *155*
Bonaccorsi, R. R. 358 (32), *375*
Bonati, F. 34 (133), *55*
Bonchev, D. 618 (282), *666*
Bondarenko, A. V. 617 (199), 635 (579), *664*, *672*
Bondarenko, B. R. 437 (43), *439*
Bondi, A. 362 (60), *376*
Bonifačić, M. 925 (29), 926 (39b), 932 (91), *933*, *934*; 977 (89a), 983 (122, 123, 125), 984 (123, 130a), 985 (89a, 130a), 986, 987 (135), *990–992*
Bonner, W. A. 516 (311), *536*; 587, 593 (239), *606*
Bono, M. R. 938 (61), *963*
Bontempelli, G. 332 (17), 339 (17, 32), 340 (36), 342 (43), *350*
Boonstra, H. J. 808 (400), *820*
Booth, G. E. 238, 239 (31), *275*
Booth, H. 241 (32), *275*
Bopp-Schön, A. 955, 961 (293), *969*
Borch, R. F. 624 (373), *668*
Borchers, F. 302 (30), 310 (30, 151), 313 (212, 213), 325 (286), *319*, *322*, *323*, *325*
Borcic, S. 419 (100), 425 (8), *438*, *440*
Bordignon, E. 554 (104), *602*
Bordwell, F. G. 419 (45), 429 (44), *439*; 548 (66), *602*; 896 (86), *902*
Borer, R. 621 (342), *667*
Borg, A. P. ter 511 (291), *536*
Borgen, G. 10, 18 (35), *53*; 883 (14), *901*
Borgers, T. R. 822 (8), *853*
Borkovski, M. 391 (187), *442*
Borleau, L. 172 (74), *174*
Bornowski, H. 313 (207), *323*
Borowitz, I. J. 688 (54), *713*
Borowitz, J. 92 (84), *149*
Borrows, E. T. 2 (9), *52*
Bors, W. 987 (141), *992*
Borstnik, B. 611 (34), *660*
Bortyan, T. A. 615 (136), 619 (294), *662*, *666*
Bory, S. 555 (117), *603*
Bos, H. J. T. 692 (102, 103), *714*
Bosch, H. W. 593 (284), *607*
Bosin, T. R. 400 (46), *439*
Bošnjak, J. 501 (219), 502 (225), *534*
Bosshardt, H. 312 (199), *323*
Bost, P. E. 616 (166), *663*
Bost, R. O. 653 (815), *677*
Boswell, D. E. 574 (197), *605*
Bothe, E. 955 (290), 958 (321–323, 325), 960 (322), *969*, *970*
Bothe, H.-K. 937, 944 (18a), *962*
Botkina, S. S. 736 (176), *756*
Botnikov, M. Ya. 916 (81), *921*
Bottari, F. 620 (313), 621 (340), *667*
Botteghi, C. 688 (55), *713*
Botteron, D. G. 723 (13), 724 (40), 727, 728 (13), *753*
Bottini, A. T. 231 (33), *275*
Bottino, F. 312 (195, 196), *323*
Bottomley, C. G. 929 (59), *934*
Bouas-Laurent, H. 9, 18 (30), *53*; 60 (9n), *145*
Bouchet, P. 658 (903), *679*
Bougault, J. 540, 592 (3), *600*
Bouget, H. 659 (923), *680*
Boulette, B. 552 (92), *602*
Bourgain, M. 525 (374), *538*; 774 (93), *813*
Bourn, A. J. R. 237 (17), *275*
Bourns, A. M. 731 (112), 742, 745 (296), *755*, *759*
Bourns, A. N. (17, 47), 380 (380), 416 (145), 429 (380), *438*, *439*, *441*, *447*
Bournsnell, J. C. 392 (48), *439*
Boussard, G. 221 (71), *276*
Boutan, P. J. 548 (66), *602*
Bovey, F. A. 826 (47), *854*
Bovio, A. 553 (97), *602*
Bowden, K. 416 (49), *439*; 482 (74), *530*
Bowen, M. W. 915 (73), *921*
Bowen, R. 422 (57), *439*
Bowen, R. D. 300 (12), 302, 303 (42), *319*
Bower, J. D. 692, 693 (106), *714*
Bowers, A. 482 (74), *530*
Bowers, C. W. 5 (21), *52*; 123 (170b), *153*; 166 (31), *173*; 312 (186), *323*
Bowers, M. T. 316, 317 (254), 318 (272), *324*
Bowie, J. H. 299 (4), 308 (116, 118), 313 (204), 314 (225–227), *318*, *321*, *323*, *324*; 842, 843 (144, 145), *856*

Bowman, M. 945 (188b), *966*
Bowman, M. I. 481 (70), *530*
Bowman, M. K. 938 (81), *964*
Bowman, N. S. (76), *440*
Bowman, R. E. 723, 725 (28), *753*
Bowman, R. M. 613 (74), *661*
Bowmann, W. G. 731 (106), *754*
Boxer, M. 592, 595, 597 (267), *607*
Boyajian, C. G. 653, 654, 658 (834), *678*
Boyd, A. W. 179 (19), *212*; 382 (86), *440*
Boyd, D. B. 222 (7, 34), *275*
Boyd, D. R. 567 (161), *604*; 613 (73, 76), 620 (327), 634 (549), 637 (327), *661*, *667*, *672*
Boyd, R. J. 823 (12), *853*
Boyer, P. D. 988 (150), *992*
Boykin, D. W. 751 (358), *760*
Boys, S. F. 279 (2b), *296*
Bradamante, S. 555, 567 (326), *608*
Bradbury, A. G. W. 952 (283), 961 (333), *968*, *970*
Bradley, C. H. 236 (18), *275*
Bradshaw, J. S. 11, 12 (44), 16 (59, 60), 19 (59), 20 (72), 21 (59), 22 (59, 72, 82–84), 23 (83), 31 (114–121), 32 (122, 124), 44 (168), *53–55*, *57*; 60 (8d, 9o,r), 83 (70a,b), 84, 92 (69, 70a,b), 93 (69), 94 (69, 70b), 101 (8d, 69), 121, 122 (165), *145*, *148*, *152*; 852, 853 (269), *858*
Brady, B. A. 614 (122), *662*
Braid, M. 60 (9s), *145*
Brakmane, M. T. 699 (164), *715*
Bram, G. 169 (59), *174*
Branchi, T. A. 163 (16), *173*
Brand, H. 139 (252), *156*; 210 (106), *214*
Brand, J. C. D. 247, 258 (12), *275*
Brandini, A. 38 (148), *56*
Brandon, J. R. 938 (94), *964*
Brandsma, L. 588, 589 (250, 251), 590 (257), *606*; 808 (400), *820*
Brandsma, L. B. 689 (67), *713*
Brandt, M. K. 825 (25), *853*
Brandt, R. 520 (334), *537*
Brannock, K. C. 785 (194), *815*
Brasen, W. R. 929 (59), *934*
Braslavsky, S. 923, 927 (5), 930 (68), *932*, *934*
Braun, H. 625 (405), *669*
Braun, M. 659 (951), *680*
Braunton, P. N. 312 (197), *323*
Brauwer, A. C. 633, 645 (512), *671*
Braye, E. H. 465, 466 (104), *468*
Bredereck, H. 785 (195), *815*
Breen, D. L. 355, 360 (23), *375*
Breig, E. L. 217 (109), *277*
Breitenkamp, M. 950 (248a), *967*
Breiter, J. J. 588 (248, 249), 590 (248), *606*
Bremer, N. 917 (86), *921*
Bremholt, T. 653, 654 (820), *677*
Bremner, J. B. 624 (374), *668*
Brendlein, W. 417 (50), *439*
Brenken, B. 832 (78), *854*
Brennan, T. M. 860 (9), *878*
Breslow, E. 295 (48), 296 (48, 60), *297*, *298*
Breslow, R. 617 (226), *665*
Bressel, U. 788 (227), *816*
Brett, T. J. 479 (62), *530*
Breuer, A. 617 (237), *665*
Brewer, F. M. 62 (19b,c), *146*
Brewster, J. H. 283 (10), *296*; 312 (178), *322*; 518 (325, 326), *537*
Bridges, A. J. 629 (454), *670*
Bridges, J. W. 420 (6), *438*
Bridges, L. 924 (14, 15), 925 (14, 15, 28), *933*
Bridgewater, A. J. 546 (43), *601*
Brige, E. K. 751 (351), *760*
Bright, D. 125 (195), 129 (212), 130 (213b), *154*
Brill, W. 616 (171), *663*
Brill, W. F. 617 (242), *665*
Brimacombe, J. S. 238 (25), *275*
Brimage, D. R. G. 943 (159), *965*
Brink, M. 833 (85), *854*
Brion, C. E. 315 (239, 240), 316 (239), *324*
Bristow, P. A. 852 (263), *858*
Britton, C. E. 731 (109), *755*
Brizuela, C. L. 636 (603b), *673*
Brizzolara, A. 782 (171), *815*
Broaddus, C. D. 431 (51), *439*
Brod, L. H. 889 (56), *901*
Brodski, L. 617 (231), *665*
Brodskii, E. S. 306, 308 (70), *320*; 977 (78), *990*
Broekhof, N. L. J. M. 508 (276), *535*
Broer, W. J. 305 (53, 54), 325 (280, 281), *320*, *325*
Brogli, F. 769 (30), *811*
Brois, S. J. 231 (35), *275*
Bron, J. 429 (52), *439*
Bronstein, J. 885 (32), *901*
Brook, A. G. 741 (234), *757*
Brooks, L. A. 524 (364), *538*
Brousie, D. 526 (379), *538*
Broussard-Simpson, J. 60 (9a), *145*
Browder, L. E. 723 (19), *753*
Brown, B. J. 917 (96), *921*; 938 (93a,b), *964*
Brown, B. R. 518 (324), *537*
Brown, C. A. 301 (25), *319*; 803 (346), *819*

Brown, E. D. 589, 590 (255), *606*; 831 (70), *854*
Brown, G. L. 496 (181), *533*
Brown, H. C. 486 (116), 519 (329), 527 (390, 392), *531*, *537*, *538*; 598 (306), *608*; 638 (623, 625, 627), 639 (646, 647), 640 (649, 650), *673*, *674*; 886 (45), *901*
Brown, M. E. 365 (90), *376*
Brown, P. 307 (84), 309 (126, 128), 311 (159), 314 (236), *320–322*, *324*
Brown, P. M. 573 (194), *605*
Brown, R. F. 726 (61, 64), *754*
Brown, R. K. 401 (53, 54), 430 (54), *439*; 780 (154), *814*
Brown, R. P. 401, 430 (54), *439*
Brown, W. H. 2 (8), *52*
Brownell, R. 512, 513 (296), *536*
Browning, H. E. 306 (67), *320*
Brownstein, S. 231 (36), *275*
Bruce, W. F. 486 (115), *531*
Bruckenstein, S. 138 (251), *156*
Bruice, P. Y. 632 (493), 634, 658 (546), *670*, *672*
Bruice, T. C. 632 (493), 634 (546, 550), 658 (546), *670*, *672*; 890, 895 (63), *902*
Bruijn, Ms. J. F. de 25, 29, 30 (96), *54*
Bruins, A. P. 313 (217–219), *323*
Brun, J. P. 307 (93), *320*; 710 (357), *720*
Brunelle, J. A. 222 (37), 263 (45), 265–267 (43), *275*, *276*
Brunfelter, B. 403 (394), *447*
Brüning, W. 943 (155), *965*
Brunissen, A. 422 (30), *439*
Brüntrup, G. 774 (95), *813*
Brusentseva, S. A. 950 (243a,b), *967*
Brutcher, F. V. 735 (204), 738 (203, 204), 740 (212), *757*
Brůza, K. J. 800 (322), 801 (324), *818*
Bryan, G. T. 402 (246), *444*
Bryce, W. A. 465 (105), *468*
Bryce-Smith, D. 618 (275), *666*; 794 (259), *817*
Brzezinska, K. 702 (231), *717*
Bub, O. 741 (233), *757*
Bubnov, N. N. 951 (263), *968*
Bubnov, Y. N. 802 (336), *819*
Buchachenko, A. L. 617 (217), *664*
Buchanan, B. G. 304 (49, 50), *319*
Buchanan, G. W. 236 (18), *275*; 835, 836 (101), 838 (106, 109, 110), 849 (110), 850 (109, 110, 225, 226), *855*, *857*
Buchanan, J. D. 988 (159, 161, 182), *992*, *993*
Buchanan, J. G. 610, 630, 632, 637, 656 (9), *659*
Buchert, A. R. 558 (130), *603*
Buchholz, B. 703 (237), *717*
Büchi, R. 92 (88), 115 (142), 142 (257), *149*, *151*, *156*
Buchman, O. 408 (367), *446*; 520 (333), *537*; 635 (590, 591), *672*
Buchs, A. 304 (50), *319*
Buck, K. W. 848 (200, 204), 849 (205), *857*
Buckwalter, B. 801 (326), *818*
Bucquoye, M. 312, 317 (189), *323*
Bucy, W. E. 217 (55), *276*
Buddenbaum, W. 422 (57), *439*
Buddenbaum, W. E. (364), *446*
Buddrus, J. 642, 643 (682), 659 (954), *675*, *681*; 795 (272), *817*
Budnik, R. A. 618 (266), *666*
Budzikiewicz, H. 299, 300 (1), 304 (44), 306 (1, 71), 307 (71, 88, 99–101), 308 (71, 108), 309 (71), 310 (44, 71), 311 (71, 163), 312 (71), *318–322*; 492 (153), *532*
Bugaenko, L. T. 939 (133b), 943 (160), *965*
Buhleier, E. 30 (113), 34 (132), 39 (149), 41 (154), *55*, *56*; 60 (9g,h), 62 (15g,i, 25c), 64 (25c,e), 92 (85d), 114 (15i, 138), 139, 142 (25c, 26e), *145–147*, *149*, *151*
Bukharov, V. G. 741, 742 (242), *758*
Buley, A. L. 951 (262), *968*
Bull, H. G. 882, 888, 889, 895, 896, 898, 899 (8), *900*
Bullitt, O. H. 550, 555 (81), *602*
Bullmann, J. F. 172 (78), *174*
Bulygin, M. G. 618 (244), *665*
Buncel, E. (55), *439*
Bunnenberg, E. 295 (46), *297*
Bunnett, J. F. 587 (247), *606*; 790 (232), *816*; 896 (90, 91), *902*
Bunton, C. A. 501 (221), *534*; 722 (6), 723 (6, 10, 12, 20), 724 (6, 12), 726 (6, 20), *752*, *753*; 852 (259), *858*
Bünzli, J.-C. G. 123 (180f,h), *153*
Burchardt, B. 655 (841), *678*; 689 (65), *713*
Burchill, C. E. 950 (249, 250), 951 (249, 259–261, 268), *968*
Burden, I. J. 11–13, 44 (43), *53*
Burdge, D. N. 587 (247), *606*
Burdon, I. J. 101 (115), *150*
Burdon, J. 847 (191, 192), *857*
Burfield, D. R. 659 (932), *680*
Burg, T. E. 19 (68), *54*
Burger, K. 797 (292), *818*
Burgermeister, W. 60, 64, 68, 69, 72, 74, 91, 92, 99, 101, 111, 115 (7b), 124, 125, 130 (190d), 140 (7b), *144*, *154*
Bürgi, H. 11 (40), *53*
Burgstahler, A. W. 593 (275), *607*

Burianek, J. (56), *439*
Burkett, H. 422 (57), *439*
Burkhardt, J. 825 (42), *854*
Burkhardt, T. J. 774 (83), *813*
Burlingame, A. L. 309 (138), 311 (164), *321*, *322*
Burmakina-Lunenok, V. A. 428 (58), *439*
Burnelle, L. 860 (3), *878*
Burnett, G. M. 452 (11), *466*
Burns, J. 403 (59), 408, 411 (425), *439*, *448*
Burr, J. G. 386 (18, 60), *438*, *439*
Burr, M. 745 (274), *758*
Burrows, E. P. 520 (334), *537*
Burrows, H. D. 424 (61), *439*
Bursey, J. T. 303 (43), *319*
Bursey, M. M. 303 (43), 309 (125), 310 (140, 141), 314 (232), 317 (260), *319*, *321*, *322*, *324*
Burstein, S. H. 481 (72), *530*
Burtle, J. G. 381 (62), *439*
Burwell, R. L. 523 (361), *538*
Burwell, R. L. Jr. 431 (118), *441*
Busch, D. H. 4 (13), 19 (13, 66, 67), 36 (13, 66, 139, 141), *52*, *54*, *56*
Busch, S. 615 (144), *662*
Buschhoff, M. 774 (90), *813*
Buse, C. 633 (527), *671*
Busetti, V. 180 (55), *213*
Bush, J. D. 485 (98), *531*
Bush, M. A. 111, 125 (135), 126 (205), 129 (135), 130 (213a,b), *151*, *154*; 196 (82), *213*
Bush, P. 15 (49), *53*
Bushaw, B. A. 168, 172 (46), *173*
Bushell, A. W. 723 (15), *753*
Bushin, A. N. 616 (165), 635 (579), *663*, *672*
Bushweller, C. H. 222 (37), 223 (88), 224 (158), 225 (40, 88, 170), 230 (41, 47), 231 (26), 232 (48), 234 (95), 236 (42, 49, 93, 94, 96), 240 (95), 244 (46, 94), 249 (96), 261 (38), 263 (39, 45), 265 (43, 44), 266 (43), 267 (39, 43), 274 (38), *275–278*; 828 (57, 58), *854*
Busing, K. H. 390 (63), *439*
Busko-Oszczapowicz, I. 407 (443), *448*
Buslova, E. M. 730, 731 (99, 100), *754*
Buss, J. H. 362 (52), *375*
Buswell, R. L. 168, 172 (46), *173*
Büthe, J. 521 (340), *537*
Butler, A. R. 422 (64), *439*
Butler, D. 809 (407), *820*
Butler, D. N. 798 (304), *818*
Butler, P. E. 301 (23), *319*
Butlerov, A. 722 (2), *752*
Butterworth, F. 494, 505 (178), *533*
Buttrill, S. E. Jr. 317 (262), *324*
Buu-Hoi, N. P. 311 (174), *322*
Buxton, G. V. 938 (63c), 939 (114), 947 (230), 950 (248b, 257, 258a), *963*, *964*, *967*, *968*
Buys, H. R. 179 (10), *212*; 237, 238, 261, 262 (153), *278*; 840 (130–132), 847 (132), 850 (131), *855*
Buys, Th. S. V. 877 (57), *879*
Buzikiewicz, H. 300 (10), *319*
Bychkova, M. K. 735, 736, 738 (175), *756*
Bychkova, T. I. 780 (153), *814*
Byers, G. W. 932 (90), *934*
Byrne, B. 693, 694 (117), 699, 700 (172), *714*, *715*
Byrne, M. P. 5 (21), *52*; 123 (170b), *153*; 312 (186), *323*
Bzhezovskii, V. M. 770, 808 (44), *812*

Cabbiness, D. K. 87 (77), *149*
Cabiddu, S. 525 (370), *538*; 834 (87), *854*
Cadioli, B. 766 (13), *811*
Caglioti, L. 500 (217), *534*
Cagniant, D. 593 (285), *607*
Cagniant, P. 593 (285), *607*
Cahiez, C. 651 (780), *677*
Cahill, P. 765 (11), *811*
Cainelli, G. 486 (118), 500 (217), 501 (222), *531*, *534*; 626 (428, 429), *669*
Calas, R. 650 (757), *676*
Calder, I. C. 311 (173), *322*
Caldwell, R. A. 692, 694 (95), *714*
Callaghan, P. 566 (155), *604*
Callear, A. B. 924–927, 931 (18), *933*
Calo, V. 641 (671), *674*
Caló, V. 550 (80), *602*
Calvert, J. G. 904, 918 (5), *919*; 924 (9), *933*
Calvin, M. 262 (50), *276*; 931 (78), *934*
Cambie, R. C. 633 (518), *671*
Cambieri, M. 798 (312), *818*
Cambillau, C. 169 (59), *174*
Cameron, A. F. B. 492 (154), *532*
Cameron, G. S. 461 (86), *468*
Camp, R. L. 863 (26), 868 (39), 873 (26), *879*
Campbell, D. E. 591 (262), *606*
Campbell, D. H. 617 (239), *665*
Campbell, J. M. 918 (112), *921*
Campbell, J. R. 494 (167), *532*
Campbell, R. G. 710, 711 (372), *720*
Campbell, T. W. 745 (288), *759*
Campion, T. A. 657 (872), *679*
Camps, F. 784 (191, 192), *815*
Canfield, N. D. 342 (42), *350*
Cannie, J. 643, 658 (693), *675*
Cannon, J. G. 705 (267), *718*

Canonica, L. 633 (507), *671*
Cantacuzene, J. 620 (315–317), 624 (316, 317), 652 (788, 791), *667*, *677*
Canter, F. C. 735, 741 (233), *757*
Cantrell, T. S. 692 (101), *714*
Capobianco, G. 330 (11), *349*
Capobiano, G. 599 (313), *608*
Capon, B. 611 (27), 645 (709), *660*, *675*; 688 (51), *713*; 774 (97), *813*; 882 (6), 890 (64), 891 (67, 68), 895 (64, 67, 68), 898 (97), *900*, *902*
Caputo, J. A. 494 (174), *532*
Carapellucci, P. A. 982 (114), *991*
Carbonnelle, P. A.-C. 850 (227), *857*
Carden, B. M. 840 (133), *855*
Cardillo, G. 171 (67), *174*; 486 (114, 118), *531*
Carduff, J. 614 (123), *662*
Carey, F. A. (65), *439*; 519 (327), *537*; 547 (49), 571 (49, 182), *601*, *604*; 809 (406), *820*
Carless, H. A. J. 692 (92–94, 97, 107), 693 (92, 93), 694 (94, 97, 107), 708 (323, 328), *714*, *719*
Carls, G. A. 435 (28b), *438*
Carlsen, L. 222 (157), *278*; 822 (3), 823 (11), *853*
Carlson, D. D. 924–926, 931, 932 (13), *933*
Carlson, G. L. 356 (28), *375*
Carlson, R. 620, 621 (312), *667*
Carlson, R. G. 639, 640 (644), *674*
Carlson, R. M. 571 (178), *604*; 844 (151), *856*
Carlyle, D. W. 658 (895), *679*
Carmack, M. 294 (37, 38, 41), 295 (37, 38, 41, 45), *297*
Carmody, M. A. 693, 708 (121), *714*
Carnahan, J. E. 745 (286), *759*
Carnduff, J. 632 (492), *670*
Caron, G. 774 (96), *813*
Carpenter, F. H. 392, 394 (434), *448*
Carpenter, G. B. 230 (179), *278*
Carpenter, J. G. 706 (286), *718*
Carpenter, W. 301 (24), 304 (48), *319*
Carr, L. J. 884 (20, 23), *901*
Carr, M. D. 658 (886), *679*; 722 (6), 723 (6, 20), 724 (6), 726 (6, 20), *752*, *753*
Carreira, L. A. 217 (55), *276*
Carrington, A. 487 (122), *531*
Carroll, G. L. 167 (37), *173*
Carruth, R. L. 22 (84), *54*
Carruthers, R. J. 587 (327), *608*
Caruso, T. C. 5 (21), *52*; 123 (170b), *153*; 312 (186), *323*
Casadevall, A. 621 (343), *667*
Casadevall, E. 621 (343), *667*
Casagrande, M. 558 (136), *603*
Caserio, M. C. 305, 318 (51), *320*; 590 (256), *606*
Casey, C. 516 (310), *536*
Casey, C. P. 774 (83), *813*
Casey, J. P. 296 (56), *297*
Cashen, M. J. 893 (72–74), 894, 895 (73), 898 (74), *902*
Cass, W. E. 507 (264, 266), *535*
Cassell, J. D. P. 943 (159), *965*
Cassol, A. 123 (180a,c), 132 (223a), *153*, *155*
Castells, J. 784 (192), *815*
Castonguay, J. 309 (130), *321*; 918 (115), *922*
Castrillon, M. P. A. 547 (57), *601*
Castrio, C. E. 436 (66), *439*
Castro, B. 623 (362, 363), *668*
Castro, E. B. 624 (371), *668*
Catalano, S. 634 (540, 543), 642 (540), *671*; 689 (66), *713*
Cate, L. A. 163 (16), *173*
Catelani, G. 656, 657 (868), *679*
Catsch, A. 119 (155), *152*
Cattalini, L. 554 (104), *602*
Cattelain, E. 540, 592 (3), *600*
Catterall, R. 946 (193), *966*
Catton, G. A. 123 (180e), *153*
Causa, A. G. 611, 612, 620, 621 (38), *660*
Cauzzo, G. 558 (136), *603*
Cava, M. P. 543 (24, 25), *601*
Cavell, E. A. 707 (312), *719*
Cavill, G. W. K. 554 (105), *602*
Cavitt, S. B. 618 (260), *665*
Cawley, J. J. 474 (22), 483 (82), 529, *530*
Cazaux, L. 735 (168, 224), 736 (168), 741, 744, 745 (224), *756*, *757*; 847 (186), 850 (222, 223, 246–248), *856–858*
Cazaux, M. 917 (83), *921*
Ceccarelli, G. 686 (18), 688 (55), *712*, *713*; 808 (397), *820*
Ceccon, A. 329 (10), *349*; (67), *439*
Ceder, O. 650 (756), *676*
Ceder, O. J. 520 (334), *537*
Cederholm, B. J. 904 (6), *919*
Ceccon, A. (281), *444*
Čeković, Ž. 499 (211), 501 (218, 219), 502 (218, 225), *533*, *534*
Cellerina, G. 799 (313), *818*
Cenci, H. J. 740 (212), *757*
Cenci, S. 545, 571 (40), *601*
Cenini, S. 618 (254), *665*
Centola, P. 618 (285), *666*
Ceraso, J. M. 21 (77), *54*; 72 (54), 120 (162b), *148*, *152*
Ceré, V. 582 (221), *605*

Cerefice, S. A. 612, 613, 637, 638 (45), *660*
Cerfontain, H. 692, 694 (91), *714*
Cerny, M. 519 (328), *537*
Cerrai, P. 700 (187), *716*
Červený, L. 611 (26), 616 (188), *660*, *664*
Cesselli, P. 329 (10), *349*
Çetinkaya, E. 904, 916, 917 (18), *920*
Chabrier, P. 540, 592 (3), *600*
Chabudzinski, Z. 621 (336), *667*
Chachaty, C. 946 (214), *967*
Challis, B. C. 422 (68), *440*
Chalvet, O. 356 (30), 359 (35), *375*
Chambenois, D. 691 (82, 83), *713*
Chamberlain, P. 306 (67), *320*; 579 (209), *605*; 613 (62), *661*
Chambers, J. Q. 342 (42), *350*
Chambers, R. D. 692, 693 (99), *714*
Chan, F. H. 693 (116), *714*
Chan, H. F. 876 (52), *879*
Chan, K. C. 492 (155), *532*
Chan, K.-C. 709 (355), *720*
Chan, K. H. 779 (138), *814*
Chan, P. C. 982 (115), *991*
Chan, S. I. 11 (37), *53*; 179 (16), 194 (78), *212*, *213*
Chan, T. H. 522 (347), *537*; 629 (449), 641 (669, 673), *669*, *674*; 825 (27), *853*; 863 (27–31), 864 (30, 32), 866 (32), 869 (30), 871–873 (32), *879*
Chan, Y. 22, 23 (83), *54*; 121, 122 (165), *152*
Chancel, P. 769 (32), *811*
Chandra, S. 426 (69), *440*
Chaney, J. 272 (163, 164), *278*
Chang, H.-M. 222 (7), *275*
Chang, L. H. 631 (478), *670*
Chang, L. L. 78, 86 (76b), *148*
Chang, T. H. 870, 871 (40), *879*
Chang, Y. C. 558 (134), *603*
Chang, Y.-H. 591 (262), *606*
Chang, Y. W. 476 (42), 484 (89), 512, 513 (296), *529*, *531*, *536*
Chanon, F. 736 (173), *756*
Chao, B. Y.-H. 573, 576, 585 (193), *605*
Chao, Y. 49 (188), *57*; 107 (122e), 109 (130b), *150*, *151*
Chapat, J. P. 611, 612, 620 (36), 621 (36, 350), *660*, *667*
Chapius, G. 264 (28), *275*
Chapman, J. H. 492 (154), *532*
Chapman, O. L. 653, 654 (822), *678*; 692 (86), *713*
Chaput, G. 39 (149), *56*; 92, 98 (86b), *149*
Charles, H. C. 614 (94), *661*
Charles, S. W. 769 (37), *812*
Charpin, P. 132 (224), *155*
Chase, W. J. 938 (49b, 53), *963*
Chassaing, G. 850 (223, 248), *857*, *858*
Chastrette, F. 6 (22), *53*
Chastrette, M. 6 (22), *53*
Chatani, Y. 9 (33), *53*; 137 (246), *156*
Chatterjee, A. 642 (679, 680), 658 (680), *674*
Chatterji, A. K. 484 (88), *530*
Chatterway, F. D. 571 (180), *604*
Chattopadhyay, J. K. 773 (72), *812*
Chattopadhyaya, J. B. 308 (120), *321*
Chatziiosifidis, I. 806 (371), *820*
Chaudet, J. H. 739 (211), *757*
Chaudhri, S. A. 938 (33), *962*
Chaudhuri, N. R. 707 (296), *718*
Chautemps, P. 612, 613 (43), 614, 638 (115, 116), *660*, *662*
Chauvette, R. R. 582 (222), *605*
Chavdarian, C. G. 802 (325), *818*
Chaykovsky, M. 625 (408), *669*
Cheema, Z. K. 723, 725 (30), *753*
Cheer, C. J. 634 (538, 539), *671*
Chen, A. 431 (90), *440*
Chen, C. H. 622 (354), *667*
Chen, H. J. 416 (211, 212), *443*; 774 (99), 775 (108), 776 (99, 108), *813*
Chen, H. L. 416 (221), 431 (222), *443*; 775, 776 (103), *813*
Chen, H. Y. 611, 612, 620, 621 (38), *660*
Chen, M. J. Y. 618 (273), *666*
Chen, T. S. 390 (70), *440*
Cheney, J. 62 (13b), 76 (60), *145*, *148*
Chenoweth, M. B. 51 (192), *57*
Chermin, H. A. G. 368 (133), *377*
Chern, C. 161 (14), 170 (14, 63, 65), 171 (65), *173*, *174*
Chern, Ch. J. 485 (96), *531*
Chernischkova, F. A. 638, 639 (635), *673*
Chernousova, N. N. 642 (686), *675*
Chernov, A. B. 798 (308), *818*
Chernyshev, E. A. 402 (415), *448*
Chernyshkova, F. A. 635 (567), *672*
Chernyuk, K. Yu. 614 (128), *662*
Chian, L. L. 39 (149), *56*
Chiang, C.-S. 885 (38), 886 (44), *901*
Chiang, Y. 416 (212, 214–218), 431 (214, 215, 218), *443*; 774 (99), 775 (103, 113), 776 (99, 103, 113), *813*; 893 (73, 75), 894 (73), 895 (73, 78), *902*
Chiasson, B. A. 613 (66), *661*
Chichkareva, G. G. 749 (343, 347), *760*
Chiellini, E. 772 (67), 808 (397), *812*, *820*
Chiesa, P. P. 22 (81), *54*
Chiglien, G. S. 769 (35), *812*
Childs, M. E. 167 (34), *173*
Ching, T.-Y. 558 (129), *603*
Chinn, L. J. 471 (6), 492 (152), *528*, *532*

