

Nucleophilic Substitution at Four-co-ordinate Sulphur. Mobility of the Leaving Group

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The leaving group effect has been measured for the reactions of benzenesulphonyl halides with aniline, n-butylamine, and hydroxide ion. The specific rate constants of displacement at 25° with I, Br, Cl, and F, respectively, as leaving groups, are the following: with aniline, 3.55×10^{-2} , 31.2×10^{-2} , 4.27×10^{-2} , and 2.6×10^{-2} ; with n-butylamine, 21.9, 103, 42.6, and 1.01×10^{-2} ; and with hydroxide ion, 43.6, 28.9, 15.5, and 3.40. The almost identical leaving group mobility of I, Br, and Cl for each nucleophile and the enormous change in relative group mobility of fluorine on changing the pK_a of the nucleophile, point to a mechanism involving an intermediate complex with bond forming or bond breaking as the rate-limiting step according to the substrate. The activation parameters are also reported and agree with this interpretation.

THE neutral and alkaline hydrolysis of sulphonyl derivatives has been discussed in terms of S_N1 ,¹ S_N2 ,² or $S_A N$ ³ mechanisms.⁴ The S_N1 mechanism was later discarded² on various grounds. The $S_A N$ mechanism was also abandoned because the sulphonyl oxygen atoms do not exchange with those of water during the solvolysis and this was taken as a proof against the formation of an addition intermediate.⁵ The mechanism was thus mostly considered to involve a direct displacement on sulphur, as was recently emphasized by Rogne,⁶ since all the kinetic features of the reaction are in accord with an S_N2 mechanism. Rogne extended the investigation to a number of nucleophiles other than water, in aqueous media,^{7,8} and the mechanism was identified as a nucleophile-catalysed hydrolysis.

For reasons given in the Discussion section, we did not consider the lack of ¹⁸O exchange a sufficient proof against an $S_A N$ mechanism in the hydrolysis of sulphonyl derivatives. One way to try to distinguish between a direct displacement and one which occurs *via* an intermediate complex is to determine the relative amount of bond

formation and breaking in the transition state. For this purpose the Brønsted coefficients for the nucleophile and for the leaving group, which have been related to the amount of bond formation and breaking, respectively, in the transition state, might be used.^{9,10} However, the values reported for nucleophilic substitution at a sulphonyl sulphur atom (0.45 for the nucleophile⁷ and -0.6 for the leaving group¹¹) are not sufficient to distinguish between the two mechanisms,^{12,13} and Rogne limits himself to the general remark⁸ that sulphur occupies an intermediate position between a saturated and a carbonyl carbon atom because of the intermediate value of the nucleophilic Brønsted coefficient, and the statement⁷ that such a value should indicate that sulphur, being highly polarizable, should be able to form bonds at a larger distance than carbonyl carbon which usually gives β values close to 0.8.

We report a study of the element effect¹⁴ in nucleophilic substitutions at four-co-ordinate sulphur. This effect is related to the amount of bond breaking in the transition state. Similar studies have already been

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¹³ A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5442.

¹⁴ J. F. Bunnett, E. W. Garbish, jun., and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385.

reported for two-co-ordinate sulphur.^{15,16} The results were discussed in terms of an S_N mechanism with bond forming as the rate-limiting step. Due to the different reactivity of sulphur in the two oxidation states we expected to find a different pattern of leaving group mobilities.

EXPERIMENTAL

Materials.—Commercial benzenesulphonyl chloride was fractionated under vacuum, b.p. 113–115° at 10 mmHg. Benzenesulphonyl fluoride [yield 80%; b.p. 55–56° at 5 mmHg; n_D^{20} 1.490 (lit.,¹⁷ 1.4922)], benzenesulphonyl bromide (yield 90%; b.p. 79–80° at 1 mmHg),¹⁸ and benzenesulphonyl iodide [yield 90%; m.p. 44–45° (lit.,¹⁹ 42–45°)] were prepared according to reported procedures. Aniline and n-butylamine were commercial products which were twice distilled from potassium hydroxide pellets. Sodium hydroxide was a reagent grade commercial product and was used without further purification. Deionized water was distilled from potassium permanganate. Acetonitrile was carefully fractionated.

