General Base and General Acid Catalyzed Intramolecular Aminolysis of Esters. Cyclization of Esters of 2-Aminomethylbenzoic Acid to Phthalimidine

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Plots of log k_0 vs pH for the cyclization of trifluoroethyl and phenyl 2-aminomethylbenzoate to phthalimidine at 30 °C in H_2O are linear with slopes of 1.0 at pH >3. The values of the second-order rate constants k_{OH} for apparent OH^- catalysis in the cyclization reactions are 1.7×10^5 and 5.7×10^7 M^{-1} s^{-1}, respectively. These rate constants are 10^5- and 10^7-fold greater than for alkaline hydrolysis of trifluoroethyl and phenyl benzoate. The k_{OH} for cyclization of the methyl ester is 7.2×10^3 M^{-1} s^{-1}. Bimolecular general base catalysis occurs in the intramolecular nucleophilic reactions of the neutral species. The value of the Bronsted coefficient β for the trifluoroethyl ester is 0.7. The rate-limiting step in the general base catalyzed reaction involves proton transfer in concert with leaving group departure. The mechanism involving rate-determining proton transfer exemplified by the methyl ester in this series ($\beta = 1.0$) can then be considered a limiting case of the concerted mechanism. General acid catalysis of the neutral species reaction or a kinetic equivalent also occurs when the leaving group is good ($pK_a \leq 12.4$). That the mechanism and/or rate-determining step of the intramolecular aminolysis reactions is different than in bimolecular reactions or the intramolecular reactions of other esters is attributed to the excellent steric fit of the nucleophile to the reaction center of the 2-aminomethylbenzoate esters.

Chemical intramolecular reactions bear a striking resemblance to the intracomplex reactions of enzymes and can give insight into the analogous enzymatic process.[1,2] Intramolecular nucleophilic reactions of acyl derivatives have been found to give large rate enhancements and large effective molarities for the neighboring group in comparison with the corresponding bimolecular reaction.[1−3] The factors responsible for the efficiency of intramolecular nucleophilic reactions are of great current interest.[4] General base catalysis, in which the catalyzing base partially abstracts a proton from a water molecule in the transition state, appears to be a much less favorable mechanism. It is generally thought that nucleophilic reactions will occur when sterically possible. Nevertheless, general base mechanisms have been frequently suggested in enzymatic reactions.[5−7] It is therefore important to gain an understanding of the factors influencing the mechanisms of intramolecular nucleophilic reactions and to compare the efficiency of these reactions with general base catalyzed reactions of analogous compounds.[8]

The bimolecular and intramolecular aminolysis reactions of esters that have been studied to date have shown large differences in the detailed mechanisms.[1,9−20] 2-Imidazolylbenzoate esters give rise to rapid intramolecular nucleophilic reactions that involve apparent hydroxide ion catalysis of the neutral species nucleophilic reaction (or the kinetically equivalent reaction of an anionic species).[17,18] The cyclization reactions of the phenyl and *n*-propylthiol 2-imidazolylbenzoate esters are general base catalyzed. Bronsted plots for general base catalysis have slopes, β, of 1.0, which indicates that a proton transfer in the thermodynamically unfavorable direction is rate determining.[21] Again, $\beta = 1.0$ in the general base catalyzed aminolysis reaction of methyl 2-aminomethylbenzoate.[13] In contrast, the intramolecular reactions of the less sterically constrained phenolic and thiol esters of γ-(4-imidazolyl)butyric acid[14] involve only the neutral species of the nucleophile, and external buffer catalysis is not observed.[14b] This is also the case in the intramolecular aminolysis reactions of phenolic bis-carbonate or carbamate esters.[15] There has not been a unifying

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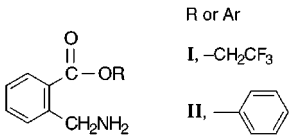
explanation of why the mechanism of ester aminolysis depends upon the type of reaction and the substrate.

The varied results in ester aminolysis reactions constitute a fundamental problem that must be resolved for proper assessment of nucleophilic mechanisms. An extensive study has now been made of intramolecular aminolysis in the 2-substituted benzoate system with the primary amine nucleophile of **I** and **II** to determine the



detailed mechanisms of these reactions. In the cyclization reactions nucleophilic amine attack proceeds via kinetically favored five-membered ring transition states.

2-Substituted benzoate esters are ideal compounds for the kinetic investigation of intramolecular reactions because of the rigid steric relationship between the substituent group and the ester carbonyl and the systematic structural variations that are possible. The kinetic investigation of the 2-aminomethylbenzoate esters has established the general relationship between the apparent OH^--catalyzed and uncatalyzed nucleophilic reactions of the neutral species in the intramolecular aminolysis reactions. Futhermore, we have found that the magnitude of the Bronsted coefficient for general base catalysis, β, depends on the leaving group when the basicity of the nucleophile is high, thereby allowing the aminolysis reactions to be interpreted in terms of a concerted mechanism.

Experimental Section

Materials. Trifluoroethyl 2-Aminomethylbenzoate Hydrochloride. Trifluoroethyl *o*-cyanobenzoate was prepared from phthalamic acid according to the general procedure of Carpino.[22] While a mixture of phthalamic acid (10 g), trifluoroethanol (18 g), and pyridine (38 g) cooled in an ice bath, 21 g of methanesulfonyl chloride was added dropwise with stirring over a period of 45 min. The ice bath was removed and stirring was continued for 8 h. The mixture was diluted with 1 L of cold water, and the white solid which separated was removed by suction filtration. The product was washed several times with water and air-dried: mp 72−74 °C; IR ν 2240 cm^{-1} (−CN); NMR ($CDCl_3$; with TMS as an internal standard, δ = 0 ppm) δ 4.72 (q, 2H), 7.73 (m, 3H), and 8.17 (m, 1H) ppm.

