Change in Rate-Determining Step in an E1cB Mechanism during Aminolysis of Sulfamate Esters in Acetonitrile

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The kinetics of the reactions of the nitrogen−sulfur(VI) esters 4-nitrophenyl *N*-methylsulfamate (NPMS) with a series of pyridines and a series of alicyclic amines and of 4-nitrophenyl *N*-benzylsulfamate (NPBS) with pyridines, alicyclic amines, and a series of quinuclidines have been investigated in acetonitrile (ACN) in the presence of excess amine at various temperatures. Pseudo-first-order rate constants (k_{obsd}) have been obtained by monitoring the release of 4-nitrophenol/4-nitrophenoxide. From the slope of a plot of k_{obsd} vs [amine], second-order rate constants (k'_2) have been obtained for the pyridinolysis of NPMS, and a Brønsted plot of log k'_2 vs pK_a of pyridine gave a straight line with $\beta = 0.45$. However, aminolysis with alicyclic amines of NPMS gave a biphasic Brønsted plot ($\beta_1 = 0.6$, $\beta_2 \approx 0$). Pyridinolysis and aminolysis with alicyclic amines and quinuclidines of NPBS also gave similar biphasic Brønsted plots. This biphasic behavior has been explained in terms of a mechanistic change within the E1cB mechanism from an $(E1cB)_{irrev}$ (less basic amines) to an $(E1cB)_{rev}$ (more basic amines), and the change occurs at approximately the pK_a's (in ACN) of NPMS (17.94) and NPBS (17.68). The straight line Brønsted plot for NPMS with pyridines occurs because the later bases are not strong enough to substantially remove the substrate proton and initiate the mechanistic change observed in the reaction of NPMS with the strong alicyclic amines and quinuclidines. An entropy study supports the change from a bimolecular to a unimolecular mechanism. This is the first clear demonstration of this E1cB mechanistic changeover involving a nitrogen acid substrate.

Introduction

Sulfamate esters, $RNHSO_2OR$[1], have been prepared and tested for a wide range of properties including uses as herbicides, pharmaceutical agents, and artificial sweeteners.[1] In the 1990s, interest has heightened because of further discoveries with regard to the efficacy of these esters, for example, in the inhibition of carbonic anhydrase[2] (an enzyme linked to abnormally high intraocular pressure causing glaucoma and leading to blindness), in the use of the clinically important sulfamate anticonvulsant topiramate,[3] in the inhibition of ACAT[4] (lowering of cholesterol levels), and most importantly in the use of certain steroidal sulfamates to inhibit estrone sulfatase[5] (the enzyme associated with the development of breast cancer). The inactivation of this enzyme by the sulfamate occurs as a result of irreversible sulfamoylation of an essential amino acid residue, and this may involve direct nucleophilic attack at the sulfur atom by the enzyme, or instead, an E1cB mechanism may be occurring.[6] In view of the established propensity of sulfamate esters to undergo elimination reactions rather than nucleophilic additions,[7,8] an elimination pathway is more likely. This probable link between the mechanism of action of these steroidal sulfamates, H_2NSO_2OR, and our present study gives added importance to this work.

Experimental Section

Materials. The substrates 4-nitrophenyl *N*-methylsulfamate (NPMS)[7,9] and 4-nitrophenyl *N*-benzylsulfamate (NPBS)[10] have been reported previously. All liquid amines were distilled under reduced pressure, and solid amines were either recrystallized from the appropriate solvent or distilled under reduced pressure on a Kugelrohr distillation unit. The acetonitrile (ACN) used in our work was HPLC grade, claimed to be 99.9% pure, and shown by Karl Fischer analysis of the separate batches used (three analyses each) to have a mean water content of 0.200%, 0.142%, 0.106%, and 0.120%.

