Hydrolysis and Aminolysis of *O*-Acylhydroxyquinolines. Intracomplex General Base-Catalyzed Aminolysis

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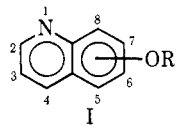
Abstract: The hydrolysis of *O*-acyl (acetyl, hexanoyl, octanoyl) 6- and 8-hydroxyquinolines was examined in the presence of various potential complexing agents. With a wide variety of ligands, binding and inhibition of the intramolecular general base-catalyzed attack of water were observed. The results are interpreted in the light of previous studies of the effect of complexation on reactivity. Aminolysis of the esters by a series of *n*-aliphatic amines indicated the presence of either preequilibrium complexing or transition state stabilization resulting from interaction of the ester and the aliphatic chains of the amines. The interaction of 8-quinolyl octanoate and octyl- or decylamine is proposed to be the first example of an intracomplex general base esterolytic reaction in water.

In the course of previous investigations,[3,4] it was found that esters of 6-and 8-hydroxyquinoline readily complex with many different buffering species, with both inhibitory and catalytic effects on the hydrolytic rate. The present work deals with the effects of complexation of the esters I on their reactivity toward H_2O and



I

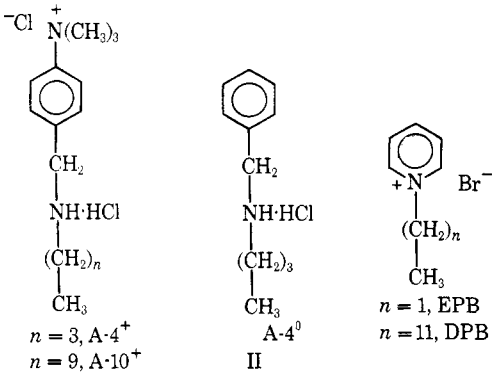
E8-Ac, R = 8-$OCCH_3$
E8-Hex, R = 8-$OC(CH_2)_4CH_3$
E8-Oct, R = 8-$OC(CH_2)_6CH_3$
E8-Dec, R = 8-$OC(CH_2)_6CH_3$
E6-Ac, R = 6-$OCCH_3$
E6-Oct, R = 6-$OC(CH_2)_6CH_3$

amines and lyophobic interaction as a factor in intramolecular general base catalysis of aminolysis.

Experimental Section

Apparatus and Materials. All apparatus used has been described in a previous paper.[4]

Ligands and salts were reagent grade or were purified by literature procedures. The 6- and 8-acetoxyquinolines[3] and the amines A-10$^+$, A-4$^+$, and A-4^0[5] (II) were from previous studies from this laboratory.



$n = 3$, A-4$^+$
$n = 9$, A-10$^+$
A-4^0
II
$n = 1$, EPB
$n = 11$, DPB

Hexylamine hydrochloride (Matheson, mp 223–225°), octylamine hydrochloride (Matheson, mp 197–200°), and decylamine hydrochloride (Eastman, mp 192–194°) were purified by the method of Kertes.[6] Collidine perchlorate (mp 239–240°) was prepared by the method of Long,[7] dodecylpyridinium bromide (DPB) (mp 50–51°) by the method of Ames and Bowman,[8] and ethylpyridinium bromide (EPB) (mp 119–122°) by the method of Willem and Nys.[9] All solids were stored in a desiccator over P_2O_5 until use. Deionized, freshly doubly glass distilled water was employed to prepare all solutions.

***N*-Dodecylimidazole (DIm).** Equimolar quantities of imidazole (Aldrich) and lauryl bromide (Matheson) were combined neat and heated at 150° for 1 hr. The residue was taken up in water, and the solution was made basic with 1.1 equiv of sodium hydroxide and extracted with ether. The ether layer was dried over $MgSO_4$, and the ether was removed on a rotary evaporator. The residue was then distilled through an annular Teflon spinning band column, yielding a clear liquid: bp 141° (0.5 mm); n 1.4712; strong ν_{max} 2900, 1500, 1450, 1225, 1075, and 725 cm^{-1}. *Anal.* Calcd for $C_{15}H_{28}N_2$: C, 76.12; H, 11.94; N, 11.85. Found:[10] C, 76.05; H, 12.09; N, 11.68.

***O*-Acylhydroxyquinolines.** Two different methods were used to prepare the esters. 8-Quinolyl hexanoate (E8-Hex) and 8-quinolyl octanoate (E8-Oct) were prepared by dissolving 1 equiv of 8-hydroxyquinoline (8-HQ) (Aldrich) in dry ether, adding 0.5 equiv of hexanoyl or octanoyl chloride (Matheson), and refluxing 24 hr. The precipitate (8-HQ·HCl) was filtered off, and the ether was removed on a rotary evaporator. The residue was taken up in ethanol, acidified with concd HCl, and purified as described below. 8-Quinolyl decanoate (E8-Dec) and 6-quinolyl octanoate (E6-Oct) were prepared by combining equimolar quantities of 8-HQ and decanoic acid or 6-hydroxyquinoline (K & K) and octanoic acid (Matheson) with an excess of trifluoroacetic anhydride and heating at 60° overnight. The liquid was then diluted with ether, washed with excess saturated sodium carbonate solution, stirred with $MgSO_4$ and Norit for 0.5 hr, and filtered, and the ether was removed on a rotary evaporator. The residue was then taken up in ethanol, acidified with concd HCl, and purified as described below.

All of the ester hydrochlorides proved to be heat sensitive. They were therefore recrystallized by dissolving them in ethanol at room temperature, diluting with ether almost to the point of precipitation, and chilling slowly. This process yielded white needles, which generally softened before melting and had somewhat broad melting ranges with decomposition. Analysis of the 8-quinolyl esters indicated the presence of water of crystallization. The ir spectra for all four esters were characterized by strong ν_{max} 3200, 2900, 1760, 1100, and 760 cm^{-1}. Additionally, the 8-quinolyl esters had a broad lowering of the spectrum above 2000 cm^{-1}, again indicative of water of crystallization.

E8-Hex·HCl had mp 72–75°. *Anal.* Calcd for $C_{15}H_{17}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 62.39; H, 6.63; N, 4.85. Found: C, 61.89; H, 6.84; N, 4.65.

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(3) S. M. Felton and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 6721 (1969).
(4) T. Maugh II and T. C. Bruice, *ibid.*, **93**, 3237 (1971).
(5) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *ibid.*, **90**, 1333 (1968).
(6) A. S. Kertes, *J. Inorg. Nucl. Chem.*, **27**, 209 (1965).
(7) J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, **79**, 2365 (1957).
(8) D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 1057 (1952).
(9) J. Willem and J. Nys, *Bull. Soc. Chim. Belg.*, **66**, 502 (1957).
(10) Analyses performed by Elek Laboratories, Torrance, Calif.

