Intramolecular General-Base-Catalyzed Hydrolysis and Aminolysis of the Ester Bond by Imidazole and Quinoline Bases[1]

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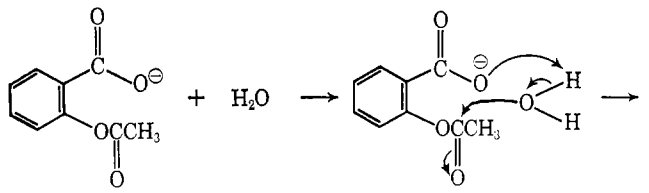
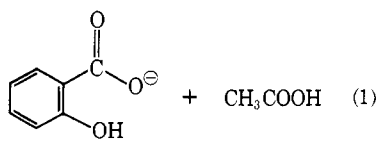
Abstract: Kinetic studies of the hydrolysis and hydrazinolysis of the esters 4-(2′-acetoxyphenyl)imidazole (II), phenyl picolinate (IIIa), phenyl isonicotinate (IIIb), 8-acetoxyquinoline (IVa), and 6-acetoxyquinoline (IVb), as well as the reactions of a series of amines with IVa and IVb, are described. Esters II and IVa (but not IIIa, IIIb, and IVb) were found to be hydrolyzed *via* intramolecular general-base catalysis by the neighboring imidazolyl and quinoline nitrogens. Thus, the values of the deuterium solvent isotope effects (k^{H_2O}/k^{D_2O}) and entropies of activation ($T\Delta S^{\mp}$ kcal mol^{-1}) were determined to be 3.23 and −8.90 for II, and 2.35 and −8.70 for IVa. The enhancements of the spontaneous rates due to intramolecular general-base catalysis have been estimated to be 10^3 for II and 5×10^2 for IVa. The reaction of II with hydrazine and the reactions of IVa and IVb with a series of eleven primary, secondary, and tertiary amines were investigated. With the conjugate acids of pyridine, imidazole, and glycylglycine, IVa and IVb exhibited marked complex formation. For primary and secondary amines the aminolysis reactions were found to occur *via* simple nucleophilic attack (k_n) as well as by amine general-base-catalyzed (k_{gb}) and protonated amine general-acid-catalyzed (k_{ga}) nucleophilic attack. From the larger than anticipated value of k_n for reaction of hydrazine with II it is suggested that the neighboring imidazolyl group assists the reaction as an intramolecular general-base catalyst. In comparing the reactions of IVa and IVb it is found that HO^- and tertiary amines are more reactive toward IVb while H_2O, primary, and secondary amines (k_n) are more reactive toward IVa. Brønsted plots constructed from values for primary and secondary amines not exhibiting the α effect are found to have slope 1.0 for IVb and 0.70 for IVa, indicating a difference in mechanism. The Brønsted equation and the point scatter (due to α effect, steric effects, electronic effects, etc.) for IVb are strikingly similar to those found for nucleophilic attack upon phenyl acetate. When the log of the second-order rate constants for reaction of H_2O, HO^-, and *all* amines with IVa is plotted *vs.* the same constants for IVb it is found that the bases are clearly separated into two groups: (a) HO^- and tertiary amines fit well a line of slope 1.0; and (b) H_2O, primary, and secondary amines provide a line of slope 0.70. The experimental data are best attributed to intramolecular general-base catalysis for the 8 isomer in reaction with primary and secondary amines and simple nucleophilic attack for the reaction of all nucleophiles with the 6 isomer and the tertiary amines (and HO^-) with the 8 isomer. These results provide the first general case of intramolecular general-base-catalyzed aminolysis of an ester. The pyridine esters (IIIa and IIIb) were found not to exhibit either intramolecular assistance to water hydrolysis or aminolysis by primary and secondary amines. A detailed discussion of the intramolecular reaction is provided.

Intramolecular catalysis in the reactions of esters with nucleophiles continues to be studied extensively. Fersht and Kirby,[4] in a reinvestigation of the mechanism of aspirin (I) hydrolysis, have shown that I hydrolyzes with intramolecular general-base assistance from the carboxylate group (1) rather than through a previously



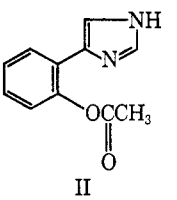
I



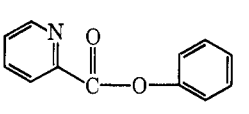
(1)

postulated nucleophilic mechanism. In a more extensive study of the reactions of I with nucleophiles, St. Pierre and Jencks[5] found that the aminolysis of I, in contrast with the hydrolysis, was not assisted by the neighboring carboxylate group except for the case of the weak base, semicarbazide. Apparently either the carboxylate group of I is not basic enough to remove a proton from the attacking amine or alternatively catalysis is felt in those reactions where it is needed most.

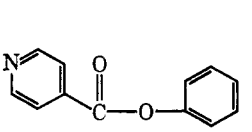
In order to understand the importance of pK_a and base type in intramolecular general-base catalysis of hydrolysis and aminolysis of esters, additional systems need be examined. Results of kinetic investigations of the hydrolysis and hydrazinolysis of the esters 4-(2′-acetoxyphenyl)imidazole (II), phenyl picolinate (IIIa), phenyl isonicotinate (IIIb), 8-acetoxyquinoline (IVa), and 6-acetoxyquinoline (IVb) are described as are the



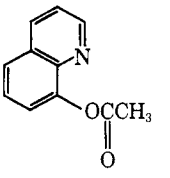
II



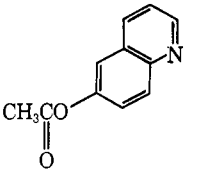
IIIa



IIIb



IVa



IVb

(1) A portion of this work appeared as a preliminary report [S. M. Felton and T. C. Bruice, *Chem. Commun.*, 907 (1968)].
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(4) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, **89**, 4853 (1967).
(5) T. St. Pierre and W. P. Jencks, *ibid.*, **90**, 3817 (1968).

reactions of esters IVa and IVb with a series of amines. The similarity of pK_a between these esters and aspirin would allow a direct comparison to be made concerning the dependence of the intramolecular catalysis on the nature of the intramolecular general base.

The use of 8-hydroxyquinoline as a chelating agent has spurred some interest in the hydrolysis of ester IVa. Elliot and coworkers[6] in a brief communication observed that 8-acetoxyquinoline when compared to 7-acetoxyquinoline exhibited an enhanced hydrolysis rate and a plateau in the pH–rate profile. Barca and Freiser[7] presented a detailed kinetic study of the hydrolysis of 8-acetoxyquinoline and proposed that the enhanced hydrolysis rate was due to an intramolecular nucleophilic catalysis. In addition, two groups[8,9] whose major interest was the use of 8-hydroxyquinoline as a leaving group in peptide synthesis observed that the reaction of esters of 8-hydroxyquinoline with certain amines was intramolecularly catalyzed. They both suggested an intramolecular general-base catalysis mechanism. Esters IIIa and IVa appeared to be suitable candidates for investigation of possible nitrogen base intramolecular catalysis of hydrolysis and aminolysis.

Experimental Section

Materials. Hydrazine hydrochloride, methylamine hydrochloride, ethylenediamine dihydrochloride, imidazole hydrochloride, and glycylglycine were recrystallized from ethanol–water several times, dried, and stored over P_2O_5 *in vacuo*. Hydroxylamine hydrochloride was recrystallized from ethanol–ether. Dimethylamine hydrochloride was extracted with chloroform and recrystallized several times from ethanol–water. Glycine (Fisher Reagent) was used without further purification. Pyridine and morpholine were distilled through a 16-in. spinning band column and the middle fractions were used. The ester, 4-(2′-acetoxyphenyl)imidazole hydrochloride, was prepared according to literature procedures.[10] 8-Acetoxyquinoline (IVa) was prepared according to the method of Salesin and Gordon,[11] mp 56.0–57.0° (lit.[11] mp 56.2–56.5°).

6-Acetoxyquinoline (IVb). To 2.0 g (0.018 mol) of 6-hydroxyquinoline (K & K Laboratories) in a 50-ml flask was added 5.2 ml (0.055 mol) of acetic anhydride with stirring. The reaction mixture was heated slowly to a pot temperature of 150° until no more distillates came over. The remaining volatile components were removed under vacuum. The pot residue was extracted with ether and the resulting solution was concentrated to a light brown mass. Recrystallization of this product from ether–petroleum ether (bp 30–60°) several times yielded a white crystalline solid, mp 68–69°.

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.27; H, 4.99; N, 7.29.

Phenyl Isonicotinate (IIIb). To 31.7 g (0.25 mol) of isonicotinic acid in a 250-ml flask was added 36.5 g (0.50 mol) of thionyl chloride with agitation over a period of 1 hr. After complete addition, the mixture was heated at 90° for 3 hr. The solid yellow crust that formed was kept at room temperature in a closed flask for 16 hr. Then 23.5 g (0.25 mol) of phenol in 75 ml of methylene chloride was slowly added with vigorous stirring, after which the mixture was refluxed for 2 hr. A solution of 21.0 g of sodium bicarbonate in 75 ml of H_2O was then added until the reaction mixture remained at a neutral pH. The methylene chloride layer was separated, dried, filtered, and concentrated. The concentrate on standing solidified and was light brown in color. Several recrystallizations from ethanol–water yielded a white crystalline solid, mp 66–67° (lit.[12] mp 70°).

