Nucleophilic Micelles. II. The Effect on the Rate of Solvolysis of Neutral, Positively, and Negatively Charged Esters of Varied Chain Length when Incorporated into Nonfunctional and Functional Micelles of Neutral, Positive, and Negative Charge

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Abstract: Phenyl esters of carboxylic acids of varied chain length have been synthesized (compounds I–IV). The phenyl head groups of esters I–IV possess the charged groups $-N^+(CH_3)_3$ and $-SO_3^-$ *para* to the ester moiety. The rate constants for the alkaline hydrolysis of esters I–IV were determined in the absence and presence of the neutral, negatively, and positively charged micelle-forming agents of VIII. The second-order rate constants for alkaline hydrolysis, in the absence of agents VIII, were found to vary as anticipated on the basis of the influence of electronic effects of substituents on the phenyl ring and the steric effect of the aliphatic chain. In all cases examined, increase in concentration of the micelle-forming agents of VIII resulted in a decrease of the observed rate constants for alkaline hydrolysis of the esters. These results establish that formation of salts, premicelles, and micelles of esters and detergents decreases the availability of the ester to nucleophilic attack by OH^-. The secondary amines of structures V–VII have been synthesized. Agents V–VII are N-*n*-alkyl-N-benzylamines in which the benzyl head groups are *para* substituted by the substituents –H, $-N^+(CH_3)_3$, and $-SO_3^-$ and the *n*-alkyl groups are of varied chain length. When *n*-alkyl = $(CH_2)_3CH_3$ and the substituent on the benzyl group is –H or $-N^+(CH_3)_3$, the disappearance of esters from solution is found to be first order in ester and first order in amine. However, when *n*-alkyl = $(CH_2)_9CH_3$ and the *para* substituent = $-N^+(CH_3)_3$, the rate of disappearance of ester from solution was found to be first order in ester and between first and fourth order in amine (depending on the ester) at low concentrations of amine and zero order (k_{p1}) in amine at higher concentrations of amine. Plots of log k_{p1} *vs.* pH have been found to resemble the pH profiles anticipated for formation of complexes, premicelles, and micelles containing ester and total amine (*i.e.*, amine plus conjugate acid in a ratio of 1:1 to 1:5, followed by reaction of ester with the amine free base species of the complex). The reactions of esters with amines is assumed to be an aminolysis reaction on the basis of deuterium solvent kinetic isotope effects though product analyses were not possible. The results are discussed with the model of structure IV in mind which considers electrostatic attraction of the charged head groups of amine and ester and lyophobic bonding of the *n*-alkyl groups of amine and ester.

The bringing together of catalyst and substrate to form a complex undoubtedly accounts for much of the efficiency of enzymatic reactions.[2] In the past, considerable effort has been expended in the syntheses and kinetic studies of intramolecular models in which a catalytic group (carboxyl, imidazole, hydroxyl, amino, amido, imide, etc.[2]) is placed in juxtaposition to a labile substrate bond in a single molecule. While these systems have been of great value in determining the rate enhancement that may be obtained on conversion of a bimolecular reaction into an intramolecular or intracomplex reaction (as in the ES complex) they suffer in that no catalytic turnover is obtained. This objection is overcome in models in which catalyst and substrate are brought together by complexation, etc. Reactions in which close association of reactants occurs prior to reaction are found in processes in frozen solution,[3-10] in inclusion compounds,[11-19] and in complexes of reactants.[20] Rates of reactions occurring in micellar solutions may be increased by including both reactants in or on the micelle or decreased by excluding one.[21-24] The influence of micellarization of a substrate on the rate constants for its hydrolysis has also been investigated.[25]

Since micelles have structure[26] it should, in principle, be possible to design a micelle possessing catalytic sites and a relative specificity toward a substrate of designated structure. Approaches to this problem appear particularly worthy since in both micelle and enzyme structure the nonpolar functional groups are located mainly in interior lyophobic regions while the polar

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functional groups are predominantly at the periphery.[26-28]

Experimental Section

Materials. Sodium lauryl sulfate and cetyltrimethylammonium sulfate were commercial samples recrystallized by the procedures of Duynstee and Grunwald.[21] The nonionic detergent, composed of dodecylphenol condensed with 18 molecules of ethylene oxide, was a gift from Professor E. H. Cordes who obtained the material as a gift of the General Aniline and Film Corp. Potassium chloride was Baker and Adamson Reagent A grade and tetramethylammonium bromide was Eastman White Label. *p*-Nitrophenyl acetate was that prepared for a previous study.[29] *o*-Nitrophenyl acetate was prepared by the mixed anhydride method employing trifluoroacetic anhydride, mp 39–40° (lit.[30] 40.5–41°). *p*-Hydroxyphenyltrimethylammonium chloride was prepared by a literature procedure.[31] Inorganic salts were Baker Analyzed Reagent grade. Carbonate free potassium hydroxide was prepared by the method of Albert and Serjeant.[32] All compounds employed in this study were stored over P_2O_5 until used.

Sodium 3-nitro-4-hydroxybenzenesulfonate was prepared from 2-nitrophenyl (Eastman) and chlorosulfonic acid by the method of Gnehm and Krecht.[33] The sulfonic acid was converted to the sodium salt by precipitation from saturated sodium chloride solution.

Fatty acid esters of sodium 3-nitro-4-hydroxybenzenesulfonate or sodium 4-hydroxybenzenesulfonate were prepared by the following general procedure.[34] Equimolar quantities of trifluoroacetic anhydride and fatty acid were allowed to react at room temperature for 30 min; a 0.5 *M* quantity of phenol was added with stirring and the mixture heated at 80° for 5 hr. The cooled reaction mixture was washed with ether to remove excess mixed anhydride and the residue recrystallized from methanol–ether or 70% aqueous methanol and ether. Nitrophenyl esters are pale yellow in color and esters of sodium 4-hydroxybenzenesulfonate are white. The esters are water soluble but easily salted out of solution by sodium chloride. The ester carbonyl band in the infrared appears at 1775 cm^{-1}; the compounds froth when vigorously shaken in water and form hydrates when exposed to air. Analyses were obtained on samples that were quantitatively dried before determinations.[35]

Sodium 3-Nitro-4-hexanoyloxybenzenesulfonate (NE_5^-). *Anal.* Calcd for $C_{12}H_{14}NO_7SNa$: C, 42.50; H, 4.15; N, 4.13. Found: C, 42.11; H, 4.39; N, 4.32.

Sodium 3-Nitro-4-octanoyloxybenzenesulfonate (NE_7^-). *Anal.* Calcd for $C_{14}H_{18}NO_7SNa$: C, 45.77; H, 4.94; N, 3.81. Found: C, 45.50; H, 5.24; N, 3.74.

Sodium 3-Nitro-4-decanoyloxybenzenesulfonate (NE_9^-). *Anal.* Calcd for $C_{16}H_{22}NO_7SNa$: C, 48.60; H, 5.56; N, 3.54; S, 8.11. Found: C, 48.61; H, 5.67; N, 3.89; S, 7.81.

Sodium 3-Nitro-4-hexadecanoyloxybenzenesulfonate (NE_{15}^-). *Anal.* Calcd for $C_{22}H_{34}NO_7SNa$: C, 55.10; H, 7.09; N, 2.92; S, 6.68. Found: C, 54.70; H, 7.42; N, 3.11; S, 6.43.

Sodium 4-Acetoxybenzenesulfonate (E_1^-). *Anal.* Calcd for $C_8H_7O_5SNa$: C, 40.44; H, 2.94; S, 13.44. Found: C, 40.19; H, 3.13; S, 13.48.

Sodium 4-Decanoyloxybenzenesulfonate (E_9^-). *Anal.* Calcd for $C_{16}H_{23}O_5SNa$: C, 54.85; H, 6.62; S, 9.15. Found: C, 54.98; H, 6.45; S, 9.30.

Sodium 3-nitro-4-acetoxybenzenesulfonate (NE_1^-) was prepared by refluxing 1 g (0.00415 mol) of sodium 3-nitro-4-hydroxybenzenesulfonate and 25 ml of acetic anhydride for 15 hr. The mixture was filtered and the precipitate crystallized from glacial acetic acid. A 92.5% yield of pale yellow solid was obtained. The compound did not melt below 300°. *Anal.* Calcd for $C_8H_6NO_7NaS$: C, 33.93; H, 2.14; N, 4.93. Found: C, 33.81; H, 2.28; N, 4.93.

4-Decanoyloxyphenyltrimethylammonium chloride (E_9^+) was prepared from decanoic acid and 4-hydroxy-3-trimethylammoniumphenyl chloride in the same manner as NE_1^-. The product was recrystallized from 75% ethanol–water and methanol–ether solvent pairs, mp 135–137°. *Anal.* Calcd for $C_{19}H_{32}NO_2Cl$: C, 66.56; H, 9.42; N, 4.12. Found: C, 65.66; H, 9.26; N, 3.84.

***p*-Trimethylammoniobenzylbutylamine Chloride Hydrochloride** (A_4^+). *p*-Carboxaldophenyltrimethylammonium iodide (CPTA) was prepared by the procedure of Hodgson and Cooper,[36] mp 149–152° (lit.[36] 152°). The infrared spectrum showed bands at 1700 (C=O) and 1605 cm^{-1} (C=C). A mixture of 8.73 g (0.03 mol) of CPTA and 2.92 g (0.04 mol) of *n*-butylamine (Eastman) in 50 ml of absolute methanol was refluxed for 0.5 hr, condensed to half its volume, cooled, layered with ether, and the precipitate collected. The crude *n*-butylimine of CPTA, 10.3 g, mp 144–146°, showed infrared bands at 1645 (C=N) and 1605 cm^{-1} (C=C). The imine was reduced with potassium borohydride by the method of Billman and Diesing.[37] Potassium borohydride (1.01 g, 0.0188 mol) was added with stirring to 6.5 g (0.0188 mol) of the imine in 25 ml of absolute methanol and the reaction allowed to proceed at ambient temperature until effervescence ceased. The solution was then refluxed for 1 hr, cooled, filtered, evaporated to one-third its volume *in vacuo*, and filtered to remove inorganic material. Saturated methanolic hydrogen chloride was added to the residue and the solution evaporated to dryness on a steam bath. The residue was dissolved in methanol and decolorized with Norit. The solution was layered with ether and cooled in a refrigerator, yielding a white solid which, after successive crystallizations and drying over P_2O_5 melted at 179–180°. The infrared spectrum showed a broad band *ca.* 3100–3200 cm^{-1} (NH^+) and the absence of the 1645-cm^{-1} band characteristic of the imine. Secondary amine chloride hydrochloride (5.2 g, 98%) was obtained. *Anal.* Calcd for $C_{14}H_{26}N_2Cl_2 \cdot 0.5\ H_2O$: C, 55.62; H, 9.00; N, 9.27. Found: C, 55.51; H, 9.24; N, 8.89.

N-Acetyl-N-(*p*-trimethylammoniobenzyl)butylamine Iodide. *p*-Dimethylaminobenzaldehyde (14.9 g, 0.1 mol) was refluxed with 7.3 g (0.1 mol) of butylamine in 100 ml of absolute methanol for 6 hr. After cooling the reaction solution was evaporated on a steam bath *in vacuo* and the yellow residue distilled to yield 15.4 g (75%) of the imine (bp 113° (0.35 mm)).

To a solution of the imine (10 g, 0.05 mol) dissolved in 50 ml of absolute methanol was added 5.4 g (0.1 mol) of potassium borohydride. After 3 hr the reaction solution was refluxed for 1 hr and solvent removed *in vacuo*. The crude amine was extracted from the residue with absolute ether and after evaporation of all solvent distilled at 125° (1.5 mm), yielding 8 g (76% yield) of *p*-dimethylaminobenzylbutylamine.

A solution of this amine (5 g, 0.025 mol) in 50 ml of chloroform containing 10 ml of acetic anhydride and a few drops of pyridine was stirred for 24 hr at room temperature. Solvent was removed *in vacuo* and the residue distilled (190° (3.75 mm)) to yield 5.2 g (86%) of the acetylated amine.

N-Acetyl-N-(*p*-dimethylaminobenzyl)butylamine (5 g, 0.0201 mol) was dissolved in dry benzene (40 ml) and 10 ml of methyl iodide added. The reaction solution was refluxed for 20 hr and cooled and the precipitate collected and crystallized from methanol–ether yielding 7.4 g (94%) of N-acetyl-N-(*p*-trimethylammoniobenzyl)butylamine iodide, mp 147°. *Anal.* Calcd for $C_{16}H_{29}N_2OI$: C, 49.23; H, 6.92; N, 7.17; I, 32.56. Found: C, 49.18; H, 7.29; N, 7.02; I, 32.53.

***p*-Trimethylammoniobenzyldecylamine Chloride Hydrochloride** (A_{10}^+). Equimolar amounts of *p*-carboxaldophenyltrimethylammonium iodide (28 g) and decylamine (15.7 g) (Eastman) were refluxed for 1 hr in 100 ml of absolute methanol, evaporated to *ca.* 50 ml, cooled, filtered, and layered with ether; the resulting solid was collected. The crude *p*-trimethylammoniobenzaldecylimine iodide, 41 g, mp 136–137°, showed a band in the infrared spectrum at 1665 cm^{-1} (C=N). The imine (8.6 g) was treated with an equimolar amount of potassium borohydride in 100 ml of absolute methanol. A calcium chloride drying tube was attached and the solution allowed to stand for 15 hr at room temperature, at which time isolation of a small amount of the material showed the absence of the 1655-cm^{-1} (C=N) band. The solution was saturated with hydrogen chloride gas and the resulting inorganic material filtered off.

