Micellar Effects upon the Hydrogen Ion and General Acid Catalyzed Hydration of 1,4-Dihydropyridines[1]

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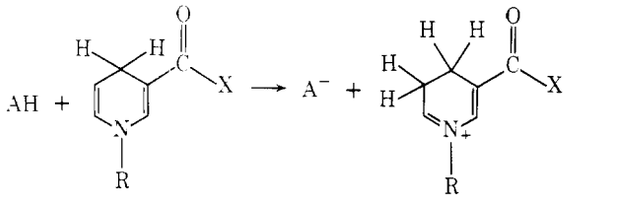
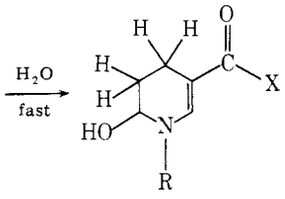
The rate-limiting step in the hydration of 1-benzyldihydronicotinamide (**1a**) and 1-benzyl-3-acetyl-1,4-dihydropyridine (**1b**) is a slow proton transfer, as shown by the kinetic deuterium solvent isotope effects and buffer catalysis. Reactions in dilute HCl are strongly inhibited by cationic micelles of cetyltrimethylammonium bromide (CTABr) and the inhibition can be related to the micellar binding of the substrates determined spectrophotometrically or by solubility. Anionic micelles of sodium lauryl sulfate (NaLS) only weakly catalyze hydration in dilute HCl, and rate constants go through maxima with increasing [NaLS]. The dependence of rate on [NaLS] can be explained quantitatively in terms of substrate and hydrogen ion incorporation in the micelle and formation of an unreactive conjugate acid in the micelle. The equilibrium constants for unproductive protonation in the micelle corrected for reagent distribution are similar to those in water but the rate constants are lower. Micelles of sodium *n*-dodecyl hydrogen phosphate are good catalysts, giving rate enhancements of $\sim 10^3$ relative to those in water.

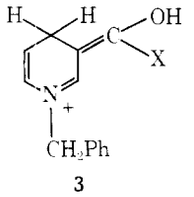
The acid hydration of dihydropyridine derivatives (**1**) in aqueous solution is an enamine addition and involves proton transfer from HA followed by rapid attack of water upon the cation (**2**).[4] Because of the biological importance of dihydropyridine nucleotides catalysis of this reaction is of considerable interest and we examined micellar effects in a model system. To date much of the mechanistic work has been on nucleotide derivatives, which are too hydrophilic to be good substrates for use with aqueous micelles, and therefore we first examined hydration of our substrates **1a,b** in the absence of surfactants for purposes of comparison with the reactions in the presence of micellized surfactants. The protonations are irreversible in aqueous acid, but not in nonpolar solvents,[5] and the reactions in aqueous solution are general acid catalyzed.[6] The slow protonation is assisted by electron release by the ring nitrogen, which is reduced by conjugation with the carbonyl group. The charge in the transition state, or the cation **2**, is delocalized, but probably it is largely on the ring nitrogen as shown, and substrate protonation, probably on the carbonyl group, **3**, should inhibit reaction.



1 **2**

R = CH_2Ph
1a, X = NH_2
1b, X = CH_3





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Micelles of anionic surfactants typically speed hydrogen ion catalyzed reactions,[7] and we were interested in micellar effects upon the hydration of dihydropyridines because to date specific hydrogen ion catalyzed reactions have generally been examined. In these reactions the proton is fully transferred in the transition state whose formation involves other bond making or breaking steps.

Cationic micelles of cetyltrimethylammonium bromide, CTABr, inhibit and anionic micelles of sodium lauryl sulfate, NaLS, weakly catalyze hydration of dihydronicotinamide derivatives.[12] These experiments were in phosphate buffer so that the micelles could affect the buffer equilibria and have different, and perhaps opposite, effects upon the hydrogen ion and the dihydrogen phosphate ion catalyzed reactions.[13] We therefore examined these reactions under conditions in which the only catalyst is the hydrogen ion, because there is information on the distribution of hydrogen ions between water and anionic micelles of NaLS.[15,16]

The apparent low catalysis by NaLS is unusual because an alkyl dihydropyridine should be sufficiently hydrophobic to be incorporated into the micelle, and one of our prime aims was to understand the significance of this small effect. In addition we planned to analyze the relation between rate and surfactant concentration in terms of the distribution of hydrogen ions between water and the micelle.[15,16] These relations have been interpreted in terms of the distribution of reagents for acetal hydrolysis[15] and for a number of nucleophilic substitutions and additions,[17] and a general theoretical model has been derived,[18] but this approach has not been used extensively for reactions of hydrophilic ions. In addition, the kinetic form of the micellar catalysis is complex because it depends not only upon the incorporation of reagents into the micelle but also upon increased formation of an unreactive conjugate acid. We also planned to use a micelle which was itself a buffer and we therefore also examined the buffer catalysis in water and the kinetic solvent isotope and electrolyte effects in the absence of micelles.

Results

Reactions in the Absence of Surfactant. Strong Acid. The first-order rate constants of hydration in aqueous acid are illustrated in Figure 1. In dilute HCl at 25.0 °C the second-order rate constants, k_H ($k_H = k_\psi/[H^+]$), are 16.0 and 0.44 M^{-1} s^{-1} for **1a** and **1b**, respectively. The small differences between these and other rate constants[6] are probably due to differences in the ionic strengths of the reaction solutions. The reaction is first order with respect to hydrogen ion concentration in dilute acid, but with increasing acid concentrations the rate constants for the acetyl derivative (**1b**) reach maxima

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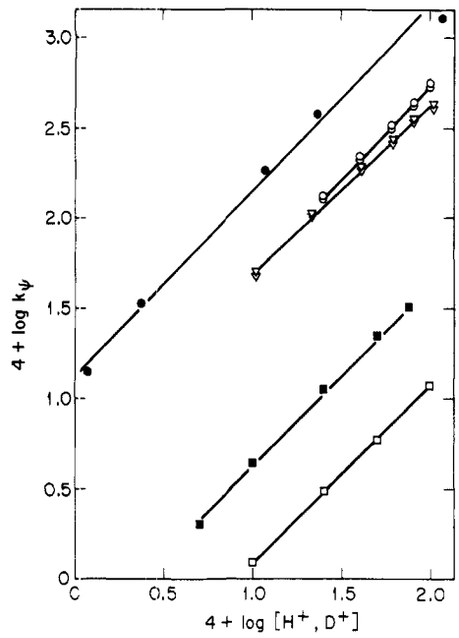


Figure 1. Hydration in dilute acid: **1a** HCl, ●; DCl, ○; D_2SO_4, ◇; **1b**, HCl, ■; DCl, □.

at ca. 1 M HCl and then fall slightly. The hydration of the acetamido derivative (**1a**) becomes too fast for us to observe a rate maximum (Figure 2).

