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Sulphonyl Transfer Reactions

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1 Introduction

Although organic sulphur compounds have a long history and many important biological compounds have sulphur-containing functional groups, their study has remained largely peripheral to main-stream organic chemistry.[1] Sulphur exists in a number of oxidation states in organic compounds and, within each, may have different coordination numbers. We shall be concerned in this review with substitution reactions in solution of the particular type of sulphur(VI) compounds shown in equation 1 where X^- and Y^- are nucleofuge and nucleophile, respectively.

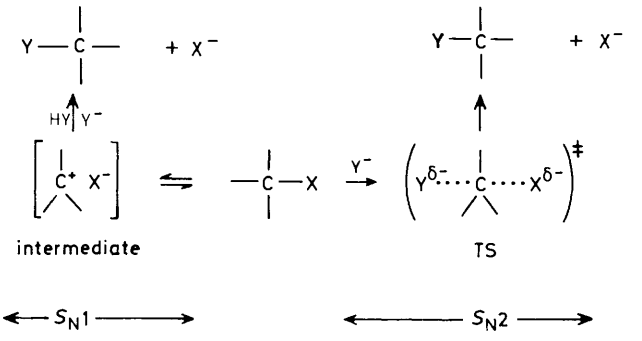
$$\mathrm{Ar(R)}\underset{\underset{\mathrm{O}}{\|}}{\overset{\overset{\mathrm{O}}{\|}}{-\mathrm{S}-}}\mathrm{X} + \mathrm{Y^-(HY)} \xrightarrow{\text{solvent}} \mathrm{Ar(R)}\underset{\underset{\mathrm{O}}{\|}}{\overset{\overset{\mathrm{O}}{\|}}{-\mathrm{S}-}}\mathrm{Y} + \mathrm{X^-(HX)} \qquad (1)$$

In this overall transformation, an arenesulphonyl (or alkanesulphonyl) group may be regarded, conceptually though not necessarily mechanistically, as undergoing transfer as a Lewis acid ($ArSO_2^+$ or RSO_2^+) from one Lewis base (X^-) to another (Y^-). Reactions of equation 1 are used as methods of enzyme modification,[1] and, given the recent and continuing redirection of chemical investigations towards biological systems, it is not surprising that we are currently witnessing a significant development of interest in their mechanisms. We shall consider in this review how such reactions are currently believed to take place, and how their mechanisms relate to those of better known reactions of other types of compounds, *e.g.* S_N1 and S_N2 substitutions of alkyl halides and arenesulphonates (Scheme 1) and substitution reactions by addition–elimination of carboxylic acid derivatives (Scheme 2).

Nucleophilic substitutions at saturated carbon were among the first to be investigated in mechanistic detail and are still discussed using the terminology described by Ingold.[2] Since Ingold's seminal work, there have been innumerable

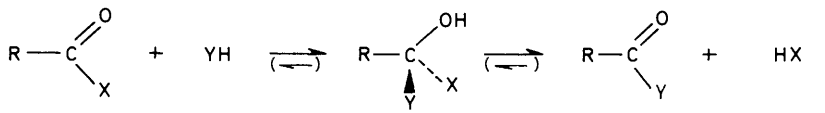
[1] 'Organic Sulphur Compounds', Pergamon Press, Vol. 1, ed. N. Kharasch, 1961; Vol. 2, ed. N. Kharasch and C. Y. Meyers, 1966; 'Organic Chemistry of Sulfur', ed. S. Oae, Plenum Press, New York and London, 1977; 'The Enzymes', 3rd Edn. ed. P. D. Boyer, Academic Press, New York, 1970, Vol. 1, Ch. 2, by E. Shaw; E. Ciuffarin and A. Fava, *Progr. Phys. Org. Chem.*, 1968, **6**, 81.

[2] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', Cornell University Press, 2nd Edn., 1969.



$X^- = Br^-$, $p\text{-}CH_3C_6H_4SO_3^-$ (TsO^-)
$Y^-(HY) = EtO^-(EtOH)$, $OH^-(H_2O)$
$Y^- = N_3^-$, SCN^-

Scheme 1



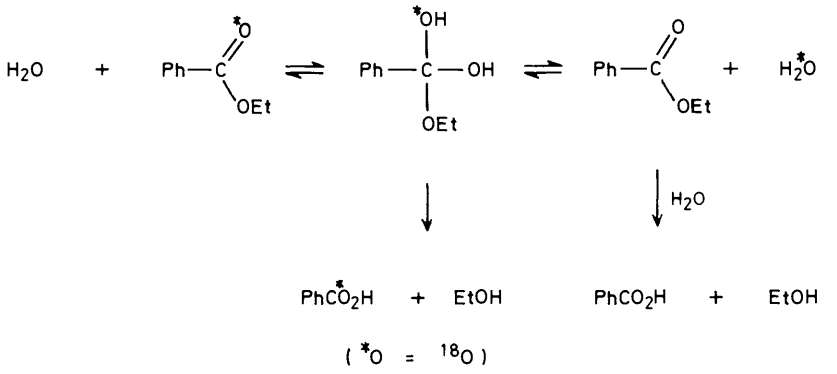
X = Cl, OR', O_2CR'
YH = H_2O, $R''NH_2$, $R''OH$

Scheme 2

investigations directed at elucidating the finer details of both S_N1 and S_N2 extremes, and also at the more difficult problem of characterizing those borderline reactions which appear to show some features of both S_N1 and S_N2 mechanisms. These are now recognized as reactions in which a postulated intermediate in the S_N1 mechanism is so reactive, *i.e.* short-lived, that there is doubt as to whether it really exists at all.[3]

The most obvious comparisons for sulphonyl transfer, however, are substitution reactions of carboxylic acid derivatives, *i.e.* acyl transfer, Scheme 2. This is a process of enormous importance and interest since it occurs in so many biological reactions catalysed by enzymes. Consequently, it has attracted attention over many years and is reasonably well understood.[4] The initial nucleophilic attack to give the tetrahedral intermediate may be reversible, as also may be the departure of the nucleofuge in the final step, depending upon the

[3] W. P. Jencks, *Chem. Soc. Rev.*, 1981, **10**, 345.
[4] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53; W. P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw-Hill, New York, 1969; C. Walsh, 'Enzymatic Reaction Mechanisms', Freeman, San Francisco, 1979.

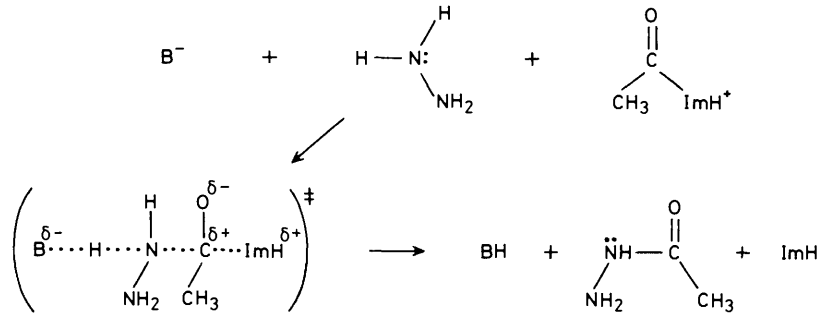


Scheme 3

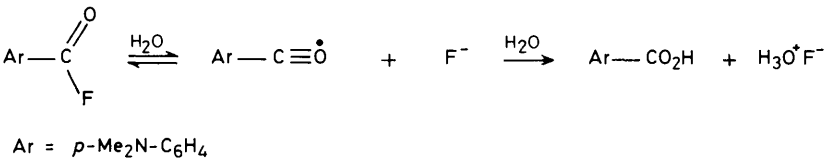
particular reaction. Also, either step may be catalysed by acids or bases, and either may be rate determining, again depending upon the natures of the reactants and the reaction conditions. In the case of the hydrolysis of esters, with either acid or base catalysis, the reversible formation of an intermediate was established by demonstrating exchange of isotopically labelled oxygen between recovered starting material and the water of the aqueous medium, Scheme 3.[5] Some stable analogues of these tetrahedral intermediates have been isolated[6] and others have been observed spectroscopically in chemical reactions.[7]

If the nature of the acyl transfer is such that there is no free-energy barrier separating the product of the initial nucleophilic attack from the product of the departure of the nucleofuge, then no intermediate exists and the mechanism has become an enforced concerted (S_N2-type) displacement, *e.g.* the base-catalysed hydrazinolysis of acetylimidazolium cation in Scheme 4.[3,8] But whereas the transition state of the S_N2 reaction of alkyl halides in Scheme 1 involves a penta-coordinated carbon atom and is trigonal bipyramidal,[9] that in the acyl transfer of Scheme 4 has a tetra-coordinated central carbon atom and a (distorted) tetrahedral structure. A non-enforced concerted mechanism for acyl transfer has also been identified by Williams and his colleagues[10] in the transfer of the acetyl group between phenolate nucleophiles. In these reactions, the transition state still involves a tetra-coordinated central carbon, but its structure is less 'intermediate-like' than in the enforced concerted process.

[5] M. L. Bender, *J. Am. Chem. Soc.*, 1951, **73**, 1626; M. L. Bender and R. J. Thomas, *ibid.*, 1961, **83**, 4189; M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *ibid.*, 1961, **83**, 4193.
[6] G. A. Rogers and T. C. Bruice, *J. Am. Chem. Soc.*, 1974, **96**, 2481; F. Khouri and M. K. Kaloustian, *ibid.*, 1979, **101**, 2249; J. Hine, D. Ricard, and R. Perz, *J. Org. Chem.*, 1973, **38**, 110.
[7] B. Capon, A. K. Ghosh, and D. M. A. Grieve, *Acc. Chem. Res.*, 1981, **14**, 306; B. Capon, M. I. Dosunmu, and M. de N. de Matos Sanchez, *Adv. Phys. Org. Chem.*, 1985, **21**, 37.
[8] M. I. Page and W. P. Jencks, *J. Am. Chem. Soc.*, 1972, **94**, 8828.
[9] J. Chandrasekhar, S. F. Smith, and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1985, **107**, 154.
[10] S. Ba-Saif, A. K. Luthra, and A. Williams, *J. Am. Chem. Soc.*, 1987, **109**, 6362.

