In principle these trapping experiments can be treated quantitatively in terms of Scheme II, which gives the rate equation (7).

$$p\text{-NPDPP} + I^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{1} + OAr^- \xrightarrow[OH^-]{k_2} \text{product}$$

$$k_1' = k_1k_2/(k_{-1} + k_2) \qquad (7)$$

In eq 7 k_1' is the observed first-order rate constant for reaction with areneimidazolide ion, and k_1, k_{-1}, and k_2 are first-order rate constants for the individual steps. We assume that k_1 is given by k_1' in the absence of added *p*-nitrophenoxide ion,[20] and k_1, k_{-1} and k_2 will depend on the concentrations of nucleophilic ions in the micellar pseudophase. The values of k_{-1}/k_2 are given in Table IV. There are several approximations in eq 7; for example it neglects competition between the various anions for the micelle, and retardation by *p*-cyano- and 2,4-dichlorophenoxide ions (Figure 4) shows that these effects are present. However, $k_{-1}/k_2[ArO^-]$ is reasonably constant for reaction of a given areneimidazolide ion (Table IV), which is reasonable because phenoxide ions bind very strongly to cationic micelles.[21] Thus in view of the complexities of micellar catalyzed reactions the relative rate constants (Table IV) fit the proposed reaction scheme satisfactorily, especially for reaction with BI^-.

An important aspect of this trapping study is that it would be very difficult to do the experiments in nonmicellar systems, because in water reactions of the areneimidazolide ions are small contributors to the overall rate (Table II). In addition trapping of the intermediate by *p*-nitrophenoxide ion is much more effective in a cationic micelle than in water because phenoxide ions bind much more strongly than hydroxide ions to cationic micelles.[13c]

Micelles appear to catalyze or inhibit reactions without materially changing mechanism, and our trapping experiments show how micelles can be used to develop mechanistic probes which may not be available for reactions in water or similar solvents.

Acknowledgment. Support of this work by the U.S. Army Office of Research is gratefully acknowledged.

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Catalysis by Hydrophobic Tetraalkylammonium Ions. Dephosphorylation of *p*-Nitrophenyl Diphenyl Phosphate

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Abstract: The phase-transfer agents tri-*n*-octylethylammonium bromide and mesylate (TEABr and TEAMs, respectively) strongly catalyze the reaction of *p*-nitrophenyl diphenyl phosphate (*p*-NPDPP) with benzimidazolide ion (BI^-) and naphth-2,3-imidazolide ion (NI^-). In dilute TEABr and TEAMs reactions are of greater than first order with respect to substrate, areneimidazole, and TEABr or TEAMs, suggesting that reaction is occurring in small aggregates of the three solutions. The reaction of *p*-NPDPP with OH^- is not catalyzed by TEABr. The solubility of TEAMs allows study of the catalysis up to 2×10^{-2} M, and the first-order rate constants, k_ψ, for reaction of the areneimidazoles with *p*-NPDPP go through maxima with increasing [TEAMs]. The constants depend upon [*p*-NPDPP] at low [TEAMs] but not at high. The rate maxima can be explained in terms of incorporation of both *p*-NPDPP and BI^- in aggregates of TEAMs, and the rate constants of reaction in the aggregates can be estimated and are similar to that for reaction in micelles of cetyltrimethylammonium bromide (CTABr). The reactions of areneimidazolide ions with *p*-NPDPP are catalyzed by CTABr at concentrations below the critical micelle concentration (cmc) in water. Under these conditions the order with respect to *p*-NPDPP is less than 1 and catalysis appears to be due to induced micelle formation.

Micellar effects upon reaction rates in aqueous solution have generally been analyzed in terms of a pseudophase model,[2-4] assuming reactants are distributed between the aqueous solvent and the micelles, with reaction occurring in either pseudophase. It was first applied to micellar inhibited bimolecular reactions[5] and then to micellar catalyzed unimolecular reactions[6] and has been extended to bimolecular micellar catalyzed reactions.[3,4,7-9]

It is implicit in these treatments that reactants do not perturb micellar structure and do not bind cooperatively to the micelle. These assumptions are reasonable, provided that surfactant is in large excess over reactants. However the quantitative treatments sometimes fail for [surfactant] close to the critical micelle concentration (cmc), especially with hydrophobic reactants which may interact strongly with micelles or premicelles.[10,11]

Piskiewicz has developed an alternative model in which rate–surfactant profiles are explained by an equation similar to the Hill equation of enzyme kinetics,[11] which stresses cooperative binding. Kunitake and co-workers found that the phase-transfer catalyst tri-*n*-octylmethylammonium chloride (TMAC) strongly accelerates deacylation of *p*-nitrophenyl acetate by hydrophobic hydroxamates or imidazoles in water.[12] The reactions in TMAC were faster than in micellized cetyltrimethylammonium bromide (CTABr), showing that nonmicellar aggregates could be catalytically active and that rate effects in very dilute surfactant might also be due to formation of submicellar aggregates. The rate enhancements

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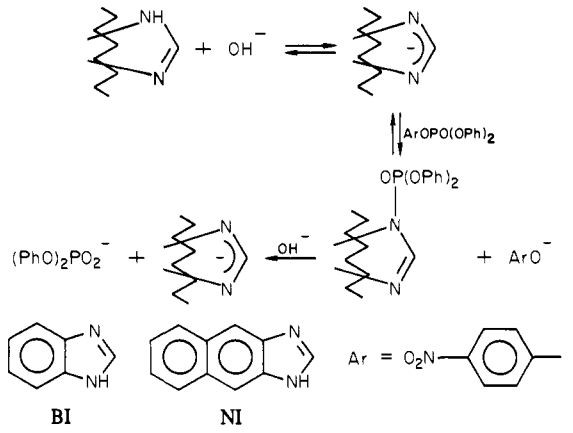
Scheme I



by micellized surfactants and by nonmicellized quaternary ammonium ions were ascribed to formation of "hydrophobic ion pairs" which were considered to be more nucleophilic than the free ions.[12] These observations were especially interesting because phase-transfer catalysis typically applies to biphasic reactions in which transport of ionic reactant across a phase boundary is of key importance.[13]

