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PAPER

Mechanisms of hydrolysis of phenyl- and benzyl 4-nitrophenyl-sulfamate esters†

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The kinetics of hydrolysis at medium acid strength (pH interval 2–5) of a series of phenylsulfamate esters **1** have been studied and they have been found to react by an associative $S_N2(S)$ mechanism with water acting as a nucleophile attacking at sulfur, cleaving the S–O bond with simultaneous formation of a new S–O bond to the oxygen of a water molecule leading to sulfamic acid and phenol as products. In neutral to moderate alkaline solution (pH ≥ ~ 6–9) a dissociative (E1cB) route is followed that involves *i*) ionization of the amino group followed by *ii*) unimolecular expulsion of the leaving group from the ionized ester to give *N*-sulfonylamine [HN═SO_2] as an intermediate. In more alkaline solution further ionization of the conjugate base of the ester occurs to give a dianionic species which expels the aryloxide leaving group to yield the novel *N*-sulfonylamine anion [$^-$N═SO_2]; in a final step, rapid attack of hydroxide ion or a water molecule on it leads again to sulfamic acid. A series of substituted benzyl 4-nitrophenylsulfamate esters **4** were hydrolysed in the pH range 6.4–14, giving rise to a Hammett relationship whose reaction constant is shown to be consistent with the E1cB mechanism.

Introduction

Sulfamate esters, RNH–SO_2–OR′ have become hugely important in the last fifteen years because of their ability to inhibit the action of certain enzymes thereby blocking a variety of enzymatic pathways.

Two of the best known early discoveries were the estrogenic emate and the non-estrogenic 667-coumate, both of which are steroidal sulfatase (STS) and carbonic anhydrase (CA) inhibitors (Fig. 1). Extensive synthetic work worldwide has led to the development of many new sulfamate inhibitors and a few of these are shown in the ESI† (see Fig. S1). EMD 486019 is a very new antitumor agent and is a strong inhibitor of certain isozymes.[1] The betulinyl-bis-sulfamate from the same laboratories is one of a series of bis-sulfamates, which have shown better inhibitory properties than the monosulfamates in certain cases.[2] KW-2581 is non-estrogenic and displayed good inhibitory activity in a number of applications.[3,4]

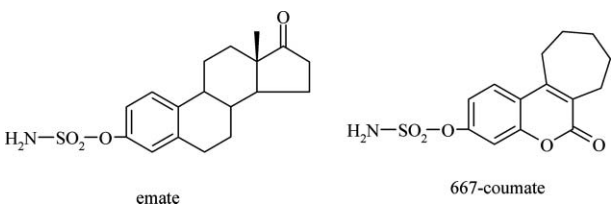

Fig. 1 First generation steroidal sulfatase (STS) and carbonic anhydrase (CA) inhibitors.

The emate derivative STX-213 showed similar potency to emate but with no estrogenic effects.[5] The diversity of structural types shown in Fig. 1 and Fig. S1 (ESI†) gives an indication of the wide range of sulfamate esters that have potential in medicinal

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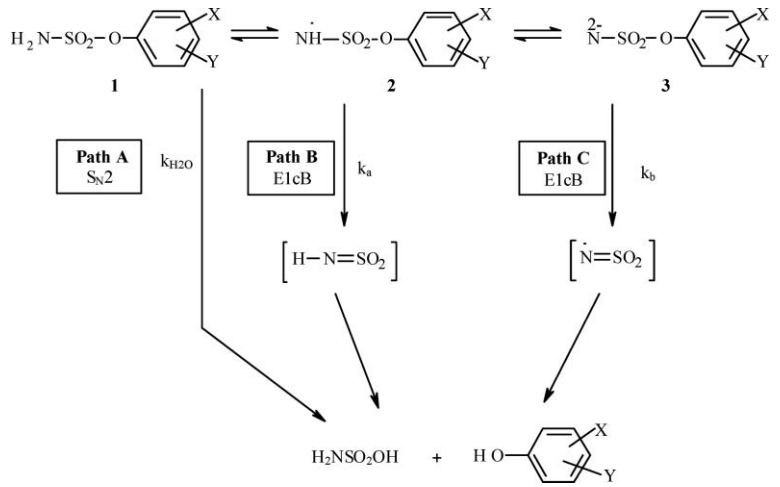
† Electronic supplementary information (ESI) available: **Fig. S1** Some newly developed sulfamate-containing inhibitors. **Fig. S2** ^{1}H NMR spectra of 4-nitrophenyl benzylsulfamates (compounds **4a–g**) in DMSO-d6 (Varian Mercury 300 MHz spectrometer). **Table S1** Experimental pK_as for the first ionization of compounds **1**. **Table S2** Experimental pK_a for the second ionization of compounds **1** in ACN. **Table S3** Spectrophotometric and kinetic pK_as for the ionization of compounds **4a–g**. **Table S4** pH-Rate profile data for the hydrolysis of compound **4a** in water at 25 °C. **Table S5** pH-Rate profile data for the hydrolysis of compound **1a** in water at 50 °C. **Table S6** Logk_{obs} for the hydrolysis of compounds **1a** and **1f–j** in water at 50 °C at pH = 2.0, the pK_a of the leaving phenols and literature Hammett σ value. **Table S7** Hydrolysis of compound **1a** in aqueous organic solvent mixtures of identical ionizing power (Y_{OTs}) but differing nucleophilicities (N_{OTs}). **Table S8** Logk_{obs} for the hydrolysis of **1a** in 50% aqueous ACN at 25 °C at high pH. **Table S9** Logk_{obs} for the hydrolysis of compounds **1a** and **1g–j** at pH = 11.7 at 25 °C in 50% aqueous ACN, the pK_a of the leaving phenols and literature Hammett σ values. **Table S10** Logk_a for the hydrolysis of compounds **4a–g i**n water at 25 °C and Hammett σ values. **Table S11** pH-Rate profile data for the hydrolysis of compounds **4b–g**. **Table S12** Effect of acetate buffer on the hydrolysis of **1a** in water at 25 °C. **Table S13** Physical and analytical data for compounds **4a–g**. See DOI: 10.1039/c0ob00362j



