Micellar Effects upon the Reaction of *p*-Nitrophenyl Diphenyl Phosphate with Hydroxide and Fluoride Ions[1]

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The reactions between *p*-nitrophenyl diphenyl phosphate and hydroxide or fluoride ions in water at 25° are catalyzed strongly by cationic micelles of cetyltrimethylammonium bromide, with the rate increasing to a maximum at *ca.* $3 \times 10^{-3}\ M$ detergent. The detergent increases the activation enthalpy, but makes the activation entropy less negative. Added salts inhibit the catalysis, and the inhibition is largest with anions of low charge density. Anionic micelles of sodium lauryl sulfate strongly inhibit the reaction, as does the uncharged detergent Igepal, but here there is marked inhibition at submicellar concentrations. The inhibition can be related to the extent of incorporation of the substrate into the micelles, or its association with the detergent.

The hydrolysis of *p*-nitrophenyl diphenyl phosphate is catalyzed by acids, and the reaction with hydroxide ion is very much faster than with water.[2] We have found that the hydrolysis of the dianions of 2,4- and 2,6-dinitrophenyl phosphate are strongly catalyzed by cetyltrimethylammonium bromide, a cationic micelle,[3] and we were interested in examining micellar effects for nucleophilic attack upon *p*-nitrophenyl diphenyl phosphate. Much of the interest in micellar catalysis and inhibition stems from analogies with enzymic reactions. The hydrolysis of dianions of dinitrophenyl phosphate is a "phosphorylation" of water in which the reactive species is considered to be a metaphosphate ion[4,5]

$$\mathrm{ArOPO_3{}^{2-}} \xrightarrow{\text{slow}} \mathrm{ArO^-} + \mathrm{PO_3{}^-} \xrightarrow[\mathrm{H_2O}]{\text{fast}} \mathrm{H_2PO_4{}^-}$$

whereas the reaction between triaryl phosphates and anionic nucleophiles involves rate-limiting attack upon a phosphoryl group[2,6] which is shown below and

$$\mathrm{ArOPO(OPh)_2} + \mathrm{X^-} \longrightarrow \mathrm{ArO^-} + \mathrm{XPO(OPh)_2}$$

mechanisms of these reactions can be considered as models for enzymic phosphorylations.[7] There are several examples of micellar effects upon the attack of nucleophilic anions upon uncharged substrates, usually carboxylic esters.[8,9] Cationic micelles generally assist these reactions, and anionic micelles retard them, as expected from electrostatic considerations. In some systems the reactive group has been incorporated into the detergent structure.[10,11] Some of these micellar studies were done using buffers to control the hydroxide ion concentration, and it is difficult to know whether the hydrogen ion activity as measured by a glass electrode in the presence of micelles can be used to determine the hydroxide ion concentration because the pH in the micelle may not be that measured in the solution, and in addition the micelle may change the autoprotolysis constant of water. Therefore in these studies we have used hydroxide or fluoride ion in known concentration as the nucleophiles. Although micelles have generally similar effects upon the anionic reactions of *p*-nitrophenyl diphenyl phosphate as upon other anion–molecule reactions, some of our results were unexpected.

Experimental Section

Materials.—The preparation of *p*-nitrophenyl diphenyl phosphate has been described. The ester after recrystallization from hexane had mp 49–50° (lit.[12] mp 49–51°).

The purification of the detergents and salts has been described.[13] The cationic detergent was cetyltrimethylammonium bromide (CTA), the anionic detergent was sodium lauryl sulfate, and the uncharged detergent was Igepal, which is a dinonylphenol condensed with ethylene oxide units, and which we designate as DNPE, and has mol wt 1404. Distilled and deionized water was used in these experiments.

Critical Micelle Concentrations.—The cmc of the ionic detergents are slightly decreased by NaOH,[13,14] and values of the cmc in water are CTA, $8 \times 10^{-4}\ M$; NaLS, $6 \times 10^{-3}\ M$; DNPE, $4.7 \times 10^{-4} M$. In 0.01 *M* NaOH they should be approximately 4.8×10^{-4}, 4.7×10^{-4}, and $4.7 \times 10^{-3}\ M$, respectively.[13]

Solubilities.—The solubility of *p*-nitrophenyl diphenyl phosphate was determined by shaking it with detergent solution. Samples were taken for periods up to 1 week, and filtered and the pH brought to 9.0 with borate buffer, so that any *p*-nitrophenol which had been formed by hydrolysis could be measured spectrophotometrically. Sodium hydroxide was then added to give a concentration of 0.1 *M* and to hydrolyze the ester and the *p*-nitrophenol was redetermined spectrophotometrically. In a few experiments the solution was diluted with ethanol before the absorbances were measured in case the phenoxide ion formed a "lake" with the detergent. No difference in absorbance was found.

Satisfactory results were obtained with DNPE (Table I) but

TABLE I

SOLUBILITY OF *p*-NITROPHENYL DIPHENYL PHOSPHATE[a]

10^3C_D, *M*	Absorbance	$\alpha/1-\alpha$
	0.035	
0.10	0.110	2.1
0.25	0.225	5.4
0.50	0.320	8.2
0.75	0.594	16
2.00	1.269	35
3.50	2.046	58
5.00	2.534	70

[a] In aqueous DNPE at 25°.

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(1) Support from the National Institute of Arthritis and Metabolic Diseases of the U. S. Public Health Service is gratefully acknowledged.

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

(3) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K-U. Yang, *J. Amer. Chem. Soc.*, **90**, 5512 (1968.

(4) A. J. Kirby and A. G. Varvoglis, *ibid.*, **89**, 415 (1967).

(5) C. A. Bunton, E. J. Fendler, and J. H. Fendler, *ibid.*, **89**, 1221 (1967).

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(7) T. C. Bruice and S. J. Benkovic, "Bio-Organic Mechanisms," Vol. VI, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter V.

