the column temperature was raised to 200 °C to elute the heavy byproducts). The first sample, taken after 2 h, showed a ratio of **5**/**6**/$C_{13}H_{22}$ of 96.8:2.4:0.7, but the peak for **7** was too small for accurate integration; therefore that data point was not included in Table I. The next sample (at 4 h) is entry 2 of Table I. To drive the reaction to equilibrium, fresh TFMSA was added after 10.5 h (150 mg), 23 h (200 mg), and 30.25 h (320 mg). The following sample (47 h) showed a **7**/**6** ratio of 25.8, which did not change to 71.5 h. **6**: M = 176 (GC-MS).

Batch II of Table I was conducted in the same way, except that 320 mg (2.81 mmol) of TFMSA was used. The first sample (entry 5) was taken after 1 h, and the last (entry 15), after 23 h.

Rearrangement of 5 with $AlBr_3$. The installation was the same as above, except that a 25-mL flask was used. **5** (0.57 g, 3.25 mmol), carbon disulfide (12 mL, reagent grade), and aluminum bromide (0.22 g, 0.825 mol, measured under nitrogen inside a drybox) were added, and then the tube to the nitrogen line was replaced with a connection to an HBr lecture bottle. The installation was flushed with HBr at the beginning of the run and occasionally thereafter. Sampling was done as described above. The first sample was taken after 20 min, and the highest concentration of **6** (checked on column B at 134 °C) was 7.9% after 50 min. The equilibrium ratio **7**/**6** (26.5) was reched after 9 h.

Rearrangement of 11 with $AlBr_3$.[10] In order to reduce the conversion rate, this reaction was run at 15 °C with more dilute catalyst. Aluminum bromide (0.5 g) was dissolved in CS_2 (25 mL) in the drybox; 5 mL of the resulting solution (0.37 mmol of $AlBr_3$) was brought to the reaction temperature and mixed with a solution of 0.35 g of **11** (2 mmol) in 5 mL of CS_2 at the same temperature. The installation and sampling technique were the same as above. Analysis was done mostly on column A at 120-250 °C; some samples were also checked on column C, as above. Samples taken at 0.25, 0.67, 2.0, 3.5, 5.0, 7.5, and 23 h are presented in Table I.

Acknowledgment. The high-field NMR spectra were run on a NR250 IBM instrument, a gift from the IBM Corp. to Clarkson University. The gas chromatograph (Perkin Elmer, Model Sigma 115) and the Vacuum-Atmospheres drybox were donated by Exxon Corp. We are also indebted to Prof. John E. Baldwin and Naresh Ghatlia for the GC-MS determinations, to Dr. Tonis Pehk for the high-resolution NMR spectra (^1H and ^{13}C), to Dr. C. S. Hsu for the high-resolution mass spectra, to Prof. Paul v. R. Schleyer for helpful discussions, and to Prof. Wolfgang Kirmse for communicating to us the results of ref 9 prior to publication.

Supplementary Material Available: An addition to the partial tricycloundecane rearrangement graph published previously[10] (Scheme III) with comments (3 pages). Ordering information is given on any current masthead page.

Mechanism of Solvolysis of Substituted Benzoyl Halides[1]

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Abstract: Most substituted benzoyl fluorides undergo hydrolysis in aqueous solution through an associative mechanism with ρ = 1.7, k_{HOH}/k_{DOD} = 2.3 ± 0.2, little dependence on the leaving group (k_{Cl}/k_F = 1.2), and general-base catalysis by fluoride ion. There is an abrupt change to a dissociative mechanism through an acylium ion intermediate for the hydrolysis of *p*-(dimethylamino)benzoyl and (in part) *p*-anisoyl fluorides, with $\rho^+ \leq -1.2$, $k_{Cl}/k_F = 10^6$-10^7, and k_{HOH}/k_{DOD} = 1.1 for *p*-$Me_2NPhCOF$. Common ion inhibition by fluoride ion traps the *p*-(dimethylamino)benzoyl acylium ion, which undergoes hydration with $k_h \sim 10^9$-10^{10} s^{-1}. The increase in the solvent isotope effect for hydrolysis of *p*-(dimethylamino)benzoyl fluoride to k_{HOH}/k_{DOD} = 1.9 in the presence of concentrated potassium fluoride is attributed to general-base-catalyzed hydration of the acylium ion intermediate. The large yield of trifluoroethyl ester from the solvolysis of *p*-anisoyl fluoride in TFE/EtOH/HOH suggests that the acylium ion reacts in a solvent-separated ion pair, with $k_h \sim 10^{12}$ s^{-1}; extrapolation predicts rate constants of $\geq 10^{13}$ s^{-1} for the hydration of less stable acylium ions. A change in sensitivity to solvent ionizing power from m = 1.4 in water to m = 0 in 60% ethanol for *p*-(dimethylamino)benzoyl fluoride suggests a change to an associative mechanism. Benzoyl fluorides and acylium ions show selectivity toward alcohols, with $\beta_{nuc} \sim 0.2$. The absence of common ion inhibition for the solvolysis of several benzoyl chlorides in water or 90% TFE/HOH is consistent with $k_h > 10^{11}$ s^{-1} for the acylium ions. Solvolysis occurs through the dissociative reaction channel, with $\rho^+ = -3.0$, even when the estimated lifetimes of the acylium ion species suggest that there is no chemical barrier for their hydration. However, there is a change to an associative mechanism for the solvolysis of *p*-nitrobenzoyl chloride in water.

In spite of intensive experimental examination of the mechanism of acyl-transfer reactions for many years, the mechanisms of most of these reactions are still not established.[2,3] Acyl-transfer reactions are commonly classified into three groups: (1) A dissociative mechanism, which may proceed through an acylium ion intermediate (S_N1)

$$\mathrm{RCOX} \longrightarrow \mathrm{RC^{+}{=}O\ X^{-}} \xrightarrow{+Nu^-} \mathrm{RCONu} \qquad (1)$$

(2) A direct displacement mechanism (S_N2)

$$\mathrm{RCOX} \xrightarrow{+Nu^-} [\mathrm{TS}]^{\ddagger} \xrightarrow{-X^-} \mathrm{RCONu} \qquad (2)$$

(3) An associative addition-elimination mechanism, which may proceed through a tetrahedral intermediate (AE).

$$\mathrm{RCOX} \xrightarrow{+Nu} \mathrm{R{-}C(O^-)(Nu){-}X} \xrightarrow{-X^-} \mathrm{RCONu} \qquad (3)$$

However, this classification of mechanisms is ambiguous because there is no clear distinction between the three mechanisms when they are concerted; all of them may be concerted displacements with added nucleophiles or solvent, which can have

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varying amounts of associative or dissociative character in the transition state. The classification does not distinguish between the *appearance* of the rate-limiting transition state and the *number and sequence of steps* in a reaction. This kind of classification is associated with terms such as "merging" and a "spectrum" of mechanisms, which are not clearly defined, as well as "borderline" mechanisms in situations when there is no defined borderline between the mechanisms.

These ambiguities may be avoided if the mechanisms are defined in terms of the number and sequence of steps, or primitive changes, of the reaction. The mechanisms for acyl transfer are then (1) dissociative, with an acylium ion intermediate; (2) concerted displacement, which can have associative or dissociative character; (3) associative, or addition–elimination, with a tetrahedral addition intermediate. The Commission on Physical Organic Chemistry of IUPAC recently proposed a system of nomenclature for the classification of organic reaction mechanisms in this way.[4]

These mechanisms are clearly defined, with a rather sharp borderline between them. The term "borderline" is meaningful in this context: it refers to a reaction series in which a small change in the structure of one of the reactants, or in the reaction conditions, causes a change from a concerted to a stepwise mechanism, or vice versa. The appearance of the transition state for each mechanism can be characterized by structure–reactivity correlations, isotope effects, and other methods. We suggest that the terms "spectrum" and "merging", as applied to reaction mechanisms, are poorly defined, ambiguous, and misleading; our understanding of the distinction between different mechanisms would be improved if they were abandoned.

