Department for their determination of spectroscopic data. Special thanks to D. Chidester for experimental assistance.

Registry No. 2, 13200-60-7; **2a**, 5269-39-6; **5**, 28752-82-1; (±)-**6**, 52183-82-1; (±)-**7**, 35677-84-0; **8**, 92345-88-5; (±)-*cis*-**9**, 92346-01-5; (±)-*trans*-**9**, 92419-26-6; (±)-**9a**, 92469-48-2; (±)-**9b**, 92345-89-6; (±)-*cis*-**10**, 92345-94-3; (±)-*trans*-**10**, 92419-25-5; **11**, 92345-90-9; (±)-**12**, 92345-91-0; (±)-**13**, 92345-92-1; (±)-**14**, 92345-93-2; (±)-**16**, 92345-95-4; (±)-**16**·HCl, 92345-96-5; (±)-**19**, 56782-26-4; **21**, 92345-97-6; **22**, 92346-00-4; **23**, 92345-98-7; **24**, 92345-99-8; **25**, 92365-83-8; 3,4-dimethoxy-α-methylstyrene, 30405-75-5; 3,4-dimethoxyacetophenone, 1131-62-0.

Nucleophilic Reactions in Solutions of Nonmicellized Hydrophobic Ammonium Ions

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Abstract: Rate constants of reactions of *p*-nitrophenyl diphenyl phosphate, 2,4-dinitrochlorobenzene, and *p*-nitrophenyl benzoate with (2-hydroxyethyl)-tri-*n*-octylammonium bromide or mesylate in aqueous solvents at high pH can be treated quantitatively in terms of binding of reactants to nonmicellar aggregates and second-order rate constants of reaction in aggregates. These rate constants are very similar to those in cationic micelles, but micelles are the more effective at binding substrate. The apparent acid dissociation constant of the hydroxyl group is also larger in the micellar system.

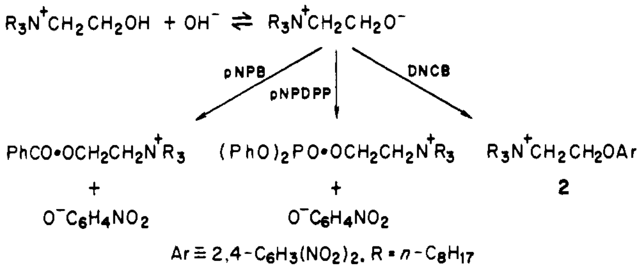
Salts of tri-*n*-octylalkylammonium ions (**1a–c**) increase the extent of deprotonation of hydrophobic weak acids and speed reactions of hydrophobic nucleophilic anions and of amphiphilic nucleophiles.[2,3] The rate enhancements involve the bringing

$(n\text{-}C_8H_{17})_3N^+R\ X^-$
1a, R = Me; X = Cl
1b, R = Et; X = Br
1c, R = Et; X = OMs
1d, R = CH_2CH_2OH; X = Br
1e, R = CH_2CH_2OH; X = OMs

together of reactants in an association complex which includes the ammonium ion or an aggregate of it, and for dephosphorylation by benzimidazolide ion second-order rate constants are similar in the aggregate and in solutions of micellized cetyltrimethylammonium bromide (CTABr).[3] The effects of these ions are similar to those of a variety of other amphiphiles which form so-called "organized assemblies", for example, many reactions are speeded by micellized surfactants, microemulsions, and vesicles.[4-7] The colloidal particles in these assemblies are relatively large and contain large numbers of monomeric amphiphiles.

Salts of **1** are surface active, but unlike surfactants they do not have a critical micelle concentration (cmc), although they are believed to aggregate.[2a,b] In some kinetic systems, but not all, the reagent has been a functionalized surfactant, which could promote formation of micelle-like species. The rate enhancements are sometimes larger than those found with comicelles of a functional and an inert surfactant, e.g., cetyltrimethylammonium bromide, and **1a** (X = Cl) has been considered to be a "better catalyst" than micellized surfactants.[2] But for such a statement to be significant it is necessary to isolate the sources of rate enhancements and to decide the extent to which size of the assembly is important.

Scheme I



Rate constants in nonfunctional and functional aqueous micelles and microemulsions can be treated quantitatively in terms of reactant concentrations and rate constants in the micelles or droplets which are treated as a pseudophase.[6,7-10] Dephosphorylation by areneimidazolide ions in solutions of **1b,c** appears to be governed by the same factors which govern micellar rate enhancements,[3,11] and the aim of the present work was to apply a similar treatment to reactions in functionalized hydrophobic ammonium ions (**1d,e**). It was necessary to demonstrate nucleophilic attack by the functional group and to estimate the relative importance of substrate binding and reactivity of bound substrate.

We used two substrates of very different hydrophobicities,[6] 2,4-dinitrochlorobenzene (DNCB) and *p*-nitrophenyl diphenyl phosphate (pNPDPP), in order to obtain information regarding the importance of substrate binding. A major problem in the study of rate enhancements by nonmicellizing, hydrophobic ammonium

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ions is that solubility of the ammonium salts is very low[2a] and for dephosphorylation and aromatic nucleophilic substitution the products derived from **1d,e** are also sparingly soluble in water. We had to use an organic cosolvent in some of these reactions, which complicated comparison with experiments with functional micelles in water. These reactions were carried out in solvents containing 10–30 vol % MeCN. However, solubility was less of a problem for reaction of *p*-nitrophenyl benzoate (pNPB), and we examined its reactions in mixtures of **1c** and **1e** in solvents of high water content. Deacylation by functionalized micelles has been extensively studied and at high pH surfactants containing a hydroxyethyl group are effective reagents.[6,10,12]

The overall reactions are shown in Scheme I. Micelles of hydroxyethylammonium ion surfactants give similar reactions, and in aromatic nucleophilic substitution the first formed ether (**2**) may go forward to 2,4-dinitrophenoxide ion.[13a,b]

The substrates react with OH^-, but alkoxide ions are better nucleophiles, so that attack by OH^- is of minor importance.[14]

Any quantitative treatment of these rate enhancements by the nonmicellizing ions (**1**) should be applicable to reactions of strongly bound pNPDPP and of less strongly bound pNPB or DNCB. In addition formation of ether or trisubstituted phosphate ester (Scheme I) demonstrates nucleophilic attack by **1d,e** rather than general base catalyzed attack by water.