(i) The pseudophase model treats the micelles as a separate reaction medium unaffected, to a first approximation, by incorporation of the reactants. An important conclusion of this model is that second-order rate constants in the micellar pseudophase are in magnitude similar to those in water, and rate enhancements of bimolecular reactions are due largely to concentration of reactants into a small volume at the micellar surface.[3,4,7-9,14] (ii) The cooperativity model emphasizes interactions between surfactant and both reactants in generating a micelle in which reaction occurs; i.e., it postulates a productive interaction between three chemically distinct solutes such that the nature of the micelle changes with reactant concentration.[11] (iii) The hydrophobic ion pair model requires that these pairs be more reactive than the free ions, but it places little emphasis on the structure and composition of the aggregate.[12]

These three models appear to be mutually incompatible, although different models may apply at different surfactant concentrations. For example in very dilute surfactant reactants may induce formation of either micelles or small submicellar aggregates, whereas in more concentrated surfactant, reactant should have little effect on micellar structure.

We have compared catalysis by a micelle forming surfactant, cetyltrimethylammonium bromide (CTABr), with that by phase-transfer catalysts. Initially we used tri-*n*-octylethylammonium bromide (TEABr),[15] but it is only sparingly soluble in water so we also used the more soluble tri-*n*-octylethylammonium mesylate (TEAMs).

The reaction was dephosphorylation of *p*-nitrophenyl diphenyl phosphate (*p*-NPDPP) by anions of benzimidazole (BI) or naphth-2,3-imidazole (NI). The anions BI^- and NI^- are effective dephosphorylating agents in solutions of micellized CTABr[16] (Scheme I). Except in very dilute CTABr the rate–surfactant profile fits the pseudophase model and rate enhancements are due wholly to concentration of reactants in the micelles, and second-order rate constants in the micellar pseudophase are similar to those in water and are independent of the total concentrations of reactants. Reaction of an areneimidazolide ion with *p*-NPDPP is reversible (Scheme I), but the reverse reaction is unimportant in very dilute *p*-nitrophenoxide ion.[17]

There is extensive catalysis at [CTABr] below the cmc in water,[16] which could be due to induced formation of normal micelles in the presence of the hydrophobic reactants, or the reactants might combine with surfactant to form small, submicellar, aggregates which are catalytically effective (cf. ref 11). One might expect CTABr at submicellar concentrations to behave similarly to the phase-transfer catalysts in its catalytic effectiveness.

Table I. Solubility of *p*-NPDPP[a]

10^2[TEAMs], M	10^5[*p*-NPDPP], M	*f*
0.	1.1	
0.1	1.75	0.35
0.25	2.3	0.52
0.4	2.8	0.59
0.5	3.1	0.63
0.75	3.7	0.68
1.0	3.9	0.70
1.25	4.4	0.73
1.5	4.2	0.72
1.75	4.6	0.75
2.0	5.0	0.76

[a] In aqueous solution at 25 °C.

Experimental Section

Materials. The preparation and properties of most of the reagents have been described.[16] The phase-transfer catalysts tri-*n*-octylethylammonium bromide and tri-*n*-octylethylammonium mesylate (TEABr and TEAMs, respectively) were prepared by alkylation of tri-*n*-octylamine with EtBr or $EtOSO_2Me$.[12] Alkylation with $EtOSO_2Me$ was carried out under reflux in a mixture of MeCN–THF–EtOH (3:2:1) for 2 days. The solvents were removed via rotary evaporation, and the salt was recrystallized (Et_2O) and dried in vacuo over P_2O_5.

Kinetics. Formation of *p*-nitrophenoxide ion was followed spectrophotometrically at 25.0 °C, generally at pH 10.7 (10^{-2} M carbonate buffer). A few experiments were run in dilute NaOH. The nucleophile was in large excess over substrate, and reactions were first order except when [substrate] was increased to 1.5×10^{-5} M, and the first-order rate plots then deviated after ca. 2 half-lives. Initial values of the first-order rate constants, k_ψ (s^{-1}), are quoted for these reactions.

The phase-transfer catalyst TEABr is sparingly soluble in water, cf. ref 12, and its solubility was decreased by buffer. We used sufficiently low concentrations of reagents that kinetic solutions were no more than faintly turbid, because we were unable to obtain consistent data when the solutions were very turbid.

Deprotonation of Benzimidazole and Naphth-2,3-imidazole. The concentrations of BI^- and NI^- in the reaction solutions were measured at 283 and 363 nm, respectively, following methods already described.[16,18] However we could not do these experiments with naphth-2,3-imidazole in the higher concentrations of TEAMs because the solutions were turbid, especially when we added sufficient NaOH to deprotonate the imidazole fully.

Substrate Binding. The solubility of *p*-NPDPP in aqueous TEAMs at 25 °C was determined at pH ca. 4 (with $MeSO_3H$) to decrease hydrolysis. After equilibration, initially with sonication, followed by standing for several hours at 25 °C, pH was increased to 8.5, to ionize *p*-nitrophenol which might have formed by hydrolysis, and the absorbance of *p*-nitrophenoxide ion at 400 nm was measured. Hydroxide ion was then added to hydrolyze *p*-NPDPP and absorbance at 400 nm was remeasured. The solubility of *p*-NPDPP was calculated from the absorbance of *p*-nitrophenoxide ion, taking $\epsilon = 13700$. We did not examine the effect of TEABr on the solubility of *p*-NPDPP, because of the low solubility of TEABr.

Results

Reactions in the Absence of Quaternary Ammonium Salts. The areneimidazolide ions BI^- and NI^- make a small contribution to

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(14) Rate effects upon spontaneous, unimolecular, reactions are however due wholly to the medium effects of micelles.[3]

(15) We use the acronym TEABr for tri-*n*-octylethylammonium bromide to conform with the designation of tri-*n*-octylmethylammonium chloride as TMAC.[12]

(16) Bunton, C. A.; Hong, Y. S.; Romsted, L. S.; Quan, C., preceding paper in this issue.