Phenyl Picolinate (IIIa). To 6.15 g (0.05 mol) of picolinic acid was added 10.50 g (0.05 mol) of trifluoroacetic anhydride. The reaction mixture immediately turned a dark green color. After 1 hr 4.70 g (0.05 mol) of phenol was added. An exothermic reaction took place and a deep red color developed. After 16 hr 100 ml of dry ether was added and the reaction mixture was neutralized with sodium carbonate. The ether layer was separated and concentrated to a light orange liquid. The concentrate was zone sublimed in a zone heated glass tube to yield a white solid, mp 78–79°. Recrystallization from ethanol–petroleum ether yielded a white crystalline product, mp 81–82° (lit.[12] 82°).

Kinetics. Reaction rates were determined spectrophotometrically with Gilford Model 2000 and 220 instruments. Autotitrimetric rates were obtained with a Radiometer TTT1b autotitrator combined with a Radiometer PHA scale expander and a specially designed thermostated cell. pH readings were determined with a Radiometer pH meter 22 equipped with a Radiometer PHA scale expander. The spectrophotometer and autotitrator instruments were kept thermostated at the desired temperature by circulating water from a large 30° bath or from a Haake bath for higher temperature work.

All reaction rates were carried out in aqueous solution at a calculated ionic strength of 1.0 *M* (with KCl) under pseudo-first-order conditions. For the hydrolysis rates the pH was kept constant by the use of HCl and KOH buffers in the extreme pH regions; formate, acetate, and phosphate buffers were used in the moderately acid region and the pH-stat method was used in the neutral to basic region. pH values of the reaction solutions were obtained using a thermostated electrode at the reaction temperature. The pH of solutions was determined prior to and in some cases at the completion of the reaction. Fresh doubly glass-distilled water was used to make up all kinetic solutions.

Solutions of the esters (0.025 *N*) were made with dioxane (Spectroquality) and kept frozen until used. For the spectrophotometric rates, cuvettes (2 or 3 ml) containing the buffer solutions were thermally equilibrated in the thermostated compartment of the instrument; then 1 drop of the ester–dioxane solution was added to each cuvette, the cuvettes were quickly shaken and returned to the cell compartment, and the reaction was followed. The appearance of the phenolic reaction product of ester II was followed at 300 mμ, that of IIIa was usually followed at 264 mμ (low pH) and 290 mμ (high pH), that of IIIb was usually followed at 288 mμ (low pH) and 240 mμ (high pH), that of IVa was usually followed at 288 mμ (low pH) and 325 mμ (high pH), and that of IVb was usually followed at 260 mμ (low pH) and 335 mμ (high pH). The absorption of the substrate usually required that the zero line be offset. For each ester a number of reactions in the acid region were followed at several wavelengths at the same time, and the calculated rate constants at each wavelength were identical.

Amines were used as their own buffers in the aminolysis experiments. An amine solution was made to approximately the desired pH by adding either HCl or KOH solution. To maintain 1 *M* ionic strength the required amount of KCl was added. Serial dilutions were made with 1 *M* KCl solution. Owing to varying pH drifts on dilution it was sometimes necessary to adjust the pH of the solutions by the addition of very small amounts of concentrated HCl or KOH. In this way the pH of the stock solution and the serial dilutions did not vary by more than 0.04 pH unit. Amine buffer solutions were prepared and used the same day. The reaction rates were followed at the same wavelengths used in the basic hydrolysis of each ester.

The pseudo-first-order rate constants were calculated from the infinity OD value or by the method of Guggenheim.[13] An Olivetti-Underwood Programma 101 desk computer was used for the calculations. Programs written for this computer were used to fit the theoretical equations to the pH profiles. The experimental data for the aminolysis experiments are presented in Table I.

Deuterium Solvent Isotope Effects. Deuterium isotope effects were determined at 55° in 99.8% deuterium oxide (Stohler Isotope Chemicals) employing an autotitrator or phosphate buffer (spectrophotometer) to maintain constant pH. The pD values were taken as the pH meter readings plus the proper correction at 55°.[14]

pK_a Determinations. The pK_a values of the amines at 30° were taken from the literature where available. The pK_a of dimethylamine hydrochloride was taken as the pH at half-neutralization.

(6) D. Elliot, L. C. Howick, B. G. Hudson, and W. K. Noyce, *Talanta*, **9**, 723 (1962).
(7) R. H. Barca and H. Freiser, *J. Amer. Chem. Soc.*, **88**, 3744 (1966).
(8) H. D. Jakubke and A. Voigt, *Chem. Ber.*, **99**, 2419 (1966).
(9) J. H. Jones and G. T. Young, *Chem. Commun.*, 35 (1967).
(10) G. L. Schmir and T. C. Bruice, *J. Amer. Chem. Soc.*, **80**, 1173 (1958).
(11) E. D. Salesin and L. Gordon, *Talanta*, **4**, 75 (1960).
(12) H. Meyer, *Rec. Trav. Chim.*, **44**, 323 (1925).
(13) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).
(14) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

Table I. Experimental Conditions for the Aminolysis of Esters II, IIIa, IIIb, IVa, and IVb

Amine (with ester)	pH range	No. of pH's	No. of k_{obsd}	Concn range, M (total amine)
Pyridine (IVa,b)	4.67–6.01	3	18	0.12–2.0
Hydroxylamine (IVa,b)	5.53–6.48	3	18	0.08–0.60
Imidazole (IVa,b)	6.62–7.58	3	18	0.12–2.0
Hydrazine (IVa,b)	7.75–8.91	6	36	0.02–0.20
Hydrazine (II)	7.75–9.06	5	30	0.01–0.20
Hydrazine (IIIa)	7.68–9.05	5	30	0.04–0.30
Hydrazine (IIIb)	7.68–9.05	5	30	0.04–0.30
Glycylglycine (IVa,b)	8.67–7.44	3	18	0.12–0.60
Morpholine (IVa,b)	8.27–9.25	3	18	0.08–0.60
Glycine (IVa,b)	9.11–10.12	3	18	0.06–0.60
Trimethylamine (IVa,b)	9.52–10.10	2	12	0.10–1.0
Ethylenediamine (IVa,b)	9.60–10.52	3	18	0.04–0.40
Methylamine (IVa,b)	10.29–11.12	3	18	0.02–0.20
Dimethylamine (IVa,b)	10.47–11.65	5	30	0.02–0.20

Table II. Hydrolytic Rate Constants

	Ester				
	II	IIIa	IIIb	IVa	IVb
$k_{OH}(55°)$, M^{-1} min^{-1}		7.18×10^3	1.45×10^4	6.27×10^2	1.76×10^3
$k_{OH}(30°)$, M^{-1} min^{-1}	1.49×10^2	2.31×10^3	1.01×10^3	9.02×10	3.04×10^2
$k_0(55°)$, min^{-1}		8.55×10^{-6}	2.50×10^{-4}	2.62×10^{-2}	2.20×10^{-4}
$k_H(55°)$, M^{-1} min^{-1}		1.62	8.70	2.36	0.83
$k_H'(55°)$, M^{-1} min^{-1}		1.4×10^{-2}	1.8×10^{-2}	2.8×10^{-2}	4.0×10^{-2}
p$K_a(55°)$[a]		1.92	3.26	3.09	
p$K_a(30°)$[b]	5.6[c]	2.20	3.30	3.64	4.44

[a] The pK_a apparent values taken from the pH profiles at 55° (Figure 1). [b] Determined by spectrophotometric titration. [c] Reference 10.

At 1 M ionic strength, 30°, and an amine concentration of 0.2 M, a value of 10.93 was obtained. Since this value was in variance with previously recorded values at 25° in the range of 10.64[15] to 10.77,[16] the pK_a of dimethylamine hydrochloride was also determined *via* spectrophotometric titration at the trailing absorption of the amine at 231 mμ, at 30°, 1 M ionic strength, and an amine concentration of 0.06 M. This determination gave an excellent OD *vs.* pH plot which was fitted to a theoretical curve of 11.10. The pK_a value of pyridine at 30° was determined by half-neutralization at a pyridine concentration of 1 M. There was an appreciable concentration dependence on the pK_a value and the value obtained at 1 M can only be regarded as an average value for the experimental conditions of the experiment.

The pK_a values of esters IIIa, IIIb, IVa, and IVb were determined *via* spectrophotometric titration at 30° and 1 M ionic strength at concentrations of about 0.003 M. Excellent plots of OD *vs.* pH were obtained for each of the esters at the following wavelengths: 216 mμ (IIIa), 240 mμ (IIIb), 264 mμ (IVa), and 260 mμ (IVb). These plots were fitted to theoretical curves for evaluation of the pK_a value. All spectrophotometric pK_a determinations were obtained using a combined autotitrator–spectrophotometer cell specially designed in this laboratory in conjunction with a Cary Model 15 spectrophotometer, a Radiometer ABUI automatic buret, and a Radiometer Model 26 pH meter.

