QUARTERLY REVIEWS

ALKYL–OXYGEN HETEROLYSIS IN CARBOXYLIC ESTERS AND RELATED COMPOUNDS

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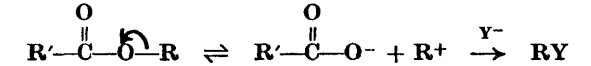
Introduction

THIS Review is restricted to that type of fission of the alkyl–oxygen bond in carboxylic esters and other oxy-compounds in which both electrons of the bond are transferred to the oxygen atom. This process usually occurs by a unimolecular ionisation to produce a carbonium ion which then attains stability by loss of a proton or, more commonly, by reaction with a nucleophilic reagent:



In view of the recent and probably future interest in the homolysis of alkyl–oxygen bonds to produce free radicals ($R\overset{\frown}{-}\overset{\frown}{O}X \rightarrow R\cdot + \cdot OX$), throughout this Review the former process is referred to as alkyl–oxygen heterolysis and the more familiar description of alkyl–oxygen fission is used only when the electronic nature of the process is not specifically implied.

Ferns and Lapworth [1] pointed out in 1912 that whereas sulphonic and sulphuric esters (I) reacted by fission of the alkyl–oxygen bond and brought about alkylation reactions similar to those of the alkyl halides, carboxylic esters (II) maintained the alkyl–oxygen bond intact in all their reactions

$$R\cdot SO_2\cdot O\text{–}\vert\text{–Alk (I)} \qquad R\cdot CO\text{–}\vert\text{–OAlk (II)}$$

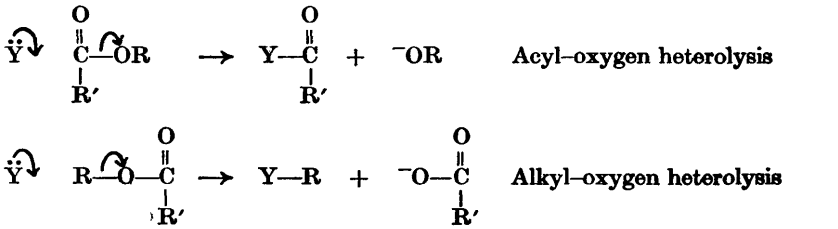
which were then known; later evidence served mainly to confirm this. Although the possible alternative of alkyl–oxygen bond fission in carboxylic esters has long been recognised,[2] it is only recently that the extent and importance of the phenomenon has been understood. Its investigation has made available a number of novel synthetic methods and has extended our understanding of the reactivity of alkyl–oxygen bonds in general. A

[1] Ferns and Lapworth, *J.*, 1912, **101**, 273.
[2] Burton and Ingold, *J.*, 1928, 904.

review of the subject at its present stage of development may help in viewing it against this wider background, and be of assistance in indicating the type of behaviour that may be encountered in the investigation of less familiar systems.

The Mechanism of the Substitution Reactions of Esters

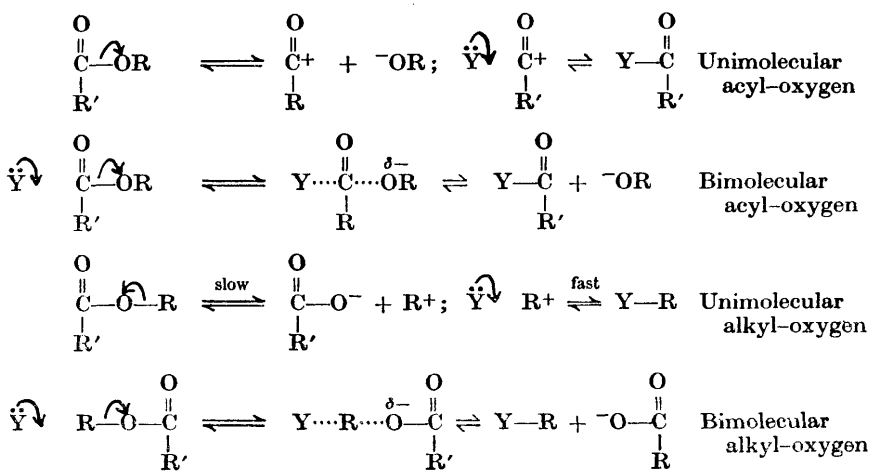
The Possible Reaction Mechanisms.—A carboxylic ester, R′·CO·OR, has two carbon atoms at which substitution can potentially occur by attack of a nucleophilic reagent. These are the acyl and the alkyl carbon atoms, substitution proceeding by heterolysis of the acyl–oxygen and the alkyl–oxygen bonds respectively,[3] *i.e.*,



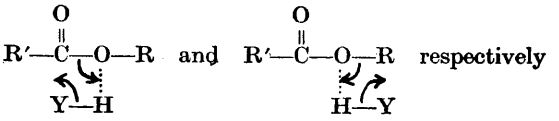
it will be noted that in general the nature of the products will be diagnostic of the process involved.

Reactions proceeding by these types of bond fission are denoted by the subscripts AC and AL respectively.[3, 4 *]

If possible mechanisms proceeding *via* carbonyl addition be neglected, either of these modes of bond heterolysis may, in principle, be accomplished by a unimolecular (S_N1-type) or a bimolecular (S_N2-type) rate process. Under neutral conditions, therefore, different combinations of site of reaction and molecularity of reaction (denoted by a suffix) give rise to the following four possible mechanisms of heterolysis :

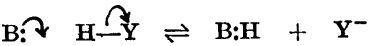


In principle a reagent HY could also bring about acyl– or alkyl–oxygen heterolysis *via* an S_Ni-type transition state :

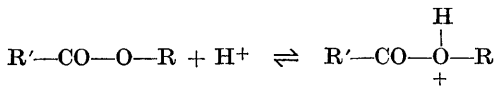


but as yet such mechanisms have not been established.

The occurrence of basic or acidic catalysis may modify these equations. Basic catalysis is possible in those bimolecular reactions proceeding *via* alkyl– or acyl–oxygen heterolysis where the reagent has the form HY, and can ionise in presence of the base to give the more strongly nucleophilic reagent Y^- :



By either a bimolecular or a unimolecular process both acyl– and alkyl–oxygen bond heterolysis will be susceptible to acid catalysis because protonation of the ester to form its conjugate acid will increase the affinity of the oxygen atom for either the alkyl–oxygen or acyl–oxygen bond electrons, and these electron shifts are involved in the kinetically significant stages of both bimolecular and unimolecular reactions :



Reactions occurring under acidic conditions on the conjugate acid of the ester are distinguished by the prefix *A*, and those under neutral or basic conditions which take place on the unprotonated ester, by the prefix *B*. Of the eight possible mechanisms ($B_{AC}1$, $B_{AC}2$, $B_{AL}1$, $B_{AL}2$; $A_{AC}1$, $A_{AC}2$, $A_{AL}1$, $A_{AL}2$), all except the first and last may be claimed to have been observed.[3] In principle, these reactions are reversible, and the same equations read from right to left will describe possible mechanisms of esterification.

When R is a simple primary or secondary saturated aliphatic group, its readiness to release the R–O bond electrons to the oxygen atom will be small, particularly in the absence of acid catalysis. These esters will thus show low reactivity by the $A_{AL}1$ and $B_{AL}1$ mechanisms. The strongly dipolar carbonyl group ($>\overset{\delta+}{C}=\overset{\delta-}{O}$), however, is susceptible to bimolecular

[3] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.

[4] Ingold, " Structure and Mechanism in Organic Chemistry ", Bell, London, 1953, p. 754.

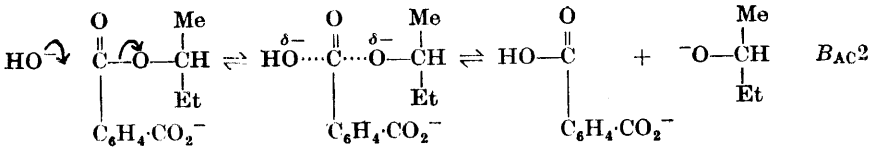
[4a] Anbar, Dostrovsky, Samuel, and Yoffe, *J.*, 1954, 3603.

* Anbar, Dostrovsky, Samuel, and Yoffe [4a] have recently proposed an alternative symbolism to accommodate the reactions of inorganic esters, using the symbols S_{NC} and S_{NX} to denote nucleophilic reaction at the C and X atoms respectively in the oxy-acid ester of generalised formula $R_3C{\cdot}O{\cdot}X$.

nucleophilic attack, whereas the relatively uncharged alkyl carbon atom is much less reactive by the same mechanism. Thus under neutral and basic conditions, or under acidic conditions, such simple esters react preferentially by bimolecular acyl–oxygen heterolysis ($B_{AC}2$ and $A_{AC}2$ respectively), and the $B_{AL}2$ mechanism will be observed only in special circumstances.

Evidence that Acyl–Oxygen Heterolysis usually occurs.—For nucleophilic reagents other than water the constitution of the products of their reactions with simple primary and secondary alkyl esters proves the occurrence of acyl–oxygen fission. For example, the ammonolysis of ethyl oxalate gives oxamide and not ethylamine (see pp. 204 and 210). However, the hydrolysis of esters by either mode of bond fission yields the same products of alcohol and acid. Evidence that this reaction also proceeded by bimolecular acyl–oxygen heterolysis was forthcoming in 1939 from the following sources:

(i) Many saturated secondary alcohols had been resolved *via* their hydrogen phthalic esters; the alcohols obtained by the hydrolysis of these esters could be re-esterified to give the hydrogen phthalates with sign and magnitude of rotation unchanged. The existence of a free carbonium ion as an intermediate in either of these reactions would result in racemisation; thus neither the alcohol nor its ester has reacted by a unimolecular alkyl–oxygen heterolysis mechanism. The alkaline hydrolysis of such simple esters is known to be of the second order, and as the $B_{AL}2$ mechanism, which could give net retention as the result of two configurational inversions, is unlikely (see above) it may be presumed that the $B_{AC}2$ mechanism is operative, *e.g.*,



(ii) It had been shown that 1-methylallyl acetate and 3-methylallyl acetate do not isomerise on hydrolysis under alkaline [5] or acid [6] conditions. The reaction of these two compounds by a unimolecular alkyl–oxygen heterolysis mechanism would proceed *via* the common mesomeric ion $CH_3—\overset{\delta+}{C}H\cdots CH\cdots\overset{\delta+}{C}H_2$, and would give a common mixture of products. Again, therefore, the reactions appear to proceed by bimolecular acyl–oxygen heterolysis.