(17) Return of the phosphorylated intermediate to reactants can be neglected when the concentration of *p*-nitrophenoxide ion is less than 10^{-5} M.[16]

(18) In dilute NaOH we estimated $pK_a = 12.8$ and 12.3 for deprotonation of benzimidazole and naphth-2,3-imidazole, respectively;[16,19a] cf. ref 19b.

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Table II. Reaction with Hydroxide Ion[a]

	10^4[TEABr], M		
[OH^-], M	1	2.5	5
0.01	5.15	4.95	5.08
0.02	9.86	9.52	10.0
0.04			19.4

[a] Values of $10^3 k_\psi$ (s^{-1}) at 25.0 °C with 3×10^{-6} M substrate.

Table III. Dephosphorylation by Benzimidazole in TEABr[a]

10^3[BI],	10^3[TEABr], M				
M	0.5	0.75	1.0	1.25	1.50
0.1	0.27	0.51	0.63	0.85	1.75
0.2	0.41	0.47	0.75	1.55	2.35
0.3	0.95	1.25	2.25	3.25	5.75
0.5	1.85	3.65	5.85	8.45	20.8
1.0	2.35	3.95	9.15	16.0	37.4
1.5	2.75	6.55	11.0	29.8	68.4
2.0	3.05	9.75	19.8	41.8	108
3.0	3.45	11.8	29.8		151

[a] Values of $10^3 k_{BI}'$ (s^{-1}) at 25.0 °C in 10^{-2} M carbonate buffer, pH 10.7, with 3×10^{-6} M *p*-NPDPP. In the absence of added nucleophile $10^3 k_\psi \approx 0.3$ s^{-1}.

reaction of *p*-NPDPP in water or in aqueous EtOH at pH 10.7, 10^{-2} M carbonate buffer, largely because areneimidazoles are very weak acids.[16,18] At 25.0 °C under these conditions $10^4 k_\psi$ is 3.2 s^{-1} in 8×10^{-3} M BI, and in H_2O–EtOH (70:30, v/v) it is ca. 2.9 s^{-1} in 2×10^{-3} M NI, whereas it is 2.6 s^{-1} in aqueous buffer. (Naphth-2,3-imidazole is too insoluble to be used in water with no solubilizing agent.[16]) In the following discussion we allow where necessary for contributions of these reactions in water to the overall rate, neglecting the effect of EtOH on reaction of NI^-.

Substrate Binding to TEAMs. The increase of solubility of p-NPDPP on addition of TEAMs (Table I) is larger than expected for a simple salt effect,[20] suggesting that there is direct interaction between substrate and the hydrophobic quaternary ammonium ion TEA^+.

The binding of hydrophobic nonionic solutes to micelles typically follows eq 1, provided that surfactant is in large excess over the

$$K_s = [S_M]/[S_W][Dn] \quad (1)$$

solute,[21] where S_W and S_M are solute in the aqueous and micellar psudeophases, respectively, and Dn is micellized surfactant (detergent). In calculating K_s from solubility measurements, one assumes that solubility in water gives $[S_W]$ and the increase of solubility on addition of surfactant gives $[S_M]$. Typically K_s is independent of surfactant concentration, but when we attempted to fit our solubility data in TEAMs to eq 1, we found that K_s varied. This result suggests that *p*-NPDPP interacts with TEAMs to form small aggregates of variable composition.

If we assume that the concentration of bound *p*-NPDPP is given by the increase of solubility, the fraction, f, of bound *p*-NPDPP is given by eq 2, where $[S_T]$ is the solubility of p-NPDPP in TEAMs and $[S_W]$ is that in water (Table I).

$$f = ([S_T] - [S_W])/[S_T] \quad (2)$$

Reaction with Hydroxide Ion in TEABr. The phase-transfer catalyst TEABr does not catalyze reaction of *p*-NPDPP with OH^- (Table II). The second-order rate constant is ca. 0.5 M^{-1} s^{-1}, in agreement with the value in the absence of catalyst.[21a]

Reaction with the Areneimidazoles in TEABr. The first-order rate constants for reaction with BI, k_{BI}', at pH 10.7 are in Table III, and the corresponding rate constants, k_{NI}', for reaction with NI are in Table IV. (These rate constants are corrected for the small contribution of reaction with OH^-.)

Table IV. Dephosphorylation by Naphth-2,3-imidazole in TEABr[a]

10^4[NI],	10^3[TEABr], M				
M	0.5	0.75	1.0	1.2	1.5
0.5	5.75	16.8	30.2	50.8	100
0.75	6.95	20.8	51.8	131	181
1.0	14.8	43.8	88	162	
1.25	22.8	72	118		
1.5	23.8	97	207		
2.0	35.8	214	313		

[a] Values of $10^3 k_{NI}'$ (s^{-1}) at 25.0 °C in 10^{-2} M carbonate buffer, pH 10.7, with 3×10^{-6} M *p*-NPDPP.

Table V. Effect of Substrate Concentration on Dephosphorylation by Benzimidazole in TEABr[a]

$10^5 \times$ [*p*-NPDPP], M	$10^3 k_\psi$, s^{-1}	$10^5 \times$ [*p*-NPDPP], M	$10^3 k_\psi$, s^{-1}
0.2	0.86 (2.0)	1.0	1.12 (6.8)
0.3	0.88 (2.3)	1.25	1.50 (11.5)
0.5	0.89 (2.8)	1.5	2.24 (13.7)
0.75	1.10		

[a] With 10^{-4} M benzimidazole in 10^{-2} M carbonate buffer, pH 10.7, at 25.0 °C. [b] The values in parentheses are for reaction in 0.02 M NaOH.

