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Elimination Mechanisms in the Aminolysis of Sulfamate Esters of the Type $NH_2SO_2OC_6H_4X$ – Models of Enzyme Inhibitors

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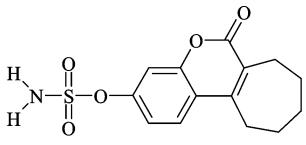
The kinetics of the reaction of 4-nitrophenyl sulfamate $NH_2SO_2OC_6H_4NO_2$-4 (**1a**) in acetonitrile (ACN) with a series of pyridines (pK_a range ca. 8 units) and alicyclic amines (pK_a range ca. 3.6 units) has been studied in the presence of excess amine at various temperatures. The compounds **1a**–**1f** are important as model substrates for the medicinally important sulfamate esters 667-coumate and emate and analogues. Pseudo-first-order rate constants ($k_{obsd.}$) have been obtained mainly by the release of 4-nitrophenol/4-nitrophenoxide. Slopes of plots of $k_{obsd.}$ vs. [amine] gave second-order rate constants (k_2), and Brönsted plots were biphasic for the aminolysis (with alicyclic amines) with an initial slope $\beta_1 = 0.53$ and a subsequent slope $\beta_2 = 0.19$. The change in slope occurs near the first pK_a of **1a** (17.9) in ACN. Leaving-group effects were probed by using the same series of phenyl sulfamates, i.e. **1a**–**f** and the alicyclic amines *N*-formylpiperazine and pyrrolidine. The reactions were considered to be dissociative in nature involving E2- and E1cB- type mechanisms with the phenyl sulfamate anion **2** being involved in pyridine and in the weaker alicyclic amines (β_1 segment) and a phenyl sulfamate dianion **3** being involved with the stronger alicyclic bases (β_2 segment). The calculation of Leffler indices (α) for bond-forming (base···H^+) and bond-breaking (S–OAr) steps allows fuller interpretation of the mechanisms occurring, which are seen as having the *N*-sulfonylamines, $HN{=}SO_2$ and $^-N{=}SO_2$ on the reaction pathways leading to products.

Introduction

There has been a renaissance of interest in sulfamate esters $RNHSO_2OR'$ over approximately the last 12 years because of their potential in medicinal chemistry where certain types of esters, particularly those of the type NH_2SO_2OR have been showing considerable promise in a wide variety of applications. To take a few important examples, some sulfamates inhibit steroidal sulfatases (STS) and carbonic anhydrase (CA), and thus the synthesis of those steroids that encourage the growth of hormone-dependent cancers like breast and prostate cancer and other diseases[1] can be blocked. The results of phase I clinical trials on 667-coumate, an STS inhibitor, which shows promise in the treatment of breast cancer have appeared recently.[2]



667-coumate

Generally, the active esters are esters of sulfamic acid, i.e. they contain the NH_2SO_2O entity. The subject has been reviewed over the years,[3,4] and several quite recent accounts have appeared.[5–7] These esters act by inhibiting or blocking enzymatic pathways in the body, and it is thought that they sulfamoylate essential amino acid residues in the enzyme, thereby rendering it inactive. Over much the same period of time, we have been investigating the hydrolysis and aminolysis mechanisms of various esters such as 4-nitrophenyl methylsulfamate, 4-nitrophenyl benzylsulfamate and a series of 4-nitrophenyl phenylsulfamates.[8,9] Latter studies have focussed more on 4-nitrophenyl sulfamate $NH_2SO_2OC_6H_4$-NO_2-4 (**1a**), because this compound could act as a simple model for the more complex and therapeutically important esters.[10] The thrust of this current work is to examine the kinetics and mechanism of reaction in acetonitrile (ACN) of compound **1a** and five other phenyl sulfamate derivatives, **1b**–**f**.