Determination of pK_a's of Amines and Sulfamate Esters. The spectrophotometric procedure of Bordwell and coworkers,[11] as modified by Cho et al.,[12] was used. As a check on the method, the pK_a's in ACN of three secondary amines

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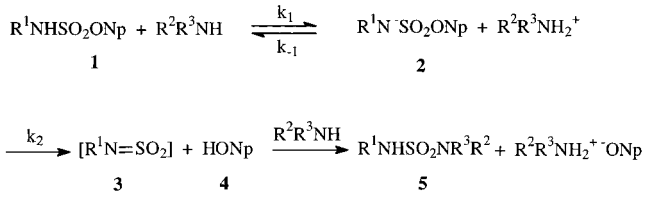
Scheme 1[a]



[a] Key: Np = $-C_6H_4NO_2$-4; R^1 = Me (NPMS), Bn (NPBS), Ph (NPPS), 2-MeO, 5-MeC_6H_3 (NPMMS).

previously determined[12] were remeasured at 25 °C with the following results (previous values in parentheses): $(^iBu)_2NH$, 17.95 ± 0.2 (18.3); $(^iPr)_2NH$, 18.4 ± 0.2 (18.5); and 2,4-dimethylpiperidine, 18.7 ± 0.2 (18.9). The pK_a values obtained for the amines used in this work are presented in Tables S1−S5 of the Supporting Information. The pK_a values were determined for NPMS and NPBS and previously prepared substrates 4-nitrophenyl *N*-phenylsulfamate[10] (NPPS) and 4-nitrophenyl *N*-2-methoxy-5-methylphenylsulfamate[13] (NPMMS).

Kinetic Measurements. Rates of aminolysis of substrates were measured on Cary 1/3 UV/Vis or Shimadzu UV-260 spectrophotometers fitted with thermostated cell holders. All reactions were carried out under pseudo-first-order conditions, i.e., in excess amine (at least 10-fold and usually 20−2000-fold). The initial substrate concentrations were 1×10^{-4} to 5×10^{-5} M, and the reaction was followed by monitoring the appearance of 4-nitrophenol (~335 nm) or 4-nitrophenoxide (~410 nm). From plots of k_{obsd} vs [amine], straight lines were obtained, and the slopes of these plots gave k'_2, the second-order rate constant for the aminolysis reactions. Some kinetic runs were followed by the disappearance of sulfamate ester, and the agreement between the rates obtained this way and those obtained by following the appearance of 4-nitrophenol or 4-nitrophenoxide was good. The initial concentration of substrate ester used did not affect the rates obtained, showing that these reactions are first-order in substrate. The precise details of the kinetic runs have been given previously.[8,10] The rate data obtained are recorded in Tables S1−S5 in the Supporting Information.

Product Studies. Partial product analysis was carried out by comparing the absorbances of spent (reacted ≥10 half-lives) kinetic solutions with spiked solutions of 4-nitrophenol in the corresponding amine solution. In previously described product studies[8,10] in ACN, $CHCl_3$, and 50% aqueous ACN, the sulfamide product has been monitored by reverse phase HPLC.

Results and Discussion

The general rate law followed for the aminolysis reactions studied in this work has the following form:

$$d[\text{NpOH } or \text{ NpO}^-]/dt = -d[\text{substrate}]/dt = k_{obsd}[\text{substrate}]$$

where $k_{obsd} = k_0 + k'_2$[amine]. The second-order rate constants for the reactions, k'_2, were obtained from plots of k_{obsd} vs [amine]. The k_0 terms for uncatalyzed reactions are negligible in most cases compared to those for the aminolysis, and they are not shown in Scheme 1.

Three sets of bases were used in this study. A set of six or nine pyridines with a pK_a range in ACN of >6 units, a set of six or seven alicyclic amines for which the pK_a range spanned ~2 or ~3 units, respectively, and a set of four quinuclidines spanning over 4 pK_a units were used. The kinetic data for the pyridinolysis of NPMS and of NPBS are given in Tables S1 and S2 of the Supporting Information, respectively. Kinetic data for aminolysis with the set of alicyclic amines are in Tables S3 and S4 of the Supporting Information, respectively, and data for the aminolysis of NPBS with quinuclidines are in Table S5 of the Supporting Information.

