Sulfonyl Transfer Reactions − A Kinetic Study on the Solvolysis of *p*-(Dimethylamino)benzenesulfonyl Chloride in Aqueous Acetic Acid

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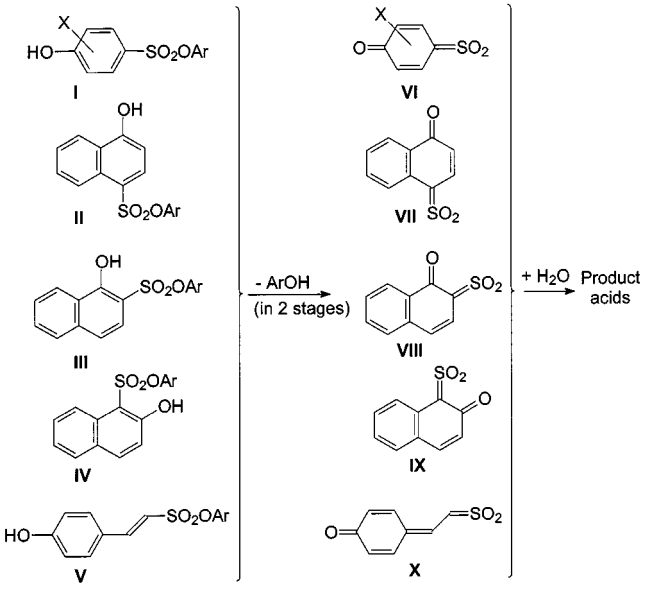
Measured activation parameters, as well as the effect on rate of adding inert electrolytes, are consistent with solvolysis of *p*-(dimethylamino)benzenesulfonyl chloride **XI** occurring through a concerted, asynchronous bimolecular mechanism, in which bond breaking takes place far ahead of bond formation in the transition state.

Introduction

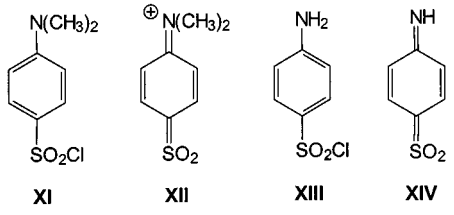
Our previous work on mechanisms of acyl transfer reactions has shown that derivatives of arenesulfonic acids bearing good leaving groups (such as nitro-substituted phenoxides) can hydrolyse in aqueous alkali by following a dissociative mechanism of the E1cB type rather than the more common, associative $S_N2(S)$-type mechanism, provided that an efficient "internal" nucleophilic centre − i.e., a powerful electron-supplying substituent, capable of stabilising the incipient sulfonylium cation − is present *para* or *ortho* to the sulfonyl group. As shown in Scheme 1, aryl phenolsulfonates **I**−**IV** (and the "extended" form **V**) have been shown, after ionisation into their conjugate bases, to hydrolyse in aqueous alkali through E1cB mechanisms involving the sulfoquinone intermediates **VI**−**X**, respectively.[1]

Solvolysis of other arenesulfonyl derivatives (e.g., 2,4,6-trimethyl-, 4-methoxy-, 2,4-dimethoxybenzenesulfonyl chlorides) had previously been proposed as occurring by S_N1 mechanisms, but these claims were subsequently disproved.[2] Solvent polarity, and also the presence of added strong nucleophilic species, however, can have some bearing on the mechanistic selection: on increasing amine nucleophilicity, a change from E1cB to $S_N2(S)$ mechanism is observed in the aminolysis of 4-hydroxy-3,5-dimethylbenzenesulfonyl chloride in acetonitrile.[3]

As far as other benzenesulfonyl chlorides possessing internal nucleophilic centres other than the hydroxy group are concerned, previously published studies on solvolysis of *p*-(dimethylamino)benzenesulfonyl chloride (**XI**) have suggested the plausibility of the occurrence of a dissociative mechanism.[4] Indeed, it has been claimed that decomposition of **XI** in 80% aqueous acetic acid takes place by an S_N1 mechanism involving the cationic sulfene intermediate **XII**. This proposal was put forward because solvolytic reactivity of **XI** was some 2200 times greater than that predicted on the basis of a Hammett correlation involving nine other, "regular" *m*- and *p*-substituted benzenesulfonyl chlorides. The observation that added sodium acetate (up to 0.5 M concentration) had a negligible effect on rate was considered to be strong additional evidence in favour of the dissociative nature of the reaction.



