Aminolysis of sulfamate esters in non-aqueous solvents. Evidence consistent with a concerted E2-type mechanism

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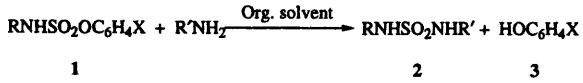
Aminolysis of 4-nitrophenyl sulfamate, *N*-phenylmethylsulfamate and *N*-phenylsulfamate esters in chloroform and acetonitrile at 37 °C using a series of pyridine, quinuclidine and cyclic amine bases has been studied. Second-order kinetics were observed and k_2 constants were obtained from plots of k_{obs} *vs.* [amine]. Brønsted-type plots gave slopes of ~0.27 for the pyridines and ~0.5 for the stronger bases. The failure of the *N*,*N*-dimethylsulfamate, $Me_2NSO_2OC_6H_4NO_2$-4, to react and the absence of steric effects when hindered pyridines were used support an elimination rather than a substitution mechanism and thus the amines act as general base catalysts. Negative entropies of activation support a bimolecular mechanism and an isokinetic temperature of 541 K was obtained from a plot of $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$. A β_{lg} of −1.25 (ρ = +2.8) has been obtained for reaction of a series of five *N*-phenylmethyl esters, $PhCH_2NHSO_2OC_6H_4X$ (X = 4-NO_2, 3-NO_2, 3-Cl, 4-Cl and H with *tert*-butylamine in chloroform and a ρ_{acyl} of −0.91 for reaction of the phenyl esters, $XC_6H_4NHSO_2OC_6H_4X$ (X = 4-MeO, 4-Me, 3-Me, H and 3-Cl) with 4-dimethylaminopyridine in chloroform. These reactions are seen as being E2 type processes with some ElcB-like character but they are not thought to involve *N*-sulfonylamines, $RN{=}SO_2$.

The study of acyl transfer reactions in aqueous and mixed aqueous media is one of the most thoroughly researched areas in organic and biological chemistry. However, such studies in non-aqueous media are much more limited and apart from the seminal work of Menger,[1] Satchell,[2] Litvinenko[3] and Lee[4] and a number of other contributions little work has been done in this area.

Sulfonyl transfer reactions in aqueous media have been recently reviewed by Gordon, Maskill and Ruasse.[5] As in the case of acyl transfer reactions work involving sulfonyl group transfer in non-aqueous media is less extensive than that carried out in aqueous media. Important studies in this area involving reactions of sulfonyl halides and sulfonate esters have been carried out by Vizgert,[6] Litvinenko,[7] Skrypnik,[8] Rogne[9] and Lee.[10] Generally, two distinct mechanisms (sometimes competing) have been delineated, *viz.* nucleophilic substitution at the sulfonyl group sulfur (S_N2 or S_AN) and elimination–addition often apparently involving a sulfene, $R^1R^2C{=}SO_2$ as a transient intermediate. In elegant work Skrypnik's group[8] have demonstrated the concurrent operation of both mechanisms in the phenolysis in various organic solvents of a series of phenylmethanesulfonyl chlorides in the presence of pyridines.

The aminolysis and hydrolysis of sulfamate esters in aqueous organic media has been closely examined by Williams' group[11] and more recently in this laboratory[12] and the predominant reaction by an ElcB elimination mechanism involving a sulfonylamine [$RN{=}SO_2$] has been established. Considering the importance of sulfamate esters and sulfamoyl halides in the pharmaceutical and agrochemical industries and remembering that most of their reactions are carried out in non-aqueous media it is surprising to find that no mechanistic studies of their aminolysis reactions have been made in such media. This paper attempts to fill this gap and to examine the nature of the mechanism of the reaction shown in Scheme 1.

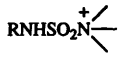


Scheme 1

Results

Product studies, often using spent kinetic solutions, showed that in chloroform or acetonitrile reaction proceeds exclusively according to Scheme 1. Both sulfamide **2** and nitrophenol **3**, X = 4-NO_2, products have been determined by HPLC and by UV spectroscopy in the case of **3**, X = 4-NO_2. Tests with spiked solutions of phenylsulfamate showed that ⩾2.5% sulfamate formation in Scheme 1 can be detected.

In many of the reactions examined the product sulfamides **2** will be of type **4** where $\overset{+}{N}\!\!<$ represents a pyridinium or a



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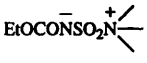
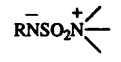
quinuclidinium ring and these may be stabilised by forming an inner salt or zwitterion **5**. Compounds such as **5** have been





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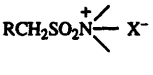
isolated and reacted[13] and in 'sulfonamide' chemistry there are many examples[8,14] of structures of the type given below which can also be regarded as precedents for **4**.