The *o*-cyano ester was catalytically reduced in tetrahydrofuran−trifluoroethanol (4:1) and chloroform employing the method of Secrist and Logue.[23] Hydrogenation was complete in 4 h at 55 psi of H_2. After the PtO_2 catalyst was removed by filtration, the solvent mixture was removed by rotary evaporation. The product was triturated several times with anhydrous ether, which yielded white crystals: mp 171−173 °C (dec); IR ν 1740 cm^{-1} (C═O); ^{1}H NMR (DMSO-d_6, TMS) δ 4.70 (q, 2H), 3.2 ppm (2H). Anal. Calcd for $C_{10}H_{11}ClF_3NO_2$: C, 44.54; H, 4.11; N, 5.19. Found: C, 44.39; H, 4.23; N, 5.37.

Phenyl 2-Aminomethylbenzoate Hydrochloride. Phenyl *o*-cyanobenzoate was obtained by the same method as above with the substitution of phenol for trifluoroethanol to yield the crystalline ester: mp 74−76 °C; IR ν 2270 cm^{-1} (−CN); ^{1}H NMR ($CDCl_3$, TMS), δ 7.18 (m, 5H), 7.59 (m, 3H), and 8.15 (1H) ppm. The cyano ester was reduced, by the same procedure employed in the synthesis of I, in tetrahydrofuran−phenol−chloroform solvent to yield the hydrochloride: mp 158 °C (dec); IR ν 1725 cm^{-1} (C═O); ^{1}H NMR (DMSO-d_6, TMS) δ 3.5 (2H) ppm. Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.52; H, 5.62; N, 4.86.

Infrared and NMR spectra were consistent with the expected ester structures. Buffers were prepared from reagent grade materials. Amine buffer components were freshly distilled or recrystallized prior to use.

Kinetic Methods. The rates of cyclization of the esters of 2-aminomethylbenzoic acid to phthalimidine at 30 °C were measured by following the absorbance change at 285 nm with a Beckman 25 recording spectrophotometer or a Durrum D110 stopped-flow apparatus equipped with a Hewlett-Packard Model 1207B storage oscilloscope. The spectra of the products of the reaction were identical with those of equivalent concentrations of phthalimidine and trifluoroethanol or phenol. In studies employing the Beckman 25 recording spectrophotometer (at pH values below 7 with **I** and below 5 with **II**) aliquots (10−20 μL) of the substrate hydrochloride dissolved in dimethyl sulfoxide were injected into 2 mL of the appropriate buffer (μ = 0.5 M with KCl) to initiate the reactions. At the higher pH values the stopped-flow apparatus was employed. The substrate hydrochloride in 10^{-3}−10^{-2} M HCl solution was placed in one drive syringe and the appropriate buffer was placed in the other syringe. The drive syringes were suspended in a water trough whose temperature was maintained at 30 °C. With each buffer four to six runs were tabulated. Infinity points were stable. The values of k_{obsd}, the pseudo-first-order rate constants, were computer calculated using a rigorous least squares procedure.

The reaction solution pH values were measured with either a Radiometer Model 22 pH meter with a GK 2303 C combination electrode or a Beckman Model 3500 pH meter with a combination electrode standardized against Mallinckrodt standard buffer solutions. The value of K_w at 30 °C was taken to be 1.47×10^{-14}.

Computer modeling of the esters was carried out with a Silicon Graphics Indigo 2 workstation and the programs Quanta 4.0−Charmm, from Molecular Simulations Inc., and Spartan 3.1, from Wavefunction Inc. Energy minimization in the Quanta−Charmm program was by the method of steepest descent and by the method of Newton−Raphson until a constant value was obtained. With the Spartan program, geometry was optimized with AM1 semiempirical calculations.

Results

In Figure 1 is shown a plot of log k_0 vs pH for cyclization of trifluoroethyl 2-aminomethylbenzoate (**I**) to phthalimidine in H_2O at 30 °C (μ = 0.5 M with KCl). The rate constant k_0 was obtained by extrapolation of k_{obsd} values to zero buffer concentration at constant pH. The plot is linear with a slope of 1.0 in the pH range 3−10, which indicates apparent OH^- catalysis in the intramolecular nucleophilic reaction. The value of k_{OH}, the second-order rate constant for the apparent OH^- reaction, is $(1.7 \pm 0.2) \times 10^5$ M^{-1} s^{-1}.

Pronounced general base catalysis was observed in the cyclization reaction of **I**. Figure 2 presents plots of k_{obsd} vs methoxyethylamine total buffer concentration ($B + BH^+$) at two constant pH values. The slope increases as the pH is increased, which indicates general base catalysis. Similar plots were obtained with all the buffers. However, the second-order rate constants for general base catalysis (k_B'), calculated as the slopes of plots of k_{obsd} vs buffer base concentration, increase as the pH is increased. A plot (not shown) of log k_B' for the imidazole-catalyzed reaction (six points in the pH range 6.27−7.84) vs pH is reasonably linear; the best fit line has a slope of 0.7. The slopes of such plots at higher pH were less (0.2 with methoxyethylamine and carbonate buffers in the pH range 9−10), which shows that the apparent OH^--

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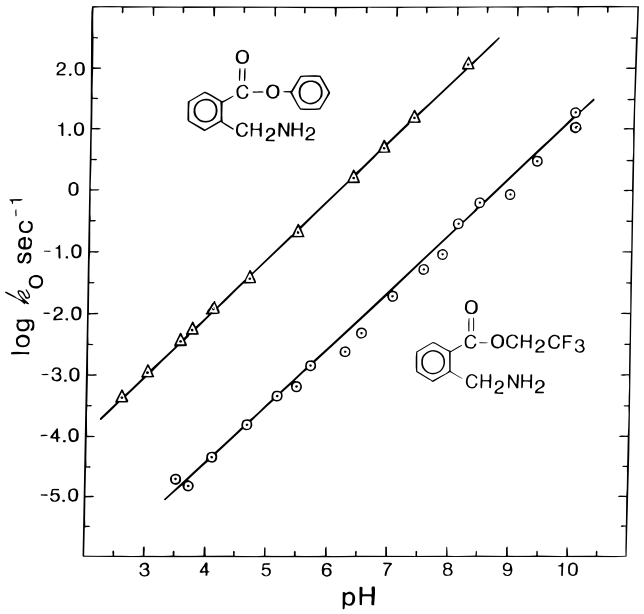

Figure 1. Plots of log k_0 vs pH for cyclization of trifluoroethyl 2-aminomethylbenzoate (○) and phenyl 2-aminomethylbenzoate (△) to phthalimidine in H_2O at 30 °C (μ = 0.5 M with KCl).

