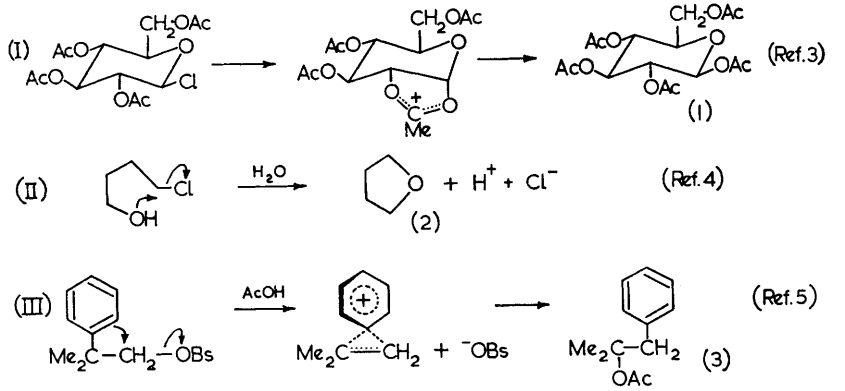
NEIGHBOURING GROUP PARTICIPATION

By BRIAN CAPON

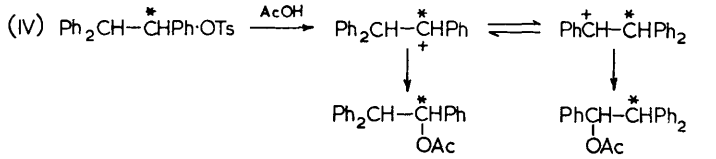
(CHEMISTRY DEPARTMENT, BIRKBECK COLLEGE, MALET STREET, LONDON, W.C.1)

THE most widely investigated effects of a substituent in an organic molecule, on the reactions of that molecule, are electronic effects transmitted through the carbon skeleton, and steric effects. In addition, however, some substituents may influence a reaction by stabilising a transition state or intermediate by becoming bonded or partially bonded to the reaction centre. This behaviour is called neighbouring group participation,[1] or sometimes, if an increased reaction rate results, intramolecular catalysis,[2] and, as with intermolecular catalysis, nucleophilic, electrophilic, and basic catalysis or participation are possible. If the transition state of a rate-determining step is stabilised in this way, an increased reaction rate results and the neighbouring group is then said to provide anchimeric assistance. Many examples of nucleophilic participation in displacement reactions at saturated carbon centres [cf. (I)—(III)] have been described, mainly by Winstein and his co-workers. One of the steps of all these reactions is an

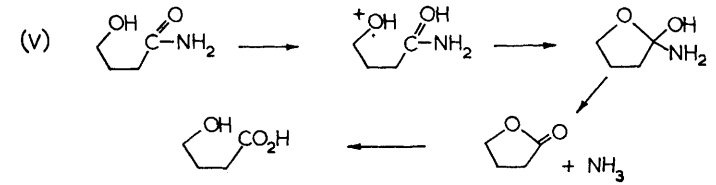


intramolecular nucleophilic displacement. Sometimes the resultant intermediate reacts to yield a product which differs from that which would be expected in the absence of participation. This may be a product with retained configuration [*e.g.*, (1)], a ring-closed product [*e.g.*, (2)], or a product in which the participating group has migrated [*e.g.*, (3)]. In some reactions [*e.g.*, (IV)[6]] participation occurs after a rate-determining ionisation; the structure of the product may then be affected but there is no anchimeric assistance. When describing nucleophilic participation it is frequently convenient to use the symbol "G-*n*", where G is the participating

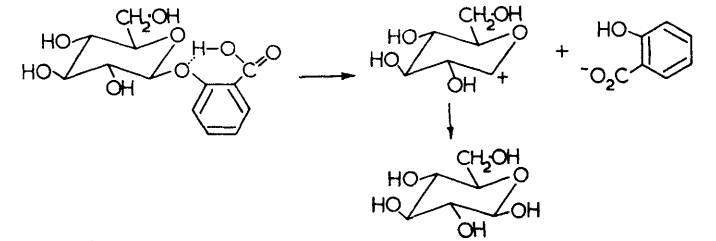
[1] Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780.
[2] Bender, *J. Amer. Chem. Soc.*, 1957, **79**, 1258.
[3] Lemieux and Brice, *Canad. J. Chem.*, 1955, **33**, 109.
[4] Heine, Miller, Barton, and Greiner, *J. Amer. Chem. Soc.*, 1953, **75**, 4778.
[5] Heck and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 3432.
[6] Collins and Bonner, *J. Amer. Chem. Soc.*, 1955, **77**, 92.



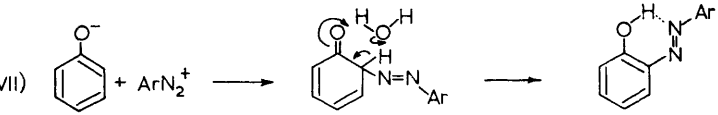
group and *n* the size of the ring formed in the transition state.[7] Reactions (I)—(III) are then examples of AcO-5, HO-5, and Ph-3 participation, respectively. Examples of displacement reactions at unsaturated carbon involving nucleophilic participation are also known [*e.g.*, (V)[8]].



The number of reactions in which a neighbouring group is known to act as an electrophile or as a general-base is much smaller. In nearly all the known examples of electrophilic participation the neighbouring group acts as a general-acid catalyst [*e.g.*, (VI)[9]]. An example of participa-



tion by a neighbouring group acting as a general-base is found in the coupling reaction of diazonium ions at the *ortho*-position of phenoxide ions, which is thought to proceed as shown in Scheme (VII).[10]



The Measurement of Anchimeric Assistance

To measure anchimeric assistance it is of course necessary to be able to estimate what the reaction rate would be in the absence of neighbouring

[7] (*a*) Heck and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 3105; (*b*) Winstein, Allred, Heck, and Glick, *Tetrahedron*, 1958, **3**, 1.

[8] Zürn, *Annalen*, 1960, **631**, 56; Martin, Hendrick, and Parcell, *J. Org. Chem.*, 1964, **29**, 158.

[9] Capon, *Tetrahedron Letters*, 1963, 911.

[10] Stamm and Zollinger, *Helv. Chim. Acta*, 1957, **40**, 1955; see also Zollinger, "Azo and Diazo Chemistry," Interscience, New York, 1961, p. 254.

group participation. In cyclic compounds the molecular geometry frequently restricts the possibility of nucleophilic participation to *trans*-isomers, and hence the unassisted rate approximates to that of the corresponding *cis*-isomer. This approximation neglects any conformational effects on the reactivities of the *cis*- and *trans*-isomers. These are probably not very large, but correction for them is not easy.

In acylic compounds in which neighbouring group and reaction centre are at adjacent carbon atoms the separation of anchimeric assistance from polar and steric effects is more difficult. The most satisfactory procedure for the separation of polar effects is that of Streitwieser,[11] using Taft's equation. Taft's equation, $\log k/k_0 = \rho^*\sigma^*$, is a linear free-energy relationship correlating reaction rates and equilibria of aliphatic compounds. σ^* is the polar substituent constant derived from the relative rates of the acid and alkaline hydrolysis of aliphatic esters, and ρ^* is a constant giving the susceptibility of a given reaction series to polar substituents.[12] Reactions in which a substituent provides anchimeric assistance, *i.e.*, stabilises the transition state through bonding to the reaction centre, will therefore show positive deviations from this relationship. However, reactions in which there is a release of non-bonding compression on going to the transition state will also show enhanced rates, *i.e.*, they will be sterically accelerated. Separation of these two effects is largely a matter of chemical intuition, and different chemists may give different assessments of their importance. As an example, consider the solvolyses of 2,2,2-triphenylethyl chloride[13] and toluene-*p*-sulphonate[14] which are accelerated to a far greater extent than can be accounted for by the inductive effects of the phenyl groups, and are accompanied by phenyl migration. The reactions, therefore, probably pass through transition states such as (4). The problem is to

$$Ph_3C{-}CH_2X \longrightarrow \underset{(4)}{Ph_2\overset{Ph}{\overset{+}{C}}{=}CH\cdots X} \longrightarrow Ph_2C{=}CHPh$$

decide how much of the enhanced rate results from stabilisation of this transition state by bonding of the phenyl group to C-1, and how much results from release of non-bonding compression on going to this or some other intermediate state. The answers that have been given range from 100% anchimeric assistance[13] to 100% steric acceleration.[15]

When the neighbouring group and the reaction centre are separated by a several-membered carbon chain, as in, *e.g.*, $HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Cl$,

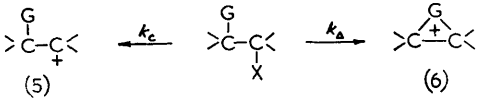
[11] Streitwieser, *Chem. Rev.*, 1956, **56**, 694.
[12] Taft in "Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, p. 586.
[13] Unpublished results reported by Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1953, p. 514.
[14] Winstein, Morse, Grunwald, Schreiber, and Corse, *J. Amer. Chem. Soc.*, 1952, **74**, 1113.
[15] Brown in "The Transition State," *Chem. Soc. Special Publ.*, No. 16, 1962, p. 152.

the polar and steric effects of a neighbouring group are generally small, and the unassisted rate is often taken to be that of the compound in which the neighbouring group is replaced by hydrogen, although a better estimate can be made more laboriously by making use of Taft's equation. With reactions of substituted benzene derivatives in which there is participation by an *ortho*-substituent the rate with the corresponding *para*-compound is, of course, a good approximation to the unassisted rate. Some workers prefer to improve this approximation a little by multiplying by the ratio of the rates with the *ortho*- and *para*-compounds found with similar non-participating substituents.[16]

When a substituent such as hydroxyl is providing assistance by acting as an intramolecular acid catalyst the rate of the corresponding methylated derivative is frequently used to give the unassisted rate. This, of course, neglects the different steric and electronic effects of H and CH_3.

It is seen from the foregoing account that it is not possible to estimate very accurately what reaction rates would be in the absence of neighbouring group participation. For this reason an increase in rate, at least five-fold and preferably more than fifty-fold, is necessary for the identification of neighbouring group participation through the recognition of anchimeric assistance.

Sometimes, when comparing the rates of reactions involving neighbouring group participation, it is frequently convenient to use three different symbols:[7b] k_Δ, the rate constant for the anchimerically assisted reaction; k_s, the rate constant for the reaction, not anchimerically assisted, but assisted by solvent (the relative importance of k_Δ and k_s of course depends upon the solvent. For instance, with a reaction involving nucleophilic participation, there will be more successful competition from the solvent when it is, say, water than when it is the much less nucleophilic formic acid);k_c is sometimes used with reactions involving nucleophilic participation; it is the rate constant for the idealised ionisation to the open ion (5), formed without neighbouring group or solvent participation. This will generally be less than k_s, and Winstein *et al.*[17] have given a method for its approximate calculation. The quantity, $L = RT\ln(k_\Delta/k_c)$, termed the driving force, is then the free-energy difference between the open and closed carbonium ions, (5) and (6).



(5) (6)

Participation by Methoxyl Groups

Displacement Reactions at Saturated Carbon.—Many of the results described in this section are due to Winstein and his co-workers who have

[16] Cf. Bender and Silver, *J. Amer. Chem. Soc.*, 1962, **84**, 4589.
[17] Winstein, Grunwald, and Ingraham, *J. Amer. Chem. Soc.*, 1948, **70**, 821.

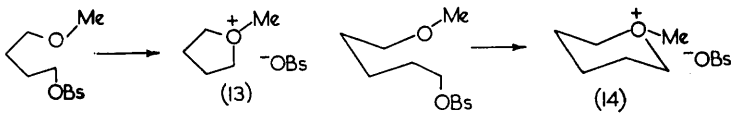
summarised[7b] their outstanding contribution. Unfortunately most of the experimental details have not yet been published.

The absence of a steady trend in the rates of solvolysis of a series of ω-methoxyalkyl *p*-bromobenzenesulphonates (see Table 1) indicates the

TABLE 1. *The relative rates of solvolyses of ω-methoxyalkyl* p-*bromobenzenesulphonates.*[7b]

Compound	Relative rate			Calc. k/k_S at 75°		
	EtOH (75°)	AcOH (25°)	HCO_2 (75°)	EtOH	AcOH	HCO_2H
Me·$[CH_2]_3$·OBs (7)	1·00	1·00	1·00	0·93	0·81	1·07
MeO·$[CH_2]_2$·OBs (8)	0·25	0·28	0·10	1·33	1·51	0·85
MeO·$[CH_2]_3$·OBs (9)	0·67	0·63	0·33	1·14	1·20	0·84
MeO·$[CH_2]_4$·OBs (10)	20·4	657·0	461·0	22·2	425·0	610·0
MeO·$[CH_2]_5$·OBs (11)	2·8	123·0	32·6	2·42	47·2	30·6
MeO·$[CH_2]_6$·OBs (12)	1·19	1·16	1·13	0·87	0·71	0·85

importance of an effect by the methoxyl groups other than the inductive effect. In particular the high rates for the 4-methoxybutyl and 5-methoxypentyl compounds [(10) and (11)] suggest nucleophilic participation, and Winstein and his co-workers have formulated these reactions as proceeding through the cyclic oxonium ions (13) (MeO-5) and (14) (MeO-6 participation).[7b] Hence, the primary methoxyl group provides assistance when a five- or six-membered cyclic oxonium ion is possible but not when this intermediate would have seven, three, or four members.



The increase in rate due to MeO-5 participation in the acetolysis of secondary *p*-bromobenzenesulphonates [cf. compounds (17) and (21) in Table 2] is about twenty-fold less than for the analogous primary com-

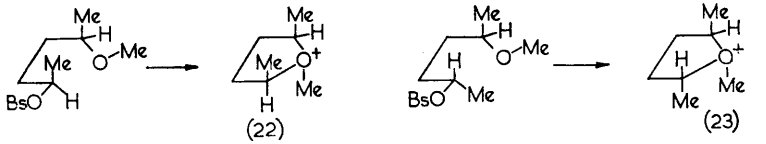
TABLE 2. *The relative rates of acetolysis of some methyl-substituted butyl* p-*bromobenzenesulphonates at* 25°.[7b]

Compound		Relative rate		
Me·$[CH_2]_4$·OBs (15)		1	—	—
MeO·$[CH_2]_4$·OBs (16)		657	1·00	—
MeO·$[CH_2]_3$·CHMe·OBs (17)		4140	6·29	30
MeO·CHMe·$[CH_2]_3$·OBs (18)		4110	6·26	—
MeO·CHMe·$[CH_2]_2$·CHMe·OBs	*erythro* (19)	9450	14·4	67
	threo (20)	$2·28 \times 10^4$	34·7	163
Me·CH_2·CHMe·OBs (21)		140	—	1·0

pounds [cf. compounds (15) and (16)]. The α-methyl group in the secondary compound helps to disperse the positive charge in the transition state and hence the need for assistance from the neighbouring methoxyl group

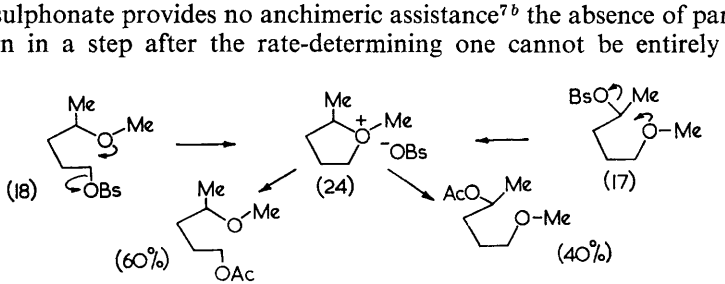
to do this is less. The compound (18), with a secondary methoxyl group, reacts faster than the corresponding compound (16), with a primary methoxyl group. This accelerating effect of alkyl substituents on ring-closure reactions is frequently encountered and is discussed on p. 109.

The slightly greater rate of acetolysis of *threo*-5-methoxy-1-methylpentyl *p*-bromobenzenesulphonate (20) than its *erythro*-isomer (19) probably results from steric retardation in the formation of the cyclic oxonium ion from the *erythro*-isomer. In the ion (22) from the *threo*-isomer the three methyl substituents may all be staggered, but in that, (23), from the *erythro*-isomer two must be eclipsed.



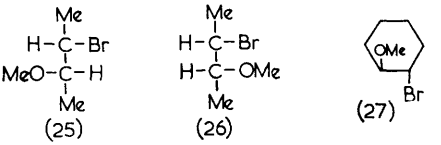
4-Methoxypentyl (18) and 4-methoxy-1-methylbutyl *p*-bromobenzenesulphonate (17) should yield the same cyclic oxonium ion (24) and hence the products of their acetolyses should be identical. Winstein and his co-workers report[7b] (without details) that this is so. The cyclic oxonium ion (24) undergoes ring cleavage but there is the possibility of methyl–oxygen cleavage as well. According to Winstein *et al.* Me–O cleavage is unimportant in MeO-5 participation but significant in MeO-6 participation; the acetolysis of 5-methoxypentyl *p*-bromobenzenesulphonate yields tetrahydropyran, methyl acetate, methyl *p*-bromobenzenesulphonate, and 5-methoxypentyl acetate.[7b]

Although the primary methoxyl group in 2-methoxyethyl *p*-bromobenzenesulphonate provides no anchimeric assistance[7b] the absence of participation in a step after the rate-determining one cannot be entirely dis-

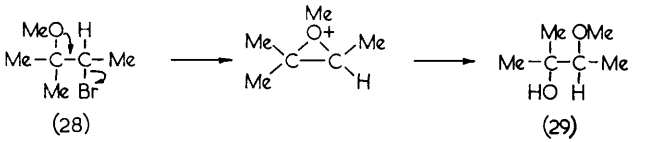


counted. MeO-3 participation by secondary and tertiary methoxyl groups, however, quite definitely occurs. Examples of participation by secondary methoxyl groups are found in the reactions of compounds (25), (26), and (27) with silver acetate in acetic acid, which yield methoxy-acetates of retained configuration.[18] The tertiary methoxyl group in 2-bromo-3-methoxy-3-methylbutane (28) participates in the hydrolysis, since it

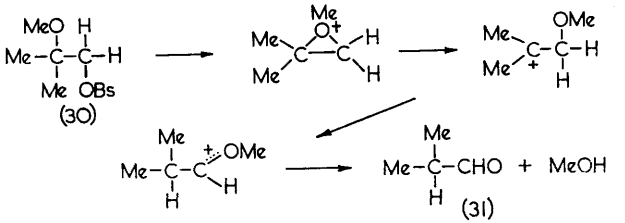
[18] Winstein and Henderson, *J. Amer. Chem. Soc.*, 1943, **65**, 2196.



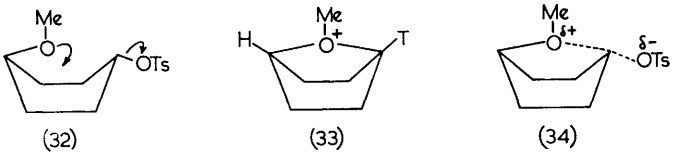
migrates and the product is 3-methoxy-2-methylbutan-2-ol (29).[19] MeO-3



participation by tertiary methoxyl groups can provide considerable anchimeric assistance; k/k_s for the acetolysis of 2-methoxy-2-methylpropyl *p*-bromobenzenesulphonate (30) is about 1500, and when the solvent is aqueous dioxan the major product is isobutyraldehyde (31).[20]



A very thorough and illuminating investigation of MeO-5 participation in the acetolysis of *trans*-4-methoxycyclohexyl toluene-*p*-sulphonate (32)



has been made by Noyce and his co-workers.[21] By comparing the reaction rate with that of the *cis*-isomer, and making a small allowance for the amount of *cis*-isomer in a conformation with the toluenesulphonyl-group in a more reactive axial position, they estimated that k/k_s for the *trans*-compound is about 5·6. Hence a large amount of the product must result from a reaction involving participation by the methoxyl group. The products are 4-methoxycyclohexene (67·7%), *cis*-4-methoxycyclohexyl acetate (8·7%), and *trans*-4-methoxycyclohexyl acetate (23·6%).

[19] Winstein and Ingraham, *J. Amer. Chem. Soc.*, 1952, **74**, 1160.
[20] Winstein, Lindegren, and Ingraham, *J. Amer. Chem. Soc.*, 1953, **75**, 155.
[21] (*a*) Noyce, Thomas, and Bastian, *J. Amer. Chem. Soc.*, 1960, **82**, 885; (*b*) Noyce and Bastian, *ibid.*, p. 1246.

It seems likely, therefore, that much of the 4-methoxycyclohexene results from a reaction involving participation. The products of acetolysis of *trans*-4-methoxy[1-^{3}H]cyclohexyl toluene-*p*-sulphonate are given in Table 3. Any products derived from the bicyclic oxonium ion (33) should have

TABLE 3. *Products of acetolysis of* trans-4-*methoxy*[1-^{3}H]*cyclohexyl toluene*-p-*sulphonate*.[21]

4-Methoxy[1-^{3}H]cyclohexene	66·4%
cis-4-Methoxy[1-^{3}H]cyclohexyl acetate	9·6%
trans-4-Methoxy[1-^{3}H]cyclohexyl acetate	13·8%
trans-4-Methoxy[4-^{3}H]cyclohexyl acetate	10·2%

the tritium scrambled equally between the 1- and the 4-position, or possibly have a slight excess in the 4-position owing to a secondary isotope effect. The *trans*-4-methoxycyclohexyl acetate has 35% more tritium in the 1-position than in the 4-position and hence some of it cannot have been formed by way of the oxonium ion (33). Also, the 4-methoxycyclohexene contains all its tritium in the 1-position but, nevertheless, as argued above from the rate data, much of it probably came from an assisted reaction. These observations led Noyce and Bastian[21b] to suggest that participation by the methoxyl group first involves partial bonding to the reaction centre to give an internally solvated ion-pair intermediate (34), the anchimeric assistance being associated with the formation of this species. This ion-pair may then react with acetic acid to give *trans*-acetate,

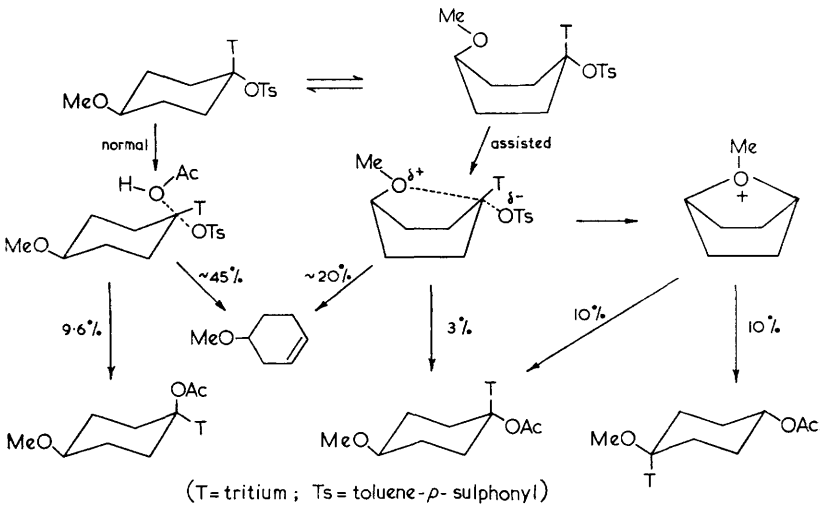


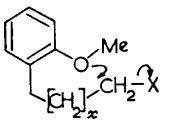
CHART 1.

collapse to give a bicyclic oxonium ion, or undergo elimination, the complete reaction scheme being as shown in Chart 1. The driving force for participation in the acetolysis of 4-methoxycyclohexyl toluene-*p*-sulphon-

ate is much less than in the acetolysis of a similar acyclic compound, 5-methoxy-2-methylpentyl *p*-bromobenzenesulphonate, for which $k/k_s = 163$ (See Table 2). This is because much of the energy gained from participation in the 4-methoxycyclohexyl compound is lost in non-bonded interactions on going over to the unfavourable boat conformation.

The work of Noyce *et al.* must throw some doubt on the details of Winstein's interpretation of methoxyl-group participation, presented in the first part of this Section. Obviously, more experimental work is needed to determine the exact proportions of methoxyl-assisted reactions which involve cyclic oxonium ions.