Brønsted-type plots of log k'_2 against amine pK_a have been made for the pyridinolysis of NPMS and NPBS in Figure 1 and for the aminolysis with alicyclic amines and quinuclidines in Figure 2. The most notable feature is the leveling off of the Brønsted plots seen in both figures for four of the five plots. This type of effect has been

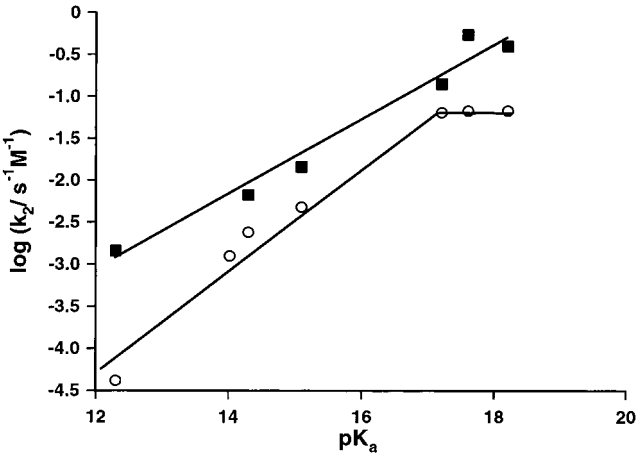


Figure 1. Brønsted-type plots for the aminolysis (pyridinolysis) of NPMS (■, Table S1 data, Supporting Information), the bases left to right being pyridine, 2-NH_2-pyridine, 2-NH_2-4-CH_3-pyridine, 4-NH_2-pyridine, 4-$(CH_3)_2$N-pyridine, and 4-pyrrolodinopyridine, and of NPBS (○, Table S2 data, Supporting Information), the bases left to right being pyridine, 4-MeO-pyridine, 2-NH_2-pyridine, 2-NH_2-4-CH_3-pyridine, 4-NH_2-pyridine, 4-$(CH_3)_2$N-pyridine, and 4-pyrrolidinopyridine in ACN at 42 and 37 °C, respectively.

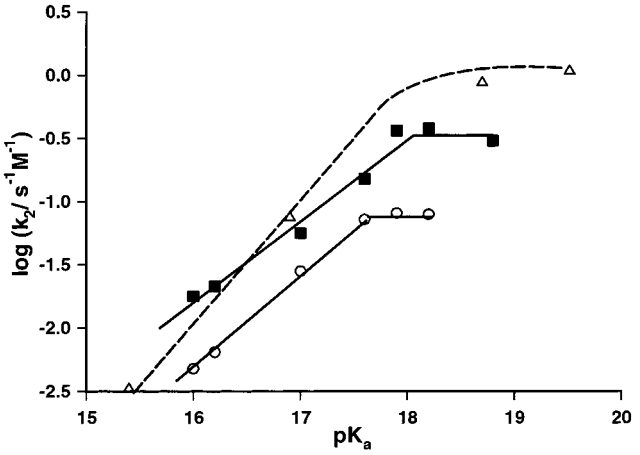


Figure 2. Brønsted-type plots for the aminolysis (alicyclic amines) of NPMS (■, Table S3 data, Supporting Information), the bases left to right being morpholine, thiomorpholine, *N*-formylpiperazine, *N*-(2-hydroxyethyl)piperazine, *N*-(2-aminoethyl)piperazine, piperazine, and piperidine, for the aminolysis (alicyclic amines) of NPBS (○, Table S4 data, Supporting Information), using the same bases excluding piperidine, and for the aminolysis (quinuclidines) of NPBS (△, Table S5 data, Supporting Information), the bases left to right being quinuclidinone, 3-chloroquinuclidine, quinuclidinol, and quinuclidine. All plots represent reactions in ACN at 37 °C.

