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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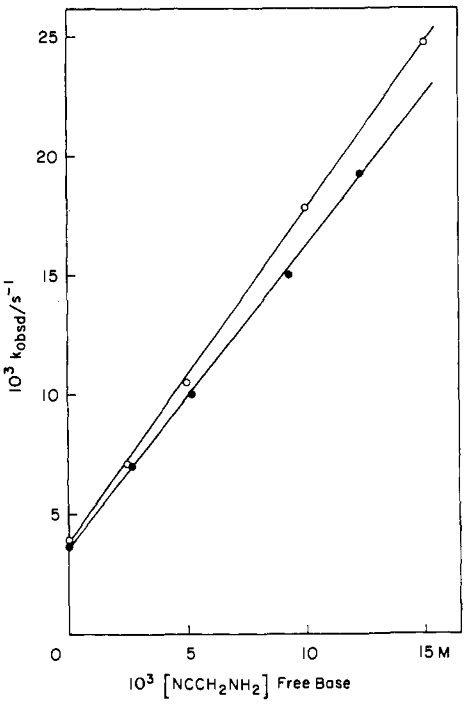

Figure 1. Dependence on aminoacetonitrile concentration of the first-order rate constants for the reaction of *p*-(dimethylamino)benzoyl fluoride with aminoacetonitrile at 25 °C and ionic strength of 1.0 (KCl): (○) aminoacetonitrile, 50% free base; (●) in the presence of 0.83 M KH_2PO_4/K_2HPO_4 (9/1), pH 5.50–5.64.

proceeds in steps through an addition intermediate with a significant lifetime.[18]

On the other hand, the absence of a change in β_{nuc} for symmetrical acyl-transfer reactions at the point at which the pK_a of attacking and leaving phenolate ions or amines is the same supports a concerted, one-step reaction with no change in rate-limiting step. This has been observed for acetyl transfer between substituted phenolate ions, with β_{nuc} = 0.75,[19] and for methoxycarbonyl transfer from isoquinoline to substituted pyridines, with β_{nuc} = 0.58.[20]

Benzoyl halides are well-known to undergo second-order reactions with amines,[21] and there is a good correlation of product yield with the observed rate constants for the reaction of benzoyl chloride with *o*-nitroaniline if account is taken of medium effects.[22] However, it is still uncertain whether these reactions proceed by direct displacement or an addition–elimination mechanism.

We report here an examination of the aminolysis of substituted benzoyl fluorides by a series of primary amines in the range pK_a = 3.9–11. These reactions show a nonlinear dependence of log *k* on the pK_a of the amine, which could be interpreted in terms of a stepwise reaction mechanism; however, we suggest that the reaction may instead proceed through a concerted bimolecular displacement in which there is a change in transition-state structure with changing amine basicity.

Experimental Section

Substrates were prepared as described in the preceding paper.[23] Amine hydrochlorides (Aldrich Chemical Co. or Eastman Organic Chemicals) were recrystallized except for 2,2,2-trifluoroethylamine hydrochloride, which was used from a freshly opened bottle; 2-methoxyethylamine was distilled. Water was glass distilled.

Table I. Second-Order Rate Constants for the Reactions of *p*-(Dimethylamino)benzoyl Fluoride with Nucleophiles[a]

nucleophile	pK_a	p*H*	10^3[nuc],[b] M	k_2, $M^{-1} s^{-1}$
semicarbazide	3.86[c]	4.80	37–190	0.08[e]
		3.78	45–220	0.15[e]
methoxyamine	4.72[d]	5.66–5.75	5.7–19	1.5
aminoacetonitrile	5.55[d]	6.49–6.55	3.0–8.9	1.4[f]
trifluoroethylamine	5.81[d]	6.55–6.58	2.0–5.7	0.52[f]
hydroxylamine	6.17[c]	6.60	0.24–0.94	65[f]
ethylenediamine-H^+	7.42[c]	6.59	0.12–0.39	12[f]
3-aminopropionitrile	8.03[d]	6.59	0.12–0.35	23[f]
glycinamide	8.32[c]	6.59	0.04–0.12	37[f]
2-chloroethylamine	8.81[d]	6.59	0.02–0.07	60[f]
2-methoxyethylamine	9.72[c]	6.68–6.87	0.006–0.038	132[f]
ethylamine	10.97[c]	7.68	0.0014–0.0060	280[f]
hydroxide ion	15.74[c]	11		15

[a] In aqueous solution at 25 °C with ionic strength of 1.0 (KCl). [b] Concentration of reactive species. [c] Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869. [d] Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572. [e] The second-order rate constant of 0.073 $M^{-1} s^{-1}$ for the reaction of neutral substrate with free base was calculated from both rate constants and the fraction of protonated substrate at each pH value, (pK_a = 1.69), by extrapolating to zero concentration of the protonated substrate. [f] Measured in 0.2 M potassium phosphate buffer.