Table VI. Effect of TEABr on Deprotonation and Rate Constants[a]

$10^3 \times$	10^{-3} M BI		10^{-4} M NI	
[TEABr], M	$10^5 \times$ [BI^-], M	$k_{BI}'/$ [BI^-]	$10^6 \times$ [NI^-], M	$10^{-3} k_{NI}'/$ [NI^-]
0.5	4.0	59	3.0	5
0.75	4.1	96	3.0	14
1.0	4.4	210	4.4	20
1.25	4.7	340	5.0	30
1.5	5.1	730		

[a] At 25.0 °C, pH 10.7, 10^{-2} M carbonate buffer.

Although reactions with 3×10^{-6} M *p*-NPDPP are first order, the rate constants depend on initial [*p*-NPDPP] (Table V). This effect is especially large for reaction in 0.02 M NaOH where BI is extensively deprotonated.[18,19]

The variations of the rate constants with [areneimidazole] or [TEABr] fit no simple kinetic equation. For example plots of log k_{BI}' against log [BI] are linear with approximately unit slope for reaction in [TEABr] < 0.75×10^{-3} M, but the slopes increase with increasing [TEABr]. The corresponding plots of log k_{BI}' against log [TEABr] are curved with slopes increasing from approximately 1 at low [BI] and [TEABr] to approximately 4 at higher [BI] and [TEABr].

The behavior is similar for reactions of NI where plots of log k_{NI}' against log [NI] had slopes increasing from ca. 1.5 to 2 with increasing concentration, whereas corresponding plots of log k_{NI}' against log [TEABr] had slopes increasing from ca. 3 to 4.

The observations suggest that small aggregates of reactants and TEABr are present in solution, rather than 1:1 adducts. In particular the curvature, and greater than unit slope, of log vs. log plots of rate constant against [TEABr] show that the monomeric ion of TEABr is not the most active form, and it appears that there is a cooperative interaction between catalyst and reactants; cf. ref 11. However these aggregates do not build up in concentration because there is no saturation effect. However with the more soluble TEAMs we see a saturation effect, consistent with buildup of an aggregate of reactants and catalyst (see below).

Formation of reactive aggregates depends upon both reactants, for example, TEABr does not catalyze reaction of OH^- with *p*-NPDPP (Table II).

Part, but not all, of the rate enhancements by TEABr may be due to increased deprotonation of the areneimidazoles, but k_{BI}'

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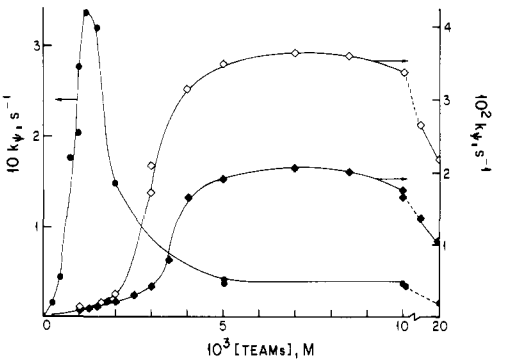

Figure 1. Dephosphorylation in TEAMs at pH 10.7 and 25.0 °C: ●, 10^{-4} M naphth-2,3-imidazole; ♦ and ◊, 10^{-4} and 2×10^{-4} M benzimidazole, respectively.

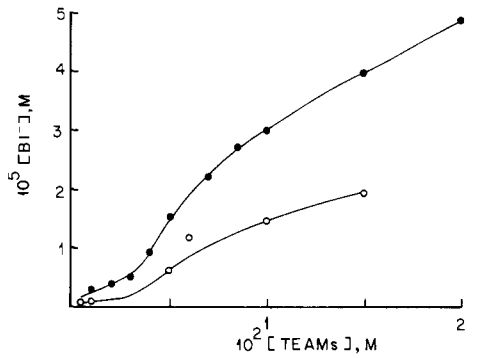

Figure 2. Deprotonation of benzimidazole in TEAMs at pH 10.7: ○ and ●, 10^{-4} and 2×10^{-4} M benzimidazole, respectively.

and k_{NI}' increase more rapidly than concentration of arene imidazolide ion with increasing [TEABr] (Table VI).

The rate enhancements by TEABr are large. For example in water and 8×10^{-3} M BI, $10^3 k_\psi \approx 0.3$ s^{-1},[16] but most of that reaction involves attack by H_2O and OH^-, and in 3×10^{-3} M BI contribution of the benzimidazole reaction to k_ψ is ca. 0.2×10^{-4} s^{-1}. On this basis 1.5×10^{-3} M TEABr is increasing the rate constant for reaction of *p*-NPDPP with 3×10^{-3} M BI (Table III) by a factor of ca. 7×10^3. The corresponding rate enhancement of reaction with NI is even larger. The contribution of 2×10^{-3} M NI to the first-order rate constant for reaction with *p*-NPDPP in H_2O–EtOH (70:30, v/v) is ca. 0.3×10^{-4} s^{-1}, and the rate constant in water should not be very different, whereas in 10^{-3} M TEABr and 2×10^{-4} M NI, $k_\psi = 0.31$ s^{-1} (see Results), so that the rate is increased by a factor of ca. 10^4.

Reaction with the Areneimidazoles in TEAMs. The solubility of TEABr in water is so low that we could only use very dilute solutions of it (Tables II–VI). However TEAMs is much more soluble and is an effective catalyst of dephosphorylation by areneimidazoles and in low concentration behaves much like TEABr (Figure 1). As with TEABr part of the rate enhancement is due to increased deprotonation of BI (Figure 2).

The striking observation is that k_ψ goes through maxima with increasing [TEAMs], as do values of k_ψ/[BI$^-$] (Table VII), and [TEAMs] at the rate maximum is smaller for reaction with NI than with BI (Figure 1). The position of the rate maximum depends upon interaction between the hydrophobic TEA^+ and areneimidazole or its anion.