Results and Discussion

pK_a Studies

In order to understand more fully the mechanism of aminolysis of these sulfamate esters, pK_a measurements in ACN at 25 °C for compound **1a** for the equilibria shown in Equations (1) and (2) were first carried out (Scheme 1). Com-

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pound **1a** was the substrate mainly used in this study. The pK_a for the ionization of **1a** was found to be 17.9, in excellent agreement with a value of 17.8 previously determined in this laboratory.[10] The pK_a value for the second ionization gave an average value of 21.08 in ACN on the basis of three determinations by using two different analytical wavelengths.

$$\underset{\mathbf{1}}{NH_2SO_2OC_6H_4X} \rightleftharpoons \underset{\mathbf{2}}{\bar{N}H\,SO_2OC_6H_4X} + H^+ \quad (1)$$

$$\underset{\mathbf{2}}{\bar{N}HSO_2OC_6H_4X} \rightleftharpoons \underset{\mathbf{3}}{^{2-}\bar{N}SO_2OC_6H_4X} + H^+ \quad (2)$$

a (X = 4-NO_2), **b** (X = 4-F), **c** (X = 4-Cl), **d** (X = 4-Br), **e** (X = H), **f** (X = 4-Me)

Scheme 1. Ionizations of phenyl sulfamate esters.

In the second ionization [Equation (2)], a higher pK_a (less acidic) would be expected because of the insulating effect of the negative nitrogen centre now present and thus greater difficulty in removing protons.

Brönsted (β), Hammett (ρ) and Thermodynamic Studies

The rate law followed for the aminolysis of the sulfamate esters used in this work had the form:

d[XC_6H_4OH or $XC_6H_4O^-$]/dt = –d[sulfamate ester]/dt = $k_{obsd.}$[sulfamate ester]

where $k_{obsd.} = k_0 + k_2$·[amine]. The k_0 terms for uncatalyzed reactions were found to be negligible in this work carried out under pseudo-first-order conditions, i.e., a large excess of amine present relative to the amount of substrate. The k_2 values are the second-order rate constants for the aminolysis reaction. Two types of bases were employed: firstly a set of pyridines with a pK_a range in ACN of ca. 8 units, and secondly a set of alicyclic amines with a range spanning ca. 3.6 pK_a units. The second-order rate constants for the pyridinolysis and aminolysis (alicyclic bases) of **1a** are given in Table 1 together with the pyridine pK_a values and the Hammett σ values used. Brönsted-type plots of log k_2 against amine pK_a values are shown in Figure 1 for the pyridinolysis and for the aminolysis of **1a**.

The Brönsted β value for the pyridinolysis plot is 0.28 (r = 0.970). This value is very close to those previously obtained when a series of 12 pyridines were treated with **1a** in chloroform.[11] Because pyridine pK_a values are not available in $CHCl_3$, sets of pK_a values for water and ACN were used instead. Plots of log k_2 against pyridine pK_a values (in water) gave a slope of 0.23 (r = 0.930), and against pyridine pK_a values (in ACN) a slope of 0.28 (r = 0.920) was obtained. [11] The point for 2,4,6-trimethypyridine is not plotted in Figure 1, because it deviates well below the line. This is not surprising, because being substituted in both *ortho* positions it may be expected to deviate somewhat due to steric effects. The data for the alicyclic amines has been published previously.[10]

Table 1. log k_2 values for pyridinolysis at 37 °C in ACN of **1a** and values of pK_a and Hammett σ used.

Pyridine	log k_2	pK_a[a]	σ_{pyr}[b]
4-Pyrrolidino	–1.06	18.2	–0.90
4-Amino	–1.75	17.2	–0.57
4-Dimethylamino	–1.26	17.6	–0.83
2-Amino-4-methyl	–2.32	15.1	–0.41
3,4-Diamino	–1.92	14.7	–0.57
2-Amino	–2.17	14.3	–0.27
2,4,6-Trimethyl	–3.07	13.9	–0.33
Pyridine	–2.87	12.3	0
3-Chloro	–3.38	10.5	0.37

[a] Measured in ACN at 25 °C.[8,9] [b] Most of the σ values were available in: D. D. Perrin, B. Dempsey, E. P. Sergeant, *pK_a Prediction for Organic Acids and Bases*, Chapman & Hall, London, **1981**; the σ value of –0.90 for 4-pyrrolidine and the σ_0 values of –0.27 and –0.13 for the 2-NH_2 and 2-Me compounds, respectively, were obtained from: C. Hansch, A. Leo, D. Hoekman, *Exploring QSAR – Hydrophobic, Electronic and Steric Constants*, American Chemical Society, Washington, DC, **1995**.

