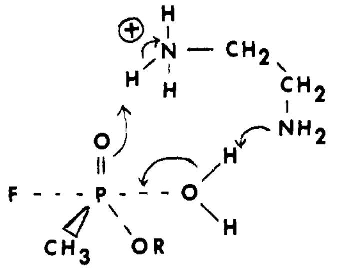
concerted hydrogen abstraction from the axial water by the unprotonated nitrogen and hydrogen donation to the equatorial phosphoryl oxygen by the protonated portion. The spatial arrangement for such an occurrence is plausible from geometric models (II).



II

In all cases, isopropylmethylphosphonic acid was the product when I and amines were present in aqueous solution. Isopropylmethylphosphonic acid may be formed by nucleophilic attack of amines[20] followed by rapid hydrolysis of the amidate or by general or specific base catalysis of a transition state containing a water molecule. In support of the latter mechanism, *O*-isopropyl *N*-benzylmethylphosphonoamidate, the intermediate expected from the nucleophilic attack of benzylamine on I, was found to be stable under the reaction conditions for several days, showing that it could not have been formed under the experimental conditions. Also, nmr studies of the reaction between I and benzylamine or 3-methoxypropylamine showed no evidence of amidate formation. A Brønsted slope of 0.50 is also consistent with a general base catalyzed hydrolysis mechanism;[17] much higher slopes have been obtained in nucleophilic displacements of fluoride ion from I (see ref 1–4). Furthermore, the linear free-energy equation reported herein is qualitatively similar to that reported for the base-catalyzed hydrolysis of diisopropylphosphorofluoridate (DFP),[9] *viz.*, $\log k_2 = 0.42\text{p}K_a - 4.9$. Marked dissimilarities between the rates of reaction of DFP and I are found in their reactions with nucleophiles where displacement on the phosphorus is the mechanistic pathway.

Finally, the "$\alpha$" amines, ethoxyamine and hydrazine, have reactivities no greater or only slightly greater than that predicted from their p$K_a$'s. If the "$\alpha$" effect is related to the polarizability of the nucleophile[3d] then its impact would be expected to be of much less importance in proton displacement reactions than in reactions involving attack on an atom which can accommodate a high electron density. For base-catalyzed hydrolyses, both the "charge" (as described in ref 1) and "$\alpha$" effects appear to be nonoperative. Use can be made of this observation, in conjunction with others, to distinguish between several base and nucleophilic catalytic mechanisms.

[20] Although amines are known to react with phosphoro- and phosphonochloridate esters to produce amidates, it should be pointed out that their reaction with the corresponding fluoridates in aqueous solution does not produce the amidate (see ref 10).

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# The Hydrolysis of *p*-Nitrophenyl Diphenyl Phosphate Catalyzed by a Nucleophilic Detergent[1]

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*Received June 20, 1970*

**Abstract:** Micelles of 1,1-phenylhydroxypropyl-2-dimethylalkylammonium bromide (I, alkyl = $n$-$C_{10}H_{21}$, $C_{12}H_{25}$) are good catalysts of the reaction of *p*-nitrophenyl diphenyl phosphate in aqueous hydroxide ion, relative to micelles of the corresponding trimethylalkylammonium bromide because of nucleophilic participation by an ionized hydroxyl group in the detergent. The variation of rate with increasing hydroxide ion concentration can be explained in terms of ionization of the hydroxyl group at high pH, and p$K_a \approx 12.7$. There is no special catalytic activity of micelles of I for reactions of fluoride ion. Micelles of 1,1-phenylmethoxypropyl-2-dimethyldodecylammonium bromide (II) are not particularly effective catalysts for reactions of hydroxide or fluoride ions with *p*-nitrophenyl diphenyl phosphate. The choline anion is approximately 35 times as reactive as hydroxide ion toward *p*-nitrophenyl diphenyl phosphate.

There are now many examples of micellar catalysis of reactions in solution, and the subject has been extensively reviewed.[2-4] In most of the catalytic systems studied the substrate is incorporated into the micellar phase where it is in a favorable position to be attacked by an external reagent,[2-4] or to decompose spontaneously.[5,6]

In a few systems the detergent contains a nucleophilic group which is the active reagent, and these systems

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[1] Support of this work by the Arthritis and Metabolic Diseases Institute of the USPHS is gratefully acknowledged.

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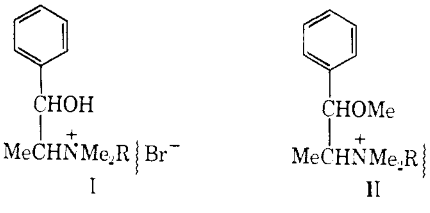
present analogies with enzymic catalysis.[7,8] Another approach has been to use a nucleophile which contains a bulky alkyl group,[9,10] so that the reagent is very readily taken up into the micellar phase, as in the reaction between *N*-myristyl-L-histidine and *p*-nitrophenyl esters,[9] or aryl phosphate dianions and *p*-nitrophenyl diphenyl phosphate.[10]

We have examined micellar effects upon the reaction of *p*-nitrophenyl diphenyl phosphate with hydroxide or fluoride ions, using the cationic detergents I and II.



I II

R = alkyl

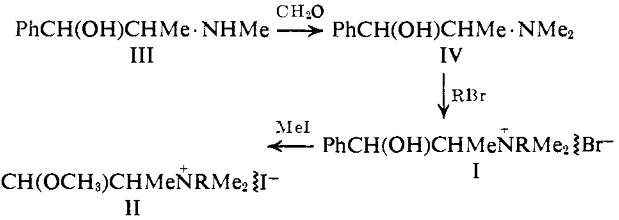
In micelles made up of these detergents the aryl group in the polar head should assist in the hydrophobic bonding of nonionic substrates to the micelle,[11] but the important feature is that the hydroxyl group in I might act as a nucleophilic reagent, particularly at high pH, where it should be ionized. The p$K_a$ of choline is 13.9,[12] and I should be more acidic than choline because of the (−)-I effect of the phenyl group,[13] and micellization should also increase the acidity. Alternatively the hydroxyl group in I might act as an electrophilic catalyst, *e.g.*, by hydrogen bonding to an anionic leaving group. One of the major problems in providing evidence for nucleophilic or electrophilic catalysis by micelles is the choice of the detergent which is to be taken as the reference compound, because a group such as hydroxyl, when substituted into a detergent, might affect the physical properties of the micelle and therefore affect its catalytic efficiency without participating chemically in the reaction. For this purpose we compared the catalytic efficiencies of I (R = $C_{10}H_{21}$,$C_{12}H_{25}$) on the reactions of *p*-nitrophenyl diphenyl phosphate with hydroxide and fluoride ions, with those of cetyl-, dodecyl-, and decyltrimethylammonium bromide and the methoxy derivative II (R = $C_{12}H_{25}$), because only micelles of I could act as nucleophilic or electrophilic catalysts. The reaction rates of fluoride and hydroxide ions with *p*-nitrophenyl diphenyl phosphate in the micellar pseudophase of several nonnucleophilic cationic detergents are not strongly affected by the nature of the polar head group, but the binding constants of the substrate to the micelle are very sensitive to it.[11,14]

