Catalysis of the Hydrolysis of Aryl Sulfonyl Fluorides by Acetate Ion and Triethylamine[1a]

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The ability of (1) acetate and (2) triethylamine to catalyze the hydrolysis of aryl sulfonyl fluorides in aqueous dioxane has been explored kinetically. Acetate ion does catalyze the hydrolysis, and the solvent isotope effect associated with the acetate-catalyzed reaction indicates that this is due to nucleophilic catalysis (eq 1). The relative effectiveness of acetate as a catalyst, as measured by the ratio of the rate constant for the acetate-catalyzed reaction to that for spontaneous hydrolysis of the sulfonyl fluoride under the same conditions, appears to be closely comparable to its relative effectiveness as a catalyst for the hydrolysis of aryl sulfonyl chlorides and α-disulfones. Catalysis by triethylamine, while detectable in competition with the normal alkaline hydrolysis of $ArSO_2F$ in 1:1 Et_3N–Et_3NH^+ buffers, is relatively much less important compared to the normal alkaline hydrolysis under these conditions than in the hydrolysis of aryl α-disulfones, but considerably more important than in the hydrolysis of *p*-nitrophenyl *p*-toluenesulfonate. The possible mechanistic significance of this result is discussed.

Although they react readily with hydroxide ion, sulfonyl fluorides hydrolyze very slowly in neutral or acidic aqueous solution.[2,3] On the other hand, when complexed to a macromolecule such as an enzyme[4] or cellulose,[5] sulfonyl fluorides can undergo rapid covalent bond formation with OH groups on the macromolecule. Catalysis of the hydrolysis of the sulfonyl fluoride by the enzyme can also occur.[4] In view of the very slow rate of spontaneous hydrolysis of sulfonyl fluorides, it would appear that there must be very effective intramolecular catalysis by functional groups on the macromolecule in each of the reactions mentioned.

This suggested to us that a study of the possible catalysis of the hydrolysis of sulfonyl fluorides by such simple species as carboxylate ions and nitrogen bases might prove interesting and informative. Functional groups of these types are present in the side chains of protein amino acid residues and have often been implicated in the catalytic activity of various enzymes. We also knew that such species as acetate ion and triethylamine are able to catalyze the hydrolysis of sulfonyl derivatives with better leaving groups than F, namely, sulfonyl chlorides[6] ($ArSO_2Cl$) and α-disulfones[7] ($ArSO_2SO_2Ar$), and so it seemed quite reasonable that catalysis by those species might also be important for the hydrolysis of aryl sulfonyl fluorides.

We have therefore investigated the hydrolysis of several aryl sulfonyl fluorides in the presence of a representative carboxylate ion, acetate ion, and in the presence of a typical tertiary amine, triethylamine, in order to see whether there was marked catalysis of the hydrolysis by either species, and to then determine, if significant catalysis was observed, whether this catalysis was nucleophilic or general base catalysis.

Results

Catalysis of the Hydrolysis of Aryl Sulfonyl Fluorides by Acetate Ion. The disappearance of the aryl sulfonyl fluoride was followed spectrophotometrically in acetate buffers in 20% dioxane (v/v) as solvent using added potassium chloride to maintain a constant ionic strength of 0.04. In runs with *m*-nitrobenzenesulfonyl fluoride a wavelength of 275 nm was used to follow the reaction; with *p*-toluenesulfonyl fluoride the wavelength used was 235 nm. Depending on the sulfonyl fluoride, the data were plotted as either log $(A - A_\infty)$ or log $(A_\infty - A)$ vs. time. Plots of this type were linear and the experimental first-order rate constant, k_1, for the disappearance of the sulfonyl fluoride was evaluated in the usual way from the slope of such plots.

Our initial studies were conducted with *p*-toluenesulfonyl fluoride as the substrate. However, the disappearance of this sulfonyl fluoride, even in the presence of 0.04 *M* acetate at 90°, was rather slow ($t_{1/2} \simeq 5$ hr), and there seemed to be difficulty in determining the infinity value of the absorbance accurately and getting reproducible rate constants. For this reason the decision was made to switch to *m*-nitrobenzenesulfonyl fluoride as the substrate. This reacts about 30 times faster than the *p*-tolyl compound, just as it undergoes spontaneous hydrolysis much more readily than $p\text{-}CH_3C_6H_4SO_2F$.[3]

Table I
Hydrolysis of *m*-Nitrobenzenesulfonyl Fluoride in Acetate Buffers in 20% Dioxane at 91°