Participation by methoxyl groups attached to benzene rings, as shown in (35), sometimes occurs. The nucleophilicity of such groups is reduced by the mesomeric interaction with the benzene ring but this is at least partly counterbalanced by the increased rigidity of the system. In compounds



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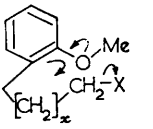


(36)

where this kind of participation is possible there is also the possibility of aryl participation [see (36)] and competition between MeO-*n* and Ar-(*n*−2) participation may occur. The rates of solvolyses (Table 4) of 2-(*o*-methoxyphenyl)-2-methylpropyl toluene-*p*-sulphonate (38) are smaller than those of the *p*-methoxy-isomer (37) but the occurrence of *o*-MeO-5 participation is clearly shown by the reaction products (Table 5) which in

TABLE 4. *Relative rates of solvolysis of methoxyphenylalkyl toluene*-p-*sulphonates.*[22]

	HCO_2H (25°)	AcOH (75°)
2-Methyl-2-phenylpropyl	1·0	1·0
2-(*p*-Methoxyphenyl)-2-methylpropyl (37)	72·0	88·0
2-(*o*-Methoxyphenyl)-2-methylpropyl (38)	6·47	5·5
2-(*o*-Methoxyphenyl)ethyl (39)	0·66	0·99
2-(*p*-Methoxyphenyl)ethyl (40)	0·67	1·3

TABLE 5. *Products of solvolysis of* 2-(o-*methoxyphenyl*)-2-*methylpropyl toluene*-p-*sulphonate.*[22]

Solvent	Temp.	Added base	Total	Alcohol			Furan (45)
				Olefin (41) + (42)	Tert. (43)	Prim. (44)	
AcOH	25°	NaOAc 0·0301M	96	8	15	4	73
HCO_2H	25°	NaOCHO 0·0515M	92	32	42	—	26

[22] Heck, Corse, Grunwald, and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 3278.

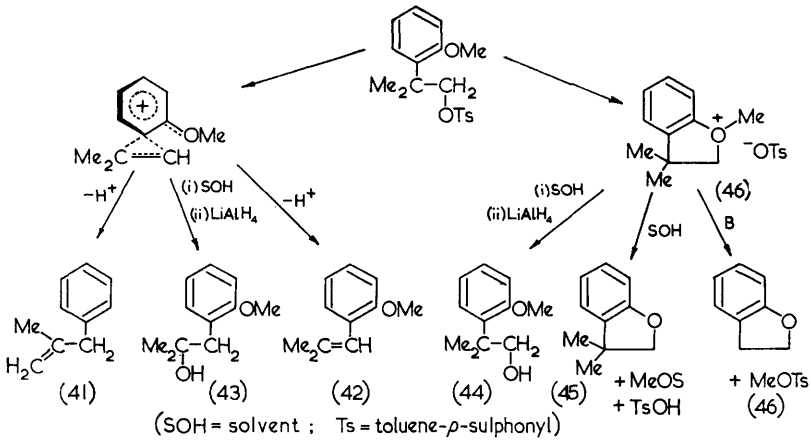


CHART 2.

acetolysis, formolysis, and ethanolysis all contain some of the benzofuran (45).[22] The solvolyses, therefore, proceed as shown in Chart 2. The ethanolysis and formolysis reactions obey the first-order rate law and give the theoretical infinity titres but the acetolysis reaction gives infinity titres (presumably after 10 half-lives) corresponding to 63% reaction. This is due to the formation of methyl toluene-*p*-sulphonate which undergoes acetolysis 500 times more slowly. In the presence of sodium acetate or lithium perchlorate fairly good infinity titres are obtained. This is not due to reaction between methyl toluene-*p*-sulphonate and sodium acetate because this is too slow. The sodium acetate or lithium perchlorate must prevent the methyl toluene-*p*-sulphonate from being formed. The following very reasonable explanation has been given by Winstein *et al.*[7b] Ionisation is thought to occur first to an ion-pair (46) which may collapse through nucleophilic attack of the toluenesulphonate ion on the methyl group to yield methyl toluene-*p*-sulphonate (Chart 2, path B); this is referred to as ion-pair return. In the presence of lithium perchlorate or sodium acetate rapid exchange of partners between ion-pairs occurs and hence the oxonium ion is paired with perchlorate or acetate and cannot yield methyl toluene-*p*-sulphonate by ion-pair return.

The rates of solvolysis in ethanol, formic acid, and acetic acid of 2-(*o*-methoxyphenyl)ethyl toluene-*p*-sulphonate (39) are approximately the same as those of its *para*-isomer (40).[23] Although no product analyses were reported, it therefore seems likely that *o*-MeO-5 participation is not important in the reactions of this compound. However, *o*-MeO-6 participation occurs extensively in the acetolysis and formolysis of the analogous 3-(*o*-methoxyphenyl)-propyl *p*-bromobenzenesulphonate (47) and 3-(*o*-

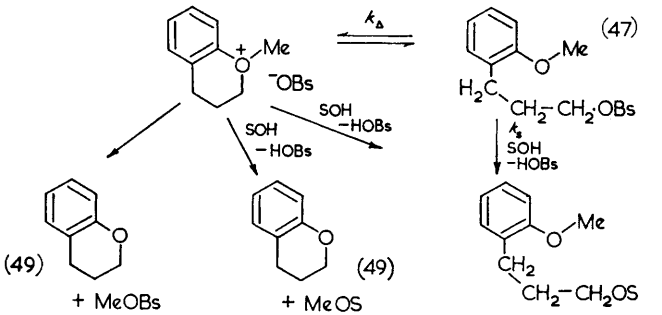
[23] Winstein, Lindegren, Marshall, and Ingraham, *J. Amer. Chem. Soc.*, 1953, **75**, 147.

methoxyphenyl)-3-methylbutyl toluene-*p*-sulphonate (48) (see Table 6).[7b] Any competing aryl participation would be Ar_1-4 participation and as

TABLE 6. *Rates and products for the formolyses of* 3-(o-*methoxyphenyl*)-*propyl* p-*bromobenzenesulphonate* (47) *and* 3-(o-*methoxyphenyl*)-3-*methylbutyl toluene*-p-*sulphonate* (48) *at* 25°.[7b]

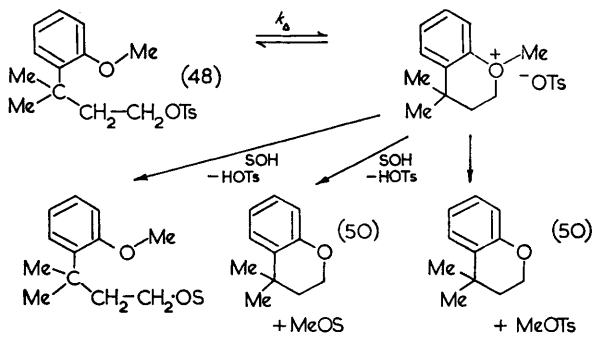
Compound	10^5k	10^5k for *para*-isomer	Products	
			Alcohol	Pyran
(47)	0·2	0·01	46%	49%
(48)	22·0	~0	<5%	>95%

shown by the reaction rates for the *para*-isomers, is unimportant. The reaction products (Table 6) contain large amounts of the pyran derivatives (49) and (50) and of the methyl arenesulphonates, and the reactions may therefore be formulated as shown in Charts 3 and 4. The infinity titres for the acetolysis of 3-(*o*-methoxyphenyl)-3-methylbutyl toluene-*p*-sulphonate correspond to 34% reaction at 75°, and this value is decreased by the addi-



(SOH = solvent ; Bs = *p*-bromobenzene sulphonyl)

CHART 3.



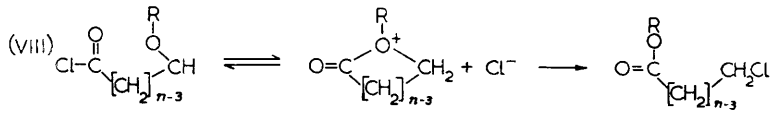
(SOH = solvent ; Ts = toluene-*p*-sulphonyl)

CHART 4.

tion of lithium toluene-*p*-sulphonate, a result which indicates that formation of methyl toluene-*p*-sulphonate involves more than just ion-pair return.

Reactions at Carbonyl Carbon.—When heated to 100—150°, γ- and δ- (but not ε) alkoxyacyl chlorides rearrange to give the alkyl γ- and δ-chloro-esters, respectively.[24,25] *cis*- 3- and -4-Methoxycyclohexanecarbonyl chloride undergo this rearrangement but their *trans*-isomers do not,[26] a result which excludes an intermolecular reaction between the acyl chloride group of one molecule and the ether group of another. The *cis*-3- and -4-methoxycyclohexanecarbonyl chlorides[26] and (+)-4-methoxyvaleryl chloride[27] yield chloro-esters with inverted configuration. All these results support a mechanism involving intramolecular nucleophilic attack by the alkoxyl group as in Scheme (VIII).

4-Ethoxybutyryl chloride rearranges about forty times faster than 5-ethoxyvalerlyl chloride[25] and so, if return to the acyl chloride occurs to the



same extent for both compounds, the assistance for EtO-5 participation is greater than for EtO-6. No example of alkoxyl cleavage of the oxonium intermediate in this type of reaction has been reported.

cis-3- and -4-Methoxycyclohexanecarboxylic acid undergo a similar rearrangement when heated in acetic anhydride containing sulphuric acid.[28]

Participation by Hydroxyl Groups

Displacement Reactions at Saturated Carbon.—The rates of hydrolysis in water of a series of ω-hydroxyalkyl halides (Table 7)[29,30] indicate that

TABLE 7. *The rates of hydrolysis of some halohydrins*, $Cl\cdot[CH_2]_n\cdot OH$, *in water at* 70·5°.[29,30]

n	2	3	4	5
10^5k (min.$^{-1}$)	1·82	7·79	1710	70

The value of 10^5k for n-propyl chloride, extrapolated from the value at 100° (Laughton and Robertson, *Canad. J. Chem.*, 1959, **37**, 1491), is~15.

neighbouring group participation is probably occurring with 4-hydroxy-

[24] Blicke, Wright, and Zienty, *J. Amer. Chem. Soc.*, 1941, **63**, 2488, for a similar but not completely analogous reaction of alkylmercaptoacyl chlorides, see Truce and Abraham, *J. Org. Chem.*, 1963, **28**, 964.
[25] Prelog and Heimback-Juhász, *Ber.*, 1941, **74**, 1702.
[26] Noyce and Weingarten, *J. Amer. Chem. Soc.*, 1957, **79**, 3093.
[27] Wiberg, *J. Amer. Chem. Soc.*, 1952, **74**, 3957.
[28] Noyce and Weingarten, *J. Amer. Chem. Soc.*, 1957, **79**, 3098.
[29] Heine, Miller, Barton, and Greiner, *J. Amer. Chem. Soc.*, 1953, **75**, 4778.
[30] Capon and Farazmand, unpublished observations.

butyl and 5-hydroxypentyl chloride, an interpretation which is supported by the isolation of tetrahydrofuran and tetrahydropyran from the reactions of these compounds. The increase in rate associated with this participation is not very great because the solvent, water, is itself fairly highly basic and nucleophilic and hence the rate in the absence of neighbouring group participation is already quite high.

In alkaline solution hydroxyl groups (pK_a 14—18) are appreciably ionised and participation by RO^- can occur (see Table 8).[30,31] Under these

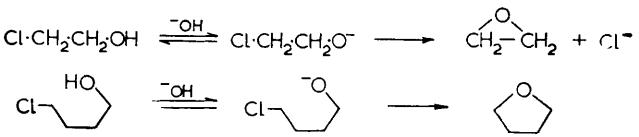
TABLE 8. *The rates of ring-closure of some halohydrins in aqueous sodium hydroxide at* 30°.[30,31]

	k_2 (l. mole^{-1}min.$^{-1}$)
$Cl{\cdot}[CH_2]_2{\cdot}OH$	0·13
$Cl{\cdot}[CH_2]_4{\cdot}OH$	0·172
$Cl{\cdot}[CH_2]_5{\cdot}OH$	0·0007*

* Extrapolated from results at higher temperatures.

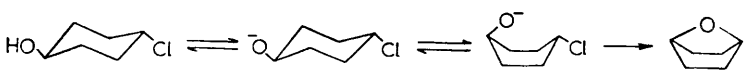
conditions the most reactive of the ω-hydroxyalkyl chlorides is 2-hydroxyethyl chloride. However, this is because there is a higher standing concentration of the conjugate base owing to the acid strengthening effect of chlorine on a carbon atom adjacent to an alcohol group.

It is claimed that the solvent deuterium isotope effect for the reaction of 2-hydroxyethyl chloride is consistent with a two-stage mechanism, as



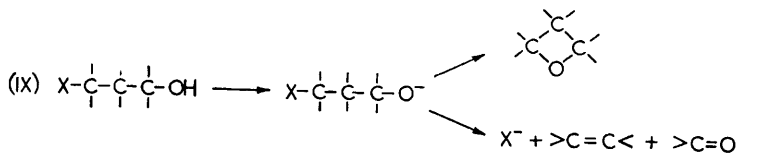
shown, but not with a mechanism in which removal of the proton and ring- closure occur synchronously.[32]

1,4-Epoxycyclohexane is the main product of the alkaline hydrolysis of *trans*-4-chlorocyclohexanol.[33] The rate of reaction is however 1100 times less than the rate of formation of tetrahydrofuran from 4-chlorobutanol under the same conditions.

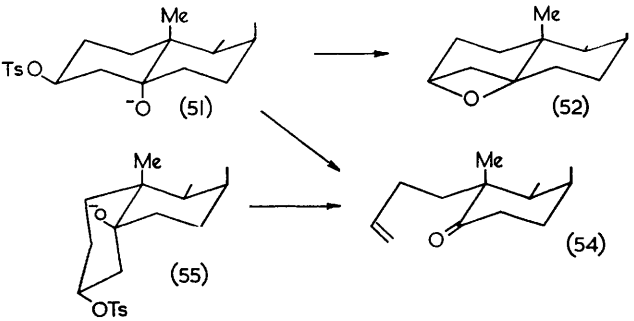


O^--4 participation occurs with compounds of suitable configuration but is frequently accompanied by fragmentation. [see Scheme (IX)] 5α-Hydroxycholestan-3β-yl toluene-*p*-sulphonate (51) reacts with potassium t-butoxide in t-butyl alcohol to yield 3α,5α-epoxycholestene (52) (55%)

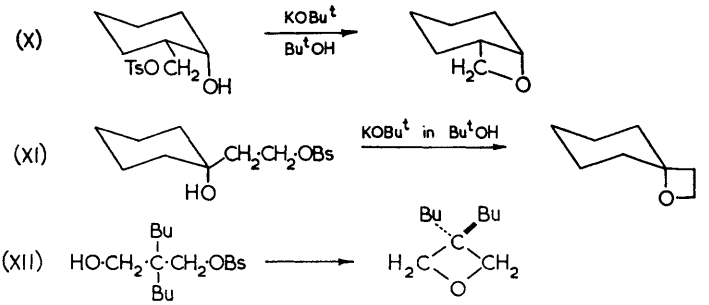
[31] Heine and Siegfried, *J. Amer. Chem. Soc.*, 1954, **76**, 489.
[32] Swain, Ketley, and Bader, *J. Amer. Chem. Soc.*, 1959, **81**, 2353; see also Ballinger and Long, *ibid.*, p. 2347.
[33] Heine, *J. Amer. Chem. Soc.*, 1957, **79**, 6268.



and 4,5-secocholest-3-en-5-one (54) (37%) at a rate much faster than that with which cholestan-3β-yl toluene-*p*-sulphonate reacts under the same conditions.[34] 5β-Hydroxycoprostan-3α-yl toluene-*p*-sulphonate (55) reacts at approximately the same rate as 5α-hydroxycholestan-3β-yl toluene-*p*-sulphonate but yields only the seco-ketone (54).[34]

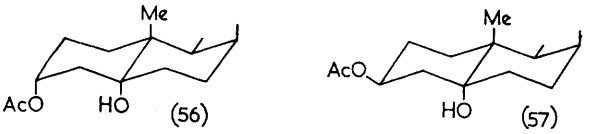


Other examples of O^--4 participation are shown in Schemes (X)—(XII).[35]



Reactions of Carboxylic Acids and their Derivatives.—Neighbouring hydroxyl-group participation in the alkaline hydrolysis of esters has frequently been reported,[36] an example[37] being the hydrolysis of 3α-acetoxycholestan-5α-ol (56) which proceeds faster than that of 3β-acetoxy-

[34] Clayton, Henbest, and Smith, *J.*, 1957, 1982.
[35] Henbest and Millward, *J.*, 1960, 3575; see also Lindegren and Winstein, Abstracts of Papers, 123rd American Chemical Society Meeting, 1953, 30M.
[36] See Kupchan, Slade, Young, and Milne, *Tetrahedron*, 1962, **18**, 499, and papers cited therein.
[37] Henbest and Lovell, *J.*, 1957, 1965.



cholestan-5α-ol (57), the usual rate order, that equatorial esters are more readily hydrolysed than axial ones,[38] being reversed. Possible mechanisms include nucleophilic participation, as (a) or (b) in Chart 5 (shown for an

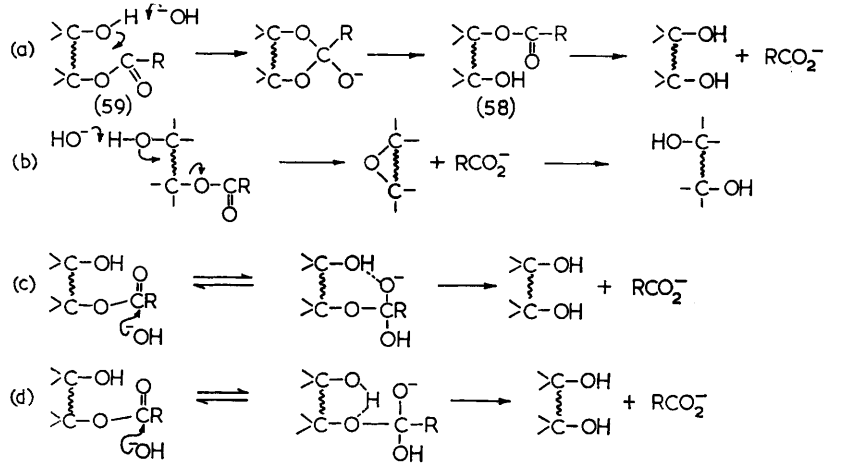
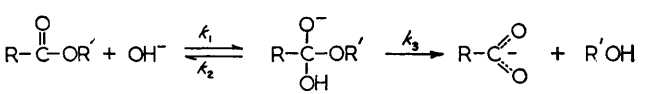


CHART 5.

ester with the hydroxyl substituent in the alkyl portion), or electrophilic participation, as (c) or (d), as well as several mechanism involving intramolecular general-base catalysis.

Participation of type (a) in Chart 5 will only result in an increase in rate if ester (58) is more reactive than ester (59). In type (b) the ester group is merely the leaving group for an intramolecular displacement at saturated carbon. In type (c) the hydroxyl group facilitates the reaction by hydrogen bonding to the carbonyl oxygen, and in type (d) by hydrogen bonding to the ether oxygen of the ester.

Generally it is easy to exclude mechanisms (a) and (b), but to distinguish between (c) and (d) is much more difficult. If the mechanism of ester hydrolysis is written:[39]



[38] See Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 222.

[39] Bender, *Chem. Rev.*, 1960, **60**, 61.

the measured rate constant, k_m, is given by $k_m = k_1(1 + k_2/k_3)$. Participation by the hydroxyl group as in (c) would result in an increased value of k_1, and as in (d) with an increased value of k_3 and k_1, although the effect on k_1 would be expected to be much less than with (c). Also, any effect on k_3 would not significantly affect the overall rate (see ref. 117) since, for the alkaline hydrolysis of esters, k_2/k_3 is never greater than about 0·2.[40] Therefore, a large increase in rate must be ascribed to a mechanism such as (c), but a small increase is consistent with both (c) and (d). Unfortunately, the rate increases that are observed are frequently small.

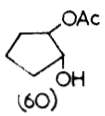
Henbest and Lovell[37] originally tried to distinguish between mechanisms (c) and (d) by examining the infrared spectra of the esters to find whether the hydroxyl group was bonded to the carbonyl or ether oxygen of the ester. However, the value of this approach is limited since the infrared spectra were always measured in aprotic solvents such as carbon tetrachloride and quite different state of affairs may prevail in the hydroxylic solvents used in the solvolyses (generally hydrolyses). More seriously, however, since the rates of reactions depend on the free-energy differences between initial and transition states, the point of interest is the relative strengths of the hydrogen bonding in these two states,[41] and hence a knowledge of the nature of the hydrogen bonding in the initial state alone in a different solvent is only partly relevant.

Bruice and Fife[42] attempted to distinguish between the two possibilities by considering the rates of hydrolyses of the esters given in Table 9, and

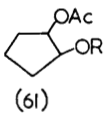
TABLE 9. *The rates of hydrolysis of some esters at* 78°.[42]

Esters	Cyclopentyl acetate	(61; R=Me)	(60)	(61; R=H)	(62)	(63; R=H)	(63; R=OH)
k (l. mole^{-1}sec.$^{-1}$)	9·3	31·6	174	309	85·1	5·0	79·4

came to the conclusion that the rate acceleration found with esters (60), (61; R=H), (62), and (63; R=OH), and with esters previously studied, resulted from a mechanism "in which a neighbouring hydroxyl group solvates the transition state for nucleophilic attack of the hydroxyl ion on the ester carbonyl group", *i.e.*, of type (c). However, they assumed that the



(60)



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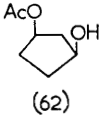

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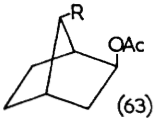


(63)

hydroxyl group participates in the same way in all these reactions, but, as pointed out by Kupchan and his co-workers,[43] this may not be so and might well vary with the geometry of the molecule. Sometimes, geometrical considerations exclude one of the possible mechanism for particular com-

[40] Bender and Thomas, *J. Amer. Chem. Soc.*, 1961, **83**, 4189.
[41] West, Korst, and Johnson, *J. Org. Chem.*, 1960, **25**, 1976.
[42] Bruice and Fife, *J. Amer. Chem. Soc.*, 1962, **84**, 1973.
[43] Kupchan, Eriksen, and Friedman, *J. Amer. Chem. Soc.*, 1962, **84**, 4159.

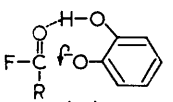
pounds, as with esters (60) and (62), in which hydrogen bonding to the ether oxygen of the ester grouping is not possible, and has been shown not to occur in carbon tetrachloride solution. For their compounds, Bruice and Fife's conclusion is therefore probably correct, but it should clearly not be generalised, particularly when the rate differences are small.

Some other examples of intramolecular electrophilic participation by hydroxyl groups are found in the reactions of salicylic acid[44] and 1′-α-hydroxylbenzylferrocenecarboxylic acid[45a] with diphenyldiazomethane.

The alkaline hydrolysis of *p*-nitrophenyl 5-nitrosalicylate occurs much faster than expected and the pH-rate profile is consistent with either a reaction of the un-ionised ester with hydroxide ion or of the ionised ester with water.[45b] The reactions of this ester with other nucleophiles are not, however, abnormally fast, which would be surprising if the fast hydrolysis involved attack of hydroxide ion on the unionised ester, the phenolic group providing intramolecular general acid catalysis. Bender, Kezdy, and Zerner,[45b] therefore, prefer a mechanism involving the intramolecularly general base-catalysed attack of water on the ionised ester. This interesting conclusion must, of course, raise the question as to whether some of the examples of intramolecular catalysis by alcoholic hydroxyl groups do not involve general base catalysis.