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The solution was concentrated to about 30 ml, resaturated with hydrogen chloride, filtered, evaporated to dryness, and decolorized with Norit in methanol. Layering with ether and cooling for a day produced a two-phase system; the oily lower layer was dispersed into the methanol–ether by vigorous shaking. Additional cooling yielded a white solid, which was recrystallized from methanol–ether and dried over P_2O_5 (2.5 mm, 20 hr), yielding 4.2 g (56%), mp 179–180°. *Anal.* Calcd for $C_{20}H_{33}Cl_2N_2$: C, 63.66; H, 10.15; N, 7.43. Found: C, 63.01; H, 10.17; N, 7.42.

4-Hydroxy-3-nitrophenyltrimethylammonium Iodide. A solution of 15.3 g (0.1 mol) of 4-amino-2-nitrophenol and 32 g (0.4 mol) of sodium acetate in 200 ml of absolute methanol was brought to pH 3.5 by addition of glacial acetic acid. After addition of 50 ml of methyl iodide the solution was refluxed for 36 hr, the solution was cooled, and the resulting crude product collected by filtration and recrystallized once from water, yielding 22 g (68% yield) of the product as lustrous orange needles, mp 220°. *Anal.* Calcd for $C_9H_{13}N_2O_3I$: C, 33.33; H, 4.01; N, 8.64; I, 39.19. Found: C, 33.11; H, 4.15; N, 8.72; I, 39.24.

All efforts to obtain the product by methylation of 4-amino-3-nitrophenol either with methyl iodide or dimethyl sulfate at pH values between 6 and 8 or by direct nitration of 4-hydroxyphenyltrimethylammonium iodide were unsuccessful.

Fatty acid esters of 4-hydroxy-3-nitrophenyltrimethylammonium iodide were prepared according to the procedure previously described for the preparation of esters of 3-nitro-4-hydroxybenzenesulfonate. Recrystallization of the products from ethanol–water (50% v/v) provided lemon yellow needles. The ester carbonyl band in the infrared appears at 1775 cm^{-1}. Analytical samples were dried *in vacuo* at 100° over P_2O_5 to constant weight.

3-Nitro-4-acetoxyphenyltrimethylammonium iodide (NE_1^+) melted at 152–155°. *Anal.* Calcd for $C_{11}H_{15}N_2O_5I$: C, 36.06; H, 4.09; N, 7.65. Found: C, 36.24; H, 4.37; N, 7.62.

3-Nitro-4-octanoyloxyphenyltrimethylammonium iodide (NE_7^+) melted at 131–133°. *Anal.* Calcd for $C_{17}H_{25}N_2O_5I$: C, 45.33; H, 6.00; N, 6.20. Found: C, 44.99; H, 5.92; N, 5.95.

Benzylbutylamine Hydrochloride (A_4^0). A solution of 10.6 g of benzaldehyde (0.1 mol) and 8 g of butylamine (0.109 mol) in 100 ml of absolute methanol was refluxed for 8 hr, and evaporated *in vacuo* to provide benzalbutylimine as a yellow oil. The imine (8.1 g) was reduced with a slight excess of potassium borohydride in the same manner as A_4^+, and the amine recrystallized from methanol to yield 6.7 g (67% over-all), mp 190° dec. *Anal.* Calcd for $C_{11}H_{18}\cdot HCl$: C, 66.16; H, 9.02; N, 7.17; Cl, 17.71. Found: C, 65.76; H, 9.20; N, 7.10; Cl, 18.43.

Apparatus. A Zeiss PMQ II spectrophotometer equipped with a brass cuvette holder through which was circulated water at 30 ± 0.1° and a Gilford 2000 recording spectrophotometer equipped with double thermospacers were used for those kinetic studies based on the rate of appearance of absorbing product. For rate determinations dependent upon liberation of protons, a Radiometer TTT 1b autotitrator and a Radiometer SBR 2c titrigraph were employed. The reaction cell was of 25-ml volume and water jacketed. The ground top of the reaction cell was equipped with ground ports which accommodated a thermometer, capillary buret, N_2 inlet and outlet, Metrohm type X ground glass electrode, and a salt bridge fitted with an asbestos wick leading to a calomel electrode. pH measurements were made with a Radiometer Model 22 pH meter equipped with a Model PHA 630 Pa scale expander. The combined glass–calomel electrode (Radiometer G.K. 2021C) and cell compartment were thermostated at the same temperature employed for all kinetic measurements. pK_a' measurements were made using a Radiometer TTT 1b autotitrator equipped with a Model PHA 630 Ta scale expander and the thermostated Metrohm microtitration cell and assembly described by Bruice and Bradbury.[38]

Kinetics. Ester was added as an aqueous solution from a micrometer syringe to solutions of amine of appropriate pH contained in ground cuvettes of 2–2.5-ml capacity, air was displaced, with N_2, and the reaction solution was mixed by inverting the stoppered cuvette. The appearance of substituted phenolate anion with time was followed spectrophotometrically (410 mμ for 2-nitrophenol-4-sulfonate). The amines employed supplied their own buffer capacity, and solutions were brought to the desired calculated ionic strength with KCl except where otherwise stipulated. All solutions were prepared from doubly glass-distilled water. In both the spectrophotometric and autotitrimetric rate determinations, the concentration of nucleophile was either constant (OH^-), or in excess (amines) of the concentration of ester (*ca.* 10^{-5} *M*) so that *pseudo*-first-order kinetics were obtained. Reaction rates were generally followed to at least three half-times. The pH of each solution was determined at the beginning of each run and was periodically checked after some runs to ensure constancy of pH. In the case of the micelle-forming agents not containing ionizable functional groups of pK_a' in the pH region of interest, buffering was supplied by a pH-Stat. Pseudo-first-order rate constants were calculated from slopes of log $(X_\infty/(X_\infty - X_t))$ *vs.* time where X refers to either OD or units of base added. All actual computations were carried out on either an IBM 1620 or an Olivetti-Underwood Programma 100 computer employing programs written by Dr. Donald Tanner, formerly of this laboratory.

pK_a' Determinations. The pK_a' of *p*-trimethylammoniobenzylbutylamine chloride hydrochloride was determined by both potentiometric titration[32] and by half-neutralization (30°, total amine at 0.05 and 0.01 *M*). The pK_a' value determined by both methods was found to be 8.87 ± 0.02 (in D_2O 9.46 ± 0.02 employing the proper electrode correction[39]) at μ = 0.1 and 8.91 ± 0.02 at μ = 0.5.

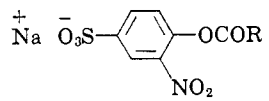
The pK_a of N-benzylbutylamine was determined potentiometrically at 0.05 *M*. The pK_a' value was calculated from ten titration points in the range of pH 7.33–9.05. Above pH 9.1 precipitation occurs. The pK_a' value so determined was found to be 9.76 ± 0.01.

The pK_a' values of *p*-trimethylammoniobenzyldecylamine chloride hydrochloride as a function of amine concentration were determined by half-neutralizing a 0.05 *M* solution of the salt (μ = 0.1 with KCl) and performing a serial dilution with 0.1 *M* KCl to provide a series of solutions 0.05–0.003 *M* in total amine. The pH of each solution was then taken as the pK_a' at that concentration. The variation of pK_a (pH) as a function of concentration is shown in Figure 4.

Product Analysis. Various modifications of the hydroxamic acid method as developed for amides[40] and employing N-acetyl-N-(*p*-trimethylammoniobenzyl)butylamine iodide as standard were employed. However, because of the ϵ of the colored products produced from the liberated phenols and the small color yield from the standard, no satisfactory procedure could be found to assay for acetylated secondary amines. Thus, we can not, on the basis of product analysis state that the reaction of amines with esters in this study produces amides.

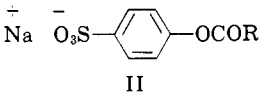
Results

Esters were generally prepared by reaction of the appropriate phenol and carboxylic acid in trifluoroacetic anhydride. Amines were obtained by condensing the appropriately substituted benzaldehyde and primary amine, and reduction of the resultant imine with potassium borohydride.



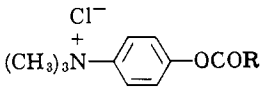
I

NE_1^-, R = CH_3
NE_5^-, R = $(CH_2)_4CH_3$
NE_7^-, R = $(CH_2)_6CH_3$
NE_9^-, R = $(CH_2)_8CH_3$
NE_{15}^-, R = $(CH_2)_{14}CH_3$



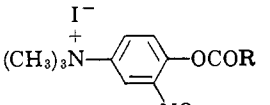
II

E_1^-, R = CH_3
E_9^-, R = $(CH_2)_8CH_3$



III

E_9^+, R = $(CH_2)_8CH_3$



IV

NE_1^+, R = CH_3
NE_7^+, R = $(CH_2)_6CH_3$

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Table I. The Effect of Initial Ester Concentration on the Pseudo-First-Order Rate Constants for Hydrolysis

NE_7^- pH 10.2 μ = 0.1		E_9^- pH 10.6 μ = 0.1		E_9^+ pH 10.16 μ = 0.1	
Concn, $M \times 10^5$	k_{obsd}, min^{-1}	Concn, $M \times 10^5$	k_{obsd}, min^{-1}	Concn, $M \times 10^5$	k_{obsd}, min^{-1}
1.25	0.123	2.58	0.124	2.56	0.130
2.08	0.156	5.2	0.126	4.27	0.152
4.16	0.157	7.8	0.124	17.1	0.121
6.25	0.187	10.4	0.125	42.7	0.147
8.33	0.185	13.0	0.102	150	0.146
12.6	0.187	13.0	0.089	275	0.133
18.8	0.205	13.0	0.088	329	0.097
31.3	0.182	18.0	0.104	490	0.071
40.6	0.185	130	0.101	613	0.045
50.0	0.179	180	0.080		
62.5	0.159	342	0.096		
72.9	0.168				
83.3	0.158				

linear Beer plots in the range of concentrations that were employed in this study at 0.1–0.5 μ, indicating that the esters either do not aggregate in the concentration range employed or that aggregation is not accompanied by a change in absorbance.

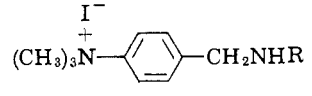
Aggregation of ester would be anticipated to be reflected in the rate of ester hydrolysis; in Table I are listed hydrolytic pseudo-first-order rate constants (k_{obsd}) for three esters at constant pH and ionic strength but varying initial ester concentration. Inspection of Table I reveals that in the approximate concentration range 10^{-5}–10^{-3} M no appreciable change in k_{obsd} is noted for the hydrolysis of NE_7^-. The average deviation of the values of k_{obsd} (0.172 ± 0.016; 9.3%) is about that anticipated when working at high pH values on the pH-Stat. For esters E_9^- and E_9^+, however, aggregation is possibly indicated at concentrations of about 1×10^{-4} and 3×10^{-2} M, respectively. However, these concentrations exceed those employed in all the kinetic studies described in this paper.

Table II. Rate Constants for the Alkaline Hydrolysis of Esters in the Absence of Micelle-Forming Agents[a]

Ester	Initial concn, $M \times 10^5$	pH	No. of k_{obsd} values determined	μ	Slope of plot of log k_{obsd} *vs.* pH	k_{OH}, l. mol^{-1} min^{-1}	k_{OH}/k_{OD}
NE_1^-	17.1	8.00–10.1	8	0.1	0.964 ± 0.044	2242	
	17.1	8.50–10.4	4	0.5	0.971 ± 0.11	2021	0.44
NE_5^-	9.5–17.1	8.00–10.1	8	0.1	0.972 ± 0.07	1053	
	17.1	8.77–10.4	7	0.5	0.983 ± 0.038	850	0.64
NE_7^-	5.0–19.8	8.53–10.5	9	0.1	0.975 ± 0.047	848	
	15.6	9.05–9.9	3	0.5	0.948 ± 0.008	589	0.88
NE_9^-	17.1	9.07–10.31	4	0.1	0.996 ± 0.12	340[b]	
E_1^-	5.0–17.1	9.0–10.5	6	0.1	0.990 ± 0.055	257	
	17.1	9.05–10.4	4	0.5	0.961 ± 0.206	312	
E_9^-	5–14	9.05–10.5	6	0.1	1.036 ± 0.152	219	
	14.2	9.0–10.41	4	0.5	0.944 ± 0.101	177	
E_9^+	4.9–17.1	9.03–10.34	8	0.1	1.034 ± 0.080	567	
	17.1	9.03–10.43	5	0.5	1.173 ± 0.070	422	0.76
NE_1^+	7	8.55–9.12	2	0.1		7270	
NE_7^+	6	8.54–9.40	2	0.1		2850	

[a] Most k_{obsd} values were obtained on the pH-Stat, and some were obtained spectrophotometrically extrapolating to zero buffer concentration. Buffers were amines employed in this study. [b] NE_9^- was not sufficiently soluble at μ = 0.5.

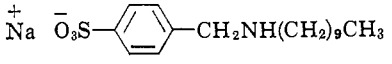
The amine A_{10}^- (preparation not included in the Experimental Section) proved too insoluble to employ as a nucleophilic micelle-forming agent.



