°C for 12 half-lives. The products were isolated as described in the preceding section. Analytical GC showed that the product distribution was 40% **15** and 60% of a mixture of **14**-$OCH_3$ and **16**-$OCH_3$. This mixture could not be resolved by analytical GC and the composition of a sample isolated by preparative GC was determined by NMR as a 1:2 mixture of **14**-$OCH_3$ and **16**-$OCH_3$. Thus, methanolysis of **11** gives 40% **15**, 20% **14**-$OCH_3$, and 40% **16**-$OCH_3$. The optical rotation of pure **15**, isolated by preparative GC, was $[\alpha]^{25}D$ −141°. The mixture of 33% **14**-$OCH_3$ and 66% **16**-$OCH_3$ had $[\alpha]^{25}D$ −2.10° (*c* 0.428, $CHCl_3$). Pure **16**-$OCH_3$ was separated from this mixture by column chromatography (80:20 mixture of $Al_2O_3$ and $AgNO_3$ with pentane as eluent) and showed no activity at 589, 578, 546, 436, or 365 nm, (*c* 0.413 $CHCl_3$): NMR ($CCl_4$) δ 3.40 (s, 1 H, C-3 methine proton), 3.16 (s, 3 H, methoxy methyl), 1.9 (s, 1 H, bridgehead), 0.8–1.76 (m, 4 H), 1.2 (s, 3 H), 1.1 (s, 3 H), 0.48 (s, 1 H, cyclopropyl). The rotation of **14**-$OCH_3$, corrected for contamination with 66% racemic **16**-$OCH_3$ is $[\alpha]^{25}D$ −6.0° (*c* 0.14, $CHCl_3$). Optical purities of the products and the average optical purity of the (−)-**11** during methanolysis (91% × $k_t/k_\alpha$) are shown under eq 2.

Authentic samples of optically active **15** and **14**-$OCH_3$[17] were shown to be optically stable under conditions of the solvolysis and isolation of the products.

**Acknowledgment.** This work was supported by the National Science Foundation (MPS75-15879) and the Air Force Office of Scientific Research (AFOSR-71-1974).

## References and Notes

(1) (a) H. L. Goering and K. Humski, *J. Am. Chem. Soc.*, **90**, 6213 (1968); (b) H. L. Goering and J. V. Clevenger, *ibid.*, **94**, 1010 (1972).
(2) H. L. Goering, C.-S. Chang, and J. V. Clevenger, *J. Am. Chem. Soc.*, **96**, 7602 (1974).
(3) H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 5004 (1964).
(4) G. D. Sargent in "Carbonium Ions", Vol. III. G. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972.
(5) The rate constant for solvolysis of 1,2-dimethyl-*exo*-2-benzonorbornenyl *p*-nitrobenzoate in 90% acetone at 100 °C ($7.62 \times 10^{-5}$ $min^{-1}$) is approximately five times larger than that for 2-methyl-*exo*-2-benzonorbornenyl *p*-nitrobenzoate ($1.44 \times 10^{-5}$ $min^{-1}$), W.-S. Chang, unpublished results.
(6) C. F. Wilcox, Jr., L. M. Loew, R. G. Jessitis, S. Belin, and J. N. C. Hsu, *J. Am. Chem. Soc.*, **96**, 4061 (1974).
(7) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 2540 (1970).
(8) H. C. Brown, E. N. Peters, and M. Ravindranathan, *J. Am. Chem. Soc.*, **97**, 7449 (1975).
(9) (a) S. Winstein and M. Shatavsky, *J. Am. Chem. Soc.*, **78**, 592 (1956); (b) J. B. Lambert and A. G. Holcomb, *ibid.*, **93**, 2994 (1971).
(10) (a) S. J. Cristol and D. A. Bermborn, *J. Am. Chem. Soc.*, **95**, 3651 (1973); (b) S. J. Cristol, T. C. Morrill, and R. A. Sanchez, *ibid.*, **88**, 3087 (1966).
(11) H. C. Brown and E. N. Peters, *J. Am. Chem. Soc.*, **97**, 7442 (1975).
(12) G. A. Olah and G. Liang, *J. Am. Chem. Soc.*, **97**, 1920 (1975).
(13) K. Mislow and J. G. Berger, *J. Am. Chem. Soc.*, **84**, 1956 (1962).
(14) Structures for active compounds show absolute configurations.
(15) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **74**, 1154 (1952).
(16) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).
(17) H. L. Goering and C.-S. Chang, *J. Org. Chem.*, **40**, 3276 (1975).
(18) For *exo*-**10** in 80% acetone at 100 °C, $k_t = 4.9 \times 10^{-4}$ $min^{-1}$.[11] For a related tertiary system, 2-methylbenzonorbornen-*exo*-2-yl *p*-nitrobenzoate, at 121 °C $k_t$ is four times larger for 80% than for 90% acetone (W.-S. Chang, unpublished results). Thus the calculated value for *exo*-**10** in 90% acetone is $1.2 \times 10^{-4}$ $min^{-1}$ or about one-third the value for **11** in Table I.
(19) H. L. Goering and K. Humski, *J. Org. Chem.*, **40**, 920 (1975).
(20) S. Bruckenstein, *Anal. Chem.*, **28**, 9920 (1956).
(21) W. L. Dilling, R. D. Kroening, and J. C. Little, *J. Am. Chem. Soc.*, **92**, 928 (1970).
(22) W. D. Closson, P. Wriede, and S. Bank, *J. Am. Chem. Soc.*, **88**, 1581 (1966).
(23) D. B. Denney and B. Goldstein, *J. Am. Chem. Soc.*, **79**, 4948 (1957).

# Positive Cooperativity in Micelle-Catalyzed Reactions

**Dennis Piszkiewicz**

*Contribution from the Department of Biological Chemistry, California College of Medicine, University of California, Irvine, California 92717.* *Received July 30, 1976*

**Abstract:** The rate constants of micelle-catalyzed reactions when plotted vs. detergent concentration give sigmoid shaped curves. This behavior is analogous to positive cooperativity in enzymatic reactions, a sigmoid shaped dependence of velocity on substrate concentration. A kinetic model analogous to the Hill model, which describes enzymatic reactions, accommodates published data on the rate constants of micellar reactions as a function of detergent concentration. According to this model, plots of log $[(k_{obsd} - k_0)/(k_m - k_{obsd})]$ vs. detergent concentration are linear, and have slopes equal to the empirical constant *n*; the term log $[D]_{50}$ is also easily ascertained from these plots as that detergent concentration at which the rate constant of micellar catalysis is one-half of its maximal value. Published data on the dependence of rate constants on detergent concentration were evaluated according to this model. Values of *n* ranged from approximately 1 to 6 with the vast majority of reactions having values of *n* below 3. For a given reaction, the nature of the detergent appeared to have an effect on both log $[D]_{50}$ and *n*. Log $[D]_{50}$ paralleled the log of the critical micelle concentration for a variety of detergents catalyzing the hydrolysis of methyl orthobenzoate, but the two were not related in a simple manner. When a single detergent was employed, and variations in the structure of the substrate were made, effects were seen on both log $[D]_{50}$ and *n*. However, major structural variations in the substrates were required; alterations of electronic inductive effects were not always sufficient. The inhibition and activation of micelle-catalyzed reactions by substances which are neither substrate nor detergent could be described in analogy with the terminology of enzymology. V-type inhibitors and activators are substances which affect the maximum attainable velocity; K-type inhibitors and activators are substances which affect the value of log $[D]_{50}$. Examples of V-type inhibitors, V-type activators, and K-type inhibitors of micelle-catalyzed reactions were found. In addition to having their effects on the maximum attainable velocity, $k_m$, and log $[D]_{50}$, these substances also affected the value of *n*. Micellar catalysis is treated here in analogy with the Hill model for enzymatic cooperativity for the sake of simplicity. Micellar catalysis may also be described in terms of the Monod-Wyman-Changeux and Koshland-Nemethy-Filmer models, which require different conformational forms of free and substrate bound catalyst.

