Abnormal Micellar Effects on Reactions of Azide and *N*-Alkyl-2-bromopyridinium Ions

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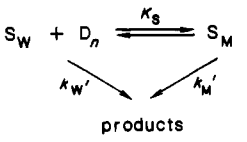
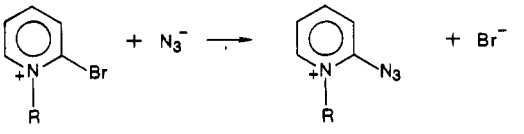
Second-order rate constants of reactions of azide ion with *N*-alkyl-2-bromopyridinium ion (**1a–d**, alkyl = Me, n-$C_{12}H_{25}$, n-$C_{14}H_{29}$, n-$C_{16}H_{33}$, respectively) are very similar in $MeCN/H_2O$ (1:1 w/w), but in water they increase very sharply with increasing [substrate] for the more hydrophobic substrates. In aqueous solutions of cetyltrimethylammonium chloride and bromide (CTACl and CTABr), first-order rate constants, k_ψ, at a given $[NaN_3]$ go through maxima with increasing [surfactant], but, unexpectedly, reactions, under some conditions, are faster in CTABr than in CTACl. The rate–surfactant profiles do not fit the pseudophase, ion-exchange model. For reactions of **1d** k_ψ increases with $[CTAN_3]$ and [**1d**]. In the absence of added surfactant with 0.005–0.01 M NaN_3, k_ψ increases with increasing [**1d**] and becomes larger than that for reactions in $CTAN_3$ or in NaN_3 + CTACl or CTABr. The rate constants for reactions of **1d** in water are greater than those for **1a** by a factor of ca. 6×10^5, and the increase is probaby due to self-association of the hydrophobic 2-bromopyridinium ion.

Ionic micelles in water typically speed bimolecular reactions of counterions with micellar-bound substrates.[2] The variation of the observed first-order rate constant, k_ψ, with concentrations of surfactant, counterion, or added inert electrolyte, can be explained in terms of a pseudophase model which treats the micelles as a reaction medium distinct from water.[2,3] The distribution of reactants between micelles and water can often be measured directly, or estimated, provided that it is assumed that the two reactants bind independently, and second-order rate constants can be calculated in the micellar psesudophase.[3-7] Assumptions have to be made regarding the appropriate measure of concentration in the micellar pseudophase, but generally second-order rate constants in the micelle are not very different from those in water. These observations suggest that micellar enhancements of rates of bimolecular reactions are due largely to concentration of both reactants in the small volume of the micelles. Aromatic substitution by azide ion is an exception to this generalization, because estimated second-order rate constants in the micelle are much larger than those in water.[6] The discrepancy is apparently not due to some anomaly in micellar binding of azide ion because for deacylation and attack on methyl benzenesulfonate or a preformed carbocation, second-order rate constants are very similar in water and on cationic micelle surfaces.[6,7]

The present work involved a search for other reactions of azide ion which might be faster in micelles than predicted from their rates in water. We examined the reaction of azide ion with *N*-alkyl-2-bromopyridinium ion (1).

Scheme I





1a, R = Me
1b, R = n-$C_{12}H_{25}$
1c, R = n-$C_{14}H_{29}$
1d, R = n-$C_{16}H_{33}$

Nucleophilic attack upon 1 has been studied in the absence of added surfactant,[8] and attack of OH^- is speeded by cationic micelles if the substrate is sufficiently hydrophobic to be micellar bound.[9] The kinetic form of these reactions can be explained in terms of the pseudophase model on the assumption that OH^- and inert anions compete for the micelle. The second-order rate constants are lower in the micelle than in water by a factor of ca. 5, and this difference could be rationalized on the basis of a negative salt effect due to the high concentration of ions at the micellar surface.[9] When the substrate (1) was very hydrophobic, e.g., R = $C_{14}H_{29}$ or $C_{16}H_{33}$, its self-association gave rate enhancements in the absence of added surfactant.

Quantitative treatment of relatively slow reactions in aqueous micelles is generally based on Scheme I.[2,3]

Provided that reactants do not perturb the micellar structure, the distribution of substrate, S, between water and micelles is given by eq 1,[2c] where D_n is micellized surfactant, whose concentration is that of total less monomeric surfactant[10] and subscripts W and M denote the

$$\frac{[S_M]}{[S_T]} = \frac{K_S[D_n]}{1 + K_S[D_n]} \quad (1)$$

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aqueous and micellar pseudophases and T denotes the total concentration. The first-order rate constants, k'_W and k'_M (Scheme I) can be written in terms of second-order rate constants and concentration of the ionic reagent in aqueous and micellar pseudophases. For reaction of azide ion in a micelle with inert counterion (X^-), the ionic distribution is assumed to follow eq 2,[2d,e,3c,d,4,5] shown for azide ion, with concentrations written in terms of molarity in the total solution.