Kinetics were carried out in the appropriate organic solvent under pseudo-first-order conditions (at least 10-fold excess of amine). A first-order dependence on the ester concentration was established for the esters **1**, R = $PhCH_2$, X = 4-NO_2, and **1**, R = Ph, X = 4-NO_2. Plots of k_{obs} *vs.* [amine] gave good straight lines over the range of amine concentrations indicated in Tables 1–4. Some of these plots are shown in Fig. 1. The second-order rate constants (k_2) for each reaction were

Table 1 Rate constants (k_2) for reaction of 4-nitrophenyl *N*-phenylmethylsulfamate with pyridines at 37 °C

Solvent	Pyridine	pK_a (H_2O)[a]	pK_a (CH_3CN)[c]	[Amine]/10^{-2} mol dm^{-3}	$10^4k_2/10^{-4}$ dm^3 mol^{-1} s^{-1}	±(10^4 S.E.)	r	n
PhMe (2.4)[d]	2-NH_2	6.71	14.51	1.0–20.0	11.0	0.96	0.991	6
PhCl (5.6)	2-NH_2	—	—	1.0–20.0	14.8	0.67	0.997	5
CH_2Cl_2 (8.9)	2-NH_2	—	—	1.0–20.0	10.5	0.62	0.993	6
Me_2CO (20.6)	2-NH_2	—	—	5.0–15.0	12.8	0.54	0.999	3
MeCN (36)	2-NH_2	—	—	1.0–20.0	12.5	0.69	0.993	6
$CHCl_3$	4-Pyrrolo	10.56[b]	19.18	3.0–10.0	63.6	0.46	0.999	3
$CHCl_3$	4-Me_2N	9.70	18.13	2.0–15.0	40.5	2.99	0.991	5
$CHCl_3$	4-NH_2	9.11	17.44	2.0–10.0	29.0	0.80	0.998	5
$CHCl_3$	2-NH_2, 4,6-Me_2	7.84	15.44	2.5–20.0	12.8	0.26	0.990	6
$CHCl_3$	2-NH_2, 4-Me	7.48	15.4	2.5–20.0	11.8	0.18	0.979	6
$CHCl_3$	3-Me	5.63	13.13	2.0–20.0	6.34	0.47	0.994	3
$CHCl_3$	Pyr[e]	5.25	12.66	3.0–20.0	4.39	0.29	0.991	6
$CHCl_3$	3-Cl	2.84	9.69	2.0–20.0	0.57	0.04	0.996	4

[a] The $pK_a(H_2O)$ values for the pyridines were taken from D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworths, London, 1965. [b] The value for 4-pyrrolopyridine was predicted using the eqn. $pK_a = 5.25–5.90\sigma$: see D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Prediction for Organic Acids and Bases*, Chapman and Hall, London, 1981. [c] The pK_a (CH_3CN) values for 2-NH_2, 4-NH_2 and 2-NH_2, 4,6-dimethylpyridines were taken from N. Foroughifar, K. T. Leffek and Y. G. Lee, *Can. J. Chem.*, 1992, **70**, 2856, the values for the other pyridines were calculated from the eqn. given in the paper: pK_a (CH_3CN) = (1.23 ± 0.03) pK_a (H_2O) + 6.2 ± 0.2. [d] Relative permittivities in brackets were taken from C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd edn., VCH, Weinheim, 1988, Table A-1, pp. 408–411. [e] Pyr = pyridine.

Table 2 Rate constants (k_2) for reaction of 4-nitrophenyl *N*-phenylmethylsulfamate with quinuclidines and alicyclic amines in chloroform at 37 °C

Amine	pK_a (H_2O)[a,b]	pK_a (CH_3CN)[c]	[Amine]/10^{-2} mol dm^{-3}	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}	±(10^3 S.E.)	r	n
Quinuclidine	11.45	19.51	1.0–10.0	40.8	2.55	0.994	5
Quinuclidinol	10.02	18.70	1.0–10.0	12.8	1.21	0.995	5
3-Chloroquinuclidine	9.03	17.17	1.0–10.0	2.1	0.15	0.994	5
Quinuclidinone	7.53	15.40	2.5–10.0	0.45	0.01	0.999	4
Piperidine	11.24	—	2.0–10.0	16.4	0.74	0.997	5
Piperazine	9.94[d]	—	2.0–10.0	4.25	0.02	0.999	5
1-(2-Aminoethyl)piperazine	9.51	—	1.0–5.0	3.51	0.04	0.999	4
Thiomorpholine	9.10	—	2.0–10.0	0.95	0.01	0.988	5
β-Hydroxyethylpiperazine	9.38	—	2.0–10.0	1.96	0.00	0.999	5
Morpholine	8.78	—	2.0–10.0	0.68	0.03	0.999	5
N-Formylpiperazine	7.98	—	1.0–5.0	0.35	0.05	0.988	4