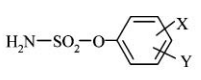
Scheme 1 Possible reaction paths for the hydrolysis of sulfamate esters.

applications. The quest to find the ideal inhibitor to combat many human ailments will continue and will encourage further syntheses of other types of sulfamate esters.

Sulfamates H_2NSO_2OAr generally tend to react by elimination–addition (EA) mechanisms because one or even both of their ionisable hydrogens are readily removed by base, and this initiates, in further mechanistic steps, the break-off of the aryloxide ion, ArO^-, and subsequent rapid reaction(s) with solvent/reagents leading to final products (Scheme 1, Paths B and C).[6–9] They may also react by a substitution S_N2 pathway and this has been shown for *N*,*N*-disubstituted sulfamates, RRN–SO_2–OR′, which lack a removable hydrogen and therefore cannot follow an eliminative pathway but react very slowly *via* a bimolecular substitution.[8] At low pH, this $S_N2(S)$ type of pathway had also been proposed over 20 years ago for sulfamates that have an acidic hydrogen[8] and this has recently been shown to occur in very recent work with phenylsulfamate[10] (Scheme 1, Path A).

Knowing the mechanism of reaction of sulfamates under chemical and biological conditions is clearly essential in order to understand the role that they play in many highly important enzymatic reactions. For some years mechanistic aspects of sulfamate ester reactions mainly in non-aqueous media such as acetonitrile (ACN) and chloroform have been the subject of study[7] but in recent studies[10] and in this present work water has been used as the reaction medium since this environment is much closer to that prevailing when the sulfamates are acting as inhibitors.

In this current work, a small segment of which has appeared in preliminary form,[10] it has been possible for the first time to demonstrate the occurrence of both eliminative and non-eliminative reaction pathways using the same set of arylsulfamate esters (compounds **1**).



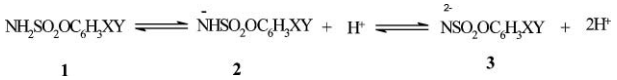
1a-j

a) X = 4-NO_2, Y= H
b) X = 3-NO_2, Y= H
c) X = 4-CN, Y= H
d) X = 3-Cl, Y= 5-Cl
e) X = 3-CN, Y= H
f) X = 4-Cl, Y= H
g) X = 4-Br, Y= H
h) X = 4-F, Y= H
i) X = Y= H
j) X = 4-Me, Y= H

Results and discussion

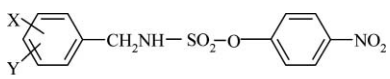
pK_a Studies

The pK_as of a series of ten phenylsulfamate esters **1** for the first ionization **1**⇆**2** (Scheme 2) were determined spectrophotometrically in water at 25 °C.



Scheme 2 Ionizations of phenylsulfamate esters.

The set of pK_a values obtained are available (see ESI,† Table S1) and the Hammett ρ for the ionization is 1.06 (r = 0.995, n = 10). A value of approximately unity might be expected since the ionization site is somewhat insulated from the ring substituents and furthermore, dissociation studies of related sulfonamides $ArNHSO_2C_6H_4X$ gave ρ values of 1.15 in water.[11] For the second ionization **2**⇆**3** higher pK_as would be expected because of the insulating effect of the negatively charged nitrogen in **2** and greater difficulty in removing the second hydrogen. The pK_a in ACN for the second ionization of **1a** is ~21.08[7] and for the six compounds **1a** and **1f–j** the average of their pK_as in ACN is 22.32 (See ESI,† Table S2) and a Hammett ρ value of 1.44 (r = 0.94, n = 6) was obtained. This value as expected is about 50% higher than the value obtained in water given above. These pK_a values were measured using an indicator method developed by Bordwell *et al.*[12a] and modified by Cho *et al.*[12b] Various relationships connecting pK_as (measured in H_2O) and pK_as (measured in ACN) for nitrogen bases have shown that the pK_as in water are about 7 to 8.5 units lower than in ACN.[13,14] Therefore the pK_a in water for the second ionization of **1a** should be ~12.5–14.