$$K_X^{N_3} = [N_3^-{}_W][X^-{}_M]/[N_3^-{}_M][X^-{}_W] \quad (2)$$

The observed first-order rate constant, k_ψ, is given by[2,3] eq 3 and the first-order rate constants k'_W and k'_M are

$$k_\psi = \frac{k'_W + k'_M K_S[D_n]}{1 + K_S[D_n]} \quad (3)$$

written in terms of second-order rate constants, eq 4 and 5, for reactions of azide ion.[2d,3d] In eq 5 concentration of

$$k'_W = k_W[N_3^-{}_W] \quad (4)$$

$$k'_M = k_M[N_3^-{}_M]/[D_n] \quad (5)$$

N_3^- in the micelles is written as a mole ratio of nucleophile to micellar head groups. Provided that β, the extent of charge neutralization of micellar head groups by counterion, is constant, eq 1–5 can be combined and the variation of k_ψ with [surfactant] can be predicted in terms of the various kinetic and equilibrium constants.[3-7]

The treatment gives satisfactory fits for many ionic reactions, including those of azide ion[6,7] and of *N*-alkyl-2-bromopyridinium ions with OH^-,[9] and we attempted to apply it to reactions of N_3^- with these substrates.

Micellar binding of counterions can also be treated by using a Poisson–Boltzman distribution of ions and considering both coulombic and specific interactions.[11] This treatment and that based on eq 2 generally give reasonable fits to the experimental data.

The second-order rate constants, k_W and k_M, eq 4 and 5, have different dimensions, but they can be compared provided that the volume element of reaction in the micelles is estimated and reagent concentrations are written as molarities in the micellar pseudophase.[2d,e,3b-e,4-6,12] When this is done, second-order rate constants are often similar in micellar and aqueous pseudophases, except for aromatic nucleophilic substitution by azide ion.[6] However, reactions of azide ion with hydrophobic *N*-alkyl-2-bromopyridinium have much larger second-order rate constants in cationic micelles than in water, and the enhancement is larger than for reaction of the halonitroarenes. In addition, rate enhancements due to substrate association are unusually large.

Experimental Section

Materials. The preparation and purification of the reagents has been described.[9] The substrates were bromide salts.

Products. The substrates (**1a–d**) were allowed to react with NaN_3 in aqueous MeCN and the azido products were identified by IR and NMR spectrometry. The isolation is described for the tetradecyl derivative (**1c**). The product was precipitated with $NaClO_4$ and the product was washed (H_2O) and dried. Anal. Calcd for $C_{19}H_{33}N_3O_4Cl$: C, 54.72; H, 7.99; N, 13.44; Cl, 8.50. Found: C, 54.82; H, 7.92; N, 13.22; Cl, 8.25.

There was a strong IR band at 2150 cm^{-1} (KBr disk) which was split due to Fermi resonance and corresponds to the asymmetric stretch in an aromatic azide and a weaker band at 1320 cm^{-1} corresponding to the symmetric stretch.[13]

The proton NMR spectrum was at 300 MHz in acetone-d_6, relative to Me_4Si: δ 8.92 (dd, 1 H, J_1 = 6.5 Hz, J_2 = 1.3 Hz, Ar H), 8.61 (td, 1 H, J_1 = 8.3 Hz, J_2 = 1.3 Hz, Ar H), 8.19 (dd, 1 H, J_1 = 8.4 Hz, J_2 = 1.3 Hz, Ar H), 7.81 (td, 1 H, J_1 = 6.5 Hz, J_2 = 1.3 Hz, Ar H), 4.85 (m, 2 H, NCH_2), 2.05–0.88 (series of m, 27 H, $CH_3(CH_2)_{12}$). The location of the azido group at C-2 was confirmed by double resonance.

Similar IR and NMR spectra were obtained with the products of reaction of the other substrates.

Kinetics. Reactions were followed spectrophotometrically at 25.0 °C on Gilford or Beckman spectrophotometers for the slower reactions and a Durrum stopped-flow spectrophotometer for the faster reactions. The substrates have λ_{max} at 276 nm and the products at 296–300 nm, and tight isosbestic points at 279 nm were observed in the course of reaction, suggesting that intermediates do not build up in concentration. The concentration of NaN_3, generally 0.01 M, was much larger than that of the substrates which was 4×10^{-5} M for most of the experiments in aqueous surfactants. The reactions were generally cleanly first order, and the rate constants, k_ψ, are in reciprocal seconds. The first formed azido product slowly forms the pyridone by reaction with OH^-, and therefore initial rate constants are quoted for the very slow kinetic runs.

Reactions were followed in solutions of cetyltrimethylammonium halides (CTAX, X = Cl, Br) or hexadecyl(cetyl)pyridinium chloride (CPCl).

Interaction of Azide and *N*-Hexadecylpyridinium Ion. The spectra of solutions of *N*-hexadecylpyridinium chloride (CPCl) in 0.05 M and 0.1 M NaN_3 have small peaks on the side of a large peak due to N_3^- at 328 and 352 nm in MeCN and CH_2Cl_2, respectively, and a broad shoulder (330–340 nm) in $CHCl_3$. When the spectra were taken with NaN_3 in the reference cell, we saw maxima at 328, 333, and 352 nm in MeCN, $CHCl_3$, and CH_2Cl_2, respectively. We saw a slight, ill-defined shoulder in 2-propanol, but no spectral shift in water. Qualitatively, the spectral shifts in the organic solvents follow Kosower's *Z* scale of solvent polarity,[14] except that *Z* for CH_2Cl_2 is slightly larger than that for $CHCl_3$.