E8-Oct·HCl had mp 74–77°. *Anal.* Calcd for $C_{17}H_{21}NO_2 \cdot HCl \cdot H_2O$: C, 62.67; H, 7.42; N, 4.30. Found: C, 63.13; H, 7.48; N, 4.55.

E8-Dec·HCl had mp 93–96°. *Anal.* Calcd for $C_{19}H_{25}NO_2 \cdot HCl \cdot H_2O$: C, 64.49; H, 7.98; N, 3.96. Found: C, 65.11; H, 8.04; N, 4.15.

E6-Oct·HCl had mp 156–158°. *Anal.* Calcd for $C_{17}H_{21}NO_2 \cdot HCl$: C, 66.33; H, 7.20; N, 4.55. Found: C, 66.24; H, 7.37; N, 4.50.

As an additional check, the E8-Hex·HCl and E8-Oct·HCl were individually heated under a vacuum in a zone sublimation apparatus,[11] yielding decomposition products and the neutral esters as clear liquids; both liquids showed strong ν_{max} 2900, 1750, 1140, 1100, 825, and 795 cm^{-1}. The uv spectra and hydrolytic properties of these liquids were identical with those of the hydrochlorides.

E8-Hex had n 1.5555. *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.44; H, 7.14; N, 5.77.

E8-Oct had n 1.5435. *Anal.* Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.12; H, 7.88; N, 5.19.

Kinetics. All kinetic measurements were performed in water at a temperature of 30 ± 0.1° and a calculated ionic strength of 1.0 (with KCl). pH values for the reaction solutions were obtained using an electrode thermostated at 30 ± 0.1°; pH values were measured before reaction and, in some cases, at the completion. The disappearance of the quinoline esters was generally followed by monitoring increase in product phenol absorbance at 250 nm. For those buffer solutions with high absorbances at 250 nm (as DPB, A-10[+]), the reaction was followed by monitoring disappearance of ester absorbance at 288 nm; at this wavelength, however, there is a much smaller absorbance change, so that an approximately fivefold higher concentration of ester is required, thereby restricting its use to the more soluble esters. For those buffers with high absorbance at 288 nm, hydrolysis of the ester was followed by monitoring uptake of hydroxide in the pH Stat. The hydrolysis experiments were generally performed at an ester concentration of about 4–6 × 10^{-6} M when followed at 250 nm, about 3 × 10^{-5} M at 288 nm, and about 1–1.5 × 10^{-6} M when the Cary 15 spectrophotometer and a Radiometer autotitrator (described elsewhere[12] by Bruice and Maley) was used. Titrimetric rates were performed at [E8-Ac] ≅ 10^{-3} M. Stock solutions of the esters were prepared in acetonitrile and kept in a freezer until use; these solutions were stable for several weeks. The reactions were initiated by the addition of a measured quantity of the ester solution—generally 10 to 20 μl—to the preequilibrated buffer with an Eppendorf pipet; care was taken to ensure that, within any one serial dilution, the concentration of the ester was the same for all reactions.

Complexing experiments at pH 4.6 were performed in 0.4 M acetate buffer; serial dilutions were made with the same buffer, ensuring good pH control with only a small (and constant) inhibition (<5%) due to buffer. Ethyl-, butyl- and hexylamines served as their own buffers in the aminolysis experiments; serial dilutions were performed with 1 M KCl adjusted to pH 10.6, so there was no pH drift on dilution. Experiments with octyl- and decylamines were performed in the autotitrator cell of the Cary 15, using the Radiometer unit to maintain pH. For all serial dilutions at either pH, where plots of k_{obsd} *vs.* [ligand] were nonlinear, rates were measured for at least 6 different ligand concentrations.

All rates were followed to at least four half-lives, and the values of the pseudo-first-order rate constants were routinely calculated by the method of Guggenheim;[13] occasionally the rate constants were also calculated from the infinity OD value to ensure that they were first order. Good agreement between the two methods was obtained in all cases.

pK_a Determinations. The acid dissociation constants of the quinoline esters were determined by spectrophotometric titration on the Cary apparatus[12] at 243 nm. All titrations were performed at the same temperature, ionic strength, and concentration of ester as the rate determinations.

Results

Hydrolysis. The esters E8-Ac and E6-Ac were readily soluble in the neutral form up to a concentration of 10^{-3} M. The E8-Hex was soluble to at least a concentration of 5 × 10^{-5} M; rate constants obtained at concentrations varying between 5 × 10^{-5} and 1.5 × 10^{-6} M were found to be identical. The esters E8-Oct and E6-Oct were found to be soluble as the neutral species only to a maximum concentration of about 7–8 × 10^{-6} M. Rate constants obtained for each of these esters at concentrations between 5 × 10^{-6} M and 1.5 × 10^{-6} M were found to be identical. The neutral species of the ester E8-Dec was found to be too insoluble for kinetic studies.

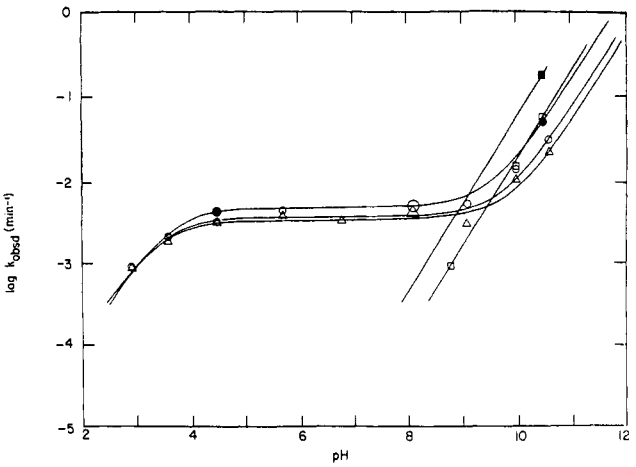


Figure 1. pH–log k_{obsd} profiles for the hydrolysis of esters E8-Ac (●), E6-Ac (■), E8-Hex (○), E8-Oct (△), and E6-Oct (□). The plots for E8-Ac and E6-Ac are derived from the data of ref 3.

The pH–log k_{obsd} profiles for the hydrolysis of esters E8-Ac and E6-Ac have previously[3] been found to follow the rate expression 1 where K_e is the acid dissociation

$$k_{obsd} = \left[\frac{1}{K_e + a_H}\right] \times [(k_{OH}[HO^-] + k_1 + k_H a_H)K_e + k_H' a_H^2] \quad (1)$$

constant for the ester, a_H is the activity of the hydrogen ion as measured at the glass electrode, k_H' represents acid-catalyzed hydrolysis of the protonated ester, and k_H, k_1, and k_{OH} represent, respectively, the acid-, spontaneous (water-catalyzed), and hydroxide-catalyzed hydrolysis of the neutral ester. Equation 1 reduces to

$$k_{obsd} = \frac{(k_1 + k_{OH}[HO^-])K_e}{K_e + a_H} \quad (2)$$

for E8-Ac in the pH region 3–12, and to

$$k_{obsd} = \frac{k_{OH}[HO^-]K_e}{K_e + a_H} \quad (3)$$

for E6-Ac in the pH region 9–12.

