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Kinetic and mechanistic studies of the hydrolysis of sulfamate esters: a non-elimination decomposition route

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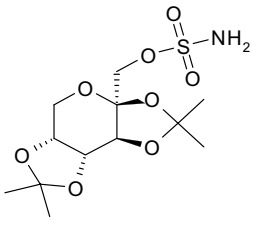
Abstract

The kinetics of hydrolysis at pH 2 and ionic strength (μ) = 1 of a series of sulfamate esters p-$XC_6H_4OSO_2NH_2$ have been examined using structure- and solvent-reactivity studies, thermodynamic data, a 'nucleophilicity test' and a kinetic solvent isotope effect to probe the mechanism of the hydrolysis. These esters can be regarded as models for the more complex medicinally and biologically important esters now under extensive study. The mechanism of hydrolysis involves the neutral ester undergoing nucleophilic attack by water in a bimolecular TS.

In the late eighties only a small number of sulfamate esters $ROSO_2NH_2$ were known to display biological and potential medicinal properties, such as anticonvulsant,[1] anti-Parkinson,[2] anti-bacterial[3] and anti-viral [4]activities.[5] Now almost twenty years on there has been a renaissance in interest in this area driven mainly by the discovery of new and more potent sulfamate esters that are or promise to be highly efficacious in the treatment of a variety of conditions. For example, Topiramate, **1**,[6] which is in clinical use, as an anti-epileptic drug and shows promise as an anti-obesity drug, 667 Coumate **2**,[7] which has completed phase 1 of clinical trials for treating hormone-dependent breast cancer[8] and Emate, **3**, which has been found to be an excellent inhibitor.[9] Several recent authoritative reviews



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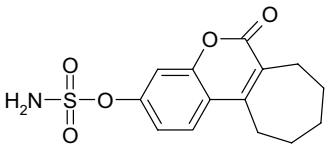

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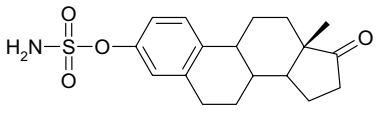

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covering various aspects of the development of biologically important sulfamate esters have appeared.[10]

The aminolysis of various sulfamate esters in non-aqueous solvents has been the subject of study over some years[11] but apart from the seminal work of Williams and Thea and their collaborators[12] over twenty years ago there has been a dearth of mechanistic studies in aqueous media on sulfamate esters. These workers explored the mechanisms mainly at intermediate and higher pHs and in a recent paper it has been pointed out that 'the major hydrolytic pathway at low pH has yet to be studied in detail'.[13] The indications are that in sharp contrast to the elimination mechanisms taking place at higher pHs and in non-aqueous media bimolecular water attack at the neutral sulfamate sulfur is occurring. In the present work we have examined the mechanism taking place at lower pH particularly at pH ~ 2 and our findings and conclusions are reported herein. A study of the decomposition mechanism in this area of pH seems especially appropriate since those

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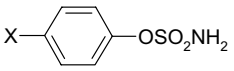
sulfamate esters in use[6] and in clinical trials[8,14] have been orally administered so they would very quickly be subjected to stomach environment where the pH is approximately 1–3.



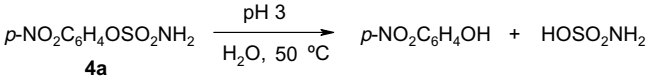
a: NO_2, **b**: Br, **c**: Cl, **d**: F, **e**: H, **f**: CH_3

4

To probe the mechanism of the reaction of sulfamates at low pHs a series of esters of type **4** were prepared by standard methods.[13,15,16] Kinetics were followed by the appearance of *p*-nitrophenol or other liberated phenols. Product studies showed that sulfamate **4a** was cleaved on hydrolysis at pH 3 according to the pathway shown in Scheme 1. A spiked pH 3 solution containing 1×10^{-4} M of *p*-nitrophenol and of sulfamic acid when compared ($\lambda_{max} = 316$ nm for *p*-nitrophenol) with a rate solution after ten half-lives at 50 °C gave an absorbance, which was within 91% of that shown by the rate solution. The sulfamic acid produced in the reaction of **4a** (conc. of 4.583×10^{-4} M) was determined gravimetrically as barium sulfate and the amount obtained corresponded to 98% of the expected sulfate. Hydrolysis of sulfamic acid will not occur under the conditions of the current rate study. In fact, at 50 °C and even at pH 1 the $t_{1/2}$ of sulfamic acid is about 18 days.[17] Thus these results clearly confirm that the main flux of the reaction proceeds as shown in Scheme 1.

H_0/pH–Rate profiles (Fig. 1) for the hydrolysis of **4a** in water at 50 °C using 3M HCl over the pH range from 0 to 10 and in 50% water–50% ACN at 25 °C from pH ~2 to ~13 were determined. The shapes of these were similar to that previously determined from pH 2 to 12 for **4a** in water at 25 °C.[12a] The rate constants cannot be compared directly because of differing temperature/medium. The absence of acid catalysis in the pH range 0–5 is evident and this is the region of most interest in the context of the current work. Structure-reactivity, solvent-reactivity, a test for nucleophilicity, thermodynamic data and deuterium kinetic solvent isotope effects (KSIE) were examined in this pH region to discern the mechanism taking place.

