Hydrolysis of Aryl *N*-Methylaminosulphonates: Evidence consistent with an *E*1cB Mechanism [1a]

By **Andrew Williams** * and **Kenneth T. Douglas**, University Chemical Laboratories, Canterbury, Kent, CT2 7NH

The following evidence is consistent with an *E*1cB mechanism for the hydrolysis of aryl *N*-methylaminosulphonates: (1) rate constants for the hydrolysis of the title esters are independent of pH in the alkaline region and obey a Brønsted type relationship with a $\beta_{1g.}$ −1·8; (2) the 4-nitrophenyl *N*-methylamino-ester shows a 10^8-fold greater reactivity to hydroxide ion than does the corresponding dimethylamino-ester; and (3) increasing the concentration of amine buffer has no effect on the rate constant for the release of 4-nitrophenol from the monomethyl ester but at 1M-amine concentration all the product is in the form of the sulphonamide.

STRONG evidence exists for the participation of an elimination mechanism in the alkaline hydrolysis of carboxylic esters,[1b-d] carbamates,[2] and phosphoramidic esters.[3] Such a pathway with little bond formation to the nucleophile is responsible for the hydrolysis of monophosphate monoanions and dianions [4] and monosulphate esters.[5] In a recent paper we discuss [2c] three factors affecting the pathway taken in acyl transfer of esters with an 'α-proton'; these are the pK_a of the α-proton, the stability of the intermediate, and the nature of the nucleophile. A fourth factor is the ability of the α-atom constituting the conjugate base to expel the leaving group; a study of the alkaline hydrolysis of alkylaminosulphonates was carried out because these esters are the nitrogen analogues of the monosulphates. Although the unsaturated intermediate $MeNSO_2$ is probably less stable than is sulphur trioxide the α-atom (MeN^-), which has a higher basicity than the oxygen analogue, is expected to expel the leaving group more effectively. It was of interest therefore to compare the oxygen and nitrogen esters for their relative propensity to hydrolyse *via* the *E*1cB pathway.

EXPERIMENTAL

Materials.—Aryl methylaminosulphonates were prepared from *N*-methylaminosulphonyl chloride,[6] b.p. 76—78° at 0·05 Torr, n^{20} 1·465 (lit.,[6b] 70° at 0·04 Torr, n^{25} 1·461) by the following general method, described for the 4-nitrophenyl ester. To a solution of *N*-methylaminosulphonyl chloride (4·3 g, 0·03 mol) in dry dichloromethane (15 ml) was added a mixture of triethylamine (3·02 g, 0·03 mol) and 4-nitrophenol (4·16 g, 0·03 mol) in dichloromethane (20 ml). The mixture was kept at room temperature overnight, filtered, and the filtrate dried (Na_2SO_4). An alternative procedure that was used occasionally was to extract the dichloromethane with 5M-hydrochloric acid solution prior to drying. Removal of the solvent gave a yellow oil which slowly crystallised. Recrystallisation (twice) from dry ether gave white crystals, m.p. 70—72°.

Aryl dimethylaminosulphonates were prepared from dimethylaminosulphonyl chloride [7] by a method similar to that for the monomethyl derivatives. The acid chloride, b.p. 46—48° at 0·03 Torr, n^{20} 1·454 (lit.,[7a] b.p. 71° at 12 Torr) had an i.r. spectrum identical with that reported in the literature.[7b]

4-Nitrophenyl benzenesulphonate was prepared similarly, m.p. 85·5—86° (lit.,[8] 88—89°).

All compounds were characterised by i.r. and n.m.r. spectroscopy and their analytical and physical properties are recorded in Table 1. AnalaR dioxan was purged of peroxides by percolating through an alumina column and tested with aqueous potassium iodide. Ethyl alcohol was dried using magnesium ethylate as described by Vogel.[9] Water enriched with oxygen-18 was commercial (B.O.C.) and was converted into sodium hydroxide solution by dissolving a cleaned pellet of sodium (0·2 g) in water (4 ml) cooled in ice. Deuterium oxide (B.O.C.) was converted into sodium deuterioxide solution in the same way.

Methods.—Rates of hydrolysis of the sulphonate esters in ethanol–water or dioxan–water (both 50% v/v) were measured spectrophotometrically using a Unicam SP 800 instrument fitted with a repetitive scanning attachment (SP 825) and a Servoscribe recording potentiometer; some rates were measured with an SP 600 machine. Scanning experiments gave the best wavelength for following the hydrolyses and also gave an indication of the reaction stoicheiometry and identity of products. Further indication of the stoicheiometry and product identification was carried out using a pH-stat to determine the number of

[1] (*a*) Preliminary account, K. T. Douglas and A. Williams, *J.C.S. Chem. Comm.*, 1973, 356; (*b*) R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956; (*c*) T. C. Bruice and B. Holmquist, *ibid.*, 1968, **90**, 7136; (*d*) *idem.*, *ibid.*, 1969, **91**, 3003.

[2] (*a*) A. Williams, *J.C.S. Perkin II*, 1972, 808; (*b*) A. F. Hegarty and L. N. Frost, *J.C.S. Chem. Comm.*, 1972, 1538; (*c*) A. Williams, *J.C.S. Perkin II*, 1973, 1244.