(8) (a) E. F. Duynstee and E. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540, 4542 (1959); *Tetrahedron*, **21**, 2401 (1965); (b) M. T. A. Behme and E. H. Cordes, *J. Amer. Chem. Soc.*, **87**, 260 (1965); M. T. A. Behme, J. G. Fullington, and E. H. Cordes, *ibid.*, **87**, 266 (1965).

(9) F. M. Menger and C. E. Portnoy, *ibid.*, **89**, 4698 (1967).

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(12) W. M. Gulich and D. H. Geske, *ibid.*, **88**, 2928 (1966).

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(14) M. L. Corrin and W. D. Harkins, *ibid.*, **69**, 679 (1947); E. W. Anacker, R. M. Rush, and J. S. Johnson, *J. Phys. Chem.*, **68**, 81 (1964).

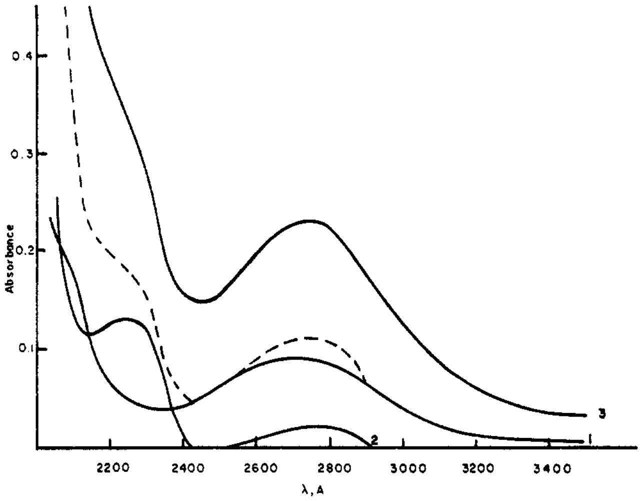

Figure 1.—Spectra of 2 × 10^{-5} M *p*-nitrophenyl diphenyl phosphate (1), DNPE (2), and the mixture (3). The broken line is the sum of curves 1 and 2.

not with CTA or NaLS. With CTA at pH 7 there is appreciable hydrolysis of *p*-nitrophenyl diphenyl phosphate during the time required for solubilization, and erratic results were obtained with NaLS, although it effectively solubilizes the substrate.

Spectra.—The ultraviolet spectra of *p*-nitrophenyl diphenyl phosphate and DNPE were measured at 25.0° in water containing 0.4% dioxane using a Gilford spectrophotometer, with solvent in the reference cell. Figure 1 shows the spectra for 2 × 10^{-5} M reagents, and a mixture of the reagents, and the absorbance of the mixture is greater than the sum of those of the components. Similar results were obtained with 1 × 10^{-5} M reagents. The low solubility of the phosphate prevented our investigating a wider range of concentration.

Kinetics.—The formation of *p*-nitrophenol was followed spectrophotometrically using a Gilford spectrophotometer fitted with a water-jacketed cell compartment.[3]

The substrate was dissolved in purified dioxane and approximately 0.015 ml of this solution was placed in small holes in a square Teflon holder which was rapidly plunged into the reaction cell which contained the detergent solution, so that the substrate concentration was *ca.* 10^{-5} M and that of dioxane was 0.4% vol. %. The nucleophile was in large excess, and first-order rate constants, k_ψ (sec^{-1}), were calculated graphically. Good linear plots were obtained for up to three half-lives. The second-order rate constants, k_2 (l. mol^{-1} sec^{-1}), were calculated from k_ψ. In the absence of detergent the reaction between *p*-nitrophenyl diphenyl phosphate and hydroxide ion is second order, except at high concentrations of hydroxide ion, and the results in Table II show that this is also true with fluoride ion. Borate buffer was used to control the pH of solutions for the experiments with fluoride ion.

Table II

Second-Order Rate Constants for Reaction between *p*-Nitrophenyl Diphenyl Phosphate and Fluoride Ion[a]

C_{NaF}, M	10^2k_2, l. mol^{-1} sec^{-1}
0.01	10.5
0.01	5.33[b]
0.01	2.29[c]
0.02	10.5
0.03	10.4
0.04	10.2
0.10	10.1

[a] At 25.0° in the absence of detergent, and in 0.015 M borate buffer, pH 9.0. [b] At 15.4°. [c] At 5.0°.

Results

Solubilities.—Both the ionic and uncharged detergents solubilize *p*-nitrophenyl diphenyl phosphate.

The incorporation of the substrate into a micellized detergent can be treated quantitatively by assuming that the aggregation number, N, and the cmc of the micelle remain constant, and that there is an equilibrium between the substrate in solution, S, and that in the micelle SD_n.[13]

$$D_n + S \overset{K}{\rightleftharpoons} SD_n$$

The concentration of micelles, C_m, is given by eq 1,

$$C_m = (C_D - \text{cmc})/N \qquad (1)$$

where C_D is the detergent concentration. These approximations are least satisfactory for detergent concentrations near the cmc, because added solutes can affect micellization.[11,15,16]

On the assumption that the increase in solubility of S is due wholly to its incorporation into the micelles and that we can calulate the amount, α, of the substrate present in the micelles from its relative solubilities in water and detegent solution, we obtain eq 2.[13]

$$K/N = [\alpha/(1 - \alpha)]\,[1/(C_D - \text{cmc})] \qquad (2)$$

The values of α are given in Table I. A plot of $\alpha/(1 - \alpha)$ against C_D is a straight line, which unexpectedly intercepts at the origin and not at the cmc as predicted by eq 2, although in the absence of substrate cmc = 4.7 × 10^{-4} M. The value of K/N calculated from the slope is 16,000; the aggregation number of DNPE is not known, and therefore we cannot calculate K.

The solubilization of the substrate at apparently

Table III

Reactions at Low Concentrations of Uncharged Detergent[a]

	Reagent	
10^2C_D, M	NaOH	NaF[b]
	48.3[c]	10.5
0.005	47.8	10.5
0.010	45.1	9.92
0.020	39.0	
0.030	38.2	7.98
0.050	29.5	6.97
0.100	21.4	5.07
0.250	12.3	2.88
0.500	7.17	1.85

[a] Values of 10^2k_2 l. mol^{-1} sec^{-1} at 25.0°, with 0.01 M reagents in DNPE. [b] In 0.015 M borate buffer, pH 9.0. [c] Mean of two values.