In Figure 1 is plotted log k_{obsd} *vs.* the constant pH at which the rate constants were determined for hydrolysis of the *O*-acylhydroxyquinolines. The plots of E8-Ac and E6-Ac are from a previous work[3] at 55°, and have been extrapolated to 30° by determining k_{obsd} at 30° for several pH values. The points of Figure 1 are experimental and the lines are theoretical, having been derived from eq 2 for the 8-quinolyl esters and from eq 3 for the 6-quinolyl esters. The values of the various rate and equilibrium constants are given in Table I.

(11) T. C. Bruice and B. Holmquist, *J. Amer. Chem. Soc.*, **89**, 4028 (1967).
(12) T. C. Bruice and J. R. Maley, *Anal. Biochem.*, **34**, 275 (1970).
(13) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

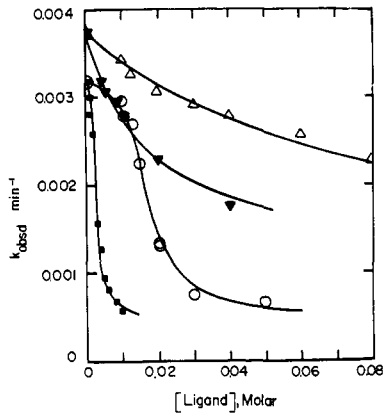


Figure 2. Plots of k_{obsd} *vs.* [ligand] for the hydrolysis of E8-Ac in the presence of A-10$^+$ (△) and DPB (▼) and for the hydrolysis of E8-Hex in the presence of A-10$^+$ (○) and DPB (■). All solutions were at pH 4.6 in 0.4 *M* acetate buffer.

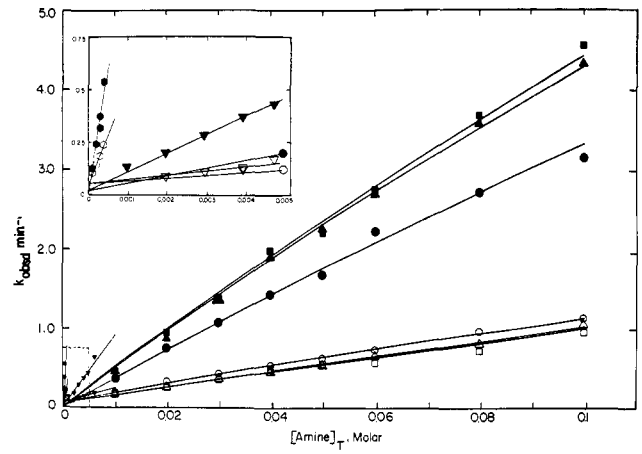


Figure 3. Plots of k_{obsd} *vs.* $[amine]_T$ for the reaction of E6-Oct (open symbols) and E8-Oct (solid symbols) with ethyl- (○), butyl- (△), hexyl- (□), octyl- (▽), and decylamines (○). The insert is a partial enlargement of the region enclosed by the dashed line. All solutions were at pH 10.60.

Repetitive scan spectra taken in the course of hydrolysis of the 8-quinolyl esters show sharp isosbestic points at 233, 267, and 307 nm, and those of the 6-quinolyl esters at 235, 260, and 313 nm, both in the absence and the presence of external buffering and/or complexing agents, indicating that absorbing intermediates do not accumulate. The magnitude of the change in absorbance resulting from hydrolysis does appear to change in the presence of some complexing agents, however.

Table I. Rate and Dissociation Constants for the Hydrolysis of *O*-Acyl hydroxyquinolines[a]

Ester	pK_e[b]	k_1, min^{-1}	k_{OH}, M^{-1} min^{-1}
E8-Ac[c]	3.64	0.0045	90.2
E6-Ac[c]	4.44		304
E8-Hex	3.52	0.0035	42.9
E8-Oct	3.44	0.0032	30.4
E6-Oct	4.19		94.6

[a] All rate constants extrapolated to zero external buffer; T = 30°; μ = 1.0 (KCl). [b] Determined by spectrophotometric titration. [c] Data from ref 3.

Complexation. All complexing studies were performed at pH 4.6 in 0.4 *M* acetate buffer; at this pH, the hydrolysis of the 8-quinolyl esters proceeds primarily *via* intramolecular general base catalysis of the attack of water.

In all cases examined where added nonnucleophilic reagent (ligand) caused a change in the observed hydrolytic rate, plots of k_{obsd} *vs.* [ligand] were found to conform to the expression 4 where k_0 is the hydrolysis rate in the absence of ligand, k' is the pseudo-first-order

$$k_{obsd} = \frac{k_0C + k'[\text{ligand}]^n}{C + [\text{ligand}]^n} \quad (4)$$

rate constant for reaction within the complex, and C is the apparent *dissociation* constant for the complex. With the exception of the reaction of ester E8-Hex with either A-10$^+$ or DPB where n = 4 was required, all experimental data were fitted with n = 1. For n = 1, a plot of $1/(k_{obsd} - k_0)$ *vs.* 1/[ligand] [avoiding very small values of $(k_{obsd} - k_0)$ where minor errors in k_{obsd} are greatly magnified] provided linear plots of slope = $C/(k' - k_0)$ and intercept = $1/(k' - k_0)$; from which C = slope/intercept, and k' = (1/intercept) + k_0.[14] As an additional check, the derived constants were then inserted into eq 4 and fitted to the data on a plot of k_{obsd} *vs.* [ligand]. In those cases where n = 4, the data were fitted directly on the plot of k_{obsd} *vs.* [ligand] by a process of trial and error.