(iii) Whitmore [7] had shown that the free *neo*pentyl cation undergoes rearrangement to the *tert.*-pentyl cation. *neo*Pentyl acetate, chloroacetate, dichloroacetate, and trichloroacetate on hydrolysis yield *neo*pentyl alcohol.[8] Again, therefore, the reaction cannot involve a free carbonium ion. Steric

[5] Prévost, *Ann. Chim.* (*France*), 1928, **10**, 147; cf. Kenyon and Snellgrove, *J.*, 1925, **127**, 1169.

[6] Ingold and Ingold, *J.*, 1932, 756.

[7] Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3431; 1939, **61**, 1586.

[8] Quayle and Norton, *ibid.*, 1940, **62**, 1170.

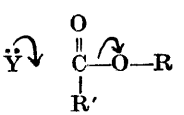
hindrance by the *neo*pentyl group would furthermore preclude the $B_{AL}2$ mechanism,[9] leaving the $B_{AC}2$ mechanism as the most probable alternative.

(iv) Direct proof that fission of the acyl–oxygen bond did in fact occur was given by Polanyi and Szabo in 1934,[10] who showed that the basic hydrolysis of pentyl acetate in water enriched with the oxygen-18 isotope yielded pentyl alcohol of normal isotopic constitution, *i.e.*,

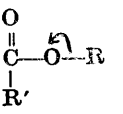
$$Me{\cdot}CO{-}|{-}O{\cdot}C_5H_{11} \quad H{-}|{-}{}^{18}OH \longrightarrow Me{\cdot}CO{\cdot}{}^{18}OH + C_5H_{11}{\cdot}OH \xrightarrow{Al_2O_3} C_5H_{10} + H_2O$$

Datta, Day, and Ingold [11] subsequently showed by a similar method that acyl–oxygen fission occurred in the acid catalysed hydrolysis of methyl hydrogen succinate, and Roberts and Urey [12] established a similar mechanism for the esterification of benzoic acid with labelled methyl alcohol.

Conditions favouring Unimolecular Alkyl–Oxygen Heterolysis.—In simple saturated primary and secondary alkyl esters, therefore, bimolecular nucleophilic attack on the acyl carbon atom (III*a*) is the primary observable process. Unimolecular alkyl–oxygen heterolysis (III*b*) may concomitantly



(III*a*)



(III*b*)

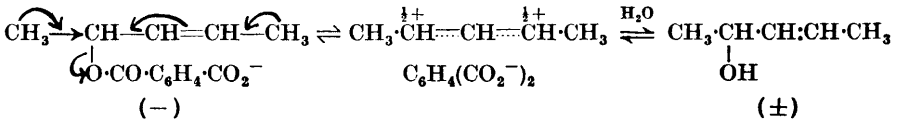
occur, but its rate is very much less than that of (*a*) and no significant number of molecules react by this process in the above examples. Let us suppose, however, that the structure of R and of R′ and the nature of the solvent are such that the ionisation (*b*) proceeds more readily. Then if the nucleophilic power of the reagent Y is progressively decreased, the rate of shift (*a*) will diminish, while that of shift (*b*) stays constant, and a point may be reached where the rate of (*b*) becomes equal to, and then greater than, that of (*a*). A transition from bimolecular acyl–oxygen heterolysis to unimolecular alkyl–oxygen heterolysis will then take place. Thus unimolecular alkyl–oxygen heterolysis which will be susceptible to acid catalysis should be observable in a highly polar solvent particularly when Y is a weak nucleophilic reagent, when the group R strongly releases electrons and when the group R′·CO strongly attracts electrons.[3, 4]

The Recognition of Alkyl–Oxygen Heterolysis in Carboxylic Esters

All the early evidence for the occurrence of unimolecular alkyl–oxygen heterolysis in carboxylic esters was derived from studies of optical activity and of anionotropic rearrangements, and from a knowledge of the constitutional and environmental factors which facilitate the analogous S_N1 reactions of alkyl halides ; it is only recently that kinetic measurements have been forthcoming to reinforce the argument.

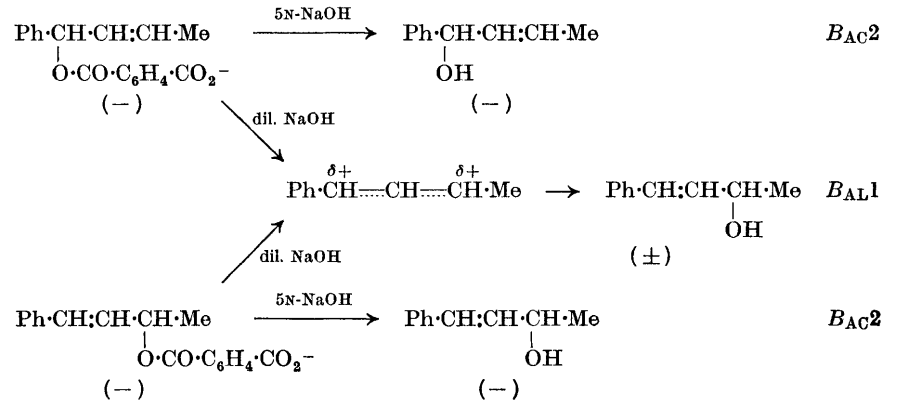
[9] Hughes, *Quart. Rev.*, 1948, **2**, 107.
[10] Polanyi and Szabo, *Trans. Faraday Soc.*, 1934, **30**, 504.
[11] Datta, Day, and Ingold, *J.*, 1938, 838.
[12] Roberts and Urey, *J. Amer. Chem. Soc.*, 1938, **60**, 2381.

Allylic Compounds.—The occurrence of unimolecular alkyl–oxygen heterolysis during the hydrolysis of carboxylic esters was first observed in experiments on the resolution of some secondary allylic alcohols. 1 : 3-Dimethylallyl alcohol had been resolved through its hydrogen phthalic ester; saponification of the ester in aqueous 5N-sodium hydroxide gave the almost optically pure alcohol, but with aqueous sodium carbonate the inactive alcohol was obtained.[13] The weakly nucleophilic aqueous sodium carbonate reacts slowly by the $B_{AC}2$ mechanism, permitting essentially all the hydrolysis to proceed by a $B_{AL}1$ mechanism, promoted by electron release from the double bond and methyl groups, and involving a free, racemising carbonium ion:



Similar racemisation accompanies the hydrolysis of 1-methyl-3-phenylallyl, 1-ethyl-3-methylallyl, and 3-methyl-1-propylallyl esters;[14] further, since the initial ionisation is reversible, after incomplete hydrolysis the portion of the ester which has not reacted is partially racemised.

In these unsymmetrically substituted allyl esters different products will result from the attack of the nucleophilic reagent on alternative ends of the mesomeric carbonium ion, with the possibility of an anionotropic rearrangement. This was observed in the hydrolysis of 3-methyl-1-phenylallyl and 1-methyl-3-phenylallyl hydrogen phthalates.[15] Hydrolysis of the esters with concentrated aqueous or alcoholic sodium hydroxide gave the almost optically pure alcohol of corresponding structure, whereas reaction of either ester with aqueous sodium carbonate gave racemic



1-methyl-3-phenylallyl alcohol as a result of nucleophilic attack upon the

[13] Hills, Kenyon, and Phillips, *J.*, 1936, 576.

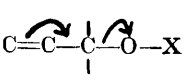
[14] Arcus and Kenyon, *J.*, 1938, 1912; Balfe, Hills, Kenyon, Phillips, and Platt, *J.*, 1942, 556.

[15] Kenyon, Partridge, and Phillips, *J.*, 1936, 85; 1937, 207.

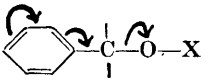
mesomeric methylphenylallylium ion, formed by unimolecular alkyl–oxygen heterolysis.

Unimolecular ionisation of this type had first been postulated by Burton and Ingold [2] in 1928 to account for the variation in the mobility of the group X in the tautomeric allylic system $R{\cdot}CHX{\cdot}CH{:}CH_2$ on variation of groups R and X.

Extension to Non-allylic Compounds.—In the esters of substituted allyl alcohols the major factor promoting heterolysis of the alkyl–oxygen bond is conjugative electron release by the C=C double bond to the "alkyl" carbon atom (IV). This same mechanism of electron supply can be afforded

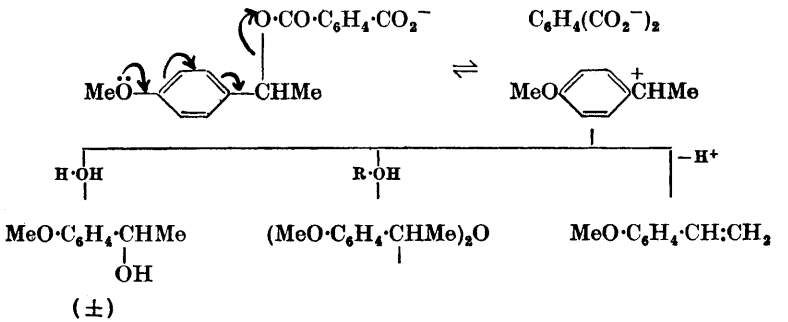


(IV)



(V)

by an aryl group (V), particularly when it carries *ortho* and/or *para* electron-releasing substituents (see Section 6), and esters of such alcohols also may react by unimolecular alkyl–oxygen heterolysis. This was first observed in experiments on optically active 1-(4-methoxyphenyl)ethanol.[16] Hydrolysis of the hydrogen phthalate of the optically pure alcohol in aqueous 3N-sodium hydroxide gave the alcohol possessing 80% of its maximum optical activity; 80% of the molecules are thus reacting by acyl–oxygen heterolysis ($B_{AC}2$) and 20% by alkyl–oxygen heterolysis ($B_{AL}1$). The use of more dilute alkali permits a greater proportion of the reaction to proceed by this latter mechanism resulting in more racemisation and increasing the proportion of olefin and ether formation:

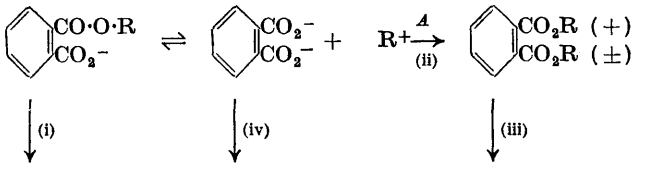


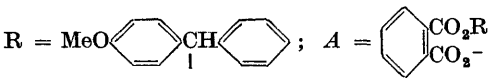
From the alkaline hydrolysis of the hydrogen phthalate a neutral derivative of phthalic acid was also isolated, which, in the analogous reaction of 4-methoxydiphenylmethyl hydrogen phthalate, was identified as the dialkyl phthalate.[17]

A solution of 4-methoxydiphenylmethyl hydrogen phthalate in aqueous 0·15N-sodium hydroxide became milky in a few minutes and gradually

[16] Balfe, Evans, Kenyon, and Nandi, *J.*, 1946, 803.
[17] Balfe, Doughty, Kenyon, and Poplett, *J.*, 1942, 605.

deposited an oil (reaction ii) consisting essentially of di-(4-methoxydiphenylmethyl) phthalate, which on hydrolysis gave the partially racemised alcohol and about 50% of the total phthalic acid (reaction iii). On acidification the upper aqueous layer yielded the remaining 50% of the phthalic acid (reaction iv).





One molecule of the hydrogen phthalate, by undergoing unimolecular alkyl–oxygen heterolysis, provided a carbonium ion which can react with the hydroxyl ions to give the racemic alcohol, or, as in this case, can be diverted to react with a second hydrogen phthalate molecule to give the dialkyl phthalate.

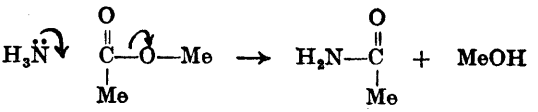
This disproportionation reaction is characteristic of acid esters, and indeed of most molecules whose electronegative group contains a nucleophilic centre and which can undergo unimolecular alkyl–oxygen heterolysis. Thus *p*-methoxyphenyl-1-naphthylmethyl hydrogen succinate, hydrogen diphenate, and hydrogen homophthalate, as well as *p*-phenoxydiphenylmethyl hydrogen diphenate and hydrogen homophthalate [16] undergo disproportionation to the corresponding dibasic acids and dialkyl esters. Similarly, methyl hydrogen sulphate forms sulphuric acid and dimethyl sulphate, alcohols are converted into water and dialkyl ethers, and some alkyl hydroperoxides form hydrogen peroxide and the dialkyl peroxide (see p. 216).

The Nucleophilic Reagent and the Product of Reaction

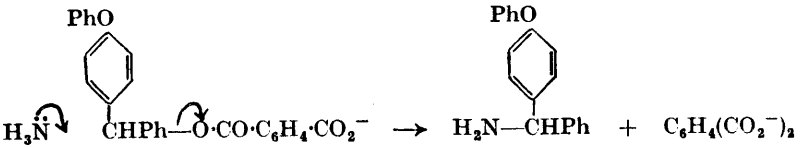
The above formation of neutral esters indicates that the presence of carbonium ions resulting from unimolecular alkyl–oxygen heterolysis, may be detected by their alkylation reactions with suitable nucleophilic reagents.* Only if the reagent Y has the structure of a symmetrical oxide, X·O·X (and then only if the oxygen atom has its normal isotopic constitution), will the products of its reaction with an ester by alkyl– and by acyl–oxygen heterolysis be the same. In all other cases, as is shown by the equations on p. 204, the mere constitution of the products will be diagnostic of

* No example appears to have been recorded of the fragments resulting from alkyl–oxygen heterolysis behaving as the addenda in addition reactions.

the site of bond fission. For example, a simple ester such as methyl acetate reacts with ammonia by acyl–oxygen heterolysis, to give an amide :

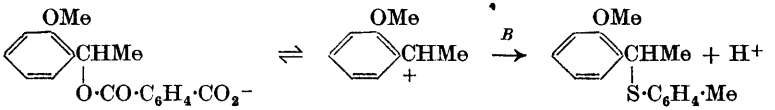


whereas *p*-phenoxydiphenylmethyl hydrogen phthalate, by alkyl–oxygen heterolysis, gives the amine.[18]



The unimolecular nature of the reaction will be demonstrated by the formation, from optically active esters, of products which are racemic or possess partly inverted configurations (see p. 218). The rates of reaction will be essentially independent of the nature of the nucleophilic reagent because the initial alkyl–oxygen heterolysis is usually slow in comparison with the subsequent rapid attack of the reagent upon the highly reactive carbonium ion. In some cases, however, where the carbonium ion is highly stabilised by resonance and the nucleophilic reagent is less reactive (*e.g.*, aromatic hydrocarbons, cf. the first-order rate of nitration of some aromatic compounds with excess of nitrating agent), the nature of the reagent may affect the reaction rate.

Thus esters which undergo unimolecular alkyl–oxygen heterolysis will alkylate alcohols to give ethers, and thiols to give sulphides. For example, triphenylmethyl acetate reacts with methanol by a reaction which has been shown to be unimolecular, to form methyl triphenylmethyl ether,[19] and 1-*o*-methoxyphenylethyl hydrogen phthalate alkylates toluene-*p*-thiol giving 1-*o*-methoxyphenylethyl *p*-tolyl sulphide : [20]

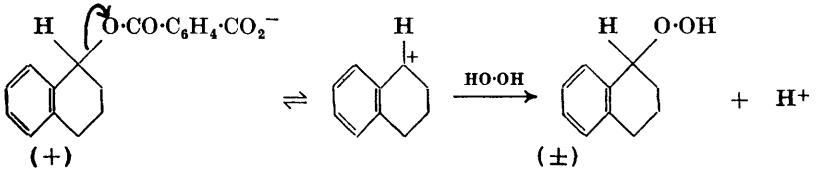


B = toluene-*p*-thiol

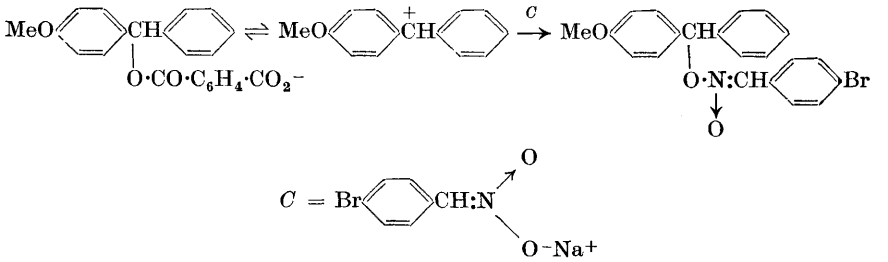
Hydrogen peroxide is alkylated to give alkyl hydroperoxides,[21] and alkyl hydroperoxides react to give dialkyl peroxides ; [22] for example, optically

[18] Balfe, Kenyon, and Wicks, *J.*, 1946, 807.
[19] Hammond and Rudesill, *J. Amer. Chem. Soc.*, 1950, **72**, 2769.
[20] Dabby, Davies, Kenyon, and Lyons, *J.*, 1953, 1541.
[21] Davies, Foster, and White, *J.*, 1953, 3619.
[22] *Idem*, *J.*, 1954, 2200.

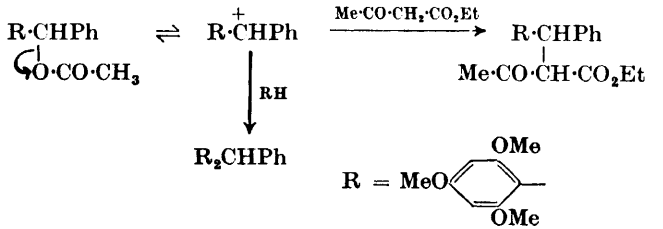
active 1 : 2 : 3 : 4-tetrahydro-1-naphthyl sodium phthalate dissolved in 90% hydrogen peroxide rapidly yields the racemic hydroperoxide.[23]



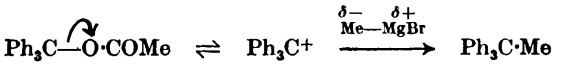
Salts of oximes and of *aci*nitro- compounds similarly undergo *O*-alkylation, *e.g.*[18]



Methyl and methylene groups which are activated by adjacent electron-attracting groups, as in acetone, benzoylacetone, acetylacetone, and ethyl acetoacetate, are alkylated, and aromatic compounds which are activated towards electrophilic substitution, such as the alkoxybenzenes, undergo ring substitution.[24]



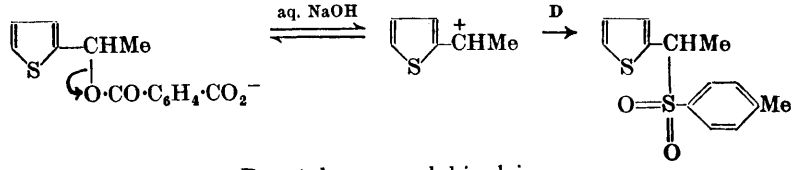
Grignard reagents similarly provide nucleophilic alkyl groups, and react with carbonium ions forming carbon–carbon bonds. Thus triphenylmethyl acetate when treated with methylmagnesium bromide is converted, not into a tertiary alcohol, but into 1 : 1 : 1-triphenylethane.[25]



Hydrochloric acid and acetyl chloride are converted into alkyl halides.

[23] Davies and White, *J.*, 1952, 3300. [24] Mason and Kenyon, *J.*, 1952, 4964.
[25] Fieser and Heymann, *J. Amer. Chem. Soc.*, 1942, **64**, 376.
[26] Anderson, Balfe, and Kenyon, *J.*, 1951, 385.
[27] Kenyon, Phillips, *et al.*, *J.*, 1925, **127**, 399, 2552; 1926, 2052; 1935, 1072; 1936, 303.
[28] Phillips, *J.*, 1923, **123**, 44.