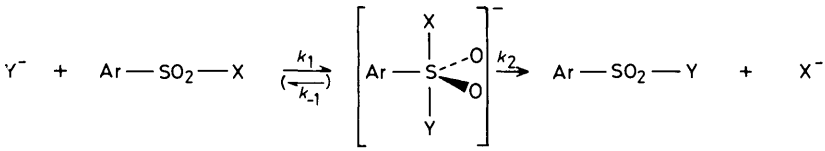


Scheme 4



Ar = *p*-Me_2N-C_6H_4

Scheme 5



(2)

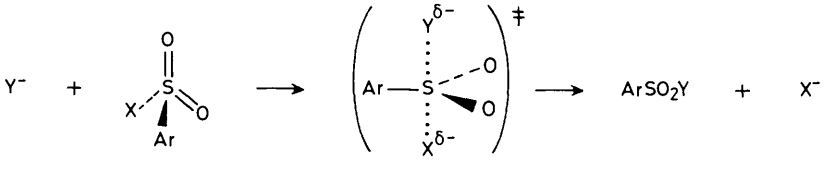
Scheme 6

Unimolecular mechanisms of acyl transfer have also been identified both in the gas phase[11] and in solution, *e.g.* Scheme 5.[12]

2 Nucleophilic Substitution at Four-coordinated Sulphur(VI)

The stepwise mechanisms corresponding to S_N1 and addition–elimination (S_AN) processes (equation 2 and Scheme 6 respectively) can be regarded as limiting cases for the sulphonyl transfer from X to Y in equation 1. Between these stepwise extremes, there is the concerted one-step S_N2 alternative (Scheme 7). These three conceptually distinct routes for the overall transformation of equation 1 are represented in the free-energy reaction map of Figure 1 from which contours have been omitted for clarity.[3,13,14]

[11] J. K. Kim and M. C. Caserio, *J. Am. Chem. Soc.*, 1981, **103**, 2124.
[12] B. D. Song and W. P. Jencks, *J. Am. Chem. Soc.*, 1987, **109**, 3160.
[13] R. A. More O'Ferrall, *J. Chem. Soc.* (*B*), 1970, 274.
[14] H. Maskill, 'The Physical Basis of Organic Chemistry', Oxford University Press, 1985.



(5)

Scheme 7

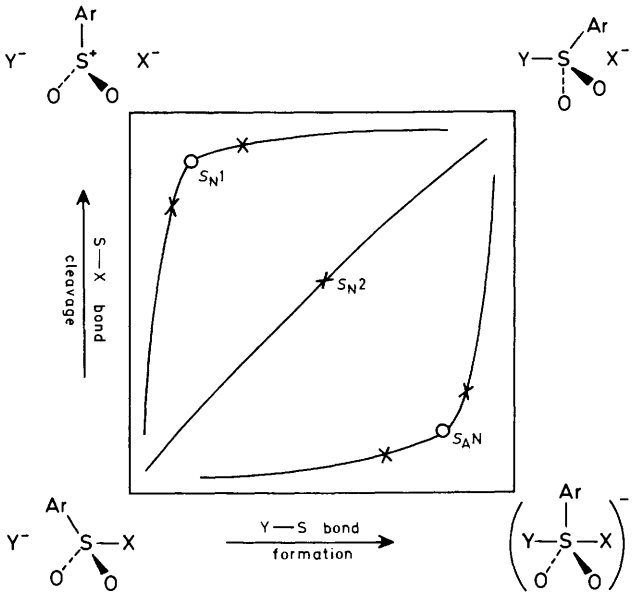


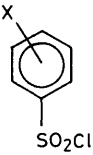
Figure 1 *Free-energy reaction map for the S_N1, S_N2, and S_AN mechanisms for the sulphonyl transfer reaction of equation 1*

$$ArSO_2X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArSO_2^+ X^- \xrightarrow[k_2]{Y^-(HY)} ArSO_2Y + X^-(HX) \qquad (2)$$

A. The S_N1 Mechanism.—There appeared to be the classic evidence in the earlier literature for an S_N1 reaction of compounds such as *N,N*-dimethylsulphamoyl chloride in equation 3, *i.e.* product formation but no rate effect upon solvolysis caused by added nucleophiles,[15] but this was subsequently shown to be in error. These are S_N2 reactions.[16]

$$Me_2NSO_2Cl + 2H_2O \xrightarrow{H_2O} Me_2NSO_3H + H_3O^+ + Cl^- \qquad (3)$$

[15] H. K. Hall, *J. Am. Chem. Soc.*, 1956, **78**, 1450.
[16] O. Rogne, *J. Chem. Soc.* (*B*), 1969, 663.



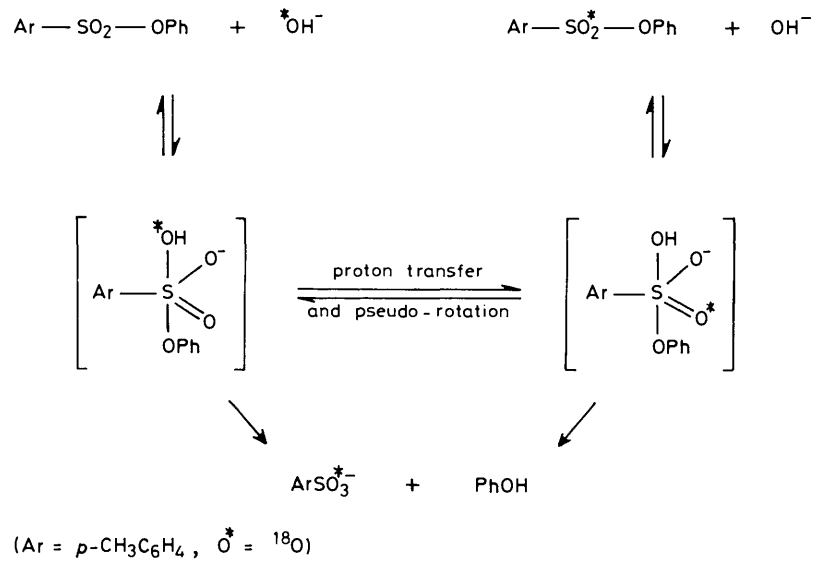
(1) a. X = 2,4,6-trimethyl
b, X = 4-methoxy
c, X = 2,4-dimethoxy

In principle, and on the basis of results for aroyl halides,[12] there ought to be an S_N1 reaction mode available to arenesulphonyl chlorides (1) if substituents in the arene ring are sufficiently electron-supplying. There have in fact been claims that the 2,4,6-trimethyl compound (1a) reacts *via* an S_N1 mechanism,[17,18] but here also the evidence has been disputed.[16,19] Tonnet and Hambly[18] predict, however, that, whereas the 4-methoxy compound (1b) does not undergo hydrolysis by an S_N1 mechanism, the 2,4-dimethoxy compound (1c) should.

B. The S_AN Mechanism.—The credibility of the S_AN mechanism, Scheme 6, for the reactions of equation 1, like that for the S_N1, has waxed and waned over the years. The intermediate in this route, (2) if it exists, will be trigonal bipyramidal, and stable analogues are known.[20] Its electronic structure could include up to twelve electrons in the valence shell of the sulphur atom through the use of *d*-orbitals.[21] In one limiting case of this mechanism, the formation of the intermediate is rate determining ($k_2 \gg k_{-1}$) and, at the other, the rate-determining step is its decomposition ($k_{-1} \gg k_2$).[14]

Isotopic labelling studies comparable with those carried out by Bender[5] in the acyl transfer reactions indicated that no exchange takes place between starting material and the aqueous solvent in the hydrolysis of phenyl tosylate.[22] However, whilst a positive result would have implicated a mechanism with a reversibly formed intermediate, the negative result does not necessarily disprove such a mechanism. The S_AN mechanism involves an intermediate (2) in which nucleophile and nucleofuge occupy apical positions. Consequently, there must be *pseudo*-rotation within this reversibly formed intermediate for there to be interchange of apical and equatorial ligands and hence isotopic exchange, Scheme 8. In contrast to the otherwise similar phosphorus compounds, it appears

[17] R. V. Vizgert, *Russ. Chem. Rev.*, 1963, **32**, 1; E. Tommila and P. Hirsjarvi, *Acta Chem. Scand.*, 1951, **5**, 659.
[18] M. L. Tonnet and A. N. Hambly, *Aust. J. Chem.*, 1971, **24**, 703.
[19] O. Rogne, *J. Chem. Soc. (B)*, 1968, 1294; 1970, 1056.
[20] E. F. Perozzi, J. C. Martin, and I. C. Paul, *J. Am. Chem. Soc.*, 1974, **96**, 6735.
[21] F. P. Ballistreri, A. Cantone, E. Maccarone, G. A. Tomaselli, and M. Tripolone, *J. Chem. Soc., Perkin Trans. 2*, 1981, 438.
[22] C. A. Bunton and C. F. Frei, *J. Chem. Soc.*, 1951, 1872; S. Oae, T. Fukumoto, and R. Kiritani, *Bull. Chem. Soc. Jpn.*, 1963, **36**, 346.



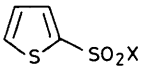
Scheme 8

that sulphonyl groups do not allow easy *pseudo*-rotation,[23,24] so even if the S_AN mechanism does operate, isotopic exchange would not be observed.

When the rates of reaction of benzenesulphonyl halides with three nucleophiles (aniline, n-butylamine, and hydroxide) were studied in aqueous acetonitrile, the relative rates for chloride, bromide, and iodide nucleofuges were found to be almost the same.[25] However, compared with these three, fluoride as a leaving group varied according to the nature of the nucleophile, *e.g.* k_{Cl}/k_F ratios for hydroxide, n-butylamine, and aniline were 4.6, 4.2×10^3, and 1.65×10^5, respectively. These leaving group mobilities were explained using the S_AN mechanism of Scheme 6. When X = Cl, Br, or I, the attack of the nucleophile, k_1, is rate determining ($k_2 \gg k_{-1}$) and the overall rate is not much influenced by the S–Hal bond strength. The mechanism is altered by changing the leaving group to fluoride whereupon k_2, the decomposition of the intermediate, becomes rate limiting ($k_{-1} \gg k_2$). The substantial positive Hammett parameter, $\rho = 2.79$, from the alkaline hydrolysis of three *para*-substituted benzenesulphonyl fluorides in aqueous dioxan was presented by the same Italian group as further evidence of this mechanism.[26]

The S_AN mechanism was also favoured, by another Italian group, from a study of the reactions of thiophen-2-sulphonyl halides (3) in methanol.[27] The sensitivity

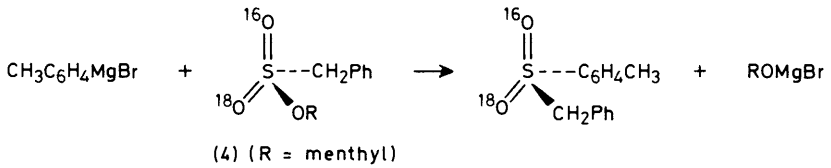
[23] R. Tang and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 5644.
[24] E. T. Kaiser, *Acc. Chem. Res.*, 1970, **3**, 145.
[25] E. Ciuffarin, L. Senatore, and M. Isola, *J. Chem. Soc., Perkin Trans. 2*, 1972, 468.
[26] E. Ciuffarin and L. Senatore, *Tetrahedron Lett.*, 1974, 1635.
[27] E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J. Org. Chem.*, 1974, **39**, 3286; A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *ibid.*, 1973, **38**, 2457.