Chiotan, C. 401 (71), *440*
Chirakadze, G. G. 972 (5, 6, 9, 21, 26, 30), 974 (26), 975 (5, 6, 21, 65), 977 (76), 987 (139), *988–990*, *992*
Chivadze, G. O. 745 (297), *759*
Chizhov, O. S. 317 (263), 325 (294), *324*, *325*
Chmielenska, K. 307 (91), *320*
Choc, C. E. 860–862 (6), *878*
Chock, P. B. 64 (30a), 69, 70 (43), 72, 73, 78, 101, 111 (48), 115 (30a), *147*, *148*
Chong, A. O. 617 (208), *664*
Chong, H.-L. 709 (355), *720*
Choo, H. 623 (365), *668*
Chorev, M. 163, 164 (19), *173*
Chovin, P. 626, 657 (432), *669*
Chow, F. 544 (30), *601*
Chrétien-Bessière, Y. 631, 638 (470a), *670*
Christau, H.-J. 772 (63), *812*
Christe, K. O. 710, 711 (373), *720*
Christeleit, W. 96 (104), *150*
Christensen, B. G. 615 (150), *663*
Christensen, J. J. 11, 12 (44), 16 (57, 60), 19, 21 (57), 22 (82–84), 23 (83), 31 (115–121), 32 (124), 44 (164, 165, 167, 168), *53–55*, *57*; 60 (3b, 7d,f, 8b, 9r), 68, 72 (7d), 78 (65), 80 (8b, 67a,b, 68), 81, 82 (67b), 83 (70a,b), 84 (69, 70a,b), 87 (65), 92 (7d, 8b, 67a,b, 68, 69, 70a,b, 87), 93 (69), 94 (69, 70a,b), 99 (7d,f), 101 (7d,f, 8b, 65, 67a,b, 69), 111–113 (65), 121 (65, 165), 122 (165), 123 (179, 183), 125 (196), 131 (217, 218), 132 (225), *144*, *145*, *148*, *149*, *152–155*; 157 (2), *172*; 187 (59), 192 (75), *213*; 852, 853 (269), *858*
Christensen, L. W. 620 (321), *667*
Christian, J. E. 405 (365), *446*
Christiansen, R. G. 401 (53), *439*
Christol, H. 613 (53), 620 (333), *660*, *667*; 723, 727, 728 (18), *753*; 772 (63), *812*
Chu, E. J.-H. 726 (56, 58), *753*
Chu, Y. 741 (252), *758*
Chuah, T. S. 526 (384), *538*
Chuche, J. 308 (109), *321*; 620 (325), 621 (334, 338), 625 (338), 634 (556, 557), 655 (334, 556, 557, 840), *667*, *672*, *678*; 689 (62, 63), 698 (160), *713*, *715*
Chukovskaya, E. T. 802 (333), *819*
Chum, K. 359 (37), *375*
Chung, D. C. 705, 706 (273), *718*; 791 (244), *817*
Chung, D. Y. 216 (3), *275*
Chung, V. V. 653, 654 (835), *678*
Chupakhin, O. N. 736 (165), *756*
Chupka, W. A. 939, 944 (127), *964*
Chwang, W. K. 774, 775 (100), *813*
Chwialkowska, W. 702 (231), *717*
Ciabattoni, J. 611 (29), *660*
Ciampolini, M. 123 (180i), 135 (238), *153*, *155*
Ciani, S. 92 (90), *149*
Cier, A. 391 (72), *440*
Ciereszko, L. S. 386 (60), *439*
Cieślak, J. 407 (443), *448*
Cifka, J. (56), *439*
Ciganeck, E. 520 (334), *537*
Cimerman, Z. 92 (83), 109 (132), *149*, *151*
Ciminale, F. 550 (80), *602*
Cinquini, M. 17 (62), 41 (155), *53*, *56*; 115 (146), *152*; 164, 166, 169, 172 (22), *173*; 547, 548, 573 (56), *601*
Ciola, O. R. 379 (100), *377*
Cistaro, C. 555, 567 (326), *608*
Claeson, G. 262 (50), *276*; 294, 295 (36, 40), *297*
Claesson, A. 518 (323), *537*
Claisen, L. 885 (28), *901*
Claiser, L. 885 (36), *901*
Clar, E. 373 (124), *377*
Clardy, J. 639 (645), 658 (897), *674*, *679*; 794 (257), *817*
Claridge, R. F. C. 918 (118–120), *922*
Clark, A. H. 180 (23), *212*
Clark, B. C. Jr. 633 (506), *671*
Clark, G. B. 273 (51), *276*
Clark, G. C. 862, 868 (17), *878*
Clark, J. 85 (74), *148*
Clark, L. B. 924, 929 (10), *933*
Clark, R. 622 (357), *668*
Clark, R. D. 739 (211), *757*; 804 (362), *819*
Clark, R. J. H. 137 (242), *155*
Clarke, J. K. 431 (73), *440*
Clarke, M. F. 738 (187), *756*
Clarke, M. J. 707, 708 (314), *719*
Clarke, T. G. 502 (230, 231), *534*
Claus, P. 426 (74), *440*
Clausnitzer, R. 526 (385), *538*
Clauson-Kaas, N. 748 (334), *760*
Cleland, J. 494, 495 (175), *532*
Cleland, J. H. 496 (180), *533*
Clemens, K. E. 865 (37), *879*
Clement, J. R. 988 (154, 172, 176), *992*, *993*
Clements, A. D. 707 (319), *719*
Clerc, G. 746 (315), *759*
Clerc, J. J. 92 (87), *149*
Cliff, G. R. 778 (133), *814*
Clifft, B. E. 938 (58), *963*
Clive, D. L. J. 629 (450, 451), *669*; 887 (47), *901*
Clough, F. B. 289 (23), *297*

Coates, R. M. 591 (263), *606*; 614 (101), 625, 626 (420), *661*, *669*; 806 (373), *820*
Coates, W. M. 486 (105), *531*
Coburn, E. R. 728, 729 (77), *754*
Coburn, M. D. 773 (74), *812*
Cochrane, W. P. 696, 699, 710 (141), *715*
Cockcroft, R. D. 655 (838), *678*
Cocker, J. D. 580 (213), *605*
Cocker, W. 614 (104), 620 (310), 621, 622 (349), *662*, *667*
Cockerill, A. F. (75), *440*
Cocu, F. G. 625 (393), *668*
Cody, R. 270, 272 (79), *276*
Coene, E. 255 (52), *276*
Coghlan, M. J. 486 (109), *531*
Cognion, J. M. 636 (596), *673*
Cohen, H. L. 741 (234), *757*
Cohen, M. D. 362 (54, 56), *376*
Cohen, S. 408 (367), *446*
Cohen, T. 591 (261), 600 (319), *606*, *608*; 808 (405), *820*
Cohoe, G. F. 707 (317), *719*
Coke, J. L. 658 (907), *679*
Cole, E. R. 554 (105), *602*
Coleman, D. L. 295 (47), *297*
Coleman, R. A. 527 (392), *538*
Coles, L. 307 (85), *320*
Collange, E. 363 (73), *376*
Collet, A. 120 (160), *152*; 172 (74), *174*
Collin, G. J. 973 (52), *990*
Collin, J. E. 829, 843 (63), 847 (195, 196), 848 (63, 195), 852 (267, 268), *854*, *857*, *858*
Collins, C. J. (76), *440*; 722 (3, 5, 7–9), 723 (3, 30, 31), 725 (9, 30, 54), *752*, *753*
Collins, J. C. 485 (101), *531*
Collins, P. M. 494 (166, 170, 176), *532*, *533*
Coloma, S. 115 (146), *152*
Colombi, S. 284 (14), *297*
Colonge, J. 745 (262, 263), 746 (315), *758*, *759*
Colonna, S. 41 (155), *56*; 547, 548, 573 (56), *601*
Coltier, L. 885 (41), *901*
Colussi, A. J. 465, 466 (101), *468*
Colvin, E. W. 803 (339), *819*
Combret, J. C. 624 (375–377, 380), 652 (787), *668*, *677*
Comer, F. 579 (217), *605*
Commerçon, A. 525 (374), *538*; 774 (93), *813*
Condé, G. 847 (196), *857*
Condé-Caprace, G. 829, 843 (63), 847 (195), 848 (63, 195), 852 (267, 268), *854*, *857*, *858*
Condon, E. 279 (2d), *296*
Conia, J. M. 875 (46), *879*
Conia, J.-M. 723, 726, 727 (34), *753*; 804 (355), 807 (387, 389), *819*, *820*
Conlon, L. E. 772 (64), *812*
Conn, R. 508 (275), *535*
Connolly, E. E. 749 (337), *760*
Connon, H. 252, 254, 255 (22), *275*
Connon, N. W. 543, 544 (21), *601*
Connor, R. 542 (16), *600*
Conover, W. W. 613, (85), *661*; 875 (48), *879*
Conrad, R. A. 622 (356), *668*
Conroy, H. 414 (77), *440*
Consiglio, G. 688 (55), *713*
Conturier, D. 706 (293), *718*
Convert, O. 777, 778 (118), *814*
Cook, A. G. 762 (6a), 787 (219), *811*, *816*
Cook, D. H. 37 (144–146), *56*; 132 (226e), 133 (226e, 227), *155*
Cook, D. M. 168, 172 (46), *173*
Cook, F. L. 4 (19), 5 (19, 21), 52 (19), *52*; 123 (170b), *153*; 166 (31), *173*; 312 (186), *323*
Cook, G. B. (96), *440*
Cook, G. L. 927, 931 (43), *933*
Cook, J. K. 491 (144), *532*
Cook, M. J. 571 (177), *604*; 840 (133), 844, 845 (152), 848, 849 (203), *855–857*
Cook, R. J. 315 (237), *324*
Cook, R. L. 847 (177), *856*
Cooke, B. 637 (614), 638, 640 (620), *673*
Cooks, R. G. 301 (26), 304 (45), 308 (26), 309 (123, 124), 311 (124, 158), 312 (180, 198), 313 (198, 202), 325 (293), *319*, *321–323*, *325*
Cookson, R. C. 412 (78), *440*; 509 (278), 511 (292), *535*, *536*; 650 (769), *676*, 693 (115), *714*; 862 (16), *878*
Coope, J. A. R. 465 (105), *468*
Cooper, A. 825–827 (43), *854*
Cooper, J. 19 (64), *53*
Cooper, J. D. 416 (79), *440*; 774 (101), *813*
Cooper, R. D. G. 573 (195), 578 (208), 579 (216), 580 (211, 212), 581 (212), *605*
Cooper, T. A. 514 (302, 303), 515 (303), *536*
Cope, A. C. 502 (224, 227), 518 (319), 520 (334), *534*, *536*, *537*; 630 (467), 631 (471, 480), *670*
Copeck, J. A. 931, 932 (80), *934*
Copeland, E. S. 988 (173, 174), *993*
Copenhaver, J. W. 785 (199), *816*
Coquelet, C. 658 (903), *679*
Corbett, J. D. 120 (163), *152*
Corbin, D. H. 707 (307), *719*
Cordes, E. H. 415 (323), *445*; 882 (2, 8), 883 (2), 888 (2, 8), 889 (2, 8, 57, 59),

893 (76, 77), 895, 896, 898, 899 (8), *900–902*

Corey, E. J. 170, 171 (62), *174*; 484 (87), 486 (107, 108, 111), 493 (163), 506 (257, 258, 260), 521 (339), 526 (379), *530–532, 535, 537, 538*; 547 (52), 556, 560 (126), 595 (293), *601, 603, 607*; 625 (403, 408), 649 (750, 752), 650 (773), 659 (941), *668, 669, 676, 680*; 705, 706 (269), 707 (295), *718*; 794 (256), *817*; 926 (35), *933*

Corey, E. R. 571, 572 (183), *604*

Corey, G. C. 484 (91), *531*

Corey, M. D. 515 (304), *536*

Cornet, D. 635 (565, 568, 569), 638 (568, 569), 639 (568, 569, 640), *672, 674*; 700 (173), *715*

Cornforth, J. W. 486 (103), 490 (135), *531, 532*; 620 (318), *667*

Cornforth, R. H. 486 (103), *531*; 637, 638 (616), *673*

Corrigan, J. R. 486 (105), *531*

Corval, M. 307 (93), *320*; 422 (30), *439*; 710 (357), *720*

Costa Novella, E. 617 (201), *664*

Costantini, M. 616 (166), *663*

Coste, J. 620 (333), *667*

Costes, R. M. 123 (182a), 132 (224), *153, 155*

Costisella, B. 659 (953), *681*

Cotton, F. A. 87, 132 (79), *149*; 216 (92), *277*

Cottrell, P. T. 340 (35), *350*

Coulombe, R. 658 (912), *680*; 846 (171), 847 (176), 851 (171), *856*

Counsell, J. F. 361 (44, 45), 362 (46), 363 (65, 68), *375, 376*

Court, A. S. 809 (406), *820*

Cousineau, C. M. E. 850 (225, 226), *857*

Coussemant, F. 415 (369), *447*

Coutrot, P. 624 (375, 380), 633 (532), 652 (787), *668, 671, 677*

Coviello, D. A. 826, 828 (54), *854*

Covitz, F. H. 327 (6), *349*

Cowell, G. W. 624 (391), *668*

Cox, B. G. 72, 74 (55), 76 (58), *148*

Cox, F. T. 31 (117), *55*

Cox, J. D. 363 (69), 366 (93), 367 (69, 97), *376, 377*; 875 (43), *879*

Cox, W. W. 639, 640 (644), *674*

Coxon, A. C. 11, 12 (43), 13 (43, 46), 43 (158), 44 (43), *53, 56*; 62 (15d), 98 (113), 99 (15d, 113), 101 (113, 115), 105 (113), *145, 150*

Coxon, J. M. 437 (37), *439*; 621 (339), 632 (495–501), 633 (500, 502), 634 (541), 653 (832), *667, 670, 671, 678*

Coyle, T. D. 231 (53), *276*

Crabb, T. A. 839, 840 (118), *855*

Cradwick, P. D. 196–198 (85), *213*

Craig, D. 798 (303), *818*

Craig, J. T. 526 (384), *538*

Craig, P. N. 741 (251), *758*

Cram, D. J. 4, 5 (19), 7 (26, 27), 8, 9 (27), 16 (52–55), 25 (95), 26 (99), 27 (102, 106, 107), 30 (110), 35 (135, 136), 46 (107), 49 (52–55, 106, 187–189), 52 (19), *52–55, 57*; 62 (16b–d, 18a,c), 85 (71), 91 (18c, 81), 92 (90), 94 (99, 101a,b), 96 (18a,c, 71, 81, 101a,b, 103a,b), 99 (18c, 81), 107 (16b–d, 18a,c, 81, 122a–g, 123, 125a, 126a), 109 (122f,g, 125a, 126a, 127–129, 130a,b, 131), 110 (16d, 133a,b), 111 (81, 134), 113 (101a,b), 114 (18a), 116 (18c, 150), 117 (81, 151), 123 (18c, 151, 170c, 184), 131 (18c), *146, 148–153*; 157 (3), 168 (52, 53), 169 (53), 172 (52, 53), *172, 174*; 188 (62), 196 (81), 201 (62, 95), 207 (81, 100, 101), 209 (100), *213, 214*; 433 (80, 81, 204), (82, 83), *440, 443*; 727 (69), *754*

Cram, J. D. 516 (307), *536*

Cram, J. M. 16, 49 (52, 55), *53*; 62, 91, 96, 99 (18c), 107 (18c, 123), 116, 123, 131 (18c), *146, 151*; 157 (3), *172*

Cramer, J. 496, 497 (185), *533*

Crandall, J. K. 613 (84, 85), 630 (458, 468), 631 (470, 478), 633 (508), 655 (848), *661, 670, 671, 678*; 770 (46), *812*; 863 (20–25), 867 (21, 22, 25), 868 (23, 25), 871 (21), 873 (21–23, 25), 874 (24, 25), 875 (45, 48), *878, 879*

Crass, G. 47 (175), *57*

Crawford, G. H. 332 (18), *350*

Crawford, H. T. 526 (383), *538*

Crawford, R. J. 634 (554, 555), 655 (554, 555, 838, 839), *672, 678*; 689 (64), *713*

Crawley, L. C. 630 (468), *670*

Creaseley, P. M. 852 (259), *858*

Creiner, A. 617, 618 (230), *665*

Cremer, D. 766 (18), *811*

Criegee, R. 499 (206, 207), 501 (206), 514 (301), *533, 536*

Crimmin, M. J. 809 (407), *820*

Cripps, H. N. 929 (59), *934*

Crisan, C. 743, 745, 747 (260), *758*

Cristol, S. J. 524 (363), *538*

Critchelow, J. E. 896 (83), *902*

Crocker, H. P. 779 (139), *814*

Cromartie, T. H. 620 (308), *667*; 686 (40), *712*

Crombie, L. 493 (158), *532*

Cromwell, N. H. 624 (367), *668*

Crook, K. R. 766, 808 (16), *811*

Crook, S. W. 380 (370), *447*
Crosby, G. A. 651 (783), *677*
Crosby, J. (84), *440*
Cross, A. D. 524 (365), *538*
Cross, J. T. D. 460 (71–74), *467*
Cross, P. C. 221 (150), *278*
Crossley, J. 493 (158), *532*; 847 (187), *856*
Crossley, N. S. 589 (252), 595 (296), *606*, *607*
Crotti, P. 656 (861-865, 867), 657 (863, 865, 867), *678*, *679*; 686 (18, 25), 710 (25), *712*
Crowe, D. F. 803 (347), *819*
Cruickshank, F. R. 362 (53), *375*
Crumine, D. S. 860 (9), *878*
Crundwell, E. 476 (45), *529*
Crutchfield, M. M. 836, 849 (103), *855*
Cuker, E. F. 436 (85), *440*
Cullen, F. C. 769 (37), *812*
Cullum, T. V. 931, 932 (77), *934*
Culp, F. B. 625 (392), *668*
Cummins, R. W. 542 (18), *600*
Cundall, R. B. 980 (109), 988 (162, 167, 179, 180), *991–993*
Cunneen, J. I. 542, 543, 546 (11), *600*
Cunningham, G. L. Jr. 179 (19), *212*; 382 (86), *440*
Curci, R. 167 (44), *173*; 542 (17), 545 (38–40), 571 (40, 173), *600*, *601*, *604*; 612, 613, 615, 619 (48), *660*; 699 (167), *715*; 848 (199), *857*
Curl, F. A. 808 (395), *820*
Curl, R. F. Jr. 182 (32), 184, 185 (48), *212*
Curphey, T. J. 426 (87), *440*
Currier, H. A. 782 (169), *815*
Curry, J. D. 36 (139), *56*
Curtin, D. Y. 362 (57), *376*; (88), *440*
Curtis, A. B. 169, 170 (60), *174*
Curtis, C. G. 406 (280), *444*
Curtis, N. F. 19 (65), *53*
Curtis, W. D. 48 (178, 179), 50 (190), *57*; 62 (15c), 107, 109 (124a–c, 125b), *145*, *151*
Cushmac, G. F. 483 (86), *530*
Cutting, J. 613, 617 (57), *661*
Cuvigny, T. 523 (358), *537*
Čveković, Ž. 741, 743, 745, 746, 748, 750 (248), *758*
Cvetanovic, R. J. 450 (8), *466*
Cvetanović, R. J. 911 (61), 917 (95, 96, 106, 107), 918 (106, 107), *920*, *921*
Czochraloka, B. 336 (27), *350*
Czuba, L. J. 803, 806 (340), *819*

Daalen, J. van 123 (177a), 132 (225), *153*, *155*
Daasvatn, K. 10 (35, 36), 11 (36), 18 (35, 36), *53*
Daasvatu, K. 123 (173), *153*
Dabdoub, A. M. 166 (33), *173*
Daccord, G. 693 (113), *714*
Dagli, D. J. 624 (372), 633 (511, 513), *668*, *671*
Dahlhoff, W. V. 956 (299), *969*
Dahmen, A. 655 (847), *678*
Daigle, J. Y. 636 (598, 599), *673*
Dailey, O. D. Jr. 547, 571 (49), *601*
Dainko, J. L. 425 (339), *446*
Dainton, F. 939 (136a), *965*
Dainton, F. S. 851 (257), *858*; 938 (41, 44–48, 96), 939 (114), 946 (215), *963*, *964*, *967*
Dakubu, M. 459 (61), *467*
Dale, J. 4, 5 (17), 9 (29), 10 (35, 36), 11 (36), 17 (17), 18 (35, 36), *52*, *53*; 123 (169, 173), *153*; 269 (54), *276*
Dalley, N. K. 44 (165, 167), *57*; 80–82 (67b), 84 (69), 92 (67b, 69), 93, 94 (69), 101 (67b, 69), 125 (196), 131 (217, 218), *148*, *154*; 192 (75), *213*
Dallinga, G. 177 (4), *211*
Dalton, J. C. 693 (116), *714*
Dalven, P. 650 (767), *676*
Daly, J. W. 613 (76), 634 (547–549), *661*, *672*
Daly, N. J. 460 (66, 67, 69, 70), *467*
Dana, G. 729 (93), 742, 743, 745, 747 (275), *754*, *758*; 777, 778 (118), *814*
Danda, H. 701 (211), 702 (214, 218), *716*
Danen, W. C. 161, 170 (14), *173*
Danesch-Khoshboo, F. 30 (112), *55*
Danesh-Khoshboo, F. 60 (9a), *145*
Danesi, P. R. 115 (146), *152*
D'Angelo, J. 707 (309), *719*; 802 (330), *819*
Danheiser, R. L. 782 (172), *815*
Daniel, D. 834 (89), *854*
Daniels, F. 371 (108), *377*
Daniewski, W. M. 591 (261), *606*
Danishefsky, S. 807 (385), *820*
Dankleff, M. A. P. 848 (199), *857*
Dann, J. R. 22 (81), *54*
Danneels, D. 839, 840 (120), *855*
Dansette, D. 620 (326), *667*
D' Antonio, P. 178 (7), 185 (51), *212*
Dapkviashvili, A. G. 972 (8, 20), 975 (8), 977 (20, 81, 82), *988–990*
Dapporto, P. 135 (238), *155*
Darby, R. A. 752 (359), *760*
Darko, L. L. 705 (267), *718*
Darnall, K. R. 614 (110), *662*
Darvich, M. R. 613 (53), *660*
Darwent, B. deB. 462, 464 (94), 465, 466

(104), *468*; 917 (87, 103–105), 918 (103–105), *921*; 924, 925 (24), *933*
Das, K. G. 310 (143), *322*
Dasch, C. 465 (107), *468*
Da Silva, J. J. F. 62 (19a), *146*
Data, J. B. 405 (365), *446*
Daub, G. H. 410 (424), *448*
Daub, J. 780 (158), *814*
Dauben, W. G. 305 (61), *320*
Daudel, R. 356 (30), *375*
Daurenbekov, D. B. 700 (184), *716*
Daves, G. D. 707 (306), *719*; 777, 778 (121), *814*
David, S. 237 (87), *276*
Davidson, A. J. 615 (151), *663*
Davies, A. R. 638 (617), *673*
Davies, D. I. 846, 851 (172), *856*
Davies, J. A. 851 (257), *858*
Davies, J. V. 988 (165), *993*
Davies, R. 555 (118), *603*
Davies, S. G. 612, 613 (46, 47), *660*
Davis, B. 309 (127), *321*
Davis, B. C. 499 (209), *533*
Davis, D. D. 650 (760), *676*
Davis, F. A. 548 (69b), *602*
Davis, F. O. 851 (255), *858*
Davis, J. E. 691 (77), *713*
Davis, M. 180, 183 (20), *212*
Davis, R. A. 823, 824 (15), *853*
Davis, R. E. 60 (9m), *145*; 427 (417), *448*; 617 (237), *665*
Davis, T. S. 899 (108), *902*
Davis, W. 583 (228), *606*
Davis, W. H. 972 (16), *989*
Dawczynski, H. 772 (57), *812*
Dawes, C. C. 883 (16), *901*
Dawson, C. R. 522 (349), *537*
Day, J. T. 382, 430 (240), *443*
Day, R. J. 325 (293), *325*
De, N. C. 825, 829, 830 (32), *853*
Dean, F. M. 625 (394), *668*; 698 (162), *715*
Dear, R. A. 742, 745 (281), *758*; 931, 932 (77), *934*
DeBacker, M. G. 172 (73), *174*
De Benneville, P. L. 643, 644 (696), *675*
Deber, C. M. 33 (128), *55*
DeBlauwe, F. 884 (20, 21, 23, 24), 885 (24), *901*
De Boer, B. G. 478 (55), *530*
De Boer, Th. J. 307 (95), 308 (114), 311 (161), *320–322*; 710 (359), *720*; 877 (57), *879*
De Bruyn, D. J. 510 (285), *536*
De Bruyn, J. F. 312 (193), *323*
De Busk, R. E. 735 (223), 741 (222, 223), *757*
Decoret, C. 353, 357, 358 (17, 18), 359 (35), 370 (103), 372 (112), *375*, *377*
Dedieu, M. 308 (117, 119), *321*
Dedio, E. L. 928 (52), *934*
De Frees, D. J. 317 (261), *324*
Degen, B. 267 (70), *276*
Degen, P. J. 274 (19), *275*
Deger, B. 703 (237), *717*
De Graff, C. 652 (795), *677*
Dehler, J. 123 (184), *153*
Dehm, D. 165 (25, 26), *173*
Dehmlow, E. V. 115 (145a,b), *152*; 169 (55c), *174*; 520 (334), *537*
DeJesus, R. 161, 170 (14), *173*
De Jong, A. J. 616, 617 (179), *663*
Delano, G. 699 (167), *715*
Delaumeny, M. 525 (374), *538*
Del Bene, J. 353 (10), *374*
Del Cima, F. 167 (43), *173*
Delektorsky, N. 726 (66), *754*
Delfino, A. B. 304 (50), *319*
Delmond, B. 620 (330), *667*
Del Pra, A. 180 (55), *213*
Del Rosso, R. 618 (285), *666*
Del'tsova, D. P. 792 (248), *817*
De Marco, P. V. 579 (216), 580 (211), *605*
De Maré, G. R. 917, 918 (111), *921*
Demback, P. 245–247 (24), *275*
De Meijere, A. 705 (263), *718*
Demerseman, P. 742, 746 (318), *759*
De Meyer, C. 310 (143), 311 (154), *322*
Demianova, E. A. 695 (137), *715*
Demina, M. M. 744 (346), 749 (345, 346), *760*
Demuth, M. R. 613 (59), *661*
Demuth, W. 418 (250), *444*; 526 (377), *538*
Demuynck, J. 217, 221 (169), *278*
Denes, V. I. 400 (42), *439*
Den Heijer, M. 137 (245), *156*
Denian, J. 524 (369), *538*
Deniau, J. 650 (755), *676*
Denisenko, V. K. 846 (166), *856*
Denisevich, E. A. 780 (153), *814*
Denisov, D. A. 437 (202), *443*
Denisov, E. T. 617 (228), *665*
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Denyer, C. V. 629 (450), *669*
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De Pasquale, R. J. 642, 643 (688), *675*
Depezay, J.-C. 801 (329), *819*
De Puy, C. H. 318 (279), *325*; (89), *440*
Derby, E. 167 (41), *173*
De Reinach-Hirtzbach, F. 659 (942), *680*
De Reinach-Hirtzbuch, F. 838 (106), *855*
Deriglazov, N. M. 415 (366), *446*
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Derrick, P. J. 309 (138), *321*
Dertinger, H. 971, 987 (2), *988*
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Deryagina, E. N. 402 (415), *448*
Désalos, J. 946 (214), *967*
De Sarlo, F. 38 (148), *56*
Deschamps, B. 624 (379), *668*
Descotes, G. 642 (678), *674*; 691 (79, 80), *713*; 885 (41), *901*
Desimoni, G. 798 (310–312), 799 (313), *818*
Desmaison-Brut, M. 735, 738, 739, 741 (208), *757*
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Dessy, R. E. 431 (90), *440*
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Devaquet, A. 798 (297), *818*
Devendra, K. 362 (50), *375*
Devissagnet, P. 317 (265), *324*
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Dewar, P. S. 573 (194), *605*
De Witt, R. 119 (157), *152*
De Wolf, N. 840 (130), *855*
De Wolfe, R. H. 882 (3), *900*
Dey, A. K. 653, 654 (825), *678*
Deyrup, J. A. 838 (108), *855*
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Diakiw, V. 317 (266), 325 (291), *324*, *325*
Dias, J. R. 313 (206), *323*; 690 (70), *713*
Diaz, Z. 912 (67), *921*
Dice, D. R. 929 (62–65), 930 (66, 67), *934*
Dick, A. W. S. 698 (162), *715*
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Dickerson, C. L. 745 (279), *758*
Dickinson, M. J. 495 (179), *533*
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Dietrich, M. W. D. 797 (289), *818*
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Dill, J. D. 302, 303 (37), *319*
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Dimroth, K. 773 (80), *813*
Dimroth, P. 742, 748 (330), *760*
Dimsdale, M. J. 624 (374), *668*
Dinur, D. 623 (366), *668*
Dismukes, G. C. 931 (70), *934*; 946 (221), *967*; 977 (84, 85), *990*
Dittmann, W. 614 (97), *661*
Dittmer, D. C. 723 (35), *753*
Dittus, G. 610, 623, 647 (1), *659*; 684 (2–4), *712*
Divjak, S. 567 (161), *604*
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Dodelet, J.-P. 945 (178, 179), *966*
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Dolin, P. I. 950 (243a,b), *967*
Dolivo, G. 938 (72b), *963*
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Domagala, J. M. 633 (515), *671*
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Dorfman, L. M. 945 (181–183), 946 (190), 948 (234), *966*, *967*; 978 (90), *991*
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Dorman, D. E. 770 (45), *812*
Dormidontova, N. V. 616 (191), *664*
Dornauer, H. 774 (82), *813*
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Doyle, T. W. 589, 590 (255), *606*; 825 (34), 826 (44), 831 (34), *853*, *854*
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Dubois, J. E. 422 (1), *438*; 723, 726 (23, 24), *753*; 772 (70), *812*
Dubois, J.-E. 778 (123–125), *814*
Dubrovskii, S. A. 640 (668), *674*
Duchek, J. R. 564, 565 (150), *604*
Duchet, J. C. 635 (565, 568, 569), 638, 639 (568, 569), *672*; 700 (173), *715*
Dudley, W. H. 412 (167), *442*
Dudzik, Z. 690 (75), 700 (181), *713*, *716*
Duerre, J. A. 398 (95), *440*
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Duggan, A. J. 621 (342), *667*; 778 (129), *814*
Duhamel, L. 620 (314), 659 (921), *667*, *680*
Duhamel, P. 620 (314), 659 (921), *667*, *680*
DuManoir, J. R. 547 (50), *601*
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Dumke, K. 706 (284), *718*
Dumont, W. 626 (422–426), *669*
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Durand, R. 477 (47), *529*; 658 (887), *679*
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Dyatkin, B. L. 620 (322), 625 (395), 658 (322), *667*, *668*
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Dye, J. L. 21 (77), *54*; 72 (54), 120 (162a–c), *148*, *152*; 172 (73), *174*
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Dyen, M. E. 643, 644 (695), *675*
Dyke, S. F. 762 (6b), *811*
Dyumaeva, T. N. 659 (926), *680*
Dzantiev, B. G. 391 (98), *440*
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Eastland, G. W. 939, 942 (128a), *965*
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Ebbon, G. P. 566 (155), *604*
Eberbach, W. 655 (841), *678*; 689 (65), *713*
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Eberson, L. 327 (4), 342 (41), 348 (4), *349*, *350*
Eberstein, K. 632 (482, 483), *670*
Ebert, M. 956, 957 (308b), *969*; 988 (165), *993*
Eccleston, G. 850 (243), *858*
Echigo, Y. 659 (937), *680*
Eckert, T. 918 (130), *922*
Eckhardt, G. 325 (289), *325*
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Edison, D. H. (336), *446*
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Edmundson, R. S. 643, 644 (698), *675*; 850 (231), *857*
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Effenberger, F. 762 (3), 764, 765 (8), 770 (8, 42), 780 (158), 786 (203, 206), 789 (229), 792 (249), 793 (42, 249), 795–797 (280), *811, 812, 814, 816, 817*
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Eggelte, H. J. 585 (232), *606*
Eggerichs, T. 561 (139), *603*
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Eibenberger, H. 948 (235a), *967*
Eibenberger, J. 955 (290), *969*
Eichenberg, H. 653 (817), *677*
Eichhorn, J. 882 (1), *900*
Eigen, M. 68 (38), 69 (39–44), 70 (43), 72 (49), 77 (62, 63), 92 (49), *147, 148*; 896 (81), *902*
Eigendorf, G. 309 (132), *321*
Eijsinga, H. 774 (92), *813*
Eilingsfeld, H. 782 (166), *815*
Einhellig, K. 797 (292), *818*
Einhorn, J. 888 (50), *901*
Eisch, J. J. 523 (362), *538*; 652 (792), *677*
Eisenhardt, W. 694 (123), *714*
Eisenman, G. 92 (84, 90), 97 (110), *149, 150*
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Elagina, N. V. 727, 728 (73), *754*
El Basyony, A. 123 (184), *153*
Elben, U. 60, 115, 143 (6e), *144*
Elemesov, E. V. 700 (183), *716*
El Gaied, M. M. 611, 612, 637 (37), *660*
El Haj, B. 24 (90), *54*; 116 (149), *152*
Eliason, R. 415 (208), 419 (100), *440, 443*; 899 (106), *902*
Eliel, E. L. 220 (59), 242 (23), 243 (63, 103), 245 (67, 172), 246, 247 (172), 248 (100, 133), 249 (63, 65, 103, 133), 250 (65), 251 (65, 133), 252 (22, 63, 103), 254 (22, 60), 255 (22), 256 (23, 62), 257–259 (62), 260 (1, 61, 66), 270 (64, 173), *275–278*; 425 (101), *440*; 479 (62), *530*; 589 (254, 255), 590 (255), 595 (296), *606, 607*; 824 (21), 825 (34, 36), 826, 827 (51), 831 (34, 36, 71), 838 (21), 844 (150), *853, 854, 856*
Elkik, E. 613 (88), *661*
Eller, P. G. 189, 193 (67), *213*
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Elliot, A. J. 924–926 (20b), 927 (20b, 49), 931, 932 (49), *933, 934*; 972–977 (38), *989*
Elliott, S. P. 787 (225), *816*
Ellis, D. R. 983 (121), 987 (145), *991, 992*
Ellison, D. H. 939 (137a), *965*
El'Naggar, G. 647 (722), *675*
Elphimoff-Felkin, I. 517 (318), 523 (354), *536, 537*
Elwood, T. A. 303 (43), *319*
Elzen, R. van den 625 (401), *668*
Eman, A. 626 (424), *669*
Emanuel, N. M. 617 (228), 618 (244, 261, 288), *665, 666*
Emblem, H. G. 659 (922), *680*
Emerson, D. W. 831 (73), *854*
Emerson, W. 852 (258), *858*
Emovon, E. U. 460 (75), 463, 464 (99), *467, 468*
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Englard, S. 289 (24), *297*
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English, J. 735 (204, 206, 207), 738 (200, 203, 204, 206, 207, 210), 739 (210), *757*
Enikolopiyan, N. S. 640 (661), *674*
Enikolopyan, N. S. 700 (190, 201), *716*
Ennis, M. D. 862 (11), 877, 878 (56), *878, 879*
Entelis, S. G. 640 (655, 657), *674*; 702 (217), *716*
Epiotis, N. D. 766 (15, 17), 768, 770 (15), *811*
Epley, T. D. 364 (86), *376*
Epling, G. A. 508 (275), *535*
Epshtein, D. I. 616 (191), *664*
Epshtein, G. L. 711 (378), *720*
Epstein, M. F. 550 (86), *602*