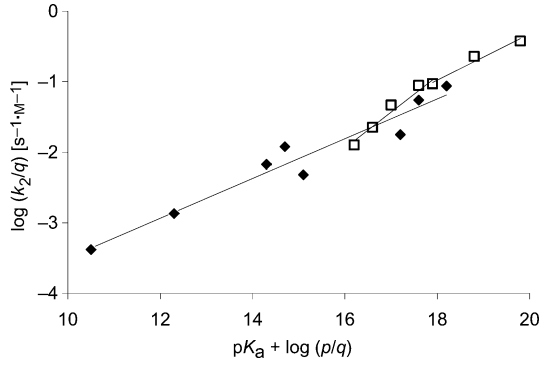


Figure 1. Brönsted-type plots for the pyridinolysis of **1a** (black diamonds), the bases left to right being 3-chloropyridine, pyridine, 2-aminopyridine, 3,4-diaminopyridine, 2-amino-4-methylpyridine, 4-aminopyridine, 4-(dimethylamino)pyridine and 4-pyrrolidinopyridine, and for the aminolysis (alicyclic amines) of **1a** (squares), the bases left to right being thiomorpholine, morpholine, *N*-formylpiperazine, *N*-(2-hydroxyethyl)piperazine, *N*-(2-aminoethyl)piperazine, piperazine, piperidine, and pyrrolidine in ACN at 37 °C. The usual correction has been applied for piperazine by using p = 1 and q = 2 and both *N*-(2-aminoethyl)piperazine and piperazine having the same pK_a values and virtually identical rates appear together in the plot.

These β values indicate a moderate transfer of proton from substrate nitrogen atom to pyridine in the reaction. From previous examination of the reactions of various sulfamate esters in ACN and other organic solvents the pyridinolysis is likely to involve an E2 mechanism with reasonable N–H cleavage in the substrate, and the aminolysis (alicyclic amines) for the Brönsted β_1 and β_2 segments will follow E2-/E1cB-type mechanisms. The plot for the aminolysis with alicyclic bases could be regarded as presenting a steady change (continuum) or two straight lines with slopes β_1 and β_2 of 0.53 (r = 0.981, 5 points) and 0.32 (r = 0.982, 3 points), respectively. Opting for the smooth continuous curve also gives a good fit to a suitable quadratic equation

Table 2. Activation parameters[a] for the aminolysis by alicyclic amines of **1a** in ACN.

Alicyclic amine[b]	$\Delta H^{\pm}$/kJmol^{-1}	$\Delta S^{\pm}$/J mol^{-1} K^{-1}	Alicyclic amine[b]	$\Delta H^{\pm}$/kJ mol^{-1}	$\Delta S^{\pm}$/J mol^{-1} K^{-1}
Thiomorpholine (16.2)	47.5 ± 5	–128.2 ± 9	*N*-(2-aminoethyl)piperazine (17.9)	49.2 ± 5	–105.7 ± 8
Morpholine (16.6)	42.9 ± 4	–138.0 ± 10	piperazine (18.2)	53.4 ± 5	–87.3 ± 7
N-Formylpiperazine (17.0)	61.2 ± 6	–75.8 ± 6	piperidine (18.8)	49.9 ± 5	–98.5 ± 8
N-(2-Hydroxy)piperazine (17.6)	59.5 ± 5	–73.5 ± 6	pyrrolidine (19.8)	60.1 ± 6	–59.5 ± 6

[a] Eyring plots (correlation coefficients were > 0.99 in all cases) were generated for each amine by using rate constants at between four and nine different temperatures and covering temperature ranges of usually 25+ °C. Thiomorpholine, which reacts very slowly, was studied over a 16 °C temperature range. The errors shown are standard deviations.. [b] The numbers in parentheses are the pK_a values in ACN for the amines.