The reactions of acyl halides illustrate these points. A dissociative mechanism has frequently been proposed for reactions of these compounds, but there are few cases in which a monomolecular mechanism with an acylium ion intermediate has been demonstrated.[2,3] There is evidence for the trapping of a carbamoyl cation by amines and azide in water under conditions in which these reagents cause little or no increase in the rate of disappearance of the starting material,[5,6] and inhibition by 60% of the hydrolysis of 2,4,6-trimethylbenzoyl chloride in the presence of 1.6 M tetra-*n*-butylammonium chloride in 99% acetonitrile has been reported and was attributed to a monomolecular mechanism.[7] However, little inhibition was observed in 95% acetone,[8] even though the hydrolysis of 4-substituted 2,6-dimethylbenzoyl chlorides has the identical sensitivity to polar substituents ($\rho^+ = -3.9$) in 99% acetonitrile and 89.1% acetone, and there is no common ion inhibition with benzoyl chloride in 67–95% acetone.[9] Competing monomolecular and bimolecular mechanisms were suggested for the reaction of benzoyl chloride with *o*-nitroaniline in 50% acetone because of the absence of a linear correlation between the rate increase and the amount of anilide formation,[10] but this may represent a medium effect of *o*-nitroaniline; there is a good correlation between the rate increase in the presence of nitroanilines and the formation of anilide product in the absence of a medium effect.[11,12]

On the other hand there is abundant evidence that the solvolysis of benzoyl chlorides and other acyl halides may occur through a transition state with dissociative character. For example, electron-donating substituents increase the rate of solvolysis of substituted benzoyl chlorides in 50% acetone,[13] formic acid,[14,15] 97% 2,2,2-trifluoroethanol,[16] 99% acetonitrile,[7] 89.1% acetone,[17] and highly aqueous solutions,[16] and the entropies of activation for the hydrolysis of isopropyl chloroformate and carbamoyl chloride are positive.[18] However, the solvolysis of benzoyl chloride shows less sensitivity (m) to solvent ionizing power (Y) than the monomolecular solvolysis of *tert*-butyl chloride and 1-adamantyl chloride, from which it was concluded that the reaction involves nucleophilic assistance in an S_N2 mechanism.[12,19] The entropies of activation for the solvolysis of most acyl halides are negative, near −10 eu, but less so than values in the range −30 to −50 eu for many esters and other acyl compounds.[2e] There is also an associative reaction pathway that becomes significant with electron-withdrawing substituents and with decreasing ionizing power of the solvent.[12-14,21-24]

Table I. Wavelengths Used for the Measurements of Reactions of Benzoyl Halides (YPhCOX)

Y	wavelength, nm X = Cl	wavelength, nm X = F	Y	wavelength, nm X = Cl	wavelength, nm X = F
p-Me_2N		330[b,c]	H	250[a]	
p-Me_2N		310[d]	*m*-MeO	310[b]	310[b]
p-MeO	290[a]	275[b,c]	*m*-Cl	300[b]	295[b,c]
p-MeO		250[d]	*p*-Me_2N	250[a]	
p-Me	260[a]	250[b]	*m*-CF_3	285[b]	
H	240[b]	240[b,d]	*p*-NO_2	265[b]	295[b]

[a] Solvolysis in 90% (v/v) 2,2,2-trifluoroethanol. [b] Hydrolysis in water. [c] Aminolysis in water. [d] Product analysis by HPLC.

We have reported evidence, from common ion inhibition by potassium fluoride, that the hydrolysis of *p*-(dimethylamino)-benzoyl fluoride in water proceeds by a stepwise mechanism through an acylium ion intermediate; potassium fluoride increases the rates of hydrolysis of *p*-anisoyl and benzoyl fluorides.[25] The dissociative mechanism is supported by the solvent deuterium isotope effect of $k_{HOH}/k_{DOD} = 1.1$ for *p*-(dimethylamino)benzoyl fluoride. The larger isotope effects of $k_{HOH}/k_{DOD} = 2.3 \pm 0.2$ for *p*-anisoyl and benzoyl fluorides in the presence and the absence of 1.0 M potassium fluoride provide evidence that these compounds react with water in a bimolecular reaction that is assisted by general-base catalysis.[25]

We report here the results of a study of the hydrolysis of substituted benzoyl fluorides and chlorides in water and of benzoyl chlorides in 90% trifluoroethanol that was carried out with the goal of characterizing the change from a dissociative to an associative pathway for these reactions and the relationship of this change to the lifetime of the acylium ion and to the reaction conditions.

Experimental Section

Materials. *p*-(Dimethylamino)benzoyl chloride was prepared according to Harada et al.;[26] other reagent-grade benzoyl chlorides and benzoyl fluoride from Aldrich were used without further purification. Substituted benzoyl fluorides were prepared according to Olah and Kuhn[27] and analyzed by mass spectra obtained with a Hewlett-Packard

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Table II. First-Order Rate Constants for the Solvolysis of Substituted Benzoyl Halides[a]

subst	$10^3k/s^{-1}$	k/s^{-1}	$10^3k/s^{-1}$	k/s^{-1}
leaving gp/ solvent	F/H_2O	Cl/H_2O	Cl/90/TFE[e]	Cl/97TFE[f]
p-Me_2N	3.5	(1.0×10^5)[g]		
p-Me_2N	3.1[b]			
p-MeO	0.29		620	0.57
p-MeO	0.12[b]			
p-Me	0.7		39	3.5×10^{-2}
H	1.8	1.1	5.7	3.6×10^{-3}
H	0.9[b]	0.77[b]		
H	1.9[c]	1.8[d]		
m-MeO	3.4	0.6		
p-Cl				4.5×10^{-4}
m-Cl	9.0	0.056	0.12	
m-CF_3		0.034		
p-NO_2	51	0.062		9.9×10^{-6}
		0.031[b]		

[a] At 25 °C and ionic strength of 0. [b] In D_2O. [c] In 1.0 M HCl. [d] Reference 16. [e] Volume percent. [f] Weight percent: Bentley, T. W.; Harris, H. C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 619. [g] Estimated by extrapolation of the Hammett plot for the hydrolysis of substituted benzoyl chlorides.

Model 5985B gas chromatograph/mass spectrometer: m^+/e = 166 (*p*-Me_2N), 154 (*m*-MeO), 138 (*p*-Me), 158 (*m*-Cl), 150 (*p*-NO_2). The ^{13}C NMR spectrum of *p*-anisoyl fluoride in $CDCl_3$ showed peaks with chemical shifts, δ (ppm) = 57, 116, 118 (d, J = 1 ppm), 135.4, 159 (d, J = 5 ppm), 167; and *p*-anisoyl chloride showed peaks at δ (ppm) = 57, 116, 126.4, 135.8, 167.2, 168. 2,2,2-Trifluoroethanol (Aldrich, 99%+, Gold label) and absolute ethanol (USI Chemicals) were used without further purification and other reagent-grade substituted ethanols were distilled. Water was glass distilled.

Methods. For hydrolysis and solvolysis, the disappearance of 0.01–0.10 mM substrate at 25 °C was followed spectrophotometrically at the wavelengths shown in Table I. For the reactions with fluoride ion in aqueous solution, the stock solution of potassium fluoride was prepared by the addition of 2.96 N HCl (2.5 mL) to 4.0 M KF (200 mL), which gave pH ~6.0 by pH indicator paper; it was stored in a polyethylene bottle. No buffer was added unless otherwise indicated. Some benzoyl halides have a low solubility, especially in the presence of salts, but the data at high salt concentrations were found to be reproducible with varying substrate concentrations, different mixing methods, and filtration of the reaction mixture immediately after mixing. Usually 30–50 μL of a solution of substrate in acetonitrile was injected into solvent in a cuvette and the cuvette was inverted two to three times for mixing. For reactions with a half-life of <10 s, the solvent was injected forcefully into a cuvette that contained a small amount of substrate in acetonitrile. Logarithmic plots of the absorbance change against time were generally linear for >90% reaction and first-order rate constants were obtained from $k_{absd} = 0.693/t_{1/2}$.

For reactions of *p*-(dimethylamino)benzoyl, *p*-anisoyl, and benzoyl fluorides with substituted ethanols in 10% mixed alcohols in water (v/v), the products were analyzed with a Waters Associates HPLC reverse-phase octadecylsilane column (Nova Pack C18 5 μm). A solvent gradient from 42 to 100% (v/v) acetonitrile was applied and the products were analyzed at the wavelengths shown in Table I. The ratios of the second-order rate constants were obtained by dividing the product ratio by the alcohol concentration ratio (eq 4) for the reactions in 3:7:90 and 6:4:90 (v/v/v) ROH/EtOH/HOH and from the alcohol/water ratios (eq 5) for the reactions in 10% ROH. The solution containing x volume % of solvent A was prepared by mixing (x/n) mL of solvent A with $(100 - x)/n$ mL of water.

$$\frac{k_2(\mathrm{ROH})}{k_2(\mathrm{EtOH})} = \left(\frac{[\mathrm{ArCOOR}]}{[\mathrm{ArCOOEt}]}\right) \Big/ \left(\frac{[\mathrm{ROH}]}{[\mathrm{EtOH}]}\right) \quad (4)$$

$$\frac{k_2(\mathrm{ROH})}{k_2(\mathrm{HOH})} = \left(\frac{[\mathrm{ArCOOR}]}{[\mathrm{ArCOOH}]}\right) \Big/ \left(\frac{[\mathrm{ROH}]}{[\mathrm{HOH}]}\right) \quad (5)$$

Results

Hydrolysis of Substituted Benzoyl Fluorides. The first-order rate constants for the hydrolysis of most substituted benzoyl fluorides (Table II) increase with electron-withdrawing substituents and follow a Hammett correlation with a slope of $\rho^+ = 1.7$, as shown in Figure 1 (diamonds). There is a change to a negative slope of the correlation at the rate constant for *p*-anisoyl fluoride, and the positive deviation by a factor of $\sim 10^3$ of the rate constant for *p*-(dimethylamino)benzoyl fluoride indicates a change to a different reaction pathway with a dissociative transition state.