Table II. Second-Order Rate Constants for the Reactions of *p*-Anisoyl Fluoride with Primary Amines[a]

nucleophile	pH	10^4[RNH_2],[b] M	k_2, $M^{-1} s^{-1}$
aminoacetonitrile	6.54	6.1–1.5	11
trifluoroethylamine	6.54	4.2–12.6	3.7
ethylenediamine-H^+	6.58	0.41–1.2	76
3-aminopropionitrile	6.54	0.42–1.2	240
glycinamide	6.58	0.30–0.89	375
2-chloroethylamine	6.54	0.18–0.53	600
2-methoxyethylamine	6.65–6.86[c]	0.09–0.41	1500
ethylamine	6.58	0.011–0.032	2920
	7.62	0.01–0.09	2820

[a] At 25 °C with ionic strength of 1.0 (KCl) and in the presence of 0.2 M potassium phosphate buffer. [b] Concentration of reactive species. [c] Three determinations in this pH range.

Table III. Second-Order Rate Constants for the Reactions of *m*-Chlorobenzoyl Fluoride with Primary Amines[a]

nucleophile	pH	10^5[RNH_2],[b] M	k_2, $M^{-1} s^{-1}$
aminoacetonitrile	5.47	9.2–17	100
trifluoroethylamine	5.47	16–310	43
ethylenediamine-H^+	5.47	0.55–1.1	1000
3-aminopropionitrile	5.48	0.22–0.52	3200
glycinamide	5.51	0.15–0.46	5500
2-chloroethylamine	5.51	0.08–0.24	7500
2-methoxyethylamine	6.56	0.02–0.09	22000
ethylamine	6.55	0.01–0.06	70000

[a] At 25 °C with ionic strength of 1.0 (KCl) and in the presence of 0.1 M potassium phosphate buffers. [b] Concentration of reactive species.

Aminolysis was followed spectrophotometrically by measuring the change in absorbance from the disappearance of substrate at the same wavelengths as for hydrolysis.[23] Other experimental conditions are recorded in the tables and figures.

Results

The pseudo-first-order rate constants for the disappearance of substituted benzoyl fluorides in the presence of a large excess of

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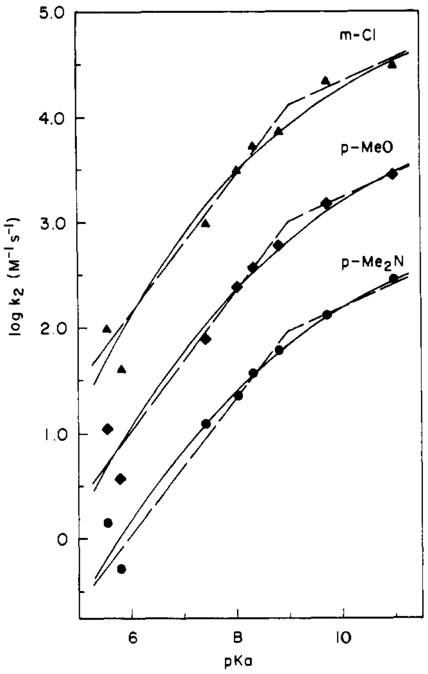

Figure 2. Dependence on amine basicity of the second-order rate constants for the reactions of substituted benzoyl fluorides with primary amines in water at 25 °C with ionic strength of 1.0 (KCl). The curved lines are calculated from log $k_2 = -5.57 + 1.23\text{p}K_a - 0.045\text{p}K_a^2$ (*p*-Me$_2$N); $-5.13 + 1.32\text{p}K_a - 0.049\text{p}K_a^2$ (*p*-MeO); $-5.27 + 1.63\text{p}K_a - 0.067\text{p}K_a^2$ (*m*-Cl). Each dashed line has slopes of 0.67 and 0.23.