Epsztein, R. 621 (337), *667*
Erdman, J. P. 172 (76), *174*
Erez, M. 408 (367), *446*
Erfontain, H. 850 (233), *857*
Erfurt, G. 659 (950), *680*
Erickson, R. E. 330 (12), 336 (26), *349*, *350*; 423 (102), *440*; 508 (272), *535*
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Ermer, O. 271, 272 (69), *276*
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Ernst, J. 618 (291), *666*
Erofeev, V. I. 795 (269), *817*
Ershov, B. A. 610, 630 (12), 647 (722, 723), *659*, *675*
Erzhanova, M. S. 700 (182–184), *716*
Eschenmoser, A. 4 (15), *52*; 473 (18), 479 (18, 60), *529*, *530*
Esfandi, A. 987 (140), *992*
Espenson, J. H. 472 (9), 474 (26), *528*, *529*
Esser, J. 972 (36), 975, 976 (72), *989*, *990*
Esteban, S. 731 (108), *755*
Estep, R. E. 624 (383, 387), *668*
Ethridge, D. R. 937, 944 (18b), *962*
Etlis, V. S. 643 (703), *675*
Eustratov, A. V. 113 (136), *151*
Evans, A. G. 706 (286), *718*
Evans, D. A. 167 (37–39), 169, 172 (54), *173*, *174*; 801 (326), *818*; 885 (39), *901*
Evans, E. A. 380 (103), *440*
Evans, E. G. 706 (288), *718*
Evans, E. R. 846 (162), *856*
Evans, M. L. 845, 846 (159), *856*
Evans, M. M. 577 (207), *605*
Evans, R. H. Jr. 207 (103), *214*
Evans, R. M. 491 (149), 492 (154), *532*
Evans, S. A. 243, 249, 252 (103), *277*; 849 (206), *857*
Evsyutina, N. G. 772 (60), *812*
Evzerikhin, E. I. 617 (202–204, 209), *664*
Ewins, R. C. 613 (72), *661*
Exner, L. J. 643, 644 (696), *675*
Exner, O. 824, 838 (20), *853*
Eyal, E. 92 (84), *149*
Eyring, H. 279 (2d,e), *296*

Fabian, J. 808 (392), *820*
Fabrichnyi, B. P. 593 (279), *607*
Fabrizzi, L. 87 (78), *149*
Faehl, L. G. 544 (321), *608*
Fahey, R. C. 610, 611 (6), *659*
Fahrni, P. 414 (104–106), (345), *440*, *446*
Faigle, J. W. 409 (107), *440*
Failes, R. L. 459 (53, 54), 461 (76), *467*
Fain, V. Ya. 919 (133), *922*
Fair, R. W. 928 (54), *934*
Fairweather, R. B. 307 (97), *321*
Faisst, W. 839–842 (111), *855*
Falanagan, V. 690 (73), *713*
Falck, J. R. 808 (405), *820*
Fales, H. M. 317 (264, 265), 318 (277), *324*, *325*
Falle, H. R. 939 (130), *965*
Falou, S. 802 (330, 331), *819*
Fanucci, R. 416 (418), *448*
Farajo, M. E. 123 (177d), 132 (225), *153*, *155*
Farberov, M. I. 616 (165, 184, 191), 617 (199, 206, 207), 635 (570, 579, 580), *663*, *664*, *672*
Farcasan, M. 400 (42), *439*
Farges, G. 614 (105), 636 (595), *662*, *673*
Fargher, R. G. 741 (228), *757*
Farhataziz 938 (66, 87), 947 (228), 948 (228, 233), *963*, *964*, *967*; 978 (91, 94), *991*
Farid, S. 692 (105), 696 (142), *714*, *715*
Farines, M. 833 (82), *854*
Farlow, M. W. 929 (59), *934*
Farmer, E. H. 736 (162), 745 (276), *756*, *758*
Farnia, G. 329 (10), 330 (11), *349*; 599 (313), *608*
Farnier, M. 593 (287), *607*
Farnum, B. W. 476 (39), *529*
Farnum, D. G. 745 (274), *758*
Farnum, S. A. 476 (39), *529*
Farona, M. F. 616 (185), *664*
Farquarson, J. 611 (27), *660*
Farrar, J. 618 (272), *666*
Farrow, M. M. 72 (50), *148*
Fateley, W. G. 356 (28), *375*
Fatiadi, A. J. 490 (139), 491 (147), *532*
Faucher, H. 852 (262), *858*
Faulkner, D. J. 577 (204), *605*
Faulkner, J. K. 410 (112), *441*
Fava, A. 245–247 (24), *275*; 582 (221), *605*
Favorskaya, T. A. 686 (21, 22, 33), 700 (22), *712*; 738 (201), 740 (216), 741 (238–240), 743 (335), 744 (238, 346), 745 (277), 747 (238, 239), 749 (335, 341–347), *757*, *758*, *760*
Favorskii, A. 772 (58), *812*
Fechner, K.-H. 316 (246, 248–250), *324*
Fedeli, E. 306 (66), *320*
Fedor, L. R. 419 (108), *440*; 825, 829, 830 (32), *853*
Fedorov, V. C. 618 (268), *666*
Fedorovits, A. D. 735, 736 (169), *756*
Fedorynski, M. 624 (381), *668*

Fedulova, L. V. 735 (160), 736 (160, 161, 176), *756*
Feenan, K. 849 (210, 212), *857*
Fehér, F. 267 (70), *276*
Feher, I. 435 (205), *443*
Feigenbaum, E. A. 304 (49, 50), *319*
Feigin, A. B. 616 (165), *663*
Feil, M. 633 (521), *671*
Feiler, L. A. 787 (216, 220), 791, 792 (216), *816*
Feinauer, R. 825 (41, 42), *853*, *854*
Feistkorn, V. 313 (207), *323*
Feit, E. D. 457 (46), *467*
Feit, P. W. 621 (335), *667*
Fel'bdlyum, V. Sh. 635 (579), *672*
Feldman, D. 640 (656), *674*; 700 (192), *716*
Felföldi, K. 696 (145), *715*; 735, 736, 738 (146), *755*
Fell, B. 658 (902), *679*
Fendler, E. J. 419 (109), *440*
Fendler, J. H. 419 (109), *440*; 956 (312), *969*
Feng, D. F. 938 (88), *964*
Fenselan, A. H. 504 (245), *534*
Fenselau, C. 301, 302, 304 (27), 308 (115), *319*, *321*; 412 (91), *440*
Fenton, D. E. 37 (144–146), *56*, 64, 115 (30c), 132 (226e), 133 (226e, 227), 138 (247), *147*, *155*, *156*
Ferdinand, G. 832 (76), *854*
Ferles, M. 746 (316), *759*
Fernandez, J. 784 (192), *815*
Fernandez, V. P. 547 (55), *601*
Fernandez-Alonso, J. I. 357 (30), *375*
Ferracutti, N. 624 (371), *668*
Ferrari, M. 633 (507), *671*
Ferreira, G. A. L. 781 (164), *815*
Ferrer-Correia, A. J. V. 305 (64), *320*; 771 (51), *812*
Ferrero, C. 745 (271), *758*
Ferretti, M. 656, 657 (866–868), *678*, *679*; 686, 710 (25), *712*
Ferrier, R. J. 614 (107), *662*
Fesenko, T. N. 918, 919 (131), *922*
Fessenden, R. W. 936 (8), 949 (239), 956, 957 (308a), *962*, *967*, *969*; 980 (104), *991*
Fetizon, M. 307 (89), 308 (106), *320*, *321*; 620 (320), 623 (359), *667*, *668*
Fétizon, M. 503 (232–234, 236, 237), *534*
Fiandanese, V. 434 (110), *440*
Fibiger, R. 804 (353), *819*
Ficini, J. 801 (329), 802 (330, 331), *819*
Fiedler, U. 64 (27f), 92 (27f, 83), 109 (132), 122 (27f), *147*, *149*, *151*
Field, F. H. 316 (258), *324*
Field, L. 544, 577 (33), *587 (242)*, *601*, *606*
Fields, E. K. 612, 613, 637, 638 (45), *660*
Fieser, L. F. 380 (111), *440*; 483, 515 (80), *530*; 587 (247), 593 (277), *606*, *607*; 729 (86), *754*; 885 (33), *901*
Fieser, M. 380 (111), *440*; 587 (247), 593 (277), *606*, *607*; 885 (33), *901*
Fife, T. H. 825, 830 (33), *853*; 882, 888 (4, 53–56), 890 (65), 891 (53, 54), 895 (4), *900–902*
Figdor, S. K. 410 (112), *441*
Figge, K. 387 (113), 392 (114), *441*
Figueruelo, J. E. 640 (667), *674*
Filimoshkina, V. A. 795 (268), *817*
Filip, G. A. 686 (30), *712*
Filippov, A. P. 617 (215), *664*
Filippova, C. B. 797 (288), *818*
Filippova, T. V. 618 (246), *665*
Filler, R. 486 (113), *531*
Filseth, S. V. 917 (110), 918 (110, 114), *921*, *922*
Findlay, M. C. 305, 318 (51), *320*
Finkelstein, M. 327 (5), 347 (52), *349*, *350*
Finkenbine, I. R. 641 (669), *674*
Finkenbine, J. R. 629 (449), 641 (673), *669*, *674*
Finnegan, R. A. 611, 620–622 (35), *660*
Firestone, R. A. 414 (77), *440*; 798 (294, 295), *818*
Firestone, R. F. 938 (94), *964*
Firouzabadi, H. 490 (134), *532*
Firth, B. E. 564, 570 (151), *604*; 633 (514), 653, 654 (833, 834), 658 (834), *671*, *678*
Fisch, M. 860 (10), *878*
Fisch, M. H. 502 (223), *534*
Fischer, A. 733 (126), *755*
Fischer, Ch.-H. 985 (132b), *992*
Fischer, F. E. 523 (355), *537*
Fischer, F. G. 507 (270), *535*
Fischer, H. 436 (97), *440*; 554 (106), 555 (110), *602*, *603*; 911, 918 (63), *920*; 949 (241), *967*
Fischer, J. 136 (239a,b), *155*
Fischer, K. F. 831, 835 (74), *854*
Fischer, L. B. 745, 749 (261), *758*
Fischer, M. 398 (115), *441*
Fischer, P. 764 (8), 765 (8, 9), 770 (8, 9, 42), 789 (229), 792 (249), 793 (42, 249), *811*, *812*, *816*, *817*
Fischer, W. 686 (20), *712*
Fish, A. 452 (17), *466*
Fish, I. Sh. 617 (204), *664*
Fish, V. B. 741 (251), *758*
Fisher, C. M. 330 (12), 336 (26), *349*, *350*
Fishman, J. 405 (116), *441*

Fittig, R. 722 (1), *752*
Fitton, P. 772 (65, 66), *812*
Fitzsimmons, C. 782 (174), *815*
Flad, G. 626, 657 (432), *669*
Flammang, R. 310 (143), *322*
Flanders, E. D. 22 (84), 31 (116), *54*, *55*
Flash, P. J. 496 (187), *533*
Flaskamp, E. 307 (101), *321*
Fleet, W. J. 486 (107), *531*
Fleischer, G. 885 (26), *901*
Fleischmann, F. K. 790 (236), *816*
Fleming, G. 911 (57), *920*
Fleming, I. 799 (316), *818*
Fleming, M. P. 627 (439), *669*
Fletcher, C. J. M. 452 (29), 453 (31), *467*
Fletcher, J. W. 939 (116), 946 (192, 193), *964*, *966*
Flid, M. R. 617 (200), *664*
Fligge, M. 642, 643 (682), *675*
Flippen, J. 790 (233), *816*
Flood, T. C. 627 (441), *669*
Florêncio, H. 309 (131), *321*
Flory, P. J. 9, 29 (34), *53*
Flowers, M. C. 635 (560), 655 (843–846), *672*, *678*
Flygare, W. H. 862 (13), *878*
Fock, V. 352 (2), *374*
Fojtik, A. 960 (328), *970*
Fok, N. V. 931, 932 (86), *934*
Fokin, A. V. 650 (758), *676*
Folcher, G. 123 (182a), 132 (224), *153*, *155*
Foley, K. M. 659 (943), *680*
Folin, M. 558 (133), *603*
Folkers, K. 586 (237), 593 (237, 271), 595 (294), *606*, *607*
Follmann, H. 773 (80), *813*
Follmann, R. 825 (40), *853*
Follows, A. G. (229), *443*
Fomina, M. V. 702 (217), *716*
Fonassier, M. 436 (117), *441*
Fonken, G. S. 566 (157), *604*
Fontana, A. 279 (1), *296*; 553 (95), *602*
Foote, C. S. 556 (125), 558 (128, 129, 134, 135), 559–561 (128, 135), 562 (125), *603*
Forbes, C. P. 506 (256), *535*
Forbes, E. J. 491 (144), *532*
Forbes, W. F. 558 (131), *603*
Forchioni, A. 946 (214), *967*
Ford, G. P. 769, 808 (38), *812*
Ford, J. A. Jr. 484 (91), *531*
Ford, R. 907 (49), *920*
Ford, S. H. 650 (764), *676*
Ford-More, A. H. 547 (54), *601*
Fore, P. E. 31 (114, 117), *55*; 60 (9o), *145*
Forel, M. T. 436 (117, 400), *441*, *447*
Forissier, F. 620, 621 (331), *667*
Fornasier, R. 62, 115 (22), *146*
Forrest, G. C. 891 (69), *902*
Forrest, J. M. 431 (118), *441*
Forrester, A. R. 573 (194), *605*
Forshult, S. 500 (212), *533*
Fort, A. W. 862 (16), *878*
Forys, M. 972, 974 (39), *989*
Forzatti, P. 616 (181, 183), 617 (214), *663*, *664*
Foss, O. 294 (43, 44), *297*
Foster, A. B. 420 (119), *441*; 848 (200–202), 849 (205), *857*
Foster, A. M. 707 (294), *718*
Foster, C. H. 544, 577 (33), *601*
Foster, H. M. 703 (238), *717*
Foster, J. F. 292 (32), *297*
Foster, R. B. 238 (25), *275*
Foster, T. 952 (282), *968*
Foti, S. 312 (195, 196), *323*
Foucard, A. 614 (120), *662*
Foucaud, A. 619 (300), 634 (559), *666*, *672*
Foulger, N. J. 650 (772), *676*; 705 (268), *718*
Fourche, G. 9, 29 (34), *53*
Fournari, P. 593 (287), *607*
Foumas, C. de 736 (164), *756*
Fowler, R. B. 798 (303), *818*
Fowler, R. G. 399 (120), *441*
Fowles, G. W. A. 137 (242), *155*; 849 (210–212), *857*
Fowles, P. 928, 930 (51), *934*
Fox, D. P. 806 (377), *820*
Fox, F. 618 (254), *665*
Fox, M. A. 562 (145b), *603*
Fox, M. F. 904 (21), *920*
Fox, N. S. 496, 497 (185), *533*
Foxall, J. 708 (343), *719*
Foy, P. 623 (359), *668*
Fraenkel, G. 172 (75), *174*
Francis, G. E. 392 (48), *439*
Francis, P. S. 476 (43), 481 (71), *529*, *530*
Frandanese, V. 168, 172 (50), *173*
Frandsen, E. G. 834 (86), *854*
Frank, F. J. 485 (101), *531*; 588, 590 (248), *606*
Frank, G. A. 862 (16), *878*
Frank, J. 311 (154), *322*
Frank, R. 554 (106), *602*
Franke, A. 736 (151), 741 (221, 229), 742 (325), 746 (319–322, 324, 325), *755*, *757*, *759*
Franklin, J. L. 315 (238), *324*; 367 (98), 372 (120), *377*; 972 (47), 973 (55), 977 (47), *989*, *990*
Franz, J. E. 797 (289), *818*

Franz, K. 615 (144), *662*

Franzen, G. R. 572 (186), *605*

Franzen, V. 509 (279), *535*

Fraser, R. R. 221 (71), *276*; 434 (121), *441*

Fraser-Reid, B. 273 (51), *276*; 774 (87), 777 (122), *813*, *814*

Frater, F. 700 (207), *716*

Frazee, W. J. 635 (564a), *672*

Frazer, W. 593 (272), *607*

Frederiksen, N. 308 (105), *321*

Freedman, M. L. 472 (8), *528*

Freeman, C. G. 918 (118–120), *922*

Freeman, G. R. 422 (289, 290), *445*; 453 (33), *467*; 935 (4), 937 (20, 24, 25), 938 (4, 32, 62, 73, 79c, 83–85, 89), 939 (62, 84, 85, 104a,c, 105, 111, 112, 113a,b, 121), 940 (121, 142, 146, 147a, 149), 944 (121, 163, 164, 171–174, 176), 945 (178, 179, 184), 946 (196, 206, 207), *961–967*; 973 (56), *990*

Freiberg, L. A. 247, 248 (4), *275*

Freidlin, L. Kh. 729, 731 (89), 734 (179), 735 (175, 181), 736 (152, 156, 175), 737 (178–181), 738 (175), 741 (179), 742 (291), 743 (290, 292), 745 (178, 290–292), 746 (178), 750 (178, 290–292, 348), 751 (178, 355, 356), *754–756*, *759*, *760*; 695 (138), 696, 697 (144), *715*

Freidlina, R. K. 802 (333), *819*

Frensch, K. 25 (93), 32 (123), *54*, *55*; 60 (9d), 62 (15i), 97 (108), 114 (15i), 143 (262b), *145*, *146*, *150*, *156*

Frensdorff, H. K. 11, 12 (42), 44 (42, 162), *53*, *56*; 60 (3c), 78, 86 (76a), 92 (76a, 90), 93, 94, 111, 114 (76a), 123 (3c), *144*, *148*, *149*; 157, 167 (1), *172*

Frendsdorff, J. K. 44 (164), *57*

Freon, P. 648 (740), 650 (755), *676*

Fréon, P. 524 (369), *538*

Freppel, C. 620 (319), 638, 639 (618), *667*, *673*

Freudenberg, B. 734, 738 (205), *757*

Frey, H. M. 707 (319), *719*

Frey, J. G. 707 (319), *719*

Friberg, L. 119 (155), *152*

Frick, W. G. 231 (149), *278*

Fridrichsons, J. 296 (61), *298*

Friebolin, H. 247, 256, 258 (73), 263 (101), 269 (72), 272 (72, 74), 273 (74, 101), *276*, *277*; 839–842 (111), *855*

Fried, J. 650 (764, 767), *676*

Friedel, P. 690 (73), *713*

Friedel, R. A. 523 (356), *537*

Friedman, B. S. 392 (171), *442*

Friedrich, L. B. 693 (114), *714*

Friedrich, L. E. 692, 693 (106), *714*

Friege, H. 769, 808 (31), *811*

Fries, K. 549 (70), *602*

Friesen, M. D. 310 (142), 325 (296), *322*, *325*

Friess, S. L. 371 (109), *377*

Frieze, D. M. 849 (206), *857*

Frimer, A. 170 (64, 66), 171 (64), *174*

Frimer, A. A. 779 (135), *814*; 885 (40), *901*

Fripiat, J. J. 618 (287), *666*

Fristad, W. E. 617, 618 (235), *665*

Frokova, N. N. 24 (91), *55*

Frolkina, I. T. 618 (280, 281), *666*

Fromm, E. 571 (175), *604*; 746 (312), *759*

Fronza, G. 555, 567 (326), *608*

Früh, P. U. 92 (87, 91), *149*

Fry, A. 380 (122, 370), 412 (123), 430 (122, 123), *441*, *447*

Fry, A. J. 327 (2, 8), *349*

Fu, W. Y. 592, 595, 597 (267), *607*

Fu, Y. C. 517 (312), *536*

Fuchs, C. 987 (141), *992*

Fuchs, P. L. 629 (453), 649 (753), 650 (453, 762), *670*, *676*

Fuchs, R. 494 (174), *532*

Fueki, K. 938 (71, 88), 939 (103, 118), *963*, *964*; 972 (27), *989*

Fueno, T. 417 (299), *445*; 634, 655 (551), *672*; 766, 767 (20), 776 (20, 107, 109), 808 (398), 809 (109, 398), 810 (107, 398, 408), 811 (408, 409), *811*, *813*, *820*

Fuhr, K. H. 639 (645), *674*

Fuhrer, H. 192, 194 (77), *213*

Fuhrhop, J. H. 618 (291), *666*

Fuji, K. 840 (121), *855*

Fujii, M. 647 (729), *675*

Fujimaki, M. 980 (111), *991*

Fujimoto, A. 614 (119), *662*

Fujino, Y. 646 (718), *675*

Fujisaki, Sh. 647 (732), *676*

Fujita, E. 555 (108), *603*; 840 (121), *855*

Fujita, K. 703 (242–244, 248), 704 (244), *717*; 723 (26), *753*

Fujita, S. 709 (352), *719*; 726, 729 (62, 63), *754*

Fujita, T. 404 (162), *442*; 526 (381), *538*; 613, 632 (82), 642 (681), *661*, *674*; 706 (287), *718*

Fujiwara, Y. 618 (271), *666*

Fukayama, T. 613 (91), *661*

Fukui, K. 354 (18a), *375*; 658 (899), *679*; 798 (296), *818*

Fukumoto, K. 528 (397), *538*; 615 (135), *662*

Fukunaga, M. 849 (217), *857*

Fukuta, K. 860 (10), *878*

Fukuyama, T. 179 (15), 183 (38), *212*

Fukuzawa, A. 696 (146), *715*
Fukuzumi, K. 695 (132, 133), *714*
Fulcher, J. G. 627 (435), *669*
Fullington, J. G. 889 (57), *893 (76), 901, 902*
Fumasoni, S. 659 (955), *681*
Fumijoto, H. 658 (899), *679*
Funabashi, F. 939 (108), *964*
Funabashi, K. 938 (72a), *963*
Funck, D. L. 488 (129), *531*
Funck, R. J. J. 64, 92, 122 (27i), *147*
Funck, Th. 69, 70 (45a,b), 78 (45a), *147, 148*
Funder, W. J. 408 (41), *439*
Funderburk, L. 898 (98), *902*
Funke, C. W. 692, 694 (91), *714*
Fürst, A. 475 (29), 483 (81), *529, 530*
Furtado, D. 25 (94), *54*
Furth, B. 693 (111–113), 694 (112), *714*
Furukawa, J. 46 (173), *57*; 96 (103c), *150*; 640 (654), *674*; 700 (208), *716*; 766, 767 (20), 776 (20, 107), 810 (107), *811, 813*
Furukawa, M. 646 (718), *675*
Furukawa, N. 570 (171), *604*
Fusco, A. 658 (882), *679*
Fusi, A. 618 (254, 264), *665, 666*
Futrell, J. H. 939 (124), *964*
Fyles, D. L. 27 (104), *54*
Fyles, T. M. 27 (104), *55*

Gabra, G. G. 640 (665), *674*; 702 (225), *717*
Gadelle, C. 618 (259, 286), *665, 666*
Gadzhieva, M. G. 849 (215), *857*
Gaertner, V. R. 645 (707), *675*
Gaeta, F. 47 (174), *57*; 62, 107 (16a), *146*
Gager, A. H. 576 (203), *605*
Gagis, A. 658 (882), *679*
Gailyunas, I. A. 616 (160, 177), 617 (177, 219, 224, 227), 637 (219), *663–665*
Gainulina, S. R. 491 (145), *532*
Gaivorouskii, L. A. 491 (145), *532*
Gajewski, R. P. 692, 694 (95), *714*
Gal, D. (288), *445*
Gál, D. 616 (176), *663*
Gal, G. 615 (151), *663*
Gal, J. 380 (124), *441*
Galakhov, I. V. 647 (730), *676*
Galik, V. 734, 740 (215), *757*
Galimov, E. M. 702 (232), *717*
Gall, M. 803, 806 (340), *819*
Galle, J. A. 652 (792), *677*
Gallivan, R. M. Jr. 519 (329), *537*
Gallo, A. A. 587 (242), *606*
Gallopo, A. R. 699 (167), *715*
Gal'pern, G. D. 306, 308 (70), *320*
Galy, J.-P. 305 (60), *320*
Gamba, A. 798 (310–312), *818*
Gambaryan, N. P. 792 (248), *817*
Gan, S. 659 (932), *680*
Ganassi, E. E. (398), *447*
Gandler, J. R. 898 (100), *902*
Gandour, R. D. 896 (84), *902*
Ganem, B. 542 (320), *608*; 620, 622 (309), *667*; 806 (376), *820*
Ganem, B. E. 493 (163), *532*
Gangwer, T. E. 938 (95), *964*
Gansow, O. A. 76 (58), *148*
Ganter, C. 576 (201), *605*
Ganter, G. 272 (107), *277*
Gaoni, H. 574 (196), *605*
Gara, W. B. 977 (89b), *990*
Garanin, V. I. 691 (76), *713*
Garbesi, A. 245–247 (24), *275*
Garbisch, E. W. Jr. 516 (307), *536*
Garcea, R. L. 624 (374), *668*
Garcia, B. J. 21 (79), *54*; 60 (9f), *145*
Gardiner, D. 494 (170), *532*
Gardner, J. O. 64 (28b), *147*
Gardy, E. M. 939 (130–132), *965*
Garg, C. P. 486 (116), *531*
Gargiulo, R. J. 587 (242), *606*
Garibyan, T. A. 917 (98), *921*
Garin, D. L. 635 (561), *672*
Garito, A. F. 543 (25), *601*
Garneau, F. X. 973 (52), *990*
Garner, A. Y. 794 (261), *817*
Garner, B. J. 506 (256), *535*
Garnett, J. L. 384 (125), *441*; 456 (45), *467*
Garrett, P. E. 613 (59), *661*
Garst, M. E. 694 (127), *714*
Garwood, D. C. 168, 172 (52), *174*
Gasaki, H. 143 (263), *156*
Gasanov, F. G. 646 (717), *675*
Gasiorek, M. 690 (75), 700 (181), *713, 716*
Gasowski, G. L. 956 (312), *969*
Gassman, P. G. 598 (307, 308), *608*
Gates, J. W. Jr. 22 (81), *54*
Gatti, C. 262 (75), *276*
Gaube, H. 574 (199), *605*
Gaucher, G. M. 988 (151, 153, 154, 172), *992, 993*
Gaumeton, A. 707 (301), *718*
Gauthier, M. 937 (19), *962*
Gautier, M. F. 405 (128), *441*
Gavrilenko, V. A. 617 (202–204, 209), *664*
Gavrilova, G. M. 769 (34), 786 (211), *812, 816*
Gawdzik, A. 618 (278), *666*
Gaydoŭ, E. M. 778 (126), *814*
Gazdar, M. 542 (15), *600*

Gaze, C. 708 (331), *719*
Gear, J. L. 731 (105), *754*
Gebhardt, H. J. 724, 725 (45), *753*
Gebicki, J. L. 938 (98), *964*
Gebreyesus, T. 314 (231), *324*
Gedra, Á. 616 (176), *663*
Gehlhaûs, J. 788 (227), *816*
Geier, G. 69 (40), *147*
Geilmann, W. 494 (169), *532*
Geise, H. J. 178 (9), 179 (12), *212*; 835, 836 (97), *855*
Geissman, T. A. 741 (218, 220), *757*
Gelan, J. 259 (76), *276*; 839 (119), 840 (119, 124, 127, 128, 134), 842 (119, 134), *855*
Gelas, J. 846 (163), *856*
Gelashvili, E. S. 706 (277), *718*
Gelboin, H. V. 658 (879, 880), *679*
Gel'bstein, A. I. 618 (280, 281), *666*
Gen, A. van der 508 (276), *535*
Geneste, P. 477 (47), *529*; 585 (234), *606*; 658 (887), *679*
Gennari, G. 558 (133, 136), 562 (145b), *603*
Gennaro, A. R. 405 (325), *445*
Gensch, K. H. 549 (76), *602*
Gensch, K.-H. 571 (174), *604*
George, C. 185 (51), *212*
George, C. F. 178 (7), *212*
George, T. J. 424 (233), (232), *443*; 561 (139), *603*
Georghiou, P. E. 521 (338), *537*
Gerasenkova, A. N. 428 (58), *439*
Gerdil, R. 245 (77), *276*; 328, 329 (9), *349*; 599 (314), *608*
Gerhard, R. P. 703 (239), *717*
Gerkin, R. M. 633 (525, 529), *671*
Gerlach, O. 795–797 (280), *817*
German, E. N. 736 (152), *755*
Gero, S. D. 847 (194), *857*
Gershanov, F. B. 617 (225), *665*
Gershman, N. E. 511 (287), *536*
Gershtein, N. A. 780 (145), *814*
Gesellchen, P. D. 165 (28), *173*
Gettys, G. A. 899 (107, 108), *902*
Gevorkyan, A. A. 691 (85), *713*
Gey, E. 771 (47), *812*
Ghaderi, E. 490 (134), *532*
Ghali, H. 482 (78), *530*
Ghatah, K. L. 647 (731), *676*
Gheniculescu, A. 513 (298), *536*
Gheorghe, N. 391, 424 (130), *441*
Ghersetti, S. 429 (126), *441*
Ghirardelli, R. G. 92 (89), *149*; 658 (908), *679*
Ghosez, L. 792 (246), *817*
Gianni, F. L. 799 (316), *818*
Gianni, M. H. 269 (80, 81), 270 (79, 80), 271 (78), 272 (78, 79), *276*; 655 (851), *678*
Gianturco, M. A. 690 (73), *713*
Gibson, D. T. 238, 239 (9), *275*
Gibson, N. A. 490 (137), *532*
Gibson, Th. A. 694 (124), *714*
Giddey, A. 625 (393), *668*
Giella, M. 395 (317), *445*
Giering, W. P. 630 (461), *670*
Giersch, W. 493 (162), *532*
Giese, B. 808 (401), *820*
Gigg, J. 774 (86), *813*
Gigg, R. 522 (345), *537*; 774 (86), *813*
Gilardeau, C. 479 (62), *530*
Gilbert, A. 709 (351), *719*; 794 (259), *817*
Gilbert, B. C. 655 (842), *678*; 708 (331, 343), *719*; 780 (146), *814*; 939 (137b,c), 951 (278), 954 (278, 287), *965*, *968*; 972 (14), 977 (88), 985 (14, 88), *989*, *990*
Gilbert, D. P. 598 (308), *608*
Gilbert, E. E. 642 (687), *675*
Giles, H. G. 932 (90), *934*
Giles, J. R. M. 977 (89b), *990*
Giles, R. G. F. 653 (827), *678*
Gilham, P. T. 554 (105), *602*
Gill, E. W. 383 (127), *441*
Gillbro, T. 972, 974, 975 (28), 977 (87a), *989*, *990*
Giller, S. A. 700 (178), *716*
Gilles, L. 938 (49a, 61), *963*
Gillet, C. L. 405 (128), *441*
Gilligan, M. F. 460 (69, 70), *467*
Gillis, B. T. 520 (334), *537*; 743, 746, 747 (309), *759*
Gillis, H. A. 925 (29), *933*; 938 (57, 97), *963*, *964*; 977 (80a, 89a), 982 (117), 985 (89a), 988 (172, 176), *990*, *991*, *993*
Gillis, R. G. 306 (78), 310 (147), *320*, *322*; 808 (399), *820*; 852 (260), *858*
Gilman, H. 522 (351), 526 (377, 379), *537*, *538*
Gilman, N. W. 493 (163), *532*
Gilman, S. 614 (112), *662*
Gilmore, J. R. 501 (221), *534*
Gilmore, W. F. 632 (484), *670*; 862 (16), *878*
Gimbarzensky, B. P. 823 (10), *853*
Ginns, I. S. 950 (249), 951 (249, 259), *968*
Ginsburg, D. 613 (68), *661*; 727, 728 (74), *754*
Ginzburg, I. M. 436 (129), *441*
Gioia, B. 633 (519), *671*
Giorgadze, N. A. (183), *442*
Girard, C. 807 (387), *820*
Girard, J. P. 611, 612, 620 (36), 621 (36, 350), *660*, *667*

