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Tests of the Pseudophase Model of Micellar Catalysis: Its Partial Failure[1]

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Abstract: Acid hydrolyses of *p*-nitrobenzaldehyde acetals are effectively catalyzed by micelles of tetradecanesulfonic acid (**1a**) and *p*-$ROC_6H_4SO_3H$, R = C_8H_{17} and $C_{12}H_{25}$ (**1b,c**, respectively). The kinetic forms are explained quantitatively in terms of reactions in the aqueous and micellar pseudophases, and the effects of added HCl can be explained qualitatively in these terms. Conductivity measurements show that ca. 75% of the hydrogen ions are bound to micelles of **1c**, and the second-order rate constants in the micellar pseudophase are in the range expected from earlier experiments using mixtures of HCl and sodium lauryl sulfate. The pseudophase model fails for reactions of 2,4-dinitrochlorobenzene and -naphthalene in *p*-$C_8H_{17}O_6H_4CH_2NMe_3OH$. The results can be explained by assuming that reaction occurs between reactants in the aqueous and micellar pseudophases, and also between OH^- in water and substrate in the micelle.

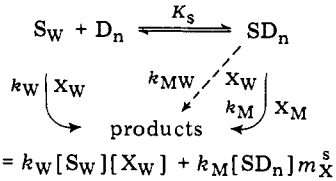
Micellar catalysis in water is generally rationalized in terms of reaction occurring either in the micellar or aqueous pseudophase.[3] The first quantitative application of this model was to the inhibition of ester saponification by anionic micelles,[8] and later to catalysis of the spontaneous hydrolyses of dinitrophenyl phosphates[9] and sulfates[10] by cationic micelles.

For micellar catalyzed bimolecular reactions it is necessary to consider the distribution of both reactants between the aqueous and micellar pseudophases (Scheme I).

In Scheme I and eq 1, S denotes organic substrate, D_n micellized surfactant (detergent), and K_s the binding of S to D_n. (The bracketed quantities are reactant concentrations in moles per liter of solution, the subscripts W and M denote water and micellar pseudophase respectively, m^s_X is the mole ratio of bound X to micellized surfactant, and k_M is the related second-order rate constant.[11])

Most models of micellar catalyzed reactions assume that the overall rate of reaction is the sum of the rates in each pseudophase, and that changes in rate with increasing surfactant concentration or added salt, for example, reflect changes in the distribution of reactants between the pseudophases. Other models also consider potential effects due to changes in the micellar surface charge on the initial and transition state free energies in the micellar pseudophase.[5a] A possible reaction path which has not been considered previously, and which we are now postulating, is reaction across the interfacial boundary, in this case, reaction between micellar bound organic substrate and an ionic reactant in the aqueous pseudophase, with a rate constant, k_{MW}, indicated by the broken line in Scheme I.

Scheme I



$$\text{rate} = k_W[S_W][X_W] + k_M[SD_n]m^s_X \quad (1)$$

The pseudophase kinetic model has been applied successfully to a number of micellar catalyzed bimolecular reactions between nonionic reactants,[11] and with partial success to reactions between neutral organic substrates and hydrophobic anionic nucleophiles.[6,12] The model correctly predicts the rate maxima which are typically observed with micellar catalyzed bimolecular reactions. However, it has not been tested extensively for micellar catalyzed bimolecular reactions involving hydrophilic ions, except for reactions involving hydrogen ions[13] and nucleophilic addition to carbocations.[14]

Much of the kinetic work on micellar catalyzed reactions involving hydrogen or hydroxide ions has been done in buffer solutions, and often with added salts.[5] Ionic micelles perturb buffer equilibria,[15] and added salts may introduce further complications, for example, by lowering the critical micelle concentration (cmc), reducing the surface potential, increasing micelle size, and generally reducing reaction rates.[5-7] To test the simple kinetic model for reactions with hydrophilic reactants we needed a micellar system which avoided, or at least minimized, these complications.

The pseudophase model explicitly assumes that changes in micelle size and shape are not very important, so that only those factors which control the distribution of reactants will significantly affect the observed reaction rate. Buffer effects are particularly difficult to interpret, so we selected reactions which would not require use of buffers. Finally, the presence of both reactive and unreactive counterions results in uncontrolled variations in distribution of the counterions between the micellar and aqueous pseudophases with concomitant changes in micelle surface potential and the cmc further complicating the interpretation. However, even with all these problems, both the rate maxima in the rate-surfactant concentration profiles

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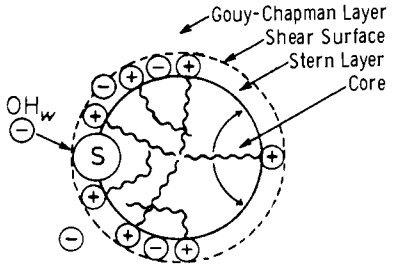


Figure 1. Model of a hypothetical cationic micelle showing the locations of head groups, surfactant chains, and counterions.[16] Curved arrows symbolize the liquid-hydrocarbon-like nature of the core. Also shown is a reaction between hydroxide ion and substrate across the interfacial boundary (shear surface).

and inhibition by added nonreactive counterions can be qualitatively interpreted by considering counterion competition (ion exchange) between reactive and nonreactive counterions for "sites" on the micelle surface.[7]

