for the ligands would undoubtedly be more pertinent than are the rates of reactions such as (21) but may be impossible to determine in reducible proton-labile solvents. Closest to the mark might be a method of measuring the energy of transferring an electron abruptly from some common source to the ligand carrier orbital of the proper symmetry. There is some hope that for a series of ligands, such as nitrogen heterocyclics, the energy of the band maximum for the electron-transfer transition[48] in the complexes with $(NH_3)_5Ru^{2+}$ will serve. The transition in question undoubtedly involves transferring an electron from the t_{2g}^6 levels of Ru to an acceptor level on the ligand, having π symmetry matching that of the t_{2g} electrons of Ru. With judicious choice of ligand, and of substituents, series can be devised to expose the relationship between the energy of the unoccupied levels of the ligands and the rates of electron transfer.

The present Account has stressed observations, but the development of the subject nevertheless has been guided by theoretical considerations. In addition to publications, already mentioned, dealing with the theory of electron transfer through bridging groups, the reader is referred to a paper[49] in which the Halpern and Orgel[13] treatment is extended to include effects other than those arising from bond conjugation, a paper by Libby[50] emphasizing the relevance to the reactions of the Franck–Condon restrictions, and a more general treatment in book form[51] of the entire subject of electron-transfer reactions. The book provides breadth of coverage, useful for placing the material in the present Account into the context of the subject as a whole; it is also recommended for the clear development of the basic principles and for the care with which the present limitations of quantitative approaches are stated. The quantitative treatment of the complex behavior is difficult, at best, and it has not been helped by the experimental errors which have confounded the subject in its formative stage. It is too much to hope for a complete quantitative treatment at the present time, but some advances toward a quantitative theory can perhaps be based on the experimental results now being generated.

(48) P. C. Ford, DeF. P. Rudd, R. G. Gaunder, and H. Taube, *J. Am. Chem. Soc.*, **90**, 1187 (1968).

(49) P. V. Manning, R. C. Jarnagin, and M. Silver, *J. Phys. Chem.* **68**, 265 (1964).

(50) W. F. Libby, *J. Chem. Phys.*, **38**, 420 (1963).

(51) W. L. Reynolds and R. W. Lumry, "Mechanisms of Electron Transfer," The Ronald Press, New York, N. Y., 1966.

Kinetics of Organic Reactions in Micellar Systems

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The chemical literature in the period 1900–1958 contains a scattering of reports concerning reaction kinetics in aqueous media containing ionic or nonionic surfactants.[1] However, substantial insight into this area was first achieved in 1959 by Duynstee and Grunwald in their study of the effects of cationic and anionic surfactants on the rate of alkaline fading of cationic triphenylmethane dyes.[2] Since that time, related studies have been appearing at an increasing rate, and interest is still growing.

Surfactants are amphipathic molecules having both pronounced hydrophobic and hydrophilic properties. Such molecules have the important property of forming over a certain small concentration range, termed the critical micelle concentration or cmc, molecular aggregates, called micelles. It is the micelles, rather than individual surfactant molecules, which are responsible for altering the rates of organic reactions in aqueous solutions of surfactants. What has generally been observed is that the proper choice of surfactant can lead to rate increases of 5- to 1000-fold compared to the same reaction in the absence of surfactant. Typically, rate increases of 10- to 100-fold are elicited by surfactant concentrations near 0.02 *M*.

Although so far not more than 50 directly relevant publications have appeared in this field, several important generalizations and conclusions seem warranted. Furthermore, a good many avenues open for exploration are now apparent. This brief review attempts both to summarize these conclusions and to point the way to these avenues. As is customary in these pages, emphasis is placed on developments in our own laboratory, and we have deliberately avoided producing a comprehensive survey.

Motivation for adding surfactants to mixtures of chemical reactants, usually organic in nature, may be considered to derive from three sources: first, to further understanding of those factors which influence the rates and courses of organic reactions; second, and closely related to the first, to gain additional insight into the exceptional catalysis characteristic of enzymatic reactions; third, to explore the utility of micellar systems for the purpose of organic synthesis. At the moment, the last of the factors remains completely unexplored and the second largely a matter of speculation.

(1) For a summary of early work and an exhaustive compilation of studies in this field through early 1968, see: R. B. Dunlap, Ph.D. Thesis, Indiana University, 1968.