V

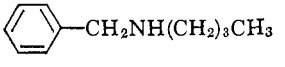
A_4^+, R = $(CH_2)_3CH_3$

A_{10}^+, R = $(CH_2)_9CH_3$



VI

A_{10}^-



VII

A_4^0

Alkaline Hydrolysis of Esters. Determination of the rate constants for the alkaline hydrolysis of the various charged esters and some knowledge of their physical state in solution was a prerequisite to the study of the rates of their hydrolyses in the presence of micelle-forming agents. Esters NE_7^-, E_1^-, and E_9^- exhibit

The values of the second-order rate constants for alkaline hydrolysis of the esters are provided in Table II at μ = 0.1 and 0.5. Ester NE_{15}^- proved too insoluble in water to determine its rate of alkaline hydrolysis in the absence of added detergent. Plots of k_{obsd} *vs.* pH (not shown) were found to be linear in the alkaline pH range employed showing that spontaneous hydrolysis is unimportant. The slopes of plots of log k_{obsd} *vs.* pH were found to be between 0.948 and 1.17 in good agreement with the theoretical value of 1.0. The per cent mean deviations of the points from the best least-square line were found to be between 0 and 14% depending upon the ester (Table II). Change in μ from 0.1 to 0.5 causes a decrease in k_{OH} of 10–20% for all esters but E_1^-, in accord with an anticipated salting out of the ground state. Ester NE_9^- is visibly salted out of solution on increase of μ to 0.5 with KCl.

The decrease in rate with chain length is as anticipated from steric considerations.[41] The greater sensitivity of the NE_n^- esters (NE_1^-:NE_5^-:NE_7^-:NE_9^- = 1.0:0.44:0.36:0.14) to chain length as compared to the

(41) M. S. Newman in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 4.

E_n^- esters (E_1^-:E_9^- = 1.0:0.85) may be related to the greater steric requirements of the transition states for hydrolysis of the former due to the presence of the *o*-nitro group. The greater rate constants for the esters NE_1^- and NE_9^- compared to E_1^- and E_9^- is to be expected on the basis of the electron-withdrawing nature of the *o*-nitro group.

Hydrolysis of Esters in the Presence of Nonfunctional Micelles. Since our objective was to prepare micelles that would act as nucleophiles or nucleophilic catalysts after inclusion of substrate it was important to ascertain: (a) whether the various esters I to IV are incorporated into micelles; (b) how formal electrostatic charges on the ester and detergent affected incorporation of the ester; and (c) how incorporation into neutral, negatively, and positively charged micelles affects the rates of alkaline hydrolysis of the various esters. For this study, the following micelle-forming agents were chosen.

VIII

NDA^0 $HOCH_2CH_2(OCH_2CH_2)_{17}OC_6H_4(CH_2)_{11}CH_3$

LS^- $\overset{+}{N}aO_3SO(CH_2)_{11}CH_3$

CTA^+ $\bar{B}r(CH_3)_3\overset{+}{N}(CH_2)_{15}CH_3$

Pseudo-first-order rate constants for the hydrolysis of NE_5^- as a function of the concentration of NDA^0 at μ = 0.5 and pH 9.55 ± 0.02 were determined on the autotitrator and presented in Table III. From Table III it is seen that k_{obsd} is not influenced by NDA^0 until the agent reaches a concentration of *ca.* 5×10^{-4} *M*, approximately three times the initial concentration of ester (1.7×10^{-4}), and that the values of k_{obsd} decrease as [NDA^0] is further increased reaching a constant value at [NDA^0] = 0.952×10^{-2} to 4.76×10^{-2} *M*. This phenomenon may be attributed to either the formation of micelles of NDA^0 or the formation of a complex of NDA^0 and substrate. From the concentration of NDA^0 at which k_{obsd} becomes minimal it may be concluded that if a micelle is formed which incorporates ester this micelle must contain not more than 20 molecules of NDA^0 for each molecule of ester.

The following kinetic scheme pertains for complex formation

$$\begin{aligned} &\text{ester} + m\text{NDA}^0 \underset{K_1}{\rightleftharpoons} \text{ester-NDA}_m^0 \\ &\text{ester-NDA}_m^0 \xrightarrow{k_1} \text{hydrolytic products} \\ &\text{ester} \xrightarrow{k_{OH}[OH^-]} \text{hydrolytic products} \end{aligned} \quad (1)$$

for which

$$+\frac{d[P]}{dt} = \frac{k_1[\text{NDA}^0]^m + k_{OH}[OH^-]K_1}{K_1 + [\text{NDA}^0]^m}[\text{ester}_{total}] \quad (2)$$

and

$$k_{obsd} = \frac{k_1[\text{NDA}^0]^m + k_{OH}[OH^-]K_1}{K_1 + [\text{NDA}^0]^m} \quad (3)$$

A very reasonable fit of (3) to the kinetic data is obtained if m = 2, k_1 = 0.0034 min^{-1}, and the complex dissociation constant (K_1) is set equal to 8.47×10^{-7} *M* (see Table III). In (3) it is assumed that all NDA^0 is undissociated. This assumption is not serious for this particular case. If the decrease in rate of hydrolysis of NE_5^- on increase of NDA^0 concentration is due to incorporation of the ester into a micellar phase then the kinetics are probably best explained through a partition of ester between the bulk aqueous phase [E_{H_2O}] and the micellar phase [E_M].

Table III. Comparison of Determined and Calculated (eq 1-3) Rate Constants for the Hydrolysis of NE_5^- in the Presence of NDA^0 [a]

[NDA^0], $M \times 10^5$	k_{obsd} min$^{-1} \times 10^2$ Calcd	Found
0.0	4.86	4.86
23.8	4.57	4.67
47.6	3.91	4.67
72.0	3.14	3.42
95.2	2.95	2.30
140	1.70	1.34
238	0.92	1.15
336	0.65	0.726
576	0.46	0.556
952	0.38	0.384
2380	0.34	0.354
4760	0.34	0.340

[a] Initial ester concentration at 1.71×10^{-4}; pH 9.57; μ = 0.5.

$$\frac{[E_M](\text{vol bulk phase})}{[E_{H_2O}](\text{vol micellar phase})} = C' \quad (4)$$

The volume of the bulk phase may be considered a constant and the volume of the micellar phase (*i.e.*, micelle-forming agent plus trapped solvent, etc.) a function of some power of the concentration of micelle-forming agent.

$$\frac{[E_{H_2O}]([M_T] - \text{cmc})^n}{[E_M]} = C \quad (5)$$

At constant pH the hydrolysis of ester in both the micellar [E_M] and aqueous phases [E_{H_2O}] is pseudo first order

$$\begin{aligned} &E_{H_2O} \xrightarrow{k_{OH}[OH^-]} \text{product} \\ &E_M \xrightarrow{k_1} \text{product} \end{aligned} \quad (6)$$

so that

$$k_{obsd} = \frac{k_{OH}[OH^-]C + k_1([M_T] - \text{cmc})^n}{C + ([M_T] - \text{cmc})^n} \quad (7)$$

The similarity of eq 3 and 7 is obvious. If m = 2 and the total concentration of micelle-forming agent [M_T] ≫ critical micelle concentration (*i.e.*, cmc) then C is found to equal 8.47×10^{-7}.

In order to determine the cmc of NDA^0, the absorbance of a 0.0027% (w/v) solution of pinacyanol chloride (610 mμ at μ = 0.5) was determined as a function of NDA^0 concentration at pH 8.84 (Figure 1).[42] A comparison of Table III and Figure 1 reveals that the increase in absorbance of the dye begins in a range of NDA^0 concentrations lower than that noted for the decrease in the rate of hydrolysis of NE_5^-. This may be ascribed to a lessened partitioning of NE_5^- into the micelles (as compared to dye) or to an induced premicelle or salt formation of dye with NDA^0.[43]

The negative micelle-forming agent LS^- was investigated with both a positively charged ester (E_9^+) at pH

(42) M. L. Corrin, H. B. Klevins, and W. D. Harkins, *J. Chem. Phys.*, **14**, 480 (1946).

(43) P. Murkerjei and K. J. Mysels, *J. Amer. Chem. Soc.*, 77, 2937 (1955).

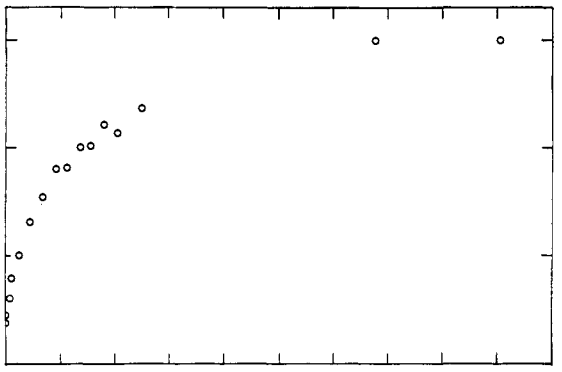


Figure 1. Absorbance of pinacyanol chloride [0.0027% (w/v); 610 mμ; μ = 0.5; pH 8.84] as a function of NDA^0 concentration. The values of OD were found to be constant from $[NDA^0] = 3.4 \times 10^{-3}$ to 9.6×10^{-3} *M* (last five points not shown).

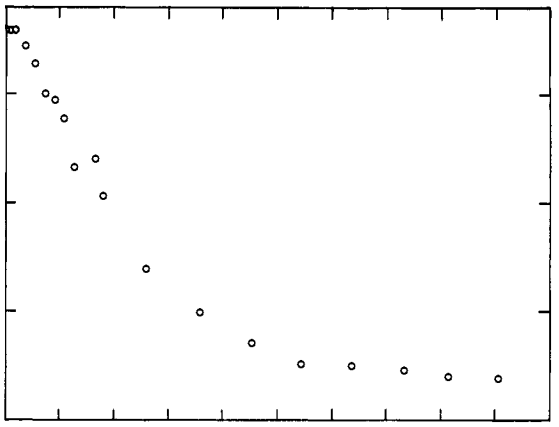


Figure 2. Absorbance of phenolphthalein [0.0022% (w/v); 560 mμ; μ = 0.5; pH 8.95] as a function of CTA^+ concentration.

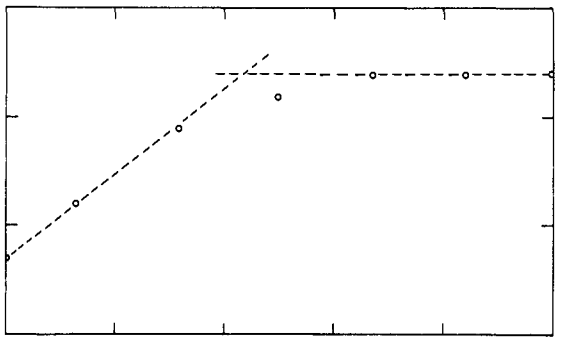


Figure 3. Dependence of the absorbance of NE_5^- on CTA^+ concentration (mμ = 250; pH 6.17; μ = 0.5).

9.60 and a negatively charged ester (NE_5^-) at pH 9.35 (μ = 0.1). It was found for both esters that at about the cmc of LS^- a precipitate is formed which is visible to the eye.[43,44] For NE_5^- no depression of rate is seen until $[LS^-] \cong 3[NE_5^-]$ at zero time (plot not shown) which is just prior to precipitate formation. In the case of E_9^+, a depression in k_{obsd} occurs before $[LS^-] = [ester]$ at zero time and continues until precipitation is noted. Earlier precipitation with NE_5^-, but greater rate depression with E_9^+ is in accord with lessened solubility of a double negatively charged ($LS\text{–}NE_5^{2-}$) complex which would have a formation constant smaller than the neutral complex ($LS\text{–}E_9$).

The influence of the concentration of the positively charged micelle-forming agent, CTA^+, on the rates of hydrolysis of negatively charged esters NE_1^-, NE_5^-, and NE_7^- was examined with the aid of the pH-Stat. At μ = 0.1, CTA^+ was found to have no effect on the hydrolysis of NE_5^-; at μ = 0.5, however, the rates of hydrolysis of the esters were depressed, attaining a constant value *when* $[CTA^+]$ *approximately equals concentration of ester* (1.7×10^{-4} *M*). The decrease in the rates of hydrolysis occurs before the cmc of CTA^+ ($\sim 4 \times 10^{-4}$ *M* at μ = 0.5 with KCl)[45] is reached. The absorbance of an 0.0022% (w/v) solution of phenolphthalein (560 mμ) as a function of $[CTA^+]$ at pH 8.95 and μ = 0.5 is shown in Figure 2. The absorbance of the indicator is seen to decrease precipitously at a concentration about 40 times less than the cmc of CTA^+ but at the same concentration at which the ester hydrolysis begins to decrease. One may therefore conclude that both ester and dye induce formation of micelles of CTA^+ or form salts with CTA^+ equally well. If the decrease in rate is due to salt formation, then there must be several molecules of ester per molecule of CTA^+ in the salt. Precedents exist for the formation of highly insoluble salts with detergents in greater than 1:1 ratio of reagent.[43] The kinetics for hydrolysis of the species E_mCTA^+ would, however, then be of the *m*th order in ester, whereas the hydrolysis is experimentally first order in ester regardless of $[CTA^+]$. The ratio of the rate constants at zero and high $[CTA^+]$ is about fivefold (Table IV). It is interesting to note that NE_9^-, though insoluble in water at μ = 0.5 (with KCl), is soluble if CTA^+ is present at a concentration greater than its cmc. The hydrolytic rates for NE_5^- as a function of $[CTA^+]$ were determined at three pH values (10.27 ± 0.02, 9.56 ± 0.03, and 8.77 ± 0.02). The dependence of the hydrolysis rate of NE_5^- on $[CTA^+]$ can be rationalized

Table IV. Ratio of k_{OH} Values for the Hydrolysis of Nitro-Substituted Esters in the Absence and Presence of High CTA^+ Concentrations (μ = 0.5)

Ester	k_{OH} l. mol^{-1} min^{-1} [CTA^+] = 0	k_{OH} l. mol^{-1} min^{-1} [CTA^+] = 0.0192 *M*	Ratio
NE_1^-	2021	434	4.6
NE_5^-	850	160	5.3
NE_7^-	589	127	4.6
NE_9^-	Insol	135	

via partitioning of the ester into the micellar phase by use of eq 7. A comparison of the values of k_{obsd} to those calculated from eq 7 when $m = 2$ or 3 and $[M_T] \gg$ cmc is provided in Table V. At a constant initial concentration of 1.61×10^{-4} *M* in NE_5^-, increase in $[CTA^+]$ brings about an increase in the optical density of the ester solution, reaching a constant value at high $[CTA^+]$. The dependence of the absorbance of NE_5^- on $[CTA^+]$ is shown in Figure 3. Inspection of Figure 3 reveals that the break in the curve of $[CTA^+]$ *vs.* absorbance of ester occurs at 1.1×10^{-4} *M* CTA^+, a concentration below that of the ester but which corresponds to the essentially complete incorporation of ester into a micellar phase of CTA^+ as predicted by eq 7 (Table

(44) E. D. Goddard, O. Harva, and T. G. Jones, *Trans. Faraday Soc.*, 49, 980 (1953).