In Figure 2 is plotted k_{obsd} *vs.* [ligand] for the hydrolysis of esters E8-Ac and E8-Hex in the presence of A-10$^+$ and DPB; the points are experimental, and the theoretical lines are derived from eq 4 with n = 1 for E8-Ac and n = 4 for E8-Hex. The results shown for E8-Ac are typical of the results obtained with all other ligands which show inhibition. The results shown for E8-Hex were obtained only with these two ligands; for reaction of esters E8-Hex and E8-Oct with all other ligands, the kinetics were similar to those obtained with E8-Ac (E8-Oct was not examined with A-10$^+$ and DPB). In Table II are provided the rate and dissociation constants used to construct Figure 2, as well as the constants obtained with the other ligands examined. For all ligands where complexation resulted in inhibition, *saturation kinetics were observed.*

Aminolysis. For those ligands where the data reflect catalysis, plots of k_{obsd} *vs.* [ligand] appear to have a slight downward curvature, similar to that shown in Figure 3 (see below). The data can be readily fitted to eq 4 as described previously, yielding the results shown in Table II. The values of C obtained, however, indicate that at the maximum concentrations of ligand employed, less than 10% of the ester was actually complexed. Second-order rate constants (k_n) were therefore calculated using data obtained at low concentrations of ligand, where the plots of k_{obsd} *vs.* [ligand] are linear. For reaction with $[E8\text{-}Ac]_T$, the second-order rate constants calculated with respect to free amine are: imidazole, k_n = 2.38 M^{-1} min^{-1}; *N*-methylimidazole, k_n = 0.75 M^{-1} min^{-1}; glycine amide, k_n = 0.022 M^{-1} min^{-1}; and triglycine, k_n = 0.46 M^{-1} min^{-1}. Second-

(14) $k_{obsd} = (k_0C + k'[\text{ligand}])/(C + [\text{ligand}]) = (k_0C + k_0[\text{ligand}] + k'[\text{ligand}] - k_0[\text{ligand}])/(C + [\text{ligand}]) = [k_0(C + [\text{ligand}])]/(C + [\text{ligand}]) + [(k' - k_0)[\text{ligand}]]/(C + [\text{ligand}])$, $1/(k_{obsd} - k_0) = 1/(k' - k_0) + C/[(k' - k_0)[\text{ligand}]]$.

Table II. Rate and *Dissociation* Constants for the Hydrolysis of *O*-Acyl-8-hydroxyquinolines in the Presence of Various Ligands[a]

Ligand[b]	Maximum [ligand], *M*	E8-Ac				E8-Hex or E8-Oct				
		C, *M*	*K*, *M*	*k'*, min^{-1}	k'/k_0	Ester	*C*, *M*	*K*, *M*	*k'*, min^{-1}	k'/k_0
None (acetate only)				0.00375		Hex			0.00318	
						Oct			0.00295	
Glycine amide·HCl	0.8	4	4[c]	0.0057	1.5					
Imidazole·HCl	0.2	2.7	2.7[c]	0.15	40	Oct	0.81	0.81[c]	0.030	10
N-Methylimidazole·HCl	0.2	0.46	0.46[c]	0.018	4.8	Oct	1.91	1.91[c]	0.0261	8.85
Sarcosine anhydride	0.5	0.44	0.44[c]	~0						
Triglycine·HCl	0.3	0.24	0.24[c]	0.005	1.4					
Hexylamine·HCl	0.3	0.097	0.0049[d]	0.0025	0.67	Oct	0.067	3.4×10^{-3}[d]	0.0018	0.6
A-10$^+$	0.1	0.093	0.0047[d]	0.00051	0.14	Hex	1.3×10^{-7}[f]	1.3×10^{-7}[f]	0.00055	0.17
2,5-Piperazinedione	0.05	0.078	0.078[c]	0.0023	0.61					
Decylamine·HCl	0.1	0.069	0.0035[d]	0.0026	0.71	Oct	0.013	6.5×10^{-4}[d]	0.00041	0.14
EPB	0.1	0.066	0.066[c]	0.0026	0.71					
A-4$^+$	0.1	0.056	0.056[c]	0.0028	0.74					
A-4^0	0.1	0.052	0.052[c]	0.0029	0.77					
Caffeine	0.1	0.038	0.038[c]	0.0021	0.55					
Collidine·$HClO_4$	0.05	0.038	0.038[c]	0.0028	0.76					
DPB	0.04	0.018	0.0009[d]	0.001	0.27	Hex	6×10^{-11}[f]	6×10^{-11}[f]	0.00065	0.2
DIm·HCl	0.01	*e*				Oct	0.00032	1.6×10^{-3}[d]	0.00035	0.012

[a] All reactions in 0.4 *M* acetate buffer, pH 4.6, μ = 1.0 (KCl), T = 30°. [b] The following compounds, at the concentrations indicated in parentheses, were examined under the same conditions and found to have no significant effect on the hydrolysis rate of E8-Ac: acetamide (0.5 *M*); *N*-acetylserine amide (0.05 *M*); *N*-acetyltyrosine amide (0.005 *M*); benzamide (0.075 *M*); 1,4-diaminobutane dihydrochloride (0.5 *M*); ethylamine hydrochloride (0.3 *M*); ethyleneurea (saturated); *N*-ethylmorpholine hydrochloride (0.1 *M*); hippuric acid (0.05 *M*); lysozyme (0.5 mg/ml); malonamide (0.25 *M*); morpholine hydrochloride (0.5 *M*); nicotinamide methiodide (0.005 *M*); phenol (0.05 *M*); phthalamide (saturated); piperidine hydrochloride (0.5 *M*); succinimide (0.25 *M*); and urea (1.0 *M*). Hexanoic acid (0.05 *M*) and ethylamine hydrochloride (0.3 *M*) were also examined with E8-Hex and E8-Oct with the same results. [c] Calculated assuming a 1:1 complex for simple ligands. [d] Calculated with N = 20; see Discussion. [e] Buffer dilution linear with slope zero. [f] Units are M^4.

Table III. Nucleophilic Rate Constants for Aminolysis of *O*-Acylhydroxyquinolines[a]

Amine	pK_a	k_n, M^{-1} min^{-1}				
		E8-Ac	E6-Ac	E8-Hex	E8-Oct	E6-Oct
Methylamine[b]	10.69[c]	290	190			
Ethylamine	10.67[c]	136	82.4	84.9	79.5	25.4
Butylamine	10.6[d]	154	68.1	101	89.8	19.1
Hexylamine	10.6[d]	154	66.4	100	88.8	19.3
Octylamine	10.6[d]	240	93.2	171	185	44.4
Decylamine	10.6[d]	318	236	556	2140	904

[a] At pH 10.6; μ = 1.0 (KCl); T = 30°; all constants calculated in terms of [free amine]. [b] Data from ref 3. [c] Reference 16. [d] Reference 17.

order rate constants for reaction of free amine with $[E8\text{-}Oct]_T$ are: imidazole, k_n = 0.04 M^{-1} min^{-1}; and *N*-methylimidazole, k_n = 0.3 M^{-1} min^{-1}.