Carboxylic acids are *O*-alkylated to give racemic esters, but sulphinic acids react at the sulphur atom to form racemic sulphones, *e.g.*,[26]



D = toluene-*p*-sulphinyl ion

The conditions under which this last reaction occurs have been widely used to indicate the reactivity of molecules by unimolecular alkyl–oxygen heterolysis.

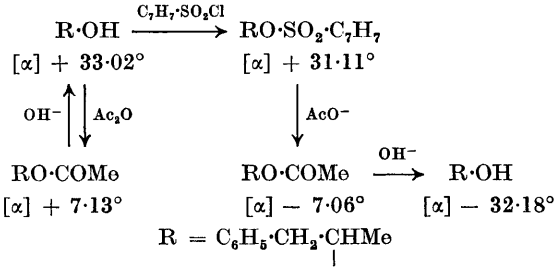
The Replaced Electronegative Group

The ease of the unimolecular displacement of the bond electrons from the alkyl group to the oxygen atom in the compound R–OX will be dependent upon the electron affinity of the group OX and the electron-releasing power of the group R. The former of these factors is discussed now and the latter on p. 219.

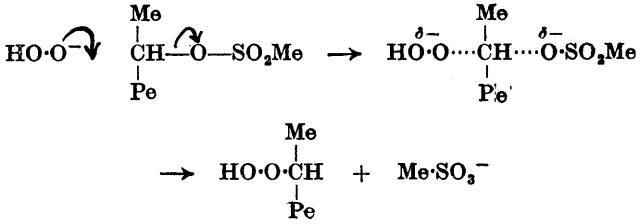
For different derivatives of any one group R, such as its esters, alcohols, acetals, ethers, epoxides, and peroxides, the relative rates of reaction will depend principally upon the electron affinity of the displaced group, which may be protonated under acidic conditions.

Esters.—On this basis the reactivity of carboxylic esters by unimolecular alkyl–oxygen heterolysis should increase with increase in strength of the esterifying acid, although under acid conditions this effect may be obscured by differences in degree of protonation. However, the criterion of the qualitative readiness of the oxy-compounds to undergo reaction, which has hitherto been used, is too insensitive to detect these differences ; their demonstration must await the application of quantitative kinetic measurements.

The mechanism of the reactions of esters of the sulphur oxy-acids was investigated in early studies of the Walden inversion. Under alkaline conditions, these esters are strong alkylating agents ; [1] for a variety of saturated alkyl groups, it has been shown that substitution under basic conditions involves configurational inversion in the alkyl group of sulphonic esters.[27] As an example, the relevant reactions of optically active derivatives of benzylmethylmethanol are summarised below : [28]



As the esterifications of the alcohol with toluene-*p*-sulphonyl chloride and with acetic anhydride both give retention of configuration, the action of acetate ions on the sulphonate must proceed with essentially complete inversion. Similar inversion of configuration occurs in the alkaline perhydrolysis of 2-heptyl methanesulphonate [29] and in the alkaline hydrolysis of *sec.*-butyl sodium sulphate,[30] and it has recently been demonstrated by the isotope method that *n*-alkyl sulphates are hydrolysed mainly by alkyl–oxygen fission.[31] These reactions therefore appear to involve bimolecular alkyl–oxygen heterolysis, *e.g.*,



However, if the alkyl group of the ester strongly releases electrons, or if the reactions occur under acidic conditions, a different mechanism may obtain. Thus the toluene-*p*-sulphonates of 1-phenylethanol and of ethyl mandelate under basic conditions undergo substitution with inversion of configuration accompanied by racemisation; [32] apparently a mechanism involving a free carbonium ion is beginning to intercede. This carbonium ion mechanism appears to dominate the rearrangement of optically active 1-phenylethyl toluene-*p*-sulphinate to inactive 1-phenyl *p*-tolyl sulphone.[33] *sec.*-Butyl sodium sulphate under acidic conditions is hydrolysed with configurational retention perhaps by a mechanism involving S–O bond fission.[30]

Of the remaining esters of inorganic oxy-acids, the nitrites and nitrates have been investigated in some detail. Using a combination of the kinetic, isotope, and optical activity methods of investigation, Allen showed that of a number of primary, secondary, and tertiary alkyl nitrites which were studied under acidic and basic conditions all except triphenylmethyl nitrite reacted by bimolecular nucleophilic attack of the reagent on the nitrogen atom.[34] In the alkyl nitrates Baker and Easty [35] demonstrated that methyl and ethyl nitrates undergo basic hydrolysis by bimolecular reaction probably involving attack at both the carbon and the nitrogen atom,[31] but that *tert.*-butyl nitrite reacted by unimolecular alkyl–oxygen heterolysis.

By the use of the ^{18}O method, Anbar, Dostrovsky, Samuel, and Yoffe

[29] Williams and Mosher, *J. Amer. Chem. Soc.*, 1954, **76**, 3495.
[30] Burwell *et al.*, *ibid.*, 1948, **70**, 878; 1952, **74**, 1462.
[31] Anbar, Dostrovsky, Samuel, and Yoffe, *J.*, 1954, 3603.
[32] Kenyon, Phillips, and Taylor, *J.*, 1933, 173; Kenyon, Phillips, and Shutt, *J.*, 1935, 1663.
[33] Kenyon and Phillips, *J.*, 1930, 1677; Arcus, Balfe, and Kenyon, *J.*, 1938, 485.
[34] Allen, *J.*, 1954, 1968.
[35] Baker and Easty, *J.*, 1952, 1193, 1208.

have carried out a broad investigation of the position of bond fission in the alkaline hydrolysis of esters of hypochlorous, hypobromous, chloric, bromic, iodic, perchloric, sulphuric, nitrous, nitric, chromic, and acetic acids.[31] Of the esters studied, only triphenylmethyl perchlorate, sulphate, and nitrate react completely by alkyl–oxygen fission. *n*-Butyl and *n*-octyl nitrates, triphenylmethyl chlorate and acetate, and diethyl sulphate are hydrolysed only partly by alkyl–oxygen fission, and the remainder retain the alkyl–oxygen bond intact during hydrolysis.

Alcohols.—Cryoscopic measurements show that aryl alcohols in sulphuric acid solution undergo heterolysis to form stable carbonium ions,[36] *e.g.*,

$$Ph_2C{\cdot}Me{-}OH + 2H_2SO_4 \longrightarrow Ph_2\overset{+}{C}{\cdot}Me + \overset{+}{H_3O} + 2HSO_4^- \qquad (i = 4)$$

In suitable examples the absorption spectrum of the carbonium ions is identifiable with that obtained from solutions of the corresponding chlorides in liquid sulphur dioxide, or of the corresponding olefins in sulphuric acid.

Under less strongly acid conditions ionisation is much less complete. Senkus and Brown [37] showed that tri-(*p*-methoxyphenyl)methanol after 43 hours at 95° under neutral conditions did not exchange its oxygen atom with water containing the oxygen-18 isotope, but in the presence of 0·1% of sulphuric acid, exchange was complete after 24 hours under the same conditions.

$$(p\text{-}MeO{\cdot}C_6H_4)_3C{\cdot}OH + H^+ \longrightarrow (p\text{-}MeO{\cdot}C_6H_4)_3C{-}\overset{+}{O}H_2$$

$$\downarrow$$

$$H^+ + (p\text{-}MeO{\cdot}C_6H_4)_3C{-}{}^{18}OH \xleftarrow{H_2{}^{18}O} (p\text{-}MeO{\cdot}C_6H_4)_3C^+ + H_2O$$

This tendency to ionise results in the optical instability of active alcohols whose asymmetry is centred on the "methyl" carbon atom. Thus, for example, 4-methoxydiphenylmethanol in homogeneous 1% aqueous solution at 90° slowly racemises without chemical change, presumably *via* unimolecular alkyl–oxygen heterolysis.[17]

$$MeO{\cdot}C_6H_4{\cdot}\underset{\displaystyle OH}{\underset{|}{C}}HPh \longrightarrow MeO{\cdot}C_6H_4{\cdot}\overset{+}{C}HPh \xrightarrow{H_2O} MeO{\cdot}C_6H_4{\cdot}\underset{\displaystyle OH}{\underset{|}{C}}HPh$$

(+) (±)

Hours of heating	0	0·5	10	30
$[\alpha]_D$	17·4°	14·2°	7·0°	0°
% Racemisation	0	18	60	100

The disproportionation of alcohols to give ethers at high temperatures, or under acidic conditions, is analogous to the formation of neutral esters from acid esters. One molecule, by undergoing unimolecular alkyl–oxygen

[36] Reviewed by Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 40.
[37] Senkus and Brown, *J. Org. Chem.*, 1938, **2**, 569.

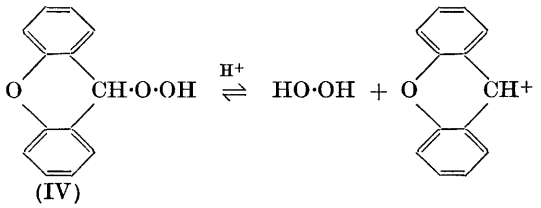
heterolysis, provides a carbonium ion for the alkylation of a second alcohol molecule, *e.g.*,[38]

$$R_2CH{-}\overset{\curvearrowleft}{\overset{+}{O}}H_2 \rightleftharpoons H_2O + R_2\overset{+}{C}H \xrightarrow{E} R_2CH{\cdot}O{\cdot}CHR_2 + H^+$$

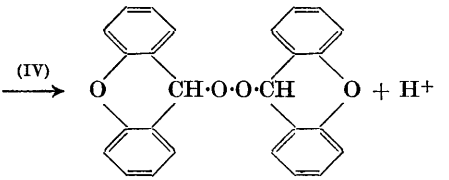
R = *p-tert.*-butylphenyl E = $R_2CH{\cdot}OH$

Under mildly acidic conditions, alcohols demonstrate all the alkylation reactions which are shown by their corresponding esters (p. 210). These reactions are discussed more fully on p. 219.