($y = -0.0668x^2 + 2.8075x - 29.815$) with $r = 0.995$. However, because biphasic Brönsted plots have been found before with some sulfamate esters,[8] and because the entropy changes measured (Table 2) do not display a continuous change, but show firstly an increase (become less negative) with a change in base, and at approximately a pK_a value of 18 again become quite negative and start to increase for a second time, we regard the plot as being most likely biphasic. With other biphasic plots involving, for example, 4-nitrophenyl benzylsulfamate in ACN with eight strong bases whose pK_a values cover a range of 4–5 units and in particular straddle p$K_a \approx 18$, we have observed very similar behaviour in entropy changes for the reaction, and for this substrate the entropy increases from –112 J mol^{-1} K^{-1}to –55 J mol^{-1} K^{-1}, and then at a point corresponding approximately to the pK_a value of the substrate the entropy decreases to –114 J mol^{-1} K^{-1} and then increases again to –15 J mol^{-1} K^{-1}.[8] When the Brönsted plot is a straight line, for example, with 4-nitrophenyl sulfamate and a set of pyridines covering a pK_a range of ca. 7 units, the entropy displays a steady increase moving to the weaker bases. The activation study in this work was carried out by using eight of the nine alicyclic amines shown in Figure 1. The $\Delta H^{\pm}$ and $\Delta S^{\pm}$ values determined from Eyring and Arrhenius plots are given in Table 2 for the aminolysis of **1a**.

The value for β_1 points to substantial proton removal during the reaction, but the value for β_2 indicates that considerably less protons are now transferred to the stronger bases. This arises, because it is more difficult to remove the second proton from **2a** than it was to remove the first proton from **1a**. It may be noted that the changeover from one plot to the other seems to be occurring at around the first pK_a value of **1a** (17.9). Around p$K_a \approx 18$ the second proton is being removed by the stronger bases, and the reactive species then becomes the dianion **3a**. Above the second pK_a value of **1a** (21.1) corresponding to the ionization **2a** ⇄ **3a**, eventually the dianion **3a** is fully formed, and general catalysis by bases should cease at that point, and a straight line parallel to the *x*-axis would be expected. Then the plot for the alicyclic bases would be triphasic (Figure 1). The strongest alicyclic base available in this study was pyrrolidine (pK_a = 19.8), and thus we were unable to demonstrate this predicted levelling off of the Brönsted plot.

The plot in Figure 1 for the pyridinolysis does not display biphasic behaviour and neither do the other plots show such behaviour. This is due to the fact that even the strongest pyridine bases are not basic enough to achieve substantial proton removal from the substrates to generate dianion **3a**. By using the log k_2 and σ_{pyr} data (Table 2) a Hammett ρ value of –1.82 ($r = 0.97$) was found, and this would indicate that the pyridines have removed the acidic NH hydrogen atom partially. Substantial removal of the proton would lead to a much larger negative ρ value of the order of –5 to –6 because the ρ value for the ionization of the pyridinium ions of the bases in Table 1 (pK_a against σ_{pyr} plot) is –6.1 ($r = 0.963$). The Brönsted β value of 0.28 for the pyridinolysis supplies the same information and corroborates this point. All the alicyclic bases used were of the required "same structural type" possessing a secondary –NH– moiety within a saturated six- or five-membered (in the case of pyrrolidine) ring system, however, one of them (octahydroindole surprisingly), like 2,4,6-trimethylpyridine, deviated considerably from the plot and is not included. Its slower reaction may be due to a substantial steric effect caused by the attached six-membered ring, and it cannot be used with the other bases.

Leaving Group Effects

To shed further light on the mechanism occurring in these aminolysis reactions, leaving group effects were probed in the "β_1 segment" and in the "β_2 segment" of the alicyclic amine plots in Figure 1. The substrates **1a**–**f** were treated with *N*-formylpiperazine, which falls about midway on the β_1 plot, and with pyrrolidine, which is the last point on the β_2 plot. By using the log k_2 and pK_a data (Table 3) Brönsted β_{lg} (*N*-formylpiperazine) and β_{lg} (pyrrolidine) values of –0.43 ($r = 0.992$) and –0.66 ($r = 0.984$), respectively, were determined and the plots are drawn (Figure 2). The

Table 3. log k_2 values for the aminolysis (pyrrolidine and *N*-formylpiperazine) at 41.5 °C in ACN of a series of 4-substituted phenyl sulfamate esters and values of pK_a and Hammett σ used.

