Aminolysis of Substituted Phenyl Quinoline-8- and -6-carboxylates with Primary and Secondary Amines. Involvement of Proton-Slide Catalysis

Paula Yurkanis Bruice and Thomas C. Bruice*

Contribution from the Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. *Received May 4, 1974*

Abstract: The reaction of primary and secondary amines with a series of substituted (p-CH_3O, H, p-Cl, p-CN, o-NO_2, p-NO_2, and 2,4-diNO_2) phenyl quinoline-8- and -6-carboxylates (Q-8 and Q-6, respectively) has been investigated (20% (v/v) acetonitrile–H_2O, μ = 0.5, 30°). Plots of log k_n *vs.* σ exhibit a diminution of ρ with increase in σ. This requires a change in rate-limiting step from collapse of the tetrahedral intermediate in the direction of products for the least reactive esters to amine attack for the most reactive esters. The stop-flow recordings obtained for the reaction of methylamine with p-CN-Q-8 evidence the formation of the tetrahedral intermediate; the initial decrease in OD due to addition of amine to ester is followed by an increase in OD as phenoxide ion is expelled from the tetrahedral intermediate. The separation of rate-limiting attack and departure becomes obvious in a plot of log k_n *vs.* ΔpK_a (ΔpK_a = pK_a(phenolic leaving group) − pK_a(amine nucleophile)) for the Q-6 esters. The 2,4-diNO_2 substituted esters fall on one line and the less reactive esters on another. A like plot for the Q-8 esters results in three lines: (1) p-CH_3O, H, and p-Cl esters which evidence rate-limiting collapse of the tetrahedral intermediate to products; (2) p-CN, o-NO_2, and p-NO_2 esters with both attack of nucleophile and departure of leaving group partially rate limiting; and (3) 2,4-diNO_2 substituted esters where nucleophilic attack is rate limiting. With the exception of the 2,4-diNO_2 substituted esters, the Q-8 esters are more reactive (by *ca.* 100-fold) toward primary and secondary amines than are the Q-6 esters. Since breakdown of the tetrahedral intermediate ceases to be rate limiting for the Q-8 esters while it is still rate limiting for the Q-6 esters and dependence of k_n on the leaving group is less for the Q-8 esters (ρ = 1.5–2.5) than for the Q-6 esters (ρ = 2.5–3.4), it follows that the quinoline nitrogen of the Q-8 esters catalyzes collapse of the tetrahedral intermediate to products. The accelerated rate of aminolysis with primary and secondary amines exhibited by the Q-8 esters when departure of the phenoxide leaving group is rate determining is independent of the pK_a of the amine. This conclusion is reached equally by inspection of plots of log k_n *vs.* ΔpK_a, log k_n^{Q-8} *vs.* log k_n^{Q-6}, and from the rate ratios k_n^{Q-8}/k_n^{Q-6}. This lack of dependence of catalysis on amine pK_a together with the observation that the weakly basic quinoline nitrogen acts as an efficient catalyst even when the amine moiety of the tetrahedral intermediate is as much as 7.0 pK_a units a stronger base leads to the conclusion that the observed catalysis cannot be due to intramolecular proton transfer from the ammonium group of the zwitterionic tetrahedral intermediate ($T^{\pm}$) to the quinoline nitrogen. *Proton-slide catalysis* in which the ammonium proton of ($T^{\pm}$) slides across the quinoline nitrogen lone pair orbital to the negatively charged oxygen to yield an uncharged tetrahedral intermediate (T) is suggested. Conversion of $T^{\pm}$ to T results in a crossover from the reaction coordinate for neutral amine attack on neutral ester to anionic amine attack on protonated ester and allows the reaction to proceed through a pathway of lower energy. Intramolecular amine catalysis is observed with esters too reactive to evidence intermolecular catalysis. Intermolecular general base catalysis (by amine) is generally observed when the amine is less than 0.8 pK_a units more basic than the leaving group and is attributed to proton removal from $T^{\pm}$ to give T^- which rapidly collapses to products. Values of k_{gb}/k_n are 2–17 and 20–50 for non-α-effect and α-effect amines, respectively, and are independent of amine or leaving group pK_a. Intramolecular catalysis by α,ω-diaminoalkanes and electrostatic effects in aminolysis reactions are also discussed. The large number of second-order rate constants collected in this study has allowed a critical evaluation of the relationship of the change in one linear free-energy parameter of a reaction series with another. For the reactions investigated herein no useful relationship is apparent between β_{nuc} and σ or between ρ (or β_{lg}) and pK_a.

A major problem in the use of activated amino acid esters in peptide synthesis is competing racemization.[1] Activating an ester by giving it a good leaving group serves to increase both the rate of amide formation and the rate of racemization (*via* oxazoline formation).[2] One approach to the problem has been to utilize esters that are too unreactive to allow oxazoline formation but whose rates of aminolysis are increased *via* "intramolecular general base catalysis." Considerable success has been achieved with o-hydroxyphenyl,[1] 8-hydroxyquinoline,[1,3] 1-piperidyl,[4] 2-mercaptopyridyl,[5] and 2-pyridyl esters.[6] These esters owe their selective activation toward aminolysis to a weakly basic oxygen or nitrogen atom situated so that it is able to act as an intramolecular catalyst in amide formation. Though facilitation of aminolysis cannot be denied, studies to date have not established that this facilitation by a weakly basic neighboring group to attack by a strongly basic amine is of a general base nature. In a study of the reaction of I with nucleophiles, St. Pierre and Jencks[7] found that though hydrolysis of I occurred with intramolecular general base assistance from the carboxylate group[8] this assistance to aminolysis occurred only in the case of the weak base, semicarbazide. On the other

(1) J. H. Jones and G. T. Young, *J. Chem. Soc. C*, 436 (1968).
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(3) (a) M. W. Williams and G. T. Young, *J. Chem. Soc., London*, 3701 (1964); (b) H.-D. Jakubke and A. Voight, *Chem. Ber.*, **99**, 2419 (1966); (c) H.-D. Jakubke, A. Voight, and S. Burkhart, *ibid.*, 100, 2367 (1967); (d) J. H. Jones and G. T. Young, *Chem. Commun.*, 35 (1967).
(4) B. O. Hanford, J. H. Jones, G. T. Young, and T. F. N. Johnson, *J. Chem. Soc., London*, 6814 (1965).
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(6) A. S. Dutta and J. S. Morley, *J. Chem. Soc. C*, 2896 (1971).
(7) T. St. Pierre and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 3817 (1968).
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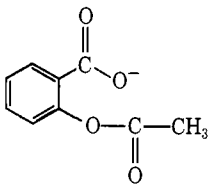
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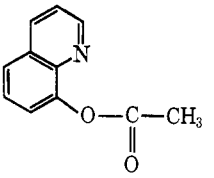
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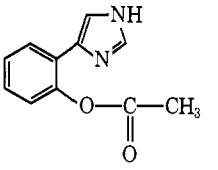
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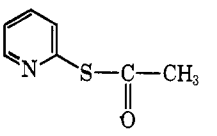
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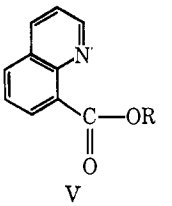
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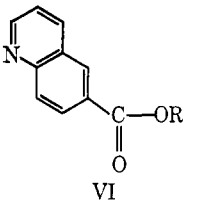
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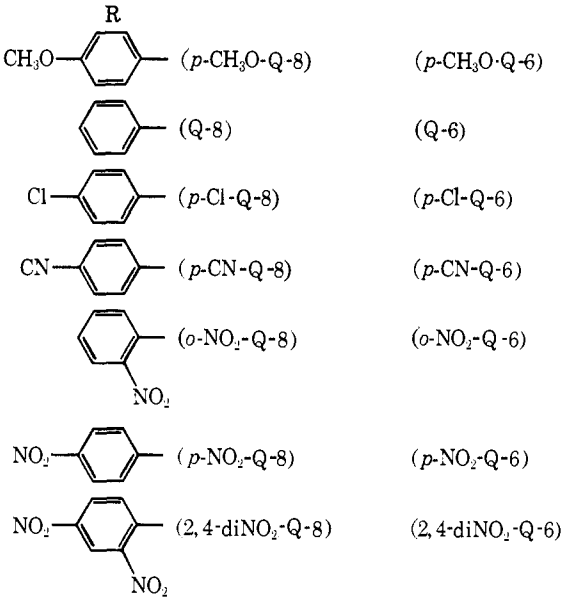


hand, Felton and Bruice[9] showed that regardless of base strength the reaction of primary and secondary amines with II (in contrast to tertiary amines) occurred more rapidly than with the electronically equivalent 6-acetoxy ester where the quinoline nitrogen is not located at the reaction site. Both the hydrolysis and hydrazinolysis of III were shown to occur with intramolecular participation by the imidazole nitrogen. Similarly, Kasperek and Bruice[10] found that 2-pyridyl thiolacetate (IV) reacted more rapidly with amines containing a dissociable proton than did the 4 isomer. These results strongly suggested the participation of the nitrogen atoms in II, III, and IV as intramolecular general base catalysts, but the possibility of the enhanced reaction rate being due to an O → N or S → N acyl shift could not be conclusively eliminated.