Scheme 1



A few years later, Forbes and Maskill carried out an investigation aimed at better definition of the factors directing competition between S_N2 and S_N1 mechanisms of sulfonyl transfer reactions. As a result, these authors suggested that solvolysis of compound **XI** in anhydrous trifluo-

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roethanol occurs through a mechanism corresponding to an "exploded" S_N2 pattern, in which bond breaking takes place well ahead of bond formation in the transition state.[5]

It is a reasonable hypothesis that the different solvents employed in the two sets of experiments could be responsible for the contrasting mechanistic conclusions.

As far as our own research is concerned, we have found that nitrogen (as part of a *p*-acetylamino or *p*-benzoylamino group) is unable to direct the reaction course toward dissociative pathways, in view of the hydrolyses of 4-nitro- and 2,4-dinitrophenyl esters of *p*-substituted benzenesulfonic acids.[1b,6] However, work in progress on the alkaline hydrolysis and aminolysis of sulfanilyl chloride **XIII** seems to suggest that in aqueous solution a dissociative mechanism proceeding through the sulfoquinone imine **XIV** might take place in competition with the $S_N2(S)$ mechanism.[7] In less polar solvents (e.g., acetonitrile) only the associative route is followed. In the light of these facts, and in order to improve our knowledge of the mechanism of this reaction, we decided to reinvestigate the hydrolysis of *p*-(dimethylamino)-benzenesulfonyl chloride in 80% aqueous acetic acid, and the effect on reactivity of addition of electrolytes.

Results and Discussion

Although suffering to some degree from ambiguity, one of the mechanistic tools generally used to distinguish between associative and dissociative pathways in sulfonyl transfer reactions is the determination of activation parameters. Comprehensive studies carried out by us on the hydrolysis of compounds closely related to those presently of interest (i.e., aryl esters of *o*- and *p*-hydroxyarenesulfonic acids[1] and *o*- and *p*-hydroxybenzoic acids[8] and their vinylogues) have provided convincing evidence that simple bimolecular processes give rise to large, negative activation entropies, counterbalanced by activation enthalpies that are relatively low in value. This can easily be explained, since the S_N2 transition state is more ordered than the reagents that are going to interact; the matching moderate value of the activation enthalpy is the result of the bond breaking involved in the leaving group departure being partly compensated by bond formation with the incoming nucleophile.

In contrast, when the acyl group transfer process is dissociative in nature, positive (or sometimes very slightly negative) values are generally found for $\Delta S^{\neq}$.

By way of example: for the hydrolysis of 2′,4′-dinitrophenyl 1-hydroxy-4-naphthalenesulfonate, $\Delta S^{\neq} = +10.8$ e.u. (solvent 20% dioxane-water, pH = 4.4).[1b] More examples are reported in refs.[1,8]

Although solvent reorganisation might well play an important role in the unimolecular expulsion of the leaving group, to the best of our knowledge its contribution to activation entropy is hardly high enough to make it as large and negative as is found in the associative processes.

Therefore, we decided to start evaluating the activation parameters for the reaction under investigation. The temperature dependencies of the pseudo-first order rate constants k_{obs} for the hydrolysis of **XI** were measured, and the rate constants and the derived activation parameters are reported in Table 1, Part A. For purposes of comparison, the reaction of sulfanilyl chloride (**XIII**) was also studied under the same conditions. Results are shown in Table 1, Part B.

Table 1. The dependence of rates on temperature, and the derived activation parameters for the solvolysis of *p*-(dimethylamino)benzenesulfonyl chloride (**XI**) (A) and sulfanilyl chloride (**XIII**) (B) in 80% aqueous acetic acid; all runs were performed in duplicate

	$10^4\ k_{obs}$ (s^{-1})	
T [°C]	A	B
18.4	16.2 ± 0.01	4.65 ± 0.02
25.0	29.3 ± 0.01	8.32 ± 0.03
35.1	64.2 ± 0.01	–
36.2	–	21.8 ± 0.01
	$\Delta H^{\neq}$ = 14.1 ± 0.26 kcal/mol	$\Delta H^{\neq}$ = 15.0 ± 0.26 kcal/mol
	$\Delta S^{\neq}$ = −22.9 ± 0.9 e.u.[a]	$\Delta S^{\neq}$ = −22.4 ± 0.3 e.u.[a]

[a] Calculated at 25 °C.