(3) X = F, Cl, Br

of these compounds towards a range of substituted anilines was claimed to be similar to those of benzenesulphonyl halides and the authors concluded that an addition–elimination mechanism operates in both cases. This group also investigated the reaction kinetics of the parent compounds (3) plus three 5-substituted derivatives with anilines in a wide range of pure solvents (protic, aprotic, and deuteriated) and in mixed solvents at 25 °C,[28] They found that two single-parameter correlations (using the dielectric constant of the solvent) best described the solvent effects: one for the protic solvents with a positive slope, and another for aprotic solvents with a negative slope. They discussed their results in terms of the mechanism of Scheme 6 with rate-determining bond making (k_1) in protic solvents, and bond breaking (k_2) in aprotic ones.

However, later publications from Italy reporting the reactivity of substituted derivatives of (3) with nucleophiles in water and methanol–acetonitrile,[29] and the kinetics of hydrolysis, methanolysis, and ethanolysis of a range of alkane-, alkene-, arene-, and heteroarene-sulphonyl halides[21] were interpreted in terms of S_N2 mechanisms with 'tight' or 'loose' transition states. These mechanisms could become S_N1-like or S_AN mechanisms according to the nature of the nucleophile, ring substituent, leaving group, and solvent. Such a description is much more in accord with a wide range of other evidence described in the next section.



(4) (R = menthyl)

Scheme 9

C. The S_N2 Mechanism.—In 1969 the isotopically labelled chiral sulphonate (4) was reported to react with *p*-tolyl Grignard reagent to give the chiral sulphone with inversion of configuration at sulphur, Scheme 9.[30] This and other stereochemical evidence[23] were entirely consistent with the bimolecular displacement reaction of Scheme 7 that had been developed from earlier kinetics[31] and

[28] A. Arcoria, V. Librando, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Tetrahedron*, 1977, **33**, 105; A. Arcoria, F. P. Ballistreri, and G. A. Tomaselli, *ibid.*, 1978, **34**, 2545.

[29] A. Arcoria, F. P. Ballistreri, G. Musumarra, and G. A. Tomaselli, *J. Chem. Soc., Perkin Trans 2*, 1981, 221.

[30] M. A. Sabol and K. K. Andersen, *J. Am. Chem. Soc.*, 1969, **91**, 3603.

[31] C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, 1953, **75**, 246; R. B. Scott and R. E. Lutz, *J. Org. Chem.*, 1954, **19**, 830; R. B. Scott and H. L. McLeod, *ibid.*, 1956, **21**, 388.

the (negative) isotope scrambling results.[22,24] During the sixties, Hambly and co-workers in Australia published an important series of papers on this subject.[18,32] From their studies of the rates of solvolysis of alkane- and arene-sulphonyl halides in solvents of varying polarity, they concluded that in all cases except, perhaps, one, an S_N2 mechanism was taking place in which there are continuous changes in the structure of the transition state according to the nature of the substrate and the polarity of the solvent. When the hydrolysis of substituted benzenesulphonyl chlorides in aqueous dioxan containing mole fractions of water above 0.9 was investigated in a Hammett-type study, substituents were found to have effects opposite from those that they had had in the media of lower polarity, *i.e.* the ρ-value changed sign.[18] A similar phenomenon was subsequently reported by Tomaselli and his colleagues.[21] Hambly's interpretation, based also on $\Delta C_p^{\ddagger}$ and $\Delta V^{\ddagger}$ results, was that under the better ionizing conditions the S–Cl bond stretching in the transition state is appreciably ahead of the S–O bond formation. Consequently, the reaction is facilitated by electron-releasing substituents which stabilize the developing positive charge on sulphur and the Hammett ρ is negative. In the less ionizing conditions, S–O bond formation is ahead of S–Cl bond rupture, and a positive ρ indicates the ability of electron-withdrawing groups to stabilize the increased electron density on sulphur in the transition state. [For 2,4,6-trimethylbenzenesulphonyl chloride, (1a),[18] and presumably other compounds with better electron-releasing substituents in the benzene ring, an S_N1 mechanism may intervene in the more ionizing media as had been proposed earlier,[17] see Section 2A above.]

About this time, Rogne in Norway was publishing his important work on sulphonyl chlorides. He observed that benzenesulphonyl chloride underwent hydrolysis in neutral and alkaline conditions, and faster direct nucleophilic substitutions with aniline, azide, thiosulphate, and fluoride to give stable products.[19] As no reaction was detected with the softer thiocyanate, bromide, and iodide, polarizability is less important in determining nucleophilic reactivity towards the hard sulphonyl electrophilic centre. With pyridine, nitrite, and acetate, the kinetics, stoicheiometry and solvent deuterium kinetic isotope effects of the reaction with arenesulphonyl chlorides were consistent with nucleophile catalysis of the hydrolytic process.

It was established from the study of the rates of hydrolysis of substituted benzenesulphonyl chlorides with substituted pyridines that this catalytic reaction occurred by an initial rate-determining formation of the unstable sulphonylpyridinium intermediate and that the rate was increased by electron-donating substituents in the pyridine and electron-attracting substituents in the benzene ring.[33] The substituent effects were correlated by Brönsted and Hammett equations and the β_{nuc} and ρ parameters were found to be interrelated and sensitive to the reactivity of the system.

[32] F. E. Jenkins and A. N. Hambly, *Aust. J. Chem.*, 1961, **14**, 190, 205; R. Foon and A. N. Hambly, *ibid.*, 1962, **15**, 668, 684; M. L. Tonnet and A. N. Hambly, *ibid.*, 1970, **23**, 2427; R. Foon and A. N. Hambly, *ibid.*, 1971, **24**, 713.

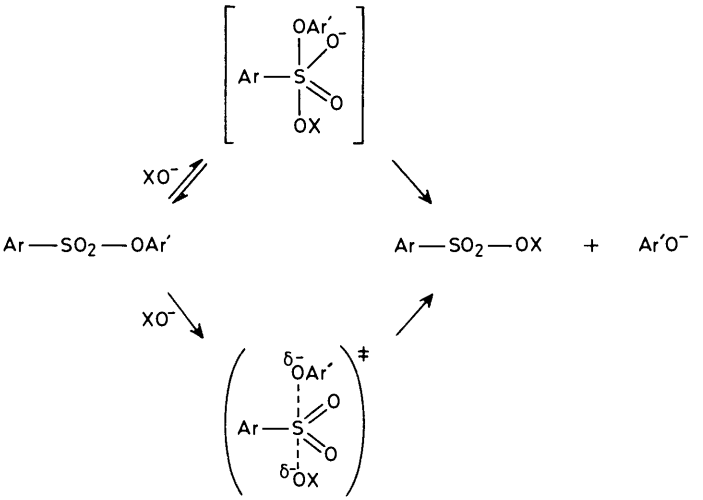
[33] O. Rogne, *J. Chem. Soc.* (*B*), 1970, 727; *J. Chem. Soc., Perkin Trans. 2*, 1972, 489.

A similar study of the rates of reactions of substituted benzenesulphonyl chlorides with a series of substituted anilines in methanol yielded very similar results.[34] Again, the values of the β_{nuc} and ρ parameters were interpreted as indicating that the reaction was a direct displacement mechanism with a tighter or looser transition state depending on the substituents present. The retarding effect of one or two *ortho*-methyl substituents in the aniline was found to decrease with increasing electron-donating ability of the substituents in the ring of the benzenesulphonyl chloride,[35] consistent with the notion that the transition state became looser when these types of substituents were present in the sulphonyl chloride.

Rogne obtained evidence in agreement with his view that substitution at sulphonyl sulphur was direct and concerted when he compared the rates and activation parameters for the reaction of imidazole with substituted benzenesulphonyl chlorides in protic and aprotic media.[36] Both the enthalpy and entropy of activation decreased in going from protic (methanol) to aprotic (acetonitrile) media, but ρ (and therefore the electronic characteristics of the reaction centre) remained unchanged. To separate the solvent effect on $\Delta H^{\ddagger}$ into initial and transition state components, the heats of solution of the reactants in the two solvents were measured. It was shown that transfer of the activated complex from methanol to acetonitrile was substantially exothermic. This result, it was claimed, indicated an activated complex in a concerted process having a charge distribution as shown in (*5*) in Scheme 7 rather than a more polar one such as those immediately leading to or from the intermediate in the alternative S_AN mechanism. Rogne supported his interpretation when a much less exothermic or actually endothermic enthalpy of transfer from protic to aprotic media was established for the activated complex in the reaction of imidazole with benzoyl chloride.[37] This reaction was known to proceed *via* a polar tetrahedral intermediate.

In 1983 Lee and Koo[38] published an investigation of the reactions of substituted benzenesulphonyl chlorides with substituted anilines in a range of methanol–acetonitrile mixtures. Their approach was similar to Hambly's and Rogne's in the 1960s and '70s. The reactions of benzenesulphonyl chlorides with a series of substituted anilines yielded linear Hammett plots (and consequently linear Brönsted plots) with large negative slopes ($\rho_{nuc} = -2.0 \rightarrow -2.9$). The reactions of anilines with the series of substituted benzenesulphonyl chlorides yielded positive Hammett parameters which were numerically smaller ($\rho_S = 0.5 \rightarrow 1.0$). This led the authors to conclude that more negative charge is transferred from the nucleophile than is developed on the sulphur in the formation of the activated complex and, therefore, that there must be a partial transfer of electron density onto the nucleofuge which is beginning to depart in

[34] O. Rogne, *J. Chem. Soc.* (*B*), 1971, 1855.
[35] O. Rogne, *J. Chem. Soc., Perkin Trans. 2*, 1972, 472. See also O. Rogne, *J. Chem. Soc.* (*B*), 1971, 1334, and J. F. Bunnett and J. Y. Bassett, *J. Org. Chem.*, 1962, **27**, 2345.
[36] O. Rogne, *J. Chem. Soc., Perkin Trans. 2*, 1973, 823 & 1760.
[37] O. Rogne, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1486.
[38] I. Lee and I. S. Koo, *Tetrahedron*, 1983, **39**, 1803.