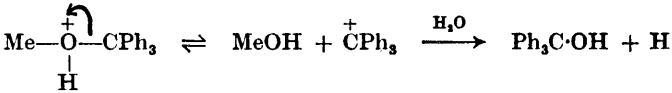
Peroxides.—Alkyl hydroperoxides and dialkyl peroxides under approximately the same conditions as the corresponding alcohols yield carbonium ions which again will alkylate sodium toluene-*p*-sulphinate, urea, aromatic hydrocarbons, and reactive methyl or methylene groups. The disproportionation of acid esters and of alcohols has its parallel in the disproportionation of xanthhydryl hydroperoxide into xanthhydryl peroxide and hydrogen peroxide : [39]

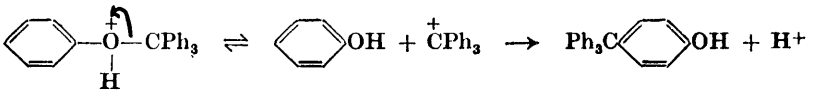


(IV)



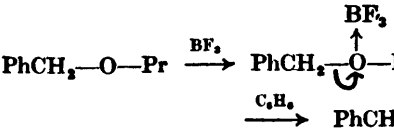
Ethers.[40]—The electron affinity of the alkoxy-group is small, even when protonated, and thus few ethers readily undergo unimolecular alkyl–oxygen heterolysis. Such a mechanism, however, is probably involved when the carbonium ion is very highly stabilised by resonance. Thus the acid-catalysed hydrolysis of methyl triphenylmethyl ether [41] probably proceeds through the triphenylmethyl cation, as does the acid-catalysed rearrangement of phenyl triphenylmethyl ether : [42]





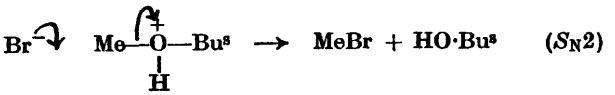
[38] Balfe, Kenyon, and Thain, *J.*, 1952, 790.
[39] Davies, Foster, and Nery, *J.*, 1954, 2204.
[40] The reactions of ethers have been reviewed by Burwell, *Chem. Rev.*, 1954, **54**, 615.
[41] Hart, *J.*, 1938, 483. [42] Burton and Cheeseman, *J.*, 1953, 832.

Similarly, benzyl ethers in the presence of Lewis acids alkylate aromatic hydrocarbons,[43] *e.g.*,

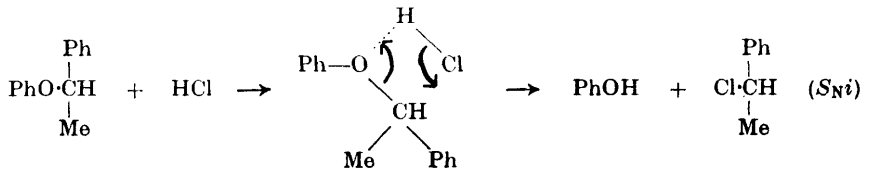


Burwell and his co-workers have shown, by the use of optically active *sec.*-butyl methyl ether, that this reaction incurs inversion with very extensive racemisation in the alkylating group.[44]

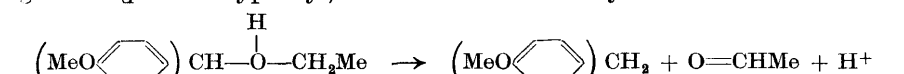
Ethers whose alkyl groups do not form such stable carbonium ions are less sensitive to acids, except those whose anions are strong nucleophilic reagents. Thus the great difference in the rate of reaction of ethers with the halogen hydracids (HCl : HBr : HI = 1 : 6 : ∞ [45]) indicates that the function of the acid is something more than mere protonation. Experiments with optically active ethers suggest that in these structures the S_N2 or S_Ni mechanisms may be operative. Thus active *sec.*-butyl methyl ether reacts with hydrogen bromide yielding optically pure *sec.*-butyl alcohol with retention of configuration, presumably by bimolecular attack of bromide ion on the methyl group of the protonated ether: [46]



On the other hand, optically active phenyl 1-phenylethyl ether on treatment with hydrogen chloride yields phenol and 1-phenylethyl chloride with retention of configuration, probably *via* a cyclic transition state (S_Ni): [47]

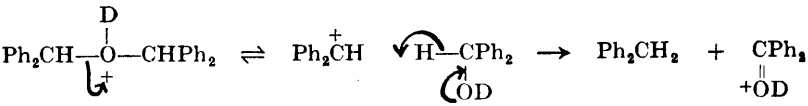


Many ethers containing strongly electron-releasing alkyl groups undergo intramolecular oxidation–reduction forming a hydrocarbon and a carbonyl compound. Thus, dixanthhydryl ether under acidic conditions dismutates into xanthen and xanthone,[48] bis(diphenylmethyl) ether forms diphenylmethane and benzophenone,[49] and di-(*p*-methoxyphenyl)methyl ethyl ether gives di-(*p*-methoxyphenyl)methane and acetaldehyde: [38]



[43] Burton and Praill, *Quart. Rev.*, 1952, **6**, 302, esp. page 317.
[44] Burwell, Elkin, and Shields, *J. Amer. Chem. Soc.*, 1952, **74**, 4570.
[45] Lüttringhaus and Sääf, *Angew. Chem.*, 1938, **51**, 916.
[46] Burwell, Elkin, and Maury, *J. Amer. Chem. Soc.*, 1951, **73**, 2428.
[47] Hart and Eleuterio, *ibid.*, 1954, **76**, 1379.
[48] Kny-Jones and Ward, *J.*, 1930, 535. [49] Burton and Cheeseman, *J.*, 1954, 986.

Baddeley and Nield have shown that the dismutation of bis(diphenylmethyl) ether in the presence of deuterium perchlorate yields diphenylmethane containing no deuterium. They conclude that the reaction proceeds by initial alkyl–oxygen heterolysis; the carbonium ion then abstracts a hydride ion from the α-position of the nucleophilic alcohol: [49a]

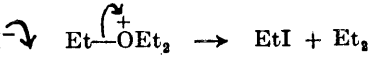


Evidence for this mechanism is provided by the fact that the addition of suitable nucleophilic reagents to the reaction mixture diverts the carbonium ions to give the products characteristic of unimolecular alkyl–oxygen heterolysis.[49b]

The trialkyloxonium salts prepared by Meerwein and his co-workers,[50] such as Et_3O^+,BF_4^-, which are analogous in structure to the protonated ethers, are powerful alkylating agents towards alcohols and phenols, carboxylic acids, and compounds containing activated methyl and methylene groups, *e.g.*,

$$Et_3O^+,BF_4^- + Me{\cdot}CO{\cdot}CHNa{\cdot}CO_2Et \longrightarrow Et_2O + Me{\cdot}CO{\cdot}CHEt{\cdot}CO_2Et$$

Only the salts containing anions which are weak nucleophilic reagents, such as BF_4^-, $SbCl_4^-$, $AlCl_4^-$, and $FeCl_4^-$, can be prepared. Attempts to isolate triethyloxonium iodide resulted in the formation of ethyl iodide and ethyl ether. The alkylation reactions would therefore appear to follow a bimolecular mechanism, *e.g.*,



The Structure of the Alkyl Group

The Stereochemical Result of Reaction.—Unimolecular heterolysis at the asymmetric centre of an optically active compound will produce a carbonium ion which will assume a planar trigonal configuration (unless this is prevented by steric strain or by intramolecular bonding). If there is equal probability of attack by the nucleophilic reagent on either side of this planar ion the product of reaction will be racemic. However, if the reagent attacks before the displaced electronegative group has receded by more than a few Ångströms, this group may exert an asymmetric shielding effect upon the reaction centre directing the reagent's attack mainly on the side distant from the replaced group, with resultant inversion of configuration. The normal stereochemical outcome of unimolecular alkyl–oxygen heterolysis will therefore be racemisation accompanied by varying amounts of inversion.[51] The resonance in carbonium ions containing electron-releasing

[49a] Baddeley and Nield, *J.*, 1954, 4684; Baddeley and Pickles, *J.*, 1953, 3726.
[49b] Davies, Feld, and Long, unpublished work.
[50] Meerwein *et al.*, *J. prakt. Chem.*, 1937, **147**, 257; 1939, **154**, 83.
[51] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252.

+ *C* groups (*e.g.*, phenyl groups) at the reaction centre will (*a*) induce coplanarity of bonds at the ionic centre and (*b*) prolong the life of the ions and permit their further separation from the displaced group before their reaction with the nucleophilic reagent ; both these tend to increase the degree of racemisation during reaction. The same factor of electron release which promotes alkyl–oxygen heterolysis thus promotes racemisation in the resulting carbonium ions. Therefore, in general, the more readily an optically active compound undergoes alkyl–oxygen heterolysis, the more nearly racemic will be the products of such reaction.