The levelling of the rate constants with increasing acidity is general for these derivatives[6] and can be ascribed to buildup of unreactive cation (**3**, $HS^{+\prime}$). The structure of $HS^{+\prime}$ is probably **3**, and of HS^+, **2**.

Scheme I leads to eq 1, provided that protonation of the substrates to HS^+ or $HS^{+\prime}$ follows hydrogen ion concentration rather than any other function of acidity. Rearrangement of eq 1 gives eq 2 which fits the experimental data reasonably well (Figure 2) and gives for the acetamido derivative (**1a**) $k_H = 15.6\ M^{-1}\ s^{-1}$ and $pK_a = 0.62$, and for the acetyl derivative (**1b**) $k_H = 0.47\ M^{-1}\ s^{-1}$ and $pK_a = 0.87$. These equilibrium constants are in the expected range and the rate constants agree with those determined in dilute HCl even though the rate and equilibrium constants in Scheme I may follow some acidity function rather than hydrogen ion concentration, and protonation may not be wholly rate limiting when the water activity begins to decrease (cf. ref 5).

Scheme I

$$HS^{+\prime} \underset{K_a}{\overset{H^+}{\rightleftharpoons}} S \xrightarrow[H^+]{k_H} HS^+ \xrightarrow[\text{fast}]{H_2O} \text{products}$$

$$k_\psi = k_H K_a[H^+]/([H^+] + K_a) \quad (1)$$

$$1/k_\psi = 1/k_\psi K_a + 1/k_H[H^+] \quad (2)$$

Kinetic Salt Effects in Strong Acids. There are positive salt effects on the hydration of **1a** in dilute HCl (Table I). Salts typically increase acidity,[19-21] and our rate effects follow the expected form of eq 3:

$$\log k_s/k_0 = K_s[\text{salt}] \quad (3)$$

where k_s and k_0 are the rate constants in the presence and absence of added salt.

We see little dependence upon the nature of the salt, although salt effects are often highly specific, especially for Al reactions. In addition, the effects are smaller than those upon many Al reactions and acidity as measured by H_0' or H_R suggesting that the magnitude of the salt effects is related to the extent of proton transfer in the transition state.[21]

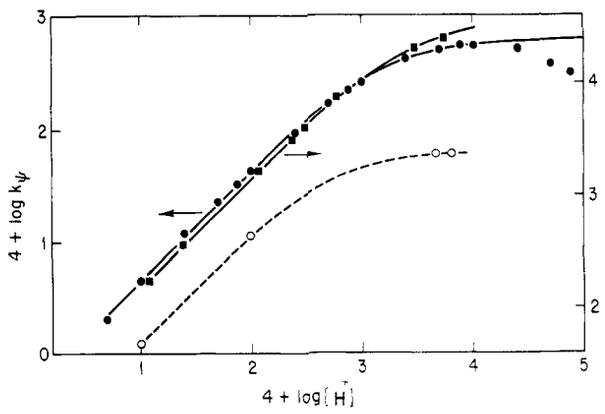


Figure 2. Hydration in moderately concentrated HCl (DCl broken line): **1a**, ■; 1b, ●, ○. The curves are calculated.

Table I. Salt Effects on Hydration in Dilute Acid[a]

Salt	K_s	Salt	K_s
LiCl	0.21	$NaClO_4$	0.23 (0.31)
LiBr	0.22	$NaNO_3$	0.23
$LiClO_4$	0.19	KCl	0.21
NaCl	0.31 (0.26)	KBr	0.31
NaBr	0.31	KNO_3	0.19

[a] At 25.0 °C with 5×10^{-3} M HCl, 0.5–2 M salt, and **1a**. The values in parentheses are for hydration of **1b**.

Table II. General Acid Catalysis[a]

Buffer	[HA]/[A]	$10^2 k_{cat}$, $M^{-1}\ s^{-1}$ 1a	1b
Acetic	2	5.07	0.13
	2[b]	5.50	
	1	4.80	0.12
Formic	2	24.2	0.73
Chloroacetic	1	101	2.44
Cyanoacetic	1	137	3.37
	0.5[c]	113	2.41
H_3O^+		1600[d]	44[d]

[a] At 25.0 °C and 0.1 ionic strength with NaCl unless specified. [b] Ionic strength 0.05. [c] Ionic strength 0.2. [d] Dilute HCl.

The situation is different for reactions of the acetyl derivative (**1b**) in 1 M HCl where added salts either have a very small positive effect or retard reaction; in the absence of salt $10^3 k_\psi = 52\ s^{-1}$ and with added 2 M NaCl and 2 M $NaClO_4$ the respective values are 56.9 and 46.2 s^{-1}. These results are readily understandable because in the more acidic solutions protonation of the substrate generates unreactive conjugate acid. Added salts increase this protonation and this inhibitory effect offsets the normal positive kinetic salt effect. Apparently with sodium perchlorate, which decreases the first-order rate constant, k_ψ, the inhibitory effect is the more important.

Buffer Catalysis. These hydrations are general acid catalyzed, and the catalytic constants are in Table II. These constants depend slightly upon the reaction media, probably because of the specific electrolyte effects of chloride and carboxylate ions. The catalytic constants for the carboxylic acids follow the Bronsted catalysis law[22] although those for the hydrogen ion in dilute HCl are low as is often found. For catalysis by carboxylic acid $\alpha = 0.6$ for both substrates, and is in the range found for other enamine protonations.