[3] A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1972, 1454; 1973, 318.

[4] (*a*) A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3209; (*b*) A. J. Kirby and A. G. Varvoglis, *ibid.*, 1967, **89**, 415.

[5] (*a*) E. J. Fendler and J. H. Fendler, *J. Org. Chem.*, 1968, **33**, 3852; (*b*) S. J. Benkovic and P. A. Benkovic, *J. Amer. Chem. Soc.*, 1968, **90**, 2646.

[6] (*a*) N. C. Hansen, *Acta Chem. Scand.*, 1963, **17**, 2141; (*b*) G. Weiss and G. Schulze, *Annalen*, 1969, **729**, 41.

[7] (*a*) E. Stein, G.P. 946,710/1956 (*Chem. Abs.*, 1959, **53**, 2260e); (*b*) E. Merian, *Helv. Chim. Acta*, 1960, **43**, 1122.

[8] S. Oae and R. Kiritani, *Bull. Chem. Soc. Japan*, 1956, **38**, 765.

[9] A. I. Vogel, 'A Textbook of Practical Organic Chemistry, Longmans, London, 1956, 3rd edn., p. 167.

TABLE 1

Analytical and physical properties of substrates and products

Compound	M.p. (°C) or b.p. [T/°C (p/Torr)]	Found (%) C	H	N	Formula	Calc. (%) C	H	N
Aryl methylaminosulphonate								
4-NO_2	70—72	36·4	3·7	12·0	$C_7H_8N_2O_5S$	36·2	3·5	12·0
3-NO_2	70—71	36·1	3·5	11·6	$C_7H_8N_2O_5S$	36·2	3·5	12·0
4-Ac	99—101	47·0	4·9	5·7	$C_9H_{11}NO_4S$	47·2	4·8	6·1
4-Cl	53—55	37·4	3·7	6·2	$C_7H_8ClNO_3S$	37·8	3·6	6·3
3-Cl	[148—150 (0·015)]	37·9	3·8	6·7	$C_7H_8ClNO_3S$	37·8	3·6	6·3
H [b]	[148—152 (0·9)]							
4-MeO [a]		44·0	5·3	6·7	$C_8H_{11}NO_4S$	44·2	5·1	6·5
Aryl dimethylaminosulphonate								
4-NO_2	124 [c]	39·2	4·4	11·4	$C_8H_{10}N_2O_5S$	39·0	4·1	11·4
2,4-$(NO_2)_2$	81—82	33·6	3·5	14·3	$C_8H_9N_3O_7S$	33·0	3·1	14·4
2-Cl-4-NO_2	78—79	34·2	3·3	9·9	$C_8H_9ClN_2O_5S$	34·2	3·2	10·0
N-(Methylaminosulphonyl)diethylamine								
	[118—120 (1·0)]	36·2	8·5	16·7	$C_5H_{14}N_2O_2S$	36·1	8·4	16·9
N-(Methylaminosulphonyl)piperidine								
	[131—132 (1·0)]	40·5	7·8	15·5	$C_6H_{14}N_2O_2S$	40·4	7·9	15·7

[a] This compound was purified by chromatography in dichloromethane over alumina (Camag); since the quantity involved was so small no attempt was made to record a b.p. [b] Lit.,[4b] b.p. 135° at 0·4 Torr. [c] C. Corral and A. M. Municio, *Anal. Real. Soc. Espan. quim.*, 1964, **60B**, 341, give m.p. 124°.

protons released per molecule hydrolysed. Product analysis in trapping experiments using amine buffers was performed using n.m.r. spectroscopy (Perkin-Elmer R10 machine) of the solution of 4-nitrophenol and sulphonamide from extraction of the aqueous product at low pH with chloroform; the 4-nitrophenol integration was used as a standard to determine the percentage of the methylaminosulphonate trapped as sulphonamide.

Pseudo-first-order rate constants were determined using plots of $\log_{10}(A_t - A_\infty)$ *versus* time and random checks with the Guggenheim method gave identical results. Very slow reactions were followed by the method of initial rates using infinity values calculated from the known extinction coefficients of the products and/or from complete hydrolysis of reactant under fast conditions (*e.g.* higher pH or temperature) and reverting to the experimental conditions to measure the optical density. Ionic strengths were kept at either 0·1 or 1·0 using sodium chloride.

Thermodynamic ionisation constants were determined from u.v. absorptions at different pH values; if the absorptions at zero and *x*M-NaOH are A_0 and A_x respectively and A_{tot} is the absorbance change for complete ionisation then equation (1) holds. Where reaction of the substrate caused

$$A_x - A_0 = A_{tot}(1 + a_{H^+}/K_a) \qquad (1)$$

the absorbances to change with time these were extrapolated to zero time. pH Measurements were made with a Radiometer 25 pH-meter fitted with an expanded scale; high pH values were corrected for sodium ion error using the nomogram supplied by Radiometer. Extremely high pH values were measured using the B-type electrode and the nomogram. Kinetic parameters requiring a knowledge of the hydroxide ion concentration were derived using K_w for water at 25°

Fitting of the experimental data to theoretical equations was accomplished using ' Basic Language ' computer programs and the Kent on-line system. Mass spectra were determined with an A.E.I. MS 902 high resolution mass spectrograph.

