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Mechanism of the acid-catalyzed hydrolysis of *N*-acylsulfamates

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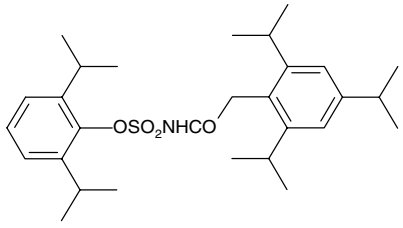
Abstract—The kinetics of hydrolysis of a series of *N*-acylsulfamate esters *p*-$XC_6H_4OSO_2NHCOR$ as models for more complex, biologically important compounds has been examined. Structure-reactivity, solvent-reactivity, thermodynamic data, etc. support a bimolecular mechanism involving water in the transition state (TS).

There has been an upsurge of interest in sulfamate esters, $R^1OSO_2NR^2R^3$, and sulfamides, $R^1R^2NSO_2NR^3R^4$, both cyclic and open chain, in the last decade or so and this is mainly, though not entirely, because of their many potential and proven uses in medicinal and biological chemistry.[1–3] So extensive is the interest in the sulfamate group in particular that it has become something of an ubiquitous group in chemistry.

Certain biomolecules possessing closely related moieties, such as the *N*-(oxycarbonyl)sulfamate esters, $–OSO_2NHCOO–$ and the *N*-(carbonyl)sulfamate esters, $–OSO_2NHCO–$, have also been shown to be very important in biological chemistry and a very thorough mechanistic study of a series of the former type of esters was made some years ago.[4] The latter class, which are broadly *N*-acylsulfamates, include the important lipid-regulating and anti-atherosclerotic agent Avasimibe **1**.[5] (Fig. 1), which reached phase III of clinical trials, the sulfamate esters **2a**–**e**, which are competitive inhibitors of the pantothenate synthetase-catalysed condensation of D-pantoate and β-alanine to form pantothenate,[6] several methionyl- and isoleucylsulfamates, which inhibit methionyl-tRNA and isoleucyl-tRNA synthetases,[7] a β-aspartyl-AMP sulfamate,[8] which inhibits human asparagine synthetase and a sulfamate analogue of luciferyl-AMP, which inhibits firefly luciferase.[9] Recently, a phosmidosine analogue, in which the proline and 8-oxoadenosine moieties are linked by an acylsulfamate bridge, has been prepared.[10] Some years ago a number of acyl derivatives of EMATE, the steroidal sulfatase inhibitor, were prepared but were generally found to be less potent than the parent compound.[11]

Despite its obvious importance, the chemistry of the acylsulfamate group has not been explored and in the



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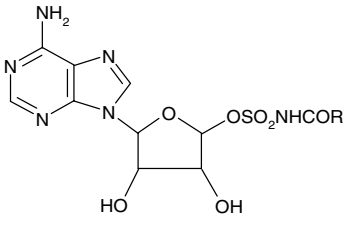

2 **a**: R = *t*-BuCO-
b: R = $MeO(CH_2)_2CHOH$-
c: R = $MeOCH_2C(CH_3)_2CHOH$-
d: R = *t*-BuCHOH-
e: R = *t*-$BuCH(NH_3^+)$-

Figure 1. Examples of biologically important *N*-acylsulfamates.

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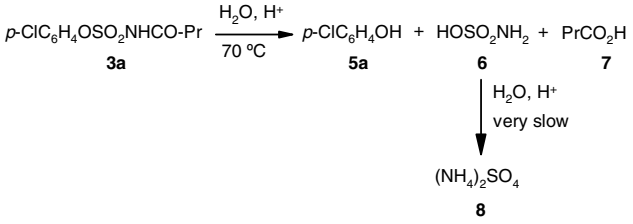
current work we have studied, particularly in acidic media, the hydrolysis of a series of aryl-substituted *N*-acylsulfamates, $XC_6H_4OSO_2NHCOR$, (R = Pr) **3**.

We prepared a series of *N*-acyl- and N-sulfonylated sulfamates of types $R^1OSO_2N(ArCH_2)COR^2$ and $R^1OSO_2N(ArCH_2)SO_2R^2$, respectively, by benzoylation/sulfonylation of the monoesters[12] but since these compounds lacked a hydrogen on the nitrogen, they were rather unreactive. More recently, because of the potential of sulfamate esters as sweeteners,[13] we have prepared several series of mainly new acylsulfamates of the general type $p\text{-}XC_6H_4OSO_2NHCOR$, including the seven compounds where R = Pr and X is **a**: Cl, **b**: Br, **c**: I, **d**: F, **e**: H, **f**: CH_3, **g**: CF_3 using general methods.[14,15]

Since several modes of cleavage could be envisaged for the acid-catalysed hydrolysis of acylsulfamates **3**, a product study was carried out using the *p*-Cl compound **3a** and this was found to hydrolyse according to the pathway shown in Scheme 1 giving rise to products **5a**, **6** and **7**. Compound **8** does not form under the kinetic conditions used, but would form under more forcing conditions.