Table I. Reaction in Absence of Added Surfactant[a]

10^3-[NaN_3], M	alkyl group			
	Me[b]	$C_{12}H_{25}$[b]	$C_{14}H_{29}$	$C_{16}H_{33}$
0.5				13.7 (2740)[c]
1.0			6.23 (623)	23.3 (2330)[c]
1.5				35.9 (2390)
2.0			12.4 (620)	60.4 (3020)
5.0		0.45 (8.9)	26.0 (520)	
6.7	0.049 (0.73)			
7.0			39.0 (557)	
8.0			41.3 (516)	
10.0	0.084 (0.84)	0.93 (9.3)		252 (2520)
20.0		1.80 (9.0)		
30.0		2.82 (9.4)		
33.0	0.28 (0.83)			
60.0	0.51 (0.85)			
100	0.83 (0.83)			

[a] Values of 10^3 k_ψ, s^{-1}, at 25.0 °C with 4×10^{-5} M substrate; values in parentheses are $10^2 k_\psi/[N_3^-]$, M^{-1} s^{-1}. [b] 5×10^{-5} M substrate. [c] With 10^{-5} M **1d**, 10^3 k_ψ = 8.24 and 17.4 s^{-1}, with 0.5 and 1.0 mM NaN_3, respectively.

Results

In water second-order rate constants, k_2, for reactions of the methyl derivative (**1a**) are independent of [sub-

(10) The concentration of monomeric surfactant is assumed to be the critical micelle concentration, cmc,[2,3] which is lowered by electrolytes and hydrophobic nonionic solutes.

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Table II. Effect of Substrate Concentration in Absence of Surfactant[a]

10^5[substrate], M	Me[b]	$C_{12}H_{25}$	$C_{16}H_{33}$
2	0.83		
4		0.93	2520
5	0.84		
8	0.84		6820
10	0.82	1.49	9400, 1810[c]
11		3.05	
12	0.83	5.68	11400
15			13600, 6680[c]
16			14200
20			20900, 10900[c]
24			24300
25			26100, 20900[c]
30			33000, 27000[c]
35			35800, 26600[c]

[a] Values of $10^3 k_\psi$, s^{-1}, at 25.0 °C with 0.01 M NaN_3 unless specified. [b] 0.1 M NaN_3. [c] 0.005 M NaN_3.

Table III. Reactions in Aqueous Acetonitrile[a]

	alkyl group			
	Me	$C_{12}H_{25}$	$C_{14}H_{29}$	$C_{16}H_{33}$
$10^3 k_\psi$, s^{-1}	10.4	9.2	10.1	10.0

[a] Initial rate constants at 25.0 °C with 4×10^{-5} M substrate in 1:1 H_2O/MeCN (w/w) and 0.01 M NaN_3.

Table IV. Salt Effects upon Reaction of *N*-Hexadecyl-2-bromopyridinium Ion in Absence of Surfactant[a]

10^5[substrate], M	no salt	0.01 M KCl	0.01 M KBr
4	2.37	1.10	1.19
10	9.40	3.29	3.86
15	13.6	4.76	6.21
20	20.9	6.48	8.36
25	26.1	7.08	

[a] Values of k_ψ, s^{-1}, at 25.0 °C with 0.01 M NaN_3.

strate] and [NaN_3] (Tables I and II), and they are essentially independent of [NaN_3] for reactions of the dodecyl and tetradecyl derivatives (**1b,c**), although rate constants increase with increasing [substrate]. There is a very striking increase in reactivity of the hexadecyl derivative (**1d**) with increasing [substrate] (Tables I and II). For example, the reactivities, relative to methyl (**1a**), are approximately R = $C_{12}H_{25}$ (**1b**), 11; R = $C_{14}H_{29}$ (**1c**), 500; R = $C_{16}H_{33}$ (**1d**), 3×10^3, with 4×10^{-5}M substrate (Table I) and the differences increase with increasing [substrate] (Table II). These rate increases are much too large to be ascribed to a kinetic salt effect. The high reactivities of the hydrophobic substrate disappear if the reaction is carried out in aqueous MeCN (Table III) and reaction of the methyl derivative (**1a**) is, as expected, faster in this solvent than in water.

The rate enhancements for the hydrophobic substrates are observed for [substrate] much lower than the critical micelle concentration, cmc, of *N*-alkylpyridinium salts, because for *N*-hexadecylpyridinium chloride and bromide cmc $\simeq 8 \times 10^{-4}$ and 6×10^{-4} M, respectively.[15] The cmc of the chloride is not markedly decreased by 0.01 M NaN_3. However, substrate aggregation of **1b–d** is clearly important in water (Tables I and II), and aggregates should be broken up by MeCN which disrupts water structure.