These rate maxima are qualitatively similar to those observed with micellar catalyzed bimolecular reactions.[16] There are however some marked differences between catalysis by TEAMs and micellized surfactants, e.g., CTABr. First, added substrate changes first-order rate constants for reaction catalyzed by TEAMs (Table VIII), as is found with TEABr (Table V). The situation is complex, and variation of k_ψ with [*p*-NPDPP] depends on [TEAMs] and hydrophobicity of the areneimidazole. Second, sodium mesylate does *not* change the rate constants in the presence

Table VII. Relation of Rate Constant to Benzimidezolide Ion for Reaction in TEAMs[a]

$10^2 \times$ [TEAMs], M	$10^{-3} k_\psi$/[BI$^-$], M^{-1} s^{-1}	$10^2 \times$ [TEAMs], M	$10^{-3} k_\psi$/[BI$^-$], M^{-1} s^{-1}
0.1	(0.4)	0.7	1.75 (1.65)
0.2	2.17 (0.8)	0.85	(1.32)
0.3	3.33 (3.53)	1.0	1.17 (1.13)
0.4	3.83 (3.30)	1.5	0.69 (0.65)
0.5	2.96 (2.29)	2.0	(0.46)

[a] For reaction with 3×10^{-6} M *p*-NPDPP and 1×10^{-4} M benzimidazole; values in parentheses are for reaction with 2×10^{-4} M benzimidazole.

Table VIII. Effect of Substrate Concentration on Reaction with Areneimidazole in TEAMs[a]

10^5[*p*-NPDPP], M	BI[b]	NI[c]
0.15	0.27	22.6 (4.1)
0.30	0.32 (1.66)	27.8 (3.7)
0.50	0.37 (1.90)	26.6 (4.4)
0.75	0.77 (1.60)	(5.0)
1.00	0.89 (1.52)	25.1 (3.9)
1.50	0.97 (1.30)	15.2 (4.3)
2.00	1.08 (1.21)	13.8

[a] Values of $10^2 k_\psi$ (s^{-1}) at 25 °C with 10^{-4} M areneimidazole, in 10^{-2} M carbonate buffer, pH 10.7. The values in parentheses are in 10^{-2} M TEAMs. [b] In 3×10^{-3} M TEAMs. [c] In 10^{-3} M TEAMs.

Table IX. Effect of Sodium Mesylate on Reaction with Benzimidazole in TEAMs[a]

$10^3 \times$ [$MeSO_3Na$], M	$10^2 k_\psi$, s^{-1}	$10^3 \times$ [$MeSO_3Na$], M	$10^2 k_\psi$, s^{-1}
.4	0.33 (1.66)	6.0	0.31 (1.66)
1.0	(1.66)	8.0	0.37 (1.75)
2.0	0.32 (1.66)	10.0	0.39 (1.55)
4.0	0.36 (1.66)		

[a] At 25.0 °C with 10^{-4} M benzimidazole in 10^{-2} M carbonate buffer, pH 10.7, with 3×10^{-6} M *p*-NPDPP and 3×10^{-3} M TEAMs. The values in parentheses are in 10^{-2} M TEAMs.

of TEAMs, either above or below the optimum [TEAMs] (Table IX), although typically inert counterions reduce micellar catalysis of bimolecular reactions.[2-4] There is however an interaction between TEAMs and imidazolide ions, because deprotonation of BI is increased by TEAMs (Figure 2). (We could not determine the extent of deprotonation of NI in TEAMs because the solutions were slightly turbid, and although we obtained reproducible rate constants, our spectrophotometric estimates of [NI$^-$] were scattered.) There is also interaction between TEAMs and *p*-NPDPP (Tables I and VIII), so that, as in micellar catalyzed bimolecular reactions, both reactants are binding to the catalytic quaternary ammonium center.

The rate enhancements by TEAMs are large. For example the first-order rate constant for dephosphorylation by 10^{-4} M NI at pH 10.7 and optimum [TEAms] (Figure 1) is greater than that in aqueous solution by a factor of 1300, but much of the reaction in water is attack of OH^-, and considering only reaction of NI the rate enhancement is by a factor of 2×10^4. This rate enhancement is much too large to be ascribed merely to increased deprotonation of areneimidazole. A direct comparison can be made of reaction with BI at optimum [TEAMs] (Figure 1 and Table VII) where k_ψ/[BI$^-$] = 3.8×10^3 M^{-1} s^{-1}, whereas the corresponding second-order rate constant in water is ca. 1 M^{-1} s^{-1}.[16] (In this comparison we neglect the small contribution of reaction with OH^- in TEAMs.)

Table VII shows that k_ψ/[BI$^-$] is not strongly dependent on [BI], except at the lowest [TEAMs], but the situation is diffeent for reaction of the more hydrophobic NI, which is more than first

Table X. Variation of Rate Constant with [Naphth-2,3-imidazole] in TEAMs[a]

10^4[NI], M	10^3[TEAMs], M		
	1	5	10
0.5	1230		162
1.0	2040	394	355
1.5		691	
2.0	6630		672

[a] Values of $10^3 k_\psi$ (s^{-1}) at 25.0 °C in 10^{-2} M carbonate buffer, pH 10.7, and 3×10^{-6} M *p*-NPDPP.

Table XI. Effect of Substrate Concentration on Reaction with Hydroxide Ion[a]

10^5[*p*-NPDPP], M	10^4[CTABr], M	
	1	2.5
0.3	3.9	30.5
0.5	4.2	29.8
0.75	4.1	27.9
1.0	3.8	27.8
1.25	2.9	26.4
1.5	2.7	24.6

[a] Values of $10^4 k_\psi$ (s^{-1}) in M 10^{-2} M carbonate buffer, pH 10.7.

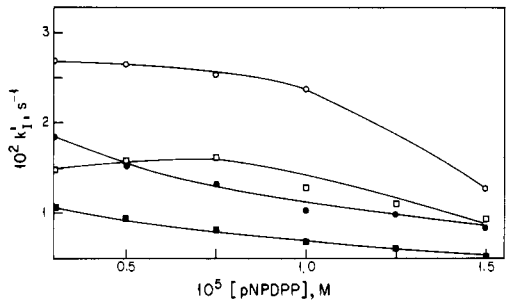

Figure 3. Effect of substrate concentration on dephosphorylation in dilute CTABr: open points, reaction in 10^{-4} M CTABr; solid points, in 2.5×10^{-4} M CTABr; ■, 5×10^{-5} BI; ●, 10^{-4} M BI; □, 5×10^{-5} M NI; ○, 10^{-4} M NI.

order with respect to areneimidazole (Table X). This difference suggests that except in very dilute TEAMs, BI has less effect than NI on the structure of the TEAMs aggregates.