Product Isolation.—The products could not be isolated from the kinetic experiments because of the small concentrations of substrate used. However, in the same solvent mixture, reaction of all substrates in preparative amounts with each nucleophile always gave the expected product in almost quantitative yield. Products were identified by analyses and i.r. spectroscopy. n-Butylbenzenesulphonamide was purified by molecular distillation. An oil was obtained whose b.p. could not be determined.²⁰ Benzenesulphonanilide was purified by crystallization (ethanol), m.p. 110–111° (lit.,²¹ 108–110°).

Kinetics.—The reactions with n-butylamine and hydroxide ion were followed by u.v. spectroscopy at the most convenient wavelength (240–265 nm) either with a Durrum stopped-flow apparatus (for the faster reactions) or with a Beckman u.v. spectrophotometer. In each case the experimental infinity spectrum was identical with that of the products. The temperature control was better than $\pm 0.1^\circ$ except perhaps for the reactions followed with the stopped-flow spectrophotometer above room temperature. In the latter cases we assumed an accuracy of $\pm 0.5^\circ$. The reactions with aniline were followed with a Metrohm E 101 conductometer in a jacketted reaction vessel equipped with a platinum conductivity cell. Care was taken to avoid contact with carbon dioxide of the air. A linear relation was found between the conductivity and the concentration of the aniline hydrohalides produced in the reaction.

Solutions of all substrates in 90% water–acetonitrile were sufficiently stable toward hydrolysis. They were used within a day after preparation. Solutions of benzenesulphonyl chloride, bromide, and iodide in 50% acetonitrile–water react slowly but measurably with water. These solutions were prepared immediately before use.

All reactions were followed directly in the reaction vessel except those between aniline and benzenesulphonyl fluoride, which were followed by sealing portions of the reacting mixture in glass vials, which were withdrawn from the

thermostat at time intervals and chilled. The conductivity was then measured at 25 °C.

RESULTS

The rates of reaction of benzenesulphonyl fluoride, chloride, bromide, and iodide with aniline, n-butylamine, and hydroxide ion have been measured in aqueous acetonitrile. In all cases the products, in quantitative yield, were those expected for a nucleophilic substitution at sulphur. The reaction is first order in all substrates and nucleophiles. The reactions were measured under pseudo-first-order conditions and were linear up to 90% completion except for the reaction of benzenesulphonyl fluoride with aniline which was followed up to 25% completion. The data are in Table 1.

TABLE 1

Velocity constants for the nucleophilic substitution of benzenesulphonyl halides with aniline, n-butylamine, and hydroxide ion^a

Leaving group	$t/^\circ\text{C}$	$10^2[\text{Nucleophile}]$ M	k $l \text{ mol}^{-1} \text{ s}^{-1}$	No. of runs
Aniline^b				
F	100	50.0	1.35×10^{-5}	1
F	108	33.0	1.88×10^{-5}	1
Cl	0.0	5.8–10.5	1.42×10^{-2}	3
Cl	12.65	11.6–16.2	2.54×10^{-2}	3
Cl	25.2	6.7–12.3	4.25×10^{-2}	3
Br	0.0	5.3–10.8	10.1×10^{-2}	3
Br	14.7	3.2–6.2	20.4×10^{-2}	3
Br	25.2	3.2–5.3	30.9×10^{-2}	3
I	0.0	8.5–16.6	1.05×10^{-2}	3
I	14.5	16.6–22.2	2.22×10^{-2}	3
I	25.0	17.4–22.1	3.48×10^{-2}	3
n-Butylamine^c				
F	25.0	11.1–27.5	1.00×10^{-2}	3
F	49.9	3.46–4.70	4.64×10^{-2}	3
Cl	22.0	0.95–2.95	38.0	5
Cl	25.0	1.16–2.50	43.0	5
Cl	32.5	0.95–2.95	52.5	3
Br	25.0	1.16–2.50	102	5
Br	48.2	1.43–2.83	237	5
I	25.0	1.16–2.50	21.8	6
I	47.8	1.73–2.35	42.0	5
Hydroxide ion^c				
F	21.7	2.56–4.27	2.5	3
F	25.0	1.71–4.27	3.5	3
F	30.8	2.56–4.27	5.0	3
F	48.0	1.71–2.56	12.6	3
Cl	22.2	2.56–4.27	13.0	3
Cl	25.0	1.0–2.0	15.3	3
Cl	30.8	2.56–4.27	21.0	3
Cl	48.2	1.71–2.56	83.5	2
Br	25.0	1.71–4.27	27.5	5
Br	30.7	1.71–4.27	44.6	2
Br	48.0	1.71–4.27	130	2
I	25.0	1.71–4.27	43.0	6
I	47.8	1.71–4.27	220	4