[a] The quinuclidine values were taken from M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6963. [b] Values for the alicyclic amines were obtained from E. A. Castro and C. Ureta, *J. Chem. Soc., Perkin Trans. 2*, 1991, 63 except for 1-(2-aminoethyl)piperazine which was obtained from D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, 1965 and thiomorpholine was determined (see Experimental). [c] K. Izutsu, *Acid-Basic Dissociation Constants in Dipolar Aprotic Solvents* IUPAC, Chem. Data series No. 35, Blackwell Scientific Publications, Oxford, 1990. The value for 3-chloroquinuclidine was calculated from the relationship: pK_a (CH_3CN) = 1.079 pK_a (H_2O) + 7.43 (see P. Beltrame, G. Gelli and A. Loi, *Gazz. Chim. Ital.*, 1980, **110**, 491). [d] If the pK_a and rate values are statistically corrected *i.e.* $pK_a = 9.94 + \log p/q$ and $k_2 = (4.25/_q)\ 10^{-3}$ (E. A. Castro, F. Ibáñez, M. Salas, J. G. Santos and P. Sepúlveda, *J. Org. Chem.*, 1993, **58**, 459) the slope of the Brønsted plot for the alicyclic amines (Fig. 2) remains the same but the correlation coefficient (r) drops from 0.968 to 0.95.

Table 3 Rate constants (k_2) for reaction of X-phenyl *N*-phenylmethylsulfamates with *tert*-butylamine in acetonitrile at 37 °C

$PhCH_2NHSO_2OC_6H_4X$	pK_a (H_2O)[a]	σ[b]	[Amine]/10^{-2} mol dm^{-3}	$k_2/10^{-5}$ dm^3 mol^{-1} s^{-1}	±(10^5 S.E.)	r	n
4-NO_2	7.15	1.27	2.0–15.0	318.67	9.175	6	0.998
3-NO_2	8.36	0.71	5.0–40.0	6.29	0.337	5	0.995
3-Cl	9.12	0.373	5.0–40.0	0.863	0.004	4	0.998
4-Cl	9.41	0.27	10.0–50.0	0.413	0.001	5	0.998
H	9.99	0	5.0–50.0	0.083	0.000	5	0.998

[a] pK_a values of the phenol leaving groups in water are taken from D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Prediction of Organic Acids and Bases*, Chapman and Hall, London, 1981. [b] The 4-NO_2 and 4-Cl are σ^- values.

calculated from the slopes of these plots and are also given in Tables 1–4 together with the standard error (S.E.), the correlation coefficient (r) for the k_{obs} *vs.* [amine] plot and the number of points (n) on the plot.

All the data in Table 1 relate to the phenylmethyl ester, **1**, R = $PhCH_2$, X = 4-NO_2. The first five entries reveal the negligible effect of solvent on the reaction. The other eight entries probe the effect in chloroform of a series of pyridines on the reaction of the ester. The most hindered pyridine, 2-amino-4,6-dimethyl shows no rate retardation compared to, say, pyridine and thus no steric effect is evident. These eight pyridines give a good 'Brønsted-type' plot (Fig. 2) with β = 0.25 ± 0.02 (r = 0.987) when the k_2 rate constants are plotted against the pK_a values in water. Interestingly, an almost identical slope β = 0.21 ± 0.02 (r = 0.984) was obtained when pK_a(CH_3CN) values were used. Fig. 2 contains two other Brønsted-type plots for the reactions of 4-nitrophenyl *N*-phenylmethanesulfamate in chloroform using sets of stronger quinuclidine bases (β = 0.52 ± 0.04, r = 0.989) and alicyclic amines (β = 0.54 ± 0.04, r = 0.968) (Table 2). For the four quinuclidines a plot using pK_a (CH_3CN) values gave β = 0.47 ± 0.03 (r = 0.994).

Table 3 contains data on the effect of leaving group. A β_{lg} of −1.25 ± 0.05 (r = 0.997) using pK_a values from water for the

Table 4 Rate constants (k_2) for reaction of 4-nitrophenyl sulfamate with pyridines in chloroform at 37 °C