In order to determine the validity of the proposal of intramolecular general base catalysis in the activated esters currently employed in peptide synthesis, additional systems need be examined in which there is no possibility of an acyl shift. Thus, we have investigated the comparative rates of aminolysis of several phenyl quinoline-8- (V) and -6-carboxylates (VI). The leaving group of the ester pair was varied to ascertain whether catalysis is felt only in those reactions where it is needed and more efficient in those reactions where it is needed most or whether a highly reactive substrate will also make use of a catalyst if it is juxtaposed to the reaction site. The esters were reacted with amines of a wide range in pK_a in order to determine the relationship between the extent of catalysis and basicity of the nucleophile. In addition, by employing a large series of esters and amines our objectives have been to determine the exact step in the aminolysis reaction subject to intermolecular general base catalysis as well as to intramolecular catalysis, the mechanism by which such catalysis occurs, and the effects of structural changes in the reactants on the mechanism of catalysis.

Experimental Section

Materials. The hydrochlorides of methylamine, glycinamide, trifluoroethylamine (Columbia), hydrazine, dimethylamine, and the dihydrochloride of ethylenediamine were recrystallized from water–ethanol. Methoxyamine hydrochloride was recrystallized from ethanol–ether. Glycine (Fisher reagent) was used without further purification. Pyrrolidine and *tert*-butylamine were distilled. The amine hydrochlorides were dried in a desiccator over P_2O_5.

Preparation of the esters, kinetic conditions, preparation of buffer solutions, pK_a determinations, and methods of calculation have been described previously.[11]

Results

The first-order rate constant for the aminolysis of an ester at constant pH and amine concentration is well correlated[12] by eq 1 where k_n represents the nucleophilic rate constant for attack of amine upon ester, k_{gb} and k_{ga} the general base and general acid catalysis of this reaction by a second molecule of amine [N] and its conjugate acid [NH^+], respectively, and $k_{HO}{}'$ the hydroxide ion catalyzed aminolysis rate constant.

$$k_{obsd} = k_{HO}[HO^-] + k_{H_2O}[H_2O] + k_n[N] + k_{gb}[N]^2 + k_{ga}[N][NH^+] + k_{HO}{}'[HO^-][N] \quad (1)$$

The aminolysis reactions were carried out under conditions of total amine concentration $[N_T] = ([N] + [NH^+]) \gg$ [ester]; thus pseudo-first-order kinetics were obtained. Since the hydrolysis rate is very slow compared to aminolysis and in no case is general acid catalysis detectable, these two terms of eq 1 can be ignored. Values of k_n, k_{gb}, and $k_{HO}{}'$ were obtained by use of plotting techniques previously discussed.[12] Each second-order rate constant was derived from buffer dilution plots at an average of three pH's, each employing five amine concentrations. Since this amounts to over 2000 rate constants, space does not allow the presentation of the singly determined k_{obsd} values or the buffer dilution plots from which the second-order rate constants were derived. Values of k_n and k_{gb} for the substituted Q-8 and Q-6 esters are given in Tables I and

(9) (a) T. C. Bruice and S. M. Felton, *J. Amer. Chem. Soc.*, **91**, 2799 (1969); (b) S. M. Felton and T. C. Bruice, *ibid.*, **91**, 6721 (1969).
(10) G. J. Kasperek and T. C. Bruice, *J. Org. Chem.*, 37, 1456 (1972).
(11) P. Y. Bruice and T. C. Bruice, *J. Amer. Chem. Soc.*, **96**, 5523 (1974).
(12) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967).

Table I. Second-Order Nucleophilic (k_n) and Third-Order General Base (k_{gb}, in Parentheses) Rate Constants for the Aminolysis of Substituted Phenyl Quinoline-8-carboxylates with Primary and Secondary Amines

Amine	pK_a[a]	k_n, M^{-1} sec^{-1}						
		p-CH_3O	H	*p*-Cl	*p*-CN	*o*-NO_2	*p*-NO_2	2,4-diNO_2
Pyrrolidine	11.20	2.58	5.91	15.6	67.0	77.5	103	90.7
Dimethylamine	10.74	4.02×10^{-1}	1.14	7.10	37.7		54.2	225
Methylamine	10.62	6.18×10^{-1}	9.73×10^{-1}	3.69	15.8		32.3	39.2
tert-Butylamine	10.61		1.24×10^{-3}					
Ethylenediamine	10.00		2.01×10^{-1}	5.78×10^{-1}			5.7	
Glycine	9.55	3.51×10^{-2}	6.88×10^{-2}	2.13×10^{-1}	6.85×10^{-1}	1.09	2.76	8.71
Morpholine	8.60	3.54×10^{-3}	1.14×10^{-2}	1.04×10^{-1}	2.94		5.46	23.5
Hydrazine	8.22	4.39×10^{-2}	1.34×10^{-1}	7.11×10^{-1}			13.0	24.0
		(1.35×10^{-1})	(2.22×10^{-1})					
Glycinamide	7.98	1.74×10^{-3}	4.27×10^{-3}	2.25×10^{-3}			4.40×10^{-1}	1.01
Ethylenediamine·HCl	7.30			1.68×10^{-2}				
Trifluoroethylamine	5.57			3.03×10^{-4}			1.28×10^{-2}	2.25×10^{-2}
Methoxyamine	4.64		6.51×10^{-3}	1.40×10^{-2}			5.08×10^{-2}	7.40×10^{-2}
			(5.03×10^{-3})					

[a] pK_a's determined by half-neutralization.

Table II. Second-Order Nucleophilic (k_n) and Third-Order General Base (k_{gb}, in Parentheses) Rate Constants for the Aminolysis of Substituted Phenyl Quinoline-6-carboxylates

Amine[a]	k_n, M^{-1} sec^{-1}						
	p-CH_3O	H	*p*-Cl	*p*-CN	*o*-NO_2	*p*-NO_2	2,4-diNO_2
Pyrrolidine	1.08×10^{-2}	5.40×10^{-2}	3.18×10^{-1}	27.4	38.3	93.9	1530
	(1.78×10^{-1})						
Dimethylamine	4.62×10^{-3}	9.97×10^{-3}	4.41×10^{-2}	9.51		12.3	523
	(1.64×10^{-2})	(5.61×10^{-2})	(1.84×10^{-1})				
Methylamine	7.11×10^{-3}	1.22×10^{-2}	5.66×10^{-2}	4.62		8.68	114
	(9.54×10^{-2})	(2.08×10^{-2})	(4.5×10^{-1})				
tert-Butylamine		1.13×10^{-4}					
Ethylenediamine		4.4×10^{-3}	1.72×10^{-2}	7.0×10^{-1}			
Glycine	4.24×10^{-4}	5.83×10^{-4}	3.16×10^{-3}	2.91×10^{-1}	2.32×10^{-1}	4.13×10^{-1}	11.6
Morpholine	4.23×10^{-5}	8.13×10^{-5}	2.35×10^{-4}	6.36×10^{-2}		6.79×10^{-2}	30.0
Hydrazine		1.93×10^{-3}	2.96×10^{-3}			1.83	40.8
		(3.93×10^{-2})	(1.48×10^{-1})				
Glycinamide	2.69×10^{-5}	5.13×10^{-5}	8.45×10^{-5}	1.14×10^{-2}		1.68×10^{-2}	1.19
	(1.63×10^{-4})	(1.61×10^{-4})	(5.06×10^{-4})				
Ethylenediamine·HCl			3.6×10^{-5}				
Trifluoroethylamine						5.23×10^{-5}	2.13×10^{-2}
Methyoxyamine						3.05×10^{-4}	1.14×10^{-1}
						(1.8×10^{-4})	

[a] pK_a values given in Table I.

