Dephosphorylation in Zwitterionic Micelles of Amine Oxide or Betaine Sulfonate Surfactants

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First-order rate constants for reaction of OH^- with *p*-nitrophenyl diphenyl phosphate (*p*-NPDPP) go through minima with increasing concentrations of dodecyldimethylamine oxide (DDMAO) or *N*-hexadecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate (SB3-16). The initial sharp decrease is ascribed to surfactant binding to submicellar aggregates and fully formed zwitterionic micelles appear to bind OH^- weakly, and this binding is decreased by added inert anions. Reaction of bound substrate is faster in micelles of DDMAO than those of SB3-16 because the amine oxide moiety participates in the reaction, probably as a nucleophile.

Effects of ionic micelles upon rates of bimolecular ionic reactions typically follow the generalization that counterions are attracted to the micellar surface and co-ions are excluded from it, with consequent effects upon reactivity.[1] These micelle–ion interactions and competition between counterions for the micellar surface can be treated quantitatively in terms of the pseudophase ion-exchange model[1] or by estimating the electrical surface potential of the micelle.[2,3] Both treatments show that Coulombic and non-Coulombic interactions must be considered, because weakly hydrated, polarizable, counterions bind most strongly to ionic micelles.

These interactions markedly reduce the micellar charge and for many ionic micelles the fractional charge, α, is ca. 0.3,[1a,b] and the fractional charge neutralization, β, is given by eq 1.

$$\beta = 1 - \alpha \quad (1)$$

The pseudophase ion-exchange model is based on the premise that β is a measure of counterion binding in the micellar Stern layer, which is the region adjacent to the surfactant head groups, and reactions in the micellar pseudophase are assumed to take place in this layer. However, other treatments consider the distribution of reactive counterions away from the micellar surface[3] and the possibility that reactions may involve ions which are not bound specifically in the Stern layer.[4]

In this paper we consider bimolecular reactions in micellized zwitterionic micelles of *N*-hexadecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate (SB3-16) and of dodecyldimethylamine oxide[5] (DDMAO) in the presence of NaOH.

n-$C_{16}H_{33}N^+Me^2(CH_2)_3SO_3^-$ SB3-16 $\quad$ n-$C_{12}H_{25}N^+Me_2{\cdot}O^-$ DDMAO

The sulfonate moiety of SB3-16 should be very weakly nucleophilic, and its micelles are analogous to cationic micelles in which the head group charge is fully neutralized, i.e., $\alpha = 0$. The oxide moiety of DDMAO may react as a base or nucleophilically as in a functional micelle.[8] At the simplest level the ion-exchange model predicts that these zwitterionic micelles will not attract reactive anions, e.g., OH^-, and therefore will not speed their reactions with micellar bound substrates. There is little evidence on ion-binding by zwitterionic micelles, except for kinetic evidence for binding of polarizable organic anions by micellized betaine surfactants derived from amino acids,[9] and deacylation in these micelles has been studied.[10]

We examined dephosphorylation of *p*-nitrophenyl phosphate (*p*-NPDPP) because it binds strongly to micelles and the reaction product, *p*-nitrophenoxide ion, is easily followed spectrophotometrically.[11]

Results and Discussion

Dodecyldimethylamine oxide can catalyze dephosphorylation of *p*-NPDPP by acting as a basic or nucleophilic catalyst, but it can also inhibit attack of OH^- on the substrate. Reaction with OH^- is virtually eliminated by working at low pH; e.g., in sodium hydrogen carbonate (at pH 7–8.5) and at surfactant concentrations for which *p*-NPDPP should be fully micellar bound the first-order rate constant, k_ψ, under these conditions is approximately half that in 0.01 M NaOH (Figure 1).[12] The amine oxide (DDMAO) at pH 7–8.5 is acting as a functional micelle, and the mechanism of its reaction is considered later.