Triaryl phosphates are reactive toward "hard" nucleophiles,[15] such as fluoride and hydroxide ions, which readily attack phosphorylphosphorus,[16] and therefore *p*-nitrophenyl diphenyl phosphate is a convenient substrate for this investigation. In addition micellar catalysis which involves nucleophilic participation by the hydroxyl group of micelles of detergents of structure I has some formal similarity to the phosphorylation of a serine hydroxyl group in alkaline phosphatase.[17]

## Experimental Section

**Materials.** The detergents were commercial samples or were prepared by quaternizing the tertiary amines with a long-chain *n*-alkyl halide, usually by heating in ethanol,[18] and the ammonium halides were purified by recrystallization in the usual way.[19]

(−)-Ephedrine (III) was N-methylated with formaldehyde by the procedure of Nakajima[20] giving *N*-methylephedrine (IV), which was purified by crystallization from methanol. It had mp 86–87° (lit.[20,21] 87–88°). It was quaternized using *n*-decyl bromide, *n*-dodecyl bromide, or *n*-hexadecyl bromide (cetyl bromide). The racemic dodecyl derivative was prepared in the same way starting from racemic ephedrine.



$$\begin{array}{ccc} \underset{\text{III}}{PhCH(OH)CHMe\cdot NHMe} & \xrightarrow{CH_2O} & \underset{\text{IV}}{PhCH(OH)CHMe\cdot NMe_2} \\ & & \downarrow{\scriptstyle RBr} \\ & \xleftarrow{MeI} & \underset{\text{I}}{PhCH(OH)CHMe\overset{+}{N}RMe_2\}Br^-} \\ \underset{\text{II}}{PhCH(OCH_3)CHMe\overset{+}{N}RMe_2\}I^-} & & \end{array}$$

The alkyltrimethylammonium halides were prepared by quaternization of trimethylamine,[18] and had the following properties: decyltrimethylammonium bromide, mp 245° dec (Br, calcd: 28.5; found: 28.1); dodecyltrimethylammonium bromide, mp 245° dec (lit.[22] 243°) (Br, calcd: 25.9; found: 25.7).

The detergents which were prepared by quaternizing *N*-methylephedrine were recrystallized from ethanol or ethanol–acetone and had the following properties: (−)-1,1-phenylhydroxypropyl-2-decyldimethylammonium bromide, mp 105–107° (*Anal.* Calcd for $C_{21}H_{38}NOBr$: C, 63.0; H, 9.6; N, 3.5; Br, 20.0. Found: C, 63.2; H, 9.7; N, 3.5; Br, 20.2); 1,1-phenylhydroxypropyl-2-dodecyldimethylammonium bromide, (−) mp 87–93°; (±) mp 135–138°. (*Anal.* Calcd for $C_{23}H_{42}NOBr$: C, 64.5; H, 9.9; N, 3.3; Br, 18.7. Found (−): C, 64.4; H, 9.9; N, 3.4; Br, 19.2; (±): C, 64.5, H, 10.1; N, 3.2; Br, 18.5). The cetyl derivative (I, R = $C_{16}H_{33}$) was very sparingly soluble in water, and therefore was not used as a micellar catalyst.

We attempted to O-methylate the hydroxy-substituted dodecylammonium bromide ((−)-I, R = $C_{12}H_{25}$) using either methyl bromide under a variety of conditions, or diazomethane with $BF_3$, but were unable to isolate crystalline products. However the methylation could be done using methyl iodide (3.0 g) in acetonitrile–1% water with KOH (1.2 g) and I, R = $C_{12}H_{25}$ (4.3 g). The mixture was heated under reflux for 6 hr, and the mixture was kept basic by further addition of KOH when necessary. The product was isolated by concentration of the reaction mixture after neutralization with HI. It was contaminated with a small amount of iodine which was removed with $SO_2$. (−)-1,1-Phenylmethoxypropyl-2-dimethyldodecylammonium iodide was then purified by several recrystallizations from hot water. Only 1.3 g was obtained but no attempt was made to recover additional product from the mother liquors because of possible contamination with KI. It had mp 178–181° (*Anal.* Calcd for $C_{24}H_{44}NOI$: C, 58.9; H, 9.1; N, 2.9; I, 26.0. Found: C, 58.7; H, 9.0; N, 3.0; I, 26.3).

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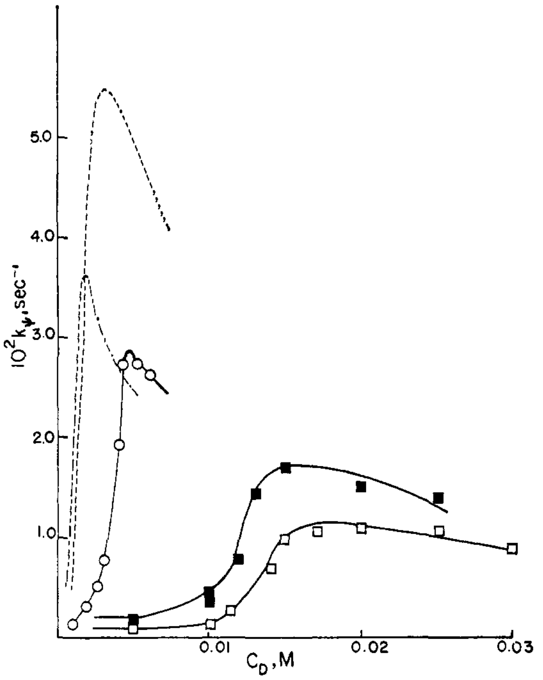

Figure 1. Micellar-catalyzed reactions of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium fluoride and hydroxide at 25.0° not involving chemical interaction with the detergent. Solid points denote reactions of hydroxide ions, open points, reactions of fluoride ions: ■, □, dodecyltrimethylammonium bromide; ○, (—)-I, R = $C_{12}H_{25}$. The broken lines denote catalysis by cetyltrimethylammonium bromide (ref 14): ----, $OH^-$; ------, $F^-$.