The relatively low value of the activation enthalpy and the large, negative value of the activation entropy suggest that the hydrolyses of both compounds might follow an associative mechanism. It is interesting to note, however, that chloride **XI** is ca. 3.5 times *more* reactive than sulfanilyl chloride; i.e., the *p*-dimethylamino group ($\sigma_p = -0.83$)[9] is a *stronger* activating group than the unsubstituted amino group ($\sigma_p = -0.57$).[9] A rough value of the Hammett sensitivity ρ as estimated from a *two-point* relationship is ca. −2.1, quite different from that reported for the associative mechanism ($\rho = +1.34$).[4] The electronic demand of the reaction is rather suggestive of a dissociative, S_N1 process, which in the transition state involves the build-up of positive charge on the sulfur atom.

In order to reconcile these apparently conflicting results, the effect on rate of adding increasing concentrations of various electrolytes (KCl, CH_3CO_2Na, $NaClO_4$) was assessed. Results are collected in Table 2, and displayed graphically in Figure 1.

Table 2. The effect of salt addition on reactivity of the sulfonyl chloride **XI**; temperature 25 °C; unless otherwise stated, no effort was made to keep the ionic strength I constant; I values, therefore, are the same as those of the salt concentration shown; in the absence of any added salt $k_{obs} = 2.93\ \ 10^{-3}\ s^{-1}$

	$10^3\ k_{obs}$ (s^{-1})			
[Salt]	CH_3CO_2Na	KCl	$NaClO_4$	CH_3CO_2Na[a]
0.10	3.44	3.59	4.01	4.98
0.20	3.99	–	–	4.94
0.30	4.33	4.22	5.52	5.11
0.40	4.87	–	–	5.13
0.50	5.03	4.75	6.61	5.03
0.75	5.91	–	–	–

[a] I was kept at 0.5 M with KCl.

Inspection of Table 2 and Figure 1 shows that, in all cases, the dependence of rate on salt concentration is virtually linear, and the accelerating effect follows the order:

$KCl \approx CH_3CO_2Na < NaClO_4$

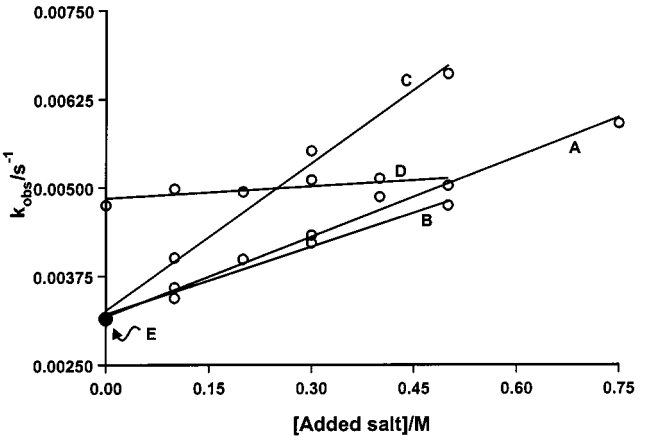


Figure 1. The effect of salt addition on reactivity in solvolysis of *p*-$(CH_3)_2NC_6H_4SO_2Cl$; solvent CH_3COOH/H_2O (80:20), T = 25 °C; legend: (A) CH_3COONa, (B) KCl, (C) $NaClO_4$, (D) CH_3COONa, I was kept constant at 0.5 M with KCl, (E) no added salt

In the protic solvent used, acetate ion is expected to be a stronger base and better nucleophile than chloride ion; nevertheless, they both have almost the same effect on rate. This is also shown by the rates being almost independent of acetate ion concentration, if ionic strength is kept constant by addition of KCl.

It is noteworthy that, despite the exceedingly weak basic and nucleophilic properties of perchlorate ion, $NaClO_4$ shows the greatest accelerating effect. These observations clearly rule out any occurrence of base catalysis, as well as nucleophilic catalysis, in this reaction.

Also the fact that rates are *lowered* by addition of perchloric acid (k_{obs} is reduced by a factor of 3.6 in the presence of 0.5 M $HClO_4$)[4] gives further support to the conclusion that a "regular" $S_N2(S)$ mechanism is not followed, since in this case, reactivity should increase as a result of the increasing concentration of protonated substrate [cf. $\sigma_p(NH_3^+) = 1.70$; $\sigma_p(NH_2) = -0.57$].[9]

Data from the literature[10] suggest that KCl and CH_3CO_2Na behave like good electrolytes in the employed solvent system, but $HClO_4$ and, quite probably, $NaClO_4$ are stronger.