The Dependence of Reactivity upon the Structure of the Alkyl Group.—The same factors of electron release in the alkyl group to the reaction centre, and any contributory steric effects, which promote the S_N1 alkyl–halogen

$$R\overset{\curvearrowright}{-}X \rightleftharpoons X^- + R^+ \xrightarrow{Y^-} RY$$

heterolysis in alkyl halides [52] also facilitate unimolecular alkyl–oxygen heterolysis. Thus on variation of the alkyl group the same sequence of reactivity by this general unimolecular mechanism should hold in a series of alkyl halides, or of esters, alcohols, ethers, and other oxy-derivatives, if allowance is made for differences in degree of protonation under acid conditions. For example, the introduction of α-methyl groups, and particularly of the more strongly electron-repelling α-phenyl groups, should increase the rate of unimolecular alkyl–oxygen heterolysis, and the reactivity of derivatives by this mechanism should increase in the sequence :

Me—, Me_2CH—, Me_3C—, Ph(Me)CH—, Ph_2CH—, Ph_3C—

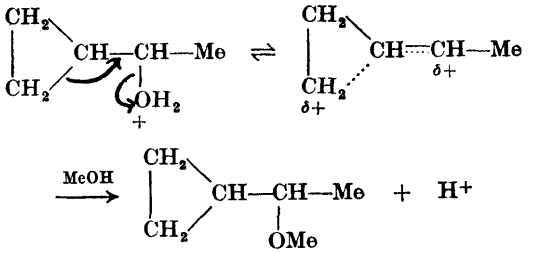
Saturated Primary Alkyl Compounds.—Simple primary alkyl esters and the corresponding alcohols show little tendency to undergo unimolecular alkyl–oxygen heterolysis, just as the corresponding alkyl halides are unreactive by the S_N1 mechanism. The few examples of alkyl–oxygen bond heterolysis which are recorded in the literature probably proceed by a bimolecular ($B_{AL}2$) mechanism. For example, the reaction of trimethylamine with methyl esters to form the tetramethylammonium ion [53] has been shown to be bimolecular. The same mechanism has been established in the reaction of sodium methoxide with methyl benzoate.[54] Here the facile attack of the methoxide ion on the acyl carbon atom regenerates methyl benzoate, thus permitting the much slower $B_{AL}2$ mechanism to be observed :

$$MeO\overset{\curvearrowright}{-} \quad \overset{\curvearrowright}{MeO}—CO—Ph \longrightarrow MeOMe + {}^-O{\cdot}CO{\cdot}Ph$$

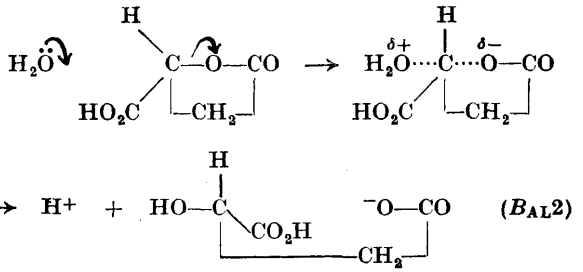
Saturated Secondary Alkyl Compounds.—Again, simple secondary alcohols and their esters show a low reactivity by unimolecular alkyl–oxygen heterolysis. For example, optically active 1-methylheptyl acetate racemises only

[52] Hughes, *Quart. Rev.*, 1951, **5**, 245.
[53] Hammett and Pfluger, *J. Amer. Chem. Soc.*, 1933, **55**, 4079.
[54] Bunnett, Robison, and Pennington, *ibid.*, 1950, **72**, 2378.

slowly when heated in the presence of strong acids,[55] and simple aliphatic secondary alcohols undergo etherification only under strongly acidic conditions.[56] The presence of an α-*cyclo*propyl group, however, greatly facilitates the reaction, and 1-*cyclo*propylethanol readily reacts with methanol under mildly acid conditions to give the methyl ether.[57] Here the carbonium ion which is produced is stabilised by resonance with the 1-allylethylium structure.



β-Lactones.—β-Lactones are unusual amongst esters in that under neutral or slightly acidic conditions they undergo hydrolysis by bimolecular alkyl–oxygen heterolysis ($B_{AL}2$); under more strongly acidic conditions or under basic conditions the usual bimolecular alkyl–oxygen heterolysis mechanisms ($A_{AC}2$ and $B_{AC}2$ respectively) are followed. This was first pointed out by Hughes and Ingold and their co-workers [51] who drew attention to the fact that the β-lactone of malic acid was hydrolysed in dilute acid with inversion of configuration in the alkyl group, *i.e.*,



Under alkaline or more strongly acidic conditions, acyl–oxygen heterolysis occurred with retention of configuration.

Similarly, β-butyrolactone and β-propiolactone are hydrolysed under neutral conditions by the $B_{AL}2$ mechanism.[58] The position of bond fission has been confirmed by the methanolysis of β-propiolactone to form β-methoxypropionic acid under neutral conditions,[59] and by the hydrolysis of

[55] Balfe, Jackman, and Kenyon, *J.*, 1954, 965.
[56] Norris and Rigby, *J. Amer. Chem. Soc.*, 1932, **54**, 2088.
[57] Pearson and Lange, *ibid.*, 1953, **75**, 1065.
[58] Olsen and Miller, *ibid.*, 1938, 60, 2687; Long and Purchase, *ibid.*, 1950, **73**, 3267.
[59] Bartlett and Rylander, *ibid.*, 1951, **73**, 4273.

β-butyrolactone with water containing an excess of the oxygen-18 isotope : [60]

$$CH_3—CH(—CH_2—)—O—CO + H_2{}^{18}O \longrightarrow CH_3—CH(—CH_2—CO_2H)—{}^{18}OH$$
$$\longrightarrow CH_3—CH{=}CH—CO_2H + H_2{}^{18}O$$

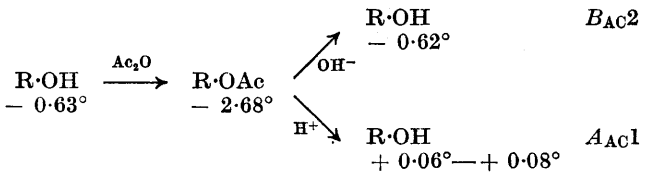
No detailed explanation can be given of why this unusual mechanism should be encountered in the β-lactones. However, it is known that strain in a small ring confers upon its constituent members the characteristics of unsaturation (as, for example, in the methanolysis of *cyclo*propylethanol quoted above). Presumably in the β-lactones ring strain so modifies the character of the alkyl and acyl carbon atoms that it renders invalid the arguments which suggest that nucleophilic attack would occur preferentially at the acyl group.[4]

Saturated Tertiary Alkyl Compounds.—In tertiary alkyl esters and alcohols inductive and hyperconjugative electron release by three alkyl residues facilitates ionisation of the alkyl–oxygen bond, just as it promotes the S_N1 reactivity of alkyl halides. Alkyl–oxygen heterolysis in *tert.*-butyl benzoate and mesitylate was demonstrated in 1941 by Cohen and Schneider [61] who showed that these esters, when boiled for some days in methanol, yield *tert.*-butyl methyl ether. The reaction is catalysed by acids,[62] but under basic conditions attack occurs at the acyl carbon atom to form *tert.*-butyl alcohol. Similarly, by the oxygen isotope method, Bunton, Comyns, and Wood [63] demonstrated that alkyl–oxygen heterolysis occurred in the acid-catalysed hydrolysis of *tert.*-butyl acetate :

$$Me{\cdot}CO{\cdot}O—CMe_3 + H{}^{18}OH \longrightarrow Me{\cdot}CO{\cdot}OH + Me_3C{\cdot}{}^{18}OH$$

Until recently, because of the absence of successful resolutions of tertiary alcohols, the stereochemical method of investigation was restricted to those tertiary alcohols which could be obtained active from natural sources.

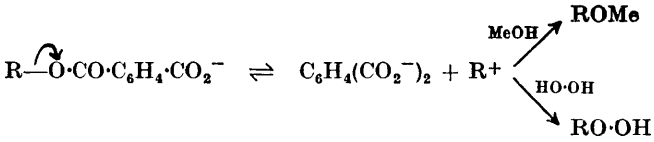
The reduction of optically active linaloöl to active 1-ethyl-1 : 5-dimethylhexanol provides a simple system for investigation. In alkaline aqueous dioxan 1-ethyl-1 : 5-dimethylhexyl acetate is hydrolysed by a $B_{AC}2$ mechanism to give the fully active alcohol with retention of configuration and optical purity, but in acidic aqueous acetone it reacts by unimolecular alkyl–oxygen heterolysis yielding the much racemised alcohol with inversion of configuration ; values of α_D^{17} (*l*, 1·0) are quoted below : [64]



R = 1-ethyl-1 : 5-dimethylhexyl

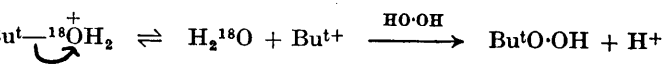
[60] Olsen and Hyde, *J. Amer. Chem. Soc.*, 1941, **63**, 2459.
[61] Cohen and Schneider, *ibid.*, 1941, **63**, 3383.
[62] Bunton, quoted by Ingold, ref. 4, page 780.
[63] Bunton, Comyns, and Wood, *Research*, 1951, **4**, 387.
[64] Bunton, Hughes, Ingold, and Meigh, *Nature*, 1950, **161**, 680.

Following their recent resolution of 1-ethyl-1 : 3-dimethylbutyl hydrogen phthalate, Doering and Zeiss have shown that this ester, when heated under reflux in methanol, undergoes alkyl–oxygen heterolysis to form the methyl ether with extensive configurational inversion ; [65] by a similar mechanism the sodium salt of this hydrogen phthalate alkylates hydrogen peroxide to yield 1-ethyl-1 : 3-dimethylbutyl hydroperoxide : [21]



R = 1-ethyl-1 : 3-dimethylbutyl

Under acidic conditions, many reactions of the corresponding tertiary alcohols proceed by alkyl–oxygen heterolysis. For example, *tert.*-butyl alcohol in the presence of 70—80% sulphuric acid alkylates benzene to form *tert.*-butylbenzene and 1 : 4-di-*tert.*-butylbenzene. Criegee and Dietrich's preparation of *tert.*-alkyl hydroperoxides by the reaction of tertiary alcohols with 90% hydrogen peroxide in the presence of sulphuric acid [66, 67] has been shown to proceed by alkyl–oxygen heterolysis by the use of alcohols labelled with the oxygen-18 isotope, whereupon the hydroperoxide which is formed is isotopically normal, and the eliminated water contains the heavy oxygen : [68]



Primary and Secondary Arylmethyl Compounds.—The introduction of α-aryl groups into the alkyl groups of esters or alcohols greatly increases the tendency of these compounds to undergo unimolecular alkyl–oxygen heterolysis (cf. the rates of the S_N1 reactions of the corresponding alkyl halides [52]). Although benzyl esters show no marked tendency to form benzyl cations, 1-phenylethyl esters are more reactive and, since they can be obtained in optically active forms, their behaviour has been closely studied.