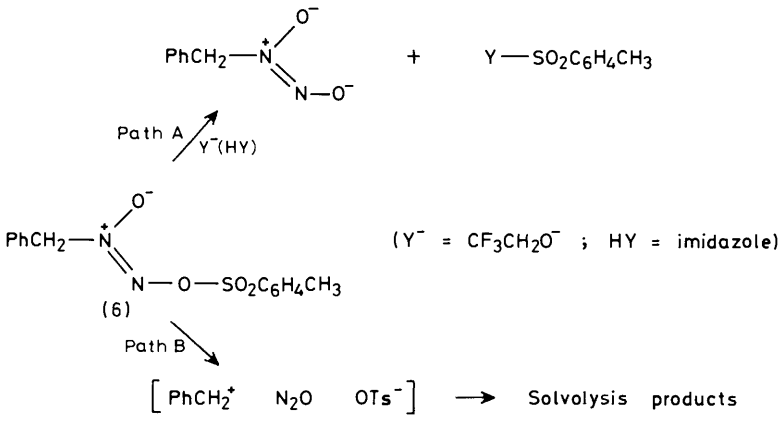
Scheme 10

the activated complex. Again, an addition–elimination mechanism was ruled out. Lee and Koo went on to increase the solvent ionizing power to its maximum (80—90% methanol v/v) where the leaving group ability of the chloride should be at its greatest. Instead of finding, as they expected, less N–S bond formation in the transition state (because less nucleophilic assistance would be required) they found ρ_{nuc} (and hence β_{nuc}) and ρ_S exhibited maximal behaviour indicating an activated complex with a much shorter N–S bond and slightly longer S–Cl bond. It appears, therefore, that an increased extent of S–Cl bond cleavage in the more ionizing solvent is actually compensated by increased N–S bond formation.

Similar work but using a series of oxygen nucleophiles with benzenesulphonyl chloride was reported in 1980 by Banjoko and Okwuiwe.[39] Rates with substituted benzoate anions were slower than with anilines but, in other respects, the results were similar and consistent with concerted bimolecular substitutions at sulphur.

Evidence that intermolecular sulphonyl transfer between two oxygen bases takes place by a concerted mechanism was provided by Williams' study of the reactions of aryl arenesulphonate esters with oxyanions, Scheme 10.[40] With *p*-nitrophenolate (pK_a *p*-$NO_2C_6H_4OH$ = 7.15) as nucleofuge and nucleophiles ranging from acetate (pK_a CH_3CO_2H = 4.76) to trifluoroethoxide (pK_a CF_3CH_2OH = 12.4), a linear Brönsted-type plot was obtained with no discontinuity at pK_a = 7.15. There was, therefore, no evidence of the stepwise mechanism also shown in Scheme 10 in which the rate-determining step changes as nucleophile and nucleofuge invert their relative base strengths.

[39] O. Banjoko and R. Okwuiwe, *J. Org. Chem.*, 1980, **45**, 4966.
[40] P. D.'Rozario, R. L. Smyth, and A. Williams, *J. Am. Chem. Soc.*, 1984, **106**, 5027.



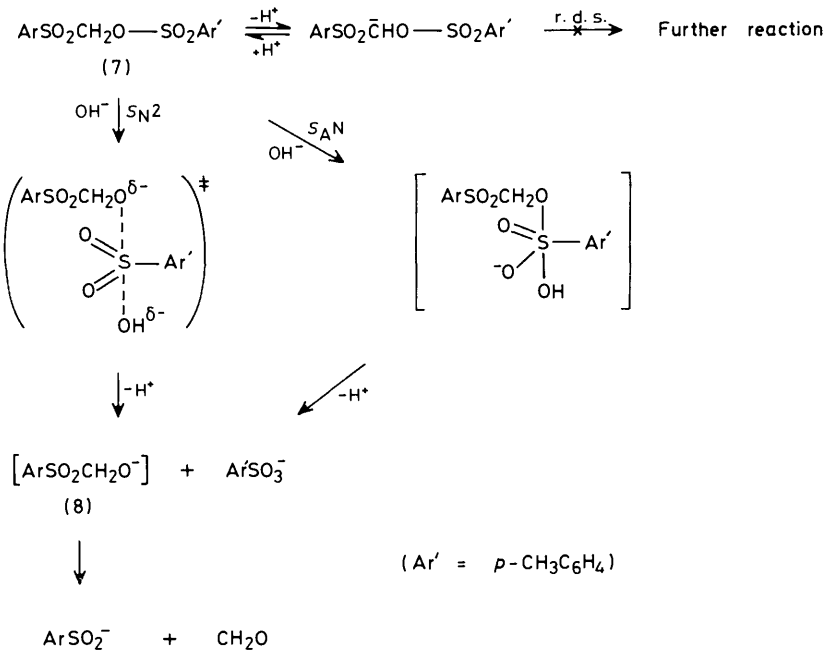
Scheme 11

Analogous results were reported from France by Monjoint and Ruasse[41] for the aminolysis of *p*-toluenesulphonyl imidazole and corresponding imidazolium cations, in which sulphonyl migrates from one nitrogen to another. As the base strength of the nucleophile ranged over 10 pK_a units from below to above that of the nucleofuge, linear Brönsted plots were obtained with very similar β parameters (~0.5) in all cases. Furthermore, the effect of the nucleofuge as expressed by the β_{lg} is virtually independent of the nature of the nucleophile.

A more obscure leaving group, *N*-benzylazoxy anion, is displaced in the substitution reaction at sulphur shown in Path A of compound (6) in Scheme 11.[42] This reaction in aqueous trifluoroethanol takes place only with harder nucleophiles such as the conjugate base of the solvent, $CF_3CH_2O^-$, and imidazole. Softer nucleophiles, *e.g.* thiocyanate, simply compete with the solvent as a trap for the electrophilic intermediates generated in the alternative reaction mode involving heterolysis of (6) in the opposite sense, Path B.

The reaction of compound (7) in Scheme 12 in aqueous solution with a specific base-catalysis rate law was interpreted earlier in terms of a rate-determining reaction of the deprotonated substrate. This has had to be rejected, however, since in ^{18}O enriched water, the ^{18}O turns up in the tosylate anion which does not exchange oxygen with the solvent under the conditions of the reaction.[43] Furthermore, ^{18}O was not incorporated into recovered starting material. Nucleophilic attack by OH^- at the sulphonyl group of (7) now seems the more probable reaction path, as shown in Scheme 12. There remains the intriguing possibility that fragmentation of the complex anionic nucleofuge (8) is concerted with its departure in this S_N2 process (or, less likely, the S_AN alternative).

[41] P. Montjoint and M.-F. Ruasse, *Tetrahedron Lett.*, 1984, **25**, 3183; *Bull. Soc. Chim. Fr.*, 1988, 356.
[42] H. Maskill, *J. Chem. Soc., Chem. Commun.*, 1986, 1433; H. Maskill and W. P. Jencks, *J. Am. Chem. Soc.*, 1987, **109**, 2062.
[43] H. A. J. Holterman and J. B. F. N. Engberts, *J. Org. Chem.*, 1977, **42**, 2792.



Scheme 12

3 Nucleophilic Substitution at the Sulphonyl Groups of α-Disulphones and Sulphonic Anhydrides

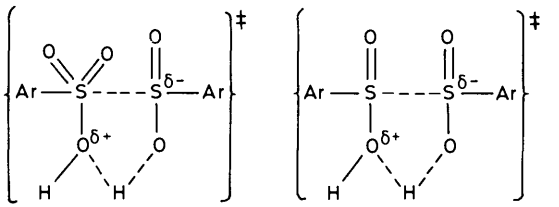
From the study of the hydrolysis of diaryl α-disulphones (9) and arylsulphinyl aryl sulphones (10) in acidic aqueous dioxane, equations 4 and 5, Kice and his co-workers[44,45] have been able to make a quantitative comparison of the influence of reaction variables on nucleophilic substitution at sulphonyl and sulphinyl sulphur.

$$\underset{(9)}{ArSO_2SO_2Ar} + H_2O \xrightarrow[\text{dioxane}]{H_2O} ArSO_3H + ArSO_2H \qquad (4)$$

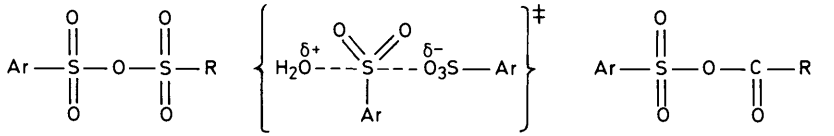
$$\underset{(10)}{ArSOSO_2Ar} + H_2O \xrightarrow[\text{dioxane}]{H_2O} 2\,ArSO_2H \qquad (5)$$

Despite the fact that nucleophilic attack at sulphinyl was found to be 10^4 faster than at sulphonyl, the reactions were otherwise very similar. They have virtually the same dependence on aryl group structure [$\rho = 3.5$ for hydrolysis of (9) and

[44] J. L. Kice, *Adv. Phys. Org. Chem.*, 1980, **17**, 65.
[45] J. L. Kice and G. J. Kasperek, *J. Am. Chem. Soc.*, 1969, **91**, 5510; J. L. Kice, *Int. J. Sulfur Chem.*, 1971, **6**, 3.



(11) (12) (13)



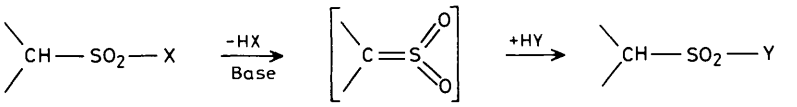
(14) (15) (16)

3.4 for (10)], and both reactions have very large negative entropies of activation (-158 and -155 JK^{-1} mol^{-1}) and substantial solvent deuterium kinetic isotope effects ($k^H/k^D = 2.3$ and 2.7). The authors proposed S_N2-like mechanisms involving intramolecular partial rate-determining proton transfers to the departing $ArSO_2^-$ group for both (9) and (10) *via* activated complexes (11) and (12).

As compounds (9) and (10) differ only in the oxidation state of the sulphur, it was possible from these reactions to make direct comparisons of their susceptibilities towards different nucleophiles. For sulphonyl sulphur[46] the order is $F^- \gg AcO^- \gg Cl^- > Br^- > H_2O$, whereas for attack at sulphinyl[47] it is $Br^- > Cl^- > AcO^- > F^- \gg H_2O$.

Hydrolysis of sulphonic anhydrides (13)[48,49] and (14)[49] have also been investigated in aqueous acetone or aqueous dioxane and the results link those for the α-disulphones[14–46] to those from other arenesulphonyl systems discussed above. For the hydrolysis of (13) in aqueous acetone, $\rho = 2.5$ compared with $\rho = 3.5$ for (9) in aqueous dioxane.[48,45] The deuterium solvent kinetic isotope effect for (13), $k^H/k^D \sim 1.2$, is also much smaller than the value of 2.3 for (9),[45] a result which must rule out proton transfer in the rate-determining step for the reactions of (13). Evidently, when the leaving group is changed from $ArSO_2^-$ to the much less basic $ArSO_3^-$, no proton transfer is necessary for departure of the nucleofuge, and a transition state such as (15) was proposed for the hydrolysis of (13). In none of these reactions was there any evidence which required other than a concerted S_N2 mechanism. Not surprisingly, mixed anhydrides such as (16)

[46] J. L. Kice, G. J. Kasperek, and D. Patterson, *J. Am. Chem. Soc.*, 1969, **91**, 5516; J. L. Kice and E. Legan, *ibid.*, 1973, **95**, 3912.
[47] J. L. Kice and G. Guaraldi, *J. Am. Chem. Soc.*, 1968, **90**, 4076.
[48] N. H. Kristensen, *Acta Chem. Scand.*, 1966, **20**, 1955; 1967, **21**, 899.
[49] R. M. Laird and M. J. Spence, *J. Chem. Soc.* (*B*), 1971, 1434.