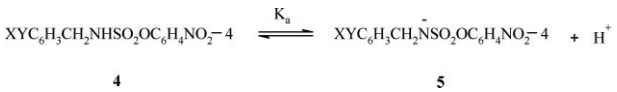


4a-g

a) X = 2-Cl, Y = 4-Cl
b) X = 4-Cl, Y = H
c) X = 2-Cl, Y = H
d) X = 4-F, Y = H
e) X = H, Y = H
f) X = 4-Me, Y = H
g) X = 4-MeO, Y = H

Values of pK_a were also determined for a series of seven benzyl 4-nitrophenylsulfamates **4**. Sulfamates **4** are an important inclusion in this mechanistic study because they cannot react by the second elimination mechanism in Scheme 1 since they lack a second hydrogen on the nitrogen of the sulfamate moiety. Compounds **4** ionize to their anions **5** (Scheme 3) and the ionization data are available (see ESI,† Table S3). There is very close agreement between the pK_as determined by UV–vis and those derived from the kinetics; this fact gives us confidence that the break of the pH-rate profile at pH *ca*. 8 is actually due to substrate ionization. Eqn (1) is of the appropriate form to fit the kinetic data in Table S4.[15,16a,b] Values of kinetic pK_as (as well as values of k_a, *vide infra*) were calculated by non-linear fitting to eqn (1) of the pH-rate profile data for compounds **4a–g** using the Fig P® program[17] (see Fig. 2 below where the profile for **4a** is shown). As compounds **4b–g** displayed very similar pH-profiles to that of **4a**, they are not shown here. In eqn (1) k_{obs} is the observed first-order rate constant, which has units of s^{-1}, k_a, is the rate constant (in s^{-1}) for the decomposition of anion **5** (see Scheme 6 below) and K_a, is the ionization constant for **4**⇆**5**

$$k_{obs} = k_a/(1+[H^+]/K_a) \quad (1)$$



Scheme 3 Ionization of benzyl 4-nitrophenylsulfamate esters.

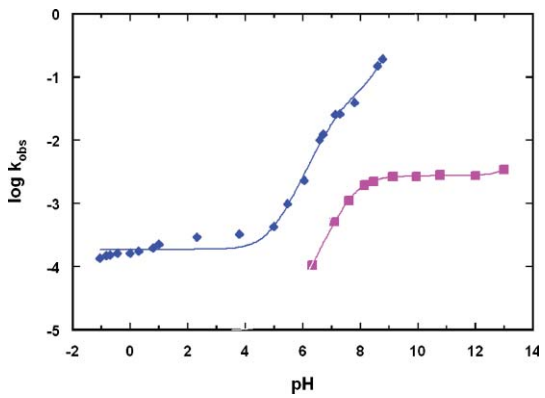


Fig. 2 pH-rate profiles for hydrolysis of **1a** (diamonds, ◆) and **4a** (squares, ■). Reaction temperatures are 50 °C for **1a** and 25 °C for **4a**. Line for **1a** is theoretical and was calculated with parameters from Table S5 using eqn (2) with the non-linear least squares Fig P® program.[17] Line for **4a** is theoretical and was calculated from eqn (1) with parameters from Table S4 using this program.[17]

pH-Rate profiles

The pH-rate profile for compound **1a** has been determined (Table S5) and the data are plotted in Fig. 2 and a curve (R factor 4.026) through the points has been drawn using eqn (2) which is the appropriate form.[6,8]

$$k_{obs} = k_{H2O} + (k_a + k_b[OH^-])/(1 + [H^+]/K_a) \quad (2)$$

K_a is the ionization constant for **1a** ⇆ **2a**; k_{H2O}, k_a and k_b are the rate constants for the processes shown in Scheme 1 (above).

The k_{obs} *vs.* pH study is similar to that reported earlier[6] except that it has been extended below pH 2 to pH 0 and beyond into the H_o region. In the alkaline region, because of the exceedingly high speed of the reactions, slightly fewer points were taken. A pH-rate profile has also been obtained for 2′,4′-dichlorobenzyl 4-nitrophenylsulfamate **4a** in the pH range 6.37 to 14 (see Table S4 and Fig. 2). As mentioned above, the pH-rate profiles of **4b–g** are very similar to that of **4a**. The pH range explored was in a more alkaline region than for compounds **1a–g** since we wanted to gain more information on the eliminative path originating in the first ionization (see Scheme 6, Path B below). As far as compound **1a** (as well as compounds **1b–g**) is concerned, this process merges into the one that follows the second ionization (Scheme 1, Path C), and this gives rise to the inflection between pH 7 and 9 shown in Fig. 2. Obviously, Path C is not allowed for compounds **4** and this accounts for the reactivity of **4a** being invariant at pH > ~9. Moreover, it should be noted that the different temperatures for the two series (50 °C for compounds **1**, 25 °C for compounds **4**) may well account for the reactivity of **1a** being higher than that of **4a** also at pH < 9 (Fig. 2).

Studies at medium acid strength (pH 2–5)

Hammett (ρ), Brønsted (β_{lg}), thermodynamic and solvent studies. Three factors prompted a study at low pH, namely earlier work concentrated on studies at intermediate and higher pHs,[6,8] a recent paper has pointed out that 'the major hydrolytic pathway at low pH has yet to be studied in detail'[18] and the sulfamate esters in use and in clinical trials are administered orally so they will be in a pH environment of ~1 to ~3. It is also worth noting that the pH-profile for **1a** shows the plot is virtually linear with the pH axis over the range pH 2–5 and acid catalysis can be ruled out in this range of pH. Hydrolysis here is due to water only. These facts determined that a major part of this study should be carried out at ~ pH 2 and much of this current work has focussed on this pH. At slightly higher pHs Path B, the E1cB breakup of the anion **2a** will come into play, leading to the final products shown (Scheme 1) and finally at higher pHs Path C with decomposition of the dianion **3a** will operate. Below pH ~1 and into the H_o region acid retards the rate somewhat.

