The quest for sulfoquinone imine intermediates in the reaction of sulfanilic acid derivatives with nucleophiles

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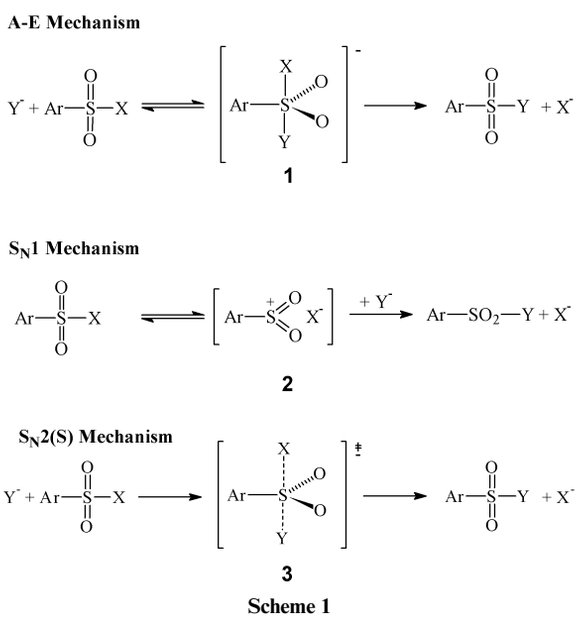
Data from kinetic and trapping studies suggest that the alkaline hydrolyses of sulfanilyl chloride and of the corresponding *N*-acetyl derivative follow different reaction pathways. While results for the latter compound are fully consistent with the occurrence of the common associative, S_N2 mechanism, the former shows somewhat different features suggesting the incursion of a mechanism of the dissociative type involving a sulfoquinone imine species as a reaction intermediate. The alkaline hydrolyses of the corresponding sulfonyl fluorides and 2,4-dinitrophenyl esters, whose leaving groups are worse than Cl^- as leaving groups, are all associative.

Introduction

Nucleophilic substitution reactions of arenesulfonyl halides and related compounds may be envisaged as processes in which a sulfonyl residue migrates from a donor, the nucleofuge X, to an acceptor, the nucleophile Y^-.

Three major types of mechanisms have been proposed for this reaction (Scheme 1).[1]



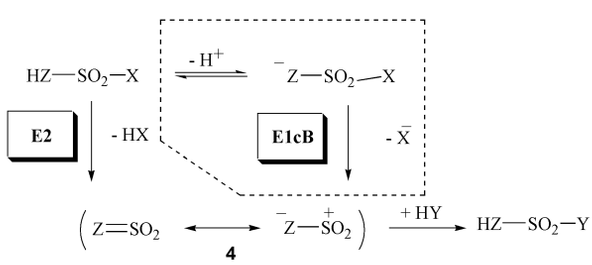
Scheme 1

i) Addition of Y^- at sulfur to yield the trigonal bipyramidal intermediate **1**, followed by departure of X^- (associative, addition–elimination or S_AN mechanism).

ii) Heterolysis of the S–X bond generating the sulfonylium cation **2**, which eventually reacts with the nucleophile Y^- (dissociative, elimination–addition, S_N1 mechanism).

iii) Concerted displacement of X^- *via* the trigonal bipyramidal transition state **3** (associative, concerted S_N2 mechanism). This can be considered, in principle, as an intermediate mechanism between the two previous ones, and it is now generally accepted that this mechanism is the most commonly occurring one in sulfonyl transfer reactions by far.

As regards the S_N1 mechanism, a particularly favourable situation takes place when the highly unstable sulfonylium cation **2** gains stabilisation by virtue of an adjacent group Z capable of neutralising the positive charge on sulfur because of the presence on it of one, or more, unshared pairs of electrons and a negative charge (Scheme 2). This is the E1cB mechanism,



Scheme 2

whose prerequisite is the presence, adjacent to the sulfur, of an acidic function HZ which ionises to yield the substrate conjugate base, from which the leaving group is subsequently expelled affording a sulfene species **4**. Following this, rapid addition of the nucleophile HY to **4** usually occurs giving rise to the substitution product. Under specific circumstances (namely, a very efficient leaving group X, or an internal strong nucleophilic centre Z^-, or both are present in the substrate) the conjugate base will not be able to exist as a discrete species any more; therefore, overall elimination of HX will take place in a single step, and the entire process will be of the E2 type. Both these mechanisms, likewise the S_N1 one seen before, are of the elimination–addition (E–A), or dissociative type.