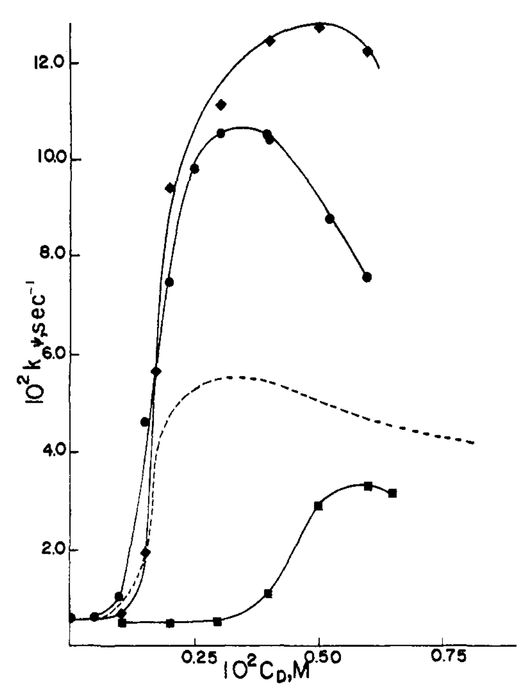

Figure 2. Micellar-catalyzed reactions of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium hydroxide at 2.50°. The broken line denotes catalysis by cetyltrimethylammonium bromide, ref 14: ●, (—)-I, R = $C_{12}H_{25}$; ◆, (±)-I, R = $C_{12}H_{25}$; ■, (—)-II, R = $C_{12}H_{25}$.

The infrared spectrum of this compound (Nujol mull) contained a prominent doublet at 1080 cm$^{-1}$, which is in the region characteristic of methoxy substituents.[23] The prominent peak at 3240 cm$^{-1}$ in the spectrum of I, R = $C_{12}H_{25}$, was not present in the spectrum of II, R = $C_{12}H_{25}$.

**Kinetics.** The reactions were followed spectrophotometrically using a Gilford spectrophotometer with a water-jacketed cell compartment.[14,24] The substrate was added as a dioxane solution using a square Teflon plunger. The final solution contained 0.5 vol % dioxane and the dioxane was purified before use.[25]

The units of the first-order rate constants, $k_\psi$, are sec$^{-1}$, and the second-order rate constants, $k_2$, were obtained by dividing $k_\psi$ by the concentration of the nucleophile. Most of the reactions were carried out at 25.0°. The low solubility of some of the detergents derived from *N*-methylephedrine caused some problems; for example the cetyl derivative could not be used, and it was necessary to use relatively high concentrations of I, R = $C_{10}H_{21}$, to catalyze the reaction of *p*-nitrophenyl diphenyl phosphate in hydroxide or fluoride ion, and solutions containing >0.02 *M* of this detergent often formed precipitates on standing. Probably for this reason with this detergent we found much more scatter in duplicate values of $k_\psi$ at high as compared with low detergent concentrations. With I, R = $C_{12}H_{25}$, sodium fluoride salted out the detergent at 25.0° at the higher concentrations, and therefore we did some experiments at 37.3°. Low solubility also prevented our examining the effect of added iodide ion over a large concentration range. Except where low solubility was a problem, duplicate values of $k_\psi$ agreed to within 3%.

**Critical Micelle Concentrations.** Detergents which contain the ephedrinyl group in the polar head group have lower critical micelle concentrations than the corresponding trimethylammonium detergents. The dye method was employed,[26,27] generally by measuring the absorbance at 5900 Å of 4 × $10^{-5}$ *M* bromophenol blue at 25.0° in 0.01 *M* NaOH. In 0.01 *M* NaOH the value of cmc for decyltrimethylammonium bromide was 0.034 *M*, which is close to that expected. (For dodecyltrimethylammonium bromide cmc = 0.016 *M* at 25.0°.)[26]

For 1,1-phenylhydroxypropyl-2-dimethyldecylammonium bromide (I, R = $C_{10}H_{21}$), cmc = 6 × $10^{-3}$ *M*, and for the corresponding dodecyl bromide (I, R = $C_{12}H_{25}$), cmc ≈ 3 × $10^{-4}$ *M*. For 1,1-phenylmethoxypropyl-2-dimethyldodecylammonium iodide (II, R = $C_{12}H_{25}$), cmc is 1.5 × $10^{-4}$ *M* with 1 × $10^{-5}$ *M* indicator and 2.5 × $10^{-4}$ *M* with 4 × $10^{-5}$ *M* indicator. This effect of the dye concentration upon the cmc has been observed in other systems.[26]

Precipitates were formed by interaction of the dye and the hydroxy- or methoxy-substituted detergents at concentrations below the cmc, and were solubilized by higher detergent concentrations. Formation of these insoluble precipitates is often observed in mixtures of ionic dyes and detergents.[28]

## Results

**Trimethylalkylammonium Bromides.** The first-order rate constants, $k_\psi$, for reactions of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium fluoride and hydroxide in the presence of dodecyltrimethylammonium bromide are given in Figure 1, together with earlier results for cetyltrimethylammonium bromide (CTABr),[14] and results for the reactions with fluoride ion in the presence of (−)-I, R = $C_{12}H_{25}$. Figures 2 and 3 give results for reactions of *p*-nitrophenyl diphenyl phosphate with hydroxide ion in the presence of I, R = $C_{12}H_{25}$ and $C_{10}H_{21}$. Figure 4 gives results for reactions with fluoride ion in the presence of I, R = $C_{12}H_{25}$, at 37.3°. (This higher temperature was used because of solubility problems.) Decyltrimethylammonium bromide has almost no kinetic effect on the reaction with 0.01 *M* sodium hydroxide at 25.0° (Table