Active 1-phenylethyl hydrogen phthalate is hydrolysed in aqueous sodium carbonate solution with about 20% of racemisation, and undergoes slow racemisation in formic acid giving the racemic *trans*-esterified products.[52] The reactivity of the hydrogen phthalate, however, is not sufficient for it to disproportionate or to form the sulphone (with sodium toluene-*p*-sulphinate) in 0·3N-sodium hydroxide solution, and it is not solvolysed in 90% hydrogen peroxide.[21] 1-Phenylethanol also, under acidic conditions, gives many of the characteristic reactions of carbonium ions, yielding 1-phenylethyl *p*-tolyl sulphone with sodium toluene-*p*-sulphinate in 90%

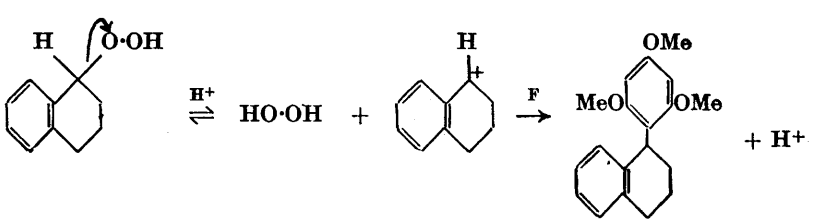
[65] Doering and Zeiss, *J. Amer. Chem. Soc.*, 1953, 75, 4733.
[66] Criegee and Dietrich, *Annalen*, 1948, **560**, 135.
[67] Davies and White, *Nature*, 1952, **170**, 668.
[68] Bassey, Bunton, Davies, Lewis, and Llewellyn, in the press.

formic acid, and the hydroperoxide with 90% hydrogen peroxide in the presence of a trace of acid.[68a] The optically active alcohol by this latter reaction yields the active hydroperoxide which can be reduced with a number of reagents, apparently without stereochemical change, to regenerate the largely racemised alcohol with inverted configuration,[69] *e.g.*,

$$\underset{\alpha_D\ -\ 43{\cdot}3^\circ}{\underset{|}{\overset{}{Ph{\cdot}CHMe}}\!\!\underset{OH}{|}} \overset{H^+}{\rightleftharpoons} H_2O + \overset{+}{Ph{\cdot}CHMe} \xrightarrow{HO{\cdot}OH} \underset{+\ 5{\cdot}2^\circ}{\underset{|}{\overset{}{Ph{\cdot}CHMe}}\!\!\underset{O{\cdot}OH}{|}} \xrightarrow{Redn.} \underset{+\ 1{\cdot}6^\circ}{\underset{|}{\overset{}{Ph{\cdot}CHMe}}\!\!\underset{OH}{|}}$$

The oxidation of the alcohol must hence involve inversion of configuration, as would be expected if a carbonium-ion mechanism is involved.[51]

1 : 2 : 3 : 4-Tetrahydro-1-naphthyl compounds are much more reactive than the corresponding 1-phenylethyl compounds. Optically active 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydrogen phthalate undergoes hydrolysis in aqueous sodium carbonate with loss of 89% of its optical purity, and is readily perhydrolysed in 90% hydrogen peroxide to give the inactive hydroperoxide. The active alcohol similarly reacts with 90% hydrogen peroxide in the absence of added acid yielding the racemic hydroperoxide, whereas 1-phenylethanol reacts only in the presence of added acid and gives a product retaining some optical asymmetry (see p. 219). The alcohol and hydrogen phthalate react with sodium toluene-*p*-sulphinate in formic acid solution to form the *p*-tolyl sulphone, and the alcohol and hydroperoxide alkylate 1 : 3 : 5-trimethoxybenzene in acetic–sulphuric acid solution : [23, 21, 22, 38]



F = 1 : 3 : 5-trimethoxybenzene

Baddiley and Chadwick have suggested that the ionisation of 1-phenylethyl compounds is inhibited because it involves an increase in the steric compression between non-bonded groups on formation of the carbonium ion. Since the carbon atoms of the 1 : 2 : 3 : 4-tetrahydro-1-naphthyl group are essentially coplanar before ionisation, this factor of instability in the ion is absent, and unimolecular heterolysis of these compounds proceeds more readily.[70]

The presence of 1-naphthyl,[71] 2-naphthyl,[72] 2-thienyl,[26] and 2-furyl [73]

[68a] Balfe, Downer, Evans, Kenyon, Poplett, Searle, and Tarnoky, *J.*, 1946, 797; Balfe, Beavan, and Kenyon, *J.*, 1951, 376.

[69] Davies, Feld, and White, *Chem. and Ind.*, 1954, 1322.

[70] Baddiley and Chadwick, *J.*, 1951, 368.

[71] Balfe, Downer, Evans, Kenyon, Poplett, Searle, and Tarnoky, *J.*, 1946, 797.

[72] Balfe, Kenyon, and Searle, *J.*, 1951, 380.

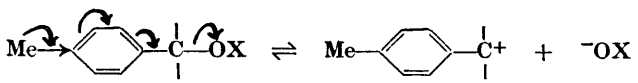
[73] Duveen and Kenyon, *J.*, 1936, 621.

groups in the alpha position similarly promotes alkyl–oxygen heterolysis. The 1-naphthyl and 2-naphthyl groups are more effective in this respect than the phenyl group. 1-1′-Naphthyl- and 1-2′-naphthyl-ethyl hydrogen phthalates suffer respectively 61% and 57% of loss of optical purity on hydrolysis in aqueous sodium carbonate, yield the methyl and ethyl ethers on heating in aqueous methanol and ethanol respectively, and are *trans*-esterified in anhydrous formic and acetic acids; under similar conditions 1-phenylethyl hydrogen phthalate is hydrolysed with a loss of only 11% of optical purity, is unreactive towards aqueous methanol and ethanol, and is *trans*-esterified only in aqueous formic and acetic acids.[74]

Diarylmethyl derivatives are more reactive by unimolecular alkyl–oxygen heterolysis than the monoarylmethyl compounds (cf. the corresponding S_N1 reactivity of the halides). The hydrogen phthalate of benzhydrol does not disproportionate in aqueous sodium hydroxide but is perhydrolysed in hydrogen peroxide to give the hydroperoxide in poor yield. 1-Naphthylbenzyl hydrogen phthalate is apparently slightly more reactive;[20] unfortunately neither of these compounds can be resolved, the former because of the symmetry of the molecule and the latter because the alkaloidal salts cannot be crystallised. The sensitive test of racemisation accompanying the hydrolysis of esters cannot therefore be applied.

Substituted Arylmethyl Compounds.—Electron release by substituents in the *ortho*- and *para*-positions of the benzene ring in arylmethyl derivatives will be relayed by conjugation to the alkyl–oxygen bond and will therefore facilitate the formation of carbonium ions; conversely, electron-attracting substituents will hinder ionisation. The effects of the more important types of substituents are now discussed.

(i) **Alkyl substituents.** Alkyl groups release electrons by the inductive and hyperconjugative effects, and 4-methyldiphenylmethyl, 2 : 4′-dimethyldiphenylmethyl, and 2 : 4 : 6-trimethyldiphenylmethyl hydrogen phthalates show progressively increasing reactivity over diphenylmethyl hydrogen phthalate:[75]

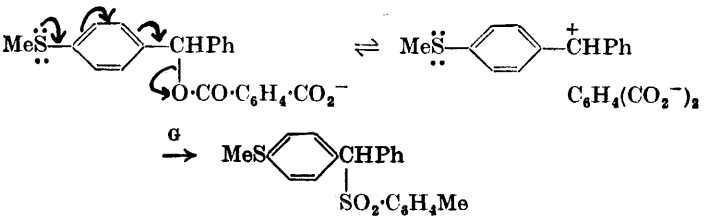


(ii) **RS and RSO_2 substituents.** The significance of the electronic effect of ring substituents is illustrated very clearly in the difference in the reactivity of the hydrogen phthalates of 4-methylthio- and 4-methylsulphonyldiphenylmethanols. The former is more reactive than diphenylmethyl hydrogen phthalate; it racemises extensively during hydrolysis in aqueous sodium hydroxide, yields a half-active neutral phthalate in aqueous 0·3N-sodium hydroxide solution or a racemic sulphone when sodium toluene-*p*-sulphinate is present, and a racemic ethyl ether when warmed in absolute ethanol. Conjugative electron release by the Me–S– group is relayed

[74] Balfe, Beavan, and Kenyon, *J.*, 1951, 376.

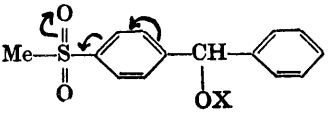
[75] Balfe, Hargreaves, and Kenyon, *J.*, 1951, 375; Davies, Kenyon, Lyons, and Rohan, *J.*, 1954, 3474.

through the benzene ring to promote alkyl–oxygen heterolysis, *e.g.*,

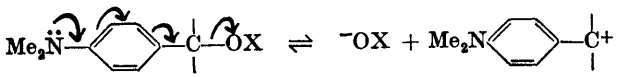


G = toluene-*p*-sulphonyl ion

Oxidation of the $CH_3–\ddot{S}–$ group to $CH_3–SO_2–$ completely changes the reactivity of the ester : the optically active hydrogen phthalate now undergoes hydrolysis without racemisation, and yields no neutral ester nor reacts with sodium toluene-*p*-sulphinate when dissolved in aqueous sodium hydroxide. The methylsulphonyl group is electron attracting (—*C*) and reverses the tendency of the phenyl groups to promote alkyl–oxygen heterolysis,[76] *i.e.*,



(iii) **R_2N substituents.** Amino-groups exert an effect similar to that of the methylthio-group. 4-Dimethylaminodiphenylmethyl hydrogen phthalate in 0·3N-sodium hydroxide solution reacts with sodium toluene-*p*-sulphinate to yield a sulphone, and the free alcohol reacts with methanol and with aqueous methanolic sodium toluene-*p*-sulphinate to yield the methyl ether and the sulphone respectively.[18, 71] Similarly bis-(4-dimethylaminophenyl)methanol disproportionates on treatment with trichloroacetic acid in acetone to form the dialkyl ether. In all these reactions conjugative electron release of the unshared electrons of the amino-group is relayed through the benzene ring to promote alkyl–oxygen heterolysis : [77]

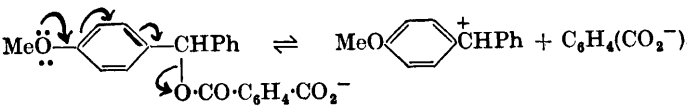


(iv) **RO substituents.** The introduction of alkoxy-groups into the *ortho-* and *para*-positions of the aromatic ring powerfully promotes alkyl–oxygen heterolysis, again by the operation of conjugative electron release. For example, whereas benzyl hydrogen phthalate shows no pronounced tendency to ionise, 4-methoxybenzyl hydrogen phthalate very readily yields the *p*-tolyl sulphone by reaction with sodium toluene-*p*-sulphinate in aqueous 0·3N-sodium hydroxide.[18, 71, 78]

1-(4-Methoxyphenyl)ethyl esters (and to a rather less extent the

[76] Balfe, Dabby, and Kenyon, *J.*, 1951, 382.
[77] Balfe, Kenyon, and Thain, *J.*, 1952, 790.
[78] Balfe, Doughty, Kenyon, and Poplett, *J.*, 1952, 605.