(45) As extrapolated from the conductometric results of J. Steigman, I. Cohen, and F. Spingola, *J. Colloid Sci.*, 20, 732 (1965).

Table V. Comparison of Determined and Calculated Values of k_{obsd} for the Hydrolysis of NE_5^- at Three pH Values as a Function of CTA^+ Concentration (μ = 0.5 with KCl)

$[CTA^+] \times 10^5$ M	k_{obsd}	k_{obsd} calcd for m = 2	k_{obsd} calcd for m = 3
	A[a]		
0.0	4.46×10^{-2}	4.46×10^{-2}	4.46×10^{-2}
1.15	4.46	4.32	4.44
3.08	4.41	3.67	4.12
5.76	3.52	2.70	3.00
5.76	2.86	2.70	3.00
7.69	2.09	2.16	2.22
7.69	2.31	2.16	2.22
9.61	1.69	1.81	1.70
11.5	1.20	1.57	1.39
23.0	0.92	0.90	0.90
30.8	0.98	0.94	0.85
87.7	0.89	0.83	0.82
384	0.85	0.82	0.82
1900	0.82	0.82	0.82
2000	0.82	0.82	0.82
	B[a]		
0.0	7.4×10^{-3}	7.40×10^{-3}	7.4×10^{-3}
1.15	7.15	6.92	7.31
1.92	7.17	6.23	7.02
3.08	6.31	5.10	6.10
3.84	4.57	4.45	5.30
5.76	3.34	3.28	3.52
7.65	3.07	2.63	2.52
9.61	2.13	2.23	2.02
11.5	1.57	2.00	1.76
38.4	1.37	1.40	1.39
57.7	1.40	1.39	1.39
76.9	1.38	1.39	1.38
96.2	1.30	1.39	1.38
154	1.46	1.38	1.38
307	1.53	1.38	1.38
1150	1.38	1.38	1.38
1920	1.38	1.38	1.38
3800	1.38	1.38	1.38
19600	1.38	1.38	1.38
	C[a]		
0.0	23.2×10^{-2}	23.2×10^{-2}	23.2×10^{-2}
0.94	23.1	22.2	23.0
1.51	21.6	20.9	22.6
2.83	20.2	17.1	19.9
2.83	23.0	17.1	19.9
3.78	17.2	14.5	16.8
4.70	13.3	12.4	13.9
4.74	14.65	12.3	13.9
5.67	11.2	10.8	11.3
5.67	12.5	10.8	11.3
6.60	8.8	9.5	9.40
7.56	8.02	8.5	8.00
9.40	6.9	7.3	6.51
18.8	6.0	5.2	4.65
37.8	5.26	4.57	4.39
151	5.30	4.37	4.39
1900	4.36	4.36	4.36

[a] Conditions: A, pH 9.53–9.59, $k_{OH}[OH^-] = 4.46 \times 10^{-2}$ min^{-1}, $k_1 = 0.818 \times 10^{-2}$ min^{-1}, $C = 3.47 \times 10^{-9}$ for m = 2, $C = 2.87 \times 10^{-13}$ for m = 3; B, pH 8.75–8.79, $k_{OH}[OH^-] = 7.4 \times 10^{-3}$ min^{-1}, $k_1 = 1.38 \times 10^{-3}$ min^{-1}, $C = 1.53 \times 10^{-9}$ for m = 2, $C = 1.05 \times 10^{-13}$ for m = 3; C, pH 10.25–10.29, $k_{OH}[OH^-] = 23.2 \times 10^{-2}$ min^{-1}, $k_1 = 4.36 \times 10^{-2}$ min^{-1}, $C = 1.66 \times 10^{-9}$ for m = 2, $C = 1.07 \times 10^{-13}$ for m = 3.

V). The phenol produced on hydrolysis of NE_n^- esters appears not to be incorporated into CTA^+, since it neither exhibits an absorbance dependent on $[CTA^+]$ nor shows a pK_a' change with $[CTA^+]$ ($pK_a' = 5.52 \pm 0.01$ when $[CTA^+]$ varies from 0.0 to 1.54×10^{-3} M).

The nonnitrated, negatively charged esters E_1^- and E_9^- also exhibit a decrease in rate of hydrolysis in the presence of CTA^+, this effect being greatly dependent on the length of the aliphatic side chain (Table VI). For the esters E_1^- and E_9^-, depression in rate occurs in the same concentration range noted previously for the esters in Table IV. For the positively charged ester E_9^+, however, no depression in the rate constant for hydrolysis was noted until $[CTA^+]$ was 20- to 30-fold greater than for the esters of Tables IV and V (*i.e.*, depression in rate is not observed until the normal cmc of CTA^+ is reached). For the complexing or incorporation of ester into micelles of CTA^+ the results of Table VI suggest the importance of lyophobic bonding (E_1^- *vs.* E_9^-) and charge type (E_9^- *vs.* E_9^+). In Table VII, the experimental k_{obsd} values are compared to calculated values on the basis of eq 7.

Table VI. Ratio of k_{OH} Values for the Hydrolysis of Nonnitrated Negatively Charged Esters and a Positively Charged Ester in the Absence and Presence of High CTA^+ Concentration[a]

Ester	k_{OH}, l. mol^{-1} min^{-1} $[CTA^+]$ = 0	k_{OH}, l. mol^{-1} min^{-1} $[CTA^+]$ = 0.0192 M	Ratio
E_1^-	312	198	1.6
E_9^-	177	20	8.9
E_9^+	422	218	1.9

[a] pH range employed 9.00–10.5.

Table VII. Experimental and Calculated Values of k_{obsd} for E_9^+ as a Function of CTA^+ Concentration[a]

$[CTA^+] \times 10^5$ M	$k_{obsd} \times 10^2$ Detd	$k_{obsd} \times 10^2$ Calcd
0.0	2.05	
3.84	2.28	
7.74	2.37	
38.4	2.41	
40.0	2.40	2.40
77.0	2.30	2.27
154	1.65	1.73
231	1.36	1.39
384	1.23	1.15
770	1.12	1.03
1152	0.965	1.01
2000	1.00	1.00

[a] pH 9.50; cmc = 4.0×10^{-4}, $k_{OH}[OH^-] = 2.40 \times 10^{-2}$, $k_1 = 1.0 \times 10^{-2}$, m = 2, $C = 1.43 \times 10^{-6}$.

Reaction of Esters with Functional Micelles and Related Agents. The reaction of the amine A_4^+ with six esters was investigated. Under conditions of constant pH and $[A_4^+] \gg$ [ester], the disappearance of ester(s) was found to be pseudo first order. The values of $k_{obsd} - k_{OH}[OH^-]$ were found to be in all cases linearly dependent on the first power of the concentration of the free base species of A_4^+.

$$v = k_A[A_4^+][\text{ester}] + k_{OH}[OH^-][\text{ester}] \quad (8)$$

No evidence for micelle or complex formation was obtained. The pertinent kinetic data is presented in Table VIII. Inspection of Table VIII reveals that the esters are more susceptible to hydroxide ion attack than aminolysis, a result anticipated from the basicities of OH^- and A_4^+. The NE^+ esters are more reactive to both bases than the NE^- esters, the ratio of k_{OH}/k_A being 2.5 times greater for NE^+ than NE^- esters. This greater reactivity of the NE^+ esters is attributed to the

Table VIII. Reaction of A_4^+ with Esters (μ = 0.5)[a]

Ester	Concn × 10^5 M	pH range	No. of k_{obsd} values	k_A, l. mol^{-1} min^{-1}	$k_A^{H_2O}/k_A^{D_2O}$[c]
NE_1^-	10	8.45, 8.90	10	16.0	1.2
NE_5^-	9.4	9.2	5	2.6	0.73
NE_7^-	7	8.53-9.30	5	2.41	0.66
NE_9^-	5	8.43, 9.00	6	1.93	
NE_1^+	7	8.55, 9.12	10	22.6	
NE_7^+	6	8.54, 9.40	10	4.71	
o-NPA[b]	6	8.62, 9.40	10	1.08	

[a] Kinetic data obtained spectrophotometrically employing A_4^+ and its conjugate acid as buffer (pK_a' = 8.87; by potentiometric titration) concentration 0.05-0.005 M. [b] *o*-Nitrophenyl acetate. [c] $k_A^{D_2O}$ obtained in the same manner as $k_A^{H_2O}$ (pK_a' in D_2O = 9.46).

greater electron withdrawal by the $N^+(CH_3)_3$ group as compared to the SO_3^- group. The determined values of $k_A^{H_2O}/k_A^{D_2O}$ are as anticipated for an aminolysis reaction unassisted by general acid or general base catalysis.[46] The inability to carry out satisfactory product analysis (see Experimental Section) precluded assay for amide products. Therefore, we can rely only on the isotope effect to distinguish between the amine acting as a general base catalyst for ester hydrolysis and as a nucleophile.

To ascertain the influence of electrostatic charge on the bimolecular aminolysis reaction the reaction of six esters with A_4^0 was investigated (Table IX). The larger

Table IX. Second-Order Rate Constants for the Reaction of Esters with the Neutral Amine A_4^0 (μ = 0.5, 30°)

Ester	pH	No. of k_{obsd} values	k_A, M^{-1} min^{-1}
NE_1^+	8.3	6	80.9
NE_1^-	8.3	6	38.65
NE_5^-	8.3	6	6.85
NE_7^+	8.3, 8.88	12	17.7
NE_7^-	8.3	6	10.2
o-NPA	8.3	6	5.08

values of the second-order rate constants with A_4^0 compared to A_4^+ can be attributed to the greater pK_a' of the former (pK_a' = 9.76 *vs.* 8.87, respectively). The positively charged esters again exhibit the larger rate constants. The ratios of k_A values for NE_7^+/NE_7^- = 1.72 and NE_1^+/NE_1^- = 2.1 with A_4^0 as compared to 1.97 and 1.41 with A_4^+ lead to the conclusion that there is little or no electrostatic facilitation for these bimolecular aminolysis reactions.

The reaction of NE_7^- with A_4^+ as a function of [CTA^+] was investigated in order to ascertain whether the positively charged micelles of CTA^+ would incorporate the oppositely charged ester while excluding the positively charged amine. As in the absence of CTA^+, the reactions were found to follow pseudo-first-order kinetics when [A_4^+] (0.005-0.025 M) > [NE_7^-] (6×10^{-5} M) and a plot of k_{obsd} *vs.* [A_4^+] at constant values of [CTA^+] and pH 8.87 afforded linear plots (not shown) from whose slopes and intercept could be calculated the CTA^+-dependent second-order aminolysis rate constant (k_A') and the CTA^+-dependent second-order rate constant for alkaline hydrolysis (k_{OH}'), respectively (see eq 8). The results are presented in Table X. On increase of [CTA^+] both k_A' and k_{OH}' decrease precipitously becoming rather constant at [CTA^+] > 1.0×10^{-4} M. The *ca.* 30- and 13-fold decrease in k_A'

Table X. Reaction of A_4^+ with NE_7^- as a Function of CTA^+ Concentration (μ = 0.5, pH 8.87)

[CTA^+] × 10^5 M	k_A', l. $mole^{-1}$ min^{-1}	k_{OH}'	No. of k_{obsd} determined
0	2.3	972	5
3.2	0.77	954	5
4	0.64	862	5
5	0.48	284	5
6	0.41	243	5
8	0.26	216	5
9	0.16	46	5
50	0.075	73	5

and k_{OH}', respectively, may be attributed to incorporation of NE_7^- into micelles of CTA^+ from which A_4^+ and OH^- are excluded. An alternate explanation for the decrease in k_A' would be that incorporation of A_4^+ into CTA^+ micelles reduces its reactivity toward the ester bond. This possibility does not appear to be in accord with the established reactivity of the ester when incorporated into micelles of A_{10}^+ (see the following). Furthermore the pK_a' of A_4^+ is not influenced by the presence of CTA^+ (μ = 0.5, [CTA^+] = 6×10^{-6} to 5×10^{-4} M), a finding more in accord with exclusion of A_4^+ from micelles of CTA^+.