Experimental Section

Materials. Tri-*n*-octyl(2-hydroxyethyl)ammonium bromide (**1d**) was prepared by reaction of 2-bromoethanol with equimolar tri-*n*-octylamine in refluxing MeCN for 5 days. The solvent was removed and the residue was recrystallized five times from Et_2O. Anal. Calcd for $C_{26}H_{56}NOBr$: C, 65.2; H, 11.8; N, 2.92; Br, 16.7. Found: C, 65.1; H, 12.0; N, 3.00; Br, 16.7.

Tri-*n*-octyl(2-hydroxyethyl)ammonium mesylate (**1e**) was prepared by reaction of 2-hydroxyethyl mesylate[15] with equimolar tri-*n*-octylamine in refluxing MeCN:THF:EtOH 3:2:1 for 5 days. The solvent was removed and the residue was recrystallized from Et_2O. Anal. Calcd for $C_{27}H_{59}NO_4S$: C, 65.7; H, 12.0; N, 2.84. Found: C, 65.5; H, 12.1; N, 2.85.

The other materials were prepared or purified by standard methods.[13]

Autoprotolysis of H_2O–MeCN. The effect of MeCN on the autoprotolysis constant of water, pK_w, was determined by measuring the difference in pH of 0.01 and 0.1 M HCl and 0.01 and 0.1 M KOH. A Corning 12 pH meter with an S and K high pH glass electrode was standardized with aqueous buffers and the apparent pH of acidic and basic H_2O:MeCN 70:30 v/v was then measured. The values of pK_w were 14.70 and 14.73, calculated from 0.01 and 0.1 M solutions, respectively. As a test of the method we obtained corresponding values of 13.95 and 14.02 in water. No correction was made for electrolyte effects.

Reaction Products. Reaction of 5×10^{-4} M pNPDPP with 0.08 M **1d** was carried to completion in 10^{-3} M NaOH and H_2O:MeCN 80:20 v/v at 25 °C. Addition of $NaClO_4$ gave a precipitate which was filtered off, washed (H_2O), and redissolved in EtOH. The ethanolic solution had absorbances at 262 and 267 nm characteristic of a diphenyl phosphoryl group.[15a,16]

Formation of ether (**2**) was demonstrated spectrophotometrically.[13b] This initial reaction was followed by a much slower conversion of **2** into 2,4-dinitrophenoxide ion by attack of OH^-.

Kinetics. Reactions were followed spectrophotometrically at 25.0 °C in Gilford or Beckman spectrometers, for the slower reactions, and in a Durrum stopped-flow spectrophotometer, for the faster reactions. Reaction of pNPDPP was followed at 405 nm, λ_{max} for *p*-nitrophenoxide ion. Reaction of DNCB was followed at 324 nm, the isosbestic point of 2,4-dinitrophenoxide ion and its ether (**2**). We were concerned with the possibility that turbidity, even though undetectable by eye, might cause problems, and we measured rate constants for reaction of DNCB in H_2O:MeCN 80:20 and 70:30 (v/v) with **1d** and 0.01 M NaOH. We estimated a few rate constants from the differences in absorbance at 324 and 500 nm in order to allow for turbidity of the solution. The rate constants estimated in this way were within experimental error of those estimated from the changing absorbance at 324 nm in 70% H_2O, but they were slightly higher in 80% H_2O.

Table I. Reaction of pNPDPP in H_2O–MeCN[a]

	MeCN vol %		
10^2[NaOH], M	0	20	30
0.5		0.83	0.60
1.0	5.0[b]	1.50	
2.0		3.57	2.28

[a] Values of 10^3k_ψ, s^{-1}, at 25.0 °C. [b] Bunton, C. A.; Farber, S. J.; Fendler, E. J. *J. Org. Chem.* **1968**, *33*, 29.

Table II. Dephosphorylation in Mixed Ammonium Ions[a]

	10^3k_ψ, s^{-1}, at H_2O vol % =	
10^4[**1e**], M	97.8	95
		0.39
2	3.66	0.72
2.6	3.52	1.10
3.0	4.14	
4.0	6.60	3.02
5.0	5.25	3.07
7.0		2.71

[a] At 25.0 °C with 10^{-3} M NaOH and [**1e**]/[**1c**] = 0.1.

The rate constants for reactions in solutions containing **1c** are means of two measurements, and some of the other reactions were run in duplicate. Duplicate runs agreed within 6%.

The first-order rate constants, k_ψ, are in reciprocal seconds, and the cosolvent, when present, was MeCN.

Results

Reaction in the Absence of Ammonium Ions. Reaction of OH^- with DNCB is speeded by addition of MeCN. In 0.01 M NaOH at 25.0 °C values of 10^6k_ψ are 1.42, 3.0, and 4.8 s^{-1} in 0, 20, and 30 vol% MeCN, respectively. The corresponding results for reaction of pNPDPP are in Table I.

Hydration of anions decreases their nucleophilicity, and therefore addition of aprotic solvents to water generally speeds nucleophilic attack.[17] Solvent effects upon the reaction of DNCB follow the expected pattern, and the retardation of the reaction of OH^- with pNPDPP by MeCN is due to the high hydrophobicity of the substrate. The decrease of the activity coefficient of the substrate, relative to that of the transition state, on addition of MeCN, more than offsets the increased reactivity of OH^-. Other nonnucleophilic organic solvents behave similarly.[18]

The second-order rate constant for reaction of OH^- with pNPB is 3.2 M^{-1} s^{-1} at 25.0 °C on the basis of rate constants in 10^{-2} M carbonate buffer (pH 9.3 and 9.9) and in 10^{-3} and 5×10^{-3} M NaOH. Under similar conditions the second-order rate constant for reaction of cholinate zwitterion is 18 M^{-1} s^{-1}, based on pK_a = 12.8 for choline.[19] A higher pK_a was used in earlier calculations of the relative reactivities of OH^- and cholinate zwitterion,[13,14c] and the new rate constants are therefore lower than the earlier values.

Reaction in Solutions of Ammonium Ions. We generally used (2-hydroxyethyl)tri-*n*-octylammonium mesylate (**1e**) which is more soluble than the bromide (**1d**), cf. ref 3. We could not follow the reaction in water because of precipitation, probably of ether (**2** or phosphorylated **1e** (Scheme I). Therefore, reactions were generally followed in aqueous acetonitrile.