Table IV

Reaction in the Presence of NaLS and DNPE[a]

Detergent	C_D	NaOH	NaF
		97.5	22.7
NaLS	0.004	31.8	1.13
NaLS	0.005	12.9	
NaLS	0.006	5.4	0.58
NaLS	0.0075	2.55	
NaLS	0.008		0.39
DNPE	0.004	5.43	1.68
DNPE	0.006	4.85	1.50
DNPE	0.008	4.80	1.35

[a] Values of 10^2k_2 l. mol^{-1} sec^{-1} at 35.8°, with 0.01 M nucleophiles.

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

(16) See ref 9 for a discussion of the validity of these approximations as applied to kinetic effects of detergents.

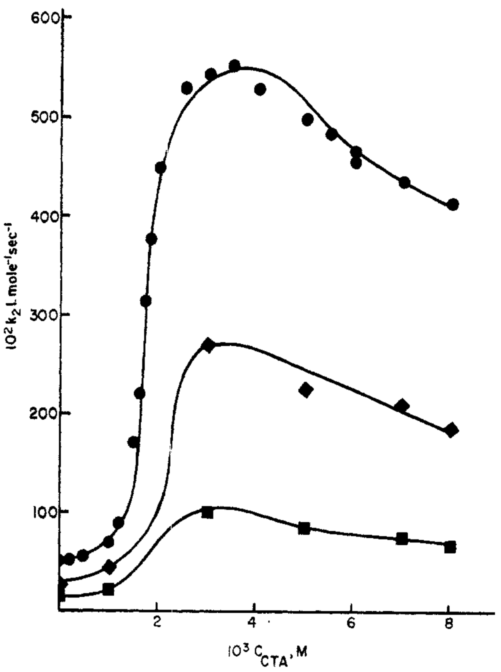

Figure 2.—Catalysis of the reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium hydroxide by CTA: ●, at 25.0°; ◆, at 15.4°; ■, at 5.0°.

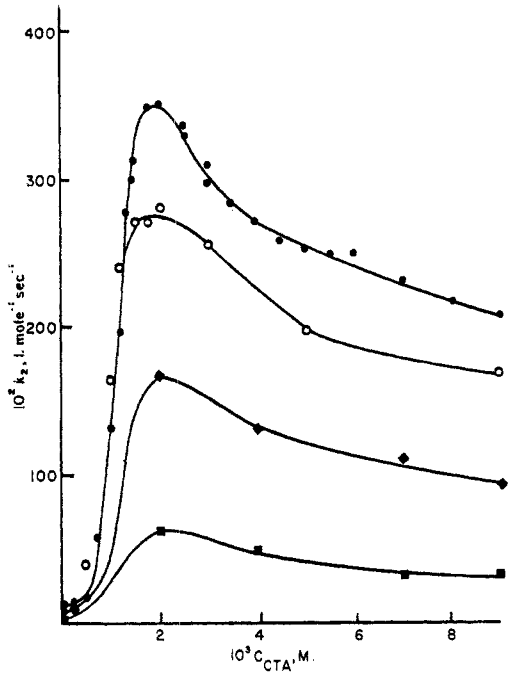

Figure 3.—Catalysis of the reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium fluoride at pH 9.0: ●, at 25.0° with 0.015 *M* borate buffer; ○, at 25.0° with 0.03 *M* borate buffer; ◆, at 15.4° with 0.015 *M* borate buffer; ■, at 5.0° with 0.015 *M* borate buffer.

submicellar detergent concentrations suggests that it is associating with the detergent (*cf.* ref 11 and 15).

Kinetics.—In the absence of detergent the reaction between the substrate and sodium hydroxide or fluoride is second order, and hydroxide is approximately five times as reactive as fluoride ion (Table II and ref 2; *cf.* ref 6). A cationic detergent, CTA, strongly catalyzes the reactions of *p*-nitrophenyl diphenyl phosphate with both hydroxide and fluoride ions, but in the presence of detergents the reactions with hydroxide are also faster than with fluoride ion (Figures 2 and 3).

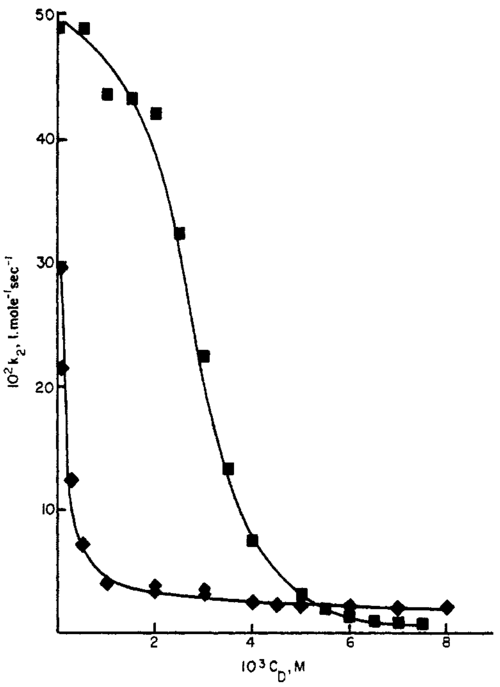

Figure 4.—Inhibition of the reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium hydroxide at 25.0°: ■, NaLS; ◆, DNPE.