The reactions of A_{10}^+ with the same esters studied with A_4^0 (Table VIII) do not follow the simple second-order kinetics scheme of eq 8 but provide evidence for the partitioning of ester into micelles of A_{10}^+. Beer plots (pH 4.01, 8.65, and 9.03) of A_{10}^+ at 256 mμ are linear providing no evidence for micelle formation to [A_{10}^+] = 5.0×10^{-2} M (μ = 0.1). The linearity of the Beer plots, however, was found to be not an index of lack of micelle formation, but an indication of lack of electronic perturbation of the aromatic ring of A_{10}^+ on micelle formation. In Figure 4 are plotted the pK_a' values of the conjugate acid of A_{10}^+, obtained by half-neutralization and serial dilution *vs.* the concentration of [A_T] (=[A_{10}^+] + [$A_{10}H^{2+}$]) (μ = 0.1). Inspection of Figure 4 reveals that pK_a' = 8.92-8.93 at [A_T] = 0.0 to 5×10^{-3} M and then abruptly decreases with increase in concentration, the lowest pK_a' determined being 8.07 at [A_T] = 5×10^{-2} M. The shape of the plot suggests micelle formation for which the cmc $\cong 5 \times 10^{-3}$. The absorbance (460 mμ) of a phenolphthalein [0.0045% (w/v)] solution at pH 9.07 and a methyl yellow (410 mμ) solution [0.00072% (w/v)] at pH 3.52 were determined as a function of [A_T] (μ = 0.1). Essentially no change of absorbance was noted at pH 3.52. This is in contrast to the observation that methyl yellow does give a decrease of 0.43 in absorbance on increase of [CTA^+] at pH 3.52 (μ = 0.5). At pH 9.07 (Figure 5) the absorbance of phenolphthalein decreases abruptly with increase in [A_T]. From the lack of absorbance change of methyl yellow at pH 3.52 it may be concluded either that only A_{10}^+ and not $A_{10}H^{2+}$ forms micelles or that methyl orange does not incorporate into micelles of $A_{10}^+ + A_{10}H^{2+}$ at μ = 0.1, even though it does into CTA^+ at μ = 0.5. The ionic strengths employed were those used in the kinetic experiments.

(46) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, 89, 2016 (1967).

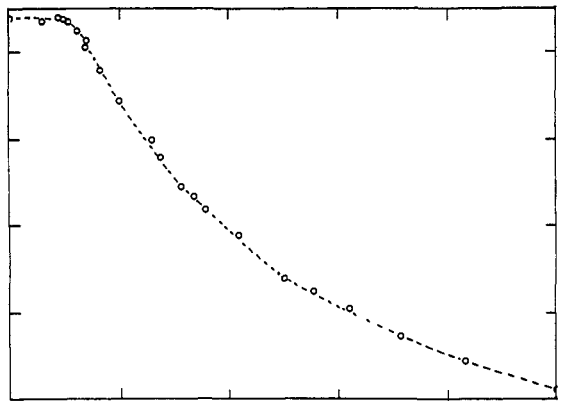


Figure 4. The pH of half-neutralized solutions of the amine hydrochloride of A_{10}^+ as a function of the concentration of A_T ($= [A_{10}^+] + [A_{10}H^{2+}]$) at $\mu = 0.1$.

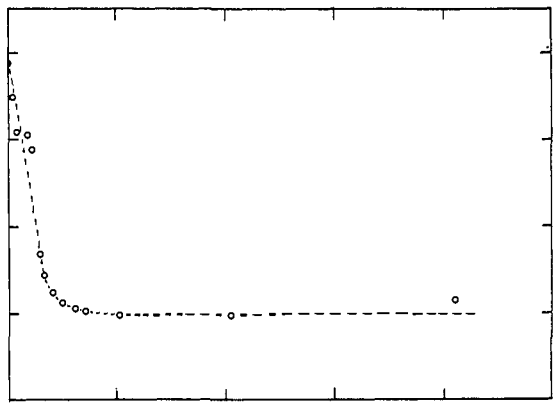


Figure 5. Absorbance of phenolphthalein [0.0045% (w/v); 560 mμ; $\mu = 0.1$; pH 9.07) as a function of the concentration of A_T ($= [A_{10}^+] + [A_{10}H^{2+}]$).

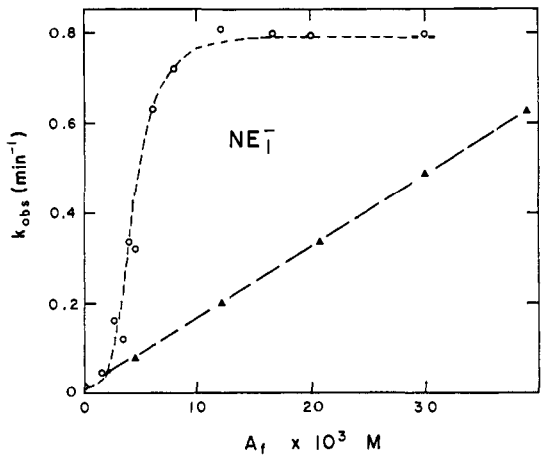


Figure 6a. Plot of the pseudo-first-order rate constants (k_{obsd}) for appearance of 3-nitro-4-hydroxybenzenesulfonate from ester (O) NE_1^- ([ester]$_0 = 5 \times 10^{-5}$ *M*) *vs.* concentration of A_{10}^+ as free base species (pH 8.63; $\mu = 0.1$). Included are the values of k_{obsd} *vs.* A_4^+ as free base (▲).

In Figure 6 are plotted the values of k_{obsd} for the appearance of 3-nitro-4-hydroxybenzenesulfonate from NE_1^-, NE_5^-, NE_7^-, NE_9^-, and NE_{15}^- as a function of $[A_{10}^+]$ as the free base species at pH 8.63. $[A_{10}^+]$ was calculated from $[A_T]$ and the pK_a' values of Figure 4. From inspection of Figure 6, we see that k_{obsd} increases with increase in $[A_{10}^+]$, leveling off at high $[A_{10}^+]$. Thus,

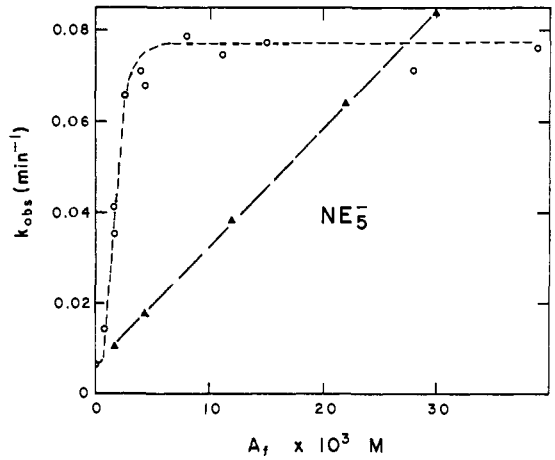


Figure 6b. Plot of the pseudo-first-order rate constants (k_{obsd}) for appearance of 3-nitro-4-hydroxybenzenesulfonate from ester (O) NE_5^- (see caption for Figure 6a). Included are the values of k_{obsd} *vs.* A_4^+ as free base (▲).

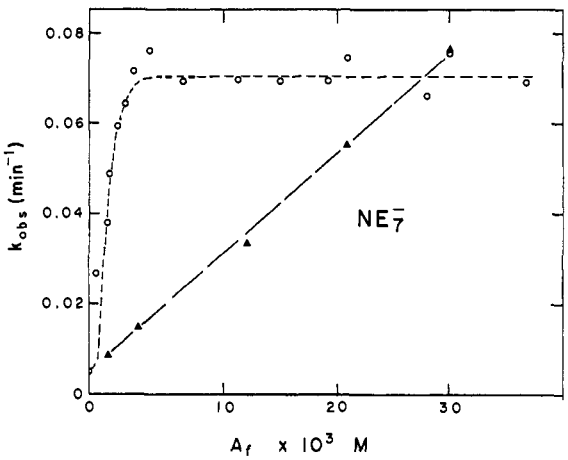


Figure 6c. Plot of the pseudo-first-order rate constants (k_{obsd}) for appearance of 3-nitro-4-hydroxybenzenesulfonate from ester (O) NE_7^- (see caption for Figure 6b). Included are the values of k_{obsd} *vs.* A_4^+ as free base (▲).

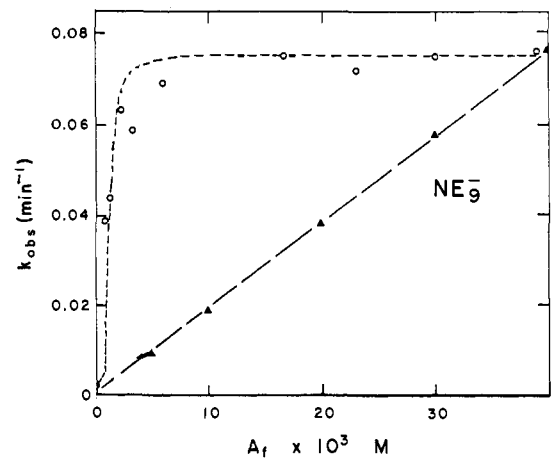


Figure 6d. Plot of the pseudo-first-order rate constants (k_{obsd}) for appearance of 3-nitro-4-hydroxybenzenesulfonate from ester (O) NE_9^- (see caption for Figure 6a). Included are the values of k_{obsd} *vs.* A_4^+ as free base (▲).

although the esters are protected from hydrolysis by nonfunctional micelles, their rate of disappearance in-

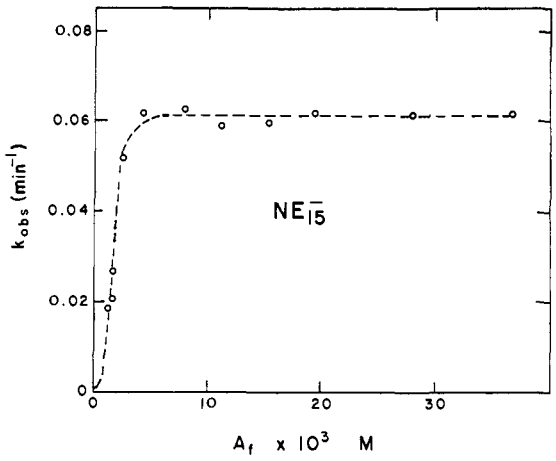


Figure 6e. Plot of the pseudo-first-order rate constants (k_{obsd}) for appearance of 3-nitro-4-hydroxybenzenesulfonate from ester (O) NE_{15}^- (see caption for Figure 6a).

creases on formation of micelles of A_{10}^+. The decrease in OD of phenolphthalein occurs at about the same concentration as seen for the increase in rate of disappearance of the NE_n^- esters in the presence of A_{10}^+. As with CTA^+, therefore, phenolphthalein and the NE_n^- esters are comparable in inducing micelle formation with A_{10}^+. The kinetics for appearance of phenol from ester can be treated *via* eq 7. For this purpose we assume that $[A_T] \gg$ cmc. In Table XI are recorded the best parameters for eq 7 to fit the experimental data of Figure 6—in which the points are experimental and the curves theoretical. Unlike the solvolysis of the esters in CTA^+ and NDA^0 where it was necessary to assume $m = 2$ or 3 and 2, respectively, for the reaction of the NE_n^- esters in A_{10}^+ a reasonable fit is obtained only if $m = 4$ (for Figure 6 the values of $[A_{10}^+]$ were employed but m remains the same if $[A_T]$ is used). The values of the calculated partition coefficient C may be seen to be quite comparable for NE_5^-, NE_7^-, NE_9^-, and NE_{15}^- (*i.e.*, $6.1 \pm 3 \times 10^{-12}$) but much greater for NE_1^- (340×10^{-12}). Thus, the partitioning of NE_1^- into micelles of A_{10}^+ is about 50 times less favorable than for all the other esters. Apparently once the chain is extended from acetyl to hexanoyl further extension does not increase the relative partitioning of the ester into A_{10}^+ micelles. The increase in k_{obsd} on incorporation of ester into micelle is shown by the ratio of $k_1/k_{OH}[OH^-]$. Inspection of Table XI reveals that although the acetyl ester NE_1^- is the most poorly absorbed into the A_{10}^+ micelle, it is quite reactive once it is incorporated. The ratio of $k_1/k_{OH}[OH^-]$ decreases in going from NE_1^- to NE_5^- but then steadily increases from NE_5^- through NE_{15}^-. The per cent increase in k_{obsd} is actually greater for NE_{15}^- than for NE_1^- on incorporation into the A_{10}^+ micelle. Because of the much more favorable partitioning of NE_{15}^- into A_{10}^+ and the greater per cent increase of k_{obsd} accompanying incorporation, the values of k_{obsd} are comparable for NE_1^- and NE_{15}^- at $[A_{10}^+] = 2 \times 10^{-3}$ M even though both $k_{OH}[OH^-]$ and k_1 are themselves about 10 times less for NE_{15}^- than for NE_1^-. Included in Figure 6 as dashed lines are the values of k_{obsd} *vs.* $[A_4^+]$. It may be seen that incorporation into the micelle makes A_{10}^+ a much better nucleophile than A_4^+ at low concentration of amine. Even though C is largest for NE_1^-, A_{10}^+ at 1.2×10^{-2} M is as good a nucleophile toward this ester as is A_4^+ at 5×10^{-2} M. For the experiments of Figure 6 and Table XI the concentration of the NE_n^- esters was 5×10^{-5} M. For NE_1^- the concentration of ester at constant $[A_{10}^+] = 5 \times 10^{-2}$ M was shown not to affect k_{obsd} (Table XII).