Dephosphorylation in Dilute CTABr. Reactions with BI and NI are strongly catalyzed by CTABr, and k_ψ goes through maxima with increasing [CTABr].[16] However there are large rate effects at [CTABr] well below the critical micelle concentration (cmc) in water.[22] We examined the rate effects of [substrate] and [CTABr] in the hope of understanding these effects.

The effect of [*p*-NPDPP] is shown in Figure 3 for reaction in [CTABr] $\leq 2.5 \times 10^{-4}$ M. Some of these reactions in the most dilute CTABr were first order for only 2 half-lives, probably because of salt effects on the products or back-reaction of *p*-nitrophenoxide ion with phosphorylated intermediate.[16] (The constants, k_1', are corrected for the contribution of reaction with OH^-.)

The first-order rate constants for reaction with the areneimidazoles decrease slightly with increasing [*p*-NPDPP] (Figure 3), and we see a similar effect for reaction with OH^- (Table XI). The effects disappear with 10^{-3} M CTABr, i.e., at [surfactant] > cmc.[24] All these reactions were much faster than in water, and the "inhibitory" effect of substrate is almost certainly due to its incomplete incorporation into CTABr aggregates at low [surfactant].

(22) The cmc of CTABr in water is ca. 8×10^{-4} M,[23] and it should be reduced by the buffer and other solutes.

(23) Mukerjee, P.; Mysels, K. J. "Critical Micelle Concentrations of Aqueous Surfactant Systems"; National Bureau of Standards: Washington, D.C., 1971.

(24) This concentration is slightly greater than the cmc in water.[23]

Table XII. Effect of Substrate Concentration on Reaction in CTABr[a]

10^5[*p*-NPDPP], M	benz-imidazole	naphth-2,3-imidazole
0.2	2.3	17.7
0.3	2.2	
0.5	2.1	16.5
0.75		17.5
1.0	2.1	17.1
1.2		16.2
1.5	2.1	15.4

[a] Values of $10^2 k_\psi$ (s^{-1}) at 25.0 °C in 10^{-4} M benz- or naphth-2,3-imidazole in 10^{-3} M CTABr and 10^{-2} M carbonate buffer, pH 10.7.

Scheme II

$$Oct_3N^+Et + BI^- \rightleftharpoons (Oct_3N^+EtBI^-)$$

$$(Oct_3N^+EtBI^-) + p\text{-NPDPP} \longrightarrow \text{products}$$

Scheme III

$$n\text{-}Oct_3N^+Et\text{-}p\text{-NPDPP} \overset{p\text{-NPDPP}}{\rightleftharpoons} n\text{-}Oct_3N^+Et + BI^- + p\text{-NPDPP} \rightleftharpoons C$$

$$C \rightleftharpoons n\text{-}Oct_3N^+EtBI^- \qquad C \longrightarrow \text{products}$$

The species involved in catalysis in very dilute CTABr could be akin to normal micelles, i.e., induced micelles, or be similar to aggregates generated by interaction of reactants and salts such as TMAC, TEABr, or TEAMs. The second explanation seems to be incorrect because the decrease of k_1' with increasing [*p*-NPDPP] in very dilute CTABr (Figure 3) contrasts sharply with the increase with TEABr or TEAMs (Tables V, VIII, and X).

Therefore catalysis at [CTABr] below the cmc in water seems to be occurring in micelles whose formation is induced by reactants. However, these micelles readily become saturated by *p*-NPDPP (Figure 3 and Table XI) so that k_ψ decreases with [*p*-NPDPP], and this saturation disappears as [CTABr] is increased (Table XII).

Discussion

Catalysis by Tri-*n*-octylethylammonium Salts. The rate maxima with increasing [TEAMs] in dephosphorylations of *p*-NPDPP by BI^- and NI^- (Figure 1) require that both reactants associate strongly with the quaternary ammonium ion. If only one reactant was strongly associated to give a reactive species, k_ψ would become constant once association was complete, even if several molecules of reactant and catalyst were incorporated into the aggregate. Therefore we cannot explain our results in terms of Scheme II, written for reaction with benzimidazolide ion.

Solubilization of *p*-NPDPP by TEAMs (Table I) suggests that there is direct association between the two solutes, and the increased deprotonation of BI by TEAMs (Figure 2) is good evidence for association between BI^- and TEA^+.

The simplest model for catalysis is in Scheme III. It assumes that both reactants associate with quaternary ammonium ion and that reaction occurs in the association complex C. The scheme is written for a 1:1:1 complex, although variations of rate constant with [reactants] and [catalyst] show that such a complex will be present only at very low solute concentrations. Under most conditions the complex will contain more than one molecule of each solute. The solution will contain productive complexes C and unproductive complexes of $n\text{-}Oct_3N^+Et$ with either *p*-NPDPP or BI^-, and rate will depend upon the amounts of *p*-NPDPP and BI^- associated in the same complex. In deriving a simplified rate equation we assume that the two reactants will not affect each other's association with the quaternary ammonium ion. We also neglect reactions with water and OH^- and reactions between nonassociated reactants.

Table XIII. Estimation of Second-Order Rate Constants for Reaction in TEAMs[a]

$10^3 \times$ [TEAMs], M	$10^3 k_\psi$, s^{-1}	$10^5 \times$ [BI^-], M	f	k_M, s^{-1}
3	3.23	0.15	0.56	12 (27)
3.5	7.6	0.27	0.59	17
4	16.8	0.36	0.61	31 (24)
5	19.1	0.58	0.63	26 (17)
7	20.6	1.14	0.68	19 (17)
8.5	20.1	1.20	0.69	21 (16)
10	17.0	1.41	0.70	17 (16)
15	13.6	1.97	0.74	14 (13)
20	10.6	2.50	0.76	11 (11)

[a] At 25.0 °C, pH 10.7, carbonate buffer, and 10^{-4} M benzimidazole. Values of k_M in parentheses are for reaction in 2×10^{-4} M benzimidazole.