(17)

α sulphene

Scheme 13

react *via* nucleophilic attack at the carbon electrophilic centre with the arenesulphonate anion as a very good leaving group.[49,50]

4 Sulphonyl Transfer *via* Sulphene Intermediates

So far, we have considered the overall reactions of equation 1 in comparison with S_N1 and S_N2 reactions of alkyl halides and arenesulphonates, and S_AN reactions of carboxylic acid derivatives. However, a proton may be abstracted from a carbonium ion in the $E1$ process which often accompanies the S_N1, and from the β-carbon of an alkyl halide or arenesulphonate in either an $E1_{CB}$ or $E2$ reaction. Furthermore, an α-proton of an acyl chloride or anhydride may also be abstracted in $E2$ or $E1_{CB}$ processes. It is not surprising, therefore, that alkanesulphonyl halides and related compounds also undergo elimination reactions, Scheme 13.[51] But in these reactions, the products, sulphenes (17), are not stable; they are themselves reactive electrophiles so they intervene in stepwise elimination–addition reactions which may also be seen as overall sulphonyl transfer processes and hence part of the broader topic covered in this review.

The intermediate sulphene (17) with general formula $R^1R^2C{=}SO_2$ may be regarded as the sulphonyl analogue of a ketene or as a derivative of sulphur trioxide formally obtained by the replacement of one oxygen by a substituted methylene group, R^1R^2C.

In 1964 King and Durst put forward evidence for the intermediacy of a sulphene in the reaction of phenylmethanesulphonyl chloride with triethylamine in deuterated isopropanol, with the observation that monodeuterated isopropyl phenylmethanesulphonate accounted for 90% of the yield.[52] The formation of such a product requires deuterium to be incorporated in an irreversible process. Further evidence was produced by Truce and his colleagues[53] when they reported in the same year that methanesulphonyl chloride reacts immediately with triethylamine in methanol but not with weaker bases. Moreover, with [*O*-^{2}H]-methanol, singly labelled $^2HCH_2SO_3CH_3$ was obtained. An elimination–addition mechanism was implicated. Investigations of these types of mechanisms with sulphonyl species were carried out mainly by two research groups led by

[50] R. M. Laird and M. J. Spence, *J. Chem. Soc.* (*B*), 1970, 388; 1971, 454.
[51] G. Opitz, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 107; T. J. Wallace, *Q. Rev. Chem. Soc.*, 1966, **20**, 67; J. F. King, *Acc. Chem. Res.*, 1975, **8**, 10.
[52] J. F. King and T. Durst, *J. Am. Chem. Soc.*, 1964, **86**, 287.
[53] W. E. Truce, R. W. Campbell, and J. R. Norell, *J. Am. Chem. Soc.*, 1964, **86**, 288.

$$B + ArCH_2SO_2OAr' \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ar\bar{C}HSO_2OAr' + BH^+$$

(18)

$$Ar\bar{C}HSO_2OAr' \xrightarrow[-Ar'O^-]{k_2} [ArCH{=}SO_2] \xrightarrow{ROH} ArCH_2SO_2OR$$

Scheme 14

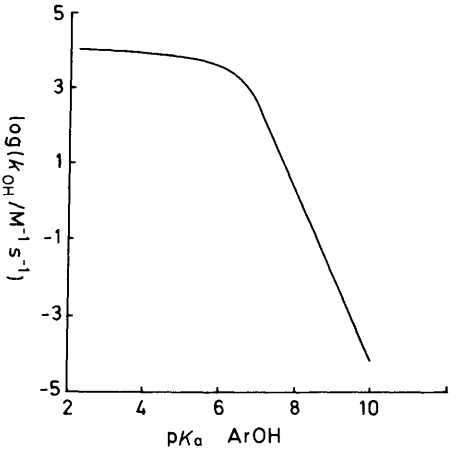


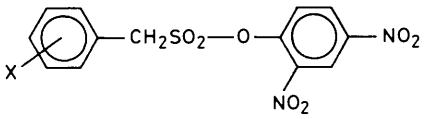
Figure 2 *Plot of* $\log(k_{OH}//M^{-1}\ s^{-1})$ vs. pK_a *of the conjugate acid of the substituted phenoxide leaving group in the* OH^-*-induced hydrolysis of aryl phenylmethanesulphonates,* $PhCH_2SO_2OAr$, 25 °C, *aqueous solution. Taken from reference* 55

King in Ontario and Williams in Kent. Their work was complementary and both came to the conclusion that, while the second-order kinetics of the dehydrohalogenation of alkanesulphonyl chlorides with tertiary amines (Scheme 13) were consistent with a concerted *E*2 elimination mechanism, sulphene formation from the reactions of aryl arylmethanesulphonates (18) could be stepwise ($E1_{CB}$, Scheme 14) or *E*2 depending upon the particular reaction. Either way, the sulphene intermediate reacted rapidly with the alcoholic solvent.

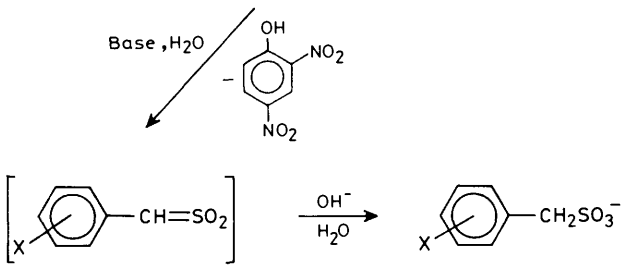
King and his colleagues studied the reactions of the esters in deuterated solvents and observed the number of deuteriums incorporated into recovered starting material and into the products of the reaction.[52,54] A different approach was used by Williams who, in part of a major investigation, obtained a discontinuous Brönsted plot, Figure 2, for the alkaline hydrolysis (and aminolysis) of aryl phenylmethanesulphonates (18; Ar = C_6H_5), Scheme 14.[55] The large

[54] J. F. King and T. W. S. Lee, *J. Am. Chem. Soc.*, 1969, **91**, 6524; J. F. King and R. P. Beatson, *Tetrahedron Lett.*, 1975, 973.

[55] A. Williams, K. T. Douglas, and J. S. Loran, *J. Chem. Soc., Chem. Commun.*, 1974, 689; M. B. Davy, K. T. Douglas, J. S. Loran, A. Steltner, and A. Williams, *J. Am. Chem. Soc.*, 1977, **99**, 1196.



(19)



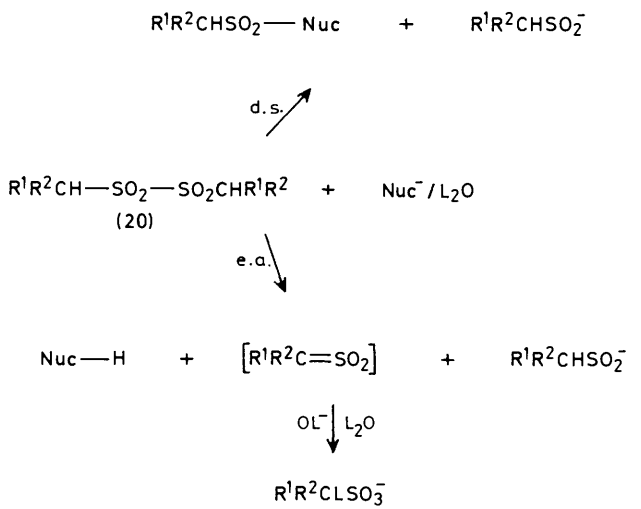
Scheme 15

Hammett [$\rho(\sigma^-) = 5.4$] and Brönsted ($\beta_{lg} = -2.4$) parameters were consistent with phenolate character in the transition state of the rate-determining step for compounds to the right of the break in Figure 2 where specific base catalysis was observed. The rate, therefore, was very sensitive to the phenolate structure, and departure of the leaving group was taken to be rate limiting. As the leaving group became a weaker base, *i.e.* as ArO^- became a better nucleofuge (towards the left of the plot in Figure 2), the gradient changed abruptly and the rate became independent of the leaving group, and the reaction became subject to general base catalysis. The deduction that proton abstraction had now become rate determining was confirmed when large primary deuterium kinetic isotope effects were observed, *e.g.* $k^H/k^D = 6.0$ with fluoride as nucleofuge, for those substrates to the left of the break in the Brönsted-type plot in Figure 2.

Williams and his colleagues have also investigated the effect of substituents upon the base-induced elimination reaction of arylmethanesulphonates with good phenolate leaving groups. A concerted elimination but with an unsymmetrical transition state was proposed for the reaction of 2,4-dinitrophenyl arylmethanesulphonates (19) with pyridine and hydroxide in aqueous solution, Scheme 15.[56] Although there is not a large development of charge at the alpha carbon in the transition state of the first step of this reaction, C–H bond cleavage is more advanced than S–O fission, *i.e.* it is an $E1_{CB}$-like $E2$ process. (Under the alkaline conditions of the reaction, the sulphene $ArCHSO_2$ will yield the corresponding arylmethanesulphonate $ArCH_2SO_3^-$).

Kice also extended his work on substitution at diaryl α-disulphones (Section 3)

[56] S. Thea and A. Williams, *J. Chem. Soc., Perkin Trans 2*, 1981, 72; S. Thea, M. G. Harun, N. Kashefi-Naini, and A. Williams, *ibid.*, p. 78.



Scheme 16

to study the reactions of nucleophiles with dialkyl α-disulphones (20) in aqueous dioxane.[44,57] When di-n-butyl α-disulphone reacted with piperidine, morpholine, glycine ethyl ester, and acetate in 60% dioxane 40% D_2O, the products contained one, and only one, deuterium bonded to carbon. Either an irreversible $E1_{CB}$ or a concerted $E2$ mechanism was taking place in an overall elimination–addition (e.a.) reaction, Scheme 16. Only with weakly basic, highly nucleophilic azide did the reaction proceed by direct substitution (d.s.). But even with azide, the preferred route switched from direct substitution to elimination–addition when the hydrogens alpha to the sulphone groups became more acidic as in $PhCH_2SO_2$-SO_2CH_2Ph.

