JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 8, 610–616 (1995)

AMINOLYSIS AND HYDROLYSIS OF SULPHAMATE ESTERS: SUBSTANTIAL N=S BONDING IN THE TRANSITION STATE LEADING TO N=SULFONYLAMINES

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The aminolysis and hydrolysis of several sulphamate esters, $RNHSO_2ONp$ (R = $PhCH_2$, Ph, 4-$MeC_6H_4$4, 3-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, H; Np = 4-$NO_2C_6H_4$) were been studied in 50% (v/v) aqueous acetonitrile at various temperatures. Reaction of the esters with an amine (R^1NH_2) gives $^-$ONp and both sulphamide, ($RNHSO_2NHR^1$) and sulphamate ($RNHSO_2O^-R^1NH_3^+$) products. First-order rates were determined by the appearance of $^-$ONp and sometimes also by the disappearance of ester. The reaction was found to be independent of amine type and concentration and at the high pHs that obtain the substrate esters are fully ionized. A Hammett ρ_{acyl} of −1·8 was obtained for the decomposition of the sulphamate anions and this is consistent with substantial N=S bonding in the transition state leading to N-sulphonylamine, $RN=SO_2$. This intermediate then partitions very rapidly, reacting with R^1NH_2 and H_2O respectively. $\Delta H‡$, $\Delta S‡$ and a deuterium solvent isotope effect were determined and were also interpreted in favour of the proposed mechanism. The dimethyl sulphamate ester (Me_2NSO_2ONp) does not react under the conditions used.

INTRODUCTION

There has been considerable interest for more than 25 years in the kinetics and mechanisms of sulphonyl transfer reactions and many groups worldwide have made important contributions. A number of reviews have appeared in this area.[1–3] The changes occurring can be generally represented as

$$RSO_2X + Y^- \rightarrow RSO_2Y + X^- \qquad (1)$$

The most studied reactions have been those involving solvolysis and/or aminolysis of sulphonyl and sulphonate systems. Various mechanisms have been supported, depending on the substrate, reagents and solvent, and these range from nucleophilic substitutions (S_N), addition–elimination (S_AN) to eliminations (*E*1, *E*2 and *E*lcb variants).

The hydrolyses of sulphamate esters of the types $MeNHSO_2OAc$, Me_2NSO_2OAr and H_2NSO_2OAr have been studied by Williams and co-workers.[4,5] For the esters of the first and third types, an *E*lcb mechanism involving *N*-sulphonylamine intermediates, $MeN=SO_2$ and $HN=SO_2$ respectively, has been proposed in aqueous organic solution and in water. Such species have generally been named *N*-sulphonylamines by most authors.[6] However, some workers have preferred the term *N*-sulphonylimines.[7] A referee has suggested the interesting and perhaps more appropriate name sulpheneimines for these intermediates, 'since the nitrogen is not an amino nor is the SO_2 a sulphonyl group.' Esters of the second type may react by an S_AN path. The hydrolysis of the sulphamoyl azides, $RNHSO_2N_3$, to sulphamic acids, $RNHSO_3H$, is also thought to occur via *N*-sulphonylamines.[8] The hydrolysis of sulphamoyl halides has been controversial with both S_N1 and S_N2 pathways being favoured by different groups.[9]

Against this background, the kinetics of the aminolysis/hydrolysis in aqueous acetonitrile of a series of sulphamate esters, $RNHSO_2OC_6H_4NO_2$-*p*, were been examined in this study.

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CCC 0894–3230/95/090610–07

Received 30 September 1994
Revised 11 May 1995

RESULTS AND DISCUSSION

The reactions occurring are

$$\underset{(1)}{RNHSO_2ONp} + R^1NH_2 \xrightarrow{H_2O} \underset{(2)}{RNHSO_2NHR^1}$$