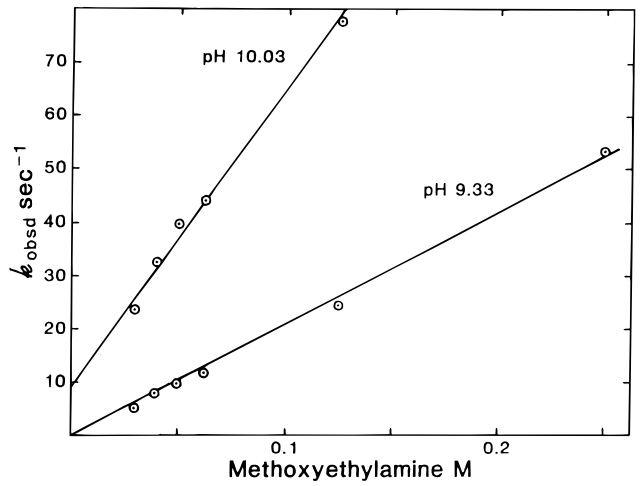

Figure 2. Plots of k_{obsd} vs total methoxyethylamine buffer concentration (B + BH^+) for cyclization of trifluoroethyl 2-aminomethylbenzoate to phthalimidine at 30 °C (μ = 0.5 M with KCl).

catalyzed general base reaction is not a third-order process involving ester, general base, and OH^-. In a general base reaction of the neutral species, the plots of log k_B' vs pH should become level ~2 pH units above the pK_a of the ester amine group conjugate acid. Thus, the pK_a of the neighboring amine group conjugate acid is near 8.5. An empirical equation for k_{obsd} would then be eq 1, where K_1 is the dissociation constant of the protonated ester.

$$k_{obsd} = k_0 + k_B[B]\left[\frac{K_1}{K_1 + a_H}\right] \quad (1)$$

The value of pK_1 cannot be directly measured because of the rapidity of the cyclization reaction, and it will be noted that there is no inflection for an apparent pK_a in the plot of log k_0 vs pH in Figure 1. The pK_1 determined

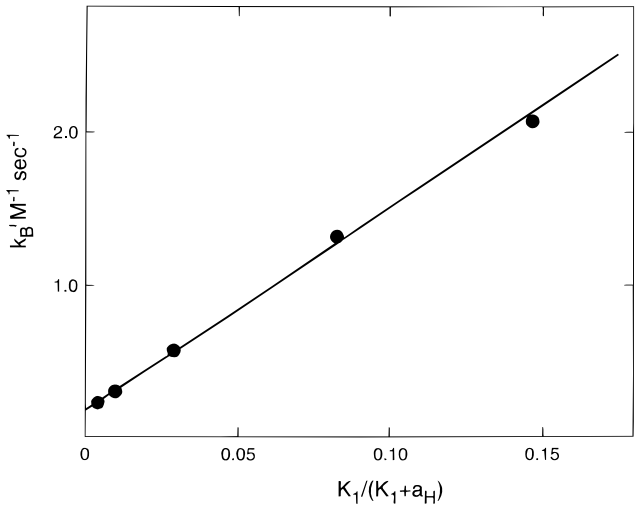

Figure 3. A plot of k_B' vs $K_1/(K_1 + a_H)$ for the imidazole-catalyzed cyclization of trifluoroethyl 2-aminomethylbenzoate to phthalimidine at 30 °C (μ = 0.5 M with KCl); pK_1 = 8.6.

from the buffer catalysis data was employed to obtain the limiting rate constants. Plots were made of k_B' vs $K_1/(K_1 + a_H)$. The intercept of such plots at $K_1/(K_1 + a_H) = 1.0$ is k_B, the limiting second-order rate constant for general base catalysis. Plots of k_B' vs $K_1/(K_1 + a_H)$ were linear, as seen in Figure 3 for imidazole buffer, when the value of pK_1 is taken to be 8.5−9.0. A pK_1 of 8.6 gave the best fit to the data and is estimated to be accurate within ±0.2. This pK_1 value is consistent with the pK_a values obtained with analogous 2-aminomethyl conjugate acid derivatives.[13,24] The pK_{app} for the cyclization of the corresponding methyl ester is 8.6,[13] and the measured pK_a at 30 °C of the conjugate acid of the corresponding 2-aminomethylbenzamide is 9.2.[24]

Extrapolation of the plot in Figure 3 to $K_1/(K_1 + a_H) = 0$ gives a positive intercept. The intercept at $K_1/(K_1 + a_H) = 0$ is the second-order rate constant for the general base catalyzed reaction of the protonated species, k_{BH}, or the kinetically equivalent, general acid catalysis of the neutral species reaction. Equation 1 predicts an intercept of zero in the plot of Figure 3 and the corresponding plots for the other buffers. Therefore, an additional term must be added to eq 1 to give eq 2. The values of these rate

$$k_{obsd} = k_0 + k_B[B]\left[\frac{K_1}{K_1 + a_H}\right] + k_{BH}[B]\left[\frac{a_H}{K_1 + a_H}\right] \quad (2)$$

constants are given in Table 1, as well as the range of buffer concentrations employed. The second-order rate constant for imidazole general base catalysis (k_{Im}) is 2.5-fold less in D_2O than in H_2O.