Nucleophilic participation by hydroxyl groups has been shown to occur in the hydrolyses of 4-hydroxybutyramide, 5-hydroxyvaleramide,[8,46a] and several aldonamides,[46b] and in the esterification of *o*-hydroxyphenoxyacetic acid.[47]

The nucleophilicity of the mono-anion of catechol is abnormally high in reactions with several aryl[48] and phosphoryl fluorides,[49] and with phenyl chloroacetate.[50] Probably the un-ionised hydroxyl group is providing assistance, as signified by (64) or (65), and (66). It is interesting to note that the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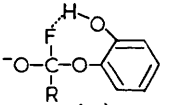
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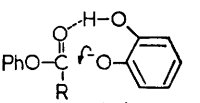

(66)

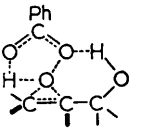
reaction of *p*-nitrophenyl acetate with several hydroxyl substituted imidazoles is not similarly facilitated.[51]

Other Reactions.—An example where an ionised hydroxyl group participates in a reaction by acting as a general-base rather than as a nucleo-

[44] Norris and Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 187.
[45] (*a*) Little and Eisenthal, *J. Amer. Chem. Soc.*, 1961, **83**, 4936; (*b*) Bender, Kezdy, and Zerner, *J. Amer. Chem. Soc.*, 1963, 85, 3017.
[46] (*a*) Bruice and Marquardt, *J. Amer. Chem. Soc.*, 1962, **84**, 365; (*b*) Wolfrom, Bennett, and Crum, *J. Amer. Chem. Soc.*, 1958, **80**, 944.
[47] Kupchan and Saettone, *Tetrahedron*, 1962, **18**, 1403.
[48] Churchill, Lapkin, Martinez, and Zaslowsky, *J. Amer. Chem. Soc.*, 1958, **80**, 1944.
[49] Epstein, Rosenblatt and Demek, *J. Amer. Chem. Soc.*, 1956, **78**, 341.
[50] Fuller, *J. Amer. Chem. Soc.*, 1963, **85**, 1777.
[51] Bruice and Schmir, *J. Amer. Chem. Soc.*, 1958, **80**, 148.

phile is found in the coupling reaction between the *o*-nitrodiazonium ion and 1-hydroxynaphthalene-3-sulphonic acid.[10] The reactions at both the *ortho*- and the *para*-positions of the phenol are general-base catalysed by external bases but extrapolation to zero buffer concentration shows that the "water"-catalysed reaction for *ortho*-coupling is considerably faster than that for *para*-coupling. Stamm and Zollinger[10] explained this as being due to the fact that proton loss from the σ-complex for *ortho*-coupling is catalysed intramolecularly by the phenoxide ion acting through a water molecule [see (VII) on p. 46].

The reaction of cyclohex-2-enol with perbenzoic acid yields the *cis*-epoxide exclusively, probably because of intramolecular electrophilic participation, the transition state being as (67).[52]



(67)

Participation by Amino-groups

Many examples of nucleophilic participation by amino-groups are known, and large rate acceleration have been observed with the formation of 3-, 4-, 5-, and 6- membered rings.[53,54] The pattern of behaviour found for the ring-closure reactions of ω-aminoalkyl halides (Table 10) is similar

TABLE 10. *The rates of ring-closure of ω-aminoalkyl halides, $Br\cdot[CH_2]_n\cdot NH_2$, in water at 25°.*[53]

n	2	3	4	5	6
k (min.$^{-1}$)	0·036	0·0005	30	0·5	0·001

TABLE 11. *The effect of chain-branching on the rates of ring-closure of ω-aminoalkyl halides.*

Rates of solvolysis* in 80% ethanol at 56°.[54]

	10^5k (sec.$^{-1}$)	k/k_{RCl}†
$Me_2N\cdot CH_2CH_2\cdot CH_2Cl$	10·5	6×10^3
$Me_2N\cdot CH_2CMe_2\cdot CH_2Cl$	98·0	5×10^6

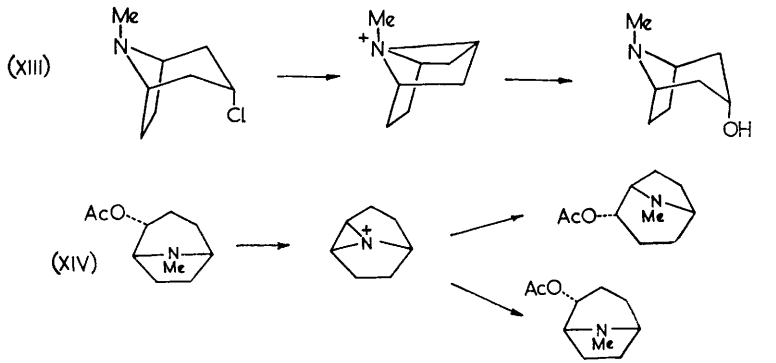
Relative rates of solvolysis in acetate buffer at 30°.[55]

	$k_{rel.}$
$H_2N\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2Br$	1
$H_2N\cdot CH_2\cdot CMe_2\cdot CH_2\cdot CH_2Br$	158
$H_2N\cdot CH_2\cdot CEt_2\cdot CH_2\cdot CH_2Br$	594
$H_2N\cdot CH_2\cdot CPr^i{}_2\cdot CH_2\cdot CH_2Br$	9790

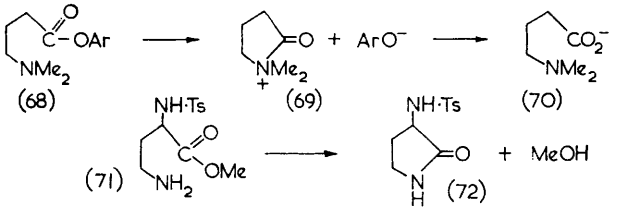
* Ring-closure occurs exclusively with these compounds. †Rate constant for the corresponding compound in which the Me_2N group is replaced by H.

[52] Henbest and Wilson, *J.*, 1957, 1958.
[53] Freundlich and Kroepelin, *Z. phys. Chem.*, 1926, **122**, 39.
[54] Grob and Jenny, *Tetrahedron Letters*, 1960, No. 23, p. 25.
[55] Brown and van Gulick, *J. Org. Chem.*, 1956, **21**, 1046.

to that found with the analogous ω-hydroxy- and ω-methoxy-compounds (see previous Sections). Branching at the non-terminal positions of the alkyl chain increases the rate of formation of the 4- and 5-membered rings. (Table 11)[54,55] (see p. 109 for a discussion of this effect). Examples of a similar participation with more complex molecules are found in the solvolysis of tropan-3α-yl chloride[56] [Scheme (XIII)] and in the racemisation of L-(+)-tropan-2α-ol by boiling acetic anhydride[57] [Scheme (XIV)].

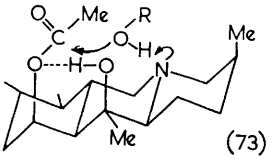


Nucleophilic participation by amino-groups in reactions of carboxylic acid derivatives is found in the hydrolysis of aryl 4-(*NN*-dimethylamino)-butyrates and 5-(*NN*-dimethylamino)valerates,[58] *e.g.*, (68)→(70), and in the hydroxyl-ion catalysed lactamisation of methyl ω-amino-α-(toluene-*p*-sulphonamido)-butyrates and -valerates,[59] *e.g.*, (71)→(72). Considerable rate accelerations result, and in the former series the rate of formation for a 5-membered ring is slightly greater than for a 6-membered ring, but with the latter compounds 6-membered-ring formation is faster.



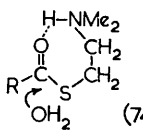
Reactions in which amino-groups participate by acting as general-bases are rare. A recently discovered example is the methanolysis of cevadine orthoacetate diacetate which is thought to proceed as shown in (73).[60]

[56] Archer, Bell, Lewis, Schulenberg, and Unser, *J. Amer. Chem. Soc.*, 1957, **79**, 6337; Grob, I.U.P.A.C. Kekulé Symposium, Butterworths, London 1959, p. 121.
[57] Archer, Lewis, Bell, and Schulenberg, *J. Amer. Chem. Soc.*, 1961, **83**, 2386.
[58] Bruice and Benkovic, *J. Amer. Chem. Soc.*, 1963, **85**, 1.
[59] Curragh and Elmore, *J.*, 1962, 2948.
[60] Kupchan, Eriksen, and Yun-Teh Shen, *J. Amer. Chem. Soc.*, 1963, **85**, 350.

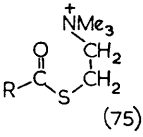


(73)

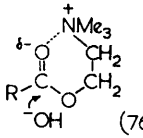
The protonated amino-group is a particularly effective intramolecular acid catalyst in the hydrolysis of 2-*NN*-dimethylaminoethyl thioacetate in acid solutions [see (74)], the rate being about 240 times greater than that for the ester (75) which lacks the acidic proton.[61] A similarly caused, but



(74)



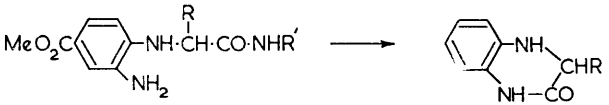
(75)



(76)

smaller (about 20-fold), rate accelerating effect is found in the hydrolysis of 2-*NN*-dimethylaminoethyl benzoate.[62] There is some evidence that the positively charged trimethylamino-group can stabilise the transition state in the alkaline hydrolysis of esters through "electrostatic bonding" as shown in (76).[63] The ester, Me_3N^+–CH_2·CH_2·OAc, is hydrolysed more slowly than ethyl acetate in acidic solutions but about 10 times faster in alkaline solutions.

Use is made of amino-group participation in a stepwise degradation of peptides devised by Holley and Holley,[64] of which several modifications have been reported.[65] The original procedure involved reaction of the free amino-groups with methyl 4-fluoro-3-nitrobenzoate, and reduction, to yield an *N*-aminophenylpeptide which reacts as shown:



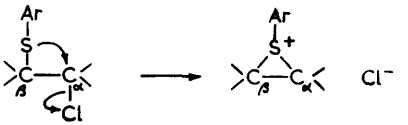
A similar reaction sequence is employed in the use of *o*-nitrophenoxyacetyl chloride as a protective group in peptide synthesis.[66] This may be removed by reduction, and hydrolysis with participation by the resulting amino-group [(77)→(78)].

[61] Hansen, *Acta Chem. Scand.*, 1958, **12**, 324.
[62] Ågren, Hedsten, and Jonsson, *Acta. Chem. Scand.*, 1961, **15**, 1532.
[63] Davis and Ross, *J.*, 1950, 3056; Butterworth, Eley, and Stone, *Biochem. J.*, 1953, **53**, 30.
[64] Holley and Holley, *J. Amer. Chem. Soc.*, 1952, **74**, 5445.
[65] Jutisz and Ritschard, *Biochem. Biophys. Acta*, 1955, **17**, 548; Scoffone Vianello, and Lorenzini, *Gazzetta*, 1957, **87**, 354.
[66] Holley and Holley, *J. Amer. Chem. Soc.*, 1952, **74**, 3069.

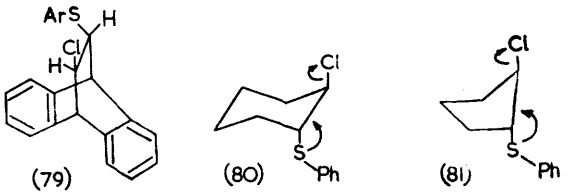
Many examples of neighbouring amino-group participation are found in the reactions of the nitrogen mustards.[67,68]

Participation by Thioether Groups*

trans-2-Chlorocyclohexyl and *trans*-2-chlorocyclopentyl phenyl sulphide undergo solvolysis in 80% aqueous ethanol 10^5—10^6-fold faster than their *cis*-isomers.[69] Electron-releasing substituents in the *para*-position of the phenyl ring increase, and electron-withdrawing substituents decrease, the rates for the *trans*-compounds (ρ values are $-1{\cdot}431$ and $-1{\cdot}388$ at 30°) but have no effect on the rates of the *cis*-isomers. The *trans*-isomers therefore react with nucleophilic participation of the thioether group:



A *trans*-configuration is, however, not a sufficient condition for participation; it is also necessary that the molecule be sufficiently flexible to allow the thioether group, α- and β-carbon atoms, and the leaving group to be in one plane in the transition state. Thus, the rigid *trans*-chloro-sulphide (79) undergoes solvolysis only four times as fast as its *cis*-isomer.[70] It therefore seems likely that the cyclohexyl and cyclopentyl compounds would have to react by way of the conformations (80) and (81).



Participation of a thioether group to yield 5- and 6-membered cyclic sulphonium ions may also occur (see results in Table 12).[71] The anchimeric assistance decreases with ring size in the order $3 > 5 > 6$.

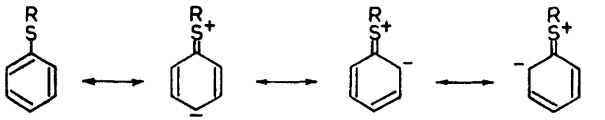
The ethylthio-group provides more anchimeric assistance than the

* For a recent review, see Gundermann, *Angew. Chem. Internat. Edn.*, 1963, **2**, 599.
[67] See papers cited by Streitwieser, *Chem. Rev.*, 1956, **56**, 678.
[68] See Chapman and Triggle, *J.*, 1963, 1385, and earlier papers.
[69] Goering and Howe, *J. Amer. Chem. Soc.*, 1957, **79**, 6542.
[70] Cristol and Arganbright, *J. Amer. Chem. Soc.*, 1957, **79**, 3441.
[71] Böhme and Sell, *Chem. Ber.*, 1948, **81**, 123.

TABLE 12. *The rates of solvolysis of some ω-chloroalkyl phenyl sulphides.*

	50% Aqueous acetone at 80°.[71] 10^2k (min.$^{-1}$)	20 mole % Aqueous dioxan at 100°.[72] 10^3k (min.$^{-1}$)
PhS·$[CH_2]_2$·Cl	—	5·5
PhS·$[CH_2]_3$·Cl	—	0·029
PhS·$[CH_2]_4$·Cl	6·5	1·1
PhS·$[CH_2]_5$·Cl	0·085	—
$C_6H_{13}Cl$	—	0·053

phenylthio-group; 2-chloroethyl ethyl sulphide, for example, undergoes solvolysis about forty times faster than 2-chloroethyl phenyl sulphide.[71] This may be ascribed to a decreased nucleophilicity of the phenylthio-groups because of delocalisation of the electrons on the sulphur throughout the phenyl ring as represented by resonance between structures (82)—(85).



(82) (83) (84) (85)

Probably the most thoroughly studied reactions involving participation by a thioether group are those of 2,2′-bischloroethyl sulphide (mustard gas) (86), which readily undergoes cyclisation to the ion (87). Competition factors of a large number of nucleophiles for the ion (87) have been measured.[67,73]

(86) (87)

Participation by Halogeno-groups

Evidence for nucleophilic participation by halogeno-groups comes both from kinetic measurements and from the configuration of certain reaction products. The rate of formation of titratable acid in acetic acid solutions of *trans*-2-bromocyclohexyl *p*-bromobenzenesulphonate[17] is appreciably faster than would be expected for its unassisted acetolysis, as estimated by the rate for the *cis*-isomer[74] and from the $\rho^*\sigma^*$ correlation for other cyclohexyl *p*-bromobenzenesulphonates.[11] *trans*-2-Iodocyclohexyl toluene-*p*-sulphonate is unstable and liberates titratable acid about 1000 times faster than cyclohexyl toluene-*p*-sulphonate when dissolved in acetic acid.[17] Unfortunately the products of these reactions have not been determined,

[72] Bennett, Heathcoat, and Mosses, *J.*, 1929, 2567.
[73] Ogston, Holiday, Philpot, and Stocken, *Trans. Faraday Soc.*, 1948, **44**, 45; see also Bartlett and Swain, *J. Amer. Chem. Soc.*, 1949, **71**, 1406.
[74] Grunwald, *J. Amer. Chem. Soc.*, 1951, **73**, 5458.

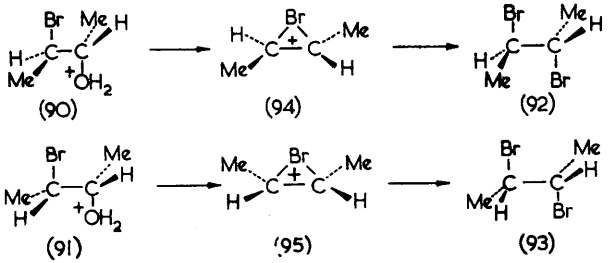
but the results at least suggest the occurrence of participation by the bromo- and iodo-groups to yield the bromonium and iodonium ions (88) and (89). (Bromonium ions have, of course, also been postulated as intermediates in the addition reaction of bromine with olefins.[75]) *trans*-2-Chlorocyclohexyl *p*-bromobenzenesulphonate does not react abnormally fast in acetic acid.[74]

Among reactions whose products suggest the incursion of bromonium ions are those of *dl-erythro-* and *dl-threo*-3-bromobutanol, (90) and (91), with concentrated hydrobromic acid.[76] These yield *meso-* and *dl*-2,3-dibromobutane, (92) and (93), respectively, and the racemic product is also


(88)


(89)

obtained from the optically active *threo*-bromobutanol. Hence these reactions proceed with retention of configuration by way of symmetrical intermediates which are most likely the bromonium ions (94) and (95). Similar results indicate the incursion of the corresponding iodonium ions in the reaction of the 3-iodobutan-2-ols with concentrated hydrochloric and hydrobromic acid.[77] The corresponding chloronium ions are, however, formed much less readily but there is some evidence for their incursion in the reactions of the 3-chlorobutan-2-ols with thionyl chloride.[78]



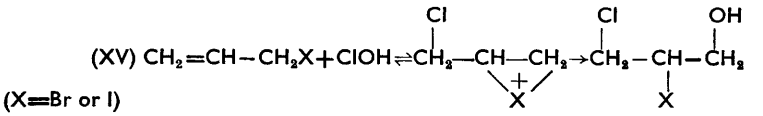
That nucleophilic participation by halogeno-groups increases in the order Cl<Br<I is, of course, to be expected from the known ease with which these elements increase their valency.

The conformational requirements for nucleophilic participation by a bromo-group were investigated by Alt and Barton.[79] They found that, whereas the diaxial 2β-bromocholestan-3α-ol readily underwent reactions (*e.g.*, with PBr_3 and PCl_3) which appeared to involve participation by the bromo-group, the di-equatorial isomer, 2α-bromocholestan-3β-ol did

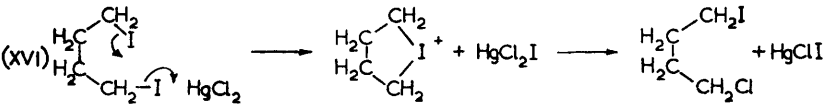
[75] Roberts and Kimball, *J. Amer. Chem. Soc.*, 1937, **59**, 947; see also Traynham, *J. Chem. Educ.*, 1963, **40**, 392.
[76] Winstein and Lucas, *J. Amer. Chem. Soc.*, 1939, **61**, 1576, 2845.
[77] Lucas and Garner, *J. Amer. Chem. Soc.*, 1950, **72**, 2145.
[78] Lucas and Gould, *J. Amer. Chem. Soc.*, 1941, **63**, 2541.
[79] Alt and Barton, *J.*, 1954, 4284.

not. It thus appears that, as found with participation by a thioether group (see p. 65), a *trans*-planar arrangement of participating and leaving groups is highly favourable for participation.

Interesting examples of bromine and iodine participation occur in the acid-catalysed addition of hypochlorous acid to allyl bromide[80] and iodide,[81] which yield, besides the normal addition products, 28% of 2-bromo-3-chloropropene and 45% of 3-chloro-2-iodopropene formed by the rearrangement shown in Scheme (XV). The corresponding reaction of allyl chloride with hypobromous acid yields very little rearranged product, because of the much smaller tendency of chlorine to participate. Participation by the hydroxyl and acetoxy-groups in the addition of chlorine and bromine to the double bonds of allyl alcohol and acetate also does not occur.[82]



Evidence of nucleophilic participation by a more remote iodo-group [see Scheme (XVI)] is provided by the observation[83] that treatment with mercuric chloride in chloroform replaces one of the iodo-groups of several 1,4-di-iodoalkanes with chloride, but that the second iodo-group is inert.



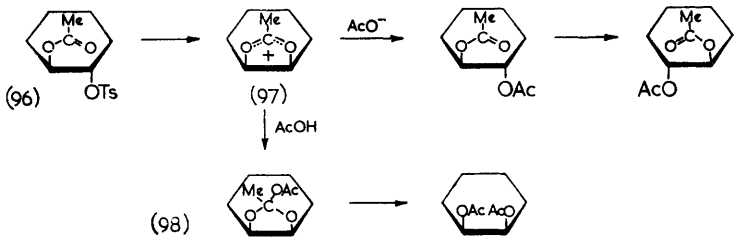
Neighbouring Ester Groups

The acetoxy-group, MeCO·O, is electron-withdrawing and has a strong retarding effect on reactions in which a carbonium ion is generated at an adjacent atom. Thus, the rate of acetolysis of *cis*-2-acetoxycyclohexyl toluene-*p*-sulphonate is about one two-thousandth that of cyclohexyl toluene-*p*-sulphonate.[84] The acetolysis of the isomeric *trans*-toluene-*p*-sulphonate (96) proceeds, however, almost as fast as that of cyclohexyl toluene-*p*-sulphonate,[84] and yields, in the presence of potassium acetate, the *trans*- diacetate, formed with retention of configuration; when optically active material is used, it yields a racemic product.[85] The symmetrical ion (97) is therefore an intermediate. Solvolyses in wet acetic acid, in absolute

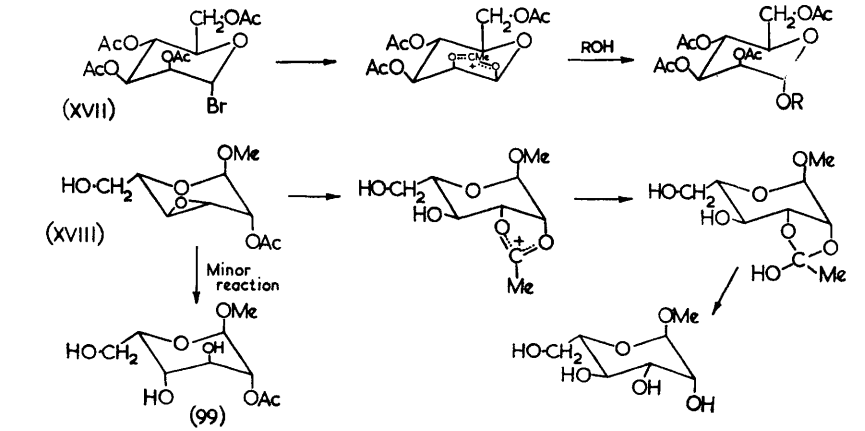
[80] de la Mare, Naylor, and Williams, *J.*, 1962, 443.
[81] de la Mare, Naylor, and Williams, *J.*, 1963, 3429.
[82] Winstein and Goodman, *J. Amer. Chem. Soc.*, 1954, **76**, 4368.
[83] Summerbell and Forrester, *J. Org. Chem.*, 1961, **26**, 4834.
[84] Winstein, Grunwald, Buckles, and Hanson, *J. Amer. Chem. Soc.*, 1948, **70**, 816.
[85] Winstein, Hess, and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2796.

alcohol, or in dry acetic acid in the absence of potassium acetate yield mainly products with a *cis*-configuration, formed probably by way of derivatives of the ortho acid [*e.g.*, (98)].[85] Similar behaviour is observed with the acyclic compounds *erythro*- and *threo*-2-acetoxy-3-bromobutane,[1] and *erythro*- and *threo*-3-acetoxybut-2-yl toluene-*p*-sulphonate.[86]

The carbohydrate field is particularly rich in examples of neighbouring acetoxy-group participation. Two recently reported examples occur in the



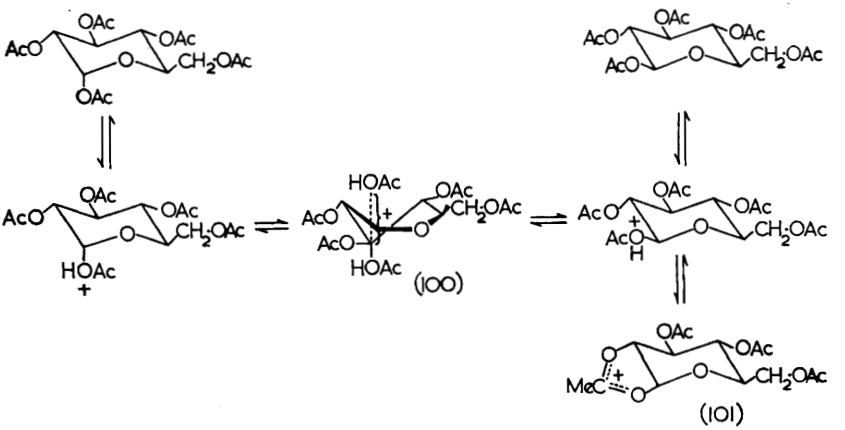
formation with retention of configuration of an α-linked disaccharide from the reaction of tetra-*O*-acetyl-α-D-mannopyranosyl bromide with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose [Scheme (XVII)],[87] and in the opening of the epoxide ring of methyl 2-*O*-acetyl-3,4-anhydro-α-D-altroside in aqueous acetic acid [Scheme (XVIII)][88] to yield a mannose derivative almost exclusively. In the absence of participation predominant formation of the idose derivative (99) would be expected, through diaxial ring-opening, similar to that found with the unacetylated epoxide.[88]



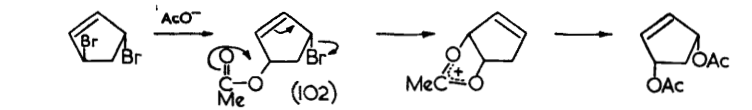
An interesting example of ionisation proceeding concurrently with and without neighbouring group participation occurs in the sulphuric acid

[86] Lucas, Mitchell, and Garner, *J. Amer. Chem. Soc.*, 1950, **72**, 2138.
[87] Gorin and Perlin, *Canad. J. Chem.*, 1959, **37**, 1930.
[88] Buchanan and Schwarz, *J.*, 1962, 4770.

catalysed anomerisation of glucose penta-acetates in acetic acid.[89] The rates of anomerisation and acetate-exchange of the α-anomer are identical, but the β-anomer undergoes acetate exchange about 15 times faster than it undergoes anomerisation. Hence, in addition to the reactions in which the α- and β-anomers are interconverted, which, by the principle of microscopic reversibility, must involve the same transition state [as (100)] the β-anomer must have a pathway for undergoing acetate exchange without anomerisation, by way of the ion (101) formed by neighbouring group participation. An example of AcO-6 participation has recently been reported.[90a]



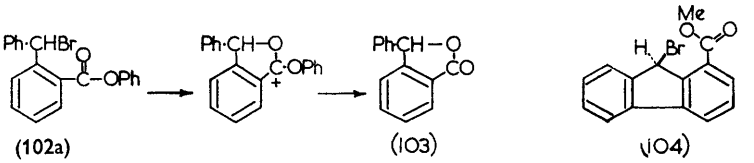
An interesting speculation has been made[90b] that an intramolecular S_N2' mechanism occurs in the second stage of the reaction of *trans*-3,5-dibromocyclopentene with tetramethylammonium acetate in acetone.[91] It is known that a *cis*-arrangement of entering and leaving groups is favourable for this mechanism,[92] and hence it is not unreasonable to suppose that the postulated intermediate (102) would react as shown to yield *cis*-3,5-diacetoxycyclopentene.