$$+ \underset{(3)}{RNHSO_2O^-R^1NH_3^+} + {}^-ONp \quad (2)$$

where $Np = p\text{-}NO_2C_6H_4$. Douglas and Williams[4b] in a very limited product study showed that in 50% aqueous ethanol **1** (R = Me) gave exclusively a sulphamide product (and ^-ONp) in the presence of 1 mol dm^{-3} Et_2NH or piperidine. However, we found that in 50% aqueous acetonitrile, **1** (R = Ph) in the presence of Et_2NH gave only 50% of **2** and 50% of **3** was also formed (first run, Table 1). We therefore decided to carry out a more detailed product analysis using HPLC and the main findings of this are shown in Table 1. Examination of the product data in Table 1 shows (i) that in most cases a reasonably quantitative product balance is maintained, i.e. the summation of the amounts of **2** and **3** corresponds to the amount of *p*-nitrophenoxide released, and this in turn corresponds more or less to the initial quantities of ester employed in the study; (ii) as expected, decreasing the amine concentration favours the formation of **3** at the expense of **2**; and (iii) increase in water content (at 0·1 mol dm^{-3} amine) of the aqueous acetonitrile promotes the formation of **3**. A referee has suggested that we might be able to use our product data to obtain useful parameters for describing the reactivity of the sulphonylamine, as has been done by King *et al.*[10] recently for sulphenes. However, our product data would not be of sufficient accuracy (see Table 1, footnote c) to do this and further, since the pH varied for various concentrations of amine (see Table 2), conformance to the appropriate equation could not be checked.

In this work, the hydrolysis reaction *per se* was not studied since this reaction has been reported on previously over a wide pH range.[4b]

Kinetic runs were carried out in 50% (v/v) aqueous acetonitrile at 37 °C and the results are given in Table 2. The strongly basic amines present ensured that the system was self-buffered. Rate constants are seen to be virtually independent of the type and concentration of amine. The slight increase in rate constant at the higher pHs is expected since the pH–rate profile found for the ester **1** (R = Me)[4b] in 20% (v/v) aqueous dioxane plateaus in the region of pH 10–12·5 and rises slightly as this alkaline pH increases. The kinetics are first order in ester since identical rates were obtained when the ester concentration was (0·2, 0·5, 1·0 and 1·5) × 10^{-4} mol dm^{-3}). Ionic strength effects using sodium perchlorate at 1·0 mol dm^{-3} and potassium chloride at 0·1 mol dm^{-3} are small or negligible.

In Table 3 some activation data for the phenyl (**1**,R = Ph) and the phenylmethane (**1**, R = $PhCH_2$) esters are given together with a solvent isotope effect (k_{H_2O}/k_{D_2O}) for **1** (R = Ph). The values of $\Delta H‡$ and $\Delta S‡$ are close to the $\Delta H‡$ (72 kJ mol^{-1}) and $\delta S‡$ (−37 J mol^{-1} K^{-1}) values reported by Douglas and Williams[4b] for the alkaline hydrolysis of the corresponding methyl ester **1** (R = Me). For the latter ester a solvent isotope effect (k_{H_2O}/k_{D_2O}) of 1·35, identical with the value of 1·4 in Table 3, has been determined.[4b]

Table 1. Product data for the reaction of *p*-nitrophenyl-*N*-phenylsulphamate[a] and -*N*-phenylmethanesulphamate[b] with diethylamine in aqueous acetonitrile at 37 °C

Sulphamate	$H_2O:CH_3CN$ (v/v)	Et_2NH (mol dm^{-3})	10^4 [Sulphamate] (mol dm^{-3})	10^4 [Sulphamide] (mol dm^{-3})	10^4 [$^-$ONp] (mol dm^{-3})
Phenyl	50:50	1·0	1·05	1·05	2·04
		0·5	1·1	0·87	2·08
		0·1[c]	1·53	0·34	1·93
		0·01	1·68	0	1·93
	10:90	0·05	0·99	1·02	2·03
	20:80	0·1	1·33	0·53	1·97
	80:20	0·1	1·74	0·27	2·09
	90:10	0·1	1·95	0	2·20
Phenylmethane	50:50	1·0	8·14	4·83	10·26
		0·20	7·34	1·63	9·57
		0·15	7·96	1·28	9·43
		0·10	7·76	1·13	10·03

[a] [Ester] 2 × 10^{-4} mol dm^{-3}.
[b] [Ester] 1 × 10^{-3} mol dm^{-3}.
[c] Duplicate injections showed that the relative standard deviations were 14% for sulphamate and sulphamide and 8% for $^-$ONp.