Pyridine	$pK_a(H_2O)^a$	$pK_a(CH_3CN)^b$	$\sigma/\Sigma\sigma^c$	[Amine]/10^{-2} mol dm^{-3}	$k_2/10^{-4}$ dm^3 mol^{-1} s^{-1}	±(10^4 S.E.)	r	n
4-Me_2N	9.61	18.13	−0.83	0.75–15.0	178.0	0.089	0.990	10
2-NH_2, 4-Me	7.53	15.4	−0.41	1.0–20.0	28.8	0.007	0.998	9
2-NH_2, 4,6-Me_2	7.84	—	−0.54	4.5–20.0	28.8	0.002	0.994	9
2-NH_2	6.71	14.51	−0.27	1.0–20.0	16.9	0.006	0.995	9
2-NH_2, 6-Me	7.41	—	—	4.0–20.0	14.0	0.003	0.997	7
3-Me	5.63	13.13	−0.06	4.0–20.0	8.3	0.004	0.992	9
2-Et	5.89	13.4	−0.13	1.0–20.0	6.9	0.005	0.977	10
2-Me	5.94	13.5	−0.13	10.0–20.0	6.7	0.003	0.996	5
Pyr	5.25	12.66	0	8.0–20.0	6.5	0.003	0.995	6
2,6-Me_2	6.60	—	—	8.0–20.0	6.5	0.006	0.986	6
3-Cl	2.84	9.69	0.37	8.0–20.0	1.5	0.001	0.994	6

[a] All values are taken from the ref. in Table 1, footnote *a*. [b] See Table 1, footnote *c*. [c] Values were taken from D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Prediction for Organic Acids and Bases*, Chapman and Hall, London, 1981. A $\sigma_{p\text{-}NH_2}$ of −0.57 was used for the Hammett plot for some of the data in Table 1. Individual σ values were added where necessary to assess cumulative electronic effects.

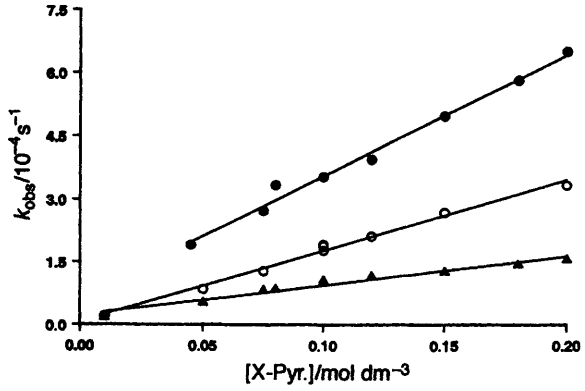


Fig. 1 Plots of k_{obs} *vs.* [amine] for aminolysis of 4-nitrophenylsulfamate in chloroform at 37 °C for 2-ethylpyridine (▲), 2-aminopyridine (○) and 2-amino-4,6-dimethylpyridine (●)

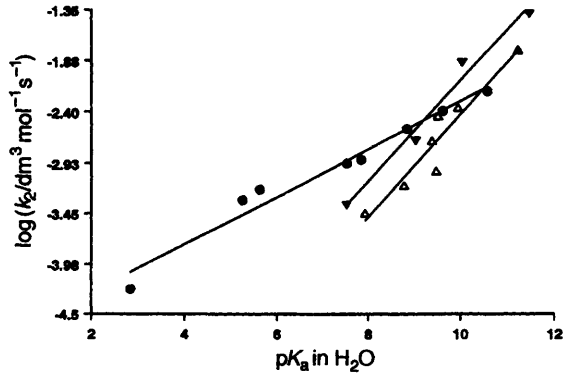


Fig. 2 Brønsted dependence for aminolysis of 4-nitrophenyl *N*-phenylmethylsulfamate in chloroform at 37 °C with pyridines (●), quinuclidines (▼) and cyclic amines (△). Data from Tables 1 and 2.

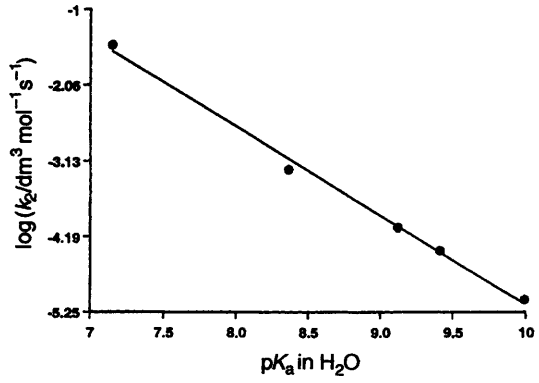


Fig. 3 Brønsted dependence for reaction of X-phenyl *N*-phenylmethylsulfamate with *tert*-butylamine in acetonitrile at 37 °C. Data from Table 3.

