

# Mechanisms of reactions of sulfonyl compounds with nucleophiles in protic media

James F. King, Manjinder S. Gill, and Darryl F. Klassen

Department of Chemistry, University of Western Ontario, London, Ontario, Canada  
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**Abstract:** The mechanism of the reaction of ethylene sulfone (thiirane 1,1-dioxide) with hydroxide in water and methoxide in methanol, been examined. Evidence has been obtained for two distinct pathways (respectively first order and second order in hydroxide), which are believed to proceed via attack of hydroxide on the sulfone to give a trigonal-bipyramidal monoanion which reacts either with water or with another hydroxide ion to form ethanesulfonate anion or ethylene plus sulfite anion in quite different proportions.

Study of the mechanisms of hydrolysis of alkanesulfonyl chlorides has been extended to (a) cyclopropanesulfonyl, (b) trimethylsilylmethanesulfonyl, (c) tris-(trimethylsilyl)-methanesulfonyl, (d) 2,2,2-trifluoroethanesulfonyl, and (e) 2-methyl-2-propanesulfonyl chlorides. The last hydrolyzes by initial *t*-butyl cation formation, while the others go by more or less precedented routes, usually by way of a sulfene.

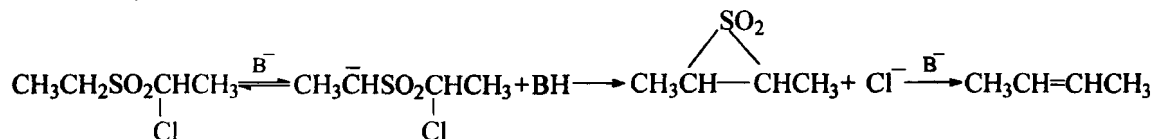
Reactions of arenesulfonyl chlorides with a number of primary and secondary amines show pH-yield profiles indicating third-order processes to the sulfonamide at high pH. The propensity for third-order reactivity increases with increasing hydrophobic character of the alkyl group(s). A practical result is that a number of amines are efficiently converted into their benzenesulfonamides using only a slight (5%) excess of benzenesulfonyl chloride in 1 M NaOH.

For a number of years we have been interested in the study of the mechanisms of reactions of the sulfonyl group, particularly those processes which lead to overall nucleophilic substitution. This paper presents three related topics each of which deals with the reactions of nucleophiles with a sulfonyl group in water. The specific topics, involve

- 1) ethylene sulfone and the final stage of the Ramberg-Bäcklund reaction,
- 2) the hydrolysis of alkanesulfonyl chlorides, and
- 3) new mechanisms of reaction of arenesulfonyl chlorides with nucleophiles.

## 1. The Ramberg-Bäcklund reaction and the reactions of ethylene sulfone with nucleophiles

The general course of the well-known Ramberg-Bäcklund reaction is shown below.



The first stages of the reaction have been extensively studied (1,2), but in virtually all Ramberg-Bäcklund reactions the episulfone intermediate is not isolated or observed, but is converted directly to the olefin. Although a thermal cheletropic extrusions of sulfur dioxide is well-precedented, it seems likely that in most Ramberg-Bäcklund reactions the episulfone is sufficiently stable that its further reaction is not the thermal reaction but rather a base-promoted process, and it is this final stage of the Ramberg-Bäcklund reaction that is relatively little understood. Bordwell and co-workers (3) have suggested that addition of methoxide to the sulfone should yield an anion with a hypervalent sulfur which might then proceed by a diradical species to the olefin; but, as we have noted elsewhere (4) the latter proposal was made prior to the recognition by Woodward and Hoffmann of the possibility of non-linear cheletropic extrusion, and such a cheletropic reaction of the hypervalent anion is a feasible pathway. To gain a clearer insight into the Ramberg-Bäcklund reaction and of

the general reactions of episulfones with nucleophiles, we have examined some of reactions of ethylene sulfone (thiirane 1,1-dioxide, **1**) with nucleophiles in protic media.