Results

Hydrolysis. A theoretical fit for the experimental points at 55° of the pH–rate profiles of esters IIIa, IIIb, IVa, and IVb (Figure 1) was calculated and the derived rate constants are given in Table II. The theoretical rate equation employed (2) was based on the presence of two reactive species, the protonated ester EH^+

$$v = k_{OH}[E][HO^-] + k_0[E] + k_H[E]a_H + k_H'[EH^+]a_H \quad (2)$$

and the neutral ester E. With the help of the acid dissociation relationship for EH^+, the pseudo-first-order rate equation can be derived

$$k_{obsd} = \frac{1}{a_H + K_a}[(k_{OH}[HO^-] + k_0 + k_H a_H)K_a + k_H' a_H^2] \quad (3)$$

where K_a represents the dissociation constants for EH^+; k_{OH}, k_0, and k_H, respectively, represent the HO^-, spontaneous (H_2O catalyzed), and acid-catalyzed hydrolysis of E, and k_H' represents the acid-catalyzed hydrolysis of EH^+ (for justification of the mechanistic assignment of k_0, see Discussion). The hydrolytic rate constants for

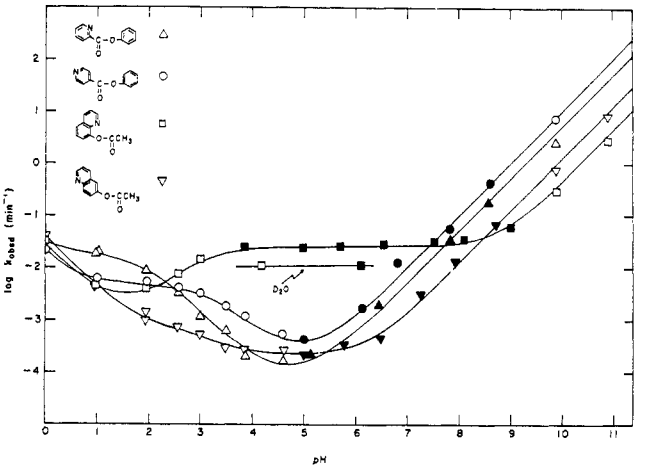


Figure 1. Plots of log k_{obsd} *vs.* pH for the hydrolysis of esters IIIa, IIIb, IVa, and IVb at 55°. The points are experimental and the lines are theoretical fits (filled points, pH-stat; open points, spectrophotometric).

(15) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 675 (1960).

(16) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962, p 140.

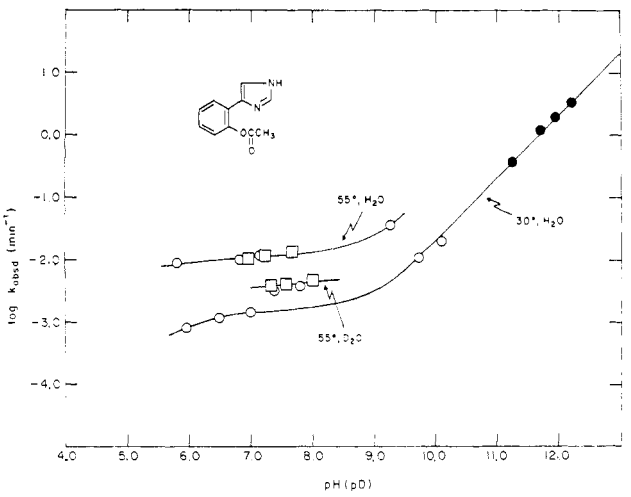


Figure 2. Plots of log k_{obsd} *vs.* pH for the hydrolysis of ester II. The filled in circles are rates obtained spectrophotometrically (hydroxide buffer); the open circles are rates obtained autotitrimetrically, and the open squares are rates obtained spectrophotometrically (phosphate buffers).

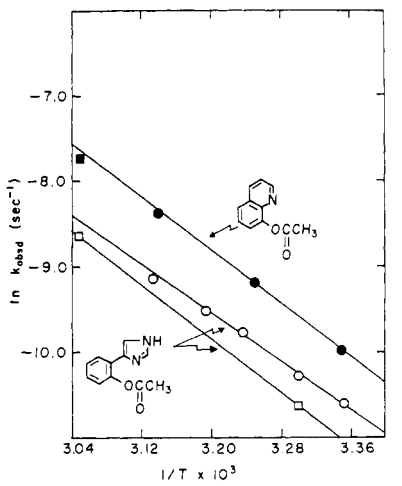


Figure 3. Plots of ln k_{obsd} *vs.* $1/T$ for the spontaneous hydrolysis (plateau rate) of esters II and IVa. Filled circles are from data of Barca and Freiser[7] at μ = 0.1 *M*, 5% EtOH–H_2O. Solid and open squares are from this study at μ = 1.0 *M*, 3% dioxane–H_2O. Open circles are from the data of Schmir and Bruice[10] at μ = 0.55, 28% (v/v) EtOH–H_2O.

IVa are in good agreement with the previously reported values[7] obtained under somewhat different conditions. The HO^--catalyzed hydrolytic rates (k_{OH}) for the above esters as well as II at 30° were determined and they are also listed in Table II. The apparent pK_a values derived from the theoretical fit of eq 3 at 55° are listed in Table II. The pK_a's of these four esters were also determined independently by the spectrophotometric technique at 30° and are also tabulated.

The k_{OH} rate constant for II at 30° was determined to be 149 min^{-1} mol^{-1}. In Figure 2 are shown hydrolytic rates of II in the pH 6–12 region at 30 and 55°. Also shown is the plateau rate of II at 55° in deuterium oxide which exhibits a significant decrease from the rate in H_2O. The deuterium solvent kinetic isotope effect and $T\Delta S^{\pm}$ values were determined for the hydrolysis of the two esters (II and IVa) which exhibited regions of pH-independent hydrolysis. A $T\Delta S^{\pm}$ (−10.8 kcal mol^{-1}) value for the hydrolysis of II at pH 7.00 in 28.5% (v/v) EtOH–H_2O and at 0.55 *M* ionic strength was derived from data in an earlier paper by Schmir and Bruice.[10] In addition, $T\Delta S^{\pm}$ for this ester was also derived from a two-point plot for the hydrolysis of II in H_2O at pH 7.00 at 1.0 ionic strength. Energy of activation plots for both cases are provided in Figure 3. Ester IVa also exhibited a significant deuterium isotope effect for spontaneous hydrolysis at 55°. A $T\Delta S^{\pm}$ (−8.70 kcal mol^{-1}) value for this hydrolysis was derived from the data of Barca and Freiser[7] whose experimental conditions were 0.1 *M* ionic strength and 5% EtOH–H_2O solvent. The rate constant from this work at 55° in H_2O at 1 *M* ionic strength fell directly on the Arrhenius line plotted from their data (Figure 3). The deuterium isotope and entropy data are presented in Table III.

The hydrolytic rates were determined by several methods depending on the pH range being studied. Automatic titration techniques were used in the neutral to alkaline region; spectrophotometric methods were used in the remaining regions. Except where acetate and formate buffers were used, the hydrolytic rates were obtained directly. The use of the carboxylate buffers, however, required an extrapolation to zero buffer concentration. This buffer catalysis was not significant in the spontaneous hydrolysis of esters II and IVa. The reason for this becomes apparent on examination of the general rate equation for hydrolysis in the neutral to basic pH range (4). For those esters that exhibit a large

$$k_{obsd} = k_0 + k_{OH}[HO^-] + k_{cat}[buffer] \quad (4)$$

spontaneous rate (k_0), due to intramolecular catalysis, the k_{cat}[buffer] term becomes barely detectable. Thus, Schmir and Bruice[10] observed that phosphate did not catalyze the hydrolysis of II at pH 6.

Table III. Deuterium Solvent Kinetic Isotope Effects and the Entropy of Activation for the Spontaneous Hydrolysis of Esters II and IVa

	Ester	
	II	IVa
k^{H_2O}/k^{D_2O}(55°)	3.23[a]	2.35[b]
$T\Delta S^{\pm}$,[c] kcal mole^{-1}	−10.8[d]	−8.70[e]
	−8.90[f]	

[a] At pH 6.00, μ = 1.0 *M*. [b] At pH 7.50, μ = 1.0 *M*. [c] Calculated for 25°. [d] From 25.2 to 46.0°, 28.5% (v/v) EtOH–H_2O, μ = 0.55 *M*, pH 7.00. [e] From 25 to 55°, 5% EtOH–H_2O, μ = 0.1 *M*. [f] 30 and 55°, H_2O, μ = 1.0 *M*, pH 7.00.

Aminolysis. The second-order rate constants (k_n) for the aminolysis of II, IIIa, IIIb, IVa, and IVb are presented in Table IV. It has been found[17] that the pseudo-first-order rate constants for the aminolysis of esters in H_2O are correlated well by the rate expression of (5), where k_{OH} represents the hydrolysis of the ester

$$k_{obsd} = k_{OH}[HO^-] + k_n[N] + k_{gb}[N]^2 + k_{ga}[N][NH^+] + k_{OH}'[N][HO^-] \quad (5)$$

catalyzed by HO^-, k_n represents the bimolecular reaction of ester and amine, k_{gb} represents catalysis of this reaction by a second molecule of amine, k_{ga} represents catalysis by a molecule of protonated amine, and k_{OH}' is the catalysis of aminolysis by HO^-. The spontaneous

(17) See Table IV, footnote *f*.