As part of our long-term interest in this field, we have been looking for systems capable of reacting through dissociative pathways, despite the fact that their acidic centre is remote from the reaction centre. Extensive studies on the alkaline hydrolysis

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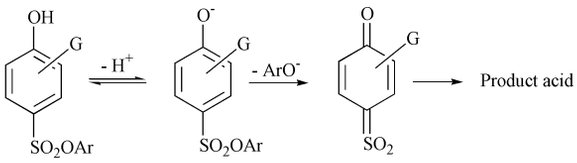
of a number of aryl hydroxybenzene-*p*-sulfonates revealed that a dissociative mechanism involving the unprecedented quinonoid sulfene species **5** shown in Scheme 3 takes place, showing



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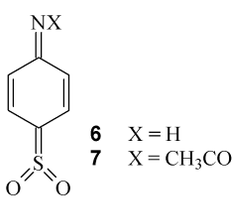
Scheme 3

that the phenoxide ion group is extremely efficient as the internal nucleophilic centre.[2]

However, it is also conceivable that other lone pair donor HZ groups may behave as internal nucleophilic centres, either in their neutral or ionised form, giving rise, respectively, to dissociative mechanisms of the S_N1 type (by virtue of intermediate stabilization by charge delocalisation) or of the E1cB type (on account of intermediate stabilisation by charge neutralization). In order to better understand the rôle played by the nature of the internal nucleophile on the E1cB mechanism of the arenesulfonyl group transfer, we have carried out an investigation into the alkaline hydrolysis of 2,4-dinitrophenyl esters as well as halides (*i.e.*, chlorides, fluorides) of sulfanilic and *N*-acetylsulfanilic acid. Our aim was to check if, in alkaline solution, *p*-amino and *p*-acetylamino groups could divert the arenesulfonyl group transfer mechanism from the usually occurring S_N2 to a dissociative one. In that case, the sulfoquinone imines **6** and **7** could be involved as reaction intermediates.



6 X = H
7 X = CH_3CO

Actually, reports on these species can be found in the literature. It was claimed, indeed, that the yellow colour arising from a strong absorption band with a maximum at 426 nm, which quickly developed on dissolving sulfanilyl chloride in pyridine, was due to accumulation of **6** in solution. This species was described as 'stable', since it seemed to disappear quite slowly to give poly(*p*-benzenesulfonamide).[3]

A subsequent, careful reinvestigation of this reaction, however, has shown that this claim was in error.[4] However, since, sometimes, the rôle played by solvent polarity may be crucial in governing the choice of the mechanism of the sulfonyl transfer process, the possibility that in aqueous alkaline solution the S_N1–E1cB mechanism, rather the commonly observed $S_N2(S)$ one, might take place, is still open.

Results and discussion

The alkaline hydrolyses of the 2,4-dinitrophenyl esters of sulfanilic and *N*-acetylsulfanilic acid were first investigated. Excellent pseudo-first order kinetics were followed over at least 90% of the entire reaction in the pH range employed. Second-order rate constants (which represent reactivity towards hydroxide ions) and Arrhenius parameters are shown in Table 1. For the sake of comparison, data taken from the literature for two model substrates, *i.e.* the 2,4-dinitrophenyl esters of benzenesulfonic acid and 3,5-dimethyl-4-hydroxybenzenesulfonic acid are also shown. Comparison of reactivity and activation entropy data reveals that there is strict similarity between the first two substrates and the benzenesulfonate, whose alkaline hydrolysis follows a S_N2 mechanism, rather than with the 4-hydroxybenzenesulfonate, which has been shown to react *via* an E1cB pathway.[2a,b] In other words, according to the well known reaction sensitivities for sulfonyl transfer reactions and substituent constants for the *p*-amino and *p*-acetylamino groups, electron releasing substituents in the acyl moiety such as the 4-amino group (either neutral or ionised) and the more acidic 4-acetylamino group are expected to increase reaction rates significantly if a dissociative route is followed. In contrast, a decelerating effect should be observed if an associative mechanism was occurring, as found in the present case. Also the observation of a negative, high value of the activation entropy is fully consistent with this hypothesis. Indeed, in sulfonyl transfer reactions, strongly negative activation entropy values are typical of associative mechanisms. In contrast, positive or, sometimes, low negative values are commonly found when dissociative mechanisms are followed.[1]