Added KCl and KBr slow reaction of the hexadecyl derivative (**1d**) with NaN_3 (Table IV), probably because

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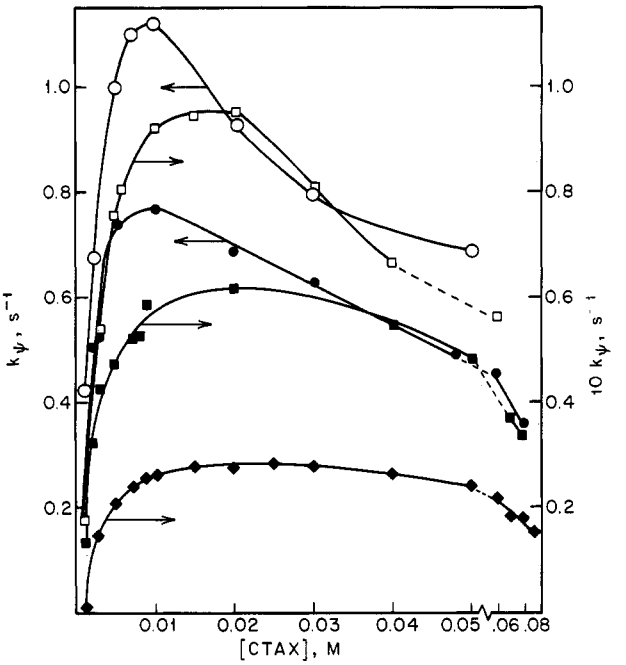

Figure 1. Reaction of *n*-dodecyl-2-bromopyridinium ion (**1b**) in cationic micelles. Open points, CTABr; solid points, CTACl. ◆, 5×10^{-4} M NaN_3; ■, □, 10^{-3} M NaN_3; ●, ○, 10^{-2} M NaN_3.

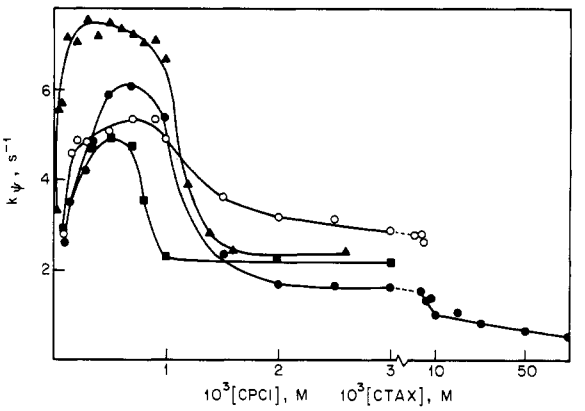

Figure 2. Reaction of *n*-hexadecyl-2-bromopyridinium ion (**1d**) in cationic micelles. ●, ▲ in CTACl, 0.01 and 0.05 M NaN_3, respectively; ○ in CTABr, 0.01 M NaN_3; ■ in CPCl, 0.01 M NaN_3.

Table V. Reaction of *n*-Tetradecyl-2-bromopyridinium Ion in CTACl[a]

10^3[CTACl], M	k_ψ, s^{-1}	10^3[CTACl], M	k_ψ, s^{-1}
0.3	1.0	4.0	1.19
0.5	1.77	5.0	1.15
0.7	2.24	6.0	1.13
0.9	2.72	8.0	0.89
1.0	2.83	10	1.06
2.0	1.20	12	0.91
3.0	0.9		

[a] At 25.0 °C with 4×10^{-4} M substrate and 0.01 M NaN_3.

of competition between inert halide ion and N_3^- for aggregated substrate. Unexpectedly reaction is slowed more by KCl than KBr,[3d] perhaps because Br^- favors substrate aggregation.

For reactions of N_3^- with the do-, tetra-, and hexadecyl substrate (Table V and Figures 1 and 2), values of k_ψ go through maxima with increasing [CTACl] and [CTABr]. Qualitatively these observations accord with the pseudophase, ion-exchange, model[3-7] but especially with the more hydrophobic substrates, k_ψ increases at [surfactant] well below the cmc in water. The maximum rate enhance-

Table VI. Maximum Micellar Rate Enhancements

substrate	alkyl group	surfactant	$[NaN_3]$, M	k_{max},[a] s^{-1}	k_{rel}[b]	$10^3[D]_{max}$,[a] M
1b	$C_{12}H_{25}$	CTACl	5×10^{-4}	0.028	7.5×10^3	25
1b	$C_{12}H_{25}$	CTACl	10^{-3}	0.063	8.4×10^3	25
1b	$C_{12}H_{25}$	CTABr	10^{-3}	0.095	1.3×10^4	17
1b	$C_{12}H_{25}$	CTACl	10^{-2}	0.77	1.0×10^4	10
1b	$C_{12}H_{25}$	CTABr	10^{-2}	1.1	1.5×10^4	10
1c	$C_{14}H_{29}$	CTACl	10^{-2}	2.7	3.6×10^4	1
1d	$C_{16}H_{33}$	CTACl	10^{-2}	6.3	8.4×10^4	0.8
1d	$C_{16}H_{33}$	CTABr	10^{-2}	5.3	7.1×10^4	0.8
m1d	$C_{16}H_{33}$	CPCl	10^{-2}	4.9	6.5×10^4	0.5
1d	$C_{16}H_{33}$	CTACl	5×10^{-2}	7.6	2.0×10^4	0.4

[a] At the rate maximum. [b] Relative to the rate constant for reaction of the methyl derivative **1a** in absence of surfactants in water.