In attempting to elucidate the mechanisms by which enzymes effect catalysis, chemists have expended a great deal of effort in studying mechanisms of simpler, model chemical reactions.[1] Among these models have been reactions catalyzed within micelles.[2,3] Although the analogy between micelle-catalyzed reactions and enzyme-catalyzed reactions is far from perfect, there are important similarities.[3] The structures of both micelles and enzymes are similar in that they have hydrophobic cores with polar groups on their surfaces. The structures of micelles are disrupted by common protein denaturing agents such as urea and guanidinium salts. Both catalytic micelles and enzymes bind substrates in a noncovalent

manner. The kinetics of micellar catalysis resemble that of enzymatic catalysis in that the micelle may be saturated by the substrate; and, conversely, the substrate may be saturated by the micelle.[3]

Recently, I have described an additional similarity of micellar and enzymatic reactions.[4] The rate constants of micelle-catalyzed reactions when plotted vs. detergent concentration give sigmoid shaped curves. This behavior is analogous to positive homotropic interactions (also termed positive cooperativity) in enzymatic reactions, a sigmoid shaped dependence of velocity on substrate concentration. A kinetic model analogous to the Hill model,[5] which describes enzymatic reactions, accommodated published data on the rate constants of many micellar reactions as a function of detergent concentration. I concluded that micelle-catalyzed reactions are models of enzyme-catalyzed reactions which show positive homotropic interactions, or positive cooperativity.

The literature is replete with data on the dependence of rate constants on detergent concentration for micellar reactions. On the basis of the mathematical treatment of micellar reactions put forward previously,[4] I have analyzed a large portion of this data. This analysis demonstrates the general applicability of the mathematical treatment, and it illustrates some uses with respect to specific examples of micellar reactions.

## Theory and Methods

**Calculations and Treatment of Data.** The kinetic model most often used to quantitatively describe the relationship of rate constant to detergent concentration assumes that the micelle, $D_n$, forms a noncovalent complex with the substrate, S, before catalysis may take place[3,6]

$$D_n + S \overset{K}{\rightleftharpoons} D_nS$$

$$D_nS \xrightarrow{k_m} \text{product}$$

$$S \xrightarrow{k_0} \text{product} \qquad (1)$$

In this scheme, $K$ is the association constant of the micelle–substrate complex, $k_m$ is the rate constant for micelle-catalyzed reaction, and $k_0$ is the rate constant for the reaction in the absence of micelle. The observed rate constant at any concentration of micelle is given by

$$k_{obsd} = \frac{k_0 + k_m K\left(\frac{[D]_{total} - cmc}{n}\right)}{1 + K\left(\frac{[D]_{total} - cmc}{n}\right)} \qquad (2)$$

where cmc is the *critical micelle concentration*, which is defined as that concentration at which micelles first appear, and $n$ is the number of detergent molecules per micelle. This relationship and its equivalents describe the dependence of rate on detergent concentration of many micelle-catalyzed reactions, especially those which are unimolecular.

Several other models have also been proposed to describe uni- and bimolecular reactions in micellar systems. Bunton[6] presented a simple empirical modification of eq 2 applicable to bimolecular reactions which often show a decrease in rate at high detergent concentrations. Berezin et al.[7] have used a pseudophase model of micelles to describe the velocities of uni- and bimolecular reactions in the presence of detergents. Romsted[8] has proposed a model based on similar assumptions which is applicable to the rates of reaction of organic substances and hydrophilic ions in micelles.

The mathematical model used in this study to describe the dependence of rate constant on detergent concentration is based on the reaction mechanism proposed by Bruice et al.[9] It begins with the assumption that a substrate, S, and a number, $n$, of detergent molecules, D, aggregate to form catalytic micelles, $D_nS$, which may then react to yield product:

$$nD + S \overset{K_D}{\rightleftharpoons} D_nS$$

$$D_nS \xrightarrow{k_m} \text{product}$$

$$S \xrightarrow{k_0} \text{product} \qquad (3)$$

$K_D$ is the dissociation constant of the micelle back to its free components, $k_m$ is the rate of reaction within the micelle, and $k_0$ is the rate of reaction in the absence of detergent. The actual reaction undoubtedly involves multiple, sequential equilibrium steps in which detergent and substrate molecules aggregate to form the catalytic micelle, $D_nS$. They are presented here as a single association step for the sake of convenience. For this reaction scheme the observed rate constant is expressed as a function of the concentration of detergent, D, by

$$k_{obsd} = \frac{k_m[D]^n + k_0 K_D}{K_D + [D]^n} \qquad (4)$$

This equation may be rearranged and its log taken to give

$$\log\left(\frac{k_{obsd} - k_0}{k_m - k_{obsd}}\right) = n \log [D] - \log K_D \qquad (5)$$

According to this equation, a plot of log $[(k_{obsd} - k_0)/(k_m - k_{obsd})]$ vs. log [D] for a micelle-catalyzed reaction is linear with a slope of $n$, and at log $[(k_{obsd} - k_0)/(k_m - k_{obsd})] = 0$, $n$ log [D] = log $K_D$. Also, at log $[(k_{obsd} - k_0)/(k_m - k_{obsd})] = 0$, catalysis by detergent shows one-half of its maximum effect on rate constant. For convenience the value of log [D] at this point is designated as log $[D]_{50}$, and it is equal to (log $K_D$)/$n$.

Data tabulated in the literature was used to construct plots of log $[(k_{obsd} - k_0)/(k_m - k_{obsd})]$ vs. log detergent concentration. Occasionally data was read from graphs of rate constants plotted vs. detergent concentration. Values of $k_0$ were taken as the observed rate constant in the absence of detergent; $k_m$ was taken as the maximum rate constant obtained in the presence of detergent. This analysis was applied only to the region of detergent concentration in which the initial sigmoid dependence of $k_{obsd}$ on detergent concentration was seen. It did not include the region at very high detergent concentration where $k_{obsd}$ often decreases in bimolecular reactions. Slopes of the double log plots, $n$, were calculated by least-squares analysis; correlation coefficients, $r$, were also calculated as indicators of how well the data fit the graphical analysis. These calculations were done with a Texas Instruments SR-51 calculator.

**Constants Describing Micellar Catalysis.** Micelle formation and the absorption of solutes into micelles takes place at rates much faster than the rates of reaction commonly observed. Therefore, micelle-catalyzed reactions may be divided into two steps: the rapid detergent–substrate ($D_nS$) complex formation and the rate limiting catalytic step. Likewise the rate constants which describe these reactions can be split into two terms. The term $k_m$ defines the latter step; $k_m/k_0$ is equal to the rate acceleration effected by micellar catalysis. These terms have been used commonly and need no further explanation here. The terms $n$, log $K_D$, and log $[D]_{50}$, which equals (log $K_D$)/$n$, pertain to detergent–substrate ($D_nS$) complex formation and should be commented on.