Table IV. Nucleophilic Rate Constants for the Aminolysis Reactions

Amine	pK_a	k_n, M^{-1} min^{-1} Ester II	Ester IIIa	Ester IIIb	Ester IVa	Ester IVb
Pyridine	5.30[a]				1.0×10^{-3}	3.4×10^{-3}
Hydroxylamine	6.04[b]				45	6.8
Imidazole	7.10[c]				0.52	3.7
Hydrazine	8.11[b]	12.8	2.7	1.7	73	9.2
Glycylglycine	8.25[d]				2.9	0.24
Morpholine	8.59[b]				4.9	0.40
Glycine	9.63[b]				30	5.4
Trimethylamine	10.08[e]				5.7×10^{-2}	1.3×10^{-1}
Ethylenediamine	10.10[b]				62	18
Methylamine	10.69[f]				2.9×10^{2}	1.9×10^{2}
Dimethylamine	10.93[a]				1.8×10^{2}	73

[a] Determined by half-neutralization. [b] See T. C. Bruice, J. J. Bruno, and W. S. Chou, *J. Amer. Chem. Soc.*, **85**, 1659 (1963). [c] See T. C. Bruice and J. J. Bruno, *ibid.*, **83**, 3494 (1961). [d] N. G. Kundu, unpublished results. [e] See T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **85**, 1 (1963). [f] T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid., Soc.*, **89**, 2106 (1967).

hydrolysis rate (k_0) is generally comparatively small and need not be included in the equation. Not all reactions exhibit detectable k_{gb}, k_{ga}, and k_{OH}' terms and in such cases a plot of k_{obsd} *vs.* [N] is linear with slope being k_n. As an example, the aminolysis of IVa by methylamine showed such behavior (Figure 4). Where k_{gb} and/or k_{ga} are significant an upward curvature is observed as in the aminolysis of IVb by methylamine (Figure 4). To derive k_{gb}, k_{ga}, and k_{OH}', $(k_{obsd} - k_{OH}[HO^-])/[N]$ *vs.* [N] is plotted to yield as slope $(k_{gb} + k_{ga}a_H/K_a)$ and as intercept $(k_n + k_{OH}[HO^-])$. From secondary plots of slope

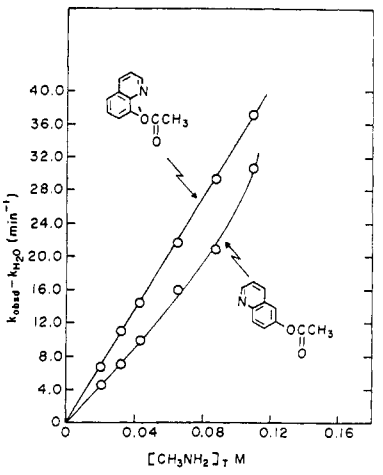


Figure 4. Plots of $(k_{obsd} - k_{H_2O})$ *vs.* total methylamine buffer concentration for the reaction of esters IVa and IVb with methylamine (3% dioxane–H_2O; μ = 1.0; 30°; pH = 10.77).

vs. a_H/K_a and the intercept *vs.* [HO^-] the various rate constants can be determined. For the reaction of II, IIIa, IIIb, IVa, and IVb, k_{obsd} was determined for six concentrations of amine at each of several pH values. Hydrazine was used as its own buffer; thus the five pH values centered around the pK_a of hydrazine. Esters IVa and IVb were also allowed to react with a series of amines; in these cases rates were determined at only three pH's centering around the pK_a of each individual amine.

The bimolecular rate constants (k_n) were ordinarily derived by the described plotting technique. The determination of k_n for the morpholinolysis of IVb is shown in Figure 5a where the intercept is plotted against [HO^-] providing k_n as the new intercept and k_{OH}' as the slope. However, in the reaction of IVa and IVb with glycylglycine, imidazole, and pyridine, k_n could not be derived by the above technique due to apparent complexing of amine and substrate. In Figure 6 a plot of k_{obsd} against total pyridine concentration reveals a satu-

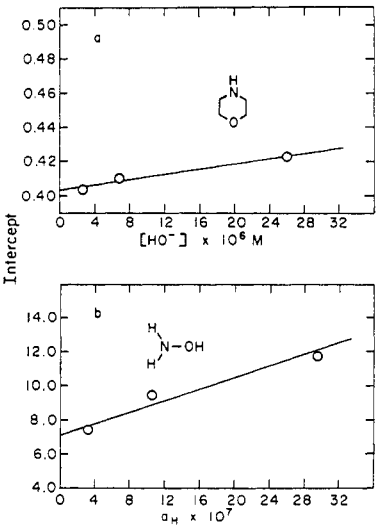


Figure 5. (a) The intercept derived from $(k_{obsd} - k_{OH}[HO^-])/[N]$ *vs.* [N] plotted against hydroxide ion concentration for the reaction of morpholine with ester IVb; (b) the like intercept plotted against hydrogen ion concentration for the reaction of hydroxylamine with ester IVb (3% dioxane–H_2O; μ = 1.0 at 30°).

ration of substrate by pyridine buffer. A detailed study of this complexing phenomenon will be presented in a forthcoming paper. Where the complexing is between the quinoline esters and the protonated form of the amine the derived rate equation is

$$k_{obsd} = k_{OH}[HO^-] + k_n[N] + k_{gb}[N]^2 + k_{ga}[N][NH^+] + k_{OH}'[N][HO^-] + [R]\frac{K'a_H[N]}{1 + K'a_H[N]} \quad (6)$$

where R represents the rate constant for disappearance of complexed ester. A similar derivation was used previously by other groups[18,19] to explain complexation

(18) A. K. Colter, F. F. Guzik, and S. H. Hui, *J. Amer. Chem. Soc.*, **88**, 5754 (1966).
(19) F. M. Menger and M. L. Bender, *ibid.*, **88**, 131 (1966).

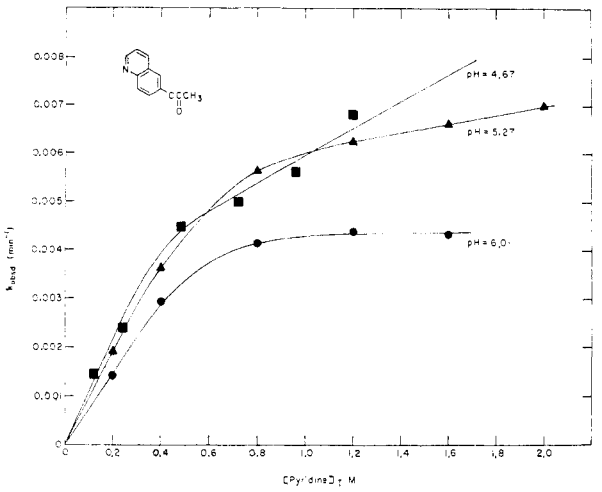


Figure 6. Plots of k_{obsd} *vs.* total pyridine buffer concentration for the reaction of ester IVb with pyridine at three pH values (3% dioxane–H_2O; μ = 1.0 at 30°).

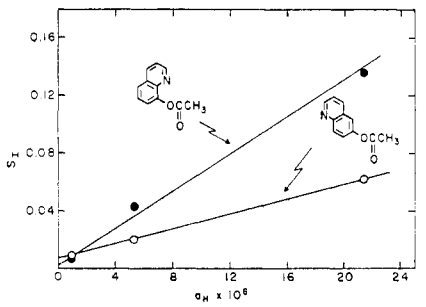


Figure 7. The initial slope derived from the plot of k_{obsd} *vs.* free pyridine concentration plotted against hydrogen ion concentration (3% dioxane–H_2O; μ = 1.0 *M* at 30°).

effects. When [N] approaches zero (and it is assumed that the $[N]^2$ term becomes insignificant) eq 6 becomes

$$k_{obsd} = k_{OH}[HO^-] + k_n[N] + k_{OH}'[N][HO^-] + [R]K'a_H[N] \quad (7)$$

If k_{OH}' is not significant the initial slope (S_1) of the k_{obsd} *vs.* [N] plot should yield $k_n + [R]K'a_H$ as a new slope (S_2). Plotting S_2 against a_H yields k_n as the intercept. In Figure 7 this plot is presented for the reactions of IVa and IVb with pyridine. The same treatment was applied in the reactions of glycylglycine and imidazole with esters IVa and IVb.

In the reaction of hydroxylamine with the quinoline esters (IVa and IVb), no downward curvature was noted in the k_{obsd} *vs.* [N] plot. However, the intercepts determined from the plot of $(k_{obsd} - k_{OH}[HO^-]/[N]$ *vs.* [N] at each pH increased as a_H increased for the reaction with IVb. The k_n value for this reaction was taken as the intercept extrapolated to 0 a_H (Figure 5b). This behavior is possibly indicative of complexing; the lack of downward curvature can be rationalized by the presence of a large k_{gb} term which causes a compensating upward curvature in the k_{obsd} *vs.* [N] plot. For this reason the values of the k_{gb}, k_{ga}, and k_{OH}' rate constants are in doubt in the reactions of the amines with the quinoline esters and only k_n values can be reported with a high degree of certainty.

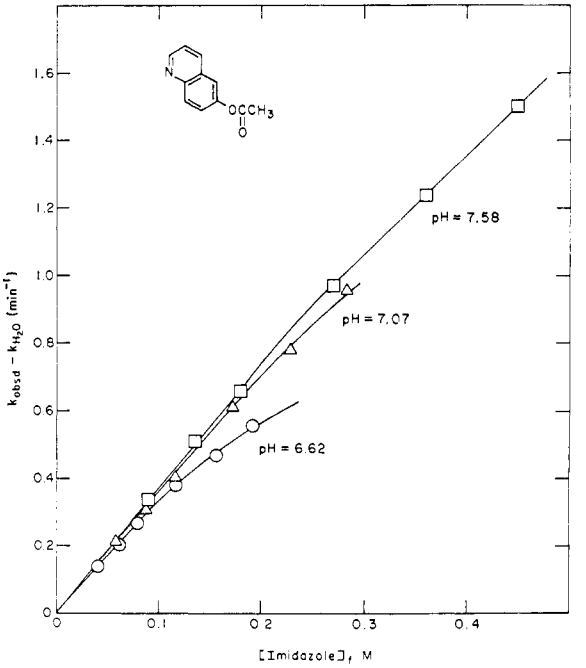


Figure 8. Plots of $k_{obsd} - k_{H2O}$ *vs.* free imidazole concentration for the reaction of ester IVb with imidazole at three pH values.