Formation of 2,4-dinitrophenoxide ion from DNCB was much slower than the initial step of ether formation.[13b] For example, in H_2O:MeCN 80:20 (v/v) 0.05 M OH^- and 0.05 M **1e** the half-life for conversion of ether **2** into 2,4-dinitrophenoxide is ca.

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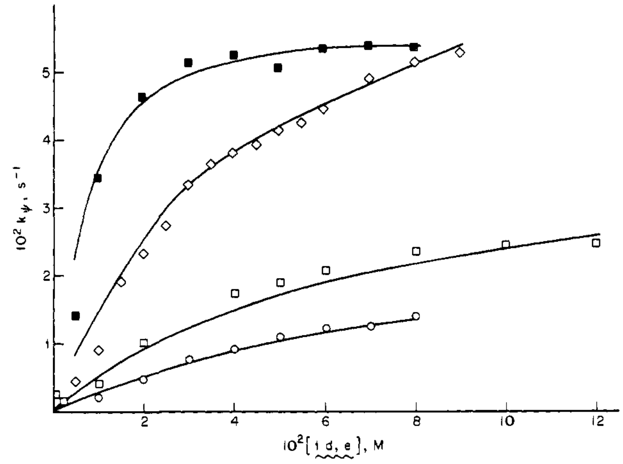

Figure 1. Reaction of pNPDPP in hydrophobic ammonium ions. Open points, H_2O:MeCN 70:30 (v/v); closed points, H_2O:MeCN 80:20 (v/v); ○, 0.005 M NaOH + **1d**; ■ and □, 0.01 M NaOH + **1e**; △, 0.02 M NaOH + **1d**. The lines are calculated, eq 1.

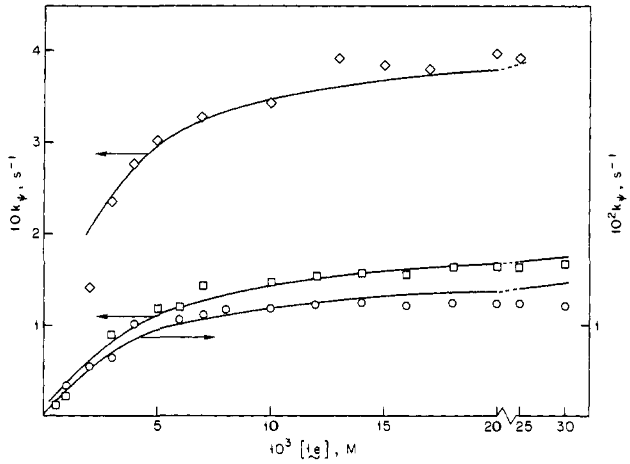

Figure 2. Reaction of pNPDPP in **1e** and H_2O:MeCN 90:10 (v/v): ○, □, and △, 0.001, 0.01, 0.02 M NaOH. The lines are calculated, eq 1.

500 s at 25.0 °C. In these conditions formation of the ether is complete within 50 s.

The overall reaction rate depends on the extent of substrate binding to aggregates of the hydrophobic ammonium ions and the extent of deprotonation of the hydroxyethyl group of **1d,e**, and we have to separate these two effects.

Effect of Ammonium Ion Concentration. Rate constants of dephosphorylation and aromatic nucleophilic substitution increase with increasing [**1d,e**], and in 70 and 80 vol % H_2O there are inflections in plots of k_ψ againt concentration (Figures 1–3 and Tables SI and SII). With mesylate counterion k_ψ tended toward limiting values as the concentration of ammonium ion is increased. Low solubility of the bromide (**1d**) made it difficult to reach limiting rates in this system. Reaction of pNPDPP in mixtures of **1c** and **1e** was slowed by addition of MeCN (Table II). The data for reaction in which k_ψ did not tend toward limiting values are in Tables SI and SII.

These rate effects are superficially similar to those observed with aqueous surfactants where rates increase as micelles form and incorporate reactants,[4–6,8–10] and for micelles rate and binding constants can be separated. These similarities lead us to apply a model similar to that which is generally used to treat micellar rate effects,[6,8,9,20,21] although we recognize that assumptions which are satisfactory in one system may be invalid for another.

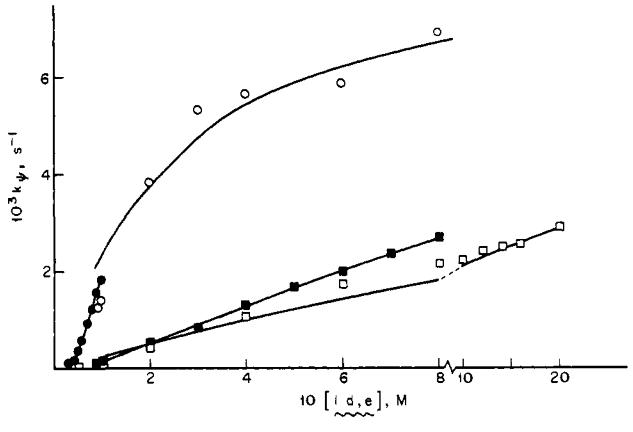

Figure 3. Reaction of DNCB in 0.01 M NaOH. Solid points in **1d**, open points in **1e**; ● and ○, H_2O:MeCN 80:20 (v/v); ■ and □, H_2O:MeCN 70:30 (v/v). The lines were calculated (eq 1) except for reaction with **1d** in 80% H_2O.

Scheme II

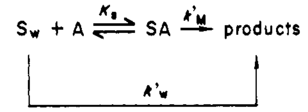

Table III. Binding and Rate Constants for Reactions in Hydrophobic Ammonium Ions[a]

substrate	[NaOH], M	H_2O vol %	[**1d,e**],[b] M	K_s, M^{-1}	k_M', s^{-1}
pNPDPP	0.001	90	0.001	210	0.017
pNPDPP	0.01	90	0.003	240	0.20
pNPDPP	0.02	90	0.004	470	0.42
pNPDPP	0.01	80	0.01	133	0.060
pNPDPP	0.005	70[c]	0.02	12	0.027
pNPDPP	0.01	70	0.02	15	0.040
pNPDPP	0.02	70[c]	0.03	25	0.077
DNCB	0.01	80	0.02	37	0.009
DNCB	0.01	70	0.06	6	0.0055

[a] Counterion is mesylate unless specified. [b] Minimum concentration used in fitting. [c] Bromide counterion.

