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The Hydrolysis of 4-Amino- and 4-Dimethylaminobenzene Sulfonyl Chlorides: An Unprecedented Case of Independence of Reactivity from pH

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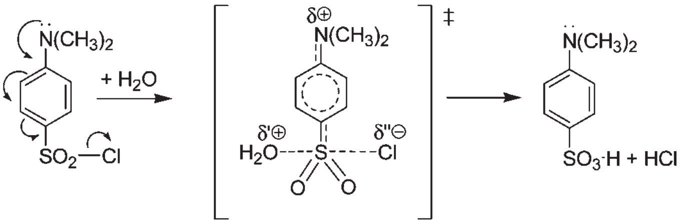
ABSTRACT

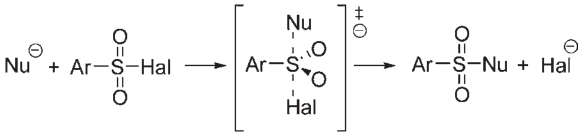
A unique hydrolytic mechanism operating in the pH range 0 – 14.7



The reactivity−pH profile for the hydrolysis of 4-aminobenzenesulfonyl chloride 1 has a sigmoid shape with a plateau extending from pH 2 to 11; reactivity of N,N-dimethyaminobenzenesulfonyl chloride 4 is invariant over an even wider pH range (0−14.7). These results, together with the activation data determined at selected pH's for compound 1, are interpreted in light of the occurrence of a reaction mechanism that is dissociative in nature, in which nucleophilic assistance by solvent molecules is given to the amino group of 1 acting as an "internal nucleophile".

Previous work[1] has shown that the alkaline hydrolysis and aminolysis of 4-aminobenzenesulfonyl chloride **1** in aqueous solution have the features of dissociative processes. In the less polar solvent acetonitrile, instead, occurrence of the usual associative, $S_N2(S)$ mechanism (shown in Scheme 1) was demonstrated.[2] Only the associative mechanism, however, was followed by the fluoride **2** and the 2,4-dinitrophenyl ester **3** of 4-aminobenzenesulfonic acid, independent of the solvent employed.[1] These conclusions were reached on the basis of results from kinetic and trapping studies and were attributed to the different abilities of chloride, fluoride, and 2,4-dinitrophenoxide as leaving groups.

Scheme 1



The question whether the dissociative mechanism found for chloride **1** is an E2, S_N1, or an "exploded"

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(1) Thea, S.; Vigo, D.; Cevasco, G. *J. Chem. Soc., Perkin Trans. 2* **2002**, 611–614.

(2) For an excellent review on sulfonyl transfer mechanisms, see: Gordon, I. M.; Maskill, G.; Ruasse, M.-F. *Chem. Soc. Rev.* **1989**, *18*, 123–151.

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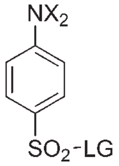
S_N2 process was left unanswered.[1] In order to shed light on this point, pH−reactivity profiles have been now generated for compounds **1** and **2** over a wide range of pHs.[3] The exceedingly high reactivity of **1** in aqueous solvent made it necessary to use a diode-array UV spectrophotometer equipped with a stopped flow apparatus. It was thus possible to measure the rate constants for the hydrolysis of **1** in pure water,[4] with a quite satisfactory degree of accuracy.



1: X = H; LG = Cl
2: X = H; LG = F
3: X = H; LG = 2,4-$(NO_2)_2C_6H_3O$
4: X = CH_3; LG = Cl

The hydrolysis of sulfonyl halides **1** and **2** in aqueous buffers obeyed excellent first-order kinetics up to at least 80% of the total reaction. No buffer catalysis was detected even when nucleophilic buffers (e.g., ammonia) were employed. Results are shown graphically in Figure 1.