Girault, J. P. 742, 743, 745, 747 (275), *758*
Giray, M. 367 (95), 373 (127), *377*
Girijavallabhan, M. 655 (853), *678*
Girodeau, J. M. 62, 107, 109 (16f), *146*
Girodeau, J.-M. 47 (176), *57*
Giroud-Abel, B. 642 (678), *674*; 691 (79), *713*
Gisler, H. J. 274 (130), *277*
Gisser, H. 977 (77), *990*
Giusti, P. 700 (187), *716*
Gladysheva, F. N. 643 (703), *675*
Gladysz, J. A. 627 (435), *669*
Glamkowski, E. J. 615 (151), *663*
Glase, W. H. 649 (747), *676*
Glass, R. S. 564 (150), 565 (150, 153), *604*
Glassman, I. 452 (30), *467*
Glazkov, Yu. V. 647 (733), *676*
Glazurina, I. I. 635 (570), *672*
Gleason, J. G. 823 (13a,b, 14), 824 (14, 20), 832 (14), 837 (13a, 14), 838 (13a, 14, 20), *853*
Gleiter, R. 788 (228), *816*; 847 (190), *856*
Glenat, R. 492 (156), *532*
Glidewell, G. 803 (350), *819*
Gloede, J. 659 (950), *680*
Glotter, E. 482 (76), *530*; 657 (871), *679*
Glue, S. 835 (92), *855*
Glusko, L. P. 659 (948), *680*
Gnanapragasam, N. S. 422 (287), *445*
Göbl, M. 984, 985 (130c), *992*
Goddard, W. A. 281 (8b), *296*
Goebel, C. G. 736 (163), *756*
Goehmann, P. 846 (170), *856*
Goerdeler, J. 794 (254), *817*
Goering, H. L. 372 (116), *377*
Goethals, E. J. 312, 317 (189), *323*; 640 (662), *674*; 700 (198), *716*
Goff, D. L. 653, 654 (829), *678*
Gogek, G. J. 749 (340), *760*
Goh, S. H. 623 (364), *668*
Goh, S.-H. 709 (355), *720*
Goheen, D. W. 548 (67), *602*
Gojković, S. 502 (225), *534*; 741, 743, 745, 746, 748, 750 (248), *758*
Gojon, G. 926 (32a), *933*
Gokel, G. W. 4, 5 (19), 7–9 (27), 16 (53), 21 (79), 30 (110), 49 (53, 187, 189), 52 (19), *52–55*, *57*; 60 (4a,b,d,f, 9f), 62 (16c, 18a), 92 (90), 96 (18a, 103b), 107 (16c, 18a, 122b,d,f,g), 109 (122f,g, 127, 131), 114 (18a), 115, 120 (4a,b,d,f), 123 (170c, 184), 143 (4a,b,d,f), *144–146*, *149–151*; 157 (8), 167 (35), *172*, *173*; 196, 207 (81), *213*
Golab, A. M. 169, 172 (54), *174*
Gold, L. P. 765 (11), *811*
Gold, V. 431 (27), *438*; 900 (109), *902*
Goldberg, I. 11 (41), *53*; 123 (185), 131 (185, 220), 134, 135 (185), *153*, *154*; 188 (65), 189, 191, 193 (71), 194, 195 (80), 201 (96, 97), 202 (96), 203 (97, 98), 204 (99), 205 (98), 206 (99), 207, 209 (102), *213*, *214*
Golden, D. M. 362 (53), *375*
Gol'dfarb, E. I. 711 (379), *720*
Goldfarb, Y. L. 593 (279, 282), *607*
Golding, B. T. 613 (80), 620 (324), *661*, *667*; 732 (114–116), *755*
Goldman, I. M. 491 (146), *532*
Goldman, J. M. 491 (141), *532*
Goldman, L. 505 (246, 249), *535*
Goldsack, R. J. 317 (266), *324*
Goldschmidt, V. M. 124 (191), *154*
Gol'dshtein, I. P. 364 (87), *376*
Goldsmith, D. J. 633 (506), *671*; 710, 711 (372), *720*
Golfier, M. 503 (232–234, 236), *534*; 620 (320), *667*
Golikov, V. I. 659 (947, 948), *680*
Golini, J. 265 (44), *275*
Golino, C. M. 686 (38), *712*
Gombos, J. 620 (323), *667*
Gomer, R. 911 (58), *920*
Gompper, R. 785 (195), *815*
Gonoboblev, L. N. 632 (487), *670*
Gonzalez, T. 158, 164, 165 (9), *172*
Gonzalez-Diaz, P. 355 (25), *375*
Goodwin, T. W. 490, 492 (140), *532*
Goon, D. J. W. (373), *447*
Goossens, H. J. M. 887 (49), *901*
Gopal, H. 494, 513 (172), *532*
Gorbatenko, V. I. 786 (207), *816*
Gorden, R. Jr. 944 (170), *966*
Gordon, A. 619 (302), *666*
Gordon, M. S. 216 (82), 221 (68), *276*
Gordon, S. 904 (20), *920*
Gordon, W. G. 558 (130), *603*
Gordy, W. 184 (43), *212*; 221 (174), *278*
Goré, J. 518 (323), *537*
Gorenstein, D. G. 220, 243, 246 (83), *276*
Gorewit, B. V. 977 (89c), *990*
Gorfinkel, M. I. 309 (134), *321*
Gorin, E. 279 (2e), *296*
Gorin, G. 987 (140), *992*
Gorman, A. A. 692 (109), *714*
Gorski, R. A. 633 (511, 513), *671*
Goshoru, R. H. 703 (237), *717*
Gosselck, J. 625 (404), *668*
Gossman, P. G. 593 (290), *607*
Gosztonyi, T. 403 (394), *447*
Goto, T. 613 (91), *661*

Gottarelli, G. 284 (13, 14), 289 (17), 291, 292 (29), 293 (34a,b), *297*
Gotthardt, H. 696 (147), *715*
Gouesnard, J. P. 776 (111), *813*
Gould, E. 616 (172), 617 (172, 198), 618 (251), *663–665*
Gould, I. A. 395 (313), *445*
Gould, W. A. 741 (253), *758*
Gouw, T. H. 52 (194), *57*
Goya, S. 621 (352), *667*
Goyal, G. C. 982 (118), *991*
Graaf, B. van de 302–304 (36a,b), 316 (251), *319*, *324*
Grabe, B. 353 (16), *375*
Grachev, S. A. 979 (98, 100), 987 (147), *991*, *992*
Gracheva, E. P. 784 (180), *815*
Gracheva, Z. D. 363 (67), *376*
Graetzel, M. 938 (33), *962*
Graf, E. 42 (157), *56*; 101 (117), 118 (117, 153), 136 (117), *150*, *152*
Grafen, P. 779 (140), *814*
Graffe, B. 689 (60), *713*
Graham, D. M. 924, 926 (25), *933*
Gralak, J. 620 (314), 659 (921), *667*, *680*
Gramain, J. C. 502 (223), 503 (234), *534*
Grand, D. 937 (19), *962*
Grandjean, J. 90, 92, 122, 140 (80), *149*
Granger, R. 611, 612, 620 (36), 621 (36, 350), *660*, *667*
Granoth, I. 312 (182), 313 (215), *322*, *323*
Grant, D. M. 248 (100), *277*
Granwehr, B. 647 (731), *676*
Granzow, A. 972, 975 (37), 977 (37, 75), 979–981 (103), *989–991*
Grasselli, P. 626 (428), 627 (440), *669*
Grässlin, D. 956, 957 (302, 303), *969*
Grätzel, M. 951 (270a), *968*
Grauer, A. 623 (366), *668*
Graves, J. M. H. 795 (267), *817*
Gravitz, N. 896, 898 (79), *902*
Gray, C. E. 650 (760), *676*
Gray, P. 452 (13, 20, 26), *466*
Gray, R. T. 6 (23), 7 (24), 25 (24, 96), 27 (23, 24), 29 (96), 30 (24, 96), *52*, *54*; 92 (88), 142 (257), *149*, *156*; 311 (155), 312 (193), 313 (155, 200, 201, 209), *322*, *323*
Grayshan, R. 526 (380), *538*; 595 (291), *607*; 625 (409), *669*
Grayson, D. H. 614 (104), 620 (310), 621, 622 (349), *662*, *667*
Grayson, J. I. 808 (403), *820*
Greef, J. van der 313 (216), 325 (283), *323*, *325*
Green, B. 527 (391), *538*
Green, B. S. 362 (56, 58), *376*
Green, C. H. 835 (95, 98, 99), 836 (98), 850 (233, 238), *855*, *857*, *858*
Green, D. T. 620 (318), *667*
Green, E. A. 138 (250), *156*
Green, G. E. 633 (524), *671*
Green, I. R. 653 (827), *678*
Green, J. C. 950 (257, 258a), *968*
Green, J. H. 381 (239), *443*
Green, J. H. S. 361 (42, 43), 362 (48), *375*
Green, M. M. 314 (235), 315 (237, 238), *324*; 570 (169), *604*; 684 (11, 12), *712*
Greenberg, A. 860, 862 (4, 5), *878*
Greenberg, R. S. 317 (260), *324*
Greene, F. D. 863 (26), 868 (39), 873 (26), *879*
Greene, P. M. 724 (39), *753*
Greene, R. N. 4, 5, 17 (18), *52*; 123 (170a), *153*
Greenfield, H. 517 (312), *536*
Greenfield, S. 482 (76), *530*
Greengrass, C. W. 613 (55), *660*
Greenlee, T. W. 516 (311), *536*
Greenwood, G. 778 (128), *814*
Greff, M. 314 (223), *323*
Gregory, B. J. 49 (186), *57*; 62 (15e), *145*
Gregory, G. E. 580 (213), *605*
Greidinger, D. S. 727, 728 (74), *754*
Grell, E. 69, 70 (45a,b), 78 (45a), *147*, *148*
Grell, W. 773 (81), *813*
Gren, A. I. 839 (117), *855*
Gren', A. I. 686 (19), *712*
Grieco, P. A. 614 (112), *662*
Griengl, H. 799 (318), *818*; 886 (42, 43), *901*
Griesbaum, K. 613, 635 (89), *661*
Grieve, D. McL. A. 891, 895 (68), *902*
Griffin, C. E. 419 (109), *440*
Griffin, G. W. 613 (56), 614 (94), 652 (800–802, 806, 807), 653 (806, 811–815, 824), *661*, *677*, *678*
Griffin, M. T. 658 (895), *679*
Griffith, M. G. 924 (21a), *933*
Griffiths, D. W. 187 (61), *213*
Grigg, R. 635 (587, 588), *672*; 708 (327), *719*
Grigorescu, S. 391, 424 (130), *441*
Grigos, V. I. 799 (315), *818*
Grimaldi, J. 613 (86, 87), 638 (87), *661*; 870, 874 (41), *879*
Grimaud, J. 585 (234), *606*
Grimm, K. G. 167 (39), *173*; 885 (39), *901*
Grimm, R. A. 587, 593 (239), *606*
Grimsrud, E. P. 429 (403), *447*; 944 (177), *966*
Grinblam, M. P. 711 (378), *720*

Grindley, T. B. 44 (169), *57*
Grisdale, E. C. 161 (11), *172*
Griswold, A. A. 772 (65), *812*
Gritter, R. J. 2 (4), *52*; 491 (142), *532*; 610, 637 (2), *659*; 684 (6), *712*; 929 (58), *934*
Grob, C. A. 621 (347), *667*; 686 (20), *712*
Gröbel, B.-T. 541 (9), *600*
Grodski, A. 416 (418), *448*
Gronowitz, S. 593 (281), *607*
Groot, Ae. De. 593 (276), *607*
Grosby, J. 419 (131, 132), *441*
Gross, H. 659 (950, 953), *680*, *681*
Gross, M. L. 325 (282, 283), *325*
Gross, P. 884 (18), *901*
Grossenbacher, L. 214 (110), *214*
Grosser, J. 652 (799), *677*
Grossert, J. S. 549, 578 (71), *602*
Grossi, L. 926 (32b), *933*
Grossweiner, L. I. 988 (155), *992*
Grotjahn, L. 307 (99), *321*
Grovenstein, E. 172 (77), *174*
Grovenstein, E. Jr. 426 (133), *441*
Grubb, S. D. 639 (641), *674*
Gruber, J. M. 804 (361), *819*
Gruen, H. 932 (90), *934*
Grue-Sorensen, G. 425 (134), *441*
Grula, R. J. 748 (332), *760*
Grundon, M. F. 613 (74), *661*; 689 (59), *713*
Grundwald, E. 896, 899 (94), *902*
Grunwald, E. 161 (13), *173*
Grunwell, J. R. 924, 931 (12), *933*
Grupe, K. H. 475 (34), *529*
Grushka, E. 165 (24), *173*
Grushko, I. E. 691 (78), *713*
Grützmacher, H.-F. 301 (20), 305 (63), 313 (63, 203), 314 (222), 315 (242, 243), 316 (244, 246–250), *319*, *320*, *323*, *324*
Grutzner, J. B. 710 (369), *720*
Gryazev, N. N. 732 (117), *755*
Gryaznov, V. M. 730, 731 (101), *754*
Guarna, A. 38 (148), *56*
Guenzi, A. 582 (221), *605*
Guerrero, A. 784 (191, 192), *815*
Guest, I. G. 634 (544), *671*
Güggi, M. 64 (27d,f), 92 (27d,f, 83, 84), 109 (132), 122 (27d,f), *147*, *149*, *151*
Guiard, B. 693 (111, 112), 694 (112), *714*
Guimaraes, A. 852 (262), *858*
Guinot, F. 830 (67, 68), *854*
Guinot, H. M. 738 (194), *756*
Gulbins, E. 825 (42), *854*
Gunning, H. E. 450 (9), 465 (106), *466*, *468*; 917 (89–94), 918 (94, 112), *921*; 923, 927 (3), 928 (3, 51–55, 56a), 930 (3, 51), 931 (3), *932*, *934*
Gunstone, F. D. 307 (87), *320*
Gupta, A. 461 (51), *467*
Gupta, B. G. B. 548 (323), *608*
Gurbanov, P. A. 659 (945), *680*
Gurdzhiyan, L. M. 918, 919 (131), *922*
Gurevich, A. V. 731 (107), *754*
Gurfein, N. S. 736 (157), *756*
Gurfeyn, N. S. 736 (177), *756*
Gurria, G. M. 658 (914), *680*
Gur'yanova, E. N. 364 (87), *376*; 388 (407a), 400, 401 (136), 435 (230), (135, 137), *441*, *443*, *448*
Gusarov, A. V. 769 (34), *812*
Gusarova, N. K. 770, 808 (44), *812*
Guseinov, I. I. 798 (302), *818*
Guseinov, Sh. L. 618 (280, 281), *666*
Gusenkov, M. V. 630 (463), *670*
Gusev, V. I. 746 (323), *759*
Gutbrod, H.-D. 884 (18), *901*
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Gvilava, S. E. 972, 975 (6), 977 (76), *988*, *990*
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Hackhofer, T. 733, 741 (120), *755*
Hackler, R. E. 62 (19k), *146*; 590 (258), *606*
Haddon, W. F. 302 (32b), *319*
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Hadwick, T. 723 (10, 12), 724 (12), *753*
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Haeuser, H. 788 (227), *816*
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Hagège, J. 904 (26), 905 (26, 31, 32), 906 (26), *920*
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Halkes, S. J. 786 (212), *816*
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Hall, M. E. 580 (213), *605*
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Hall, S. S. 517 (314–317), *536*; 778 (129), *814*
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Hamaoka, T. 886 (45), *901*
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Hamlin, K. E. 523 (355), *537*
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Hammerli, M. 939 (114), *964*
Hammond, G. S. 696 (147), 709 (348), *715*, *719*; 896, 899 (95), *902*
Hammond, J. A. S. 749 (336), *760*
Hamon, A. 576 (202), *605*
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Hartmann, A. A. 260 (61), *276*
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Highet, R. J. 493 (161), *532*
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Hirano, S. 505 (251), *535*
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Ho, A. C. 842, 843 (144), *856*
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Hochstetler, A. R. 613, 619 (52), *660*
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Hoffmann, R. W. 788 (227), *816*
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Jha, K. N. 938 (84), 939 (84, 104a, 111), 940 (146, 147a, 149), *964*, *965*
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Jiricek, B. 618 (274), *666*
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Johnson, C. A. F. 909 (52), *920*
Johnson, C. K. 860–862 (6), *878*
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Johnson, D. C. 496, 497 (184), *533*
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Johnson, D. T. 475 (35), *529*
Johnson, D. W. 939 (137d), 940 (147b), *965*
Johnson, H. E. 520 (334), *537*
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Johnson, K. W. 938 (58), *963*
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Johnson, R. A. 170 (61), *174*; 566 (157), *604*
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Jonah, C. D. 938 (52, 77), *963*
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Jones, A. 452 (26), *466*; 927, 932 (50), *934*
Jones, A. J. 248 (100), *277*
Jones, A. R. 382 (175), *442*; 687 (48), *713*
Jones, D. N. 567 (165), *604*
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Jones, E. R. H. 482 (74), *530*
Jones, G. 383 (127), *441*; 634, 653 (553), *672*; 692, 708 (90), 710 (358), *714*, *720*
Jones, G. II 693 (121), 707 (316), 708 (121, 316, 324), *714*, *719*
Jones, G. H. 48 (178, 179), 50 (190), *57*; 107, 109 (124a–c, 125b), *151*
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Jones, J. B. 526 (380), *538*; 595 (291), *607*
Jones, J. Bryan 625 (409), *669*
Jones, J. K. N. 597 (300), *607*
Jones, J. R. 499 (201, 205), *533*
Jones, M. P. 550 (88), *602*
Jones, M. U. 706 (288), *718*
Jones, P. W. 423 (176), *442*; 950 (250), *968*
Jones, R. B. 305, 306 (65), *320*
Jones, R. G. 885 (25), *901*
Jones, R. L. 587 (245), *606*
Jones, S. O. 391 (177), *442*

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Jones, T. K. 640 (652), *674*
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Jonsson, B.-Ö. 944 (169b), *966*
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Jori, G. 558 (133), 562 (145b), 603
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Jou, F.-Y. 938 (79c, 85), 939 (85), 945 (179, 181–184), *963*, *964*, *966*
Jouanne, J. v. 790 (235), *816*
Jowko, A. 939 (136b), *965*
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Judd, C. J. 522 (346), *537*
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Kagan, J. 633 (509, 514), 653, 654 (833, 834), 658 (834), *671*, *678*
Kagan, Y. B. 777 (116), *813*
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Kakis, F. J. 503 (233), *534*
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Kalabina, A. V. 780 (153), 798 (308), *814*, *818*
Kalberer, F. (179, 180), *442*
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Kaliko, O. R. 615 (136), *662*
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Kaliyan, O. L. 918, 919 (131), *922*
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Kamai, G. 782 (170), *815*
Kaman, A. J. 615 (141), *662*
Kamata, S. 4 (16), *52*; 591 (261), *606*
Kamber, B. 295 (49), *297*
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Kaneko, K. 555 (108), *603*
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Kang, R. 627 (443), *669*
Kang, S. 860 (3, 5), 862 (5), *878*
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Karakhanov, E. A. 695 (136, 137), *715*
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Kashman, Y. 613 (70), *661*
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Kaufman, W. I. 643 (694), *675*
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Kaufmann, H. 314 (299), *324*
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Kazanskii, B. A. 727, 728 (73), *754*
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Keskinen, R. 307 (94), *320*; 825 (29–31), 826 (29–31, 45, 49, 52, 53), 827 (29–31, 49, 52), 828 (52, 55), 833 (83), *853*, *854*
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Khan, S. A. 571 (181, 182), *604*
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Kingsbury, W. D. 550 (83), *602*
Kingsley, G. 223, 225 (88), *277*
Kingston, D. G. I. 311 (177), *322*
Kinnel, R. B. 502 (224), *534*
Kinoshita, M. 427 (228), *443*; 567 (163), 570 (170), 571 (172), 573 (163), *604*
Kinstle, T. H. 312 (183), *322*
Kinzig, C. M. 658 (914), *680*
Kipping, F. B. 745 (267), *758*
Kipps, M. R. 835 (92), *855*
Kiprianova, L. A. 415 (200), *442*
Kira, A. 939 (117), *964*
Kirchoff, R. A. 625 (400), *668*
Kirik, T. M. 617 (199), *664*
Kiritani, R. 384 (142), *441*
Kirk, D. N. 281 (9), *296*; 610 (7, 14), 611 (7), 633, 634 (517), *659*, *671*
Kirk, K. 422 (57), *439*
Kirkpatrick, D. 659 (936), *680*
Kirkwood, J. G. 279 (2c), *296*
Kirkwood, S. 401, 430 (54), *439*
Kirmse, W. 642 (675), *674*; 774 (90), *813*
Kirrmann, A. 658 (896), *679*; 687 (49), *713*; 769 (32), *811*
Kirsankina, E. I. 731 (107), *754*
Kirsanov, A. V. 659 (935), *680*
Kirsanova, A. I. 699 (166), *715*
Kirsch, A. 949 (242), *967*
Kirsch, N. N. L. 64 (27g), 92 (27g, 91), 122, 142 (27g), *147*, *149*
Kirschke, K. 643 (704), *675*
Kiseleva, M. M. 735 (160), 736 (154, 155, 160, 161, 176), *755*, *756*
Kishi, M. 552 (91), 568 (91, 168), 573 (91), *602*, *604*
Kishi, Y. 613 (91), *661*
Kishida, Y. 592, 595 (268), *607*
Kiso, Y. 659 (933), *680*
Kiss, A. I. 353 (13), *374*
Kiss, F. 946 (208, 212), *966*, *967*
Kissel, C. L. 631 (474), *670*
Kistiakovsky, G. B. 383, 413 (201), *443*
Kistiakowsky, G. B. 455, 456 (39), *467*
Kitaeva, V. G. 736 (165), *756*
Kitagawa, Y. 527 (388), *538*
Kitahara, T. 807 (385), *820*
Kitamura, E. 730, 746 (102), *754*
Kitaoka, Y. 435 (169), *442*
Kitatani, K. 795 (266), *817*

Kitazawa, E. 785 (193), *815*
Kitazume, T. 583 (227), *605*
Kitchin, R. W. 847 (177), *856*
Kito, R. 780 (144), *814*
Kito, Y. 951 (274), 953 (285), *968*
Kiu, J.-C. 561 (140), *603*
Kiwi, J. 914 (72), *921*; 936 (11a), 946 (203), *962*, *966*
Kiyoura, T. 618 (277), *666*
Kizan, G. K. 391 (98), *440*
Kizawa, K. 695 (134), *715*
Kizilkilic, N. 909, 910, 912, 913 (53), *920*
Kjaer, A. 425 (134), *441*
Klaassen, J. 615 (144), *662*
Klaboe, P. 847 (178), *856*
Klabunde, K. J. 628 (446), *669*
Klabunde, K. Y. 695 (130), *714*
Klages, F. 372 (119), *377*; 972 (11), *989*
Klammar, D. 642, 643 (682), *675*
Kläning, U. 472 (11), *529*
Klasino, L. (9), *438*
Klassen, N. V. 938 (57), 948 (232), *963*, *967*; 982 (117), 988 (172, 176), *991*, *993*
Klaus, M. 653 (828), *678*
Klausner, Y. S. 163, 164 (19), *173*
Klautke, G. 60 (5a), 110 (133c), 143 (5a), *144*, *151*
Kleemola, S. 710 (368), *720*
Kleiman, Yu. L. 647 (723), *675*
Klein, F. M. 826 (44), *854*
Klein, G. W. 305, 306, 315 (62), *320*; 947 (231), *967*
Klein, J. 885 (35), *901*
Klein, K. 774 (92), *813*
Kleinfelter, D. C. 723 (21), 725 (50), *753*
Kleinman, H. H. 707, 708 (316), *719*
Kleinpeter, E. 641 (672), *674*
Klemm, L. H. 598 (304), *608*
Klemm, O. 741 (217), *757*
Klessinger, M. 769, 808 (31), *811*
Klimes, J. 123 (177b, 184), 132 (225), *153*, *155*
Klimov, A. P. 702 (232), *717*
Klimovitskii, E. N. 707 (303), *718*; 849 (216), *857*
Kline, S. A. 658 (904), *679*
Klinot, J. 621 (351), *667*
Kloetzel, M. C. 741 (250), 745 (250, 278), *758*
Klonka, J. H. 628 (446), *669*; 695 (130), *714*
Klopman, G. 356 (29), *375*
Klosová, E. 944 (165), *966*
Klug, J. T. 564, 565 (150), *604*
Klug-Roth, D. 958 (319), *969*
Klump, G. 567 (164), *604*
Klyne, W. 289 (18b), *297*; 829 (61), *854*
Kmet, T. J. 723, 725 (28, 29), *753*
Knapp, S. 543 (26), *601*
Knegt, A. C. 123 (177a), 132 (225), *153*, *155*
Knight, A. R. 905 (33, 39), 917 (89–94), 918 (94, 117), *920–922*; 923 (1), 924 (1, 13), 925 (13), 926 (13, 33, 34), 927 (33, 34, 46–48), 931, 932 (13, 80–82), *932–934*; 976 (74), *990*
Knipe, A. C. 60, 115, 120, 143 (4c), *144*; 419 (45), *439*
Knöchel, A. 115 (144), 119 (156), 120 (164), 123 (177b, 184, 186), 132 (225, 226d), 134 (186), 135 (231), *152*, *153*, *155*; 159, 161 (10), *172*; 189 (69, 70), 191 (70), 193 (69, 70), *213*
Knoeber, M. C. 248 (100), 249–251 (65), 270 (64), *276*, *277*
Knof, H. 937, 938, 940 (31b), 944 (31b, 166b), *962*, *966*; 972, 974 (49, 50), *989*
Knof, S. 288 (16), *297*
Knoll, R. 553 (100), *602*
Knop, D. 76 (59a), *148*
Knorr, R. 272 (107), *277*
Knothe, L. 658 (898), *679*
Knox, B. E. 452 (14), *466*
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Knunyants, I. L. 613 (90), 620 (322), 625 (395), 647 (730), 658 (322), *661*, *667*, *668*, *676*
Knutsen, R. S. 705 (270), *718*
Knyazev, D. A. 437 (202, 412), *443*, *448*
Kobayashi, A. 126 (203), *154*; 189, 193, 201 (68), *213*
Kobayashi, E. 780 (156), *814*
Kobayashi, J. 615 (137), *662*
Kobayashi, M. 591 (265), *605*; 811 (409), *820*; 847 (190), *856*
Kobayashi, S. 700 (194, 205), 701 (211), 702 (214, 218–220), *716*
Kobayashi, Y. 618 (290), *666*
Kober, W. 803 (341), *819*
Kobrich, G. 652 (799), *667*
Köbrich, G. 526 (382), *538*
Kobuke, Y. 46 (173), *57*; 96 (103c), *150*
Kobylinski, T. P. 746, 751 (306), *759*
Koch, D. 779 (142), *814*
Kochi, J. K. 507 (261), *535*; 616 (162), 618 (266, 273), 627 (436), *663*, *666*, *669*; 955 (294), *969*; 972 (16), *989*
Kochmann, W. 659 (950), *680*
Kodama, M. 590 (259), *606*
Kodicek, E. 614 (127), *662*
Koehler, K. 889 (59), 893 (77), *901*, *902*
Koehler, R. E. 580, 581 (212), *605*

Koenig, K. E. 26 (99), *54*; 94, 96, 113 (101b), *150*
Koeppl, G. W. 416 (217), *443*
Koga, K. 49 (187–189), *57*; 62, 91 (16n), 107 (16n, 122d,e), 109 (130a), *146*, *150*, *151*
Kogan, V. E. 736 (166), *756*
Kogane, T. 707 (298), *718*
Kögel, W. 60 (9p), *145*
Kogure, T. 803 (348), *819*
Kohji, Y. 736 (147), *755*
Kohl, D. A. 179 (18), 212
Kohmoto, S. 561 (143), *603*
Kohn, M. 736 (151), *755*
Köhnlein, W. 987 (148), *992*
Kohrman, R. E. 931 (71), *934*
Koida, K. 172 (69), *174*
Koinuma, H. 642, 643 (689), 659 (956), *657*, *681*; 702 (213), *716*
Kojima, T. 182 (34), 186 (54), *212*; 217 (108, 109), *277*; 639, 640 (643), *674*
Kok, P. 617 (216), *664*
Kokoshko, Z. Yu. 736 (165), *756*
Kokotailo, G. T. 60 (9s), *145*
Kokubo, T. 567 (325), *608*
Kokuryo, Y. 786 (201), *816*
Kolaczinki, G. 633 (503), *671*
Kolar, G. F. 430 (203), *443*
Kolarikol, A. 494 (176), *533*
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Kolchin, A. M. 437 (253), *444*
Kolenko, I. P. 633 (504), *671*
Kolesnikov, I. M. 617 (223), *665*
Kollman, P. A. 355 (26), 360 (40), *375*
Kollmeyer, W. D. 433 (204), *443*
Kolmakova, E. F. 780 (153), *814*
Kolomiet, A. F. 650 (758), *676*
Kolosov, V. A. 617 (209), *664*
Kolthoff, I. M. 138 (251), *156*
Koltzenburg, G. 951 (279, 280), 954 (289), 955 (289, 290), *968*, *969*
Kolyaskina, Z. N. 306 (82), *320*
Komalenkova, N. G. 617 (227), *665*
Komarov, V. G. 706 (292), 707 (292, 300), *718*
Komeno, T. 291, 293 (28), *297*; 552 (91), 568 (91, 168), 573 (91), *602*, *604*
Komin, J. B. 613 (85), *661*
Kominami, S. 975 (69), *990*
Komissarova, N. L. 688, 700 (53), *713*
Komratov, G. N. 702 (215), *716*
Konakahara, T. 312 (184), *322*
Konasewich, D. E. (209), *443*
Kondo, K. 540 (5), 543, 585 (23), *600*, *601*; 694 (128), *714*
Kondrat'ev, L. T. 658 (892–894), *679*
Kondrat'eva, G. Ya. 742 (299), 744 (349), 745 (289, 298, 299), 750 (349), *759*, *760*
Konno, K. 516, 522 (308), *536*
Konoike, T. 805 (363), *819*
Konstantinović, S. 502 (225), *534*
Konyasheva, N. V. 659 (924), *680*
Köpf, H. 267 (110), *277*
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Koppikar, D. K. 123 (181), *153*
Koptyng, V. A. 309 (134), *321*
Koptyug, V. A. 372 (114), *377*
Kopylevich, G. M. 735, 736, 738 (175), *756*
Koreck, S. 546 (46), *601*
Korchagova, E. Kh. 700 (178), *715*
Kormarynsky, M. A. 172 (74), *174*
Kornblum, N. 504 (242), *534*
Kornfeld, R. 302 (32a,b), *319*
Korngold, G. 634, 653 (553), *672*
Korobitsyna, I. K. 745 (273), 751 (351), *758*, *760*
Koros, E. 435 (205), *443*
Korostova, S. E. 705 (266), *718*; 771 (53), *812*
Korotaeva, I. M. 706, 707 (292), *718*
Korovina, G. 640 (657), *674*
Korovina, G. V. 700 (201), *716*
Korsakova, I. S. 593 (282), *607*
Koshel, G. N. 635 (570), *672*
Kositsyna, E. I. 771 (53), *812*
Kositsyna, Z. I. 769 (34), *812*
Koskimies, J. K. 260 (66), *276*; 844 (150), *856*
Kosolapova, N. A. 390, 401 (260), *444*
Kosoloski, C. L. 885 (32), *901*
Kosower, E. M. 161 (13), *173*
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Kostelnik, R. J. 705, 706 (273), *718*
Koster, R. J. C. 692 (102, 103), *714*
Kostikov, R. R. 169 (55c), *174*
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Kotimoto, S. 561 (143), *603*
Kotlyarevskii, I. L. 741 (247), 744 (247, 264), 745 (247, 261, 264), 746 (264), 749 (247, 261, 264), *758*
Kourim, P. 926 (42), *933*
Kovac, P. 522 (350), *537*
Kovács, K. 686 (35, 42), 687 (43, 44), 690 (74), 696 (140), 697 (140, 150, 152), 702 (234b), 707 (322), *712*, *713*, *715*, *717*, *719*