The kinetics of hydrolysis of six compounds **1** with a spread of σ values of almost unity and of leaving group (phenol) pK_a values of more than 3 units were determined in water at pH = 2.0 at 50 °C (Table S6). A Hammett plot of log k_{obs} *vs.* σ gave a ρ of 1.41 (r = 0.984, n = 6) (*vide infra*, Fig. 3) and a Brønsted plot of log k_{obs} *vs.* pK_a of the corresponding phenols gave a β_{lg} of –0.41(r = 0.989).

Activation enthalpies ($\Delta H^{\neq}$) of ~105 kJ mol^{-1} for **1a–j** and activation entropies ($\Delta S^{\neq}$) of –22 J $mol^{-1}K^{-1}$(for **1a**) increasing with diminishing electron withdrawal to 7 (for **1j**) J $mol^{-1}K^{-1}$ have been determined previously[10] over a temperature range of at least 30 °C at pH 2 and μ = 1.0 M KCl for the six compounds in Table S6 using Eyring plots which have correlation coefficients ≥0.99. A kinetic solvent isotope effect (KSIE) of k_{H2O}/k_{D2O} of 2.6 has been reported for **1a** in earlier work.[10]

The effect of solvent on reactivity has been examined using aqueous ACN and aqueous acetone with the water content varying from 100% to 25% and from 100% to 20% (v/v) respectively. Though the Grünwald–Winstein plots of log k_{obs} *vs.* Y_{OTs} values showed some scatter and downward curvature they gave slopes m_s

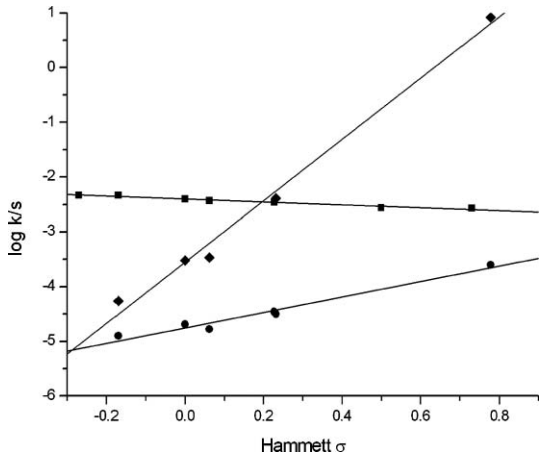


Fig. 3 Hammett plots for hydrolysis of (i) compounds **1a** and **1f–j** (●) in water at 50 °C, pH = 2.0, $k = k_{obs}$ (ii) compounds **1a** and **1g–j** (◆) in 50% aqueous ACN 25 °C, pH = 11.7, $k = k_{obs}$ and (iii) compounds **4a–g** (■) in water at 25 °C, $k = k_a$.

of ~0.1 indicating that the ionizing power of the solvent appears to play a minor role in the reaction.[19]

To examine the likely major role of water as a nucleophile in the hydrolysis of compounds **1a** a "nucleophilicity test"[20,21] in which two solvent mixtures with identical Y_{OTs} values but very different nucleophilicity values (N_{OTs}) were used in the reaction. 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 results are shown in Table S7 (ESI†). The hydrolysis rates of **1a** are much faster in the ethanol, methanol and ACN aqueous solvent mixtures of higher nucleophilicity than in aqueous trifluoroethanol (TFE) and aqueous hexafluoroisopropanol (HFIP), which are very poor nucleophiles as indicated by their N_{OTs} values. The rate ratios of $k_{\text{solvent mixture}}/k_{97\%\text{ TFE or }97\%\text{ HFIP}}$ vary from 95 to 21 (Table S7) and differences of this magnitude are clearly very significant and point to nucleophilic attack by water in the rate-limiting step. These ratios can be compared with values of 78 for the solvolysis of 2,4,6-trimethylbenzenesulfonyl chloride,[20] 13.2 for the solvolysis of benzoyl chloride[21] and of ~300, which may be calculated for the solvolysis of *N*,*N*-dimethylsulfamoyl chloride[22,23] In our earlier report[10] a value of 48.2 was given for the ratio $k_{45.8\%\text{ aq. ethanol}}/k_{97\%\text{ TFE}}$ but this was in error and the correct figure is approximately 95 (Table S7).

Studies in Alkaline Medium

Hammett (ρ), Brønsted (β_{lg}) and thermodynamic studies. Studies in the strong alkaline region at pH = 11.7 in 50% aqueous ACN were carried out at 25 °C. This judicious change in medium and temperature slowed the reactions and allowed accurate rates to be measured. The results at various pHs are given in the ESI† Table S8. Table S9 shows the kinetic results obtained for compounds **1a** and **1g–j** together with the pK_a values of the leaving phenols and the Hammett σ values for the substituents in each compound. These data give a very large Hammett ρ value of 5.6 ($r = 0.995$, $n = 5$) (*vide infra*, Fig. 3) and a substantial Brønsted β_{lg} value of –1.6 ($r = 0.997$) when the log k_{obs} values were plotted against σ values and pK_as respectively.

Table 1 Activation parameters[a] for the hydrolysis of compounds **1f–j** at pH = 11.7 in 50% aqueous ACN

Compound	$\Delta H^{\pm}$ kJ mol^{-1}	$\Delta S^{\pm}$ J mol^{-1} K^{-1}
1f	101	41
1g	113	80
1h	101	24
1i	101	22
1j	106	25

[a] Rates were determined over a temperature range of 20 °C. Five temperatures were used for each compound. Eyring plots had correlation coefficients ≥0.996 and the $\Delta H^{\pm}$ and $\Delta S^{\pm}$ are accurate to within ± 6%.