Ethylene sulfone (**1**) is obtained by two procedures, (a) diazomethane and sulfur dioxide (**5**), and (b) methanesulfonyl chloride and triethylamine in ether (**6**); both reactions evidently proceed via sulfene,  $\text{CH}_2=\text{SO}_2$ ; **1** is obtained as a distillable, low-melting solid which undergoes thermal decomposition on heating ( $k = 3.27 \times 10^{-5} \text{ s}^{-1}$  at  $77.8^\circ\text{C}$  (**7**)). The original paper of Hesse, *et al.* (**5**) reported that **1** with aqueous barium hydroxide gave the 2-hydroxyethanesulfinate anion,  $\text{HOCH}_2\text{CH}_2\text{SO}_2^-$ . We subsequently showed (**4**) that the sulfinate was, in fact, only a minor component of the reaction mixture and that the principal products were roughly comparable amounts of (a) ethanesulfonate anion (**4**) and (b) ethylene and sulfite dianion, the latter products recalling the Ramberg-Bäcklund reaction. Vilsmeier and co-workers (**8**) showed that a number of nucleophiles such as thiolates gave the 2-substituted ethanesulfinate anion while organometallic reagents led to desulfonylation with formation of ethylene and the alkanesulfinate anion.

Our studies of **1** were prompted by two questions. One was simply, what factors control attack by nucleophiles of sulfonyl groups at sulfur vs attack at other centres? The second question was, will any sulfonyl compound undergo attack at the sulfur atom to form a transient species which is itself attacked by a nucleophile to lead to the final product? This process is essentially Corriu's nucleophilic activation or nucleophilic assistance mechanism, evidence for which has been obtained with silicon and phosphorus species (**9**) but not, to our knowledge, with sulfur. Attack of hydroxide (for example), on **1** to form a species with a hypervalent trigonal-byramidal sulfur atom would be expected to be accompanied by release of ring strain, and hence a reaction of **1** might be expected to be a suitable place to look for nucleophilic assistance.

The rate of hydrolysis of **1** was measured conveniently by the pH-stat technique at  $70^\circ\text{C}$  and found to show good pseudo-first order kinetics. The pH-rate profile is shown in Fig. 1, and is consistent with the rate law  $k_{\text{obs}} = k_w + k_{\text{OH}}[\text{OH}^-]$ . The products at high pH ( $>11$ ) were ethanesulfonate (**4**), ethylene, and sulfite anion, along with a small amount of 2-hydroxyethane-sulfinate anion, as previously reported (**4**). At low pH ( $<9$ ), however, the only product observed with low concentrations of **1**, is 2-hydroxyethanesulfinate; higher concentrations of **1** lead to apparently polymeric materials. The  $k_w$  term evidently refers to the attack of water at the carbon with C-S bond cleavage, while the  $k_{\text{OH}}$  term describes a composite of three reactions. These and other observations suggested that S vs C attack of the nucleophile was related to the  $\text{pK}_a$  of the nucleophile, with highly basic O-nucleophiles attacking at carbon.

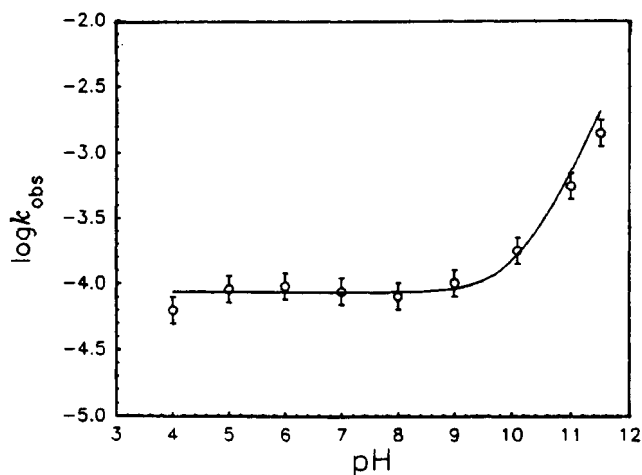


Fig. 1 pH-rate profile for the hydrolysis of ethylene sulfone (**1**) at  $70^\circ\text{C}$ .