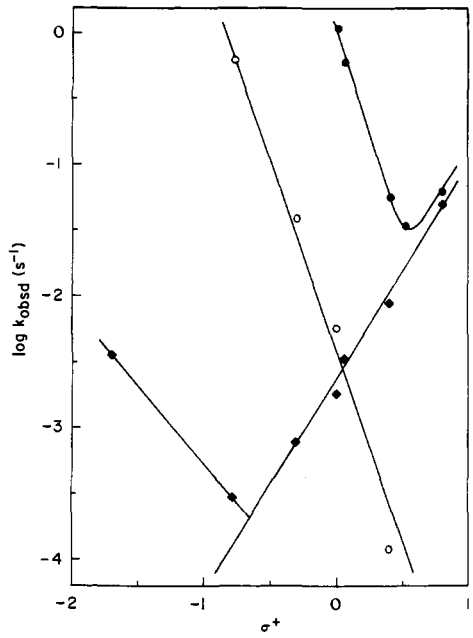

Figure 1. Hammett plots for the solvolysis of substituted benzoyl chlorides (●, in water; ○, in 90% 2,2,2-trifluoroethanol) and fluorides (◆, in water) at 25 °C and ionic strength of 0. The σ^+ values are from Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323.

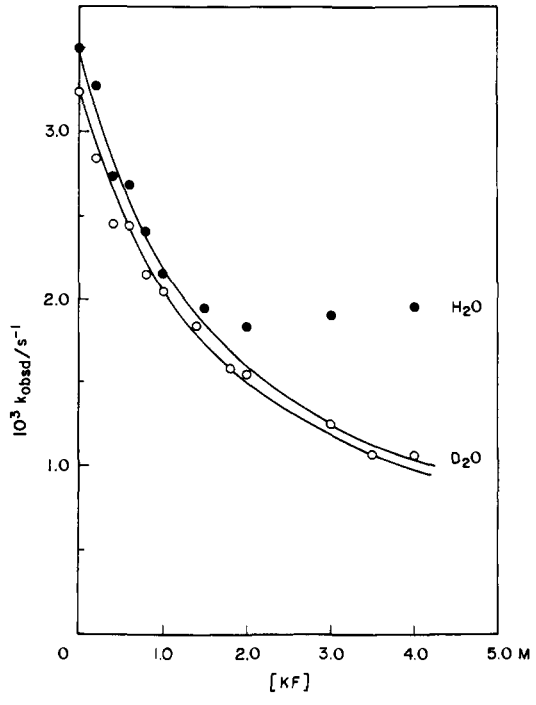

Figure 2. Dependence on potassium fluoride concentration of the hydrolysis of *p*-(dimethylamino)benzoyl fluoride in water and in deuterium oxide at 25 °C. Ionic strength of 2.0 was maintained with KCl up to 2.0 M KF; KF is the only salt at higher concentrations. The solid lines are calculated from eq 6.

Figure 2 shows that the hydrolysis of *p*-(dimethylamino)benzoyl fluoride in water and in deuterium oxide exhibits common ion inhibition in the presence of potassium fluoride at concentrations up to 2 M, as reported previously.[25] In contrast, the hydrolysis

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Table III. Effect of Salts on the Rate Constants for Reactions of *p*-Anisoyl and Benzoyl Fluorides in Water at 25 °C

salt		concn, M	substituent: *p*-MeO, $10^3k_{obsd}/s^{-1}$	substituent: H, $10^3k_{obsd}/s^{-1}$
no salt			2.9	1.8
no salt	D_2O		1.2	0.92
				1.7[a]
KH_2PO_4/K_2HPO_4 (1:1)		0.5		35
KH_2PO_4/K_2HPO_4 (1:1)	D_2O			33
KF		1.0	20	12
KF	D_2O		9.2	5.4
C_2H_5COONa		1.0		17
CH_3COONa		1.0		22
HCOONa		1.0	92	53
HCOONa	D_2O		81	43
NaCl		1.0		1.9
NaBr		1.0		1.6
Na_2SO_4		0.33		2.5
$NaClO_4$		1.0		1.3

[a] In the presence of 1.0 M HCl.

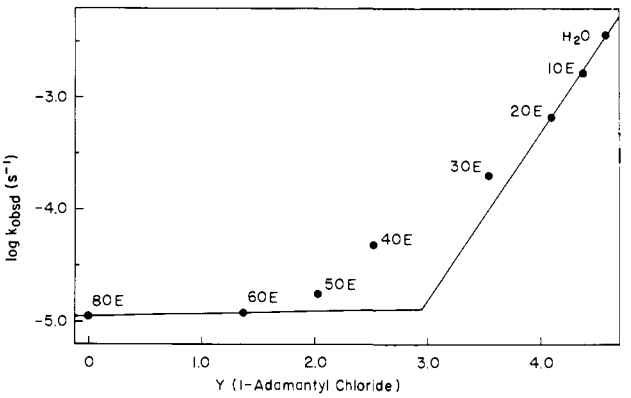

Figure 3. Sensitivity to solvent ionizing power of the solvolysis of *p*-(dimethylamino)benzoyl fluoride in aqueous ethanol at 25 °C. E: (v/v) ethanol/water, in percent.

rates of *p*-anisoyl and benzoyl fluorides are increased in the presence of 1.0 M potassium fluoride.[25] Above 2 M potassium fluoride the rate constants continue to decrease in deuterium oxide but level off in water. This corresponds to the appearance of a solvent deuterium isotope effect that increases from k_{HOH}/k_{DOD} = 1.1 in the absence of fluoride to 1.9 at 4 M potassium fluoride. The solvent deuterium isotope effect is k_{HOH}/k_{DOD} = 2.3 ± 0.2 for the hydrolysis of *p*-anisoyl and benzoyl fluorides, both in the presence and in the absence of 1.0 M potassium fluoride (Table III).

The hydrolysis rate of *p*-(dimethylamino)benzoyl fluoride was found to be independent of the concentration of potassium phosphate, 50% dianion, up to 1.0 M, but there is a 20-fold increase in the rate of disappearance of benzoyl fluoride under the same conditions (Table III). There is little effect of NaCl, NaBr, or HCl, but other basic anions also increase the rate with both benzoyl and *p*-anisoyl fluoride. The solvent deuterium isotope effect of 1.1 ± 0.1 for these salts shows that the reactions are predominantly nucleophilic. This is in contrast to the rate increases and solvent deuterium isotope effects in the presence of potassium fluoride that were described above, which provide evidence for general-base catalysis of hydrolysis.

Figure 3 shows that the hydrolysis of *p*-(dimethylamino)benzoyl fluoride is very sensitive to solvent ionizing power, *Y*, in predominantly aqueous solution, with an *m* value of 1.4, but becomes insensitive to *Y* in the presence of high concentrations of ethanol; the *Y* values are for 1-adamantyl chloride.[28] Again, this change suggests a change in reaction mechanism. The hydrolysis rate was also found to be inhibited by 17–34% in the presence of 1.0 M CH_3CN, CH_3CONH_2, CF_3CH_2OH, CH_3CH_2OH, and CH_3OH.

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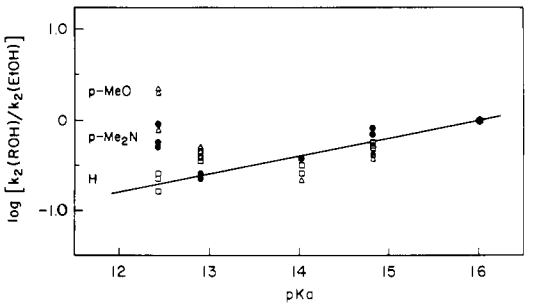

Figure 4. Dependence on alcohol basicity of the solvent selectivity for the solvolysis of substituted benzoyl fluorides in 90:3:7, 90:6:4, 90:10:0 (v/v/v) HOH/ROH/EtOH at 25 °C: (●) *p*-(dimethylamino)benzoyl fluoride, (△) *p*-anisoyl fluoride, (□) *m*-chlorobenzoyl fluoride. The individual points represent replicate determinations.