Kinetic Solvent Hydrogen Isotope Effects. Hydrations in dilute strong acid show normal hydrogen isotope effects[23]

Table III. Hydrogen Solvent Isotope Effects in Moderately Concentrated Acid[a]

[HCl], [DCl], M	$10^4 k_\psi$, s^{-1} H_2O	D_2O	k_{H_2O}/k_{D_2O}
0.46	48	58.8	8.2
0.69	52	59.2	8.8
0.92	52	58.9	8.8
2.30	50	56.6	8.8

[a] At 25.0 °C with the acetyl derivative (**1b**) in HCl and DCl. The values of k_{H_2O} are interpolated where necessary.

(Figure 1) with k_{H_2O}/k_{D_2O} = 3.67 for the acetyl derivative (**1b**) and 3.2 for the acetamido derivative (**1a**) in the range HCl (DCl) of 0.001–0.01 M, but there are larger effects for the formic acid catalyzed reaction. In D_2O with sodium formate–formic acid 1:2, formic acid 0.02–0.1 M, and ionic strength 0.1 (NaCl), k_{cat} = 0.0457 and 0.00119 M^{-1} s^{-1}, for **1a** and **1b**, respectively, giving k_{H_2O}/k_{D_2O} = 5.3 and 6.2. These differences could be related both to differences in the extents of proton transfer in the transition state and to the secondary solvent isotope effects.

For lyonium ion transfer the normal primary isotope effect will be opposed by an inverse secondary isotope effect as the lyonium ion is converted into water with proton transfer.[24] The maximum inverse isotope effect has been estimated as k_{H_2O}/k_{D_2O} = 0.61,[24] on the assumption that the positive charge of the hydronium ion is largely lost in the transition state. The overall normal isotope effects of 3.2 and 3.67 for proton transfer to **1a** and **1b**, respectively, from lyonium ion suggest that there is a primary hydrogen isotope effect of ca. 6 which is partially offset by the inverse secondary effect. This secondary effect should be much less important in the formic acid catalyzed hydration (cf. ref 6).

These normal isotope effects upon the proton transfers are in the range expected for a reaction in which the zero point energy of the proton is lost in forming the transition state, and are consistent with the Bronsted α value of 0.6.

The kinetic solvent deuterium isotope effects on hydration of **1b** increase with increasing acid concentration (Figure 2 and Table III) where the unreactive conjugate acid (**3**) builds up in concentration because this conjugate acid is weaker in deuterium oxide than in water.[24] This additional secondary solvent isotope effect therefore augments the usual primary isotope effect in the hydrogen ion transfer, and the overall isotope effect reaches a maximum value of 8.8 when the bulk of the substrate is protonated.

In dilute hydrochloric or formic acid buffer where there is no substrate protonation the kinetic solvent deuterium isotope effect is smaller for the acetamido derivative (**1a**) than for the acetyl derivative (**1b**). The differences may depend on the extents of proton transfer, but there could also be a secondary effect due to isotopic exchange into the acetamido group, because this group is conjugated with the forming cationic center in the transition state.

Micellar Effects. As expected, anionic micelles catalyze and cationic micelles inhibit the hydrogen ion catalyzed hydration.[8-12] Although we see extensive inhibition the catalysis by NaLS is small, and in order to understand this behavior we need evidence on substrate incorporation in the micelles (see Experimental Section).

Substrate Incorporation. The extent of substrate binding to the micelles has been estimated spectrophotometrically[25] and by solubility,[17,26] and we write the binding constant K as:[27]

$$K_M = [S_M]/[S]([D] - cmc) \quad (4)$$

Table IV. Binding Constants[a]

Solute	Surfactant CTABr		NaLS	
1a	453	460[c]	285	
1b	409	488[b] 370[c]	405	423[b]

[a] Values of K, M^{-1}, determined spectrophotometrically except where specified. [b] Determined by solubility. [c] Determined kinetically.

where S and S_M are the substrate in water and in the micelle, respectively, D is the surfactant (detergent), and cmc is the critical micelle concentration.

Determination of binding constants by the solubility method (Experimental Section) assumes that any increase in solubility is caused by incorporation of the substrate into the micelles, and that there is no material change in the micellar properties. In addition, the substrate should be only slightly soluble in water so that it does not change the nature of the bulk solvent. This method fails if the substrate is decomposed, and therefore we only used it with the less reactive **1b**. However, the spectrophotometric and solubility methods agree (Table IV), and they also agree with gel filtration results for incorporation of **1a** into CTABr.[28]

The binding constants of the acetyl derivative (**1b**) toward micellized CTABr and NaLS are very similar (Table IV), but the acetamido derivative (**1a**) binds more strongly to CTABr than to NaLS. Quaternary ammonium ions interact strongly with polarizable solutes, and cationic micelles readily incorporate aromatic solutes, especially those which have electron releasing and hydrophobic groups.[14,29] The acetyl group is more hydrophobic than the acetamido group, and therefore **1b** should be bound more strongly than **1a** to a micelle, as with anionic micelles of NaLS, but not with CTABr. The greater binding to CTABr of the acetamido derivative (**1a**) is therefore probably due to the greater electron withdrawing power of the acetyl group, which would reduce the interaction of the dihydropyridine group with the quaternary ammonium head groups of micellized CTABr.[29]

Inhibition by Cationic Micelles. The inhibition (Figure 3) can be treated quantitatively on the assumption that the substrate is partitioned between water and the micelles but that hydrogen ions are excluded from the micelle (Scheme II, where D_M is a micelle).[8-11,30]

The usual treatment of the inhibition follows eq 5:

$$k_\psi = \{k_W' + k_M' K_M([D] - cmc)\}/\{1 + K_M([D] - cmc)\} \quad (5)$$

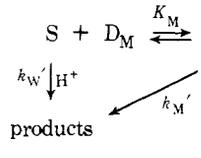
where k_W' and k_M' are first-order rate constants in water and the micelle, respectively. Although this equation works well in some systems it fails with hydrophobic substrates which decrease the cmc,[26] as is the case with these dihydropyridines. However, if we assume that $k_M' = 0$ we obtain eq 6:

$$(k_W'/k_\psi) - 1 = ([D] - cmc)K_M \quad (6)$$

Plots of $(k_W'/k_\psi) - 1$ against [D] are linear with slopes K_M given in Table IV, and the intercepts at ca. 4×10^{-4} M CTABr show that these substrates strongly decrease the cmc.