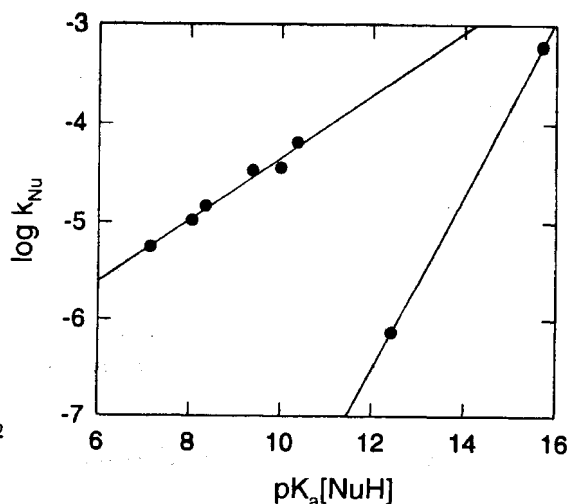


Fig. 2 Brønsted plot for the reaction of **1** with nucleophiles; left line: aryloxides, attack at carbon  $\beta_{\text{NuC}} = 0.27$ ; right line attack at sulfur  $\beta_{\text{NuS}} \approx 0.85$ .

For a series of aryloxide anions a Brønsted-type plot made from a set of competition experiments showed a good correlation of  $\log k$  with the  $\text{pK}_a$ 's of the phenols; (Fig. 2); the slope of the line gave  $\beta_{\text{NuC}} = 0.27$ , a value in good accord with those noted earlier (**10**) for  $\text{S}_{\text{N}}2$  processes of aryloxides. A rough estimate of  $\beta_{\text{NuS}}$  for the reaction at sulfur was obtained from a competition experiment which gave a  $\beta_{\text{NuS}}$  value of  $0.85 \pm 0.1$ . The very high  $\beta_{\text{Nu}}$  value is consistent with a very "tight" transition state with complete (or almost complete) C-S bond formation.

To gain further insight into the S-attack reaction, we examined the rates (at 25°C) at high hydroxide concentrations. A plot of  $k_{\text{obs}}$  vs either  $[\text{OH}^-]$  or the hydroxide activity,  $a_{\text{OH}^-}$ , as determined by Yagil (11), showed curved plots, pointing to a reaction both first and second order in hydroxide.

At this point it was noticed that the product composition varied with hydroxide concentration; this was conveniently followed by iodimetric titration of the sulfite (and sulfinate) anions. The results are shown in Fig. 3 as a pH-yield profile, and clearly to point to a change in mechanism for the formation of the products. The observed kinetics and yield variation may be accounted for in terms of the reaction pathway shown in the scheme below; at hydroxide concentrations below 1.5 M the major reaction is the decomposition of the monoanionic intermediate 2, whereas when  $[\text{OH}^-] \geq 2$  M the principal processes are the two modes of reaction of the dianion - either 3 or 4 (or both?).