RESULTS

Spectral data for both sets of esters are recorded in Table 2; good isosbestic wavelengths were obtained by repetitive scanning for the methylamino-series and the more reactive members of the dimethylamino-series and indicated 1 : 1 stoicheiometry in the reaction. Isosbestic wavelengths for the methylaminosulphonates are dependent on the concentration of the sodium hydroxide buffers as a consequence of

TABLE 2

Hydrolysis of sulphonate substrates [a]

Compound	$\lambda_{kinetic}$/nm	$\lambda_{isosbestic}$/nm	pK_a [c]	k'/s^{-1} [b]
Aryl methylaminosulphonates				
4-NO_2	400	338 [e]	8·88 [j]	1·4 × 10^{-1}
4-Ac	330	289, 241 [f]		2·9 × 10^{-3}
3-NO_2	390	287, 268 [f]	8·70 [g]	1·1 × 10^{-3}
3-Cl	295	None	9·48 [g]	5·0 × 10^{-5}
4-Cl	303	None	9·80 [h]	1·4 × 10^{-5}
H	292	None	10·53 [i]	9·9 × 10^{-6}
4-MeO	325	None		5·6 × 10^{-6}
				k_{OH}/l mol^{-1} s^{-1} [b]
Aryl dimethylaminosulphonates				
4-NO_2	400			2·4 × 10^{-6}
2,4-(NO_2)	400	335		5·8 × 10^{-3}
2-Cl-4-NO_2	320	286, 248		9·1 × 10^{-4}

[a] See text for general experimental conditions. [b] 60°, μ 1·0, 50% ethanol–water (v/v). [c] 25°, μ 0·1, 50% ethanol–water. A Hammett relationship is obeyed: $pK_a = -2{\cdot}5\,\sigma + 10{\cdot}5$; although the phenyl derivative deviates in the Hammett k' correlation there is no reason to expect a deviation in the Hammett plot for ionisation and the correlation is normal in that respect. The thermodynamic pK_a values of the 4-nitro- and 4-acetyl-phenyl derivatives were not measured owing to the rapid hydrolysis of these esters even at 25°; no good absorption change was observed for the ionisation of the 4-methoxyphenyl derivative. The spread of σ is however sufficient to ensure a reasonably accurate selectivity to be measured. We note here that the Hammett ρ value indicates considerably more linkage between NH and the substituent than in benzoic acids and refer to our previous sytems where a higher degree of bonding has also been observed (ref. 3 and A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1972, 2112). The cause of this apparently greater linkage may reside in the effect of solvent which can be considerable (P. R. Wells, ' Linear Free Energy Relationships,' Academic Press, London, 1968, p. 12). [d] $k'_H/k'_D = 1{\cdot}35$; 4-nitrophenyl benzenesulphonate has $k_{OD}/k_{OH} = 1{\cdot}26$ and $k_{OH} = 1{\cdot}7 \times 10^{-2}$ l mol^{-1} s^{-1}, 20% dioxan–water (v/v), 25°, μ 1·02. [e] 0·1M-NaOH. [f] 1·0M-NaOH. [g] Measured at 300 nm. [h] Measured at 250 nm. [i] Measured at 290 nm. [j] Kinetically determined pK_a for 50% dioxan–water, μ 0·1, 25°.

the ionisation of the NH group. The absorption at 400 nm for the product of hydrolysis of the 4-nitrophenyl esters agreed with the absorbance calculated from the extinction coefficient for the 4-nitrophenolate anion under these conditions. The identity of the other hydrolytic product from the methylaminosulphonates is with little doubt methylaminosulphonate anion ($MeNHSO_3^-$) and this was checked by determining the number of protons released in experiments at different pH values using the pH-stat; above pH 9 the anionic substrate yields *one* equivalent proton [equation (2)]; between pH 7 and 8 the acid released may be calculated from the pK_a of the 4-nitrophenol and of the substrate and rises to two equivalents of protons [equation (3)]. Below pH 7 the acid released is one equivalent [equation (4)].

$$\text{pH} > 9 \quad MeNHSO_2\text{–O-}p\text{-Np} + H_2O \longrightarrow MeNHSO_3^- + p\text{-NpO}^- + H^+ \quad (2)$$

$$7 < \text{pH} < 8 \quad MeNHSO_2\text{–O-}p\text{-Np} + H_2O \longrightarrow MeNHSO_3^- + p\text{-NpO}^- + 2H^+ \quad (3)$$

$$\text{pH} < 7 \quad MeNHSO_2\text{–O-}p\text{-Np} + H_2O \longrightarrow MeNHSO_3^- + p\text{-NpOH} + H^+ \quad (4)$$

p-Np = p-nitrophenyl.