A Bronsted plot of log k_B vs the pK_a of the conjugate acid of the base catalyst is presented in Figure 4 for the cyclization of **I**. The slope β is 0.67 (r = 0.98). The slope of the Bronsted plot is not sensitive to the value of pK_1. Points for the amine bases, carbonate, and cacodylate fit well on the same line. Acetate buffers were employed at four pH values in the pH range 4.09−5.48 with the total buffer concentration varied from 0.06 to 0.5 M, but significant catalysis was observed only at pH 5.48 (225%). The catalysis was only 16% with 0.5 M total acetate at pH 5.16.

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Table 1. Rate Constants for the General Base Catalyzed Cyclization of Trifluoroethyl 2-Aminomethylbenzoate and Phenyl 2-Aminomethylbenzoate to Phthalimidine at 30 °C in H_2O (μ = 0.5 M with KCl)

compd	base	pK_a[a]	buffer concn range (M)	k_B (M^{-1} s^{-1})	k_{BH} (M^{-1} s^{-1})
I	carbonate	10.25	0.019−0.10	2500 ± 40	
	methoxyethylamine	9.45	0.03−0.25	650 ± 40	
	morpholine	8.60	0.02−0.06	140 ± 20	
	tris	8.15	0.062−0.50	45 ± 2	
	imidazole[b]	7.05	0.062−0.50	12.7 ± 0.5	0.2
	cacodylate	6.28	0.075−0.60	6.5 ± 0.5	
	acetate[c,d]	4.75	0.062−0.50	0.0029 ± 0.0001	
II	acetate[e]	4.75	0.062−0.50		0.098 ± 0.01
	formate	3.57	0.062−0.50		0.016 ± 0.001

[a] Determined at the same temperature and ionic strength as the rate measurements. [b] Studied at six pH values. [c] Studied at four pH values. Catalysis was observed only at pH 5.48. [d] The reported rate constant is k_B'. [e] Studied at three pH values.

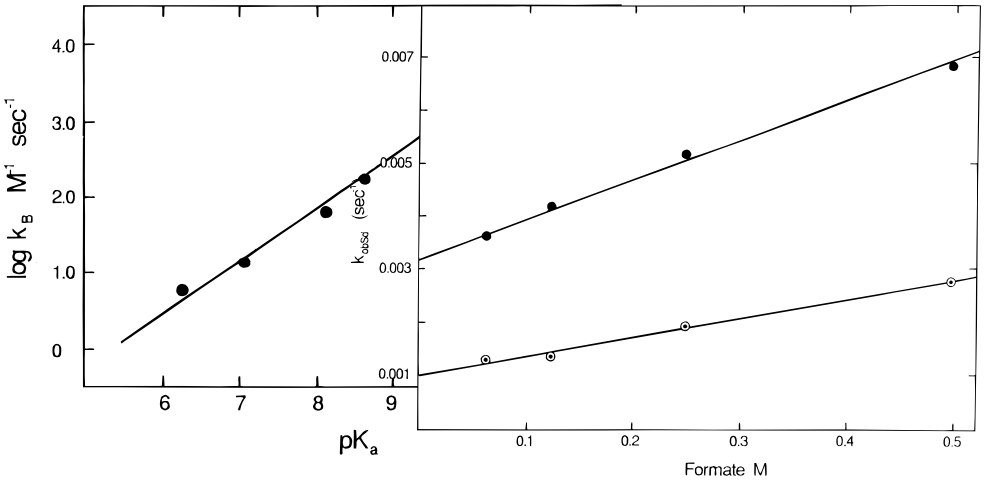


Figure 4. A plot of log k_B vs the pK_a of the conjugate acid of the general base catalyst in the cyclization of trifluoroethyl 2-aminomethylbenzoate to phthalimidine at 30 °C (μ = 0.5 M with KCl).

Figure 5. Plots of k_{obsd} vs total formate buffer concentration at pH 3.0 (○) and 3.57 (●) in the cyclization of phenyl 2-aminomethylbenzoate to phthalimidine at 30 °C (μ = 0.5 M with KCl).

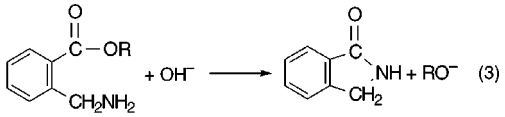
A plot is also shown in Figure 1 of log k_0 vs pH for the cyclization of phenyl 2-aminomethylbenzoate (**II**) to phthalimidine in H_2O at 30 °C. The plot is linear with a slope of 1.0 in the pH range 3−8.5. The value of k_{OH} is $(5.7 \pm 0.35) \times 10^7$ M^{-1} s^{-1}. By reducing the temperature to 15 °C, rate measurements could be made at higher pH values. In that manner it was demonstrated that OH^- catalysis still occurs at pH values above 9. No curvature was detected in the plot of log k_0 vs pH at the limit of the stopped-flow instrument.

Catalysis by buffer was also found in the cyclization reaction of **II**, and rate constants are given in Table 1. In view of the rapidity of the reactions, complete buffer dilutions were carried out only with acetate and formate buffers (0.062−0.50 M). In contrast with **I**, significant catalysis was found with acetate buffers at three pH values ranging from 3.7 to 4.7 and with formate buffer even at pH 3.0. Plots are shown in Figure 5 of k_{obsd} vs total formate buffer concentration at pH 3.0 and 3.57. As is also the case in acetate buffer, the slope is increased at the higher pH, which indicates general base catalysis or a kinetic equivalent. However, with both buffers, k_B' is reasonably constant at the various pH values. Thus, the reaction involves general base catalysis of the protonated species reaction or the kinetically equivalent general acid catalysis in the neutral species reaction. The values of k_{BH} for **II** in Table 1 are given as the rate constants for general base catalyzed cyclization of the protonated species. With other buffers, at pH greater than 5.4, k_0 values were determined in 0.03−0.062 M total buffer.