Up to now only reactions involving intramolecular nucleophilic displacement of a group in the alcohol portion of esters have been considered, but reactions in which the displaced group is in the acid portion are also

[89] Lemieux, Brice, and Huber, *Canad. J. Chem.*, 1955, **33**, 134; see Capon and Overend, *Adv. Carbohydrate Chem.*, 1960, **15**, 42, for a mechanistic interpretation.
[90] (*a*) Kovács, Schneider, and Láng, *Proc. Chem. Soc.*, 1963, 374; (*b*) Saegebarth, *J. Org. Chem.*, 1960, **25**, 2212.
[91] Owen and Smith, *J.*, 1952, 4042.
[92] Stork and White, *J. Amer. Chem. Soc.*, 1953, **75**, 4119; 1956, **78**, 4609.

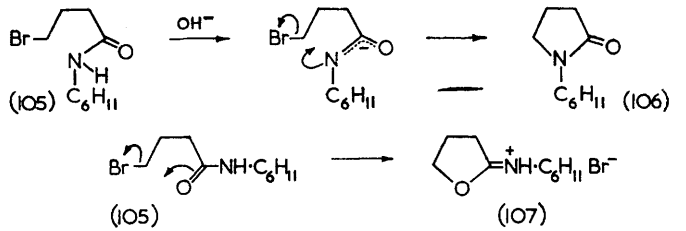
possible. An example of such a reaction is the solvolysis of 2-phenoxycarbonyldiphenylmethyl bromide (102a) in aqueous acetone which is 60—80 times faster than that of its 4-isomer and yields 3-phenylphthalide (103).[93] The corresponding *o*-methoxy-carbonyl compound is so reactive that attempts to prepare it yield only 3-phenylphthalide.[93] Participation does not occur in the solvolysis of the fluorene ester (104),[94] presumably because the geometry of the molecule does not allow rearside attack by the ester group at position 9.



A similar intramolecular nucleophilic attack by an ester group on iodine occurs in the dissociation of the dichloride of methyl 2-iodobenzoate in acetic acid, as shown in Scheme (XIX).[95]

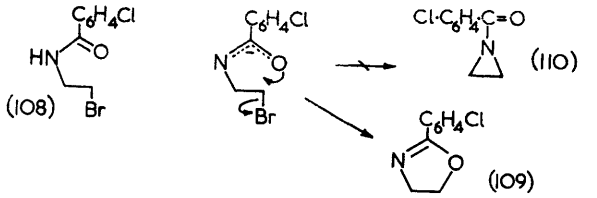
Participation by Amide Groups

Amides are ambident nucleophiles, and examples of nucleophilic participation involving attack by both the nitrogen and oxygen atoms of amide groups are known. When rings of the same size would result from either *O*- or *N*-attack, *O*-attack is generally favoured with un-ionised amide groups but *N*-attack is favoured with their conjugate bases. Thus, when fused with alkali, 4-bromo-*N*-cyclohexylbutyramide (105) yields the pyrrolidone (106), but when fused alone it yields the tetrahydrofuran derivative (107).[96] The relative importance of *N*- and *O*-attack may, however, be governed by the sizes of the resulting rings when these are different. For example,



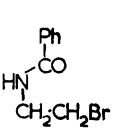
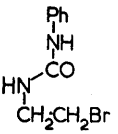
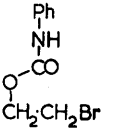
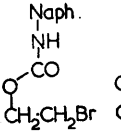
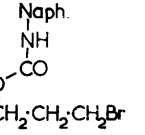
[93] Singh, Andrews, and Keefer, *J. Amer. Chem. Soc.*, 1962, **84**, 1179.
[94] Lovins, Andrews, and Keefer, *J. Amer. Chem. Soc.*, 1962, **94**, 3959.
[95] Andrews and Keefer, *J, Amer. Chem. Soc.*, 1959, **81**, 4218, 5329.
[96] Stirling, *J.*, 1960, 255.

N-(2-bromoethyl)-4-chlorobenzamide (108), on reaction with sodium methoxide in methanol, yields the oxazoline (109) by O⁻-5 participation rather than the aziridine (110) by N⁻-3 participation.[97a] *trans*-2-Benzamidocyclohexyl toluene-*p*-sulphonate with sodium ethoxide in ethanol, however, yields a mixture of the corresponding aziridine and oxazoline.[97b]



The ethanolysis of *trans*-2-benzamidocyclohexyl toluene-*p*-sulphonate, in the presence of potassium acetate, which yields an oxazolinium ion, is about 1000 times faster than that of the *cis*-isomer and about 200 times faster than that of *trans*-2-acetoxycyclohexyl toluene-*p*-sulphonate.[98,99] In the presence of strong bases, participation by amide groups becomes much more effective owing to conversion into the more highly nucleophilic conjugate bases (see Table 13).[100] The measured second order rate constant, k_m, is then equal to the product of the equilibrium constant for the formation of the conjugate base and the rate constant for its ring-closure, $k_m = Kk$. The rate-accelerating effect of an ionised amide group may be judged by comparing the value of k_m for the reaction of 4-bromo-*N*-phenylbutyramide with sodium methoxide in methanol at 22·90° (3 ×

TABLE 13. *Participation by ureido- and urethano-groups.*[100]

Compound	 (111)	 (112)	 (113)	 (114)	 (115)
	Solvolysis in 80% ethanol at 50°				
10^5k_1 (sec.$^{-1}$)	110	45·4	2·56	3·36	0·18
Type of participation	O-5	O-5	O-5	O-5	O-6
	Solvolysis in absolute ethanol containing sodium ethoxide. at 25°.				
10^5k_2 (l. mole^{-1}sec.$^{-1}$)	13000	1360	1·5 × 10^5	1·2 × 10^6	>10^5
Type of participation	O⁻-5	N⁻-5	N⁻-5	N⁻-5	N⁻-6

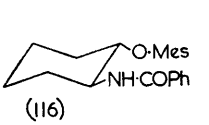
[97] (*a*) Heine, *J. Amer. Chem. Soc.*, 1956, **78**, 3708; (*b*) Taguchi and Kojima, *ibid.*, 1959, **81**, 4316; see also Buss, Hough, and Richardson, *J.*, 1963, 5295.
[98] Winstein, Goodman, and Boschan, *J. Amer. Chem. Soc.*, 1950, **72**, 2311.
[99] Winstein and Boschan, *J. Amer. Chem. Soc.*, 1950, **72**, 4669.
[100] Scott, Glick, and Winstein, *Experientia*, 1957, **13**, 183.

10^{-3} l. mole^{-1}sec.$^{-1}$)[101] with the second-order constant for the displacement reaction of propyl bromide with sodium ethoxide in ethanol at 55° ($5{\cdot}5 \times 10^{-4}$ l. mole^{-1}sec.$^{-1}$).[102]

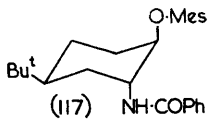
A preliminary report of an investigation on the participation of ureido- and urethano-groups appeared in 1957[100] but at the time of writing (June 1963) full details are still awaited. In neutral solution both these groups provide less anchimeric assistance than the amido-group [cf. compounds (111), (112), and (113) in Table 13], and *O*-attack predominates. In basic solution *N*-attack occurs and the values of k_m decrease in the order urethano > amido > ureido. Comparison of the results for compounds (114) and (115) (Table 13) shows that O-5 is more effective than O-6 urethano-participation.

Sicher and his co-workers have made an interesting investigation on the neutral ethanolysis of some 2-benzamidocyclohexyl methanesulphonates in which conformational movements were restricted by a t-butyl group in the 4-position (Table 14).[103] The high rate for the di-axial compound (117)

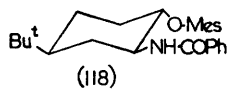
TABLE 14. *Rates of ethanolysis of some 2-benzamidocyclohexyl methanesulphonates in the presence of potassium acetate.*[103]



(116)

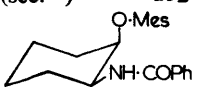


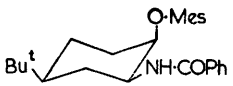
(117)

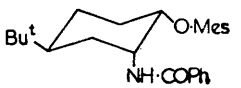


(118)

10^6k (sec.$^{-1}$) 252 6280 76·2





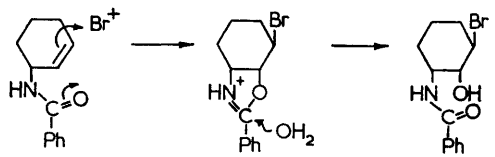


10^6k (sec.$^{-1}$) 0·687 0·692 2·95

shows that such an arrangement is highly favourable for participation, but the only slightly slower rate for compound (118) compared to compound (116) indicates that in these di-equatorial compounds participation can occur without inversion to the other chair conformation.

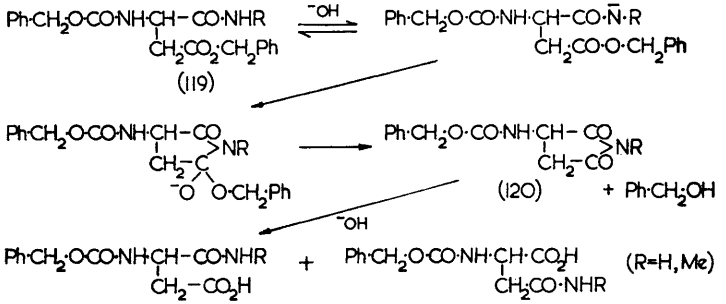
Examples of participation of amido-groups in addition reactions to olefinic double bonds are also known.[98,104] [See, *e.g.*, Scheme (XX)].

(XX)

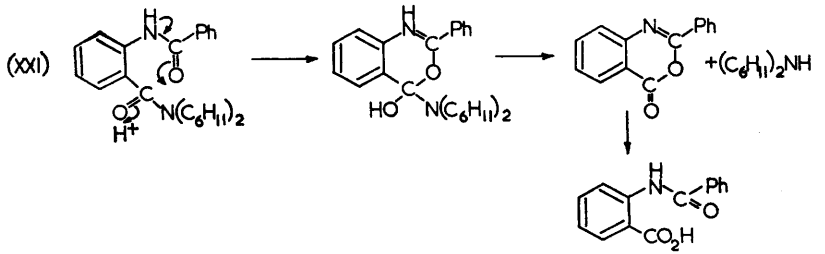


[101] Heine, Love, and Bore, *J. Amer. Chem. Soc.*, 1955, **77**, 5420.
[102] Dhar, Hughes, Ingold, and Masterman, *J.* 1948, 2055.
[103] Sicher, Tichý, Šipoš, and Pańková, *Proc. Chem. Soc.*, 1960, 384; *Coll. Czech. Chem. Comm.*, 1961, **26**, 2418.
[104] Goodman and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 4788.

The importance of amide participation in the reactions of peptides and their derivatives is becoming increasingly recognised.[105] A striking example is afforded by the hydrolyses of the β-benzyl esters of *N*-benzyloxycarbonyl-L-aspartyl amide and methylamide (119) which occur in alkaline solutions with nucleophilic participation by the amide groups (*N*-attack).[106] The hydrolyses of the resulting imides (120) are the slow steps, and the imides have been isolated from the reaction solutions. Nucleophilic participation by an amide group with *O*-attack occurs in the acid-catalysed

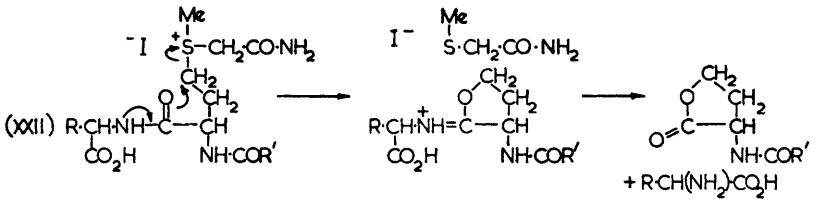


hydrolysis of *O*-benzamido-*NN*-dicyclohexylbenzamide [see Scheme (XXI) for the probable mechanism].[107] The rate of hydrolysis of this compound is at least 10^4 times greater than that for *NN*-dicyclohexylbenzamide, but part of this increase in rate may be due to steric acceleration.

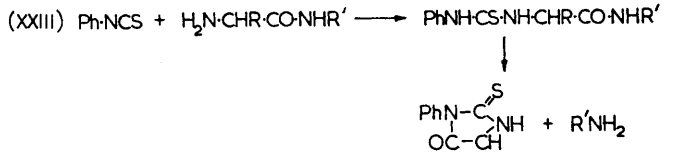


Other examples of amide participation in peptide chemistry are found in the specific cleavage of the peptide linkage adjacent to an *S*-alkylated methionine residue[108] [see Scheme (XXII)] and in the Edman procedure for the removal of terminal amino-acid residues.[109] In this procedure the free amino-groups of the peptide are allowed to react with phenyl isothio-

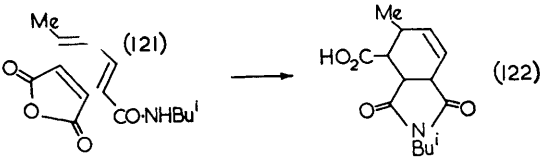
[105] See Cohen and Witkop, *Angew. Chem.*, 1961, **73**, 253.
[106] Bernhard, Berger, Carter, Katchalski, Sela, and Shalitin, *J. Amer. Chem. Soc.*, 1962, **84**, 2421.
[107] Cohen and Lipowitz, *J. Amer. Chem. Soc.*, 1961, **83**, 4866; see also Shafer and Morawetz, *J. Org. Chem.*, 1963, **28**, 1899.
[108] Lawson, Gross, Foltz, and Witkop, *J. Amer. Chem. Soc.*, 1962, **84**, 1716.
[109] Edman, *Acta. Chem. Scand.*, 1950, **4**, 283.



cyanate and the resulting thiourea derivative is allowed to hydrolyse with N^--participation [See Scheme (XXIII)].



An interesting example of amide participation occurs in the Diels–Alder reaction between *N*-isobutylsorbamide (121) and maleic anhydride, which yields compound (122).[110] It is not known whether the amide participation occurs concurrently with, or subsequent to, the Diels–Alder addition.



Neighbouring Carboxyl and Carboxylate Groups

Reactions at Saturated Carbon Centres.—There appears to be no clear evidence for participation by the un-ionised carboxyl group in substitution reactions at saturated carbon. The ionised carboxyl group, however, provides considerable anchimeric assistance, as is seen from the high rates of hydrolysis of 5-chlorovaleric and 4-chlorobutyric acid in sodium hydroxide solution, and the independence of these rates on the concentration of sodium hydroxide (Table 15).[30] If this participation were nucleophilic the initially formed products would be the corresponding lactones [see Scheme (XXIV)], and this is almost certainly so, since it has been shown that in neutral solution sodium 4-bromobutyrate yields the lactone,[111] but, of course, in alkaline solutions the lactones are rapidly saponified.

[110] Crombie and Manzoor-I-Khuda, *J.*, 1957, 2767.
[111] Caldin and Wolfenden, *J.*, 1936, 1239.

The occurrence of CO_2^--4 participation is shown by the isolation of several β-lactones from the hydrolysis of salts of the corresponding bromo-acids.[112] The anchimeric assistance, however, is not large; sodium 3-bromobutyrate, for instance, is hydrolysed about five-fold faster than isopropyl bromide (see Table 15).[113]

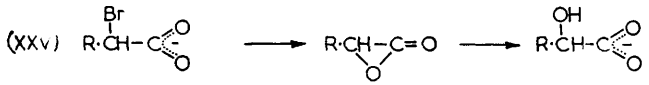
TABLE 15. *The kinetics of solvolysis of halogeno-acids.*

	First-order rate constants ($sec.^{-1}$)		
Solvent	4-Chlorobutyric acid at 37·5°[30]	5-Chlorovaleric acid[30] at 50·0°	Propyl chloride in water at 100°†
0·2M-NaOH	$4·05 \times 10^{-5}$	$1·73 \times 10^{-4}$	$6·81 \times 10^{-5}$
0·5M-NaOH	$3·96 \times 10^{-5}$	$1·70 \times 10^{-4}$	—

	3-Bromobutyrate ion[113]	2-Bromopropionate ion[115]	Isopropyl bromide
H_2O at 38°	$1·5 \times 10^{-4}$	—	$3·0 \times 10^{-5}$*
H_2O at 25°	—	$4·2 \times 10^{-7}$	$7·0 \times 10^{-6}$*
MeOH at 64°	—	$5·12 \times 10^{-5}$	$2·3 \times 10^{-6}$*

*Extrapolated from results at higher temperatures; Leffek, Robertson, and Sugamori, *Canad. J. Chem.*, 1961, **39**, 1989. † Laughton and Robertson, *Canad. J. Chem.*, 1959, **37**, 1491.

The solvolyses of the anions of α-halogeno-carboxylic acids in slightly alkaline solutions yield products of retained configuration[114] and hence CO_2^--3 participation is occurring [Scheme (XXV)]. The intermediate α-lactones have, however, never been isolated. The rate of methanolysis of the 2-bromopropionate ion is about twenty times greater than that



(XXV)

expected for isopropyl bromide[115] (see Table 15). For hydrolysis in water, however, these reactivities are reversed because the solvolysis of isopropyl bromide is sensitive to solvent effects but that of the 2-bromopropionate ion is not.[115] This insensitivity to solvent effects and to salt effects, and the high rate in methanol, are good evidence that the rate-determining step of the solvolyses of the α-bromopropionate ion involves a direct intramolecular displacement by the carboxylate group. If the reaction involved a prior ionisation followed by ring-closure the typical high dependance of S_N1 reactions on solvent effects would be expected.

Reactions of Carboxylic Acid Derivatives.—Examples of intramolecular participation by the carboxylate ion in displacement reactions at carboxyl

[112] Johansson, *Ber.*, 1915, **48**, 1262; Johansson and Hagman, *ibid.*, 1922, **55**, 647.
[113] Lane and Heine, *J. Amer. Chem. Soc.*, 1951, **73**, 1348; Heine, Becker, and Lane, *ibid.*, 1953, **75**, 4514.
[114] Cowdrey, Hughes, and Ingold, *J.*, 1937, 1208, 1243 and references cited by Cowdrey, Hughes, Ingold, Masterman, and Scott, *ibid.*, p. 1262.
[115] Grunwald and Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 841.

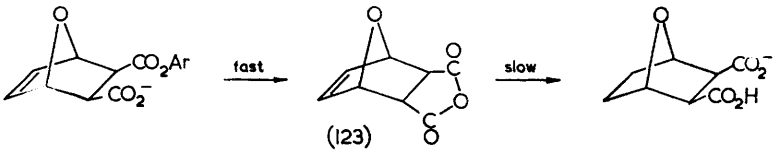
carbon are also known. The hydrolyses of phenyl hydrogen succinate and glutarate are particularly fast at pH's at which the carboxyl group is ionised (see Table 16).[116] The rate for phenyl hydrogen succinate is almost

TABLE 16. *The kinetics of the hydrolyses of phenyl hydrogen succinate and glutarate.*[116]

	10^4k (sec.$^{-1}$) at 25·3°	
	pH 5·0	pH 7·0
Phenyl hydrogen succinate	11	14·2
Phenyl hydrogen glutarate	—	0·1

k for phenyl acetate in 0·05M-acetate buffer at pH 5·27 and 60·8° = 1·25 × 10^{-6}sec.$^{-1}$

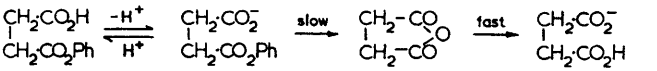
independent of pH in the region 5—10 and decreases at lower pH's where the carboxyl group becomes protonated. Hence, intramolecular participation by the carboxylate-ion group is occurring. Although no definite evidence has been provided for these reactions, there is evidence for nucleophilic participation in the hydrolyses of two closely analogous esters. These are acetylsalicylic acid, discussed below, and the mono-*p*-methoxyphenyl ester of 7-oxabicyclo[2,2,1]hept-2-ene-5,6-*exo*-dicarboxylic acid. The hydrolysis of the latter has been shown[117] to yield phenol and a neutral



(123)

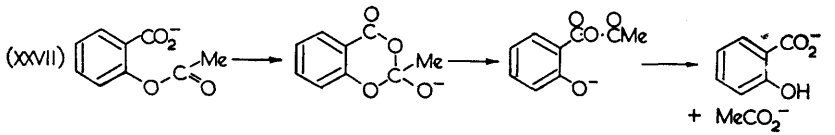
intermediate which is itself hydrolysed at rates identical with those of the anhydride (123), and, hence, is presumably the anhydride. The hydrolysis of the succinate and glutarate may, therefore, be formulated similarly, as in Scheme (XXVI), but with these the subsequent hydrolyses of the anhydrides are fast compared to the ring closures.

Participation by the carboxylate ion also occurs in the hydrolysis of acetylsalicylic acid[118,119] and probably in that of methyl hydrogen phthalate.[119] The pH–rate profiles between 2·5 and 7·0 for these reactions follow the ionisation curves for the carboxylic acid groups; the rates being proportional to the concentration of the ionised forms. (The results for methyl

(XXV 

[116] Gaetjens and Morawetz, *J. Amer. Chem. Soc.*, 1960, **82**, 5328.
[117] Bruice and Pandit, *J. Amer. Chem. Soc.*, 1960, **82**, 5858.
[118] Edwards, *Trans. Faraday Soc.*, 1950, **46**, 723; 1952, **48**, 696; Garrett, *J. Amer. Chem. Soc.*, 1957, **79**, 3401.
[119] Bender, Chloupek, and Neveu, *J. Amer. Chem. Soc.*, 1958, **80**, 5384.

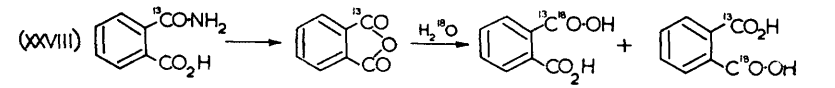
hydrogen phthalate[119] have been questioned[62] on the grounds that similar results were not obtained with ethyl hydrogen phthalate.) At pH 6·0 acetylsalicylic acid is hydrolysed about eighty times faster than *p*-acetoxybenzoic acid,[120] and at pH 5·5 methyl hydrogen phthalate is hydrolysed about ten times faster than methyl benzoate.[119] Hydrolysis of acetylsalicylic acid in water enriched in oxygen-18 yields salicylic acid enriched in oxygen-18 approximately to the (small) extent that would be expected if acetylsalicylic anhydride were an intermediate.[119] The hydrolysis, therefore, probably proceeds as shown in Scheme (XXVII).