Table III. Values of β_{nuc} Obtained from Slopes of Plots of Log k_n for Primary and Secondary Amines *vs.* pK_a of the Amine[a]

Substituent	$\beta_{nuc(Q\text{-}8)}$	$\beta_{nuc(Q\text{-}6)}$
p-CH_3O	0.99 (0.992)	0.88 (0.990)
H	0.95 (0.993)	0.96 (0.988)
p-Cl	0.80 (0.988)	1.06 (0.994)
p-CN	0.64 (0.818)	1.03 (0.995)
p-NO_2	0.68 (0.990)	1.05 (0.992)
2,4-diNO_2	0.68 (0.985)	0.83 (0.985)

[a] Correlation coefficients given in parentheses.

Table IV. Deuterium Solvent Kinetic Isotope Effects for Aminolysis with Glycine[a]

Ester	pK_a^H	pK_a^D [b]	k_n^H [c]	k_n^D [c]	k_n^H/k_n^D
p-Cl-Q-8	9.55	10.13	2.13×10^{-1}	2.23×10^{-1}	1.0
p-Cl-Q-6			3.16×10^{-3}	2.94×10^{-3}	1.1
2,4-diNO_2-Q-8			8.71	10.2	0.9
2,4-diNO_2-Q-6			11.6	13.5	0.9

[a] Determined in 20% acetonitrile, $\mu = 0.5$, $T = 30°$. [b] Determined by half-neutralization employing the electrode correction: pD = pH meter reading + 0.38 (T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961)). [c] Units in M^{-1} sec^{-1}.

II, respectively. With ethylenediamine aminolysis can occur with both neutral (n) and monoprotonated (n^+) species. The apparent second-order nucleophilic rate constant (k_n') obtained in the manner described above is a composite constant containing the second-order nucleophilic rate constants for n and n^+ where K_1 and K_2 are the first and second acid dissociation constants of

$$k_n' = \frac{k_n K_1 K_2 + k_{n^+} K_1 a_H}{K_1 K_2 + K_1 a_H + a_H^2}$$

ethylenediamine. The values of K_1, K_2, k_n, and k_{n^+} were obtained by successive approximations and are given in Tables I and II.

Values of β_{nuc} obtained from plots of log k_n for the reaction of primary and secondary amines *vs.* the pK_a of the conjugate acid of the nucleophile are given in Table III. In Table IV are found the deuterium solvent kinetic isotope effects obtained for reaction of the *p*-Cl and 2,4-diNO_2 substituted esters with glycine.

Examples of typical Hammett $\sigma\rho$ plots obtained from reaction of primary or secondary amines with the substituted Q-8 and Q-6 esters are given in Figure 1. The curvature evidenced in these plots is observed with all the primary and secondary amines employed in this

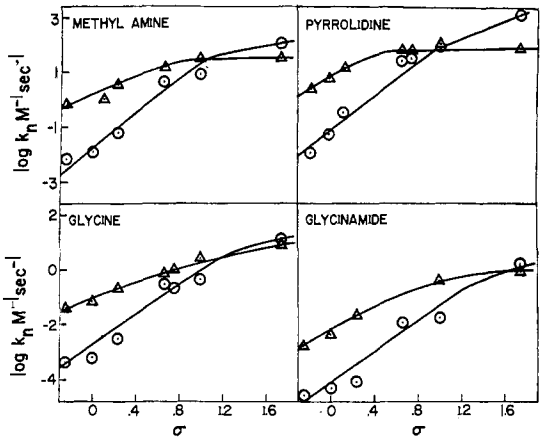


Figure 1. Hammett $\sigma\rho$ plots of the second-order rate constant for nucleophilic attack for several primary and secondary amines on substituted Q-8 (△) and Q-6 (○) esters.

study. This curvature is equally apparent when σ is replaced by pK_a. The ρ values obtained from these plots are given in Table V together with the particular esters employed in their calculation.

Table V. Values of Hammett ρ Obtained from Reaction of Primary and Secondary Amines with a Series of Substituted Phenyl Quinoline-8- and -6-carboxylates[a]

Nucleophile	log k_n vs. σ $\rho_{Q\text{-}8}$	log k_n vs. σ $\rho_{Q\text{-}6}$	log k_{gb} vs. σ $\rho_{Q\text{-}6}$
Pyrrolidine	1.6 (0.996)[b]	3.4 (0.990)[c]	
Dimethylamine	2.5 (0.981)[b]	3.1 (0.964)[c]	2.1 (1.00)[b]
Methylamine	1.5 (0.949)[b]	2.8 (0.973)[c]	1.3 (0.999)[b]
Glycine	1.5 (0.981)[b]	2.8 (0.969)[c]	
Glycinamide	2.2 (0.977)[b]	2.5 (0.955)[c]	1.0 (0.842)[b]

[a] Correlation coefficients given in parentheses. [b] Calculated for p-CH_3O, H, and p-Cl. [c] Calculated for p-CH_3O, H, p-Cl, p-CN, and p-NO_2 (o-NO_2 included in those cases where data for that ester had been obtained).

Discussion

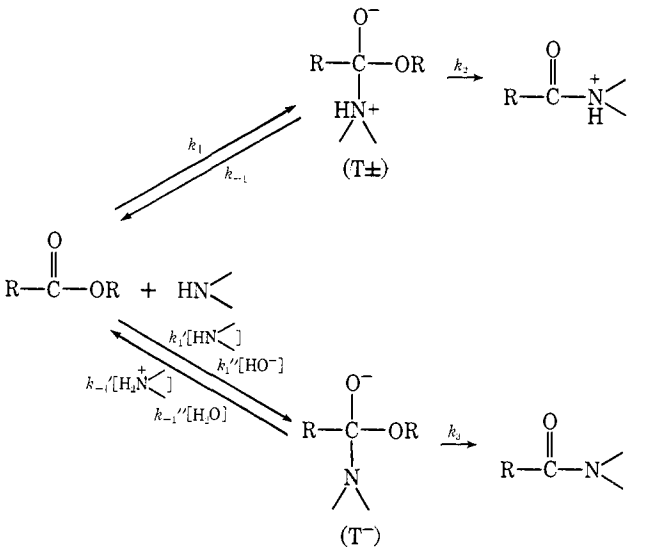
Aminolysis with Primary and Secondary Amines. Mechanisms that would account for the observed dependence of ester aminolysis on [N], $[N]^2$, and [N][HO^-] terms are given in Schemes I and II, the two differing only in whether the general base catalysis is concerted with nucleophilic addition (Scheme I) or follows nucleophilic addition (Scheme II). *The latter will be referred to as general base catalysis of the breakdown of the tetrahedral intermediate in the direction of products, although strictly speaking the catalysis occurs at an intermediate step between attack and breakdown.* It recently has been proposed[13] that the mechanism given in Scheme II is the preferred pathway for the general base catalyzed aminolysis of carbonyl compounds. Prior to this proposal mechanistic arguments generally centered around Scheme I[14] although concerted proton transfer from attacking to leaving group has also been considered,[14a] and Bunnett,[15] in his studies of the aminolysis

(13) (a) J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *J. Amer. Chem. Soc.*, 94, 4729 (1972); (b) W. P. Jencks, *ibid.*, 94, 4731 (1972); (c) W. P. Jencks, *Chem. Rev.*, 72, 705 (1972).