The structure of the esters **I** and **II** and the corresponding cyclization products were investigated through computer modeling. These studies revealed that the neighboring amino group of the energy minimized structures of **I** and **II** is 3.51 and 3.53 Å, respectively, from the ester carbonyl carbon. Other relatively less stable conformations produced by rotation about the C−N bond can be obtained in which the amine group is 3.14 to 4.44 Å (**I**) and 3.17 to 4.42 Å (**II**) from the carbonyl carbon. These values were obtained with the Quanta−Charmm program. With AM1 semiempirical geometry optimization, **I** and **II** have nonbonded distances between the amine nitrogen and the carbonyl carbon of 3.57 and 3.46 Å. The C−N bond length in the tetrahedral intermediate produced by cyclization is 1.47−1.49 Å.

Discussion

Intramolecular Aminolysis. In the cyclization of **I** and **II** to phthalimidine, the plots of log k_0 vs pH are linear with comparable slopes of 1.0, which indicates apparent hydroxide ion catalysis (eq 3). Removal of a proton from



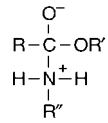
the molecule is, therefore, an essential feature of the reaction. The second-order rate constant for alkaline hydrolysis of trifluoroethyl benzoate is 6.56 M^{-1} s^{-1} at

50 °C.[17] In comparison, k_{OH} for the cyclization reaction of **I**, in which the same leaving group is released, is 1.7×10^5 M^{-1} s^{-1} at 30 °C, 3×10^4-fold larger, even with a temperature difference of 20 °C. The k_{OH} for the cyclization of **II** is more than 10^7-fold larger than that for hydrolysis of phenyl benzoate[25] if a reasonable allowance is made for differences in temperature and solvent. Thus, the neighboring amine group of these esters gives rise to extremely facile intramolecular nucleophilic reactions with very large rate enhancements.

The intramolecular nucleophilic amine group attack at the ester carbonyl might take place via either the neutral species or the amine anion. However, the high pK_a of the neutral amine would limit the concentration of the amine anion to an exceedingly low level at any pH.[26] Also, a reaction via an amine anion would demand a slope of 2.0 in the plot of log k_0 vs pH at pH values less than the pK_a of the amine group conjugate acid. Amine anion attack at high pH would generate an anionic tetrahedral intermediate directly, whereas nucleophilic attack by the neutral amine group would require proton transfer subsequent to or concurrent with nucleophilic attack. The general base catalyzed cyclization of the phenyl and *n*-propylthiol esters of *o*-(2-imidazolyl)benzoic acid, with which the pK_a of the nucleophile (~12) is much less than that of **I** and **II**, proceeds with rate-determining proton transfer ($\beta = 1.0$) that does *not* involve proton abstraction from the nucleophile.[17,18]

The phenyl ester **II** cyclizes 335 times faster than the trifluoroethyl ester **I** in the apparent OH^--catalyzed intramolecular reactions and 10^4-fold faster than the OH^--catalyzed cyclization of the corresponding methyl ester.[13] The k_{OH} for cyclization of the cyclohexyl ester is 4-fold less than that of the methyl ester,[27] which may indicate a steric effect in the reaction. In view of the pK_a values of phenol (10),[28] trifluoroethanol (12.4),[29] and methanol (15.5),[29] the difference in the rate constants corresponds to a Bronsted β_{1g} for the leaving group of ca. −1.0,[30] which implies considerable C−O bond breaking in the critical transition states. An *o*-aminomethyl group gives rate constants that are 100-fold greater than those found with a neighboring imidazolyl group,[17] thereby indicating that β_{nuc} for the nucleophile is also 1.0 or greater. Rate constants for these reactions are summarized in Table 2. The simplest explanation is that breakdown of a tetrahedral intermediate is rate-determining in the apparent OH^--catalyzed intramolecular aminolysis reactions.

Intermediates between the reactants and the neutral tetrahedral intermediate could occur. A zwitterionic intermediate (**III**) has been suggested in bimolecular aminolysis reactions of esters.[12] The rate-determining step was suggested to be proton abstraction from this intermediate by a general base, a proton transfer through water giving a neutral tetrahedral intermediate (alkyl esters), or direct breakdown of the intermediate to products (phenyl esters). Such an intermediate might also be formed in the reactions of **I** and **II**, or proton transfer and nucleophilic attack could be concerted to give a neutral tetrahedral intermediate without the formation of a zwitterion. A concerted reaction would avoid the unstable zwitterion as an intermediate. A rate-determining reaction of a zwitterion can be ruled out in the intramolecular reactions of **I**. The log k_0 vs pH profile is linear with a slope of 1.0, whereas the rate-limiting proton switch of a zwitterion would give rise to a pH-independent region in the pH−rate constant profile. The Bronsted plot for general base catalysis in the diffusion-controlled reactions of the zwitterion would change the slope from 1.0 to zero at the pK_a, which is contrary to observation; the Bronsted plot of Figure 4 is linear to at least p$K_a = 10.25$ with $\beta = 0.7$. The zwitterion pK_a should be comparable to that of the amine group conjugate acid of the reactant,[12] or less because of the electron withdrawal of −OR′.



III

Table 2. Summary of Second-Order Rate Constants k_{OH} for Apparent Hydroxide Ion Catalyzed Intramolecular Aminolysis Reactions in Water at 30 °C

compd	k_{OH}[a] (M^{-1} s^{-1})
methyl 2-aminomethylbenzoate[b]	7.2×10^3
cyclohexyl 2-aminomethylbenzoate[c]	$(1.7 \pm 0.3) \times 10^3$
I	$(1.7 \pm 0.2) \times 10^5$
II	$(5.7 \pm 0.35) \times 10^7$
trifluoroethyl *o*-(2-imidazolyl) benzoate[d]	1.9×10^3
phenyl *o*-(2-imidazolyl)benzoate[d]	1.2×10^5

[a] From linear plots of log k_0 vs pH. [b] Reference 13. [c] Reference 27. [d] Reference 17.