(2) E. F. J. Duynstee and E. Grunwald, *J. Am. Chem. Soc.*, **81**, 4540, 4542 (1959).

Many features of the kinetics of reactions in micellar systems are related to those of reactions in monolayers and to those in the presence of polyelectrolytes. Excellent reviews of these topics are available.[3,4]

Micellar Organization and Properties

A prerequisite to understanding reaction kinetics in micellar systems is the understanding of the structures and properties of the micelles themselves. On the whole, this background information is much less complete than one might wish. For micelles derived from surfactants of simple structure, a good deal is known that is relevant to our considerations. This information has been summarized in the excellent short review of Mukerjee.[5]

Basically, surfactants capable of forming aggregates (micelles) in aqueous solution are molecules of the type RX, in which R is a hydrophobic moiety, usually a straight-chain alkyl group of 8 to 18 carbon atoms, and X is a hydrophilic group. Further classification depends on the nature of X: in cationic surfactants, X is typically a quaternary ammonium or phosphonium group; in anionic surfactants, usually a sulfate, sulfonate, or carboxylate group; in nonionic surfactants, generally a polyoxyethylene group. Great structural variation is, of course, possible.

Micelle formation is accompanied by an abrupt, almost discontinuous, change in many solution properties; these include surface tension, conductivity, ability to solubilize certain dyes, viscosity, light scattering, and the like. These properties may be employed to determine the cmc for a particular surfactant under a specified set of conditions.

A number of factors affect the cmc for a surfactant and the size of the micelles formed. Increasingly hydrophobic surfactants have decreasing values of the cmc and form increasingly large micelles (in terms of both molecular weight and number of molecules per micelle). Increasing both the electrolyte concentration and the surfactant concentration leads to decreases in cmc and to increases in micellar size as does increasing the hydrophobicity of the counterion. At very high concentrations of certain electrolytes, micellar structure changes dramatically. The small spherical micelles may become large rod-shaped structures with molecular weights of one million or more. At sufficiently high surfactant concentrations, a liquid crystalline phase may be obtained.

Micelles formed from simple surfactants such as sodium dodecyl sulfate are generally roughly spherical and contain 50–100 surfactant molecules per micelle under most conditions. The hydrophilic groups occupy the surface of the micelle and are exposed to the solvent, while the hydrophobic chains of the surfactant molecules occupy the interior. Most physical measurements suggest that the interior of the micelle has substantially the properties of a liquid hydrocarbon.[5]

While the hydrocarbon-like portion of the micellar phase may have great importance for the association of certain organic substrates with that phase, it seems likely that most bond-changing reactions occur at the micellar surface (see below). The properties of this surface are, consequently, of great interest. A substantial fraction of the charged groups on the surface are neutralized through the inclusion of counterions.

With respect to these counterions, we may distinguish two regions. Immediately adjacent to the hydrocarbon core of the micelle, there is a highly charged layer in which the counterions are tightly bound to the micelle itself. This layer, usually referred to as the Stern layer, generally has its outer boundary at or slightly within the shear surface of the micelle. Beyond the Stern layer, the remainder of the counterions exist relatively unorganized with respect to the micellar surface. Their concentration decreases as one recedes from the surface according to the Boltzmann distribution law. Generally about 60–70% of the charges on the micellar surface are neutralized by counterions in the Stern layer. This value is, however, a sensitive function of the nature and concentration of counterions in the solution: the greater the concentration of counterions and the more pronounced their hydrophobic properties, the more nearly completely neutralized will be the micellar surface charge.

The hydration of the charged groups within the Stern layer is similar to that of the charged groups alone[6,7] and the thickness of the Stern layer is about equal to that of the ionic heads.[7] The potential difference between the bulk and micellar phases is usually in the range 50–100 mV. The surface of the micelles is rough.[8,9] Proton nmr and other evidence indicates that a portion of the hydrocarbon chain is, transiently at least, exposed to solvent, regardless of the nature of the micellar interior.[10] As a result of the rough-surfaced character of the micellar surface, molecules adsorbed at the surface may experience hydrophobic interactions with the surfactant molecules. The surface of micelles appears to be quite a polar environment, though not so polar as water itself. Mukerjee and Ray have assigned an approximate value of 36 for the dielectric constant of the surface of micelles derived from N-alkylpyridinium ions on the basis of measurements of the positions of charge-transfer bands between the pyridinium group and certain anions.[11]