These kinetically derived association constants agree with the binding constants calculated physically, which supports

Scheme II



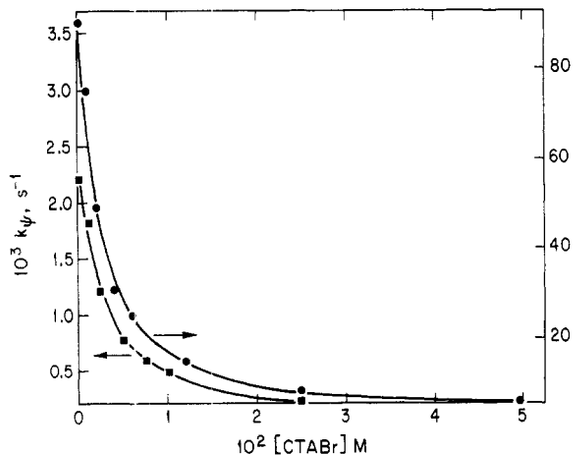


Figure 3. Micellar inhibition by CTABr: ●, **1a** in 0.0058 M HCl: □, **1b** in 0.005 M HCl. The curves are calculated.

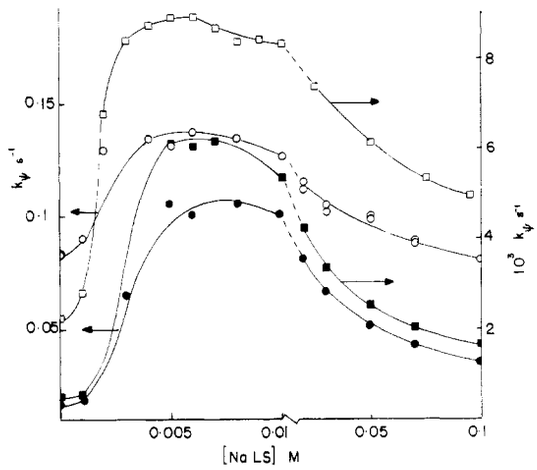


Figure 4. Micellar catalysis by NaLS. Solid points in 0.001 M HCl, open points in 0.005 M HCl: **1a**, ●, ○; **1b**, ■, □.

the validity of our kinetic treatment. Our kinetically estimated cmc for CTABr of ca. 4×10^{-4} M is lower than the values of 7×10^{-4} M estimated spectrophotometrically (Experimental Section) in part because of the effect of the added HCl. The curves in Figure 3 were calculated using these parameters and eq 6.

Catalysis by Micelles of Sodium Lauryl Sulfate. The rate enchancements by NaLS are unusually small (Figure 4 and Table V) and the rate maxima are reached at low surfactant concentrations below the cmc of NaLS in water.[31]

Micellar catalysis is generally discussed in terms of the maximum rate enhancement of the micelle, but this approach is clearly inadequate for these reactions. For example, although the hydrations are second order in dilute aqueous HCl (Figure 1) the maximum rate constants in NaLS are almost the same in 0.001 and 0.005 M HCl (Figure 4 and Table V). Bimolecular reactions in aqueous surfactant solutions are often less than first order with respect to an ionic reagent,[8-11,15,26] but this large effect is unusual.

Therefore a dissection of the effects which govern micellar catalysis of bimolecular reactions is needed. In principle, the relation between rate constant and surfactant concentration can be treated quantitatively if we can estimate the concentrations of both reactants in the micellar and aqueous pseudo phases. The reaction is too fast for us to estimate the substrate concentration on the micelles in acidic solution, and so we are forced to carry out this determination in neutral solution.

The distribution of hydrogen ions between water and micelles of NaLS has been estimated by pH,[15] conductivity, and indicator measurements on the ionization of maleic acid[16] for a range of acid and surfactant concentrations. These three methods agreed well and a plot of $m^s_{H^+}$ against $[H^+]/([H^+] + [Na^+])$ was linear with slope 0.82 ($m^s_{H^+}$ is the number of hydrogen ions per micellized sulfate head group). This relation gives $m^s_{H^+}$ in terms of the total concentrations of HCl and NaLS and its significance will be discussed elsewhere.

The first-order rate constants k_W' and k_M', Scheme II, will depend on the concentrations of hydrogen ion in the aqueous and micellar pseudo phase, which are $[H^+_W]$ and $m^s_{H^+}$, respectively. For convenience we write $[H^+_W]$ as a molarity, and assume that the volume of the micelles is much less than that of water, but we write $m^s_{H^+}$ as a ratio of bound hydrogen ions to head groups in the micelle. We could alternatively use a different measure of concentration; for example, we could estimate the hydrogen ion concentration in terms of micellar volume, and this approach is discussed later.

The second-order rate constants for reaction in water, k_H, and in the micelle, k_M, are given by:

$$k_W' = k_H[H^+_W]; k_M' = k_M m^s_{H^+} \quad (7)$$

Table V. Maximum First-Order Rate Constants in Anionic Micelles[a]

	[HCl], M	
Substrate	0.001	0.005
1a	10.6 (6.6)	13.3 (1.7)
1b	0.63 (14.3)	0.88 (4)

[a] Maximum values of $10^2 k_\psi$, s^{-1}; the values in parentheses are the enhancements over the rate constants in the absence of surfactants.

(The units of k_H are M^{-1} s^{-1} and those of k_M are s^{-1}.)

The total molarity of hydrogen ions $[H^+_T]$ is:

$$[H^+_T] = [H^+_W] + m^s_{H^+}([D] - \text{cmc}) \quad (8)$$

Equations 5 and 8 relate the first-order rate constant, k_ψ, to the constants K_M, k_{H^+}, and k_M, and the concentrations of hydrogen ions in water and the micelles.