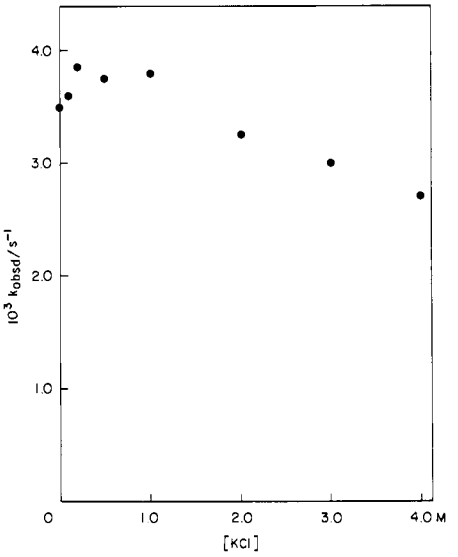

Figure 5. Dependence on ionic strength of the hydrolysis of *p*-(dimethylamino)benzoyl fluoride at 25 °C.

The selectivities of substituted benzoyl fluorides toward different alcohols in 90% water were obtained from product analysis by HPLC. The ratios of the second-order rate constants, $k_2(ROH)/k_2(EtOH)$, are shown in Table IV and are plotted as a function of the pK_a of the alcohol in the Brønsted-type plot of Figure 4. The selectivities toward the unsubstituted compound, which reacts with water through an associative mechanism (Figure 1), are consistent with a modest dependence on the basicity of the alcohol, with a slope of β_{nuc} = 0.2. The selectivities for the π-anisoyl- and *p*-dimethylamino-substituted compounds are similar for most alcohols, but show large positive deviations for trifluoroethanol and, to a lesser extent, for dichloroethanol. This is consistent with catalysis by the leaving fluoride ion of the attack of these acidic alcohols on an acylium ion intermediate in a solvent-separated ion pair.

Figure 5 shows that there is little effect of ionic strength on the rate of hydrolysis of *p*-(dimethylamino)benzoyl fluoride up to 1 M potassium chloride; there is a small decrease in rate at higher concentrations of potassium chloride.

The rate of hydrolysis of *p*-(dimethylamino)benzoyl fluoride increases with increasing acidity below pH 3, with an inflection point at pH 1.7 and a rate constant for hydrolysis of the protonated substrate of 0.016 s^{-1} (Figure 6). The dependence on pH is consistent with a value of pK_a = 1.69 ± 0.04 for this species, which was determined spectrophotometrically from the absorbance at 330 mM immediately after adding samples of the substrate to solutions of varying acidity.

The entropy and enthalpy of activation for the hydrolysis of *p*-(dimethylamino)benzoyl fluoride in water, $\Delta S^* = -12$ eu and

Table IV. Solvent Selectivities, $k_2(ROH)/k_2(EtOH)$, for the Solvolysis of Substituted Benzoyl Fluorides in 10% Mixed Alcohols in Water[a]

		R =			
substituent	solvent[b]	CF_3CH_2	$CHCl_2CH_2$	$NCCH_2CH_2$	$MeOCH_2CH_2$
p-Me_2N	3ROH	0.51	0.24	0.35	0.77
p-Me_2N	6ROH	0.87	0.20	0.34	0.74
p-Me_2N	10ROH	0.56	0.24	0.35	0.79
p-MeO	3ROH	0.78	0.72	0.23	0.42
p-MeO	6ROH	2.28	0.53	0.22	0.42
p-MeO	10ROH	2.01	0.43	0.22	0.42
H	3ROH	0.16	0.41	0.35	0.53
H	6ROH	0.21	0.36	0.33	0.53
H	10ROH	0.27	0.39	0.23	0.57

[a] Each number is the average of three analyses by HPLC. [b] The xROH is x:(10 − x):90 (v/v/v) ROH/EtOH/HOH.

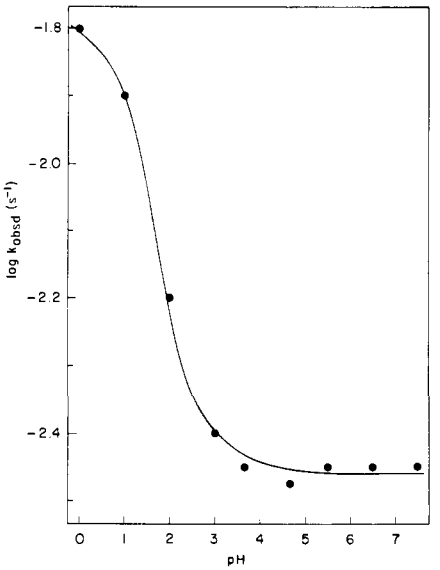

Figure 6. Dependence on pH of the rate constants for hydrolysis of p-(dimethylamino)benzoyl fluoride at 25 °C and ionic strength of 1.0 (KCl).

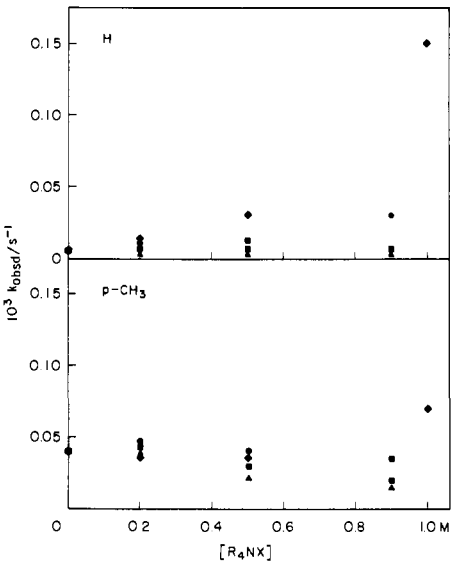

Figure 7. Effects of increasing concentrations of different salts on the solvolysis of p-toluoyl and benzoyl chlorides in 90% (v/v) 2,2,2-trifluoroethanol at 25 °C. (◆) Me_4NF, (●) Me_4NBr, (■) Et_4NClO_4, (▲) Me_4NCl.

$\Delta H^{\ddagger}$ = 17.2 kcal mol^{-1}, were calculated from rate constants of $10^3k_{obsd}/s^{-1}$ = 0.88 (10 °C), 1.8 (15 °C), 3.9 (25 °C), 13.6 (36 °C), and 26 (45 °C).

Solvolysis of Benzoyl Chlorides. In 90% trifluoroethanol electron-donating substituents cause a large increase in the rate of solvolysis of substituted benzoyl chlorides; a correlation of the rate constants with σ^+ has a slope of $\rho^+ = -3.0$ (Figure 1, open circles; Table II). Benzoyl chloride was found to give 57% benzoic acid under these conditions, from product analysis by HPLC; this corresponds to a selectivity of $k_2(HOH)/k_2(TFE)$ = 2.9. Added salts have variable effects on the rate of solvolysis of benzoyl chlorides in this solvent, as shown in Figure 7. Most salts inhibit solvolysis, presumably because of a salt-induced medium effect.[29] The inhibition by tetramethylammonium chloride cannot be ascribed to common ion inhibition because similar inhibition is observed with other salts. Tetramethylammonium fluoride was found to cause a large increase in the rate with benzoyl chloride but did not affect the product yield (λ_{max} 230 nm), which was found to be different from that obtained from benzoyl fluoride (λ_{max} 245 nm).

Figure 1 shows that the solvolysis of most substituted benzoyl chlorides in water is ~500 times faster than in 90% trifluoroethanol and shows the same dependence on substrate structure. However, the electron-withdrawing substituent on p-nitrobenzoyl chloride causes a change in the reaction pathway, with a rate constant and structure–reactivity behavior that are similar to those for most of the benzoyl fluorides; the rate constant is consistent with a change to ρ^+ = 1.7. This change is accompanied by an increase in the solvent deuterium isotope effect from k_{HOH}/k_{DOD} = 1.4 for benzoyl chloride to 2.0 for p-nitrobenzoyl chloride (Table II). The observed rate constant of 1.1 s^{-1} for the hydrolysis of benzoyl chloride in water is somewhat smaller than previously reported values of 1.4–1.8 s^{-1}.[16,19] There is no common ion inhibition of the hydrolysis of benzoyl chloride by 1.0 M potassium chloride and no significant effect of 1.0 M potassium bromide; however, 1.0 M potassium fluoride causes a 90-fold decrease in rate that is attributed to a rapid nucleophilic reaction to form benzoyl fluoride[30] (Table V).

Table V. Effects of Salts on the Solvolysis of Substituted Benzoyl Chlorides at 25 °C

salt	M		$10^2k/s^{-1}$	$10^3k/s^{-1}$	k/s^{-1}
	subst/solvent[a]	p-MeO/90TFE	p-Me/90TFE	H/90TFE	H/H_2O
no salt		0.64	3.9	5.8	1.1
KF	1.0				0.012
Me_4NF	1.0	0.18	6.8	150	
KCl	1.0				1.3
Me_4NCl	0.9	0.21	1.5	3.0	
KBr	1.0				1.1
Me_4NBr	0.9	0.39	3.5	28	
Et_4NClO_4	0.9	0.29	1.9	2.8	

[a] Volume percent.