Rate constants for release of 4-nitrophenol from the methylamino-ester in glycine, piperidine, and diethylamine buffers at different concentrations are given in Table 3; since

TABLE 3

Effect of buffer concentration on products and rate of release of 4-nitrophenol from the methylaminosulphonate ester [a]

Piperidine					
pH	11·23	11·25	11·21	11·24	11·20 [b]
Concentration/M	1·00	0·75	0·50	0·25	0·00
$10^3 k_{obs}/s^{-1}$	3·85	3·80	3·90	3·75	3·80
Glycine					
pH	9·64	9·53	9·43	9·53	9·50 [b]
Concentration/M	0·232	0·046	0·023	0·009	0·000
$10^3 k_{obs}/s^{-1}$	3·83	3·70	3·66	3·76	3·70
Diethylamine					
pH	10·70	10·71	10·70	10·73	10·70 [b]
Concentration/M	1·00	0·75	0·50	0·25	0·00
$10^3 k_{obs}/s^{-1}$	3·80	3·90	3·85	3·83	3·85

Product analysis (1M-amine buffer [a])

	4-Nitrophenol : sulphonamide [c,d]
Piperidine	1 : 0·98
Diethylamine	1 : 1·01

[a] Fraction of base in buffer solutions is 0·5, μ 0·1, 25°, 50% ethanol–water (v/v). [b] This measurement was recorded in the pH-stat; one equivalent of acid is released per one equivalent of ester consumed. [c] Estimated error in measuring area under n.m.r. peaks is <5%. [d] $CDCl_3$ was the solvent for measuring the n.m.r. spectra and the peaks used were the aromatic absorptions of the 4-nitrophenol and the NCH_2 absorptions in the diethylamine and piperidine cases.

the buffer effect is negligible, rate constants for release of 4-nitrophenol were not extrapolated to zero buffer concentration in the study of the effect of pH on hydrolysis [Figure 1, and Supplementary Publication No. SUP 21133 (6 pp.) *]. The rate constants with buffer are the same, within experimental error, as those determined in the pH-stat without added buffer. Product analysis using n.m.r. spectroscopy (Table 3) indicates that all the 4-nitrophenyl methylaminosulphonate is converted into sulphonamide in the presence of 1M-piperidine and diethylamine buffer whereas the rate constant for 4-nitrophenolate release is identical with that in the absence of amine buffer (within experimental error).

Ionic strength has no sensible effect on reactivity. The rate constants fit a theoretical equation (5) and the values of k_{H_2O}, k', and k_{OH} are $3·5 \times 10^{-6}$ s^{-1}, $8·4 \times 10^{-3}$ s^{-1}, and $8·0 \times 10^{-1}$ l mol^{-1} s^{-1} respectively; the kinetic pK_a (8·88) is higher than that extrapolated from the equation in footnote

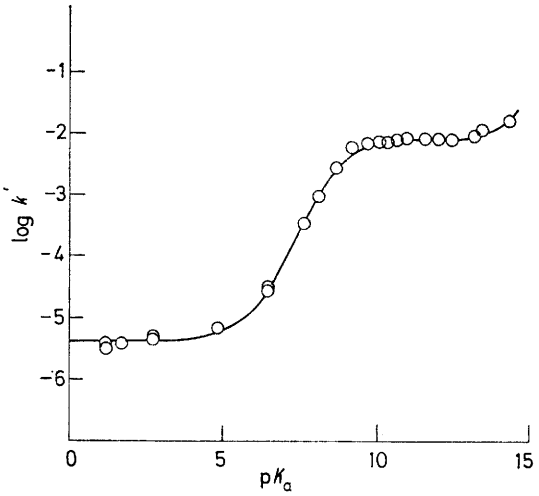


FIGURE 1 pH Dependence for the hydrolysis of 4-nitrophenyl methylaminosulphonate in 20% dioxan–water (v/v) at 25°; line is theoretical from data in the text and equation (5)

c of Table 2 (8·48). The difference reflects the different media; although the kinetics were done with different ionic

$$k_{obs} = k_{H_2O} + k'/(1 + a_{H^+}/K_a) + k_{OH}[OH] \quad (5)$$

strengths the medium was constant in the pH region where the kinetic pK_a dominates. The alkaline 'plateau' rate constants (k', Table 2) for the other aryl esters were obtained from results over a range of hydroxide ion concentrations (Supplementary Publication). The k' parameters fit a Hammett σ^- relationship [Figure 2(a)] and a Brønsted type relationship [Figure 2(b)] and the equations governing the parameters are: $\log_{10} k' = 3·9\sigma^- - 5·7 = -1·8\ pK_a - 11·6$ (the correlation coefficients r are respectively 0·999 and 0·997). The values of the selectivities are for the most reactive esters and do not include the phenyl and 4-methoxyphenyl cases. When these compounds are included in the correlation the selectivities become 3·0 and −1·5 respectively. [The slopes quoted here are slightly lower than those in the preliminary communication (4·04 and −1·85) [1a] because the kinetic parameters have been subsequently refined.]