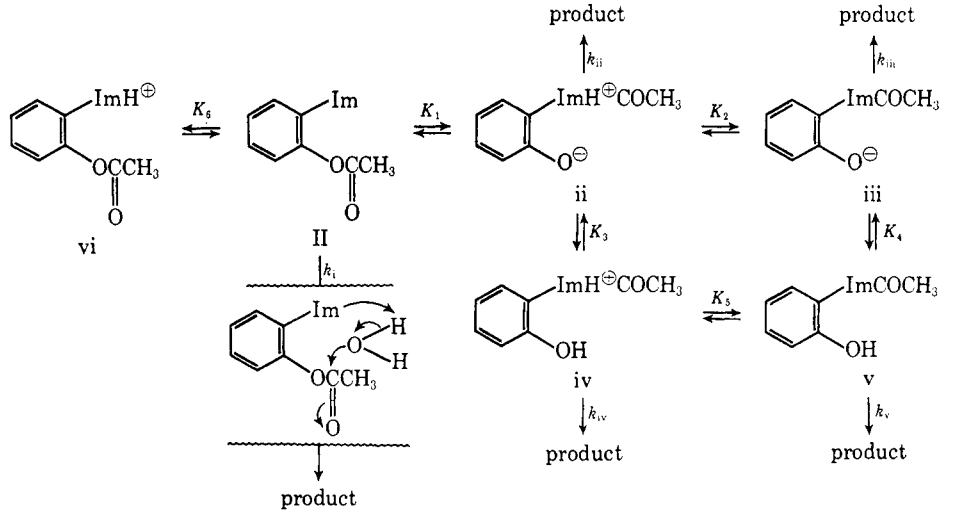
Evidence that the complexing involves the quinoline ester and the protonated amine can be inferred from the plot of the pseudo-first-order rate constant corrected for hydrolysis by H_2O and HO^- ($k_{obsd} - k_{H_2O}$) against the concentration of free imidazole (Figure 8), where the leveling of the plot increases as the pH is decreased.

Discussion

Intramolecular Catalysis in the Reactions of 4-(2′-Acetoxyphenyl)imidazole (II). A summary of the intermolecular reactions of imidazole with phenyl esters has been presented by Bruice and Benkovic.[20] With esters containing good leaving groups, such as *p*-nitrophenyl acetate, a nucleophilic mechanism involving rate-determining attack of imidazole on the ester carbon has been established.[21] As the leaving group becomes poorer a general-base mechanism is observed involving one or two molecules of imidazole in the transition state.[22] The kinetically indistinguishable mechanisms have been differentiated on the basis of deuterium isotope effects and the actual observation of the N-acylimidazole intermediates. The energy barrier to nucleophilic displacement becomes prohibitive as the leaving group becomes poorer than phenoxy[23] so that a general-base mechanism prevails. On this basis it seems reasonable that compound II would hydrolyze through a nucleophilic mechanism,[10] since the leaving group in this case is better than phenoxy. However, the deuterium isotope effect (k^{H_2O}/k^{D_2O} = 3.23) certainly indicates the participation of H_2O in the transition state, which would rule out rate-determining formation of the N-acetylimidazole. This conclusion is also supported by a $T\Delta S^{\pm}$ value of −8.90 kcal mol^{-1} in H_2O which in-

(20) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 46.
(21) T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **80**, 148 (1958).
(22) (a) T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964); (b) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 833 (1964).
(23) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 837 (1964).

Scheme I



dicates the presence of a bimolecular reaction, whereas rate-determining formation of the N-acetylimidazole is a unimolecular reaction. For comparison, the bimolecular reaction of phenyl acetate and imidazole has a $T\Delta S^{\ddagger}$ value of -11.6 kcal mol^{-1},[22a] and the intramolecular nucleophilic catalysis in monophenyl hydrogen glutarate exhibits a $T\Delta S^{\ddagger}$ value of -3.1 kcal mol^{-1}.[24] Since imidazole will attack the ester carbon of phenyl acetate, it is highly probable that I *does* unimolecularly form the N-acetylimidazole (K_1 equilibrium in Scheme I); however, the reverse reaction involving intramolecular nucleophilic attack of phenoxide or phenol on the N-acetylimidazole would be expected to be more facile. Consequently, the equilibrium concentration of the N-acyl compound must be quite small.

As in the case of I the entropy and deuterium isotope effect do not distinguish between general-base catalysis in the O-acyl compound (II) and rate-determining general-base catalysis in one of the possible N-acyl intermediates (ii, iii, iv, and v in Scheme I). The lack of incorporation of ^{18}O into the salicylate product in the hydrolysis of I provides evidence that in this case the anhydride intermediate is not on the reaction path. Trapping an N-acyl intermediate in this way is not feasible in the hydrolysis of II. It is of considerable interest to ascertain the rate enhancement for H_2O-catalyzed hydrolysis brought about by intramolecular general-base participation of nitrogen base. Thus, in the deacylation step for enzymic activity of the serine esterases it is thought that the imidazolyl group of a histidine residue acts as a general-base catalyst to assist the attack of H_2O upon the acylserine intermediate.[25] In the case of the hydrolysis of II this type process is involved. In order to estimate the rate enhancement for spontaneous hydrolysis brought about by participation of the imidazolyl group it is necessary to ascertain what the rate constant for spontaneous hydrolysis of II would be if the *o*-imidazolyl group were acting as a normal substituent with no catalytic role. In what follows the steric and inductive contributions of the *o*-imidazolyl group are first evaluated, thus allowing the calculation of the hypothetic rate constant for the case when the *o*-imidazolyl group is noncatalytic.

The rate retardation of HO^- attack caused by the steric effect of an *o*-carboxylate group in the aspirin molecule has been found to be about two- or threefold.[5] The imidazolyl group, although slightly larger, has a similar geometry, and based on CPK atomic models of the two esters, it does not introduce significantly greater steric interactions than the *o*-carboxylate group. Indeed, the solvation of the negative carboxylate by H_2O may increase its over-all bulk to make it even more comparable to the *o*-imidazolyl group. Thus, a rate retardation of two- to threefold caused by the *ortho* positioning of the imidazolyl group in II is qualitatively correct.

The magnitude of the inductive effect of the *o*-imidazolyl group can be evaluated from the rate constant for hydroxide-catalyzed hydrolysis (k_{HO}) of II (145 M^{-1} min^{-1} at 30°). Assuming that the HO^- rate is retarded two- or threefold by the steric effect of the *o*-imidazolyl group, a value of *ca.* 400 M^{-1} min^{-1} would be expected for the *para* isomer. The inductive effect can now be evaluated as a σ^- value from the Hammett[26] $\sigma\rho$ plot for the hydrolysis of substituted phenyl acetates derived from the data of Bruice and Mayahi[27] employing the proper σ^- values for *ortho*- and *para*-substituted phenyl acetates.[22a] By this means a σ^- value of $+0.3$ was obtained for the imidazolyl group. This evaluation is based on the assumption that electrostatic repulsion of the nucleophile (HO^-) is not significant. This is a reasonable assumption since the imidazole moiety is present entirely as a neutral species in the moderately basic pH range. Also, it has been demonstrated that *o*-nitrophenyl esters containing positively and negatively charged acyl groups do not exhibit electrostatic effects in their reactions with HO^-.[28,29]

A measure of the degree of rate enhancement over that for the hypothetical uncatalyzed reaction of II with H_2O can now be estimated if it is assumed that phenyl acetates with substituents of similar steric and inductive effects will have comparable hydrolysis rates. In a study of a large series of *o*-nitrophenyl esters, Holmquist and Bruice[29] have shown that the HO^- rate and the

(24) T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, **90**, 3808 (1968).
(25) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 2.
(26) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 188.
(27) T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, **82**, 3067 (1960).
(28) T. C. Bruice and B. Holmquist, *ibid.*, **89**, 4028 (1967).
(29) B. Holmquist and T. C. Bruice, *ibid.*, **91**, 2982 (1969).

H_2O rate are related by $\log k_{OH} = 0.84 \log k_{H_2O} + 8.0$. This relationship indicates a similar sensitivity of k_{OH} and k_{H_2O} to electronic and steric effects. Applying this relationship to the known k_{OH} (149 M^{-1} min^{-1}) value of II, a k_{H_2O} value of 4.5×10^{-8} M^{-1} min^{-1} is derived. The validity of this value is supported by the H_2O-catalyzed hydrolysis rate constant of 1.8×10^{-8} M^{-1} min^{-1} for *o*-carboxyphenyl acetate methyl ester (V) and a k_{OH} value of 130 M^{-1} min^{-1} at 25°.[5] In Table V the H_2O and HO^- rate constants for II, V, and an *o*-nitrophenyl ester that was used to derive the $\log k_{OH} - \log k_{H_2O}$ relationship[29] are presented. Thus, if the value of 10^{-8} M^{-1} min^{-1} is taken as the lower limit for the uncatalyzed H_2O reaction of II, and the plateau rate at 30° (divided by 54.76 M)[30] from Figure 2 is taken as the catalyzed H_2O rate (2.9×10^{-5}), a *maximum* rate acceleration of 10^3 can be attributed to intramolecular catalysis by the *o*-imidazolyl group. This compares to a *ca.* 50-fold rate enhancement in the hydrolysis of I (compared to its *para* isomer), and a *ca.* 500-fold rate enhancement in the hydrolysis of IVa (compared to the 6 isomer; see following discussion and Figure 10). The most important conclusion to be made from this discussion is that the efficiency of the intramolecular catalysis in II and IVa is of *ca.* the same order and somewhat larger than in I and perhaps approaches the limit of catalytic efficiency that can be attained in simple intramolecular general-base-catalyzed ester hydrolysis in H_2O.