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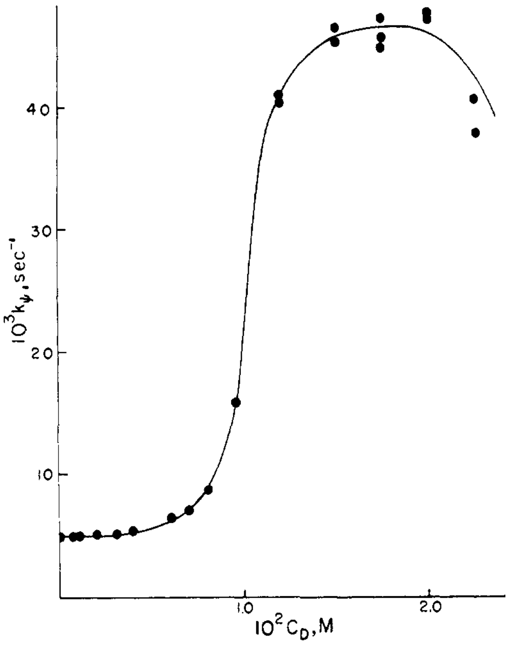

Figure 3. Micellar-catalyzed reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium hydroxide at 25.0° in the presence of (−)-I, R = $C_{10}H_{21}$.

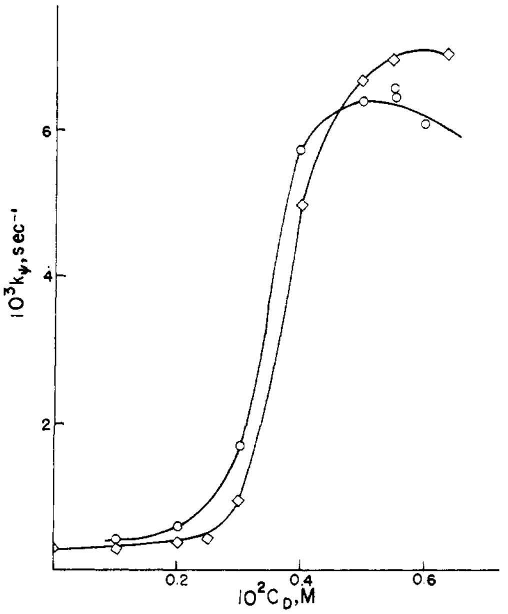

Figure 4. Micellar-catalyzed reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium fluoride at 37.3°: ○, (−)-I, R = $C_{12}H_{25}$; ◇, (±)-I, R = $C_{12}H_{25}$.

I). An initial slight decrease in rate is followed by a small increase, and micelles of this detergent are ineffective catalysts, possibly because they do not incorporate the substrate strongly. These results show that for a given chain length in the detergent a hydroxyl group in the polar head assists some, but not all, reactions, and this question will be discussed later. The results agree with earlier results in showing that the catalytic efficiencies of micelles derived from detergents of similar structure increase with increasing length of the alkyl chain.[2-4,29] In part these effects can be related to differences in the critical micelle concentration (cmc),[26] because on the simplest interpretation there should be no catalysis until micelles are present in the solution.[2-4] Two other factors are also important: (i) the magnitude of the binding constant between substrate and micelle and (ii) the rate constant for reaction in the micellar phase. The binding constant will affect the steepness of the rate increase with detergent concentration, for concentrations above the cmc, but the maximum value of $k_\psi$ for the micellar-catalyzed reaction will be approximately the rate constant, *k*, for reaction in the micellar phase, and will be obtained when all the substrate is taken up by the micelles.[2-4] Although the values of the maximum rate constants increase with increasing chain length of the alkyl group, our earlier results on the reaction of *p*-nitrophenyl diphenyl phosphate showed that the rates in the micellar phase are not particularly sensitive to the nature of the polar head group attached to the quaternary nitrogen atom, although it affects the binding constants[11] (*cf.* ref 30). It is not at first sight obvious why if reaction occurs at or near the micellar surface the rate constant in the micellar phase should depend upon the length of an alkyl group which is buried deeply in the micelle. However, for an approximately spherical micelle the charge density at the surface should decrease with increasing length of the alkyl group, assuming that the alkyl chains are arranged approximately radially in the micelle.[31] For attack of hydroxide or fluoride ion upon a phosphate ester the initial state includes a small high charge density anion, while the transition state is a large low charge density anion which should be stabilized, relative to the initial state, by interaction with a cation of low charge density. We see this effect in the behavior of electrolytes upon nucleophilic displacements by anions where the anionic transition state is stabilized relative to the nucleophilic anion by large low charge density cations, although this effect is much smaller than that given by cationic micelles.[32] In addition the micellar surface is probably rough,[2,31b] and the roughness will increase with increasing asymmetry in the head group and increasing alkyl chain length, and substrate incorporation and reaction could

**Table I.** Reaction with Hydroxide Ion in Decyltrimethylammonium Bromide[a]

| $C_D$, *M* | $10^3k_\psi$, sec$^{-1}$ |
|---|---|
|  | 4.83 |
| 0.005 | 4.73 |
| 0.010 | 4.51 |
| 0.020 | 3.93 |
| 0.050 | 3.96 |
| 0.075 | 5.16 |
| 0.100 | 5.07 |
| 0.125 | 4.10 |
| 0.150 | 3.60 |

[a] At 25.0° with 0.01 *M* NaOH.

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very well take place in these voids on the micellar surface.