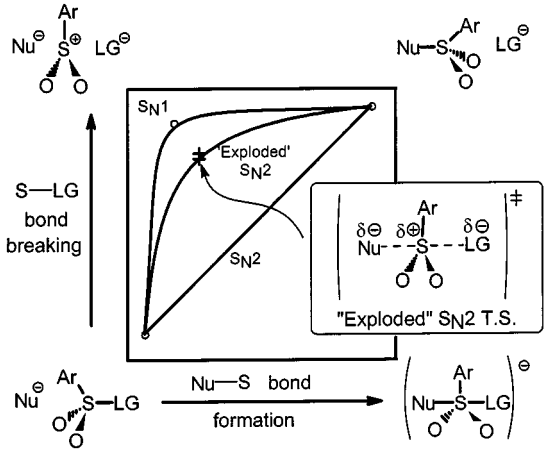
It is therefore confirmed that, while the observed rate increase is independent of the nucleophilic power of the added species, it is to some degree related to the "effective" ionic strength of the medium, to which the above salts are expected to make increasing contributions as follows:

$$KCl \approx CH_3CO_2Na < NaClO_4$$

that is the same as the observed order of the accelerating effect. In other words, the reaction is subject to a positive salt effect, which is consistent with a considerable degree of charge separation in the transition state.[11]

These results seem to suggest that, in the transition state, both the leaving chloride ion and the nucleophile (a solvent molecule, most probably water) are bound to sulfur, although the last-mentioned has a strong sulfonylium ion character, thus accounting for the very substantial, negative entropy of activation found. This would correspond to a concerted, asynchronous bimolecular mechanism proceeding through a transition state in which bond breaking takes place far ahead of bond formation ("exploded" transition state).

A simple depiction of the transition state, together with a reasonable location for it on the pathway followed by the reaction under investigation, are illustrated in the Jencks–MoreO'Ferrall plot shown in Scheme 2. For purposes of comparison, paths corresponding to the dissociative, S_N1 process and to the associative, "synchronous" S_N2 process are also displayed in the same Scheme.



Scheme 2. Jencks–MoreO'Ferrall diagram and reaction coordinates for S_N1, S_N2 and solvent-assisted S_N2 ("exploded" S_N2) mechanisms for the sulfonyl-transfer process; contour lines are omitted for clarity

Conclusion

Our results are consistent with the solvolysis in 80% aqueous acetic acid of *p*-(dimethylamino)benzenesulfonyl chloride (**XI**) [and presumably also that of sulfanilyl chloride (**XIII**)] occurring through an "exploded" S_N2 mechanism, similar to that proposed by Forbes and Maskill for the solvolysis of **XI** in trifluoroethanol.[5]

A referee has suggested that electrostriction of solvent generated by developing charge separation might suffice to account for the negative value of activation entropy found. Although this possibility cannot definitely be ruled out at the moment, we believe that the close similarity between the system studied here and those investigated in refs.[1,8], for which a relationship between $\Delta S^{\neq}$ and molecularity of the hydrolytic mechanism has been firmly established, lends good support to our conclusions.

It seems reasonable to suppose that this "exploded" S_N2 mechanism is a "smooth" transition between the two extremes represented by proper S_N1 and S_N2 mechanisms. Previous work has shown that, in the alkaline hydrolysis of the aryl esters of *o*- and *p*-hydroxyarenesulfonic acids, a sudden changeover from the E1cB to an S_N2 mechanism occurs in which nucleophilic attack of the hydroxide ion onto the sulfonyl group of the substrate conjugate base takes place. This would imply that no assistance from an

"external" nucleophile is needed because the powerful "internal" nucleophile (the oxy anion) is able to expel the leaving group on its own.

In essence, the E1cB mechanism can be regarded as an S_N1 mechanism taking place on the negatively charged conjugate base of the substrate. This confers extra stability onto the reaction intermediate, which is neutral in this case, since the positive charge of the S_N1 intermediate is compensated by the pre-existing negative charge.

This does not seem to occur when the *p*-dimethylamino function, which is less efficient as an electron-releasing group, is involved. In this case, cooperation of a solvent molecule would be required for the expulsion of the leaving group. The failure of the amino group to promote the S_N1 solvolysis of **XIII** can easily be explained, as it is somewhat weaker than the dimethylamino group as an electron donor. On the other hand, the acidity of the NH_2 group is far too low as to allow accumulation of a sufficient concentration of the substrate conjugate base in aqueous solution, which is prerequisite for the E1cB process.