10^5 [$ArSO_2F$]$_0$, *M*	[AcO^-], *M*	[AcOH], *M*	[KCl], *M*[a]	$10^4 k_1$, sec^{-1}
8.0	0.00	0.00	0.04	0.51 ± 0.03
	0.01	0.01	0.03	3.4 ± 0.3
				2.3 (D_2O)
	0.02	0.02	0.02	4.7 ± 0.4
				4.6 (D_2O)
	0.03	0.03	0.01	6.1 ± 0.5
				6.4 (D_2O)
	0.04	0.04	0.00	8.7 ± 0.6
				8.9 (D_2O)
	0.04	0.02	0.00	9.9

[a] The same rates were obtained when $LiClO_4$ was used in place of KCl to maintain ionic strength in the AcO^-–AcOH buffers.

The *m*-nitro compound underwent hydrolysis in 1:1 acetate–acetic acid buffers at a convenient rate at 91°. The results are shown in Table I, along with the rates of hydrolysis under identical conditions in 20% dioxane–80% D_2O. Evidence that acetate, and *not* acetic acid, is the species responsible for the catalysis of the hydrolysis of the sulfonyl fluoride in these buffers was provided by an experiment using a 2:1 AcO^-–AcOH buffer containing 0.04 *M* AcO^-. The rate of hydrolysis was not less than that found for a 1:1 buffer containing 0.04 *M* AcO^-.

Salomaa and coworkers[8] have pointed out that in mixed dioxane–water solvents apparent catalysis by a buffer component can *sometimes* result from accidental salt effects involved with the control of ionic strength. Their results, however, indicate that, if one gets the same rates for a series of experiments of the type shown in Table I when the ionic strength is maintained with an alkali metal perchlorate as when it is maintained with an alkali metal chloride, one can feel quite confident that an effect of this type is

Table II
Hydrolysis of Aryl Sulfonyl Fluorides in Triethylamine Buffers in 60% Dioxane at 25°

$ArSO_2F$, Ar =	10^4 $[ArSO_2F]_0$, M	$[Et_3N]$, M	$[Et_3NH^+]$, M	$[LiClO_4]$, M	$10^4 k_1$, sec^{-1}
m-$O_2NC_6H_4$	8.0	0.01	0.01	0.2375	7.2 ± 0.1
		0.02	0.02	0.2275	8.3 ± 0.3
		0.04	0.04	0.2075	9.8 ± 0.2
		0.06	0.06	0.1875	11.0 ± 0.1
p-BrC_6H_4	6.0	0.02	0.02	0.2275	0.95 ± 0.07
		0.04	0.04	0.2075	1.10 ± 0.01
		0.06	0.06	0.1875	1.21 ± 0.01

not operating and that one is observing true catalysis by the buffer component. In the present work we observed no change in rate when lithium perchlorate was used instead of potassium chloride to maintain ionic strength in the AcO^-–AcOH buffers. Therefore we are confident that the catalysis being observed here with acetate ion is in fact either nucleophilic or general base catalysis, and *not* an accidental salt effect.

Plots of k_1 vs. $[AcO^-]$ for both the runs in 20% dioxane–80% H_2O and 20% dioxane–80% D_2O are satisfactorily linear, indicating a first-order dependence of the rate of the catalyzed reaction on acetate concentration. From the slopes of the plots $k_{OAc}(H_2O)$ is estimated to be 0.020 ± 0.002 M^{-1} sec^{-1}, and $k_{OAc}(D_2O)$ as 0.022 ± 0.001 M^{-1} sec^{-1}, giving a solvent isotope effect for catalysis by acetate, $k_{OAc}(H_2O)/k_{OAc}(D_2O)$, of 0.9 ± 0.2.

Hydrolysis of Aryl Sulfonyl Fluorides in Triethylamine Buffers. Rates of disappearance of the sulfonyl fluorides were followed spectrophotometrically in 1:1 Et_3N–Et_3NH^+ buffers in 60% dioxane (v/v) at 25°, using lithium perchlorate to maintain a constant total ionic strength of 0.25. The triethylamine concentration was varied between 0.01 and 0.06 *M*. *m*-Nitrobenzenesulfonyl fluoride and *p*-bromobenzenesulfonyl fluoride were used as substrates. The disappearance of the sulfonyl fluorides followed good first-order kinetics, and the experimental first-order rate constants, k_1, for the different conditions are shown in Table II.