The model for reaction at a given stoichiometric concentration of OH^- is shown in Scheme II, where A denotes ammonium ion in an unspecified state of aggregation, S is substrate, K_s is a binding constant, and k'_w and k'_M are the first-order rate constants respectively in water and the complex SA. Reactions in water are relatively slow and make a minor contribution (Table I and Results). (The values of k'_W and k'_M depend on [OH^-]).

Scheme II leads to eq 1 which is similar to that applied to micellar systems except that we do not include the critical micelle concentration (cmc).[23,24]

$$k_\psi = \frac{k'_w + k'_M K_s[A]}{1 + K_s[A]} \tag{1}$$

Equation 1 can be rearranged to the reciprocal form, eq 2, cf. ref 23:

$$\frac{1}{k_\psi - k'_w} = \frac{1}{k'_M - k'_w} + \frac{1}{(k'_M - k'_w)K_s[A]} \tag{2}$$

The rate constants fit eq 2 only over a specified range of concentrations of **1d,e**, and values of k'_M and K_s calculated from a least-squares fit to eq 2 are in Table III.

The values of k_ψ predicted from K_s and k'_M and eq 2 are shown in Figures 1–3, mostly for reaction in solutions of the mesylate (**1e**).

We observe linear reciprocal plots only over a limited concentration range (Figures 1–3 and Table III), and predicted values of k_ψ are higher than those observed for dilute quaternary am-

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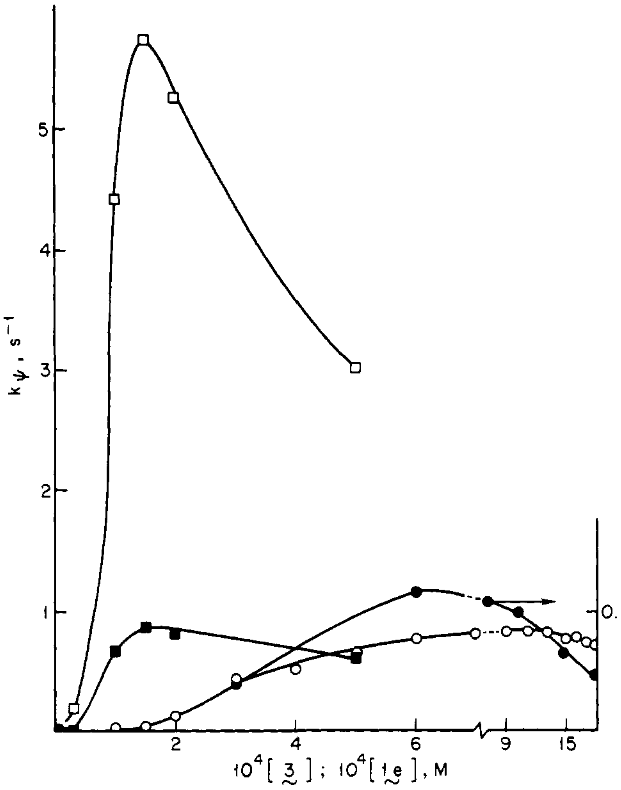

Figure 4. Reaction of pNPB in 0.001 M NaOH: ○, **1e**; ●, [**1c**]/[**1e**] = 10 in 97. vol % H_2O; □, **3**; ■, [CTABr]/[**3**] = 10.

monium ions. With micelles linear plots can be observed over wide ranges of surfactant concentrations.[6,8-11,20-23] This difference and the points of inflection in Figures 1–3 are probably the result of the hydrophobic ammonium ions forming relatively small aggregates whose size and solubilizing capacity increase with increasing concentration.

The rate constants, k'_M, are not very different in the various solvents. They depend upon the extent of deprotonation of the hydroxy group, and this question is related to the effect of OH^- upon reaction rate.

Deacylation of pNPB in mixtures of **1c** and **1e** could be followed in a solvent containing only 2.2 vol% MeCN (Figure 4).

We did not attempt to treat the binding quantitatively, because the rate maxima (Figure 4) show that there is competition between OH^- and mesylate ion which complicates the analysis. This competition is less important in the less aqueous media (Figures 1–3). Approximate values of K_s are given by the reciprocal of the concentration of tri-*n*-octylammonium ion required for 50% rate increase.[25] On this basis $K_s \approx 3 \times 10^2$ M^{-1} for binding to **1c** or **1e** in 97.8% water (Figure 4).

The nonfunctional salt **1c** only weakly speeds reaction of pNPB with OH^- (Table SIII), but it is much faster in mixtures of **1c** and **1e**.

Effect of Hydroxide Ion. Reaction rates increase with increasing $[OH^-]$, because of increasing formation of alkoxide zwitterion (Scheme I).

Plots of k_ψ against $[OH^-]$ are initially linear, but curve at higher $[OH^-]$ (Figures 5 and 6). Generally we write the variation of k_ψ with $[OH^-]$ in terms of eq 3, which neglects possible effects of OH^- upon rate and binding constants, due to its nucleophilicity or medium effects.[13a,26] where the rate constant, k', is a function

$$k_\psi = k'[OH^-]/(K_B + [OH^-]) \tag{3}$$

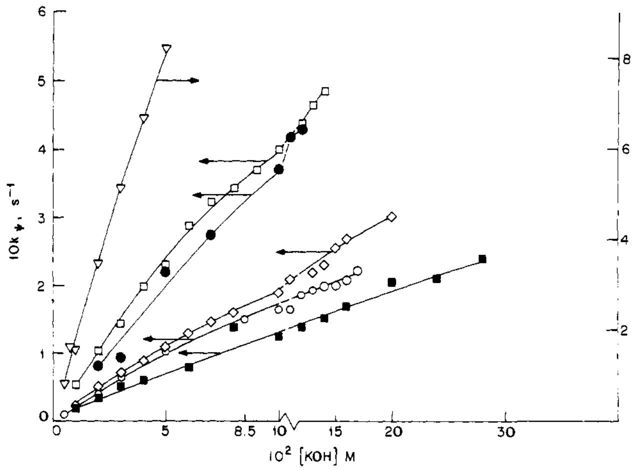

Figure 5. Effect of KOH upon reaction of pNPDPP: <<tvd, 0.01 M **1e**, 90 vol % H_2O; (●), 0.008 M **1d** and (□) 0.04 M **1e** in 80 vol% H_2O; (○) 0.05 M **1d** (■), 0.05 M **1e**, and (<<tvd) 0.01 M **1e** in 70 vol % H_2O. Lines for 70 and 80 vol % H_2O are calculated.