The log k_0 vs pH profiles for cyclization of **I** and **II** are also still linear at pH values as low as 3 and have no break in the pH region near 8.6, where the pK_a of the amine group conjugate acid occurs. If the cyclization of **I** and **II** only involved OH^- catalysis of the reaction of the neutral species (or an amine anion reaction), then at the pK_a of the protonated amine group the slope would change to 2.0, as observed in the cyclization of the methyl ester.[13] Thus, a reaction must be occurring at a low pH that will give a profile of slope 1.0. Such a reaction would be a water-promoted cyclization of the neutral species or the kinetic equivalent OH^--catalyzed reaction of the protonated species. The equation for k_0 at all pH values in the former case would be eq 4, where k_{H_2O} and k_{OH} are

$$k_0 = (k_{H_2O} + k_{OH}K_w/a_H)\left[\frac{K_1}{K_1 + a_H}\right] \qquad (4)$$

rate constants for the water- and OH^--catalyzed reactions, respectively, and K_1 is the dissociation constant of the amine group conjugate acid. Since the pH−log rate constant profiles are linear at the pH values, the contributions of the two reactions to k_0 are a function of pH

(25) The-second-order rate constant for hydroxide ion catalyzed hydrolysis of phenyl benzoate in 50% dioxane−H_2O at 20 °C is 4.2×10^{-2} M^{-1} s^{-1}; G. D. Cooper; B. Williams *J. Org. Chem.* **1962**, *27*, 3717. In 33% acetonitrile−H_2O at 25 °C the rate constant is 5.6×10^{-2} M^{-1} s^{-1}: Kirsch, J. F.; Clewell, W.; Simon, A. *J. Org. Chem.* **1968**, *33*, 127. This comparison is meant only to show the great facility of leaving group departure in the intramolecular reaction. Note that OH^- attack on a reference ester should be much more favorable than attack by an amine of pK_a ~ 9. The relative rate values are therefore minimum values.

(26) The pK_a of the amine group would reasonably be greater than 25. A low concentration of a reactive species does not, of course, rule out a unimolecular reaction via that species if the rate constant is very large.

(27) Bembi, R.; Fife, T. H. Unpublished data. The plot of log k_0 vs pH is linear with a slope of 1.0 from pH 11.3 to 8.5 (8 points).

(28) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1962**, *84*, 2910.

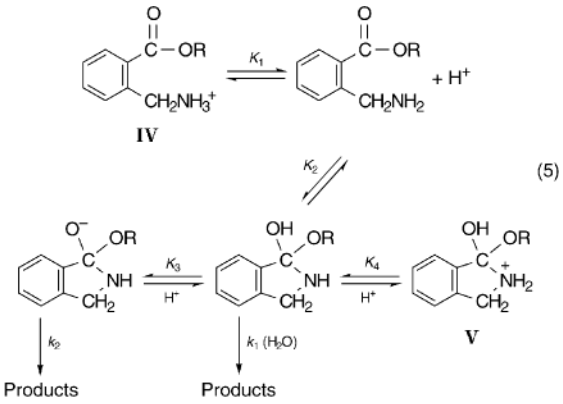
(29) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.

(30) β_{1g} is the slope of a plot of the log of the rate constant vs the pK_a of the leaving group.

and will be nearly equal at pK_1. This result is not coincidental. We have now observed linear log k_0 vs pH profiles with slopes of 1.0 through the pK_a of the amine nucleophile conjugate acid with four different 2-substituted benzoate esters, including the two 2-imidazole-substituted esters listed in Table 2. The log k_0 vs pH profiles for the latter two esters are linear with slopes of 1.0 from pH 4 to 11.

The uncatalyzed neutral species reaction or kinetic equivalent that is predominant at pH values below the pK_1 of the esters **I** and **II** does not occur in cyclization of the corresponding methyl ester.[13] Thus, a water reaction of the neutral species or kinetic equivalent is significant only with leaving groups better than methanol (pK_a < 15.5). Presumably, the neutral tetrahedral intermediate will not break down to products when the leaving group is very poor. The leaving groups of **I** and **II** are of much lower pK_a than methanol; C−O bond breaking is therefore sufficiently favorable that a neutral species reaction or kinetic equivalent can occur.

From the scheme of eq 5, which assumes equilibrium between the reactant and the tetrahedral intermediate, eq 6



(5)

$$k_0 = \frac{k_1K_1K_2a_H + k_2K_1K_2K_3}{a_H^2 + K_1a_H + K_1K_2a_H + K_1K_2K_3} \qquad (6)$$

can be derived considering that $K_4 \gg K_1K_2$. At low pH ($a_H > K_1$), this equation reduces to eq 7,

$$k_0 = \frac{k_1K_1K_2}{a_H} \qquad (7)$$

if $a_H > K_1K_2$. On the other hand, at high pH ($a_H < K_1$ and $a_H > K_3$) eq 8

$$k_0 = \frac{k_2K_2K_3}{a_H} \qquad (8)$$

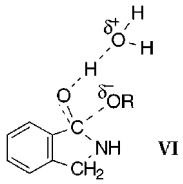
is obtained if K_2 is less than unity. Thus, the scheme of eq 5 is consistent with the linear log k_0 vs pH profiles and the slope of 1.0 if eq 9 holds at pK_1.

$$k_1K_1K_2 \cong k_2K_2K_3 \qquad (9)$$

The rate and equilibrium constants compensate.

Equation 9 must hold independent of the basicity of the leaving group for leaving groups of p$K_a \leq 12.4$. That is also the case when an *o*-imidazolyl group is the nucleophile. The leaving group is, of course, the same in the reactions governed by k_1 and k_2, and the respective intermediates differ by only one proton. Consequently, the two reactions should be mechanistically related. Successive water- and OH^--promoted reactions of the neutral species need not give significant inflections in the plots of log k_0 vs pH.