Kovtun, G. A. 973 (53), *990*
Kowalczyk, J. 395 (334), *446*
Kowanko, N. 597 (303), *607*
Kozak, I. 391 (224, 225), 443
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Kozik, T. A. 437 (411, 413), *448*
Kozlov, N. S. 659 (929), *680*
Koźluk, T. 697 (148), *715*
Kozma, B. 686 (16, 17, 29, 34), 697 (149, 151), 707 (302, 315, 318), *712*, *715*, *718*, *719*; 733, 734 (135), *755*
Kozuka, S. 549, 573 (75), *602*
Krafft, D. 937, 938, 940, 944 (31b), *962*
Kraft, J. P. 365 (89), *376*
Kraft, L. 499 (207), *533*
Kraij, B. 507 (268), *535*
Krainov, I. S. 618 (261, 288), *665*, *666*
Kramarova, E. P. 806 (383), *820*
Kramer, J. K. G. 301 (19), *319*
Kramer, V. 507 (268), *535*
Krane, J. 123 (173), *153*; 274 (19), *275*
Kranzfelder, A. L. 523 (355), *537*
Krapcho, A. P. 723, 727, 728 (18), *753*
Krasne, S. J. 97 (110), *150*
Krasnoslobodskaya, L. D. 615 (136), *662*
Krasnov, B. P. 699 (165), *715*
Krauch, C. H. 507 (267), *535*; 558 (127), *603*
Kraus, C. A. 540, 587 (2), *600*
Kravets, E. Kh. 916 (81), *921*
Krawczyk, A. R. 426 (206), *443*
Kray, L. R. 705 (271), *718*
Krayushkin, M. M. 805 (369), *819*
Kreevoy, M. M. 415 (208, 210), 431 (207), (209), *443*; 899 (103, 106), *902*
Kreile, D. P. 699 (164), *715*
Kreiser, W. 488 (129), *531*; 800 (323), *818*
Krejči, F. 709 (346), *719*
Krenmayr, P. 771 (49), *812*
Krepski, L. 625 (416), *669*
Kresge, A. J. 416 (211, 212, 214–218, 220, 221), 431 (214, 215, 218–220, 222), *443*; 774 (99, 100), 775 (100, 103, 108, 113), 776 (99, 103, 108, 113), *813*; 889 (58), 893 (72–75), 894 (73), 895 (73, 78), 896 (80), 898 (74), 899 (104), *901*, *902*
Krespan, C. G. 21 (80), 43 (159, 161), *54*, *56*; 123 (172c,d), *153*; 792 (247), *817*; 929 (59), *934*
Kresse, J. 399 (40), *439*
Kresze, G. 625 (405), *669*
Kretchmer, R. A. 622 (356), 635 (564a), *668*, *672*
Kretzschmann, G. 437 (227), *443*
Krief, A. 626 (422–427), *669*
Krinszky, P. 657 (871), *679*
Krishnamachari, S. L. N. G. 917, 918 (97), *921*
Krishnamurthy, S. 527 (392), *538*; 595 (296), *607*; 640 (650), *674*
Krishnan, S. 619 (302), *666*
Kristian, P. 401 (11), *438*
Kristiansen, P. O. 4, 5, 17 (17), *52*; 123 (169, 173), *153*
Kristinsson, H. 653 (813, 824), *677*, *678*
Krivenko, V. G. 974 (60), *990*
Kroeber, H. 808 (392), *820*
Kroh, J. 938 (63c, 72c, 98), 939 (100), 946 (198), *963*, *964*, *966*
Krolikiewicz, K. 803 (342), *819*
Kron, A. A. 772 (62), *812*
Kron, V. A. 798 (308), *818*
Kronberg, J. E. 975, 977 (71), *990*
Kronrad, L. 391 (224, 225), 992 (223), *443*
Kropachev, E. V. 979 (98, 100), 987 (147), *991*, *992*
Kröper, H. 684 (5), *712*
Kropf, H. 617 (241), 636 (604), *665*, *673*
Kroposki, L. M. 706 (283), *718*
Kropp, P. 633 (516), *671*; 860 (9), *878*
Kroupa, A. 742 (325), 746 (321, 322, 325), *759*
Krouse, H. R. (264), *444*
Krow, G. R. 638 (619), *673*
Krueger, P. J. 192, 194 (77), *213*
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Krumbiegel, P. 423 (419), *448*
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Krysin, E. P. 616 (173), *663*
Kryukov, S. I. 616 (165, 184), 635 (580), *663*, *664*, *672*
Krzyminiewski, R. 977 (86), *990*
Kubasov, A. A. 703 (246), *717*
Kubicka, R. 618 (274), *666*
Kubisa, P. 702 (231), *717*
Kubler, D. G. 784 (188), *815*; 899 (107, 108), *902*
Kubo, M. 177, 184 (1), *211*; 220 (167), *278*
Kubota, T. 692 (108, 110), 694 (108), *714*
Kucherov, V. T. 785 (198), *815*
Kuchitsu, K. 179 (15), 183 (37, 38), *212*; 822 (7), *853*
Kucsman, A. 550 (84, 85), *602*
Kuda, Y. 516, 522 (308), *536*
Kudesia, V. P. 422 (226), *443*
Kudo, H. 832 (79), *854*
Kuehl, F. A. 615 (150), *663*
Kuehne, M. E. 614 (125), *662*

Kugel, A. R. 658 (888), *679*
Kuhn, D. A. 686 (39), *712*; 899 (105), *902*
Kuhn, W. 279 (2a), *296*
Kuiper, H. 478 (56), *530*
Kuivila, H. G. 269 (81), 270 (79), 271 (78), 272 (78, 79), *276*; 479 (63), *530*
Kukhar, V. P. 659 (935), *680*
Kukui, N. M. 367 (99), *377*
Kulevsky, N. 918 (125, 126, 129), *922*
Kulicke, P. 437 (227), *443*
Kulkarni, C. L. 314 (236), *324*
Kumada, M. 774 (94). 804 (357), *813*, *819*
Kumai, S. 723 (26), *753*
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Kumar, K. S. 619 (297), *666*
Kumar, R. 928 (57), *934*
Kumasawa, T. 618 (284), *666*
Kumta, U. S. 984 (129), *991*
Kunakova, R. V. 573 (190), *605*
Kundu, N. G. 658 (876), *679*
Kunert, F. R. 510 (286), *536*
Kung, C.-C. 437 (191), *442*
Küng, W. 752 (360), *760*
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Kunowskaya, D. M. 781 (163), *815*
Kuntz, R. R. 979 (96, 99), *991*
Kuo, P. L. 123 (170f), *153*
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Kuosmanen, P. 829, 843, 848 (64), *854*
Kupchan, S. M. 627 (437, 438), *669*
Kuppermann, A. 936 (15), *962*
Kuran, W. 648 (742), *676*
Kurbanov, S. E. 646 (717), *675*
Kurgane, B. 332 (16), *350*
Kuri, Z. 939 (103, 118), *964*
Kuri, Z.-I. 972 (27), *989*
Kurita, Y. 220 (167), *278*
Kuriyama, K. 291 (27, 28), 293 (28), *297*
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Kurokawa, T. 627 (438), *669*
Kuroki, Y. 805 (364, 365), 806 (382), *819*, *820*
Kurono, M. 659 (940), *680*
Kurooka, A. 695 (132), *714*
Kurosawa, E. 696 (146), 700 (175), *715*
Kurowsky, S. R. 751, 752 (357), *760*
Kurozumi, S. 591 (265), *607*
Kurr, B. G. 592, 595, 597 (267), *607*
Kursanov, D. N. 782 (173), *815*
Kurts, A. L. 169 (58), *174*
Kurtz, B. E. (229), *443*
Kushnarev, D. F. 770 (44), 795 (271), 808 (44), *812*, *817*
Kuthalingam, P. 544 (322), *608*
Kutney, J. P. 309 (132), *321*
Kutyreva, V. S. 643 (703), *675*
Kuwa, M. 617 (233), *665*
Kuwajima, I. 591 (264), *607*; 803 (343, 344), 806 (374, 375), *819*, *820*
Kuwata, T. 729 (87), *754*
Kuyper, L. F. 260 (1), *275*
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Kuznetsova, E. M. 437 (231), *443*
Kuznetsova, T. S. 749 (342), *760*
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Lynn, K. R. 723 (36, 37), *753*; 988 (152), *992*
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Lyons, J. 617 (220, 222), 618, 638 (222), *664*, *665*
Lyons, J. E. 616, 617 (164), 618 (164, 257, 265, 289), *663*, *665*, *666*
Lyons, W. E. 931 (74), *934*
Lyper, L. 502 (231), *534*
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Macchia, F. 611 (21), 621 (341), 656 (860–865, 867), 657 (863, 865, 867), 658 (873), 659 (341), *660*, *667*, *678*, *679*; 686 (18, 25), 710 (25), *712*; 723, 726 (25), *753*
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Mahajan, J. R. 561 (142), *603*; 781 (164), *815*
Mahalanabis, K. M. 723, 728 (22), *753*
Maier, R. 786 (202), *816*
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Porter, Q. N. 306–308 (83), *320*; 540 (7), *600*
Porter, R. F. 520 (334), *537*
Porter, R. P. 905 (30), *920*
Porter, S. 639 (645), *674*
Porter, S. K. 658 (897), *679*
Portnyagin, Yu. M. 686 (21–24, 33), 696 (143), 700 (22), 710 (24), *712*, *715*; 738 (201), 740 (216), *757*
Portoghese, P. S. 687 (45), *713*
Porzig, D. 306 (68), *320*
Porzio, M. A. 889, 895 (61), *901*
Posner, G. H. 649 (745), 658 (914–916), *676*, *680*
Pospelov, M. V. 615 (136), 619 (294), *662*, *666*
Post, H. W. 882 (10), *900*
Posternak, Th. 625 (393), *668*
Postovskii, I. Ya. 24 (91), *54*
Posynkiewicz, S. 648 (742), *676*
Potenza, J. 693 (118), *714*
Potolovskii, L. A. 367 (99), *377*
Potter, D. E. 706 (283), *718*
Potter, N. H. 515 (306), *536*
Pottie, R. F. 917, 918 (88), *921*
Pouet, M. 164 (18), *173*
Poulson, R. 904 (23), *920*
Povarov, L. S. 783 (175), 784 (183, 184, 187), 799 (315), *815*, *818*
Povodyreva, T. P. 637, 638 (615), *673*
Powell, M. F. 893 (72, 73), 894, 895 (73), *902*
Powers, J. W. 504 (242), *534*
Powers, P. J. 635 (564), *672*
Pownall, H. J. 407 (321), *445*
Pozdnyakova, T. E. 741, 742 (242), *758*
Pozharskaya, A. M. 390, 401 (260), *444*
Pradhan, S. K. 655 (853), *678*
Praefcke, K. 314 (233), *324*
Prágai, B. 733 (138), *755*
Prager, R. H. 638 (626), *673*
Prahl, H. 774 (85), *813*
Prajer-Janczewska, L. 307 (91), *320*
Prasad, N. 614 (107), *662*
Prášil, Z. 944 (165, 168a,b), *966*
Pratt, E. F. 491 (150), *532*
Pratt, N. H. 852 (259), *858*
Prauge, T. 503 (233), *534*
Preckel, M. 633 (530), *671*
Preiss, D. M. 479 (66), *530*
Preite, S. 617 (214), *664*
Prelog, V. 62, 107 (18d), 109 (132), *146*, *151*; 752 (360), *760*
Preobrazhenskaya, L. B. 437 (202), *443*
Pressman, B. C. 60 (6b), 92 (90), 115, 143 (6b), *144*, *149*
Preto, R. J. 889 (58), *901*
Pretsch, E. 60 (6c), 64 (27a–f,h–k), 92 (6c, 27a–f,h–k, 83, 84, 88), 96 (105), 98 (27k), 106 (119), 109 (132), 115 (6c, 141, 142), 122 (27a–f,h–k), 142 (257), 143 (6c), *144*, *147*, *149–151*, *156*
Prévost, C. 751 (352), *760*
Prey, V. 523 (357), *537*
Pri-Bar, I. 520 (333), *537*
Pribush, A. G. 950 (243a,b), *967*
Price, C. C. 2 (1), *52*; 431 (322), *445*; 550, 555 (81), *602*; 774 (84), 808 (399), *813*, *820*
Price, D. R. W. 904 (10), *919*
Price, M. J. 416 (49), *439*
Price, M. L. 415 (323), *445*
Priéto, J. 735, 737 (185), *756*
Prikle, W. H. 613 (79), *661*
Prilezhaeva, E. N. 576 (200), *605*; 610, 611 (18), *660*; 772 (62), 780 (148, 149), *812*, *814*
Prinzbach, H. 613 (54), 653 (828), 658 (898), *660*, *678*, *679*; 769 (30), *811*
Prishchepenko, V. B. 659 (929), *680*
Pritchard, J. G. 382 (259), *444*; 658 (884), *679*; 850 (221), *857*
Pritchett, R. J. 951 (262), *968*
Pritzkow, W. 548 (62), *602*
Privalova, I. M. 737 (180), *756*
Procházka, M. 543, 560 (19), 583 (229), *600*, *606*
Prokop'ev, B. V. 415 (366), *446*
Pronicheva, L. D. 835 (96), *855*
Prösch, U. 980 (107), *991*
Prossel, G. 770 (42), 792 (249), 793 (42, 249), *812*, *817*
Protopopova, T. V. 784 (186), *815*
Pruckmayr, G. 312, 317 (188), *323*; 700 (189), 701 (212), 702 (212, 222, 228), *716*, *717*
Pruss, G. M. 168, 172 (46), *173*
Prütz, W. A. 988 (183), *993*
Pryor, W. A. 923 (2), 924 (21a,b, 22, 23), 925 (23), 926 (32a), 931, 932 (2, 23), *932*, *933*; 973 (51), *989*
Przybytek, J. T. 653, 654 (833), *678*
Puce, G. 700 (187), *716*
Pudel', M. E. 618 (270), *666*
Pulatova, M. K. 974 (60), *990*
Pullen, K. M. 774 (91), *813*
Pullin, A. D. E. 436 (23), *438*
Pullman, A. 372 (122), 373 (125), *377*
Pullman, B. 372 (122), 373 (125), *377*
Pummerer, R. 548 (59), *601*

Purdie, J. W. 982 (117), 987 (144), *991*, *992*
Purdie, N. 72 (50), *148*
Purick, R. 615 (151), *663*
Purves, C. B. 749 (340), *760*
Pushas, I. 240 (58), *276*
Pushkareva, Z. V. 736 (165), *756*
Pusset, J. 167 (40), *173*
Puzanova, V. E. 706 (289), *718*
P'yankova, G. V. 686 (30), *712*
Pyradi, T. 884, 885 (24), *901*
Pyun, H.-Y. 848 (199), *857*

Qadir, M. H. 848 (202), 849 (205), *857*
Quaglia, M. G. 690 (71), *713*
Qudrat-i-Khuda, M. 727 (67), *754*
Quin, L. D. 613 (71), *661*
Quinn, C. B. 769 (29), *811*
Quinn, M. J. 946 (202), *966*
Quintiliani, M. 987 (140), 988 (160), *992*

Raaen, H. P. (324), *445*
Raaen, V. F. (324), *445*
Raban, M. 570 (169), *604*
Rabani, J. 938 (33), 958 (319, 320), *962*, *969*
Rabinovich, E. A. 398, 432 (358, 359), *446*
Rabinovitz, R. 926 (31), *933*
Rabinowitz, J. L. 405 (325), *445*
Rabinsohn, Y. 482 (76), *530*
Rachele, J. R. 392, 394 (434), *448*
Raciszewski, Z. 615 (145), *662*
Radatus, B. 774 (87), *813*
Radau, M. 643 (700), *675*
Radchenko, E. D. 973 (53), *990*
Radeglia, R. 771 (47), *812*
Rademacher, L. E. 524 (363), *538*
Radics, L. 550 (84), *602*
Radkowsky, A. 483 (83), *530*
Radkowsky, A. E. 474 (24), 475 (30), *529*
Radlick, R. 526 (383), *538*
Rado, M. 618 (251), *665*
Radom, L. 216, 220, 221 (147), *278*; 353, 355 (15), 356 (28), *375*
Radzabov, D. T. 646 (717), *675*
Rafikov, S. R. 617 (225), *665*
Raghavan, N. V. 956, 957 (311b), *969*
Rahkamaa, E. 850 (228), *857*
Rahman, M. 474, 475 (25), *529*
Rai, D. K. 359 (36), *375*
Rai, K. D. 362 (50), *375*
Rainey, W. T. 722, 725 (9), *753*
Raithby, P. R. 131 (222), *154*
Raj, R. K. 426 (326), *445*
Rakhmankulov, D. L. 711 (387), *720*; 840 (122, 123), *855*; 916 (80, 81), *921*
Ramage, R. 613 (55), *660*
Ramakrishnan, L. 123 (181), *153*
Ramakrishnan, V. 931 (89), *934*
Ramamurthy, V. 794 (258), *817*
Ramana, D. V. 309, 313 (133), *321*
Rama Rao, A. V. 308 (120), *321*
Rama Rao, K. V. S. 960 (329), *970*
Ramaswamy, Vaidhyanathan 362 (51), *375*
Ramey, K. C. 274 (130), *277*
Ramsay, G. C. 972 (13), *989*
Ramsay, O. B. (159), *442*
Raney, M. 592 (270), *607*
Rank, B. 499 (207), *533*
Rankin, D. W. H. 803 (350), *819*
Ranky, W. O. 548 (60), *601*
Ranneva, Yu. I. 431 (355), *446*
Ransom, C. J. 4–6 (20), *52*
Ranz, J. A. 623 (361), *668*
Rao, A. S. 613 (61), *661*
Rao, G. U. 236 (42), 265 (44), *275*; 828 (57), *854*
Rao, P. M. 927 (46), 931, 932 (80, 82), *933*, *934*
Rao, P. S. 723, 725 (29), *753*
Rao, V. S. 884 (23), *901*
Rao, V. S. R. 292 (32), *297*
Rao, Y. 486 (113), *531*
Raphael, R. A. 518 (321), *536*
Rapoport, H. 492 (155), *532*
Rapoport, I. B. 738 (188), *756*
Rapp, U. 314 (229), *324*
Rappond, K. D. 380 (370), *447*
Rappoport, Z. 415 (327), *445*
Raptis, M. 476, 479 (40), *529*
Rasmussen, J. K. 803 (338), 805 (366–368), 806, 807 (338), *819*
Rasshofer, W. 38 (147), 39 (149), *56*; 60 (9g,k), 62 (25a,b), 64 (25a,b, 26c,f), 123 (170e, 174, 189), 139, 142 (25a,b, 26c,f), 143 (189), *145*, *147*, *153*, *154*
Rastrup-Andersen, N. 621 (335), *667*
Ratajczyk, J. F. 169 (57), *174*
Ratcliffe, R. 486 (102), 522 (343), *531*, *537*
Ratouis, R. 745 (268), *758*
Raufast, C. 640 (664), *674*; 702 (224), *717*
Rauhut, M. M. 782 (169), *815*
Rauk, A. 230 (148), 231 (149), 240, 241 (176), *278*
Raulins, R. 414 (328), *445*
Rawlinson, D. J. 347 (50), *350*; 507 (261, 262), *535*
Ray, A. K. 727 (67), *754*
Ray, D. J. M. 618 (245), *665*
Rây, P. C. 20, 22 (73), *54*
Raynal, S. 120 (160), *152*
Raynol, S. 172 (74), *174*

Ražem, D. 939 (108), *964*
Razina, R. S. 655 (852), 658 (901), *678*, *679*
Razumovskii, S. D. 556 (120), *603*
Réamonn, L. S. S. 581 (220), *605*
Rebek, J. 614 (108), *662*
Rechnitz, G. A. 92 (84), *149*
Reddy, G. S. 310 (143), *322*; 884 (23), *901*
Redington, R. L. 221 (150), *278*
Redpath, J. L. 980 (109, 110), 981, 982 (110), 987 (149), 988 (162, 179–181), *991–993*
Reed, D. 566 (159), *604*
Reed, J. 617 (198), *664*
Reed, S. F. Jr. 550 (79), *602*
Reeder, R. A. 22 (84), 31 (115), *54*, *55*
Rees, N. H. 706 (286, 288), *718*
Reese, C. B. 4–6 (20), *52*; 794 (264), *817*
Reetz, M. T. 313 (214), 325 (288), *323*, *325*; 805 (370), 806 (370, 371), *820*
Reeve, W. 728, 729 (79), *754*
Reeves, W. P. 867, 868, 873 (38), *879*
Regen, S. L. 490 (138), *532*
Reggel, L. 523 (356), *537*
Regitz, M. 795 (285), *818*
Reich, H. J. 544 (30), *601*
Reichel, D. M. 728, 729 (79), *754*
Reichert, K. H. W. 702 (227, 230), *717*
Reid, E. 391 (177), *442*
Reid, E. E. 20, 22 (74), *54*; 542, 549 (14), *600*
Reid, G. L. 891, 895 (67), *902*
Reifegerste, D. 641 (672), *674*
Reihard, G. 398 (115), *441*
Reijerkerk, R. J. 850 (233), *857*
Reilly, J. 638 (619), *673*
Reimann, I. 918 (130), *922*
Reinach-Hirtzbach, F. de 824, 837 (19), *853*
Reinecke, M. G. 705 (271), *718*
Reiner, M. D. 562 (145b), *603*
Reinhold, G. 587 (244), *606*
Reinhoudt, D. N. 6 (23), 7 (24), 25 (24, 96), 27 (23, 24), 29 (96), 30 (24, 96), *52*, *54*; 68, 71, 72 (36), 92 (88), 99 (36), 122 (167), 142 (257); *147*, *149*, *152*, *156*; 312 (193), *323*
Reischer, R. J. 625 (400), *668*
Reisinger, G. W. 365 (90), *376*
Reistad, T. 294 (43), *297*
Reit, H. 617 (240), *665*
Reitano, M. 508 (275), *535*
Reiter, P. L. 795–797 (280), *817*
Rejtoe, M. 657 (871), *679*
Rekasheva, A. F. 415 (200), 416 (34), *439*, *442*
Remberg, G. 301 (16), *319*
Remizov, A. B. 707 (303), *718*; 850 (241), *858*
Remport, V. 686 (31, 32), *712*
Renard, A. 123 (180d), *153*
Renge, T. 807 (388), *820*
Renken, T. L. 571, 572 (183), *604*
Rennekamp, M. E. 309 (123), *321*
Renold, W. 511 (291), *536*
Rens, J. 620 (320), *667*
Repkin, A. I. 650 (758), *676*
Replogle, L. L. 547 (51), *601*
Reppe, W. 733 (131, 132), 738 (190), 741, 742 (249), 745 (249, 257, 258, 265, 280), 746, 750, 751 (249), *755*, *756*, *758*; 772 (59), *812*
Reshetova, I. G. 614 (128), *662*
Rest, A. J. 123 (171), *153*
Reusch, W. 632 (485), *670*
Reuss, R. H. 804 (359), *819*
Reuss, R. M. 804 (356), *819*
Reutebuch, G. 956, 957 (307), *969*
Reuter, J. M. 413 (332), *446*; 512 (294), *536*
Reutov, O. A. 169 (58), *174*; 381 (362), *446*
Reutrakul, V. 624 (384), *668*
Revelle, L. K. 544 (33, 34), 572 (187), 577 (33, 34), *601*, *605*
Revenko, O. M. 742 (300), 743 (301), 745 (300, 301), *759*
Revinskii, I. F. 614 (117), *662*
Reynolds, R. D. 414 (328), *445*
Rhee, H. K. 490 (137), *532*
Rhee, J. U. 490 (137), *532*
Rhoads, S. J. 414 (328), *445*; 773 (72), *812*
Ribnikar, S. V. 436 (85), *440*
Ricard, M. 307 (93), *320*; 710 (357), *720*
Rice, D. A. 137 (242), *155*
Rice, K. C. 550 (82), *602*
Rice, S. A. 938 (99), 939 (109), *964*
Richards, F. E. 860 (10), *878*
Richards, K. E. 632 (496, 499), 633 (502), 634 (541), *670*, *671*
Richards, P. J. 939 (116), *964*
Richardson, F. S. 295 (53), *297*
Richardson, W. H. 497 (194), *533*; 686 (38), *712*
Riche, C. 130 (214), *154*
Richer, J. C. 309 (130), *321*; 476 (38), 479 (62, 63), 482 (78), 485 (38), *529*, *530*; 620 (319), 638, 639 (618), *667*, *673*
Richey, F. A. 862 (16), *878*
Richey, W. F. 618 (283), *666*
Richman, J. E. 19, 21 (70), *54*; 571 (179a), *604*

Richmond, G. 310 (142), *322*
Richter, P. 726, 729 (65), *754*
Richter, W. J. 311 (164, 165), 312, 317 (191), *322, 323*
Rickborn, B. 433 (80), *440*; 631 (469, 472, 474, 481), 633 (529), 638 (622, 628), 649 (751), 651 (781), *670, 671, 673, 676, 677*
Rickborn, R. 633 (525), *671*
Riddell, F. G. 238 (151), 248 (104, 152), 270 (151), 274 (119), *277, 278*; 825–827 (30), 828 (56), 840 (136), 841 (137), *853–855*
Riedel, J. T. 437 (329), *446*
Rieder, W. 426 (74), *440*
Riehl, J. J. 624 (389), *668*
Rieker, A. 218 (106), *277*
Rifi, M. R. 327 (6), *349*
Rigau, J. J. 545, 546 (41), 550, 551 (89), 555, 567 (115), *601–603*
Rigaudy, J. 356 (30), *375*
Rigbi, M. 296 (58), *298*
Rigby, R. B. 582 (223), *605*
Righetti, P. P. 798 (311), *818*
Rigny, P. 123 (182a), *153*
Rinaldi, P. L. 613 (79), *661*
Rincon, M. T. 745, 749, 750 (295), *759*
Ringold, H. J. 481 (72), *530*
Ringold, M. J. 885 (29), *901*
Riobe, O. 707 (305), *719*
Rios, A. 636 (603a), *673*
Riskin, M. I. 736 (161), *756*
Ritchie, C. D. 161 (13), *173*
Ritter, A. 954, 955 (289), *968*
Rivera, J. 784 (191), *815*
Rivett, D. E. 927, 931 (45), *933*
Rix, M. 733 (123), *755*
Ro, R. S. 524 (363), *538*
Roach, J. A. G. 987 (143, 145), *992*
Roberge, P. C. 904 (26), 905 (26, 32), 906 (26), *920*
Robert, A. 614 (120), 619 (300), 634 (558, 559), 645 (710), 646 (716), 647 (720), 655 (716), *662, 666, 672, 675*
Robert, F. 850 (227), *857*
Robert, H. 745 (262), *758*
Roberti, G. 659 (955), *681*
Roberts, B. P. 916 (79), *921*; 977 (89b), *990*
Roberts, F. E. 597 (299), *607*
Roberts, J. D. 231 (33), 267 (15), 272 (107), *275, 277*; 421 (307), *445*; 593 (272), *607*; 770 (45), *812*
Roberts, J. S. 628 (446), *669*; 695 (130), *714*
Roberts, M. L. 579 (209), *605*; 613 (62), *661*
Roberts, P. B. 988 (163), *992*
Roberts, R. M. 414 (139), *441*
Robertson, A. V. 316 (245), *324*
Robiette, A. G. 803 (350), *819*
Robin, M. 119 (155), *152*
Robin, M. B. 281 (8a), *296*; 903, 904 (1a), *919*; 923, 929 (8), *933*
Robins, P. A. 749 (339), *760*
Robinson, A. G. 735, 741 (223), *757*
Robinson, C. H. 308 (115), *321*; 640 (648), *674*; 829 (61), *854*
Robinson, J. M. 29 (109), *55*
Robinson, M. G. 938 (84), 939 (84, 113a), *964*
Robinson, M. J. T. 238, 270 (151), *278*; 828 (56), *854*
Robinson, M. L. 698 (162), *715*
Robson, A. C. 25 (94), *54*
Robson, P. 544, 578, 585 (32), *601*
Roček, J. 473 (18), 474 (24, 25), 475 (25, 30–33), 476 (41, 44, 46), 477 (41, 48, 51), 478 (32, 52–55, 57), 479 (18), 481 (69), 483 (79, 83, 86), 484 (90), 488 (128), 496, 498 (186), 499 (128), *529–531, 533*
Rochester, C. H. 363 (74, 78–80, 82, 83), *376*
Rodehorst, R. 486 (102), *531*
Rodgers, A. S. 362 (53), *375*
Rodgers, M. A. J. 692 (109), *714*; 936 (7b), 945 (189), 946 (189, 199, 209, 218), *962, 966, 967*
Rodriguez, M. 640 (667), *674*; 987 (143), *992*
Roeske, R. W. 165 (28), *173*
Roger, R. 724 (43), 725 (43, 49), 741, 745 (235), *753, 757*
Rogers, D. Z. 658 (914–916), *680*
Rogers, M. E. 550 (82), *602*
Rogers, N. R. 693 (115), *714*
Rogers, P. E. 625 (397), *668*
Rogers, R. B. 400 (46), *439*
Rogers, T. 564, 570 (151), *604*
Rogić, M. M. 780 (159), 781 (162), *814, 815*
Rogier, E. R. 525 (371), *538*
Roginsky, S. Z. (330), *446*
Rogozina, S. V. 847 (189), *856*
Röhm, D. 940, 941 (150), *965*
Roitman, J. N. 168, 169, 172 (53), *174*; 433 (81), *440*
Rojas, A. C. 770 (46), *812*
Rojo, E. A. 946 (219), *967*
Rokhlin, E. M. 613 (90), *661*
Rolla, F. 62 (15k), *146*
Rollefson, G. K. 453 (31), *467*
Roller, P. P. 658 (879), *679*
Röllgen, F. W. 325 (286), *325*

Rollin, G. 486 (117), *531*
Romanet, R. 393 (405, 406), *447*
Romanovska, E. 939 (100), *964*
Romanovskii, B. V. 630 (463), *670*
Romanskii, I. A. 431 (355), (360, 361), *446*
Romaskina, L. L. 658 (892–894), *679*
Römer, J. 407 (320), *445*
Romers, C. 179 (10), *212*; 237, 238 (153), 244, 258 (102), 261, 262 (153), *277*, *278*; 847 (181–185), *856*
Rona, R. J. 630 (455, 456), 633 (531), 652 (455), 658 (911), *670*, *671*, *680*
Ronald, B. P. 623 (358), *668*; 724, 725 (46, 47), *753*
Ronchi, A. U. 626 (428, 429), *669*
Roncucci, R. R. 405 (128), *441*
Ronzini, L. 163 (17), *173*
Roosevelt, C. S. 804 (352), *819*
Roper, J. M. 16, 30 (58), *53*; 60, 101 (8f), *145*
Ropp, G. A. (324), *445*
Roque, J. P. 477 (47), *529*; 658 (887), *679*
Roquitte, B. C. 911 (59), 912 (65, 66), 916 (76), *920*, *921*
Rosalky, J. M. 136 (241), *155*
Rosall, B. 363 (78), *376*
Rose, C. B. 651 (782), *677*
Rosenberger, M. 621 (342), *667*
Rosenblum, M. 630 (460, 461), *670*
Rosenfeld, J. J. 634 (542), *671*
Rosenfeld, S. M. 931, 932 (85), *934*
Rosenfield, J. S. 291 (26), *297*
Rosengren, K. J. 931 (75), *934*
Rosenkranz, G. 492 (153), *532*
Rosenstock, H. M. 300 (15), *319*
Rosenthal, I. 170 (64, 66), 171 (64), *174*; 708, 709 (338), *719*
Rosenthal, S. 334 (21), *350*
Ross, A. B. 947 (226–228), 948 (226, 228, 233), *967*; 978 (91–94), *991*
Ross, J. A. 232 (48, 154), *276*, *278*; 585 (236), *606*
Ross, R. A. 459 (52), 461 (82, 83), *467*, *468*
Ross, S. D. 327 (5), 347 (52), *349*, *350*
Rosscup, R. J. 419 (160), *442*
Rossi, A. 309 (130), *321*
Rossi, J. C. 611, 612, 620 (36), 621 (36, 350), *660*, *667*
Rossi, R. A. 587 (246), *606*
Rossini, F. D. 370 (106), *377*
Rossiter, B. E. 11, 12 (44), *53*
Rossmanith, K. 707 (297), *718*
Rossy, P. A. 521 (338), *537*
Rostock, K. 774 (82), *813*
Rostoker, M. 647 (725), *675*
Rostron, A. 363 (82), *376*
Roth, W. D. 797 (292), *818*
Rothenberg, S. 355 (26), 360 (40), *375*
Röttele, H. 48 (184), *57*; 62, 107 (16o), *146*
Rouchaud, J. 610, 611 (11), 618 (255, 287), *659*, *665*, *666*
Rouessac, F. 633 (522), *671*
Roush, P. B. 543 (22), 563 (146), 571 (22), *601*, *604*; 977 (89c,d), *990*, *991*
Rousseau, A. D. 693, 694 (117), *714*
Rousseau, Y. 309 (130), *321*; 917 (101), 918 (101, 115), *921*, *922*
Roussi, G. 167 (40), *173*
Roux, A. 624 (370), *668*
Roux-Schmitt, M. C. 624 (370), *668*
Rowbotham, J. B. 359 (37), *375*
Rowland, S. P. 653 (812), *677*
Roy, C. R. 938 (82), *964*
Roy, R. B. 315 (237), *324*
Roy, S. 939 (120), *964*
Royer, J. 359 (35), *375*
Royer, R. 742, 746 (318), *759*
Ruben, H. 265–267 (43), *275*
Rubottom, G. M. 804 (358, 360, 361), *819*
Rubstov, M. V. 728 (85), *754*
Ruby, P. R. 522 (349), *537*
Rudd, E. J. 327 (5), 347 (52), *349*, *350*
Rudenko, B. A. 785 (198), *815*
Rudler, H. 706 (285), *718*
Rudnev, A. V. 938 (76), *963*
Rudolph, G. 115 (144), 120 (164), 123 (177b, 184, 186), 132 (225, 226d), 134 (186), 135 (231), *152*, *153*, *155*; 159, 161 (10), *172*; 189 (69, 70), 191 (70), 193 (69, 70), *213*
Ruecker, Ch. 613 (54), *660*
Rüegg, R. 784 (182), *815*
Ruff, F. 550 (85), *602*
Rulinda, J. B. 364, 365 (88), *376*
Rumanowski, E. J. 642 (687), *675*
Rumquist, O. A. 238 (139), *278*
Rundel, W. 218 (106), *277*
Runowski, R. F. 938 (58), *963*
Ruotsalainen, H. 307 (92), *320*; 699 (170), 710 (356, 364–366), *715*, *720*; 822 (5), *853*
Rupe, H. 741 (217, 219, 227), *757*
Ruska, W. E. W. 972, 977 (47), *989*
Rus Martinez, E. 617 (201), *664*
Russel, C. A. 738 (203), *757*
Russel, G. B. 294, 295 (42), *297*
Russel, J. P. 729 (91), *754*
Russel, P. J. 500 (213), *533*
Russell, D. H. 325 (282, 283), *325*
Russell, G. A. 574, 576 (198), *605*; 614 (100), *661*