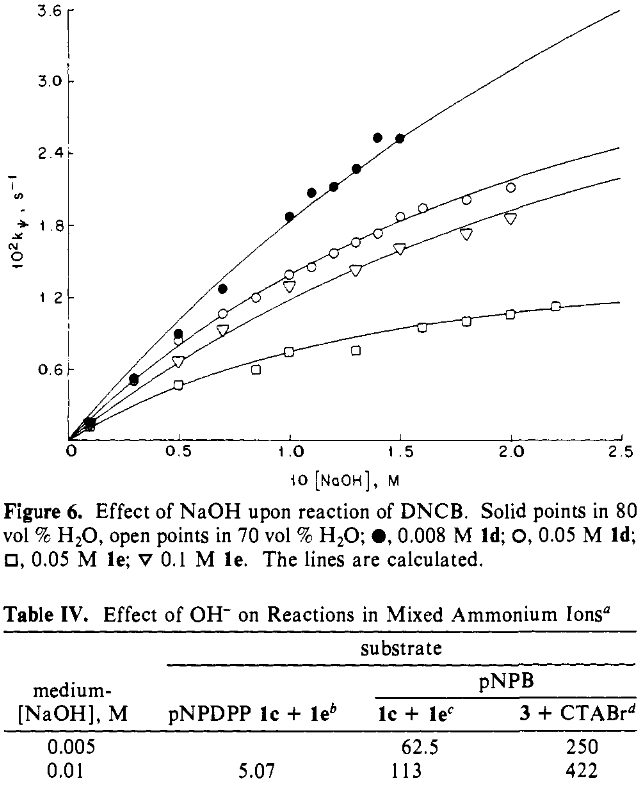

Figure 6. Effect of NaOH upon reaction of DNCB. Solid points in 80 vol % H_2O, open points in 70 vol % H_2O; ●, 0.008 M **1d**; ○, 0.05 M **1d**; □, 0.05 M **1e**; ▽ 0.1 M **1e**. The lines are calculated.

Table IV. Effect of OH^- on Reactions in Mixed Ammonium Ions[a]

medium-[NaOH], M	substrate		
		pNPB	
	pNPDPP **1c** + **1e**[b]	**1c** + **1e**[c]	**3** + CTABr[d]
0.005		62.5	250
0.01	5.07	113	422
0.02	8.64	189	585
0.05	13.2	329	933
0.1		516	1100

[a] Values of 10^2k_ψ, s^{-1}, at 25.0 °C. [b] 4×10^{-3} M **1c**, 4×10^{-4} M **1e**, and 2.2 vol % MeCN. [c] 6×10^{-3} M **1c**, 6×10^{-4} M **1e**, and 2.2 vol % MeCN. [d] 1.5×10^{-3} M CTABr, 1.5×10^{-4} M **3**, 0.08 vol % MeCN.

of [**1d,e**], and K_B is an apparent base-dissociation constant. Provided that $[OH^-]$ is much larger than $[R'O^-]$ k' and K_B can be calculated by using the reciprocal form of eq 3:

$$1/k_\psi = 1/k' + K_B/(k'[OH^-]) \tag{4}$$

and plots of $1/k_\psi$ against $[OH^-]^{-1}$ are generally linear. Alternatively we can allow for depletion of OH^-, eq 5,

$$[OH^-] = [OH^-_T] - [R'O^-] \tag{5}$$

where $R' = (n\text{-}C_8H_{17})_3N^+CH_2CH_2$ and subscript T denotes the stoichiometric concentration of OH^-. Computer simulation of the plots of k_ψ against $[OH^-]$ is then used to estimate k' and K_B. The two methods of calculation give similar results, except for

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(22) The symbols for rate and equilibrium constants are similar to those used in treatments of micellar and microemulsion rate enhancements.[6,21]

(23) Menger, F. M.; Portnoy, C. E. *J. Am. Chem. Soc.* **1967**, *89*, 4968.

(24) Hydrophobic ammonium salts (**1a**) are surface active, but surface tension vs. concentration plots do not show breaks characteristics of a cmc.[2a]

(25) Romsted, L. S.; Cordes, E. H. *J. Am. Chem. Soc.* **1968**, *90*, 1898.

Table V. Rate and Apparent Deprotonation Constants

substrate	solvent % H_2O	reagent	pK_b	pK_a[a]	k', s^{-1}
DNCB	80	0.008 M **1d**	0.36 (0.36)	≈14	0.1 (0.1)
DNCB	70	0.05 M **1d**	0.7 (0.7)	14.0	0.042 (0.042)
DNCB	70	0.05 M **1e**	1.0 (0.85)	13.7	0.017 (0.018)
DNCB	70	0.1 M **1e**	0.7 (0.42)	14.3	0.044 (0.06)
pNPDPP	80	0.04 M **1e**	(0.34)	≈14	(1.25)
pNPDPP	70	0.05 M **1d**	0.85 (0.78)	13.8	0.46 (0.44)
pNPDPP	70	0.05 M **1e**	0.5 (0.46)	14.2	0.54 (0.53)
pNPDPP	70	0.1 M **1e**	0.7	14.0	0.7
pNPDPP	98	4×10^{-4} M **1e**[b]	1.5	12.5	0.22
pNPB	98	6×10^{-4} M **1e**[b]	1.3	12.7	6.9
pNPB	100	1.5×10^{-4} M **3**[c]	1.7	12.3	13.5

[a] Based on $K_aK_b = K_w$. [b] With 10-fold excess **1c**. [c] With 1.5×10^{-3} M CTABr.

Table VI. Inhibition by Sodium Mesylate[a]

	reaction	
10^3[NaOMs], M	dephosphorylation[b]	deacylation[c]
	24.5	116
0.5		104
5.0		69
10		71
20	23.9	
40	23.1	
60	22.6	
80	21.6	

reaction in 0.1 M OH^- where there is most deprotonation.[27]

The plots of k_ψ vs. [OH^-] (Figures 5 and 6) are calculated from the values of k' and pK_b in Table V. The values of pK_b and k' in parentheses are based on eq 4. This table includes results from experiments in functional micelles which are described later.