Table XI. Values of Rate Parameters Which Provide a Correlation of the Values of k_{obsd} to the Concentration of A_{10}^+ Species at pH 8.63 ($T = 30°$; $\mu = 0.1$)

$$k_{obsd} = \frac{k_{OH}[OH^-]C + k_1[A_{10}^+]^4}{C + [A_{10}^+]^4}$$

Ester	No. of k_{obsd} values	$k_{OH}[OH^-]$, min^{-1}	k_1, min^{-1}	$k_1/k_{OH}[OH^-]$	C
NE_1^-	11	0.014	0.793	56.6	3.40×10^{-12}
NE_5^-	11	0.00662	0.0775	11.7	8.40×10^{-12}
NE_7^-	15	0.00533	0.071	13.3	8.02×10^{-12}
NE_9^-	9	0.00224	0.075	33.5	3.09×10^{-12}
NE_{15}^-	11	0.001	0.062	62[a]	9.16×10^{-12}

[a] The value of $k_{OH}[OH^-]$ was obtained from best fit of eq 7 to kinetic data.

Table XII. Values of k_{obsd} Determined at Various Values of $[NE_1^-]$ and $A_{10}^+ = 5 \times 10^{-2}$ M ($\mu = 0.1$; pH 8.70; $T = 30°$)

Concn of ester $\times 10^5$ M	k_{obsd}, min^{-1}	Concn of ester $\times 10^5$ M	k_{obsd}, min^{-1}
4.01	0.935	35.6	0.940
6.60	0.960	39.8	1.13
7.40	0.938	47.8	0.896
14.20	0.960	60.0	0.915
15.40	0.911		
29.0	0.926		

The influence of the ester charge type on reaction with A_{10}^+ has been studied employing esters NE_1^+, NE_7^+, and *o*-nitrophenyl acetate (*o*-NPA). The values of k_{obsd} as a function of $[A_{10}^+]$ are shown in Figure 7 and the best fits of the experimental data to eq 7 are provided in Table XIII. Comparison of the results reported in Tables XI and XIII reveals that the best fit to the experimental data is obtained when $m = 4$ for NE_n^- esters and $m = 2$ for NE_n^+ esters. The value of m, as well as that of C appears, therefore, to be an index of the association of ester with amine, the lower value being obtained when the association is not electrostatically facilitated by unlike charges on ester and amine. On comparison of $k_1/k_{OH}[OH^-]$ it is found that electrostatic

Table XIII. Values of Rate Parameters Which Provide a Correlation of Values of k_{obsd} to the Concentration of A_{10}^+ at pH 8.63 ($T = 30°$; $\mu = 0.1$)

$$k_{obsd} = \frac{k_{OH}[OH^-]C + k_1[A_{10}^+]^2}{C + [A_{10}^+]^2}$$

Ester	No. of k_{obsd} values	$k_{OH}[OH^-]$, min^{-1}	k_1, min^{-1}	$k_1/k_{OH}[OH^-]$	C
NE_1^+	12	0.0448	0.18	4.0	1.67×10^{-5}
NE_7^+	11	0.0179	0.30	17	7.81×10^{-5}
o-NPA	21	0.00646	0.064	9.9	10.0×10^{-5}

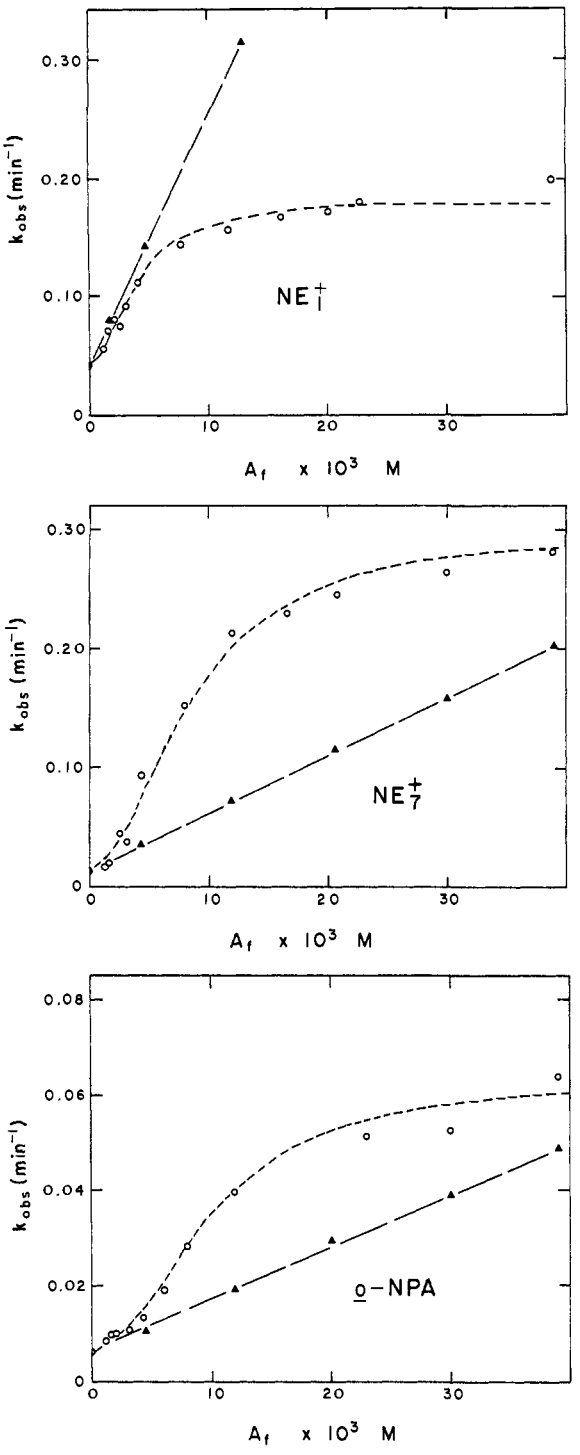


Figure 7. Plot of the pseudo-first-order rate constants (k_{obsd}) for appearance of 4-hydroxy-3-nitrophenyltrimethylammonium from esters NE_1^+ and NE_7^+ and *o*-nitrophenol from *o*-NPA *vs.* $[A_{10}^+]$ as free base (pH 8.63; μ = 0.1) as determined on the autotitrator (○). Included are the values of k_{obsd} *vs.* $[A_4^+]$ as free base (▲).

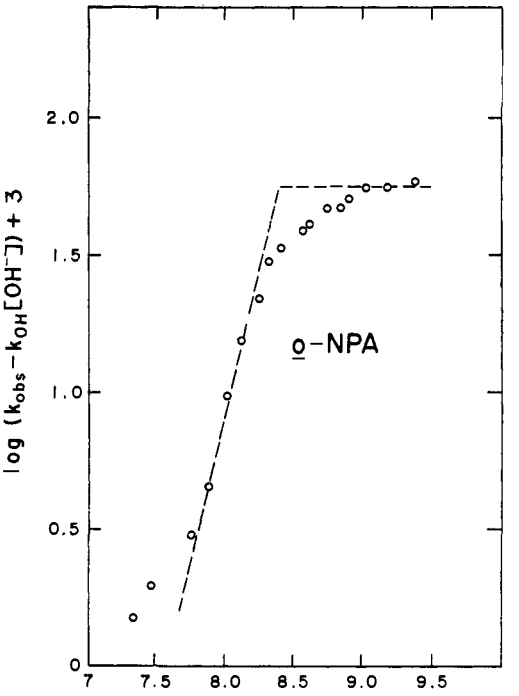


Figure 8a. The log k_1 *vs.* pH profiles for the reaction of ester *o*-NPA with A_T ($=[A_{10}^+] + [A_{10}H^{2+}]$ = 0.025 *M*), μ = 0.1.

attraction is of much more importance for the short-chain esters NE_1^+ and NE_1^- than for the longer chain esters as NE_7^+ and NE_7^-. Thus, $k_1/k_{OH}[OH^-]$ is 14.5-fold greater for NE_1^- than for NE_1^+ while the ratios are comparable for NE_7^- and NE_7^+. Also, inspection of Figures 6 and 7 reveals that A_4^+ approaches A_{10}^+ as a nucleophile toward NE_1^- at high concentrations while, toward NE_1^+, A_4^+ is a better nucleophile than A_{10}^+ at all concentrations. With NE_7^- and NE_7^+, however, A_{10}^+ is the better nucleophile at low concentrations. For the short-chain esters, attraction of A_{10}^+ and NE_1^- must be primarily electrostatic, while for NE_7^-, lyophobic. On the basis of the values of *m*, *C*, and $k_1/k_{OH}[OH^-]$ the best substrates (Tables XI and XIII) for micelles of A_{10}^+ are NE_1^- and NE_{15}^-. Incorporation of NE_{15}^- is much more favorable than NE_1^- and the values of $k_1/k_{OH}[OH^-]$ are comparable for the two esters but the values of both k_1 and $k_{OH}[OH^-]$ are greater for NE_1^-. It should be noted that for the plots of Figures 6 and 7 and the parameters derived therefrom (Tables XI and XIII), k_{obsd} is not corrected for $k_{OH}[OH^-]$. This may be an error on our part, but it is not obvious what correction should be made. In the hydrolysis of esters in the presence of NDA^0, LS^-, and CTA^+ the value of k_{OH} decreases when ester is complexed or incorporated into the micelles. It is, therefore, reasonable to assume that this would be the case for reaction with A_{10}^+. If this is so, the rate constant for reaction of ester incorporated into micelles of A_{10}^+ is not $k_{OH}\cdot[OH^-] - k_1$ but is essentially k_1. The ratio of $k_1/k_{OH}\cdot[OH^-]$ is a legitimate constant with which to compare the reactivities of esters, however, since it represents the ratio of $V_m/k_{OH}[OH^-]$ at a constant pH and levels electronic effects on the reactivity of esters due to their differential substitution.

The data presented to this point have dealt with the reactions of A_{10}^+ with ester at the pH of 8.6–8.70. Since the reactions are aminolytic, *a priori*, the rates should be sensitive to the ratio of $A_{10}^+/A_{10}H^{2+}$.

In Figure 8 are presented log k_1–pH profiles for the reaction of esters *o*-NPA, NE_1^+, NE_1^-, NE_5^-, and NE_7^- with A_T ($[A_T] = [A_{10}^+] + [A_{10}H^{2+}]$ = 0.025 *M*; μ = 0.1; T = 30°). The plots are seen to resemble titration curves. For the reaction of a base species B with ester

$$v = k_2[E][B] \qquad (9)$$

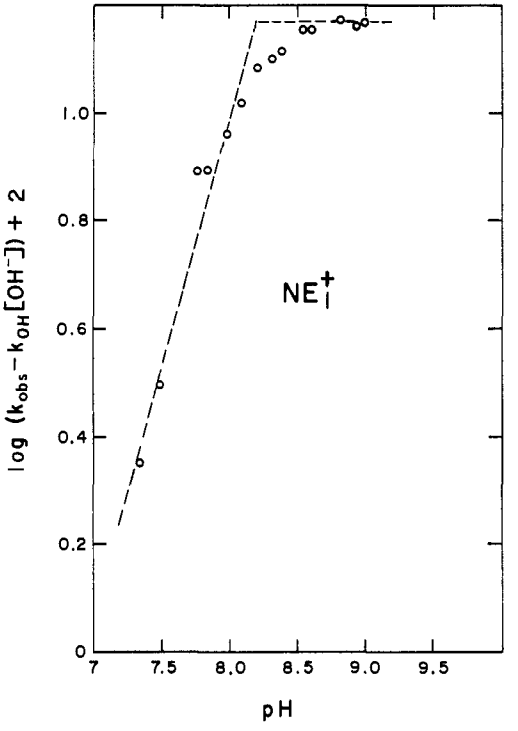


Figure 8b. The log k_1 *vs.* pH profiles for the reaction of ester NE_1^+ with A_T (see caption for Figure 8a).

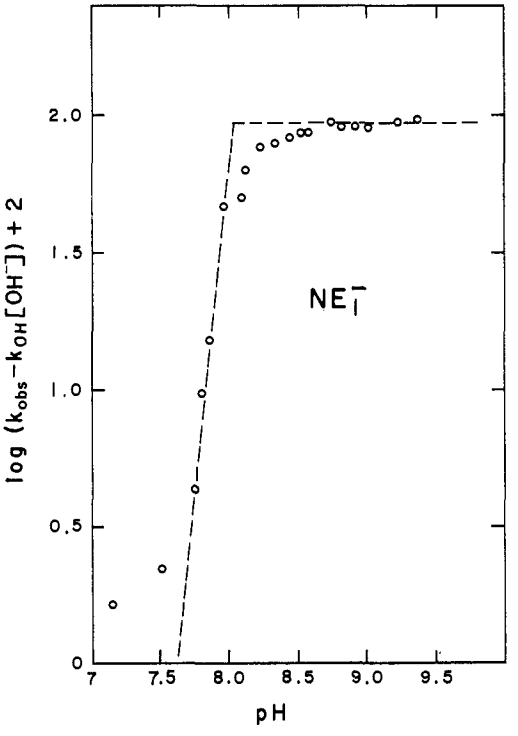


Figure 8c. The log k_1 *vs.* pH profiles for the reaction of ester NE_1^- with A_T (see caption for Figure 8a).