Russell, J. C. 937 (20), 940 (142), *962*, *965*

Russell, M. E. 302 (35), *319*; 939, 944 (127), *964*

Rutenburg, A. M. 394, 395 (350), *446*

Rutgers, J. G. 909–911 (54), *920*

Ruth, J. M. 311 (175), *322*

Rutman, G. I. 616 (165), *663*

Ruzicka, L. 483 (81), *530*

Ruzicka, S. 497 (195), *533*

Ruzicka, V. 726, 729 (65), *754*

Růžička, V. 611 (26), 616 (188), *660*, *664*

Ryabova, I. D. 113 (136), *151*

Ryan, K. R. 939 (124), *964*

Ryan, T. G. 937 (24, 25), *962*

Ryba, O. 92 (92), 96 (106), 123 (172b), *149*, *150*, *153*

Rybakov, Z. 437 (308), *445*

Rydzy, M. 437 (245), *444*

Ryhage, R. 301 (21), *319*

Rykowski, Z. 621 (336), *667*

Rylander, P. N. 494, 513 (168), *532*

Ryono, D. E. 776 (104), *813*

Ryskin, M. I. 736 (176), *756*

Rytting, J. H. 44 (164), *57*; 80, 92, 101 (67a), *148*

Ryzhova, N. P. 741 (238, 239), 744 (238), 747 (238, 239), *757*

Rzhevskaya, N. N. 617 (205, 217), *664*

Sääf, G. v. 525 (373), *538*

Saakyan, A. S. 917 (98), *921*

Saavedra, J. 269 (80, 81), 270 (80), *276*

Sabate-Alduy, C. 647 (727), *675*

Sabatino, E. C. 929 (58), *934*

Sabetay, S. 738 (186), *756*

Sable, H. Z. 610, 630, 632, 637, 656 (9), *659*

Sabourin, R. 626, 657 (432), *669*

Sacquet, M. C. 689 (60), *713*

Sadeh, S. 574 (196), *605*

Sadovaya, N. K. 745 (298), *759*

Saegusa, T. 640 (654), *674*; 700 (194, 204, 205, 208), 701 (211), 702 (214, 218–220, 233), *716*, *717*

Saenger, W. 133, 134 (228), 139 (252), 140 (228, 253, 254), 141 (228), 143 (259), *155*, *156*; 210 (106), 214 (111), *214*; 705 (263), *718*

Safarik, I. 928 (55, 56b), 931 (69), *934*

Safe, S. 311 (176), *322*

Safranova, L. P. 749 (344, 345), *760*

Sagatys, D. S. 416 (221), 431 (222), *443*; 775, 776 (103), *813*

Sager, W. F. 483 (79), *530*

Saidi, M. R. 630 (460), *670*

Saigo, K. 785 (193), *815*

Saines, G. S. 509 (281), *535*

Saint-Ruf, G. 311 (174), *322*

Saito, E. 907 (45), *920*

Saito, I. 561 (143), 585 (233), *603*, *606*

Saito, K. 561 (143), *603*

Saito, S. 731 (113), *755*

Saito, Y. 137 (246), *156*

Sajus, L. 616 (153–156), 617 (156), *663*

Sakai, H. 427 (331), *446*

Sakai, I. 302 (32b, 34), 304, 305 (34), *319*

Sakai, M. 780 (143), *814*

Sakai, S. 700 (203), 710 (374), *716*, *720*

Sakakibara, H. 695 (133), *714*

Sakakibara, M. 194 (79), *213*; 769 (36), *812*

Sakakibara, T. 546 (42), *601*

Sakata, R. 780 (156), *814*

Sakembaeva, S. M. 169 (58), *174*

Sakharov, A. M. 702 (232), *717*

Sakikawa, N. 598 (305), *608*

Sakrika, S. 620 (324), *667*

Sakurai, H. 692 (108, 110), 694 (108), *714*

Salahub, D. R. 904 (8), *919*; 929 (60), *934*

Salaun, J. R. 875 (46), *879*

Salegusa, T. 805 (363), *819*

Salem, L. 237 (87), *276*; 798 (297), *818*

Sallo, J. S. 905 (27), *921*

Salmon, G. A. 938 (44–48, 63c), 939 (136a, 137a,d), 940 (147b), 946 (191, 192, 215), *963*, *965–967*

Salmona, G. 305 (60), *320*

Salmond, W. G. 486 (110), *531*; 613 (65), *661*

Salomaa, P. 773 (71), 774 (98), 775, 776 (102), *812*, *813*

Salomaa, S. 895 (78), *902*

Salomon, R. G. 413 (332), *446*; 512 (294), *536*

Saltiel, J. 305 (61), *320*; 694 (125), *714*

Salvadori, G. 370 (102), *377*; 416 (333), *446*

Salvadori, P. 289 (18a), 298 (65), *297*, *298*

Salvatore, F. 398 (437), *448*

Salvatori, T. 633 (507), *671*

Salzmann, J. J. 124 (193), *154*

Salzmann, T. N. 615 (132), *662*

Sam, D. J. 115 (143, 144), *151*, *152*; 164, 168, 171 (20), *173*; 490 (136), *532*

Sambhi, M. 709 (345), *719*

Sambrook, T. E. M. 937 (24), *962*

Samdal, S. 181, 182 (30), *212*; 766, 769, 808 (14), *811*

Samitov, Yu. Yu. 686 (19, 30), *712*; 850 (239), *858*

Sammes, P. G. 579 (217), *605*

Samochocka, K. 395 (334), *446*

Samokhvalov, G. I. 737 (180), *756*

Samorì, B. 284 (13, 14), 289 (17), 293 (34a,b), *297*
Samoshin, V. V. 9 (28), *53*
Sample, S. 301, 303, 304 (28), *319*
Sample-Woodgate, S. D. 311 (162), *322*
Samson, M. 621, 657 (348), *667*
Samter, L. N. 617 (212), *664*
Samuni, A. 951 (281), *968*
Samusenko, Y. V. 581 (219), *605*
Sande, C. C. van de 771 (50), *812*
Sandefur, L. O. 806 (373), *820*
Sandell, E. B. 138 (251), *156*
Sandhu, H. S. 465 (106), *468*; 918 (112), *921*; 928 (56a), *934*
Sandin, R. B. 401 (53, 54), 430 (54), *439*
Sandler, S. R. 2 (3), *52*
Sandorfy, C. 769, 808 (26), *811*; 903 (1b), 904 (1b, 8, 13), *919*; 929 (60), *934*
Sandra, P. 318 (274), *325*
Sandri, E. 582 (221), *605*
Sandri, S. 171 (67), *174*; 486 (114, 118), *531*
Sands, R. D. 723, 727, 728 (13, 14), *753*
Sane, P. P. 613 (61), *661*
San Filippo, J. 170 (63, 65), 171 (65), *174*
San Filippo, J. Jr. 161, 170 (14), *173*; 485 (96), *531*
Sänger, D. 904 (22, 24), 905 (24, 38, 40, 41), 906 (41), 907 (38, 40, 41), *920*; 942 (153), *965*
Sangster, D. F. 938 (93a,b), 956 (305), *964*, *969*
Santambrogio, A. 615 (138), *662*
Santiago, E. 338 (30), *350*
Santosusso, T. M. 636 (606), 658 (875), *673*, *679*
Santry, D. P. 352 (7), *374*
Sapre, A. V. 960 (329), *970*
Sapunov, V. N. 615 (142), 617 (197, 205, 218), *662*, *664*
Sarac, S. A. 497 (193), *533*
Saran, M. 987 (141), *992*
Sarda, P. 517 (318), 523 (354), *536*, *537*
Sarel, S. 825 (23), 835, 836 (100), *853*, *855*
Sarett, L. H. 485 (99), *531*
Sargent, F. P. 939 (130–132, 134b, 135), *965*
Sarilova, M. E. 730, 731 (101), *754*
Sarin, V. N. 362 (49), *375*
Sarkanen, S. 766 (17), *811*
Sarkar, I. 653 (813), *677*
Sarkar, T. 723, 728 (22), *753*
Sarner, S. F. 412 (234), *443*; 708 (329), *719*
Sarr, M. 455 (43), *467*
Sarthow, P. 169 (59), *174*
Sasai, K. 980 (111), *991*
Sasaki, A. 121 (166), *152*
Sasaki, H. 91 (82c), *149*
Sasaki, M. 702 (229), *717*
Sasaki, S. 311 (170), *322*
Sasaki, T. 169 (55c), *174*; 806 (371), *820*; 939 (101), *964*
Sasaki, Y. 126 (203), *154*; 189, 193, 201 (68), *213*
Sasse, W. H. F. 597 (303), *607*
Sato, H. 280, 293 (7c), *296*
Sato, M. 618 (290), *666*
Sato, S. 918, 919 (121a,b), *922*
Sato, T. 611–613, 618 (40), *660*
Sato, Y. 416, 431 (218), *443*; 567 (163), 570 (170), 571 (172), 573 (163), *604*
Satsumabayashi, S. 784 (190), *815*; 832 (79), *854*
Saucy, G. 621 (342), *667*
Sauer, D. T. 583 (224, 226), *605*
Sauer, J. 769 (27), 774 (85), 790, 791 (239), 798 (301, 305, 309), 808 (27), *811*, *813*, *817*, *818*
Sauer, J. D. 16, 30 (58), *53*; 60, 101 (8f), *145*; 884 (19), *901*
Sauers, R. R. 693 (117, 118, 120), 694 (117), 699, 700 (172), *714*, *715*
Sauleau, J. 659 (923), *680*
Saunders, A. D. 650 (769), *676*
Saunders, B. B. 984 (128), 985 (134), *991*, *992*
Saunders, J. K. 221 (71), *276*
Saunders, K. J. 2 (2), *52*
Saunders, W. H. Jr. 425 (335), (336), *446*; 896 (87), *902*
Saus, A. 658 (902), *679*
Sauvage, J. P. 47 (176), *57*; 62 (12a,b, 13c, 14b, 16f), 72 (53), 84, 86 (75), 92 (85a), 98 (112), 99, 100 (85a), 101 (14b, 85a), 107, 109 (16f), 111, 113 (85a), 114 (112, 140), 120 (53), 121 (75, 85a), 123 (177d, 178), 124 (14b, 190d), 125, 130 (190d), 132 (225), 135 (12b, 13c, 53), *145*, *146*, *148–151*, *153–155*
Sauvage, J.-P. 23, 24 (86), 40 (150), 41 (86, 152), *54*, *56*
Sauvageau, P. 904 (13), *919*
Savard, J. B. 482 (78), *530*
Savidan, L. 736 (173), *756*
Savige, W. E. 553 (95), 558 (131), *602*, *603*; 927 (45), 931 (45, 83), *933*, *934*
Savinykh, Y. V. 795 (273), *817*
Savoy, J. 269 (80, 81), 270 (80), *276*
Savushkina, V. I. 402 (415), *448*
Sawada, H. 625 (414), *669*
Sawada, S. 972 (27), *989*
Sawaki, Y. 509 (280), *535*

Sayamol, K. 931, 932 (81), *934*; 976 (74), *990*
Sayer, J. M. 898 (99), *902*
Saytzeff, A. 540, 548 (1), *600*
Scanlon, B. 502 (230, 231), *534*
Scaplehorn, A. W. 707 (312), *719*
Scartazzini, R. 231 (155), *278*
Scartom, V. 612 (41), *660*
Scartoni, V. 634, 642 (540), *671*; 689 (66), *713*
Scatturin, A. 554 (104), *602*
Scettri, A. 698 (161), *715*
Schaal, C. 307 (93), *320*; 686 (14), 699 (168), 710 (357), 711 (381), *712*, *715*, *720*
Schaap, A. 647 (736), *676*
Schaefer, A. D. 169 (57), *174*
Schaefer, H. 555 (111), *603*; 779 (142), *814*
Schaefer, J. 312 (187), *323*
Schaefer, T. 359 (37), *375*
Schaefer, W. 808 (390, 394), *820*
Schaefer, W. E. 779 (136), *814*
Schäfer, H. 327, 348 (4), *349*; 472 (12), 474, 475 (27), *529*
Schäfer, H. J. 339 (31), *350*
Schäfer, K. 741 (219), *757*; 926 (39b), 932 (91), *933*, *934*; 980 (112, 113), 982 (113), 983 (112, 113, 123), 984 (123), 986, 987 (135), *991*, *992*
Schäfer, R. 527 (394), 538
Schaffner, K. 500 (215, 217), *533*, *534*
Schaleger, L. L. 889, 895 (61, 62), *901*
Schamp, N. 308 (104), *321*
Schank, K. 832 (76), *854*
Scharf, D. J. 638 (621), *673*
Scharf, H. D. 692 (98), *714*
Schauble, J. H. 692 (100), *714*
Scheeren, J. W. 887 (49), *901*
Scheffold, R. 647 (731), *676*
Schefter, E. 11 (40), *53*
Schellman, J. A. 988 (166), *993*
Schenck, G. O. 558 (127), *603*
Schenk, G. O. 507 (267), *535*
Schenk, H. 794 (254), *817*
Scherer, K. V. 169, 170 (55b), *174*
Scherowsky, G. 642, 643 (682), *675*
Scherrer, F. 396 (337), *446*
Scherz, H. 951 (271), *968*
Scheurs, H. 652 (795), *677*
Schiebel, H. M. 314 (228), *324*
Schiess, P. 655 (849), *678*
Schiff, L. J. 310 (139), *321*
Schiketanz, I. I. 630 (465), *670*
Schildknecht, C. E. 777 (119), *814*
Schiller, W. R. 435 (338), *446*
Schilling, W. 4 (16), *52*
Schindewolf, U. 938 (36a,b), *962*
Schindler, J. G. 60, 92, 115, 143 (6d), *144*
Schinski, W. 699, 700 (172), *715*
Schinz, H. 745 (271), *758*
Schlegel, H. B. 766, 768, 770 (15), *811*
Schlenk, F. 398 (340, 437), 425 (339), (341), *446*, *448*
Schlessinger, R. H. 571 (179a), 585 (231), *604*, *606*
Schleyer, P. R. 725 (50), *753*
Schleyer, P. v. R. 875 (44), *879*
Schlochoff, P. 741 (227), *757*
Schlögl, K. 743, 744, 746, 747, 749 (311), *759*
Schloman, W. W. Jr. 825 (38), *853*
Schlosser, M. 381 (342), *446*; 650, 658 (776), *677*; 773 (78), 801 (327, 328), *813*, *818*, *819*
Schlözer, R. 618 (291), *666*
Schmalzhofer, F. X. 733 (119), *755*
Schmid, G. H. 356 (30), *375*
Schmid, H. 385 (343, 344, 347), 386 (346), 414 (104–106, 139, 140, 343, 344, 409), (179, 180, 345), *440–442*, *446*, *448*
Schmid, H. G. 838–842 (111), *855*
Schmid, K. 385 (343, 344, 347), 346 (386), 414 (104, 343, 344), (180, 345), *440*, *442*, *446*
Schmidbaur, H. 643, 644 (697), *675*
Schmidt, C. L. A. 397 (392), *447*
Schmidt, E. A. 865 (37), *879*
Schmidt, G. 437 (227), *443*
Schmidt, G. M. J. 362 (54, 58), *376*
Schmidt, H. 398 (115), *441*
Schmidt, M. 267 (110), *277*; 938 (61), *963*
Schmidt, O. 733 (133), *755*
Schmidt, U. 779 (140), *814*
Schmidt, W. 348 (53), *350*; 585 (231), *606*
Schmidtchen, F. P. 118 (152), *152*
Schmitt, J. L. 172 (78), *174*
Schmitt, R. J. 318 (279), 325 (295), *325*
Schmitt-Fumian, W. W. 710 (371), *720*
Schmitz, E. 882 (1), *900*
Schmitz, P. 313 (207), *323*
Schnabel, W. 936 (11a,b, 12), *962*
Schneider, D. R. 795 (274), *817*
Schneider, E. 789 (229), *816*
Schneider, Gy. 658 (909), *679*; 686 (27), 702 (234b), 710 (375), *712*, *717*, *720*
Schneider, H. 72, 74 (55), 76 (59a), *148*
Schneider, J. A. 553 (99), *602*
Schneider, P. 780 (155), *814*; 846 (164, 165), *856*
Schneiders, J. 741 (241), *758*
Schnepp, O. 289 (19), 298 (65), *297*, *298*
Schöbel, A. G. 686 (29), 705 (262), *712*, *718*

Schöberl, A. 542 (13), *600*; 984 (126, 127), *991*
Schoeller, W. W. 764, 765, 770 (8), *811*
Schoellkopf, U. 643, 644 (701), *675*; 800 (320), *818*
Schoemaker, H. E. 313 (202), *323*
Schöllkopf, K. 649 (744), *676*
Schöllkopf, U. 526 (382), *538*; 705 (264), *718*; 823 (16), *853*
Scholten, D. J. 510 (285), *536*
Scholten, G. 60, 143 (5a), *144*
Scholz, H. 696 (142), *715*
Schomburg, G. 907–909, 912 (46), *920*; 946 (222), 951, 953 (273), *967*, *968*
Schönberg, A. 311 (171), *322*
Schönecker, B. 658 (909), *679*
Schoner, W. 114 (139), *151*
Schore, N. E. 794 (255), *817*
Schossig, J. 659 (949), *680*
Schott, H. N. 932 (90), *934*
Schowen, R. L. 686 (39), *712*; 896 (84), 899 (102, 105), *902*
Schram, C. W. A. 616, 617 (179), *663*
Schreiber, J. 473 (18), 479 (18, 60), *529*, *530*
Schreiber, K. C. 547 (55), *601*
Schreiner, H. 399 (348), *446*
Schreurs, P. H. M. 689 (67), *713*
Schröder, G. 48 (184), *57*; 60 (9p), 62, 107 (16o), *145*, *146*
Schröder, L. 735, 741 (225), *757*
Schröder, N. 314 (228), *324*
Schroeck, C. W. 625 (412, 413), *669*
Schroeder, H. 636 (604), *673*
Schroeder, L. 846 (170), *856*
Schröer, H. P. 137 (242), *155*
Schroeter, S. H. 479 (62), *530*; 699, 705 (171), *715*
Schroll, G. 304 (49), 308 (105), *319*, *321*
Schroth, W. 587 (244), *606*
Schubert, F. 738 (209), *757*
Schubert, H. 846 (170), *856*
Schubert, R. M. 640 (650), *674*
Schubert, W. M. 422 (57), *439*
Schuchardt, W. 725 (52), *753*
Schuchmann, H.-P. 904 (4, 9, 12, 15–18, 25), 905 (4, 25, 42), 907 (9, 12, 25, 46, 47, 49), 908 (4, 9, 12, 46, 47), 909 (4, 9, 12, 15, 46, 47, 53, 55, 56), 910 (15, 53, 55, 56), 912 (46, 53), 913 (53, 55, 56), 914 (15, 56, 68b), 915 (15–17, 75), 916 (18, 75), 917 (18, 82), 918 (127), *919–922*; 937 (22, 23, 28), 946 (22, 222), 949 (28), 954 (288), 955 (295), *962*, *967–969*
Schuchmann, M. N. 953 (284), 958 (284, 323, 324, 326), 960 (284, 324), *968–970*
Schuddemage, H. D. R. 302 (32b), *319*
Schue, F. 172 (74), *174*
Schué, F. 120 (160), *152*
Schuessler, H. 988 (165), *993*
Schug, R. 789 (230, 231), 790 (230, 233, 238), 791 (238), *816*, *817*
Schugar, H. J. 693 (118), *714*
Schuijl, P. J. W. 588, 589 (250), *606*
Schuijl-Laros, D. 588, 589 (250), *606*
Schukovskaya, L. L. 803 (349), *819*
Schulek, E. 435 (205), *443*
Schuler, R. H. 947 (231), *967*; 976 (73), *990*
Schulte-Elke, K. H. 870, 874 (42), *879*
Schulte-Elte, K. H. 507 (267), *535*; 746 (327, 328), *759*
Schulte-Frohlinde, D. 904 (24, 25), 905 (24, 25, 29, 42), 907 (25), 911, 918 (62), *920*; 939 (110), 940 (141, 148), 942 (148), 948 (235a), 949 (242), 951 (265, 277, 279, 280), 954 (289), 955 (289–293, 296), 956 (299, 301–303, 306, 307, 311a, 315–317, 318a,b), 957 (301–303, 306, 307, 311a, 315–317, 318a,b), 958 (321–323, 325), 960 (322), 961 (293, 332, 335, 336), *964*, *965*, *967–970*; 972 (31, 32), *989*
Schultz, A. G. 592, 595, 597 (267), *607*
Schultz, G. 180 (21), 183 (39), *212*; 847 (179, 180), *856*
Schultz, R. C. 567 (164), *604*
Schultz, R. F. 455, 456 (39), *467*
Schultze, G. R. 427 (349), *446*
Schulz, M. 643 (704), *675*
Schulze, P. 311 (165), *322*
Schulze-Panier, H. 311 (171), *322*
Schuster, C. 746 (326), *759*
Schuster, G. B. 693 (114), *714*
Schut, J. 597 (301), *607*
Schuttenberg, H. 567 (164), *604*
Schuyl, P. J. W. 316 (251), *324*
Schwab, J. M. 315 (237), *324*
Schwartz, L. H. 633 (521), *671*
Schwartz, M. A. 520 (332), *537*
Schwartz, N. 492 (151), *532*
Schwartz, R. H. 658 (911), *680*
Schwartz, R. N. 938 (81), *964*
Schwartz, S. B. 708 (324), *719*
Schwartz, S. J. 802 (332), *819*
Schwartzman, S. M. 506 (255), *535*
Schwarz, H. 302 (32c), 310 (145, 150), 311 (171), 312 (191), 313 (207, 211, 214), 314 (145, 150, 224, 228–230, 233), 317 (191), 325 (284, 288), *319*, *322–325*
Schwarzenbach, G. 79, 92 (66, 94), 94 (94), *148*, *149*
Schweig, A. 808 (390, 394), *820*

Schweikert, O. 769 (30), *811*
Schweizer, E. E. 794 (265), *817*
Schwellnus, J. 806 (371), *820*
Schwenk, E. 885 (26), *901*
Schwing-Weill, M. J. 87 (78), 94, 95, 115 (97), 137 (244), *149*, *150*, *155*
Schwyzer, R. 295 (49, 50), 296 (50), *297*
Sciacovelli, O. 168, 172 (50), *173*
Sclove, D. B. 868 (39), *879*
Scopes, P. M. 281 (9), 289 (18b), *296*, *297*
Scott, C. B. 161 (13), *173*
Scott, D. A. (82), *440*
Scott, G. 546 (44), *601*
Scott, R. A. 707 (311, 320), 708 (320), *719*
Scott, W. D. 745 (276), *758*
Screttas, C. G. 591 (261), *606*
Scrocco, E. 358 (32), *375*
Sealy, R. C. 954 (287), *968*
Searles, S. 524 (368), 526 (378), *538*; 909–911 (54), *920*
Searles, S. Jr. 92 (93), *149*; 553 (93), *602*; 709 (348), *719*
Secci, A. 834 (87), *854*
Secci, M. 525 (370), *538*
Sechrest, R. C. 243, 249, 252 (63), *276*
Seddon, W. A. 939 (116), 946 (191–193), *964*, *966*
Sedea, L. 549 (74), *602*
Sedgwick, R. D. 944 (167), *966*
Sedzik-Hibner, D. 621 (336), *667*
Seebach, D. 47 (175), *57*; 541 (9), *600*; 650 (773), 659 (951), *676*, *680*; 705, 706 (269), *718*; 769, 808 (27), *811*
Seefelder, M. 780 (157), 782 (166), *814*, *815*
Seeker, R. 342 (43), *350*
Seeley, D. A 622 (355), *668*
Segal, G. A. 352 (7), *374*
Segebarth, G. 836 (102), *855*
Segre, A. L. 262 (75), *276*
Sehested, K. 956 (313), *969*
Sehon, A. H. 462, 464 (94), 465, 466 (104), *468*
Seiders, R. P. 232 (154), *278*; 585 (236), *606*
Seidler, F. 951 (266), *968*
Seiler, P. 11 (38, 39), *53*; 125 (194, 198, 199), 126 (200, 203), 132 (200), *154*; 189, 191–194 (66), *213*
Seip, H. M. 177 (5), 179 (13), 181 (30), 182 (30, 36), *211*, *212*; 765 (12), 766 (14), 769 (12, 14), 808 (14), *811*
Seitz, U. 702 (230), *717*
Seki, H. 943 (161), *965*
Seki, K. 493 (164), *532*
Selander, H. G. 632 (493), *670*
Seligman, A. M. 394, 395 (350), *446*; 729 (86), *754*
Sell, C. S. 732 (115, 116), *755*
Sellars, P. J. 613 (80), *661*; 732 (115, 116), *755*
Sellers, R. M. 950 (248b), *968*
Selling, H. A. 390 (351), *446*
Seltzer, S. 412 (423), *448*
Selve, C. 656 (855), *678*
Semenov, V. P. 796 (286), 797 (288, 291), *818*
Semerdzhi, L. S. 686 (30), *712*
Seminaro, A. 123 (180a,c), *153*
Semsel, A. M. 782 (169), *815*
Senda, Y. 516, 522 (308), *536*
Senderens, J. B. 736, 749 (172), *756*
Sénéchal, G. 635 (565), 639 (640), *672*, *674*
Senning, A. 780 (152), *814*
Seno, M. 611 (25), *660*
Sen Sharma, D. R. 305 (64), *320*
Sepp, D. T. 169, 170 (55b), *174*; 238, 239 (10), *275*
Sepulcher, M. 700 (200), *716*
Sepulchre, A. M. 847 (194), *857*
Sepulchre, M. 640 (658), *674*
Serebryanskaya, A. I. 432 (352), *446*
Seree de Roch, I. 616 (153–156), 617 (156), 618 (259, 286), *663*, *665*, *666*
Sergeev, G. B. 659 (944), *680*
Sergievskaya, O. V. 741 (239), 743 (335), 747 (239), 749 (335, 341), *757*, *760*
Serum, J. W. 311 (166), *322*
Servis, K. L. 272 (156), *278*
Serzyho, J. 648 (742), *676*
Sethi, S. 618 (252), *665*
Sethi, S. C. 653, 654 (836), 658 (918), *678*, *680*
Setkina, V. N. 433 (353), *446*
Setser, D. W. 309 (123), *321*
Settineri, W. J. 335 (24), *350*
Sevand, O. 504 (242), *534*
Severin, M. G. 330 (11), *349*; 599 (313), *608*
Severs, W. L. 979 (101), *991*
Sevost'janova, V. V. 805 (369), *819*
Sexton, M. 479 (62), *530*
Sexton, M. D. 546 (43), *601*
Seyden-Penne, J. 624 (370, 378, 379), *668*; 699 (168, 169), *715*
Sezi, R. 314 (229), *324*
Sghibartz, C. M. 900 (109), *902*
Sha, C. K. 517 (317), *536*
Shabanov, A. L. 653, 654 (837), 659 (944, 945), *678*, *680*
Shabarov, Yu. S. 614 (103), *662*
Shabyro, O. I. 955 (297b), *969*

Shackelford, S. A. 619 (303), *666*
Shafferman, A. 982 (120), *991*
Shagidullin, R. R. 642 (676), *674*
Shah, R. H. 388 (354), *446*
Shahak, I. 658 (905), *679*; 808 (404), *820*
Shalavina, I. F. 593 (279), *607*
Shalom, E. 799 (317), *818*
Shanah, I. 641 (674), *674*
Shanker, R. 499 (210), *533*
Shankland, R. V. 725 (53), *753*
Shanklin, J. R. 625 (420, 421), 626 (420), *669*
Shannon, J. S. 308, 309 (121), 317 (266), 325 (291), *321*, *324*, *325*
Shapiro, E. S. 780 (148), *814*
Shapiro, I. O. 431 (355), (360, 361), *446*
Shapiro, R. H. 309 (129), 318 (279), 325 (295), *321*, *325*
Shapiro, U. G. 896 (89), *902*
Shapovalova, T. M. 736 (177), *756*
Sharf, V. Z. 695 (138), 696, 697 (144), *715*; 729, 731 (89), 734 (179), 735 (175, 181), 736 (152, 156, 175), 737 (178–181), 738 (175), 741 (179), 742 (291), 743 (290, 292), 745 (178, 290–292), 746 (178), 750 (178, 290–292, 348), 751 (178, 355, 356), *754–756*, *759*, *760*
Sharma, A. K. 506 (253), *535*
Sharma, C. 618 (252), *665*
Sharma, D. K. S. 771 (51), *812*
Sharma, N. 822 (9), *853*
Sharma, N. K. 824 (18, 19), 837 (19), 838 (106), *853*, *855*
Sharman, E. H. 298 (65), *298*
Sharman, S. H. 630 (467), *670*
Sharp, J. C. 555, 568 (114), *603*
Sharp, J. H. 943 (159), *965*
Sharpe, P. H. G. 938 (59, 63a, 90), *963*, *964*
Sharpless, K. 616 (159), 617 (159, 221), *663*, *665*
Sharpless, K. B. 485 (97), 520 (332), *531*, *537*; 616 (192), 617 (208), 625 (419), 627 (441), 632, 650, 658 (491), *664*, *669*, *670*
Sharpless, R. 613, 617 (57), *661*
Sharvit, J. 315 (241), *324*
Shatenshtein, A. I. 398 (358, 359), 431 (355), 432 (352, 356–359), 436 (129), (360, 361), *441*, *446*
Shatenshtein, D. I. 432 (138), *441*
Shatokhina, E. I. 556 (120), *603*
Shatzmiller, S. 799 (317), *818*
Shaw, R. 362 (53), *375*; 452 (20), *466*
Shchekut'eva, L. F. 381 (362), *446*
Shcherbakova, E. S. 364 (87), *376*
Shcherbakova, N. D. 731 (107), *754*
Shcherbinskaya, N. V. 745 (277), *758*
Shchori, E. 72, 73 (51), 92 (51, 86a), 116 (148), 123 (183, 187), *148*, *149*, *152*, *153*
Shchukina, M. N. 390 (252, 260), 395 (252), 401 (260), *444*
Shealer, S. E. 692 (105), *714*
Shearer, G. O. 611 (30), *660*
Shearing, D. J. 420 (166), 433 (165), *442*
Sheehan, M. 314 (220), *323*
Shefer, E. A. 736 (156), *756*
Sheikh, Y. M. 311 (156), *322*
Shekhtman, N. M. 786 (204), *816*
Sheldon, J. C. 548 (64), *602*
Sheldon, R. 617 (195, 210), *664*
Sheldon, R. A. 616 (162, 178, 179, 187), 617 (178, 179), *663*, *664*
Sheldrick, G. M. 803 (350), *819*
Shellhamer, D. F. 875 (47), *879*
Shelly, T. A. 168, 172 (46), *173*
Shelton, G. 635 (587), *672*
Shelton, J. R. 778 (127), *814*
Shemyakin, M. M. 113 (136), *151*
Shen, C.-M. 505 (248), *535*
Sheng, M. N. 616 (169, 174, 180), 617 (174, 196), 635 (581), *663*, *664*, *672*
Shepard, A. F. 741, 751 (231), *757*
Shepard, D. 899 (107), *902*
Shepherd, D. M. 741, 745 (235), *757*
Shepherd, J. P. 490 (137), *532*
Sheppard, N. 765, 769 (10), *811*
Sherbanenko, B. T. 617 (223), *665*
Shergina, C. I. 744–746, 749 (264), *758*
Shergina, N. I. 769 (34), 771 (53), *812*
Shering, D. J. 168, 172 (49), *173*
Sherman, W. V. 940 (140), 946 (217), 950 (252–254, 255a,b, 256), *965*, *967*, *968*
Sherwin, P. F. 571, 572 (183), *604*
Sherwood, A. G. 928 (56b), *934*
Sherwood, J. E. 456 (45), *467*
Shetlar, M. D. 709 (347), *719*
Shevlin, P. B. 628 (445, 447), *669*; 862 (14), *878*
Shibasaki, M. 170, 171 (62), *174*
Shida, T. 938 (67), *963*; 975 (67, 68), *990*
Shiefer, S. 403 (363), *446*
Shigeru, T. 614 (113), *662*
Shigesato, H. 612 (42), *660*
Shih, E. 653 (830, 831), *678*
Shih, N. Y. 653, 654, 658 (834), *678*
Shil'nikova, L. N. 646 (714), *675*
Shim, B. K. C. 431 (118), *441*
Shima, K. 692 (96, 108, 110), 694 (108), *714*
Shimada, K. 621 (352), *667*
Shimada, M. 703 (242, 245), *717*
Shimada, O. 946 (224), *967*