Pyrrolidine	log k_2 *N*-Formylpiperazine	Leaving group X in $H_2NSO_2OC_6H_4X$-4	pK_a[a]	σ
–5.00	–4.16	Me	27.45	–0.17
–4.52	[b]	H	27.2	0.0
–4.00	–3.40	F	26.57	0.062
–3.00	–3.05	Br	25.53	0.227
–2.92	–3.05	Cl	25.44	0.232
–0.324	–1.11	NO_2	20.7	0.778

[a] pK_a value in ACN of the leaving phenol. [b] Substantial overlap between the absorbances of the amine and the leaving phenol precluded rate measurements.

same log k_2 values and the appropriate σ values (Table 3) gave Hammett ρ_{lg} values for *N*-formylpiperazine of 3.2 (r = 0.995) and for pyrrolidine of 5.1 (r = 0.996).

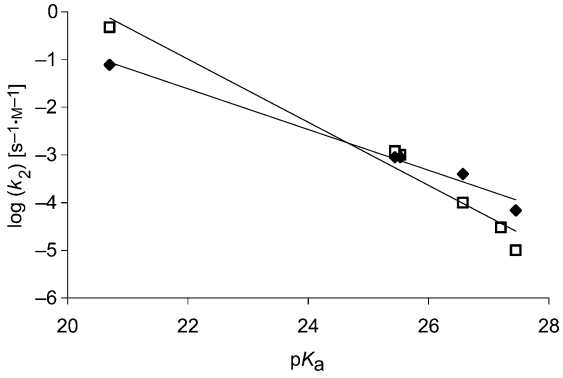


Figure 2. Brönsted leaving-group plot for aminolysis at 41.5 °C in ACN with *N*-formylpiperazine (black diamonds) the substrates from left to right being **1a**, **1c**, **1d**, **1b** and **1e**, and with pyrrolidine (squares) the substrates from left to right being **1a**, **1c**, **1d**, **1b**, **1e** and **1f**. The pK_a values in ACN of the corresponding phenolic leaving groups[12] are used in the plot. The value for 4-fluorophenol in ACN was estimated from a plot of the pK_a values in water against ten pK_a values available in ACN.[12]

Mechanism of Aminolysis

A substitution mechanism where the amines act not as bases but as nucleophiles attacking the sulfur atom leading to a pentavalent intermediate can be ruled out under the present circumstances. This is because the NH proton is quite acidic (ca. 8 in aqueous organic media[13]) and the aryl oxides are good leaving groups. However, an S_N-type reaction is very likely in certain situations (i) for those esters that do not possess an acidic hydrogen atom, e.g. Me_2N-SO_2Oar, because they have to choose an associative route;[9,14] and (ii) current work has shown that at pH = 2 the neutral form of the esters **1a**–**1f** react by nucleophilic attack by water in a bimolecular TS.[15]

The two values of β_{lg} (–0.43 and –0.66) for the two amines used (Figure 2) would indicate a reasonable degree of S–O bond cleavage and phenolate-ion character in the transition states, both in the "β_1 and β_2" segments of the reaction. Recent work[16] has suggested that in the scissile S–O bond there is significant lengthening in the slow step, and that the dissociative TS is sulfur-trioxide-like. Thea and Williams interpreted the β_{lg} values of –1.21 (intermediate pH) and –1.79 (high pH) in water as supporting E1cB dissociative processes for the hydrolysis/aminolysis of compounds **1**.[13] The Hammett ρ_{lg} values (Figure 3) are 3.2 (using *N*-formylpiperazine) and 5.1 (using pyrrolidine). Both suggest that a substantial amount of negative charge is being carried in the transition states and may support the breakup of an anionic substrate **2** via an *N*-sulfonylamine **4** (path A) and of the dianion **3** to give the anionic sulfonylamine **5** (Scheme 2). Hammett ρ values at intermediate and high pH levels can be calculated from the data by Thea and Williams,[17] and the values obtained were 2.32 and 3.66, respectively.[17] These values relate to the measurement in water and are therefore lower than the values obtained in ACN, but nevertheless they also point to substantial negative charge buildup in the transition states for the Paths A and B.