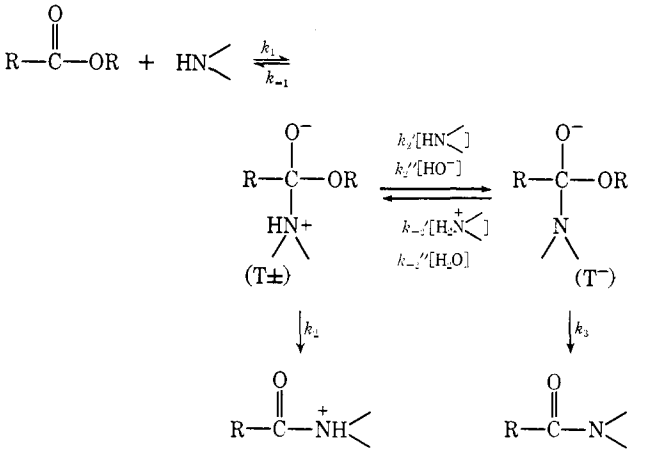
(14) (a) T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, 82, 3607 (1960); (b) W. P. Jencks and J. Carriuolo, *ibid.*, 82, 675 (1960).

(15) J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.*, 82, 665 (1960).

Scheme I



Scheme II



reaction in alcoholic solution, specifically favored general catalysis to occur after amine addition although his proposals differ in kind from Scheme II.

The curvature of the Hammett plots for the second-order reaction of primary and secondary amines with both the substituted Q-8 and Q-6 esters (Figure 1) suggests that a change in rate-limiting step occurs as the leaving ability of the phenoxide ion is changed with the value of log k_n being considerably more dependent on the leaving ability of the phenoxide ion when the leaving group is poor. Thus, for esters with poor leaving groups collapse of the tetrahedral intermediate is rate limiting. As the pK_a of the leaving group is decreased, breakdown of the tetrahedral intermediate to products can better compete with its breakdown to regenerate starting materials. In the case of very good leaving groups, collapse of the tetrahedral intermediate in the direction of products is so rapid that the rate-limiting step becomes attack of amine on the carbonyl carbon. The curvature of the Hammett plots reflects the decreased sensitivity of k_n to the leaving group as the rate-limiting step changes from tetrahedral intermediate breakdown to amine attack with increase in σ. For the Q-6 esters attack does not become important until the leaving group is 2,4-dinitrophenolate ion while for the Q-8 esters curvature is evidenced with poorer leaving groups. The β_{nuc} values of Table III also reflect a change in rate-limiting step at about p-cyanophenol for

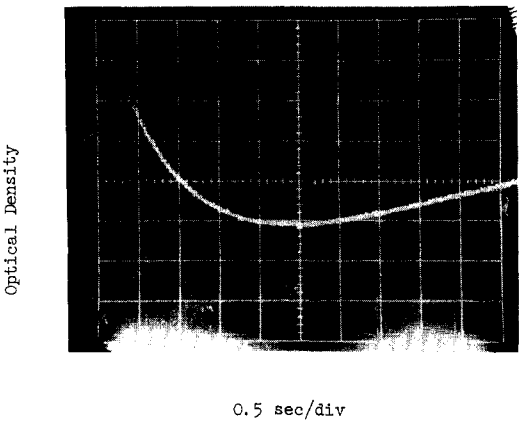


Figure 2. An oscillograph tracing obtained from the reaction of *p*-CN-Q-8 with 0.2 *M* total methylamine buffer, pH 10.62.

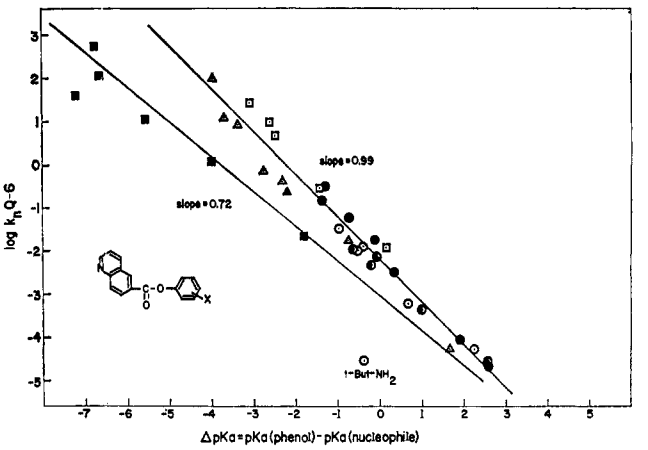
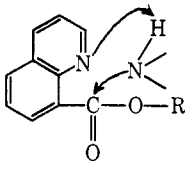


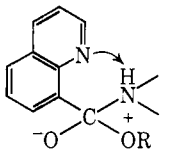
Figure 3. A plot of the log of the second-order rate constants for the reaction of primary and secondary amines with substituted Q-6 esters *vs.* (pK_a of the phenolic leaving group − pK_a of the attacking nucleophile): ◐, *p*-CH_3O; ●, H; ⊙, *p*-Cl; ⊡, *p*-CN; ▲, *o*-NO_2; ◬, *p*-NO_2; ■, 2,4-diNO_2.

the Q-8 esters and at 2,4-dinitrophenol for the Q-6 esters. The curvature in the Hammett plots cannot be attributed to steric effects in the 2,4-diNO_2 substituted esters; the second-order rate constant for the reaction of pyrrolidine with *p*-Cl-Q-8 is sixfold greater than for reaction with *p*-CH_3-Q-8 with the difference in basicities of the two leaving groups being only 0.66 pK_a units while the 2,4-diNO_2-Q-8 and *o*-NO_2-Q-8 esters with similar steric requirements evidence only a 1.2-fold rate difference although ΔpK_a of the leaving groups is 3.37. A change in rate-limiting step is clearly seen in the aminolysis of *p*-CN-Q-8 with methylamine. In the stop-flow recordings (see for example Figure 2) of the progress of the reaction of methylamine with this ester a decrease in OD due to addition of amine to ester is followed by an increase in OD as the resultant tetrahedral intermediate loses phenoxide ion. The period of time required for the OD to decrease to a minimum in these experiments exceeded the mixing time of the apparatus employed by *ca.* eightfold. The k_n value given in Table I for this reaction was obtained from k_{obsd} values calculated from the initial portions of the stop-flow recordings which exhibit decreasing OD *vs.* time. A more extensive investigation of this unusually stable tetrahedral intermediate is in progress.

Intramolecular Catalyzed Aminolysis. A comparison of the k_n values obtained for the aminolysis of the substituted Q-8 esters with primary and secondary amines with those for the Q-6 esters (Tables I and II) shows that, except for the 2,4-diNO_2 substituted esters, the 8 isomers are the more reactive. On the basis of steric factors alone the amines should be more reactive toward the 6 isomers.[11] When, however, the amine possesses a dissociable proton, the quinoline nitrogen can participate in intramolecular catalysis in the case of the 8 isomers but is not in a position to accelerate the aminolysis of the 6 isomers. Attributing the intramolecular catalysis evidenced in the aminolysis of the 8 isomer to concerted proton removal from the attacking nucleophile (VII) requires an amine of $pK_a = 4.26$ (the quinoline nitrogen) to pull a proton from an amine of $pK_a = 5$–11 (depending on the nucleophile) to give a product with approximately the same pK_a as the attacking nucleophile. This is clearly against the proposition put forth by Jencks[13] that for concerted general base catalysis to occur the pK_a of the catalyst must be between that of the substrate and product. In other words there is no advantage to concerted catalysis unless the stepwise pathway involves the formation of high energy intermediates. Stepwise proton removal after nucleophilic attack (VIII) results in catalysis since it prevents



VII



VIII

collapse of the zwitterionic tetrahedral intermediate back to starting materials. It should be noted that proton transfers such as those in VII and VIII likely take place through one or more water molecules. *This may well be the case for proton transfers in all general base catalyzed aminolysis reactions.*[16]

Several observations suggest that intramolecular catalysis by the quinoline nitrogen follows nucleophilic attack. In Figure 3 log k_n for aminolysis of the substituted Q-6 esters with primary and secondary amines is plotted against the pK_a of the phenolic leaving group minus the pK_a of the amine nucleophile (ΔpK_a). Because of the large amount of data presented in this figure, points for α-effect nucleophiles as well as for morpholine, which has been found in this and in other studies to be a poorly behaved nucleophile, have been omitted to avoid confusion. The second-order rate constants are well correlated with ΔpK_a with the points falling on one of two lines. The 2,4-diNO_2 substituted esters which undergo rate-limiting carbonyl addition fall on one line, and all the other substituted Q-6 esters fall on another line suggesting that these all have breakdown of the tetrahedral intermediate as the rate-limiting step. In the case of the Q-8 esters (Figure 4), the points fall on three lines. The 2,4-diNO_2 substituted esters are subject to rate-limiting amine attack, collapse of the tetrahedral intermediate to product is rate-limiting for *p*-CH_3O, H, and *p*-Cl substituted esters, and both steps are important for the esters with leaving groups of intermediate pK_a, the *p*-CN, *o*-NO_2, and *p*-NO_2 substituted

(16) E. Grunwald, C. F. Jumper, and S. Meiboom, *J. Amer. Chem. Soc.*, 85, 522 (1963), and references therein.