The betaine sulfonate (SB3-16) is chemically inert and under conditions in which *p*-NPDPP should be fully micellar bound reaction with OH^- is inhibited (Figure 2) but inhibition is much less than that by anionic or nonionic micelles, which almost stop the reaction.[11] The contribution of the hydroxide ion reaction on micelles of the amine oxide is obtained by making a correction for direct reaction of the functionalized micelles. With 0.01 M DDMAO 10^3k_ψ = 2.9 and 1.5 s^{-1} in 0.01 M + OH^- and at pH 8.5, respectively (Figure 1). Reaction with OH^- can be neglected at pH 8.5 so the first-order rate constant in 0.01 M OH^- is 1.4×10^{-3} s^{-1}, which is very similar to the rate constant of 1.7×10^{-3} s^{-1} for reaction with 0.01 M OH^- in micelles of SB3-16 (Figure 2). Therefore despite structural differ-

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(5) Amine oxides are weak bases and are zwitterionic except at low pH.[6]

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(12) The binding constants of *p*-NPDPP with a variety of micelles are ca. 10^4 M^{-1} per micellized surfactant.[11]

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Table I. Salt Effects upon Reaction in the Amine Oxide[a]

	[DDMAO], M							
salt	0.005	0.001	0.002	0.003	0.004	0.005	0.01	0.02
none	4.54	1.60		2.31		2.41	2.97	
LiCl						2.42	2.30	2.51
NaCl	2.71	2.51		2.19		2.31	2.42	2.46
NaBr	3.03	2.48		1.99		2.09	2.09	2.09
Et_4NBr		4.28	2.76	2.27	1.99	2.04	2.03	2.03

[a] Values of 10^3k_ψ, s^{-1}, in 0.01 M NaOH and 0.2 M salt unless specified.

Table II. Salt Effects upon Reaction in the Betaine Sulfonate[a]

[salt], M	NaCl	NaBr	KBr	Et_4NBr	$Na(SO_4)_{1/2}$
0.005	13.7	9.4	10.1	9.6	15.9
0.01	10.9	8.8	9.3	8.9	14.4
0.05	8.3	6.0	5.3	5.3	10.6
0.10	7.1	5.2		4.6	10.6
0.15	6.8	4.6		4.4	10.7
0.20	7.3	4.0		4.0	11.4

[a] Values of 10^4k_ψ, s^{-1}, in 0.01 M SB3-16 and 0.1 M NaOH. In the absence of added salt $10^4k_\psi = 15.8$ s^{-1}.

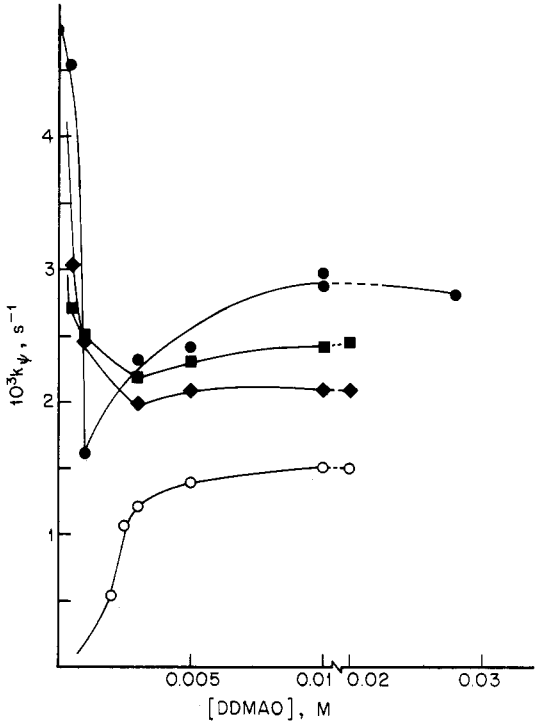

Figure 1. Effect of the amine oxide (DDMAO) on dephosphorylation. Solid points in 0.01 M NaOH: (●) no salt; (■) 0.2 M NaCl; (◆) 0.2 M NaBr. Open points: (○) 0.01 M $NaHCO_3$.