**Hydroxy- and Methoxy-Substituted Detergents.** The hydroxy-substituted detergents (I, R = $C_{10}H_{21}$ and $C_{12}H_{25}$) are considerably better catalysts than the other detergents of corresponding chain length for reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium hydroxide at 25.0° (Figure 2). In fact the decyl compound ((−)-I, R = $C_{10}H_{21}$) is almost as good a catalyst as CTABr, and both (−)- and (±)-I, R = $C_{12}H_{25}$, are better catalysts (Figures 2 and 3), despite the shorter alkyl chains. The dodecyl compound, (−)-I, R = $C_{12}H_{25}$, is not an especially effective catalyst for reactions with fluoride ion (Figures 1 and 2). It is less effective than CTABr, and is only about twice as effective as dodecyltrimethylammonium bromide (Figure 1). However detergents of structure I exhibit their catalyses at low concentrations, simply because they have lower critical micelle concentrations than the corresponding alkyltrimethylammonium bromides (Experimental Section), and as noted earlier catalysis generally increases for a given head group with increasing length of the alkyl group.[2–4,29]

Although most of the experiments on catalysis by 1,1-phenylhydroxypropyl-2-dimethyldodecylammonium bromide (I, R = $C_{12}H_{25}$) were made using the (−) entantiomer the racemic mixture was also used in a few experiments. It is less soluble than the optically active material, and there are differences between the catalytic efficiencies of the racemic and optically active detergents for reactions of both fluoride and hydroxide ions. (Because of solubility problems caused by added sodium fluoride some of the results were obtained at 37.3° (Figures 2 and 4).) These results show that the racemic detergent gives micelles which contain both entantiomers, rather than a mixture of micelles which individually are optically pure. These physical and chemical differences are currently being examined further.

(−)-1,1-Phenylmethoxypropyl-2-dimethyldodecylammonium iodide (II, R = $C_{12}H_{25}$) is not a particularly effective catalyst for reactions of either fluoride or hydroxide ion with *p*-nitrophenyl diphenyl phosphate (Figure 2 and Table II); indeed it behaves similarly to I, R = $C_{12}H_{25}$, and dodecyltrimethylammonium bromide for both reactions. Replacement of bromide by iodide as the counterion should reduce the catalytic effectiveness of the detergent, but the effect should not be large, as is shown by the small retardations observed when iodide ion is added to solutions of I, R = $C_{12}H_{25}$ (Table III). The maximum concentration that could be used was 6.5 × $10^{-3}$ *M*, and we could not therefore go much past the rate maximum. The catalytic effectiveness of the methoxy-substituted detergent (II) is very similar to that of I, R = $C_{12}H_{25}$, and dodecyltrimethylammonium bromide for reactions of both fluoride and hydroxide ion (Figures 1 and 2 and Table II).

The maximum values of the rate enhancements with the various detergents at 25.0° (the values in parentheses are at 37.3°) are: (i) reactions of hydroxide ion: (−)-I, R = $C_{12}H_{25}$, 22; (±)-I, R = $C_{12}H_{25}$, 26; (−)-I, R = $C_{10}H_{21}$, 10; II, R = $C_{12}H_{25}$, 6; cetyltrimethylammonium bromide, 12; dodecyltrimethylammonium bromide, 3.5; decyltrimethylammonium bromide, no effect; (ii) reactions of fluoride ion: (−)-I, R = $C_{12}H_{25}$, 26 (21); (±)-I, R = $C_{12}H_{25}$ (24); (−)-I, R = $C_{10}H_{21}$, 10; II, R = $C_{12}H_{25}$, 26; cetyltrimethylammonium bromide, 35; dodecyltrimethylammonium bromide, 11. (The values for CTABr are from ref 14 and it should be noted that the concentrations for the rate maxima vary considerably from one detergent to another, and for a given length of alkyl group decrease with substitution into the polar head group). These results show that a hydroxyl group in the head increases the catalytic effectiveness of the detergent for reactions in the presence of hydroxide, but not fluoride, ion.

**Table II.** Reactions of Fluoride Ion with *p*-Nitrophenyl Diphenyl Phosphate in Detergent Solutions[a]

| Detergent $10^2C_D$, *M* | $\overset{+}{R}$'OMe$\}\overset{-}{I}$[b] | $\overset{+}{R}$'OH$\}\overset{-}{Br}$[b] |
|---|---|---|
| | 0.11 | 0.11 |
| 0.10 | | 0.14<br>0.13 |
| 0.20 | 0.21 | 0.32 |
| 0.25 | | 0.52 |
| 0.30 | 0.41 | 0.78 |
| 0.40 | 1.18 | 1.96 |
| 0.45 | | 2.73 |
| 0.50 | 2.28 | |
| 0.525 | | 2.76 |
| 0.60 | 2.73 | 2.65 |
| 0.65 | 2.04 | |

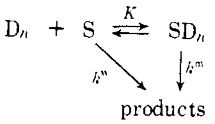
[a] Values of $10^2k_\psi$, $sec^{-1}$, at 25.0° with 0.01 *M* NaF in 0.015 *M* sodium borate buffer at pH 9.0. [b] R' = $C_6H_5CH \cdot CHMeNMe_2C_{12}H_{25}$.

**Table III.** Effect of Iodide Ion[a]

| $C_D$, *M* | $C_{NaI}$, *M* | $10^2k_\psi$, $sec^{-1}$ |
|---|---|---|
| 0.002[b] | | 9.11, 9.35 |
| 0.002[b] | 0.001 | 8.50 |
| 0.004[c] | | 10.5, 10.4 |
| 0.004[c] | 0.0015 | 8.40 |

[a] With 0.01 *M* NaOH at 25.0° and I, R = $C_{12}H_{25}$. [b] Racemic entantiomer. [c] (−) enantiomer.

Micellar catalysis depends upon both the extent of incorporation of substrate, S, into the micelles, $D_n$, and the reaction rates in the micellar and aqueous phases[2–5,24] (where $k^w$ and $k^m$ are first-order rate



constants with respect to the substrate, and $C_m$ is the concentration of micelles).

The overall first-order rate constant, $k_\psi$, is given by

$$k_\psi = \frac{k^w + k^mKC_m}{1 + KC_m} \tag{1}$$

In practice, eq 1 is inadequate for reactions which involve an external reagent,[2–4,24] although it is satisfactory for spontaneous hydrolyses of, for example, dinitrophenyl phosphates.[5] For most micellar-catalyzed reactions $k_\psi$ decreases at high detergent concentrations, because of either a negative salt effect of the counterion of the detergent,[29b,33] or a deactivation

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[33] L. R. Romsted and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 4404 (1968).