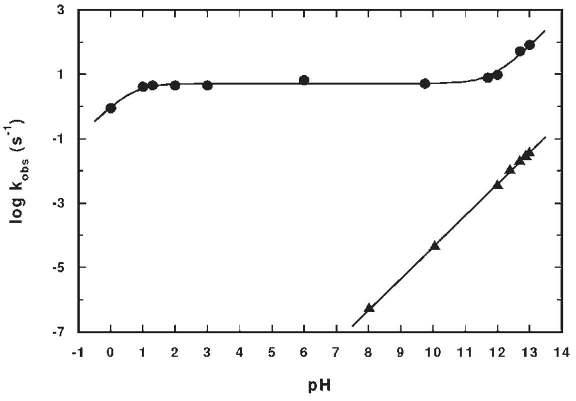


Figure 1. pH−rate profiles for the hydrolysis of 4-aminobenzenesulfonyl chloride **1** (●) and fluoride **2** (▲) in water solution, ionic strength = 1 M (KCl), temperature 25.0 ± 0.1 °C. Rate measurements were performed with a conventional spectrophotometer or with a stopped-flow apparatus equipped with a parallel diode-array detector operating in the wavelength range 250−330 nm.

Inspection of Figure 1 shows that the pH−rate profiles for chloride **1** and fluoride **2** have a notably different shape.

As far as the hydrolysis of **1** is concerned, the pseudo-first-order rate constant k_{obs} was independent of buffer concentrations and changed with pH according to the classical rate law shown in eq 1.

On the contrary, the pH profile for compound **2** indicated that a simple second-order rate law in hydroxide ion and ester concentrations was obeyed (eq 2). The derived constants are as follows: $k_a = (5.13 \pm 0.40)\ s^{-1}$, $k_b = (740 \pm 90)\ M^{-1}s^{-1}$, $pK_a = (0.64 \pm 0.10)$, $k_{OH} = (0.367 \pm 0.011)\ M^{-1}\ s^{-1}$.

$$k_{obs} = (k_a + k_b[OH^-])/(1 + [H^+]/10^{-pK_a}) \qquad (1)$$

$$k_{obs} = k_{OH}[OH^-] \qquad (2)$$

The exceptionally wide plateau (extending from below pH 2 to 12) obtained for the chloride **1** is not consistent with the associative, $S_N2(S)$ mechanism, for which a linear dependence of reactivity (as expressed by log k_{obs}) on pH is expected (indeed, this behavior is observed for fluoride **2**). Moreover, should the associative mechanism occur, reactivity would increase as a result of protonation of the amino group, due to the strong electron-withdrawing effect of the positively charged ammonium group. In the present case, on the contrary, reactivity decreases at pH < 1, i.e., in the region where substrate undergoes protonation. Indeed, a pK_a of ca. 0.5 can be calculated for **1** from literature data,[5] in nice agreement with the value obtained from the present data (i.e., 0.64). The observed rate decrease is well consistent with the dissociative mechanism, as protonation makes unavailable the lone pair of the amino group, whose availability is prerequisite to expulsion of the leaving group.

Aimed at ascertaining whether the rate increase observed at pH > 11 is due to the incursion of an associative mechanism (viz., attack of OH^- onto the neutral, nonionized substrate) or to the kinetically equivalent dissociative mechanism, i.e., the eliminative expulsion of the leaving chloride ion subsequent to the ionization of the amino group), the pH−rate profiles were obtained for the nonionizable 4-dimethyaminobenzenesulfonyl chloride **4**, as well as for 4-aminobenzenesulfonyl chloride **1**, in dioxane−water 20:80 (v/v) solvent (the difficulty caused by the inconveniently low solubility of **4** in water was solved

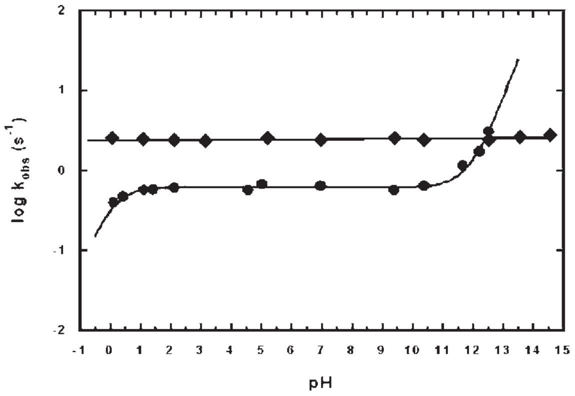


Figure 2. pH−rate profiles for 4-aminobenzenesulfonyl chloride 1 (●) and 4-dimethylaminobenzenesulfonyl chloride 4 (♦): solvent, dioxane−water 20:80 (v/v); ionic strength, 1 M (KCl); temperature, 25.0 ± 0.1 °C; stopped-flow kinetics; λ_{exptl} = 309 nm; pK_w = 14.51.[6]