Aminolysis of the five esters by ethyl-, butyl-, hexyl-, octyl-, and decylamines was performed at pH 10.6, which is near the pK_a of all the amines.[15] For ethyl-, butyl-, and hexylamines, plots of k_{obsd} *vs.* [total amine] appear to have a slight downward curvature, similar to that discussed for imidazole and glycinamide in the preceding paragraph. The values of C obtained for these compounds indicate that from 5 to 15% of the ester is actually complexed at the maximum concentrations of amine. Second-order rate constants were therefore calculated in the same manner. The low solubility of free octyl- and decylamines severely limited the concentration ranges over which their reactions could be studied. For experiments performed at $[octylamine]_T \leq 0.006$ *M* and $[decylamine]_T \leq 0.0004$ *M*, plots of k_{obsd} *vs.* $[amine]_T$ were linear, and extrapolated directly to the values of k_0 obtained independently on the Cary spectrophotometer–Radiometer pH-Stat assembly.[12] Values of k_n for these amines were obtained as described above.

In Table III are listed the values of k_n obtained for aminolysis of the five esters by the five amines, as well as data previously obtained[3] for aminolysis of E8-Ac and E6-Ac by methylamine. Also, as a visual aid, in Figure 3 is plotted k_{obsd} *vs.* $[amine]_T$ for aminolysis of esters E8-Oct and E6-Oct by the five amines. The points are experimental, and the lines are the theoretical lines derived from eq 4. These plots are typical of those for reaction of the amines with the remaining esters.

Discussion

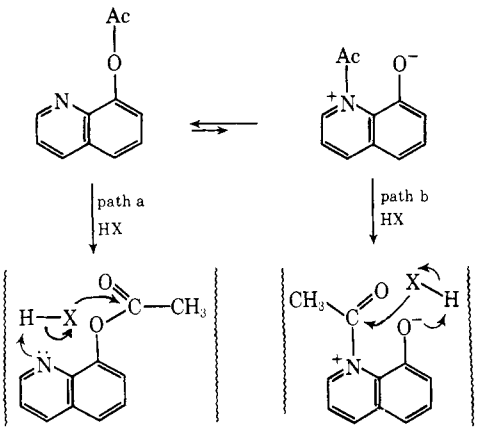
Hydrolysis. The mechanism of the pH-independent hydrolysis of E8-Ac has been discussed extensively in ref 3. Briefly, the deuterium solvent isotope effect (k^{H_2O}/k^{D_2O} = 2.35), the entropy of activation ($T\Delta S^{\pm} = -8.7$ kcal/mole at 25°), and the different mode of reaction with water and primary and secondary amines compared to HO^- and tertiary amines dictate an intramolecular general base-catalyzed attack of water and primary and secondary amines. Two kinet-

(15) Ethylamine, pK_a = 10.7;[16] butyl-, hexyl-, octyl- and decylamines, pK_a = 10.6.[17]

(16) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967).

(17) H. C. Brown, *et al.*, in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955.

Scheme I



ically indistingushable mechanisms were considered (Scheme I). The mechanism proceeding through path a is favored over that through path b primarily on three considerations: (a) any reasonable value for the pK_a of the quinolyl hydroxyl group would require an exceptionally facile intramolecularly catalyzed hydrolysis by the oxyanion species at the low pH end of the plateau; (b) in analogy with the general base catalysis mechanisms for the hydrolysis of substituted aspirins[18,19] path a should be favored over path b due to the magnitude of the ΔpK_a difference between the conjugate acids of the quinoline nitrogen and hydroxyl groups; (c) in the hydrolysis of 8-quinolyl hydrogen glutarates and succinates, which may also undergo a preequilibrium O → N acyl shift prior to nucleophilic attack by the carboxyl anion, it has been demonstrated[4] by comparison with other substituted phenyl succinates and glutarates that the phenolic oxygen is the leaving group; by implication, then, the phenolic oxygen, rather than the quinoline nitrogen, should be the leaving group for hydrolysis of E8-Ac.

The identical shapes of the pH–log k_{obsd} profiles for the hydrolysis of esters E8-Hex, E8-Oct, and E8-Ac and of those for E6-Oct and E6-Ac, and the similarity of the calculated rate constants, indicate that the hydrolytic mechanisms for the acetates and the longer chained esters are identical. The two- to threefold rate ratios for hydroxide attack on the acetates and the longer chained esters are similar to the rate ratios previously observed in the hydrolysis of the sodium salts of 3-nitro-4-acetoxybenzenesulfonate and 3-nitro-4-octanoyloxybenzenesulfonate,[5] *p*-nitrophenyl acetate (PNPA) and octanoate,[20] and PNPA and *p*-nitrophenyl decanoate (PNPD).[21,22]

The similarity of rate constants for long- and short-chain esters would also appear to indicate that there are no self-association phenomena occurring; large changes in the rate of alkaline hydrolysis resulting from self-association have previously been observed for 4-decanoyloxyphenyltrimethylammonium chloride and sodium 4-decanoyloxybenzenesulfonate[5] and for *p*-nitrophenyl laurate.[23] It would thus appear that, at the concentrations employed, the long-chained esters examined in this study exist in solution primarily as monomers. Reference to the Results section indicates that k_{obsd} is not dependent upon ester concentration.

Complexation. A large number of systems have been studied in which complexation with a ligand changes the reactivity of a substrate toward nucleophilic attack.[24] In almost all cases it has been found that complexation lowers the reactivity of the substrate, although a very few cases of increased reactivity have been noted.[24,25]

Assuming that an ester complexes with one or more molecules of ligand, and that the reactivity of the complexed ester is different from that of the free ester, one may write the following scheme[5]

$$\text{ester} + n\ \text{ligand} \underset{C}{\rightleftharpoons} \text{ester}\cdot\text{ligand}_n \qquad (5a)$$

$$\text{ester}\cdot\text{ligand}_n \xrightarrow{k'} \text{hydrolytic products} \qquad (5b)$$

$$\text{ester} \xrightarrow{k_0} \text{hydrolytic products} \qquad (5c)$$

The observed first-order rate constant for this mechanism is then given by eq 4. If the ligand first undergoes self-association to form a micelle, which then complexes with the ester, 5a and 5b then become

$$\text{ester} + \text{micelle} \underset{K}{\rightleftharpoons} \text{ester}\cdot\text{micelle} \qquad (6a)$$

$$\text{ester}\cdot\text{micelle} \xrightarrow{k'} \text{hydrolytic products} \qquad (6b)$$

for which we may write

$$k_{obsd} = \frac{k_0K + k'[\text{micelle}]}{K + [\text{micelle}]} \qquad (7)$$

The concentration of micelles is then given[26] by

$$[\text{micelle}] = \frac{[\text{ligand}] - cmc}{N} \qquad (8)$$

where *cmc* is the critical micelle concentration (*i.e.*, the concentration of ligand at which micelles begin to form), and N is the aggregation number (the number of molecules of ligand per micelle). Under conditions where [ligand] $\gg$ *cmc*, we obtain

$$k_{obsd} = \frac{k_0K + k'[\text{ligand}]/N}{K + [\text{ligand}]/N} = \frac{k_0KN + k'[\text{ligand}]}{KN + [\text{ligand}]} \qquad (9)$$

which is identical with eq 4 with $C = KN$. In those cases where the ligand forms micelles, therefore, the true binding constant to the micelle, K, is obtained by dividing the experimentally determined value of C (eq 4) by the number of monomers in the micelle. Values of K in Table II have been obtained using an average value for N of 20; since, however, N may vary from