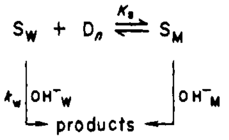
The small effect of replacement of bromide by mesylate ion upon the apparent pK_B (Table V), suggests that competition between OH^- and inert counteranions is not of major importance in the mixed solvents. This conclusion is consistent with small inhibition of the reaction of PNPDPP in **1e** by addition of sodium mesylate (Table VI). In addition reactions are faster in solutions of the bromide, **1d**, than in the mesylate, **1e** (Figures 1–3 and Tables SI and SII). If competition were all important, reaction should be slower in the bromide salt. Reaction rates and deprotonation equilibria in solutions of cationic micelles are very sensitive to added anions which compete with OH^- for the micelle, and bromide ion competes much more effectively than does a more hydrophilic ion such as mesylate.[6,9,21,28,29]

Values of pK_b are solvent dependent (Table V), but part of the effect is due to medium effects upon pK_w (Experimental Section).

Inhibition by Mesylate Ion. Sodium mesylate inhibits dephosphorylation of pNPDPP and deacylation (Table VI). Inhibition is larger for deacylation of pNPB in the more aqueous solvent.

Effect of Substrate and Nonionic Solute. An increase in [DNCB] decreases values of k_ψ, but the effect is small (Table SIV). Added *m*-dinitrobenzene (DNB) also slightly slows the reaction (Table SV). These inhibitions probably arise because binding of nonionic solutes decreases the charge densities of the hydrophobic ammonium ions, or clusters of them. This decrease in charge density decreases binding of anions, e.g., OH^-, and deprotonation of the hydroxyl group of **1d,e**. Nonionic, hydrophobic solutes inhibit reactions in ionic micelles, and reactions in microemulsion droplets are often slower than in otherwise similar ionic micelles.[7,18,30,31] All these phenomena are associated with a lowering of the charge density of the micelle or droplet.

Scheme III



Micellar Effects upon Deacylation. Reaction of pNPB with OH^- is speeded by micelles of cetyltrimethylammonium bromide (Table SVI). Rate constants go through a maximum with increasing CTABr, as is typical of micellar effects upon bimolecular reactions.[6,8,9,30] These rate constant–surfactant profiles can be understood in terms of Scheme III.

In Scheme III subscripts W and M denote aqueous and micellar pseudophases, respectively, k_W and k_M are the second-order rate constants in water and the micellar pseudophase, with the concentration of OH^- written as a mole ratio, and K_s is a binding constant.

The distribution of OH^- and Br^- between water and micelles is written in terms of eq 6:[9,21,29]

$$K_{Br}{}^{OH} = [OH^-_W][Br^-_M]/([OH^-_M][Br^-_W]) \qquad (6)$$

From the variation of k_ψ with [CTABr] (Table S VI), we estimate $K_s = 1400$ M^{-1} and $k_M = 2.2$ s^{-1}, taking $\beta = 0.75$, $K_{Br}{}^{OH} = 10$, the kinetic cmc $= 6 \times 10^{-4}$ M, and $k_W = 3.2$ M^{-1} s^{-1}.[32]

Other combinations of k_M, $K_{Br}{}^{OH}$, and β fit the data equally well, as is often found for micellar rate enhancements, but K_s is affected little by these changes, and our value is in the range observed for substrates of similar hydrophobicity.[6,8,9,20,21]

Micelles of (2-hydroxyethyl)hexadecyldimethylammonium bromide (**3**) are effective deacylating agents at high pH.[12,33] They

$$C_{16}H_{33}N^+Me_2CH_2CH_2OH\ Br^-$$

3

speed deacylation of pNPB, and the rate enhancement is decreased by admixture with CTABr (Figure 4). The rate constants go through maxima with increasing [surfactant], but it is difficult to apply equations such as (6) to these systems because deprotonation generates a zwitterionic surfactant which complicates treatment of the ion exchange. Reaction in the micellar system is considerably faster than that in the hydrophobic ammonium ions (**1c**, **1e**) (Figure 4).

Reaction is speeded by an increase in [OH^-] which increase deprotonation of **3** (Table IV). We estimate a deprotonation constant, pK_a = 12.3 (apparent), from the variation of k_ψ with [OH^-], eq 3 and 4. This value is similar to those observed earlier.[13a,33]

Discussion

Qualitatively hydrophobic quaternary ammonium ions (**1a–e**) behave like micellized cationic surfactants in speeding nucleophilic reactions even though micelles are relatively large aggregates

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(26) This assumption is least satisfactory for reaction of the relatively weakly bound substrate DNCB.

(27) The rate data for deacylation (Table IV) were treated by using eq 4 because there is little depletion of OH^- in this system.

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

(29) Quina, F. H.; Chaimovich, H. *J. Phys. Chem.* **1979**, *83*, 1844. Bartet, E.; Gamboa, C.f Sepulveda, L. *Ibid.* **1980**, *84*, 272.

(30) Cordes, E. H.; Gitler, C. *Progr. Bioorg. Chem.* **1973**, *2*, 1.

(31) Bunton, C. A.; de Buzzaccarini, F.; Hamed, F. H. *J. Org. Chem.* **1983**, *48*, 2457.

containing ca. 10^2 monomers,[4] whereas ions such as **1** appear to form only small aggregates.[2,34] Micellar rate enhancements can be treated quantitatively, and it is useful to see to what extent values of rate and equilibrium constants are similar for the various amphiphiles.

Substrate Binding. Values of K_s (Table III) are smaller than those for binding to aqueous micelles. For example, K_s for pNPDPP is ca. 10^4 M^{-1} for binding to cationic micelles.[36] Other differences are that binding of nonionic solutes to micelles is not very sensitive to added electrolytes, although there is a small effect which is probably due to "salting-out" of the solute from the aqueous pseudophase.[37] Hydroxide ion increases K_s for binding of pNPDPP to **1d,e** (Table III). Two factors could be at work, (i) electrolyte "salts-out" pNPDPP and (ii) it increases the size of the aggregate and therefore its ability to take up pNPDPP. This second effect is probably the more important because eq 1, with constant K_s, fits the data only in more concentrated **1d,e** (Results), suggesting that the aggregates grow, and their solubilizing power increases, with increasing [**1d,e**].

Values of K_s decrease markedly as the solvent becomes less aqueous, because organic solvents increase the solubility of hydrophobic solutes, an effect which is especially important with pNPDPP (Table III), and break up aggregates of **1** because of disruption of water structure.

The binding constant, K_s, for pNPB to **1c** + **1e** is ca. 300 M^{-1}, and it is smaller than K_s = 1400 M^{-1} for binding to CTABr. These results are for solvents of very low content of MeCN, so that even in water a cationic micelle binds substrate better than does an aggregate of hydrophobic ammonium ions. We assume that micellar binding of pNPB will be similar in **3** and CTABr.