Table VII. Reaction of *N*-Hexadecyl-2-bromopyridinium Ion in $CTAN_3$[a]

	10^5[substrate], M			
$10^3[CTAN_3]$, M	0.5	1	4	8
0.9			0.31	
1.0		0.20	0.68	1.50
1.5			1.13	
2.0		1.07	1.20	
3.0			1.56	
4.0	1.66		1.81	
5.0		2.12	2.42	
6.0	1.97	2.17	2.46	2.96
8.0	2.55	2.75	3.11	3.74
10.0	2.89	3.13	3.48	4.06

[a] Values of k_ψ, s^{-1}, at 25.0 °C.

Table VIII. Effect of Substrate Concentration on Reaction of 1d in CTACl[a]

	10^5[**1d**], M	
10^3[CTACl], M	0.7	4
0.1	2.49	2.63
0.15		3.5
0.2	3.44	
0.25		4.16
0.3	4.00	4.89
0.36	4.60	4.84
0.5	4.62	5.55
0.6	4.80	
0.7	4.91	6.08
0.9	4.85	
1.0		5.34
1.5	2.94	2.21
2.0	2.00	1.68
3.0	1.69	1.63

[a] Values of k_ψ, s^{-1}, at 25.0 °C with 0.01 M NaN_3.

ments, relative to the reactivity of the methyl substrate (**1a**) in water, are very much larger than those generally found in micellar-assisted reactions (Table VI). For reaction of **1d** with 0.01 M OH^- in CTACl, the maximum rate enhancement is by a factor of ca. 30,[9] whereas for reactions with N_3^- it is ca. 8×10^4. Generally micellar rate enhancements of bimolecular reactions of hydrophilic ions are by factors of $10-10^2$.[1-4]

We could not fit all the rate–surfactant profiles for any given substrate to the pseudophase, ion-exchange model, based on independently estimated values of K_S,[9] $K_{Br}^{N_3}$, or $K_{Cl}^{N_3}$,[6] and fractional ionization, α, even though this treatment is satisfactory for reactions of OH^- with **1c,d**[9] and for reactions of N_3^- with other substrates.[6,7] Its failure to account for micellar effects upon these reactions of azide ion is understandable in view of the observation that under some conditions reaction is faster in CTABr than in CTACl (Figures 1 and 2), which is against the predictions of the ion-exchange model.[2d,e,3c,d,4]

Values of k_ψ increase steadily with increasing $[CTAN_3]$ even under conditions for which **1d** should be extensively micellar bound, although rate constants generally become constant under these conditions.[6] For a given $[CTAN_3]$ k_ψ increases with increasing substrate, which is unusual for micellar-assisted reactions.[2d,3d] Similar substrate effects were observed for reaction of **1d** in CTACl (Tables VII and VIII).

Discussion

The striking increase in k_ψ for attack of azide ion upon the more hydrophobic 2-bromopyridinium ions with increasing [substrate] (Tables I and II) is evidence for reaction of aggregated, rather than free, substrate. The increase is much sharper than that found for attack of OH^- upon **1c,d**[9] which suggests that aggregation is a cooperative phenomenon involving pyridinium and azide ions. Hydroxide is much more hydrophilic and less polarizable than azide ion and is therefore less able to interact with and stabilize a cluster of *N*-alkylbromopyridinium ions, as with binding to cationic micelles.[3d,6]

These rate increases (Table II) are probably not due to substrate micellization because they are observed at concentrations much lower than an expected cmc.[15]

Reactions with substrate aggregates of **1b,c,d** are approximately first order in azide ion (Tables I and II). However at the higher [**1d**], reaction is less than first order in azide ion, suggesting that it is binding to the aggregates and tending to saturate them.

The unusual anion order and overall salt inhibition suggest that the halide ions are competing with N_3^- for substrate aggregates, but that Br^-, in particular, can also stabilize micelles or aggregates, which should assist reaction (Table IV).

The "normal" behavior of the methyl, dodecyl, and hexadecyl derivatives in aqueous MeCN (Table III) confirms that substrate association of the more hydrophobic substrates in water is all-important. The reactions also show the expected kinetic solvent effects because for the methyl derivative (**1a**) where self-association should be unimportant, even in water, reaction is considerably faster in aqueous MeCN than in water (Tables I–III).

The rate maxima with increasing [CTACl] or [CTABr] (Figures 1 and 2 and Table V) and the increasing rate enhancements (k_{rel}) with increasing substrate hydrophobicity are qualitatively as predicted by the pseudophase model (eq 1–5). The rate increases in very dilute surfactant could be ascribed to induced micellization, but other features are less easily explained. As noted earlier, treatments based on eq 1–5 do not fit the rate–surfactant profiles, unless we assume that parameters such as K_S or the ion-exchange parameter (eq 2) vary with surfactant or reactant concentrations, although such variations were not observed for reactions of OH^- with **1c,d**.[9]

Bimolecular, ionic reactions are nearly always faster in CTACl than in CTABr, because Br^- is a better competitor

than Cl^- for reactive anions.[1-3] This anion order is followed under some conditions, but not others (Figures 1 and 2 and Table VI). However, the maximum rate enhancements decrease at high [NaN_3] as in reactions of **1b,d** in CTACl (Table VI), which is consistent with micelles becoming saturated with N_3^-.