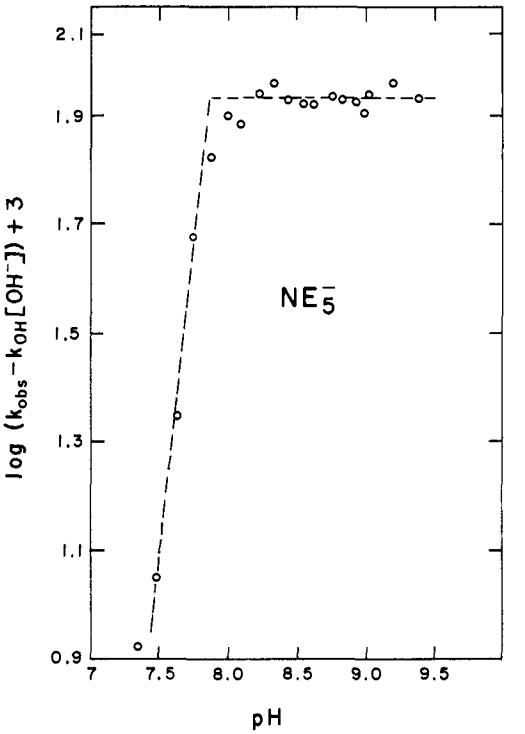


Figure 8d. The log k_1 *vs.* pH profiles for the reaction of ester NE_5^- with A_T (see caption for Figure 8a).

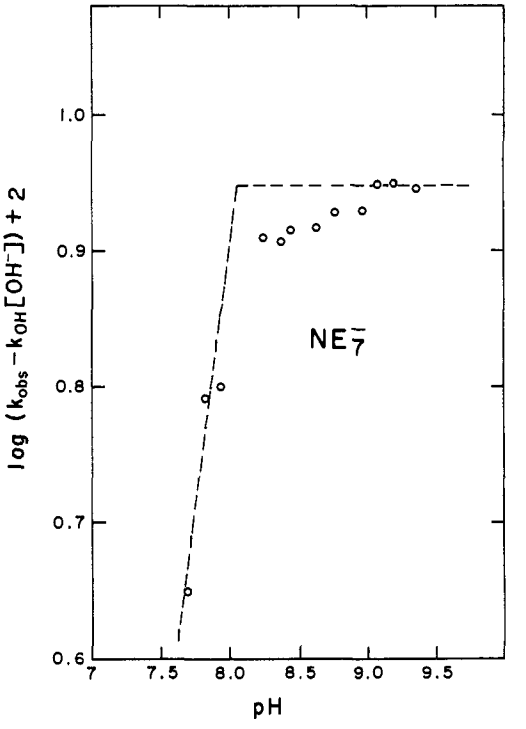


Figure 8e. The log k_1 *vs.* pH profiles for the reaction of ester NE_7^- with A_T (see caption for Figure 8a).

Under the pseudo-first-order conditions of ([B] + [BH] = [B_T]) ≫ [E]

$$k_{obsd} = k_2[B] = k_2[B_T]\frac{K_a'}{K_a' + a_H} \qquad (10)$$

and when [B_T] = constant

$$\log k_{obsd} = \log k_2'K_a' + \log \frac{1}{K_a' + a_H} \qquad (11)$$

When $a_H \gg K_a'$

$$\log k_{obsd} = \log k_2'K_a' + \text{pH} \qquad (12)$$

and when $K_a' \gg a_H$

$$\log k_{obsd} = \log k_2' \qquad (13)$$

From (12) and (13) it is anticipated that a plot of log

k_{obsd} *vs.* pH should be linear of slope 1 when $a_H \gg K_a'$ and that at $K_a' \gg a_H$ a plateau should be reached with log k_{obsd} = log k_2'. When $K_a = a_H$ then pH = pK_a so that the intersection of tangents to the plateau and ascending portion of the plot should occur at pH = pK_a'. The plots of Figure 8 do plateau above the pH range where $K_a' \gg a_H$ and have a positive slope in the pH range where $a_H \gg K_a'$, but not necessarily a unit slope. In Table XIV are recorded the plateau rate constants (k_2), the pK_{app}'s and slopes of the ascending legs of the log k_1–pH profiles. The value of pK_a' for A_{10}^+ has been established to depend upon A_T concentration (see Figure 4), varying from 8.92 to 8.07 in going from $[A_T] = 0$ to 5×10^{-3} to $[A_T] = 5 \times 10^{-2}$ *M*. At the $[A_T] = 0.025$, pK_a' = 8.32. This value is reasonably close to the pK'_{app}'s listed in Table XIV. We may conclude that only the species A_{10}^+ is involved in the aminolysis reaction. The slopes of the pH *vs.* log k_1 plots of Figure 8 appear to have some relationship to the values of *m* necessary to fit eq 7 to the experimental data for the reaction of esters with A_{10}^+ at constant pH and varying amine concentration (*i.e.*, for NE_1^+ and *o*-NPA slopes = 1.0 and 2.2 and *m* = 2 while for NE_1^- and NE_5^- slopes = 5 and 4 and *m* = 4, respectively).

In the construction of Figure 8 and the derivation of the parameters of Table XIV, log ($k_{obsd} - k_{OH}[OH^-]$), *i.e.*, log ($k_1 - k_{OH}[OH^-]$) at high $[A_T]$, has been plotted *vs.* pH. This procedure differs from that employed for Figures 6 and 7 and Tables XI and XIII. The change in convention was dictated by the large alteration of $[OH^-]$ with change of pH for the data of Figure 8 and, as explained previously, by the expectation that $k_{OH} \cdot [OH^-]$ should decrease on increase of $[A_T]$ at constant pH. The convention employed, plus the known concentration dependence of pK_a' of $A_{10}H^{2+}$ undoubtedly effects the slopes of the pH profiles recorded in Table XIV. From the data of Tables XI, XIII, and XIV, however, it is obvious that the relative values of k_1 and k_2 are comparable regardless of the convention employed in their derivation (Table XV) and that, regardless of charge type and chain length, these constants are quite similar, with the single exception of NE_1^-, whose reaction with A_{10}^+ is most facile. If $k_{2_{rel}}$ is compared to $k_{A_{rel}}$, it is seen that the reaction of NE_1^+ with A_4^+ and A_4^0 in a bimolecular aminolysis reaction is relatively more efficient than the reaction of NE_1^+ with A_{10}^+ in an "intramicellar" aminolysis reaction (see also Figures 6 and 7). The values of $k_{2_{rel}}$ and $k_{A_{rel}}$ are, however, comparable for the neutral and negatively charged esters. This lessened relative reactivity of NE_1^+ with A_{10}^+ may be due to repulsion of like charges, a factor of little importance in the less structured transition state of the bimolecular reaction.[47]

In Figure 8 the maximum velocities obtained under saturating $[A_T]$ and constant pH are plotted *vs.* pH. If association of esters and the ensuing reaction involves A_{10}^+ and not $A_{10}H^{2+}$ then the maximum velocity should be pH independent (as the mole fraction of A_{10}^+ decreases a larger value of $[A_T]$ would be required to saturate the ester but the maximum velocity would be the same). Since this is clearly not the case *we must assume association of ester with both* A_{10}^+ *and* $A_{10}H^{2+}$ but that the ensuing chemical transformation involves only A_{10}^+. An alternate and kinetically identical mechanism would involve association of ester with $A_{10}^+ + A_{10}H^{2+}$ and the bond-breaking mechanism involving the species ester + $A_{10}H^{2+}$ + OH^-.

Table XIV. Constants Obtained from the Log k_1 *vs.* pH Profile for the Reaction of Esters ($[E] = 5 \times 10^{-5}$ *M*) with A_{10}^+ ($[A_T] = 0.025$ *M*; $\mu = 0$; $T = 30°$)

Ester	No. k_{obsd}	Slope	pK_{app}'	k_2, min^{-1}
NE_1^+	14	1.0	8.2	0.148
NE_1^-	19	5.0	8.0	0.933
NE_5^-	19	4.0	7.9	0.084
NE_7^-	12	1.0	8.0	0.088
o-NPA	17	2.2	8.4	0.056

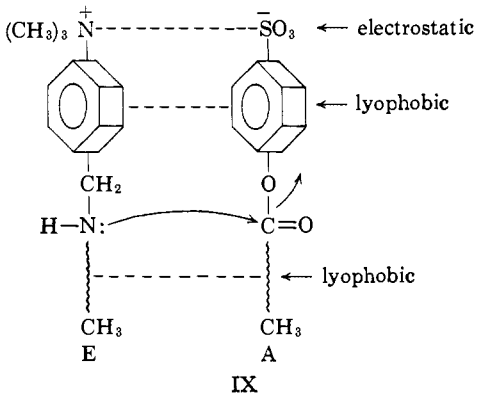
Table XV. Relative Values of the Apparent (k_1) and True (k_2) Rate Constants for Reactions of Esters within Micelles of A_{10}^+ and the Relative Second-Order Rate Constant (k_A) for Reaction of Esters with A_4^+ and A_4^0

Ester	k_{1rel}	k_{2rel}	$k_{ArelA_4^+}$	$k_{ArelA_4^0}$
NE_1^+	2.8	2.31	20.9	15.9
NE_1^-	12.2	14.55	14.8	7.2
NE_5^-	1.21	1.31	2.41	1.35
NE_7^-	1.11	1.375	2.23	2.03
NE_9^-	1.17			
NE_{15}^-	0.97			
o-NPA[a]	1.0	1.0	1.00	1.00

[a] Rate constants relative to *o*-NPA for k_2 and k_1.

Discussion

The purpose of this initial study has been to determine the feasibility of designing substrates and nucleophiles which would exhibit a significant heightening of chemical interaction due to salt or micelle formation resulting from properly oriented electrostatic and hydrophobic attraction. The structures of the esters as well as the shorthand symbolism employed are given in I–IV and those of the amines in V and VII. The sought for interaction of esters and amines is shown in IX. To our knowledge this represents the first instance of an investigation of this nature.[48,49]



IX

Kinetic studies have revealed that at the concentrations employed in this study the various esters do not

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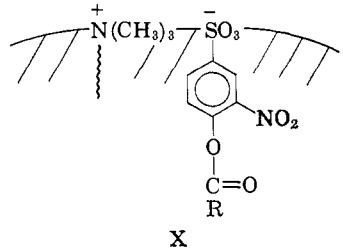
(48) A portion of this study was reported in a communication (T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Phys. Chem.*, **71**, 1961 (1967)).

(49) A. Ochoa-Solano, G. Romero, and C. Gitler, *Science*, **156**, 1243 (1967), have recently reported studies of the hydrolyses of *p*-nitrophenyl acetate and *p*-nitrophenyl carpylate by N-α-myristoyl-L-histidine when incorporated into micelle of acetyltrimethylammonium bromide. The micelle-forming nucleophile (N-α-myristoyl-L-histidine) itself was found not to be a nucleophilic catalyst for ester hydrolysis.

exist as aggregates. As a prelude to the investigation of IX the hydrolysis of various of the esters of I and IV in the presence of nonnucleophilic micelle-forming agents was studied. For this purpose pseudo-first-order rate constants for ester hydrolysis as a function of the concentration of the neutral (NDA^0), negative (LS^-), and positive (CTA^+) micelle-forming agents VIII were determined. For all cases investigated the value of $k_{OH}[OH^-]$, at constant pH, was found *to decrease* with increasing concentration of the micelle-forming agents, reaching a constant minimum value at high detergent concentrations (Tables III, IV, V, VI, and VII). Therefore, association with or incorporation of esters into nonnucleophilic micelles must either decrease the availability of the esters to OH^- attack or provide a less favorable media for the hydrolytic reaction. Previous investigations have revealed that the observed pseudo-first-order rates for OH^- attack on substrate in a micellar phase are generally increased if the micelle is of positive charge but decreased if the micelle is of negative charge.[21,24,25] Since in the present study $k_{OH}[OH^-]$ is decreased regardless of the charge of the micelle the kinetic effect presumably has nothing to do with the concentration of or restriction of hydroxyl ions from the Stern layer. This observation might suggest that the ester bond is buried and not near the surface of the micelle. A similar explanation has been suggested for the marked decrease in the spontaneous rate of hydrolysis of ethyl trichloroacetate.[50] It should be noted that the inclusion of a substrate molecule within a micelle is not strictly akin to placing the molecule in an organic phase since nmr studies have clearly shown that the interior of micelles are quite wet.[51,52] Apparently the nature of the substrate may determine its positioning within a micelle By nmr methods it has been concluded[53] that CTA^+ absorbs cyclohexane and cumene into the inner hydrocarbon portion of the micelles, whereas N,N-dimethylaniline and nitrobenzene residues are absorbed in the aqueous section of the interior not far from the surface. This would imply that the very polar esters of the present investigation should also be in the aqueous section of the interior not far from the surface. This, however, would not appear to be the case. For the various esters investigated the charged head groups may be at the Stern layer but the ester bond must be inside the micelle.