(18) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, **89**, 4853 (1967).
(19) A. R. Fersht and A. J. Kirby, *ibid.*, **90**, 5818 (1968).
(20) F. M. Menger and C. E. Portnoy, *ibid.*, **89**, 4698 (1967).
(21) J. R. Knowles and C. A. Parsons, *Chem. Commun.*, 755 (1967).
(22) See also M. S. Newman, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 4.
(23) F. M. Menger and C. E. Portnoy, *J. Amer. Chem. Soc.*, **90**, 1875 (1968).
(24) A partial list of examples might include: (a) F. M. Menger and M. L. Bender, *ibid.*, **88**, 131 (1966); (b) A. K. Colter, S. S. Wang, G. H. Megerle, and P. S. Ossip, *ibid.*, **86**, 3106 (1964); (c) K. A. Connors and J. A. Mollica, Jr., *ibid.*, **89**, 308 (1967); (d) T. Higuchi and L. Lachman, *J. Amer. Pharm. Ass.*, **44**, 521 (1955); (e) references listed in each.
(25) P. A. Kramer and K. A. Connors, *J. Amer. Chem. Soc.*, **91**, 2600 (1969).
(26) C. A. Bunton and L. Robinson, *ibid.*, **90**, 5972 (1968).

about 15 to several hundred,[27,28] these values represent only the upper limits of the dissociation constants.

With ligands which form micelles, eq 4 with $n = 1$ may be interpreted either as a partitioning of the ester into the micelle or as formation of a premicelle with a 1:1 stoichiometry of ester and ligand. The assumptions leading to eq 9 also involve partitioning of the ester into the micelle. The most suitable explanation of eq 4 with $n > 1$ is that the ester associates with n monomers to form a salt or premicelle, thereby inducing micelle formation. Such induced micelle formation with a stoichiometry of three or five detergent molecules to one dye molecule[29] has previously been shown to occur for the interaction of various dyes with sodium lauryl sulfate (NaLS). Similar salts with an apparent 1:1 ratio have been observed for the interaction of nonyl xanthate and cetyltrimethylammonium bromide (CTABr), NaLS and CTABr, and sodium laurate and CTABr.[30] The amine A-10$^+$ has also been found[5] to react with various acyloxybenzenesulfonates and acyloxynitrobenzenesulfonates with kinetics governed by eq 4 with $n = 4$; values for C were found to be on the order of 10^{-12} M^4. The two instances of induced micelle formation in the present study involved the interaction of ester E8-Hex with A-10$^+$ and DPB, for which binding constants of 10^{-7} M^4 and 6×10^{-11} M^4, respectively, were obtained. For those cases where interaction of the esters with surfactant is governed by eq 4 with $n = 1$, it may be argued that the data reflect a premicelle with a 1:1 stoichiometry, rather than partitioning into a micelle. The observed values of C (Table II) would then be the dissociation constants for these 1:1 complexes. The fact that the reactions were performed above the *cmc* of the ligand suggests that simple partitioning is the preferred explanation. The decrease in reactivity resulting from complexation with most of the ligands studied can be rationalized in the same fashion as in the previous studies.[4]

The large sensitivity of the hydrolytic rates of the 8-quinolyl esters to complexing effects (as indicated by the data of Table II) as compared to the benzoate and glutarate derivatives examined by Kramer and Connors[25] probably results from the fact that the catalytic quinoline nitrogen is an integral part of the complexed aryl ring system whereas, in the benzoate systems, the catalytic carboxylate extends from the ring.

Aminolysis. The observed apparent second-order rate constant, calculated at low free amine concentration, for reaction of free imidazole with $[E8\text{-}Ac]_T$ at pH 4.6 ($k_n = 2.38$ M^{-1} min^{-1}) is larger than the true second-order rate constant for reaction of free imidazole with the neutral ester ($k_p = 0.52$ M^{-1} min^{-1}). N-Protonated quinoline monoesters of dicarboxylic acids are at least 100 times more susceptible to nongeneral base-catalyzed carboxyl anion intramolecular nucleophilic attack than the neutral esters. It has also been demonstrated[3] that protonated imidazole complexes with neutral E8-Ac and by analogy with the results obtained for collidinium ion (Table II), this complexation should result in inhibition. The overall reaction may then be described by eq 10.

$$\text{ester} + \text{amine H}^+ \underset{K_i}{\rightleftharpoons} \text{ester}\cdot\text{amine H}^+ \qquad (10a)$$

$$\text{ester H}^+ + \text{amine} \xrightarrow{k_r} \text{hydrolytic products} \qquad (10b)$$

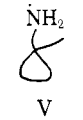
$$\text{ester} \xrightarrow{k_0} \text{hydrolytic products} \qquad (10c)$$

If K_a is the acid dissociation constant of the amine and K_e that of the ester, we obtain for low concentrations of ester

$$k_{obsd} = \frac{\dfrac{k_0 K_i (K_a + a_H)}{a_H} + \dfrac{k_r K_a K_i [A_T]}{K_e}}{\dfrac{K_i (K_a + a_H)(K_e + a_H)}{K_e a_H} + [A_T]} \qquad (11)$$

which, at constant pH, is kinetically equivalent to eq 4 for $n = 1$.

In the absence of complexation interactions, the second-order rate constants (k_n) for aminolysis of a simple substrate by primary alkyl amines would be expected to decrease as the length of the alkyl chain increases. The ratio of the rate constants for aminolysis of phenyl acetate by propyl- and methylamines, for example, is about 0.25.[16] Long hydrocarbon chains in water tend to undergo intramolecular hydrophobic bonding to form a coil,[31] so that the conformation of decylamine in water is probably similar to that of V, and its reactivity might be expected to be similar to that



V

of *tert*-butylamine. The ratio of k_n for the aminolysis of PNPA by *tert*-butyl- and methylamine is about 0.059,[32,33] so that we might expect a similar ratio of rate constants for aminolysis of simple substrates by methyl- and decylamines, or a ratio about half as large for ethyl- and decylamines.