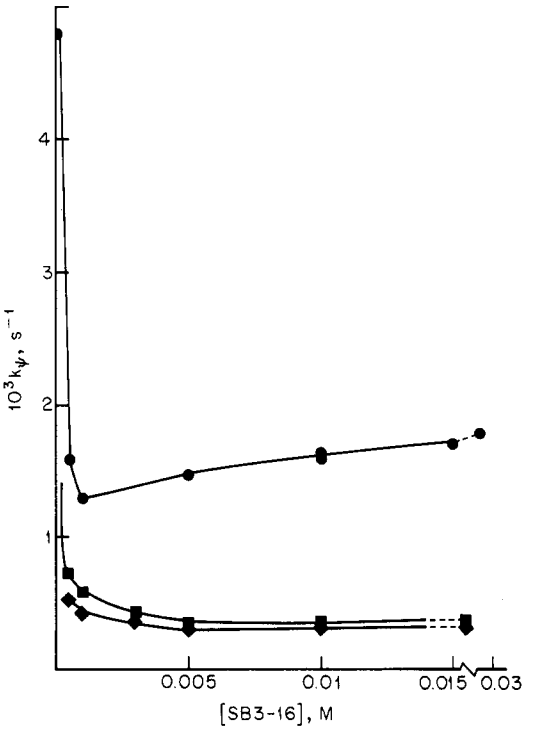

Figure 2. Effect of the betaine sulfonate, SB3-16, on dephosphorylation in 0.01 M NaOH: (●) no salt; (■) 0.2 M NaCl; (◆) 0.2 M NaBr.

Table III. Salt Effects upon Reactions in Zwitterionic Micelles[a]

	surfactant			
salt[b]	SB3-16	DDMAO	DDMAO[c]	DDMAO[d]
NaCl	0.46	0.83	0.88	0.91
NaBr[e]	0.25	0.72	0.85	0.89

[a] Values of k_s/k_o where k_s and k_o are rate constants in presence and absence of salt in 0.01 M NaOH and 0.01 M surfactant unless specified. [b] 0.2 M salt. [c] pH 8.5 in 0.01 M carbonate. [d] pH 7.0 in 0.01 M carbonate. [e] $k_s/k_o = 0.2$ for reaction of *p*-NPDPP in 0.008 M CTABr and 0.03 M NaBr.[11]

ences, both zwitterionic micelles have similar effects upon reaction with OH^-.

Added salts inhibit reaction in the zwitterionic micelles (Tables I and II), and the anion order is similar to that for reactions of OH^- with *p*-NPDPP in cationic micelles,[11] but the effects are very much smaller. Reactions of OH^- in cationic micelles are almost completely suppressed by 0.2 M NaBr.[1b] The inhibition is larger for reaction of OH^- in the betaine sulfonate than for reactions in the amine oxide where nucleophilic participation contributes to the overall reaction. Added anions should not affect nucleophilic participation by the amine oxide moiety (Table III). The salt inhibition in micelles of the betaine sulfonate is consistent with weak interaction of the inert anion with the quaternary ammonium center in the micelle which decreases binding of OH^-. Interactions of salt cations are nonspecific and are probably small (Tables I and II). Hydration of the sulfonate or oxide residues will reduce their specific interactions with cations by hydrophobic or dispersive forces.[3b]

These observations suggest that the betaine sulfonate or amine oxide micellar head groups attract OH^- and other anions from the aqueous region. Anion binding to cationic micellar head groups is due to both nonspecific Coulombic attractions and specific interactions which are largest for polarizable, low charge density, anions.[1,3,13] Very hydrophilic anions, e.g., OH^- and F^-, are largely Coulombically bound, whereas specific interactions are important with