The hydrolysis of phthalamic acid differs from those of the esters, just discussed, in being more rapid at pH's at which the carboxyl group is un-ionised than at those where it is ionised;[121] in 10^{-3}M-hydrochloric acid the rate is 75,800 times greater than that for benzamide. The reaction involves intramolecular nucleophilic participation with phthalic anhydride as an intermediate, since when phthalamic acid, in which the amide carboxyl group is specifically enriched in carbon-13, is allowed to hydrolyse in water enriched in oxygen-18, the oxygen-18-enriched carbon dioxide, obtained from the resulting phthalic acid, comes from both carbon-13-enriched and non-enriched carboxyl groups [see Scheme (XXVIII)].[121] The rate law may be written:

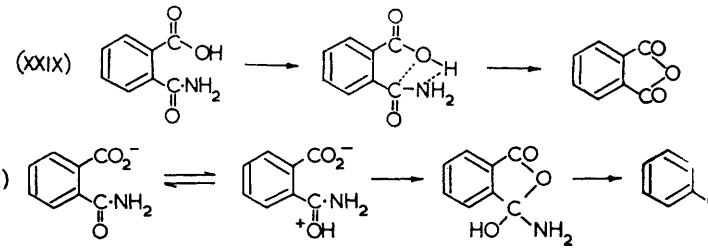
$$\text{Rate} = k\left[C_6H_4\begin{matrix}CO\cdot NH_2\\CO_2H\end{matrix}\right] = \frac{k}{K_a}\left[C_6H_4\begin{matrix}CO\cdot NH_2\\CO_2^-\end{matrix}\right]\left[H_3O^+\right]$$

$$\text{where } K_a = \left[C_6H_4\begin{matrix}CO\cdot NH_2\\CO_2^-\end{matrix}\right]\left[H_3O^+\right] \Big/ \left[C_6H_4\begin{matrix}CO\cdot NH_2\\CO_2H\end{matrix}\right]$$

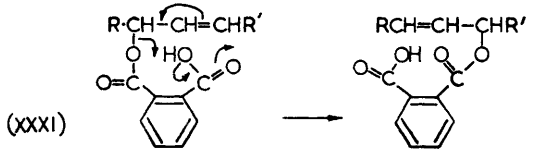


The reaction cannot involve a simple intramolecular displacement by the carboxyl group since if this were so the carboxylate group would be expected to be more effective. Bender *et al.*[121] prefer a mechanism [Scheme (XXIX)] involving simultaneous nucleophilic attack and proton transfer to the amide nitrogen ("intramolecular nucleophilic–electrophilic catalysis"), but the results are equally consistent with an intramolecular displacement by the carboxylate group on the protonated amide [Scheme (XXX)].

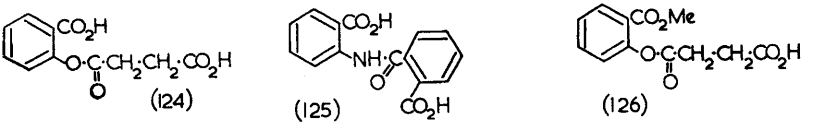
[120] Schmir and Bruice, *J. Amer. Chem. Soc.*, 1958, **80**, 1173.
[121] Bender, Yuan-Lang Chow, and Chloupek, *J. Amer. Chem. Soc.*, 1958, **80**, 5380.



The Carboxyl-group as an Intramolecular Acid Catalyst.—The possibility of participation by a carboxyl group acting as an intramolecular general-acid catalyst seems to have been first considered by Ingold for the rearrangement of substituted alkyl hydrogen phthalates [as in Scheme (XXXI)], but the suggestion was not pursued.[122] More recently Morawetz and his co-workers have demonstrated that such participation occurs



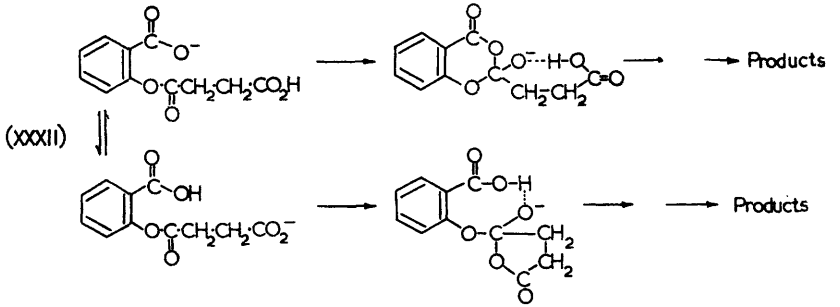
concurrently with nucleophilic participation by an ionised carboxyl group in the hydrolysis of the ester (124)[123] and the amide (125)[124] (intramolecular bifunctional catalysis). The pH–rate profiles for both of these reactions are bell-shaped curves, indicating that the half-ionised forms are



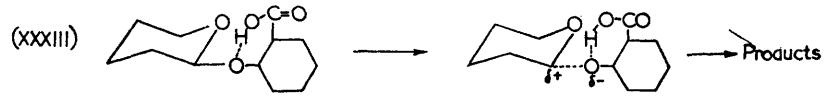
more reactive than either the un-ionised or the fully ionised. At the rate maximum at pH 3·8 the ester (124) is hydrolysed 24,000 times more rapidly than acetylsalicyclic acid and 66 times more rapidly than the di-ester (126). The high reactivity of the half-ionised form could result from reaction by way of either of two pathways (see Scheme (XXXII)], differing in which group acts as nucleophile and which as general acid. Kinetically these pathways are equivalent and hence additional information, such as the trapping of an intermediate, is required to distinguish between them. Similar pathways are available for the hydrolysis of the amide (125).

However, what is probably the most striking example occurs in the hydrolysis of *o*-carboxyphenyl β-D-glucopyranoside.[125] This reaction shows

[122] Ingold "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1953, p. 596.
[123] Morawetz and Oreskes, *J. Amer. Chem. Soc.*, 1958, **80**, 2591.
[124] Morawetz and Shafer, *J. Amer. Chem. Soc.*, 1962, **84**, 3783.
[125] Capon, *Tetrahedron Letters*, 1963, 911.

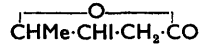
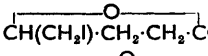
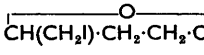


a sigmoid pH–rate profile, indicating a dependence of rate on the concentration of the un-ionised species, and at pH 3·5 the rate is about 10^4 times faster than that for *p*-carboxyphenyl β-D-glucopyranoside. As in the hydrolysis of phthalamic acid, the rate law is consistent with the reactive species being the un-ionised form or with a specific acid-catalysed reaction of the ionised form. In view of the known susceptibility of glycoside hydrolysis to acid catalysis and the lack of reactivity of glucopyranose derivatives to nucleophilic attack at C_1, it seems reasonable to ascribe the high reactivity to general-acid catalysis operating as shown in Scheme (XXXIII).



Addition Reactions.—Neighbouring group participation by a carboxyl group in the addition of halogens to olefinic double bonds has been observed by several workers.[126,127] The addition of iodine in the presence of sodium iodide and sodium hydrogen carbonate is probably the most systematically studied of these reactions, and the results obtained (Table 17) indicate that the formation of γ-iodo-lactone occurs most readily.[127]

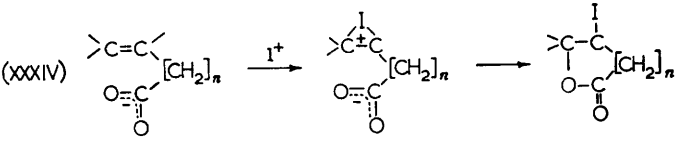
TABLE 17. *Carboxylate participation in the addition of iodine to olefinic double bonds.*[127]

Reactant	Product
$CH_3{\cdot}CH{=}CH{\cdot}CO_2H$	No iodo-lactone
$CH_2{=}CH{\cdot}CH_2{\cdot}CO_2{\cdot}H$	No iodo-lactone
$CH_3{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CO_2H$	
$CH_2{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	
$CH_2{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	

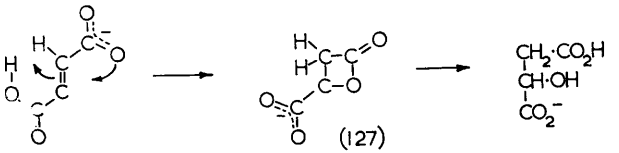
[126] Arnold, de Moura Campos, and Lindsay, *J. Amer. Chem. Soc.*, 1953, **75**, 1044; Arnold and Lindsay, *ibid.*, p. 1048; de Moura Campos, *ibid.*, 1954, **76**, 4480; Tarbell and Bartlett, *ibid.*, 1937, **59**, 407.

[127] van Tamelen and Shamma, *J. Amer. Chem. Soc.*, 1954, **76**, 2315.

The mechanism is probably as shown in Scheme (XXXIV).

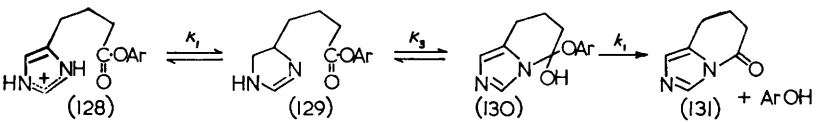


The pH–rate profile for the hydration of fumaric to malic acid is a bell-shaped curve, indicating that the mono-anion is especially reactive. It has been suggested[128] that both the carboxylic acid and carboxylate groups participate, the reaction proceeding through the lactonic acid (127) as shown:



Participation by Imidazole Groups

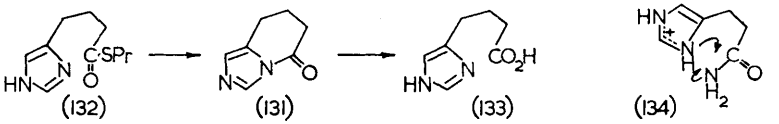
Several examples of neighbouring group participation by an imidazole nucleus in ester and amide hydrolyses have been investigated by Bruice and his co-workers. Interest in these reactions has been stimulated by the likely possibility of participation by an imidazole group of histidine in reactions catalysed by several esterases and proteinases. Aryl esters (129), but not the methyl ester, of 4-4′-imidazolylbutyric acid are hydrolysed at greatly enhanced rates in neutral solution, the rate increase for the *p*-nitrophenyl ester being approximately 3×10^4.[129a] The pH–rate profiles for the hydrolyses of the aryl esters show that the rates are approximately proportional to the concentration of the unprotonated forms of the imidazoles, but they do not follow exactly the expected ionisation curve (as determined for the methyl ester), and the apparent pK_a's vary with the substituents in the aryl residue. Since these substituents would not be expected to influence the true pK_a of the imidazoyl group, these results suggest that there is an additional substituent-dependent equilibrium, and Bruice and Sturtevant have suggested[129a] that this is the formation of the tetrahedral intermediate (130). Kinetic analysis of the reaction series (128)→(131) then shows that $K_{app.} = K_1(K_3 + 1)$. In this mechanism the imidazole group participates by acting as a nucleophile, but a kinetically



[128] Bender and Connors, *J. Amer. Chem. Soc.*, 1962, **84**, 1980.

[129] (*a*) Bruice and Sturtevant, *J. Amer. Chem. Soc.*, 1959, **81**, 2860; (*b*) See Bender, *Chem. Rev.*, 1960, **60**, 78.

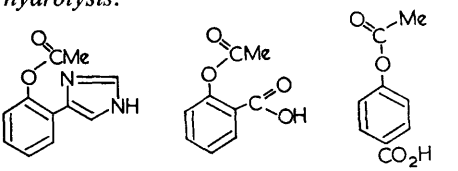
equivalent scheme in which it acts as a general base is formally possible, although unlikely in view of the known tendency of imidazole itself to act as an intermolecular nucleophilic catalyst in the reactions of aryl esters.[129b] In the hydrolysis of the analogous thiol ester (132), however, nucleophilic participation has been demonstrated unequivocally by following the formation and decomposition of the intermediate lactam (131) spectrophotometrically.[130] This ester hydrolyses at a rate 3×10^6 times that expected in the absence of imidazole participation.



The pH–rate profile for the hydrolysis of the amide of 4-4′-imidazolylbutyric acid differs from that for the aryl ester and n-propyl thiol-ester in showing a rate-dependence on the concentration of the protonated form.[129a] This behaviour is analogous to that found in participation by the carboxyl group (see p. 78), and in the amide hydrolysis the imidazole group possibly acts as an intramolecular nucleophilic–electrophilic catalyst [see (134)].

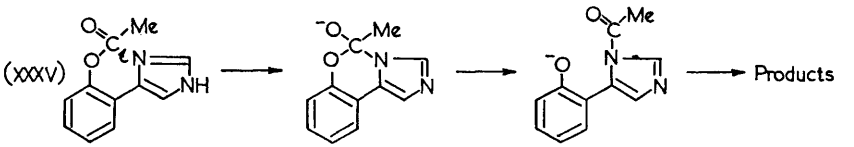
Examples of imidazole participation in ester hydrolysis when the imidazole group is in the phenol portion of the ester are also known. The rate of hydrolysis of 4-(2-acetoxyphenyl)imidazole depends on the concentration of the unprotonated imidazole.[120,131] At pH 6 at 30° the rate of hydrolysis is slightly faster than that for acetylsalicylic acid (Table 18)

TABLE 18. *A comparison of imidazole and carboxyl group participation in ester hydrolysis.*[120]



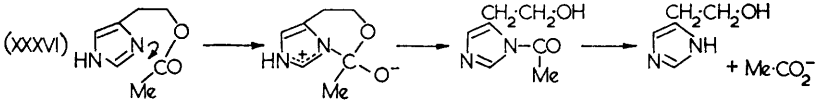
10^4k (min.$^{-1}$) at pH 6 and 30°	15	40	0·05

and the hydrolysis probably involves intramolecular nucleophilic participation as shown in Scheme (XXXV).

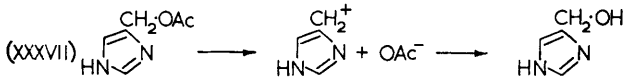


[130] Bruice, *J. Amer. Chem. Soc.*, 1959, **81**, 5444.
[131] Pandit and Bruice, *J. Amer. Chem. Soc.*, 1960, **82**, 3386.

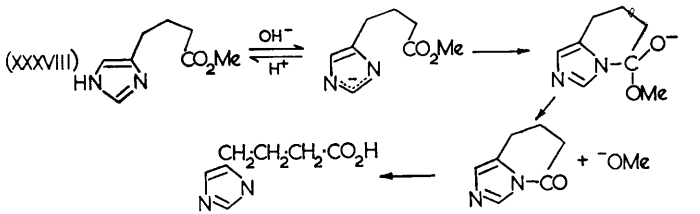
Intramolecular imidazole participation occurs in the hydrolysis of the alkyl ester, 4-(2-acetoxyethyl)imidazole[129a] [see Scheme (XXXVI)]. Comparison of Im-6 participation observed with this ester, and Im-5 participation, which might be expected to occur in the hydrolysis of 4-(acetoxymethyl)-imidazole, is precluded because the latter undergoes hydrolysis with alkyl–oxygen fission[132] [see Scheme (XXXVII)]. Although methyl



4-4′-imidazolylbutyrate apparently does not undergo hydrolysis with

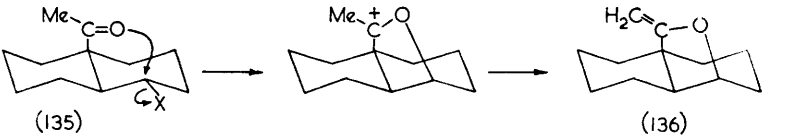


participation of the un-ionised imidazole group, like the phenyl esters, since a plot of $k_{obs.}$ against a_{OH^-} goes through the origin, the second-order rate constant for hydrolysis by OH^- is about 20 times greater than that for methyl butyrate. This may be due to participation by the ionised imidazole group as shown in Scheme (XXXVIII).[129a]



Neighbouring Aldehydo- and Keto-groups

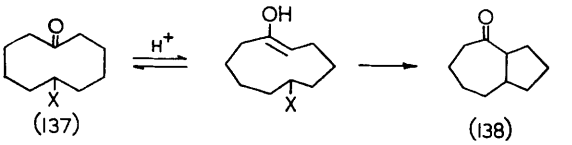
Nucleophilic participation by an aldehydo- or keto-group can occur in several ways. First, by direct displacement by the oxygen, as in the solvolysis of the bromo-ketone (135) which is anchimerically assisted and yields the vinyl ether (136) as one of the products.[133] Alternatively, participation by the enol form may occur, as in the ethanolysis of 6-oxo-cyclodecyl



toluene-*p*-sulphonate (137), which yields a mixture of *cis*- and *trans*-bicyclo[5,3,0]decan-2-one (138).[134] The rate of this reaction depends

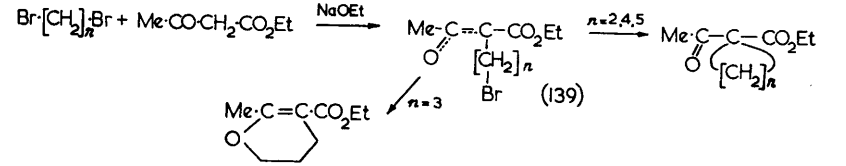
[132] Bruice and Fife, *J. Amer. Chem. Soc.*, 1961, **83**, 1124.
[133] Baddeley, Baylis, Heaton, and Rasburn, *Proc. Chem. Soc.*, 1961, 451.
[134] Goering, Olson, and Espy, *J. Amer. Chem. Soc.*, 1956, **78**, 5371.

partly on the rate of enolisation, and hence the reaction is acid-catalysed.

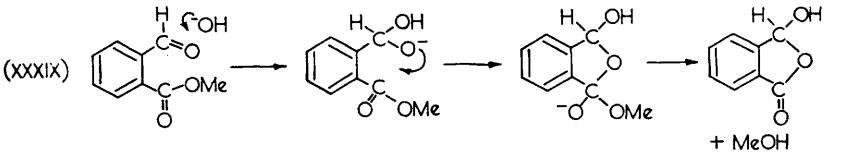


(137) (138)

In the presence of bases ionisation to an ambient enolate ion can occur, and intramolecular displacement by both the carbon and oxygen ends of this ion is possible. The ion (139), formed by reaction of acetoacetic ester with α,ω-dihalides, undergoes cyclisation at carbon, when $n = 2$, 4, or 5, to yield a 3-, 5-, or 6-membered ring, but at oxygen if $n = 3$, when the alternative product of carbon participation would be a four-membered ring.[135]



Participation in a completely different way can occur through the addition products with nucleophiles. The most striking example to date is the hydroxyl-ion catalysed hydrolysis of methyl 2-formylbenzoate which proceeds 10^5 times faster than would be expected from the electronic and steric effects of a formyl substituent.[136] Probably, the mechanism shown in Scheme (XXXIX) is followed.



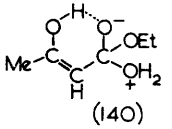
(XXXIX)

The hydrolysis is also catalysed by morpholine, and here the incursion of an intermediate has been demonstrated spectrophotometrically.[136] Similar participation occurs in the hydrolysis of certain methyl substituted *o*-benzoylbenzoates[137] and of dimethylphosphoacetoin.[138]

Participation by the ketone-carbonyl group frequently occurs in reactions at the acid-carbonyl group of keto-acids. Examples are found in the hydrolysis of ethyl acetoacetate, which probably owes its high rate[139] to

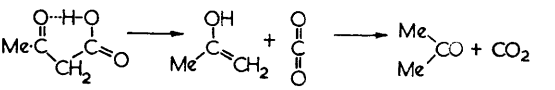
[135] See Perkin, *J.*, 1929, 1347.
[136] Bender and Silver, *J. Amer. Chem. Soc.*, 1962, **84**, 4589.
[137] Newman and Shinzaburo Hishida, *J. Amer. Chem. Soc.*, 1962, **84**, 3582.
[138] Ramirez, Hansen, and Desai, *J. Amer. Chem. Soc.*, 1962, **84**, 4588.
[139] Goodhue and Dunlap, *J. Amer. Chem. Soc.*, 1928, **50**, 1920.

stabilisation of the transition state as shown in (140),[140] and in the decarboxylation of acetoacetic acid in which the ketone group is thought to act as a general base as shown in Scheme (XL).[141]



(140)

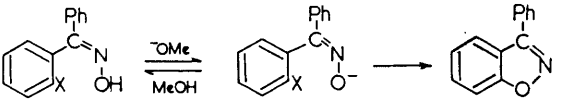
(XL)



Participation by Oxime Groups

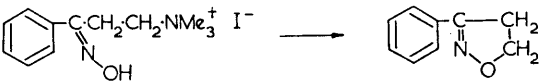
Intramolecular displacement reactions by the ionised oxime group are an important synthetic method for isoxazoles [see Schemes (XLI) and (XLII)].[142] A kinetic investigation of the reactions shown in Scheme (XLII) has been made by Bunnett and Yih.[143]

(XLI)



(X=F, Cl, Br, or I)

(XLII)

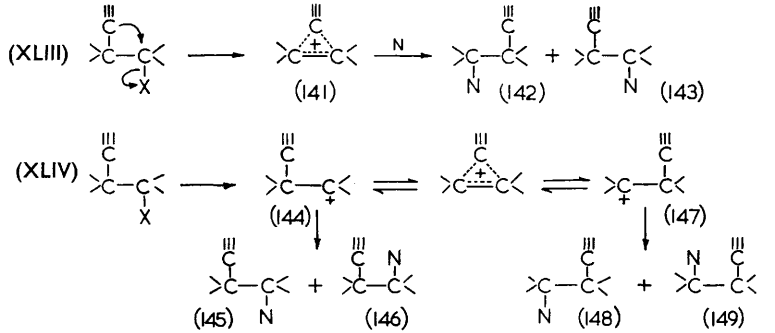


Participation by Neighbouring Carbon

The subject of nucleophilic participation by carbon in reactions occurring at saturated carbon centres is intimately bound up with the roles played by classical and non-classical or bridged carbonium ions.[144] The question to be answered for any reaction in which carbon migrates or is thought to participate is "does ionisation to the bridged ion occur directly [as in Scheme (XLIII)], or is a classical ion formed first, followed by interconversion with another classical ion, the bridged ion, though, possibly being the transition state [as Scheme (XLIV)]?" Direct formation of a non-classical ion would mean that it is of lower free energy than the alternative classical ion, and hence its formation should be associated with an increased rate. Hence reactions of this type which show enhanced rates are frequently written as involving direct ionisation to a bridged ion. The difficulty is, however, to decide what is an enhanced rate and to exclude

[140] Bender, *Chem. Rev.*, 1960, **60**, 70.
[141] See Gould, "Mechanism and Structure in Organic Chemistry," H. Holt and Company, New York, 1959, 346.
[142] See Quilico, Speroni, Behr, and McKee, "Five and Six-Membered Compounds with Nitrogen and Oxygen," Interscience, New York, 1962; Scott, Riordan, and Hegarty, *Tetrahedron Letters*, 1963, 537.
[143] Bunnett and Yih, *J. Amer. Chem. Soc.*, 1961, **83**, 3805.
[144] See Bethell and Gold, *Quart. Rev.*, 1958, **12**, 173.

other causes for it, especially steric acceleration. Product formation by nucleophilic attack on a bridged ion must be stereospecific [*e.g.*, (141)→(142) and (143) only], but nucleophilic attack on classical ions can be non-stereospecific [*e.g.* (144)→(145) and (146); (147)→(148) and (149)].