Log $[D]_{50}$, or (log $K_D$)/$n$, is equal to the log of the detergent concentration at which half maximal velocity is obtained. Generally, it can be obtained with a high degree of precision from a linear plot according to eq 5 as that value of log detergent concentration at which log $[(k_{obsd} - k_0)/(k_m - k_{obsd})] = 0$. The term $n$ is the slope of the linear plot according to eq

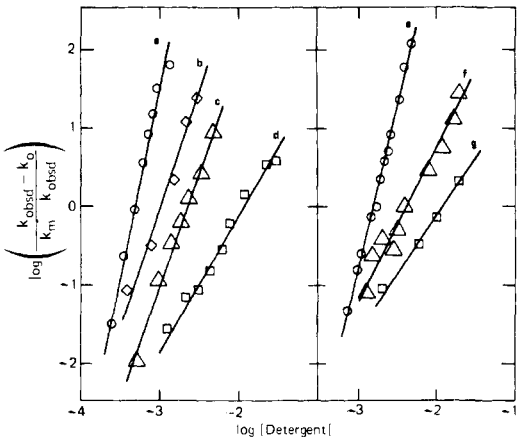



Figure 1. Plots of log $[(k_{obsd} - k_0)/(k_m - k_{obsd})]$ vs. log of detergent concentration according to eq 5 for reactions catalyzed by detergents: (a) base-catalyzed hydrolysis of bis-*p*-nitrophenyl phosphonate in polyoxyethylene(20)nonylphenol, $n = 4.43$, log $[D]_{50} = -3.30$ (data from ref 33); (b) hydrolysis of *p*-nitrophenyl hexanoate in cetyltrimethylammonium bromide, $n = 2.78$, log $[D]_{50} = -2.97$ (data from ref 28); (c) reaction of $e_{aq}^-$ with benzene in cetyltrimethylammonium bromide, $n = 2.83$, log $[D]_{50} = -2.63$ (data from ref 38); (d) solvolysis of *o*-nitrophenyl acetate in *p*-trimethylammoniobenzyldecylamine chloride hydrochloride, $n = 1.58$, log $[D]_{50} = -1.92$ (data from ref 9); (e) hydrolysis of 2,6-dinitrophenyl phosphate in cetyltrimethylammonium bromide, $n = 4.09$, log $[D]_{50} = -2.79$ (data from ref 21); (f) solvolysis of 3-nitro-4-acetoxyphenyltrimethylammonium iodide in *p*-trimethylammoniobenzyldecylamine chloride hydrochloride, $n = 1.92$, log $[D]_{50} = -2.38$ (data from ref 9); (g) inhibition of the hydrolysis of methyl orthobenzoate by dimethyldodecylphosphine oxide, $n = 1.38$, log $[D]_{50} = -1.90$ (data from ref 13).

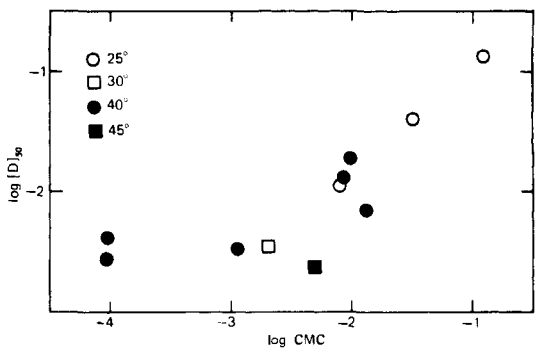



Figure 2. Data for the hydrolysis of methyl orthobenzoate in the presence of various detergents; a plot of log $[D]_{50}$ determined at the temperatures indicated vs. the log of the critical micelle concentration for these detergents.

5. Formally, $n$ describes the stoichiometry of the reaction given by eq 3. Functionally, it is probably more accurate to consider $n$ an "index of cooperativity" in micelle formation by analogy to cooperativity in enzymatic reactions.[10] The term $n$ is subject to a higher degree of uncertainty than log $[D]_{50}$, since it is dependent on data obtained at high and low as well as intermediate detergent concentrations. The use of log $[(k_{obsd} - k_0)/(k_m - k_{obsd})]$ results in considerable scale expansion at both ends, but very little distortion in the middle range. In the range where the rate constants being subtracted are within approximately an order of magnitude of each other, a reasonable value of $n$ may be expected. However, outside this range the precision of points on the linear plot decays sharply. This decay of precision at the extremes can contribute to a lack of precision in the value of $n$. Similar problems in the evaluation of constants from Hill plots for enzymatic reactions have been discussed by Cornish-Bowden and Koshland.[11] The term log $K_D$ is equal to $n$ log $[D]_{50}$. Since it is the product of two terms, it reflects the uncertainty in both. Furthermore, the units of $K_D$ vary with $n$ from reaction to reaction. These factors seriously limit the usefulness of log $K_D$ for comparing different micelle-catalyzed reactions.

## Results and Discussion

**General Applicability of the Treatment.** Data from the literature was used to construct plots of log $[(k_{obsd} - k_0)/(k_m - k_{obsd})]$ vs. the log of the detergent concentration. Several representative plots are shown in Figure 1. A large number of additional reactions have been subjected to this graphical analysis and found to be linear. Figures for all of these reactions are not shown for the sake of brevity; however, these reactions and the constants derived from them are summarized in Table I and later tables in this paper. The general linearity of these plots (Figure 1) and the generally high correlation coefficients of the data to the linear treatment (Table I) indicate that the quantitative expression which describes the plots (eq 5) describes, at least empirically, a large number of micelle-catalyzed reactions.

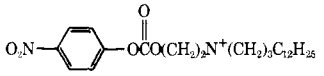
The slopes of these plots, $n$, range from approximately 1 to 6 with the vast majority below 3. These values are far less than the number of 10 to 100 detergent molecules which are found in micelles and which would be predicted on the basis of eq 3.[3] Such low exponential terms in eq 4 have previously been interpreted as indicating the existence of catalytically productive submicellar aggregates.[9] A logical extension of this deduction is that there are in reality a multiplicity of catalytically functional aggregates which are related by multiple association steps. Clearly then, the mathematical treatment of eq 3–5 is a simplification of the physical reality. Nevertheless, it serves as a useful empirical relationship.

**Effects of Variation of Detergent Structure.** In view of the fact that in the reactions under consideration detergents function as catalysts via a mechanism of micelle formation, one would expect the structures of the detergents to influence the kinetic constants. This has long been recognized to be the case with respect to overall rate accelerations and the maximal rate of reaction in the presence of detergent, $k_m$. It is not surprising that detergent structure also influences the values of log $[D]_{50}$ and $n$ which are derived on the basis of the model of eq 3. The variability of log $[D]_{50}$ and $n$ with detergent structure is indicated by the data (Table I) for the hydrolyses of 3-nitro-4-hexanoyl benzenesulfonate and bis-*p*-nitrophenyl phenylphosphonate and for the mutarotation of 2,3,4,6-tetramethyl-α-D-glucose in various detergents. However, the small amount of data available for these reactions does not allow any generalizations to be drawn.

The acid-catalyzed hydrolysis of methyl orthobenzoate has been studied in the presence of a large number of detergents. The values of log $[D]_{50}$ and $n$ for these reactions were calculated from the data published by Cordes and his co-workers,[12,13] and are presented in Table II. Several limited conclusions may be drawn from this data. First, $[D]_{50}$ parallels the critical micelle concentration, cmc, of the detergent, but is not related to it in a simple manner. This conclusion is illustrated by a plot of log $[D]_{50}$ vs. log cmc (Figure 2) for the hydrolysis of methyl orthobenzoate by a number of detergents. While there is clearly a trend, log $[D]_{50}$ does not vary with the log cmc in a linear manner, and the points show substantial scatter. These deviations should not be surprising since log $[D]_{50}$ is related to the catalytic micelle, $D_nS$, which contains both detergent and substrate, and cmc relates only to the detergent concentration.