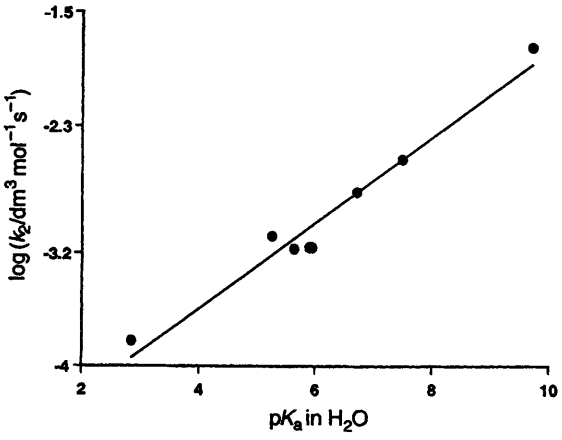


Fig. 4 Brønsted dependence for aminolysis of 4-nitrophenyl sulfamate in chloroform at 37 °C with the pyridines: 4-Me_2N; 2-NH_2, 4-Me; 2-NH_2, 3-Me; 2-Et, 2-Me; H; 3-Cl. Data from Table 4.

five phenolic leaving groups is shown in Fig. 3. A Hammett plot of these data using σ^- values for the 4-nitro and 4-chloro groups gave a ρ_- of +2.8 ± 0.15 (r = 0.995). Acetonitrile had to be used as solvent rather than chloroform in order to obtain measurable rates of reaction. *tert*-Butylamine was used because other bases interfered with the UV absorbances of the leaving phenols.

Table 4 contains data on the reaction of 4-nitrophenylsulfamate **1**, R = H, X = 4-NO_2, in chloroform with a set of eleven pyridines. The absence of a steric effect on the rates is again evident, for example, pyridine and the severely hindered 2,6-dimethylpyridine have identical rates and 2-amino-4,6-dimethylpyridine reacts at a similar rate to the less hindered 2-amino-4-methylpyridine. A Brønsted-type plot for eight of the pyridines is shown in Fig. 4. This gives β = 0.31 ± 0.02 (r = 0.985) using pK_a (H_2O) values and β = 0.30 ± 0.02 (r = 0.994) using pK_a (CH_3CN) values. A Hammett plot for the same set of pyridines using the $\sigma/\Sigma\sigma$ values given in Table 4 gave a ρ of −1.71 ± 0.1 (r = 0.989). A Hammett plot for seven of the eight pyridines in Table 1 (the 4-pyrrolo was omitted since a σ value was not available) gave a ρ of −1.4 ± 0.2 (r = 0.960).

Table 5 contains thermodynamic data on the reaction of **1**, R = H, X = 4-NO_2, in chloroform with a varying set of amines including some of differing structural types and with pK_a (H_2O) varying over almost 8 units. A $\Delta H^‡$ *vs.* $\Delta S^‡$ plot for the seven amines gave a good straight line (r = 0.985) with an isokinetic temperature of 541 ± 65 K being obtained from the plot.

Table 6 contains rate data for variation of substituents in the sulfamate (acyl) part of the ester (**1**, R = XC_6H_4, X = 4-NO_2) for reaction in chloroform with 4-dimethylaminopyridine. A ρ

value of -0.91 ± 0.004 ($r = 0.997$) was obtained from the slope of the plot (Fig. 5). When the stronger base piperidine was used instead of 4-dimethylaminopyridine, the ρ value was -1.19 ± 0.04 ($r = 0.997$) indicating an expected slightly greater interaction between the 'acyl' substituents and the reaction centre.

The ester 4-nitrophenyl *N,N*-dimethylsulfamate (1.0×10^{-4} mol dm^{-3}) failed to react with diethylamine (10.0×10^{-2} mol dm^{-3}) in acetonitrile at 37 °C over 5 d and with cyclopentylamine (15.0×10^{-2} mol dm^{-3}) in chloroform at 37 °C over 7 d. The spectra showed no change and no 4-nitrophenolate/4-nitrophenol could be detected.