Reaction Kinetics in Micellar Systems

The kinetics of organic reactions occurring in micellar systems are dominated by two factors: *electrostatic* interactions and *hydrophobic* interactions between the micellar phase and reactants, transition states, and

(3) H. Morawetz, *Advan. Catalysis*, in press.
(4) J. T. Davis, *ibid.*, **6**, 1 (1954).
(5) P. Mukerjee, *Advan. Colloid Interface Sci.*, **1**, 241 (1967).
(6) P. Mukerjee, *J. Colloid Sci.*, **19**, 722 (1964).
(7) D. Stigter, *J. Phys. Chem.*, **68**, 3603 (1964).
(8) D. Stigter and K. J. Mysels, *ibid.*, **59**, 45 (1955).
(9) D. Stigter, *J. Colloid Interface Sci.*, **23**, 379 (1967).
(10) J. Clifford, *Trans. Faraday Sci.*, **61**, 1276 (1965).
(11) P. Mukerjee and A. Ray, *J. Phys. Chem.*, **70**, 2144 (1966).

products. Prior to examining the individual aspects of these systems, let us focus briefly on these generalizations.

Kinetic studies performed thus far in solutions of micelle-forming surfactants can be grouped into two classes. The first includes those cases in which the surfactant provides a medium for the reaction but does not participate directly in it. For example, the kinetics of hydrolysis of methyl orthobenzoate are very substantially altered by the addition of small concentrations of sodium dodecyl sulfate to the reaction medium, although this surfactant does not react with the ortho ester. The second class includes those reactions in which the surfactant does participate directly in the reaction, either as a catalyst or as a substrate. Thus, the kinetics of acid-catalyzed hydrolysis of sodium dodecyl sulfate are markedly modified upon micellation of this material. In a related case, the nucleophilicity of long-chain N-acylhistidines toward *p*-nitrophenyl esters is enhanced upon the incorporation of the histidines into micelles. In the first case, the surfactant is itself the substrate and is consumed in the course of the reaction while, in the second, the surfactant is transiently modified through interaction with the substrate but is subsequently regenerated. As we shall see, the basic characteristics of both classes of reaction are related. We may also note at this point that, generally, one of the substrates will be uncharged and, hence, will interact with the micellar phase by virtue of its hydrophobic properties, and another will be charged and, hence, interact electrostatically with this phase. With these points in mind, then, we turn to the general aspects of these reactions noted above.

The electrostatic basis of kinetic effects in micellar systems may be appreciated on the basis of the following few examples. First, the acid-catalyzed hydrolysis of sodium alkyl sulfates is markedly promoted by micellation of the substrates while the uncatalyzed reaction is unaffected and the base-catalyzed reaction is strongly inhibited.[12] Second, the hydrolysis of the dianions of 2,4- and 2,6-dinitrophenyl phosphates is promoted by cationic surfactants but unaffected by anionic or nonionic surfactants.[13] Third, the acid-catalyzed hydrolysis of methyl orthobenzoate is subject to catalysis by anionic surfactants but is inhibited by cationic ones.[14-16] Fourth, the attack of anionic species on carboxylic esters is promoted by cationic surfactants but inhibited by anionic surfactants while the reaction of neutral species with these substrates is little affected by ionic surfactants of any charge.[17-23] Fifth, the addition of hydroxide ion to cationic dyes is subject to catalysis by cationic surfactants but to inhibition by anionic ones.[2] While this list can readily be expanded, the principal point is clear: the effects can be qualitatively understood in terms of electrostatic stabilization of the transition state, which possesses a charge or partial charge, relative to the reactant state, which is generally an uncharged substrate in the micellar phase and a charged one in aqueous solution. Not all reactions thus far examined fit neatly into this situation, but the majority of them do.