Bimolecular rate constants for the alkaline hydrolysis of aryl dimethylaminosulphonates (Table 2) obey a Brønsted type dependence on pK_a of the leaving phenol: $\log_{10} k_{OH} = -1·1pK_a + 2·3$ (r 0·967). The hydrolysis of 4-nitrophenyl benzenesulphonate was proportional to the hydroxide ion concentration.

Other results are presented in the Supplementary Publication and the derived parameters necessary for an understanding of this paper are quoted in Table 2 and in the text.

4-Nitrophenol extracted from the acidified solution after hydrolysis of the methylaminosulphonate ester in enriched

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin II*, 1973, Index issue. Items less than 10 pp. are supplied as full size copies.

(% excess of ^{18}O = 1·019) and non-enriched water was analysed in the mass spectrograph and the following figures refer to the percentage of mass 141/139 (Calc. for S–O cleavage, 0·800; Ar–O cleavage, 3·258. Observed: with enrichment, 0·908; with no enrichment, 0·887).

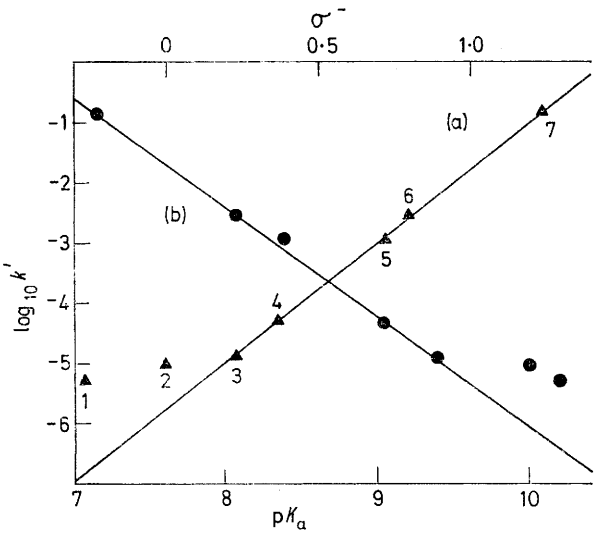


FIGURE 2 Dependence of k' for aryl methylaminosulphonates at 60° in 50% ethanol–water (v/v) on (a) σ^- ▲ and on (b) the pK_a of the phenol leaving group ●: 1, 4-methoxyphenyl; 2, phenyl; 3, 4-chlorophenyl; 4, 3-chlorophenyl; 5, 3-nitrophenyl; 6, 4-acetylphenyl; 7, 4-nitrophenyl

DISCUSSION

The elimination–addition pathway for alkaline hydrolysis of aryl methylaminosulphonates is depicted in equation (6). Consistent with this mechanism is the high positive ρ value for k' (identified in the mechanism as k_1); moreover the Hammett relationship is with σ^- indicating considerable phenolate ion character in the

$$MeNHSO_2\text{–}OAr \overset{K_a}{\rightleftharpoons} MeN\tilde{S}O_2\text{–}OAr \xrightarrow{k_1} MeNSO_2 \xrightarrow[H_2O]{fast} MeNHSO_3^- \quad (6)$$

transition-state as expected for k_1 being rate limiting. Perusal of Figure 2 indicates that quite a good correlation exists for all the esters except the phenyl and 4-methoxyphenyl cases and we shall discuss the discrepancies later; the selectivities quoted do not involve the deviant points but their inclusion would not affect our arguments significantly. Oxygen-18 studies confirm that the high ρ and σ^- dependence are not a result of aryl–oxygen cleavage and the likelihood of S–N cleavage in aqueous base is small since strong nucleophiles are generally required for such a process.[10] Comparison of the Brønsted $\beta_{l.g.}$ for k_{OH} ($k'K_a/K_w$) for aryl methylaminosulphonates (−2·9) * with that for the alkaline hydrolysis of the corresponding *NN*-dimethylamino-series (−1·1) indicates a different mechanistic path for the two ester types and the latter series presumably hydrolyses *via* an addition–elimination type of process.† The Brønsted type relationship for alkaline hydrolysis of aryl sulphonates also has a low $\beta_{l.g.}$ and the Hammett relationship correlates with σ [12] rather than σ^-. Further evidence against an identity of mechanistic type is a 10^8-fold larger apparent hydroxide rate constant for the 4-nitrophenyl ester of the monomethylaminosulphonate ($k'K_a/K_w$) than that for the dimethyl analogue ($2·4 \times 10^{-6}$ l mol^{-1} s^{-1}). Steric hindrance effects are unlikely candidates for such a large difference.[12,13]

The ' titration ' curve of Figure 1 could arise from an addition–elimination reaction of hydroxide with the neutral ester, k_2, which is inhibited as the substrate ionises; the plateau rate constant k' would then be equivalent to $K_w k_2/K_a$ and since ρ values for K_a and k' are known (2·5 and 3·9 respectively) a ρ value of 6·4 ‡ for k_2 can be calculated by adding the respective ρ selectivities. The alkaline hydrolysis of aryl sulphonates possesses a Hammett selectivity of *ca.* +2·5, *e.g.* aryl benzenesulphonates and aryl 4-phenylbenzenesulphonates have ρ 2·75 [12] and 2·56 [14] respectively. Although we do not have a Hammett selectivity for the aryl dimethylaminosulphonates a value may be calculated from the known Brønsted $\beta_{l.g.}$ (−1·1) to be +2·4 using the Hammett selectivity of −2·2 for the ionisation of phenols.[14] Thus the calculated value for ρ for the monomethylamino-series is substantially larger than the expected value if a bimolecular mechanism were involved with hydroxide attacking sulphur and expelling the phenolate anion. Moreover the nature of the Hammett dependencies differs in so far as σ^- is involved in one and σ in the other.