^a Substrate concentration, 10^{-4} – 10^{-3} M. ^b In acetonitrile–water (9 : 1). ^c In acetonitrile–water (1 : 1).

Because of the solubility properties of the reagents, a single solvent could not be used. 50% (w/w) Acetonitrile–water was chosen for n-butylamine and hydroxide ion (a

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¹⁸ A. C. Poskus, J. E. Herweh, and F. A. Magnotta, *J. Org. Chem.*, 1963, **28**, 2766.

¹⁹ F. C. Whitmore and N. Thurman, *J. Amer. Chem. Soc.*, 1923, **45**, 1068.

²⁰ W. Ssolonina, *J. Russ. Phys. Chem. Ges.*, 31, 640 (*Chem. Zentr.*, 1899, II, 867).

²¹ A. Ginzberg, *Ber.*, 1903, **36**, 2706.

smaller proportion of water would not dissolve 0.1M-sodium hydroxide). The proportion of water was decreased to 10% for aniline in order to minimize the rate of the neutral hydrolysis for the slower reactions. The neutral hydrolysis was in all cases much slower than the measured reaction and therefore did not influence the kinetics. The alkaline hydrolysis was also negligible at the pH values of the solutions when aniline or n-butylamine were used as nucleophiles.

The average specific rate constants (Table 1) do not possess the same degree of accuracy. We estimate a range from a minimum of 2–3% for reactions with good temperature control, followed up to 90% completion, and a large number of runs, to a maximum of 10% in other cases. Such errors in the rates are too small to affect the discussion in any way.

Enthalpy and entropy of activation are reported in Table 2 along with the maximum error ²² (the small number

TABLE 2

Activation parameters and summary of the leaving group mobility at 25 °C for nucleophilic substitutions of benzenesulphonyl halides with aniline, n-butylamine, and hydroxide ion

Leaving group	ΔH^\ddagger ^a kcal mol ⁻¹	$-\Delta S^\ddagger$ ^a cal K ⁻¹ mol ⁻¹	k ^b l mol ⁻¹ s ⁻¹
Aniline ^c			
F	11.1 (5.6)	51.4 (15.2)	0.26×10^{-6}
Cl	6.5 (0.7)	43.2 (2.6)	4.27×10^{-2}
Br	6.6 (0.7)	38.7 (2.6)	31.2×10^{-2}
I	7.2 (0.7)	41.1 (2.6)	3.55×10^{-2}
n-Butylamine ^d			
F	11.4 (0.8)	29.5 (2.7)	1.01×10^{-2}
Cl	5.1 (1.8)	34.0 (6.2)	42.6
Br	6.3 (1.6)	28.1 (5.7)	103
I	4.9 (1.6)	36.0 (5.7)	21.9
Hydroxide ion ^d			
F	10.6 (1.4)	20.5 (4.8)	3.40
Cl	13.0 (1.5)	9.4 (5.1)	15.5
Br	12.1 (1.6)	11.4 (5.5)	28.9
I	13.0 (1.7)	7.4 (5.8)	43.6

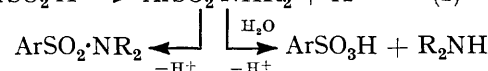
^a Maximum error in parentheses. ^b Calculated from the activation parameters. ^c In acetonitrile–water (9 : 1). ^d In acetonitrile–water (1 : 1).

of experimental temperatures does not permit the calculation of a meaningful standard deviation). However, while to report the maximum error is sometimes of mechanistic significance,²² in the present case the method of joint confidence regions²³ is more suited. Such a method clearly shows that, while the entropy and enthalpy of activation of Cl, Br, and I as leaving groups are the same within experimental error for each nucleophile, the activation parameters of benzenesulphonyl fluoride are quite different from those of other sulphonyl halides in all cases.