Experimental Section

General Remarks: Starting reagents and solvents were of analytical reagent grade; when necessary, salts were dried prior to use. Water was doubly distilled and preboiled to free it from dissolved carbon dioxide. Dioxane (used for the preparation of stock solutions of substrates) was purged of peroxides by passage of the analytical-grade product through an activated-alumina column. The absence of peroxides was assessed by the KI test. − NMR spectra were recorded with a Varian Gemini 200 spectrometer (200 MHz) with TMS as internal standard and [D_6]acetone or $CDCl_3$ as solvent.

Starting Materials: Compounds **XI**[12] and **XIII**[13] were synthesized according to published procedures, and had ^{1}H NMR spectra consistent with their structures.

Rate Measurements: The technique generally employed for measuring reaction rates has already been described in previous papers.[1] Reactions were monitored by following the decrease of absorbance due to substrate consumption at either 330 nm (compound **XI**) or 305 nm (compound **XIII**). The rates of hydrolysis obeyed pseudo-first order kinetics over at least 80% of the total reaction. Tight isobestic points were observed during the spectral scanning, indicating that reaction intermediates were either absent or at a negligible concentration. "Infinity" spectra matched well with those of the corresponding sulfonic acids, thus showing that simple hydrolysis was being followed. The solvent employed was prepared by mixing together 8 volumes of acetic acid and 2 volumes of doubly distilled water. Special care was taken in measuring exact volumes, since preliminary experiments revealed that rates are influenced significantly even by small differences in solvent composition.

[1] [1a] S. Thea, G. Guanti, A. Hopkins, A. Williams, *J. Am. Chem. Soc.* **1982**, *104*, 1128−1129. − [1b] S. Thea, G. Cevasco, G. Guanti, A. Hopkins, N. Kashefi-Naini, A. Williams, *J. Org. Chem.* **1985**, *50*, 2158−2165. − [1c] G. Cevasco, S. Thea, *J. Org. Chem.* **1998**, *63*, 2125−2129.

[2] For a comprehensive review on this and related subjects see: I. M. Gordon, H. Maskill, M. F. Ruasse, *Chem. Soc. Rev.* **1989**, *18*, 123−151.

[3] S. Thea, G. Cevasco, S. Penco, *Gazz. Chim. Ital.* **1996**, *126*, 7−10.

[4] P. Sanecki, E. Rokaszewski, *Can. J. Chem.* **1987**, *65*, 2263−2267.

[5] R. M. Forbes, H. Maskill, *J. Chem. Soc., Chem. Commun.* **1991**, 854−856.

[6] S. Thea, G. Guanti, A. R. Hopkins, A. Williams, *J. Org. Chem.* **1985**, *50*, 3336−3341.

[7] G. Cevasco, S. Thea, unpublished results.

[8] [8a] G. Cevasco, G. Guanti, A. R. Hopkins, S. Thea, A. Williams, *J. Org. Chem.* **1985**, *50*, 479−484. − [8b] G. Cevasco, S. Thea, *J. Org. Chem.* **1994**, *59*, 6274−6278. − [8c] G. Cevasco, S. Thea, *J. Org. Chem.* **1995**, *60*, 70−73. − [8d] G. Cevasco, R. Pardini, S. Thea, *Eur. J. Org. Chem.* **1998**, 665−669. − [8e] G. Cevasco, D. Vigo, S. Thea, *Org. Lett.* **1999**, *1*, 1165−1167.

[9] D. D. Perrin, B. Dempsey, E. P. Serjeant, *pK_a Prediction for Organic Acids and Bases*, Chapman and Hall, London, **1981**, p. 109.

[10] [10a] I. M. Kolthoff, A. Willman, *J. Am. Chem. Soc.* **1934**, *56*, 1007−1013. − [10b] I. M. Kolthoff, A. Willman, *J. Am. Chem. Soc.* **1934**, *56*, 1014−1016.

[11] [11a] E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York, **1959**, chapter 6. − [11b] An interesting case in which an "inert" salt added to the reaction mixture significantly affects the structure of an S_N2 transition state has been described recently: T. V. Pham, K. C. Westaway, *Can. J. Chem.* **1996**, *74*, 2528−2530.

[12] C. N. Sukenik, J. A. P. Bonapace, N. S. Mandel, Pui-Yan Lau, G. Wood, R. G. Bergman, *J. Am. Chem. Soc.* **1977**, *99*, 851−858.

[13] J. Contreras, J. I. Jones, *Brit. Polym. J.* **1980**, 192−198.

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