Table 2. Effect of amine and ester concentrations on rates in 50% (v/v) aqueous acetonitrile for *p*-nitrophenyl-*N*-phenylsulphamate[a] and -*N*-phenylmethanesulphamate[a]

Sulphamate	Amine	Concentration (mol dm^{-3})	pH[b]	$10^5 k_{obs}$ (s^{-1})
Phenyl	cyc-$C_5H_9NH_2$	0·01	11·45 ± 0·02	5·8
		0·03	11·65 ± 0·02	6·1
		0·05	11·67 ± 0·02	6·3
		0·15	12·13 ± 0·01	7·3(7·3, 7·2, 7·2)[c]
	Et_2NH	0·01	11·57 ± 0·01	6·11(5·63)[d],(5·3)[e]
		0·10	12·21 ± 0·01	6·3(6·33)[d],(6·03)[e]
		0·15	12·69 ± 0·02	6·12
		0·50	13·09 ± 0·02	7·6
Phenylmethane	Et_2NH	0·01	11·36 ± 0·02	507·0(493·3)[d]
		0·03	11·66 ± 0·02	522·1
		0·05	11·95 ± 0·02	523·0
		0·10	12·20 ± 0·01	548·0

[a] [Ester] was 1×10^{-4} mol dm^{-3}.
[b] Mean of readings taken before and after reaction.
[c] The rates in parentheses were obtained with ester concentrations of (0·2, 0·5 and 1·5) $\times 10^{-4}$ mol dm^{-3}, respectively.
[d] Ionic strength (μ) = 1·0 mol dm^{-3} $NaClO_4$.
[e] Ionic strength (μ) = 0·1 mol dm^{-3} KCl.

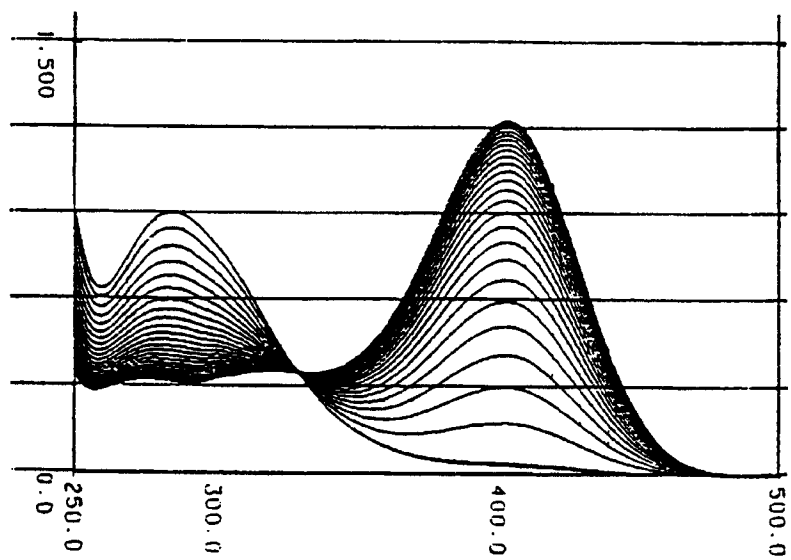


Figure 1. UV absorption spectrum for the reaction of *p*-nitrophenyl-*N*-phenylsulphamate ($1{\cdot}0 \times 10^{-4}$ mol dm^{-3}) with 4-methylimidazole (0·15 mol dm^{-3}) in 50% (v/v) aqueous acetonitrile at 37 °C

Table 3. Activation parameters and deuterium solvent isotope effect for reaction of *p*-nitrophenyl-*N*-phenylsulphamate[a] and -*N*-phenylmethanesulphamate[a]