A useful physical picture for interpreting counterion effects is based on Stigter's model, which interprets the effect of added salt on the surface potential of micelles (Figure 1).[16] Counterions are assumed to be distributed in an ionic bilayer composed of two discrete sections: (1) the Stern layer, which contains tightly bound counterions that move with the micellar aggregate (the kinetic micelle), and (2) the Gouy-Chapman layer, which contains the remaining counterions loosely arranged according to a Boltzmann distribution extending radially into the aqueous phase. Similar double-layer models describe counterion distributions around planar interfaces, charged electrodes, and lyophobic colloids.[17] Stigter's theoretical calculations suggest that the potential drop across the Stern layer is relatively insensitive to increased counterion concentration so that the counterion concentration in the Stern layer and the fraction of counterions bound to the micelle surface, β, will be approximately constant. Experimentally estimated values of β are 0.6–0.9, and, although various methods give different values of β, they are relatively insensitive to added counterion.[7,18]

To test the pseudophase model of micellar catalysis for reactions of hydrophilic ions we examined systems in which the counterion is also the reactant. Consequently, its distribution between the micellar and aqueous pseudophases should depend only upon β, uncomplicated by nonreactive counterions.[20] Within the approximations of the model the concentration of reactive counterion at the micelle surface should be constant and independent of changes in surfactant or reactive counterion concentration. Thus, the simple kinetic model (eq 1) predicts that the rate constants of an ion–molecule reaction in these systems will be constant once all the substrate is micellar bound, because the concentration of both reactants at the micelle surface will then be constant, and we should see the plateaux typical of unimolecular reactions, and not the rate maxima observed for bimolecular micellar catalyzed reactions.[5,6]

Two reactions were chosen because their mechanisms are well understood and because the kinetic effect of micelles has already been studied in detail.

First, in micellized sulfonic acids, **1**, we measured the hydrolysis of *p*-nitrobenzaldehyde dialkyl acetals, **2**, for comparison with the effect of sodium lauryl sulfate (NaLS) micelles on this reaction.[13a,22]

$$RSO_3H$$

1

1a, R = $C_{14}H_{29}$; **1b**, R = *p*-$C_8H_{17}OC_6H_4$; **1c**, R = *p*-$C_{12}H_{25}OC_6H_4$

$$p\text{-}O_2NC_6H_4CH(OR')_2 \xrightarrow[H_2O]{H^+} p\text{-}O_2NC_6H_4CHO + 2R'OH$$

2

2a, R′ = Me; **2b**, R′ = Et

Second, we measured the effect of the micellized quaternary ammonium hydroxide ion surfactant, **3a**, on the reaction of hydroxide ion with dinitrochloroarenes, **4**, for comparison with the effects of the quaternary ammonium bromide, **3b**, and cetyltrimethylammonium bromide (CTABr).[24,25]

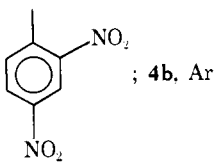
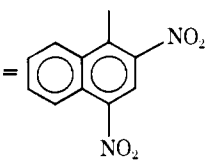
$$p\text{-}C_8H_{17}OC_6H_4CH_2\overset{+}{N}Me_3X^-$$

3

3a, X = OH; **3b**, X = Br

$$ArCl \xrightarrow{OH^-} ArO^- + Cl^-$$

4

4a, Ar =  ; **4b**, Ar = 

The reactions of **2b** in solutions of HCl and NaLS and **4a** with OH^- in CTABr show rate maxima in their rate–surfactant profiles because mixtures of counterions are present, and as expected added nonreactive counterions reduce the micellar catalysis.[13a,24] When only reactive counterion is present the rate–surfactant profiles for acetal hydrolysis approach plateaux as predicted by the simple pseudophase kinetic model; however, for reactions of **4a,b** we see evidence for an additional reaction path.

Experimental Section

Materials. *n*-Tetradecanesulfonic Acid (1a). This compound was extremely difficult to obtain in pure form. The product of the Strecker synthesis[26] (alkyl bromide plus Na_2SO_3, followed by transformation to the acid) always gave a minimum in the surface tension curve even after repeated recrystallization and extraction of the sodium salt followed by recrystallization and distillation of the acid.

A product with no minimum in the surface tension curve was obtained using a modification of the method of Noller and Gordon.[27] Vacuum-distilled *n*-bromotetradecane (Aldrich) was treated with 1 equiv of thiourea in EtOH giving *n*-tetradecylthiouronium bromide, which was twice recrystallized (EtOH–Et_2O). This salt was hydrolyzed (OH^-) to *n*-tetradecanethiol, which was treated with Zn–H_2SO_4 to reduce disulfide and was treated immediately with excess $Pb(OAc)_2$ to give a yellow precipitate of $(C_{14}H_{29}S)_2Pb$, which was oxidized in hot HNO_3 to $(C_{14}H_{29}SO_3)_2Pb$. Both the lead sulfide and lead sulfonate solids were extracted many times with warm acetone to remove unidentified white solids.