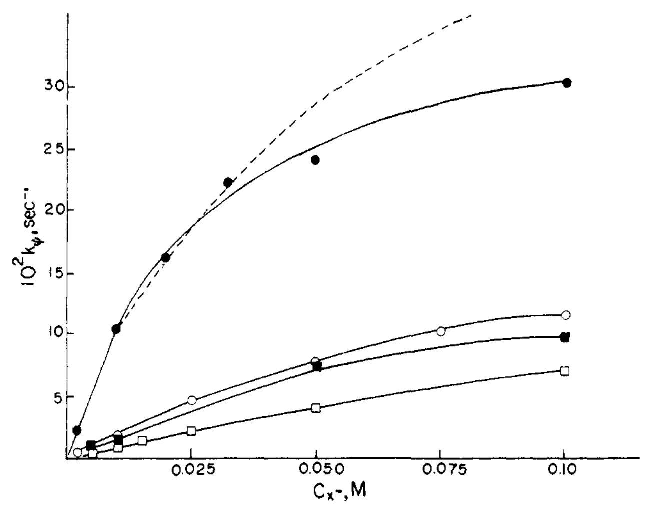


Figure 5. Effect of changes in the concentration of nucleophilic anions in micellar-catalyzed reactions of *p*-nitrophenyl diphenyl phosphate with sodium fluoride and hydroxide at 25.0°: solid points, hydroxide ion; open points, fluoride ion; ●, ○, (–)-I, R = $C_{12}H_{25}$, $C_D = 0.35 \times 10^2$ *M*; ■, □, $1.5 \times 10^{-2}$ *M* and $1.8 \times 10^{-2}$ *M* dodecyltrimethylammonium bromide, respectively. The broken line is calculated.

of the external reagent.[24,34] In favorable cases it is possible to evaluate $k^m$ even when eq 1 is only approximately followed, provided that $K$ can be determined independently. Unfortunately we cannot determine $K$ independently in the present system,[14] and therefore we will use the maximum values of $k_\psi$ as the value of $k^m$. The error caused by this assumption is probably not serious because it should be approximately the same for all the compounds and conditions used.

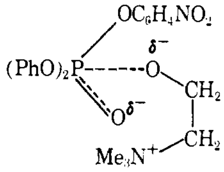
For a given detergent concentration the first-order rate constant does not increase linearly with the concentration of the nucleophilic anion (Figure 5 and Table IV). These decreases in the second-order rate constants with increasing nucleophile concentration are quite general for this type of reaction,[14,24] but they are much more marked in alkaline solutions when the detergent I contains an ionizable hydroxyl group. The values of $k_\psi^{0.025}/k_\psi^{0.01}$ in Table IV are the relative first-order rate constants in 0.025 and 0.01 *M* sodium hydroxide, and are independent of a limited change in detergent concentration, up to 0.02 *M* of I, R = $C_{10}H_{21}$. The variations of $k_\psi$ with nucleophile concentration under conditions in which there is no ionization of a hydroxyl group or in which the head group contains no hydroxyl group (Figure 5) are very similar to those generally observed for reactions of anionic nucleophiles in the presence of simple tetraalkylammonium ionic detergents.[14,24]

Table IV. Variation of Rate Constant with Hydroxide Ion Concentration[a]

| $10^2C_D$, *M* | $C_{OH^-}$, *M* | $10^3k_\psi$, sec$^{-1}$ | $k_\psi^{0.025}/k_\psi^{0.01}$ |
|---|---|---|---|
| 1.20 | 0.010 | 40.7 | 2.07 |
| 1.20 | 0.025 | 84.4 | |
| 1.50 | 0.010 | 46.0 | 1.95 |
| 1.50 | 0.025 | 89.2 | |
| 1.75 | 0.010 | 46.0 | 2.03 |
| 1.75 | 0.025 | 93.6 | |
| 2.00 | 0.010 | 47.5 | 1.76 |
| 2.00 | 0.025 | 83.3 | |

[a] At 25.0° with (–)-1,1-phenylhydroxypropyl-2-dimethyldecylammonium bromide.

**Nucleophilicity of Choline.** Choline is a very effective reagent toward *p*-nitrophenyl diphenyl phosphate at pH 12.0 in nominally 0.01 *M* NaOH. At 25.0° the first-order rate constant, $k_\psi$, in the absence of choline is $0.48 \times 10^{-2}$ sec$^{-1}$, with the second-order rate constant for hydroxide ion being 0.48 l. mol$^{-1}$ sec$^{-1}$. With 0.01 *M* choline at pH 12.0 $k_\psi = 0.58 \times 10^{-2}$ sec$^{-1}$, and with 0.05 *M* choline $k_\psi = 1.56 \times 10^{-2}$ sec$^{-1}$. For choline $pK_a = 13.9$,[12] and therefore if we assume that choline anion is the reactive species the second-order rate constant for its attack upon *p*-nitrophenyl diphenyl phosphate is 17 l. mol$^{-1}$ sec$^{-1}$ (based on reaction with 0.05 *M* reagent) showing that the choline anion is approximately 35 times as reactive as hydroxide ion. This comparison ignores electrolyte effects, which should in any effect be much smaller than those observed, but in general alkoxide ions are better nucleophiles than hydroxide ion in terms of their basicities.[35] An additional factor is that tetraalkylammonium ions have a positive salt effect upon the attack of hydroxide ion upon *p*-nitrophenyl diphenyl phosphate,[36] and insofar as some of the negative charge in the transition state will be dispersed over the phosphoryl oxygen atom or the leaving nitrophenoxide ion there may be favorable electrostatic interactions between these atoms or groups and the quaternary ammonium ion residue of choline, for example as shown below. Because of this favorable interaction in the transition state the positive charge does not reduce the nucleophilicity of the choline monoanion toward phosphorus, although it reduces its basicity by an inductive effect.



## Discussion

**Nature of the Catalysis.** A micelle derived from a detergent of general structure (I) could exhibit enhanced catalytic activity by virtue of the hydroxyl group acting (i) as a nucleophile especially at high pH when it could be ionized (Scheme I), or (ii) as a general acid (Scheme II).[37]

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(34) The absence of rate maxima in spontaneous hydrolysis of dinitrophenyl phosphate supports the latter explanation.[5]

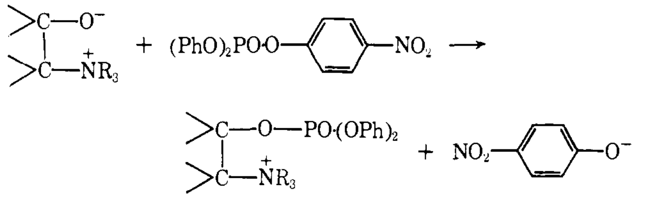
(35) T. C. Bruice and S. Benkovic, "Bio-organic Mechanisms," Benjamin, New York, N. Y., 1966, Chapter 1.