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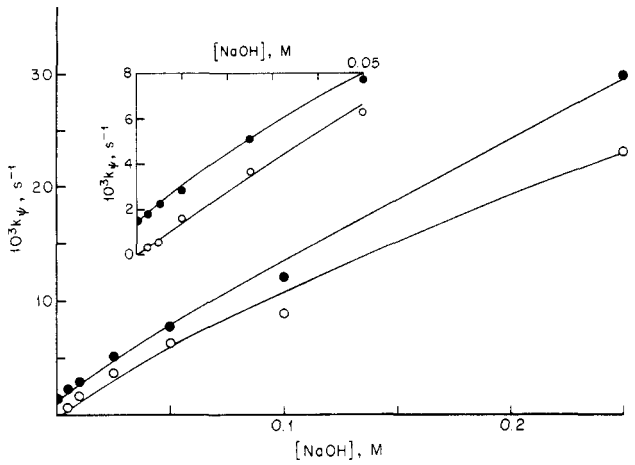

Figure 3. Dephosphorylation in 0.01 M surfactant, with added NaOH: (●) in DDMAO; (○) in SB3-16. Insert is for reaction in dilute NaOH.

Br^- and, to a lesser extent, Cl^-. These specific interactions between anion and quaternary ammonium ion should also be present in the zwitterionic micelles, but Coulombic attractions should be relatively small. Divalent counterions interact strongly with ionic micelles because of strong Coulombic attractions.[2,3] Specific attractions seem to be relatively unimportant, and sulfate ion does not strongly inhibit reaction of OH^- in SB3-16 (Table II).

Zwitterionic micelles are formally neutral, but Coulombic interactions between micelles and free ions depend to a high degree upon he charge density at the micellar surface.[2,3] If we treat zwitterionic micelles as smooth spheres with the anionic residues extending from the quaternary ammonium centers the charge density at the spherical surface through these cationic centers will be greater than that at the spherical surface through the anionic centers, and there will be a net attraction of anions. This "smooth" micellar model is only a crude approximation, because we do not know the conformation of the zwitterionic head group in the micelle, but it indicates how zwitterionic micelles could bind OH^-, albeit weakly, and why there is interionic competition.

The postulated weak binding of OH^- to zwitterionic micelles of the betaine sulfonate of the amine oxide is consistent with the almost linear increase of k_ψ with $[OH^-]$ (Figure 3) and the similarity of the slopes of the plots for the two surfactants. In micellar solutions in which there is extensive binding of the counterion, plots of k_ψ against [anion] curve down as counterions build up at the micellar surface.[1a,b]

Overall inhibition of the reaction of OH^- with micellar bound *p*-NPDPP is not inconsistent with weak binding of OH^- by the zwitterionic micelles. The second-order rate constant for this reaction at the surface of cationic micelles can be calculated from the concentration of reactants at the surface and is lower than that in water by a factor of ca. 9,[3] but because of the increased concentration of OH^- there is an overall rate increase. However, the concentration effect in zwitterionic micelles is so small that the overall reaction is inhibited.

These considerations do not explain the striking rate minimum in very dilute surfactant, but *p*-NPDPP is very hydrophobic, and it may bind to monomeric surfactant or small submicellar aggregates.[14,15] Such small zwitterionic aggregates would be formally neutral and should not attract OH^-, and the consequent inhibition should decrease as the surfactant concentration increases and micelles form and OH^- is attracted to their surfaces.

Scheme I

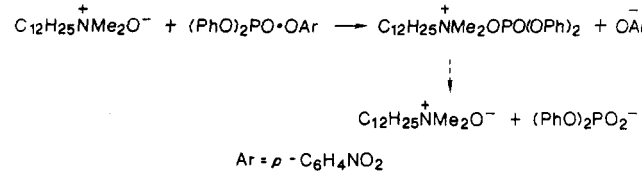

Table IV. Reaction in Comicelles of DDMAO with Excess *p*-NPDPP[a]

	[CTABr], M			
	0.001	0.003	0.005	0.01
10^5k_ψ, s^{-1}	28.4	10.3	7.15	3.66
10^7k_ψ[CTABr]	2.8	3.3	3.6	3.7

[a] At 25.0 °C with 1.5×10^{-4} M DDMAO, 3×10^{-4} M *p*-NPDPP, and 0.01 M carbonate buffer, pH 7.