Deprotonation of the Hydroxyl Group. The values of pK_a(app) of **1d,e** in solvents of relatively high content of MeCN (20–30 vol %) are more positive than those of the micellized hydroxyethyl surfactant (**3**) in water, but the differences are much smaller in water or water containing only 2% MeCN (Table V). This result differs from the observations of Kunitake and co-workers, who reported that in some systems changes in pK_a of added weak acids were larger with **1a** than with CTABr.[2c] However, these observations were on acids which were present in low concentration.

Extents of deprotonation of weak acids in cationic micelles can be treated quantitatively in terms of binding of OH^- to the micellar surface.[37,38] On this basis the variation of pK_a with solvent (Table V) suggests that increasing the amount of MeCN in the solvent decreases binding of OH^-, and this difference is probably related to the solvent effect upon aggregate size.

Binding of Hydrophilic Anions. Ionic micelles bind counterions strongly and specifically, and the counterions compete for the micelle,[9] as for an ion exchange resin (eq 6). This competition plays a key role in micellar-mediated reactions involving ionic reagents, and both kinetic and equilibrium studies show that counterion binding decreases with increasing hydrophilicity of the ion.[9,28,29]

The situation is less obvious for nonmicellizing cations such as **1a–e**. They bind hydrophobic organic anions, perhaps by forming ion pairs or clusters, but they are less effective than micelles at binding hydrophilic anions, e.g., OH^-. For example, whereas cationic micelles speed reactions of OH^- with organic substrates, salts of **1a–c** are less effective in this role, although they strongly speed corresponding reactions of hydrophobic anions.[2,3]

Table VII. Rate Constants of Bound Substrate Based on K_s

substrate	H_2O vol %	reagent	K_s	k_M, s^{-1}
pNPDPP	80	0.04 M **1e**	133	1.5
pNPDPP	70	0.05 M **1d**	12	1.2
pNPDPP	70	0.05 M **1e**	15	1.3
pNPDPP	70	0.1 M **1e**	15	1.2
DNCB	70	0.05 M **1e**	6	0.074
DNCB	70	0.1 M **1e**	6	0.12

Table VIII. Rate Constants of Substrate Bound to Micellar or Mixed Systems[a]

substrate	k_M, s^{-1}	k_2^m, M^{-1} s^{-1}	k_W^{ch}, M^{-1} s^{-1}
pNPDPP[b]	3		3
pNPDPP[c]	5.6	0.8	3
pNPDPP[d]	3.7	0.5	3
pNPB[e]	113		18
pNPB[f]	264	38	18
DNCB[c]	0.3	0.04	0.0008

[a] In water at 25.0 °C unless specified; values of k_W^{ch} are recalculated from original data taking pK_a = 12.8.[19] [b] 4×10^{-4} M **1e** + 4×10^{-3} N **1c** in 97.8 vol % H_2O. [c] In **3** counterion OH^-, ref 39c. [d] In **3** counterion, Br^- + NaOH, ref 13a. [e] 6×10^{-4} M **1e** + 6×10^{-3} M **1c** in 97.8 vol % H_2O. [f] 1.5×10^{-4} M **3** + 1.5×10^{-3} M CTABr.

Observation of inhibition by inert counterions is good evidence for ion binding by micelles,[28] but added mesylate ion did not markedly inhibit nucleophilic reactions of benzimidazolide ion in aqueous **1c**,[3] suggesting that the mesylate ion did not bind strongly to the hydrophobic ammonium ions.

Our present results show that binding of the mesylate ion, and probably of other hydrophilic anions, depends on the solvent. In 97.8 vol % H_2O rates of reaction of pNPDPP and pNPB go through pronounced maxima as the concentration of **1c** and **1e**, and therefore of mesylate ion, is increased. In addition, at constant [**1c** + **1e**] added sodium mesylate inhibits reaction of pNPB (Table VI). The inhibition by sodium mesylate is smaller for reaction of pNPDPP in H_2O:MeCN 70:30 (Table VI), and there are no pronounced rate maxima for reactions in solutions of either bromide or mesylate salt (Figures 1 and 2) in solvents containing appreciable amounts of MeCN.

These results support the view that aggregates of **1** grow as the water content of the solvent is increased and that their ability to attract counterions increases with their size and increasing density of ammonium head groups at their surface. The limited amount of data on reactivity in the hydrophobic ammonium bromide (**1d**) (Figures 1 and 2 and Tables SI and SII) is consistent with this hypothesis. Reaction is faster in the bromide **1d** than in the mesylate **1e**, which is opposite to what would be observed if interionic competition was all important.[9,28,29] It is probable that the bromide gives larger aggregates than the mesylate, which is consistent with lower solubility of the halid salts.[2,3]

Comparison with Micellar Rate Effects. Deacylation by **1a** plus functionalized surfactants is often faster when the surfactant is mixed with **1a** rather than with the cationic surfactant CTABr,[2] and similar observations were made on dephosphorylation by the areneimidazolide ion.[3]

However, generalizations based on overall rate enhancements can be misleading. Rate constants of reactions of DNCB in solutions of **3** are similar in magnitude to those of the corresponding reactions in aggregates of the tri-*n*-octyl derivative (**1e**). For example, for reaction of DNCB in 0.01 M NaOH and 7×10^{-3} M **3**, $k_\psi \simeq 2 \times 10^{-2}$ s^{-1} in water and is only larger than k_ψ in H_2O:MeCN 80:20 (v/v) 0.01 M NaOH and 8×10^{-3} M **1e** by a factor of ca. 3 (Figure 3 and ref 13b). However, reactions of pNPDPP and pNPB are consistently faster in functional micelles than in functionalized ammonium ions (**1d,e**) under similar conditions (Figures 1, 2 and 4 and ref 13a).

The rate constants, k' in eq 3 (Table V), take into account deprotonation of **1d,e**, but not partial binding of the substrate to ammonium ion, or aggregates of it, and a correction has to be applied, eq 7. The second-order rate constants for (hypothetically)

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[32] If K_{Br}^{OH} = 20, k_M = 3.5 s^{-1}. The fraction of micellar head groups neutralized by counterions is designated β.

[33] Bunton, C. A.; McAneny, M. *J. Org. Chem.* **1977**, *42*, 475.