Neighbouring Aryl Groups.—(a) Ar⁻-*participation.* Participation by neighbouring aryl groups occurs in the solvolysis of the conjugate bases of 2-(*p*-hydroxyphenyl)ethyl bromide (150)[145] and 4-(*p*-hydroxyphenyl)butyl *p*-bromobenzenesulphonate (151).[146] In favourable instances the intermediate dienones (152) and (153) have been isolated, and the formation and decomposition of the dienone (152) has been followed spectrophotometrically.[145] The anchimeric assistance for Ar_1^--3 participation is considerably greater than that for Ar_1^--5 participation (see Table 19). The

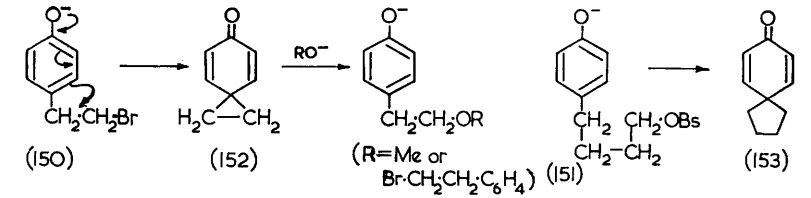


TABLE 19. *A comparison of* Ar_1^--3 *and* Ar_1^--5 *participation.*[145,146]

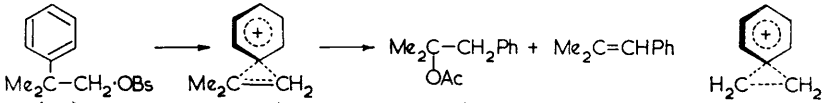
	$^-O{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2Br$	$MeO{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2Br$
Methanolysis 10^3k at 25°	0·86	—
Ethanolysis 10^3k at 25°	1·3	2×10^{-6}
	$^-O{\cdot}C_6H_4{\cdot}[CH_2]_4{\cdot}OBs$	$MeO{\cdot}C_6H_4{\cdot}[CH_2]_4{\cdot}OBs$
Methanolysis 10^5k at 50°	8·9	1·08

analogous six-membered spirodienone is formed much less readily but has been prepared by heating the potassium salt of 5-(*p*-hydroxyphenyl)-pentyl bromide to 170° in t-butyl alcohol.[147]

(b) Ar-3 *participation in reactions at primary carbon centres.* Participation by uncharged aryl rings also occurs but the anchimeric assistance is much

[145] Baird and Winstein, *J. Amer. Chem. Soc.*, 1963, **85**, 567.
[146] Baird and Winstein, *J. Amer. Chem. Soc.*, 1962, **84**, 788.
[147] Dreiding, *Helv. Chim. Acta*, 1957, **40**, 1812.

less. A well investigated example occurs in the acetolysis of 2-methyl-2-phenypropyl (neophyl) *p*-bromobenzenesulphonate (154) which proceeds about 80 times faster than that of isobutyl *p*-bromobenzenesulphonate, to yield 33·4% of the rearranged acetate (156) and 66·3% of the rearranged olefin (157).[148] The rate is increased by electron-releasing substituents in the *p*-position of the phenyl ring and decreased by electron-withdrawing substituents, the rates being correlated by the σ^+ constants and the ρ constant being −2·96.[148] Thus, the rate-determining step involves an electrophilic attack on the aryl ring, the ring acting as a nucleophile to give the phenonium ion (155). The two methyl groups in the neophyl compounds facilitate aryl participation (see p. 109 for a discussion of this



(154) (155) (156) (157) (158)

effect), which occurs much less in the reactions of 2-phenylethyl compounds. The toluene-*p*-sulphonate, for instance, undergoes ethanolysis and acetolysis more slowly than ethyl toluene-*p*-sulphonate,[149] and experiments with the ^{14}C-labelled compound show that little phenyl migration occurs (Table 20).[150] In formolysis, however, the 2-phenylethyl

TABLE 20. *Rates of solvolysis of 2-phenylethyl and ethyl toluene-p-sulphonates at* 75°.[149,150,151]

Solvent	Ethyl toluene-*p*-sulphonate		2-Phenylethyl toluene-*p*-sulphonate		
	k	$\Delta S^{\ddagger}$	k	$\Delta S^{\ddagger}$	% Phenyl migration
EtOH	$2{\cdot}95 \times 10^{-5}$	−17·5	$7{\cdot}08 \times 10^{-6}$	−20·2	0·2
HCO_2H	$1{\cdot}85 \times 10^{-5}$	−16·5	$3{\cdot}94 \times 10^{-5}$	− 9·5	43·3
AcOH	$7{\cdot}7 \times 10^{-7}$	−16·7	$2{\cdot}88 \times 10^{-7}$	−17·3	4·6

compound reacts faster[149] and there is considerable phenyl migration.[150] Direct ionisation to the phenonium ion (158) therefore only occurs in the formolysis reaction, and the ethanolysis and acetolysis probably proceed mainly by the S_N2 mechanism. Unreacted ^{14}C-labelled 2-phenylethyl toluene-*p*-sulphonate from the formolysis reaction is also partly rearranged,[152] and in the presence of ^{35}S-labelled sodium toluene-*p*-sulphonate there is partial incorporation of the label into the rearranged 2-phenylethyl toluene-*p*-sulphonate. This result indicates that the rearrangement probably proceeds partly through an intimate ion-pair and partly through

[148] Heck and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 3432.
[149] (*a*) Winstein, Lindegren, Marshall, and Ingraham, *J. Amer. Chem. Soc.*, 1953, **75**, 147; (*b*) Winstein and Marshall, *J. Amer. Chem. Soc.*, 1952, **74**, 1120.
[150] Lee, Slater, and Spinks, *Canad. J. Chem.*, 1957, **35**, 1417; see also Saunders, Asperger, Edison, *J. Amer. Chem. Soc.*, 1958, **80**, 2421.
[151] Winstein and Heck, *J. Amer. Chem. Soc.*, 1956, **78**, 4801; see also Cram and Singer, *ibid.*, 1963, **85**, 1075.
[152] Lee, Tkachuk, and Slater, *Tetrahedron*, 1959, **7**, 206.

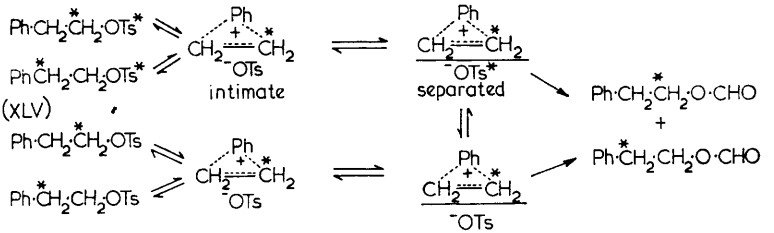
solvent-separated ion-pairs or free ions [see Scheme (XLV)]. The entropy of activation for the formolysis of 2-phenylethyl toluene-*p*-sulphonate (Table 20) is more positive than that for acetolysis and ethanolysis, and also than that for the solvolysis of the ethyl compound,[152] there being less loss of randomness on going to the transition state for the intramolecular than for the intermolecular displacements.

Further β-phenyl substitution in ethyl arenesulphonates and halides results in increased solvolysis rates (see Table 21).[13,14] This probably

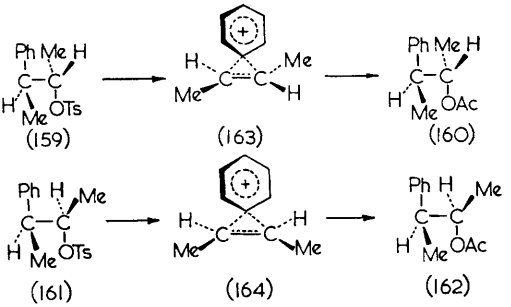
TABLE 21. *The effect of β-phenyl substituents on the rate of acetolysis of ethyl toluene-*p*-sulphonate at 75°.*

	$CH_3{\cdot}CH_2{\cdot}OTs$	$PhCH_2{\cdot}CH_2{\cdot}OTs$	$Ph_2CH{\cdot}CH_2{\cdot}OTs$	$Ph_3C{\cdot}CH_2{\cdot}OTs$
10^7k (sec.$^{-1}$)	7·7	2·9	27	3200
Ref.	149*b*	23	14	14

results from both an increased stability of the bridge ion (*i.e.*, decreased transition-state free-energy) and from release of steric strain on going to this ion (*i.e.*, increased initial-state free-energy).



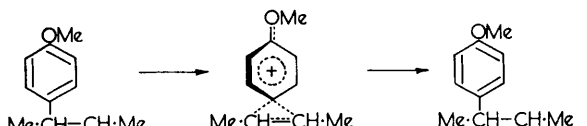
(c) Ar-3 *participation in reactions at secondary carbon centres.* Solvolysis studies on secondary arylalkyl arenesulphonates enable the steric course of reactions, for which aryl participation is suspected, to be studied. The first proposal for the incursion of a phenonium ion came, in fact, from such studies by Cram on the acetolysis of optically active *erythro*-1-methyl-2-phenylpropyl toluene-*p*-sulphonate (159), which yields the optically active *erythro*-acetate (160) with about 94% retention of configuration, and of the optically active *threo*-isomer (161), which yields



almost racemic *threo*-acetate (162).[153] These results may be explained by postulating the incursion of the intermediate phenonium ions (163) and (164),[153] but are, however, also consistent with a rapidly equilibrating pair of classical ions [*e.g.*, (165a) and (165b)], if their rate of interconversion were considerably faster than the rate of rotation about the C_2–C_3 bond, and

(165a) (165b)

if attack from the phenyl sides of the ions were prevented sterically. It has been argued[154] that this might be so by analogy with the results obtained in the acetolysis of 1,2,2-triphenylethyl toluene-*p*-sulphonate, which almost certainly reacts through a pair of classical ions (see below p. 90) and which also yields acetate with some retention of configuration. The amount of retention observed[155] (55%) is, however, considerably less than that found with the 1-methyl-2-phenylpropyl compounds. The rates of acetolysis of the 1-methyl-2-phenylpropyl *p*-bromobenzenesulphonates are less than that of 1-methylpropyl *p*-bromobenzenesulphonate although, when allowance is made for the rate decelerating effect of the phenyl group, they are probably greater than would be expected if the reactions involved a direct ionisation to classical ions.[14] The balance of evidence would therefore seem to support weakly anchimerically assisted ionisations to the phenonium ions (163) and (164). The acetolysis of one of the 2-(*p*-methoxyphenyl)-1-methylpropyl toluene-*p*-sulphonates (166a) proceeds about 45 times faster than 1-methylpropyl toluene-*p*-sulphonate, and hence almost certainly involves ionisation to the *p*-methoxyphenonium ion (166b).[156]



(166a) (166b)

In a very interesting investigation Collins and Bonner showed that the rate constants for the equilibration of the carbon-14 labels in 1,2,2-triphenyl[1-^{14}C]ethyl acetate (167) and 1-[^{14}C]phenyl-2,2-diphenylethyl acetate (168) to the randomly labelled mixtures of 50% (169) and 50% (170) and of 66·7% (172) and 33·3% (171) respectively, and the rate constant for acetate exchange of 1,2,2-triphenylethyl [*carbonyl*-^{14}C]acetate (173) in acetic acid in the presence of toluene-*p*-sulphonic acid are

[153] Cram, *J. Amer. Chem. Soc.*, 1949, **71**, 3863.
[154] Brown in "The Transition State," *Chem. Soc. Special Publ.*, No. 16, 1962, p. 152.
[155] Collins, Bonner, and Lester, *J. Amer. Chem. Soc.*, 1959, **81**, 466.
[156] Winstein, Brown, Schreiber, and Schlesinger, *J. Amer. Chem. Soc.*, 1952, **74**, 1140.

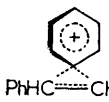
identical.[157] Hence, "statistical equilibration of each label occurs each time an acetoxyl group is removed from the discretely labelled starting material".

$$\underset{(167)}{Ph_2CH{-}C^*HPh{\cdot}OAc} \rightarrow \underset{(169)\ 50\%}{Ph_2CH{-}C^*HPh{\cdot}OAc} + \underset{(170)\ 50\%}{Ph_2C^*H{-}CHPh{\cdot}OAc}$$

$$\underset{(168)}{Ph_2CH{-}CHPh^*{\cdot}OAc} \rightarrow \underset{(171)\ 33.3\%}{Ph_2CH{-}CHPh^*{\cdot}OAc} + \underset{(172)\ 66.7\%}{Ph_2{}^*CH{-}CHPh{\cdot}OAc}$$

$$\underset{(173)}{Ph_2CH{-}CHPh{\cdot}OAc^*} \rightarrow Ph_2CH{-}CHPh{\cdot}OAc$$

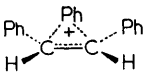
The reaction cannot therefore proceed by way of the phenonium ion (174) since this would yield a 50:50 mixture of the phenyl-labelled acetates.



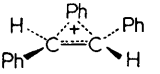
(174)

$$\underset{(175)}{Ph_2CH{-}\overset{+}{C}HPh} \rightleftharpoons \underset{(176)}{Ph\overset{+}{C}H{-}CHPh_2}$$

However, incursion of a rapidly equilibrating pair of classical ions (175) and (176) would allow complete randomisation of each label before the product-forming step. A similar mechanism also probably operates in the acetolysis of 1,2,2-triphenylethyl toluene-*p*-sulphonate,[158] for which the chain-labelled compound yields 40% and the ring-labelled 47% of the rearranged acetates. These results were shown to be mutually consistent if the reaction proceeded through a pair of rapidly equilibrating classical ions in which either phenyl group had an equal chance of migrating. The results are only consistent with the incursion of non-classical ions in the unlikely event that the acetolysis were preceded by a rapid equilibration of the toluene-*p*-sulphonates by internal return involving the *cis*- and the *trans*-ion (177) and (178) equally. This elegant demonstration of the



(177)



(178)

non-incursion of bridged ions should, however, not be generalised to other systems; undoubtedly the high degree of phenyl substitution strongly favours the formation of classical ions.

(d) *Participation by more remote aryl rings.* The rates of acetolysis and formolysis of 3-phenylpropyl, 4-phenylbutyl, and 5-phenylpentyl *p*-bromobenzenesulphonate are similar to those of propyl and butyl *p*-bromobenzenesulphonate, indicating that, for these reactions, Ar_1-4, Ar_1-5, and Ar_1-6 participation are not very important.[159] In an attempt to observe such participation Winstein studied the effect of introducing methoxyl substituents into the phenyl ring (Table 22).[159] This would be expected

[157] Bonner and Collins, *J. Amer. Chem. Soc.*, 1955, **77**, 99.
[158] Collins and Bonner, *J. Amer. Chem. Soc.*, 1955, **77**, 92.
[159] Heck and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 3105.

TABLE 22. *The effects of methoxyl substituents on the rates of solvolysis of some ω-phenylalkyl* p-*bromobenzenesulphonates.*[159]

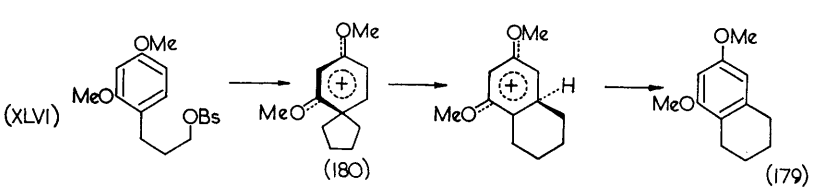
Solvent	Relative rates Ph·[CH_2]$_2$·OBs			Relative rates Ph·[CH_2]$_3$·OBs		
	H	4-MeO	2,4-$(MeO)_2$	H	4-MeO	2,4-$(MeO)_2$
AcOH	1·00	81	1590	1·00	1·07	3·69*
HCO_2H	1·00	53	672			

	Ph·[CH_2]$_4$·OBs			Ph·[CH_2]$_5$·OBs	
	H	4-MeO	2,4-$(MeO)_2$	H	2,4-$(MeO)_2$
AcOH	1·00	1·31	4·32	1·00	1·05
HCO_2H	1·00	1·77	9·91	1·00	1·07

* Reaction involves *o*-MeO-6 participation.

to increase the rate of the aryl-assisted reaction by increasing the nucleophilicity of the ring, but not greatly to affect the rate of the bimolecular reaction with solvent. It is seen that Ar_1-3 participation occurs most readily, and then Ar_1-5 participation, but that Ar_1-4 and Ar_1-6 participation are unimportant.

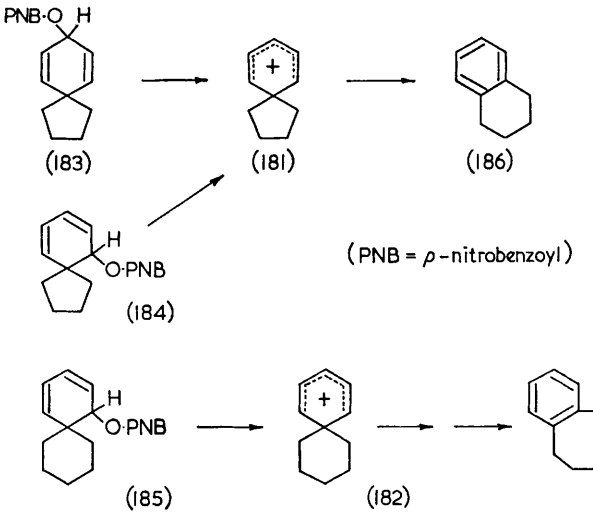
The products of formolysis of the 2,4-dimethoxyphenyl, *p*-methoxyphenyl, and unsubstituted 4-phenylbutyl *p*-bromobenzenesulphonate contain 76%, 51%, and 16·5% of the corresponding tetralins [*e.g.*, (179)], which are thought to arise from the spirocarbonium ion [*e.g.*, (180)] by ring-expansion as shown in Scheme (XLVI).[159] The spirocarbonium ion



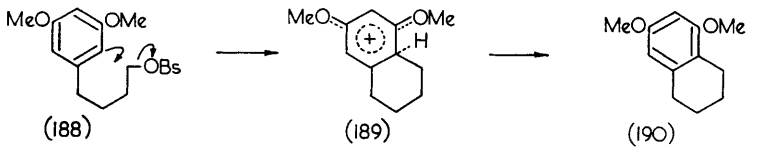
(181) from 4-phenylbutyl *p*-bromobenzenesulphonate and the corresponding six-membered-ring ion (182) have also been generated by solvolysis of the *p*-nitrobenzoates (183), (184), and (185) in aqueous acetone.[160] The five-membered-ring ion (181) rearranges exclusively to the decalin (186) but the six-membered-ring ion (182) yields only 40% of the benzocycloheptene (187), the expansion of a five-membered to a six-membered ring occurring much more readily than that of a six-membered to a seven-membered one.

5,7-Dimethoxytetralin also results from the formolysis of 4-(3,5-dimethoxyphenyl)butyl *p*-bromobenzenesulphonate (188) which proceeds about 6 times faster than that of the 4-phenylbutyl compound.[161] These results have been attributed to intramolecular nucleophilic attack by the 2-position of the aryl ring (Ar_2-6 participation) [see (188)→(190)]. Similar

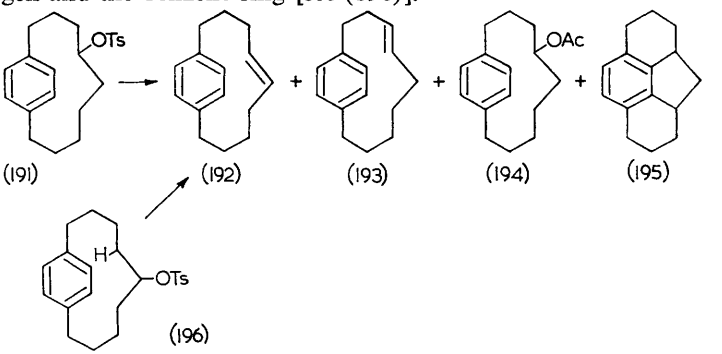
[160] Friedrich and Winstein, *Tetrahedron Letters*, 1962, 475.
[161] Heck and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 3114.



experiments with the analogous ω-aryl-propyl and -pentyl compounds show that Ar_2-5 and Ar_2-7 participation are unimportant.[161]

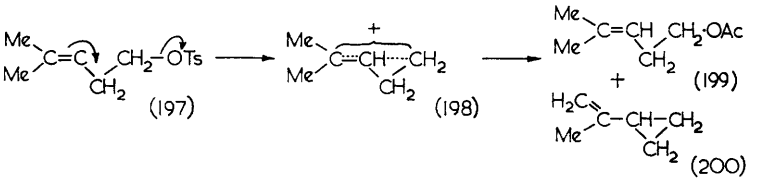


An interesting example of Ar_2-6 participation occurs in the acetolysis of [9]paracyclophen-4-yl toluene-*p*-sulphonate (191) which has a high rate and yields, besides the olefins (192) and (193), the tricyclic hydrocarbon (195) and the acetate (194) with retention of configuration.[162] The analogous 5-toluene-*p*-sulphonate also yields these products but in different proportions and probably reacts with simultaneous participation of hydrogen and the benzene ring [see (196)].

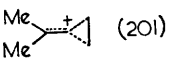


[162] Cram and Goldstein, *J. Amer. Chem. Soc.*, 1963, **85**, 1063.

Neighbouring Olefinic Double Bonds.—Acetolysis of 4-methylpent-3-enyl toluene-*p*-sulphonate (197) proceeds 1200 times faster than that of ethyl toluene-*p*-sulphonate and yields 2-cyclopropylpropene (200) and 4-methylpent-3-enyl acetate (199).[163] The reaction therefore proceeds with participation by the double bond, the homoallylic cation (198) being an intermediate. The entropy of activation, −7·8 cal. deg.$^{-1}$, also supports this interpretation, being similar to that found for reactions which involve phenyl participation (see p. 88). The ion (198) has also been considered



as an intermediate in the reaction of 4-methylpent-3-enyl chloride with phenol,[164] but, since chloride which is specifically deuterated in the 1-position yields a product in which the deuterium is scrambled, the symmetrical structure (201) is probably a better representation. The two



terminal methyl groups must lend considerable stability to this ion, since the analogous allylcarbinyl chloride and benzenesulphonate do not undergo solvolyses at enhanced rates.

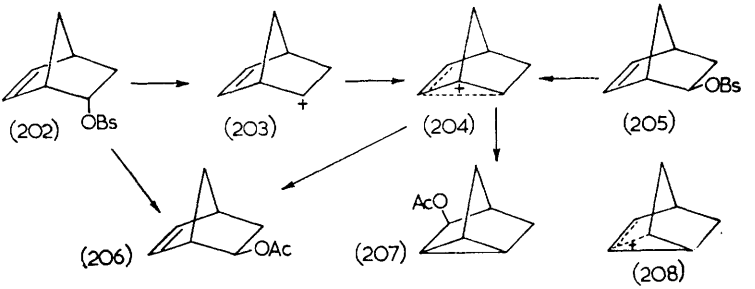
Among the first reactions in which homoallylic participation was thought to occur are those of cholester-3β-yl[165] and *exo*-norborn-5-en-2-yl[166,167] derivatives (see Table 23). With these compounds, however, the amount of anchimeric assistance which results is more difficult to assess. Acetolysis of both *endo*- and *exo*-norborn-5-en-2-yl *p*-bromobenzenesulphonates, (202) and (205), yields 3-acetoxytricyclo[2,2,1,0]heptane (207)[167] and *exo*-norborn-5-en-2-yl acetate (206), slightly more of the latter resulting from the *endo*-isomer, probably from a direct displacement reaction.[168] The *exo*-isomer reacts about 8000 times more rapidly,[169] a result which it is difficult to explain without invoking anchimeric assistance due to the formation of the bridged ion (204), but it reacts more slowly than the analogous saturated compound, *exo*-norborn-2-yl *p*-bromobenzenesulphon-

[163] Rogan, *J. Org. Chem.*, 1962, **27**, 3910.
[164] Corbin, Hart, and Wagner, *J. Amer. Chem. Soc.*, 1962, **84**, 1741.
[165] See Fieser and Fieser, "Steroids," Reinhold, New York, 1959, p. 314.
[166] Roberts, Bennett, and Armstrong, *J. Amer. Chem. Soc.*, 1950, **72**, 3329.
[167] Winstein, Walborsky, and Schreiber, *J. Amer. Chem. Soc.*, 1950, **72**, 5795.
[168] Roberts, Lee, and Saunders, *J. Amer. Chem. Soc.*, 1955, **77**, 3034.
[169] Unpublished work of H. J. Schmid and K. C. Schreiber reported by Winstein and Shatavsky, *J. Amer. Chem. Soc.*, 1956, **78**, 595.