Rearranging eq 5 and 8 gives:

$$\frac{k_\psi\{1 + K_M([D] - \text{cmc})\} - k_H[H^+_T]}{([D] - \text{cmc})} = m^s_{H^+}(k_M K_M - k_H) \quad (9)$$

Several assumptions are made in deriving eq 9. (i) The value of k_W is that determined in dilute aqueous acid; i.e., we identify k_W with the second-order rate constant k_H. (ii) The association constant K_M is not affected by dilute HCl. This assumption turns out to be reasonable at the higher surfactant concentrations, but it may not be so when [NaLS] → cmc. (iii) The value of $m^s_{H^+}$ is unaffected by added substrate. (iv) The cmc for the reaction solution can be estimated from the values in the presence of dilute HCl and substrate, and we used 10^{-3} and 2×10^{-3} M as the cmc for reaction in 5×10^{-3} and 10^{-3} M HCl, respectively (cf. ref 15). These assumptions are those often made in treating micellar catalysis and inhibition, but they complicate analysis of the rate constants near the rate maxima where the surfactant concentrations are not much greater than the cmc under the kinetic conditions.

The left-hand side of eq 9 can be calculated from the experimental data and the values of $m^s_{H^+}$ are known from independent physical measurement.[15,16]

An example of our method of estimating k_M is given in Table VI. These values are not constant but decrease with increasing concentration of hydrogen ions in the micelle, $m^s_{H^+}$. However, the important feature is that our values of k_M at a given $m^s_{H^+}$ are not directly related to the total hydrogen ion

Table VI. Analysis of Rate Constants for Reaction of the Acetyl Derivative (1b) in NaLS[a]

10^3[NaLS], M	10^3k_Ψ, s^{-1}	$10k_M$, s^{-1}	$m^s_{H^+}$	$10k_\Psi/m^s_{H^+}$, s^{-1}
4	8.69	0.30	0.45	0.19
5	8.82	0.30	0.41	0.22
6	8.82	0.31	0.37	0.24
	(6.05)	(0.82)	(0.12)	(0.53)
7	8.62	0.32	0.34	0.25
8	8.38	0.32	0.32	0.27
8	(6.19)	(0.94)	(0.090)	(0.69)
9	8.43	0.34	0.29	0.29
10	8.32	0.36	0.27	0.31
10	(5.37)	(0.91)	(0.075)	(0.72)
20	(4.23)	(1.18)	(0.040)	(1.06)
25	7.37	0.57	0.14	0.54
30	(3.35)	(1.35)	(0.027)	(1.24)
50	6.12	0.84	0.074	0.83
50	(2.53)	(1.64)	(0.016)	(1.58)
70	(2.01)	(1.77)	(0.012)	(1.68)
75	5.32	1.05	0.051	1.04
95	4.93	1.21	0.041	1.20
100	(1.61)	(2.01)	(0.008)	(1.99)

[a] In 5×10^{-3} M HCl, except for values in parentheses which are for 10^{-3} M HCl.

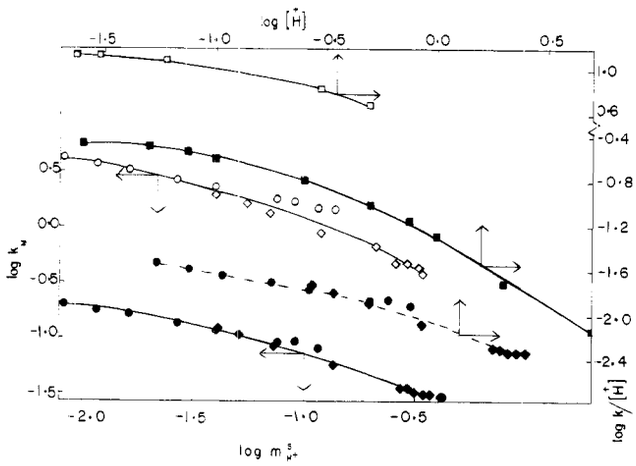


Figure 5. Variation of second-order rate constants for reactions in micelles of NaLS and in aqueous HCl. Open points are for reaction of **1a**, solid of **1b**. Reaction in aqueous HCl, □, ■; reaction in NaLS + 0.001 M HCl, ○, ●; reaction in NaLS + 0.005 M HCl.

concentration within the uncertainties of the method (Figure 5).

This behavior is similar to that shown in water where the second-order rate constant, $k_\Psi/[H^+]$, decreases steadily with increasing hydrogen ion concentration (Figure 2) because of formation of the unreactive cation (**3**), and anionic micelles should increase the protonation of the substrates just as they assist attack of hydrogen ions upon them.

In both water and the Stern layer of a micelle, hydrogen ions act in two ways: (i) they add to the double bond of the enamine substrate giving the cation (**2**) which is rapidly hydrated, and (ii) they convert the substrate into the unreactive cation (**3**). The kinetic form is very similar in both systems as shown in Figure 5 where we plot log k_M against log $m^s_{H^+}$ for reaction in the Stern layer and log $k/[H^+]$ against log $[H^+]$ for reaction in water (k is the first-order rate constant). In water it is easy to follow the reactions in solutions which are sufficiently dilute for there to be almost no buildup of unreactive cation and where we observe second-order kinetics (Figures 1 and 2).

The anionic micelle concentrates hydrogen ions into the

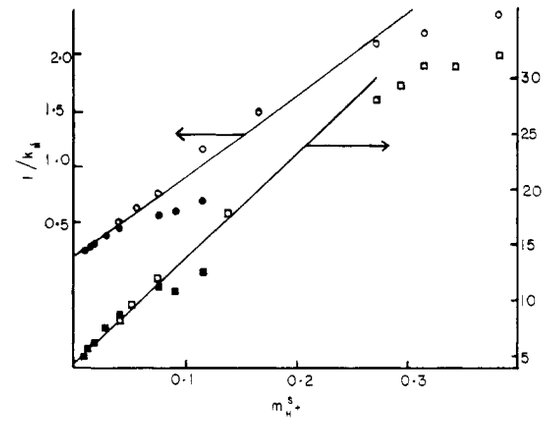


Figure 6. Estimation of rate and equilibrium constants for reactions in micelles of NaLS. Solid points in 0.001 M HCl, open in 0.005 M HCl: **1a**, ●, ○; **1b**, ■, □.

Stern layer so that there is extensive buildup of the unreactive cation (**3**) even when the total hydrogen ion concentration is only 10^{-3} M HCl.

The unreactive cation (**3**) should bind more strongly than nonionic substrate to the anionic micelle, but our binding constant, k_M, is for the substrate. However, ca. 90% of the substrate should be micellar bound at surfactant concentrations above those corresponding to the rate maxima (Figure 4).