With the substrates examined in this study, the ratios of k_n are found to be opposite to what is predicted: that is, for decyl- and ethylamines, ratios of k_n are 35.6 for ester E6-Oct and 27 for E8-Oct, rather than the ~0.125 expected. Thus, it would appear that there are factors other than steric suggesting that association may be occurring between the ester and the nucleophile. The fact that simple second-order kinetics are observed indicates that the value of the dissociation constant for the complex is much larger than the concentration of either ligand or ester.

Knowles and Parsons[21] have examined the aminolysis of PNPA and PNPD with similar results; they found ratios of k_n values for decyl- and ethylamines of 7 for PNPA and 700 for PNPD, compared to the values of 2.3 for E8-Ac and 27 for E8-Oct obtained in this sudy. In both cases the reactions were performed at concentrations of amine well below the *cmc* for formation of micelles of decylamine hydrochloride (*ca.* $4\text{–}6 \times 10^{-2}$ M).[34,35] The enhanced rates for decylamine with the

(27) G. S. Hartley and D. F. Runnicles, *Proc. Roy. Soc., Ser. A*, **168**, 420 (1938).
(28) E. W. Anacker and H. M. Ghose, *J. Amer. Chem. Soc.*, **90**, 3161 (1968).
(29) P. Mukerjee and K. J. Mysels, *ibid.*, 77, 2937 (1955).
(30) R. V. Scowen and J. Leja, *Can. J. Chem.*, **45**, 2821 (1967).
(31) G. Némethy and H. Scheraga, *J. Chem. Phys.*, **36**, 3382 (1962).
(32) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).
(33) W. P. Jencks and M. Gilchrist, *ibid.*, **88**, 104 (1966).

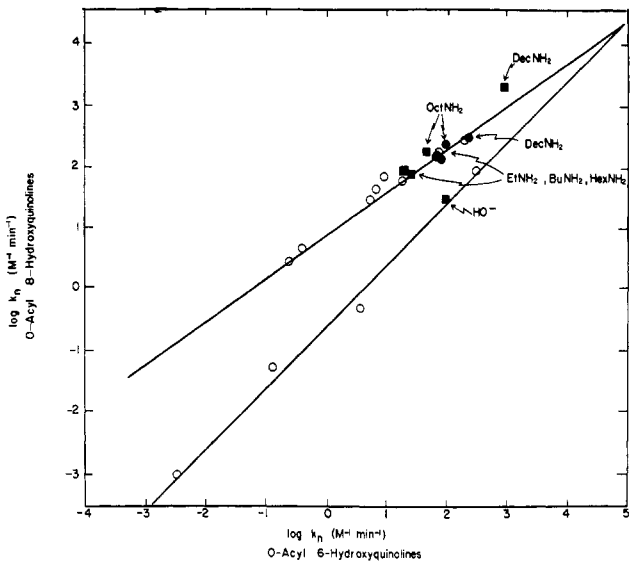


Figure 4. Plot of log k_n for the reaction of nucleophiles wth E8-Ac *vs.* log k_n for reaction of the same nucleophiles with E6-Ac. The open circles represent data for various nucleophiles taken from ref 3. The solid squares are values obtained in this study for octanoates; the solid circles are values for the acetates.

short-chained esters were attributed[21] to a nonspecific association of the aliphatic decyl chain with the aryl ring, while the larger enhancement with PNPD was thought to arise from a juxtapositioning of the aliphatic side chains of substrate and ligand.

Two different methods may be employed to assess the contribution of each methylene group to the overall rate enhancement: (a) by comparing rate constants for the reaction of a long-chained nucleophile with a long- and a short-chained ester, or (b) by comparing the rate constants for reaction of long- and short-chained nucleophiles with a long-chained ester. The decrease in the free energy of activation ($\Delta\Delta F^{\pm}$) on increase in chain length of ester or amine may then be obtained from eq 12.[36] The conclusion reached in

$$\Delta\Delta F^{\pm} = -RT \ln (k_n^{\text{long chain}}/k_n^{\text{short chain}}) \quad (12)$$

either fashion is that the majority of the binding energy arises from interaction of the amine side chain with the aromatic portion of the ester.

For reaction of decylamine with PNPD and PNPA, $\Delta\Delta F^{\pm} = -736$ cal/mole (-92 cal/mole per methylene group), while for reaction of decylamine with E8-Oct and E8-Ac, $\Delta\Delta F^{\pm} = -1145$ cal/mole (-190 cal/mole per methylene). These values are considerably less negative than those previously calculated for the transfer of surfactant monomers from the bulk to the micellar phase (-650 cal/mole per methylene)[37] or for hydrophobic binding *via* a minimum contact (-300 cal/mole per methylene),[38] and also considerably less negative than the values of -442 cal/mole per methylene obtained for the reaction of *p*-nitrophenyl esters with complexes of N^{α}-myristoylhistidine (NMH) and CTABr,[39] and -550 cal/mole per methylene for the reaction of N^{α}-acetylhistidine (NAH) and N^{α}-stearoylhistidine (NSH) with *p*-nitrophenyl alkyl carbonates.[40] The less negative values of $\Delta\Delta F^{\pm}$ for addition of a methylene group to the ester side chain, in conjunction with the previously discussed enhanced reactivity of decylamine (as compared to ethylamine) with the *p*-nitrophenyl or quinolyl acetates, indicate that the greatest contributing force to the lowering of $\Delta F^{\pm}$ results from interaction of the amine side chain and aryl ring. Additions to the ester side chain thus appear to serve more for positioning than for binding.

Employing the second approach, we may consider the reactions of decyl- and ethylamine with PNPD or E8-Oct. For these reactions, increments in $\Delta\Delta F^{\pm}$ of -493 cal/mole per methylene for the former and -250 cal/mole per methylene for the latter are obtained. Both values are within the range of values for either insertion into a micelle or for minimal contact, as in a complex. Comparing these to the values calculated above, we find contributions of $\Delta\Delta F^{\pm}$ of $-493 + 92 = -401$ cal/mole per methylene for PNPD and $-250 + 190 = -60$ cal/mole per methylene for E8-Oct for binding of the amine side chain to the ester head group; again, the remainder of the binding energy is then used for positioning of the nucleophile within the complex.

Finally, we must consider the nature of the differences in aminolysis rates between corresponding 8- and 6-quinolyl esters. A distinction in mechanism for nucleophilic attack on E8-Ac and E6-Ac has been made[3] by plotting log k_n for nucleophilic attack on the former *vs.* log k_n for the latter. It was observed that the points for water and all primary and secondary amines fall on a line provided by eq 13, while the points for tertiary

$$\log k_{n8} = 0.7 \log k_{n6} + 0.9 \quad (13)$$

amines and hydroxide fall on a separate line provided by eq 14. It may then be argued that the difference in

$$\log k_{n8} = 1.0 \log k_{n6} - 0.6 \quad (14)$$

mechanism for the two esters is best attributed to intramolecular general base catalysis for the reaction of E8-Ac with water and primary and secondary amines, and simple nucleophilic attack for the reaction of all nucleophiles with E6-Ac, and hydroxide and tertiary amines with E8-Ac.

