The Anionic Sulphonylamine Mechanism in the Hydrolysis of Aryl Sulphamates

Sergio Thea,[a]* Giorgio Cevasco,[a] Giuseppe Guanti,[a] and Andrew Williams[b]

[a] *Istituto di Chimica Organica dell'Universitá, C.N.R., Centro di Studio sui Diariloidi e loro Applicazioni, Corso Europa 26, Genova, Italy*

[b] *University Chemical Laboratory, Canterbury, Kent CT2 7NH, U.K.*

Evidence from studies on reactivity, linear free energy relationships, trapping with an amine, and activation data indicates that the unprecedented anionic sulphonylamine (**2**) is involved in the alkaline hydrolysis of aryl sulphamates.

The existence of a neutral sulphonylamine intermediate has been demonstrated in the hydrolysis of aryl *N*-methylsulphamates;[1] the present work confirms the existence of the parent sulphonylamine (**1**) and provides firm evidence for the involvement of the anionic sulphonylamine (**2**) in the alkaline hydrolysis of aryl sulphamate esters (**3**)† in aqueous solution.

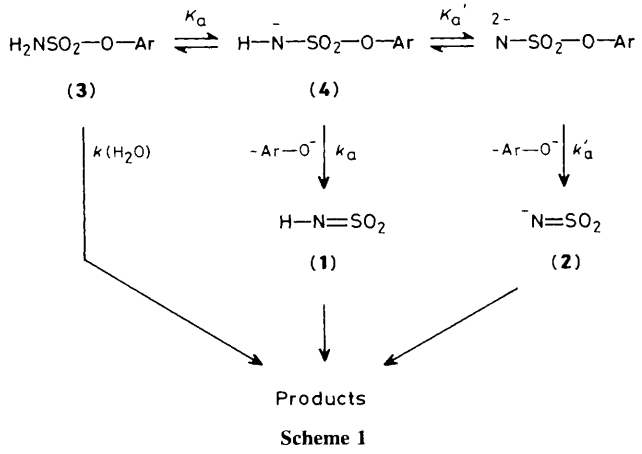
The hydrolyses of aryl sulphamates (**3**) in aqueous buffers obey excellent pseudo-first order kinetics up to at least 80% of the total reaction. No buffer catalysis is detected even when nucleophilic buffers such as ammonia or glycine are employed in the hydrolysis of the 4-nitrophenyl ester. The pH-dependence of the hydrolysis of the 4-nitrophenyl ester is shown in Figure 1 (line a). There is no inflexion due to the ionisation of the sulphonamido group although this has a pK_a, measured spectrophotometrically, of 7.29; this interesting phenomenon occurs because the hydrolysis of the aryl esters obeys the kinetic expression given in equation (1), where the values of k_a, k_b, and K_a combine to give an apparently linear plot in the ionisation range, as shown in Figure 1 for the 4-nitrophenyl ester.

$$k_{obs} = k(H_2O) + (k_a + k_b[OH^-])/(1 + [H^+]/K_a) \quad (1)$$

Three mechanistic paths giving rise to kinetic parameters $k(H_2O)$, k_a, k_b take the major part of the reaction flux at respectively low, intermediate, and high pH. The $k(H_2O)$ path probably derives from bimolecular attack of water on the neutral ester as seen for related substrates.[2]

The hydrolytic path corresponding to the K_a parameter involves ionisation of the neutral ester followed by rate-limiting decomposition of the conjugate base (**4**) to sulphonylamine (**1**) which rapidly adds water or nucleophile to give products. The apparent second order rate constant for bimolecular attack of hydroxide ion on the neutral 4-nitrophenyl ester ($k_aK_a/K_w = 3.9 \times 10^3$ mol^{-1} dm^3 s^{-1}) would be some 9 orders of magnitude larger than that for the known bimolecular attack of hydroxide ion on 4-nitrophenyl *N*,*N*-dimethylsulphamate (2.4×10^{-6} mol^{-1} dm^3 s^{-1}).[1] Such a large difference cannot be accounted for on steric grounds alone. The absence of buffer catalysis and the magnitude of the sensitivity of k_a to the leaving group ($p K_a$ ($\beta_{lg} = -1.2$) are consistent with the *E1cB* process (Scheme 1).