Table V. A Comparison of Hydrolytic Rate Constants

Ester	k_{OH}, M^{-1} min^{-1}	k_{H_2O}, M^{-1} min^{-1}
II	149[a]	4.5×10^{-8} [a,b]
V	130[c]	1.8×10^{-8} [c]
o-Nitrophenyl propionate	822[a]	41.0×10^{-8} [a]

[a] At 30°. [b] An estimated value for the uncatalyzed hydrolysis. [c] At 25°.

The second-order rate constant in the reaction of II with hydrazine is 12.8 M^{-1} min^{-1} at 30°. Inspection of a Hammett plot for the hydrazinolysis of phenyl esters at 30°, derived from the data of Bruice and Benkovic,[22a] reveals that II is *ca.* 20 times more reactive than expected. This evaluation is based on the assumption that the reaction of II with HO^- is a valid measure of its nucleophilic reactivity relative to other phenyl acetates (*i.e.*, σ for the *o*-imidazolyl group may be derived from a knowledge of ρ and k_{OH}). Such a small apparent rate enhancement does not allow for a definitive judgment as to whether II is undergoing intramolecular catalyzed hydrazinolysis, although this mechanism does seem likely.

If the general-base catalysis of hydrolysis of II does indeed occur in a rate-determining reaction of the N-acyl intermediate, the only N-acyl species that would exhibit the observed sigmoid dependence of k_{obsd} upon pH[10] are ii and v (in Scheme I). This conclusion is derived from the kinetic expression for Scheme I. Assuming that species II, ii, iii, iv, v, and vi are in equilibrium with each other and that steps k_{ii}, k_{iii}, k_{iv}, and k_v represent rate-determining formation of product, the following expressions are derived from the material balance and the acid–base equilibria

$$k_{obsd(ii)} = k_{ii} \times \left[\frac{K_3 a_H}{K_2K_3 + (K_3/K_1 + K_3 + K_5)a_H + (K_3/K_6K_1 + 1)a_H^2}\right] \quad (8)$$

$$k_{obsd(iii)} = k_{iii} \times \left[\frac{K_2K_3}{K_2K_3 + (K_3/K_1 + K_3 + K_5)a_H + (K_3/K_6K_1 + 1)a_H^2}\right] \quad (9)$$

$$k_{obsd(iv)} = k_{iv} \times \left[\frac{a_H^2}{K_2K_3 + (K_3/K_1 + K_3 + K_5)a_H + (K_3/K_6K_1 + 1)a_H^2}\right] \quad (10)$$

$$k_{obsd(v)} = k_v \times \left[\frac{K_5 a_H}{K_2K_3 + (K_3/K_1 + K_3 + K_5)a_H + (K_3/K_6K_1 + 1)}\right] \quad (11)$$

Both $k_{obsd(ii)}$ and $k_{obsd(v)}$ have the mathmetical form

$$k_{obsd} = k\left[\frac{K'}{K'' + a_H}\right] \quad (12)$$

which describes the ascending sigmoid that is observed in the pH profile of II. The expression for $k_{obsd(iii)}$ can be simplified to

$$k_{obsd} = k\left[\frac{K'}{K''a_H + a_H^2}\right] \quad (13)$$

which is further simplified to

$$k_{obsd} = k'[HO^-]\left[\frac{K'}{K'' + a_H}\right] \quad (14)$$

This relationship requires that k_{obsd} is proportional to $[HO^-]$ and the mole fraction of II as the neutral ester species, which is not the case in the pH profile; thus, the k_{iii} step is insignificant in this reaction. The expression derived for $k_{obsd(iv)}$ reduces to the form

$$k_{obsd} = k\left[\frac{a_H}{K' + a_H}\right] \quad (15)$$

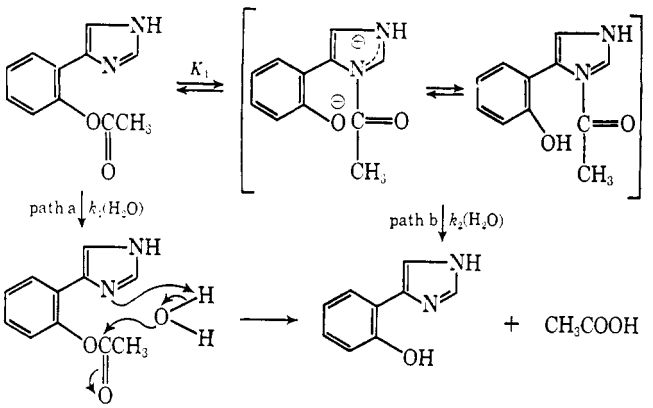
This relationship describes a proportionality to the mole fraction of ester in the acid form and a descending sigmoid which is not observed in the k_{obsd} *vs.* pH profile. Thus, the k_{iv} step is eliminated as a significant reaction path and the hydrolysis of II is limited to the following two reactions (path a and path b, Scheme II).

The reaction of either species ii or v would exhibit a deuterium isotope effect and entropy of activation in accord with the observed values. The reaction of N-acetylimidazolium ion with H_2O exhibits a deuterium isotope effect of 2.5 and an entropy of activation of −9.0 kcal mol^{-1}.[31] The difference in pK between the at-

(30) Calculated from the density of water at 55°; see R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd ed, Butterworth and Co., Ltd., London, 1959, p 457.

(31) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).

Scheme II

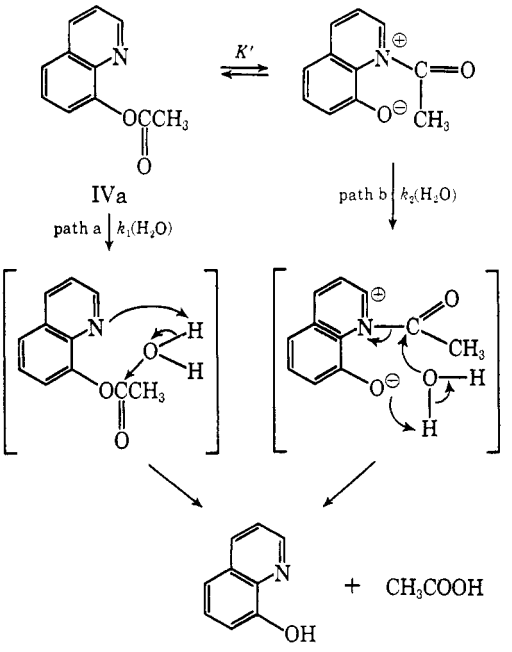


tacking imidazole group and the leaving phenoxy group in the formation of the N-acyl intermediate from II is about 5 pK units. Fersht and Kirby[32] have demonstrated that in the case of substituted aspirins where the attacking group is carboxylate a changeover from the analog path a to path b occurs as the difference in pK between the attacking group and the leaving group approaches zero. In the intermolecular catalyzed reaction of acetate ion and substituted phenyl acetates, Gold, *et al.*,[33] has shown that the general-base hydrolysis mechanism predominates over the nucleophilic mechanism if the leaving group is 3–4 pK_a units more basic than acetate. From these data Fersht and Kirby[32] have proposed, on the basis of entropy arguments, that the relative advantage in the corresponding intramolecular reaction (aspirin hydrolysis) requires that the leaving group be better by about 3–4 pK units than that in the intermolecular reaction to maintain a nucleophilic mechanism. Thus, in aspirins the nucleophilic mechanism becomes significant in 3,5-dinitroaspirin (by ^{18}O and methanolysis studies) where the attacking group and leaving group differ by about 1 pK unit. A completely similar situation exists in the imidazole analog (II). The changeover from a nucleophilic-catalyzed hydrolysis to a general-base-catalyzed hydrolysis in the intermolecular reactions of imidazole and substituted phenyl acetates has been shown to occur when the pK_a of the leaving group becomes about 5 units greater than the attacking group.[23] Thus, in II where the pK_a difference is about 5 units, path a may well be favored.

The substitution of a nitro group on II would shift the equilibrium (K_1) to the right and path b (Scheme II) should become the predominant mechanism.

Intramolecular Catalysis in the Reactions of 8-Acetoxyquinoline (IVa). The deuterium solvent kinetic isotope effect data and the entropy data ($k^{H_2O}/k^{D_2O} = 2.35$, $T\Delta S^{\ddagger} = -8.70$ kcal mol^{-1}) suggest, as in II, that the spontaneous hydrolysis of IVa is a general-base-catalyzed, bimolecular reaction.[34] A rate-determining unimolecular formation of the N-acetyl intermediate as proposed by Barca and Freiser[7] is not in accord with these data. Thus, an identical situation exists as in the hydrolysis of II; namely either path a or path b in Scheme III will satisfy the condition of a general-base-catalyzed bimolecular reaction. In this case, however, only the positively charged N-acetylpyridinium ion can be the reactive N-acyl species.

Scheme III



The spontaneous hydrolysis rate for IVa is *ca.* 500 times greater than that for IVb at 55° as seen in the pH profiles (Figure 1). Since no intramolecular catalysis can take place in the 6 isomer, the rate enhancement due to such catalysis in the 8 isomer is *ca.* 5×10^2. The π-electron densities of quinoline calculated by the MO method indicate that the position which best resembles the 8 position electronically is the 6 position (1.003 and 0.989 charge distributions, respectively).[35] Thus, electronically IVa and IVb should be similar. Sterically, the rate retardation in IVa should be about two- or threefold, as in I.[32] The hydroxide-catalyzed hydrolysis rates (k_{OH}) at 30° for IVa and IVb (90.2 and 304 M^{-1} min^{-1}, respectively) are indicative of this steric effect, since the 6 isomer reacts about three times faster. The quinoline ester can be thought of as a phenyl ester substituted with a pyridyl group; on this basis the σ value for this substituent can be estimated from the k_{OH} value of the 6 isomer. Placing this k_{OH} value on a Hammett plot of the hydrolysis of phenyl acetates[27] a σ value of +0.2 is obtained. This agrees well with the estimated σ value of +0.3 for the imidazolyl substituent in II, and agrees exactly with a σ^- value of 0.23 deter-

(32) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, **90**, 5818 (1968).