The purified lead tetradecanesulfonate in dry Et_2O was treated with dry HCl gas with agitation for about 30 min. The $PbCl_2$ was filtered off and the excess Et_2O and HCl were pumped off. The resulting low melting point solid contained Pb^{2+}. The acid was neutralized with NaOH in hot 1:1 H_2O–MeOH, Na_2S (1 M) was added in small amounts to precipitate PbS, and the solution was filtered hot to prevent precipitation of the surfactant. The filtrate gave no precipitate on further addition of Na_2S. The sodium salt of **1a** was collected and recrystallized twice (95% EtOH). It then was treated with dry HCl gas in dry Et_2O with vigorous stirring for 30 min. The volatiles were pumped off and **1a** was dehydrated under vacuum and was then molecularly distilled under high vacuum (≤5 mTorr) at 120–135 °C. The purified anhydrous solid sulfonic acid was handled under N_2 to prevent the absorption of moisture. Stock solution concentrations agreed within 1% by titration and by weight. The cmc by surface tension was 1.97 mM (lit.[28] 1.36 mM) and there was no minimum in the surface tension curve.

***p*-Dodecyloxybenzenesulfonic Acid (1c).** The recrystallized disodium salt of *p*-hydroxybenzenesulfonic acid was refluxed with distilled *n*-dodecyl bromide (Aldrich) in H_2O–*i*-PrOH for 3 days. The sodium salt of **1c** was isolated, recrystallized once from hot water, and ex-

tracted with dry Et_2O (Soxhlet) for 24 h, removing a small amount of oily material. A second extraction with hexane for 24 h removed a trace of a foul-smelling oil. The dried salt was treated in dry Et_2O with HCl gas for 30 min with vigorous stirring. Formation of the sulfonic acid was slow and the process had to be repeated several times. Purified **1c** contained one water of hydration, and without water the exchange of hydrogen for sodium ions in ether is probably very slow. After complete reaction, the precipitate of NaCl was removed by filtration and the volatiles were pumped off. The white **1c** was recrystallized twice from hexane and dried under vacuum. The cmc by surface tension was 1.00 mM without a minimum.

***p*-Octyloxybenzenesulfonic Acid (1b).** This surfactant was prepared in the same way as the dodecyl derivative except that the conversion to the acid was from the lead instead of the sodium salt. However, the surfactant contained no Pb^{2+} as shown by addition of Na_2S. The surface tension curve had a small minimum (about 1 dyn) even after repeated recrystallizations from Et_2O-petroleum ether solutions. The cmc estimated from surface tension was 9 mM.

***p*-Octyloxybenzyltrimethylammonium Hydroxide (3a).** Equimolar amounts of Ag_2O and *p*-octyloxybenzyltrimethylammonium bromide (**3b**)[29] in 1:1 aqueous MeOH were stirred for 3 min and the filtrate was centrifuged at 4500 rpm at 5 °C for 25 min. Methanol was removed by repeatedly distilling the resulting clear supernatant under vacuum and adding water after each distillation. The removal of MeOH was monitored by observing formation of a Meisenheimer complex on addition of **4b**. When all the MeOH had been removed we saw only 2,4-dinitronaphthoxide ion, λ_{max} 390 nm. All synthetic steps were carried out under nitrogen. The water was deionized, distilled, and degassed by boiling under N_2 to remove CO_2.

Substrates. 2,4-Dinitrochlorobenzene (**4a**) (Aldrich) and 2,4-dinitrochloronaphthalene (**4b**) (Eastman) were recrystallized twice. 1-Nitronaphthalene was recrystallized twice (EtOH), chromatographed once on silica gel, eluted (EtOH), and then recrystallized twice from petroleum ether-Et_2O. Dimethyl and diethyl *p*-nitrobenzaldehyde acetals **2a,b** were synthesized from *p*-nitrobenzaldehyde and dimethyl or diethyl orthoformate with a catalytic amount of polystyrenesulfonic acid and were isolated and vacuum distilled.[30]

Kinetics. All solutions were made with deionized, distilled water. All kinetic measurements were performed on a Gilford 2400 spectrophotometer thermostated at 25.0 ± 0.1 °C.

Acetal Hydrolysis. To avoid interference by the absorption of the surfactants **1b** and **1c**, hydrolyses were followed at 318 nm instead of at λ_{max} of the aldehyde at 267 nm. Hydrolyses in **1a** were run at 267 nm.[13a] Reactions were started by injecting 3–5 μL of 0.06 M acetal in MeCN into 3 mL of surfactant solution giving final substrate concentrations of ca. 10^{-4} M. Surfactant solutions were standardized by precipitation of the sulfonate with excess $BaCl_2$ followed by potentiometric titration of the acid.

Aromatic Nucleophilic Substitution. Reactions in **3a** and **3b** were monitored at 358 nm for 2,4-dinitrochlorobenzene[24] and at 390 nm for 2,4-dinitrochloronaphthalene. Hydroxide ion concentrations were determined by precipitation of the surfactant with excess standardized $HClO_4$ followed by potentiometric back-titration with standard base. Reactions were started by injection of 5 μL of 5 mM substrate in MeCN into 2 mL of surfactant solution in 1-cm cuvettes capped with serum stoppers.

Surface Tension Measurements. Surface tensions were measured on a Fischer, du Nouy type tensiometer, Model 20, at ambient temperature, using deionized, distilled water. All glassware was carefully cleaned and dried. The platinum ring was flamed before each run and the surface tension of water was used to test the cleanliness of the equipment.