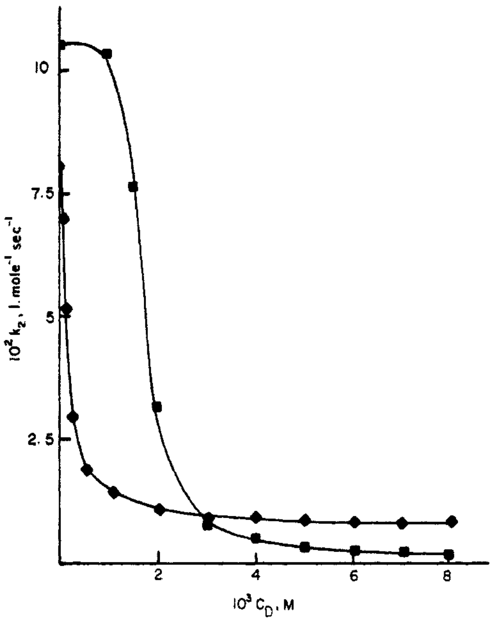

Figure 5.—Inhibition of the reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium fluoride in 0.015 *M* borate buffer at 25.0°: ■, NaLS; ◆, DNPE.

The second-order rate constants increase to a maximum at a detergent concentration of 3×10^{-3} *M* for sodium hydroxide (Figure 2) and 2×10^{-3} *M* for sodium fluoride (Figure 3). Anionic and nonionic detergents NaLS and DNPE decrease the reactivity of both hydroxide and fluoride ion toward the substrate (Figures 4 and 5). Because the effect of DNPE in low concentration is very large the values of k_2 cannot be plotted conveniently at low detergent concentration, and they are given in Table III. A few experiments were carried out at 35.8° with NaLS and DNPE. The rate constants are given in Table IV. The general effects of these detergents do not depend upon temperature.

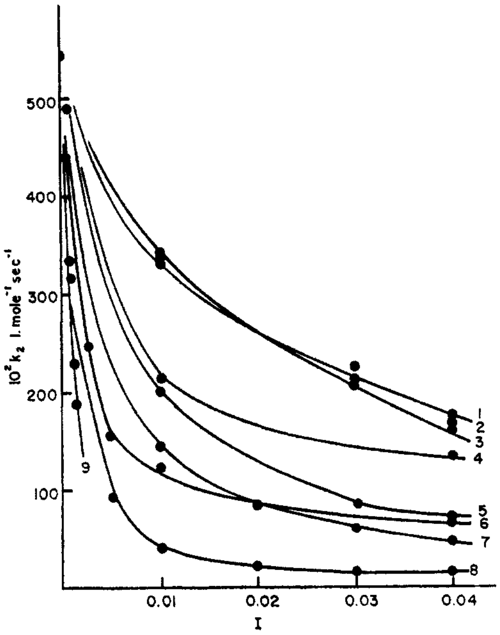

Figure 6.—Ionic strength effects upon the CTA-catalyzed reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium hydroxide in 0.0035 *M* CTA at 25.0°: 1, CH_3SO_3Na; 2, $(CH_3)_4NCl$; 3, NaCl; 4, Na_2SO_4; 5, NaBr; 6, $o\text{-}C_6H_4(CO_2Na)_2$; 7, $NaNO_3$; 8, NaOTos; 9, 1-$C_{10}H_7SO_3Na$.

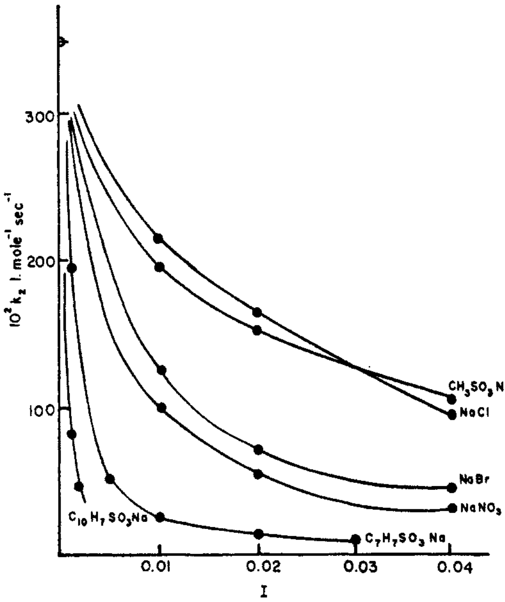

Figure 7.—Ionic strength effects upon the CTA-catalyzed reaction of *p*-nitrophenyl diphenyl phosphate with 0.01 *M* sodium fluoride in 0.002 *M* CTA and 0.015 *M* borate buffer at 25.0°.

Added salts have marked effects on the reaction rate. The results are given in Figures 6 and 7 for 0.0035 *M* CTA and for NaOH and 0.002 *M* CTA for NaF, and in Table V for 0.008 *M* CTA. They show that all added salts inhibit the reactions. In addition the over-all first-order rate constants, k_ψ, in a mixture of sodium fluoride and hydroxide ion are generally less than the sum of the individual first-order rate constants for reaction of fluoride and hydroxide ion taken separately (Table VI), showing that fluoride and hydroxide ions inhibit each other's reactions, and borate buffer slightly inhibits the reaction between the substrate and sodium fluoride (Figure 3).

Table V

Salt Effects upon the Detergent-Catalyzed Reaction between *p*-Nitrophenyl Diphenyl Phosphate and Hydroxide Ion[a]

Salt	C_{salt}, *M*	
	0.01	0.03
NaCl	277	168
NaBr	171	84
$NaNO_3$	135	60

[a] Values of 10^2k_2 l. mol^{-1} sec^{-1} at 25.0° with 0.01 *M* NaOH and 0.008/CTA *M*; in the absence of added salt $10^2k_2 = 414$ l. mol^{-1} sec^{-1}.

Table VI

Detergent-Catalyzed Reaction in Mixtures of Sodium Fluoride and Hydroxide[a]

C_{NaF}	10^2k_ψ, sec^{-1} Obsd	Calcd[b]
	5.51	
0.01	8.40	8.35
0.02	9.75	11.2
0.03	11.0	14.0
0.04	12.4	16.8

[a] At 25.0° with 0.01 *M* NaOH and 0.0035 *M* CTA. [b] Calculated from the relation $k_\psi = k_2^{OH}C_{OH} + k_2^{F}C_F$.