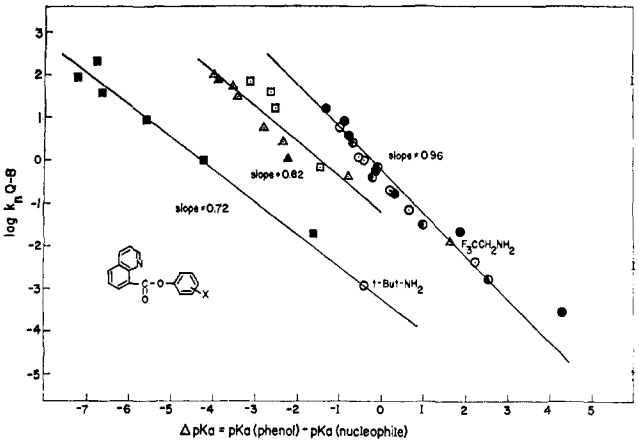


Figure 4. A plot of the log of the second-order rate constants for the reaction of primary and secondary amines with substituted Q-8 esters *vs.* (pK_a of the phenolic leaving group − pK_a of the attacking nucleophile): ◐, *p*-CH_3O; ●, H; ⊙, *p*-Cl; ⊡, *p*-CN; ▲, *o*-NO_2; ◬, *p*-NO_2; ■, 2,4-diNO_2.

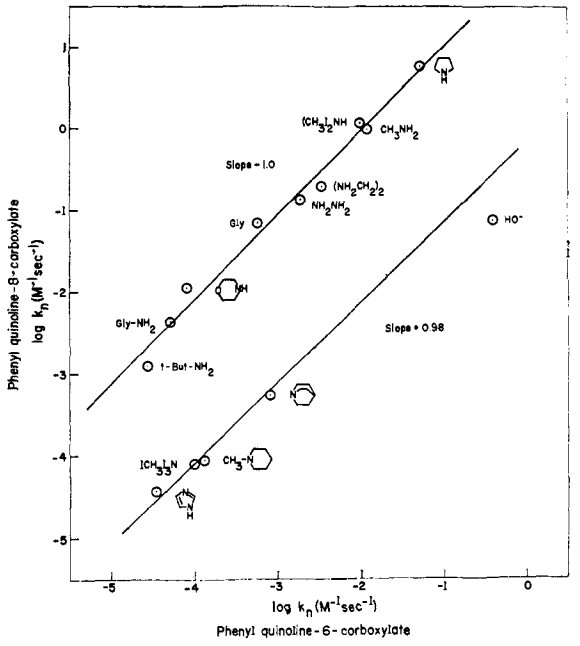


Figure 5. A plot of the log of the second-order rate constants for reaction of nucleophiles with phenyl quinoline-8-carboxylate (Q-8) *vs.* the same function for phenyl quinoline-6-carboxylate (Q-6).

esters. That breakdown of the tetrahedral intermediate ceases to be rate limiting with poorer leaving groups for the Q-8 esters than for the Q-6 esters indicates that the quinoline nitrogen of the Q-8 esters is able to catalyze collapse of the tetrahedral intermediate to products. It should be noted that in a few instances an ester does not fall on the same line with the other esters of its type. For example, the point for the reaction of *p*-NO_2-Q-8 with trifluoroethylamine falls with the esters that evidence breakdown of the tetrahedral intermediate as the rate-limiting step. This deviation is the result of the low pK_a of trifluoroethylamine which encourages the tetrahedral intermediate to return to starting materials thereby maintaining collapse of the tetrahedral intermediate in the direction of products as the rate-limiting step. Likewise the reaction of *tert*-butylamine with Q-8 shows nucleophilic attack as its rate-limiting step as a result of the bulkiness of the amine. This novel treatment of data leads to some interesting observations. For example, when collapse of the tetrahedral intermediate to products is rate limiting, a plot of log k_n *vs.* ΔpK_a results in a slope of close to unity for both the Q-6 and Q-8 esters. This linear relationship is not unexpected in the case of the Q-6 esters since partitioning of the intermediate tetrahedral compound in the direction of products should be favored equally by a given increase in pK_a of the amine or decrease in pK_a of the phenol. That a linear plot of identical slope is obtained for the Q-8 esters implies that the tendency for intramolecular catalysis by the quinoline nitrogen is independent of the pK_a of the amine; otherwise, an increase in amine pK_a should have less of an effect on k_n than a decrease in phenol pK_a. Further evidence to support the proposition that the quinoline nitrogen is able to assist in the transfer of a proton equally well from a strong base as from a weak base is presented below. From the present data it would be expected that if it were possible to employ nucleophiles of a sufficiently wide variation in pK_a with a single ester, a nonlinear ΔpK_a plot would result with a slope of 1.0 for the least basic amines gradually changing to a slope of 0.7 for the most basic amines.

The Hammett plots of Figure 1 agree with the conclusion arrived at from the ΔpK_a plots (Figures 3 and 4) that the change from rate-limiting breakdown of the tetrahedral intermediate to rate-limiting amine attack occurs with a poorer leaving group for the Q-8 esters than for the Q-6 esters. Additional evidence which suggests that the quinoline nitrogen promotes collapse of the tetrahedral intermediate to products comes from the ρ values (Table V) obtained from the Hammett plots. The values range from 1.5 to 2.5 for the reaction of amines with the 8 isomers and from 2.5 to 3.4 for reaction with the 6 isomers. The smaller dependence of k_n on the leaving group exhibited by the 8 isomers suggests that the quinoline nitrogen is acting as an intramolecular catalyst to transfer a proton from the nitrogen of $T^{\pm}$ making less important the decrease in leaving ability which occurs on increasing the pK_a of the leaving group as compared to the Q-6 esters where intramolecular facilitation is not possible.

A means for comparing nucleophilicities which normalizes scattering of points due to steric effects, electronic effects, and the α effect is to plot log k_n for the reaction of the nucleophiles with one substrate *vs.* like values for a *second* substrate.[17] Such a plot for the reactions of HO^-, primary, secondary, and tertiary amines with Q-8 and Q-6 is given in Figure 5. The nucleophilic bases fall on two separate lines both of unit slope, the primary and secondary amines which allow intramolecular catalysis by the 8 isomer on one line and the tertiary amines where no intramolecular catalysis is possible on another. In Figure 6 is given a similar plot for the reaction of primary and secondary amines with all the esters investigated in this study. The dashed lines in Figure 6 correspond to the reaction of tertiary amines and hydroxide ion with the series of Q-8 and Q-6 esters (see preceding paper, Figure 5). The points for primary and secondary amines fall on three lines of approximately unit slope. The top line results from both esters undergoing rate-limiting decomposition

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

of the tetrahedral intermediate, the middle line from those pairs for which breakdown of the tetrahedral intermediate to products is rate-limiting for the 6 isomer but amine attack has become important for the 8 isomer, and the bottom line from both esters undergoing rate-limiting amine attack. The lines show some rounding off with the most basic nucleophiles as the result of a change in rate-limiting step for one or both of the isomers. The slope of unity suggests again that intramolecular participation by the quinoline nitrogen is independent of amine pK_a. That the rate constants for 2,4-diNO_2 substituted esters which are subject to rate-limiting attack by primary and secondary amines fall on the line defined by the rate constants for tertiary amine attack on the other esters gives further support to the conclusion that the quinoline nitrogen is not able to remove a proton from a primary or secondary amine in the attack step; *i.e.*, its catalytic influence is felt in the breakdown of the zwitterionic tetrahedral intermediate to products.