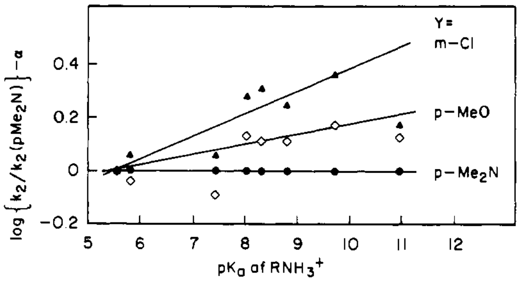

Figure 3. The effects of substituents on $\beta_{\text{nuc}} = \partial \log k/\partial \text{p}K_a$ for the reactions of Y-PhCOF with primary amines in water, with (Y, α) = (*p*-Me$_2$N, 0), (*p*-MeO, 0.89), (*m*-Cl, 1.85).

amine buffer were found to show a linear dependence on the concentration of free amine; a typical example is shown in Figure 1. Phosphate buffer (0.83 M, 9/1 KH_2PO_4/K_2HPO_4) does not affect the second-order rate constant for the reaction of *p*-(dimethylamino)benzoyl fluoride with aminoacetonitrile (Figure 1). The second-order rate constants are listed in Tables I–III. The second-order rate constant for the reaction of *p*-anisoyl fluoride with ethylamine is independent of pH (Table II).

Discussion

Figure 2 shows that the rate constants for aminolysis of substituted benzoyl fluorides by eight primary amines increase with increasing basicity of the amine and with electron-withdrawing substituents on the benzoyl fluoride. The large effect of substituents on the acyl substrate corresponds to a value of $\rho = 1.6$–1.9 for all of the amines. This is similar to the values of $\rho = 1.8$ for the formation of a tetrahedral addition compound at equilibrium from semicarbazide and substituted benzaldehydes[24] and $\rho = 1.9$ for the ammonolysis of *p*-chlorophenyl benzoates catalyzed by NH_3, which may represent formation of the addition intermediate, $T^{\pm}$, at equilibrium with rate-limiting deprotonation by NH_3; it is larger than the values of $\rho = 1.1$ and 1.4 for the uncatalyzed ammonolysis of substituted *p*-chlorophenyl and *p*-nitrophenyl benzoates, respectively,[25] and $\rho = 1.1$ for the reaction of benzylamine with *N*-hydroxysuccinimide benzoates in dioxane.[26] The value of β_{lg} is $-(0.8$–$0.9)$ for ammonolysis of the phenyl benzoates and both reactions are believed to involve rate-limiting expulsion of the leaving group from $T^{\pm}$.[25,26] It is also larger than $\rho = 1.2$ for the reaction of substituted benzoyl chlorides with anilines in benzene.[21] This shows that the reaction mechanism for the three benzoyl fluorides is associative, with a considerable amount of bond formation to the incoming nucleophile and a modest amount of bond breaking to the leaving group in the rate-limiting transition state; the value of ρ is the same as for the hydrolysis of most benzoyl fluorides through an associative mechanism.[23] However, the mechanism for the *p*-dimethylamino compound has changed from dissociative for hydrolysis[23] to associative for aminolysis. Similar large values of $\rho = 1.4$–2.2 have recently been reported by Lee and co-workers for the reactions of substituted benzoyl fluorides with substituted anilines in methanol.[27]