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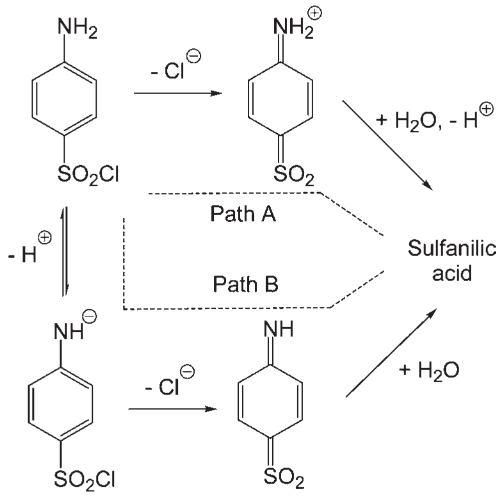
(3) Sulfanilic derivatives **1**, **2**, and **4** were prepared as already described in refs 1 and 9.

(4) Indeed, a small amount (1−2%) of dioxane was present as it was used to dissolve the substrate prior to addition to aqueous buffer.

making recourse to such solvent composition). Rate data are displayed in Figure 2.

The derived rate constants (eq 1) are as follows for compound **1**: $k_a = (0.62 \pm 0.02)\ s^{-1}$; $k_b = (318 \pm 27)\ M^{-1}s^{-1}$, p$K_a$ could not be measured, vide infra; for compound **4**, $k_a = (2.46 \pm 0.04)\ s^{-1}$.

Scheme 2



Although compound **1** is slightly less reactive in 20% dioxane−water solvent than in pure water, in both solvent systems the corresponding pH−rate profiles are quite similar. Instead, the profile from the dimethylamino derivative **4** displays somehow different characteristics. No increase in rate is observed in the high pH limb of the profile. This fact suggests that, most likely, the rate increase observed for compound **1** in both solvent systems can be ascribed to a dissociative, E1cB mechanism, shown as path B in Scheme 2. Of course, this reaction path is not allowed to the dimethylamino derivative **4**, whose ionization cannot occur as it is devoid of acidic hydrogens. In fact, reactivity is virtually invariant over the entire, extraordinarily wide pH range explored (0−14.7).

Another piece of evidence in favor of the above proposed mechanism is given by the large value (≈2000) found for the ratio between the second-order rate constants k_b for chloride **1** [(740 ± 90) $M^{-1}\ s^{-1}$, eq 1] and k_{OH} for fluoride **2** [(0.367 ± 0.011) $M^{-1}\ s^{-1}$, eq 2]. Such a value is much higher than that (3.7) reported for the reactivity with hydroxide ion of toluene-*p*-sulfonyl chloride vs toluene-*p*-sulfonyl fluoride in water,[1] both $S_N2(S)$ processes, thus giving strong support to our proposal that the mechanism followed by **1** *is not* of the S_N2 type.[7]

Such behavior is quite uncommon and, to the best of our knowledge, has been never reported previously in the literature, at least for similar systems. Indeed, under strongly acidic conditions (at pH < 0) a rate decrease was observed that would not be consistent with an associative mechanism (similar to what was previously discussed for compound **1**). These data were not included in the profile as, in order to get such a low pH, very concentrated HCl solutions were employed, whose ionic strength values were higher than that (1.0 M) employed throughout this work. For this reason comparison with the other rate data is not allowed; nevertheless, this result may well suggest that the proposed dissociative mechanism could occur. Indeed, invariance of log k_{obs} even at the lowest pH value reached seems to suggest the conclusion, apparently conflicting with the common knowledge, that basicity of the *N*,*N*-dimethylamino derivative **4** is *lower* than that of the unsubstituted compound **1**. Anyway, it should be taken into account that in the presence of strongly electron-withdrawing groups in the ring (e.g., SO_2Cl, $\sigma_p = 1.04$), *N*,*N*-dimethylanilines are predicted to be *less basic* than the correspondingly substituted anilines. Indeed, from the Hammett relationships reported in the literature for substituted anilines and *N*,*N*-dimethylanilines,[5] one can predict that the isobasic point occurs when $\Sigma\sigma = 0.83$.