X

The dissociation constant of water is known[54] to be markedly suppressed on addition of dioxane and the micellar media is best characterized as a mixed aqueous-organic solvent.[51] Possibly the most satisfactory explanation for the observed decrease in rates of hydrolysis is found in a decrease in the autoprotolysis constant of water within the micelle, which would be akin to a lessened incorporation of OH^- into the micelle.

For the hydrolysis of NE_5^- in the presence of NDA^0 the rate constant for alkaline hydrolysis decreased at an NDA^0 concentration higher than that found for the increase of absorbance of pinacyanol (Figure 1). It is known that the dye method[55] does not provide a true cmc but that the change in absorbance of the dye solution on increase of micelle-forming reagent is due to salt and premicelle formation followed by micelle formation.[43,56] Undoubtedly the same is true for the esters employed in this study. For LS^- the esters E_9^+ and NE_5^- form insoluble salts. With the esters NE_1^-, NE_5^-, NE_7^-, E_1^-, and E_9^+ no decrease of the hydrolytic rate was noted at $\mu = 0.1$ on increase of concentration of CTA^+ but at $\mu = 0.5$ the values of k_{obsd} decrease as previously described. Increase in μ is known to increase the association of detergent molecules as attested to by the accompanying decrease in the cmc and increase in the number of molecules composing the micelle.[57] At $\mu = 0.5$ with CTA^+, the decrease in the values of k_{obsd} for the hydrolysis of the negatively charged esters at constant pH occurs below the true cmc of the detergent[45] but at the same concentration of CTA^+ at which the absorbance of phenolphthalein precipitously decreased (Figure 2). Thus, both phenolphthalein and the negatively charged esters have similar tendencies to induce micelle formation and/or form salts with CTA^+. In contrast, with the positively charged ester E_9^+ no depression in the rate constant for hydrolysis was noted (Table VII) until a concentration of CTA^+ was reached which is 20- to 30-fold greater than for the esters of negative charge. Clearly electrostatic attraction appears to play a role in the combination of ester and CTA^+. The depression in rate on incorporation into micelles of CTA^+ (*i.e.*, at high CTA^+ concentration) is 5.5-fold greater for E_9^- than for E_1^- but about equal for NE_1^-, NE_5^-, and NE_7^-. Lyophobic bonding apparently orients the less polar E_n^- esters in the salt or micelle more unfavorably than the NE_n^- esters.

In this study we have considered the alteration of rate constants on increase of micelle-forming agent as either a salt formation (eq 1–3) or a partitioning of ester into a micellar phase (eq 4–7). It is, of course, unlikely that either situation prevails alone but that the esters probably form salts which induce micelle formation and that the micelles formed at higher concentration of detergent then dissolve the salts and premicelles. However, assumption of either limiting case leads to kinetic equations of the same mathematical form. The decrease in rate of ester hydrolysis is found to be dependent upon the second or third power of NDA^0 (Table I) or CTA^+ concentration (Table V). This infers that the salt or induced micelle has a composition of ester:detergent = 1:2 (or 3).[24]

For the amines of V and VII reactions with esters NE_1^-, NE_5^-, NE_7^-, NE_9^-, NE_1^+, and NE_7^+ were found to be first order in amine and first order in ester when the butylamines A_4^+ and A_4^0 were employed (Tables VIII and IX). No evidence for association of ester with

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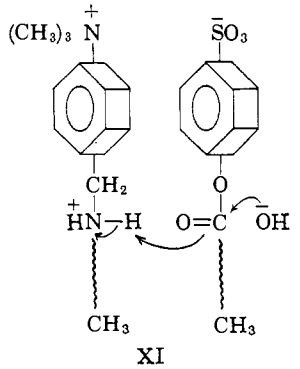
the butylamines could be detected; moreover, electrostatic attraction or repulsion was not found to contribute to the determined second-order aminolysis rate constants. The latter result is in accord with our previous findings[46] that electrostatic attraction between nucleophile and *o*-nitrophenyl hydrogen oxalate anion is unimportant.

When the reaction of NE_7^- with A_4^+ was carried out at constant pH but increasing $[CTA^+]$, it was found that the second-order rate of aminolysis decreases in the same manner as the second-order rate constant for alkaline hydrolysis (Table X). Furthermore, the decreases parallel each other. For the aminolysis reaction it can be shown (from the fact that the dissociation constant for A_4H^{2+} is not influenced by CTA^+) that positive amine is not incorporated into CTA^+.

Unlike A_4H^{2+} the pK_a' of $A_{10}H^{2+}$ is markedly concentration dependent above $[A_T] = 5 \times 10^{-3}$ *M* (Figure 4); in addition, the absorbance of a phenolphthalein solution exhibits a marked decrease, becoming independent of $[A_T]$ at about 5×10^{-3} *M* (Figure 5). These results establish association of the decylamine and/or its conjugate acid. The rates of appearance of 3-nitro-4-hydroxybenzene sulfonate from esters NE_1^-, NE_5^-, NE_7^-, NE_9^-, and NE_{15}^- (Figure 6); of 4-hydroxy-3-nitrophenyltrimethylammonium from the esters NE_1^+, NE_7^+; and of *o*-nitrophenol from *o*-nitrophenyl acetate (Figure 7) were found to depend on the concentration of the decylamine at constant pH. For the NE_n^- esters, the increase in k_{obsd} was found to depend on the fourth power of $[A_T]$ at low concentrations of amine (Table XI) and to become independent of $[A_T]$ at the higher concentrations employed. For the NE_n^+ esters and *o*-NPA the increase in k_{obsd} at low amine concentration was dependent on the second power of $[A_T]$ and independent of $[A_T]$ at its higher concentrations (Table XIII). It would thus appear that salts or premicelles are formed in the former case with stoichiometry $NE_n^-(A_T)_4$ while in the latter complexes of the type $NE_n^+(A_T)_2$ are involved. It is not unreasonable to suppose, *a priori*, that the negative esters might be associated with more molecules of the positive amine than would the positive esters. For the esters *o*-NPA, NE_1^+, NE_1^-, NE_5^-, and NE_7^- it was found that plots of the log of the constant rate constants obtained at the higher values of $[A_T]$ *vs.* pH provided curves (Figure 8) resembling log k_r *vs.* pH profiles for the intramolecular participation of a functional group of pK_{app}'.[2] The values of pK_{app}' were found to resemble closely the pK_a' of $A_{10}H^{2+}$ at the concentration of A_T employed (Figure 8; Table XIV). The slopes of the ascending portion of the curves were found to be similar to the power



XI

in $[A_T]$ necessary to fit the value of k_{obsd} to plots of k_{obsd} *vs.* $[A_T]$ at constant initial ester concentration and constant pH. Thus, esters studied are associated with *m* numbers of A_T and the rate of aminolysis is dependent on the mole fraction of A_T as A_{10}^+. The dependence of the maximum velocities at saturation by A_T on the mole fraction of A_T in the form of A_{10}^+ is in agreement with the aminolysis reaction of IX. An alternate mechanism which is kinetically indistinguishable from IX is XI in which OH^- attack is facilitated *via* intramicellar general acid catalysis (ester + $A_{10}H^{2+}$ + OH^-). The equation of (14) provides an approximate correlation of the reaction of esters with the decylamine in buffers prepared from the amine and its conjugate acid

$$k_{obsd} - k_{OH}[OH^-] = \frac{\frac{V}{C}\left(\frac{K_a[A_T]}{K_a + a_H}\right)^m}{C + \left(\frac{[A_T]K_a}{K_a + a_H}\right)^m} \qquad (14)$$

where *C* is a partition coefficient, *m* the number of A_{10}^+ and $A_{10}H^{2+}$ molecules per ester in the premicelle, and K_a the dissociation constant of $A_{10}H^{2+}$. At constant pH, (14) reduces to (7) and at constant $[A_T]$ to a form which provides the essence of the theoretical plots of Figure 8.

Though NE_1^- is poorly absorbed by micelles of the decylamine, the esters NE_5^- and NE_{15}^- are strongly absorbed and to about the same extent indicating the chain length is of little significance beyond hexanoyl. The relative rate (*i.e.*, relative to $k_{OH}[OH^-]$ in the absence of A_{10}^+) of disappearance of esters once absorbed into micelles of A_{10}^+ was found to be dependent upon the chain length of the acyl moiety (Table XI). The order of maximum rate for disappearance of NE_n^- esters in A_{10}^+ is $NE_1^- \gg NE_5^- \cong NE_7^- \cong NE_9^- \geq NE_{15}^-$ while for hydroxide ion catalyzed hydrolysis (Table II) the order is $NE_1^- > NE_5^- \geq NE_9^- > NE_{15}^-$. Intramicellar aminolysis is, therefore, less sensitive to steric effects than alkaline hydrolysis. Since A_{10}^+ is of much greater bulk than OH^- it might be supposed that the lessened steric demand of A_{10}^+ may be due to alignment of the esters and amines as shown in IX. Electrostatic attraction of ester and amine *within the micelle* of amine is of *kinetic* significance for the short-chain ester NE_1^- but not for NE_7^-. This conclusion stems from a comparison of the maximum rate of reaction, at high $[A_T]$ and constant pH, of NE_1^- *vs.* NE_1^+ and NE_7^- *vs.* NE_7^+. Thus, the NE_n^+ esters exhibit the greater rate constants in bimolecular reactions with OH^-, A_4^0, and A_4^+, but the ester NE_1^- exhibits a rate constant 4.4 times greater than that of NE_1^+ on reaction with A_{10}^+. On the other hand, the rate constant for reaction of A_{10}^+ with NE_7^- is 4.3 times less than that for NE_7^+—a ratio comparable to the ratio of rate constants for alkaline hydrolysis (3.4) of the same two esters. For the longer chain esters, therefore, electrostatic effects are important only in the incorporation of ester into micelles of $A_{10}^+ + A_{10}H^{2+}$ and have no effect on the ensuing reaction of ester with A_{10}^+ within the micelle.

The results of our studies with the amine A_{10}^+ bear some semblance to enzymic catalysis. Substrates at low concentration ($\sim 5 \times 10^{-5}$ *M*) have been shown to be effectively complexed by positive amine–amine conjugate acid (A_T), half-saturation of substrate occurring at ~ 1 to 5×10^{-3} *M* in A_T. Some specificity

has been established which involves lyophobic and electrostatic binding. The ester in the resulting complex has been shown to undergo an "intramicellar" displacement, the rate of which is dependent upon the mole fraction of A_T as A_{10}^+. The maximum first-order rate constants for ester disappearance ($\sim$0.06 to 0.2 min^{-1}) are comparable to those for the poorer substrates of esteratic enzymes. We believe our initial endeavors in this new field show sufficient promise to pursue the topic further.

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

Communications to the Editor

Synthesis by the Merrifield Method of a Protected Nonapeptide Amide with the Amino Acid Sequence of Oxytocin[1]

Sir:

Since the synthesis of oxytocin was first accomplished by du Vigneaud, *et al.*,[2] several other syntheses have been reported,[3-12] all utilizing the same nonapeptide intermediate as was used in the original synthesis but, in some cases, with different protecting groups. With all of these approaches, in which the classical methods of peptide chemistry are employed, many weeks and, in some cases, months are required for the synthesis of the required protected nonapeptide amide intermediate and the over-all yields are low. Using the method of solid-phase peptide synthesis recently introduced by Merrifield,[13] a protected nonapeptide has been synthesized in high yield in a few days. Removal of the protecting groups followed by oxidation and purification yielded oxytocin.

The protected nonapeptide was synthesized in a stepwise manner beginning with 6 g of *t*-butyloxycarbonylglycyl resin containing 1.236 mmoles of glycine according to the general procedure of Merrifield,[13,14] with the following modifications. (1) Chloroform was used as a solvent for the triethylamine neutralization steps and for the washes immediately preceding and following these steps.[15] (2) Trifluoroacetic acid was used to remove the *t*-butyloxycarbonyl (Boc) group from the glutamine residue before the addition of the next protected amino acid residue.[16] (3) All coupling reactions were allowed to proceed for 4 hr. (4) The protected peptide was cleaved from the resin by ammonolysis.[17] Eight cycles of deprotection, neutralization, and coupling were carried out with appropriate Boc-amino acids,[18] producing the protected nonapeptide esterified to the resin. Boc-amino acids with protected side chains were S-Bzl-Cys and O-Bzl-Tyr. The final cysteine residue was added as the N-carbobenzoxy-S-benzyl (N-Z-S-Bzl) derivative. All coupling reactions to form peptide bonds were mediated by dicyclohexylcarbodiimide[19] in methylene chloride except those involving the carboxyl groups of Asn and Gln, which were allowed to react in dimethylformamide (DMF) as their nitrophenyl esters.[7b]

Following the coupling of the final residue, the dried resin weighed 7.24 g. The weight increase of 1.24 g represents the incorporation of 1.00 mmole of protected nonapeptide on the resin. This is 81% of the amount expected, based on the original glycine content of 1.236 mmoles of the esterified resin. Ammonolytic cleavage was effected as follows: the protected nonapeptide resin (2.5 g) was suspended in 85 ml of anhydrous methanol and the stirred suspension was bubbled with a stream of ammonia from a refluxing solution of ammonia, which contained sodium as a drying agent, at a temperature of $-5°$ for 2.5 hr with exclusion of moisture. Stirring at 4° was continued overnight and subsequently at 23° for 2 hr. The flask containing

(1) Supported by grants from the Medical Research Council of Canada and the Quebec Medical Research Council.

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