Another apparent trend in this data (Table II) is the dependence of $n$ on temperature; the average value of $n$ appears to increase as temperature decreases. Detergents (16) were used to catalyze the hydrolysis of methyl orthobenzoate at 40 °C; they had an average value of $n$ of 1.87 with only one over

Table I. Summary of Micelle-Catalyzed Reactions and Derived Constants

| Reaction | Detergent | Temp, °C | No. of $k_{obsd}$ values used | Log $[D]_{50}$ | $n$ | $r$ | Ref |
|---|---|---|---|---|---|---|---|
| Hydrolysis of | | | | | | | |
| *p*-Nitrophenyl acetate | Cetyltrimethylammonium bromide | 25 | 5 | −2.76 | 1.72 | 0.9007 | 28 |
| *p*-Nitrophenyl hexanoate | Cetyltrimethylammonium bromide | 25 | 5 | −2.97 | 2.78 | 0.9916 | 28 |
| Mono-*p*-nitrophenyl dodecanodioate | Laurate | 50 | 7 | −1.80 | 2.46 | 0.9158 | 29 |
| 3-Nitro-4-hexanoyl benzenesulfonate | $HOCH_2CH_2(OCH_2CH_2)_{17}OC_6H_4(CH_2)_{11}CH_3$ | 30 | 8 | −3.00 | 1.91 | 0.9914 | 9 |
| 3-Nitro-4-hexanoyl benzenesulfonate | Cetyltrimethylammonium bromide, pH 9.56 | 30 | 11 | −4.16 | 3.89 | 0.9663 | 9 |
| 3-Nitro-4-hexanoyl benzenesulfonate | Cetyltrimethylammonium bromide, pH 8.77 | 30 | 9 | −4.33 | 2.52 | 0.9753 | 9 |
| 3-Nitro-4-hexanoyl benzenesulfonate | Cetyltrimethylammonium bromide, pH 10.27 | 30 | 14 | −4.33 | 2.88 | 0.9829 | 9 |
|  | *N*-α-Stearoyl histidine | 25 | 9 | −4.63 | 5.4 | 0.9462 | 30 |
| 2,6-Dinitrophenyl phosphate cyclohexylamine salt | 2,4-Dimethyloxyphenylacetyl-dimethylammonium bromide | 25 | 13 | −3.51 | 1.81 | 0.9916 | 31 |
| 2,6-Dinitrophenyl phosphate | 2,4-Dimethyloxyphenylacetyl-dimethylammonium bromide | 25 | 8 | −3.78 | 2.33 | 0.9871 | 31 |
| 2-Methoxymethoxy-3-methylbenzoic acid | Sodium lauryl sulfate | 30 | 6 | −1.82 | 2.01 | 0.9667 | 32 |
| $OH^-$ catalyzed hydrolysis of bis-*p*-nitrophenyl phenylphosphonate | Sodium lauryl sulfate | | 7 | −3.09 | 4.84 | 0.9472 | 33 |
| $OH^-$ catalyzed hydrolysis of bis-*p*-nitrophenyl phenylphosphonate[a] | Polyoxyethylene(20)nonylphenol | | 8 | −3.30 | 4.43 | 0.9887 | 33 |
| $OH^-$ catalyzed hydrolysis of bis-*p*-nitrophenyl phenylphosphonate[a] | Sodium lauryl sulfate | | 5 | −2.42 | 9.66 | 0.9129 | 33 |
| Photobleaching of riboflavin in $O_2$ saturated soln | Sodium dodecyl sulfate | | 3 | −1.40 | 6.2 | 0.9828 | 34 |
| Oxidation (by $O_2$) of benzaldehyde | Polyoxyethylene(24)hexadecanol | | 8 | −2.24 | 1.52 | 0.9901 | 35 |
| Mutarotation of 2,3,4,6-tetramethyl-α-D-glucose | | | | | | | |
| In benzene | Dodecylammonium propionate | 24.6 | 7 | −2.68 | 1.32 | 0.9978 | 36 |
| In cyclohexane | Dodecylammonium propionate | 24.6 | 7 | −2.84 | 0.96 | 0.9554 | 36 |
| In benzene | Dodecylammonium butyrate | 24.6 | 7 | −2.30 | 0.93 | 0.8266 | 36 |
| In benzene | Dodecylammonium butyrate | 24.6 | 7 | −2.49 | 1.32 | 0.9945 | 36 |
| Decomposition of 1,1-dimethyloxy-2,4,6-trinitrocyclohexadienyl ion in benzene | Dodecylammonium benzoate | 24.5 | 6 | −3.63 | 1.91 | 0.9919 | 37 |
| Reaction of $e_{aq}^-$ with benzene[a] | Sodium lauryl sulfate | | 5 | −2.04 | 3.29 | 0.9103 | 38 |
| Reaction of $e_{aq}^-$ with benzene[a] | Cetyltrimethylammonium bromide | | 7 | −2.63 | 2.83 | 0.9971 | 38 |

[a] These reactions were inhibited by these detergents.

2.14. On the other hand, six detergents were used to catalyze the hydrolysis of the substrate at 25 °C; they gave an average value of $n$ of 3.48. However, three detergents which inhibited hydrolysis of methyl orthobenzoate had an average value of $n$ of 1.41. While this data seems to indicate that $n$ is temperature dependent, the possibility must also be recognized that this trend might be related to the different chemical structures of the detergents employed at these temperatures.

No other simple correlations could be extracted from the data of Table II, although their existence could be masked by the great variety of detergent structures and the effects of the structures studied. As noted above, log $[D]_{50}$ and $n$ represent a simplified description of catalytic micelle, $D_nS$, formation. The actual physical process undoubtedly involves multiple equilibria, and the structure of the detergent could influence any or all of the individual equilibrium steps.

**Effects of Changes of Substrate Structure.** Several series of reactions have been studied in which a single detergent was employed within the series, but subtle variations in the structure of the substrate were made. One such series of reactions is the hydrolyses of para-substituted benzaldehyde diethylacetals in sodium dodecyl sulfate which were reported by Dunlap et al.[14] Table III summarizes the derived constants, log $[D]_{50}$ and $n$, for these reactions which were calculated from the original data. These parameters were calculated from a relatively small number of points, and the correlation coefficients for these reactions are relatively low. Nevertheless, some significant conclusions can be drawn. The value of log $[D]_{50}$ remains virtually constant as the inductive substituent constant, $\sigma$, of the para substituent is varied from −0.069 for *p*-methyl to 0.710 for *p*-nitro. Also, although the derived data show variation, there is no consistent variation of $n$ with $\sigma$. Similarly, for the hydrolyses of para-substituted methyl orthobenzoates, log $[D]_{50}$ appears to be independent of $\sigma$ (Table IV). There appears to be a trend in that $n$ increases roughly as $\sigma$ decreases (Table IV). However, the number of data points used to calculate $n$ ranged from 2 to 4, and better correlation coefficients would have been desirable. Consequently, this apparent trend may be fortuitous.