The k_1 step may involve bond breaking and proton transfer, as in **VI**. As the leaving group becomes better,



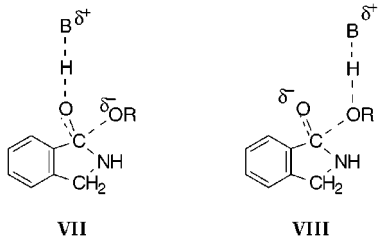
the C−O bond will break more easily, but proton transfer from oxygen will then not need to be as advanced in the transition state. A similar type of reaction takes place in the water reactions of hemiacetals.[31] The linear profiles then reflect the highly favorable intramolecular nucleophilic reactions and the reactivity of the tetrahedral intermediates when the leaving group is good.[32]

An extended linear pH−log rate constant profile would also result if the tetrahedral intermediate only breaks down to products via the anionic species (eq 5 with $k_1 = 0$) and K_2 is greater than unity. In that case, k_0 will be given by eq 10 at $a_H < K_1K_2$. For the profile to still be

$$k_0 = \frac{k_2K_3}{a_H} \qquad (10)$$

linear with a slope of 1.0 at low pH, K_2 would then necessarily be improbably large, since the plot would bend at $a_H > K_1K_2$.

Bimolecular General Base Catalysis. The Bronsted β coefficient for general base catalyzed cyclization of **I** is 0.7, which indicates considerable proton transfer in the transition state. The value of β between 0 and 1.0 shows that the general base catalyzed proton transfer reactions are concerted with C−O bond breaking.[33] The mechanisms **VII** and **VIII** for general base catalyzed breakdown



of a tetrahedral intermediate are kinetically equivalent. That β decreases from 1.0 to 0.7 as the leaving group is improved in the methyl and trifluoroethyl esters indicates that the most likely mechanism involves proton transfer

(31) Przystas, T. J.; Fife, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 4884.

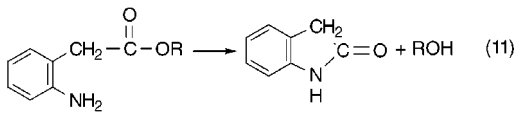
(32) A change in rate-limiting step at the pK_a to attack of the neutral amine at the carbonyl is highly improbable. The linear Bronsted plot of Figure 4 indicates that no change in rate-determining step occurs in the general base catalyzed cyclization of **I**.

(33) Values of β of 0 or 1.0 imply rate-determining proton transfer in the general base catalyzed reaction, whereas β values between 0 and 1.0 imply that bond making or breaking processes are occurring in concert with proton transfer.

from the neutral tetrahedral intermediate[34] in concert with C−O bond breaking (**VII**), rather than the kinetically equivalent donation of a proton by a general acid to the anionic intermediate. Since $\alpha = (1 - \beta)$, the kinetically equivalent mechanism **VIII** would demand that α would increase as the leaving group is improved. However, as C−O bond breaking becomes easier, there will be less proton transfer to the leaving group in the transition state of a concerted reaction, and therefore α should not increase. That α might increase as the leaving group is improved cannot be rigorously ruled out. But in the related general acid catalyzed C−O bond breaking reactions of acetals[35] and ortho esters,[36] α decreases greatly as the leaving group is improved.

It can be concluded that in the intramolecular aminolysis reactions of 2-aminomethylbenzoate esters, the magnitude of the Bronsted β for general base catalysis is a function of the leaving group. With methyl 2-aminomethylbenzoate ($\beta = 1.0$), bond breaking must be sufficiently difficult that proton transfer from the neutral tetrahedral intermediate is nearly complete in the rate-determining step, i.e., the proton must be almost completely removed before bond breaking can commence. The driving force provided by electron release from the oxyanion will then increase the ease of C−O bond breaking greatly. Therefore, the proton transfer from the tetrahedral intermediate is rate-determining in the general base catalyzed reactions, and there is little or no C−O bond breaking in the transition state. As the leaving group is improved to trifluoroethyl, C−O bond breaking becomes easier. Less proton transfer is then required for the C−O bond to begin to break, and as a consequence, proton transfer from the tetrahedral intermediate and C−O bond breaking become concerted. The β value then decreases.

In the cyclization of the trifluoroethyl ester of *o*-aminophenylacetic acid to 2-oxindole (eq 11),[20] the nucleophile has a pK_a that is less than that of **I**. However, the phenylacetate carbonyl is less deactivated than the benzoate ester carbonyl, and a 5-membered ring transition state can be formed by nucleophilic attack. The cyclization reactions of phenylacetate esters are general base catalyzed, and $\beta < 1.0$. There is kinetic evidence for the formation of a tetrahedral intermediate in these reactions, and its breakdown must be rate-determining at pH >4. Thus, these reactions and the general base catalyzed cyclization of the esters of 2-aminomethylbenzoic acid are mechanistically related, although there are large kinetic differences due to the basicities of the nucleophiles.



(11)

When the pK_a of a neighboring amine group conjugate acid is high in an aliphatic ester and the steric situation is very favorable for intramolecular nucleophilic attack, proton transfer reactions in which a zwitterionic intermediate is stabilized are not rate-determining, as in corresponding bimolecular reactions.[12] Diffusion-controlled proton transfer reactions do not have an appreciable activation energy.[37] Therefore, the peak on a free energy reaction-coordinate diagram for proton transfer to or from a zwitterion should not be the highest point unless the preceeding equilibrium (nucleophilic attack) is very unfavorable, as it is in bimolecular reactions. A subsequent step in the reaction sequence can then be rate-limiting in sterically favorable intramolecular reactions. However, when the pK_a of the nucleophile is low and the steric situation is unfavorable, the equilibrium concentration of a zwitterionic intermediate will be small. Proton transfer to or from this intermediate can then be rate-determining, as in the mechanism suggested for the cyclization of methyl 3-(2-aminophenyl)propionate.[16,38] The reaction will then be similar to a bimolecular reaction rather than the intramolecular reactions of 2-aminomethylbenzoate esters. Thus, the ease of nucleophilic attack at the carbonyl carbon is crucial not only to the rate of the reaction but also to the mechanism.