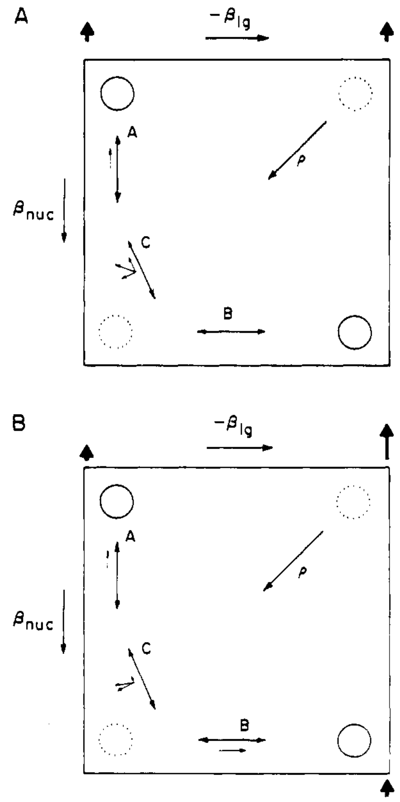

Figure 4. Reaction coordinate–energy diagrams to show how the position of the transition state changes with increasing amine basicity (A) and increasing electron-withdrawing ability of the acyl substituent (B). The short heavy arrows represent an increase in pK_a of the nucleophile (A) and an increase in σ for the substituent on the acyl group (B), which cause an increase in the energy of the indicated parts of the diagram. The short arrows on the reaction coordinates represent movement of the transition state perpendicular and parallel to the direction of the reaction coordinate.

There is a large dependence of the rate on amine basicity with weakly basic amines, but this dependence decreases with the more basic amines. The data are consistent with the dashed lines in Figure 2, which have slopes of $\beta_{\text{nuc}} = 0.67$ for weakly basic amines and 0.23 for basic amines with p$K_a > 8.8$. Correction for desolvation of the amines[28] gives values of $\beta_{\text{nuc}} = 0.7$ and 0.4. However, the rate constants are also consistent with a gradual change in β_{nuc} with increasing amine basicity, as shown by the solid lines in the figure. The rate constants for reactions of the

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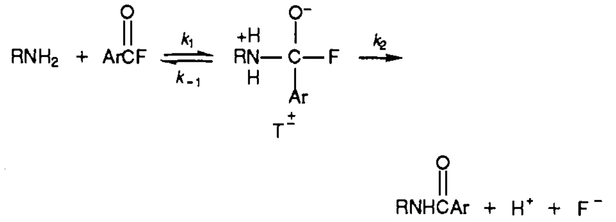
α-effect compounds semicarbazide, methoxyamine, and hydroxylamine with p-(dimethylamino)benzoyl fluoride are 2, 10, and 30 times larger, respectively, than predicted by the correlation in Figure 2.

These structure–reactivity parameters correspond to a transition state that is close to the lower left corner of the reaction coordinate-energy contour diagram of Figure 4, which is similar to that in the previous paper. This diagram describes the amount of bond formation, as estimated from β_{nuc}, by the position of the transition state along the y axis, proceeding downward from the reactants in the upper left corner toward a tetrahedral addition species in the lower left corner. The x axis corresponds to the amount of bond breaking, as indicated by $-\beta_{lg}$. The associative character of the transition state is indicated by ρ, which is negative for a dissociative transition state that resembles the acylium ion in the upper right corner and positive in the lower left corner. The large observed value of ρ could correspond to the transition state for rate-limiting addition (A) or leaving group expulsion (B) in an addition–elimination mechanism, or to a concerted mechanism that does not proceed through an addition intermediate (C).

The changing slopes of the Brønsted-type plots in Figure 2 with increasing basicity of the amine exclude an addition–elimination mechanism in which the rate-limiting step is either the formation or the breakdown of a tetrahedral addition intermediate for all amines. Rate-limiting addition of the amine, k_1 in eq 1, corresponds to transition state A in Figure 4 and has a small dependence on amine basicity; the observed value of β_{nuc} is 0.2–0.3 for many reactions of acyl compounds when nucleophilic attack of the amine is believed to be rate limiting.[4,5,8,13] For example, the reaction of acetyl chloride with primary amines follows a constant value of $\beta_{nuc} = 0.23$ for amines in the range of pK = 4–11.[16] Rate-limiting breakdown of the addition intermediate, k_2 in eq 1, corresponds to transition state B in Figure 4 and requires rapid formation of $T^{\pm}$ in an equilibrium step, with $\beta_{nuc} = 0.8$–1.0, followed by slow expulsion of the leaving group that is aided by electron-donating substituents so that the observed value of β_{nuc} would be ≥ 0.8 for all amines. Furthermore, if either addition or elimination were rate limiting with all amines, the large change in the amount of bond formation in the transition state that is indicated by the curvature in Figure 2 would be expected to cause a corresponding change in ρ with changing basicity of the amine, but there is no large change in ρ.