Figure 1 shows a plot of k_1 vs. $[Et_3N]$ for the data in Table II. One can see that, while there is some increase in rate with increasing $[Et_3N]$, the intercept on the k_1 axis at $[Et_3N]$ = 0.00, which represents the contribution to k_1 from the reaction of the sulfonyl fluoride with hydroxide ion present in the Et_3N–Et_3NH^+ buffers, is in both cases equal to, or larger than, the increase in rate brought on by the addition of 0.06 *M* Et_3N. Because in each case the triethylamine-catalyzed reaction constituted only a relatively modest portion of the total rate of disappearance of the sulfonyl fluoride, even at high triethylamine concentrations, we did not attempt to determine the solvent isotope effect associated with it. From the slopes of the plots in Figure 1 k_{Et_3N} is estimated to be about 7×10^{-3} M^{-1} sec^{-1} for the reaction involving *m*-$O_2NC_6H_4SO_2F$ and $\sim 6 \times 10^{-4}$ M^{-1} sec^{-1} for the *p*-bromo compound.

Discussion

Catalysis of the Hydrolysis of Aryl Sulfonyl Fluorides by Acetate Ion. The results in Table I show that the hydrolysis of an aryl sulfonyl fluoride can definitely be catalyzed by acetate ion. In principle, this could be either general base catalysis or nucleophilic catalysis, but the observation that the solvent isotope effect associated with the acetate-catalyzed reaction is 0.9 ± 0.2 suggests that nucleophilic catalysis (eq 1) is what is involved in the present

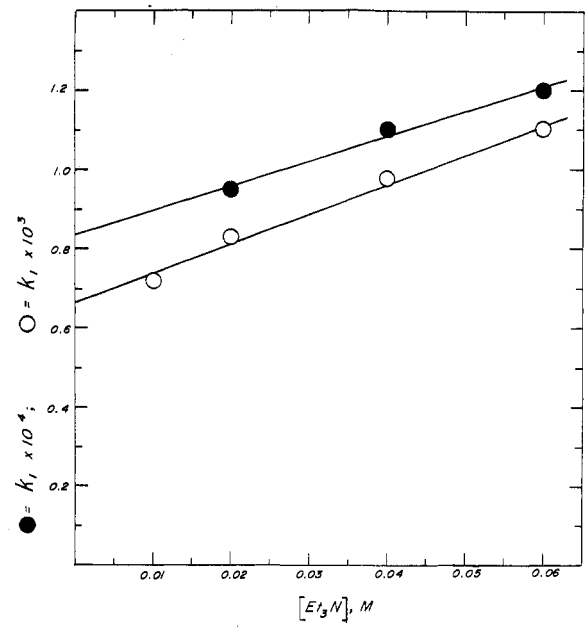

Figure 1. Rates of hydrolysis of aryl sulfonyl fluorides in 1:1 Et_3N–Et_3NH^+ buffers in 60% dioxane at 25° as a function of $[Et_3N]$: data for *m*-nitrobenzenesulfonyl fluoride, ○; data for *p*-bromobenzenesulfonyl fluoride, ●.

case.[9] This is the same type of catalysis observed with acetate in the hydrolysis of aryl sulfonyl chlorides[6] and α-disulfones.[7a]

$$AcO^- + ArSO_2F \xrightarrow{k_{OAc}} F^- + ArSO_2OAc \xrightarrow[\text{fast}]{H_2O} ArSO_3^- + AcO^- + 2H^+ \quad (1)$$

Presumably the reason that $ArSO_2OAc$ hydrolyzes more rapidly than either $ArSO_2F$, $ArSO_2Cl$, or $ArSO_2SO_2Ar$ is because attack of water on the *carbonyl* group of $CH_3C(O)OSO_2Ar$ is much faster than attack of water on the sulfonyl group of any of the sulfonyl substrates. That this should be the case is not surprising, since $ArSO_2O$ represents an excellent leaving group, and nucleophilic attack on a carbonyl carbon is generally much more rapid than attack on an equivalent sulfonyl sulfur.[10]