A Hammett plot (Fig. 2) for the hydrolysis of compounds **4** gave a ρ of 1.4 ($r = 0.982$) and a Bronsted plot (Fig. 3) gave a β_{lg} of −0.41 ($r = 0.989$). Rate measurements were carried out at pH 2 and at constant ionic strength $\mu = 1.0$ M (with KCl). These ρ and β_{lg} values indicate that a moderate amount of negative charge builds up on the phenolic oxygen in the TS of the reaction.



Scheme 1.

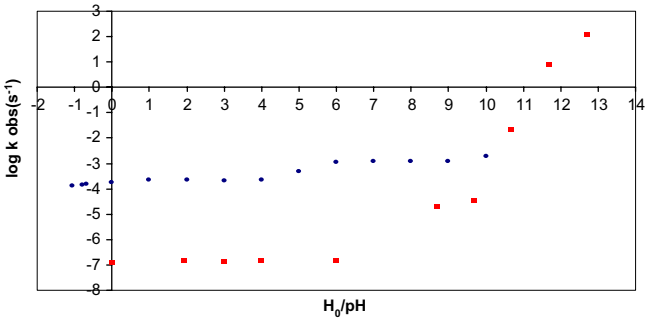


Fig. 1. H_0/pH–Rate profiles for the hydrolysis of **4a** in water (●) at 50 °C and in 50% water–50% ACN (■) at 25 °C.

Thermodynamic data for the hydrolysis of compounds **4** under similar conditions are given in Table 1. The enthalpy data display little variation as the substituent is varied but the entropies change from being reasonably negative to being slightly positive. Similar negative entropies have been interpreted as pointing towards a bimolecular S_N2 mechanism in related systems. Thus, for the hydrolysis of the named compounds the following entropies (J mol^{-1} K^{-1}) have been measured: *N*,*N*-dimethylsulfamoyl chloride, −14.5,[18] potassium *p*-nitrophenylsulfate, −18.5,[19] sodium thiosulfate, −16[20] and *p*-nitrophenyl *N*-methylsulfamate, −14.7.[12b]

The effect of solvent on reactivity was explored through a series of Grunwald–Winstein plots using compound **4a** in a range of water/ACN from 100% to 25% H_2O and water/acetone from 100% to 20% H_2O (v/v) mixtures in which the pH was maintained at 2–2.7. Plots of log*k* versus Y_{OTs} values showed downward curvature with slopes (m_s) ~ 0.1 indicating that the ionizing power of the solvent plays a minimal role. In a very recent work on the closely related acylsulfamates, $ArOSO_2NHCOR$ a similar low value of m_s for hydrolysis in water/ethanol was observed. This was interpreted as indicating that a water molecule plays an important role as a nucleophile in the TS, which in turn was substantiated by other evidence.[21]

To further examine the likely major role of solvent as a nucleophile in the hydrolysis of **4a** we have used a 'nucleophilicity test' pioneered by Bentley[22–24] in which two

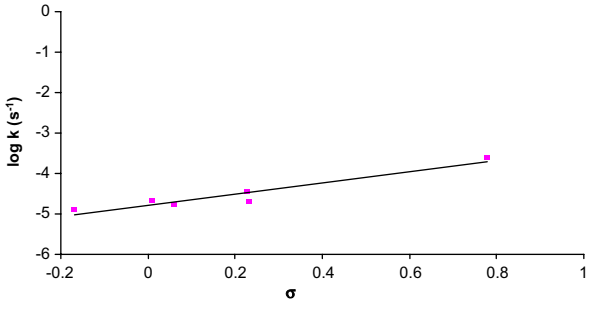


Fig. 2. Hammett plot for the hydrolysis of compounds **4** in water at pH 2, $\mu = 1.0$ M at 50 °C.

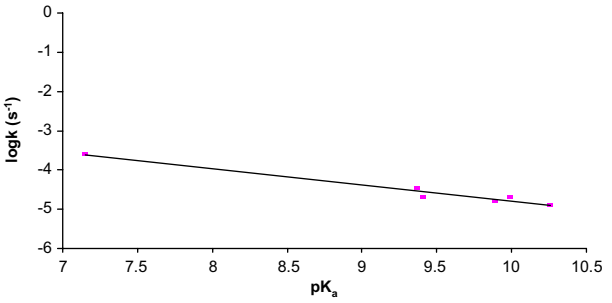


Fig. 3. Bronsted plot for the hydrolysis of compounds **4** in water at pH 2, $\mu = 1.0$ M at 50 °C.