The second-order rate constants for a given CTA concentration decrease with increasing concentrations of fluoride or hydroxide ion (Table VII), but the effects of changes in the anion concentrations are small, as compared with the over-all effects of the detergent, and are probably caused by salt effects upon the micellization of the detergent. Such properties as the aggregation number and critical micelle concentration of detergents are sensitive to added electrolytes. For example, Anacker and Ghose have shown that added salts can increase the aggregation number of cetyl pyridinium micelles.[17] However, the electrolyte concentrations which they used were larger than those used in this work. Changes in substrate concentration have no effect on k_2 (Table VII). The addition of *t*-butyl alcohol decreases k_2 (Table VIII), but the effects are much smaller than those of DNPE.

Table VII

Effect of Reagent Concentration on Reaction between Anions and *p*-Nitrophenyl Diphenyl Phosphate[a]

C_{X^-}, *M*	Reagent NaOH[b]	NaF[c]
0.010	542	334[d]
0.010	543[e]	
0.010	486[e,f]	
0.010	482[f,g]	
0.010	455[h]	
0.0125	520	
0.0150	519	307
0.0175	495	291
0.020		290

[a] Values of 10^2k_2 l. mol^{-1} sec^{-1}, at 25.0° with 10^{-5} *M* substrate. [b] With 3×10^{-3} *M* CTA. [c] At pH 9.0 with 0.015 *M* borate buffer and 2×10^{-3} *M* CTA. [d] Mean of three values. [e] 2.7×10^{-6} *M* substrate. [f] 5×10^{-3} *M* CTA. [g] 2×10^{-6} *M* substrate. [h] 3×10^{-6} *M* substrate, 7×10^{-3} *M* CTA.

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

TABLE VIII
REACTION WITH HYDROXIDE ION IN AQUEOUS *t*-BUTYL ALCOHOL[a]

t-Butyl alcohol, wt %	0	10	15	20	25
$10^2 k_2$, l. mol^{-1}	48.3	35.3	22.6	13.8	9.60

[a] At 25.0° with 0.01 *M* NaOH.

Activation Parameters.—The enthalpies of activation for the reactions of hydroxide and fluoride ions with *p*-nitrophenyl diphenyl phosphates in the absence of detergent are low (Table IX) as is generally found for nucleophilic attack upon the phosphorus atom of trisubstituted phosphate esters.[2,6]

TABLE IX
ACTIVATION PARAMETERS

Detergent	C_D, *M*	NaOH ΔH^*	NaOH ΔS^*	NaF ΔH^*	NaF ΔS^*
		10.1	−26	11.9	−23
CTA	0.002			13.6	−10.5
CTA	0.003	13.4	−10		
CTA	0.004			13.9	−10
CTA	0.005	14.0	−8.5		
CTA	0.007	14.0	−8.5	14.0	−10
CTA	0.008	14.2	−8.5		
CTA	0.009			14.6	−8.5
NaLS	0.004	24.0	+16	18.7	−3
NaLS	0.005	22.9	+11		
NaLS	0.006	22.8	+9	20.4	−3
NaLS	0.0075	21.8	+4.3		
NaLS	0.008			19.9	−5.5
DNPE	0.004	12.9	−23	10.5	−32
DNPE	0.006	12.9	−23	10.2	−34
DNPE	0.008	13.7	−21	8.5	−40

Added CTA increases the enthalpy of activation, and the rate enhancement arises from a much more favorable entropy of activation (Table IX), in contrast to the results for other detergent-catalyzed reactions between uncharged substrates and nucleophilic anions,[13] where cationic micelles decrease ΔH^*. The results with NaLS and DNPE are complicated because changes in temperature can affect the rate of that part of the reaction which occurs in the aqueous phase as well as the equilibrium constant for incorporation of the substrate into the micelles and the properties of the micelle. Because of the small temperature range the values of ΔH^* and ΔS^* for NaLS and DNPE are not very accurate.

Discussion

Reactions between nucleophilic anions and uncharged substrates are generally catalyzed by cationic micelles and inhibited by anionic micelles[8–11,13] (Figures 2–5), and the reactions under discussion follow this general pattern, but, contrary to expectation, an uncharged detergent is also a powerful inhibitor (Figures 4 and 5). The general approach to an understanding of micellar catalysis and anticatalysis is based on a consideration of the reaction rates in the micellar and aqueous phases, and we will follow it,[9,13] except that we could not measure the solubilization of *p*-nitrophenyl diphenyl phosphate by the ionic detergents.

$$\begin{tikzcd}
D_n + S \arrow[r, shift left] \arrow[d, "X^-"', "k_2^{w}"] & SD_n \arrow[l, shift left] \arrow[dl, "X^-"', "k_2^{m}"] \\
\text{products} &
\end{tikzcd}$$

Anticatalysis.—We assume that nucleophile X⁻ can react with the substrate in both the aqueous and micellar phases and, following the usual approximations,[9,13] we write eq 3, which predicts that the plots

$$1/(k^{w}_2 - k_2) = [1/(k_2{}^{w} - k_2{}^{m})] + [1/(k_2{}^{w} - k_2{}^{m})]\,[N/K(C_D - \text{cmc})] \quad (3)$$

of $1/(k_2{}^{w} - k_2)$ against $1/(C_D - \text{cmc})$ should be linear.[9,13]

The results for NaLS appear not to fit eq 3, because there is inhibition below the cmc, as measured by conventional methods.[14] This problem has not appeared with other substrates, *e.g.*, carboxylic esters[9] and 2,4-dinitrochloro- and -fluorobenzene.[13] *p*-Nitrophenyl diphenyl phosphate is taken up so strongly by micelles or submicellar aggregates that the reaction cannot be studied at detergent concentrations much above the cmc, because it becomes too slow, whereas, with the other substrates which are less soluble in aqueous detergent, it is possible to work at higher detergent concentrations where approximations made in deriving eq 3 are relatively unimportant.