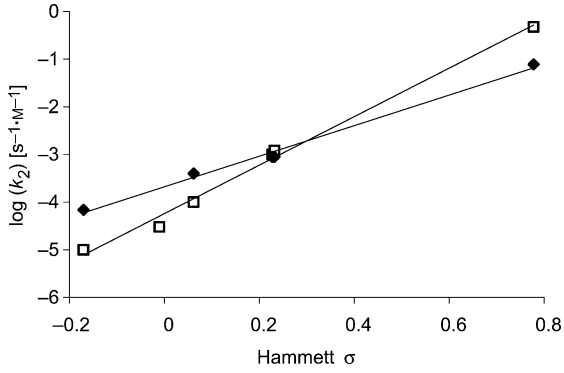


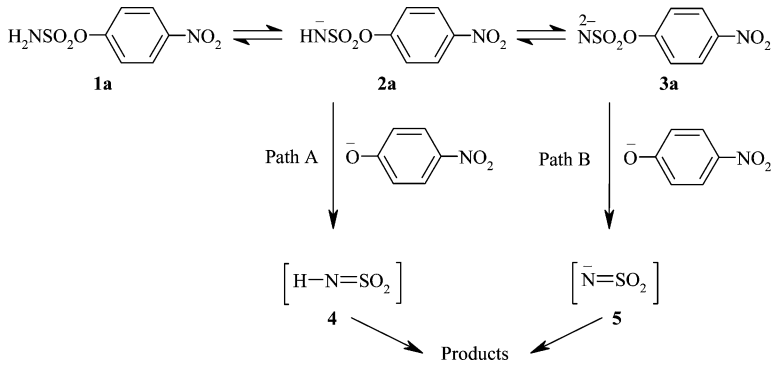
Figure 3. Hammett leaving-group plot for the aminolysis at 41.5 °C in ACN with *N*-formylpiperazine (black diamonds) the substrates from left to right being **1e**, **1b**, **1d**, **1c** and **1a**, and with pyrrolidine (squares) the substrates from left to right being **1f**, **1e**, **1b**, **1d**, **1c** and **1a**.

A likely mechanistic scenario for the reactions outlined above of **1a**, its anion **2a**, and the dianion **3a** would be the scheme proposed by Thea and Williams[13] some years ago for the reaction in water (Scheme 2). In this two major pathways involving an *N*-sulfonylamine **4** and a unique anionic sulfonylamine **5** leading to identical products were proposed and supported with kinetic evidence. In ACN in the presence of moderate bases a mechanism (Path A) involving the anions **2** and *N*-sulfonylamine (**4**) seems probable, and with the stronger bases (pK_a > ca. 18) the mechanism is likely to involve the dianion **3**, albeit in very low concentration, because the pK_a value of **2a** is ca. 21.1, and the anionic sulfonylamine **5** (Path B).

For this present work calculation of the Leffler indices (α) for the bond-forming (base···H^+) and bond-breaking (S···OAr) steps is possible if β_1 and β_{lg} are added to give β_{eq}, and β_2 and β_{lg} are added to give β_{eq}. These calculations give further insights into the reactions under study, namely, **1a** → **2a** → **4** → products, and **2a** → **3a** → **5** → products. The value of β_1 and the associated β_{lg} and β_{eq} values are 0.53, –0.43 and 0.96, respectively, and β_2 and its associated β_{lg} and β_{eq} values are 0.19, –0.66 and 0.85, respectively.