$$\mathrm{RNH_2 + ArC(=O)F \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RN^{+}H_2{-}C(O^-)(Ar){-}F \ (T^{\pm}) \xrightarrow{k_2} RNHC(=O)Ar + H^+ + F^-} \quad (1)$$

The nonlinear Brønsted-type correlations in Figure 2 could be accounted for by a concerted substitution reaction in which the slope, β_{nuc}, decreases with increasing reactivity of the nucleophile, as shown by the solid lines, or by a stepwise mechanism in which expulsion of fluoride ion from an addition intermediate is rate limiting with weakly basic amines and nucleophilic attack is rate limiting with strongly basic amines, shown by the dashed lines in Figure 2. The concerted mechanism is supported by (1) the small limiting slopes of these correlations and (2) the absence of a change in the position of the "break" in the structure–reactivity correlations with different substituents on the acyl group:

(1) The slopes of 0.67 and 0.23 for the dashed lines in Figure 2 might be assigned to rate-limiting breakdown and formation of a tetrahedral intermediate through transition states B and A, respectively, with a change in rate-limiting step for amines of pK = 9. Qualitatively similar behavior has been observed for aminolysis reactions of a number of related compounds, including the reactions of pyridines with substituted phenyl benzoates and acetates[8,9] and substituted diphenyl carbonates,[5] as well as methyl chloroformate[15] and acetyl chloride.[16] However, the limiting values of $\beta_{nuc} = 0.6$–0.7 for the reactions of weakly basic amines with substituted benzoyl fluorides are significantly smaller than the slopes of β_{nuc} in the range 0.8–1.0 that have been observed for other acyl-transfer reactions in which leaving group expulsion or proton transfer in a tetrahedral addition intermediate is believed to be rate limiting: $\beta_{nuc} = 0.8$–1.0 for substituted phenyl benzoates and acetates,[6,8,9,15,29] 1.0 for diphenyl carbonates,[5] 1.0 for acetic anhydride,[12,13] 0.8–0.93 for methyl chloroformate,[9,16] and 0.9 for acetylpyridinium ions;[11] values of β_{nuc} = 1.3, 1.3, and 1.6 have been observed for the aminolysis of methyl phenyl carbonate, acetyltriazole, and acetylimidazole, respectively, when leaving group expulsion is rate limiting.[30,31]

This suggests that the substituted benzoyl fluorides may not react through a stepwise mechanism with a tetrahedral intermediate and a change in rate-limiting step. The observed limiting values of $\beta_{nuc} = 0.6$–0.7 agree with the values of $\beta_{nuc} = 0.58$ and 0.75 for methoxycarbonyl transfer between isoquinoline and pyridines and for acetyl transfer between substituted phenolate ions, which are believed to proceed through a concerted mechanism.[19,20] The values of ρ obtained by Lee and co-workers for the reactions of four substituted anilines with benzoyl fluorides in methanol[27] and $\rho = -4.20$ for the dissociation of protonated anilines in ethanol[32] give β = 0.69, 0.74, and 0.85 for reaction with p-methyl-, unsubstituted, and p-chlorobenzoyl fluorides, respectively. These slopes are similar to our results for weakly basic amines; curvature was not detected over the range of <2 pK units that was examined.[27]

(2) The change in rate-limiting step of the stepwise mechanism occurs at the break of the structure–reactivity correlation, pK_0, which corresponds to the point at which the rate constants for expulsion of the attacking and leaving groups, k_{-1} and k_2, are equal. The partitioning of the intermediate to reactants and products has been shown to be influenced by substituents on the acyl group, because the rate of expulsion of anions is increased more than that of amines by electron donation from the acyl group. This causes a change in pK_0 of ~2 units with changing acyl substituents in the aminolysis of diaryl carbonates,[5] and an analogous change has been observed for the reaction of pyridines with acyl-substituted 2,4-dinitrophenyl benzoates.[9,29] The absence of any indication for such a change with the substituted benzoyl fluorides (Figure 2) is consistent with the concerted mechanism, with a change in transition-state structure as the basicity of the amine increases.