Discussion

The transition state for the expulsion of fluoride ion from p-(dimethylamino)benzoyl and p-anisoyl fluorides to form the

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(30) The observed rate constant of 0.012 s^{-1} is larger than the rate constant for hydrolysis of benzoyl fluoride in water, 0.0018 s^{-1}, because of catalysis by 1 M fluoride ion; it agrees with the expected rate constant for this reaction under these conditions.

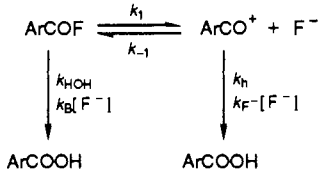
corresponding acylium ions shows the expected stabilization by electron-donating substituents (Figure 1). The value of ρ^+ from a two-point Hammett plot is −1.2, but this is an upper limit because *p*-anisoyl fluoride reacts, in part, by a different mechanism (see below). The other substituted benzoyl fluorides react through a different, associative mechanism with $\rho^+ = 1.7$ (Figure 1).

These conclusions are consistent with the negligible solvent isotope effect of $k_{HOH}/k_{DOD} = 1.1$ for *p*-(dimethylamino)benzoyl fluoride, compared with $k_{HOH}/k_{DOD} = 2.3$ for the *p*-anisoyl- and unsubstituted benzoyl fluorides, and with the strong general-base catalysis for hydrolysis of the latter compounds by 1.0 M fluoride ion, which increases the rate of hydrolysis by 6–8-fold and also shows a solvent deuterium isotope effect of $k_{HOH}/k_{DOD} = 2.3$ (Table III).[25] The hydrolysis of acetyl fluoride is also catalyzed by fluoride ion.[31] The associative pathway involves nucleophilic attack of water on these acyl fluorides that is assisted by proton removal from the attacking water molecule by fluoride ion or another water molecule in the transition state.[32]

Dissociative Reaction Pathway. The solvolysis of *p*-(dimethylamino)benzoyl fluoride is extremely sensitive to solvent ionizing power. The value of $m = 1.4$ in predominantly aqueous solutions (Figure 3) is almost half again larger than that of the reference compound, 1-adamantyl chloride. This may be ascribed to a requirement for strong solvation of the basic fluoride ion as it is expelled in the transition state.[33] However, the charge is probably not fully developed in the transition state because the effect of increasing ionic strength is small (Figure 5). Strong solvation of the leaving fluoride ion is also consistent with the negative entropy of activation of −12 eu for the reaction in water.[25]

The value of *m* shows a large decrease with increasing ethanol concentration and approaches zero in 60–80% ethanol (Figure 3). This suggests that the monomolecular formation of acylium ion is a true "borderline" reaction and that a change to an associative mechanism occurs with a modest change in the nature of the solvent, as well as with changing substituents.

The common ion inhibition of the hydrolysis of *p*-(dimethylamino)benzoyl fluoride in the presence of fluoride ion at concentrations up to 4 M, shown in Figure 2, is described by the mechanism shown in eq 6. In the presence of added fluoride ion



(6)

a fraction of the acylium ion is trapped by fluoride (k_{-1}), instead of reacting with water (k_h), so that it returns to starting material and hydrolysis is inhibited. The results confirm the earlier report of common ion inhibition at potassium fluoride concentrations of up to 2 M[25] and show that the rate of hydrolysis in D_2O continues to follow the solid line calculated from eq 6, with $k_h = k_{-1}/0.6$ M^{-1}. However, in H_2O the rate levels off at >2 M fluoride. The difference corresponds to a large increase in the observed solvent isotope effect of the reaction, from $k_{HOH}/k_{DOD} = 1.1$ at low concentrations to 1.9 in 4 M potassium fluoride.

This behavior might represent either general-base catalysis of hydrolysis of the acylium ion by fluoride ion at high concentrations of potassium fluoride, k_F in eq 6, or the appearance of a concurrent bimolecular reaction of the acyl fluoride with water that is catalyzed by fluoride ion, k_{HOH} and k_B in eq 6. However, the limiting rate constant at high fluoride concentration is much faster than the predicted rate constant for a bimolecular reaction (Figure 1) and the good fit of the data in D_2O to the calculated line for simple

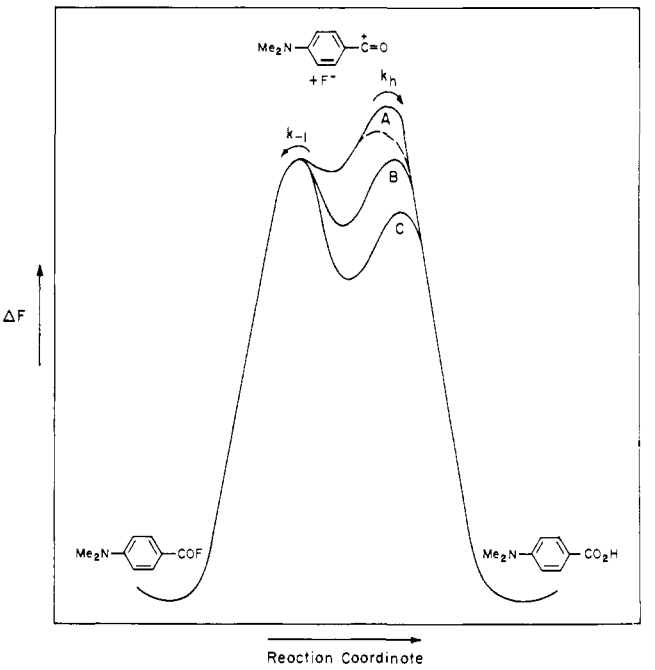
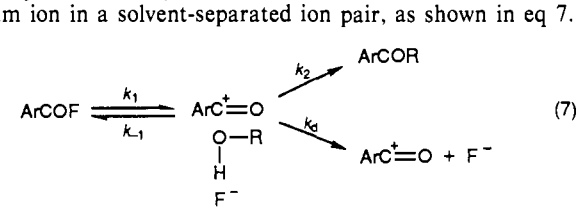


Figure 8. Reaction coordinate diagram for the hydrolysis of *p*-(dimethylamino)benzoyl fluoride to show the change in rate-limiting step at different fluoride ion concentrations: (A) [F$^-$] = >1.7 M, (B) [F$^-$] = 1.7 M ($k_h = k_{-1}$ in eq 6), (C) [F$^-$] = <1.7 M.

common ion inhibition provides no evidence for concurrent direct hydrolysis of the acyl fluoride; this supports general-base catalysis of the hydrolysis of the acylium ion by fluoride ion as the explanation for the leveling off of k_{obsd} in H_2O.

General-base catalysis of the hydrolysis of carbenium ions has been observed previously.[33] At low fluoride concentration formation of the acylium ion is rate limiting for hydrolysis (Figure 8, C), but as the concentration of fluoride ion is increased the back-reaction to regenerate acyl fluoride, k_{-1} in eq 6, becomes increasingly important (Figure 8, B) and at >1.7 M [F$^-$] hydrolysis of the acylium ion intermediate, k_h, becomes largely rate limiting (Figure 8, A). Catalysis of this hydrolysis by fluoride ion (k_F in eq 6, dashed line in Figure 8) decreases the inhibition, and at high [F$^-$] the observed rate in H_2O levels off. There is no evidence for significant general-base catalysis in D_2O. This can be attributed, at least in part, to a decrease in rate because of a solvent deuterium isotope effect for the general-base-catalyzed reaction; however, some catalysis may be offset by a rate decrease at the very high ionic strength of these solutions (Figure 5).

Solvolysis of the *p*-anisoyl and *p*-(dimethylamino)benzoyl fluorides in 9:1 water/alcohol mixtures gives a sharp increase in the yields of the trifluoroethyl esters, compared with other benzoyl fluorides and other alcohols (Figure 4). This result provides further support for a dissociative mechanism for *p*-(dimethylamino)-benzoyl fluoride and shows that *p*-anisoyl fluoride reacts, in part, by a dissociative mechanism. The increased yields can be explained by general-base catalysis by fluoride ion of nucleophilic attack by the relatively acidic trifluoroethanol molecule on the acylium ion in a solvent-separated ion pair, as shown in eq 7.