Sulphamate	Amine	Concentration (mol dm^{-3})	10^5k_{obs} (s^{-1})				$\Delta H‡$ (kJ mol^{-1})	$\Delta S‡$ (J mol^{-1} K)
Phenyl	cyc-$C_5H_9NH_2$	0·15	1·69	7·3	14·41	31·91	90 ± 1·5	−35 ± 1·0
Phenylmethane	Et_2NH	0·01	292 K	298 K	310 K	318 K	69 ± 1·0	−66 ± 1·0
			125·6	169·3	507·0	1200·0		
			k_{H_2O}[b]	k_{D_2O}[b]			k_{H_2O}/k_{D_2O}	
Phenyl	cyc-$C_5H_9NH_2$	0·15	7·3	5·22			1·4	
		0·0015	5·8	4·18			1·4	

[a] Concentration 1×10^{-4} mol dm^{-3}.
[b] At 37 °C.

The effect of the substituents in the phenyl ester on the rate is given in Table 4 and the Hammett plot of these data is shown in Figure 2. A Hammett ρ_{acyl} value of −1·8 ($r = 0·997$, standard deviation = 0·071) was obtained.

In 50% (v/v) aqueous acetonitrile the 'parent' ester **1** (R = H) reacted virtually instantaneously at 37 °C in 0·15 mol dm^{-3} cyclopentylamine whereas the dimethyl ester, Me_2NSO_2ONp, failed to show any reaction after 1 week under these conditions. An elimination mechanism is supported by (i) the failure of the dimethyl ester to react (it can only react by an addition–elimination or S_N-type pathway) and by (ii) the absence of amine catalysis. Compounds **1** are fairly acidic with pK_a in the range 7–11,[4b,5] which makes them ideal substrates for eliminative processes. The pK_a of **1** (R = Ph) in 50% (v/v) aqueous acetonitrile is 7·05 ± 0·03 (see Experimental). Thus, at the high pHs used in this study, the substrates will exist as anions, $R\bar{N}SO_2ONp$. In a rate-determining step, the anion eliminates nitrophenoxide to give an *N*-sulphonylamine which is attacked very rapidly by amine and water to give products (Scheme 1). Effectively this is an *E*lcb-type mechanism, as proposed previously[4] for alkaline hydrolysis of **1** (R = Me). The small $\Delta S‡$ values in Table 3 support a unimolecular mechanism and the similarity of the solvent isotope effect in alkaline hydrolysis and in this work points to a comparable *E*lcb mechanism. Finally, Douglas and Williams[4b] reported a large positive ρ_{lg} value (using σ^-) of +3·9 for a series of leaving groups in **1** (R = Me). This was interpreted in favour of extensive S—OAr bond breaking in the transition state. Our ρ_{acyl} of −1·8 for 'the other side' of the reacting molecule appears to complement this and suggests that in the transition state not only is S—O bond breaking well advanced but also N=S bond making in the incipient sulphonylamine is substantial (see Scheme 1).

The reactivity sequence $H_2NSO_2ONp \gg PhCH_2NHSO_2ONp \gg PhNHSO_2ONp \gg Me_2NSO_2ONp$ can be explained as follows. The only reaction routes available to the latter are non-eliminative and clearly energetically unfavourable. The phenyl ester is *ca* 80 times less reactive (Table 2) than the phenylmethane ester, which may be due to the ability of the former to

Table 4. Rate data for the reaction of *p*-nitrophenyl-*N*-X-phenylsulphamates[a] with cyclopentylamine[b] in 50% (v/v) aqueous acetonitrile at 37 °C[c]

Substituent (X)	σ	10^5k_{obs} (s^{-1})	Substituent (X)	σ	10^5k_{obs} (s^{-1})
4-CH_3	−0·17	12·88	4-F	+0·06	5·87
3-CH_3	−0·06	8·97	4-Cl	+0·22	2·8
H	0·0	7·3	3-Cl	+0·37	1·4

[a] Concentration 1×10^{-4} mol dm^{-3}.
[b] Concentration 0·15 mol dm^{-3}.
[c] The mean pH measured before and after reaction was 12·14 ± 0·02.