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Table 1. Activation Parameters for the Aminolysis of 4-Nitrophenyl *N*-Benzylsulfamate (NPBS) in ACN

pyridine[a]	$\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta S^{\ddagger}$, J mol^{-1} K^{-1}	alicyclic amine	$\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta S^{\ddagger}$, J mol^{-1} K^{-1}
2-NH_2	58.9 ± 6	−112 ± 10	morpholine	46 ± 5	−140 ± 15
2-NH_2-4-CH_3	63 ± 5	−90 ± 8	*N*-formylpiperazine	43 ± 4	−143 ± 15
4-$(CH_3)_2N$	66 ± 7	−55 ± 6	*N*-(2-aminoethyl)piperazine	77 ± 8	−10 ± 1
4-pyrrolidino	66 ± 6	−55 ± 6	piperazine	75 ± 7	−15 ± 1

[a] Arrhenius plots were made using the four or five temperatures and corresponding k'_2 values in Table S2 (pyridines) and in Table S4 (alicyclic amines) of the Supporting Information. The errors shown are standard deviations.

observed by a number of groups[14−17] using carbon substrates and has been interpreted in terms of a mechanistic change within the E1cB mechanism. At the lower amine pK_a values, an $(E1cB)_{irrev}$ reaction takes place with $k_2 \gg k_{-1}[R^2R^3NH_2^+]$, and at higher p$K_a$ values, a change to an $(E1cB)_{rev}$ mechanism occurs when $k_{-1}[R^2R^3NH_2^+] \gg k_2$ (Scheme 1). Thus at lower pK_a values, bimolecular formation of the conjugate base **2** of substrate **1** followed by rapid leaving group departure occurs. At higher amine pK_a values, departure of ONp from **2** is rate-determining and $\beta_2 \approx 0$. In both cases, the products are nitrophenol **4** and the sulfamide **5** (Scheme 1). A sulfonylamine **3**[7] may be involved.

The β value for the straight line obtained for NPMS with a set of six pyridines (Figure 1) is 0.45 ($r = 0.966$). The β_1 value for the lower part of the NPBS plot with pyridines is 0.6 ($r = 0.983$, five points), and β_2 is approximately 0 (Figure 1). Two of the pyridines in Table S2 (Supporting Information), 2,4,6-trimethyl- and 2-amino-4,6-dimethylpyridine, are not plotted because they both deviate well below the line in the figure. Because both are quite hindered at either side of the pyridine ring nitrogen, i.e., the 2- and 6-positions, their deviation is understandable.

In Figure 2, the lower part of the NPMS plot with alicyclic amines gives a β_1 value of 0.64 ($r = 0.990$, six points), the lower part of the NPBS plot with quinuclidines gives a β_1 value of 0.7 ($r = 0.992$, three points), and for NPBS with alicyclic amines, the β_1 value is 0.7 ($r = 0.999$, four points).

The change from a general to a specific base catalysis situation expected for such a mechanistic change within the E1cB mechanism[18] is clear from Figures 1 and 2. This changeover can also be supported by examining the entropy changes taking place. The expectation would be that there should be a shift from a dependence on base (bimolecular) to no dependence on base (unimolecular) and that there should be an increase (less negative values) in entropy. This is borne out by activation parameters (Table 1) that were calculated from rate data at various temperatures for NPBS (Tables S2 and S4, Supporting Information). For the pyridines, the entropy is seen to change from approximately −100 J mol^{-1} K^{-1} (lower pK_a values) to approximately −55 J mol^{-1} K^{-1} (higher pK_a values in the plateau region of Figure 1), and for the alicyclic amines, the variation is even greater ranging from about −140 J mol^{-1} K^{-1} (lower pK_a values) to about −12 J mol^{-1} K^{-1} (higher pK_a values in the plateau region of Figure 2). Examination of the literature supports this use of entropy changes. Thus, typical E2, $(E1cB)_{irrev}$, $B_{AC}2$, and S_N2 processes have entropies in the range of about −55 to about −170 J mol^{-1} K^{-1}, while less negative values in the range of −40 to +150 J mol^{-1} K^{-1} have been associated with the $(E1cB)_{rev}$ mechanism.[19] Some of the entropies calculated previously in this laboratory were in error, though the conclusions regarding the role of entropy in the mechanism were correct.[20] The correct values are presented in Table 1.