Attack of water on the conjugate base (MeN$\tilde{S}O_2$–C-*p*-Np) *via* an addition–elimination process could give rise to the observed pH profile (Figure 1) but the rate constant k' is 1000-fold larger than that for water attack on the neutral species (k_{H_2O}); if the mechanisms associated with these parameters were similar the reverse order would be expected because an anion is being attacked in the reaction corresponding to k' and a neutral species in k_{H_2O}. It is assumed that water attack on the neutral species involves considerable bond formation in the transition-state (I) and we are effectively excluding for the conjugate base reaction (k') a transition state with similar bonding characteristics. Our evidence does not exclude a transition state involving little bonding with the attacking nucleophile (II) but

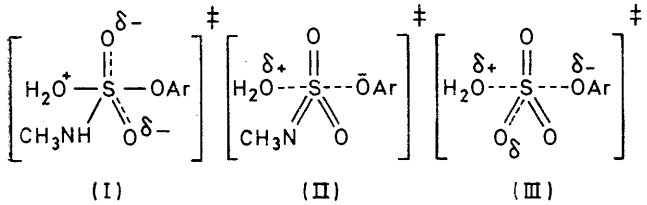
* The value of $\beta_{l.g.}$ for k_{OH} is obtained by adding $\beta_{l.g.}$ for k' and for K_a; the latter may be derived from the ρ value for K_a in Table 2 by division by 2·2, the magnitude of ρ for the ionisation of phenols (see ref. 11). In experimental terms the k_{OH} term for the methylaminosulphonates refers to the hydroxide dependent region of the pH profile prior to ionisation of the NH group. The value, −2·3, is noted as an error in the preliminary communication.[1a]

† Brønsted plots are compared here since the dimethylamino-esters are so unreactive that normal Hammett type substituents give inconveniently small rates.

‡ This ρ value is calculated from figures obtained using different media and temperatures.

[10] J. Strating in ' Organic Sulphur Compounds,' ed. N. Kharasch, Pergamon Press, Oxford, 1961, vol. 1, p. 146.
[11] G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 820.
[12] R. V. Vizgert, *Uspekhi Khim.*, 1963, **32**, 1.
[13] R. B. Scott and M. S. Heller, *J. Org. Chem.*, 1955, **20**, 1159.
[14] R. V. Vizgert and I. E. Katchanko, *React. spos. org. Soedinenii*, 1968, **5**, 9 (*Chem. Abs.*, 1968, **69**, 76,105).

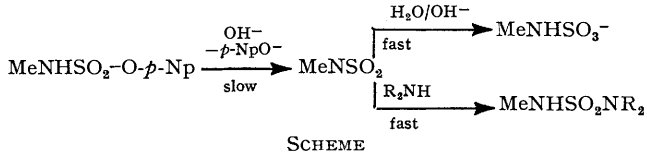
trapping experiments with amine nucleophiles (see later) do not support this. We cannot say much about the S=O and S–O–Ar bonding in (I) but it is probable that the S–OAr bond is not much broken in the transition state for alkaline hydrolysis of aryl sulphonates and we have kept this bond full in the diagram. For (II) our evidence, if it applies to this scheme, points to considerable S–OAr cleavage and we denote this bond with a dotted line.



(I) (II) (III)

There is ample evidence that the corresponding sulphate transfer has a transition state similar to (II) for attack of nitrogen nucleophiles.[15] In the sulphate case the oxyanion of pK_a *ca.* 1 is a much weaker nucleophile (see later) than the amine anion and there is a substituent effect on amine attack at 4-nitrophenyl sulphate pointing to participation of amine in the reaction (*i.e.*, weak bond formation to sulphur) and hence, by analogy, to participation of water in the hydrolysis reaction [(III)]. In the aminosulphonate case the extra energy provided by the bonding with the water to expel the leaving group as in (II) is probably not necessary. Indeed, amine attack is shown in the next section not to involve any bonding between sulphur and nitrogen in the transition state of the rate-determining step.