The parameter k_b ($= k_a'K_a'/K_w$) arises from the ionisation of the monoanion (**4**) to give a dianion which then decomposes unimolecularly to the anionic sulphonylamine (**2**) in a rate limiting step (Scheme 1). The apparent second-order rate constant (k_b) for hydroxide ion attack on the anion of the 4-nitrophenyl ester (**4**) is 9 orders of magnitude larger than that of hydroxide ion on the corresponding *N*,*N*-dimethylsulphamate ester. This value is a lower limit because the anion–anion electrostatic repulsion effect is neglected in the



Scheme 1

† Esters were prepared from substituted phenols and chlorosulphonyl isocyanate by standard procedure; structures were confirmed by n.m.r. and i.r. spectroscopy and by elemental analysis.

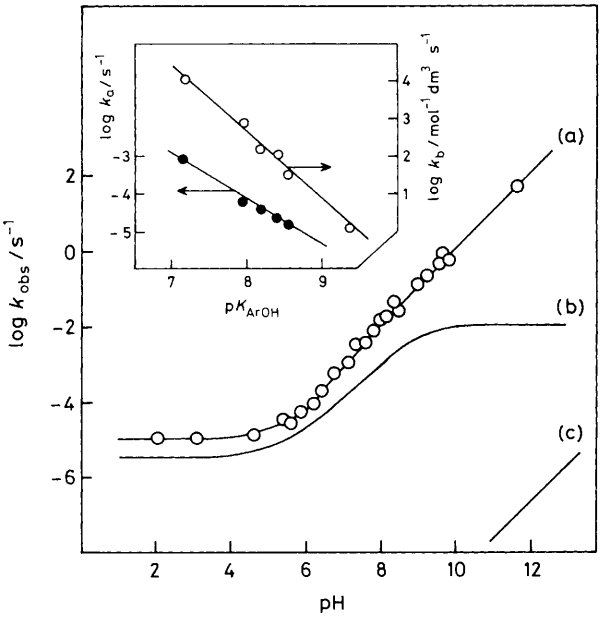


Figure 1. Dependence on pH of the hydrolysis of 4-nitrophenyl sulphamate in aqueous solution at 25 °C and ionic strength made up to 1 M with KCl. The line (a) is calculated from equation (1) with the parameters: $k(H_2O)$, 9.85×10^{-6} s^{-1}; k_a, 7.71×10^{-4} s^{-1}; k_b, 1.1×10^4 mol^{-1} dm^3 s^{-1}; K_a, 5.11×10^{-8} M. Line (b) is the pH-dependence of the hydrolysis of 4-nitrophenyl *N*-methyl sulphamate (data from ref. 1), and line (c) is the pH dependence of the hydrolysis of *N*,*N*-dimethyl sulphamate ester (data from ref. 1).

Inset: Brønsted dependence of k_a and k_b; linear regression equations relevant to this work are:

$\log k_a = (5.43 \pm 0.55) - (1.20 \pm 0.07)\ pK_{ArOH}$

$\log k_b = (16.9 \pm 0.5) - (1.79 \pm 0.06)\ pK_{ArOH}$

$pK_a = (5.32 \pm 0.43) - (2.67 \pm 0.05)\ pK_{ArOH}$

neutral ester analogue.[3,4] Activation parameters for k_b for the 4-nitrophenyl ester are $\Delta H^{\ddagger}$ = 15.2 kcal mol^{-1} and $\Delta S^{\ddagger}$ = +11.6 cal K^{-1} mol^{-1} at 25 °C, consistent with a dissociative route. The parameter k_b is very sensitive to the pK_a of the phenol leaving group (β_{lg} = −1.79) indicating considerable negative charge on the oxygen in the transition-state of the rate limiting step. Alkaline hydrolysis of aryl benzenesulphonates is an associative process and possesses a much lower β_{lg} (−0.78)[5] than does k_b. Although added *p*-toluidine had no effect on the rate of 4-nitrophenol release from 4-nitrophenyl sulphamate at pH 9.11 (where k_b term is the major contributor to reactivity), product analysis using ^{1}H n.m.r. spectroscopy showed that, in the presence of 23 mM amine, all the sulphamate is converted into *p*-tolylsulphamide. This result is consistent with attack of *p*-toluidine on an intermediate ($^-$N=SO$_2$) *after* *p*-nitrophenol liberation.

The existence of the sulphonylamine intermediates demonstrated in the present work is of interest owing to their analogy to metaphosphate ion and sulphur trioxide, which are putative intermediates in phosphoryl- and sulphuryl-group transfer reactions possessing dissociative nature.

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