We have attempted to solve this problem by assuming that $k_2{}^{m} \sim 0$, for reactions of fluoride or hydroxide ion with *p*-nitrophenyl diphenyl phosphate in solutions of NaLS. This assumption is correct for other anion–molecule reactions.[9,13] Equation 3 then gives eq 3a,

$$(k_2{}^{w}/k_2) - 1 = (C_D - \text{cmc})\,K/N \quad (3a)$$

and we find that plots of $k_2{}^{w}/(k_2 - 1)$ against C_D curve sharply upward at detergent concentrations above 0.003 *M* for NaOH and 0.002 *M* for NaF, and then become approximately linear, and the slopes give $K/N \sim 20{,}000$ for NaOH and 15,000 for NaF (Figure 8). The differences in these slopes for the different nucleophiles could arise from electrolyte effects upon the properties of the micelle, and in particular upon its interactions with the substrate. In addition the assumption that $k_2{}^{m} = 0$ may be incorrect, and the consequent error would be most important at the higher detergent concentrations. To this extent it is better to

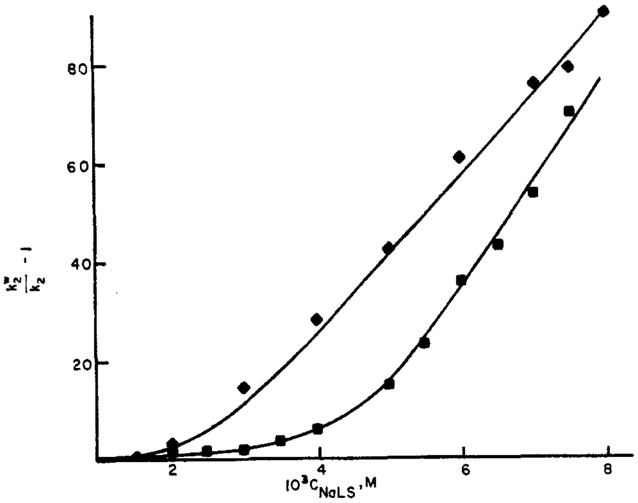

Figure 8.—Plot of $(k_2{}^{w}/k_2) - 1$ against concentration of NaLS at 25.0°: ■, 0.01 *M* NaOH; ◆, 0.01 *M* NaF.

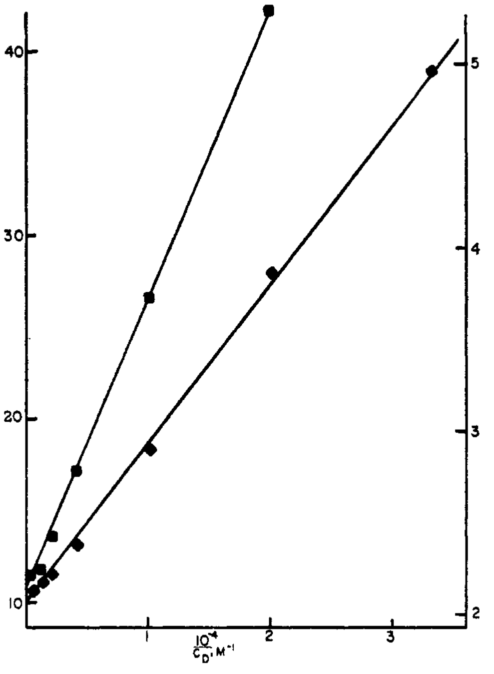

Figure 9.—Plot of $1/(k_2^{w} - k_2)$ sec mol l.$^{-1}$ against the reciprocal of the concentration of DNPE at 25.0°. Left-hand scale relates to sodium fluoride, the right to sodium hydroxide: ■, 0.01 M NaOH; ◆, 0.01 M NaF.

use eq 3 rather than eq 3a, provided that $C_D \gg$ cmc, so that uncertainties in the value of the cmc can be ignored, as can be done for most reactions.[9,13] Because of the powerful inhibition by NaLS the values of k_2 are very small at high detergent concentrations and there is considerable error in $(k_2^{w}/k_2) - 1$. The aggregation number, N, for NaLS is *ca.* 62,[18] giving $K \sim 10^6$. Although eq 3a is derived from eq 3, its application uses the rate constants obtained at the higher detergent concentrations, whereas in a plot based on eq 3 these data are bunched very close to the intercept.[9,13]

An unexpected result of this work is the powerful inhibition by the uncharged detergent, DNPE, because in other systems uncharged detergents have had little effect on the rates on anion–molecule reactions, as expected from electrostatic considerations.[8,11–13] Nmr studies have shown that nonpolar aromatic compounds are absorbed into the interior of micelles, whereas polar aromatic compounds tend to stay in the exterior water rich region.[19] On this basis, as well as in terms of solubilities, we would expect a triaryl phosphate to be absorbed more deeply into a michelle, as compared with smaller compounds, such as dinitrohalobenzenes.[13]

The inhibition by DNPE is very strong even at concentrations below cmc (measured in the absence of the substrate[13]), and, assuming that under these conditions cmc ≈ 0, we find that eq 3 fits the results reasonably well (Figure 9). For reaction with 0.01 M sodium hydroxide $K/N \approx 14{,}000$, and for 0.01 M sodium fluoride $K/N \approx 11{,}000$ and for both reactions $k_2^{m} \approx 0$, as shown by the value of the intercept. The value of K/N, determined by solubility is *ca.* 16,000 (see Results), and the differences between these three values may be caused by the approximations which we have made, *e.g.*, by assuming that cmc ≈ 0, but they may represent real effects caused by the differences between the anionic nucleophiles.

The anticatalysis by DNPE at concentrations below the cmc (Figures 4 and 5) could be caused by interactions between the substrate and submicellar aggregates of the detergent which stabilize the initial, relative to the transition state, or the substrate might promote micellization of the detergent, but rate inhibitions can be caused by the formation of 1:1 molecular complexes between reagent and inhibitor.[20]

In many of these cases it seems that charge-transfer interactions are important. A charge-transfer complex could be formed between *p*-nitrophenyl diphenyl phosphate and the phenoxy residue of DNPE, but this explanation seems improbable, because there is no evidence for formation of such 1:1 complexes between this detergent and either 2,4-dinitrofluoro- or -chlorobenzene.[13] However, we found that the absorbances of 1:1 mixtures of the substrate and DNPE are greater than the sum of the individual absorbances (Figure 1). The differences and the absorbances are small over most of the spectrum, but they are well within the range that can be measured accurately using a Gilford spectrophotometer. We cannot tell whether these changes are caused by formation of a complex or whether there is a large spectral solvent shift caused by submicellar concentrations of the uncharged detergent.