Activation enthalpies and entropies were determined for compounds **1f–j** under the same conditions and all the activation data obtained are given in Table 1. The activation enthalpy values obtained are all ~100 kJ mol^{-1} and the activation entropies are all quite positive in marked contrast to those obtained at pH = 2.0 (see above).

The kinetics of hydrolysis of seven benzyl phenyl esters **4a–g** were studied in the pH region 6.4 to 14.0 at 25 °C, in order to get a better knowledge of the dissociative mechanism occurring in the neutral to alkaline range (see Scheme 6, Path B below). Rate data are shown in Table S10. Rate data were already shown in Table S4 for compound **4a**, and those for compounds **4b–g** are reported as Table S11 in the ESI.† As stated before, ionization of the acidic benzylamino group gives rise to the sigmoid dependence shown in Fig. 2 for **4a** that is described by eqn (1). Values of log k_a were calculated from eqn (1) and are reported in Table S10. A plot of log k_a values from Table S10 against σ values gave a good Hammett plot with a low, negative ρ value of –0.27 ($r = 0.982$, $n = 7$) (*vide infra*, Fig. 3) showing that the role played by substituents is moderate due to their distance from the reaction centre.

Mechanisms of hydrolysis

In medium acid strength (pH 2–5) for (1). In the medium acid region pH 2–5 acid catalysis of the hydrolysis of **1a** does not occur (Fig. 2) and the reactive form of **1a** will be the neutral, unionized form, $NH_2SO_2OC_6H_4NO_2$-4. The calculated pK_a for the ionization of the protonated form, $^+NH_3SO_2OC_6H_4NO_2$-4 is –9.36 (see Experimental) and thus it will not be present in medium acid. The Hammett ρ and Brønsted β_{lg} values indicate a moderate amount of charge build-up on the phenolic oxygen and some S–O cleavage in the transition state (TS) of the reaction. The activation enthalpies of ~105 (kJ mol^{-1}) show little change as the substituent is varied but the activation entropies change somewhat from –22 to 7 J mol^{-1}K^{-1}. Similar negative activation entropies have been interpreted for the hydrolysis of related compounds as indicating a bimolecular mechanism with water involvement in the TS. Thus, for the following compounds the activation entropies (J mol^{-1}K^{-1}) shown have been reported: *N*,*N*-dimethylsulfamoyl chloride –14.5,[22] potassium 4-nitrophenylsulfate –18.5,[24] sodium thiosulfate –16[25] and 4-nitrophenyl *N*-methylsulfamate –14.7.[26]

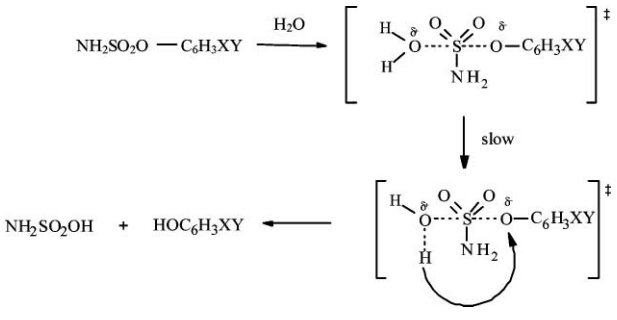
The kinetic solvent isotope effect (KSIE), k_{H2O}/k_{D2O} obtained for reaction of **1a** at 60 °C [pH(pD) 2, (μ) = 1.0 M KCl] was 2.6, the individual average k_{obs} (×10^4) values and errors based on three determinations in water and deuterium oxide being 6.16 ± 0.09 and 2.39 ± 0.06 respectively and this may be interpreted as support for an S_N2 type mechanism.[10] Schowen[27] has indicated that values

from approximately 1 to 3 support an S_N2 mechanism but those in the range of 1–1.4 may indicate an S_N1 mechanism. Values of KSIE of ~3 have been predicted[28a,b] and realised with various substrates. The spontaneous hydrolysis of acetic anhydride had a KSIE of ~3[28b] and the neutral hydrolysis of several alkyl trifluoroacetates showed values greater than 3.[28c] The pH-independent hydrolysis of ethyl trifluoroacetate gave a value of 2.8,[29a] and of bis(4-nitrophenyl) carbonate gave values in the range of 2.2–2.9.[29b]

Grünwald–Winstein plots using reactivity data from a wide range of aqueous ACN (100–25% water content) and aqueous acetone (100–20% water) mixtures with a pH variation from 2–2.7 showed downward curvature and a little scatter in plots of log k_{obs} against Y_{OTs} values, but approximate m_s values of 0.1 could be estimated which would indicate that the ionizing power of the solvent plays a small role. A similar low value of m_s has been found for the hydrolysis in aqueous ethanol of the related *N*-acylsulfamates, $ArOSO_2NHCOR$.[30] These results point to the involvement of water as a nucleophile in the TS. 'Nucleophilicity plots' gave $k_{\text{solvent mixture}}/k_{97\%\text{ TFE or }97\%\text{ HFIP}}$ ratios (Table S7) which clearly indicate the important role of water as a nucleophile in the TS for the hydrolysis of **1a**.