The hydrophobic component of kinetic effects in micellar systems may be appreciated in terms of a few examples related to those indicated just above. First, the degree of rate augmentation experienced on micellation for the hydrolysis of sodium alkyl sulfates increases very substantially as the length of the alkyl chain is increased from 10 to 18 carbon atoms.[12] Second, the acid-catalyzed hydrolysis of methyl orthobenzoate and methyl orthovalerate is subject to catalysis by anionic surfactants while that for methyl orthoformate is not.[16] Third, the attack of N-myristoyl-L-histidine on *p*-nitrophenyl esters is markedly accelerated in the presence of micelles formed from hexadecyltrimethylammonium bromide while the attack of N-acetyl-L-histidine is not and, furthermore, the reaction of the former nucleophile with *p*-nitrophenyl hexanoate is much faster than that with the corresponding acetate.[19] Finally, rate and equilibrium constants for the addition of cyanide ion to N-alkylpyridinium ions are markedly increased by cationic surfactants and the magnitude of the change is accentuated with increasing chain length in the surfactants and with increasing chain length of the N-alkylpyridinium ion.[24] Again, this list might be expanded, but the point is clear: kinetic effects in micellar systems are accentuated when hydrophobic interactions between substrate and surfactant are accentuated. We shall focus our attention on the more thoroughly studied systems, including: (i) hydrolysis of ortho esters and acetals; (ii) nucleophilic reactions of carboxylic esters; (iii) hydrolysis of phosphates and sulfates; and (iv) addition of cyanide ion to pyridinium ions. From these investigations, a number of aspects of kinetic behavior in micellar systems have proved interesting: (i) the reaction site; (ii) surfactant concentration–rate profiles; (iii) substrate concentration–rate profiles; (iv) surfactant structure; (v) substrate structure; and (vi) salt effects. These points are discussed sequentially below.

The Reaction Site. Several lines of evidence strongly suggest that most reactions occur on the surface of the micelle, at or near the highly charged double layer which surrounds the hydrocarbon core and not within the hy-

(12) J. L. Kurz, *J. Phys. Chem.*, **66**, 2239 (1962).
(13) C. A. Bunton, E. J. Fendler, L. Sepulvada, and K.-U. Yang, *J. Am. Chem. Soc.*, **90**, 5512 (1968).
(14) R. B. Dunlap and E. H. Cordes, *ibid.*, **90**, 4395 (1968).
(15) R. B. Dunlap and E. H. Cordes, *J. Phys. Chem.*, **73**, 361 (1969).
(16) M. T. A. Behme, J. G. Fullington, R. Noel, and E. H. Cordes, *J. Am. Chem. Soc.*, **87**, 266 (1965).
(17) L. R. Romsted and E. H. Cordes, *ibid.*, **90**, 4404 (1968).
(18) E. F. J. Duynstee and E. Grunwald, *Tetrahedron*, **21**, 2401 (1965).
(19) C. Gitler and A. Ochoa-Solano, *J. Am. Chem. Soc.*, **90**, 5004 (1968).
(20) A. Ochoa-Solano, G. Romero, and C. Gitler, *Science*, **156**, 1243 (1967).
(21) P. Heitmann, *European J. Biochem.*, **5**, 305 (1968).
(22) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Am. Chem. Soc.*, **90**, 1333 (1968).
(23) F. M. Menger and C. E. Portnoy, *ibid.*, **89**, 4698 (1967).
(24) D. Dunham, P. Head, and E. H. Cordes, unpublished observations.

drocarbon core itself. It is true that no very clear line can be drawn between the micelle surface and the micelle interior as noted above.[8-10] We shall include the first two or three methylene groups of the hydrocarbon chain of the surfactant molecules as well as the hydrated charged groups (or polar nonionic head groups) as comprising the micellar surface. The distinction that we really wish to make is whether the reactions occur in a region of appreciable aqueous character or not. In the first place, there is substantial evidence that organic molecules possessing appreciable polar character are localized predominantly on the micellar surface. The interesting proton magnetic resonance studies of Eriksson and Gillberg strongly suggest that molecules such as benzene and nitrobenzene are solubilized at the micellar surface while molecules such as cyclohexane are solubilized in the micellar interior.[25] Note that, as a consequence of the rough surfaced nature of the micelles, the statement that a particular molecule exists predominantly at the micellar surface does not preclude strong hydrophobic interactions between the molecule and the micelle. Indeed, interpretation of a substantial amount of kinetic data requires that just such interactions must exist. In the second place, it is a bit difficult to visualize reactions involving ionic species occurring readily within the hydrocarbon-like interior. Even if the interior should prove to be somewhat wet, we know of no evidence to suggest that ions from the bulk phase are included within this interior. In the third place, the rate of certain organic reactions is unaffected when one of the reactants is incorporated into the micellar phase and another is excluded from it.[26] In the fourth place, the striking salt effects noted below are readily accommodated in terms of reactions occurring at the micellar surface but are more difficult to account for in terms of reactions occurring in the micellar interior. Taken as a whole, these results suggest that most reactions studied thus far in micellar systems do occur at the micellar surface and, furthermore, that the micellar surface is probably the principal habitat of the organic substrates (clearly, the principal site of occupation and site of reaction need not be the same). Exceptions may occur.