[34] Although **1a–e** are generally assumed to form small aggregates, evidence from dynamic light scattering has been interpreted as indicating formation of large aggregates.[2b] The use of this technique for estimating the size of ionic colloidal aggregates has been discussed.[35]

[35] Corti, M.; Degiorgio, V. *J. Phys. Chem.* **1981**, *85*, 711. Dorshow, R.; Briggs, J.; Bunton, C. A.; Nicoli, D. F. *Ibid.* **1982**, *86*, 2388. Dorshow, R. B., Bunton, C. A.; Nicoli, D. F. *Ibid.* **1983**, *87*, 1409.

[36] Bunton, C. A.; Cerichelli, G.; Ihara, Y.; Sepulveda, L. *J. Am. Chem. Soc.* **1979**, *101*, 2429.

[37] Bunton, C. A.; Hong, Y.-S.; Romsted, L. S. In "Solution Behavior of Surfactants;" Mittal, K. L., Fendler, E. J., Eds.; Plenum Publishing Corp.: New York, 1982, Vol. 2, p 1137.

[38] Funasaki, N. *J. Phys. Chem.* **1979**, *83*, 1998.

fully bound substrate, k_M, are given by

$$k_M = k'(1 + K_s[A])/K_s[A] \quad (7)$$

and values of k_M (Table VII) are calculated from values of k' and K_s (Tables III and V) and eq 7.

Table VIII gives results in solvents of high water content for reactions in micelles[39,40] and in mixtures of **1c** and **1e**. We calculated k_M only for systems in which we had estimated K_s and calculated k' from the effect of OH^- on reaction rate. With such a weakly bound substrate as DNCB there is the problem that binding is affected by added electrolyte. Our values of k_M for DNCB are therefore less reliable than those for the more hydrophobic substrates. In calculating k_M in mixed micelles or ammonium ions we take into account the mole fraction of functionalized ammonium ion.

The rate constants, k_M, for reactions in micelles or hydrophobic ammonium ions are calculated in terms of reagent concentrations calculated as mole ratios,[41] and therefore they cannot be compared directly with second-order rate constants in solutions whose dimensions are conventionally s^{-1} M^{-1}. The comparison can be made for micelles by estimating the volume element of reaction, which may be that of the Stern layer or of the micelle, and is generally assumed to be in the range 0.14–0.35 L M^{-1}.[6,8-10,20,42] But it is not obvious how to estimate the volume element of reaction for substrate bound to **1**. The values of k_2^m for reactions in micelles (Table VIII) are based on an assumed molar volume of the Stern layer of 0.14 L,[6,42] so that:

$$k_2^m = 0.14k_M \quad (8)$$

Our conclusions are not significantly affected by use of other volume factors in eq 8. For deacylation of pNPB k_2^m is slightly larger than k_W^{ch}, the second-order rate constant for reaction of cholinate zwitterion in water (Results), which is consistent with other observations on deacylation in functional and nonfunctional micelles.[10,20a] For dephosphorylation rate constants are lower in the micelles than in water, and the opposite behavior is observed for aromatic nucleophilic substitution.[39,43] These differences suggest that the transition state for aromatic nucleophilic substitution by anions is stabilized by cationic micelles, but substrate hydrophobicity is probably also important.

Values of k_M for deacylation and dephosphorylation in micelles and in mixtures of hydrophobic ammonium ions are not very different in water, where values of k_M are within factors of ca. 2 (Tables VII and VIII). Reactions mediated by the hydroxyethylammonium ion (**1d,e**) were run in solvents containing 20–30 vol % MeCN (Figures 1 and 2), and the values of k_M are smaller than those in water by factors of 2–3. The values of k_M for reactions in the mixed solvents are sensitive to K_s, which defines substrate binding, so the differences in k_M (Tables VII and VIII) may be more apparent than real.

A key point of our analysis is that values of k_M are insensitive to the nature of the amphiphile, the counterion, and addition of appreciable amounts of organic solvent. The size of the colloidal particle also seems to be of minor importance, because amphiphiles such as **1a–e** form aggregates which appear to be much smaller than normal micelles in water.[2]

Micelles, and similar colloidal particles, are often classified as "organized assemblies"[4] which is a very useful descriptive term, but the present, and earlier,[3] work suggests that reaction rates in these systems do not depend upon the state of organization of the particle. It is possible that some minimum particle size is necessary for rate enhancement, but beyond that rate appears to depend on the concentration of amphiphile regardless of its state of aggregation.

As with micellar systems overall reaction rates provide little information on the sources of rate enhancements of bimolecular reactions, and separation of the various effects shows that the key factors are the bringing together of reactants, which always speeds reaction, and submicroscopic medium effects which may assist or retard reaction, together with increases in deprotonation which generate reactive nucleophiles.[6] Effects upon inherent reactivities are generally of minor importance.

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Supplementary Material Available: Table SI, reaction of pNPDPP in **1d**; Table SII, reaction of DNCB in **1d**; Table SIII, deacylation in mixtures of hydrophobic ammonium ions; Table SIV, effect of DNCB on reaction with **1d**; Table SV, effect of *m*-dinitrobenzene; Table SVI, deacylation in CTABr (6 pages). Ordering information is given on any current masthead page.

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[39] (a) Bunton, C. A.; Hamed, F. H.; Romsted, L. S. *Tetrahedron Lett.* **1980**, *21*, 1217. (b) Bunton, C. A.; Hamed, F. H.; Romsted, L. S. *J. Phys. Chem.* **1982**, *86*, 2103. (c) Bunton, C. A.; Gan, L.-H.; Savelli, G. *J. Phys. Chem.* **1983**, *87*, 5491.

[40] The value of K_s' for pNPDPP in **1c** and **1e** is assumed to be 10^3 M^{-1}, by analogy with binding of pNPDPP and pNPB in other systems,[36] but the value of k_M is insensitive to that of K_s for a substrate as hydrophobic as pNPDPP.

[41] The advantage of writing concentration as a mole ratio is that this quantity can be specified unambiguously regardless of the shape or size of the colloidal aggregate.[42]

[42] Bunton, C. A.; Carrasco, N.; Huang, S. K.; Paik, C.; Romsted, L. S. *J. Am. Chem. Soc.* **1978**, *100*, 5420.

[43] Bunton, C. A. *Pure Appl. Chem.* **1977**, *49*, 969. Bunton, C. A.; Moffatt, J. R.; Rodenas, E. *J. Am. Chem. Soc.* **1982**, *104*, 2653.