Most quantitative treatments of micellar effects upon bimolecular reactions in water involve the assumption that the two reactants bind independently to the micelle and that their effects upon micellar structure are relatively unimportant.[2-7] For example, micellar rate enhancements of reactions of OH^- upon **1c,d** were analyzed by assuming that *N*-alkylbromopyridinium ion was partitioned between micelle and water according to the equation developed for binding of neutral molecules (eq 1). It was assumed that the unfavorable coulombic interaction was much less important than the hydrophobic interaction.

These simplifications are not justified if there are interactions between reactants and this is probably the situation for a mixture of azide and an *N*-alkyl-2-bromopyridinium ion. If these ions form pairs, or larger clusters, each will assist the binding of the other and in addition they may bind to monomeric surfactant or to submicellar aggregates of it. The spectral shifts for mixtures of N_3^- and CPCl in aprotic solvents (Experimental Section) suggest that N_3^- and substrate could interact preferentially in a micelle. Thus rates will be increased at [surfactant] well below the cmc in water, because reactants promote formation of micelles or submicellar clusters.

There is precedent for the observation of cooperative binding of counterions from anomalous effects of inert salts upon micellar reactions of carbocations[12,16] and the demonstration that inert salts, in high concentration, will force even such a hydrophilic anion as OH^- to bind to anionic micelles, based on kinetic evidence.[17] However, these effects are generally small.

The decrease of k_ψ with increasing [surfactant] for the more hydrophobic substrates (Figure 2 and Table V) is much less marked than predicted by a model based on eq 1–5.[2d,e,3c,d,4-6] Reactions of nonionic nucleophiles show relatively modest rate decreases at high [surfactant],[3b,18] because there is no interionic competition,[3c,d] and the slow decreases in k_ψ (Figures 1 and 2) are understandable if N_3^- and the bromopyridinium ion enter the micelle as a pair, or if one assists the binding of the other. This hypothesis is consistent with the observation that in micelles of CTABr or $CTAN_3$ k_ψ increases with increasing concentration of the very hydrophobic hexadecyl substrate, **1d** (Tables VII and VIII).

Relative reactivities in CTACl and CTABr depend upon the reaction conditions, which is inconsistent with the ion-exchange model (Figures 1 and 2). Reaction is slower in CPCl than in CTACl (Figure 2), although we see no reason for the change in head group to strongly affect reactivity, unless interaction with the pyridinium moiety in a CPCl micelle reduces nucleophilicity of N_3^-. This explanation is consistent with spectral shifts in aprotic solvents (Experimental Section).

The usual assumption made in describing micellar rate effects is that reaction occurs either in the micellar or aqueous pseudophase and that reactions involving monomeric or submicellar surfactant can be neglected. Reactions of inorganic substrates provide kinetic evidence for interactions of reactants with submicellar species.[19] There is also physical evidence for these interactions or induced micellization,[20] and rate effects below the cmc are also common in reactions of hydrophobic organic substrates.[3d,12,21] Rate increases in nonmicellizing hydrophobic ammonium ions are also well-documented.[22,23] However, effects due to induced micellization or interactions with submicellar aggregates are generally observed only with very dilute surfactant.

Qualitatively the rate–surfactant profiles for reactions of **1c,d** with N_3^- in CTACl or CTABr (Figure 2 and Table V) seem to be made up of two regions. In the first, in dilute surfactant, k_ψ increases very sharply and there are rate maxima at ca. 4×10^{-3} M CTACl for reactions of **1c** and at $0.3–0.8 \times 10^{-3}$ M CTACl or CTABr for reaction of **1d**. The rate then decreases and in the second region falls off only slowly with increasing [surfactant] and much more slowly than predicted by an ion-exchange model. We know of no precedent for this behavior, although the approximate constancy of k_ψ at high [surfactant] is consistent with an interaction between N_3^- and substrate, in the micelle, which negates the expected displacement of N_3^- by inert halide ion, eq 2.

Submicellar aggregates of the hexadecyl derivative (**1d**) seem to be responsible for the marked dependence of the rate constant on [**1d**] in the absence of added surfactant (Table II) and for the sharp rate increase in very dilute surfactant (Figure 2). There are double rate maxima with increasing [surfactant] for reactions of 2,4-dinitrochloronaphthalene with OH^- and N_3^- in solutions of hexadecyltrialkylammonium salts.[24] The first maximum is observed in [surfactant] well below the cmc and almost certainly involves interaction of the substrate with monomeric surfactant or small aggregates of it. Similar interactions are probably important in reactions of **1d**, although there is only a single rate maximum.

The high reactivities of the hydrophobic substrates, especially **1d**, lead to the paradox that the question of micellar rate enhancement depends upon the basis of the rate comparison. For example, if comparison is based on values of k_ψ, as in Tables I and II and Figure 2, we conclude that reaction is speeded by cationic surfactant but only with dilute substrate, ca. 10^{-5} M. But the maximum value of $k_\psi \simeq 6$ s^{-1} in 7×10^{-4} M CTACl and 0.01 M NaN_3 is lower than that of ca. 38 s^{-1} with 3.5×10^{-4} M **1d** with no added surfactant (Table II). Another comparison involves reaction in $CTAN_3$ (Table VII). In 0.01 M $CTAN_3$ and 8×10^{-5} M **1d**, $k_\psi = 4.06$ s^{-1}, but without added surfactant $k_\psi = 6.82$ s^{-1} with same [substrate] and [N_3^-] (Table II). Again reaction is faster in the absence of inert surfactant.