The relative effectiveness of acetate as a catalyst for the hydrolysis of an aryl sulfonyl fluoride seems to be very similar to its effectiveness as a catalyst for the hydrolysis of aryl sulfonyl chlorides[6] or α-disulfones.[7a] Thus, using as a measure of effectiveness the ratio k_{OAc}/k_{H_2O}, where k_{H_2O} is the rate constant for the spontaneous hydrolysis of the sulfonyl derivative under the same reaction conditions, the values of k_{OAc}/k_{H_2O} are 400, 500, and 2000 for the hydrolyses of the sulfonyl fluoride, sulfonyl chloride,[6] and α-disulfone,[7a] respectively. Clearly, then, while acetate, and presumably other carboxylate ions, can catalyze the hydrolysis of a sulfonyl fluoride, their ability to do this parallels their ability to catalyze the hydrolyses of other sulfonyl derivatives having better leaving groups, and there is no special synergism associated with the carboxylate ion–sulfonyl fluoride system. The origin of the rapid rate of reaction of sulfonyl fluorides with OH groups in certain macromolecules vis-à-vis their slow rate of spontaneous hydrolysis does not therefore have its origin in some unusual rate enhancement due to neighboring carboxylate groups in the macromolecule, at least insofar as being the result of some particularly favorable rate for reaction of a carboxylate ion with a sulfonyl fluoride, as compared to the ease of reaction of $RCOO^-$ with hydrolytically more reactive sulfonyl derivatives.

Hydrolysis of Aryl Sulfonyl Fluorides in Triethyl-

amine Buffers. As is evident from Figure 1, most of the rate of hydrolysis of an aryl sulfonyl fluoride in a 1:1 Et_3N–Et_3NH^+ buffer in 60% dioxane is due to the reaction of hydroxide ion with the sulfonyl fluoride (eq 2) and not to a

$$HO^- + ArSO_2F \xrightarrow{k_{OH}} F^- + ArSO_3H \xrightarrow[\text{fast}]{OH^-} ArSO_3^- \quad (2)$$

triethylamine-catalyzed reaction. This contrasts with the behavior of phenyl α-disulfone under the same conditions,[7b] where most of the rate was due to a triethylamine-catalyzed reaction. On the other hand, while a kinetic term dependent on $[Et_3N]$ is still clearly detectable in the hydrolyses of the two sulfonyl fluorides in Table II, no triethylamine-dependent term could be observed in the hydrolysis of *p*-nitrophenyl *p*-toluenesulfonate, $ArSO_2OC_6H_4NO_2$-*p*, in the same buffer and solvent medium.[11] These several results suggest that as the leaving group gets poorer it becomes more difficult for a triethylamine-catalyzed reaction to compete kinetically in a 1:1 Et_3N–Et_3NH^+ buffer with the normal alkaline hydrolysis of the sulfonyl derivative (eq 2 for $ArSO_2F$).

This would seem to be more consistent with the idea that any catalysis of the hydrolysis of these sulfonyl derivatives by triethylamine involves nucleophilic catalysis, rather than general base catalysis, as was originally suggested,[7b] since, with general base catalysis, all else being equal, one normally finds that such catalysis is more important the poorer the leaving group.[12]

We had originally hoped that the hydrolysis of aryl sulfonyl fluorides might prove just as good a system in which to explore catalysis of the hydrolysis of sulfonyl derivatives as the hydrolysis of sulfonyl chlorides[6] or α-disulfones.[7] The experiments outlined in the present paper strongly suggest, however, that this is not so, and have discouraged us from undertaking any further current work in this area. Despite their somewhat esoteric nature the aryl α-disulfones appear to provide a considerably more versatile system in which to study catalysis[7] of substitution at sulfonyl sulfur, as well as nucleophilic reactivity.[13]

Experimental Section

Preparation and Purification of Reagents. *p*-Bromobenzenesulfonyl fluoride was prepared by the method of Aberlin and Bunton,[3] mp 64–65° (lit.[3] mp 65–66°). The other sulfonyl fluorides were obtained from commercial sources, *m*-nitrobenzene- (Alfred Bader) and *p*-toluene (Aldrich), and were recrystallized from ethanol–water prior to use. Triethylamine and dioxane were purified by previously described procedures.[11] Sodium acetate, acetic acid, lithium perchlorate, and potassium chloride were all analytical reagent grade and were used without further purification.

Procedure for Kinetic Runs in Acetate Buffers. The runs were carried out under nitrogen in a reaction vessel of a type previously used[14] which permits an aliquot of the reaction solution to be withdrawn without exposing the rest of the solution to the atmosphere. Fifty milliliters of a solution containing the proper amounts of sodium acetate, acetic acid, and either potassium chloride or lithium perchlorate in 20% dioxane (v/v) as solvent was placed in the reaction vessel, 0.5 ml of a 0.008 *M* solution of the sulfonyl fluoride in pure dioxane was added and thoroughly mixed with the acetate buffer, and the final reaction solution was then deaerated by passing a stream of nitrogen through the cooled solution for a number of minutes. The flask containing the reaction solution was then placed in a constant-temperature bath at 91° and aliquots of the reaction solution were removed at appropriate time intervals, stoppered, and quickly cooled in ice to stop further reaction, and then kept at 0° until all the aliquots that were going to be taken in that particular run had been removed. Their absorbance, and that of the aliquot removed after reaction was complete, was then measured at an appropriate wavelength using either a Cary Model 14 or Perkin-Elmer Model 402 spectrophotometer. Runs involving *m*-nitrobenzenesulfonyl fluoride were followed at 275 nm, those with *p*-toluenesulfonyl fluoride at 235 nm.