Shimanouchi, T. 194 (79), *213*; 769 (36), *812*; 822 (4a), *853*
Shimanskaya, M. V. 700 (178), *716*
Shimazu, F. 984 (129), *991*
Shimazu, M. 806 (375), *820*
Shimizu, F. 860 (10), *878*
Shimizu, K. 938 (72c), *963*
Shimizu, M. 803 (343), *819*
Shimizu, N. 91 (82d), *149*; 617, 618 (236),*665*; 694 (126), 707, 708 (321), *714*, *719*
Shimoda, K. 135 (217), *278*
Shimozato, Y. 611 (25), *660*
Shin, K. 618 (263), *665*
Shine, H. J. 342 (40), *350*; 563 (147), 564 (148), *604*; 779 (136), *814*
Shiner, C. S. 170, 171 (62), *174*
Shiner, V. J. Jr. (364), *446*
Shingaki, T. 709 (353), *719*
Shingu, H. 354 (18a), *375*
Shinohara, Y. 635 (583), *672*
Shioda, H. 786 (201), *816*
Shiotani, M. 708 (330), *719*; 939 (134a,c), 946 (220), *965*, *967*
Shiozuka, M. 91 (82d), *149*
Shipman, J. J. 798 (303), *818*
Shipp, B. D. 405 (365), *446*
Shippey, M. A. 630 (457), *670*
Shishkov, A. V. 391 (98), *440*
Shizuka, H. 435 (16), *438*
Shkrob, A. M. 60 (6a), 113 (136), 115, 143 (6a), *144*, *151*
Shode, L. G. 658 (889), *679*
Shokina, V. V. 647 (730), *676*
Shono, F. 409 (436), *448*
Shono, T. 330 (13), 331 (13–15), 334 (23), 336 (28), 337 (28, 29), 343 (46), 345 (47, 48), 346 (48, 49), 347 (49, 51), 349 (54–56), *350*; 508 (273), *535*; 564 (324), 599 (316), *608*; 723 (26), 745, 752 (269), *753*, *758*; 887 (48), *901*
Shoolery, J. N. 779 (136), *814*
Shor, S. 835, 836 (100), *855*
Short, M. R. 611, 612, 639 (39), *660*
Shostakovskii, M. F. 415 (366), *446*; 744, 749 (346), *760*; 772 (61), 777 (116, 117), 780 (145, 148, 149), 784 (180), 798 (307), *812–815*, *818*
Shostakovskii, S. M. 774 (89), 795 (269–271, 275), *813*, *817*
Shostakovskii, V. M. 684, 690, 691, 695–697, 699, 704 (7), *712*; 742–744, 746 (304), *759*
Shoulders, B. A. 847 (173), *856*
Shporer, M. 72, 73, 92 (51), *148*
Shreeve, J. M. 583 (224, 226, 227), *605*
Shriner, R. L. 522 (349), *537*
Shroeck, C. W. 625 (396, 418, 421), *668*, *669*
Shtacher, G. 408 (367), *446*
Shubin, V. N. 950 (243a,b), *967*
Shue, R. S. 658 (907), *679*
Shuikin, N. I. 686 (16, 17, 34), 688 (53), 697 (152), 700 (53), 704 (254–258, 260, 261), 707 (302, 310, 315), 708 (333–336), *712*, *713*, *715*, *717–719*
Shur, V. B. 431 (368), *447*
Shuykin, N. I. 742–744, 746 (304), *759*
Shvarts, I. S. 805 (369), *819*
Shvartsberg, M. S. 741, 744 (247), 745, 749 (247, 261), *758*
Shvedova, G. N. 931 (73), *934*
Shvets, V. F. 658 (881, 888, 890–894), *679*
Sianesi, D. 659 (919), *680*
Sibbio, B. A. 915 (74), *921*
Sicher, J. 479 (61), *530*
Sidall, J. B. 798 (304), *818*
Siddall, J. B. 795 (267), *817*
Siddiqi, J. A. 596 (298), *607*
Siddiqui, I. A. 658 (884), *679*
Sidel'kovskaya, F. P. 777 (116, 117), *813*, *814*
Sidgwick, N. V. 62 (19c), *146*
Sidhu, K. S. 928 (53, 57), *934*
Sidyakova, G. V. 738 (188), *756*
Sie, B. K. T. 924, 926 (25), *933*
Sieck, L. W. 939 (124), 944 (170), *964*, *966*
Siegel, G. 980 (107), 991
Siegel, M. 725 (51), *753*
Siegel, M. G. 27 (106), 49 (106, 187–189), *55*, *57*; 62 (16b,d), 107 (16b,d, 122d,e), 110 (16d), *146*, *150*
Sieger, H. 39 (149), *56*; 64 (26b, 32, 33a,b), 77, 80, 87–89 (64), 90 (64, 80), 92 (33b, 64, 80), 96 (107), 97 (33a,b), 112, 113 (64), 122 (80), 138 (32, 33a), 139 (26b), 140 (80, 107, 253), 141, 142 (26b), *147–150*, *156*; 210 (105), 214 (111), *214*
Siegfried, B. 422 (92), *440*; 510 (285), *536*
Siegl, W. O. 555, 567 (116), *603*
Sieiro, C. 355 (25), *375*
Sigsby, M. L. 325 (293), *325*
Sigwalt, P. 640 (658, 659), *674*; 700 (200), *716*
Sih, C. J. 566 (159), *604*
Sih, J. C. 650 (767), *676*
Sikata, J. 806 (375), *820*
Silakova, A. A. 695 (135), *715*
Sil'chenko, L. A. 618 (246), *665*
Sile, M. K. 703 (240), *717*
Sillen, L. G. 34 (133), *55*

Silverman, R. B. 780 (147), *814*
Silvestri, M. 520 (332a), *537*
Simandoux, J. C. 415 (369), *447*
Simchen, G. 803 (341), *819*
Simmons, D. E. 802 (337), *819*
Simmons, H. E. 40 (151), *56*; 60 (11a,b), 115 (143, 144), 118 (11b), 135 (11a), *145*, *151*, *152*; 164, 168, 171 (20), *173*
Simmons, H. F. 490 (136), *532*
Simmons, T. 567 (167), *604*
Simon, J. 41, 42 (156), 51 (191), *56*, *57*; 62 (15a, 17), 101 (116), 107 (17, 120), 110, 111, 120 (120), *145*, *146*, *150*
Simon, M. J. E. 405 (128), *441*
Simon, W. 60 (6c,d, 7c), 62 (20), 64 (27a–k, 30b), 92 (6c,d, 27a–k, 83, 84, 87, 88, 91), 96 (105), 98 (27k, 111), 99, 101 (7c), 106 (119), 109 (132), 114 (20), 115 (6c,d, 30b, 141, 142), 122 (27a–k), 129 (211a), 140 (7c), 142 (27g, 257), 143 (6c,d), *144*, *146*, *147*, *149–151*, *154*, *156*; 187 (60), *213*
Simonet, J. 335 (25), 338 (30), *350*
Simonidze, M. Sh. 972, 975 (5, 33), 987 (138), *988*, *989*, *992*
Simonnin, M. 164 (18), *173*
Simons, B. K. 313 (204), *323*
Simons, J. H. 332 (18), *350*
Simpson, J. B. 30 (112), *55*
Simpson, W. T. 924, 929 (10), *933*
Sims, L. B. 380 (370), *447*
Sims, R. J. 138 (247), *156*; 926 (38), *933*; 987 (137), *992*
Sims, S. K. 165 (27), *173*
Simwell, V. 120 (164), *152*
Sinekov, A. P. 643 (703), *675*
Singer, E. 311 (171), *322*
Singh, A. 946 (202), *966*
Singh, J. 702 (226), *717*
Singh, S. P. 633 (509, 514), 653, 654 (833), *671*, *678*
Singleton, D. M. 627 (436), *669*
Sinke, G. C. 361, 366, 368 (41), *375*
Sinnreich, D. 562 (145a), *603*
Sinta, R. 24 (90), *54*
Sipess, B. 94, 95, 115 (97), *150*
Sipos, F. 479 (61), *530*
Siracusa, G. 123 (180c), *153*
Sirling, V. 91 (82a), *149*
Sisler, H. H. 485 (98), *531*; 548 (65), *602*
Sivade, A. 656 (855), *678*
Sivapullaiah, P. V. 123 (181), *153*
Sivertz, C. 926 (36), *933*
Skattebøl, L. 552 (92), *602*; 794 (260), *817*
Skell, P. S. (371, 372), *447*; 550 (86), *602*; 628 (446), *669*; 695 (130), *714*; 794 (261), *817*
Skelton, J. 924–927 (20a), *933*; 972 (34), *989*
Skibida, I. P. 617 (216), *664*
Skingle, D. C. 457 (47), *467*
Skinner, L. J. 365 (89), *376*
Skobtsova, G. E. 704 (254, 255, 258), *717*
Skold, C. N. 585 (231), *606*
Skoldinov, A. P. 784 (186), *815*
Skorianetz, W. 870, 874 (42), *879*
Skuballa, W. 520, 521 (336), *537*
Skvarchenko, V. R. 727 (70), *754*
Skvortsova, G. G. 772 (61), 780 (150), *812*, *814*
Slae, S. 416, 431 (220), *443*
Slavinskaya, V. A. 699 (164), *715*
Slawjanow, A. 738 (202), *757*
Sletzinger, M. 615 (151), *663*
Slivon, L. E. 305 (59), *320*
Sloan, R. B. 634, 653 (552), *672*
Slopianka, M. 658 (910), *679*
Slutsky, J. 412 (234), *443*; 708 (329), *719*
Smakman, R. 307 (95), 308 (114), *320*, *321*; 710 (359), *720*
Small, G. H. 517 (314, 315), *536*
Smallcombe, S. 502 (223), *534*
Smalley, J. F. 938 (63b), *963*
Smegal, J. 167 (41), *173*
Smetana, R. D. 556, 558 (123), *603*; 618 (262), *665*
Smeyers, Y. G. 355 (25), *375*
Smid, J. 24 (90), 39 (149), *54*, *56*; 78, 86 (76b), 113 (137a,b), 116 (149), 120 (161), 143 (137a,b), *148*, *151*, *152*
Smiles, S. 542 (15), *600*
Smiley, S. H. 437 (275), *444*
Smillie, R. D. 806 (373), *820*
Smirnov, V. S. 730, 731 (101), *754*
Smirnov, V. V. 703 (252), *717*
Smirnova, M. G. 699 (166), *715*
Smissman, E. E. 931 (79), *934*
Smit, C. J. 6 (23), 7, 25 (24), 27 (23, 24), 30 (24), *52*; 92 (88), 122 (167), 142 (257), *149*, *152*, *156*
Smith, Ch. A. 710 (369), *720*
Smith, C. S. 918 (117), *922*; 926 (34), 927 (34, 48), *933*
Smith, D. E. 44 (165), *57*; 131 (218), *154*
Smith, G. 509 (283), *535*
Smith, G. A. 302, 303 (29), *319*
Smith, G. E. 972–977 (38), *989*
Smith, G. F. 87 (78), *149*
Smith, G. G. 458 (49), *467*
Smith, G. M. 138 (250), *156*
Smith, J. R. L. 643 (690), *675*
Smith, J. S. 44 (167), *57*; 125 (196), 131 (217), *154*; 192 (75), *213*
Smith, J. W. 639 (641), *674*

Smith, K. 158, 164, 165 (9), *172*
Smith, L. M. 496 (187), *533*
Smith, P. G. 692 (109), *714*
Smith, P. J. (47), *439*
Smith, R. D. 518 (319), *536*
Smith, R. I. 653 (815), *677*
Smith, S. 702 (221), *717*
Smith, S. G. 169 (56), *174*; (373), *447*
Smith, V. F. 305, 306, 315 (62), *320*
Smith, W. B. 722 (9), 723 (28, 29), 725 (9, 28, 29), *753*; 847 (173), *856*
Smith, Z. 179 (18), *212*
Smithers, R. H. 659 (932), *680*; 865 (36, 37), *879*
Smolina, G. I. 780 (153), *814*
Smolina, T. A. 381 (362), *446*
Smolina, Z. I. 307 (102, 103), *321*; 659 (926), *680*
Smuszkovicz, J. 483, 515 (80), *530*
Smyslova, E. P. 745 (289), *759*
Snapp, T. C. 748 (331), *760*
Snatzke, G. 486 (112), *531*; 829 (61), *854*
Sneeden, R. P. A. 740 (213), *757*
Snoble, K. A. J. 650 (762), *676*
Snow, J. W. 31 (119), *55*
Snow, N. W. 437 (276), *444*
Snyder, E. 518 (322), *537*
Snyder, H. R. 524 (364), *538*
Snyder, J. P. 222 (157), *278*; 822 (3), 823 (11), *853*
Snyder, P. A. 280 (4, 5), 281 (5), *296*
Snyder, R. G. 9 (32), *53*
Snyder, W. H. 774 (84), *813*
Soai, K. 806 (381), *820*
Sobala, M. C. 613 (65), *661*
Sobkowski, J. 972 (41, 42), *989*
Sochilin, E. G. 711 (378), *720*
Sogah, D. Y. 107 (122d,e), *150*
Sogah, G. D. Y. 27 (106), 49 (106, 187–189), *55*, *57*; 62 (16b), 107 (16b, 122a), 110 (122a), *146*, *150*; 207 (101), *214*
Sogah, Y. 110 (133a,b), *151*
Sohma, A. 639 (639), *673*
Sohma, J. 708 (330), *719*; 939 (134a,c), 946 (220), *965*, *967*
Söhngen, B. 267 (70), *276*
Sojka, S. A. 613 (84), *661*; 863, 867, 868, 873, 874 (25), *878*
Sokolov, A. G. 617 (212), *664*
Sokolov, S. D. 433 (353), *446*
Sokol'skii, D. V. 700 (182, 184), *716*
Sokova, K. M. 618 (292), *666*
Sokovishina, I. F. 645 (711), *675*
Sokovykh, V. D. 325 (294), *325*
Soleiman, M. 772 (63), *812*
Solka, B. H. 302 (35), *319*
Solodar, A. J. 787 (226), *816*
Solomon, A. K. 390 (99), *440*
Solomon, D. H. 554 (105), *602*
Solomon, J. 316 (258), *324*
Solomon, S. 552 (92), *602*
Solouki, B. 544, 577 (33), *601*
Solov'eva, N. I. 617 (227), *665*
Solov'yanov, A. A. 640 (655), *674*
Solov'yov, A. A. 317 (263), *324*
Soloway, A. H. 636 (603b), *673*
Sommer, J. 723, 734–736, 738 (16), *753*
Sommerfield, C. D. 617 (237), *665*
Sonawane, H. R. 653, 654 (836), 658 (918), *678*, *680*
Sondheimer, F. 492 (153), 518 (321), *532*, *536*
Soneda, R. 784 (190), *815*
Songstad, J. 161 (13), *173*
Sonida, N. 805 (363), *819*
Sonnenschein, W. 390 (63), *439*
Sonnet, P. E. 659 (939), *680*
Sonntag, C. von 904 (4, 9, 12, 15–18, 24, 25), 905 (4, 24, 25, 28, 29, 34–38, 40–43), 906 (37, 41), 907 (9, 12, 25, 38, 40, 41, 46, 47, 49), 908 (4, 9, 12, 46, 47), 909 (4, 9, 12, 15, 46, 47, 53, 55, 56), 910 (15, 53, 55, 56), 912 (46, 53), 913 (53, 55, 56), 914 (15, 56, 68b, 71), 915 (15–17, 71, 75), 916 (18, 75), 917 (18, 82), 918 (127), *919–922*; 935 (2), 937 (22, 23, 28), 940 (141, 145, 148, 150), 941 (150), 942 (145, 148, 153), 943 (155–158), 946 (22, 222), 949 (28, 242), 950 (258b), 951 (266, 267, 271, 273, 275, 276), 952 (267, 283), 953 (273, 284, 286), 954 (288), 955 (291–293, 295, 296, 297a), 956 (298–300, 307), 957 (307), 958 (284, 322–324, 326), 960 (284, 322, 324), 961 (293, 331–336), *961*, *962*, *965*, *967–970*
Sonoda, A. 640 (651), *674*
Sonoda, N. 807 (384, 388), *820*
Sonveaux, E. 41 (153), *56*; 118 (154), *152*
Sopchichin, F. C. 946 (193), *966*
Sorenson, J. R. J. 931 (79), *934*
Šorm, F. 785 (196), *185*
Sorochinskaya, E. I. 614 (102), *661*
Sorokin, M. F. 658 (889), *679*
Sorokin, V. G. 973 (53), *990*
Sosnovsky, G. 347 (50), *350*; 507 (261–263), *535*
Soth, S. 593 (287), *607*
Soundaravajan, S. 123 (181), *153*
Sousa, L. R. 16 (53), 27 (105, 106), 49 (53, 106, 187, 189), *53*, *55*, *57*; 62 (16b, 18a), 96 (18a), 97 (108), 107 (16b, 18a, 122a,d, 126a), 109 (126a), 110 (122a), 114 (18a), *146*, *150*, *151*; 207 (101), *214*

Souza Gomes, A. de 312 (194), *323*
Sova, V. V. 686, 710 (24), *712*
Sovocool, G. W. 692, 694 (95), *714*
Sowa, F. J. 523 (355), *537*
Sowa, J. R. 431 (322), *445*
Söylemez, T. 950 (258b), *968*
Spaargaren, K. 25, 29, 30 (96), *54*; 312 (193), *323*
Spanger, L. A. 580 (211), *605*
Spangler, R. J. 313 (200), 314 (220), *323*
Spassky, N. 640 (658), *674*; 700 (200), *716*
Spaziano, V. T. 483 (82), *530*
Speakman, P. R. H. 544, 578, 585 (32), *601*
Speck, D. H. 5 (21), *52*; 123 (170b), *153*; 312 (186), *323*
Speltz, L. M. 509 (284), *535*
Spencer, C. 595 (294), *607*
Spencer, J. N. 365 (90), *376*
Spencer, T. A. 694 (127), *714*
Speroni, G. P. 38 (148), *56*
Spialter, L. 728 (83), *754*
Spillett, M. J. (20), *438*
Spinks, J. W. T. 936 (14), *962*
Spirikhin, L. V. 544 (35), *601*; 617, 637 (219), *664*
Spiteller, G. 300 (6), 301 (16), 302, 304 (41), *318*, *319*
Spiteller-Friedmann, M. 302, 304 (41), *319*
Spitzer, U. A. 481 (68), 494, 495 (175), *530*, *532*
Sprake, C. H. S. 363, 367 (70, 71), *376*
Spry, D. O. 555 (112), 573 (195), 578 (208), 579 (112, 216), *603*, *605*
Spurny, F. 946 (204), *966*
Srednev, S. S. 616 (184), 635 (580), *664*, *672*
Srinivasan, C. 544 (322), *608*
Srinivasan, K. G. 477 (48), *529*
Srinivasan, V. 632 (488, 489), *670*
Srivastava, R. M. 849 (218, 219), *857*
Stack, R. 484 (88), *530*
Stadler, P. A. 598 (311), *608*
Staehle, M. 801 (328), *819*
Staffeldt, J. 520, 521 (336), *537*
Stafford, G. 487 (125), *531*
Stahl, W. A. 301, 303, 304 (17), *319*
Stahly, E. E. 735, 738 (199), *757*
Stahnecker, E. 526 (385), *538*
Staires, S. C. 692, 708 (90), *714*
Staley, R. H. 316, 317 (255), *324*
Staley, S. W. 172 (76), *174*
Stanaceo, N. Z. 522 (347), *537*
Stanbury, P. 792, 793 (250), *817*
Stang, P. J. 806 (377), *820*; 864 (33), *879*
Stanhuis, E. J. 427 (374), *447*
Stanishevskii, L. S. 647 (733), *676*
Stanley, J. P. 924 (21b, 22), 926 (32a), *933*
Stanulonis, J. 412 (235, 236), 424 (235), *443*
Stapleton, B. J. 302, 303 (42), *319*
Starcher, P. S. 611 (33), *660*
Starkovskii, A. V. 695 (136), *715*
Starks, C. M. 157, 162 (7), *172*; 490 (137), *532*
Starnes, W. H. Jr. 500, 501 (214), *533*
Staroscik, J. 651 (781), *677*
Stary, F. E. 556, 558 (123), *603*
Staude, E. 527 (389), *538*
Staudinger, H. 791 (245), *817*
Stautzenberger, A. L. 616 (168), *663*
Steacie, E. W. R. 917, 918 (103–105), *921*
Steckham, E. 348 (53), *350*
Steckhan, E. 779 (142), *814*
Steele, L. P. 460 (66, 67), *467*
Steen, H. B. 938 (60), *963*
Steenken, S. 948 (235a), 951 (265, 270b), 955 (295), 956, 957 (309, 310, 311a,b, 315–317, 318a,b), *967–969*
Steer, R. P. 929 (62–65), 930 (66, 67), *934*
Stefani, A. 688 (55), *713*
Stefanovic, D. (9), *438*
Steiger, T. 771 (47), *812*
Stein, G. 988 (156, 157, 170, 171), *992*, *993*
Stein, W. 633 (503), *671*
Steinberg, D. 493 (160), *532*
Steinberg, H. 727 (69), *754*; 877 (57), *879*
Steiner, B. W. 300 (15), *319*
Steiner, G. 787, 788 (224), 789 (224, 231), 790 (234), 791 (240), *816*, *817*
Steingaszner, P. 742, 746 (303), *759*
Steinhofer, A. 745 (280), *758*
Steinke, W. 659 (950), *680*
Steinkopf, W. 399 (375), *447*
Stekol, J. A. 396 (377), 397 (376), *447*
Stelter, L. 961 (332), *970*
Stenberg, V. I. 918 (125, 126, 129), *922*
Stenlake, J. B. 553, 554 (101), *602*
Stensiö, K. E. 486 (104), *531*
Stepanov, D. E. 772 (60), 798 (308), *812*, *818*
Stepanov, G. A. 635 (579), *672*
Stepanov, I. P. 653 (810), *677*
Stepanova, I. P. 635 (579), *672*
Stephens, J. R. 262 (160, 161), *278*
Stephenson, L M. 694 (124), *714*
Stephenson, R. A. 651 (783), *677*
Sternhell, S. 885 (27), *901*
Sternson, L. A. 826, 828 (54), *854*
Steuck, M. J. 884 (22), *901*
Stevens, C. L. 636 (597), *673*; 779 (137), *814*

Stevens, C. M. 392, 394 (434), *448*
Stevens, H. C. 615 (141), *662*
Stevens, I. D. R. 862 (16), *878*
Stevens, J. D. 420 (119), *441*
Stevens, J. D. R. 509 (278), *535*
Stevens, T. S. 696, 699, 710 (141), *715*
Stevenson, C. D. 658 (886), *679*
Stevenson, P. E. 224 (158), 230 (41), *275*, *278*; 828 (57, 58), *854*
Stewart, D. G. 2 (9), *52*
Stewart, R. 471 (2), 472 (10), 473 (20), 475 (10), 483 (85), 487 (119, 121, 123), 488 (130), 489 (131), 490 (119, 121, 132), *528–531*
Stewart, R. F. 85 (72), *148*; 353 (11), *374*
Stiles, D. A. 931 (69), *934*
Stiles, M. 723 (38), *753*
Still, I. W. J. 311 (169), *322*; 394 (378), *447*
Stille, J. K. 791 (243, 244), *817*
Stillings, M. R. 643 (690), *675*
Stimson, V. R. 457 (47), 459 (53–58, 60), 460 (62–65, 67, 68, 71–74), 461 (77–82, 84–86), *467*, *468*
Stirling, C. J. M. 419 (131, 132), (84), *440*, *441*
Stirling, D. A. 925, 926 (27), *933*; 979 (97), *991*
St. Jacques, M. 271 (159), *278*
Stockemer, J. 60, 143 (5a), *144*
Stocker, J. H. 885 (30), *901*
Stockhausen, K. 960 (328), *970*
Stöcklin, G. (379), *447*
Stoddart, J. F. 9 (28, 31), 11, 12 (43), 13 (31, 43, 45, 46), 15 (31, 45), 16 (31, 45, 56), 27 (103), 34 (130), 43 (158), 44 (43, 169, 170), 47 (31, 56), 48 (178–183, 185), 50 (190), *53–57*; 62 (15c,d, 16i,k), 72 (47), 94 (98), 97 (108), 98 (113), 99 (15d, 98, 113), 101 (113, 115), 105 (113), 107 (16i,k, 124a–g, 125b), 109 (16i, 124a–g, 125b), 131 (217), *145*, *146*, *148*, *150*, *151*, *154*
Stogryn, E. L. 655 (851), *678*
Stohrer, W.-D. 764, 765, 770 (8), *811*
Stokozenko, V. N. 658 (889), *679*
Stolevik, R. 183 (42), *212*
Stolzenberg, G. E. 408 (390), *447*
Stone, F. G. A. 231 (53), *276*
Stone, J. A. 926 (41), *933*; 972 (36), 975 (71, 72), 976 (72), 977 (71), 979 (101), 982 (116), *989–991*
Stone, T. E. 707 (306), *719*; 777, 778 (121), *814*
Stonkus, V. V. 700 (178), *715*
Stork, G. 593 (289), *607*; 762 (5), 782 (5, 171, 172), 806 (372, 376), 807 (389), *811*, *815*, *820*
Story, P. R. 15 (49), *53*; 262, 267 (132), *277*; 491 (148), *532*
Stothers, J. B. 380 (380), 429 (52, 380), *439*, *447*; 838, 849, 850 (110), *855*
Stott, P. E. 52 (193, 194), *57*; 115 (146), *152*
Stotter, P. L. 593 (289), 595 (297), *607*
Stout, C. A. 709 (348), *719*
Stouwe, C. V. d. 339 (31), *350*
Stozhkova, G. A. 617 (199), *664*
St. Pfau, A. 736, 737 (170), *756*
Stradins, J. 332 (16), *350*
Stradowski, C. 939 (106), *964*
Stradowski, Cz. 939 (100), *964*
Stransky, W. 613 (49), *660*; 705 (272), *718*
Strating, J. 623 (360), *668*
Straub, H. 652 (784), *677*
Strauss, H. L. 180, 189, 194 (25), *212*; 267 (137), 268–270 (29, 30), *275*, *278*; 822 (8), *853*
Strausz, O. P. 450 (9, 10), 465 (106), *466*, *468*; 918 (112), *921*; 923 (3), 925 (30b), 927 (3), 928 (3, 51–55, 56a,b), 930 (3, 51), 931 (3, 69), *932–934*
Strautinya, A. K. 699 (164), *715*
Streckert, G. 509 (282), *535*
Streefkerk, D. G. 692 (102), *714*
Strege, P. E. 592 (266), *607*
Strehlow, W. 585 (231), *606*
Streicher, W. 833, 834 (80), *854*
Streinz, L. 621 (351), *667*
Streitweiser, A. Jr. 161 (13), *173*
Strickland, R. W. 295 (53), *297*
Stroebel, G. G. 867, 868, 873 (38), *879*
Strojny, E. J. 423 (381), *447*
Stroka, J. 72, 74 (55), *148*
Štrouf, O. 746 (316), *759*
Strunin, V. P. 977 (83), *990*
Strunkin, V. A. 919 (133), *922*
Stubbs, J. M. 76 (61), *148*
Stubbs, M. E. 41, 42 (156), *56*
Studner, Yu. N. 650 (758), *676*
Stull, D. R. 361, 366, 368 (41), *375*
Stump, E. C. 786 (210), *816*
Stumpf, K. 62 (19i), *146*
Sturmer, D. 705 (270), *718*
Stutz, P. 598 (311), *608*
Su, A. C. L. 132, 133 (226a), *155*
Su, C. 617 (198), *664*
Su, H. C. F. 836 (102), *855*
Suarez, C. 956, 957 (306), *969*
Suarez, V. 392 (382), *447*
Subbaram, M. R. 596 (298), *607*
Subba Rao, K. V. 939 (119), *964*
Subbotin, O. A. 9 (28), *53*
Subramanyam, V. 636 (603b), *673*
Sucrow, W. 658 (910), *679*

Sudakova, G. A. 659 (944), *680*
Sudo, I. 616 (170), *663*
Suenram, R. D. 916 (78), *921*
Suga, K. 526 (381), *538*; 613, 632 (82), 642 (681), *661*, *674*; 706 (287), *718*
Suga, S. 659 (934), *680*
Suga, T. 485 (94, 95), *531*
Sugi, Y. 638, 639 (631, 638), *673*
Sugimoto, T. 91 (82d), *149*; 567 (325), *608*
Sugioka, M. 464 (100), *468*
Sugishita, M. 648 (737), *676*
Sugita, T. 659 (933), *680*
Sugiura, S. 613 (91), *661*
Sugiyama, Sh. 647 (732), *676*
Suh, I. H. 143 (259), *156*
Suh, J. T. 522 (346), *537*
Sukhomazova, E. N. 795 (275), *817*
Sulser, U. 659 (931), *680*
Sultanova, D. B. 782 (170), *815*
Sümegi, L. 616 (176), *663*
Sumitomo, H. 883 (15), *901*
Summerbell, R. K. 748 (332), *760*; 846 (168), *856*
Summerfield, R. K. 262 (160, 161), *278*
Summers, G. H. R. 638 (617), *673*
Sumoto, K. 625 (417), *669*
Sunaga, M. 625 (410), *669*
Sundararaman, P. 482, 486 (77), *530*
Sundberg, R. J. (65), *439*
Sundermeyer, W. 650 (759), *676*
Sundholm, G. 343 (44, 45), *350*
Sunko, D. E. 419 (100), *440*
Sunner, S. 931, 932 (76), *934*
Surkova, L. N. 613, 637 (51), *660*
Surnova, T. P. 735 (160), 736 (160, 161), *756*
Surova, N. S. 847 (188), *856*
Sustmann, R. 787, 792 (217), 798 (297), *816*, *818*
Sutcliffe, L. H. 500 (213), *533*
Suter, E. 791 (245), *817*
Sutherland, B. L. S. 632 (495), *670*
Sutherland, G. L. 304 (49), *319*
Sutherland, I. O. 26 (101), *54*; 269 (162), *278*
Sutton, L. E. 189 (72), *213*
Suzuki, A. 427 (228), *443*; 638, 639 (637), 652 (793), 653 (818, 835), 654 (835), *673*, *677*, *678*
Suzuki, E. 972 (13), *989*
Suzuki, F. 566 (159), *604*
Suzuki, H. 553 (98), 562 (144), *602*, *603*
Suzuki, J. 561 (141), *603*
Suzuki, M. 493 (164), *532*
Suzuki, S. 638 (632), *673*; 870, 874 (42), *879*
Suzuki, Sh. 689 (61), *713*
Suzuki, Y. 485 (94), *531*
Suzuoki, K. 417 (158), *442*
Svahn, C. M. 622 (353), *667*
Svanholm, U. 415 (383), *447*
Svec, H. J. 300 (7), *319*
Svensson, S. 299 (3), *318*
Sviridova, A. V. 576 (200), *605*
Svitych, R. B. 617 (205, 217), *664*
Svoboda, M. 168, 172 (47, 48), *173*; 659 (927), *680*
Swaelens, G. 840 (124, 128), *855*
Swain, C. G. 161 (13), *173*; (384), *447*; 620 (308), *667*; 686 (39, 40), *712*; 899 (105), *902*
Swallow, A. J. 925, 926 (27), *933*; 935 (6a,b), 936 (13), *962*; 971, 977 (4b), 979 (97), *988*, *991*
Swallow, W. H. 633 (502), *671*
Swaminathan, S. 788 (228), *816*
Swedo, R. J. 475 (31), *529*
Sweeney, A. 635 (588), *672*
Sweigart, D. A. 848 (197), *857*
Sweigart, J. R. 365 (90), *376*
Swenton, J. S. 794 (257), *817*
Swerdloff, M. D. 781 (162), *815*
Swern, D. 506 (253), *535*; 610, 611, 614 (3), 636 (601, 606), 643, 644 (695), 658 (874, 875), *659*, *673*, *675*, *679*
Swiderski, J. 388 (385), *447*
Swift, H. E. 616 (190), *664*
Swistak, E. 732, 746 (118), *755*
Sword, I. P. 404 (143), *441*
Sykes, A. 694 (125), *714*
Sykes, P. C. 363 (82), *376*
Symmes, C. 313 (215), *323*
Symmes, C. Jr. 613 (71), *661*
Symons, M. C. R. 472 (10, 11), 475 (10), 487 (122), *528*, *529*, *531*; 939 (119, 128a), 942 (128a), 943 (159), 950 (244), *964*, *965*, *967*; 972 (12, 17), 973, 974 (17), 975 (70), 976 (17, 70), 977 (12, 70), 985 (70), *989*, *990*
Syrov, A. A. 617 (229), *665*
Sysak, P. K. 558 (129), *603*
Sytilin, M. S. 611 (28), *660*
Sytin, V. N. 614 (117), *662*
Szabo, G. 92 (90), *149*
Szabó, I. 635 (566), *672*; 690 (74), 697, 700 (153a), *713*, *715*
Szafranski, A. 363 (66), *376*
Szarek, W. A. 44 (169), *57*; 847 (194), *857*
Szczepanski, H. 576 (201), *605*
Szeimies, G. 476 (37), *529*; 795 (279, 281, 282), 796 (281), 797 (279), *817*
Szilagyi, P. J. 710 (377), *720*