Conductance Measurements. An Industrial Instruments Conductivity Bridge, Model RC-17, was used with a Yellow Spring Instrument Co. 3403 cell with blackened platinum electrodes. The conductivity of **1c** was measured by progressively diluting a 0.1 M solution to a concentration below the cmc as measured by surface tension. The effect of added HCl was determined by progressively diluting a solution of 0.2 M HCl and 0.01 M **1c** with 0.01 M **1c**.

Solubility Measurements. Saturated solutions of **4b** and 1-nitronaphthalene were made by injecting small amounts of concentrated solutions of these substrates in MeCN into surfactant solutions, sonicating each mixture for about 45 min (final temperature ~40 °C), then cooling to 25 °C and centrifuging. A small aliquot of the supernatant was diluted with excess spectral grade MeCN to break up the micelles and the substrate absorbance was measured at 380 nm for 1-nitronaphthalene and 355 nm for **4b**. Plots of absorbance vs. surfactant concentration were linear. Solubilities of the substrates in water were measured directly for 1-nitronaphthalene (0.167 mM) and for **4b** (0.0048 mM) by extrapolation from H_2O-MeCN to pure water.

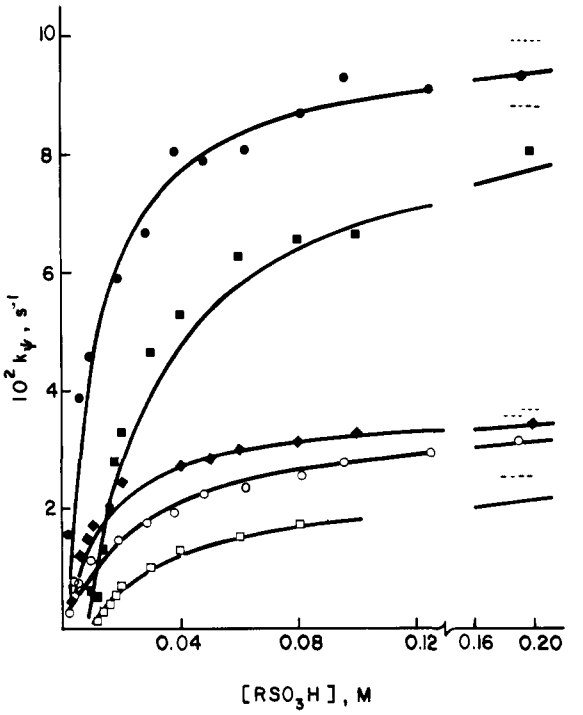


Figure 2. Hydrolyses of the acetals **2a,b.** Open points denote **2a**, closed **2b**. ♦, **1a**; ■ □, **1b**; ● ○, **1c**. The solid lines are predicted, and the broken lines are predicted k_ψ at total substrate incorporation.

Results

Acetal Hydrolyses. Figure 2 shows the rate-surfactant profiles for the acid-catalyzed hydrolyses of acetals **2a** and **2b** in the micellized sulfonic acids **1a–c**, and in each case the rate constants approach the predicted plateaux.

Following the equations applied to micellar catalyzed unimolecular and inhibited reactions, eq 1 gives

$$k_\psi = \frac{k_W[H_W^+] + k_{H^+}^m K_s([D] - \text{cmc})}{1 + K_s([D] - \text{cmc})} \qquad (2)$$

In deriving eq 2 we use the generally accepted assumption that the concentration of monomeric surfactant is given by the cmc.[31]

The extent of hydrogen ion binding to the micelle surface was estimated from the conductance data for **1c**, from the cmc to 0.01 M (Table S1; see paragraph at end of paper regarding supplementary material), by the method of Evans.[32,33] The calculation usually requires solving a quadratic equation using estimated or experimental values of the aggregation number. However, because the hydrogen ion is very mobile, higher order terms can be neglected. The simplified expression is

$$1000S_2 = (1 - \beta)\Lambda_{H^+} \qquad (3)$$

where S_2 is the slope of the specific conductivity-surfactant concentration plot above the cmc and Λ_{H^+} is the equivalent conductance of the hydrogen ion at infinite dilution. With this approximation β is 0.75. If values of 50 and 100 are assumed for the aggregation number and the complete equation is used,[32] β = 0.75 and 0.77, respectively. These small differences accord with Evans' observation that the calculated degree of counterion binding is insensitive to the aggregation number.[32]

Table I. Binding, Micellar Rate Constants, and Relative Rates Calculated from Observed Rate Constants for Acetal Hydrolysis by Micellized Long-Chained Sulfonic Acids

surfactant	substrate	K_s, M^{-1}	k_M, s^{-1}	$10^3 k_2^m$, $M\ s^{-1}$ [a]	k_2^m/k_W [b]
$C_{14}H_{29}SO_3H$	**2b**	73	0.042	5.9	0.020
p-$C_8H_{17}OC_6H_4SO_3H$	**2a**	27	0.029	4.1	0.055
	2b	36	0.101	14.1	0.049
p-$C_{12}H_{25}OC_6H_4SO_3H$	**2a**	37	0.041	5.7	0.076
	2b	91	0.115	16.1	0.056
$C_{12}H_{25}SO_4Na$ [13a]	**2b**		0.096	13.4	0.046
$C_{12}H_{25}SO_4Na$ [c]	$C_6H_5C(OCH_3)_3$	73			

[a] k_2^m ($M^{-1}\ s^{-1}$) = $0.14k_M$ (s^{-1}); 0.14 M^{-1} is a conversion factor relating the rate constant expressed in terms of the mole ratio of H^+ per micellized surfactant head groups to that in terms of moles of H^+ per liter of Stern layer. [b] k_W for **2a** = 0.075 $M^{-1}\ s^{-1}$, for **2b** = 0.29 $M^{-1}\ s^{-1}$. [c] R. B. Dunlap and E. H. Cordes, *J. Am. Chem. Soc.*, **90**, 4395 (1968).