A somewhat different situation is seen for the solvolyses of several esters by the nucleophilic detergent *p*-trimethylammoniobenzyldecylamine chloride hydrochloride as reported by Bruice et al.[9] Table V summarizes the parameters for these reactions which were calculated from the original data. In these reactions both log $[D]_{50}$ and $n$ are clearly a function of the structure of the substrate; several generalizations may be made. First, log $[D]_{50}$ increases as the chain length of the carboxylic acid portion of the negatively charged ester increases. This is no doubt the result of better binding of the longer chain substrates within the catalytic micelle complex, $D_nS$, by hydrophobic interactions. Second, $n$ appears to decrease as the chain length of the carboxylic acid moiety increases. The only striking exception to these generalizations is the data for the substrate 3-nitro-4-hexadecanoyl benzenesulfonate. This reaction yields an anomalously low value of log $[D]_{50}$ and an anomalously high value of $n$. In this reaction, unlike the others

Table II. Constants for the Hydrolysis of Methyl Orthobenzoate in the Presence of Various Detergents

| Detergent | cmc, M[a] | Temp, °C | No. of $k_{obsd}$ values used | Log $[D]_{50}$ | $n$ | $r$ | Ref |
|---|---|---|---|---|---|---|---|
| Sodium octyl sulfate | $1.3 \times 10^{-1}$ | 25 | 4 | −0.91 | 3.30 | 0.9677 | 12 |
| Sodium decyl sulfate | $3.3 \times 10^{-2}$ | 25 | 3 | −1.42 | 5.46 | 0.9999 | 12 |
| Sodium dodecyl sulfate | $8.1 \times 10^{-3}$ | 25 | 8 | −1.96 | 3.67 | 0.9638 | 12 |
| Sodium tetradecyl sulfate | $2.08 \times 10^{-3}$ | 30 | 5 | −2.48 | 1.77 | 0.9840 | 12 |
| Sodium hexadecyl sulfate | $5 \times 10^{-3}$ | 45 | 7 | −2.65 | 1.31 | 0.9987 | 12 |
| 2-Hexadecyl sodium sulfate | | 40 | 5 | −2.50 | 1.61 | 0.9986 | 13 |
| 3-Hexadecyl sodium sulfate | | 40 | 5 | −2.45 | 1.55 | 0.9950 | 13 |
| 5-Hexadecyl sodium sulfate | | 40 | 5 | −2.35 | 1.82 | 0.9972 | 13 |
| Sodium 2-hexadecyloxy-1-methylethyl sulfate | | 40 | 7 | −2.69 | 1.63 | 0.9873 | 13 |
| Sodium hexadecyloxyethyl sulfate | | 40 | 8 | −2.61 | 1.36 | 0.9966 | 13 |
| Sodium 2-oleyloxy-1-methylethyl sulfate | | 40 | 8 | −2.76 | 1.47 | 0.9756 | 13 |
| Sodium 2-hexadecyloxyl-1-ethylethyl sulfate | | 40 | 7 | −2.69 | 1.53 | 0.9877 | 13 |
| Disodium 2-sulfooctadecyl sulfate | | 25 | 3 | −2.21 | 3.76 | 0.9993 | 13 |
| Disodium 2-sulfoethyl-α-sulfopalmitate | | 25 | 3 | −1.98 | 3.64 | 0.9977 | 13 |
| Disodium 2-sulfoethyl-α-sulfostearate | | 25 | 3 | −2.71 | 1.02 | 0.9274 | 13 |
| Disodium 2-sulfo-2-butyltetradodecanoate | | 40 | 5 | −1.79 | 2.13 | 0.9952 | 13 |
| Disodium 2-sulfo-2-methyloctadecanoate | | 40 | 4 | −2.52 | 2.14 | 0.9896 | 13 |
| Sodium methyl-α-sulfopalmitate | $1.34 \times 10^{-2}$ | 40 | 6 | −2.18 | 1.37 | 0.9979 | 13 |
| Sodium propyl-α-sulfopalmitate | $9.9 \times 10^{-5}$ | 40 | 4 | −2.38 | 1.35 | 0.9977 | 13 |
| Sodium butyl-α-sulfopalmitate | | 40 | 6 | −2.28 | 1.26 | 0.9910 | 13 |
| Sodium methyl-α-sulfostearate | $9.9 \times 10^{-5}$ | 40 | 4 | −2.56 | 1.43 | 0.9953 | 13 |
| Sodium dodecyl sulfate | $8.6 \times 10^{-3}$ | 40 | 4 | −1.90 | 5.86 | 0.9433 | 13 |
| Sodium 2-dodecylbenzenesulfonate | $1.17 \times 10^{-3}$ | 40 | 4 | −2.49 | 1.75 | 0.9884 | 13 |
| Sodium 2-dodecylbenzenesulfonate | | 40 | 4 | −2.45 | 1.58 | 0.9939 | 13 |
| Sodium dodecyl sulfonate | $1.0 \times 10^{-2}$ | 39.1 | 4 | −1.73 | 4.47 | 0.9833 | 13 |
| Dimethyldodecylammonium propanesulfonate[b] | | 25 | 6 | −1.68 | 1.03 | 0.9732 | 13 |
| Dimethyldodecylphosphine oxide[b] | | 25 | 4 | −1.90 | 1.38 | 0.9958 | 13 |
| Dimethyldodecylammonium acetate[b] | | 25 | 3 | −1.85 | 1.82 | 0.9999 | 13 |

[a] Critical micelle concentrations tabulated by Mukerjee and Mysels (ref 39). [b] Hydrolysis of methyl orthobenzoate was inhibited by these detergents.

**Table III.** Derived Constants for Hydrolyses of Para-Substituted Benzaldehyde Diethylacetals in Sodium Dodecyl Sulfate[a]

| Substituent | $\sigma^b$ | No. of $k_{obsd}$ values used | log $[D]_{50}$ | $n$ | $r$ |
|---|---|---|---|---|---|
| $p$-$NO_2$ | 0.710 | 2 | −2.06 | 4.47 | |
| $p$-Cl | 0.373 | 4 | −2.03 | 5.02 | 0.9759 |
| $p$-F | 0.337 | 5 | −1.96 | 3.74 | 0.8912 |
| $p$-$OCH_3$ | 0.115 | 4 | −2.01 | 4.52 | 0.9467 |
| $p$-H | 0 | 4 | −1.98 | 5.41 | 0.9835 |
| $p$-$CH_3$ | −0.069 | 5 | −1.99 | 4.33 | 0.9085 |

[a] Data from Dunlap et al. (ref 14). Reactions were carried out at 25 °C in various buffers. [b] Values tabulated by Hine (ref 40).

**Table IV.** Derived Constants for Hydrolyses of Para-Substituted Methyl Orthobenzoates in Sodium Dodecyl Sulfate[a]

| Substituent | $\sigma^b$ | No. of $k_{obsd}$ values used | log $[D]_{50}$ | $n$ | $r$ |
|---|---|---|---|---|---|
| $p$-$NO_2$ | 0.710 | 2 | −2.06 | 4.47 | |
| $p$-F | 0.337 | 4 | −1.98 | 5.85 | 0.9528 |
| $p$-$OCH_3$ | 0.115 | 4 | −1.98 | 6.26 | 0.9557 |
| $p$-H | 0 | 4 | −1.95 | 5.49 | 0.9611 |
| $p$-$CH_3$ | −0.067 | 3 | −2.06 | 8.44 | 0.9847 |

[a] Data from Dunlap and Cordes (ref 12). Reactions were carried out at 25 °C in various buffers. [b] Values tabulated by Hine (ref 40).

of this series, the substrate has a much longer aliphatic chain than does the detergent. It is probable that this structural difference radically alters the mechanism of formation of the catalytic micelle, $D_nS$. It is possible, although not substantiated, that substrate molecules first aggregate then include the nucleophilic detergent molecules to form the catalytically active complex.

In viewing the effects of changes of substrate structure it is clear that a major structural alteration is required to change log $[D]_{50}$ or $n$. Alterations of electronic inductive effects may not be sufficient. Furthermore, the relationship of the nature of the change in log $[D]_{50}$ and $n$ is a complex function of the nature of the structural alteration.