Discussion

The rate law is of the type: rate = k_2[ester][amine] which supports a bimolecular mechanism. The negative entropies in Table 5 lend further support to such a mechanism. Several mechanistic possibilities arise: S_N2/S_AN, ElcB and E2 and the possible involvement of *N*-sulfonylamine. A concerted $S_N2(S)$ displacement process has been supported in the ammonolysis of the aryl toluenesulfonates 4-$MeC_6H_4SO_2OAr$ [15] in aqueous solution and in the reaction of 2-hydroxy-5-nitrotoluene-α-sulfonic acid sultone [16] (5-nitro-3*H*-1,2-benzoxathiole *S,S*-dioxide) with nucleophiles in water. The involvement of hypervalent intermediates resulting from such processses has recently [17] received strong kinetic support in the acid-catalysed hydrolysis of the arylbenzenesulfinamides, PhSONHAr, and cyclic sulfinate esters. Substitution or addition–elimination mechanisms are not supported in this work for three main reasons. Firstly, the dimethyl ester Me_2NSO_2ONp (Np = $-C_6H_4NO_2$-4) which can only react by such a mechanism fails to react even after one week under conditions where the other esters **1** readily undergo reaction. Secondly, if an S_N-type process were occurring some steric hindrance would be expected [18] in the aminolysis reaction but this is not the case, *e.g.* the eight pyridines reacting with 4-nitrophenyl *N*-phenyl methanesulfamate give a good Brønsted plot and even the most hindered pyridine namely, 2-amino-4,6-dimethylpyridine, does not deviate (Fig. 2). The identical reactivity of pyridine and 2,6-dimethylpyridine and of 2-amino-4,6-dimethyl- and 2-amino-4-methyl-pyridines with 4-nitrophenylsulfamate (Table 4) again illustrates the absence of steric effects and does not support a mechanism involving attack at sulfur where appreciable steric effects have been demonstrated.[9b] Thirdly, where nucleophilic attack at sulfonyl or sulfonate sulfur is occurring or proposed to be occurring a substantial body of work seems to indicate that the β_{nuc} values determined are generally somewhat larger than the values of β of 0.2–0.5 that we have determined in the present work. Thus, Rogne reports a β_{nuc} of *ca.* 0.7 [19] for attack of substituted anilines on benzenesulfonyl chlorides in methanol and of *ca.* 0.55 [20] for attack of substituted pyridines; Oae [21] finds a β_{nuc} value of 0.89 for reaction of various amines with toluene-*p*-sulfonyl chloride in acetonitrile and Kim [22] gives a value of 0.77 for reaction of substituted anilines with anthracene-1-sulfonyl chloride in acetone; Lee [23] shows that reaction of substituted benzenesulfonyl chlorides in methanol gives β_{nuc} values of 0.72 (substituted anilines) and 1.40 (ring-substituted benzylamines).

In the light of the above points an eliminative mechanism must again be favoured for the present reactions and clearly the amines employed are functioning as general base catalysts. The β values of 0.25 (Fig. 2) and 0.31 (Fig. 4) found for the phenylmethyl and 'parent' sulfamates respectively with pyridines indicate a reasonable degree of proton transfer of the substrate's hydrogen atom to the base. With the stronger quinuclidine/cyclic amine bases this transfer should be greater and this is reflected in the larger β values of 0.52 and 0.54 (Fig. 2) observed. For the substituted pyridine catalysed reactions Hammett ρ values of -1.4 and -1.7 also indicate a substantial degree of positive charge formation at the pyridine nitrogen. It may be noted that almost similar values of -1.42 and -1.8 respectively can be obtained by multiplying the β values by 5.70, the ρ value reported [24] for the ionisation of pyridinium ions.

Table 5 Activation data for reactions of 4-nitrophenyl sulfamate[a] with amines in chloroform

Amine[c]	T/K	n[b]	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
Cyclopentylamine	298–323	5	69 ± 2	−71 ± 2
β-Hydroxyethylpiperazine[d]	298–323	5	68 ± 2	−70 + 2
4-Me_2NPyr[e]	298–318	4	71 ± 4	−48 ± 5
2-NH_2,4,6-dimePyr	298–318	4	82 ± 5	−29 ± 5
3-MePyr	298–318	4	84 ± 3	−32 ± 4
Pyr	298–318	4	91 ± 5	−15 ± 3
3-ClPyr	298–318	4	96 ± 6	−9 ± 1

[a] 1×10^{-4} mol dm^{-3}. [b] No. of points used in Arrhenius plots ($r \geqslant 0.99$ in all cases). [c] Using second-order rate constants (k_2) calculated from k_{obs} *vs.* [amine] plots; cyclo-pentylamine, 0.015–0.15 mol dm^{-3}. [d] Using k_{obs} values determined at 0.05 mol dm^{-3} amine concentration. [e] Using the amine concentrations shown in Table 4 for the five pyridines.

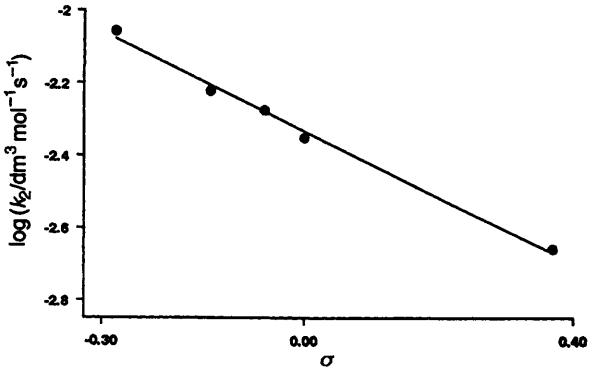


Fig. 5 Hammett plot for aminolysis of 4-nitrophenyl *N*-X-phenylsulfamates with 4-dimethylaminopyridine in chloroform at 37 °C. Data from Table 6.