Table 2. Experimental pK_a Values in ACN for Sulfamates NPBS, NPMS, NPMMS, and NPPS

ester	exp[a]
NPBS[b]	17.68 ± 0.5
NPMS[c]	17.94 ± 0.5
NPMMS[d]	18.56 ± 0.3
NPPS[e]	19.1 ± 0.1

[a] The method of ref 12 was modified. [b] 4-Nitrophenyl *N*-benzylsulfamate. [c] 4-Nitrophenyl *N*-methylsulfamate. [d] 4-Nitrophenyl *N*-2-methoxy-5-methylphenylsulfamate. [e] 4-Nitrophenyl *N*-phenylsulfamate.

In Figure 1, the reaction of NPMS with a set of pyridines does not show biphasic Brønsted behavior. However, in Figure 2 with a set of (stronger) alicyclic amines, NPMS produces a biphasic Brønsted plot. In earlier work[20] using NPPS with alicyclic amines and NPMMS with a set of pyridine bases, straight line Brønsted plots were obtained in each case.

The reason for this contrasting behavior became apparent when the pK_a's in ACN were measured for NPMS, NPBS, NPMMS, and NPPS (Table 2). For NPBS, the series of bases used are in all cases sufficient to achieve substantial proton removal from the substrate, and thus, the change in rate-determining step within the E1cB mechanism is observed. With NPMS, this is not realized with pyridines, but when a stronger set of bases is employed, biphasic Brønsted behavior again occurs. With NPPS and NPMMS, the sets of bases used were not sufficient to achieve substantial removal of the substrate proton, and thus, the more usual straight line Brønsted plots were observed.[20,22]

The change in the rate-determining step seen in four of the Brønsted plots in Figures 1 and 2 occurs at approximately the point where the substrate pK_a is equal to the pK_a of the catalytic amine, i.e.,

$$\Delta pK_a = pK_{R^2R^3NH_2^+} - pK_a(\text{sulfamate}) \approx 0$$

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Scheme 2[a]

$$\underset{a}{AH + B} \rightleftharpoons \underset{b}{AH\|B} \rightleftharpoons \underset{c}{AH\cdots B} \rightleftharpoons \underset{d}{A^-\cdots HB^+} \rightleftharpoons \underset{e}{A^-\|HB^+} \rightleftharpoons \underset{f}{A^- + HB^+}$$

Encounter complex; H-bonded complex; Ion-pair; Solvent separated ion-pair; Free ions

[a] Key: AH = substrate; B = catalytic base.

One cannot pinpoint this exactly, and in the case of the quinuclidines, this is particularly so because there is a substantial difference between the pK_a of each quinuclidine.

Finally, in connection with this work, a few other points need to be addressed. A referee has pointed out that a more adequate picture of the proton-transfer process, which is central to the reaction mechanism, can be represented by Scheme 2. In an aprotic solvent such as ACN (dielectric constant of 36.6), the diffusion apart of the ions (d → f) is a slow process and this may well be the actual crucial rate-determining step with amines of lower pK_a (β_1 part) in the curved Brønsted plots in Figures 1 and 2. These curved plots should be classical Eigen diagrams because the leveling off of the line arises at approximately $\Delta pK_a = 0$.

On the plateau (β_2 area), the proton transfer process should be very rapid (diffusion-controlled) and the kinetics are now determined by the unimolecular breakup of the sulfamate anion. From Figures 1 and 2, it is clear that the sulfamate esters react more rapidly with the alicyclic amines and the quinuclidines than with the pyridines. This arises because the former bases are stronger than the pyridines.