**Inhibitors and Activators of Micelle-Catalyzed Reactions.** The rates of micelle-catalyzed reactions, like enzyme-catalyzed reactions, are subject to inhibition or activation by substances which are neither substrate nor detergent. The inhibition or activation of enzymatic reactions which show positive cooperativity may be described in terms of the two kinetic constants by which enzymatic reactions are defined.[15] V-type inhibitors and activators either lower or raise the maximum velocity, $V_{max}$, which can be achieved. $V_{max}$ in the enzymatic reaction is analogous to $k_m$ in the micellar reaction. K-type inhibitors and activators increase or decrease the Michaelis–Menten constant, $K_m$, of the enzymatic reaction. $K_m$ is analogous to log $[D]_{50}$ in the micellar system. Inhibitors and activators of enzymatic reactions may alter $V_{max}$ or $K_m$ or both, but generally have no effect on the index of cooperativity, $n$.

The chemical literature contains numerous examples of micellar reactions which are either inhibited or activated by the addition of substances, which are neither detergent nor substrate. There are examples of V-type inhibitors and activators and K-type inhibitors. No attempt will be made here to present a complete survey of the literature, nor will an attempt be made to explain on a molecular level the precise mechanisms by which inhibition or activation is brought about. These mechanisms are likely to be varied and complex. This discussion will stress the qualitative similarities in kinetics of the

**Table V.** Derived Constants for Solvolyses of Various Esters in Nucleophilic Micelles of *p*-Trimethylammoniobenzyldecylamine Chloride Hydrochloride[a]

| Ester | No. of $k_{obsd}$ values used | log $[D]_{50}$ | $n$ | $r$ |
|---|---|---|---|---|
| 3-Nitro-4-acetoxy benzenesulfonate | 7 | −2.34 | 4.14 | 0.9814 |
| 3-Nitro-4-hexanoyloxy benzenesulfonate | 6 | −2.69 | 3.01 | 0.9763 |
| 3-Nitro-4-octanoyloxy benzenesulfonate | 5 | −3.05 | 1.63 | 0.9794 |
| 3-Nitro-4-decanoyloxy benzenesulfonate | 5 | −3.03 | 1.25 | 0.9479 |
| 3-Nitro-4-hexadecanoyloxy benzenesulfonate | 4 | −2.76 | 4.87 | 0.8916 |
| 3-Nitro-4-acetoxyphenyltrimethylammonium iodide | 10 | −2.38 | 1.91 | 0.9901 |
| 3-Nitro-4-octanoyloxyphenyltrimethylammonium iodide | 9 | −2.03 | 1.80 | 0.9983 |
| *o*-Nitrophenyl acetate | 10 | −1.92 | 1.58 | 0.9876 |

[a] Data from Bruice et al. (ref 9). Reactions were carried out at 30 °C in 0.1 μm buffer at pH 8.63.

**Table VI.** Hydrolyses of Dinitrophenyl Phosphates in Cetyltrimethylammonium Bromide in the Presence of Added Electrolytes[a]

| Substrate (initial concn) | Added electrolyte | No. of $k_{obsd}$ values used | log $[D]_{50}$ | $n$ | $r$ |
|---|---|---|---|---|---|
| 2,4-Dinitrophenyl phosphate ($6.3 \times 10^{-5}$ M) | | 11 | −2.93 | 3.80 | 0.9920 |
| 2,6-Dinitrophenyl phosphate ($9.4 \times 10^{-5}$ M) | | 12 | −2.79 | 4.09 | 0.9870 |
| 2,6-Dinitrophenyl phosphate ($1.8 \times 10^{-5}$ M) | | 7 | −2.83 | 4.58 | 0.9761 |
| | 0.1 M NaOH | 7 | −2.66 | 4.45 | 0.9833 |
| | $10^{-3}$ M Na oleate | 4 | −2.58 | 3.68 | 0.9999 |
| | $2 \times 10^{-3}$ M Na oleate | 5 | −2.44 | 7.43 | 0.9788 |
| | $10^{-3}$ M $Na_2$ *tert*-butylphenyl phosphate | 4 | −2.64 | 3.51 | 0.9964 |
| | $2 \times 10^{-3}$ M $Na_2$ *tert*-butylphenyl phosphate | 4 | −2.48 | 3.02 | 0.9858 |

[a] Data has been taken from Bunton et al. (ref 21). Hydrolyses were carried out at 25 °C in $2.5 \times 10^{-3}$ M borate buffer at pH 9.0 unless noted otherwise.

inhibition and activation of micellar and enzymatic reactions.

The inhibitors of micellar reactions which have been studied in the greatest detail are of the V-type. It is commonly recognized that for most reactions the maximum rate constant, $k_m$, is inhibited by counterions; this behavior has been rationalized by assuming a competition between substrate and inhibitor for a "binding site" on or in the micelle.[3,6] Some examples of micellar reactions which show this V-type inhibition by salts are the hydrolysis of methyl orthobenzoate by sodium dodecyl sulfate,[12] the reaction between glycylglycinate and 2,4-dinitrofluorobenzene, which is catalyzed by cetyltrimethylammonium bromide,[16] and the reaction of *p*-nitrophenyl diphenyl phosphate with hydroxide and fluoride ions in cetyltrimethylammonium bromide.[17]

The maximum rate constants, $k_m$, of some micellar reactions are enhanced by added salts, which may be considered to be V-type activators. For example, the maximum rate constant of reaction, $k_m$, of 2,4-dinitrofluorobenzene with hydroxide ion in cetyltrimethylammonium bromide is enhanced by salts which have cations of low or anions of high charge density; other electrolytes retard the rate of reaction.[18] Also, micellar catalysis of the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion is enhanced by electrolytes;[19] and the hydrolysis of bis-2,4-dinitrophenyl phosphate in the presence of cetyltrimethylammonium bromide is approximately doubled by 1.5 vol % dioxane.[20]

While there are numerous examples of V-type inhibitors and activators of micellar reactions in the literature, there are only a few examples of K-type inhibitors. This author is unaware of any examples of K-type activators of micellar reactions. Bunton et al.[21] have found that for the hydrolysis of 2,6-dinitrophenyl phosphate in cetyltrimethylammonium bromide, electrolytes may affect the dependence of the observed rate of reaction, $k_{obsd}$, on detergent concentration without significantly altering the maximum attainable rate constant, $k_m$. Therefore, they may be viewed as K-type inhibitors. The constants log $[D]_{50}$ and $n$ for this reaction under varying conditions are given in Table VI. Examination of the data for these reactions indicate that the presence of added electrolyte clearly and consistently causes an increase in log $[D]_{50}$. The effects of electrolyte on $n$ is less clear. Added 0.1 M NaOH causes a small, possibly insignificant decrease in $n$. The value of $n$ decreases as the concentration of disodium *tert*-butylphenylphosphate increases. If $n$ is viewed as a measure of cooperativity in micelle formation, this electrolyte interferes with the cooperative nature of catalytic micelle, $D_nS$, formation. The inhibitory effect of sodium oleate is more complex. The value of $n$ appears to drop initially then rises as sodium oleate concentration increases. It is probable that this substance, because of its partial aliphatic structure, causes its effects by entering into the process of micelle formation. The mechanisms by which sodium oleate may affect $n$ are observed by the numerous possible equilibria which could involve the substrate, 2,6-dinitrophenyl phosphate, the detergent, cetyltrimethylammonium bromide, and the inhibitor.