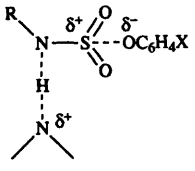
Table 6 Rate constants (k_2) for reaction of 4-nitrophenyl *N*-X-phenylsulfamates with 4-dimethylaminopyridine[a] and piperidine[b] in chloroform at 37 °C

Substituent (X)	σ	$k_2/10^{-4}$ dm^3 mol^{-1} s^{-1}	Substituent (X)	σ	$k_2/10^{-4}$ dm^3 mol^{-1} s^{-1}
[a]4-MeO	−0.28	87.6	H	0	44.6
4-Me	−0.14	60.0	3-Cl	0.37	22.0
3-Me	−0.06	53.1			
[b]4-MeO	−0.28	163.3	H	0	76.3
4-Me	−0.14	98.6	3-Cl	0.22	38.6
3-Me	−0.06	81.6	4-Br	0.37	27.1

[a] The ranges of amine concentrations used to determine k_{obs} were as follows: 4-MeO, 0.06–0.2, 4-Me and H, 0.04–0.15 and 3-Me and 3-Cl, 0.05–0.2 mol dm^{-3}. [b] The ranges of amine concentrations used to determine k_{obs} were as follows: 4-MeO, 0.05–0.18; 4-Me, 3-Me and H, 0.05–0.2; 3-Cl, 0.1–0.3 and 4-Br, 0.05–0.25 mol dm^{-3}.

A β_{lg} for a series of the phenylmethyl esters, $PhCH_2NHSO_2OAr$, gave a value of -1.25 (Fig. 5) and a Hammett ρ of $+2.8$ was obtained for the same five phenolate groups. Multiplying the β_{lg} by 2.2,[25] the ρ for the ionization of phenols, also gives a figure of 2.8. If an ElcB sulfonyl amine mechanism was involved in the breakup of these esters much larger β_{lg} and ρ values would be expected. Thus, for the hydrolysis of a series of *N*-methylsulfamate esters Williams[11a] obtained a β_{lg} of -1.8 ($\rho_- = +3.9$) and in the ElcB hydrolysis/aminolysis of aryl phenylmethanesulfonates $PhCH_2SO_2OAr$, which involves the sulfene, $PhCH{=}SO_2$, a β_{lg} of -2.4 ($\rho_- = +5.4$) has been reported.[26] The present reactions are more likely to be E2 processes with some ElcB-like character. The S–OAr bond is weakened and does possess some phenolate character but in the transition state leading to sulfonylamines this is much more substantial. The Hammett ρ_{acyl} values of -0.91 (Fig. 5) and -1.19 which were obtained using 4-dimethylaminopyridine (pK_a 9.7) and piperidine (pK_a 11.24) indicate that there is less positive charge at the reaction centre than when an ElcB (sulfonylamine) mechanism is involved. A value of ρ_{acyl} of -1.8 has been measured for the latter.[12] Finally, if a sulfonylamine was forming, a large dependence on the polarity of the medium might be expected since Skrypnik and co-workers[8] have shown that a change in relative permittivity from ~4 to ~35 produced a 120-fold acceleration in the rate of reaction by a sulfene mechanism. An almost identical change in relative permittivity in the present study (Table 1, first five entries) produced no change in rate.

The transition state leading to products is best represented by Scheme 2. The degree of S–OAr bond-breaking and of proton



Scheme 2

transfer to the base will vary depending on R, the leaving group and the type of base.

Thus, these sulfamate esters appear to be almost predisposed to undergo reaction by an elimination rather than an apparently energetically unfavourable substitution process. Substitution can only be achieved where elimination is blocked *e.g.* in Me_2NSO_2ONp. The relatively high acidity of compounds 1 (pK_a ~ 8 in aqueous organic media) coupled with the presence of a good leaving group are the reasons for this preferred elimination pathway. When the NH of the sulfamate is replaced by a CH_2 group which has a $pK_a \approx 25$[26] substitution can compete with elimination.

Experimental

Materials

Amines and reagents were obtained commercially and were redistilled or recrystallised before used. Chloroform was shaken five to six times with half its volume of water, isolated and dried over calcium chloride for 48 h. It was filtered, distilled and stored over activated 4A molecular sieves. It was used within 8 weeks of distillation. Acetonitrile was of HPLC reagent grade. Dichloromethane was dried over calcium chloride, filtered and fractionally distilled onto activated molecular sieves. Quinuclidinone and 3-chloroquinuclidine were obtained as their hydrochloride salts and were converted to their free amine forms.