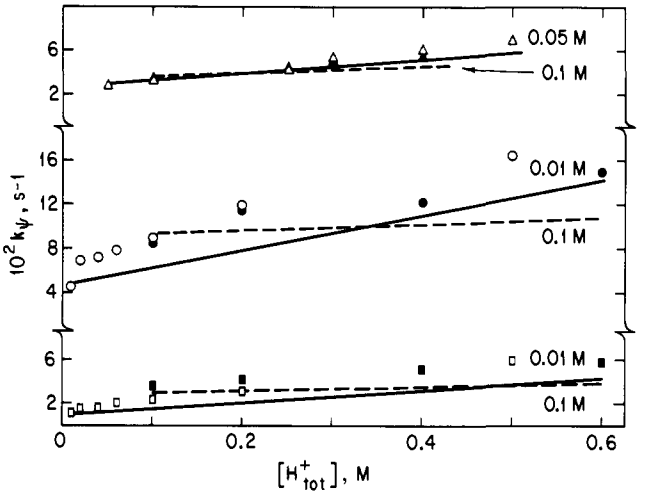


Figure 3. Hydrolysis of the acetals **2a,b** with added HCl: △, **2b** and 0.05 M **1b**; ▲, **2a** and 0.1 M **1b**; □, **2b** and 0.01 M **1c**; ■, **2b** and 0.1 M **1c**. The solid lines are predicted for the lower and the broken lines for the higher surfactant concentrations.

We will assume that $\beta = 0.75 = m^s_{H+}$ for all three sulfonic acids and does not change significantly with either sulfonic acid concentration or added HCl. This approximation no doubt fails at higher surfactant concentrations. For **1c**, the specific conductivity increases more rapidly than the surfactant concentration above 0.01 M, so that at 0.1 M, $\beta = 0.67$. This apparent increase in specific conductivity at high surfactant concentration has been observed before with many surfactants,[21] and has been interpreted as an increase in the degree of ionization of the micelle, the so-called "retrograde dissociation".[35] If, however, the micellar surface is a better conductor of hydrogen ions than the aqueous phase, then an increase in conductivity would occur at higher surfactant concentration without the need to invoke "retrograde dissociation". No evidence is available on this point.

When all the substrate is bound to the micelle eq 2 reduces to

$$k_\psi = k_M m^s_{H+} \qquad (4)$$

We did not reach this limit in any of the acetal hydrolyses (Figure 2). Nonetheless, the linear relation between the reciprocal of the observed second-order rate constant, k_2, and [D] derived from eq 2 can be used to calculate K_s and k_M, and the results are listed in Table I. The lines drawn in Figure 2 are calculated using eq 2, the cmc determined by surface tension, $\beta = 0.75$ from conductance data, and the constants in Table I.

The values of K_s and k_M are reasonable in view of the values obtained in similar systems (Table I), but with micellized NaLS.

Experiments were also done with added HCl and 0.01 and 0.1 M dodecyloxybenzenesulfonic acid and 0.05 and 0.1 M *n*-tetradecanesulfonic acid. The observed rate constants increase essentially linearly with added HCl up to ~0.5 M (Figure 3). The surfactant solutions become progressively more viscous with added acid and are gelatinous above 1.0 M HCl, preventing reliable rate measurements. In addition, the increase in rate with added acid was less at the higher surfactant concentrations. The trends in k_ψ are qualitatively in accord with the assumptions of the simple kinetic model and eq 2 which attribute the entire rate increase to increased rate of reaction in the aqueous pseudophase.

The effect of HCl on k_ψ, at constant surfactant concentration, was also calculated using eq 2 from the values of K_s and k_M (Table I) assuming that the cmc remained constant,[36] and the results are the solid lines shown in Figure 3. Given the relative small change in the observed rate, the high [HCl], and the approximations in the treatment, especially that the extent of substrate binding is independent of added HCl, these results are in reasonable agreement with theory. Apparently, the main effect of added HCl is to speed reaction in the aqueous pseudophase without significantly affecting that in the micelles. The greater than predicted rate increase with added HCl is consistent with the change in specific conductivity with added HCl. At 0.01 M **1c**, the conductivity of **1c** plus HCl minus that of equivalent amounts of HCl decreased about 10% in going from zero to 0.02 M HCl and then increased rapidly so that at 0.2 M HCl it was 40% greater than predicted by additivity (Table S2). If this increase is due to "retrograde dissociation" of the micelles,[35] there would be a larger than predicted hydrogen ion concentration in the aqueous pseudophase, which might account for part of the larger than expected rate increase for surfactants **1b** and **1c**.