In addition to the above mentioned evidence, actual comparison of the second-order rate constants in Tables I and II indicates lack of sensitivity by the quinoline nitrogen to the pK_a of the amine moiety of the tetrahedral intermediate; *e.g.*, k_n^{Q-8}/k_n^{Q-6} = 109, 114, 80, 118, 83 for pyrrolidine pK_a = 11.20, dimethylamine pK_a = 10.74, methylamine pK_a = 10.62, glycine pK_a = 9.55, and glycinamide pK_a = 7.98, respectively. This observation together with the surprising result that the weakly basic quinoline nitrogen acts as an efficient catalyst even when the amine moiety of the tetrahedral intermediate is as much as 7.0 pK_a units stronger a base leads to the conclusion that the observed intramolecular catalysis cannot be the result of proton transfer from the amino group to the quinoline nitrogen. The weakly basic quinoline nitrogen (pK_a = 4.26) should not be able to remove a proton from an amine of pK_a = 11 as easily as it does from one of pK_a = 8. Yet the quinoline nitrogen is responsible for a 100-fold (and more if steric factors are taken into account) rate enhancement in the breakdown of the tetrahedral intermediate, and there is no abating of this catalysis with decreasing amine strength. In studies of the aminolysis of 8-acetoxyquinoline[9] and 2-pyridyl thiolacetate,[10] intramolecular catalysis was also found to persist when the pK_a of the conjugate acid of the primary or secondary amine was considerably more basic than the quinoline and pyridyl nitrogens, but intramolecular participation was found to be greatest for the most weakly basic amines.

To explain the equally efficient intramolecular catalysis obtained in aminolysis with strongly and weakly basic amines we should like to propose that the function of the quinoline nitrogen is to allow the ammonium proton of $T^{\pm}$ to slide through its (the quinoline nitrogen's) orbital to the adjacent negatively charged oxygen as in IX (proton-slide catalysis). This mechanism is analogous to that proposed for general-acid catalysis of aminolysis reactions where protonation of $-O^-$ and removal of a proton from $-NH^+$ occur in a stepwise fashion.[13c] Both CPK and Fisher-Hershfelder molecular models show that the preferred conformation for the zwitterionic tetrahedral intermediate is one in which the orbital containing the unshared electrons of the quinoline nitrogen is locked between the proton of the

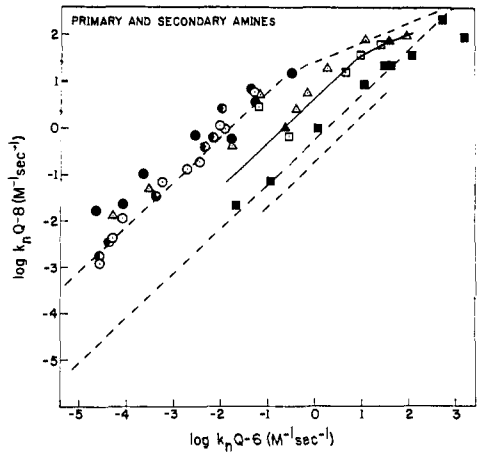
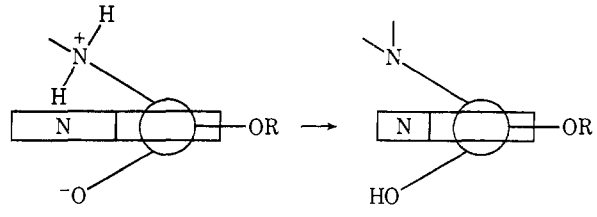


Figure 6. A plot of the log of the second-order rate constants for reaction of primary and secondary amines with substituted Q-8 esters *vs.* the same function for substituted Q-6 esters: ◐, *p*-CH_3O; ●, H; ○, *p*-Cl; □, *p*-CN; ▲, *o*-NO_2; △, *p*-NO_2; ■, 2,4-diNO_2. The dashed lines correspond to the reaction of tertiary amines and hydroxide ion.[11]



IX

amino group and the negatively charged oxygen. Thus the quinoline nitrogen electron pair is in position to conduct the proton from the nitrogen to the oxygen in the tetrahedral intermediate. Rotation of $T^{\pm}$ to a conformation favoring proton-slide catalysis may be kinetically significant.[18] Catalysis occurring *via* such a mechanism would evidence no dependence on the pK_a of the amino nitrogen since the basicity of the $-O^-$ of $T^{\pm}$ will always exceed that of the amino function of T. Lack of a deuterium solvent kinetic isotope effect (Table IV) for this mechanism is not surprising since the k_{gb} term for aminolysis is known not to be associated with an isotope effect.[12] The analogy between proton-slide and general base catalysis is obvious. In 8-acetoxyquinoline and 2-pyridyl thioacetate the molecular geometries appear not to allow proton-slide catalysis. Thus the efficiency of the observed intramolecular general base catalysis for these compounds is dependent on the pK_a of the ammonium group of $T^{\pm}$. It is not apparent why the neighboring carboxyl ion in acetyl salicylate acts as an intramolecular general base only when the pK_a of the $-COOH$ group is not too far below that of the conjugate acid of the nucleophilic amine[7] while intramolecular catalysis by amines occurs even when the nucleophile is a considerably more basic amine than the intramolecular catalyst.

In Figure 7 is given a reaction coordinate diagram for the aminolysis of an ester involving proton-slide catalysis. The most favorable pathway involves the reaction of neutral amine with neutral ester to give a zwitter-

(18) (a) P. Deslongchamps, P. Atlani, D. Fréhel, and A. Malaval, *Can. J. Chem.*, 50, 3405 (1972); (b) P. Deslongchamps, C. Lebreux, and R. Taillefer, *ibid.*, 51, 1665 (1973).

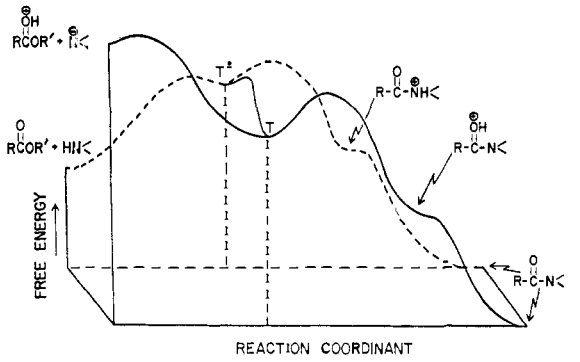


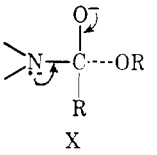
Figure 7. Reaction coordinant diagram for the aminolysis of an ester involving proton-slide catalysis. The favored reaction path is neutral amine + neutral ester going to $T^{\pm}$ which crosses over to T *via* proton-slide catalysis, T then proceeding to products.

ionic tetrahedral intermediate ($T^{\pm}$). Conversion of $T^{\pm}$ to T *via* proton-slide catalysis prevents $T^{\pm}$ from returning to starting materials and results in a crossover to the reaction coordinate given in the figure for reaction of anionic amine with protonated ester. A crossover between parallel reactions as the result of acid–base equilibria of tetrahedral intermediates has previously been proposed by Bruice and Fedor.[19] The pK_a of $T^{\pm}$ is at least 3 pK_a units[20] less than the pK_a of T so proton transfer is thermodynamically favorable. Although expulsion of phenoxide ion is more difficult from T than $T^{\pm}$, conversion of $T^{\pm}$ to T allows the reaction to proceed through a lower energy pathway since the free energy of the transition state leading from $T^{\pm}$ to products is considerably greater than that from T due to the greater free energy of initially formed N-protonated as compared to O-protonated amide.