Trapping Experiments.—The non-acceleratory effect of increasing concentrations of glycine, diethylamine, and piperidine buffers on the rate constant for release of 4-nitrophenol from the corresponding methylaminosulphonate ester combined with the fact that at 1M-buffer (at a fraction of base of 0·5) no acid product was detectable and that all observable product is sulphonamide points to a rate-limiting release of 4-nitrophenol followed by a fast reaction of the amine with an intermediate. The rate constant in the presence of buffers is identical within experimental error with that in the absence of buffers (measured in a pH-stat). We describe this behaviour in the Scheme; the analytical technique



SCHEME

was not suitable to work with low amine concentrations so that a relative value $(k_{H_2O} + k_{OH^-})/k_{R_2NH}$ was not obtained by product analysis. An upper limit for this ratio for diethylamine and piperidine is 1/5500 assuming an error of 1% in measuring the product ratio (essentially from *p*-NpOH/MeNHSO$_2$NR$_2$). This value is consistent with selectivities determined for water and hydroxide *versus* piperidine and other amines of similar pK_a.[4a,16,17] There is of course no sensitivity of the reaction to amine structure and a description of the transition state of the rate-determining step in the Scheme is that it possesses no nitrogen–sulphur bonding.

The deuterium oxide solvent isotope effect on k' for 4-nitrophenyl methylaminosulphonate hydrolysis (k'_H/k'_D 1·35) provides a further example where an *E*1 process has a non-zero effect. The assumption that the *E*1 step should be insensitive to solvent isotope effects was the basis of a proposed diagnostic method to distinguish addition–elimination from *E*1cB mechanisms.[18] We can say that a large solvation change from ground to transition state in the *E*1 process is consistent with the solvent isotope effect and this could be expected from the highly charged ground-state which must disperse its charge in the transition state. The solvent isotope effect of 1·26 (k_{OD}/k_{OH}) for the hydrolysis of 4-nitrophenyl benzenesulphonate is expected for lyoxide attack on a neutral ester.

Recently, Matier and his co-workers [19] postulated that some aminosulphonyl azides also hydrolyse in alkali *via* an *E*1cB path and the large difference in rate constants between mono- and di-substituted amide was cited as evidence. Perusal of the data [19] shows that a series of azides (RNHSO$_2$N$_3$; R = Me, Pr^i, Bu^s, Bu^t, or Pr^n) hydrolyse in alkali with closely similar rate constants. Reactivity to hydroxide in the analogous carboxylic ester series (RCH$_2$CO$_2$Et) ranges over nearly 100-fold for a similar series of R groups.[20a] Bunnett and Bassett,[20b] however, observed relatively little *ortho*-effect on the rate constants for alkaline hydrolysis of 4-nitrophenylbenzenesulphonates, suggesting that steric effects on nucleophilic attack at the sulphonyl group are small. The insensitivity to steric effects is a result of the *ortho*-substituents merely 'fixing' the conformation of an already highly hindered electrophile and more reasonable models of Matier's azides are the substituted acetates already suggested. The insensitivity of the substituted azides to steric effects is consistent with the *E*1cB mechanism. Data from Casida *et al.*[20c] are in agreement with the absence of a steric effect as diagnostic of the *E*1cB mechanism (RNHCO$_2$-*p*-Np has k_{OH} in the order 1, 1·23, 1·23, and 1·46 for R = Me, Et, Pr^n, and Pr^i respectively; R$_2$NCO$_2$-*p*-Np has the order 1, 1·8 × 10^{-2}, 8·5 × 10^{-3}, 2·55 × 10^{-4}, and 1·25 × 10^{-3} for R = Me, Et, Pr^n, Pr^i, and Bu^n).

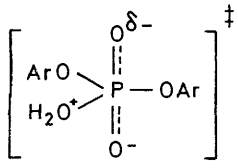
The rate constant for alkaline hydrolysis of methylaminosulphonyl azide [19] is greater than that for the 4-nitrophenyl ester (4 × 10^4 at 29 and 1·1 × 10^3 l mol^{-1} s^{-1} at

[15] S. J. Benkovic and P. A. Benkovic, *J. Amer. Chem. Soc.*, 1966, **88**, 5504.
[16] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **28**, 1778.
[17] E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, 1970, **35**, 3063, 3069.
[18] P. S. Tobias and F. J. Kezdy, *J. Amer. Chem. Soc.*, 1969, **91**, 5171.
[19] W. L. Matier, W. T. Comer, and D. Deitchmann, *J. Medicin. Chem.*, 1972, **15**, 538.
[20] (*a*) A. Williams and G. Salvadori, *J. Chem. Soc.* (*B*), 1971, 2401; (*b*) J. F. Bunnett and J. Y. Bassett, *J. Org. Chem.*, 1962, **27**, 2345; (*c*) J. E. Casida, K. B. Augustinsson, and G. Jonsson, *J. Econ. Entomol.*, 1960, **53**, 205.