(36) C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, 33, 29 (1968).

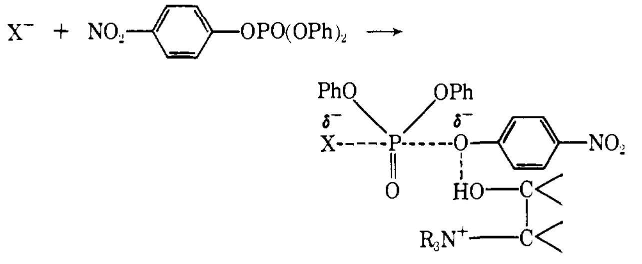
(37) For general discussions of intramolecular catalysis see ref 35 and 38.

(38) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

**Scheme I**



**Scheme II**



If the hydroxy group acted as a general acid we should find enhanced catalytic activity of detergents of structure I even when the external reagent $X^-$ is a fluoride ion, whereas if it is effective as a nucleophile enhanced catalysis should not be found for reactions of fluoride ions.

A third possibility is that the hydroxy group of I can act as a general base and activate a water molecule toward the substrate. Such a reaction would be kinetically indistinguishable from that of i, but it seems improbable because water is very much less reactive than hydroxide ion toward triaryl phosphates,[36] and general base catalysis does not seem to be of major importance in phosphate ester hydrolysis, although it has been observed in some reactions.[16]

The presence of the hydroxyl group in the head group of the detergent does not markedly increase the catalytic effectiveness of an alkyltrimethylammonium ionic detergent for reactions of fluoride ions (Figure 1), suggesting that the hydroxyl group is not markedly affecting the properties of the micelle or acting as a general acid, possibly because the driving force for the reaction comes largely from the strength of the forming fluorine–phosphorus bond. The small rate increase over the trimethylammonium ion detergent could be related to differences in the roughness of the surface, although the rate maximum is observed at low detergent concentration because of the low critical micelle concentrations for I, R = $C_{12}H_{25}$. (An aryl substituent in the polar head group reduces the cmc and leads to micellar catalysis at low detergent concentrations.[11])

The possibility that nonbonding interactions involving the head group are responsible for the high reactivity of detergents of structure I for hydroxide ion reactions is further reduced by the observation that 1,1-phenylmethoxypropyl-2-dimethyldodecylammonium iodide (II, R = $C_{12}H_{25}$) is considerably less catalytically effective than I, R = $C_{12}H_{25}$, for reactions of hydroxide, but not of fluoride ion (Figure 2 and Table II). All the evidence therefore suggests that the hydroxy group of I is ionized at high pH and attacks phosphoryl phosphorus.

**Reaction with Hydroxide Ion.** In the following discussion we will assume that the oxide ion (V) formed by ionization of a hydroxy-substituted detergent (I) will attack the phosphoryl group of a substrate molecule which is incorporated into the micelle (Scheme I). It is also possible that one ionized detergent molecule could be attacking the substrate nucleophilically, while another detergent molecule is hydrogen bonding to the leaving group through its hydroxyl group, but as already noted electrophilic catalysis seems unlikely, and it should not affect the kinetic order with respect to hydroxide ion, except at very high pH. There is evidence for such bifunctional catalysis in hydrolyses of *p*-nitrophenyl acetate catalyzed by copolymers of vinyl imidazole and vinyl phenol in alcohol.[3]

The variation of rate constant with hydroxide ion concentration for reaction when all the substrate is incorporated into the micellar phase can be treated quite simply, on the assumption that all the reaction follows Scheme I. At low pH the concentration of oxide ion V, and therefore the reaction rate, will be proportional to hydroxide ion concentration, until pH $\approx$ p$K_a$ for ionization of the hydroxyl group, and if the ionized form of the detergent is the reagent, the kinetic scheme for reaction in the micellar phase is

$$(\mathrm{DOH})_{n+1} + \mathrm{O\bar{H}} \overset{K'}{\rightleftarrows} (\mathrm{DOH})_n\mathrm{D\bar{O}}$$

$$(\mathrm{DOH})_n\mathrm{D\bar{O}} + \mathrm{S_m} \xrightarrow{k'} \text{products}$$

where D = PhCHCHMe·$N^+Me_2R$, and $S_m$ is the substrate in the micellar phase and $K' = K_a/K_w$. We will assume that $k^m$ is given by the value of $k_\psi$ at the rate maximum in plots of $k_\psi$ against $C_D$. The error introduced by this assumption (Results) should not be too serious because it should be approximately constant over the range of hydroxide concentrations used.

Provided that $C_{\mathrm{O\bar{H}}} \gg$ detergent concentration, the overall first-order rate constant, $k^m$, for reaction in the micellar phase is given by

$$k^m = \frac{k'C_{\mathrm{O\bar{H}}}(K_a/K_w)}{1 + C_{\mathrm{O\bar{H}}}(K_a/K_w)} \qquad (2)$$

where $K_a$ is the acid dissociation constant of the micellized detergent.

Equation 2 is generally used in the reciprocal form (eq 2a)[39] and the values of $k'$ and therefore $K_a$ can be

$$1/k^m = 1/k' + \frac{K_w}{k'K_aC_{\mathrm{O\bar{H}}}} \qquad (2a)$$

obtained by extrapolation to infinite reagent concentration. Unfortunately this procedure is unpractical in the present system because high concentrations of electrolytes affect the value of the second-order rate constant for reaction in the micellar phase, as shown for example by the nonlinearity of the plots of $k_\psi$ against nucleophile concentration in cases in which there is no acid dissociation of the detergent (Figure 5 and ref 11, 14, and 24). However these plots are linear for low concentrations of nucleophilic anions, and we can obtain $k'K_a/K_w$ when $C_{\mathrm{O\bar{H}}} \rightarrow 0$ (Figure 5), and $k'K_a/K_w$ = 11.1 $\mathrm{mol^{-1}\ sec^{-1}}$ on the assumption that $k^m$, the first-order rate constant for overall reaction in the micellar phase, is given by the values of $k_\psi$ for detergent concentrations = $3.5 \times 10^{-3}$ *M*, *i.e.*, that all the substrate is then in the micellar phase.