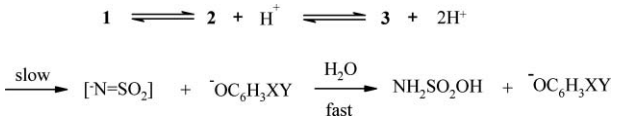
In the pH-independent region the effect of acetate buffer concentration on the rate of hydrolysis of **1a** in water at one pH was probed and the results are shown in the ESI,† Table S12. The absence of a buffer concentration effect on the rate demonstrates the absence of general acid catalysis.[31]

Thus, in the pH region ~2–5 the accumulated evidence supports an $S_N2(S)$ process in which a water molecule attacks at sulfur in the TS leading to a pentacoordinated sulfur species (with trigonal biyrimidal geometry) and ultimately to sulfamic acid and 4-nitrophenol products (Scheme 4) probably with a proton transfer in the slow step from water to the leaving group. Page *et al.*[32] have in recent times probed this type of sulfonyl transfer reaction and thrown a good deal of light on it using a series of N-aroyl β-sultams and comparing their mechanisms with those of the better known N-aryl β-lactams. Associative (such as shown in Scheme 4) rather than dissociative mechanisms are normally favoured. Such a non-eliminative decomposition route is unusual in sulfamate chemistry and in the past has only been recognized in the limited case of the hydrolysis of *N*,*N*-dimethylsulfamate esters.[8]



Scheme 4 Reaction path and TS for $S_N2(S)$ reaction of compounds **1**.

In alkaline medium for (1). The hydrolysis of compounds **1** in strong alkaline media presents a strikingly different situation. As seen from the pH-rate profile (Fig. 2) rates are much faster in strong alkali but can be slowed somewhat by changing from water to 50% aqueous ACN and by reducing the temperature from 50 °C to 25 °C. The effect of substituents on the hydrolysis is very substantial and from the data in Table S9 a Hammett ρ of 5.6 (r = 0.995, n = 5) and a Brønsted β_{lg} of −1.6 (r = 0.997) are obtained. These figures strongly support the development of a substantial negative charge on the oxygen of the S–O bond and the advanced cleavage of this bond in the TS. A β_{lg} of −1.79 has been reported for the hydrolysis of compounds **1** in water without organic solvent under strong alkaline conditions.[6] This number in conjunction with other data was interpreted in favour of a novel E1cB mechanism involving a dianionic sulfamate leading to an anionic *N*-sulfonylamine, $^-N{=}SO_2$ (Scheme 1). It is likely that the difference found between this latter value (−1.79) and the value calculated here (−1.6) could be ascribed to change of solvent from water to 50% aqueous ACN in the present work. The activation parameters obtained for reaction in 50% aqueous ACN are given in Table 1. The entropy values which are seen to be quite positive would support the operation of an E1cB mechanism. In the earlier work a $\Delta S^{\ddagger}$ (J mol^{-1} K^{-1}) of 49 was obtained which is broadly in the same range as those given in Table 1 and a $\Delta H^{\ddagger}$ (kJ mol^{-1}) of 64 was reported. There is previous evidence too from a kinetic/trapping experiment at pH 9.11 with 4-toluidine that ArO–S cleavage occurs largely *before* attack by the amine on an intermediate $^-N{=}SO_2$. In a recent report a β_{lg} of −1.1 has been obtained from kinetic data for inactivation by various arylsulfamates, including 667-coumate, of *Pseudomonas aeruginosa* arylsulfatase and the authors conclude *inter alia* that the chemical step of inactivation involves a high degree of ArO–S cleavage.[33] All of this provides strong support for an E1cB mechanism in alkaline media and a mechanism involving initial loss of proton successively from **1** and then **2**, the formation of dianion **3**, which cleaves in the slow step to give an anionic *N*-sulfonylamine and aryloxide ion, leading to products sulfamic acid and aryloxide (Scheme 5).

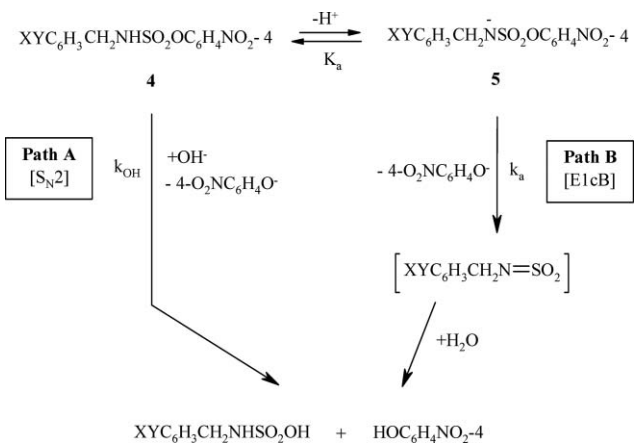


Scheme 5 E1cB mechanism of hydrolysis for compounds **1**.

For benzyl phenylsulfamates, (4). The sigmoid shape of the pH-rate profile of the benzyl phenylsulfamate esters **4**, that is described by eqn (1), could be due to either the E1cB process (Scheme 6, Path B, first order rate constant, k_a) or to the kinetically equivalent $S_N2(S)$ bimolecular process due to OH^- attacking the undissociated ester at sulfur (apparent second order rate constant: $k_{OH} = k_aK_a/K_w$). However, reactivity of the latter (k_{OH} = 3980 M^{-1}s^{-1}) would be some 10^9-fold larger than that for the bimolecular attack of OH^- on 4-nitrophenyl *N*,*N*-dimethylsulfamate, Me_2NSO_2O–$C_6H_4NO_2$-4 ($k_{OH} = 2.4 \times 10^{-6}$ M^{-1}s^{-1}), a *bona fide* $S_N2(S)$ process.[8] Such a huge difference between calculated and experimental reactivity cannot be accounted for simply on the grounds of the steric effects exerted by the benzylamino group in a mechanism of the S_N2-type.