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Similar behavior has been observed in other systems[34] and it has

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been suggested that the low values of k_{EtOH}/k_{HOH} for *p*-anisoyl chloride in ethanol/water mixtures arise from reaction of a solvent-separated ion pair.[24] The high yield of trifluoroethyl ester from the *p*-anisoyl fluoride provides evidence that a significant fraction of the reaction of this compound proceeds through a dissociative mechanism to give an intermediate that reacts with solvent (k_2, eq 7) before the leaving group diffuses out of the solvent-separated ion pair. The smaller increase with the *p*-dimethylamino compound suggests that there is competition between nucleophilic attack on this more stable intermediate in the ion pair, k_2, and dissociation to give a free ion, k_d, which can be trapped by reaction with fluoride ion in the bulk solvent.

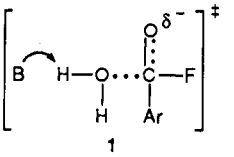
The reactivity of trifluoroethanol in these reactions is large, even larger than that of ethanol with *p*-anisoyl fluoride. This reflects the large susceptibility of this acidic alcohol to general-base catalysis.[35] It may also arise from facilitation of the expulsion of fluoride ion by hydrogen bonding to trifluoroethanol, so that trifluoroethanol is close to the acylium ion when it is formed and has an increased probability of reacting to give the trifluoroethyl ester. The normal behavior of more basic alcohols with $pK_a > 13$ (Figure 4) indicates that catalysis of their attack on the acylium ion in the ion pair is not significant, and the good fit of the observed rate constants for hydrolysis in D_2O to the theoretical line, up to 4 M fluoride ion (Figure 2), gives no indication of any hydrolysis of the *p*-(dimethylamino)benzoyl acylium ion in an ion pair that cannot be inhibited by added fluoride ion.

These reactions illustrate the power of common ion inhibition as a tool for establishing reaction mechanism, because it would be difficult or impossible to establish the monomolecular mechanism of hydrolysis of *p*-(dimethylamino)benzoyl fluoride by any other technique. An extensive search failed to identify any other nucleophilic solutes that could be used to trap the *p*-(dimethylamino)benzoyl acylium ion, because they were all found to undergo bimolecular reactions with the starting material. Carbonyl carbon is highly electrophilic and very susceptible to nucleophilic attack; the ratio of the rate constants for reaction with acetyl chloride compared with methyl chloride is 10^9 for hydroxide ion and 5×10^{10} for water.[36,37] The second-order rate constant for the nucleophilic reaction of *p*-(dimethylamino)benzoyl fluoride with fluoride ion was estimated to be $(1-6) \times 10^{-3}$ M^{-1} s^{-1} from the ratios of the second-order rate constants for fluoride and hydroxide ions of $k_2(F^-)/k_2(HO^-) = 5.9 \times 10^{-5}$ for 2,4-dinitrophenyl acetate,[38] 3.9×10^{-4} for 1-acetoxy-4-methoxypyridinium ion,[36] and 1.6×10^{-4} for acetic anhydride.[39] Thus, the rate constant for the nucleophilic reaction of fluoride ion with *p*-(dimethylamino)benzoyl fluoride is comparable to the rate of solvolysis under the conditions for common ion inhibition, and fluoride can be used as a trap for the acylium ion only because its nucleophilic reaction with *p*-(dimethylamino)benzoyl fluoride regenerates starting material.

Associative Reaction Pathway. Other substituted benzoyl fluorides show a large increase in the rate of hydrolysis with electron-withdrawing substituents and follow a Hammett correlation with $\rho^+ = 1.65$ (Figure 1). This is evidence for an associative transition state that involves bimolecular attack of water on the acyl halide. This mechanism is also consistent with the observed general-base catalysis by 1.0 M fluoride ion of the hydrolysis of *p*-anisoyl and benzoyl fluorides, by factors of 7.7- and 6.6-fold, respectively, and the solvent deuterium isotope effects of $k_{HOH}/k_{DOD} = 2.3 \pm 0.2$ for these reactions, both in the presence and in the absence of 1.0 M potassium fluoride.[25]

There is no significant dependence of the rate constant for the hydrolysis of *p*-nitrobenzoyl halides in aqueous solution on the leaving ability of fluoride and chloride ions. The value of $k_{Cl}/k_F = 1.2$ for these compounds may be compared with the ratio $k_{Cl}/k_F = 3 \times 10^7$ for *p*-(dimethylamino)benzoyl halides (Table II). The ratio of 1.2 is also much smaller than values of k_{Cl}/k_F in the range 10^1–10^3 for S_N2 substitution, such as the reaction of methyl halides with water (35),[40] iodide ion (830),[41] and hydroxide ion (11.4).[42] No catalysis of fluoride expulsion was observed for the hydrolysis of benzoyl fluoride in the presence of 1 M HCl in water. However, catalysis by HCl has been observed in aqueous acetone,[43] which is a poor solvent for a basic anion, and the hydrolysis of acetyl fluoride is catalyzed by acid in aqueous solution.[31]

These results show that there is little or no bond breaking to the leaving group in the rate-limiting transition states of these associative reactions in aqueous solution. The rate-limiting transition state involves attack of water on the carbonyl group that is assisted by partial proton removal to a base catalyst or solvent (**1**).



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This corresponds to the initial step of an addition–elimination mechanism, but we do not know if there is an addition intermediate with a significant lifetime on the reaction path. There may be such an intermediate, or the reaction may be "uncoupled concerted", in which there is no intermediate with a significant lifetime but bond formation and bond cleavage are not balanced or "synchronous"; i.e., bond making and bond breaking have not occurred to the same extent at the same time.

Potassium phosphate, 50% dianion, and several carboxylate salts increase the rate of disappearance of benzoyl fluoride (Table III), but the solvent deuterium isotope effect of $k_{HOH}/k_{DOD} = 1.2 \pm 0.1$ for the reactions with potassium phosphate and sodium formate is not significant. We conclude, therefore, that these compounds also react by bimolecular nucleophilic substitution.

Solvolysis of Benzoyl Chlorides in 90% 2,2,2-Trifluoroethanol. The large negative Hammett slope of $\rho^+ = -3.0$ for the solvolysis of *p*-anisoyl, *p*-toluoyl, benzoyl, and *m*-chlorobenzoyl chlorides in 90% trifluoroethanol (Figure 1) agrees with a previously reported value of $\rho^+ = -3.1$ for the solvolysis of benzoyl chlorides, including *p*-nitrobenzoyl chloride in 97% trifluoroethanol.[16] These large negative values show that the transition state for solvolysis under these conditions has a large amount of dissociative character. However, the addition of salts causes a *decrease* in the solvolysis rate of *p*-anisoyl chloride in this solvent by ~2–3-fold (Table V), which can be attributed to a salt-induced medium effect.[29] There is no evidence for inhibition that is specific for chloride ion and could be attributed to a common ion effect. The absence of significant common ion inhibition by 0.9 M chloride ion shows that no intermediate is formed with a sufficiently long lifetime that it can be trapped by chloride ion. There is also no evidence for common ion inhibition of the solvolysis of *p*-toluoyl or benzoyl chloride.

Fluoride ion causes a large increase in the rate of disappearance of benzoyl chloride, a smaller increase with *p*-toluoyl chloride, and no increase with *p*-anisoyl chloride. Furthermore, the absolute rate in the presence of fluoride ion is faster for benzoyl than for *p*-toluoyl chloride. The rate increase with fluoride ion in this solvent indicates that there is general-base catalysis of nucleophilic attack by solvent on the acyl chloride. It does not represent the formation of benzoyl fluoride because the disappearance of acyl halide is first order and the observed rate constant is much larger

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than the rate constant for solvolysis of benzoyl fluoride (Table II). This result provides strong evidence for nucleophilic participation by solvent in this reaction, in spite of the predominantly dissociative nature of the transition state that is indicated by the value of $\rho^+ = -3.0$.

Benzoyl chloride also shows a 10-fold increase in rate in the presence of 0.9 M Me_4NBr compared with Et_4NClO_4; much smaller increases are observed for the compounds with electron-donating substituents. These results are consistent with the appearance of bimolecular nucleophilic reactions with substituted benzoyl chlorides when the substituents are not electron-donating.

We conclude that in 90% trifluoroethanol *p*-anisoyl chloride undergoes ionization to give a short-lived acylium ion intermediate that cannot be trapped by a common ion, in agreement with the results for solvolysis of *p*-anisoyl fluoride in water, and that the lifetime of this intermediate becomes progressively shorter with less electron-donating substituents on the benzoyl group until it ceases to have a significant lifetime. The lifetime of the intermediate will be decreased still further in the presence of stronger nucleophilic reagents, such as Br^-, and the data are consistent with the notion that the intermediate has no lifetime in the presence of nucleophilic reagents that give rise to bimolecular reactions.