Aiming at enforcing the system under study to react through dissociative pathways, we directed our interest to the more reactive sulfonyl fluorides and chlorides. It is well known, indeed, that the dissociative mechanisms are strongly favoured over the associative ones as the nucleofugality of the leaving group increases.[5] Rate constants for the alkaline hydrolysis of chlorides and fluorides of sulfanilic and *N*-acetylsulfanilic acid are shown in Table 2, as well as ratios between them. For the sake of comparison, data are also shown for toluene-*p*-sulfonyl and phenylmethanesulfonyl chlorides and fluorides, which are models for the associative and dissociative mechanisms respectively. Since, as stated before, sensitivity to leaving group basicity is much higher for the dissociative than for the associative mechanisms, rate ratios are expected to be significantly higher for the former than for the latter ones: these ratios, therefore, may represent a useful mechanistic probe.

As regards *p*-acetylaminosulfanilyl halides, the chloride to fluoride reactivity ratio is virtually the same (3.4) as that (3.7) found for the tosyl derivatives (which hydrolyse through the associative, $S_N2(S)$ mechanism) and it is much lower than the one (45) related to the two phenylmethanesulfonyl halides, which have been suggested to react through a dissociative mechanism, most probably an 'asynchronous' E2.[6] In the case of the two sulfanilyl halides, the reactivity ratio is 700, and this value is even higher than the one found for the corresponding two phenylmethanesulfonic acid derivatives. Clearly, this outcome is not consistent with sulfanilyl chloride reacting through the $S_N2(S)$ mechanism. Comparison of the rate constants within each group of arenesulfonyl halides (*i.e.*, chlorides and fluorides) further substantiates this conclusion. The reactivity order found for fluorides (*p*-AcNH > *p*-Me > *p*-NH_2) is fully consistent with the occurrence of the associative, $S_N2(S)$ mechanism (for which the Hammett ρ constant is positive).[7] The same is not found in the chloride series, where the reactivity order is *p*-NH_2 > *p*-AcNH > *p*-Me. Once again, this fact suggests that, unlike sulfanilyl fluoride, sulfanilyl chloride decomposes in alkaline solution through a pathway different from that followed by the other two members of the same group.

In order to gain a better understanding of this point, we resorted to competition experiments, in which sulfanilyl and *N*-acetylsulfanilyl chlorides were allowed to react with excess, equimolar amounts of isopropylamine (Pr^iNH_2) and *tert*-butylamine (Bu^tNH_2). Our idea was that, owing to their different steric requirements, the associative, $S_N2(S)$ mechanism would involve larger discrimination between the two amines than the dissociative one. Indeed, steric crowding at the nucleophilic centre would be hardly felt when amine attacks the highly reactive, planar sulfene-type intermediate as compared to the much less reactive, more hindered tetrahedral sulfonyl chloride.

To find support for this idea we have carried out this experiment also on toluene-*p*-sulfonyl and phenylmethanesulfonyl chloride, which, as already stated before, react *via* the

Table 1 Second-order rate constants (T = 25 °C) and activation parameters[a] for the alkaline hydrolysis of some 2,4-dinitrophenyl esters of substituted benzenesulfonic acids

Substituent	k_{OH}/mol^{-1} dm^3 s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}
4-Amino[b]	8.6×10^{-2}	14.3 ± 0.2	−19.8 ± 0.6
4-Acetylamino[b]	1.0	13.3 ± 0.1	−18.8 ± 0.2
None	2.0[c]	11.3[d]	−19.2[d]
3,5-Dimethyl-4-hydroxy[e]	4.7×10^4	21.4 ± 0.5	+1.7 ± 1.6

[a] Values referring to the 4-amino- and 4-acetylamino substituted derivatives were calculated from rate data at three temperatures in the range 17.3–34.5 °C. [b] Solvent: water, ionic strength (I) was kept up at 0.1 mol dm^{-3} with KCl. [c] Solvent: 20% dioxane–water (v/v), I was kept at 0.2 mol dm^{-3}. [d] Solvent: 70% dioxane–water (v/v); calculated from rate data taken from ref. 12. [e] Solvent: 20% dioxane–water (v/v), I was kept at 1.0 mol dm^{-3} with KCl. Data are taken from ref. 2*b*.