Concerted Mechanism. The nonlinear correlations in Figure 2 can be accounted for by a gradual decrease in β_{nuc} with increasing pK_a of the attacking amine in a concerted mechanism, as shown by the solid lines in Figure 2. This downward curvature of a structure–reactivity correlation represents a normal Hammond effect for a concerted reaction, transition state C in Figure 4, with an earlier transition state for a more reactive nucleophile. The decrease in β_{nuc} can be described by $\partial\beta_{nuc}/\partial \mathrm{p}K_{nuc} = -0.11 \pm 0.02 = p_x$.[33] A Hammond effect is plausible if bond formation is largely rate limiting in the transition state, corresponding to reaction coordinates A and C in Figure 4, but a change in β_{nuc} from

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(34) The p_{xy} coefficient for substitution on benzyl halides (Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288–3294) is 0.23 when it is defined by the pK_a values of substituted anilines ($\rho = 4.2$ for the dissociation of protonated anilines).

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0.67 to 0.23 is not expected for the horizontal reaction coordinate B that represents rate-limiting leaving group expulsion from $T^{\ddagger}$. An increase in the basicity of the amine represents an increase in the energy of the reactants at the upper part of the diagram. This increase will tend to move the reaction coordinate in the direction toward the position of higher energy, parallel to the reaction coordinate, as shown by the light arrows in the diagram. In the case of reaction coordinate C, there will also be a movement perpendicular to the reaction coordinate that will tend to increase β_{nuc}.

The large change in β_{nuc} suggests that there is an important vertical component to the reaction coordinate and that the reaction coordinate may be in a narrow col with larger curvature perpendicular rather than parallel to the reaction coordinate, so that the predominant movement of the transition state is along the *y* axis.[33]

There is also a small but significant increase in β_{nuc} with electron-withdrawing substituents on the benzene ring of the benzoyl fluorides that is consistent with the concerted mechanism of transition state C. This change is best illustrated by changes in the ratios of rate constants for aminolysis of the different benzoyl fluorides, normalized to the rate constants for reaction with aminoacetonitrile, as shown in Figure 3. The increase in β_{nuc} is consistent with a value of $\partial\beta_{nuc}/\partial\sigma = 0.07$, which is shown by the solid lines. The data also correspond to an increase in ρ with increasing pK_a of the amine, as required by the $p_{xy'}$ coefficient and eq 2;[33] this is evident from the increased rate constants for

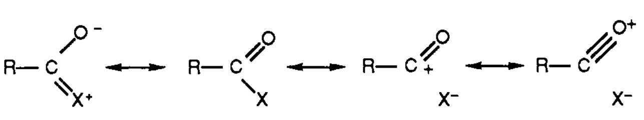
$$p_{xy'} = \frac{\partial\beta_{nuc}}{\partial\sigma} = \frac{\partial\rho}{\partial\,pK_{nuc}} \qquad (2)$$

the reactions of basic amines and benzoyl fluorides with electron-withdrawing substituents shown in Figure 3. The changes in β_{nuc} that were noted above for the reactions of four anilines with benzoyl fluorides in methanol, reported by Lee and coworkers[27] after the completion of this work,[37] correspond to a much larger interaction coefficient of $p_{xy} = 0.40$; for the corresponding benzoyl chlorides the values of p_{xy} is 0.18.

A positive $p_{xy'}$ coefficient is characteristic of concerted nucleophilic substitution on benzyl halides, in which its existence has been confirmed by measurement of α-secondary deuterium isotope effects.[33-36] An increase in ρ corresponds to an increase in the amount of bond formation in the transition state, proceeding from the acylium ion in the upper right corner to $T^{\pm}$ in the lower left corner (diagonal arrow in Figure 4). The small increase in ρ that is observed with basic amines is consistent with movement of the transition state perpendicular to reaction coordinate C for a concerted mechanism; it is not expected for the vertical reaction coordinate A, with rate-limiting amine attack, which predicts a decrease in ρ.