Finally, the observation that $k_a(\mathbf{4}) > k_a(\mathbf{1})$ (ratio ≅ 4) is fully consistent with the dissociative mechanism, as the dimethylamino group ($\sigma_p = -0.8$) is a better electron donor as compared to the amino group ($\sigma_p = -0.66$).[8]

The proposed overall mechanistic scheme concerning the reaction of 4-aminobenzenesulfonyl chloride **1** is shown in Scheme 2, where path A, prevailing at pH < 11, can also be followed by the 4-dimethylaminobenzenesulfonyl chloride **4** in the entire range of pHs; incursion of path B, that can be accessed only by the unsubstituted chloride **1**, occurs at pH > 11. In order to gain deeper insight into the mechanism of this reaction, the activation parameters for the hydrolysis of the 4-aminobenzenesulfonyl chloride **1** have been obtained at two different pH's, i.e., in the plateau region (at pH 6.95) where $k_{obs} \cong k_a$, as well as in the alkaline region (at pH = 12.2), where $k_{obs} \cong k_b$. At either pH, high, negative values of $\Delta S^{\ddagger}$ were found at $-99{,}6 \pm 0.6\ J\ K^{-1}\ mol^{-1}$ and $-86.6 \pm 7.5\ J\ K^{-1}\ mol^{-1}$, respectively). At first glance, this finding is not consistent with the mechanistic hypothesis seen before, as positive, or at least slightly negative, entropy values are generally associated to dissociative mechanisms; on the contrary, large, negative values like those found in this work are typical of associative processes such as the $S_N2(S)$ one.[9]

The complex of these results point to a mechanism that is dissociative in nature, but where other molecules different from the substrate (or its conjugate base) take part into the

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(5) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK Prediction of Organic acids and Bases*; Chapman & Hall: London, 1982; p 133.

(6) Harned, S.; Fallon, L. D. *J. Am. Chem. Soc.* **1939**, *61*, 2374–2377.

(7) Linearity of the pH−rate profile of sulfonyl fluoride **2** in the pH range 8−13 strongly suggests that a single mechanism (i.e., $S_N2(S)$) is followed, also at high pHs. Such a different mechanistic behavior with respect to that of chloride **1** can be easily explained if it is taken into account that dissociative (E1, E1cB) processes are much more sensitive to leaving group nucleofugality than the associative ($S_N2(S)$) one, and F is quite worse than Cl as a leaving group.

(8) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

(9) (a) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969. (c) Douglas, K. T. *Prog. Bioorg. Chem.* **1976**, *4*, 194–238. (d) Safraoui, A.; Calmon, M.; Calmon, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1349–1352. (e) Broxton, T. J. *Aust. J. Chem.* **1985**, *38*, 77–83.

transition state. An extensive solvent reorganization accompanying the dissociation of substrate into charged species (i.e., chloride ion and the positively charged sulfoquinone imine, path A), although possible, seems unlikely on the basis of our previous findings on similar systems.[10]

The simplest explanation takes into account the occurrence of an "exploded" $S_N2(S)$ (in other words, an S_N2, S_N1-like) mechanism, encompassing a loose transition state in which both the leaving atom *and* one (or more) water molecule interacts weakly with the reaction center.

A similar mechanism was previously proposed by ourselves[10] and others[11] for the solvolysis of **4** under acidic (80% aqueous acetic acid solvent) and neutral (anhydrous trifluoroethanol solvent) conditions, respectively. Our present results not only confirm our previous mechanistic hypothesis but also provide an indication about the generality of such a mechanism, that seems to be operating in an extremely wide pH range and in quite different solvent systems (trifluoroethanol, 80% aqueous acetic acid, 20% aqueous dioxane).

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Supporting Information Available. Experimental procedures, primary kinetic data for calculation of kinetic and activation parameters, and UV data related to stopped-flow rate measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Thea, S.; Carpanelli, C.; Cevasco, G. *Eur. J. Org. Chem.* **2001**, 151–154.

[11] Forbes, R.; Maskill, H. *J. Chem. Soc., Chem. Commun.* **1991**, 854–856.