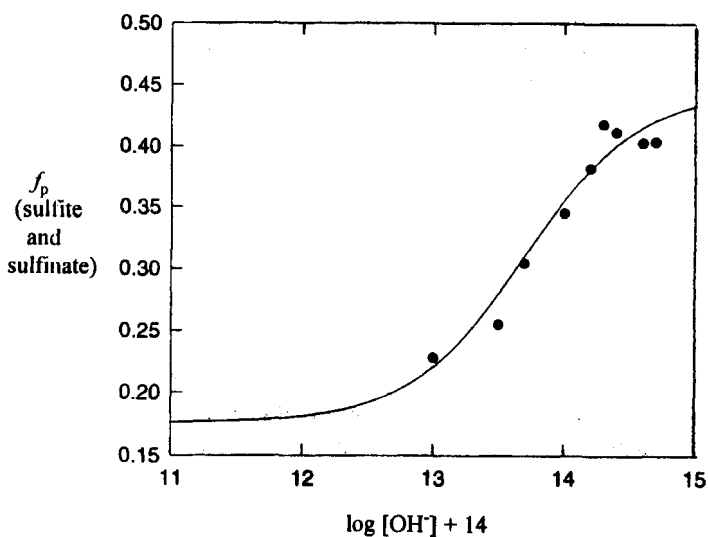
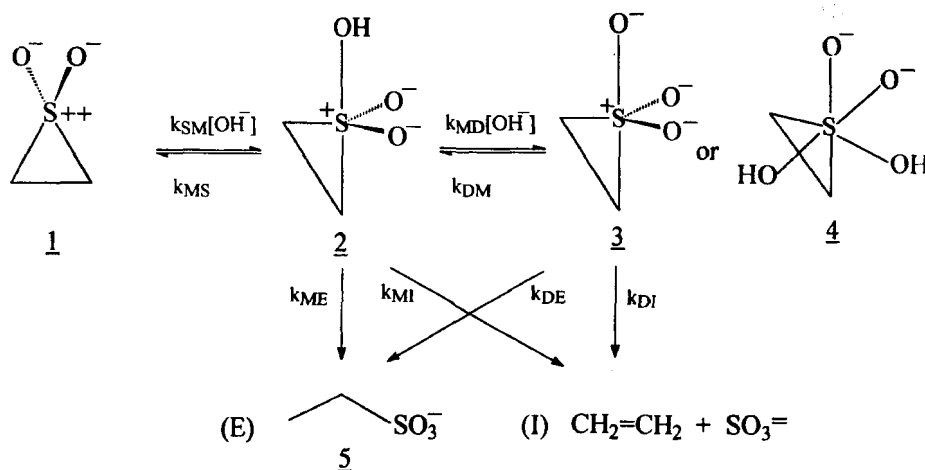


Fig. 3 pH-yield profile for the formation of sulfite and sulfinate from 1 and hydroxide.

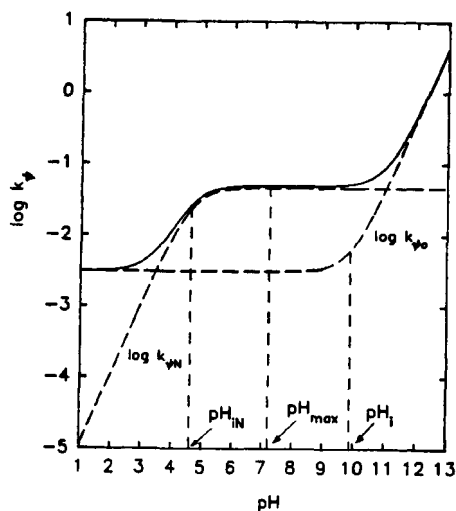


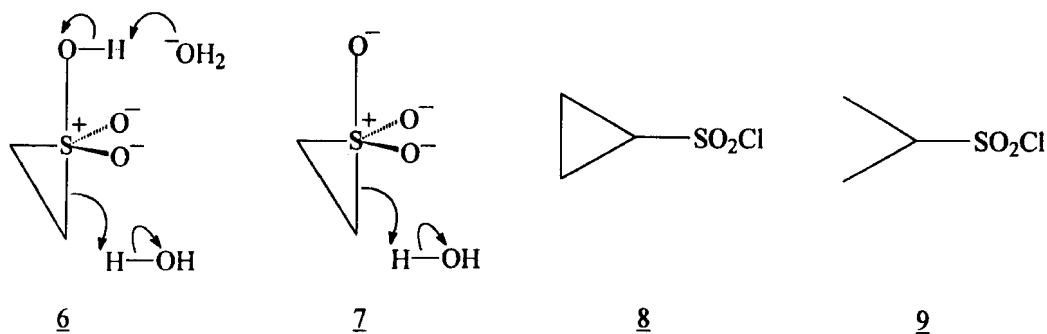
Fig. 4 pH-rate profiles for the reaction of aniline with benzenesulfonyl chloride.

With the idea of possibly distinguishing between a mechanism involving deprotonation (e.g. via 3) from one involving nucleophilic attack (e.g. via 4), we examined the reactions of 1 with sodium methoxide; the variation of the yield of sulfite (and sulfinate) with change in methoxide concentration was comparatively small, changing roughly linearly from about 45-50% with 0.1 to 0.2 M sodium methoxide to <60% with methoxide concentrations around 3 to 4 M. Reactions of sodium ethoxide were qualitatively similar.