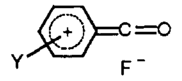
Unfortunately, a positive $p_{xy'}$ coefficient also may arise from an electrostatic interaction. A similar interaction coefficient was observed for the exchange of substituted alcohols with substituted 1-phenylethyl alkyl ethers at equilibrium and was ascribed to an electrostatic interaction between polar substituents on the phenylethyl and alcohol groups.[38] However, more recent work of Kirby and co-workers has suggested that such changes may arise from resonance that results in changes in C–O bond length in similar systems.[39] Therefore, the positive $p_{xy'}$ coefficient for substitution is consistent with, but does not prove a concerted mechanism for the aminolysis of benzoyl fluorides. The $p_{xy'}$ coefficient for substitution on benzyl systems is approximately 3 times larger and cannot be accounted for by an electrostatic effect.[34]

Effect of the Leaving Group. The greater C–O vibrational frequency and shorter C–O bond length of acid halides compared with aldehydes and acyl cyanides, and the longer C–X bond length than expected for an sp^2 hybridized C–X bond,[40,41] suggest that the ionic structures **4** and **5** contribute significantly to the structure



2 **3** **4** **5**

of acid halides in the ground state.[42,43] The electronegative fluorine atom and the benzene ring of benzoyl fluorides are expected to provide additional stabilization from a contribution of the nonbonded structure **6**; this is supported by the change in the ^{13}C NMR chemical shift of the carbonyl carbon atom from 168 ppm for *p*-anisoyl chloride to 159 ppm for p-anisoyl fluoride.[44]



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These resonance structures are expected to stabilize the ground state and a transition state with C–F bond breaking; they will result in destabilization of a tetrahedral addition intermediate. This is consistent with the rapid reactions of benzoyl fluorides through a concerted displacement mechanism. In fact, anisoyl fluoride reacts 3–5 times faster with primary amines of pK_a = 5.5–11 than *p*-anisoate picoline *N*-oxide ester, in spite of the greater basicity of fluoride (pK_a = 3.2) than of the oxygen leaving group (pK_a = 2.1). The curvature of the Brønsted-type plot for the ester is very similar to that for the fluoride, so that aminolysis of this reactive ester may also occur with a concerted mechanism.[45] The reactions of anilines with substituted benzoyl chlorides at 35 °C are $>10^3$ faster than with benzoyl fluorides at 55 °C in methanol, so that it is likely that the chlorides also react by a concerted mechanism.[27] This large effect of the leaving group is very different from the ratio of $k_{Cl}/k_F = 1.2$ for the hydrolysis of benzoyl halides through an associative pathway and a transition state that involves primarily bond formation to the nucleophile.[23]

The absence of detectable general-base catalysis of aminolysis is expected for these rapid reactions with a good leaving group. The uncatalyzed aminolysis of benzoate esters is very sensitive to the nature of the leaving group. For example, the rate constants for the uncatalyzed ammonolysis of *p*-chlorophenyl and *p*-nitrophenyl benzoates correspond to $\beta_{lg} = -0.85 \pm 0.05$. General-base catalysis is significant for the *p*-chlorophenyl but not the *p*-nitrophenyl ester,[25] so that it would not be expected to be observed with benzoyl fluorides. General-base catalysis that removes the proton from $T^{\ddagger}$ is frequently observed in stepwise aminolysis reactions, but it is not diagnostic for a reaction intermediate unless it can be shown to involve diffusion-controlled proton transfer; it has been observed in a reaction that appears to be concerted.[46]

Conclusion. The data suggest that the aminolysis of benzoyl fluorides proceeds by a concerted substitution mechanism, A_ND_N,[47] although a stepwise mechanism with an unstable addition intermediate, $A_N{*}D_N$,[47] is not rigorously excluded. It was suggested in the previous paper[23] that the hydrolysis of most benzoyl fluorides

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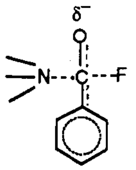
[47] The terms A_ND_N and $A_N{*}D_N$ refer to concerted and stepwise nucleophilic substitution reactions, respectively (Commission on Physical Organic Chemistry, IUPAC *Pure Appl. Chem.* **1989**, *61*, 23–56). The terms A and D refer to association and dissociation, respectively, the subscript N refers to nucleophilic, the absence of punctuation indicates a concerted process, and the asterisk indicates a short-lived intermediate.

and some benzoyl chlorides with a positive value of ρ also occurs through an associative transition state.