On the basis of one criterion surfactant is speeding reaction, but on another it is inhibiting it. In the absence

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of surfactant the hexadecyl derivative (**1d**) appears to form an aggregate which brings reactants together, and this proximity effect promotes reaction more effectively than in a mixture of **1d** and CTACl, CTABr, or $CTAN_3$, where added surfactant, in effect, "dilutes" the substrate in the aggregate.

For reaction in the absence of added surfactant the rate enhancements due to substrate aggregation are unusually large, ranging up to a factor of ca. 6×10^5 (for reaction of **1d** with 0.005 M NaN_3, for which $k_\psi/[N_3^-] = 5.3 \times 10^3$ M^{-1} s^{-1}), relative to reaction of the methyl derivative (**1a**) for which $k_\psi/[N_3^-] = 8.3 \times 10^{-3}$ M^{-1} s^{-1} (Tables I and II).

Generally rate enhancements due to substrate aggregation are much smaller than those observed here, and for acid hydrolysis of monoalkylsulfates,[25] deacylation by OH^- and reaction of OH^- with **1** they are by factors of $10–10^2$.[9,26]

The rate enhancements by factors of almost 10^6 of reaction of **1d** with N_3^- in the presence (or absence) of surfactant (Tables I, II, and VI) are similar in magnitude to rate enhancements in intramolecular as compared with intermolecular reactions.[27,28]

We cannot use the pseudophase, ion-exchange model to estimate second-order rate constants in the micellar pseudophase, because it does not explain the rate–surfactant profiles quantitatively. However, we can estimate *minimum* values of k_M by assuming that *N*-hexadecyl-2-bromopyridinium and azide ion are fully micellar bound at high [surfactant]. For this purpose we consider reactions of **1d** in 2×10^{-3} M CTACl or CTABr and 0.01 M NaN_3. The binding constant, $K_S = 850$ M^{-1} in CTACl, estimated by ultrafiltration,[9] so substrate binding should be extensive.

In these conditions $k_\psi = 1.63$ and 3.16 s^{-1} in CTACl and CTABr, respectively (Figure 2). For fully bound substrate:

$$k_\psi = k_M m_{N_3}{}^s = k_M[N_3^-M]/[D_n]$$

so that if the micelle is saturated in N_3^-, i.e., $m_{N_3} = \beta \simeq 0.8$, k_M will be ca. 2 and 4 s^{-1} in CTACl and CTABr, respectively. The actual value should be higher because substrate is probably not fully bound and the micelle is not saturated with N_3^-. These values of k_M do not change markedly if the calculation is based on data at higher [surfactant]. The second-order rate constant k_M is based on concentration written as a molar ratio, but if the molar volume element of reaction in the micelle is 0.14 L,[3d,12] the second-order rate constant, $k_2 = 0.14k_M$, based on the molarity of N_3^- in the micellar pseudophase is ca. 0.5 M^{-1} s^{-1}, as a *minimum*. The actual value will almost certainly be higher. Competition between N_3^- and (excess) Br^- suggests that N_3^- will not be fully bound unless cooperative binding with the substrate is important.[6]

In any event the value of $k_2^m = 0.5$ M^{-1} s^{-1} is very much larger than that of $k_W \simeq 0.008$ M^{-1} s^{-1} for reaction of the *N*-methyl derivative (**1a**)[29] in water (Tables I and II). This very large difference between the reactivity of N_3^- in water and in cationic micelles is similar to, but larger than, that observed for reactions of N_3^- with 2,4-dinitrochloroarenes.[6] Calculation of the second-order rate constants in the micellar pseudophase is based on the assumption that both reagents are distributed uniformly at the micellar surface and do not bind cooperatively.[30]

The reactivity of N_3^- toward nitrohalobenzenes in aqueous or alcoholic solvents is much lower than that predicted by Ritchie's N_+ scale,[31] although this scale fits relative reactivities of other nucleophiles. For example N_+ values are 4.75 and 7.6 for OH^- and N_3^-, respectively, in water, but for reactions with 2,4-dinitrochlorobenzene log $k_{OH} = -3.85$ and log $k_{N_3} = -4.34$.[6,32] We see a similar anomaly for reactions with *N*-methyl-2-bromopyridinium ion in water, where log $k_{OH} = -0.16$ and log $k_{N_3} = -2.12$ (Table I and ref 9). The large micellar rate enhancements of these azide ion reactions, relative to reaction in water, may be due to an abnormally *low* reactivity of N_3^- to aromatic or pyridinium ion substrates in water. If comparisons are based on estimated second-order rate constants in a micellar pseudophase, we see a very different reactivity pattern in that N_3^- is no longer much less reactive than OH^-.[33] These differences do not seem to be related to differences in anion hydration in water and micelles. Ions are considered to be extensively hydrated in micelles,[2,3,35] and any decrease in hydration should favor reaction of the more hydrophilic ion, in this case OH^-. In addition, decrease of hydration should increase the nucleophilicity of N_3^- in deacylation and S_N reactions.