For the reaction **1a** → **2a** → **4** → products, α (bond-forming step) will be 0.53/0.96 = 0.55, and α (bond-breaking step) will be 0.43/0.96 = 0.44. These values of the Leffler indices indicate that removal of the proton to the base is slightly more advanced than the cleavage of the sulfur–oxygen bond for this reaction, and there is a small imbalance between the two steps.

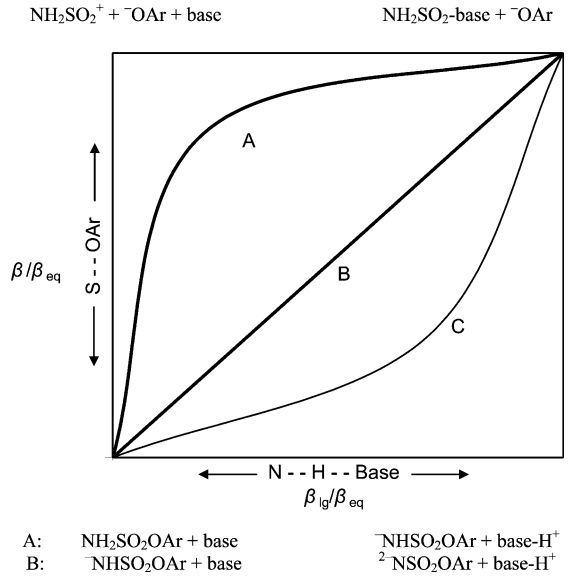
For the second reaction in stronger bases **2a** → **3a** → **5** → products, α (bond-forming step) is 0.19/0.85 = 0.22 and α (bond-breaking step) is 0.66/0.85 = 0.78. This indicates that for this reaction there is a very substantial imbalance between the progress of these two crucial steps, and the proton is only about 20% removed from the substrate, while



Scheme 2. Favoured mechanistic pathways for the hydrolysis of **1a** and other derivatives **1b**–**1f**.

the S–OAr bond is cleaved to almost 80%. The removal of the second proton would be expected to be much more difficult than the removal of the first proton from **1a** because of the negative charge on **2a**, and thus it is not surprising to find that in the TS for Path B this lags well behind the sulfur–oxygen bond-breaking step.

A free energy diagram for these elimination processes serves to illustrate more clearly the changes occurring during the reaction of these sulfamate esters in moderate bases and stronger bases. Such reaction maps have been used to follow more easily the changes taking place during the course of elimination reactions,[18,19] and the changes taking place during the elimination reactions in this work have been delineated now in Scheme 3.



Scheme 3. Free energy reaction map for the elimination of proton(s) and $^-$OAr from sulfamate esters NH_2SO_2OAr (**1**). Line C represents Path A, i.e. **1a** → **2a** → **4** → products (see Scheme 2), and shows how bond-forming between base and H^+ is somewhat more advanced than S–OAr bond-breaking and the line is pulled off a little off centre towards the bottom right hand corner of the diagram. Line A represents Path B, i.e. **2a** → **3a** → **5** → products (see Scheme 2), and this line is dragged substantially towards the top left hand corner reflecting the facts that S–OAr bond breaking is well ahead of base and proton bond forming. Line B shows a "central" E2 mechanism where bond-breaking and bond-forming both occur to the same extent in the TS.

The TS for Path A should lie on or somewhat below line C, and the TS for Path B should be on or below line A but well above line B. The TSs for Path A and Path B should resemble those shown in Scheme 4:

Scheme 4. TSs for Path A and Path B in Scheme 2. In Path B the larger δ symbols represent substantial bond cleavage, and in both TSs the distances between the various atoms/groups attempt to show the variable length of the bonds.

Finally, Path A should be seen as an E2-/E1cB-type mechanism and Path B as an E2 mechanism in which little bond formation but extensive bond breaking has occurred, and both are likely to involve very transient *N*-sulfonylamine intermediates as shown in Scheme 2.