The preparation and characterisation of 4-nitrophenyl sulfamate, *N*-phenylmethanesulfamate, *N*,*N*-dimethylsulfamate and four of the *N*-X-phenylsulfamate esters have been described previously.[12]

The substituted X-phenyl *N*-phenylmethanesulfamate esters were prepared by the following general method, described for 4-chlorophenyl *N*-phenylmethanesulfamate ester. To a mixture of 4-chlorophenol (0.71 g, 5.5 mmol) and triethylamine (0.51 g, 5 mmol) in dry dichloromethane was added a solution of *N*-phenylmethylsulfamoyl chloride (1.00 g, 5 mmol) in dry dichloromethane (7 ml) under an atmosphere of nitrogen. The mixture was stirred at room temperature overnight. Filtration of the mixture was followed by extraction with dilute HCl and the organic layer was dried with anhydrous Na_2SO_4. Removal of the dichloromethane gave an oil which slowly crystallised. Purification of the resultant ester by flash chromatography and recrystallisation from a mixture of light petroleum (bp 40–60 °C) and diethyl ether gave pure crystals.

IR, ^1H NMR and C, H and N microanalytical data for the esters used were consistent with the ester structure. The microanalytical data were generally within ±0.3% and always within ±0.4%. The melting points for the previously unreported esters are as follows: $C_6H_5CH_2NHSO_2OC_6H_4X$, X = 3-NO_2-, 79–81 °C; X = 3-Cl-, 83–85 °C; X = 4-Cl-, 105.5–108.5 °C; X = H-, 56.5–59.5 °C. The 4-nitrophenyl *N*-4-methoxyphenyl- and *N*-4-bromophenyl-sulfamates were prepared by the method previously described for the other phenylsulfamates. Their melting points were 139–142 °C and 132–136 °C respectively.

Product studies

HPLC analysis of products **2** and **3** was performed as previously described[12] except that *N*,*N*′-di-4-tolylsulfamide was used as an internal standard in runs with $CHCl_3$ as solvent and *N*-phenyl-*N*′-butylsulfamide was used for runs in acetonitrile. In a typical run **1**, R = Ph, X = 4-NO_2 (2.0×10^{-4} mol dm^{-3}), with diethylamine (10.0×10^{-2} mol dm^{-3}) in $CHCl_3$ were reacted at 37 °C for ≥10 halflives. Analysis of the reaction mixture showed that *N*-phenyl-*N*′,*N*′-diethylsulfamide (1.9×10^{-4} mol dm^{-3}) and 4-nitrophenol (2.1×10^{-4} mol dm^{-3}) had formed. Spiking solutions with sodium *N*-phenylsulfamate showed that ≤2.5% could be detected by this method. Generally, the accuracy of analysis for products **2** and **3** were ±10 and ±5%, respectively.

In another method of partial product analysis, the absorbances of 4-nitrophenol in spent (reacted ≥10 halflives) kinetic solutions were compared with spiked 4-nitrophenol solutions. Agreement was within ±5%.

Kinetic measurements

The rates of aminolysis were measured with Shimadzu UV-260 or Cary 1/3 spectrophotometers. Solutions (2 ml) of the appropriate amine in the solvent medium were introduced into the 1 cm cells and placed in the thermostatted cell compartment, which was maintained at constant temperature (±0.2 °C). After thermal equilibrium, a stock of the substrate ester in the organic solvent (20 μl) was injected into the reaction solution. The reactions were followed by monitoring the increase in the absorbance of the phenol/phenolate ion and in some cases by the disappearance of the ester absorbance. In all cases with excess of amine good pseudo-first-order rate constants (k_{obs}) were obtained. These were calculated from the slopes of the plots of log ($A_\infty - A_t$) *vs.* time or by using a three-parameter curve-fitting program. The standard deviation of the individual runs was never greater than 5% and usually within 3%.

In a few runs the kinetic equation is of the form $k_{obs} = k_2[\text{amine}] + k_1$ where k_1 is the intercept on the k_{obs} axis (see Fig. 1, where one such example is shown). A rate law of the type $k_{obs} = k_2[\text{amine}] + k_3[\text{amine}]^2$ does not give a good fit of the data and plots of k_{obs}/[amine] *vs.* [amine] were not linear and gave poorer correlation coefficients than plots of

k_{obs} *vs.* [amine]. In the case shown in Fig. 1 $k_2 = 28.8 \times 10^{-4}$ mol^{-1} dm^3 s^{-1} and $k_1 = 0.69 \times 10^{-4}$ s^{-1}. Therefore the uncatalysed portion of the rate is small and may be due to the presence of small quantities of water in the organic solvent used. The value of k_1 was never more than 10% of k_2 and further study of this component of the rate was not pursued.

pK_a determination

A 1.0×10^{-2} mol dm^{-3} solution of thiomorpholine in water at 25 °C was prepared and its pH read. The titrant (1.0×10^{-3} mol dm^{-3} HCl) was then added in equal portions and the pH recorded after each addition (PT1-6 Universal Digital pH meter) when equilibrium was reached. The pK_a was determined according to the procedure of Albert and Serjeant.[27]

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