(33) D. G. Oakenfull, J. Riley, and V. Gold, *Chem. Commun.*, 385 (1966); *J. Chem. Soc., B*, 515 (1968).

(34) The assignment of the term k_0[E] to an intramolecular mechanism in eq 2 and 3 rather than to a kinetically equivalent specific base–general acid (k_r[EH$^+$][HO$^-$]) catalysis must rest on other than the deuterium kinetic solvent isotope effect and entropy data. This is so since the isotope effect indicates only that a proton is being transported in the transition state but does not stipulate the mechanistic mode. Much the same argument can be made concerning $T\Delta S^{\ddagger}$ and kinetic order. The specific base–general acid mechanism (SBGA) is made unlikely through the following considerations: the ester IVa, but not the isomeric IVb, could be involved in a SBGA mechanism. Furthermore, nucleophiles other than [HO$^-$] should be assisted in their attack on IVa by intramolecular general-acid catalysis. It is found for the tertiary amines pyridine, imidazole, and trimethylamine that nucleophilic attack on IVa is two- to sixfold *slower* than upon IVb. This is particularly significant in the case of pyridine since its pK_a approaches that of IVa most closely. In contrast to tertiary amines, primary and secondary amines show greatest reactivity toward IVa as compared to IVb. This is in accord with a general-base-catalyzed assistance involving amines with a dissociable proton.

(35) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, 43, 87 (1947).

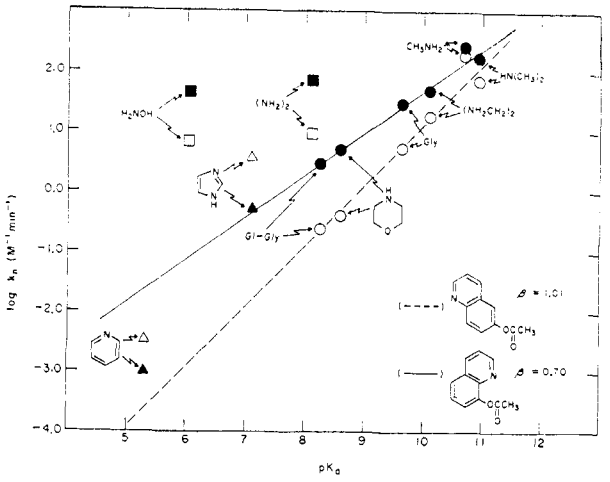
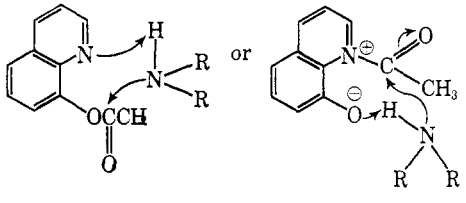


Figure 9. Brønsted plots for the second-order aminolysis rate constant (k_n) *vs.* pK_a of the amine nucleophile. The filled points represent reaction with ester IVa and the open points represent reaction with ester IVb. The circles and squares represent primary and secondary amines and the triangles represent tertiary amines. The square points represent amines that exhibit the α effect.

mined from a variety of data by Elderfield and Siegel.[36] Thus, the inductive effect is similar to that of a *p*-Cl substituent ($\sigma^- = 0.23$).

Intramolecular General-Base-Catalyzed Aminolysis. The results for the aminolysis of IVa and IVb are highly significant. Primary and secondary amines are seen to react more rapidly with IVa and tertiary amines react more rapidly with IVb. For steric reasons amines will react faster (from two to six times) with the 6 isomer, except when the amine has a dissociable proton that can enter into an intramolecular general-base-catalyzed mechanism in which case a faster reaction is observed with the 8 isomer. The extent of the rate acceleration is seen only in the second-order aminolysis rate constant (k_n), since the transition state for intramolecular general-base-catalyzed aminolysis is bimolecular as in VI. On the other hand the third-order general-base



VI

aminolysis rate constant (k_{gb}) is not increased significantly over the same rate constant for the 6 isomer, or it becomes undetectable due to the large size of k_n. The aminolysis results provide definitive evidence that in the case of IVa the aminolysis reaction involves an intramolecular general-base-catalyzed mechanism.

The general-base mechanism of hydrolysis of IVa predominates to below pH 3. At this low pH the mole fraction of the ionized N-acetyl species in Scheme III should be minuscule. This follows from the fact that the pK_a of the hydroxyl group should be far removed $pK_a = 3$ and that the equilibrium constant K_1 should be much smaller than the corresponding value for II (Scheme II). It is probable that the value of k_2 would not be great enough to offset these factors in order to favor path b of Scheme III. Extrapolation from the established mechanism of hydrolysis of I would also favor path a for the hydrolysis of IVa. However, in employing this criteria, one must keep in mind that inference concerning a nitrogen base is drawn from data concerning a carboxyl base. With this well in mind, application of Fersht and Kirby's criteria[32] of the large pK_a difference (*ca.* 6 units) between the attacking and leaving groups would strongly favor path a (Scheme III).

In Figure 9 the Brønsted plots for the bimolecular aminolysis of IVa and IVb are presented. The lines are drawn through the points for the primary and secondary amines which do not exhibit the α effect.[37] The scatter of these points from the line is similar to that observed in the Brønsted plot for the aminolysis of phenyl acetate.[17] Indeed, the deviations of all the amines from the line drawn for IVb are strikingly similar to those for phenyl acetate, emphasizing the closeness of mechanism for the two esters. The Brønsted equation for IVb derived from Figure 9 is

$$\log k_n = 1.01pK_a' - 8.80 \quad (16)$$

The corresponding relationship for phenyl acetate[17] is

$$\log k_n = 1.05pK_a' - 10.4 \quad (17)$$

Thus, the only significant difference between these two esters is that IVb is about 40 times more reactive than phenyl acetate. The Brønsted equation for the aminolysis of IVa, however, is quite different

$$\log k_n = 0.70pK_a' - 5.30 \quad (18)$$

The markedly different β value indicates that the aminolysis mechanism for IVa is different from that for phenyl acetate and IVb.

A means for comparing nucleophilicities which normalizes scattering of points due to the α effect, steric effects, electronic effects, etc., is to plot log k_n for the reaction of the nucleophiles with one substrate *vs.* log k_n for reaction of nucleophiles with a second substrate.[38] In Figure 10 such a plot is presented for reaction of H_2O, HO^-, and the 11 assorted amines of this study with IVa and IVb. Importantly, H_2O and all primary and secondary amines fall on a line provided by eq 19

$$\log k_{n_s} = 0.7 \log k_{n_b} + 0.9 \quad (19)$$

while the tertiary amines and HO^- ion fit well a line of eq 20. From the slopes of eq 19 and eq 20 we may sur-

$$\log k_{n_s} = 1.0 \log k_{n_b} - 0.6 \quad (20)$$

mise that ($\Delta F_8^{\pm} - \Delta F_6^{\pm}$) is a constant for the tertiary amines and HO^-. This indicates a similarity in mechanism. For H_2O, primary, and secondary amines, however, ($\Delta F_8^{\pm} - \Delta F_6^{\pm}$) is not constant but is a linear function of $\Delta F_6^{\pm}$ and, therefore, the nature of the transition states differ. The plot of Figure 10 clearly establishes the greater relative reactivity of H_2O, primary, and secondary amines with IVa. The difference in mechanism for IVa and IVb is best attributed to intramolecular general-base catalysis for the 8 isomer in reaction with H_2O, primary, and secondary amines and

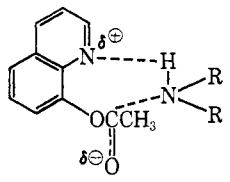
(36) R. C. Elderfield and M. Siegel, *J. Amer. Chem. Soc.*, 73, 5622 (1951).

(37) See ref 17 for a discussion of the α effect.

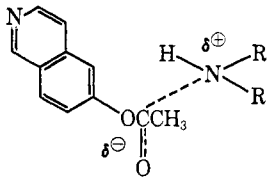
(38) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, 89, 2121 (1967).

simple nucleophilic attack for the reaction of all nucleophiles with the 6 isomer and the tertiary amines as well as HO^- with the 8 isomer.

From the Hammond postulate[39] it follows that as the transition state in a reaction becomes more stable it resembles the starting reactants more closely. Thus, the transition state in the aminolysis of 8-acetoxyquinoline (VII) resembles starting reactants more so than the



VII



VIII

transition state from 6-acetoxyquinoline (VIII). This means that less N–C bond formation takes place in VII, thus, a lower Brønsted β value. Based on Jencks and Gilchrist's proposal[40] that complete bond formation in reaction of amines with phenyl esters corresponds to a β value of 1.7, one might conclude that in the transition state of VII N–C bond formation has proceeded halfway to completion. The lower β coefficient for IVa can also be rationalized in terms of the quinoline nitrogen being less able to act as a general base as the attacking amine becomes more basic.