The rates of production of *p*-chlorophenol **5a** (UV measurements) and of *n*-butyric acid **7** (GC measurements) were almost identical. Thus there is concomitant breakage of the S–O and the C–N bonds in **3a**. In aqueous acid sulfamic acid **6** decomposes much more slowly, but it eventually produces the quantity of sulfate **8** expected from a known amount of **3a**. A number of groups have studied the acid-catalysed hydrolysis of sulfamic acid in various acids and over a range of temperatures.[16–18] At 70 °C, the temperature at which most rate studies were carried out in this work, in 1 M acid a half-life of 34.7 h was determined for the hydrolysis of sulfamic acid.[17] The half-lives of compounds **3** to give sulfamic acid, phenol and *n*-butyric acid (Scheme 1) vary from 0.65 to 1.6 h so hydrolysis of the sulfamic acid is very slow and is not an issue in the time scale of the kinetic runs.

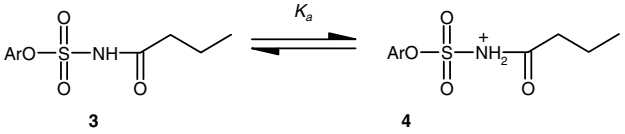


Scheme 1. Hydrolysis pathway.

Partial H_o/pH-rate profiles for compounds **3** have been determined (Fig. 2). These rate profiles show that acid-catalysis ceases at approximately pH 0.5, at which point the substrate should be substantially protonated. Apparent pK_as for the equilibrium in Scheme 2 for **3a**–**f** can be obtained from the pH-rate profiles[19] and values between 0.5 (**3a**) and 0.8 (**3f**) were calculated. A value could not be obtained for **3g** since it did not show the curvature that characterises the other plots.

When the pK_a values were plotted against Hammett δ values, a ρ value of −0.61 ($r = 0.981$) was obtained. This ρ is much lower than that for the protonation of arylsulfonamides, $ArSO_2NR_2$ (R = H, Me), which gave a value of ∼−2 for two limited series.[20] This is due to the extra oxygen atom between the aryl-substituents and the protonation site in compounds **3** compared to the arylsulfonamides. Since the effects are principally inductive, the insertion of an extra atom or group can cause a dramatic falling off in ρ, for example, the protonation of substituted anilines has a ρ of about −2.7, while that of a series of ring-substituted benzylamines is about −0.7.[21]

Structure-reactivity effects were examined by studying the effect of varying the substituents (X) in compounds **3** in 1 M HCl at 70 °C on the rates of reaction. Hammett (Fig. 3) and Brönsted (Fig. 4) plots, respectively,



Scheme 2.

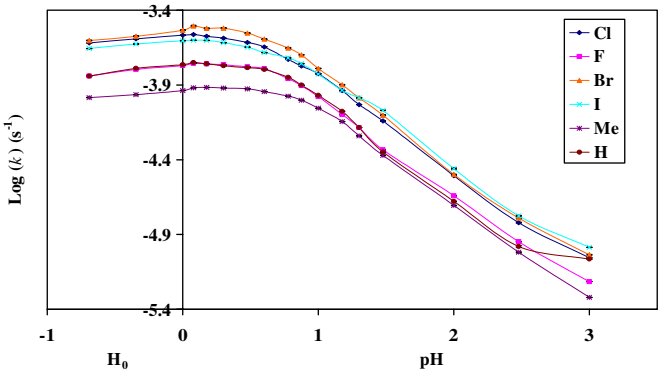


Figure 2. Partial H_0/pH rate profiles of **3a** to **3f**.

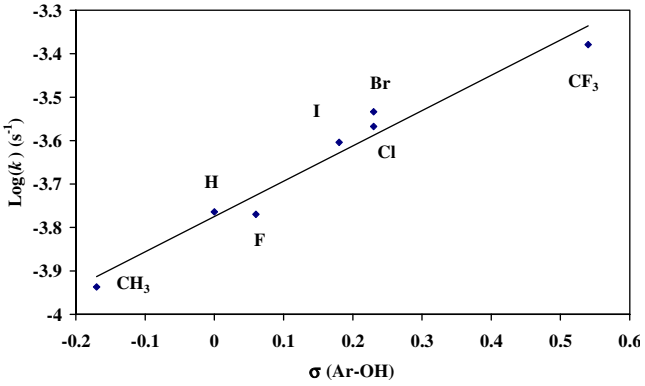


Figure 3. Hammett plot of the leaving group in the hydrolysis of **3a**–**g**.