Binding of cationic substrates, e.g., **1b–d**, to a cationic micelle is coulombically unfavorable and the repulsions should decrease with attack by an anion.[36] This hypothesis is attractive, but it fails for reactions of nucleophiles with other cationic substrates[9,12,37] and does not explain micellar effects upon reactions of N_3^- with dinitrochloroarenes.[6]

Another example of the high reactivity of N_3^- in aromatic substitution in a cationic pseudophase involves reactions in a macrotricyclic ammonium salt,[38] which behaves like a cationic micelle.

Aromatic nucleophilic substitution involves prior addition, but the Meisenheimer intermediate formed by anionic attack is believed to go rapidly to products in polar hydroxylic solvents.[39] Azide ion is a very good leaving group and cationic micelles could affect the partitioning of an intermediate between reactants and products, but halide ions should be much better leaving groups than azide ion, so it is difficult to ascribe the large micellar rate enhancements to a more favorable partitioning of a Meisenheimer intermediate to products.

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There is strong evidence for interactions between N_3^- and substrate in these pyridinium ion reactions, and submicellar aggregates are probably involved. It is difficult to obtain pysical evidence on these systems, in part because of the high reaction rates but also because techniques such as light scattering are unsatisfactory for such dilute solutions. There is a similar problem for reactions in nonmicellizing hydrophobic ammonium ions where formation of small aggregates is assumed,[22,23] although the aggregates have not been detected by physical measurement.

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A Study and Mechanistic Interpretation of the Electronic and Steric Effects That Determine the Stereochemical Outcome of the Reaction of Schiff Bases with Homophthalic Anhydride and 3-Phenylsuccinic Anhydride

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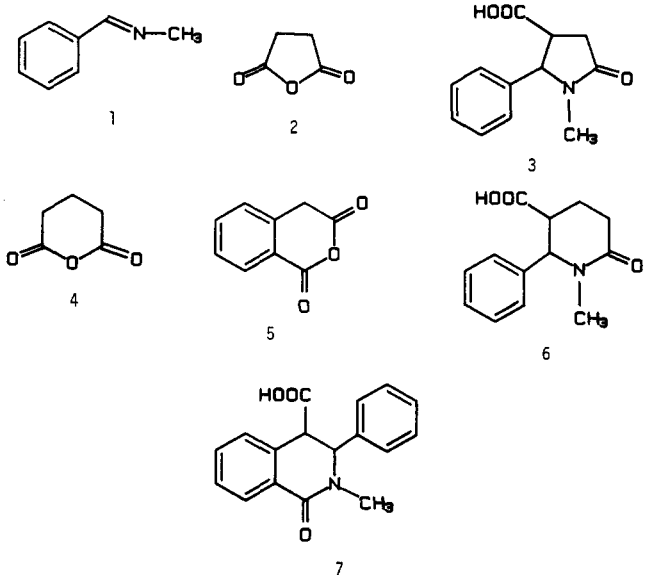
A study has been undertaken of the electronic and steric effects that determine the ratios of *cis*- and *trans*-isoquinolones **9** formed in the condensation of para-substituted Schiff bases **8** with homophthalic anhydride (**5**). A linear correlation between the ratios of the *cis*- and *trans*-isoquinolones formed and the Hammett σ^+ constants of the substituents in the aromatic ring has been observed. Electron-donating substituents have been found to favor formation of the cis diastereomers, while electron-attracting substituents result in the production of greater amounts of the trans diastereomers. In addition, it has been found that bulky substituents on the nitrogen atom of the Schiff bases result in the exclusive formation of the cis diastereomers. A mechanistic interpretation of these results has been proposed involving iminolysis of the anhydride as the initial event in which the *E* imines give rise to *cis*-isoquinolones and the *Z* imines result in formation of the trans diastereomers. The linear Hammett relationship observed between the ratios of diastereomers formed and the σ^+ values of substituents in the para position of the imines **8** means that there is a higher carbocationic character in the transition state of the rate-limiting step leading to the cis product than that leading to the trans product. This indicates that the rate-limiting step in the production of the cis diastereomer is probably the initial iminolysis of the anhydride **5**, while the rate-limiting step in production of the trans isomer is likely the *E*-*Z* isomerization of the Schiff base. Similar, although weaker, trends were observed in reactions involving 3-phenylsuccinic anhydride (**18**).

Since the discovery of the condensation of benzylidenemethylamine (**1**) with succinic anhydride (**2**) to form



substituted 2-pyrrolidinones **3**,[1] the reaction has been extended to glutaric[2] and homophthalic anhydrides (**4**, **5**), resulting in piperidinones and isoquinolones of general structures **6** and **7**, respectively. The latter reaction has been utilized in the preparation of a variety of protoberberine,[3] benzophenanthridine,[4] and B-secoprotoberberine[5] alkaloids as well as certain indenoisoquinolines possessing significant antitumor activity.[6] These reactions along with several related condensations have recently been reviewed.[7]

The reaction products resulting from these condensations possess two asymmetric centers and are therefore capable of existing as cis and trans diastereomers. Although an empirical relationship between solvent polarities

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