The proposed reaction mechanism is similar to that for substitution on benzyl halides, except that the reacting carbon atom is tricoordinate instead of tetracoordinate. This allows a large amount of electron donation and bond formation with the nucleophile in the associative transition state, **7**. It is well-known



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that electron-withdrawing substituents on benzyl halides increase the amount of electron donation from the nucleophile in the transition state, as measured by β_{nuc},[34,35] and the carbonyl group on acyl halides might be regarded as an extreme example of such a substituent. The carbonyl group can easily accept negative charge in the transition state, and the development of a bond to the nucleophile requires the breaking of only a π bond, rather than the σ bond to the leaving group. The reaction may also be favored by the "benzyl effect", which brings about rate increases of 10^2–10^3 in substitution reactions and is believed to involve resonance with the benzene ring in the transition state.[48]

The associative transition state arises from a perturbation perpendicular to the reaction coordinate (Figure 4). Delocalization of charge into the carbonyl group and benzene ring results in stabilization of a transition state in which such delocalization takes place, just as stabilization by electron-donating substituents gives rise to a dissociative transition state that is stabilized by these substituents in substitution reactions.[49]

The structure of the transition state may resemble a tetrahedral addition compound or a trigonal bipyramid; calculations have shown that these two structures do not differ greatly in energy for the reaction of chloride ion with formyl chloride,[50] and displacement reactions of halide ions with acyl halides in the gas phase can be described by two potential wells with no evidence for an addition intermediate;[51] however, the tetrahedral structure is more stable for fluoride ion and formyl fluoride.[50]

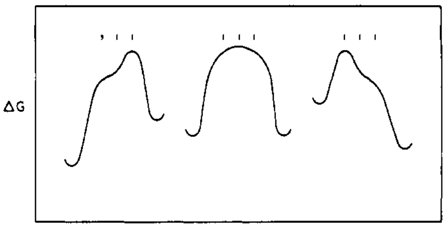
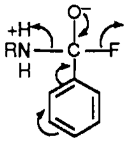


Figure 5. Reaction coordinate diagram to show how the position of the transition state may undergo a large change with changing amine basicity for a concerted reaction that is near the borderline for a stepwise addition–elimination mechanism.[18]

The reaction may occur through a concerted mechanism because the tetrahedral species $T^{\pm}$ is too unstable to exist. The addition intermediates $T^{\pm}$ formed from *p*-tolyl acetate and methylamine or dimethylamine expel the amine very rapidly,[4] with $k \geq 3 \times 10^9\ \text{s}^{-1}$, and the decomposition of benzoate adducts is expected to be considerably faster because of resonance from the benzene ring (**8**). Therefore, it is likely that $T^{\pm}$ does not have a significant lifetime and that the concerted mechanism is enforced, at least for the reactions with weakly basic amines that will be expelled much faster than methylamine. It has been suggested previously that the reaction of pyrazole with phenyl acetate, which is subject to general-acid and general-base catalysis, also proceeds through a concerted mechanism because pyrazole is a very good leaving group and the addition intermediate $T^{\pm}$ is too unstable to exist.[46]



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Electron donation from the acyl group that destabilizes $T^{\pm}$ may also account for a change from a stepwise to a concerted mechanism for acyl transfer between pyridines. The aminolysis of acetylpyridinium ions shows a large change in the Brønsted slope, from $\beta_{\text{nuc}} = 0.9$ for weak nucleophiles to $\beta_{\text{nuc}} = 0$ for strong nucleophiles,[11] while the slower transfer of a methoxycarbonyl group from isoquinoline to substituted pyridines follows a linear Brønsted relationship with a smaller dependence on amine basicity, $\beta_{\text{nuc}} = 0.58$, for nucleophiles of larger and smaller pK_a than the pK_a of isoquinoline and is believed to be concerted.[20]

It is certain that these reactions are near the mechanistic borderline for a change from a stepwise to a concerted mechanism. Following an earlier suggestion,[18] we speculate that the reaction coordinate profile resembles that for the stepwise mechanism, except that the intermediate does not exist because there is not a significant barrier for its decomposition (Figure 5). This can account for the large change in transition-state structure over a comparatively small range of reactivity, as shown in Figure 5. When the tetrahedral structure becomes still less stable, the curvature of the reaction coordinate profile will be sharper and there will be less tendency for movement of the transition state with changing structure of the nucleophile and leaving group.[33,49] This may account for the essentially linear Brønsted-type correlations for acetyl transfer between substituted phenolate ions and methoxycarbonyl transfer between isoquinoline and substituted pyridines that were observed by Williams and co-workers.[20]

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