From a comparison of the rates of elimination from α-disulphones RCH_2SO_2-SO_2CH_2R with the rates of base-catalysed hydrogen exchange with the solvent in the corresponding trifluoromethyl sulphones $RCH_2SO_2CF_3$, Kice and his colleagues concluded that the eliminations were either $E1_{CB}$ or very $E1_{CB}$-like $E2$ processes. This view was fully in accord with observed variations in the rates of eliminations from $RR'CHSO_2SO_2R''$ with changes in R and R′.

A. Modified Sulphenes.—The rate constant for the hydrolysis of 2,4-dinitrophenyl 3,5-dimethyl-4-hydroxybenzenesulphonate (21) was found to have the dependence on pH shown in Figure 3.[58] This effect could be attributed either to an associative mechanism (Path A, Scheme 17) where nucleophilic attack by hydroxide on (21) is inhibited as (21) undergoes ionization, or to a dissociative mechanism where the step which is rate limiting is the breakdown of the conjugate base (22) (elementary rate constant k_1 in Path B, Scheme 17). From an

[57] L. O. Farng and J. L. Kice, *J. Am. Chem. Soc.*, 1981, **103**, 1137.
[58] S. Thea, G. Guanti, A. Hopkins, and A. Williams, *J. Am. Chem. Soc.*, 1982, **104**, 1128.

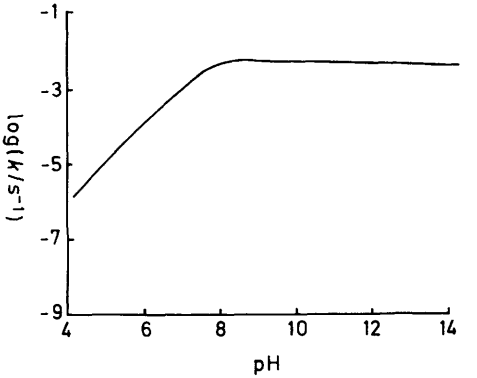
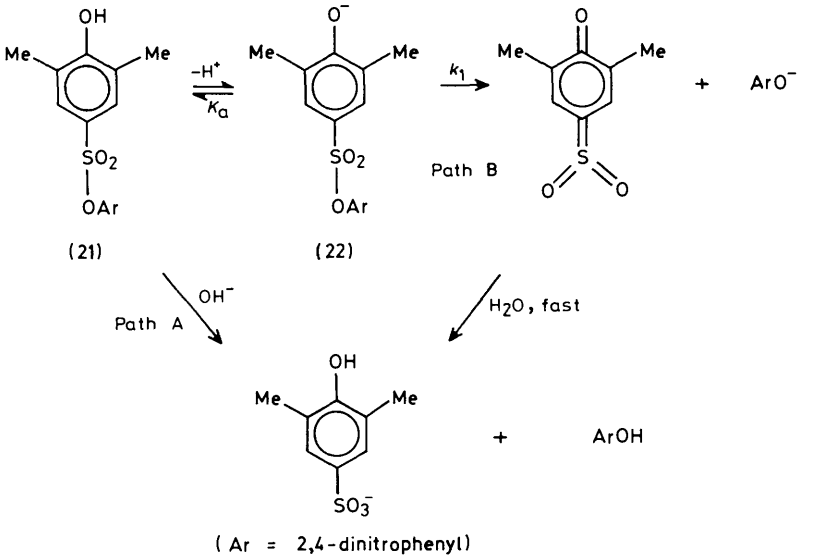


Figure 3 *Dependence on* pH *of the hydrolysis of* 2,4-*dinitrophenyl* 3,5-*dimethyl*-4-*hydroxybenzenesulphonate*, (21), *in dioxane–water*, 25 °C. *Taken from reference* 58

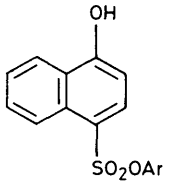


Scheme 17

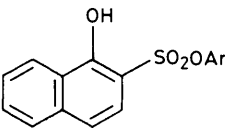
estimate of the second-order rate constant for path A on the basis of the known reactivity of 2,4-dinitrophenyl benzenesulphonate, the authors concluded that only path B *via* the sulphoquinone intermediate was operating.[58] This is the first sound evidence for such intermediates even though they had been proposed earlier.[59]

A study of the reaction pathways of other aryl esters of *ortho*- and *para*-

[59] T. Zincke and R. Brüne, *Chem. Ber.*, 1908, **41**, 902; W. L. Hall, *J. Org. Chem.*, 1966, **31**, 2672.



(23)



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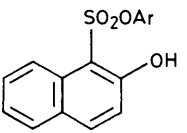

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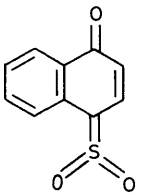
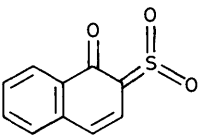
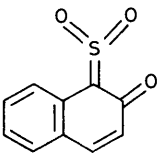


(26)



(27)



(28)

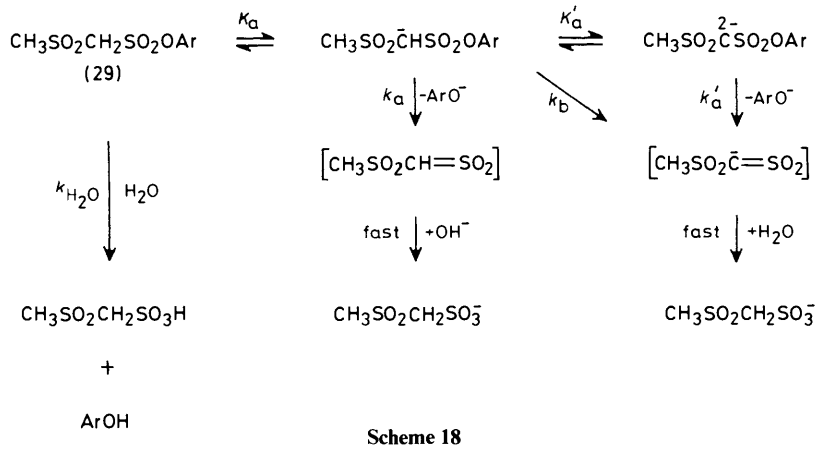
hydroxyarenesulphonic acids (23), (24), and (25) has also been made.[60] As before, the observed second-order rate constants for hydroxide attack on the ionized hydroxyesters were many orders of magnitude larger than those for hydroxide attack on the corresponding *O*-methylated compounds indicating that the same mechanism was not operative for both. The positive entropies of activation for the hydroxy compounds are also good evidence that a simple bimolecular process is not involved in these reactions. Esters (23), (24), and (25) also appear, therefore, to hydrolyse under basic conditions through $E1_{CB}$ mechanisms *via* sulphoquinone intermediates (26), (27), and (28). There does appear to be, however, an additional route for hydrolysis of (23)—(25) under alkaline conditions through hydroxide attack at the sulphonyl residues of their ionized forms since a more complex rate law was observed for these compounds than for (21).

Anionic sulphene intermediates were invoked to account for the alkaline hydrolytic reactivity of aryl (methylsulphonyl)methanesulphonates (29), *i.e.* substrates in which the acidity of the α-CH_2 is so enhanced by the second sulphonyl group that they yield a dianion in basic aqueous solution.[61] As for compounds (23)—(25), two hydroxide-induced mechanisms were indicated by the log*k*–pH profile and the results were fitted to the rate law

$$k_{obs} = k_{H_2O} + \frac{(k_a + k_b[OH^-])}{(1 + [H^+]/K_a)}$$

[60] S. Thea, G. Cevasco, G. Guanti, A. Hopkins, N. Kashefi-Naini, and A. Williams, *J. Org. Chem.*, 1985, **50**, 2158.

[61] S. Thea, G. Guanti, A. R. Hopkins, and A. Williams, *J. Org. Chem.*, 1985, **50**, 5592; S. Thea, G. Guanti, and A. Williams, *J. Chem. Soc., Chem. Commun.*, 1981, 535.



Scheme 18

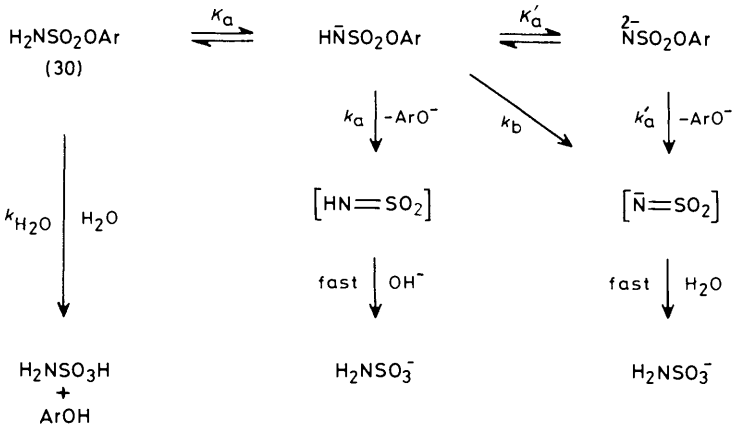
where k_{H_2O}, k_a, and k_b are indicated in Scheme 18. Williams and Thea and their colleagues were able to extract reactivity parameters for both k_a and k_b from their comprehensive results and show that an $E1_{CB}$ mechanism is required. At pH $\sim$10 the reaction is principally *via* k_a whereas, at higher alkalinity (pH $\sim$12—14), the route *via* k_b is required through the previously unknown anionic sulphene.

Related to this is the investigation of the hydrolysis of aryl sulphamates (30) (Scheme 19). Previous work[62] had demonstrated the intermediacy of the neutral sulphonylamine $CH_3N{=}SO_2$ in the hydrolysis of aryl (*N*-methyl)aminosulphonates through an $E1_{CB}$ mechanism. Compounds (30) were found to be many orders of magnitude more reactive than the *N,N*-dimethyl derivatives which could react only by direct bimolecular attack at the sulphonyl group.[63] By a strategy parallel with that employed in the investigation of (29) in Scheme 18, the joint Kent–Genova group present convincing evidence that both specific base-catalysed routes of Scheme 19 are required as well as an uncatalysed route [presumably *via* nucleophilic attack by water at the sulphonyl group of (30) itself]. At low, intermediate, and high pH, the predominant paths are those *via* k_{H_2O}, k_a, and k_b respectively.