Table 2 Alkaline hydrolysis of some substituted benzene- and phenylmethanesulfonyl chlorides and fluorides. Solvent: water (unless otherwise stated), T = 25 °C

Sulfonyl halide	[OH$^-$] range/mol dm^{-3}[a]	k_{OH}/dm^3 mol^{-1} s^{-1}	Chloride : fluoride reactivity ratio
p-$NH_2C_6H_4SO_2Cl$	5.7×10^{-5} – 3.2×10^{-3}	260 ± 20[b]	700
p-$NH_2C_6H_4SO_2F$	1×10^{-3} – 0.001	0.37 ± 0.01[c]	
p-$CH_3CONHC_6H_4SO_2Cl$	2×10^{-3} – 0.1	20.9 ± 0.1[c]	3.4
p-$CH_3CONHC_6H_4SO_2F$	5×10^{-3} – 0.1	6.2 ± 0.3[c]	
p-$CH_3C_6H_4SO_2Cl$	2×10^{-3} – 0.01	18.8 ± 0.3[c]	3.7
p-$CH_3C_6H_4SO_2F$	5×10^{-3} – 0.1	5.1 ± 0.3[c]	
$C_6H_5CH_2SO_2Cl$	—	2.6×10^{-3}[d]	45
$C_6H_5CH_2SO_2F$	—	5.8×10^{-5}[d]	

[a] Buffers (phosphate, carbonate) were employed to keep hydroxide ion concentration constant when lower than 10^{-2} mol dm^{-3}. [b] Solvent: aqueous dioxane 21.4 % (v/v), ionic strength (I) was kept at 1.0 mol dm^{-3} with KCl. The choice of this solvent composition was imposed by the use of the rapid kinetic accessory cited in the Experimental section. The pK_w value of 14.62 for 20% aqueous dioxane used for calculating the [OH$^-$] values is from ref. 13. [c] I was kept at 0.1 mol dm^{-3} with KCl. [d] I was kept at 1.0 mol dm^{-3} with NaCl. Data are from ref. 6.

associative and the dissociative routes respectively. As far as these two model substrates are concerned, our expectations were nicely fulfilled.

Indeed, either in aqueous or in pure acetonitrile toluene-*p*-sulfonyl chloride shows strong preference for Pr^iNH_2; in contrast, phenylmethanesulfonyl chloride exhibits only a small preference for the less hindered amine, consistent with the participation of a sulfene species in the reaction. It is interesting to note, however, that, on going from the highly polar aqueous acetonitrile to the less polar acetonitrile, selectivity increases considerably. This observation is in line with the results of Skripnik *et al.*,[8] who found that in the pyridine-catalysed phenolysis of phenylmethanesulfonyl chloride in organic solvents spanning a broad range of medium polarity, although both the elimination–addition and the addition–elimination mechanisms are followed competitively, the contribution of the former increases sharply as solvent polarity increases.

As far as *N*-acetylsulfanilyl chloride is concerned, it appears that its selectivity features are almost the same as those of *p*-tosyl chloride, *i.e.*, the mechanism is $S_N2(S)$ under these conditions too. Therefore, it can be concluded that the *p*-acetylamino group is unable to feed the E–A mechanism, even in the very favourable reaction conditions we made use of (*i.e.*, strong alkaline solution, very good leaving group). In contrast, depending on solvent polarity, sulfanilyl chloride responds in different ways to the steric hindrance of the nucleophile: whereas selectivity is as high as that of the corresponding acetyl derivative (as well as that of tosyl chloride) in pure acetonitrile, in aqueous acetonitrile it becomes considerably lower, thus getting closer to that found for phenylmethanesulfonyl chloride. This finding, as well as those discussed previously, is not consistent with an associative route being followed. Incursion of a pathway having the characteristics of a dissociative mechanism is a reasonable possibility.

Whether it is a proper E2 (or, perhaps, S_N1) mechanism or an 'exploded' S_N2 process, as suggested for the solvolysis of sulfanilyl chloride in 20% aqueous acetic acid,[9] is still an open question.

It is likely that widening of the pH range explored so far, as well as performing accurate measurements of the activation parameters (in particular $\Delta S^{\ddagger}$), which is made difficult by the exceedingly high reactivity under the present experimental conditions, will throw light on this matter.