## Conclusions

The model of micellar catalysis explored in this paper (eq 3-5) has several features which makes it a desirable method for describing these reactions. First, the method allows for a more accurate description of the dependence of observed rate

constant on detergent concentration, especially at low detergent concentration, than previously possible. The validity of this model is substantiated by the generally high correlation coefficients of observed data to the linear equation (eq 5). Second, the data may be treated without reference to the critical micelle concentration (as in eq 2), which would have to be determined independently. Third, the method allows calculation of two constants, log $[D]_{50}$ and $n$, which may be used to compare different micelle-catalyzed reactions. Fourth, the model more accurately describes physical reality in that it considers substrate as participating in the formation of the catalytically active micelle, $D_nS$ (eq 3), rather than being adsorbed by an existing micelle, $D_n$, prior to reaction (eq 1). This treatment does, of course, simplify into one step the multiple steps which must be involved in the formation of the reactive species, $D_nS$. The validity of this simplification is supported by the finding of Muller[22] that micellization of several detergents in nonaqueous solvents may be fit equally well by a single equilibrium model analogous to eq 3 or a more complex model involving multiple steps in aggregate formation.

Micellar reactions may be viewed as models of enzymatic reactions which show positive cooperativity. They have been treated quantitatively by a model (eq 3–5) which is analogous to the Hill model.[5] When applied to micellar reactions this model has theoretical shortcomings, but it also has advantages in that it allows simple evaluation of the empirical parameters $n$ and log $[D]_{50}$. It allows the analogy between micellar and enzymatic reaction to be drawn on a simple mathematical basis.

One might also look to more modern models of cooperativity in enzymatic reactions to draw this analogy. The model of Monod, Wyman, and Changeux[15] requires two distinct conformations of the enzyme and its subunits. One conformation would not bind substrate significantly, and a second conformation would have a high affinity for substrate. Koshland, Nemethy, and Filmer[23] refined this model by postulating that the subunits of the enzyme could change their conformations sequentially and bind substrate with varying affinities between the two extreme conformational states. It is probable that catalytic micelles have different shapes in the absence of and in the presence of substrates.[24] Consequently, the kinetics of micelle-catalyzed reactions could be treated analogously with either of the two enzymatic conformation models, although such a treatment would be extremely complex.

An apparent shortcoming of the alternative mechanism of micellar catalysis (eq 3) as a model for enzymatic positive cooperativity is that the phenomenon results from cooperativity in aggregation of the subunits of the catalytic micelle, the detergent and substrate molecules, rather than association of the substrate to the detergent. This apparent shortcoming is reconcilable, at least in a qualitative sense, with a model proposed by Frieden.[25] Frieden has noted that many enzymatic homotropic interactions can be related to the degree of aggregation of a polymeric enzyme. One form of the enzyme, either dissociated or aggregated, would have the greater catalytic activity. He also noted that his model was analogous to the model of Monod, Wyman, and Changeux,[15] the only difference being that the two conformational forms which exist in equilibrium are monomer and oligomer. Several enzymes[25] as well as the polymeric catalyst *N*-benzoylhistidine poly(oxyethylene) ester[26] have been shown to function in accord with this model.

In viewing enzymatic reactions it should be noted that positive cooperativity and negative cooperativity have been observed, and that these are both accommodated by the model of Koshland, Nemethy, and Filmer.[23] Positive cooperativity implies the stimulation of the interaction of additional substrate molecules by interaction of the first molecule with the enzyme; positive cooperativity is indicated by a value of the enzymatic index of cooperativity, $n$, greater than 1.0. Negative cooperativity implies the inhibition of the interaction of additional molecules of substrate by the interaction of the first molecule with the enzyme; negative cooperativity is indicated by a value of $n$ less than 1.0. All of the micelle-catalyzed reactions analyzed in this manuscript and its predecessor gave values of $n$ equal to or greater than 1.0; negative cooperativity has not been seen in micellar reactions. That this is the case should not be surprising. The cooperativity seen in the micellar reaction is in the aggregation of detergent and substrate molecules. If negative cooperativity were to take place, catalytic micelle, $D_nS$, formation would be inhibited, and no catalytic effect could take place.

The occurrence of homotropic interactions in enzymatic reactions has often been associated with the fact that enzymes which catalyze these reactions are always composed of subunits. A causal relationship between the association of subunits to form functional aggregates which show cooperative interactions has been inferred.[27] Micellar systems which catalyze chemical reactions are simple models of such systems. The micelle differs from the enzyme in that the subunit is a simple detergent molecule rather than a complex polypeptide chain. Thus, the causes of positive homotropic interactions in enzymatic and micelle-catalyzed reactions are related; they can be traced to self-assembly of subunits in both cases.

The micellar reactions examined to date are not perfect models of enzymatic cooperativity. Nevertheless they serve to illustrate the principle which leads to cooperativity in enzymatic reactions: the self-assembly of subunits into a functional aggregate. With this as a basis, it may be possible to design a micellar catalyst which is a more accurate model of enzymatic cooperativity, one which shows cooperativity as a function of substrate concentration rather than detergent concentration.

## References and Notes


(1) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. 1 and 2, W. A. Benjamin, New York, N.Y., 1966; W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969; M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley, New York, N.Y., 1971; T. C. Bruice in "The Enzymes", 3rd ed, Vol. 2, P. D. Boyer, Ed., Academic Press, New York, N.Y., 1970, p 217.
(2) E. H. Cordes and R. B. Dunlap, *Acc. Chem. Res.*, **2**, 329 (1969).
(3) E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, **8**, 271 (1970); J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, N.Y., 1975.
(4) D. Piszkiewicz, *J. Am. Chem. Soc.*, **98**, 3053 (1976).
(5) A. V. Hill, *J. Physiol. (London)*, **40**, iv (1910).
(6) C. A. Bunton, *Prog. Solid State Chem.*, **8**, 239 (1973).
(7) I. V. Berezin, K. Martinek, and A. K. Yatsimirskii, *Russ. Chem. Rev.*, **42**, 787 (1973).
(8) L. Romsted, Ph.D. Dissertation, Indiana University, Bloomington, 1975.
(9) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Am. Chem. Soc.*, **90**, 1333 (1968).
(10) In reference to enzymes, cooperativity is defined as a stimulation (or inhibition) of the interaction of additional molecule(s) of the same substance to an enzyme as a result of interaction of the first molecule(s) of the ligand with the enzyme. By analogy, in reference to micellar catalysis, cooperativity is defined as a stimulation of association of additional detergent molecules to an aggregate as a result of interaction of the first detergent molecules.
(11) A. Cornish-Bowden and D. E. Koshland, Jr., *J. Mol. Biol.*, **95**, 201 (1975).
(12) R. B. Dunlap and E. H. Cordes, *J. Am. Chem. Soc.*, **90**, 4395 (1968).
(13) R. B. Dunlap and E. H. Cordes, *J. Phys. Chem.*, **73**, 361 (1969).
(14) R. B. Dunlap, G. A. Ghanim, and E. H. Cordes, *J. Phys. Chem.*, **73**, 1898 (1969).
(15) J. Monod, J. Wyman, and J. P. Changeux, *J. Mol. Biol.*, **12**, 88 (1965).
(16) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **92**, 356 (1970).
(17) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969).
(18) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 780 (1969).
(19) C. A. Bunton, M. Minch, and L. Sepulveda, *J. Phys. Chem.*, **75**, 2707 (1971); C. A. Bunton, A. Kamego, and M. J. Minch, *J. Org. Chem.*, **37**, 1388 (1972).
(20) G. J. Buist, C. A. Bunton, L. Robinson, L. Sepulveda, and M. Stam, *J. Am. Chem. Soc.*, **92**, 4072 (1970).
(21) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K.-U. Yang, *J. Am. Chem. Soc.*, **90**, 5512 (1968).
(22) N. Muller, *J. Phys. Chem.*, **79**, 287 (1975).