The rate minima in the zwitterionic micelles seem to be less marked in salt solution (Figures 1 and 2). Added salts reduce critical micelle concentrations (cmc) of ionic surfactants,[16] and they probably also promote micellization of the zwitterionic surfactants. The cmc of the amine oxide is 2.1×10^{-3} M,[16] and there is inhibition at much lower [DDMAO] (Figure 1).

Rate constants increase smoothly with increasing concentration of the amine oxide (DDMAO) in hydrogen carbonate buffer, pH 8.5 (Figure 1). The increase corresponds to uptake of *p*-NPDPP by the micelles, and the rate constant for reaction of fully bound *p*-NPDPP is 1.5×10^{-3} s^{-1}. A decrease of pH to 7.0 only slightly decreases k_ψ to 1.38×10^{-3} s^{-1} because the amine oxide residue should not be protonated under these conditions. Second-order rate constants, k_M, at the surface of a micelle can be written with concentration of the reagent expressed as a mole ratio of reagent to micellized surfactant which is 1 for the amine oxide as reagent.[1b,e] For fully-bound substrate, eq 2 obtains.

$$k_\psi = k_M \quad (2)$$

This value of $k_M = 1.5 \times 10^{-3}$ s^{-1} can be compared with values of k_M for dephosphorylation of *p*-NDPP in functional comicelles of oximates or hydroxamates with CTABr. In these comicelles values of k_M are ca. 1 and 2 s^{-1} for hydroxamate and oximate, respectively, after correction for concentration of the functional group in the comicelle.[17] The lower nucleophilicity of the amine oxide, as compared with hydroxamate or oximate ions is consistent with its lower basicity.[6]

Enhanced rates of dephosphorylation by functional micelles typically involve nucleophilic participation,[1b,e,f,8] although general base catalysis was postulated for reaction of *p*-NPDPP in a histidine-functionalized micelle.[18] The amine oxide is participating as a nucleophile (Scheme I), and the phosphorylated amine oxide does not decompose readily in carbonate buffer because with excess *p*-NPDPP

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overall reaction becomes very slow when all the amine oxide is phosphorylated (see Experimental Section).

The reaction was followed in carbonate buffer with *p*-NPDPP in excess over DDMAO in CTABr. (It was necessary to use excess CTABr to solubilize the substrate). The reactions followed reasonably good first-order kinetics for approximately two half-lives, and the first-order rate constants decreased with increasing [CTABr] (Table IV). Values of k_ψ varied linearly with [DDMAO]/[CTABr], i.e., with the concentration of amine oxide in the comicelle. The absorbance after ca. 7 half-lives was approximately 60% of that calculated for complete decomposition of *p*-NPDPP (Experimental Section), so that there is apparently a small contribution from reaction with OH^- or buffer or some turnover of phosphorylated amine oxide. Despite these complications values of k_ψ in the comicelles agree reasonably well with those in DDMAO alone.

Substrate should be fully bound at the higher [CTABr], and under these conditions k_ψ is given by eq 3[1b,e,17] and

$$k_\psi = k_M[\text{DDMAO}]/([\text{CTABr}] + [\text{DDMAO}]) \quad (2)$$

from the data in Table IV, $k_M \approx 2.4 \times 10^{-3}$ s^{-1}, which is similar to that of $k_M = 1.5 \times 10^{-3}$ s^{-1} for reaction in DDMAO (Figure 1). The higher value in the comicelles is probably due to incursion of reaction with buffer or OH^-. The rate constant depends upon reagent concentration at the micellar surface and micellar charge has little or no effect.