We interpret the distinctly different shapes of the yield vs concentration curves shown by the hydroxide and methoxide reactions as probably indicating different mechanisms. For the reaction first order in hydroxide it is reasonable that monoanion 2 is subject to (a) simultaneous general base and general acid assistance by

water as indicated by **6** to give ethanesulfonate (**5**), and (b) simple cheletropic extrusion to yield ethylene and bisulfite anion. For the reaction second order in hydroxide the dianion **3** could react as in **7** with general acid assistance by water, or (b) with cheletropic extrusion to yield ethylene and bisulfite anion. There is, however, no requirement of a discrete dianionic intermediate (**3**), and the processes is second order in hydroxide could involve general base reactions with species akin to **3** as a transition states.

Finally, we note that the sequence **1** → **2** → **3** → products, proposed for the hydroxide reaction, can also be regarded as a form of nucleophilic activation; the further reaction of the "activated" species (**2**), however, involves the hydroxide acting as a base, rather than as a nucleophile, as is the case with Corriu's examples.



## 2. Mechanistic variation in the hydrolysis of alkanesulfonyl chlorides.

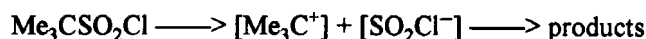
The hydrolysis of a number of alkanesulfonyl chlorides had been shown earlier (12) to obey the following rate law,  $k_{\text{obs}} = k_w + k_{\text{OH}} [\text{OH}^-]$ , with each of the two terms referring to a single, distinct process. The first order reaction is a simple attack by water on the sulfur atom, probably assisted by a second molecule of water acting as a general base, whereas the second order term describes an attack of the hydroxide anion with elimination of HCl to form the sulfene,  $\text{RR}'\text{C}=\text{SO}_2$ , which subsequently reacts with water or hydroxide; in the examples studied the  $k_w$  term involves >99% direct displacement at sulfur and the  $k_{\text{OH}}$  term >97% sulfene formation.

In extending our study to cyclopropanesulfonyl chloride (**8**), we found the same mechanisms at work, with a particular feature of interest being a notable change in the structure of the transition state occurring on changing the sulfene-forming base from hydroxide (in water) to triethylamine (in  $\text{CH}_2\text{Cl}_2$ ). In comparison with 2-propanesulfonyl chloride (**9**) we found  $(k_{\text{OH}})_8/(k_{\text{OH}})_9 = 1.5$  whereas with the corresponding triethylamine rate constants ( $k_{\text{EN}}$ ),  $(k_{\text{EN}})_8/(k_{\text{EN}})_9 = 0.015$ , a change of 100-fold! The kinetic isotope effects for  $\text{R}_2\text{CHSO}_2\text{Cl}$  vs  $\text{R}_2\text{CDSO}_2\text{Cl}$  were also informative,  $k_{\text{H}}/k_{\text{D}}$  values for **8** and **9** with  $\text{OH}^-/\text{H}_2\text{O}$  were, respectively, 5.1 and 4.0, but with  $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$  were very much smaller, 1.4 and 1.2, respectively. These observations are in good accord with a very "product-like" transition state for the  $\text{Et}_3\text{N}$  reactions, but with the hydroxide processes, a transition state with a greater negative charge on carbon and only a partly developed C-S double bond.

Trimethylsilymethanesulfonyl chloride was found to show the same rate law as the other alkanesulfonyl chlorides (14), but the only product from the  $k_w$  term and the major product from the hydroxide reaction was  $\text{CH}_3\text{SO}_3^-$ , presumably via sulfene ( $\text{CH}_2=\text{SO}_2$ ) formed from silicophilic attack of water and hydroxide. With hydroxide the minor product was  $\text{Me}_3\text{SiCH}_2\text{SO}_3^-$ , evidently from  $\text{Me}_3\text{SiCH}=\text{SO}_2$ . Fluoride ion in water (like CsF in acetonitrile (15)), also gave sulfene (14).