Solvolysis of Benzoyl Chlorides in Water. The value of $\rho^+ = -3.0$ for the solvolysis of four substituted benzoyl chlorides in water is the same as in 90% trifluoroethanol, although the rates are 200–500 times faster (Figure 1). The extrapolated rate constants for the *p*-MeO and *p*-Me_2N compounds are faster than those for the corresponding benzoyl fluorides by factors of $10^{5.9}$ and $10^{7.5}$, respectively. These differences are in marked contrast to the ratios of $k_{Cl}/k_F = 1.2$ for the associative reactions of the *p*-nitrobenzoyl halides and confirm the strongly dissociative nature of the transition state.

However, the solvent-independent value of $\rho^+ = -3.0$ is considerably less negative than the values of $\rho^+ = -4.5$ for the solvolysis of *p*-substituted cumyl chlorides,[45] on which the ρ^+ scale is based, and $\rho = -5.6$ for the solvolysis of 1-phenylethyl chlorides in 20% acetonitrile in water.[46] The relatively small negative value of ρ^+ for the benzoyl halides may reflect electron movement from oxygen toward the central carbon atom by polarization or resonance (**2**) and/or nucleophilic interaction of these relatively unhindered molecules with solvent in the transition state.

$$\underset{\mathbf{2}}{\mathrm{Ar{-}{}^{+}C{=}O} \leftrightarrow \mathrm{Ar{-}C{\equiv}O^{+}}}$$

There is no common ion inhibition of the hydrolysis of benzoyl chloride in the presence of 1 M potassium chloride. In contrast to the reaction in 90% trifluoroethanol, fluoride ion undergoes a rapid bimolecular reaction with benzoyl chloride to give benzoyl fluoride, which undergoes slow hydrolysis (Table V). There is a small, but significant, solvent deuterium isotope effect on hydrolysis of $k_{HOH}/k_{DOD} = 1.4$, compared to 1.1 for the monomolecular hydrolysis of *p*-(dimethylamino)benzoyl fluoride (Table II). These results are consistent with solvolysis in a concerted reaction through a predominantly dissociative transition state in which there is weak nucleophilic interaction with a water molecule.[11,12,22,47] The absence of common ion inhibition by chloride ion shows that no intermediate has a long enough lifetime to account for the reaction with fluoride ion by capture of this intermediate.

There is a sharp break in the Hammett plot of Figure 1 for *p*-nitrobenzoyl chloride, which reacts faster than *m*-(trifluoromethyl)benzoyl chloride in water. This is evidence for hydrolysis through a different reaction channel with an associative transition state, similar to that for hydrolysis of most of the substituted benzoyl fluorides; the rate increase is consistent with the Hammett slope of $\rho^+ = 1.65$ that was observed for the benzoyl fluorides. The solvent deuterium isotope effect of $k_{HOH}/k_{DOD} = 2.0$, which is the same as that for the benzoyl fluorides, provides evidence for general-base catalysis by water of the attack of water on the acid chloride. It has been suggested previously that the rate maximum of a correlation with Y in alcohol/water mixtures and the dependence on [ROH] in aprotic solvents represent general-base catalysis by solvent in a third-order reaction.[23] As noted above, the chloride–fluoride ratio of rate constants is small, 1.2, compared with a ratio of 3×10^7 for the corresponding *p*-(dimethylamino)benzoyl halides in water that was calculated from an extrapolation of the Hammett plot for other benzoyl chlorides in water. This provides evidence for an associative transition state with rate-limiting attack of the nucleophilic reagent and little or no bond breaking in the transition state. This is the behavior expected for an addition–elimination mechanism, as with the benzoyl fluorides, but we do not know whether or not the reaction proceeds through an addition intermediate with a significant lifetime.

Lifetimes of Acylium Ions and Reaction Mechanisms. Approximate lifetimes can be estimated for the *p*-(dimethylamino)benzoyl and *p*-anisoyl acylium ions, and extrapolation to less stable ions suggests that substituted benzoyl chlorides react through a dissociative reaction pathway even when the acylium ion does not have a significant lifetime in the presence of solvent. More electron-withdrawing substituents cause a shift to the associative reaction channel; this occurs sooner for benzoyl fluorides than for chlorides because the relatively poor leaving ability of fluoride ion decreases the rate constant for the dissociative pathway.

The observed trapping of the *p*-(dimethylamino)benzoyl acylium ion by fluoride ion shows that this ion has a lifetime that is long enough to allow diffusional combination with fluoride ion at high concentrations, and the selectivity for reaction with four substituted alcohols, with $\beta_{nuc} \sim 0.2$ (Figure 4), shows that it has a sufficient lifetime to discriminate between different alcohols. On the other hand, the reaction with trifluoroethanol in a solvent-separated ion pair indicates that some reaction occurs before complete diffusional equilibration with the solvent, so that k_h must be $> \sim 10^9\ s^{-1}$. The ratio $k_{-1}/k_h = 0.6\ M^{-1}$ for common ion inhibition by fluoride (eq 6) gives a rate constant for hydrolysis of the acylium ion of $k_h = 8 \times 10^9\ s^{-1}$ if k_{-1} for trapping of the acylium ion by fluoride ion is $5 \times 10^9\ s^{-1}$, which is the approximate rate constant for trapping of carbocations by azide ion, and $k_h = 8 \times 10^8\ s^{-1}$ if fluoride ion has a 10-fold smaller rate constant for trapping, the same as for acetate ion, because of strong hydrogen bonding to the solvent.[48] We conclude that the *p*-(dimethylamino)benzoyl acylium ion undergoes hydrolysis with $k_h \sim 10^9$–$10^{10}\ s^{-1}$.

The *p*-anisoyl acylium ion cannot be trapped by F^- and reacts with trifluoroethanol in a solvent-separated ion pair faster than diffusional separation of the ion pair, so that it probably reacts with water at $> 10^{11}\ s^{-1}$. This is consistent with general-base catalysis by fluoride ion and the solvent isotope effect of $k_{HOH}/k_{DOD} = 2.4$ for the hydrolysis of this compound, which suggest that it can also undergo direct nucleophilic attack by water. It is conceivable that the acylium ion has a significant lifetime in the presence of a weakly nucleophilic trifluoroethanol molecule, so that reaction occurs through the ion pair, while the more nucleophilic water molecule attacks the acyl group directly. In any case, the solvolysis of *p*-anisoyl fluoride appears to qualify as a true "borderline" reaction.

The carbocations that are formed from substituted 1-phenylethyl chlorides react with 50% trifluoroethanol/water with rate constants that follow a Hammett slope of $\rho^+ = 4.0$.[49] A rate constant of $k_h = 10^9\ s^{-1}$ for solvolysis of the *p*-(dimethylamino)benzoyl acylium ion and $\rho^+ = 4.0$ gives calculated rate constants of $k_h = 2 \times 10^{12}\ s^{-1}$ for *p*-anisoyl, $2 \times 10^{14}\ s^{-1}$ for toluoyl, and $10^{16}\ s^{-1}$ for benzoyl acylium ions. This correlation is crude, but it should be adequate

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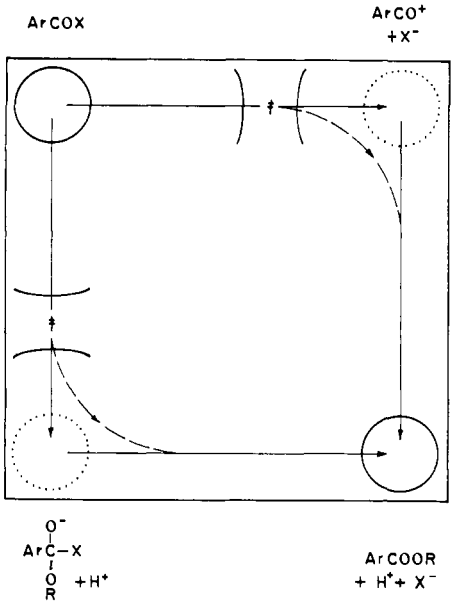

Figure 9. Reaction–coordinate energy contour diagram for the solvolysis of acyl halides. The upper right pathway is dissociative and the lower left pathway is associative. The dotted circles indicate an acylium ion and a tetrahedral addition intermediate that may or may not exist with a barrier for collapse and a significant lifetime.

to allow a prediction of a change in mechanism over a large range of reactivity. Structure–reactivity correlations for reactions of carbocations are linear up to very large rate constants, as large as $\sim 10^{10}$ M^{-1} s^{-1}.[48-50] The rate constant for the *p*-anisoyl acylium ion corresponds to a small but significant lifetime for this intermediate in water, although not enough to allow diffusion through the solvent or reaction with dilute solutes. The much larger "rate constants" for the toluoyl and benzoyl acylium ions suggest that there is little or no chemical barrier for the reaction of these ions with solvent. The very short or insignificant lifetimes also explain why there is no detectible common ion inhibition by trapping of an acylium ion intermediate in the solvolysis of substituted benzoyl chlorides or *p*-anisoyl fluoride.