DISCUSSION

The order of the reaction and the nature of the products show that a nucleophilic displacement on sulphur occurs. In the alkaline hydrolysis, which was

already identified as a nucleophilic displacement on sulphur,^{6,24} the displacement yields the products directly [equation (1)]. With amines as nucleophiles the re-



action involves the formation of an unstable sulphonyl-ammonium intermediate [equation (2)].⁷ Such an intermediate can either lose a proton to give the corresponding sulphonamide,²⁵ or be attacked by water (in aqueous media) to give hydrolysis products.⁷ When tertiary amines are used, owing to the absence of hydrogen on the nucleophilic nitrogen atom, only hydrolysis products are observed.⁷ When primary or secondary amines²⁵ are used, both reactions are possible. However, the fact that the sulphonamides are obtained in quantitative yield indicates that loss of a proton is a much faster process than attack by water (already considered a fast step⁷). Thus, the sulphonylammonium intermediate does not revert to the starting materials and in each case the reaction is a simple displacement on sulphur. The leaving group mobilities are therefore directly related to the first step of the nucleophilic substitution.

The leaving group mobility of benzenesulphonyl chloride and fluoride in neutral and alkaline hydrolysis has already been measured by Swain and Scott.²⁴ They discussed the $k_{\text{Cl}} : k_{\text{F}}$ ratio of neutral hydrolysis for a series of substrates in terms of a larger tendency for bond breaking giving a larger $k_{\text{Cl}} : k_{\text{F}}$ ratio. The ratio for the benzenesulphonyl derivatives is quite large ($>4.8 \times 10^3$); therefore the reaction was considered to proceed with a large degree of bond breaking.²⁴ The $k_{\text{Cl}} : k_{\text{F}}$ ratio for alkaline hydrolysis²⁴ was found to be much smaller (*ca.* 6), an indication that bond breaking is much less pronounced in this case. In the case of alkaline hydrolysis of benzoyl halides, where the fluoride reacts faster than the chloride, Swain and Scott suggested that fluorine facilitates the formation of the bond with the nucleophile by making the electrophilic centre more electron-deficient and positive.²⁴ These ideas are similar to those expressed by Bunnett on the 'element effect'.¹⁴ However, the element effect can give more detailed information because the number of leaving groups is not limited to two. Swain and Scott's data are in agreement with ours but are insufficient for a comprehensive discussion of the element effect on sulphonyl sulphur. For example, the $k_{\text{Cl}} : k_{\text{F}}$ ratio measured by Swain and Scott for neutral hydrolysis of sulphonyl halides suggests large bond breaking in the transition state for both leaving groups. Consideration of more than two leaving groups shows that, while bond

²⁴ G. Swain and C. G. Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 246.

²² K. B. Wiberg, 'Physical Organic Chemistry,' Wiley, New York, 1964, pp. 377–379.

²⁵ J. F. Bunnett and J. Y. Bassett, jun., *J. Amer. Chem. Soc.*, 1959, **81**, 2104; *J. Org. Chem.*, 1962, **27**, 2345.

²³ J. Mandel and F. J. Linnig, *Analyt. Chem.*, 1957, **29**, 743.

breaking in the transition state is extensive for the fluoride, it is much less pronounced for the chloride.

Table 2 shows that the leaving group mobilities of I, Br, and Cl for each nucleophile are almost identical. The maximum relative mobility changes from 2.8 for hydroxide ion, to 4.7 for n-butylamine, to 8.8 for aniline. On the other hand the relative mobility of fluorine changes on changing the nucleophile. The $k_{Cl}:k_F$ ratios for hydroxide ion, n-butylamine, and aniline, are 4.6, 4.2×10^3 , and 1.65×10^5 . The slight variation relative to the $k_{Cl}:k_F$ ratio previously determined for the alkaline hydrolysis in aqueous acetone²⁴ can be attributed to the different solvent. Clearly, on changing the nature of the nucleophile, the strength of the S-F bond influences the reaction rate to a very different degree. Breaking of the S-F bond is important for aniline and becomes less important for n-butylamine until for hydroxide ion it is almost of no importance. For the three other leaving groups on the other hand the strength of the S-halogen bond is always unimportant.