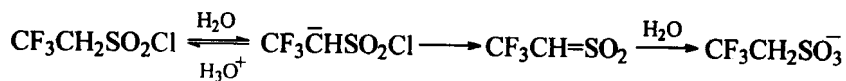
In a collaborative study with Dr. K.M. Baines, tris(trimethylsilyl)methanesulfonyl chloride,  $(\text{Me}_3\text{Si})_3\text{CSO}_2\text{Cl}$ , has been prepared (16). It has been found to react very rapidly with water to give products evidently derived from the sulfene,  $(\text{Me}_3\text{Si})_2\text{C}=\text{SO}_2$ ; this sulfene though carrying two bulky groups on the carbon, appeared to react readily and normally with nucleophiles.

2-Methyl-2-propanesulfonyl chloride,  $\text{Me}_3\text{CSO}_2\text{Cl}$ , is of interest because it is the simplest alkanesulfonyl chloride which lacks an  $\alpha$ -hydrogen and hence cannot undergo dehydrohalogenation to form a sulfene. The considerable array of hydrolysis products, including  $\text{Me}_3\text{COH}$ ,  $\text{Me}_3\text{CCl}$ ,  $\text{Me}_2\text{C}=\text{CH}_2$ , and  $\text{Me}_3\text{CSO}_2^-$  all evidently originate from an initial ionization (17):



Trifluoroethanesulfonyl chloride ("tresyl" chloride,  $\text{CF}_3\text{CH}_2\text{SO}_2\text{Cl}$ ) shows the typical pH-rate profile, but with the interesting feature that the product in  $\text{D}_2\text{O}$  over both the  $k_w$  and  $k_{\text{OH}}$  ranges, is  $\text{CF}_3\text{CHDSO}_3^-$ .

Taken with the observation of H-D exchange in the tresyl chloride itself in either 4 M DCl or 5 M D<sub>2</sub>SO<sub>4</sub>, these observations are consistent with a carbanion process reminiscent of one originally suggested for Cl<sub>2</sub>CHSO<sub>2</sub>Cl hydrolysis by Seifert, *et al.* (18):



We have no evidence yet about the mechanism of the reaction of hydroxide with tresyl chloride.

### 3. pH-yield profiles and new mechanisms of reaction of arenesulfonyl chlorides with nucleophiles.

We have recently shown (19) that for the reaction of a hydrolysable electrophile (e.g. PhCOCl, PhSO<sub>2</sub>Cl) with a basic nucleophile in water, one may readily predict the optimal pH for the reaction (pH<sub>max</sub>) from eq. 1.

$$\text{pH}_{\text{max}} = \frac{1}{2}(\log k_w/k_{\text{OH}} + \text{p}K_w + \text{p}K_a) \quad (1)$$

In eq. 1  $k_w$  and  $k_{\text{OH}}$  are the rate constants for the hydrolysis of the electrophile by water and hydroxide,  $K_w$  is the ionization constant of water, and  $K_a$  the dissociation constant of the conjugate acid of the nucleophile. Fig. 4 shows the pH-rate profile for the reaction of benzenesulfonyl chloride with aniline in water; since it is easy to show that  $\text{pH}_i = \log k_w/k_{\text{OH}} + \text{p}K_w$  and  $\text{p}K_{\text{IN}} = \text{p}K_a$ , eq. 1 follows from inspection of Fig. 4.

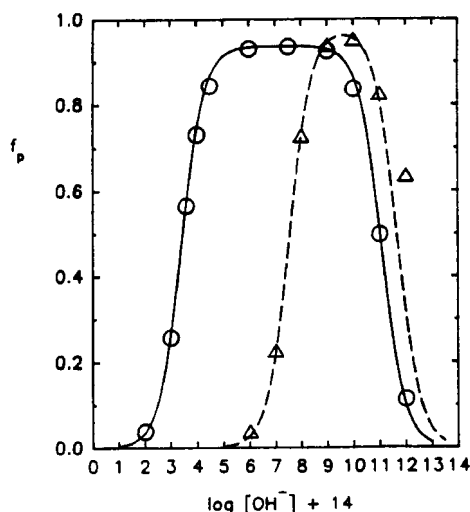


Fig. 5 pH-yield profiles for the reactions, under pseudo-first order conditions, of PhSO<sub>2</sub>Cl with PhNH<sub>2</sub> (solid) and PhCH<sub>2</sub>NH<sub>2</sub> (broken).