Experimental Section

Materials. Dodecyldimethylamine oxide (DDMAO) (Aldrich) was purified by recrystallization (EtOAc). This and unpurified material gave the same values of k_ψ for reaction in NaOH. The preparation or purification of the other materials has been described.[11,15] Reactions were followed in redistilled, deionized, CO_2-free water.

Kinetics. The reaction was followed spectrophotometrically at 405 nm or at the isosbestic point between *p*-nitrophenol and phenoxide ion, 347 nm. Except where noted the substrate concentration was 10^{-5} M, and substrate was added in MeCN so that the reaction solution contained 0.3% MeCN. The first-order rate constants, k_ψ, are in reciprocal seconds.

The reaction was followed with 3×10^{-4} M *p*-NPDPP, 1.5×10^{-4} M DDMAO, and 0.01 M carbonate buffer, pH 7.0 with 0.003, 0.005, and 0.01 M CTABr, and after ca. 7 half-lives absorbances at 347 nm were respectively 60%, 70%, and 62% of those of solutions in which *p*-NPDPP was replaced by equimolar *p*-nitrophenol. In the reactions in buffer 3 mL of reaction solution contained 1 mL of carbonate of the specified pH.

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The Bis Cycloadduct of Hexamethyl-2,4-cyclohexadienone and a 1,4-Benzadiyne Equivalent

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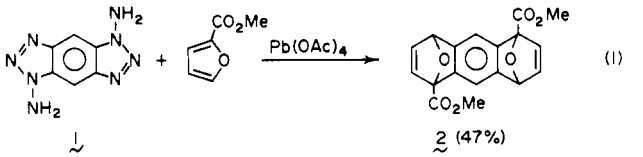
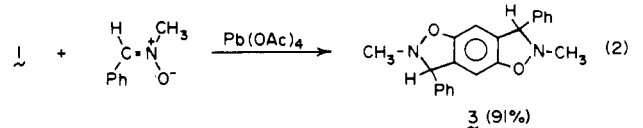
A single bis adduct **5** (*anti*-1,2,3,4,5,6,7,8,12,12,14,14-dodecamethyl-1,4:5,8-diethano-1,4,5,8-tetrahydroanthracene-11,13-dione) was obtained from the reaction of 1,4-benzadiyne equivalent **1** (1,5-diamino-1,5-dihydrobenzo[1,2-*d*:4,5-*d*']bistriazole) with hexamethyl-2,4-cyclohexadienone (**4**) and lead tetraacetate. Possible reasons for this remarkable regioselectivity in an aryne cycloaddition are discussed. Bis adduct **5** rearranges in neat trifluoroacetic acid to a mixture of isomeric diketones **13–16**. Irradiation of **16** through Pyrex gives the novel heptacyclic diketone **17**.

DABT (1,5-diamino-1,5-dihydrobenzo[1,2-*d*:4,5-*d*']bistriazole, **1**) is a useful 1,4-benzadiyne equivalent.[1] On treatment with dienes or 1,3-dipoles and lead tetraacetate, DABT gives good yields of bis(aryne) adducts. With unsymmetric dienes or 1,3-dipoles, the cycloadditions may be quite regioselective, as illustrated in eq 1 and 2. Although some secondary questions remain about the full structures of the adducts (oxygens syn or anti in **2**, phenyls cis or trans in **3**), the regiochemistry with regard to the cycloaddition was unequivocally established in both exammples. The cycloadditions to **1** probably occur stepwise, the observed regioselectivity arising in the second cycloaddition step.



(1)

1 **2** (47%)



(2)

3 (91%)

Many aryne cycloadditions occur without a high degree of selectivity.[2] In those examples where the regioselectivity is high, the factors which control it are still not entirely understood and are a matter of current interest.[2,3] We report here an example of truly remarkable regioselectivity in a cycloaddition involving benzadiyne equivalent **1**.

Results and Discussion

Cycloaddition of Hexamethyl-2,4-cyclohexadienone (4) with 1. Treatment of **1** with 2 equiv of **4**[4] and slightly

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