In proton-slide catalysis the pK_a of the conjugate acid of the catalyzing base may, as in the present study, be below that of the pK_a of the acid from which the proton is being transferred. This type of general catalysis is, therefore, not under the relative pK_a restrictions pertinent in intermolecular general catalysis. Proton-slide catalysis has an obvious analogy in the conducted tour mechanism seen in certain prototropic rearrangements,[21] and, along with spectator catalysis,[22] could well be of considerable significance in enzymatic reactions.

Although intermolecular general base catalysis has not been observed[14] in the aminolysis of an ester as labile as *p*-nitrophenyl acetate, it is obvious from the second-order rate constants given in Tables I and II that the quinoline nitrogen still catalyzes the breakdown of $T^{\pm}$ when the leaving group is *p*-nitrophenol. This suggests that examination of second and higher order reactions in which the catalytic species must be brought into the transition state over a translational kinetic energy barrier may not necessarily pertain to intramolecular or enzymatic reaction in which the catalytic entity is built into the molecule or active site and need not overcome a translational kinetic energy barrier. It has been calculated by Bruice and Benkovic[23] that it requires approximately 3–7 kcal/mol to bring each species into the transition state. Removal of this kinetic energy barrier by juxtaposing the catalytic entity to the reaction site should allow weaker bases to participate in proton transfer than would be the case in intermolecular reactions and also allow catalysis to be felt by substrates that would not be subject to catalysis in intermolecular reactions. Thus a continued examination of intramolecular reactions is most pertinent to an understanding of the mechanism of enzymatic catalysis.

Intermolecular General Base Catalyzed Aminolysis. The Q-6 esters frequently evidence third-order general base catalyzed aminolysis terms. Since this third-order term (k_{gb}) is seen only with esters containing phenoxide groups of poor leaving ability (Table II) where collapse of the tetrahedral intermediate to products is rate limiting, the mechanisms given in Schemes I and II are kinetically indistinguishable. However, the following would suggest that Scheme II in which proton removal follows nucleophilic attack is the preferred pathway for *intermolecular* general base catalysis: (a) the occurrence of general base catalysis in the attack step would result in an anionic tetrahedral intermediate whose decomposition to products would not be expected to be rate limiting as observed; (b) the Q-8 esters should exhibit k_{gb} terms if intermolecular catalysis is concerted with nucleophilic attack; and (c) transfer of a proton, in water, from RNH_2 to RNH_2 to yield RNH^- and RN^+H_3 is considered energetically far less favorable than addition of RNH_2 to the carbonyl group while transfer of a proton from $T^{\pm}$ to RNH_2 is thermodynamically favorable. It has been suggested[24] that proton removal from $T^{\pm}$ is probably not concerted with loss of phenoxide ion but most likely is the rate-limiting step in the breakdown of the zwitterionic tetrahedral intermediate. Removal of a proton would not only prevent $T^{\pm}$ from returning to starting materials but would increase the rate of expulsion of phenoxide from the anionic tetrahedral intermediate X since the driving



X

force for expulsion can come from both the negatively charged oxygen and the unshared electrons on nitrogen. From Figures 1 and 3 it is apparent that the same step is rate limiting in the aminolysis of the *p*-CH_3O, H, *p*-Cl, *p*-CN, *o*-NO_2, and *p*-NO_2-Q-6 esters. However, the data of Table II show that only the three least reactive esters exhibit a third-order general base catalyzed term (k_{gb}). Earlier studies have also shown that in a given series of phenyl esters only the least reactive are subject to intermolecular general base catalysis.[14,22] From the data of the present study it appears that amine general base catalysis of amine displacement will be observed, unless special circumstances mask its significance, when the amine is less than *ca.* 0.8 pK_a units more basic than the phenolic leaving group. Intermolecular general base catalysis is not detectable with *tert*-butylamine presumably because of the steric

(19) T. C. Bruice and L. R. Fedor, *J. Amer. Chem. Soc.*, **86**, 4886 (1964).
(20) J. P. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 1436 (1974).
(21) J. Almy, R. T. Uyeda, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 6768 (1967), and references therein.
(22) (a) M. Eigen, *Discuss. Faraday Soc.*, No. **39**, 7 (1965); (b) L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, **93**, 2014 (1971); (c) D. Drake, R. L. Schowen, and H. Jayaraman, *ibid.*, **95**, 454 (1973).
(23) T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86**, 418 (1964).
(24) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8828 (1972).

hindrance that would result if a second molecule of this bulky amine were present in the transition state.[14b] Values of k_{gb} have been observed to decrease with increasing chain length for *n*-alkylamines.[25,26] It is not clear why morpholine fails to show intermolecular general base catalysis since it is observed in the aminolysis of phenyl acetate[12] unless the greater steric requirements of the quinoline ester prevent its occurrence. Glycine also exhibits intermolecular general base catalysis with phenyl acetate[12,14b] but not with the quinoline esters. Since glycinamide shows a significant k_{gb} term with the latter, it might be that the steric bulk of the quinoline ring encourages intramolecular removal of a proton from $T^{\pm}$ by the glycine carboxyl group. The failure of ethylenediamine to exhibit a k_{gb} term may also be attributed to intramolecular general base catalysis.[27]

Using the mechanism given in Scheme II, a steady state assumption in both $T^{\pm}$ and T^{-} leads to the relationships $k_{gb} = k_1k_2'/(k_{-1} + k_2)$ and $k_n = k_1k_2/(k_{-1} + k_2)$ so that $k_{gb}/k_n = k_2'/k_2$ = the ratio of conversion of $T^{\pm}$ to amide with and without general base proton removal. From the values of k_{gb} and k_n given in Table II it can be calculated that $T^{\pm}$ yields amide 2–17 times more rapidly *via* intermolecular general base catalysis than in its absence. This agrees with the k_{gb}/k_n ratios of 5–10 M^{-1} obtained from the aminolysis of phenyl acetates.[12] Values of k_{gb}/k_n are much larger for α-effect nucleophiles, ranging from 20 to 50 M^{-1} for their reaction with phenyl acetates.[12] The only primary or secondary amine with which a p-NO_2 substituted ester exhibits a general base term is methoxyamine. In addition, methoxyamine and hydrazine evidence intermolecular general base catalysis with phenyl quinoline-8-carboxylate implying that their reactivity as general bases is such that they can complete with the intramolecular catalysis associated with the 8 isomer. These results are in agreement with previous studies[12,23,28] that have shown that the α effect is more important in the k_{gb} term than in the k_n term. It should be noted that there is no α effect in proton abstraction from *tert*-butylmalonitrile[29] (or, less importantly, nitroethane[30]) by either nitrogen or oxygen α-effect bases. Hibbert, Long, and Walters[31] have suggested, on the basis of the observation of a very small tritium isotope effect and near diffusion-controlled reprotonation of carbanion indicating little delocalization of the carbanion electron pair, that in the ionization of cyanocarbon acids β is an index of the position of the transition state as is the case with the conjugate acids of oxygen and nitrogen bases. The enhancement of the α effect in k_{gb} as compared to k_n is not, therefore, likely due to the proton abstraction step from $T^{\pm}$.

The rate constant for the intermolecular general base catalysis evidenced by the Q-6 esters does not appear to decrease as the leaving group becomes better as was found by Bruice and Mayahi[14a] in the reaction of NH_3 with phenyl acetates; k_{gb}/k_n for glycinamide = 6.1, 3.1, and 6.0 M^{-1} for p-CH_3O-Q-6, Q-6, and p-Cl-Q-6, respectively. Also, the relative importance of general base catalysis appears to be independent of amine pK_a; k_{gb}/k_n for p-CH_3O-Q-6 = 16.5, 3.5, 13.4, and 6.1 M^{-1} for pyrrolidine, dimethylamine, methylamine, and glycinamide. This finds ready explanation in the fact that the rate of proton transfer from $T^{\pm}$ to amine should remain the same since the difference in pK_a between the two should be independent of the amine employed. As found in the aminolysis of phenyl acetates where breakdown of the tetrahedral intermediate is also rate limiting,[14a,23] the ρ values for intermolecular general base catalysis are smaller than those for reaction of the nucleophiles (Table V).