Our experiments are at a pH well below pK_A of BI,[18,19] and we assume that increased deprotonation is due solely to association between BI^- and n-Oct_3N^+Et, i.e., that at pH 10.7 essentially all the BI^- is paired to the cation. In much the same way we assume that solubilization of *p*-NPDPP by TEAMs measures the fraction of substrate associated with the cation (Table XIII).

If we consider only reactions involving the productive complex C, Scheme III, the first-order rate constant is given by eq 3, where

$$k_\psi = k_M f[BI^-]/[\text{TEAMs}] \quad (3)$$

f is the fraction of bound *p*-NPDPP (Table XIII) and k_M is a second-order rate constant written in terms of the mole ratio of BI^- to quaternary ammonium ion, i.e., in terms of the probability of the nucleophile, BI^-, being associated with any given quaternary ammonium ion. This formalism has been applied to bimolecular reactions in micellar pseudophases; however, the second-order rate constants k_M cannot be compared directly with second-order rate constants in homogeneous solution because of differences in dimensions.[3,21b]

The estimation of k_M is illustrated in Table XIII for reaction with 10^{-4} M BI. The values of k_M in parentheses are for reaction with 2×10^{-4} M BI (Figure 1).

The values of k_M decrease with increasing TEAMs, but the changes are not large considering the approximations, and values of k_M are of similar magnitudes for reactions in 10^{-4} and 2×10^{-4} M BI. In addition values of k_M (Table XIII) are not very different from that of 7 s^{-1} for reaction of *p*-NPDPP with BI^- in the micellar pseudophase of CTABr.[16,25]

The treatment which leads to eq 3 appears to be qualitatively satisfactory, but it has several weaknesses, both experimental and theoretical. (i) Our estimate of the association of *p*-NPDPP with TEAMs is based on solubility measurements and is, of necessity, for a solution saturated with *p*-NPDPP, whereas [substrate] in the kinetic experiments is lower than those in the solubilization experiments, which almost certainly affects the binding (cf. Tables I and XIII and Figure 2). (ii) Interactions of the two reactants with the quaternary ammonium ion are probably not mutually independent. For example a (TEA^+BI^-) ion pair may bind *p*-NPDPP better than does TEAMs; cf. ref 11. (iii) Equation 3 is based on the assumption that k_M is independent of the size of the ion pair or aggregate, i.e., of the productive complex C, Scheme III. This is almost certainly incorrect, because values of k_ψ do not vary linearly with [reactants] or [catalyst] (Tables II–V, VIII, and X), suggesting that size and catalytic activity of the aggregates varies with [solute].

In some respects this situation is similar to that observed with so-called reverse micelles where size of the aggregates depends upon [solute].[26] These variations are taken care of by multiple equilibria relations, but our binding evidence with TEAMs is inadequate for application of such a treatment.

The apparent decrease in k_M (Table XIII) with increasing [TEAMs] suggests that the efficiency of TEAMs as a catalyst decreases slightly with increasing size of the aggregates, but in view of the approximations we do not attach much significance to this change. Despite these approximations, in both systems the rate depends primarily on the probability of the two reactants coming into close proximity by associating with a quaternary ammonium ion of TEAMs, TEABr, or their aggregates. This means that in aqueous solution, phase-transfer catalysts, and micelle-forming surfactants, e.g., CTABr, increase rates primarily by concentrating reactants rather than by increasing their reactivity.

Comparison of Phase-Transfer and Surfactant Catalysis. Micellar rate enhancements in aqueous systems fit the pseudophase model, provided that [surfactant] >> cmc, and the reactants do not materially perturb micellar structure.[3-9] However surfactants in submicellar concentrations are often effective catalysts, and Piskiewicz's model of micellar catalysis, based on general cooperative association,[11] seems to be qualitatively applicable to reactions in solutions of the phase-transfer catalysts TEABr or TEAMs. In particular, dephosphorylations in TEABr are greater than first order with respect to areneimidazoles at their higher concentrations (see Results), and the greater than first-order rate dependences upon [TEABr] and [TEAMs] are consistent with formation of small aggregates. High-order dependences upon [surfactant] are also often observed in very dilute surfactant, i.e., below the cmc.[11]

One obvious difference between catalysis by micelles and hydrophobic cations in aqueous solution is, that at a given concentration, micelles are relatively uniform in size[27] and their structures are not very sensitive to the reactants, provided that [surfactant] >> [reactants]. First-order rate constants in micellar solutions are then independent of [substrate]. But aggregation of hydrophobic quaternary ammonium ions, e.g., TEA^+, should be affected by other hydrophobic solutes, leading to high kinetic orders with respect to reactants and catalysts.

We can construct a general explanation of catalysis by cationic micelles and hydrophobic quaternary ammonium ions, on the assumption that concentration of reactants into a small volume, at a hydrophobic ionic center, will of itself speed reaction. Bimolecular reactions in micellar pseudophases generally have second-order rate constants similar in magnitude to those in water, and rates follow reactant concentrations in the Stern layer.[28] Therefore the initial effect of micellized surfactant is to incorporate reactants from the aqueous pseudophase, but eventually, when reactants are largely micellar bound, an increase in [surfactant] merely dilutes them in the micellar pseudophase. The suggestion of Kunitake and co-workers that cationic surfactants, or phase-transfer catalysts, form reactive ion pairs with anionic nucleophiles contradicts evidence that ion pairing reduces nucleophilicity.[30] A more serious problem is that the ion pair model, in its simplest form, cannot explain the rate maximum in Figure 1.