TABLE 23. *The acetolysis of norborn-5-en-2-yl and cholester-3-yl derivatives.*

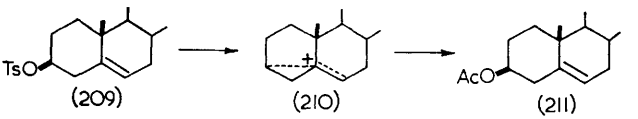
	exo-norborn-5-en-2-yl *p*-bromobenzenesulphonate (205)	*endo*-norborn-5-en-2-yl *p*-bromobenzenesulphonate (202)	*exo*-norborn-2-yl *p*-bromobenzene-sulphonate	*endo*-norborn-2-yl *p*-bromobenzene-sulphonate
k at 25° (sec.$^{-1}$)	$4{\cdot}5 \times 10^{-5}$ (ref. 169)	$5{\cdot}7 \times 10^{-9}$ (ref. 169)	$8{\cdot}82 \times 10^{-5}$ (ref. 170)	$2{\cdot}5 \times 10^{-7}$ (ref. 170)
Product	3-acetoxytricyclo[2,2,1,0]heptane and *exo*-norborn-5-en-2-yl acetate (ref. 167, 168)		*exo*-norborn-2-yl acetate (188, 189)	
	cholester-3β-yl toluene-*p*-sulphonate (209)	cholester-3α-yl toluene-*p*-sulphonate	cholestan-3β-yl toluene-*p*-sulphonate	cholestan-3α-yl toluene-*p*-sulphonate
k at 50° (sec.$^{-1}$)	$1{\cdot}32 \times 10^{-4}$ (ref. 171[a])	$2{\cdot}55 \times 10^{-5}$ (ref. 173)	$1{\cdot}1 \times 10^{-6}$ (ref. 171[b])	$7{\cdot}3 \times 10^{-6}$ (ref. 171[b])
	cholester-3-β-yl acetate (ref. 172)	cholesta-2,5-diene (ref. 173)	—	—

ate.[170] This is because acetolysis of the latter is itself considerably assisted through formation of the bridged ion (233) (see p. 98). The acetolysis of the



endo-isomer probably proceeds with ionisation to the classical ion (203) followed by rearrangement to the bridged ion (204), since rearranged acetate is formed.[167] Acetolysis of both the *endo*- and *exo*-*p*-bromobenzenesulphonates labelled at C-2 and C-3 with carbon-14 yields *exo*-acetate which has lost about one third of the label at these positions, and formolysis of the *exo*-isomer results in about 50% loss.[168] These results were explained as resulting from rearrangement of ion (204) to its enantiomorph (208), but since the exact locations of the label in the products were not determined the occurrence of hydride-ion shifts, as well, like those found in the reactions of *exo*-norbornyl compounds (see p. 99) cannot be excluded.

Evidence for participation by the double bond in the acetolysis of cholester-3β-yl toluene-*p*-sulphonate [see (209)→(211)] is provided by the increased rate,[171a] compared with that for cholester-3β-yl toluene-*p*-sulphonate,[171b] and the product,[172] cholester-3β-yl acetate, which is formed with retention of configuration (see Table 23). The rate is, however, only about five times greater than that for cholester-3α-yl toluene-*p*-sulphonate which undergoes a particularly facile elimination of the axially disposed toluene-*p*-sulphonate and hydrogen groups at C-2 and C-3 to yield cholesta-2,5-diene.[173] Solvolyses of cholester-3β-yl compounds in buffered media frequently yield derivatives of 3,5-cyclocholestan-6β-ol.[165]

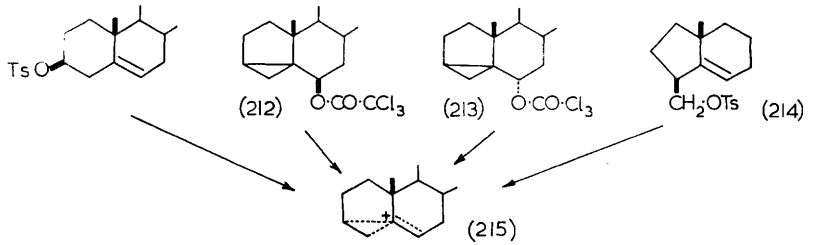


Thus, methanolysis of cholester-3β-yl toluene-*p*-sulphonate in the presence of potassium acetate yields 90% of the methyl ether of 3,5-cyclocholestan-6β-ol and 10% of that of cholester-3β-ol. The same mixture is obtained

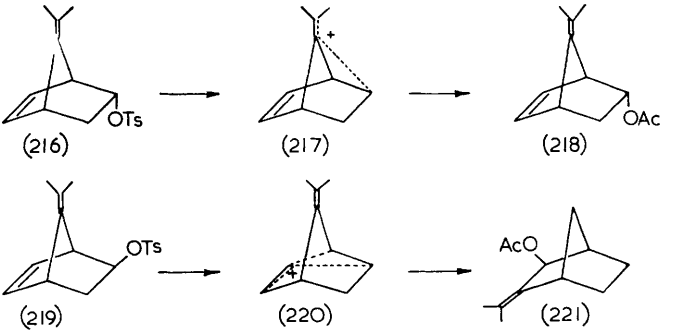
[170] Winstein, Morse, Grunwald, Jones, Corse, Trifan, and Marshall, *J. Amer. Chem. Soc.*, 1952, **74**, 1127.
[171] (*a*) Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; (*b*) Winstein, personal communication to Shoppee and Johnston, *J.*, 1961, 3265.
[172] Shoppee and Summers, *J.*, 1952, 3361.
[173] Shoppee and Williams, *J.*, 1955, 686.

from 3,5-cyclocholestan-6α- and -6β-yl trichloroacetate (213) and (212),[174] and a similar mixture of the corresponding alcohols is obtained from the hydrolysis of the toluene-*p*-sulphonate of 3β-hydroxymethyl-A-norcholest-5-ene (214).[175] These four compounds must therefore react by way of a rapidly equilibrating set of ions or through a symmetrical ion (215). The 3,5-cyclocholestanyl chlorides undergo solvolysis 10^7—10^8 times faster than cholester-3β-yl chloride, owing to their higher initial-state free-energies.[176]

A pair of structurally related homoallylic ions which are not interconverted are those formed in the acetolyses of *exo*- and *endo*-7-isopropylidenenorborn-5-en-2-yl toluene-*p*-sulphonate (219) and (216).[177] These



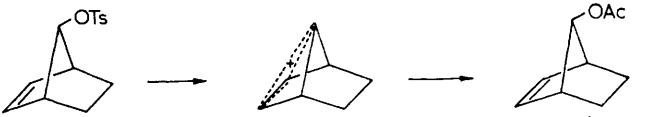
reactions are anchimercially assisted and yield different products, (221) and (218). Hence, ions (220) and (217), formed by participation of the 5,6- and 7,8-double bonds, respectively, are completely independent.



A striking example of homoallylic participation is found in the acetolysis of *anti*-norborn-2-en-7-yl toluene-*p*-sulphonate (222)[178] which proceeds 10^{11} times faster than that of the analogous saturated compound, norborn-7-yl toluene-*p*-sulphonate.[179] The π-electron cloud of the double bond in this compound is particularly well placed to interact with the developing

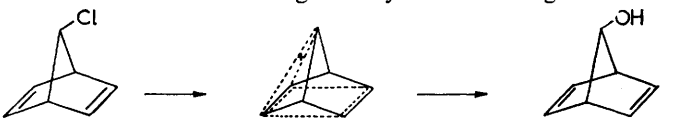
[174] Kosower and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 4347.
[175] Whitham, *Proc. Chem. Soc.*, 1961, 422.
[176] Winstein and Kosower, *J. Amer. Chem. Soc.*, 1959, **81**, 4399.
[177] De Puy, Ogawa, and McDaniel, *J. Amer. Chem. Soc.*, 1961, **83**, 1668.
[178] Winstein, Shatavsky, Norton, and Woodward, *J. Amer. Chem. Soc.*, 1955, **77**, 4183; see also Brown and Bell, *ibid.*, 1963, **85**, 2324; Winstein, Lewin, and Pande, *ibid.*, 1963 **85**, 2324.
[179] Winstein and Shatavsky, *J. Amer. Chem. Soc.*, 1956, **78**, 592; Winstein and Stafford, *ibid.*, 1957, **79**, 505.

carbonium ion at position 7 to yield the ion (223), the intervention of which is also indicated by the reaction product, *anti*-norborn-2-en-7-yl acetate (224), obtained with retention of configuration.[178] Norbornadien-7-yl



(222) (223) (224)

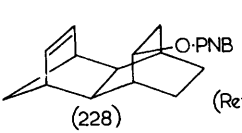
derivatives undergo solvolysis even more readily than *anti*-norborn-2-en-7-yl ones, the hydrolysis of the chloride (225) in aqueous acetone to yield norborndien-7-ol (227) being faster by a factor of about 750.[180] The intermediate carbonium ion, written as (226), forms a stable fluoroborate whose structure has been investigated by nuclear magnetic resonance



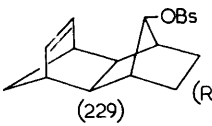
(225) (226) (227)

spectroscopy.[181] The results obtained support an unsymmetrical non-classical structure, the lack of symmetry possibly resulting from the compound being an ion-pair.

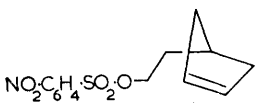
Participation by more remote double bonds is also possible and has been shown to occur in the solvolyses of compounds (228)—(232).[182–187]



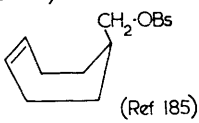
(228) (Ref. 182)



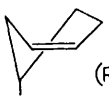
(229) (Ref. 183)



(230) (Ref. 184)



(231) (Ref 185)

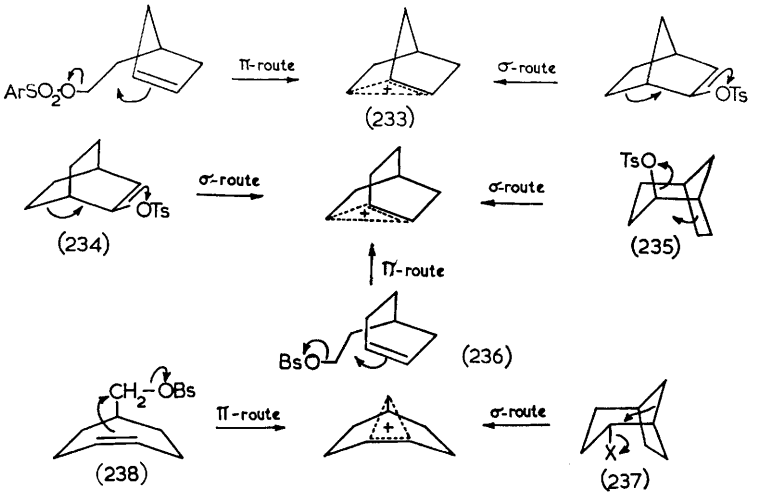


(232) CH_2CH_2OBs (Ref. 186)

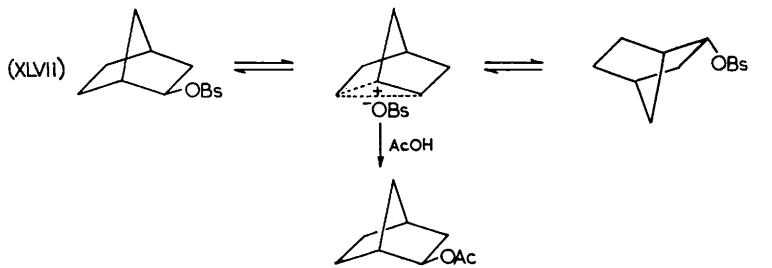
2-(Cyclopent-3-enyl)ethyl *p*-nitrobenzenesulphonate, for example, undergoes acetolysis 95 times faster than the analogous saturated compound, and yields *exo*-norbornyl acetate.[184] It is difficult to see any explanation of this result, other than that the reaction is anchimerically assisted through formation of a bridged ion as (233). This ion has also been postulated as an

[180] Winstein and Ordronneau, *J. Amer. Chem. Soc.*, 1960, **82**, 2084.
[181] Story and Saunders, *J. Amer. Chem. Soc.*, 1962, **84**, 4876; Story, Snyder, Douglass, Anderson, and Kornegay, *ibid.*, 1963, **85**, 3680.
[182] Bruck, Thompson, and Winstein, *Chem. and Ind.*, 1960, 590.
[183] Winstein and Hansen, *Tetrahedron Letters*, 1960, No. 25, 4.
[184] Lawton, *J. Amer. Chem. Soc.*, 1961, **83**, 2399; Bartlett and Bank, *ibid.*, p. 2591.
[185] Le Ny, *Compt. rend.*, 1960, **251**, 1526.
[186] Winstein and Carter, *J. Amer. Chem. Soc.*, 1961, **83**, 4485.
[187] See also Bartlett, *Annalen*, 1962, **653**, 45; Allred and Schreiber, *Tetrahedron Letters*, 1963, 949

intermediate in the acetolysis of *exo*-norbornyl *p*-bromobenzenesulphonate,[188] which proceeds 350 times faster than that of its *endo*-isomer[189] and which yields the *exo*-acetate. Winstein has designated these two routes to the same bridged ion, the π-route and σ-route, respectively.[186] The bicyclo[2,2,2]oct-2-yl (234), *trans*-bicyclo[3,2,1]oct-2-yl (235), and 2-(cyclohex-4-enyl)ethyl (236) systems, and the *cis*-bicyclo[3,2,1]oct-2-yl (237) and cycloheptyl-4-enylmethyl (238) systems are similarly related.[186]

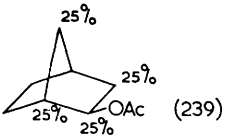


Additional information about the mechanism of the acetolysis of *exo*-norbornyl *p*-bromobenzenesulphonate comes from an investigation[188] using the optically active compound, which yields racemic acetate, as would be expected if the symmetrical ion (233) were an intermediate. The rate of loss of optical activity is however about 3 times faster than the rate of formation of *p*-bromobenzenesulphonic acid. Racemisation of the *p*-bromobenzenesulphonate, probably by ion-pair return, is therefore occurring concurrently with the acetolysis [see Scheme (XLVII)]. Hydride-ion shifts also occur, since the product obtained from the *p*-bromobenzenesulphonate, labelled specifically in the 2- and 3-positions with

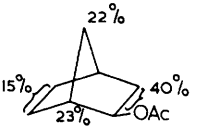


[188] Winstein and Trifan, *J. Amer. Chem. Soc.*, 1952, **74**, 1154.
[189] Winstein and Trifan, *J. Amer. Chem. Soc.*, 1952, **74**, 1147.

carbon-14, contains radioactivity in the 1-, 2-, 3-, 5-, 6-, and 7-positions as shown in (240), whereas in the absence of hydride shifts the ion (233) would be expected to yield acetate labelled only in the 1-, 2-, 3-, and 7-positions as (239).[190]

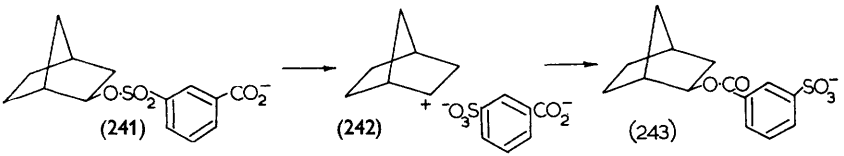


(239)



(240)

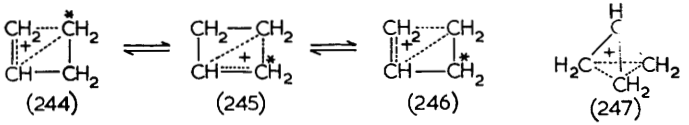
A very elegant experiment by Corey and his co-workers supports the formation of the symmetrical ion (233) as the initially formed intermediate in the solvolyses of *exo*-norbornyl arenesulphonates.[191] The optically active compound (241) with a nucleophilic *meta*-carboxylate-ion group was used, so that the product, the carboxylic ester (243), would be formed with only the slightest molecular movement after ionisation. Hence, if an initially formed unsymmetrical intermediate [*e.g.*, (242)] of an appreciable lifetime were formed it should react to yield active product, but the product was, in fact, wholly racemic.



Neighbouring Small Rings.—The solvolyses of cyclopropylmethyl chloride and benzenesulphonate proceed at high rates for primary compounds,[192,193] the ethanolysis of the benzenesulphonate, for instance, proceeding 500 times faster than that of ethyl benzenesulphonate.[193] The acetolysis of the chloride yields cyclopropylmethyl and cyclobutyl acetate in the ratio 2·6:1, a small amount of but-3-enyl acetate, and a 1·7:1 mixture of cyclobutyl and but-3-enyl chloride, which do not undergo acetolysis under the conditions used and could not, therefore, have been precursors of the corresponding acetates.[192] Cyclobutyl toluene-*p*-sulphonate behaves similarly, yielding 65% of cyclopropylmethyl acetate, 22% of cyclobutyl acetate, and 13% of but-3-enyl toluene-*p*-sulphonate.[194] An experiment with specifically deuterated cyclopropylmethyl chloride indicated considerable skeletal rearrangement in the cyclopropylmethyl chloride, isolated from a partly solvolysed reaction mixture.[195] These results suggest that ionisation of the cyclopropylmethyl and cyclobutyl compounds yield the same ion, or readily interconvertible ions, which may either react with solvent or may re-form chloride or toluene-*p*-sulphonate

[190] Roberts, Lee, and Saunders, *J. Amer. Chem. Soc.*, 1954, **76**, 4501.
[191] Corey, Casanova, Vatakencherry, and Winter, *J. Amer. Chem. Soc.*, 1963, **85**, 169.
[192] Roberts and Mazur, *J. Amer. Chem. Soc.*, 1951, **73**, 2509.
[193] Bergstrom and Siegel, *J. Amer. Chem. Soc.*, 1952, **74**, 145.
[194] Roberts and Chambers, *J. Amer. Chem. Soc.*, 1951, **73**, 5034.
[195] Caserio, Graham, and Roberts, *Tetrahedron*, 1960, **11**, 171.

by ion-pair return. It is more difficult, however, to decide whether these ions are classical or non-classical. Roberts and his co-workers favoured[195] direct ionisation to one of the non-classical ions (244), (245), and (246), which undergo a rapid but not instantaneous equilibration, this interpretation being preferred to one which involves the symmetrical ion (247)

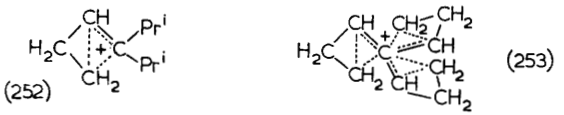


because in certain non-solvolytic reactions there is incomplete equilibration of the methylene groups. This explanation, however, has been rendered unlikely by the results of Hart *et al.*[196] who showed that each replacement of an isopropyl group by a cyclopropyl group in the series of compounds (248)—(251) (Table 24) produced a similar increase in the rate of solvolysis.

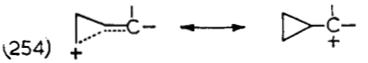
TABLE 24. *The effect of cyclopropyl groups on the rates of solvolysis of tertiary-alkyl* p*-nitrobenzoates.*[196]

	Pr^i_3CX (248)	$C_3H_5 \cdot CPr^i_2 \cdot X$ (249)	$(C_3H_5)_2 \cdot CPr^i \cdot X$ (250)	$(C_3H_5)_3CX$ (251)
Relative rate (X = *p*-nitrobenzoate)	1	240	23,500	23,500 × 1080

Hence, if the increased rate produced by one cyclopropyl group were due to stabilisation of the intermediate ion by non-classical resonance, as implied by structure (252), the ion derived from the tri(cyclopropyl)methyl compound would have to have the unlikely structure (253).* In the Reviewer's opinion, a more likely explanation is that of Gould,[197] that there is



a rapidly interconvertible set of classical ions, stabilised by the direct field effects of the electrons in the bent bonds which make up these small rings,[198] or that of Hart *et al.*[196] that the ions are stabilised by hyperconjugative electron-release as expressed by structures (254)—(255). Both these explanations are consistent with the cumulative effects of successive insertions of cyclopropyl groups (Table 24) and account for the very high reactivity of the tri(cyclopropyl)methyl compound. The tri(cyclopropyl)methyl car-



*The opposite view has recently been taken as to the likelihood of this structure, see Breslow in "Molecular Rearrangements," ed. de Mayo, Interscience, New York, 1963, p. 270.

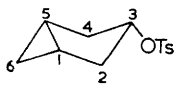
[196] Hart and Sandri, *J. Amer. Chem. Soc.*, 1959, **81**, 320; Hart and Law, *ibid.*, 1962, **84**, 2462.

[197] Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, New York, 1959, p. 588.

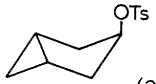
[198] Coulson and Goodwin, *J.*, 1962, 2851; 1963, 3161.

bonium ion is stable in concentrated sulphuric acid solutions,[199] and it is to be hoped that investigations on these solutions will provide more definite evidence on the mechanism by which cyclopropyl groups stabilise carbonium ions.

Another reaction in which participation by a cyclopropyl ring has been considered to occur is the acetolysis of *cis*-bicyclo[3,1,0]hex-3-yl toluene-*p*-sulphonate (256), which proceeds at a slightly enhanced rate, shows special salt effects, and yields the *cis*-acetate with retention of configuration.[200a] The *trans*-toluene-*p*-sulphonate (257) reacts somewhat more slowly, shows no special salt effect and yields a mixture of olefin and *cis*-acetate formed with inversion of configuration. When toluene-*p*-sulphonates deuterated at position 3 are used, acetate obtained from the *cis*-isomer



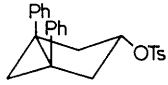
(256)



(257)

has deuterium equally distributed at positions 1, 3, and 5, but in that from the *trans*-isomer there is little redistribution. These results led Winstein and Sonnenberg[200a] to suggest that the solvolysis of the *cis*-isomer proceeded by way of the symmetrical trishomocyclopropenyl cation (258a) related to the cyclopropenyl cation by the interpolation of a CH_2 group between the CH groups on all three sides of the molecule. Some doubt has, however, been thrown on this interpretation by the observation of Corey and Hisashi Uda[200b] that the 1,5-diphenyl substituted compound (258b) does not react with an increased rate. Phenyl substitution stabilises the

(258a)



(258b)

cyclopropenyl cation[200c] and, therefore, would presumably be expected to stabilise a trishomocyclopropenyl cation. Hence, if this ion were the initially formed intermediate, phenyl substitution should cause an increased rate. Corey, therefore, prefers a mechanism involving a rapidly equilibrating set of isomeric ions (258c), in which there is a weak interaction between the vacant orbital at position 3 and the loose electrons of the three-membered ring. It is clear, though, that more work on this system is required.

(258c)

[199] Deno, Richey, Liu, Hodge, Houser, and Wisotsky, *J. Amer. Chem. Soc.*, 1962, **84**, 2016.

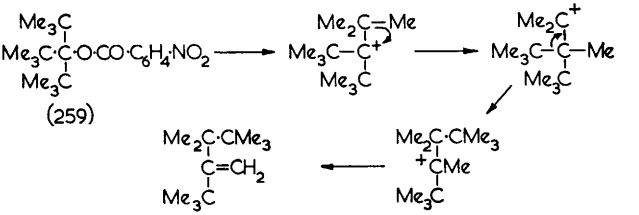
[200] (*a*) Winstein and Sonnenberg, *J. Amer. Chem. Soc.*, 1961, **83**, 3235, 3244; (*b*) Corey and Hisashi Uda, *J. Amer. Chem. Soc.*, 1963, **85**, 1788; (*c*) Breslow, Lockhart, and Chang, *J. Amer. Chem. Soc.*, 1961, **83**, 2375; (*d*) Corey and Dawson, *J. Amer. Chem. Soc.*, 1963, **85**, 1782.

The deamination of *cis*-bicyclo[3,1,0]hex-3-ylamine definitely does not involve a trishomocyclopropenyl cation since experiments with the deuterated compound show that the *cis*-bicyclo[3,1,0]hexan-3-ol obtained is formed with very little rearrangement.[200d]

Participation by Alkyl Groups.—Migration of a methyl group in reactions of neopentyl derivatives occurs frequently [*e.g.*, as Scheme (XLVIII)], but there is no evidence for any rate enhancement associated with these

(XLVIII) $Me_3C{-}CH_2Cl \xrightarrow{EtOH} Me_2C(OEt){-}CH_2Me + Me_2C{=}CHMe$

migrations.[201] The methyl group must, therefore, commence its migration after the rate-determining step. In reactions of more highly branched molecules [*e.g.*, (259)] alkyl-group migration is sometimes associated with a rate enhancement.[202] However, the familiar problem as to whether



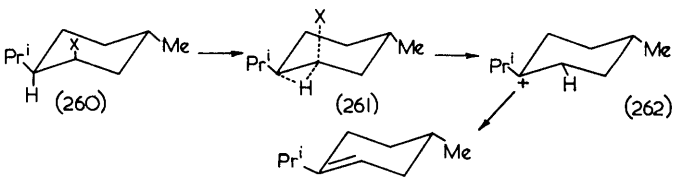
(259)

to ascribe this to steric acceleration or anchimeric assistance generally remains unsolved.