The leaving group mobility in the various cases is paralleled by the activation parameters (Table 2). Enthalpies and entropies of activation are the same within experimental error for chlorine, bromine, and iodine as leaving groups (considered separately for each nucleophile). Fluorine has in each case quite different activation parameters.

The relative mobility and the activation parameters for the different leaving groups can be accounted for only by an S_N mechanism, which, depending on the leaving group, allows either bond forming or bond breaking as the rate-limiting step.¹⁴ Bond forming is the rate limiting step with all nucleophiles for benzenesulphonyl chloride, bromide, and iodide as shown by the almost identical rate and activation parameters. When this mechanism is operative, the rate of reaction is little influenced by the S-X bond strength. Benzenesulphonyl fluoride on the other hand, reacts *via* an S_N mechanism with bond breaking as the rate-limiting step as shown by the different mobilities of fluorine with various nucleophiles. The variation in activation parameters on changing the pK_a value of the nucleophile cannot be easily interpreted. However, an interesting feature is the difference in reaction rate between benzenesulphonyl fluoride and the other sulphonyl halides, which becomes smaller, the higher the pK_a values of the nucleophile. The decomposition of the intermediate towards reagents or products depends on the relative basicity of nucleophile and leaving group. A nucleophile of higher pK_a value is a relatively worse leaving group. Thus, the decomposition of the intermediate changes from largely exclusive return to reagents for the reaction of benzenesulphonyl fluoride with aniline, to a more balanced situation on increasing the pK_a value of the nucleophile.

A comment about the difference in mobility of I, Br, and Cl found for two-^{15,16} and four-co-ordinate sulphur

seems in order. For sulphenyl sulphur, larger ratios of leaving group mobilities were found (400 in one case) and the order of leaving group mobility follows the electronegativity. However, we have assumed for both types of sulphur that iodine, bromine, and chlorine are almost fully bound to the sulphur atom in the transition state. Clearly, while the electronegativity is quite important for two-co-ordinate sulphur, the incoming nucleophile is not affected by it in reactions at sulphonyl sulphur where the order of leaving group mobility is determined both by the (small) influence of the electronegativity and by stretching of the S-halogen bond in the transition state, as shown by the slight inversion in leaving group mobility on changing the nucleophile. As far as two-co-ordinate sulphur is concerned, the influence of a small S-X stretching in the transition state is overwhelmed by the electronegativity of the leaving group, which influences the formation of the intermediate much more easily through the much more polarizable sulphenyl sulphur atom.

The Brønsted coefficient for the leaving group measured by Vizgert¹¹ for alkaline hydrolysis of *para*-substituted phenyl benzenesulphonates ($\beta -0.6$) should be an indication of fairly large bond breaking in the transition state. However, we have suggested¹⁶ that for reactions which occur *via* an intermediate complex with bond making as the rate limiting step, β values might be linked to the ability of the leaving group to facilitate the formation of the intermediate complex.

One of the reasons put forward to exclude an intermediate complex in the solvolysis of benzenesulphonyl derivatives was the absence of ¹⁸O exchange between substrate and solvent during the reaction.⁵ However, a mechanism which assumes the fast decomposition of the intermediate to products cannot give rise to exchange of solvent with nucleophile since the intermediate never returns to starting materials. Such an exchange might be observed in the hydrolysis of benzenesulphonyl fluoride, since in this case the intermediate decomposes more easily to reagents than to products. However, in the trigonal bipyramidal intermediate the entering and leaving groups lie in apical positions while the sulphonyl oxygen atoms and the remainder of the molecule lie in radial positions.²⁶ Since the two positions are not equivalent, in order to observe exchange without contradicting the principle of microscopic reversibility, another condition must be fulfilled. The intermediate must pseudorotate before reverting to reagents. Up to now, pseudorotation, while very common for phosphorus,²⁷ has not been observed with sulphur substrates.²⁸ Thus, the ¹⁸O exchange experiments, while indicative of intermediate formation when they are positive, are inconclusive when they are negative.

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²⁷ E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1966, **88**, 3431; 3432.

²⁸ R. Tang and K. Mislow, *J. Amer. Chem. Soc.*, 1969, **91**, 5644.