The similarity of the micellar rate constant k_M for reaction of BI^- in micelles of CTABr (k_M = 7 s^{-1}) and in TEAMs (k_M = 11–31 s^{-1}) suggests that reaction rate, for reactants bound to aggregates of phase-transfer catalysts, depends upon the mole ratios of reactants to quaternary ammonium ion, as it does for micellar reactions.[3,16] The main difference is that for micelles k_M is essentially independent of [surfactant] and [reactant], primarily because [reactant] in the micellar pseudophase is not high enough to perturb the micelle–water interface. But k_M varies with [TEAMs] (Table XIII), because TEAMs is not in large excess over the reactants, so that structure and catalytic activity

(25) The values of k_M for reaction in CTABr are much more reliable than those in TEAMs, because the concentrations of micellar bound reactants can be measured directly.

(26) Kertes, A. S.; Gutman, H. In "Surface and Colloid Science"; Matijevic, E., Ed.; Wiley: New York, 1976; Vol. 8.

(27) Mukerjee, P. In ref 7; Vol 1, p 171. Tanford, C. *J. Phys. Chem.* **1974**, *78*, 2469.

(28) The actual comparison depends on the choice of the volume element for reaction in a micelle,[3,8,9] and some rate constants in a micelle are lower than those in water because of the lower polarity of the Stern layer as compared with that of water.[29]

(29) Mukerjee, P.; Ray, A. *J. Phys. Chem.* **1966**, *70*, 2144. Cordes, E. H.; Gitler, C. *Prog. Bioorg. Chem.* **1973**, *2*, 1.

(30) Alder, R. W.; Baker, R.; Brown, J. M. "Mechanism in Organic Chemistry"; Wiley-Interscience: New York, 1971; Chapter 3.

of the aggregate are concentration dependent.

Although micellar catalysis of bimolecular reactions can be interpreted quantitatively in terms of concentration of reactants in the micellar pseudophase, one could just as well describe it in terms of a more favorable entropy of activation.[31] This description is often applied to intramolecular as compared to otherwise similar bimolecular reactions[32] and can be extended to catalysis by micelles and aggregates of reactants and hydrophobic cations.

Effectiveness of Phase-Transfer Catalysts and Micellized Surfactants. Comparison of rate enhancements by TEAMS, TEABr, and micellized CTABr shows that overall rate enhancements give little insight into the role of the catalysts. Micelles effectively bind hydrophobic solutes and counterions, but, because reactions are generally followed with [surfactant] >> [reactants], the latter are distributed over a large number of cationic head groups. But in an aggregate of, for example, substrate, BI^-, and TEAMs or TEABr, the reactants are associated with at most a few cationic head groups, so that for some reactions these types of catalysts should give larger rate enhancements than micelles.[12]

The question of whether micelles or hydrophobic tetraalkylammonium ions are the most effective catalysts depends upon the reaction and its conditions. In reactions of *p*-nitrophenyl acetate with functional surfactants Kunitake and co-workers found TMAC more effective than micellized CTABr.[12] We see a similar situation for dephosphorylation by the imidazoles in TEABr and CTABr (Tables II and III and ref 16). But the order of effectiveness is reversed by changing the hydrophobicity of the nucleophile because reaction of OH^- with *p*-NPDPP is catalyzed by CTABr[21a] but not by TEABr. This difference is understandable in terms of a concentration effect, because although micelles and hydrophobic cations associate with hydrophobic solutes, micelles are much the more effective at binding hydrophilic counterions. The fact that $MeSO_3^-$ ion does not reduce catalysis by TEAMs (Table IX), although inert counterions typically reduce catalysis by ionic micelles,[7,33] is consistent with our interpretation.

It is useful to compare our results on reactions of arene-imidazoles with *p*-NPDPP with those of Kunitake and co-workers on reactions of *p*-nitrophenyl acetate with lauryl-substituted imidazole or hydroxamate.[12] In our system the substrate (*p*-NPDPP) is very hydrophobic, and the nucleophilic imidazoles less so, whereas in Kunitake's system the substrate, *p*-nitrophenyl acetate, is relatively hydrophilic, but the hydrophobic nucleophile is an imidazole or hydroxamate surfactant. For example deacylation by BI is not catalyzed by TMAC,[12] whereas a micelle of CTABr is an effective catalyst.[8]

Thus it appears that formation of catalytically active aggregates from a quaternary ammonium ion of TMAC, TEABr, or TEAMs requires the presence of a hydrophobic solute, either substrate, e.g., *p*-NPDPP, or nucleophile, e.g., a lauryl imidazole or hydroxamate.

These conclusions regarding the formation of catalytically active aggregates by interaction of a tri-*n*-octylalkylammonium ion with hydrophobic solutes are consistent with available physical evidence.[12] (i) The conductivity of TMAC varies linearly up to ca. 2×10^{-4} M, which is probably the solubility limit. We see the same behavior with both TEABr and TEAMs, up to 1.75×10^{-3} M. (ii) The surface tension of water is reduced by TMAC, which is therefore surface active, but there is no break which could be associated with a cmc and formation of large aggregates. (iii) The absorbance of Methyl Orange is shifted by TMAC, which also increases deprotonation of 2,6-dichlorophenol indophenol just as TEAMs increases deprotonation of BI (Figure 2), showing that aggregation of salts of TMA^+ or TEA^+ depends on interaction with added solutes.

Acknowledgment. Support of this work by the National Science Foundation (Chemical Dynamics) and the Army Office of Research is gratefully acknowledged.

(31) Bunton, C. A.; Romsted, L. S. In "The Chemistry of Functional Groups"; Patai, S., Ed.; Wiley: New York, 1979; Supplement B, Part 2, Chapter 17.

(32) Jencks, W. P. "Advances in Enzymology"; Meister, A., Ed.; Wiley: New York, 1975; p 219. Bruice, T. C. *Annu. Rev. Biochem.* **1976**, *45*, 331. Page, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 449.

(33) Bunton, C. A. In "Reaction Kinetics in Micelles"; Cordes, E. H., Ed.; Plenum Press: New York, 1973; p 73.