In Figure 4 is shown the plot from ref 3, with the addition of the data from this study. The values of k_{OH} for E8-Oct and E6-Oct are seen to fall on the line given by eq 14, indicating that lengthening the ester side chain from acetate to octanoate has approximately the same effect for both esters; this observation provides justification for placing data for the octanoates on a plot derived from results with acetates. The values of k_n for reaction of the five amines with E8-Ac and E6-Ac and with E8-Oct and E6-Oct are found to fall either on or very close to the line given by eq 13, indicating that, for all the amines examined, the preferred mechanism for reaction with the 8-quinolyl esters is intramolecular general base catalysis of nucleophilic attack. The fact that the values of k_n for the longer amines fall on the line also indicates that either the dissociation constants for the amine–ester complexes or the contribu-

(34) H. W. Hoyer and A. Greenfield, *J. Phys. Chem.*, **61**, 818 (1957).
(35) A. Vies and C. W. Hoerr, *J. Colloid Sci.*, **15**, 427 (1960).
(36) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 11.
(37) P. Molyneux, C. T. Rhodes, and J. Swarbick, *Trans. Faraday Soc.*, **61**, 1043 (1965).
(38) G. Némethy and H. Scheraga, *J. Phys. Chem.*, **66**, 1773 (1962).
(39) C. Gitler and A. Ochoa- Solano, *J. Amer. Chem. Soc.*, **90**, 5004 (1968).
(40) R. G. Shorentstein, C. S. Pratt, C.-J. Hsu, and T. E. Wagner, *ibid.*, **90**, 6199 (1968).

tions in stability to the transition states must be very similar for the 6- and 8-esters; this should not be surprising, since the sizes and shapes of each pair of esters should be similar. Thus, in light of the results discussed in ref 4, it would appear that this is the first documented case of an intracomplex general base-catalyzed esterolytic reaction in water.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

Appendix

In the catalysis of the hydrolysis of *p*-nitrophenyl hexanoate (PNPH) by mixed micelles of N^{α}-myristoylhistidine (NMH) and cetyltrimethylammonium bromide (CTABr)[39] the authors postulate an active region (Ma) of the micelle in which bimolecular reaction with ester occurs, and an inactive region (Mi) in which the ester is protected from hydrolysis, as in eq A-1.

$$\text{Mi} + \text{ester} \underset{K_1}{\rightleftharpoons} \text{Mi}\cdot\text{ester} \qquad \text{(A-1a)}$$

$$\text{Ma} + \text{ester} \xrightarrow{k_1} \text{products} \qquad \text{(A-1b)}$$

It was assumed that the rate enhancement was a result of interaction between the acyl chain of the ester and that of the NMH; this feature may be taken into account by substituting eq A-2 for A-1b. In this

$$\text{Ma} + \text{ester} \underset{K_2}{\rightleftharpoons} \text{Ma}\cdot\text{ester} \qquad \text{(A-2a)}$$

$$\text{Ma}\cdot\text{ester} \xrightarrow{k_2} \text{products} \qquad \text{(A-2b)}$$

scheme, k_2 is now a first-order rate constant.

The arbitrary separation of the micelle into active and inactive portions is open to question; a micelle is a highly mobile system undergoing rapid positional changes of monomer within the micelle and rapid interchange of aggregated monomer with monomer in the bulk phase,[41,42] so that

$$\text{Mi} \underset{}{\overset{K_e}{\rightleftharpoons}} \text{Ma} \qquad \text{(A-3)}$$

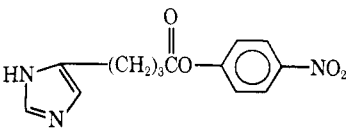
Incorporating this feature, we find that, for $[M_T] = [Mi] + [Ma]$ eq A-4 obtains. Equation A-4 is now kinetically equivalent to the rate expression for the mechanism of A-1.

$$k_{obsd} = \frac{\dfrac{k_2K_1K_e}{(K_2 + K_1K_e)}[M_T]}{\dfrac{K_1K_2(K_e + 1)}{(K_2 + K_1K_e)} + [M_T]} \qquad \text{(A-4)}$$

A much simpler mechanism, kinetically equivalent to eq A-4,[43] is provided by eq A-5, for which no as-

$$M_T + \text{ester} \underset{}{\overset{K_m}{\rightleftharpoons}} M_T\cdot\text{ester} \xrightarrow{k_r} \text{products} \qquad \text{(A-5)}$$

sumptions are required since it has been demonstrated that ester *is* incorporated into micelles;[39] furthermore, all experimental evidence can be explained by A-5. The authors'[39] primary objection to schemes incorporating eq A-2 or A-5 is that these schemes predict saturation kinetics, which were not observed. Failure to observe saturation kinetics could result from a value of $1/K_m$ larger than the concentration of ester or ligand. This would not be surprising, considering the shortness of the acyl chains used in the study (C_1–C_6). It is instructive to note that the ratio of k_1 for the reaction of NMH with PNPH to k_1 for the reaction of N^{α}-acetylhistidine with PNPH[39] is essentially identical with the ratio of the first-order rate constant[44] for the hydrolysis of VI to the second-order rate constant for reaction of PNPA with imidazole. Moreover, the



VI

ratio of the rate constant (quoted as a second-order rate constant) for reaction of N^{α}-stearoylhistidine with *p*-nitrophenyl *N*-dodecyl-*N*,*N*-dimethylammonioethyl carbonate bromide in an assumed 1:1 complex to the second-order rate constant for reaction of N^{α}-acetylhistidine (NAH) with the same ester is identical with the ratios discussed above. It is apparent that the rate increase associated with approximation of an imidazole nucleophile and an ester within the mixed micelle is very much the same as that for conversion of a bimolecular to an intramolecular imidazolyl catalyzed reaction in which nucleophile and ester bond are not restricted, by structural features, to be in close approximation.

(41) G. C. Kresheck, E. Hamori, G. Davenport, and H. A. Scheraga, *J. Amer. Chem. Soc.*, **88**, 246 (1966).

(42) B. C. Bunnion, L. K. J. Tong, L. P. Holmes, and E. M. Eyring, *J. Phys. Chem.*, **73**, 3288 (1969).

(43) T. Maugh II, Ph.D. dissertation, University of California, Santa Barbara, 1970. A critical discussion of the results of ref 40 and 41 may also be found in the dissertation.

(44) T. C. Bruice and J. M. Sturtevant, *J. Amer. Chem. Soc.*, **81**, 2860 (1959).