Procedure for Kinetic Runs with Triethylamine Buffers. The kinetics of the hydrolyses in the 1:1 Et_3N–Et_3NH^+ buffers were followed by monitoring continuously the absorbance of a solution of the sulfonyl fluoride in the appropriate buffer in a thermostatted 1-cm cell in the cell compartment of either a Cary Model 14 or Perkin-Elmer Model 402 spectrophotometer. For each run the proper volume of a stock solution containing 0.12 *M* Et_3N and 0.12 *M* $Et_3NH^+ClO_4^-$ in 60% dioxane was pipetted into the reaction cell, followed by the necessary amount of a 0.75 *M* stock solution of lithium perchlorate in the same solvent. After mixing, the cell containing the solution was placed in the thermostatted cell holder in the spectrophotometer and allowed to come to 25°. A small, known amount of a freshly prepared stock solution of the sulfonyl fluoride, which had also been brought to 25°, was then quickly added to the spectrophotometer cell, the cell was shaken vigorously to ensure complete mixing and quickly replaced in the cell holder, and measurements of absorbance vs. time were then started.

Registry No.—*p*-Bromobenzenesulfonyl fluoride, 498-83-9; *m*-nitrobenzenesulfonyl fluoride, 349-78-0; *p*-toluenesulfonyl fluoride, 455-16-3; acetate ion, 71-50-1; triethylamine, 121-44-8.

References and Notes

(1) (a) This research was supported by the National Science Foundation, Grant GP-35927X. (b) Address correspondence to Department of Chemistry, Texas Tech University, Lubbock, Texas 79409.
(2) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 246 (1953).
(3) M. E. Aberlin and C. A. Bunton, *J. Org. Chem.*, **35**, 1825 (1970).
(4) B. R. Baker, *Acc. Chem. Res.*, **2**, 129 (1969), and references cited therein.
(5) B. Krazer and H. Zollinger, *Helv. Chim. Acta*, **43**, 1513 (1960); (b) B. R. Baker and G. J. Lourens, *J. Med. Chem.*, **10**, 1113 (1967).
(6) O. Rogne, *J. Chem. Soc. B*, 1056 (1970).
(7) (a) J. L. Kice, G. J. Kasperek, and D. Patterson, *J. Am. Chem. Soc.*, **91**, 5516 (1969); (b) J. L. Kice and G. J. Kasperek, *ibid.*, **92**, 3393 (1970).
(8) P. Salomaa, A. Kankaanperä, and M. Lahti, *J. Am. Chem. Soc.*, **93**, 2084 (1971).
(9) A referee has noted that an extrapolation from known room temperature data to 91° would suggest that general base catalysis by acetate ion at that temperature would generate a solvent isotope effect in the range 1.4–1.8. He feels that the lower limit of this range is close enough to the upper limit of the actual measured solvent isotope effect of 0.9 ± 0.2 so that drawing the conclusion from the solvent isotope effect that the catalysis by acetate is nucleophilic in character rather than general base, while probably correct, is subject to some risk.
(10) J. L. Kice, "Inorganic Reaction Mechanisms, Part II", J. O. Edwards, Ed., Wiley, New York, N.Y., 1972, p 162.
(11) J. L. Kice, C. A. Walters, and S. B. Burton, *J. Org. Chem.*, **39**, 349 (1974).
(12) It is possible, of course that a change in the leaving group might have a larger effect on k_{OH} than it does on the rate constant for a general base catalyzed reaction involving triethylamine, although, since attack of OH^- on the sulfonyl compound should almost certainly be rate determining for reaction of hydroxide ion with each substrate, we find this rather difficult to believe. A decrease in k_{Et_3N}/k_{OH} with nature of the leaving group is, however, readily explicable if triethylamine catalysis is nucleophilic catalysis.[11]
(13) J. L. Kice and E. Legan, *J. Am. Chem. Soc.*, **95**, 3912 (1973).
(14) J. L. Kice and K. W. Bowers, *J. Am. Chem. Soc.*, **84**, 605 (1962).