Aromatic Nucleophilic Substitution. Experiments were done with **4a** and **4b** and added NaOH and the bromide form of the surfactant (**3b**), and the expected rate maxima were observed (Figures 4 and 5).

Although the simple pseudophase kinetic model as represented by eq 1 and 2 is satisfactory for acetal hydrolysis, it fails for reactions of **4** in solutions of the hydroxide form of the surfactant, **3a** (Figures 4 and 5), because k_ψ increases steadily with increasing **3a** even when there is strong evidence that the substrate is fully micellar bound. The variation of k_ψ with **3a** can be fitted to an equation akin to eq 2, but this treatment leads to unreasonably low values of the binding constant, K_s, which would have to be about 6 for **4a** and 15 for **4b**, whereas K_s for **4b** as estimated by comparison of its solubility with that of the model compound, 1-nitronaphthalene, is much higher (Table II).[37] While 1-nitronaphthalene does not bind as tightly to **3a** as it does to **3b** and CTABr, the differences are nowhere large enough to accord with the very small binding constants estimated from the kinetic data and the simple kinetic model.

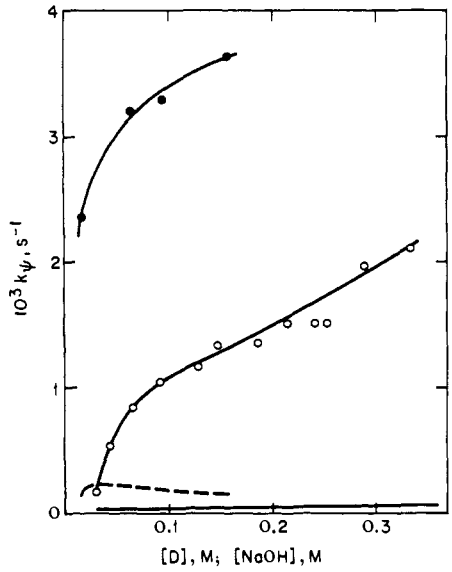


Figure 4. Reaction of 2,4-dinitrochlorobenzene (**4a**) in surfactant **3a**: ○, no added NaOH; ●, 0.5 M NaOH. Broken line, reaction of **4a** in surfactant **3b** and 0.05 M NaOH. Solid line, reaction in 0.05 M NaOH in the absence of surfactant.

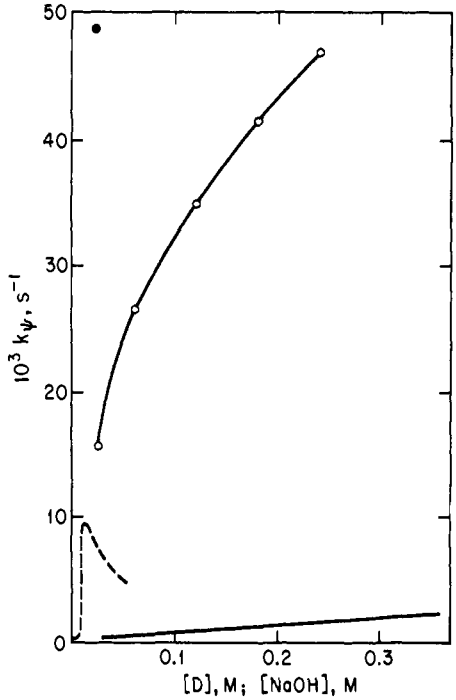


Figure 5. Reaction of 2,4-dinitro-1-chloronaphthalene (**4b**) in surfactant **3a**: ○, no added NaOH; ●, 0.185 M NaOH. Broken line, reaction of **4b** in surfactant **3b** and 0.05 M NaOH. Solid line, reaction in 0.05 M NaOH in the absence of surfactant.

Table II. Binding Constants Determined from Solubility Measurements[a]

substrate	surfactant		
	CTABr	**3b**	**3a**
2,4-dinitrochlorobenzene	75[b]	91	
2,4-dinitro-1-chloronaphthalene	1610	1640	
1-nitronaphthalene	1930	1660 (2010)	1000 (1500)

[a] Binding constants, K_s (M^{-1}). Values in parentheses were determined in the presence of 0.5 M NaOH. [b] Reference 24.

Moreover, unlike the effect of added H^+ on the acetal hydrolyses, added OH^- sharply increases k_ψ even though the reactions of **4a** and **4b** with hydroxide ion in water are much too slow to contribute materially to the overall reaction. In the absence of surfactant the second-order rate constants at 25 °C follow: **4a**, 1.42×10^{-4} [24]; **4b**, 6.4×10^{-3} M^{-1} s^{-1}.

Discussion

There are several possible reasons for the failure of the simple kinetic model in the hydroxide ion reactions (Figures 4 and 5). One is that replacement of the bromide counterion by hydroxide ion dramatically lowers the binding constants of the substrates. However, the extremely small substrate binding constants required to fit the kinetic data are difficult to reconcile with the solubility data (Table II).