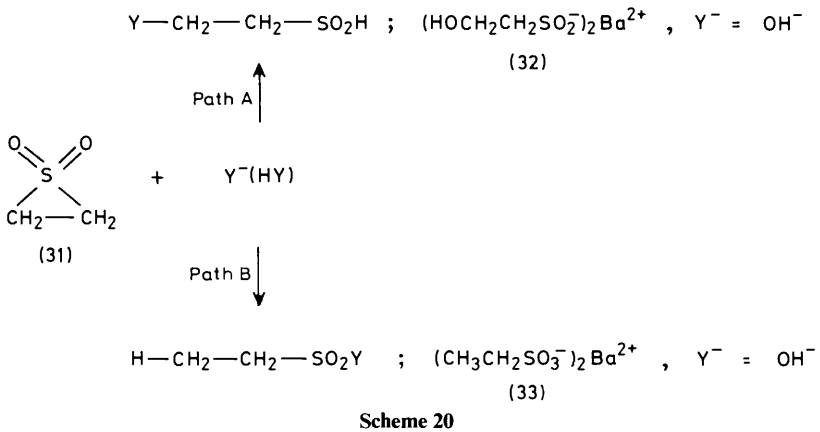
5 Bifunctionality and Alternative Reactivity

Simple sulphones RSO_2R' are not readily susceptible to nucleophilic attack. The electrophilic reactivity of the sulphone group in thiirane-1,1-dioxide (31), however, is enhanced by the prospect of ring-opening and release of strain. Two possible modes of reaction are indicated in Scheme 20: nucleophilic attack at a ring carbon and protonation of oxygen to give a 2-substituted sulphinic acid

[62] A. Williams and K. T. Douglas, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1727.
[63] S. Thea, G. Cevasco, G. Guanti, and A. Williams, *J. Chem. Soc., Chem. Commun.*, 1986, 1582.



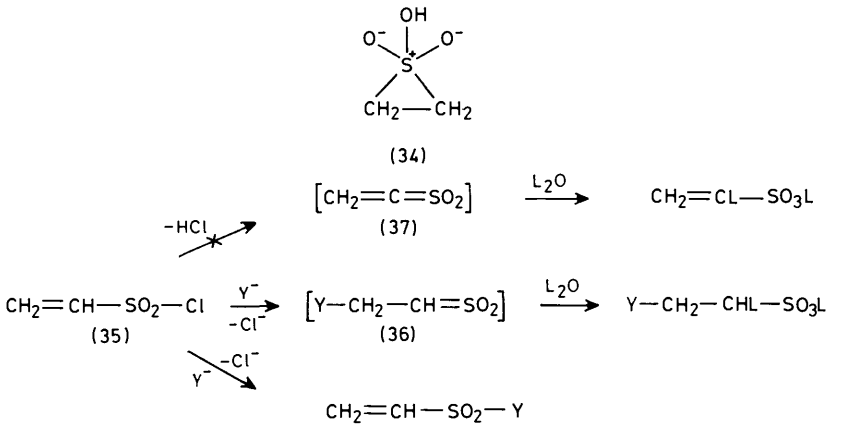
Scheme 19



Scheme 20

(Path A), and nucleophilic attack at sulphur and protonation on carbon to give an ethanesulphonic acid derivative (Path B). King's group have re-examined the reaction of (31) with aqueous barium hydroxide following an earlier report[64] that the product is barium 2-hydroxyethanesulphinate (32), presumably *via* Path A. The later workers established,[65] however, that the main product is, in fact, barium ethanesulphonate (33) *via* Path B. They demonstrated that a common penta-coordinated intermediate (34) in a stepwise process accounts for both the major reaction shown in Scheme 20 (Path B) and also the minor formation of ethene and, presumably, sulphite (the last step of the Bordwell mechanism for the Ramberg–Bäcklund reaction). For reasons mentioned earlier (Section 2B), failure

[64] G. Hesse, E. Reichold, and S. Majmuder, *Chem. Ber.*, 1957, **90**, 2106.
[65] J. F. King, J. H. Hillhouse, and K. C. Khemani, *Can. J. Chem.*, 1985, **63**, 1.



Scheme 21

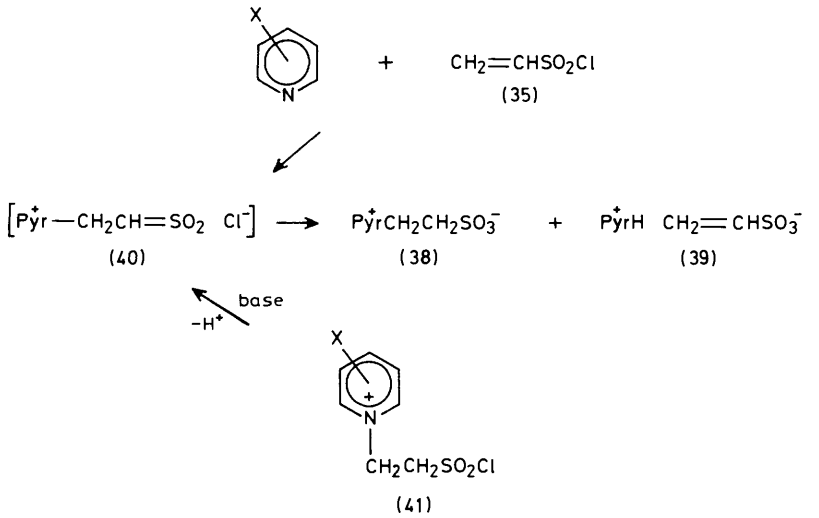
to detect the intermediate by ^{18}O exchange in recovered starting material does not disprove this mechanism.

Just as thiirane-1,1-dioxide has two possible sites of direct nucleophilic attack, so also do 1-alkene-1-sulphonyl chlorides, *e.g.* (35) in Scheme 21. The nucleophile could bond at the sulphur or, in a vinylogous alternative, at carbon-2 to give (36). In addition, a third reaction mode is conceivable for (35): elimination–addition *via* a cumulated sulphene intermediate (37). It appears that, for (35) itself in aqueous hydroxide, 90% of the reaction is to give ethenesulphonate anion *via* direct nucleophilic displacement at sulphur.[66] However, the formation of small amounts (~10%) of 2-hydroxyethanesulphonate at both high and low pH indicated a second route. In D_2O, the absence of deuterium in the ethenesulphonate showed that it could not have been formed through the cumulated sulphene, and the single deuterium bonded to carbon in the 2-hydroxyethanesulphonate was consistent with it having been formed exclusively through (36; Y = OH).

The addition of a tertiary amine, *e.g.* a pyridine, leads to a faster reaction and an altered product distribution (Scheme 22). In most cases, the betaine (38) is the major product (~80%) and the salt (39) the minor one, the exact ratios depending upon the substituent in the pyridine and the pH of the medium.[66] The simplest mechanism to account for the betaine is attack of the pyridine at C-2 of (35) to form the cationic sulphene (40) in either a concerted or stepwise process.[67] Formation of monodeuterated betaine in D_2O supported this mechanism.[66]

Four possible routes to the salt were considered, although the one *via* a cumulated sulphene [(37) in Scheme 21] was easily ruled out as no deuterium was found in the salt when the reaction was carried out in D_2O. General base catalysis was also dismissed as pyridines substituted in position 2 gave a reduced

[66] J. F. King, J. H. Hillhouse, and S. Skonieczny, *Can. J. Chem.*, 1984, **62**, 1977.
[67] A. Le Berre, A. Etienne, and B. Dumaitre, *Bull. Soc. Chim. Fr.*, 1970, 954.



Scheme 22

rate, and no solvent deuterium kinetic isotope effect was observed. Vinylogous catalysis was established (rather than catalysis *via* direct attack of the nucleophile at sulphur) when the intermediate sulphene (40) was generated from another source, (41). In reactions under identical conditions, betaine (38) and salt (39) were produced in the same ratios from (41) and from (35) plus pyridine, implicating a common intermediate, *i.e.* (40). This reaction appears to be the first well-supported example of vinylogous nucleophilic catalysis.

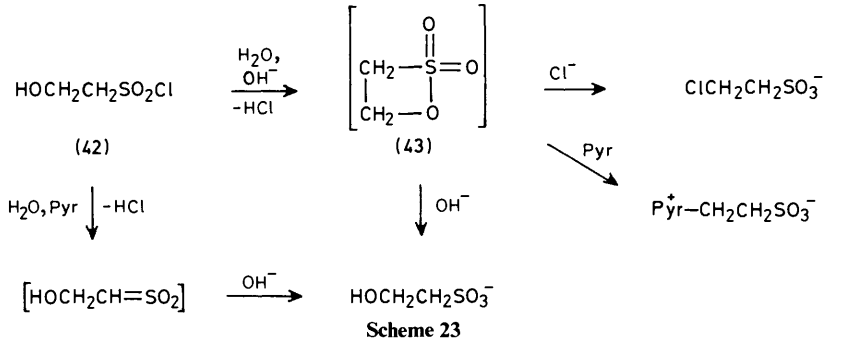
6 Intramolecular Effects

The hydrolysis of 2-hydroxyethanesulphonyl chloride (42) under alkaline conditions takes place largely through an intramolecular S_N2-like route *via* the transient β-sultone (43) which then suffers ring opening, Scheme 23.[68] In the presence of tertiary amines, *e.g.* pyridine, a minor extent of reaction (15—20%) occurs *via* the hydroxymethylsulphene as was shown by isotopic labelling in D_2O. Pyridine also intercepts the β-sultone. Reactions in alcoholic media are closely similar.

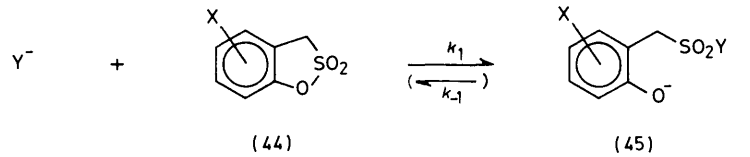
Sultones more stable than (43), which bear the same relationship to sulphonate esters as lactones do to carboxylic esters, have been studied and compared with their acyclic analogues and the corresponding phosphorus compounds. Compound (44) with X = H reacts in alkaline solution (Scheme 24; $Y^- = OH^-$) with k_1 almost 10^6 faster than its acyclic analogue, phenyl phenylmethanesulphonate.[24] This compares with ratios of up to 10^7 in the phosphorus series.

2-Hydroxy-5-nitrotoluene-α-sulphonic acid sultone (44; X = 5-NO_2), although having benzylic hydrogens next to the sulphonyl group, did not react *via* an $E1_{CB}$

[68] J. F. King and J. H. Hillhouse, *Can. J. Chem.*, 1983, **61**, 1583.