The sulfamide product **5** from the alicyclic base will be of the type $R^2R^3NSO_2-$, and the products from the quinuclidines and pyridines will be of the type $\geqslant N^+SO_2-$.

The latter have been discussed by us previously.[8] When the pyridine contains a second basic group such as 4-amino, the situation is the same because the ring nitrogen in 4-aminopyridine has a pK_a in water of 9.12, while the pK_a for the dissociation of the protonated amino group is −6.1 and thus the more basic site is at the ring nitrogen.[21]

The possibility that the biphasic behavior observed in this work might be due to a change in mechanism from E2 to $(E1cB)_{rev}$ seems unlikely because in much of our other work[22] we have found straight-line Brønsted plots with β values of 0.2−0.4 and these have been interpreted in terms of E2 mechanisms with some degree of "carbanionic" E1cB-like character. In eliminations, β values of 0.2−0.4 are associated with transition states with carbocation-type character (E2-type), while larger β values (0.6−0.9) are considered to be indicators of more carbanion-like transition states.[23]

The possibility of an S_N2-type mechanism arising has been dismissed before,[7] principally upon the basis that

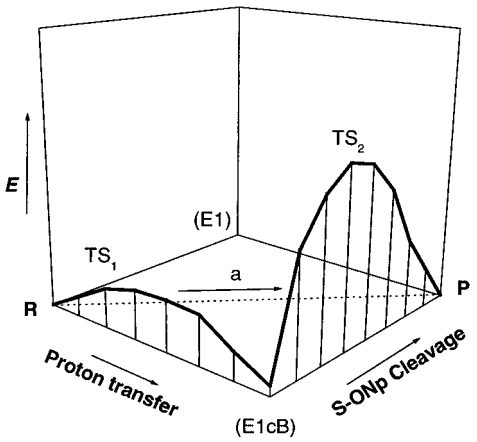

Figure 3. More O'Ferrall−Jencks-type plot for the situation when the first step (TS_1) is kinetically unimportant and the second step (expulsion of −ONp, TS_2) dominates.

4-nitrophenyl *N*,*N*-dimethylsulfamate, Me_2NSO_2ONp, which cannot undergo an elimination reaction, reacts far more slowly than other esters having the same leaving group and containing an −NH entity.

Sulfamate esters of type **1** bearing a hydrogen on the nitrogen have pK_a values of ∼8 in aqueous organic media,[7,9] and this coupled with a good leaving group appears to predispose them toward elimination.

When a More O'Ferrall−Jencks-type plot is used, the situations arising during the E1cB changeover in mechanism can be represented in Figure 3. In the bottom left-hand corner (R), the substrate and base are located, and the upper right-hand corner (P) represents the final products. Path a represents a concerted E2-type mechanism, and the paths for E1 and E1cB mechanisms are marked. The figure (shaded area) shows the $(E1cB)_{rev}$ pathway when $\beta_2 = 0$ and removal of the substrate proton is unimportant kinetically but expulsion of the leaving group is rate-determining. This is represented by a much smaller TS_1 (step 1) area compared to the TS_2 (step 2) area. The situation would be reversed, area TS_1 greater than area TS_2, for weaker bases for which $\beta_1 \approx 0.7$, and the $(E1cB)_{irrev}$ mechanism would operate.

This current work appears to be the first example of an E1cB mechanistic change involving a nitrogen substrate. Though a similar type of plot to those in Figures 1 and 2 has been observed for the decomposition of carbamates some years ago, this was interpreted in another way.[24]

Acknowledgment. Andrew B. O'Byrne, Chris Brack, and Paul McGrath thank Enterprise Ireland for research grants received. Dr. A. Bruzzi of the Public Analysts Laboratory, Galway, is thanked for carrying out the Karl Fischer analysis.

Supporting Information Available: Tables S1−S5 containing k'_2 and k_{obsd} data. This material is available free of charge via the Internet at http://pubs.acs.org.

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