Another way to treat these results is to assume that there is an additional reaction path, with rate constant, k_{MW}, involving attack of hydroxide ion in water upon substrate in the micelle, as indicated by the broken line in Scheme I and illustrated in Figure 1. Scheme I gives

$$k_\psi = \frac{\{k_W + k_{MW}K_s([D] - cmc)\}\{cmc + \alpha([D] - cmc)\} + k_M K_s(1 - \alpha)([D] - cmc)}{1 + K_s([D] - cmc)} \quad (5)$$

and at high surfactant concentration ([D] ≫ cmc) and

$$k_\psi = \alpha k_{MW}[D] + k_M(1 - \alpha) \quad (6)$$

i.e., k_ψ should increase linearly with [D] as observed with **4a** (Figures 4 and 5).

The reaction represented by k_{MW} could probably be described equally well in terms of a Guy-Chapman model of counterion ion distribution without a Stern layer, making the hydroxide ion concentration at the surface a sensitive function of that in the aqueous phase.[6b] These descriptions are essentially equivalent because there is no shear boundary between the Gouy-Chapman layer and water, making the qualitative predictions the same. The rate enhancements by added hydroxide ion are too large to be ascribed solely to an increase in the concentration of hydroxide ion at the micelle surface. Simply filling the surface with hydroxide ion would probably not markedly increase its concentration and therefore the rate.[38]

Implicit in the current quantitative discussions of micellar catalysis is the assumption that the micellar structure is insensitive to changes in surfactant and reactant concentration, or that any structural changes do not affect rate constants in the micellar pseudophase. Support for these assumptions stems from the observation that the partial molar volumes of micelles are insensitive to changes in surfactant concentration,[39] and that there are a number of spontaneous, unimolecular micellar catalyzed reactions for which the rate constants do not change with large changes in surfactant concentration once the substrate is fully bound, even though there are changes in micellar shape and size.[9b]

It is difficult to account for all these results. Our incorporation evidence (Table II) strongly suggests that the dinitrohaloarenes bind strongly to cationic micelles regardless of counterion type and there is extensive evidence that the degree of counterion binding is relatively insensitive to surfactant and counterion concentration,[7] although, to date, there are no experimental data on cationic surfactants with only hydroxide counterions. When mixtures of counterions are present, the simple model is reasonably satisfactory (eq 1 and 2). For example, the rate-surfactant profiles for the reaction of OH^- with Malachite Green can be treated reasonably well in terms

of these equations and experimentally determined micellar incorporation of the substrate.[14] In addition, the rate-surfactant profiles for a number of micellar catalyzed hydroxide ion reactions can be approximated using equations which are essentially identical with eq 1 and 2.[7]

The apparent success of the model in treating acetal hydrolysis may be the result of micellized alkanesulfonic acids not being strong. For example, the striking effect of substrate micellization on the acid hydrolysis of monoalkyl sulfates suggests that the covalent sulfuric acids are present under these conditions,[41] and in addition the hydrogen ion (or its chemical equivalent) in micellized NaLS seems to be less reactive than in water (i.e., $k_2^m < k_W$; see Table I and ref 13). Therefore we measured the solvent deuterium isotope effect on the hydrolysis of **2b** in 0.006, 0.10, and 0.20 M **1c**. Values of k_{D_2O}/k_{H_2O} were 2.77, 2.59, and 2.39, respectively, which agree with that of 2.72 in 50% D_2O-dioxane at 30 °C.[42] This value suggests that the reaction is specific rather than general acid catalyzed at the micelle surface as in water, i.e., that proton transfer is essentially complete in the transition state.

The absence of earlier evidence for reaction between reactants in two pseudophases is readily understandable. First, its observation requires high concentration of surfactant and most studies of micellar catalyzed reactions have been done at relatively low surfactant concentrations, usually well below 0.1 M.[5] Second, the ion exchange effect produced by nonreactive counterions will obscure the qualitative observation of a rate enhancement produced by added reactive ions, such as hydroxide ion, in addition to complications due to the exchange of ions at the micelle surface.

Although the pseudophase model fails for these hydroxide ion reactions, we do not know whether this failure is general for hydrophilic anions and we are currently examining this question. It may be that the abnormally high mobility of hydroxide ion in water causes it to behave differently from other anions in micellar solutions.

Rate Comparisons for Acetal Hydrolysis. For micellar catalyzed spontaneous, unimolecular reactions the maximum reaction rate occurs when the substrate is fully micellar bound, and the value of k_Ψ is then the first-order rate constant in the micellar pseudophase. This rate enhancement must be due to a medium effect (i.e., the micelle behaves as if it were a submicroscopic solvent). However, for bimolecular reactions the catalysis depends upon the extents of incorporation of both reactants in the micellar pseudophase and the second-order rate constant in the pseudophase. Consequently, to compare these rate constants with those in water we must define our units of concentration. In deriving eq 2 and 4 we avoided this problem by defining concentration of the ionic reactant as its mole ratio to the ionic head groups of the micelle, m^s.

The second-order rate constants, k_M (s^{-1}), cannot be compared directly with second-order rate constants, k_w, if the latter are measured conventionally in the units of $M^{-1}\,s^{-1}$. The comparison can be made by choosing a volume element for the reaction in the micelles and we have estimated a molar volume of ca. 140 mL for the Stern layer using Stigter's model of a spherical micelle[16] and the assumption that micellar density is 1 g mL^{-1}.[40] For CTABr and NaLS the second-order rate constant, k_2^m ($M^{-1}\,s^{-1}$), is given by

$$k_2^m \approx 0.14 k_M \qquad (7)$$

Values for k_2^m are listed in Table I.