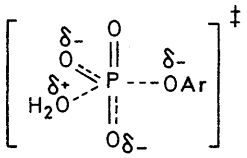
25° respectively) but lies below the Brønsted slope (−2·9) through the phenyl esters. This is not unexpected since the leaving groups are of different types and the azide point *lies below* the Brønsted line for phenols in the alkaline hydrolysis of carbamates.[21a] This reaction yields as products the phenol or alcohol and cyanate ion [21b] and is generally thought to involve an *E*1cB mechanism; it therefore ought to show similarities with the reaction under investigation.

$$NH_2COX \xrightarrow{OH^-} \bar{N}HCOX \longrightarrow NCO^- + XH \quad (7)$$

Recent reports describe the isolation of $RNSO_2$ species analogous to the postulated intermediates [22] and these species are exceedingly reactive to nitrogen nucleophiles and are probably too reactive to be observed even transiently in aqueous solution; the lower stability compared to isoelectronic sulphur trioxide, due in part to electronegatively differences, is not reflected in the relative rates for the *E*1 reactions of $Me\bar{N}SO_2$–OAr and $\bar{O}$–SO_2–OAr which are in the ratio $1 : 10^{-7}$ respectively for the 4-nitrophenyl esters.[5b] In terms of basicity the nitrogen anion (pK_a *ca.* 9) should be more nucleophilic than the oxyanion (pK_a *ca.* 2) of the sulphate half-ester; we propose that if the ' internal nucleophilicity ' of the α-atom is related to the pK_a of the conjugate acid then, other things being equal, the *E*1cB mechanism becomes most efficient at an ' intermediate ' value for the pK_a. For a high pK_a the mechanism is not efficient because there is only little conjugate base in solution; for example alkaline hydrolysis of 4-nitrophenyl acetate *via* the keten is not the preferred mechanism largely due to the extremely high pK_a (*ca.* 25) of the carbon acid. At low pK_a the internal nucleophilicity of the α-atom is only weak as in the aryl monosulphate esters and a consequence of this is that weak bonding with the nucleophile aids leaving-group expulsion. A similar interpretation may be made on the observations that the monoanions of diaryl phosphates (IV) hydrolyse [23] *via* addition–elimination whereas in the hydrolysis of the dianion of monoaryl phosphates (V) the elimination process is far advanced compared with the addition of the water.[4] The pK_a of the monoanion (*ca.* 1) is far less than that for the dianion (*ca.* 7) and therefore would be expected to possess less



(IV)



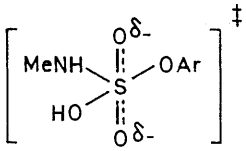
(V)

' internal nucleophilicity ' in accord with the observations. Extra driving force for the expulsion of phenol is obtained in the dianion (V) because there is a statistical factor of two; the effect of the second oxyanion (V) which can donate more charge and aid the expulsion also provides extra driving force over the monoanion (IV) which only has an ether oxygen. The driving force needed to expel the leaving group in (IV) is so great that more bond formation with the nucleophile occurs giving rise to higher selectivities to the pK_a of the ammonium ion in amine attack at diesters.[17]

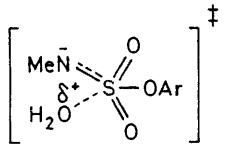
Entropy of activation has been discussed as a possible diagnostic tool for mechanisms of unimolecular reactions in water; [24] the advantage of k' over k_{H_2O} for 4-nitrophenyl methylaminosulphate hydrolysis is in both entropy (−8·9 cal mol^{-1} K^{-1}) and enthalpy (17·2 kcal mol^{-1}) terms compared with −14·7 and 19·9 respectively; the entropy for k' is consistent with the *E*1cB mechanism.

Concerted general base catalysis is not observed and is not expected for bases of pK_a *ca.* 9 according to the rule recently proposed by Jencks.[25] Concerted general base catalysis can only occur when the pK_a of the basic species lies well within the pK_a values of reactants and products; since the pK_a of $MeNHSO_2$ is probably less than zero such catalysis could take place only with very weak bases. We define concerted as meaning simultaneous breaking of the O–Ar bond and breaking of the N–H bond and formation of the base–hydrogen bond.

The phenyl and 4-methoxyphenyl methylaminosulphonates deviate from the Hammett and Brønsted correlations in a positive direction. If the deviation is meaningful it cannot represent a change in rate-determining step but must indicate the operation of an additional mechanism. The deviation cannot refer to a change to displacement at the sulphur by hydroxide ion (VI) because the rate constants for these esters are considerably larger than those calculated for the dimethylamino-analogues from the Brønsted equation in the results



(VI)



(VII)

where this mechanism is followed. A possible mechanism involves increased bond formation between water and the sulphur as in the transition state (VII) and the function of this increased bond formation would be to provide more driving force for the expulsion of the more strongly basic leaving groups.

The help of Mr. K. T. Taylor and Dr. D. Cook in the writing and use of computer programs is gratefully acknowledged. K. T. D. thanks the Government of Northern Ireland for a Research Studentship.

[4/736 *Received*, 10*th April*, 1974]

[21] (*a*) A. Williams, unpublished observations; (*b*) E. A. Werner, *J. Chem. Soc.*, 1918, 622.

[22] G. M. Atkins and E. M. Burgess, *J. Amer. Chem. Soc.*, 1967, **89**, 2502; 1968, **90**, 4744; 1972, **94**, 6135; (*b*) E. M. Burgess and W. M. Williams, *ibid.*, 1972, **94**, 4386.

[23] A. J. Kirby and M. Younas, *J. Chem. Soc.* (*B*), 1970, 510.

[24] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

[25] (*a*) W. P. Jencks, *Chem. Rev.*, 1972, **72**, 7053; (*b*) *J. Amer. Chem. Soc.*, 1972, **94**, 4731.