We use eq 2b, and plot the left-hand side, *i.e.*, ($11C_{\mathrm{O\bar{H}}}/k^m$) against $C_{\mathrm{O\bar{H}}}$ (Figure 6). The plot is

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[39] F. R. Duke, *J. Amer. Chem. Soc.*, **69**, 3054 (1947).

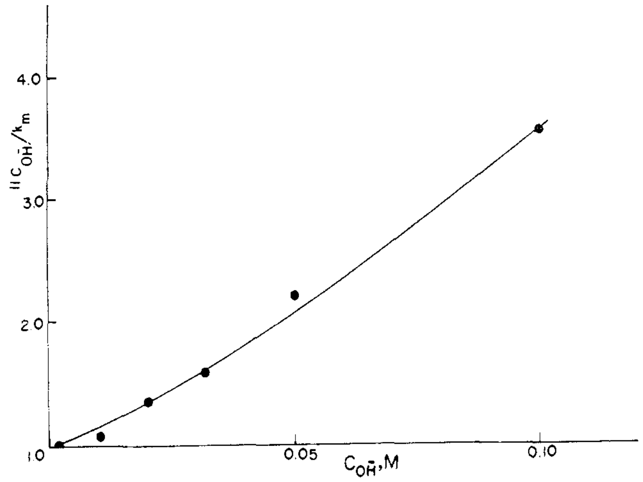

Figure 6. Kinetic analysis of the reaction of *p*-nitrophenyl diphenyl phosphate with varying concentrations of sodium hydroxide in the presence of $0.35 \times 10^{-2}$ *M* (–)-I, R = $C_{12}H_{25}$.

linear for low hydroxide ion concentrations and the initial slope gives $K_a/K_w$ = 18 l. mol$^{-1}$. We can use the

$$\frac{k'K_aC_{O\bar{H}}}{k^mK_w} = 1 + \frac{K_aC_{O\bar{H}}}{K_w} \qquad (2b)$$

values of $k'K_a/K_w$ and $K_a$ to calculate $k_\psi$ at various hydroxide ion concentrations (Figure 5, broken line) and they fit the experimental values up to *ca.* 0.05 *M* sodium hydroxide ion where electrolyte effects begin to be important. Such electrolyte effects generally appear at concentrations of anionic nucleophile greater than 0.05 *M* even when there is no nucleophilic participation by the micelles (Figure 5 and ref 11, 14, and 24). The upward curvature in Figure 6 is the result of electrolyte effects and the assumptions made in deriving eq 1 and 2. The kinetic interference caused by the electrolyte effects cannot be removed by the maintenance of ionic strength because of the specificity of electrolyte effects upon micellar catalysis,[2,5,40] but it should not be particularly important at $C_{O\bar{H}} < 0.05$ *M*. Using the value of $K_a/K_w \approx 18$ l. mol$^{-1}$, we calculate $K' \approx 0.6$ sec$^{-1}$, and comparison of this value with that of 0.48 l. mol$^{-1}$ sec$^{-1}$ for the reaction of hydroxide ion with *p*-nitrophenyl diphenyl phosphate at 25.0° in the absence of detergent,[42] shows that the rate of reaction of this triaryl phosphate with the alkoxide ion of I, R = $C_{12}H_{25}$, in the micellar phase is equal to that in aqueous 1.25 *M* aqueous hydroxide ion (assuming that a second-order kinetic form is followed at such a high concentration of hydroxide ion). This rate enhancement is in the lower range of values generally found for intramolecular nucleophilic attack.[35,38] It probably underestimates the catalytic effectiveness of a micelle derived from a nucleophilic detergent, because the negative charge on the alkoxide ion should be able to move rapidly by proton transfer around the surface of the micelle and should only be adjacent to the substrate for a small fraction of the time. If we assume that each micelle incorporates only one substrate molecule and has only one ionized hydroxyl group, and that they do not interact except when reacting chemically, the reactants will be adjacent to each other for only $^1/_N$ of the time, where $N$ is the aggregation number of the micelle, and is probably 50–100.[26]

In order to calculate the acid dissociation constant $K_a$, using eq 2, we have to assume that the detergent does not affect the autoprotolysis constant of water. On this assumption $K_a = 1.8 \times 10^{-13}$, *i.e.*, p$K_a \approx 12.7$. For choline p$K_a$ = 13.9,[12] and the greater acidity of I in the micellar form is understandable in terms of the effects of the phenyl group[13] and the positive charge of the micelle.

So far as reactions in the micellar phase are concerned an ionized hydroxyl group in the detergent is more reactive than an external hydroxide ion. For micelles of dodecyltrimethylammonium bromide $k_2$ = 1.65 l. mol$^{-1}$ sec$^{-1}$ at the rate maximum for reaction of hydroxide ion with *p*-nitrophenyl diphenyl phosphate (Figure 1), and for the corresponding first-order reaction with the ionized form of (–)-I, R = $C_{12}H_{25}$, in the micellar phase $k' \approx 0.6$ sec$^{-1}$, *i.e.*, the rate is that calculated for *ca.* 0.3 *M* hydroxide ion in the micellar phase of dodecyltrimethylammonium bromide. Two opposing factors are involved in these differences: (i) alkoxide ions are generally more nucleophilic than hydroxide ions, in terms of basicity[43] and (ii) there will probably not be more than one ionized hydroxyl group per micelle, except at high pH, whereas there will be a large number of hydroxide ions in the Stern layer of a cationic micelle. (Approximately two-thirds of the charge of a cationic micelle is neutralized by counterions,[26] and if the surface of the micelle is assumed to be "rough" these counterions could be very close to the substrate in the micellar phase, and in a favorable environment for chemical reaction.[2–4]) These comparisons ignore the differences between micelles with the same long-chain alkyl group, but different head groups, but the fluoride ion results suggest that these differences should not be large.

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[40] Added electrolytes could affect reaction rate in the micellar phase directly or indirectly by affecting the physical properties of the micelles.[41]

[41] E. W. Anacker and M. H. Ghose, *J. Amer. Chem. Soc.*, **90**, 3161 (1968).

[42] C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).

[43] Reference 35, Chapter 1.