Scheme 23



Scheme 24

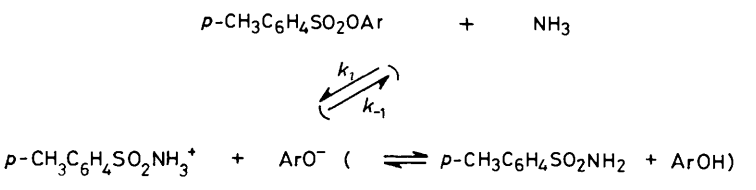
mechanism, but *via* direct nucleophilic attack at sulphur.[24,55] Suppression of the $E1_{CB}$ route was ascribed to stereoelectronic effects. The sulphene that would have been formed by proton abstraction and expulsion of the leaving group would have been constrained by the five-membered ring to be in an unstable perpendicular configuration rather than the preferred planar one. On the basis of the β_{nuc} and the solvent deuterium kinetic isotope effect in aqueous solution, sultone (44) appears to react with nucleophiles by general base catalysis and direct nucleophile catalysis routes *via* transition states with advanced S–Nuc bond formation.[69] A study of the reverse reaction was also made (k_{-1}, Scheme 24 with $Y^- = PhO^-$).[70] Intramolecular nucleophilic participation (rather than general base catalysis) by the phenoxide of (45; X = 5-NO_2) occurs to form the sultone which then goes on to suffer hydrolysis itself. The equilibrium constant ($K = 1.4 \times 10^5\ M^{-1}$) for the reaction as written in Scheme 24 was derived from forward and reverse rate constants. The stability of the sulphonate compared with the sultone was a further indication of ring strain in (44), especially as there is a translational entropy loss on going from two species on the left to one on the right of the equation as written.

The way was then open to attempt a Brönsted-type study of the effect on the reactivity of the system in Scheme 24 of substituents X and of substituents in Y^-.[71] As normally employed, the absolute values of the Brönsted parameters β_{nuc} or β_{lg} are of restricted use. Empirically, they indicate the extent to which structural changes in a reactant, *e.g.* substituents, affect the rate of the reaction,

[69] T. Deacon, A. Steltner, and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1778.
[70] C. R. Farrar and A. Williams, *J. Am. Chem. Soc.*, 1977, **99**, 1912.
[71] T. Deacon, C. R. Farrar, B. J. Sikkel, and A. Williams, *J. Am. Chem. Soc.*, 1978, **100**, 2525.

Table 1

Reaction of Scheme 24	$\beta(k_1)$	$\beta(k_{-1})$
ArO^- + 5-nitrosultone	0.81	−1.03
PhO^- + substituted sultones	−0.85	0.84



Scheme 25

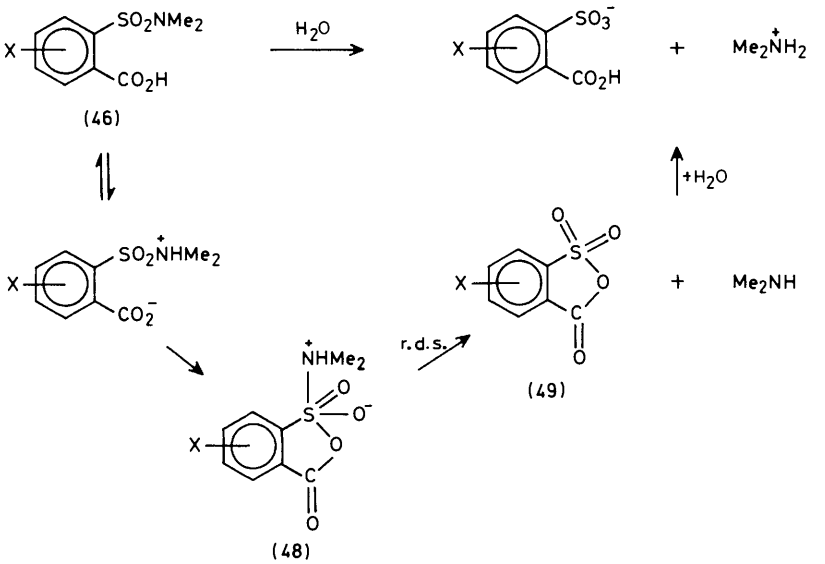
i.e. how they affect the transformation of reactant into activated complex. If we wish to interpret this parameter mechanistically, it is much more useful to know how the effect of the structural changes on the rate process compares with the effect of the same changes upon the overall equilibrium, *i.e.* the transformation of reactant into product.[72] Since, in the present context, the effects of substituents upon both k_1 and k_{-1} were determinable, *i.e.* $\beta(k_1)$ and $\beta(k_{-1})$, the effects of substituents upon the equilibrium are determinable, *i.e.* $\beta(\text{eq}) = \beta(k_1) - \beta(k_{-1})$. And, in a comprehensive investigation, this was done both for substituents X and for those in the phenolate Y^- as shown in Table 1.

The sensitivity of the equilibrium as written (left to right) (Scheme 24) towards changes in the pK_a of the conjugate acid of the phenolate (45) is, therefore, $\beta_{1g}(\text{eq}) = \beta_{1g}(k_1) - \beta_{nuc}(k_{-1}) = -0.85 - 0.84 = -1.69$. In the same way, the sensitivity of the equilibrium as written towards the pK_a of the conjugate acid of the external nucleophile Y^- in Scheme 24 is $\beta_{nuc}(\text{eq}) = \beta_{nuc}(k_1) - \beta_{1g}(k_{-1}) = 0.81 - (-1.03) = 1.84$. The Leffler parameters for the equilibrium as written, therefore, are $\alpha_{1g} = \beta_{1g}(k_1)/\beta_{1g}(\text{eq}) = -0.85/-1.69 = 0.50$, and, correspondingly, $\alpha_{nuc} = \beta_{nuc}(k_1)/\beta_{nuc}(\text{eq}) = 0.81/1.84 = 0.44$. These results indicate considerable extents of bond cleavage and formation in the transition state, consistent with a highly symmetrical electronic structure around sulphur.

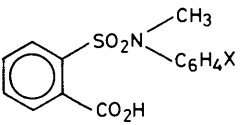
For the ammonolysis reaction of Scheme 25, $\beta_{1g}(k_1) = -1.08$ but $\beta_{nuc}(k_{-1})$ results are not available so the data cannot be used in the Leffler sense. However, by using the comprehensive results for the related reaction of Scheme 24, and literature results for $\beta_{nuc}(k_1)$ of similar reactions but using arylamines as nucleophiles, Suttle and Williams[73] conclude that the reaction of Scheme 25 is also best described as an S_N2 process.

One of the more strongly argued cases for an S_AN mechanism is the hydrolysis of a sulphonamide (46), nucleophilically catalysed by an intramolecular carboxylate, Scheme 26.[74] The authors separated the effects of substituents upon the

[72] J. E. Leffler, *Science*, 1953, **117**, 340; A. Williams, *Acc. Chem. Res.*, 1984, **17**, 425; S. Thea and A. Williams, *Chem. Soc. Rev.*, 1986, **15**, 125.
[73] N. A. Suttle and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1563.
[74] T. Graafland, A. Wagenaar, A. J. Kirby, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1979, **101**, 6981.



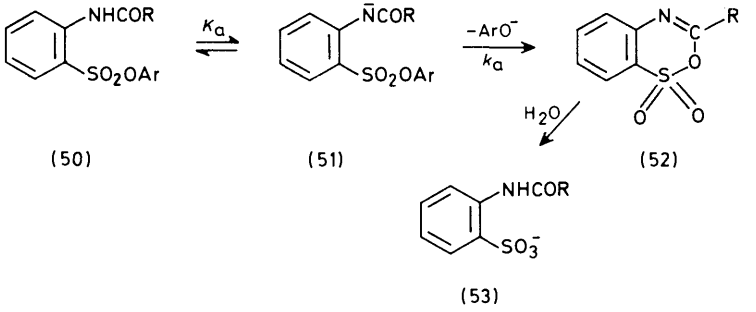
Scheme 26



(47)

overall kinetic process of (46) into an effect through the carboxyl ($\rho = -0.54$) and an effect through the sulphonamide ($\rho = -0.58$). These reaction constants indicate that both the carboxyl and the sulphonyl have lower electron densities in the activated complex than in the reactant. Furthermore, results for substituents in the leaving group of (47) lead to a three-point Hammett plot with $\rho = -0.76$ which, though nothing like as negative as the value for protonation of anilines ($\rho = -2.89$), does indicate that the nitrogen also suffers a reduction of electron density upon formation of the activated complex. These results are presented as indicating a stepwise mechanism as shown in Scheme 26 with breakdown of the intermediate (48) as the rate-determining step. However, if this reaction is actually concerted, then, structurally, the transition state must closely resemble (48). The mixed anhydride (49) will proceed to react very rapidly to give the final hydrolysis products.[49,50]

The intramolecular reaction of Scheme 27 bears some resemblances to that of Scheme 26 but, for the former, an intramolecular S_N2-type of mechanism is indicated. The hydrolysis of the *ortho*-substituted compound (50) under alkaline



(50) (51) (52) (53)

Scheme 27

conditions was found to be 10^3 times faster than that of the *para*-isomer, so the propinquity of the amide residue and the sulphonyl group clearly facilitates the reaction in some way.[75] Kinetic analysis of the reaction according to the *pseudo*-first-order rate law

$$k_{obs} = \frac{(k_a + k_b[OH^-])}{(1 + [H^+]/K_a)}$$

allowed comprehensive reaction parameters for the two routes to be obtained. The major route (k_a) is indicated in Scheme 27 and involves rate-determining expulsion of the phenolate anion from the conjugate base of the amide function of the reactant (51). All the evidence could be accommodated by this being an intramolecular concerted process. The minor route (k_b) was less well characterized but appears to involve specific intermolecular facilitation of the departure of the phenoxide from (51) by OH^-, but to give the same intermediate that is obtained in the intramolecular route. Previous work had implicated compound (52; R = CH_3) as an intermediate in the hydrolysis of 2-acetamidobenzenesulphonyl fluoride (although, in that reaction, the amide function also suffered hydrolysis).[76] Virtually all the oxygen of the amide in (53) was found to be derived from the aqueous solvent by an ^{18}O labelling study as required by this mechanism. (The product, once formed, would not be expected to undergo oxygen exchange.) When ammonia was used as a nucleophilic trap, indeed, (52) was intercepted, but there was no rate increase.

7 Conclusions

The evidence available for the reactions of equation 1 overwhelmingly suggests that the mechanisms are concerted bimolecular displacements at the sulphonyl group. There are indications, however, that an S_N1 mechanism may be induced if substituents in the arene group are sufficiently electron supplying. The use of

[75] S. Thea, G. Guanti, A. R. Hopkins, and A. Williams, *J. Org. Chem.*, 1985, **50**, 3336.
[76] M. E. Aberlin and C. A. Bunton, *J. Org. Chem.*, 1970, **35**, 1825.

highly ionizing weakly nucleophilic media should help in the characterization of such a process. At the other extreme, there is evidence that some reactions may be adequately explained by an S_AN mechanism through a penta-coordinate intermediate, but there is none, so far, that actually requires such a mechanism. Here again, it should be possible to build into the substrate certain features which, under the appropriate reaction conditions, cause the S_AN mechanism to be the most favourable reaction. At this extreme, however, the evidence necessary to confirm the S_AN mechanism may be more difficult to acquire.

Acknowledgements. It is a pleasure to acknowledge helpful discussions with Dr. P. Monjoint and Professor A. Williams.