Some information concerning the degree of proton abstraction by the quinoline nitrogen in the transition state (VII) is obtained from the β coefficient for this reaction. The Brønsted line drawn for the aminolysis of IVa can be considered to be the sum of two Brønsted lines, one involving proton abstraction from the attacking amine by the general base which would yield an α coefficient in the Brønsted equation, and the other involving nucleophilic attack by the amine species. Since nucleophilic attack with no general-base catalysis as in the reaction with IVb is associated with a β value of 1.0, the reduction to a β value of 0.7 as a result of intramolecular general-base catalysis represents an α value of 0.3 for the proton abstraction Brønsted relationship. Since the theoretical α value for complete proton transfer is 1.0, it follows that in the transition state, VII, the proton is only less than one-third of the way toward complete abstraction. These rationales are predicated on the basis of no large dependence of bond length on pK_a. Although this type assumption is implicit in all cases where linear free energy plots are employed to determine the nature of bonding in transition states it may, in many cases, be incorrect.

The pyridine esters (IIIa and IIIb) were studied to determine whether intramolecular catalysis occurs in phenyl picolinate. The lack of a plateau rate in the hydrolysis of this ester (Figure 1) and the similarity of reaction rates in the hydrolysis and aminolysis of IIIa and IIIb (where no intramolecular catalysis can occur) demonstrate that no special effects are in operation. Models of the intermediate in intramolecular general-base catalysis in IIIa indicate that a nonlinear hydrogen bond (*ca.* 90°) would be required. The model for IVa allows for an almost linear hydrogen bond, thus allowing a more efficient orbital overlap.

(39) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).
(40) W. P. Jencks and M. Gilchrist, *ibid.*, 90, 2622 (1968).

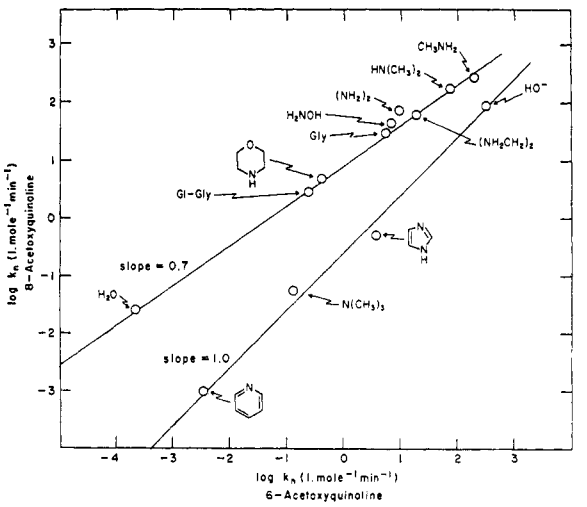


Figure 10. A plot of the log of the second-order rate constants (k_n) for reaction of bases with 8-acetoxyquinoline *vs.* the same function for 6-acetoxyquinoline.

One of the most interesting results to come out of this study of intramolecular general-base-catalyzed aminolysis is the fact that it exists at all. St. Pierre and Jencks[5] in their study of the analogous aspirin molecule (I) have established that no intramolecular general-base-catalysis takes place in the reactions of I with the amines hydroxylamine, morpholine, and methylamine. They infer that in I the carboxylate group (pK_a = 3.4) is not basic enough to act as a catalyst in the removal of protons from basic amines. In IVa the intramolecular base has a pK_a of 3.6 which means it is about as basic as the *o*-carboxyl group in I, and yet intramolecular catalysis is observed even in the reaction with dimethylamine (pK_a = 10.93). From the previous discussion on the β coefficient associated with the aminolysis of IVa, it was proposed that the intramolecular base must abstract the amine proton less than one-third of the way for catalysis to take place. Thus, the basicity of the intramolecular base need not be high in order to observe catalysis. Apparently a nitrogen base can act as an intramolecular catalyst with highly basic amines whereas a carboxyl group of similar pK_a may not.

It would appear that the aminolysis of IVa by primary and secondary amines represents the first instances of intramolecular catalysis of aminolysis reactions involving basic amines. The inability to detect intramolecular catalysis of aminolysis of I by basic amines has already been mentioned.[5] Other failures to detect intramolecular catalysis of the aminolysis reaction with basic amines include the reaction of α,ω-diaminoalkanes,[41] lysine,[42] and *trans*-1,2-diaminocyclohexane[42] with phenyl acetate. In view of the importance of the term k_{gb}[amine]^2[ester] in the reaction of primary amines with phenyl acetate and the observation of intramolecular catalysis of the aminolysis of IVa, one can only surmise that for the α,ω-diaminoalkanes the preferred conformation in H_2O does not favor proper juxtapositioning of the two amino groups. For *trans*-1,2-diaminocyclohexane CPK and Stuart–Breigleb atomic models indicate the geometry for the formation of a hy-

(41) T. C. Bruice and R. G. Willis, *ibid.*, 87, 531 (1965).
(42) R. W. Huffman, A. Donzel, and T. C. Bruice, *J. Org. Chem.*, 32, 1973 (1967).

drogen bridging between the two equatorial and vicinal amino groups is not optimal.

The inability to detect, in general, intramolecular general-base-catalyzed aminolysis in the case of I[5] finds a possible explanation in the lessened efficiency of catalysis in this system as compared to IVa. Inspection of Figures 9 and 10 reveals that the efficiency of intramolecular general-base-catalysis over simple nucleophilic attack increases as the basicity of the nucleophile decreases. This of course is as expected. The lines of Figure 10 intersect at pK_a of the base $\cong$ 12 so that for primary and secondary amines of pK_a greater than *ca.* 12 intramolecular general-base catalysis should give way to simple unassisted nucleophilic attack. The data of St. Pierre and Jencks[5] reveal that no significant catalysis is present in the reaction of I with basic amines including hydroxylamine (pK_a = 6). Thus, in terms of Figure 9 a similar plot for I (and *p*-carboxyaspirin) would require that the line correlating intramolecular general-base catalysis intersect the line correlating unassisted nucleophilic attack at about a pK_a (of attacking amine) of 5–6 or lower (the point of intersection is not clearly definable due to the fact that relatively few amines were studied). This represents an unusual situation since in I and IVa the base strengths of the intramolecular bases are similar, yet ester IVa appears to be a great deal more efficient than I in catalyzing its reaction with amines. A possible explanation may lie in the nature of the solvation shells of the amine and carboxylate groups. The greater water solvation of the anionic carboxylate group in I could presumably result in the enhanced reaction with H_2O due to intramolecular general-base hydrolysis, and could also inhibit the intramolecular carboxylate-catalyzed reaction of I with nucleophiles that must first penetrate the aqueous solvation shell as in aminolysis. Alternatively, the difference in the susceptability of primary and secondary amines to intramolecular general-base-catalyzed aminolysis of I and IVa may reside in the fact that the mechanism for IVa is actually that of path b of Scheme III. We may only state that this alternative does not appear to be supported by presently existing experimental data.

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Solvolysis of Five-Membered Sultones. Methods for Determining the Intermediacy of Carbanions in the Hydrolysis of Esters with Labile α-Protons

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Abstract: We have examined the question whether carbanions and/or sulfenes are reactive intermediates in the alkaline hydrolysis of labile five-membered sultones which have readily ionizable α-protons. The pK_a values for the ionization of these protons in the compounds studied are above 14. We have developed several general methods for carbon acids with pK values greater than 14 which enable us to conclude that mechanisms involving carbanion intermediates do not appear to be the predominant pathways by which five-membered cyclic sulfonates hydrolyze. We believe therefore that the large rate enhancements we have observed for the alkaline hydrolyses of these compounds relative to their open-chain analogs reflect the differences in the rates of attack of hydroxide ion at the sulfur atoms in the cyclic and acylic systems.

The hydrolysis of catechol cyclic sulfate (I) shows an enormous rate acceleration in alkaline solution compared to that of the acyclic analog, diphenyl sulfate (II).[3] From measurements in oxygen-18-enriched media it has been demonstrated that the observed rate acceleration reflects the difference in the rates of attack of hydroxide ion at the sulfur atoms in a five-membered cyclic sulfate and an open-chain sulfate.[4] A large rate enhancement for the hydroxide-catalyzed hydrolysis of the five-membered sultone, *o*-hydroxy-α-toluenesulfonic acid sultone (III), relative to that of the open-chain compound, phenyl α-toluenesulfonate (IV), also has been found.[5,6] However, in the case of the sulfonate esters, III and IV, hydrolytic mechanisms which do not involve the direct attack of hydroxide ion at sulfur must be considered. Specifically, the mechanisms outlined in eq 1 and 2 where carbanions and/or sulfenes may be reactive intermediates in the hydrolytic pathway can be proposed.[7] Recently, mechanisms analogous to eq 1, involving either isocyanate[8] or ketene[9] intermediates, have been suggested as the pathways for the alkaline hydrolysis of certain esters pos-

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(5) O. R. Zaborsky and E. T. Kaiser, *ibid.*, **88**, 3084 (1966).
(6) E. T. Kaiser, K. Kudo, and O. R. Zaborsky, *ibid.*, **89**, 1393 (1967).
(7) The intermediacy of sulfenes in the solvolyses of some sulfonyl halides has been established by studies done in deuterated solvents; see W. E. Truce, R. W. Campbell, and J. R. Norell, *ibid.*, **86**, 288 (1964); **88**, 3599 (1966); J. F. King and T. Durst, *ibid.*, **86**, 287 (1964); **87**, 5684 (1965).
(8) M. L. Bender and R. B. Homer, *J. Org. Chem.*, **30**, 3975 (1965).
(9) T. C. Bruice and B. Holmquist, *J. Amer. Chem. Soc.*, **90**, 7136 (1968).