The reaction constant ρ obtained by plotting log k_a values for compounds **4a–g** against σ is low (–0.27), thus indicating that the substituents play a reduced role.

From this value, however, ρ for the 'apparent' bimolecular rate constant k_{OH} ($= k_aK_a/K_w$) can be calculated as $\rho(\log k_{OH}) = \rho(\log k_a)$



Scheme 6 Pathways for the hydrolysis of compounds **4**.

– $\rho(pK_a) = +0.17$. This result allows us to compare the hydrolysis of 4-nitrophenyl benzylsulfamates with those of phenyl esters of substituted benzenesulfonic acids and phenylmethanesulfonic acids, whose dependencies of log k_{OH} to σ constants have been previously reported in the literature ($\rho = +2.24$ for the first series, whose alkaline hydrolysis follows an associative (S_N2) mechanism and $\rho = +0.43$ for the second series, which follows a dissociative (EA) hydrolytic mechanism.[34] From this comparison it emerges that, as far as substituent effects are involved, aryl benzylsulfamates are much closer to aryl phenylmethanesulfonates than to aryl benzenesulfonates, especially if one takes into account that, in our case, an extra methylene group is interposed between substituents and the ionizable group. Indeed, if the attenuation factor for the intervening CH_2 group (0.47)[35] is taken into account, a 'corrected' ρ value of +0.36 can be calculated, that is reasonably close to that found for the dissociative hydrolysis of phenyl esters of substituted phenylmethanesulfonic acids (+0.43) (the difference between the two ρ values can be considered negligible, especially if differences in solvent composition (water *vs.* 70% aqueous dioxane) and temperature (25 °C *vs.* 50 °C) are taken into account. All these results support the occurrence, for the esters **4** in the pH range explored here, of the elimination–addition (E1cB) mechanism depicted as Path B in Scheme 6.

Conclusions

At medium acid strength (pH 2–5) phenylsulfamate esters **1** have been found to react by an associative $S_N2(S)$ mechanism with water acting as a nucleophile attacking at sulfur and rupturing the S–O bond with concurrent formation of a new S–O bond to the oxygen of the H_2O molecule leading to sulfamic acid and phenol products. Conversely, at alkaline pH ≥ ~ 9, esters **1** undergo reaction *via* an eliminative route which involves first loss of proton(s) and then rate-determining ArO–S breakage followed by formation of an *N*-sulfonylamine anion and rapid attack on it leading again to sulfamic acid and aryloxide products. In neutral to strongly alkaline solutions the 4-nitrophenyl benzylsulfamates **4** hydrolyse through a dissociative E1cB pathway. It is most likely that at low pHs, like the aryl sulfamates, **1**, an associative, $S_N2(S)$ mechanism is followed.

Experimental Section

Substrates and reagents

The syntheses of compounds **1a**, **1f**, **1g**, **1h**, **1i** and **1j** has been described previously[7] as have the syntheses of **1b** and **1c**.[18] **1d** and **1e** were synthesised by the same methods. All compounds gave satisfactory C, H and N microanalytical analysis. Compounds **4a–g** are new and their synthesis has been carried out by slight modification of standard methods by reaction of the corresponding sulfamoyl chlorides with the appropriate phenols.[36] A typical example for the synthesis of **4e** involved the following procedure: tetrabutylammonium bromide (0.5 g, 1.55 mmol) and anhydrous potassium carbonate (0.8 g, 5.8 mmol) were sequentially added to a solution of 4-nitrophenol (0.3 g, 2.16 mmol) in benzene (5 ml) kept under nitrogen. The mixture was magnetically stirred over half an hour, after which period a solution of *N*-benzylsulfamoyl chloride (0.45 g, 2.19 mmol) in benzene (5 ml) was added dropwise. The reaction mixture was kept under stirring over three days at room temperature, and the solvent was eventually removed under reduced pressure. Purification by column chromatography (silica gel, eluent dichloromethane) afforded a solid which, after recrystallization from toluene, melted at 111–112 °C. All of these new compounds **4a–g** have been fully characterized (see ESI,† Table S13) giving sharp mps and excellent C, H and N microanalytical data. The ^{1}H NMR spectra for **4a–g** are shown in the ESI data in Fig. S2 and they are fully consistent with the proposed structures.

Methanol, ethanol, acetone and ACN solvents were all HPLC grade. HCl, KOH and KCl were analytical grade. TFE was ReagentPlus grade and HFIP was 99.8% both from Aldrich.