Methylene migrations in reactions of bicyclic systems* are commonly found, *e.g.*, in the Wagner–Meerwein rearrangement of camphene hydrochloride to isobornyl chloride.[203] The most thoroughly investigated are probably those of norborn-2-yl derivatives, which have been discussed in an earlier section (see p. 98).

Neighbouring Hydrogen

Although many reactions are known, in which migration of hydrogen occurs between carbon centres, it would appear that direct nucleophilic participation in a rate-determining step occurs in only very few, if any, of them. The 40—80 fold greater rates of solvolyses of neomenthyl chloride[204]



(260) (261) (262)

*For an excellent review of carbonium ion rearrangements in bridged bicyclic systems, see Berson in "Molecular Rearrangements," ed. de Mayo, Interscience, New York, 1963, p. 111.

[201] See Streitwieser, *Chem. Rev.*, 1956, **56**, 706.

[202] Bartlett and Stiles, *J. Amer. Chem. Soc.*, 1955, **77**, 2806.

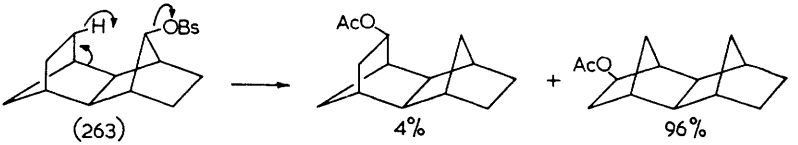
[203] See Streitwieser, *Chem. Rev.*, 1956, **56**, 698.

[204] Hughes, Ingold, and Rose, *J.*, 1953, 3839.

and arenenesulphonates (260)[170] over those of the corresponding menthyl derivatives have been ascribed to hydrogen participation [as (261)],[170] but since the major product is menth-3-ene the high rates may equally well be due to a facile elimination of the diaxial hydrogen and halogeno- or arenesulphonate groups.[204] It has been claimed[205] that the formolysis of optically active neomenthyl toluene-*p*-sulphonate yields racemic menth-3-ene, although, under the solvolysis conditions used, menth-3-ene is optically stable. Unfortunately, details of this work have not been published, but if correct it would be strong evidence for hydrogen participation, since it indicates the intervention of a symmetrical intermediate, which would most likely be carbonium ion (262), formed by hydrogen migration.

It has also been claimed that participation by the tertiary hydrogen atoms of 1,2-dimethylpropyl toluene-*p*-sulphonate[205b] and of the 2-cyclohexyl-1-methylpropyl toluene-*p*-sulphonate[205c] occurs in the rate-determining ionisations of their solvolyses, all of which yield large amounts of olefins.

Transannular hydride-shifts occur in the reactions of a number of medium-ring compounds,[206] some of which proceed at enhanced rates, but these are most probably due to steric acceleration (decrease in *I*-strain) and not to the formation of a hydrogen-bridged ion in the rate-determining step. Apparently conclusive evidence that this is so for the acetolysis of cyclodecyl toluene-*p*-sulphonate has been claimed by Prelog,[207] who reported that when the migrating hydrogen is replaced by deuterium there is no observable isotope effect.* An example of a reaction which does show an isotope effect ($k_H/k_D = 1{\cdot}24$) when the migrating hydrogen is replaced by deuterium is the acetolysis of the *p*-bromobenzenesulphonate (263), which proceeds about 10^3 times faster than that of norborn-7-yl *p*-bromobenzenesulphonate.[208] However, in the Reviewer's opinion, the possibility that this is due to steric acceleration, there being less acceleration with the



(263) 4% 96%

*It would now appear that there is, in fact, a small isotope effect, but this does not result from a difference in the rate of C–H and C–D bond breaking since the proportion of products formed with transannular migration is unchanged. (Prelog and Borcic, unpublished observations reported by Prelog and Traynham in "Molecular Rearrangements," ed. de Mayo, Interscience, New York, 1963, p. 612.)

[205] (*a*) Winstein and Schwartz, unpublished results quoted by Streitwieser, *Chem. Rev.*, 1956, **56**, 715; (*b*) Winstein and Takahashi, *Tetrahedron*, 1958, **2**, 316; (*c*) Cram and Tadanier, *J. Amer. Chem. Soc.*, 1959, **81**, 2737.

[206] See Sicher, *Progr. Stereochem.*, 1962, **3**, 243.

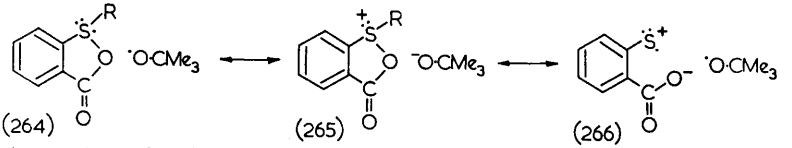
[207] Unpublished observations of Borčić reported by Prelog, *Record of Chemical Progress*, 1957, **18**, 256.

[208] Winstein and Hansen, *J. Amer. Chem. Soc.*, 1960 ,**82**, 6206.

deuterated compound, because of the smaller steric requirements of deuterium,[209] has not been excluded.

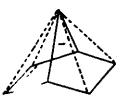
Neighbouring Group Participation in Radical Reactions

So far only neighbouring group participation in heterolytic reactions has been considered, but there is increasing interest in participation in radical reactions. The best authenticated example of anchimeric assistance in a radical reaction was discovered by Bentrude and Martin,[210a] who showed that the introduction of an *o*-phenylthio- or *o*-methylthio-substituent into t-butyl perbenzoate causes a 10^3—10^4-fold increase in the rate of radical decomposition, but that the introduction of a *p*-methylthio-substituent causes only a 3-fold increase. Reaction products include 3,1-benzoxathian-4-one and di-2-carboxyphenyl disulphide. The reactions are considered to involve a transition state which is a hybrid among structures (264)—(266), with structure (265) as the most important contributor.[210b] *o*-Iodo-substituents, which also increase the rate of radical decomposition of aromatic peresters,[211] although not so powerfully, may act similarly.



A number of radical-migrations by aryl residues have been observed[212] but there appears to be no clear evidence for anchimeric assistance in any of these reactions. Migration by a methylene group to yield isocamphane occurs in the radical decomposition of 2-azobornane[213] but not in that of 2-formylbornane.[214]

It has been suggested that the facile reaction of norbornadiene with t-butyl perbenzoate to yield 7-t-butoxynorbornadiene proceeds through an anchimerically assisted hydrogen abstraction to yield the radical (267).[215]


(267)

[209] See Brown in "The Transition State," *Chem. Soc. Special Publ.*, No. 16, 1962, p. 89; *Chem. Eng. News.*, July 8th, 1963, p. 44; Mislow, Graeve, Gordon, and Wahl, *J. Amer. Chem. Soc.*, 1963, **85**, 1199.

[210] (*a*) Bentrude and Martin, *J. Amer. Chem. Soc.*, 1962, **84**, 1561; (*b*) Tuleen, Bentrude, and Martin, *J. Amer. Chem. Soc.*, 1963, **85**, 1938.

[211] Leffler, Faulkner, and Petropoulos, *J. Amer. Chem. Soc.*, 1958, **80**, 5435.

[212] See, *e.g.*, Winstein, Heck, Lapporte, and Baird, *Experientia*, 1956, **12**, 138; Smith and Anderson, *J. Amer. Chem. Soc.*, 1960, **82**, 656; Martin, *ibid.*, 1962, **84**, 1986; Wilt and Schneider, *J. Org. Chem.*, 1961, **26**, 4196; Rüchardt and Hecht, *Tetrahedron Letters*, 1962, 957, 961; Rüchardt and Trautwein, *Chem. Ber.*, 1963, **96**, 160; Bonner and Mango, *J. Org. Chem.*, 1964, **29**, 29.

[213] Berson, Olsen, and Walia, *J. Amer. Chem. Soc.*, 1962, **84**, 3337.

[214] Berson and Olsen, *J. Amer. Chem. Soc.*, 1962, **84**, 3178.

[215] Story, *J. Org. Chem.*, 1961, **26**, 287.

Factors Influencing the Ease of Ring-closure

Many of the reactions, discussed in the previous sections, involve ring closure of acyclic compounds through intramolecular nucleophilic displacements. The rates at which these reactions take place depend markedly on the size of the ring that is formed, but, as the reader will have noted, the ring size which is associated with the fastest rate varies from one reaction to another. Also, the rates of these ring-closure reactions depend on the degree of alkyl substitution of the chain, the rate generally increasing with increasing number of alkyl substituents. These two factors will now be discussed in more detail.

Ring Size.—The dependence on ring size is determined by an interplay of several quantities.[216] First, formation of a ring results in loss of rotational freedom and hence is accompanied by an entropy decrease. With increasing length of the chain that is closed, the loss of rotational freedom increases. Hence there is an increasing unfavourable loss of entropy on ring-closure, with increasing ring size. There is also an unfavourable strain factor on ring formation, which decreases on going from a three- to a six-membered ring, then increases with ring size up to nine members and decreases again with rings of larger size. Finally, there are the electronic effects of the leaving and neighbouring groups on one another. Since most leaving and neighbouring groups are electron-withdrawing inductively, these effects act to decrease the nucleophilicity of the neighbouring group and to decrease the tendency of the leaving group to depart. They therefore tend to decrease the rate of ring formation, the decrease being greatest for three-membered rings, when neighbouring and leaving group are attached to adjacent carbon atoms, and decreasing with increasing ring size. The results given in Table 25 indicate that the balance of these factors may result in formation of three-, five-, or six-membered rings being most rapid, depending on the reaction type.*

With ring-closures of unsubstituted polymethylene chains involving an intramolecular nucleophilic attack on a saturated carbon centre, five-membered-ring formation is most highly favoured when the element of the nucleophilic group is oxygen or nitrogen [reactions (1)—(4) in Table 25]. With the more highly polarisable thioether group [reactions (5) and (6)] or an aryl ring [reactions (7)—(9)] the ring-strain factor and the electronic effect appear to have decreased since the three-membered ring is most readily formed. It would be interesting to know if this more rapid

*An interesting example of the interplay of entropy and enthalpy factors is given by the $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ values for the acid-catalysed formation of δ-valerolactone (ΔS = −25·4 cal. deg^{-1}, ΔH = 13·8 kcal. mole^{-1}) and γ-butyrolactone ($\Delta S^{\ddagger}$ = −11·5 cal. deg.$^{-1}$, $\Delta H^{\ddagger}$ = 18·9 kcal. mole^{-1}) in aqueous 1,2-dimethyoxethane.[217] The entropy of activation is more favourable for the formation of the five-membered ring but the enthalpy of activation favours six-membered-ring formation. The result, for this reaction, is that the six-membered ring is formed fastest.

[216] See Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 198.

[217] Matuszak, Thesis, Ohio State University, 1957; *Diss. Abs.*, 1958, **18**, 792.

TABLE 25. *The rates of ring-closure reactions as a function of ring size.*

	Temp.	Relative rates* $n=3$	4	5	6	7	Ref.
1. The Acetolysis of $MeO\cdot[CH_2]_{n-1}\cdot OBs$	25°	[0·00043]	[0·00096]	1·00	0·187	0·0018	7*b*
2. The hydrolysis of $HO\cdot[CH_2]_{n-1}\cdot Cl$	70·5°	[0·0010]	[0·0045]	1·00	0·041	—	29, 30
3. The cyclisation of $H_2N\cdot[CH_2]_{n-1}\cdot Br$	25°	0·0012	[0·00002]	1·00	0·017	0·00003	53
4. The cyclisation of $^-O\cdot[CH_2]_{n-1}\cdot Cl$	18°	0·2	—	1·0	0·001	—	30, 31
5. The solvolysis of $PhS\cdot[CH_2]_{n-1}\cdot Cl$ in 50% aqueous acetone	80°	—	—	1·0	0·013	—	71
6. The solvolysis of $PhS\cdot[CH_2]_{n-1}\cdot Cl$ in aqueous dioxan	100°	5·0	[0·026]	1·0	—	—	72
7. The Ar^--*n* ring-closure of $^-O\cdot C_6H_4\cdot[CH_2]_{n-1}\cdot Br$ in methanol†	25°	~1100	—	1·0	—	—	145, 146
8. The Ar_1-*n* ring-closure of *p*-$MeO\cdot C_6H_4\cdot[CH_2]_{n-1}\cdot OBs$ in acetic acid	75°	147	0·2	1·0	—	—	159
9. The Ar_1-*n* ring-closure of 2,4-$(MeO)_2\cdot C_6H_3\cdot[CH_2]_{n-1}\cdot OBs$ in acetic acid	75°	262	—	1·0	0·014	—	159

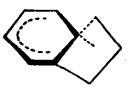
* The values in brackets, probably, do not refer to ring-closure reactions, which, therefore, have even smaller relative rates. † The rate for the methanolysis of the anion of 4-(*p*-hydroxyphenyl)butyl bromide was assumed to be one-tenth that for the corresponding *p*-bromobenzenesulphonate.

TABLE 25.—*continued*

10. The hydrolysis of $^{-}O_2C\cdot[CH_2]_{n-2}\cdot Cl$	37·5°	—	—	1·0	0·9	—	30
11. The hydrolysis of $^{-}O_2C\cdot[CH_2]_{n-3}\cdot CHBrMe$	25°	0·00008	0·00006	1·0	—	—	31
12. The acetolysis of *o*-$MeO\cdot C_6H_4\cdot[CH_2]_{n-3}\cdot OBs$; MeO-*n* participation	75°	—	—	—	1·0	0·20	7*b*
13. The acetolysis of *o*-$MeO\cdot C_6H_4\cdot CMe_2\cdot[CH_2]_{n-4}\cdot OTs$; MeO-*n* participation	75°	—	—	1·0	1·2	—	7*b*
14. The Ar_2-*n* ring-closure of 3,5-$(MeO)_2\cdot C_6H_3\cdot[CH_2]_{n-2}\cdot OBs$ in formic acid	75°	—	—	1·0	100	—	161
15. The Ar_2-*n* ring-closure of *m*-$MeO\cdot C_6H_4\cdot[CH_2]_{n-2}\cdot OBs$ in formic acid	75°	—	—	1·0	17	—	161
16. The lactonisation of $HO\cdot[CH_2]_{n-2}\cdot CO_2H$	25°	—	—	1·00	6·4	—	217
17. The hydrolysis of $HO\cdot[CH_2]_{n-2}\cdot CO\cdot NH_2$	20°	—	—	1·00	2·6	—	8
18. The hydrolysis of $Me_2N\cdot[CH_2]_{n-2}\cdot CO_2Ph$	25°	—	—	1·00	0·389	—	58
19. The lactamisation of $H_2N\cdot[CH_2]_{n-3}\cdot CH(NHTs)\cdot CO_2Me$	25°	—	—	1·00	3·03	—	59
20. The hydrolysis of $^{-}O_2C\cdot[CH_2]_{n-3}\cdot CO_2\cdot C_6H_4\cdot OMe$-*p*	25°	—	—	1·00	0·0066	—	116

formation of three-membered rings also occurs with other intramolecular nucleophiles containing elements of Group II and higher Groups. For instance, does I-3 and Br-3 participation provide more anchimeric assistance than I-5 and Br-5 participation?*

Introduction of an unsaturated group into the chain undergoing ring-closure increases its rigidity, and hence the entropy loss on ring-closure is reduced, but ring formation is now probably accompanied by a greater increase in strain. These two factors favour formation of six-membered rings relative to that of five- or three-membered rings, so that with reactions (10)—(19) the ratios k_6/k_5 are greater than with reactions (1)—(9), and with several reactions six-membered rings are formed fastest of all. The steric-strain factor is particularly significant in determining the rate of ring-closure reactions at aromatic centres [reactions (14) and (15)]. Here perpendicular approach to the ring is necessary and the transition state for the formation of the five-membered ring (268) is highly strained. Qualitative results on other reactions of this type, *viz.*, intramolecular acylation[218] and ring-closure of the nitrenes, $Ph{\cdot}[CH_2]_{n-3}{\cdot}N:$,[219] also indicate a greater ease of formation of six-membered over five-membered rings.



(268)

The only reactions in Table 25 of compounds with two unsaturated groups are the hydrolyses of the half-esters of succinic and glutaric acids [reaction (20)] which are thought to proceed by way of the cyclic anhydrides. The ring-closure of the succinate proceeds 10^2—10^3 times faster than that of the glutarate, owing to a more favourable entropy of activation. A possible explanation is that the close proximity of the carboxylate

TABLE 26. *The effects of methyl substituents on the rates of ring-closure of chlorohydrins and chloroethylamines.*

Epoxide formation in aqueous alkali at 18°*	10^3k_2 (l. mole^{-1} sec.$^{-1}$)	Estimated k_1 for ring-closure of the anion[223]		Ring-closure at 25°† 10^6k_1 (sec.$^{-1}$)
$Cl{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	5	5	$Cl{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	8
$Cl{\cdot}CH_2{\cdot}CH{\cdot}Me{\cdot}OH$	110	130	$Cl{\cdot}CH_2{\cdot}CHMe{\cdot}NH_2$	250
$Cl{\cdot}CH_2{\cdot}CMe_2{\cdot}OH$	1300	2500	$Cl{\cdot}CH_2{\cdot}CMe_2{\cdot}NH_2$	7500

* Nilsson and Smith, *Z. phys. Chem.* (*Leipzig*), 1933, **166A**, 136. † Freundlich and Salomon, *Z. phys. Chem.* (*Leipzig*), 1933, **166A**, 175.

*It has recently been disclosed that there is some evidence that the driving force for the formation of five-membered halonium rings is not large (unpublished studies by Winstein and Glick, reported by Peterson and Allen, *J. Amer. Chem. Soc.*, 1963, **85**, 3611, footnote 15).

[218] See Johnson, *Org. Reactions*, 1944, **2**, 114.

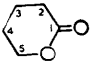
[219] Barton and Morgan, *J.*, 1962, 622.

and ester groups in the succinate restrict rotational freedom so that there is a decreased loss in entropy on going to the transition state.

Alkyl Substitution.—It has been known for many years that substituents, especially geminal substituents, increase the rate of ring-closure reactions and the thermodynamic stability of ring forms over acyclic forms (see Tables 11 and 26—28 for examples). This was widely studied qualitatively

TABLE 27. *The effect of methyl substituents on the stability and rate of formation of lactones in acqueous solution at 25°.*

(A)



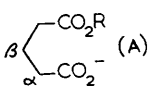
(B)

Lactones (A)	Unsubst.	2-Me	4-Me	4,4-Me_2
% Lactone at equilibrium	72·8	95·4	93·0	98·2
Rate of formation, k ($min.^{-1}$)	0·0377	0·2	0·010	0·465

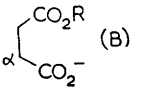
Lactones (B)	Unsubst.	2-Me	5-Me	5,5-Me_2	3-Me-5,5-Me_2	4-Me-5,5-Me_2
% Lactone at equilibrium	9·0	16·5	21·2	25·1	95·5	75·0
k ($min.^{-1}$)	0·24	0·36	0·56	0·052	3·02	0·399

* Sebelius, Inaugural Dissertation, Lund, 1927, quoted by Hückel "Theoretical Principals of Organic Chemistry," trans. Rathmann, Elsevier, Amsterdam, 1958, p. 895.

TABLE 28. *The effect of methyl substituents on the rates of hydrolyses of mono-*p*-bromophenyl esters of glutaric and succinic acid.*[117]



(A)



(B)

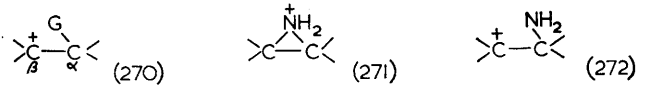
	(A) Unsubst.	(A) β-Me	(A) $\beta\beta$-Me_2	(A) $\alpha\alpha$-Me_2	(B) Unsubst.	(B) $\alpha\alpha$-Me_2
10^5k ($sec.^{-1}$)	7·4	32·3	142	26·7	170	500

by Ingold, Thorpe, and their co-workers,[220] and Ingold suggested[221] that it was due to the fact that the substituents decreased the bond angle between the remaining valencies hence bringing the groups undergoing ring-closure "into closer proximity". Alternatively, alkyl substituents may be regarded as distorting the angle between the remaining valencies towards the value found in the ring. Some evidence for this effect has recently been produced by Schleyer[222] who studied hydrogen-bonding in alkyl-substituted propane-1,3-diols. It can be of only minor importance in ring-closure reactions, however, since the influence of alkyl substituents on the formation of five- and six-membered rings, which are almost free of angle strain, is almost as great as on the formation of the highly strained smaller rings.

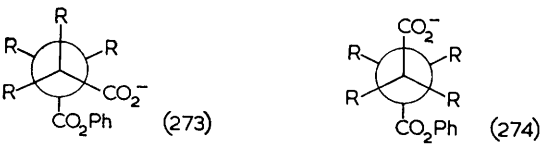
[220] See Ingold and Thorpe, *J.*, 1928, 1318, and previous papers.
[221] Ingold, *J.*, 1921, 308.
[222] Schleyer, *J. Amer. Chem. Soc.*, 1961, **83**, 1368.

Another explanation was advanced by Winstein,[223] who observed that the anchimeric assistance provided by several neighbouring groups (*e.g.*, halogen, methoxyl, aryl) in reactions of the type shown in Scheme (XLIX) was greatly increased by β-alkyl substituents. It was suggested that this

was due to stabilisation of the intermediate ion (269) by resonance with structures of type (270) which would be greatest when C_β is tertiary. However, large enhancements of rate are also observed when the substituents are attached to carbon atoms other than that bearing the neighbouring group (see Tables 6 and 11), and these, clearly, cannot be caused in this way. Also the effect of alkyl substituents is as large when the neighbouring group is alkoxide or amino (see Tables 11 and 26) as when it is carbon, although less stabilisation would be expected for an ion such as (271), bearing a positive charge on nitrogen, by resonance with structure (272), bearing a positive charge on carbon. It is clear, therefore, that stabilisation of an intermediate in this way can only be a minor contributing factor to the "gem di-alkyl effect."



More recently it has been suggested by Bruice and Pandit[117] that "the ring closure proceeds at a higher rate on geminal (or alkyl) substitution because of the resultant decrease in unprofitable rotamer distribution." Thus, it is argued, with an aryl hydrogen succinate the population of the profitable rotamer (273) is increased relative to that of the unprofitable rotamer (274) when R is alkyl instead of hydrogen because of non-bonded interactions between the alkyl groups. In terms of the transition-state



theory, this would seem to imply that the increased rate of alkyl substitution is due to an increased initial-state free-energy, because the participating group and reaction centre are brought closer together. This could be due to repulsion between these groups or to desolvation of one or both of them.

Another explanation, which is probably more satisfactory since it is formulated thermodynamically, is that of Allinger and Zalkow.[224] These

[223] Winstein and Grunwald, *J. Amer. Chem. Soc.*, 1948, **70**, 828.
[224] Allinger and Zalkow, *J. Org. Chem.*, 1960, **25**, 701.

workers showed that alkyl substitution causes a decrease in ΔH and an increase in ΔS for the reaction, hexane→cyclohexane + hydrogen, and were able to explain both changes quantitatively. On formation of cyclohexane from hexane there will be six additional *gauche*-interactions but on ring-closure of an alkyl substituted cyclohexane the additional *gauche*-interactions will be less than six. Hence, ΔH for the formation of a six-membered ring, and $\Delta H^{\ddagger}$ for the formation of a six-membered cyclic transition state, should be decreased on alkyl substitution. In addition, alkyl substituents will restrict rotation in the acyclic form[225] and thus decrease the rotational entropy. Hence, loss of rotational entropy on ring-closure of an alkyl substituted chain, or on going to the transition state for such a ring-closure, will be less than for an unsubstituted chain. Therefore alkyl substitution will cause a decrease in the free-energy of formation of a six-membered ring from an open chain through more favourable ΔH and $T\Delta S$ terms. With rings of other sizes it is more difficult to decide what the effect of alkyl substituents on ΔH and $\Delta H^{\ddagger}$ will be, but a qualitative parallelism of five-membered rings with six-membered rings is claimed.[224] The effect of alkyl substituents on ΔS or $\Delta S^{\ddagger}$, however, would be expected to be such, so as to favour ring-closure whatever the ring size, since alkyl substituents will always reduce rotational freedom in the acyclic form, and it is suggested that this factor is the most important one in the operation of the *gem*-dialkyl effect.

I thank Dr. C. W. Rees for many stimulating discussions.

[225] See Hammond in "Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, p. 468.