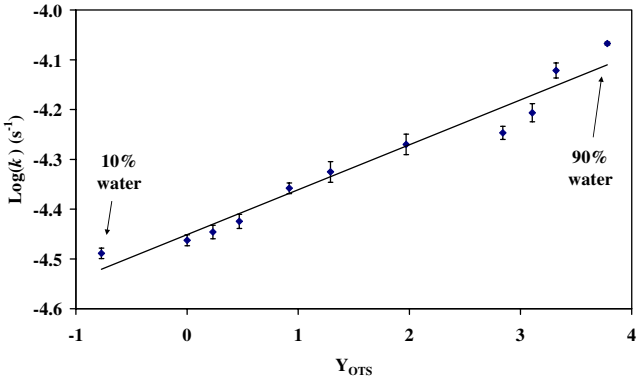


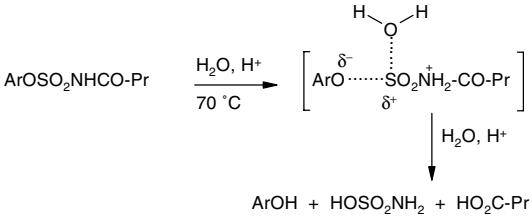
Figure 5. Grunwald–Winstein plot of the hydrolysis of **3a**.

illustrate these effects. A Hammett ρ of 0.81 ($r = 0.986$) and a β_{lg} of -0.27 ($r = 0.971$) were obtained for seven compounds.

Solvent-reactivity effects were looked at by changing the water–ethanol ratio of the medium from 10% to 90% in 0.1 M HCl at 65 °C, and the rates for the hydrolysis of **3a** were plotted against Grunwald–Winstein Y_{OTS} values[22] giving the plot shown in Figure 5. This gives a slope, m, of 0.09 ($r = 0.973$) which is very low and points to the minimal effect of the ionizing power of the solvent, suggesting instead that a water molecule plays an important role as a nucleophile in the TS.

The substantially negative entropies for the hydrolysis measured at various temperatures are given in Table 1 for **3a**–**g** compounds and they also suggest that the TS includes a water molecule. The larger value for the strongly electron-withdrawing CF_3 compound may arise from stronger binding of water in its TS compared to the other compounds.

The accumulated evidence from the above studies indicates that at low pH 0–1 the mechanism involves attack of a water molecule at the protonated substrate **4**, which will be substantially present at these pHs. The β_{lg} value of -0.27 supports a small degree of cleavage of the



Scheme 3. Proposed reaction mechanism.

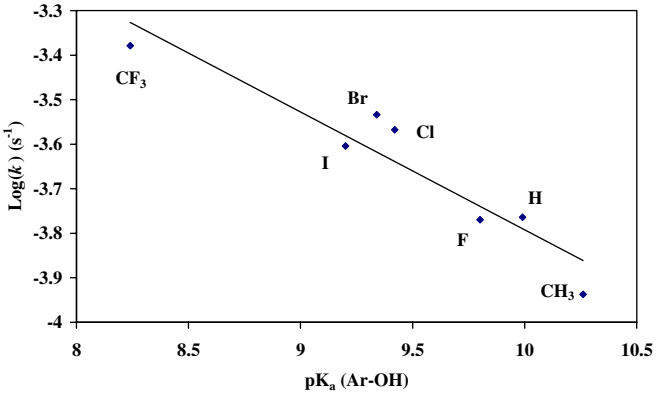


Figure 4. Brönsted plot (β_{lg}) of the hydrolysis of **3a**–**g**.

Table 1. Activation parameters for the acid-catalysed (1 M HCl) hydrolysis of *p*-X-phenyl-*N*-(*n*-propylcarbonyl)sulfamates (**3a** to **3g**)[a]

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}
CF_3	88.7 ± 5	−53.5 ± 3	F	100.4 ± 6	−14.5 ± 1
Br	100.4 ± 6	−22.5 ± 1	H	101.4 ± 5	−23.3 ± 2
I	99.4 ± 5	−26.3 ± 2	CH_3	104.0 ± 6	−20.0 ± 1
Cl	98.6 ± 5	−28.3 ± 2			

[a] Eyring plots (correlation coefficients >0.99) using seven points at temperatures between 40 °C and 70 °C. The errors shown are standard deviations.

O–SO_2 bond in the TS and the ρ value of 0.81, while small, points to the development of some negative charge at the phenolic oxygen during reaction. The thermodynamic results together with the low Grunwald–Winstein *m* value are consistent with the participation of water in the TS and a plausible S_N2 or as the compounds are esters this could be described as an A-2 reaction mechanism as shown in Scheme 3.

Acknowledgements

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