Correlation of β_{nuc} Values with Variation in Leaving Group and β_{lg} Values with Variation in Nucleophile. Various algebraic relationships are derivable[32] by simultaneous solution of linear free energy expressions (Hammett, Brønsted, Swain–Scott, etc.) which relate the anticipated change in one parameter of a reaction series (β, ρ, etc.) with another (σ, pK_a, etc.). To truly determine the usefulness of these expressions a large amount of experimental data is required. The data of the present investigation allow a test of the relationship of β_{nuc} and σ as well as of ρ (or β_{lg}) and pK_a.

Slopes (β_{nuc}) of plots of log k_n *vs.* pK_a of the nucleophile allow a determination of the sensitivity of a reaction to the base strength of the nucleophile. A combination of the Hammett and Brønsted relationships in conjunction with the Hammond postulate predicts that an increase in the reactivity of a given substrate results in a decreased sensitivity to amine base strength. Such a trend has been well demonstrated for the base catalyzed halogenation of ketones and keto esters.[33] Examination of the β_{nuc} values of Table III for the substituted Q-6 esters, where no intramolecular facilitation or change in rate-limiting step (except for the 2,4-diNO_2 substituted ester) occurs, establishes that either there is no significant change in β_{nuc} as the reactivity of the ester increases or that the change in β_{nuc} is in the opposite direction to that predicted. The β_{nuc} values for the substituted Q-8 esters where intramolecular facilitation is occurring decrease as the leaving group is changed from p-methoxyphenol to p-chlorophenol. However, the further decrease in β_{nuc} as the leaving group is changed to p-cyanophenol cannot be considered to

(25) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 104 (1966).

(26) When the ionic strength is maintained at 1.0 with KCl, the k_{gb} term exhibited by methyl-and ethylamine is not seen with *n*-propyl- or *n*-butylamine. When, however, the ionic strength is maintained with trimethylammonium chloride, all four amines exhibit marked k_{gb} terms (ref 12). This would be an indication that solvent structure plays a major role in determining the ratio of k_{gb}/k_n, possibly by controlling the conformation of the *n*-alkylamine.

(27) The reaction of phenyl acetate with $H_2N(CH_2)_nNH_2$ shows a tenfold rate enhancement due to intramolecular general base catalysis: T. C. Bruice and R. G. Willis, *J. Amer. Chem. Soc.*, **87**, 531 (1965). The rate enhancement increases to 100-fold in going from phenyl acetate to *N*-acetylimidazole with the effective normality of the second amino group in $H_2N(CH_2)_nNH_2$ estimated to be between 0.2 and 1.0: M. I. Page and W. P. Jencks, *ibid.*, **94**, 8818 (1972). Since k_{gb}/k_n for the reaction of amines with phenyl acetates is between 5 and 10 M^{-1},[12] at 1 M amine free base, $T^{\pm}$ should yield amide five to ten times more rapidly *via* general base catalysis than in its absence. Thus the observed rate enhancement due to general catalysis obtained by Bruice and Willis represents the maximum possible rate enhancement due to intramolecular catalysis. That the importance of this catalysis increases with *N*-acetylimidazole is due to the increase in basicity of the leaving group by 10^4.

(28) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **86**, 4117 (1964).

(29) R. F. Pratt and T. C. Bruice, *J. Org. Chem.*, 37, 3563 (1972).

(30) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2327 (1967).

(31) F. Hibbert, F. A. Long, and E. A. Walters, *J. Amer. Chem. Soc.*, **93**, 2829 (1971).

(32) (a) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 84, 4319 (1962); (b) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **88**, 2225 (1966).

(33) (a) R. P. Bell, E. Gelles, and E. Moller, *Proc. Roy. Soc., Ser. A*, **198**, 310 (1949); (b) R. P. Bell and H. L. Goldsmith, *ibid.*, 210, 322 (1952).

extend the trend since a change in rate-limiting step occurs in this region. Further increases in ester reactivity have no effect on β_{nuc}.

A combination of the Hammett and Brønsted relationships also predicts that the slopes (ρ or β_{lg}) of plots of log k_n *vs.* σ or pK_a of the leaving group decrease as the basicity of the nucleophile increases. In a study of the reaction of several nucleophiles with acetyl-4-methylpyridinium and acetyl-3,4-lutidinium ions Fersht and Jencks[34] found such a trend to occur. However, the ρ values given in Table V for the reaction of several primary and secondary amines whose pK_a's range from 7.98 to 11.08 are not in agreement with the predicted relationship. The ρ values for the Q-6 esters increase as the basicity of the nucleophile increases and those for the Q-8 esters are independent of the pK_a of the nucleophile. An increase in ρ with increasing amine basicity is also apparent for the general-base catalyzed rate constants for the Q-6 esters. It should be pointed out that the ρ values for the Q-6 esters were obtained from the reaction of a given nucleophile with five or six esters (ΔpK_a = 3.32) and those for the Q-8 esters from reaction with three esters (ΔpK_a = 0.66). The β_{lg} values of Fersht and Jencks were obtained from the reaction of nucleophiles with only two acetylpyridinium ions of ΔpK_a = 0.46. Amine attack on the acetylpyridinium ions is suggested to be rate limiting while the ρ values of Table V pertain to rate-limiting breakdown of the tetrahedral intermediate. However, since the reaction of both hydroxide ion and water with the quinoline esters is presumably *via* rate-limiting attack on the carbonyl group[11] and the ρ values for these two nucleophiles of widely different pK_a are essentially the same, the discrepancy of the results obtained in this study with those of the earlier study[34] cannot be accounted for by the difference in rate-limiting step. The pK_a range of the nucleophiles employed in the present study is not as great as that employed by Fersht and Jencks but again the near identity of the ρ values for water and hydroxide ion[11] argue against any correlation between ρ and nucleophilic strength. Lack of any correlation between selectivity and reactivity has recently been reported for the tertiary amine catalyzed E2 elimination of benzisoxazoles where the total difference in rate was 10^{11}.[35]

(34) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5442 (1970).

Electrostatic Effects. In a study of the reaction of a large series of α-substituted *o*-nitrophenyl acetates Holmquist and Bruice[36] found that when the α substituent possessed a positive charge, negatively charged oxyanions were more reactive and neutral amine nucleophiles less reactive than anticipated on the basis of the rate constants obtained for those esters in which the α substituent possessed no formal charge. Since the amines bear no charge in the ground state, electrostatic effects on collision frequencies were ruled out as responsible and the phenomena were attributed to electrostatic attraction or repulsion in the transition state. From the present study it is apparent that the rate-determining step in the reaction of amines with *o*-nitrophenyl acetates may be nucleophilic attack, collapse of the tetrahedral intermediate, or both. In a further investigation[37] it was found that with α-substituted phenyl acetates a large decrease in rate was again obtained in the aminolysis of those esters in which the α substituent possessed a formal positive charge. In addition it was noted that the electrostatic inhibition was not present in amine general base catalyzed aminolysis. From the present study and those of Jencks and coworkers[13] the rate-determining step for aminolysis of phenyl acetates is known to be collapse of the zwitterionic tetrahedral intermediate to products. Thus the electrostatic effect on k_n must be due to a dimunition in concentration of the tetrahedral intermediate as a result of electrostatic repulsion between the ammonium function of the tetrahedral intermediate and the positive charge of the α substituent. The lack of an electrostatic effect in k_{gb} must then be due to the tetrahedral intermediate's increased acidity, brought about by this charge repulsion, which assists proton removal by the catalytic amine molecule. Apparently for k_{gb} the lower concentration of the tetrahedral intermediate is compensated by a lowering of the energy barrier to proton transfer.

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(35) D. S. Kemp and M. L. Casey, *J. Amer. Chem. Soc.*, **95**, 6670 (1973).

(36) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2982 (1969).

(37) T. C. Bruice, A. F. Hegarty, S. M. Felton, A. Donzel, and N. G. Kundu, *J. Amer. Chem. Soc.*, **92**, 1370 (1970).