Under these conditions essentially all the reaction occurs in the micelle and eq 9 can be approximated by eq 10:

$$k_\Psi = k_M m^s_{H^+} \tag{10}$$

The values of $k_\Psi/m^s_{H^+}$ approach those of k_M as the surfactant concentration increases (Table VI), suggesting that our values of k_M are not particularly sensitive to the value of the binding constant, K_M. An additional problem which we have already noted is that our treatment is least satisfactory for low surfactant concentrations because eq 7–9 involve the term [D] − cmc which is most subject to error at low surfactant concentrations.

Two distinct effects must be considered in explaining the small micellar catalysis of these hydrations. The micelle concentrates hydrogen ions in the small volume of the Stern layer, which increases the rate of attack on the double bond, but also increases the concentration of unreactive cation. This situation is different from the typical situation for bimolecular reactions where the rate maxima arise because of a "dilution" of reagents in the micellar pseudophase[15,17,18,26] with increasing surfactant concentration. In the present situation we have to consider both "dilution" of the reagents and unproductive substrate protonation.

On this hypothesis we should be able to treat reactions in the micellar pseudophase in terms of Scheme I for reaction in aqueous acid, and write:

$$1/k_M = 1/k_H{}^M + m^s_{H^+}/k_H{}^M K_a{}^M \tag{11}$$

(where $k_H{}^M$ is the second-order rate constant in the micelle, corrected for substrate protonation, and $K_a{}^M$ is the acid dissociation constant in the micelle. Both constants are related to the concentration in terms of hydrogen ion per sulfate head group.)

This approach is shown in Figure 6. It fails for low concentrations of NaLS, because of the approximations of our treatment which underestimates the extent of substrate binding at low surfactant concentration. The points for this region deviate from the line, and these plots would be nearer to linearity had we used values of $k_\Psi/m^s_{H^+}$ (Table VI) instead

of k_M, i.e., had we assumed total micellar incorporation of the substrate.

From the slopes and intercepts in Figure 6 we calculate for **1a** $k_H^M = 4.8\ s^{-1}$ and $K_a^M = 0.029$ and for **1b** $k_H^M = 0.22\ s^{-1}$ and $K_a^M = 0.048$. There is considerable uncertainty in these constants, but their magnitudes are not unreasonable, and their relation to the corresponding values in water will be discussed later. However, we note that these are true rather than apparent constants, which represent behavior in the micellar pseudophase.

All these observations suggest that the situation should be completely different for the micellar reactions followed at lower acidity. It is impracticable to do this by using very dilute strong acid and the usual approach of using buffers is unsatisfactory because micelles affect buffer equilibria. We therefore used *n*-dodecyl phosphate which micellizes and also forms its own buffer.

Reaction in Micellized Dodecyl Phosphate. Dodecylphosphoric acid is almost insoluble in water at 25 °C, and our aim was to use micelles of the monoanion. Unfortunately, the monosodium salt is also only sparingly soluble, but we were able to use a limited range of concentrations of the monopotassium salt (Table VII). We also tried to use large chain alkanecarboxylic acids in the same way, but although the alkali metal salts are soluble precipitation occurs when carboxylic acid is present. In both systems hydrogen bonding between acid and anion probably causes the low solubility.

The monopotassium salt is an effective catalyst for the hydrations when related to the measured pH of the solutions, which is ca. 7. (The low acidity in the water is understandable because most of the acidic species should be in the micelle.)

We cannot measure the binding constants of our substrate to micelles of potassium dodecyl phosphate, but comparison with binding to micellized NaLS (Table IV) suggests that the bulk of the substrate is bound at the higher surfactant concentrations.

The first-order rate constants decrease at relatively high surfactant concentration (Table VII), and added KCl inhibits the reaction. The rate constants also decrease as the monoanion is partially converted into the dianion, but the solubility increases so that we can follow a wider concentration range and observe a rate maximum.

Although the surfactant is largely monanionic we cannot assume that the head groups in the micelle are monoanionic. If we treat the micelle as a separate phase (i.e., as a pseudophase) we must also consider acid–base equilibria in that phase. Coulombic repulsions between head groups will be reduced if some of the hydrogen phosphate monoanions are converted into undissociated phosphoric acid, with release of an equivalent number of hydroxide ions to the water. This acid–base equilibrium on the micellar surface will be affected by added potassium ions which enter the Stern layer and reduce the coulombic repulsions between anionic head groups and so favor the acid dissociation of phosphate head groups in the micelle.

These qualitative considerations show how potassium ions can reduce the catalysis by promoting dissociation of acidic groups in the Stern layer, although it is difficult to account quantitatively for the effects, because added cations will change the micellar structure. It is also implicitly assumed that the micelles do not contain appreciable amounts of hydrogen ions, in view of the relatively high pH of the water. The solubility behavior of potassium hydrogen dodecyl phosphate in water makes it difficult to study the micellar structure by such physical methods as cmc measurement, but monomeric surfactant at pH 7 should be largely dianionic while that in the micelle will be monoanionic and undissociated acid.

The reactions are slow at pH 7 in the absence of added catalysts. For example, the reaction due to hydrogen ion catalysis would have first-order rate constants of ca. 1.6×10^{-6} and $4.4 \times 10^{-8}\ s^{-1}$ for **1a** and **1b**, respectively, and for reaction in 1 M KCl the first-order rate constants of the water-catalyzed reactions are ca. 8×10^{-7} and $2 \times 10^{-7}\ s^{-1}$ for **1a** and **1b**, respectively.[6] Therefore the reactions in the presence of micelles of potassium hydrogen *n*-dodecyl phosphate are faster than those in the aqueous pseudophase by factors of approximately 10^3. Our initial rate constants in unbuffered water at pH 5.7 and in low concentrations of the surfactant (Table VII) are consistent with this estimate.