Conclusions

In this work an eliminative route in the aminolysis of compounds **1a**–**f** is strongly supported and the likely decomposition pathways (A and B) are shown above (Scheme 2). The establishment and interpretation of several structure–reactivity relationships (Hammett and Brönsted plots) point to substantial scission of the S–O bonds in compounds **1** in both pathways to products. The breakup of these compounds in ACN (studied by Thea and Williams et al. in water) appear to follow E2-/E1cB-type and E2-type mechanisms with the involvement of *N*-sulfonylamine intermediates as outlined in Scheme 2. These important findings throw light on the likely mechanisms involved in the inhibition of various enzymes such as STS and CA which certain sulfamates such as 667-coumate, emate etc. can bring about.

Experimental Section

Substrates and Reagents: The amines used in this work were purified by distillation under reduced pressure or recrystallization from an appropriate solvent. The six substrates used, i.e **1a**–**f**, were synthesised according to a literature method[20] and gave yields of 70+%. Briefly, the method involved cooling of a stirred mixture of

the appropriate phenol in dimethylacetamide with sulfamoyl chloride and allowing the reaction to occur at room temperature (monitored by TLC). After the reaction was deemed to be complete, the mixture was poured into brine, extracted with three aliquots of ethyl acetate, washed exhaustively with brine, dried with magnesium sulfate and concentrated under reduced pressure. Final purification was performed by column chromatography and, if necessary, recrystallization from toluene. The purified materials gave C, H, N microanalyses within ± 0.5 of the calculated values except for **1b** (N 0.89), **1e** (C 0.99) and **1f** (C 0.55). Melting points were generally close to the literature values,[16,21] and the ^{1}H NMR and IR spectra were in agreement with their structures. The ACN used in this work was HPLC grade, and Karl Fischer analysis showed that the water content (as *a*% by volume) in ACN for four samples from different batches was 0.058, 0.048, 0.122 and 0.099. As a check on the effects of these small amounts of water in these ACN samples on pK_a values we measured the pK_a values of five amines (diisopropylamine, piperidine, morpholine, 4-DMAP and 4-pyrrolopyridine) in the four samples and found only small variations within the experimental error of the pK_a determination. The largest variation was for 4-DMAP, which was 17.56 ± 0.07, but most were much lower.

Determination of pK_a Values in ACN: The ionizations shown (Scheme 1) in Equations (1) and (2) were measured at 25 °C by using the procedures previously described.[8] The pK_a value of the first ionization of **1a** ⇄ **2a** [Equation (1)] was measured by using 4-nitrophenol as indicator and $\lambda_{analytical}$ = 220 nm. A value of 17.9 was obtained. The pK_a value of the second ionization of **2a** ⇄ **3a** [Equation (2)] by using in each case 2,4-dinitrophenol as indicator gave values of ($\lambda_{analytical}$ in nm in parentheses): 20.96 (325), 21.13 (325) and 21.16 (305). This gives an average value of 21.08. The pK_a values in ACN of the amines used have been reported previously (see Table 1, footnote [a]) except that of 3,4-diaminopyridine which was measured in this work as 14.7.

Kinetics: Rates were measured by using Cary 1 or Cary 50 UV spectrophotometers fitted with thermostatted cell holders. All reactions were carried out under pseudo-first-order conditions, i.e. excess amine (typically 0.2 to 0.02 M) with an initial substrate concentration from 1×10^{-4} to 5×10^{-5} M. The initial concentration of substrate used did not effect the rates. The reactions were generally monitored by the detection of the appropriate X-phenol/X-phenoxide ion. A few kinetic runs were monitored by the disappearance of sulfamate ester and the agreement between the rates obtained this way and those obtained by monitoring the appearance of X-phenol/X-phenoxide was good. From plots of $k_{obsd.}$ vs. [amine], straight lines were obtained, and the slopes of these plots gave k_2, the second-order rate constants for the aminolysis reactions. The small amounts of water in the ACN did not lead to a hydrolysis term in the rate law for these reactions, because plots of $k_{obsd.}$ vs. [amine] passed through the origin or very close to it.

Product Studies: In earlier product studies conducted in ACN, $CHCl_3$ and 50% aqueous ACN, the sulfamide product has been monitored by reversed-phase HPLC,[9,22] and in ACN the absorbances of spent kinetic solutions of 4-nitrophenol in amine were almost identical with those of spiked solutions.[8,9]

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