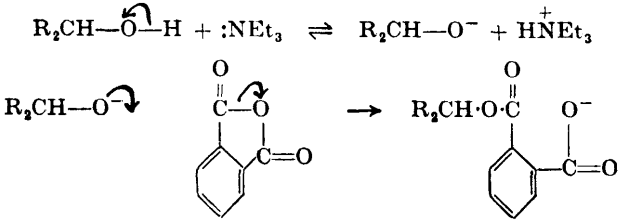
corresponding 2-methoxy-compounds) are similarly more reactive than 1-phenylethyl compounds, undergoing hydrolysis with racemisation, and yielding sulphones and neutral esters from alkaline solution. The 4-methoxydiphenylmethyl esters have been very fully investigated and again demonstrate all the usual reactions; again the isomeric 2-methoxy-compounds are somewhat less reactive. A similar difference in the reactivities of the *ortho*- and *para*-substituted compounds has been observed in the properties of 2- and 4-methoxyphenyl-1-naphthylmethyl compounds. In all these examples the *ortho*- or *para*-methoxy groups facilitate alkyl–oxygen heterolysis by conjugative electron release to the alkyl–oxygen bond, *e.g.*,



The reduced effectiveness of the methoxy-group in the *ortho*-position may probably be ascribed to the superposition of the inductive electron attraction of the group ($-I$, CH_3–O←) upon its more powerful conjugative electron release ($+C$, CH_3–$\ddot{O}$→); this inductive effect will undergo attenuation on relay round the aromatic ring and hence will operate more effectively from the *ortho* than from the *para* position in decreasing the electron-releasing power of the "alkyl" carbon atom and reducing its tendency to ionise.

In contrast to the 2- and 4-methoxydiphenylmethyl compounds, 3-methoxydiphenylmethyl hydrogen phthalate shows little tendency to react by alkyl–oxygen heterolysis; the $+C$ effect of the methoxyl group cannot be relayed to the alkyl–oxygen bond from the *meta* position, and hence cannot facilitate ionisation.[17, 20, 71]

The arylmethyl compounds containing more than one *ortho* or *para* alkoxy-group are the most reactive compounds known to undergo alkyl–oxygen heterolysis. As the tendency of an alcohol to yield a carbonium ion is increased, the tendency towards oxygen–hydrogen heterolysis (—O→H) decreases. Pyridine ceases to be a strong enough base to remove the proton and catalyse esterification by a $B_{AC}2$ mechanism, but a stronger base may be effective. For example di-(4-methoxyphenyl)methanol is unreactive towards phthalic anhydride in the presence of pyridine but is esterified in the presence of triethylamine under similar conditions.[79]



R = *p*-methoxyphenyl

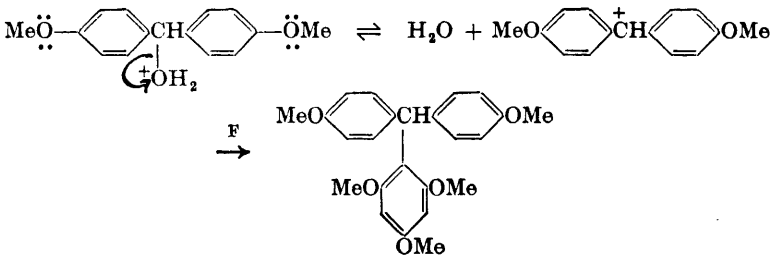
[79] Balfe, Kenyon, and Thain, *J.*, 1951, 386.

Esterification involving alkyl–oxygen heterolysis in the alcohol, however, proceeds readily by the formation of the acetate in acetic acid solution (the $A_{AL}1$ mechanism) :

$$R_2CH{\cdot}OH + H^+ \rightleftharpoons R_2CH^+ + H_2O$$
$$R_2CH^+ + AcOH \rightleftharpoons R_2CH{\cdot}OAc + H^+$$

R = *p*-methoxyphenyl

Di-(4-methoxyphenyl)methyl hydrogen phthalate is unstable and both in the solid state or in solution disproportionates into phthalic acid and the neutral phthalate ; similarly the alcohol under mildly acidic conditions readily decomposes into water and the dialkyl ether. Attempts to prepare the hydroperoxide from the alcohol resulted in the isolation of only the dialkyl peroxide, which may result either from disproportionation of the hydroperoxide or from its alkylation by the alcohol. The alcohol, its esters, and the peroxide all undergo the reactions typical of alkyl–oxygen heterolysis extremely readily. For example, the hydrogen phthalate in aqueous acetone solution reacts with sodium toluene-*p*-sulphinate to form the *p*-tolyl sulphone in 92% yield in one minute, and the alcohol and the peroxide in acetic acid solution alkylate *s*-trimethoxybenzene yielding 2 : 4 : 6 : 4′ : 4″-pentamethoxytriphenylmethane : [38, 39, 79]



F = 1 : 3 : 5-trimethoxybenzene

Derivatives of alcohols carrying the 2 : 4 : 6-trimethoxyphenyl group are similarly very reactive, and behave as powerful alkylating agents. All attempts to prepare the hydrogen phthalate or succinate of 1-(2 : 4 : 6-trimethoxyphenyl)ethanol with pyridine or triethylamine as catalysts, or *via* the potassium salt of the alcohol—reactions which would involve oxygen–hydrogen fission—were unsuccessful, but the alcohol reacted readily with acetic acid, presumably again by an $A_{AL}1$ mechanism, to yield the acetate. The alcohol alkylates thionacetic acid, thiolacetic acid (on the SH group), thiols, sulphinic acids, sulphonamides, activated methylene groups, and trialkoxybenzenes ; similarly the acetate alkylates alcohols and phenols, oximes, ammonia (to give the dialkylamine), ethyl acetoacetate, *o*-bromobenzoic acid, and sodium toluene-*p*-sulphinate.[24]

Xanthhydrol, which may be regarded as an *ortho*-alkoxybenzhydrol, and the corresponding hydroperoxide and peroxide also very readily yield carbonium ions. Under mildly acidic conditions the alcohol will alkylate

hydrogen peroxide, hydrogen sulphide, amides, reactive methylene and methyl groups, aromatic compounds, sulphinates, and similar nucleophilic reagents ; [38, 39] the derivatives which it forms with amides [80] and with alkyl hydroperoxides [22] have been used for the characterisation of these compounds.

Tertiary Arylmethyl Compounds.—Much physical evidence is available that solutions of tertiary di- and tri-aryl methanols in strong acids yield high concentrations of carbonium ions,[36] and even under much more mildly acidic conditions these alcohols behave as powerful aralkylating agents towards aromatic compounds, sulphinic acids, thiols, hydrogen peroxide, hydrazoic acid,[81] and other nucleophilic reagents.

The reactions of the corresponding esters have received much less attention partly because of the absence till recently of suitable methods for their resolution.[82] The results which have been obtained indicate that the behaviour of these compounds is similar to that of the esters of the more reactive secondary alcohols. For example the solvolysis of triphenylmethyl benzoate in ethanol and of triphenylmethyl acetate in methanol to form the corresponding ethers has been shown to be kinetically of the first order, the rates of reaction being unchanged by the addition of small amounts of the corresponding alkoxide ions.[83] The reaction therefore proceeds *via* unimolecular alkyl–oxygen heterolysis. Like di-(4-methoxyphenyl)methanol, 1-methyl-1-phenylpropanol can be esterified with phthalic anhydride in the presence of triethylamine but not of pyridine. The active hydrogen phthalate racemises in acidic acetone, reacts in 90% formic acid solution with *tert.*-butyl hydroperoxide and with sodium toluene-*p*-sulphinate to yield the dialkyl peroxide and sulphone respectively, and in 90% hydrogen peroxide yields the alkyl hydroperoxide. Complete or extensive racemisation accompanies these reactions indicating that at least a large proportion of the reaction proceeds by a carbonium ion mechanism.[84]

Conclusion

From the foregoing account it may be concluded that whereas the broad outline of the phenomenon of alkyl–oxygen heterolysis is apparent, much consolidation is required in matters of detail. The factors which govern which of the possible mechanisms (S_N1, S_N2, or S_Ni) is followed particularly need clarification, and much work needs to be done on the esters of inorganic oxy-acids. With the increasing availability of the oxygen-18 isotope for tracer studies, and the application of the kinetic method, advances in these directions should soon be forthcoming.

[80] Phillips and Pitt, *J. Amer. Chem. Soc.*, 1943, **65**, 1355 ; Phillips and Frank, *J. Org. Chem.*, 1944, **9**, 9.

[81] Arcus and Mesley, *J.*, 1953, 178.

[82] Zeiss, *J. Amer. Chem. Soc.*, 1951, **73**, 2391.

[83] Hammett and Rudesill, *J. Amer. Chem. Soc.*, 1950, **72**, 7269 ; Gomberg and Davies, *Ber.*, 1903, **36**, 3926 ; Bunton, quoted by Ingold, ref. 4, page 764.

[84] Kenyon and Salamé, unpublished work ; Davies, unpublished work.