Sziman, O. 421 (386), *447*
Szmant, H. H. 542 (12), 545, 546 (41), 547 (12, 57), 553, 554 (12), *600, 601*; 852 (258), *858*
Szmuszkovicz, J. 762 (5), 782 (5, 171), *811, 815*
Szymoniak, K. 407 (443), *448*

Taagepera, M. 316, 317 (255), *324*
Tabenko, B. M. 402 (415), *448*
Tabet, J.-C. 308 (106), *321*
Tabushi, I. 20 (71), 21, 23 (78), *54*; 91 (82c,d), 143 (263), *149, 156*; 183 (38), *212*; 659 (938), *680*; 787 (226), *816*
Tacconi, G. 798 (310–312), 799 (313), *818*
Tack, J. J. 364 (85), *376*
Taddei, F. 355, 360 (24), *375*
Tadokoro, H. 9 (33), *53*; 137 (246), *156*; 210 (107), *214*
Tadokoro, M. 220 (168), *278*
Tadwalkar, V. R. 613 (61), *661*
Taft, R. W. 316, 317 (255), *324*
Tagaki, W. 383 (292), 394 (294), (293, 295), *445*; 549 (75), 550 (78), 573 (75, 78), *602*; 625 (410), *669*
Taganov, N. G. 702 (215), *716*
Tagg, J. 420 (283), *444*
Tahara, S. 9 (33), *53*; 137 (246), *156*
Tai, A. 107 (121), *150*
Tajima, M. 980 (111), *991*
Takacs, F. 833, 834 (80), *854*
Takagi, T. 296 (57, 59), *297, 298*
Takahashi, S. 182 (34), *212*
Takahashi, T. 424 (387, 388), *447*; 540 (4), *600*; 616 (170), *663*
Takahasi, M. 909 (51b), *920*
Takaishi, N. 702 (233), *717*
Takaki, U. 39 (149), *56*; 78, 86 (76b), *148*
Takao, K. 618 (271), *666*
Takasaka, N. 613, 632 (82), *661*
Takashaki, T. 618 (277), *666*
Takaya, H. 709 (352), *719*; 860 (10), *878*
Takeda, A. 647 (729), *675*
Takeda, K. 291, 293 (28), *297*
Takeda, T. 613 (92), *661*
Takeda, Y. 121 (166), *152*
Takegami, Y. 630 (459), *670*
Takeshita, H. 617 (234), *665*
Takeshita, M. 770 (40), *812*
Takeyama, Y. 703, 703 (250), *717*
Takezaki, Y. 911 (60), 917, 918 (108), *920, 921*; 931 (84), *934*
Takitani, S. 833 (84), *854*
Takken, H. J. 849 (214), *857*
Tam, S. W. 312 (180), *322*
Tam, S. Y. K. 774 (87), *813*
Tamao, K. 774 (94), 804 (357), *813, 819*
Tamaoki, A. 618 (277), *666*
Tamaru, K. 433 (168), *442*
Tamaru, Y. 183 (38), *212*
Tamba, M. 987 (140), 988 (160), *992*
Tamelen, E. E. van 593 (273a), *607*
Tamres, M. 92 (93), *149*
Tamura, K. 724 (41), *753*
Tamura, Y. 169 (55c), *174*; 625 (417), *669*
Tamvelius, H. 363 (72), *376*
Tanabe, K. 633 (526), 635 (526, 574–577), *671, 672*; 692 (96), *714*
Tanabe, M. 420 (283), *444*; 803 (347), *819*
Tanaka, F. S. 408 (389, 390), *447*
Tanaka, H. 647 (729), *675*; 710 (374), *720*
Tanaka, J. 904, 918 (11), *919*
Tanaka, K. 918, 919 (121b), *922*
Tanaka, N. 435 (391), *447*
Tanaka, S. 613, 617 (57), 631 (473), *661, 670*
Tanaka, Y. 702 (216, 219, 220), *716*
Tancrede, J. 630 (461), *670*
Tang, D. P. C. 905 (27), *920*
Tang, F. Y. N. 634, 653 (552), *672*
Tang, R. 231 (149), *278*
Tangari, N. 626 (429), *669*
Tanguy, M. 363 (77), *376*
Taniguchi, Y. 20 (71), *54*
Tanimoto, S. 567 (325), *608*
Tanino, H. 613 (91), *661*
Tappel, A. L. 931 (87), *934*; 984 (129), *991*
Tarasov, A. N. 640 (668), *674*
Tarbell, D. S. 650 (770), *676*; 808 (402), *820*
Tark, S. Y. 611, 612, 620, 621 (38), *660*
Tarka, S. M. 549 (72), *602*
Tarli, F. 659 (919), *680*
Tarnorutskii, M. M. 659 (924), *680*
Tarnouski, T. L. 111 (134), *151*
Tarnowski, T. L. 7–9 (27), 26 (99), 27 (102), *52, 54*; 116 (150), *152*
Tarrant, P. 786 (210), *816*
Tarte, P. 852 (264, 266), *858*
Tarver, H. 396 (272), 397 (392), *444, 447*
Tarvin, R. F. 791 (243), *817*
Tasker, P. A. 36 (138, 140), *56*; 132 (226c), *155*
Taskinen, E. 698 (159), *715*; 767 (21–25), 768 (21–23), *811*; 826 (46), *854*
Tate, D. P. 587 (247), *606*
Tatikolov, A. S. 618 (261, 288), *665, 666*
Tatsumi, C. 435 (169), *442*
Tatsumi, T. 695 (134), *715*
Tausch-Treml, R. 950 (245), *967*
Tavares, D. F. 624 (383, 385, 387), *668*
Tavernier, D. 839, 840 (120), *855*
Taylor, D. R. 634 (545), *672*

Taylor, E. C. 461 (81, 85), *468*; 885 (38), 886 (44), *901*

Taylor, G. 709 (351), *719*

Taylor, G. F. 383 (198), *442*

Taylor, H. A. 462 (91, 92), *468*

Taylor, J. W. 308 (107), *321*; 380 (178, 429), 429 (178, 403), *442*, *447*, *448*

Taylor, K. G. 272 (163, 164), *278*

Taylor, R. 432 (393), *447*

Taylor, S. K. 651 (782), *677*

Taylor, W. I. 373 (128), *377*

Taylor, W. J. 370 (106), *377*

Tazuma, J. 779 (137), *814*

Tchelitcheff, S. 781 (161), 786 (205), 798 (299), 799 (319), *815*, *816*, *818*

Tchernyshova, T. M. 919 (133), *922*

Teather, G. G. 938 (57), 948 (232), *963*, *967*; 977 (80a), *990*

Tebby, J. C. 312 (197), 325 (287), *323*, *325*

Tedeschi, G. 691 (80), *713*

Tehan, F. J. 21 (77), *54*; 120 (162c), *152*; 172 (73), *174*; 946 (194), *966*

Tele, A. 403 (394), *447*

Temeriusz, A. 388 (385), *447*

Temkin, M. I. 618 (279), *666*

Temnikova, T. I. 610 (8), 620 (307), 641 (8), 642 (684), 643 (691, 692), 653 (810), *659*, *667*, *675*, *677*

Temple, R. D. 614 (114), *662*

Templeton, D. H. 220 (136), 264 (28), 265–267 (43), *275*, *278*

Templeton, W. 476 (45), *529*

Tenenitsyna, E. P. 616 (191), *664*

Téoule, R. 987 (148), *992*

Tepenitsina, E. P. 635 (579), *672*

Teplý, J. 935 (1), 944 (165), 945 (1), 946 (197, 208, 212, 213), *961*, *966*, *967*

Teptina, N. V. 642 (676), *674*

Teranishi, H. 618 (250), *665*

Teranishi, S. 613 (81), 618 (267, 271), 635 (582, 585), *661*, *666*, *672*; 734–736, 745 (145), *755*

Terashima, Sh. 616 (193), *664*

Terent'ev, A. B. 931 (73), *934*

Terent'ev, A. P. 780 (160), 782 (165), *814*, *815*

Terlouw, J. K. 306, 307 (73), *320*

Termens, G. 956, 957 (301), *969*

Ternay, A. L. Jr. 567 (167), *604*

Terpugova, M. P. 745, 749 (261), *758*

Terrell, R. 762 (5), 782 (5, 171), *811*, *815*

Terrier, F. 164 (18), *173*

Terry, R. E. 80–82 (67b), 84 (69), 92 (67b, 69), 93, 94 (69), 101 (67b, 69), 121, 122 (165), *148*, *152*

Terry, V. O. 653 (816), *677*; 911 (64), *921*

Ter-Sarkisyan, G. S. 784 (185), *815*

Ter Wiel, J. 615 (133), *662*

Terwilliger, M. A. 904 (6), *919*

Testi, R. 545 (38), *601*

Tevzadze, G. A. 437 (414), *448*

Teyssie, P. 700 (196), *716*

Tezuka, T. 553 (98), 562 (144), *602*, *603*

Thakker, D. R. 658 (878), *679*

Thap Do Minh 652, 653 (806), *677*; 905 (27), *921*

Theilacker, W. 585 (231), *606*

Theissling, C. B. 310 (151, 152), 313 (216), *322*, *323*

Thepenier, J. 708 (340, 341), *719*

Thich, J. A. 693 (118), *714*

Thide, K. H. 849 (209), *857*

Thierry, J. C. 135 (236), *155*

Thiers, G. V. D. 431 (395), *447*

Thiers, J. H. 431 (395), *447*

Thijs, L. 633, 645 (512), 653 (819), *671*, *677*

Thil, L. 624 (389), *668*

Thi Tham Oanh, H. 123 (180h), *153*

Thoai, N. 709 (350), *719*

Thoma, A. P. 60, 99, 101 (7c), 109 (132), 140 (7c), *144*, *151*

Thomas, A. F. (396), *447*

Thomas, C. 182 (33), *212*

Thomas, J. D. R. 92 (84), *149*

Thomas, J. K. 939 (117), *964*

Thomas, M. J. 863, 867, 873 (22), *878*

Thomas, M. T. 311 (169), *322*

Thomas, P. 420 (119), *441*

Thomas, P. J. 453–456, 458, 459 (35), *467*

Thomas, R. C. Jr. 406 (164), *442*

Thomassen, L. M. 167 (42), *173*

Thompson, C. J. 463, 464 (96), *468*

Thompson, D. P. 94 (96), *149*

Thompson, G. F. 951 (260), *968*

Thompson, H. W. 769 (28), *811*; 862 (16), *878*

Thompson, J. W. 645 (709), *675*

Thompson, M. D. 22 (84), 31 (115, 117, 119), 32 (122), *54*, *55*

Thompson, M. E. 25 (94), *54*; 60 (91), 94 (96), *145*, *149*

Thompson, Q. E. 556 (122), *603*; 836, 849 (103), *855*

Thompson, R. M. 695 (139), *715*

Thompson, S. D. 931 (89), *934*

Thoms, E. 951, 952 (267), *968*

Thomson, J. B. 313 (208), *323*

Thomson, J. W. 688 (51), *713*

Thomson, R. H. 573 (194), *605*

Thon, N. 808 (390), *820*

Thornton, E. R. (384, 397), *447*; 896, 899 (93), *902*

Thorstenson, T. 850 (252), *858*
Thozet, A. 187 (56), *213*
Thuan, S. L. T. 503 (235), *534*
Thummel, R. P. 631 (469, 472, 481), *670*
Thynne, J. C. J. 452 (20), *466*; 939 (125), *964*; 972, 975 (46), *989*
Tichenor, R. L. 383, 413 (201), *443*
Tichy, M. 479 (61), *530*
Tiffeneau, M. 724 (42), 725 (48), *753*
Till, A. R. 384 (125), *441*
Tillett, J. G. 825 (22, 24), 838 (22), 852 (259, 263), *853*, *858*
Tilley, J. W. 461 (78–81), *467*, *468*
Timko, J. M. 16 (53), 27 (102, 107), 30 (110), 46 (107), 49 (53, 189), *53–55*, *57*; 62 (16c, 18a), 85 (71), 92 (90), 96 (18a, 71, 103a), 107 (16c, 18a, 122b–d,f,g, 125a), 109 (122f,g, 125a, 127, 128, 130a, 131), 114 (18a), *146*, *148–151*; 196 (81), 201 (95), 207 (81), *213*, *214*
Timmons, R. B. 412 (270), *444*; 909 (51a), *920*
Timoshchuk, T. 616 (158), *663*
Tinland, B. 360 (38), *375*
Tinsley, S. W. 611 (33), *660*
Tipper, C. F. H. 372 (113), *377*; 452 (12), *466*
Tipping, A. E. 582 (223), *605*
Tiripicchio, A. 284 (14), *297*
Tisenko, I. G. 659 (930), *680*
Tishchenko, I. G. 614 (117), 647 (733), *662*, *676*
Tishler, M. 395 (317), *445*
Tissier, F. 907 (45), *920*
Tissington, P. 709, 710 (354), *719*
Titowa, A. N. 749 (338), *760*
Titus, E. O. 64, 115 (30a), *147*
Tjomsland, O. 294 (44), *297*
Tobias, I. 289 (23), *297*
Tobler, E. 659 (920), *680*
Tochtermann, W. 269 (165), *278*
Todesco, P. E. 429 (126), *441*; 550 (80), *602*
Toga, T. 407 (146), *441*
Togashi, S. 627 (435), *669*
Tohma, M. 615 (152), *663*
Toi, H. 640 (651), *674*
Toki, S. 692, 694 (108), *714*
Tokmadzhyan, G. G. 691 (85), *713*
Tokuda, M. 653 (818, 835), 654 (835), *677*, *678*
Tokunaga, H. 634, 655 (555), *672*
Tolbert, B. M. 988 (164, 168), *992*, *993*
Tolkacheva, E. N. (398), *447*
Tolkien, G. 316 (247), *324*
Tolman, V. 403 (399), *447*
Tolstikov, G. A. 544 (35–37), 573 (190), *601*, *605*; 616 (160, 177), 617 (177, 219, 224, 225), 637 (219), *663–665*
Tomaja, L. 123 (182b), *153*
Tomasi, J. 358 (32), *375*
Tomboulian, P. 706 (284), *718*
Tomer, K. B. 306 (77), 310 (149), 314 (231), *320*, *322*, *324*
Tomie, M. 419 (100), *440*
Tomita, T. 615 (152), *663*
Tomoi, M. 34 (131), *55*; 60 (9q), *145*
Tonellato, U. (67, 281), *439*, *444*
Toneman, L. H. 177 (4), *211*
Tong, J. Y. P. 471 (7), *528*
Tong, Y.-C. 547 (53), *601*
Tonge, A. P. 571 (177), *604*; 844, 845 (152), *856*
Toniolo, C. 279 (1), *296*
Top, A. W. H. 887 (49), *901*
Topchieva, K. V. 703 (246), *717*
Topsom, R. D. 769 (38), 808 (38, 396), *812*, *820*
Torck, B. 415 (369), *447*
Torgov, I. V. 784 (181), *815*
Torii, S. 650 (774), *677*
Torikai, A. 972 (27), *989*
Torimoto, K. 939 (118), *964*
Torimoto, N. 709 (353), *719*
Toriyama, K. 939 (128b, 129), 942 (128b), *965*
Török, I. 635 (566), *672*; 697 (153a), 700 (153a, 174), *715*
Torre, G. 293 (34a,b), *297*; 613 (75, 77, 78), *661*
Torssel, K. 500 (212), *533*
Toru, T. 591 (265), *607*
Tosch, W. C. 258 (131), *277*
Toullec, J. 778 (123–125), *814*
Toullex, J. 772 (70), *812*
Touzin, A.-M. 802 (330, 331), *819*
Towle, J. L. 526 (379), *538*
Townsend, D. E. 694 (125), *714*
Townsend, J. 616, 617 (159), *663*
Townsend, J. M. 625 (419), *669*
Toyoshima, K. 810, 811 (408), *820*
Trahanovsky, W. S. 474, 475 (23), 496 (23, 181, 182, 185, 187, 189), 497 (23, 185, 191, 194, 196), 498 (23), 501 (221), *529*, *533*, *534*
Tramp, D. 639 (641), *674*
Tranquille, M. 436 (400), *447*
Traynelis, V. J. 728, 734–737, 746 (82), *754*
Traynellis, V. J. 549 (72), *602*
Traynham, J. G. 724 (39), *753*
Treger, Yu. A. 617 (200), *664*
Tremper, H. S. 519 (327), *537*

Trenke, K. M. 736 (153–155), *755*, *756*
Trenner, N. R. 462 (91), *468*
Trenwith, A. B. 458 (50), *467*
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Trieschmann, H. G. 745 (257, 265), *758*
Trifilieff, E. 508 (271), *535*
Trifiro, F. 616 (181, 183), 617 (214), *663*, *664*
Trifunac, A. D. 936 (9a,b), *962*
Triplatt, K. M. 76 (58), *148*
Trocha-Grimshaw, J. 571 (184), *604*
Trockmorton, P. E. 706, 707 (279), *718*
Troesch, J. 706 (282), *718*
Trofimov, B. A. 415 (366), 417 (402, 416), 426, 427 (401), *446–448*; 705 (266), *718*; 769 (34), 770 (44), 771 (52–54), 777 (115), 786 (211), 808 (44), *812*, *813*, *816*
Trofimov, V. I. 708 (332), *719*
Tronchet, J. 503 (239), *534*
Tronchet, J. M. J. 503 (239), *534*
Tronova, V. A. 746 (323), *759*
Trost, B. M. 592 (266), *607*; 615 (132), 625 (402, 407, 415, 416), 633 (530), *662*, *668*, *669*, *671*; 809 (407), *820*; 875 (49–51), 876 (50, 51), *879*
Trotman-Dickenson, A. F. 452 (15, 18), *466*
Trotsenko, Z. P. 741, 744, 745, 749 (247), *758*
Trozzolo, A. M. 652 (806), 653 (806, 813), *677*
Truax, D. R. 230 (166), *278*
Truby, F. K. 975 (66), *990*
Truce, W. E. 587 (247), 588 (248, 249), 590 (248), 596 (298), 597 (299), *606*, *607*; 620 (321), *667*
Trudell, J. R. 311 (162), *322*
Trueblood, K. N. 214 (110), *214*
Truesdale, L. K. 167 (37–39), *173*; 885 (39), *901*
Trumbore, C. N. 926 (38), *933*; 987 (137), *992*
Trumbull, E. R. 631 (480), *670*
Trumbull, P. A. 631 (480), *670*
Truong, T. B. 940 (151), *965*
Truter, M. R. 44 (166), 45 (172), *57*; 62 (14a, 19e,f), 64 (28a), 101 (14a), 111 (135), 123 (172a, 176), 124 (14a, 190a,b,d), 125 (135, 190a,b,d, 195), 126 (204, 205), 127 (207), 128 (210), 129 (135, 212), 130 (190a,b,d, 213a,b, 216a), 131 (219), 138 (248a–d), 141 (28a, 255), *145–147*, *151*, *153*, *154*, *156*; 189 (73), 192 (74), 196 (82, 83), 197 (83), 198 (89, 91), 200 (89, 91, 92), *213*
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Tsao, J. C. Y. 917, 918 (102), *921*
Tsatsas, G. 405 (173), *442*
Tshitsugu, S. 637 (613), *673*
Tsivunin, V. S. 782 (170), *815*
Ts'O, T. O. T. 51 (192), *57*
Tsolis, A. 405 (173), *442*
Tsomaya, N. N. 972 (22, 35), *989*
Tsou, K. C. 836 (102), *855*
Tsubata, K. 336 (28), 337 (28, 29), *350*
Tsubomura, H. 904 (11), 918 (11, 128), *919*, *922*
Tsuboyama, K. 19 (69), *54*
Tsuboyama, S. 19 (69), *54*
Tsuchihashi, G. 546 (42), *601*
Tsuchiya, F. 617 (238, 253), 618 (238), *665*
Tsuchiya, K. 180 (22), *212*
Tsuchiya, S. 181 (27), *212*; 909 (51b), *920*
Tsuji, J. 540 (4), *600*
Tsuji, T. 636 (605), *673*
Tsujimoto, K. 832 (79), *854*
Tsunashima, S. 918, 919 (121a), *922*
Tsurugi, J. 399 (2), *438*
Tsuruta, T. 640 (660), *674*
Tsutsumi, S. 624, 635 (390), *668*; 805 (364, 365), 806 (382), *819*, *820*
Tsuzuki, Y. 833 (84), *854*
Tsvetkov, Yu. D. 945 (188b), *966*
Tsykovskii, V. K. 618 (268), *666*
Tsyrlina, E. M. 617 (227), *665*
Tucker, J. R. 547, 571 (49), *601*
Tulagin, V. 741 (220), *757*
Tuleen, D. L. 845 (157), *856*
Tulupov, V. A. 618 (256), *665*
Tulyaganov, M. M. 746 (317), *759*
Tumlinson, J. H. 317 (268), *324*
Tummler, B. 210 (104), *214*
Tümmler, B. 41 (154), *56*; 68, 72 (37), 74, 75 (57), 77 (57, 64), 80, 87–90 (64), 92 (37, 57, 64), 112 (64), 113 (57, 64), *147*, *148*
Tumolo, A. L. 695 (131), *714*
Tundo, P. 17 (62), *53*; 62 (22), 115 (22, 146), *146*, *152*; 164, 166, 169, 172 (22), *173*
Tung, T.-L. 926 (41), *933*; 979 (96, 99, 101), 982 (116), *991*
Turcant, A. 647 (721), *675*
Turcanu, C. N. 390 (29), *439*
Turek, W. N. 381 (62), *439*
Turley, P. C. 231 (84), *276*; 862, 868 (17), *878*
Turnbull, K. 394 (378), *447*

Turner, D. W. 848 (197), *857*
Turner, J. A. 632 (490), *670*
Turner, J. O. 618 (265), *666*
Turner, L. P. 917 (85), *921*
Turner, S. R. 567 (164), *604*
Turnquist, C. R. 429 (403), *447*
Turro, N. J. 794 (255), *817*; 860, 868 (8), *878*
Turyanskaya, A. M. 839 (117), *855*
Tušek, L. 115 (146), *152*
Tushurashvili, R. G. 972 (8, 20), 975 (8), 977 (20), *988*, *989*
Tutane, I. 332 (16), *350*
Tuzimura, K. 291 (30, 31), *297*
Tveritneva, V. V. 977 (78), *990*
Tycholiz, D. R. 926 (33), 927 (33, 47), *933*
Tyerman, W. J. R. 931 (69), *934*
Tyminski, L. J. 838 (107), *855*
Tyrrell, H. 794 (259), *817*
Tyukova, O. A. 658 (881), *679*

Ubbelohde, A. R. 362 (61), *376*
Ubertini, F. M. 846 (161), *856*
Uchida, T. 220 (167, 168), *278*
Uda, H. 870, 874 (42), *879*
Udenfriend, S. 634 (547), *672*
Uebel, J. J. 247 (129), *277*
Ueda, M. 840 (121), *855*
Ueda, T. 709 (344), *719*; 822 (4a), *853*
Uemura, S. 711 (382, 383), *720*; 780 (144), *814*
Ueno, H. 870, 874 (42), *879*
Ueno, T. 931 (84), *934*
Ueno, Y. 555, 578 (109), *603*
Ugelstad, J. 167 (42), *173*
Ugo, R. 618 (254, 264), *665*, *666*
Uh, H. 486 (106), *531*
Uhde, G. 614 (130), *662*
Uhrich, R. 488 (129), *531*
Ulaste, V. K. 703 (240), *717*
Ulteé, W. J. 548 (69a), *602*
Umbreit, M. A. 627 (441), *669*
Umemoto, K. 121 (166), *152*
Undheim, K. 309 (122), *321*; 621, 633 (345), *667*
Uneyama, K. 650 (774), *677*
Ung, S. N. 585 (234), *606*
Ungar, B. 571 (175), *604*; 746 (312), *759*
Ungaro, R. 116 (149), *152*
Unkovskii, B. V. 307 (102, 103), *321*; 659 (926), *680*
Uramoto, M. 522 (348), *537*
Urry, D. W. 113 (136), *151*
Usachev, N. Ya. 973 (53), *990*
Ushakova, T. M. 798 (307), *818*
Ushio, S. 637 (613), *673*
Usieli, V. 835, 836 (100), *855*
Usuki, A. 806 (371), *820*
Utawanit, T. 415 (196), *442*
Utebaer, V. 613 (90), *661*
Utimoto, K. 650 (766), *676*
Utley, J. H. P. 540 (7), *600*
Utyanskaya, E. Z. 700 (188), *716*; 736 (158, 159), *756*
Uyeo, S. 591 (261), *606*
Uzarewicz, A. 519 (330), *537*; 638 (629), *673*
Uzarewicz, J. 519 (330), *537*
Uzlyaner-Neglo, A. L. 772 (68), *812*

Vacek, K. 946 (212), *967*
Vagabov, M. V. 695 (136), *715*
Vahrenholt, F. 787, 792 (217), *816*
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Valade, J. 620 (330), *667*
Valentine, J. S. 169 (60), 170 (60, 63, 65), 171 (65), *174*
Valet, A. 738 (194), *756*
Valette, A. 751 (353, 354), *760*
Valicenti, J. A. 728, 734–737, 746 (82), *754*
Vallet, A. 393 (405, 406), *447*
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Van Acker, L. 567, 569 (166), *604*; 839, 840 (120), 844, 845 (153), *855*, *856*
Van Allan, J. A. 885 (34), *901*
Van Asten, J. J. A. 548 (69a), *602*
Van Bekkum, H. 316 (251), *324*
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Van de Castle, J. F. 491 (150), *532*
Van der Linde, L. M. 849 (214), *857*
Van der Plas, H. C. 610, 641 (19), *660*; 684 (9), *712*
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Van Doorn, J. A. 616 (178, 179, 187), 617 (178, 179), *663*, *664*
Van Dort, H. M. 849 (214), *857*
Van Duuren, B. L. 658 (904), *679*
Van Ende, D. 626 (423, 424, 426, 427), *669*
Van Gaever, F. 312 (189), 313 (210c), 317 (189), 318 (210c, 274–276, 278), *323*, *325*
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Van Haverbeke, Y. 310 (143), *322*

Van Heyningen, E. M. 580 (212, 214), 581 (212), *605*
Vanhooren, M. 313, 318 (210c), *323*
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Van Krevelen, D. W. 368 (133), *377*
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Vannikov, A. V. 938 (42a, 76), *963*
Van Schaick, E. J. M. 178 (9), *212*
Vanstone, A. E. 486 (116), *531*
Van Tamelen, E. E. 520 (332), *537*
Van Woerden, H. F. 835 (93), *855*
Varde, E. 931, 932 (76), *934*
Varenne, P. 325 (292), *325*
Vasileff, R. T. 580 (214), *605*
Vasil'ev, G. N. 955 (297b), *969*
Vasil'ev, G. S. 798 (302), *818*
Vasil'ev, V. V. 658 (901), *679*
Vasil'eva, E. V. 796 (286), *818*
Vasil'eva, V. F. 798 (300), *818*
Vasil'eva, V. N. 367 (99), *377*; 388 (407a), *448*
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Vass, A. 702 (234b), *717*
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Vermeer, P. 652 (795), *677* 689 (67), *713*; 774 (92), *813*
Vermeer, R. A. 946 (196), *966*
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Volkova, L. N. 736 (166, 177), *756*
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Voropaeva, T. K. 795 (270, 271), *817*
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Vukov, V. 634 (555), 655 (555, 839), *672*, *678*; 689 (64), *713*
Vul'fson, A. N. 659 (926), *680*
Vulf'son, A. N. 307 (102, 103), *321*
Vulf'son, N. S. 307 (102, 103), *321*
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Vylegzhanin, O. N. 417 (402, 416), *447*, *448*; 771 (53, 54), *812*
Vysotskii, V. A. 711 (378), *720*
Vystrčil, A. 621 (351), *667*
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Waard, E. R. de 545, 546 (41), *601*
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Wada, S. 647 (729), *675*
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Wageman, R. 945 (181), *966*
Wagenknecht, J. H. 334 (22), *350*
Wagman, D. D. 370 (106), *377*
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Wagner, E. S. 427 (417), *448*
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Wagner, H. 407 (320), *445*
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Wagner, P. J. 709 (348), *719*
Wagner, W. 325 (284), *325*; 542 (13), *600*
Wähäsilta, J. 839–843 (115), *855*
Wahren, M. 306 (68), *320*
Waight, E. S. 305, 306 (65), *320*
Waisser, K. 621 (351), *667*
Wakano, H. 137, 138 (244), *156*; 211 (109), *214*
Wakefield, B. J. 650 (772), *676*; 705 (268), *718*
Wakselmann, C. 652 (798), *677*
Walba, D. M. 27 (107), 30 (110), 46 (107), *55*; 85, 96 (71), *148*; 201 (95), *214*
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Walker, B. H. 484 (92), *531*
Walker, P. E. 37 (146), *56*; 133 (227), *155*
Walker, R. W. 452 (27), *467*

Walker, S. 847 (187), *856*
Walker, T. 492 (154), *532*
Wallace, D. C. 975 (66), *990*
Wallace, T. J. 491 (142), *532*
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Wallis, S. R. 412 (78), *440*; 511 (292), *536*; 829 (61), *854*
Walsh, E. J. 167 (41), *173*
Walsh, R. 362 (53), *375*
Walter, C. R. 727 (68), *754*
Walter, J. 279 (2e), *296*
Walter, W. F. 593 (273b), *607*
Walters, W. D. 450 (6a), *466*; 707 (317), *719*
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Walton, R. A. 849 (211, 213), *857*
Walton, R. W. 137 (242), *155*
Wan, C. 635 (563), *672*
Wan, C. N. 650 (771), *676*; 706 (280), 708 (325), *718*, *719*
Wang, C. T. 918 (125, 126, 129), *922*
Wang, C. Y. 225 (170), *278*
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Warashina, T. 938 (64), *963*
Ward, H. R. 931, 932 (85), *934*
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Ward, R. S. 311 (158), *322*
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Ware, W. R. 914 (70), *921*; 946 (201), *966*
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Warman, J. M. 976 (73), *990*
Warner, R. J. 161, 170 (14), *173*
Warnhoff, E. W. 486 (115), *531*; 632 (488, 489), *670*
Warren, C. D. 522 (345), *537*
Warren, S. 571 (179b), *604*; 773 (79), 808 (403), *813*, *820*
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Watanabe, S. 526 (381), *538*; 613, 632 (82), 642 (681), *661*, *674*; 706 (287), *718*
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Watanabe, W. 473 (21), *529*
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Watanabe, Y. 567 (325), *608*; 615 (137), 630 (459), 659 (937), *662*, *670*, *680*
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Watkins, S. H. 729 (88), *754*
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Supplement E The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
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