The incorporation of the substrate into the uncharged micelles of DNPE has analogies with the incorporation of various substrates into cyclodextrins, which can lead to either catalysis or inhibition depending upon the nature of the reaction.[20,21]

The micelles are very effective at incorporating *p*-nitrophenyl diphenyl phosphate, as can be seen from the large value of K for incorporation into NaLS, *e.g.*, with 2,4-dinitrochlorobenzene $K \approx 2700$ for NaLS, and $K/N \approx 88$ for DNPE,[13] as compared with $K \approx 10^6$ for NaLS and $K/N \approx 16{,}000$ for DNPE for incorporation of *p*-nitrophenyl diphenyl phosphate. The high solubility of the triaryl phosphate in the micellar phase, relative to that in water, could be caused by the hydrophobic properties of the phenyl groups, which should make it easier for the triaryl phosphate to penetrate the micelle and so be protected from the strongly hydrated fluoride and hydroxide ions. These observations, and the kinetic salt effects, agree with other observations which show that hydrophobic interactions[22,23] are very important in determining reaction rates in micelles,[3,8–11,13] and can be more important than the simple electrostatic interactions between point charge ions. We examined *t*-butyl alcohol as a cosolvent, on the possibility that DNPE might be hindering the reaction merely by exerting a very strong solvent effect, but, although *t*-butyl alcohol decreases k_2 for the reaction with hydroxide ion, its effect is very much less than that of the uncharged detergent (Table VIII and Figures 4 and 5), showing

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(19) J. C. Eriksson and G. Gilberg, *Acta Chem. Scand.*, **20**, 2019 (1966).

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(21) J. L. Lach and T. Chin, *J. Amer. Pharm. Assoc.*, **44**, 521 (1964); F. D. Cramer and W. Kornpe, *J. Amer. Chem. Soc.*, **87**, 1115, (1965).

(22) G. Nemethy and H. A. Scheraga, *J. Phys. Chem.*, **66**, 1173 (1962).

(23) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitions: The Organic Chemistry of the Active-Site," John Wiley & Sons, Inc., New York, N. Y., 1967, Chapter II.

that DNPE is exerting more than a solvent effect, even at submicellar concentrations.

Catalysis.—It is generally assumed that the incorporation of the substrate into a cationic micelle makes it easy for it to be attacked by a nucleophilic anion, and the inhibition of this catalysis by added salts is readily understandable on electrostatic considerations.

However the results do not fit the predictions of the simple kinetic scheme which leads to eq 4, which is a rearranged form of eq 3.

$$k_2 = (k_2^{w} + k_2^{m}KC_m)/(1 + KC_m) \qquad (4)$$

Equation 4 predicts that k_2 should increase to a plateau value when all the substrate is incorporated into the micelle. For the reactions studied here, and for a number of other anion–molecular reactions, the rate in fact goes through a maximum,[8b,9,13] and we have suggested that when the bulk of the substrate is incorporated into the micelle addition of more detergent generates more cationic micelles which simply take up the nucleophilic anions into a Stern layer, and thereby deactivate them, because a substrate in one micelle should not react with an anion in another.[13,24,25] Micelles of CTA catalyze the reactions of hydroxide and fluoride ions to similar extents, but the rate maxima occur at different detergent concentrations.

Detergents affect the properties of water itself,[26] and therefore should change the rate (and activation parameters) of that part of the reaction which goes on in the aqueous phase. In general these effects appear to be of less importance than those caused by incorporation into the micellar phase, because the retardation of reaction by an anionic micelle, for example, is that expected in terms of the changing solubility of the substrate, and also because with cationic micelles the reaction is going on largely in the micellar phase. In addition detergent catalysis persists even in aqueous organic solvents in which the water structure has been disrupted by the cosolvent.[8a,13]

Activation Parameters.—The variation of the activation parameters in CTA as compared with water (Table IX) was unexpected, because one might expect electrostatic attraction between the nucleophilic anion and the cationic micelle to reduce the activation enthalpy when the substrate is in the micellar phase. This *increase* in activation enthalpy with increasing CTA concentration may be related to the high solubility of the substrate in the micellar phase, relative to that in water. Incorporation of the substrate into the micellar or any nonaqueous phase lowers the free energy of the initial state, and of itself must always reduce the reaction rate although its effect may be more than offset by changes in the free energy of the transition state. Relative to the reaction in water this incorporation could increase the enthalpy of activation by an amount equal to the greater enthalpy of solution in the micellar as compared with the aqueous phase, and will increase with increasing solubility of the substrate in the micellar phase relative to the aqueous. We have shown that p-nitrophenyl diphenyl phosphate has a much higher solubility in these micelles, relative to water, than has 2,4-dinitrochlorobenzene (see Results), where the cationic micelle decreases the activation energy for reaction with hydroxide ion.[13] The foregoing discussion is equivalent to saying that the change in the enthalpy of solution of the transition state in the micelle is less than the sum of the changes in the enthalpies of solution of the reactants (relative to water). The enthalpies of activation for reaction in DNPE (Table IX) also reflect the high solubilities of the substrate in the micellar phase, and for reaction in NaLS electrostatic repulsions and the high substrate solubilities combine to make the increase in ΔH^* very large. One factor which could lead to the more positive entropy of activation is that the water molecules which were attached to the hydroxide ion in water could be lost when it is incorporated into the transition state in the micelle. A complete account of all the factors which influence the activation parameters for reactions in micellar phases does not seem possible at present, because we need to know how the properties of the micelles themselves, *e.g.*, the shapes and aggregation numbers, vary with temperature, but the accuracy with which for example aggregation numbers can be measured is not good enough for this purpose.