Table VII. Catalysis by Potassium Dodecyl Phosphate[a]

10^3[surfactant], M	KCl, M	Substrate 1a	Substrate 1b
		~2	
0.5		~4	
1.0		~6	
7.0		(62.3)	
8.0		(66.1)	
9.0		(70.0)	
10.0		(72.4)	
20.0		(66.9)	
50.0		252.0 (49.9)	8.99
50.0	0.025	133.0	4.83
50.0	0.05	115.0	4.09
50.0	0.10	96.7	3.59
70.0		192.0	6.72
70.0	0.025	108.0	3.84
70.0	0.050	96.6	3.65
70.0	0.10	87.7	3.48
100		158.0	5.27
100	0.025	97.4	3.10
100	0.050	91.8	2.83
100	0.10	87.2	2.78

[a] Values of $10^5 k_\Psi$, s^{-1} at 25.0 °C with *n*-$C_{12}H_{25}OPO_3HK$. The values in parentheses are for comicelles of 70% monoanion and 30% dianion.

Although we could not reach the optimum concentration of micellized monoanionic dodecyl phosphate (Table VII), the first-order rate constants in 0.05 M surfactant are approximately the same as those estimated for pH 3.5–4 in water. The pH of a solution of a monoanionic monoalkyl phosphate in water is ca. 4; e.g., for *n*-butyl phosphate $pK_1 = 1.8$ and $pK_2 = 6.84$,[33] so that the first-order rate constants in micellized dodecyl phosphate are, perhaps fortuitously, almost the same as those estimated for reaction in water at the pH of aqueous monoalkyl phosphate monoanion.

These results show that the micelle allows a marked difference in acidity to exist at its surface over that in bulk solvent. This situation is well understood in polyelectrolyte chemistry and is probably also important in catalysis by general acids at active sites of enzymes.

Kinetic Form of the Reaction in NaLS. The second-order rate constants in the micelle, k_M, s^{-1}, cannot be compared directly with those in water, k_{H^+} ($M^{-1}\ s^{-1}$). One approach is to express the concentration of hydrogen ions in water as a mole fraction and to compare k_M with $k_{H^+}/55.5$. Another is to express the second-order rate constants in the micelle in terms of the molarity of hydrogen ions in the micellar pseudophase. Reaction occurs in the Stern layer of the micelle and to follow this second approach we estimate the volume of this layer in 1 mol of micellized surfactant. Micelles have a density of approximately 1, and Romsted has estimated that the volume of the Stern layer of a micelle of NaLS is 51% of the total volume of the micelle.[18] These estimated values and the molecular weight of NaLS give a volume of Stern layer of 0.149 L mol^{-1}. Therefore the concentration of hydrogen ions in the Stern layer is $6.71 m^s_{H^+}$ M, and the corresponding second-order rate constant is 0.149 k_M, $M^{-1}\ s^{-1}$.

Table VIII. Comparison of Rate and Equilibrium Constants in the Micelle and in Water[a]

	H_2O		NaLS	
Substrate	k_H	K_a	k_H^M	K_a^M
1a	16.0	0.24	0.7 (4.8)	0.20 (0.029)
1b	0.44	0.13	0.033 (0.22)	0.32 (0.048)

[a] Calculated in terms of molarities; the values in parentheses are calculated in terms of mole fractions.

We have converted our values of k_M and $m^s_{H^+}$ for reaction in micelles of NaLS to a molar scale, and the results for **1b** are shown as the broken line in Figure 5. The pattern is similar for reaction of **1a.** The important point is that the second-order rate constants for reaction in the Stern layer are smaller than in water. They are also smaller in the Stern layer if comparison is based on values of $m^s_{H^+}$ and the mole fraction of hydrogen ions in water. Similar differences in rate constants were found for the hydrogen ion catalyzed hydrolysis of *p*-nitrobenzaldehyde diethyl acetal in micellized NaLS.[15]

The overall rate constants, k_M, depend upon the extent of unproductive substrate protonation, which gives **3.**

It is therefore necessary to compare the corrected rate, k_H^M, and equilibrium constant, K_A^M, for the reactions in the micelle, obtained using eq 11 and Figure 6, with those of k_H and K_a in water. This is done by correcting the constants for reactions in the micelle following Romsted's approach.[18] The comparisons are shown in Table VIII.

The acid dissociation constants are similar in the micelle and in water, and although it may not be realistic to compare concentrations in terms of these arbitrary volume elements the results suggest that micellar effects on protonation depend largely on the concentration of the bases **1a,b** and the hydrogen ions in the Stern layer. The corrected second-order rate constants, k_M^H, are considerably lower in the micelle than in water.

These decreases in rate constants probably arise in part from the Stern layer of the micelle having a lower polarity than water;[8,34] i.e., they can be ascribed to a microsolvent effect. Another possibility is that micellized laurylsulfuric acid is not strong and that it is a poorer catalyst than the solvated hydrogen ion, although this is not consistent with the effective catalysis by dodecyl hydrogen phosphate, or the evidence for substrate protonation. Addition of water to the first formed intermediate (**2**) may become slow in the Stern layer, but this too seems improbable because the micellar surface is hydrophilic and water addition is slow only in solvents of low water content.[5] Our results are not in accord with the plausible suggestion that the reactivity of hydrogen ions at a micellar surface is increased by partial or complete dehydration.

The decrease in the second-order rate constants in going from water to the micelle means that the micelle stabilizes the rectants more than the transition state relative to water. Extensive reactant incorporation in the micelles requires reactants to be more stable there than in the water, based on unit concentration, and this unfavorable initial state effect may overcome any favorable interactions between the micelle and the transition state.

Micellar Catalysis of Bimolecular Reactions. The high rates of many intramolecular reactions, relative to similar intermolecular reactions, are often explained in terms of favorable entropy effects.[35] Similar explanations are often applied to enzymic reactions, and they can be applied to micellar catalysis. However, the description which we use depends to some extent on our choice of standard state. Bimolecular reactions in the Stern layer of micelles are often no faster and may even be slower than in water,[15-18] once allowance is made for reactant concentrations in the Stern layer, and this concentration can be considered as an entropy effect. These general principles also apply to protonation equilibria; for example, we require ca. 1 M HCl to convert these dihydropyridines into their unreactive conjugate acids (**3**), but there is extensive protonation in micelles of NaLS even when the total hydrogen ion concentration is only 10^{-3} M.