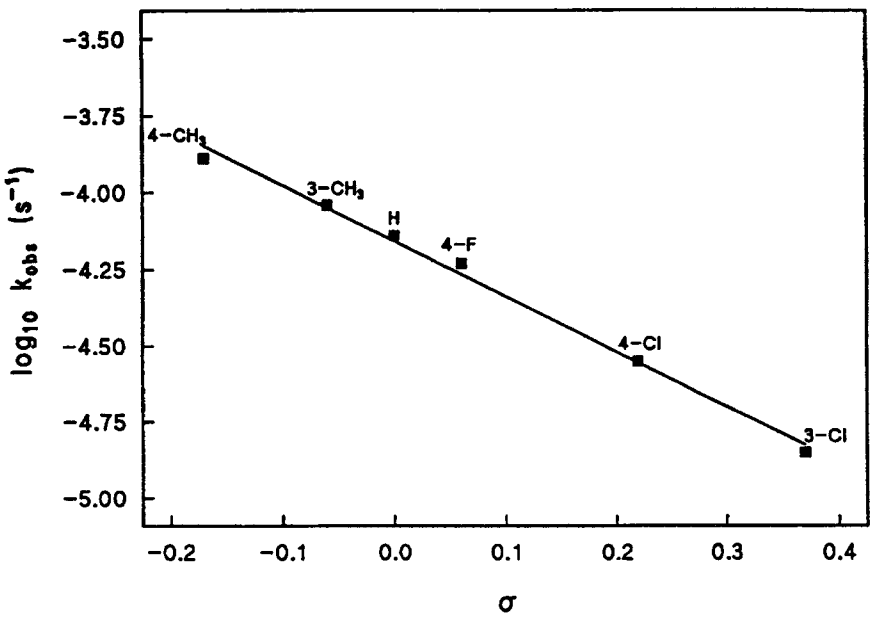
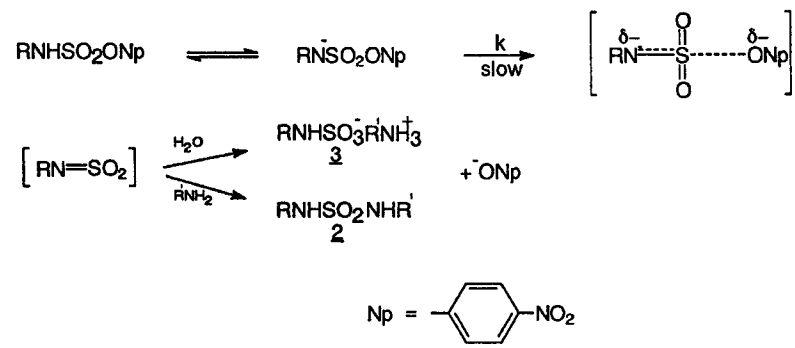


Figure 2. Hammett plot for the reaction of *p*-nitrophenyl-*N*-x-phenylsulphamates (1×10^{-4} mol dm^{-3}) with cyclopentylamine (0·15 mol dm^{-3}) in 50% (v/v) aqueous acetonitrile at 37 °C



Scheme 1

delocalize and therefore stabilize the negative charge of the anion on the ring. Such stabilization is not available in the phenylmethanesulphamate anion or to the 'parent' ester anion, $H\bar{N}SO_2ONp$. The greater reactivity of the latter may also be due to the fact that at high pH such as in this work a second anionic sulphonylamine [$\bar{N}$=SO_2] path is available to it for reaction.[5]

EXPERIMENTAL

Materials. *p*-Nicrophenyl *N*-phenylsulphamate, the substituted *N*-phenylsulphamate ester and the *N*-phenylmethane ester were prepared by first synthesizing the appropriate *N*-phenylsulphamoyl chlorides. The latter were prepared by treating the sodium salts of the *N*-phenylsulphamic acids (see Ref. 11 for the synthesis of the two sodium *N*-tolylsulphamates and Ref. 12 for that of other sulphamates) with phosphorus pentachloride in benzene.[13]