(23) D. E. Koshland, G. Nemethy, and D. Filmer, *Biochemistry*, **5**, 365 (1966).
(24) C. A. Bunton in "Reaction Kinetics in Micelles", E. H. Cordes, Ed., Plenum Press, New York, N.Y., 1973, p 73.
(25) C. Frieden, *J. Biol. Chem.*, **242**, 4045 (1967).
(26) I. N. Topchieva, A. B. Solov'eva, B. I. Kurganov, and V. A. Kabanov, *Vysokomol. Soedin., Ser. A*, **14**, 825 (1972).
(27) D. E. Koshland, Jr., and K. E. Neet, *Ann. Rev. Biochem.*, **37**, 359 (1968).
(28) M. T. A. Behme, J. G. Fullington, R. Noel, and E. H. Cordes, *J. Am. Chem. Soc.*, **87**, 266 (1965).
(29) F. M. Menger and C. E. Portnoy, *J. Am. Chem. Soc.*, **89**, 4698 (1967).
(30) T. E. Wayner, C.-J. Hsu, and C. S. Pratt, *J. Am. Chem. Soc.*, **89**, 6366 (1967).
(31) C. A. Bunton, L. Robinson, and L. Sepulveda, *J. Org. Chem.*, **35**, 108 (1970).
(32) B. M. Dunn and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 6589 (1970).
(33) E. P. Mazzola, Ph.D. Dissertation, University of Pittsburgh, Pittsburgh, Penna. (1971) as reported in J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, N.Y., 1975, p 160.
(34) H. B. Kostenbauer, P. P. DeLuca, and C. R. Kowarski, *J. Pharm. Sci.*, **54**, 1243 (1965).
(35) A. G. Mitchell and L. S. C. Wan, *J. Pharm. Sci.*, **54**, 699 (1965).
(36) J. H. Fendler, E. J. Fendler, R. T. Medary, and V. A. Woods, *J. Am. Chem. Soc.*, **94**, 7288 (1972).
(37) J. H. Fendler, *J. Chem. Soc., Chem. Commun.*, 269 (1972).
(38) J. H. Fendler, G. W. Bogan, E. J. Fendler, G. A. Infante, and P. Jirathana in "Reaction Kinetics in Micelles", E. H. Cordes, Ed., Plenum Press, New York, N.Y., 1973, p 53.
(39) P. Mukerjee and K. J. Mysels, *Natl. Stand. Ref. Data Ser., Natl. Bur. Stand.*, **No. 36**, 1 (1971).
(40) J. Hine, "Physical Organic Chemistry", 2nd ed, McGraw-Hill, New York, N.Y., 1962, p 87.

# Effects of Surfactants on the Interaction of Vitamin $B_{12a}$ with Cysteine and *N*-Alkanoylcysteines in Water and in Benzene. Influence of Aqueous Micelles and Solvent Restrictions

**Faruk Nome and Janos H. Fendler***

*Contribution from the Department of Chemistry, Texas A&M University, College Station, Texas 77843.* *Received August 9, 1976*

**Abstract:** Aqueous micellar hexadecyltrimethylammonium bromide, CTABr, and sodium dodecyl sulfate, SDS, show only a modest rate retardation of the anation of vitamin $B_{12a}$ by L-cysteine. Rate constants for the interaction of vitamin $B_{12a}$ with *N*-butanoyl-L-cysteine, NBC, *N*-octanoyl-D,L-cysteine, NOC, and *N*-decanoyl-D,L-cysteine, NDC, are markedly affected, however, by these micelles. CTABr has the most pronounced effect on the reactivities of NOC and NDC; anation rate constants are smaller by factors of 58 and 185 than those in water. SDS decreases the rate constants for the attack of NBC and NOC on vitamin $B_{12a}$ by factors of 6 and 2, but it does not influence the reactivity of NDC. The determined partition coefficients for the reactant between the micellar pseudo-phase and bulk water account well for the observed micellar effects. Vitamin $B_{12a}$ and L-cysteine do not bind at all to micellar CTABr. Binding constants for the interaction of NBC, NOC, and NDC with CTABr are: 100, 2600, and 5500 $M^{-1}$, respectively. Micellar SDS binds vitamin $B_{12a}$ ($K$ = 125 $M^{-1}$), but it does not appreciably bind any of the thiols investigated. Effects of CTABr on the interaction of NOC with vitamin $B_{12a}$ has been satisfactorily treated in terms of equations which describe micellar effects on bimolecular reactions. Rate constants for the anation of vitamin $B_{12a}$ by NOC and by NDC in 0.55 M dodecylammonium propionate surfactant solubilized water pools in benzene are factors of 1100- and 1400-fold faster than those of vitamin $B_{12b}$. In water the rate constant for anation of vitamin $B_{12a}$ by L-cysteine is only eightfold faster than that of vitamin $B_{12b}$. Reversed micellar effects on anation are essentially due to concentrating the thiols in the micelle solubilized water pools. Decomposition of the vitamin $B_{12}$ thiol complexes are, however, 3000-fold faster in the reversed micelle solubilized water pool in benzene than that in bulk water.

The bioinorganic chemistry of vitamin $B_{12a}$ and related molecules are well documented.[1-4] Kinetic parameters for anation, governed by $k_1$, of vitamin $B_{12a}$, aquocobalamin (Bzm-Co-$OH_2$), and those for the aquation of the formed vitamin $B_{12}$ complexes, Bzm-Co-L, governed by $k_{-1}$, have been determined for the ligands (L) $N_3^-$, $OCN^-$, $SCN^-$, $SO_3^{2-}$, $NCO^-$, $I^-$, $Br^-$, imidazole, and glycine:[5-11]

$$\text{Bzm-Co-OH}_2 + \text{L} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Bzm-Co-L} + \text{H}_2\text{O} \qquad (1)$$

Interest in vitamin $B_{12}$ mediated enzymatic processes has prompted investigations of the interactions of thiols with aquo and alkylcobalamins.[12-17] We have recently determined rate and equilibrium constants for the interaction of L-cysteine with vitamin $B_{12a}$ in water as a function of pH.[18] The obtained data allow us to examine the effects of surfactant aggregates or micelles on this reaction.

Surfactant aggregates in water[19] and in nonpolar solvents[20] have been utilized to mimic the microenvironments of biomacromolecular ensembles. Indeed, the effective polarity of the environment of vitamin $B_{12}$ in dodecylammonium propionate solubilized water pools in benzene has been found to vary between those resembling water and benzene.[11] Changes in microscopic polarities depended on the concentration of the cosolubilized water, i.e., on the size of the water pool. The larger the water pool, the more closely its polarity approximated that of bulk water. Rate constants for reaction 1, using glycine, imidazole, and sodium azide as ligands, were found to be substantially and selectively affected in surfactant solubilized water pools in benzene.[11] As expected, the most pronounced rate effects were observed in the smallest water pool. Conversely, these rate constants were only slightly altered by aqueous micellar hexadecyltrimethylammonium bromide and sodium dodecyl sulfate. The rate effect in surfactant solubilized water pools in benzene is the consequence of partitioning both reactants in the restricted water pool, whose effective polarity differs from that of bulk water and wherein favorable and often concerted proton transfer and dipole–dipole interactions facilitate the reaction. Effects of aqueous micelles essentially originate in electrostatic interactions.

The purpose of the present work was to examine the effects of both solvent restrictions and aqueous micelles on the attack