Salt Effects on the Micellar-Catalyzed Reaction.—In discussing the way in which salts inhibited the reactions between 2,4-dinitrochloro- and -fluorobenzene and hydroxide ion in the presence of CTA we speculated that the anion of salt tended to exclude the hydroxide ion from the neighborhood of the micelle,[13] and this explanation could also be applied to the salt inhibition of the CTA-catalyzed hydrolysis of 2,4-dinitrophenyl phosphate, where the anion inhibited incorporation of the substrate itself.[3] We concluded that one anion was hindering incorporation of another into the cationic micelle, rather than affecting the incorporation of uncharged substrates into the micelle. (Independent solubility measurements showed that added salts slightly affected the solubility of uncharged substrates in aqueous detergents.[13]) The present results fit the earlier postulate because similar salt effects are observed for the reactions of hydroxide ion with 2,4-dinitrochloro- and -fluorobenzenes and for these reactions of p-nitrophenyl diphenyl phosphate, although there are marked differences in the solubilities of the neutral substrates in the micelles.[13] In all the reactions which we have examined we find that it is the bulky anions of low charge density which are the best inhibitors, as expected in terms of the ability of organic residues to promote hydrophobic bonding.[22,23]

Added salts could also inhibit the micellar-catalyzed reaction by increasing the aggregation number, and therefore decreasing the number of micelles,[17] but this does not appear to be of overriding importance because added salts do not markedly affect solubility in aqueous detergents,[13] and the electrolyte concentrations are generally lower than those used in experiments which showed these salt effects upon aggregation number. However, our results show that the quantitative kinetic treatment of micellar catalysis and inhibition may be complicated by the effects of the reagents upon the

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[24] Romsted and Cordes[25] have explained these rate maxima in terms of inhibition by the counteranion of the cationic detergent. However, this explanation does not account for the absence of rate maxima in the CTA-catalyzed hydrolyses of dinitrophenyl phosphates where there are large inhibitions by added anions.[3]

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

[26] K. Shinoda, T. Nakagawa, B-U. Tamamushi, and T. Isemura, "Colloidal Surfactants," Academic Press, New York, N. Y., 1963, Chapters I and II.

micelles, and these effects seem to be much more important with a bulky substrate such as a triaryl phosphate than with an aryl halide. These complications are important at detergent concentrations close to the cmc. Our kinetic salt effects also suggest that caution should be exercised in using buffers to control pH for acid- or base-catalyzed reactions in the presence of detergents, because of adventitious inhibition by anions of the buffer, and the pH in the micelle may be different from that in the bulk of the solution.[27]

A major problem in interpreting the kinetic effects of detergents is that reaction can occur in either the aqueous or micellar phase, and it is generally assumed that the part of the reaction which continues in the micellar phase is to a first approximation unaffected by the detergent. This crude approximation appears to be warranted in our present system where the over-all effects are much larger than expected in terms of simple solvent or electrolyte effects, but it may not be satisfactory in other systems.

Registry No.—*p*-Nitrophenyl diphenyl phosphate, 10359-36-1; hydroxide ion, 1428-30-9; fluoride ion, 16984-48-8.

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Electrolyte and Micellar Effects upon the Reaction of 2,4-Dinitrofluorobenzene with Hydroxide Ion[1]

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The electrolyte effects upon the rate of reaction between hydroxide ion and 2,4-dinitrofluorobenzene in water can be separated into effects upon the activity coefficient of the organic substrate and the relative activity coefficients of the hydroxide ion and the transition state; for example, large cations, *e.g.*, $(CH_3)_4N^+$, stabilize the transition state relative to the hydroxide ion. Cationic micelles of cetyltrimethylammonium bromide catalyze the reaction strongly but anionic micelles of sodium lauryl sulfate retard it, and nonionic micelles have almost no effect. With cationic micelles there is a rate maximum at a detergent concentration of *ca.* 0.025 *M*. The cationic micelle decreases the activation enthalpy.

The reaction between 2,4-dinitrofluorobenzene and nucleophiles has been studied very extensively, but largely in organic and aqueous organic solvents.[2,3] The reaction is a two-stage process involving nucleophilic addition followed by loss of the fluoride ion, and in some systems this second step can be slow, although it appears to be rapid in polar hydroxylic solvents. We have examined electrolyte and micellar effects upon the reaction between hydroxide ion and 2,4-dinitrochlorobenzene,[4] and we chose this reaction for initial study because loss of chloride ion from the tetrahedral intermediate is fast,[2] except in a few special cases.[5] Some electrolytes affect the rate of reaction between hydroxide ion and 2,4-dinitrochlorobenzene by changing the activity coefficient of the organic substrate, but ions of low charge density, *e.g.*, tetraalkylammonium or perchlorate, also change the ratio of the activity coefficients of the hydroxide ion and the transition state.[4]

The kinetic effects of micelles upon the reaction between hydroxide ion and 2,4-dinitrochlorobenzene are simple: a cationic micelle increases the rate sharply, an anionic micelle decreases it, and a nonionic micelle has little effect,[4] as expected on a simple electrostatic picture of incorporation of the organic substrate into the micelle changing the probability of attack upon it by hydroxide ion.[6–8]

The aim of the present work was to find out whether 2,4-dinitrofluorobenzene behaved similarly to the chloro compound with regard to effects of electrolytes and micelles, or whether these agents changed the nature of the rate-limiting step.

Richards and his coworkers have shown that micelles profoundly affect the rate of reaction between 2,4-dinitrofluorobenzene and amines,[9] and their interest in the use of this reagent for protein modification made it desirable to study its reactions in molecular aggregates.

Experimental Section

Materials.—2,4-Dinitrofluorobenzene (Aldrich) was redistilled, bp 121.5–122° (3 mm) [lit.[10] bp 140–141° (5 mm)]. The detergents used in the present work were cetyltrimethylammonium

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