Although the micelle does not provide a favorable submicroscopic environment for these, and other, reactions of hydrogen ions there are many examples of favorable environmental micellar effects, as in unimolecular micellar catalyzed reactions.[11]

Experimental Section

Materials. The dihydropyridines were prepared by reduction of the pyridinium salts and were purified by crystallization from EtOH–H_2O[4a] or by dissolving the product in CH_2Cl_2, separating the impurities in the insoluble red layer, and then precipitating the product with petroleum ether (bp 30–60 °C). The melting points were: **1b,** 113.5–114.5 °C (lit.[4a] 110–114 °); **1b,** 63–67 °C (lit.[4a] 61–67 °C). The λ_{max}(EtOH) of 358 and 371 nm for **1a** and **1b**, respectively, agreed with literature values. The surfactants were prepared and purified by standard methods.[26,36]

Kinetics. The reactions at 25.0 °C were followed spectrophotometrically at 359 nm for **1a** and 377 nm for **1b.** The first-order rate constants, k_ψ, are in s^{-1}. Solutions were made up using redistilled deionized water, and for the buffer-catalyzed reactions the ionic strength was maintained with NaCl. For reactions in NaLS and HCl freshly made up solutions were always used to avoid hydrolysis of the surfactant.[37] The substrate concentrations were 6.7×10^{-5} M.

Incorporation Experiments. Solubility Method. The solubilities were determined in deoxygenated water and in a range of surfactant solutions. The solutions were saturated and left at 25.0 °C, and the relative solubilities were determined spectrophotometrically.

From eq 4 we obtain:

$$\alpha = \frac{C_0K([D_T] - \text{cmc})}{1 + C_0K} \tag{12}$$

where α is the amount of substrate taken up by the micelles and C_0 is the solubility in water. The maximum total surfactant concentration $[D_T]$ was 0.1 M for NaLS and 0.02 M for CTABr, and the relative solubility of **1b** was determined from the absorbance at 377 nm, after sufficient dilution to break up the micelles.

Spectrophotometry. This method requires that the substrate has different absorbances in water and in the micelle, and that Beer's law is obeyed. For the equilibrium between substrate in water (S) and in the micelle (S_M) eq 4 gives:

$$K = f/\{(1 - f)([D] - \text{cmc}) - f(1 - f)[S_T]\} \tag{13}$$

where $f = [S_M]/[S_T]$. Under our conditions $[D] - \text{cmc} \gg f[S_T]$, so that

$$K = f/(1 - f)([D] - \text{cmc}) \tag{14}$$

and assuming that Beer's law is obeyed:

$$f = (A - A_{H_2O})/(A_M - A_{H_2O})$$

where A is the observed absorbance, A_{H_2O} is that in water, and A_M is that when all the substrate is incorporated into the micelle.

The wavelengths were: for **1a,** 358 nm in CTABr, 390 nm in NaLS; and for **1b,** 395 nm in CTABr, 395 and 405 nm in NaLS. Maximum [NaLS] was 0.3 M and the maximum [CTABr] was 0.09 M. A plot of $f/(1 - f)$ vs. [D] was linear and the intercept gave the cmc. The concentration of the dihydropyridines was 6.7×10^{-5} M.

The cmc calculated using eq 14 are: with **1a,** CTABr, 7×10^{-4} M, NaLS, 2×10^{-3} M; and with **1b,** CTABr, 7×10^{-4} M, NaLS, 3×10^{-3} M.

Registry No.—**1a,** 952-92-1; **1b,** 19350-64-2; NaLS, 151-21-3; potassium dodecyl phosphate, 65045-37-6; CTABr, 54-09-0.

References and Notes

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Isoxazoles. 4. Hydrolysis of Sulfonamide Isoxazole Derivatives in Concentrated Sulfuric Acid Solutions. A New Treatment of the Medium Effects on Protonation Equilibria and Reaction Rates

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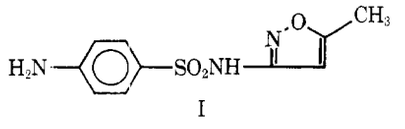
The acid hydrolysis of N^1-(5-methyl-3-isoxazolyl)sulfanilamide (I) and N^1-(3,5-dimethyl-4-isoxazolyl)sulfanilamide (II) to sulfanilic acid and their respective amino isoxazole derivatives in concentrated solutions of sulfuric acid was studied. An approach to correlate the medium effects on equilibria and reaction rates was made by introduction of a function, which represents the protonating ability of sulfuric acid solutions. The medium effects study has shown that I undergoes hydrolysis through protonation on the heterocyclic N atom, while II needs to be protonated on the sulfonamide group. The lower reactivity of II can be explained as mainly due to a more weakly basic site of protonation and a lower log ($f_S/f_{\pm}$) response toward changes in acidity.

We have previously reported[1-3] that the acid-catalyzed degradation of N^1-(3,4-dimethyl-5-isoxazolyl)sulfanilamide (III) in concentrated mineral acids occurs through two parallel pathways, one is the sulfonamide moiety hydrolysis and the other the isoxazole ring rupture. Both pathways can be associated with a preprotonation on the isoxazole N atom.

We here report a kinetic study of the hydrolysis of I and II in concentrated sulfuric acid solutions. Since Zuker and Hammett works[4] the study of medium effects on reaction rates in concentrated solutions of mineral acids has been focused by a method involving the correlation of rates with acidity functions[5,6] ($H_x = -\log (a_{H^+} f_X / f_{XH^+})$) or related magnitudes.[7] Such functions are built up from the measurements of the protonation equilibria of structurally related indicators and they involve the assumption that the ratio of activity coefficients of the acidic and basic forms of the indicators are the same within each set; however, this is not strictly true and few differences are found even within the set.



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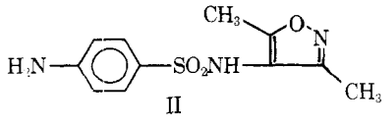

II

On the other hand, some efforts have been made in order to rationalize medium effects on reaction rates correlating them with representative magnitudes of some properties of the acid solutions, namely water activity[8] (a_{H_2O}) and more recently sulfuric acid activity[9,10] ($a_{H_2SO_4}$). However, there is no representative variable of some acid solution properties, with the exception of acidity functions, which can be applied in a wide concentration range. In this paper an alternative treatment is proposed.

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