Determination of pK_a values

Values of pH were measured either with a Jenway 3510 meter or with an Orion SA520 instrument equipped with an Orion Semi-micro Ross combination electrode, 0–14 pH. A correction was applied to readings >12 according to the manufacturer's instructions. Values of pK_a were determined at 25 °C using Cary 50 and 100 UV–vis and Kontron Uvikon 941 spectrophotometers. Aqueous buffered solutions of the sulfamate esters were made up to pH 7.2 containing 0.01 M Tris-cacodylate buffer solution and the solution was adjusted to the desired pH using 0.5 M HCl or KOH as required. Buffered solutions were made up in KCl so that each solution had a constant ionic strength of 1.0 M. Two ml of a buffered solution was added to each cuvette and 20 μl of a 1×10^{-2} M sulfamate ester solution was added to give a final concentration of 1×10^{-4} M in sulfamate ester. Control pH readings were carried out at the end of each absorption measurement to ensure that no change in pH had occurred. From a plot of absorbance *vs.* pH and using the Henderson–Hasselbalch equation the pK_a of each sulfamate ester was calculated.

$$pK_a = pH + \log[(A - A_M)(A_I - A)]$$

where A_M = absorbance of molecular species, A_I = absorbance of ionic species and A = absorbance at a particular pH. A_M and A_I were obtained by averaging a number of points from the molecular species and the ionised species from the lower and the upper ends of the titration curve respectively and A was taken from the points along the slope of the curve. A pK_a was calculated for each

point (~10) from the slope of the curve and the average of these readings was taken as the pK_a for the sulfamate. A pK_a value for $^{+}NH_3SO_2OC_6H_4NO_2$-4 was calculated using the Advanced Chemistry Development (ACD) computer program.[37]

Kinetics

The Cary 100 and the Kontron Uvikon 941 UV–vis instruments were used mainly for the rate studies. The substrate concentration was normally 1×10^{-4} M. A suitable $\lambda_{anal.}$ was chosen and the increase in absorbance due to the production of phenol/phenoxide product against time was plotted and from this the infinity absorbance was deduced. A plot of $\log(A_{inf} - A_t)$ *vs.* t, where A_{inf} = the absorbance at infinity and A_t = absorbance at time, t, was then made and from the slope of the straight line the rate constant was obtained using a linear least square method. Runs were repeated in duplicate or triplicate and followed for at least 4 half lives. The rate constants obtained were usually reproducible to within the limits stated in the Table S5 footnotes. Where comparison is possible with other independent work the agreement between the rate constants determined in this current work and literature data is very good. For example, Blans and Vigroux[38] report a rate constant of 1.8×10^{-5} s^{-1} for hydrolysis of compound **1i** under identical conditions to those used in Table S6; the value from this Table is 2.06×10^{-5} s^{-1}. Thus, the two rate constants are within 7% of each other. A rate constant of 9.85×10^{-6} s^{-1} has been reported for the hydrolysis of **1a** at pH 2, μ = 1.0 M KCl at 25 °C[6] and in this work a rate constant of 10.1×10^{-6} s^{-1} was found under the same conditions and thus the difference in rates is less than 3%. Using the same conditions the rate of *disappearance* of **1a** was followed at 265 nm to give a rate constant of 8.64×10^{-6} s^{-1} in the present studies which is in reasonable agreement with the above values.

Some very fast rates were measured using a stopped flow apparatus. Solutions of 2×10^{-4} M substrate were made up in ACN and placed in one syringe and deionized water was placed in the other syringe. The mixing vessel was thermostatically controlled at 25 °C and on mixing the two solutions voltage is recorded at millisecond intervals and the OLIS-KINFIT programme converts this to absorbance at 400 nm and produces a rate constant.

Solutions for the rate measurements at 50°C in the binary solvent mixtures (Table S7) were made up by mixing the organic solvent with water (v/v) except for TFE and HFIP which were made up w/w. In order to obtain the same Y_{OTs} for the various aqueous solvent (MeOH, EtOH, ACN) mixtures several types of plot were made from literature data.[39] All the plots constructed gave excellent straight lines and by interpolating it was possible to read off the correct % organic solvent in order to obtain the desired Y_{OTs} value. All solvent mixtures were made up using deionised water of pH 2 giving a final pH for the solution of 2.5 ± 0.5 depending on the particular mixtures thus ensuring that kinetics were carried out in the uncatalysed region of the pH-rate profile.

Product studies

Reaction of **1a** in aqueous ACN at 37 °C with Et_2NH present gave quantitative recoveries by HPLC of sulfamate, sulfamide and 4-nitrophenoxide with varying mixtures of water and ACN and varying concentrations of Et_2NH.[9] In a partial product run a spent rate (a solution that has been allowed to react for ≥10 half lives) in water solution of **1a** (original concentration 1×10^{-4} M) which had been reacted at 50 °C at pH 3 gave an absorbance for 4-nitrophenol which was within 91% of a 'mock infinity' solution at pH 3 made up with 1×10^{-4} M 4-nitrophenol and 1×10^{-4} M sulfamic acid. In another type of 'bulked-up' product run the sulfamic acid produced on complete reaction of **1a** (initial concentration 4.58×10^{-4} M) was determined gravimetrically as barium sulfate and the amount of $BaSO_4$ obtained corresponded to 98% of the expected sulfate. It is important to note that hydrolysis of sulfamic acid produced in the rate runs in this current work will not occur under the prevailing conditions. At 50 °C and even at pH 1 the $t_{1/2}$ of sulfamic acid is ~18 days.[40]

For compounds **4**, reaction stoichiometry was checked by comparing the UV–vis spectra of spent reaction mixtures with those of "mock infinity" solutions prepared from calculated amounts of 4-nitrophenol and the relevant *N*-benzylsulfamic acid at some selected pHs. In all cases, calculated yields were close to 100%.

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