Computer modeling of amino group substituted esters provides additional support for the above interpretations. The neighboring amino group nitrogen of the energy-minimized structures of **I** and **II** is held 3.51 and 3.53 Å, respectively, from the ester carbonyl carbon in the favored conformations. Very similar results were obtained with the corresponding methyl ester in the series (the preferred conformation has the amino group 3.63 Å from the carbonyl carbon). That distance is 3.10 Å in methyl *o*-aminophenylacetate. Thus, cyclization proceeds readily with **I** and **II** and the latter ester, in part because of the proximity of the nucleophile to the reaction center. In contrast, with analogous, but sterically less restricted, straight chain esters, the most stable conformation of the molecule can be extended. An extended conformation is possible with methyl 3-(2-aminophenyl)propionate, in which the distance of the amino group from the carbonyl carbon is 5.19 Å. The computer analysis indicates that nucleophilic attack would be favored with the 2-substituted benzoate esters.

Bimolecular General Acid Catalysis. In addition to general base catalysis of the reaction of the neutral species, there is also general base catalysis in the cyclization of the protonated species of **I** and **II**, or the kinetically equivalent general acid catalysis in the reaction of the neutral species. Cyclization should not proceed readily via the protonated amine species (**IV**). Therefore, a protonated species reaction would demand dissociation of the proton from nitrogen and transfer to another site in the molecule. Note that a pH-independent reaction of a protonated species below the pK_1 is not observed. The N-protonated tetrahedral intermediate (**V** in eq 5) would be present at low pH.[39] The buffer catalysis of the reaction of the phenyl ester at low pH could then involve proton abstraction from **V** by the buffer base, but such a

(34) General base catalysis of this type may be significant when $k_B[B]$ is comparable to or greater than k_2K_3/a_H, where K_3 is the dissociation constant of the neutral tetrahedral intermediate, and k_2 is the rate constant for breakdown of the anionic intermediate. When β is less than 1.0, the percent of catalysis will become greater for constant base concentrations as pH is lowered, since k_2K_3/a_H will decline by a factor of 10 for every pH unit, while that will not be the case for $k_B[B]$.

(35) Fife, T. H.; Brod, L. H. *J. Am. Chem. Soc.* **1970**, *92*, 1681. Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1113.

(36) Anderson, E.; Fife, T. H. *J. Org. Chem.* **1972**, *37*, 1993.

(37) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; pp 207−211.

(38) A detailed discussion of the mechanistic differences in the intramolecular nucleophilic reactions of methyl 2-aminophenylacetate and methyl 2-aminophenylpropionate was presented in ref 20. See also references cited therein.

mechanism does not occur at low pH with the trifluoroethyl ester **I**. Buffer catalysis is only detected experimentally in the reactions of **I** at pH ≥5.1. At higher pH the reactions may involve general acid catalysis of the neutral species reaction.

The general base catalyzed reaction of **I** is greatly favored over the general acid reaction with buffers of high pK_a. With **II**, however, buffer catalysis is large, even at pH 3, and it is the general acid reaction that is of greatest magnitude. The general acid catalyzed reaction is clearly dependent on the pK_a of the leaving group. General acid catalysis is not observed with any buffer in the reactions of the methyl ester and is relatively weak with the trifluoroethyl ester but becomes strong with the phenyl ester. This is exactly the sequence that is observed in general acid catalyzed acetal hydrolysis.[40−42] General acid catalysis in the hydrolysis of acetals is only observed when the leaving group is good[40] or when C−O bond breaking is facile.[40−44] Thus, the similarities are striking in these reactions of different type, but which each have a C−O bond breaking step.

Conclusions. The steric fit of the nucleophile to the carbonyl, the pK_a of the nucleophile, and the ease of leaving group departure all play important mechanistic roles in the intramolecular aminolysis reactions. Steric constraint of the nucleophile close to the carbonyl appears to be critical in leading to a high equilibrium concentration of tetrahedral intermediate and the ensuing mechanistic consequences that distinguish these intramolecular aminolysis reactions from bimolecular aminolysis or the intramolecular aminolysis reactions of esters having numerous degrees of freedom for rotation of the nucleophile away from the reaction center. When the steric fit of a nucleophile to the reaction center is very good, breakdown of a tetrahedral intermediate to products will be rate-determining. The nature and reactivity of the intermediate is therefore of critical importance in regard to high nucleophilic efficiency.

That the mechanism and/or rate-determining step of intramolecular reactions is highly dependent on the steric situation[45] has important consequences for the understanding of enzymatic catalysis. It is generally considered that the structure of the active site of a hydrolytic enzyme serves to maximize the rate constant for the reaction of the ES complex. However, the mechanism of an enzymatic reaction may be a unique function of the relationship between the active site structure and the particular substrate. Attempts to understand the mechanism and the magnitude of the enzymatic rate constants will then depend on prior understanding of the specific effects of the spatial relationships between functional groups and the substrate.

Acknowledgment. This work was supported by research grants from the National Science Foundation and the National Institutes of Health.

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(39) (a) The pK_a of the −OH group of **V** will be reduced by ∼5 pK_a units in comparison with the corresponding neutral species. Fox, J. P.; Jencks. W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436. Estimates of the pK_a values of **V** (R = phenyl) are $-NH_2^+$, 5.5; −OH, 6.3. (b) The pK_a values of the intermediate analogous to **V** in the reaction of methylamine and *p*-tolyl acetate were calculated to be −OH, 7, and $-NH_2^+$, 5.6−6.3. Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7031.

(40) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 4081. Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264.

(41) Anderson, E.; Fife, T. H. *J. Am. Chem. Soc.* **1969**, *91*, 7163.

(42) Fife, T. H.; Anderson, E. *J. Org. Chem.* **1971**, *36*, 2357.

(43) Fife, T. H.; Natarajan, R. *J. Am. Chem. Soc.* **1986**, *108*, 8050.

(44) Fife, T. H.; Bembi, R.; Natarajan, R. *J. Am. Chem. Soc.* **1996**, *118*, 12956.

(45) Intramolecular nucleophilic attack does not occur via a 4-membered ring transition state in the corresponding 2-aminobenzoate esters. Fife, T.; Bembi, R. Unpublished data.