Experimental

General

Starting reagents were of analytical reagent grade or were redistilled or recrystallized from bench quality materials. Deionised water was glass distilled and preboiled immediately prior to use to free it from dissolved carbon dioxide. Acetonitrile (Fluka, UV spectroscopic grade) was stored over 4 Å molecular sieves. Dioxane (Aldrich, spectrophotometric grade) was freed from peroxides by passage through an activated alumina column, and the absence of peroxides was assessed by the KI test. UV–Vis spectra were taken either with a Perkin–Elmer 554 or a Kontron Uvikon 941 spectrophotometer. The ^{1}H NMR spectra were recorded with a Varian Gemini 200 spectrometer (200 MHz) with TMS as internal standard and $CDCl_3$ as solvent. TLC on Merck silica-gel precoated plates (eluant: $CHCl_3$) was routinely used to follow the progress of the reactions and to check preliminarily the composition of the final reaction mixtures in competitive experiments. Methods reported in the literature were employed for the synthesis of the sulfonyl chlorides[3,6,9,10] and fluorides,[6,11] investigated here. The 2,4-dinitrophenyl sulfonates were prepared from the corresponding sulfonyl chlorides and 2,4-dinitrophenol through standard methods; 2,4-dinitrophenyl sulfanilate, which had not been described previously in the literature, had mp 185 °C (from EtOH). Found: C, 42.3; H, 2.7; N, 12.2. $C_{12}H_9N_3O_7S$ requires C, 42.5; H, 2.7; N, 12.4%. Model amide products were prepared by reacting excess amine (either isopropyl or *tert*-butyl) with the appropriate sulfonyl chloride in acetonitrile; ^{1}H NMR spectra were fully consistent with their structures.

Table 3 Ratios of the sulfonamide products [y^i/y^t = yield(RSO_2NHPr^i)/yield(RSO_2NHBu^t)] from competitive reactions of RSO_2Cl with Pr^iNH_2–Bu^tNH_2. Conditions: $[RSO_2Cl] = 0.1$ mol dm^{-3}, $[Pr^iNH_2] = [Bu^tNH_2] = 1.0$ mol dm^{-3}

	y^i/y^t	
R	17% aqueous CH_3CN	100% CH_3CN
4-Aminophenyl	7.3	19
4-Acetylaminophenyl	19	24
p-Tolyl	17	25
Benzyl	1.4	2.6

Rate measurements

The technique generally employed for measuring reaction rates has already been described previously.[2] A SFA-11 Rapid Kinetic Accessory (HI-TECH SCIENTIFIC Ltd.) coupled with the Kontron Uvikon 941 machine was employed to follow sulfanilyl chloride hydrolysis, as reaction rates were exceedingly fast to measure by standard procedures.† Reactions were monitored by following either the absorbance decrease due to substrate consumption (sulfonyl chlorides and fluorides) or the increase, due to liberation of 2,4-dinitrophenoxide ion (2,4-dinitrophenyl sulfonates).

Competitive experiments

Competitive reactions were carried out by adding at 0 °C the sulfonyl chloride (either as an acetonitrile solution or a finely powdered solid) to an equimolar mixture of Pr^iNH_2 and Bu^tNH_2 (1 M in each amine) in pure acetonitrile, or aqueous acetonitrile, or water. When necessary, appropriate volumes of acetonitrile and water were employed to yield 17% aqueous acetonitrile as the final solvent mixture. In all cases, each amine was in a 10-fold molar excess with respect to the substrate. After reaction completion (as assessed by TLC) the mixture was rotaryevaporated to dryness under reduced pressure, the white solid was washed once with dilute HCl and twice with water, and finally dried under vacuum. The product mixture was examined by ^{1}H NMR spectroscopy with the aid of pure samples of the corresponding pair of amide products. The $NHPr^i$: $NHBu^t$ product ratios (y^i/y^t in Table 3) were evaluated from the relative areas of peaks of the methyl groups of the *N*-isopropyl arenesulfonamides (δ_H 1.08, d) and of the *N*-*tert*-butyl arenesulfonamides (δ_H 1.22, s); in the case of isopropyl and *tert*-butyl phenylmethanesulfonamides these signals were shifted to δ_H 1.16 and 1.36 respectively

† As shown by preliminary experiments, sulfanilyl chloride and the corresponding hydrochloride exhibited, as expected, identical behaviour in the basic solutions used for experiments. The hydrochloride is easier to prepare than the free base and can be stored in a desiccator without decomposition even for a long period of time. Furthermore, as it is soluble enough either in acetonitrile or dioxane, stable stock solutions for rate measurements and trapping experiments can be prepared easily. For this reason, in most experiments, the hydrochloride was employed instead of the free base.

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