There is probably no chemical barrier for the collapse of an intimate ion pair of the *p*-anisoyl cation and fluoride ion. Therefore, the first stable intermediate in the solvolysis of *p*-anisoyl fluoride may be the solvent-separated ion pair, which gives a high yield of trifluoroethyl ester from catalysis by fluoride ion.

The change from a dissociative to an associative reaction path with increasingly electron-withdrawing substituents occurs much later for benzoyl chlorides than for benzoyl fluorides (Figure 1) because the rate of the associative reaction is independent of the leaving group, while the dissociative reaction is strongly dependent on the leaving group (Figure 1). The consequence of this is that the dissociative pathway is followed for many substituted benzoyl chlorides that certainly do not give rise to acylium ion intermediates with a significant chemical barrier for their collapse in the presence of a currently positioned solvent molecule. Nevertheless, Figure 1 shows no evidence for a change in the structure–reactivity behavior, or the structure of the transition state, with changing substituents for as long as the dissociative pathway is followed.

This situation may be illustrated by the upper pathway on the energy contour diagram of Figure 9 (the contour lines are omitted). The *p*-(dimethylamino)benzoyl and *p*-anisoyl halides react through a dissociative transition state to give an acylium ion intermediate, which is indicated by the dotted potential well; the intermediate then reacts rapidly with solvent. With electron-withdrawing substituents there is no barrier for reaction of the acylium ion and the potential well no longer exists, although the rate-limiting transition state is essentially the same. The reaction may then follow the path that is indicated by the dashed line in the diagram.

Electron-withdrawing substituents or a decrease in leaving group ability will raise the energy of the acylium ion in the upper right corner of the diagram and of the transition state for the dissociative pathway while they will stabilize the lower left corner and the transition state for the associative pathway.[51] This will eventually cause a switch to the associative reaction channel. This reaction pathway may correspond to an addition–elimination mechanism through a tetrahedral intermediate, which is indicated by a dotted circle on the lower left of the diagram. However, the reaction path may bypass this corner if the addition intermediate does not have a significant lifetime, as shown by the dashed line. A change to a less polar solvent can also cause a change from the dissociative to the associative reaction channel (Figure 3).

The associative reactions certainly do not follow a coupled concerted displacement mechanism with a large amount of bond breaking in the transition state, which is commonly called "S_N2 displacement". These reactions illustrate the difficulty of describing reaction mechanisms by a nomenclature that was designed to describe the observed properties, not the mechanism, of a reaction. The reaction is a bimolecular nucleophilic substitution, but it is not what is usually called "S_N2 displacement".

The mechanisms of these and other reactions can be described more clearly with the nomenclature for reaction mechanisms that has recently been proposed by the Commission on Physical Organic Chemistry of IUPAC.[4] This nomenclature provides a simple description of the sequence of processes that take place in the course of a reaction and the extent to which they are separated. The dissociative pathway for the solvolysis of benzoyl halides could proceed through mechanisms described by

$$D_N + A_N$$

$$D_N{}^*A_N$$

$$A_ND_N$$

in which D is dissociation and A_N is nucleophilic association.

The solvolysis of *p*-(dimethylamino)benzoyl fluoride proceeds by a $D_N + A_N$ mechanism, in which dissociation and association occur in separate steps. *p*-Anisoyl fluoride reacts with trifluoroethanol by a $D_N{}^*A_N$ mechanism, in which dissociation precedes association but the intermediate reacts with its immediate neighbors before diffusional equilibration with the solvent. This mechanism could be described by $D_N{}^*A_{Nssip}$ to indicate reaction through a solvent-separated ion pair. Concerted reactions with a dissociative transition state, in which there is no intermediate with a significant lifetime, are A_ND_N (the reactions occur in one step, so that neither process precedes the other, and the A is placed before the D by convention).

Mechanisms for the associative pathway are described by

$$A_N + D_N$$

$$A_N{}^*D_N$$

$$A_ND_N$$

in which the punctuation again indicates the nature or existence of an intermediate. An addition–elimination mechanism is described by $A_N + D_N$ if there is a long-lived intermediate, by $A_N{}^*D_N$ if the intermediate is too unstable to allow diffusional equilibration with the bulk solvent, and by A_ND_N if there is no intermediate with a significant lifetime.

The facile reactions of benzoyl halides through this pathway probably proceed through an associative, A_ND_N mechanism with no intermediate and with little or no bond breaking in the transition state; however, an $A_N{}^*D_N$ mechanism with an unstable tetrahedral addition intermediate is not rigorously excluded. The presence of the carbonyl group at the reaction center facilitates the reaction by allowing negative charge to develop on the oxygen atom by breaking a π bond, instead of on the leaving group by breaking

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a σ bond, which is more difficult. When bond formation to carbon has occurred and a proton has been removed from the nucleophile, the reaction is not easily reversible and the leaving group is expelled rapidly.

It is important to distinguish between the *mechanism* of the reaction and the *appearance* of the transition state, as indicated by structure–reactivity correlations and other techniques. The reactions described here provide one of many examples of reactions in which there is not a simple relationship between the reaction mechanism and the appearance of the rate-limiting transition state. It is possible, at least in principle for a reaction to proceed concurrently through two different reaction *channels*, such as the associative and dissociative pathways shown in Figure 9, with concerted, A_ND_N, mechanisms for both channels.

The energy contour diagram provides a simple way to illustrate both the mechanism of a reaction and the structure of its transition state, in terms of the relative amounts of bond making and bond breaking that are indicated by structure–reactivity parameters. The location of the transition state on the reaction surface can also be described by a "tightness" or "disparity" parameter, γ, which describes the amount by which it is displaced perpendicularly from a diagonal line between the reactants and products.[52] The reactions described here have large positive and negative values of γ for the associative and dissociative channels, respectively.

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Aminolysis of Benzoyl Fluorides in Water[1]

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Abstract: The reactions of benzoyl fluorides (*p*-Me_2N, *p*-MeO, *m*-Cl) with primary amines of pK_a = 3.9–11 in aqueous solution follow a first-order dependence on amine concentration and the addition of 0.83 M potassium phosphate, 10% dianion, does not affect the second-order rate constant for the reaction of aminoacetonitrile with *p*-(dimethylamino)benzoyl fluoride. The large values of ρ = 1.6–1.9 show that the transition state is strongly associative. The dependence on amine basicity, β_{nuc}, decreases gradually from 0.6–0.7 for weak nucleophiles to 0.2–0.3 for strong nucleophiles and increases with increasing σ. There is no shift in the midpoint of the curvature in the Brønsted-type plot with changing substituents on the acyl group, in contrast to the behavior of stepwise aminolysis reactions. These observation are consistent with a concerted displacement mechanism (A_ND_N) for the aminolysis of benzoyl fluorides, although a stepwise addition–elimination mechanism is not rigorously excluded. The concerted mechanism may be followed because resonance with the benzene ring destabilizes the tetrahedral addition species by accelerating departure of the nucleophile and F^-, a good leaving group, so that the addition "intermediate" does not have a significant lifetime and the concerted mechanism is enforced.

The aminolysis of activated acyl compounds is generally believed to proceed through a two-step mechanism in which a tetrahedral addition intermediate is formed by nucleophilic attack of the amine and the leaving group is expelled in the second step.[2] The reaction can be facilitated by protonation or deprotonation of an addition intermediate by a buffer catalyst, and this catalysis can provide evidence for a stepwise mechanism if it can be shown to involve diffusion-controlled combination with the intermediate.[3,4] An addition intermediate has also been demonstrated by the observation of identical partitioning ratios when it is generated from two directions,[5] from a change in rate-limiting step with changing pH,[4-6] and from partitioning of the intermediate in imidate hydrolysis.[7] The aminolysis reactions of acetate and benzoate esters,[8-10] acetylpyridinium ions,[11] anhydrides,[10,12,13] carbonate esters,[5,10,13,14] methyl chloroformate,[15] and acetyl chloride[16] show a large dependence of the rate on the basicity of weakly basic amines, with $\beta_{nuc} = 0.9 \pm 0.1$, and an abrupt change to a much smaller dependence on the basicity of strongly basic amines, with $\beta_{nuc} = 0.2 \pm 0.1$. Analogous correlations have been observed for the aminolysis of a series of substituted methoxycarbonylpyridinium ions.[17] This behavior has generally been interpreted as evidence for a change in rate-limiting step of a multistep reaction, from rate-limiting formation of the intermediate, with $\beta_{nuc} \sim 0.2$, to rate-limiting expulsion of the leaving group or proton transfer in the tetrahedral intermediate, with $\beta_{nuc} \sim 0.9$. However, the change in β_{nuc} only shows that there is a change in the charge distribution of the rate-limiting transition state with changing structure of the reactants; it does not prove that the reaction

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