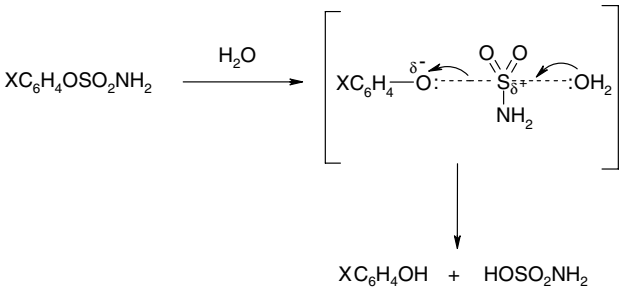
Table 1
Activation parameters for hydrolysis of sulfamates **4a**–**4f**[a,b]

p-X	$\Delta H^{\pm}$ (kJ mol^{-1})	$\Delta S^{\pm}$ (J mol^{-1} K^{-1})	*p*-X	$\Delta H^{\pm}$ (kJ mol^{-1})	$\Delta S^{\pm}$ (J mol^{-1} K^{-1})
NO_2[c]	95 ± 6	−22 ± 2	F	109 ± 6	1 ± 1
Br	101 ± 6	−19 ± 2	H	109 ± 6	2 ± 0.7
Cl	104 ± 6	−8 ± 1	CH_3	112 ± 6	7 ± 1

[a] pH 2 and ionic strength ($\mu = 1.0$ M).
[b] Eyring plots (correlation coefficients >0.99) using four or five points at temperatures between 40 °C and 70 °C. The errors shown are standard deviations.
[c] A temperature range between 30 °C and 70 °C was used.

solvent mixtures with identical Y_{OTs} values but very different N (nucleophilicity) values are used: if the reaction is significantly slowed down in the solvent of lower nucleophilicity, this suggests that the solvent is playing an important role as a nucleophile. The ratio of the rates of hydrolysis of **4a** at 50 °C in 45.8% ethanol/H_2O (v/v) ($Y_{OTs} = 1.83$, $N = -2.79$) and 97% trifluoroethanol/H_2O (v/v) ($Y_{OTs} = 1.83$, $N = 0.28$) is 48.2. The rate ratios reported with different systems vary considerably but a value of 48 is certainly significant and may be compared with values of 78 for the solvolysis of 2,4,6-trimethylbenzenesulfonyl chloride,[22] of 13.2 for the solvolysis of benzoyl chloride,[23] and of ~300, which may be calculated for the solvolysis of *N*,*N*-dimethylsulfamoyl chloride in an array of aqueous binary mixtures.[18,25] Ratios even <1 have been noted with some aromatic systems[24] such as diphenylmethyl chloride and *p*-methoxybenzyl chloride.

A kinetic solvent isotope effect (KSIE) has been measured for the reaction of **4a** using data (average of three runs) in water and deuterium oxide with an ionic strength (μ) = 1 (KCl), pH (pD) 2 (HCl/DCl) at 60 °C: $10^4 k_{H_2O} = 6.164 \pm 0.091$ and $10^4 k_{D_2O} = 2.368 \pm 0.06$ giving $k_{H_2O}/k_{D_2O} = 2.6$. The interpretation of KSIEs is difficult but broadly speaking values in the range of 1–3 support an S_N2 bimolecular reaction and values in the range of 1–1.4 may indicate an S_N1 unimolecular mechanism.[26] Bruice reported a value of ~2.8 for the pH-independent (2.5–7.6) hydrolysis of ethyl trifluorothioacetate at 30 °C ($\mu = 1$)[27] and values from 2.88 to 2.20 for the hydrolysis



Scheme 2.

of bis(*p*-nitrophenyl) carbonate at pHs from 1 to 3 have been reported.[28] These values have all been interpreted in favour of water involvement in the TS. However, values of 0.96 in the hydrolysis ($\mu = 1$) of the bis-sulfamate, $H_2NSO_2OCH_2$–$(CH_2)_5$–$CH_2OSO_2NH_2$[29] and of 1.26 for the neutral hydrolysis of potassium *p*-nitrophenylsulfate,[19] have been interpreted as evidence for unimolecular mechanisms with very little bond formation in the TS.

The reactive form of the ester at pH 2 will be the neutral molecule since the calculated pK_a for the ionization

$$p\text{-}NO_2C_6H_4OSO_2NH_3^+ \rightleftharpoons H^+ + p\text{-}NO_2C_6H_4OSO_2NH_2$$

is ~−9.36.

Finally, S–O cleavage in the TS is more likely than C–O cleavage because (i) with *p*-nitrophenyl *N*-methylsulfamate S–O cleavage has been shown to take place[12b] and (ii) examination of a large number of papers dealing with S–O versus C–O fission in *aryl* sulfonate and -sulfate esters indicates that in most cases S–O breakage occurs. Interestingly, for the aliphatic bis-sulfamate mentioned above exclusive C–O fission is found.[29]

In conclusion, this work has shown that these sulfamate esters hydrolyze to give a phenol and sulfamic acid as exclusive reaction products (Scheme 1). The linear free energy plots suggest that a moderate amount of negative charge should be formed at the phenolic oxygen in the TS so extensive bond-breaking of the S–OAr bond does not occur at that stage. The entropies, the Grunwald–Winstein m_s values, the effect of reducing nucleophilicity and the KSIE in general support the binding of a water molecule in the TS. Thus, in summary, it is felt that a mechanism of the type shown in Scheme 2 where a nucleophilic water molecule attacks at sulfur leading to concomitant S–OAr cleavage is well supported by the experimental evidence in this Letter.

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