The *p*-nitrophenylsulphamate esters were prepared by the following general method, described for the *N*-phenylsulphamate ester. To a mixture of *p*-nitrophenol (0·65 g, 5·5 mmol), 4-dimethylaminopyridine (0·09 g, 0·75 mmol) and triethylamine (0·51 g, 5 mmol) in dry dichloromethane (15 ml) was added dropwise a solution

of *N*-phenylsulphamoyl chloride (0·96 g, 5 mmol) in dry dichloromethane (6 ml) under an atmosphere of nitrogen. The mixture was left at ambient temperature overnight. Filtration of the mixture was followed by extraction with dilute hydrochloric acid and the organic layer was dried with anhydrous Na_2SO_4. Removal of the dichloromethane gave an oil which slowly crystallized. Purification of the resultant ester by flash chromatography and recrystallization from a mixture of light petroleum (b.p. 40–60 °C) and diethyl ether gave crystals, m.p. 95–97 °C.

p-Nitrophenyl *N*-sulphamate was prepared by the method given above from *N*-sulphamoyl chloride,[14] m.p. 38–39 °C (lit.,[14] 40 °C).

p-Nitrophenyl *N,N*-dimethylsulphamate was prepared from *N,N*-dimethylsulphamoyl chloride, obtained commercially, by a method similar to that for the other 4-nitrophenyl ester derivatives. The crystals had m.p. 117–118 °C (lit.,[4b,15] 124 °C).

IR, H^1-NMR and C, H and N microanalytical data for the nine sulphamate esters were consistent with the ester structure. The microanalytical data were generally within ±0·3% and always within 0·4%. The melting points of the esters not reported above are as follows: $XC_6H_4NHSO_2ONp$, X = 4-Cl, 122–125; X = 3-Cl, 109–112; X = 4-Me, 125–128; X = 3-Me, 93–96; X = 4-F, 127–129; $PhCH_2NHSO_2ONp$, 93–95; and H_2NSO_2ONp, 94–96 °C.

Other materials, i.e. amines and reagents, were obtained commercially and were redistilled or recrystallized before use. Water was doubly distilled from glass and acetonitrile was of HPLC reagent grade.

Kinetic measurements. The rates of aminolysis and hydrolysis were measured with a Shimadzu UV-260 or a Cary 1/3 spectrophotometer.

Solutions (2 ml) of the appropriate amine in the aqueous acetonitrile medium were introduced into 1 cm cells and placed in the thermostated cell compartment, which was maintained at constant temperature (±0·2 °C) by circulating water. After thermal equilibration, a stock solution of the substrate ester in acetonitrile (20 µl) was injected into the reaction solution.

The reactions were followed by monitoring the decrease in absorbance of the substrate ester at 280 nm or the increase in absorbance of the phenolate ion at 400 nm.

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 $\log(A_\infty - A_t)$ versus time or by using a three-parameter curve-fitting program. The standard deviation of individual runs was never greater than 5% and usually within 3%.

Product analysis. *p*-Nitrophenoxide and the sulphamates and sulphamides produced in the reaction in equation (2) with diethylamine were analyzed on a Waters Model 501 high-performance liquid chromatograph using a Waters Model 484 tunable absorbance detector at a wavelength of 254 nm. Samples of the above reaction (after ≥10 half-lives) were injected on to a C_{18} column using a Hamilton microlitre syringe. The ester concentration was either 2×10^{-4} or 1×10^{-3} mol dm^{-3} at the start of all reactions (see Table 1). A solution of sodium *p*-iodophenylsulphamate (1×10^{-4} mol dm^{-3}) was injected into each of the reacted samples before analysis. This acted as an internal standard. The mobile phase was prepared by making up a 0·025 mol dm^{-3} sodium acetate and a 0·01 mol dm^{-3} tetrapentylammonium bromide solution in methanol (HPLC grade) – distilled water (55 : 45, v/v). This solution was adjusted to pH 5 with acetic acid and filtered through a 0·45 µm membrane filter. Concentrations of each of the products were calculated for all subsequent samples using sodium *p*-iodophenylsulphamate as internal standard.

pK_a determination. The pK_a of 4-nitrophenyl-*N*-phenylsulphamate was measured in 50% (v/v) aqueous acetonitrile on a Metrohm 716 Autotitrator and calculated with the aid of the SUPERQUAD pK_a determination program.[15]

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