The volume of the Stern layer can be estimated in other ways. For example, Tanford,[43] using a spheroidal instead of a spherical micellar model, estimates a surface area of 60–65 Å per head group for a micellized dodecyl cationic surfactant. If the thickness of the head is ca. 4.2 Å,[44] then the volume of the Stern layer in 1 mol of micellized surfactant would be between 0.15 and 0.16 L, which is similar to our earlier estimate, so that our original form (eq 7) seems reasonable.

We do not know the dimensions of micelles of the sulfonic acids, **1a–c**, so that there is considerable uncertainty in the factor for the conversion of k_M to k_2^m, especially because it was estimated from the dimensions of micelles of sodium lauryl sulfate. However, the magnitudes of k_2^m/k_W are similar for all the acetal hydrolyses (Table I).

We should not expect the factor for conversion of k_M to k_2^m to be exactly the same for all the surfactants considered, in part because of uncertainties in the precise location of solutes in the micelle, but also because the micellar surface is rough[4,16] and its structure will depend upon the natures of the surfactant and counterion. Our estimated volume of the Stern layer is approximately half that of the micelle.

Supplementary Material Available: Specific conductance of *p*-dodecyloxybenzenesulfonic acid (**1c**) solutions, 0.007–0.1 M (Table S1), and the specific conductance of **1c** plus HCl solutions, up to 0.2 M HCl, and 0.01 M **1c** (Table S2) (3 pages). Ordering information is given on any current masthead page.

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(38) Even if β is in the low range of ca. 0.6 for a hydroxide ion surfactant, saturation of the Stern layer by OH^- would only increase the concentration of micellar-bound OH^- by ca. 66%, which would not account for the observed rate effects. It would give a micelle of zero net charge which would be unexpected with a hydrophilic counterion.
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Synthesis of Anatoxin *a* via Intramolecular Cyclization of Iminium Salts

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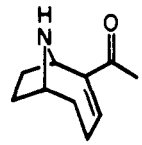
Abstract: Anatoxin *a* (**1**) has been synthesized by exploiting intramolecular cyclization between an iminium salt and a nucleophilic carbon to construct the 9-azabicyclo[4.2.1]nonane ring system. Cyclization of malonate iminium salt **16** at alkaline pH afforded a low yield of bicyclic malonate **18** owing to an unfavorable equilibrium constant and lability of the iminium salt in base. In contrast, cyclization of ketoiminium salt **31** afforded a good yield of bicyclic ketone **34** in acidic methanol. Dihydropyrrolium salts **16** and **31** were generated quantitatively by decarbonylation of substituted *N*-methylprolines **15** and **30b**, obtained by reduction of the corresponding pyrroles.

Certain strains of *Anabaena flos-aquae*, a fresh-water blue-green alga, produce a potent postsynaptic depolarizing neuromuscular toxin known as very fast death factor (VFDF) or anatoxin *a* (**1**),[1] the structure of which was determined by



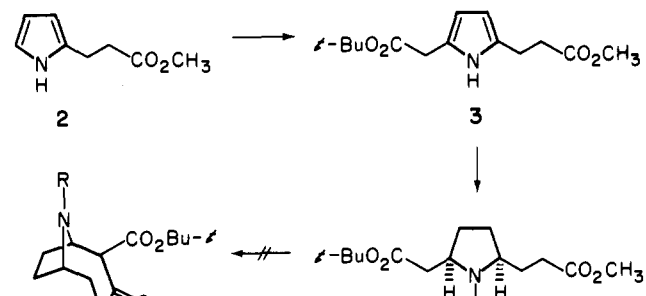
1, Anatoxin-a

X-ray crystallography and spectroscopy.[2,3] Fatal poisoning of various animals has been caused by ingestion of water from eutrophic ponds containing high concentrations of this alga.

In contrast to the many examples of the 8-azabicyclo[3.2.1]octane ring system found in the diverse and widely distributed atropine alkaloids, anatoxin *a* is the only naturally occurring representative of the homologous 9-azabicyclo[4.2.1]nonane series. Only two syntheses of this class of compounds have been reported, and both utilized ring expansion of the more readily available 8-azabicyclo[3.2.1]-octanes. Thus 9-azabicyclo[4.2.1]nonan-3-one was first prepared by Tiffeneau ring expansion from tropinone.[4] More recently, a partial synthesis of anatoxin *a* via ring expansion from cocaine was reported.[5]

We chose to examine a direct and potentially broader approach to anatoxin *a* involving closure of the eight-membered carbon ring (seven-membered, counting through nitrogen) into

Scheme I



an appropriately substituted pyrrolidine. Initially, we considered ring closure via a Dieckmann cyclization of the appropriate pyrrolidine-2,5-diester **4b** as shown in Scheme I. However, this was unsuccessful, as might have been anticipated from the low yield of the analogous Dieckmann cyclization leading to tropinone-2-carboxylate[6,7] and the known difficulty of extending this reaction to medium-sized rings.

This paper describes the successful synthesis of anatoxin *a* via intramolecular cyclization between an iminium salt and a carbon atom bearing electron-withdrawing substituents as shown in the generalized Scheme II. Similar cyclizations have been successfully employed for the closure of relatively unstrained five- and six-membered rings, and occasionally

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