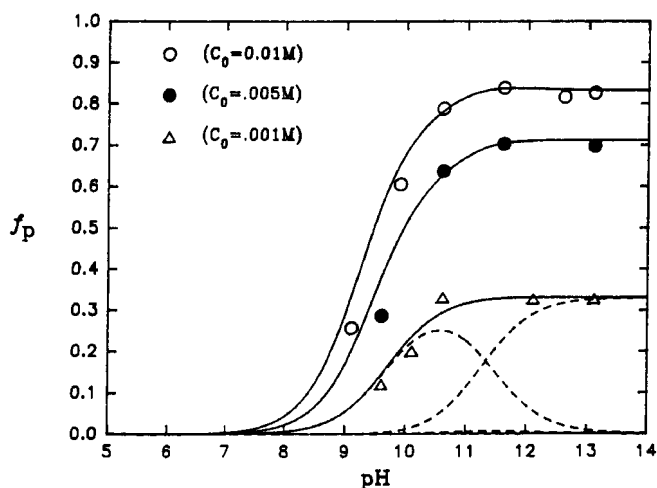


Fig. 6. pH-yield profiles for the reaction of PhSO<sub>2</sub>Cl and Bu<sub>2</sub>NH, under pseudo-first order conditions.

Under pseudo-first-order conditions it is also possible to obtain a pH-yield profile (Fig. 5) for the formation of PhSO<sub>2</sub>NHPh (solid line) in this reaction; the equation for the lines is readily derived from the rate law (19).

We have subsequently found that pH-yield profiles can be useful indicators of mechanism. Our first examples involved (a) arenesulfonyl chloride with phenoxide anion (20), and (b) acetic anhydride with primary and secondary amines (21). In both of these cases plots from the equation for  $f_p$  vs pH (19) gave poor agreement with experiment until the rate law (and the equation for  $f_p$ ) was modified to include a term for general-base promoted hydrolysis of the electrophile by the nucleophile; kinetic studies fully confirmed the role of the general-base term (20,21).

We have more recently undertaken further study of the reaction of benzenesulfonyl chloride and amines in water and obtained surprising results. In addition to curves like those in Fig. 5 we find from many amines curves showing unexpectedly high yields at high pH, e.g. as shown in Fig. 6. These curves may be interpreted with the aid of two additional reactions, both third order overall, leading to the following rate law.

$$k_{\text{obs}} = k_w + k_{\text{OH}}[\text{OH}^-] + k_{\text{N}}[\text{Nu}^-] + k_{\text{NN}}[\text{Nu}^-]^2 + k_{\text{NOH}}[\text{Nu}^-][\text{OH}^-]$$

We regard the third-order reactions as involving general-base assistance of the nucleophilic attack of the amine by either hydroxide ion or a second molecule of the nucleophile. The observed trend is that  $k_N$ ,  $k_{NN}$ ,  $k_{NOH}$  all increase with the 'size' of the alkyl group, e.g. in the series diethylamine, dipropylamine, and so on. This suggests the intervention of hydrophobic effects and of aggregates of the organic species.

In practical terms these reactions make it possible to carry out preparations with benzenesulfonyl chloride (and benzoyl chloride) at high pH. This may be illustrated by the yields of sulfonamides obtained under the following conditions in the reaction of benzenesulfonyl chloride (0.105 M) with the following specified amines (0.10 M) in 1 M aqueous NaOH at 25°C, reaction times varying from 0.5 to 1 h: diethylamine, 87%; dibutylamine, 94%; hexamethylenimine, 97%; octylamine, 98%. Butylamine under these conditions gave only a 45% yield, but at pH 10.2 ( $pH_{max}$  based on eq. 1) gave a 99% yield of the amide. These reactions in 1 M NaOH are essentially milder and less wasteful versions of the Schotten-Baumann conditions, and suggest that the success of the Schotten-Baumann procedure may have its roots in the tendency of these reactants to associate in aqueous media and hence to react via third- and higher-order processes.

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