Surfactant Concentration–Rate Profiles. In Figure 1, second-order rate constants for the hydrolysis of methyl orthobenzoate in dilute aqueous solutions of sodium dodecyl sulfate are plotted against the concentration of the surfactant.[14] The concentration–rate profile is multiphasic: below the cmc for the surfactant, the rate constants are independent of surfactant concentration. Above the cmc, the rate constants rise rapidly with increasing concentration of this surfactant. At the optimal surfactant concentration, a rate augmentation of 85-fold is observed for this reaction. While not all concentration–rate profiles show all of these features, they do seem to be the general ones for reactions in micellar systems.[14,15,17,27-30] Profiles of this type can be rationalized on the basis of (i) the necessity of micelles for catalysis, (ii) adsorption of a progressively greater fraction of the substrate into the micellar phase until that fraction approaches unity with increasing surfactant concentration, and (iii) inhibition of the micellar reaction by the counterions of the surfactant itself. In the case of methyl orthobenzoate hydrolysis in the presence of sodium dodecyl sulfate, it has been shown that this interpretation must be substantially correct.[14] Employing molecular sieve chromatography,[26] the equilibrium constant for the association of substrate with surfactant was evaluated: $K_{assoc} = 73\ M^{-1}$. This value accounts quantitatively for the increase in rate constant with increasing surfactant concentration. That is, when the substrate is predicted to be 50% associated with the micellar phase on the basis of the equilibrium constant, about 50% of the maximum catalysis is experienced, and so on. Furthermore, when the total concentration of sodium ion is maintained constant by the addition of the necessary quantities of inorganic sodium salts, the inhibition of the reaction at high surfactant concentrations disappears.

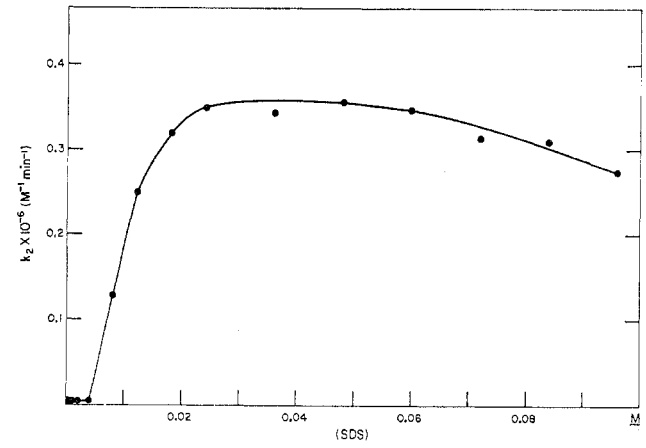


Figure 1. Second-order rate constants for hydrolysis of methyl orthobenzoate in aqueous solution at 25° plotted against the concentration of sodium dodecyl sulfate.

The general aspects of the profile in Figure 1 may change in two ways for other reactions. In some cases, there is evidence for the formation of small complexes between surfactant molecules and substrates at concentrations of the surfactant below the cmc and, in addition, for the induction of micelle formation by the substrate.[13,22] In such instances, catalysis, or, for that matter inhibition, will occur at surfactant concentrations lower than that for the cmc.

A very interesting case of the dependence of rate on surfactant concentration is provided in the work of Gitler and Ochoa-Solano concerning the hydrolysis of *p*-nitrophenyl esters in the presence of mixed micelles of

(25) J. C. Eriksson and G. Gillberg, *Acta Chem. Scand.*, **20**, 2019 (1966).
(26) D. G. Herries, W. Bishop, and F. M. Richards, *J. Phys. Chem.*, **68**, 1842 (1964).
(27) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **90**, 5972 (1968).
(28) M. T. A. Behme and E. H. Cordes, *ibid.*, **87**, 260 (1965).
(29) L. R. Cramer and J. C. Berg, *J. Phys. Chem.*, **72**, 3686 (1968).
(30) R. B. Dunlap, G. A. Ghanim, and E. H. Cordes, *ibid.*, **73**, 1898 (1969).

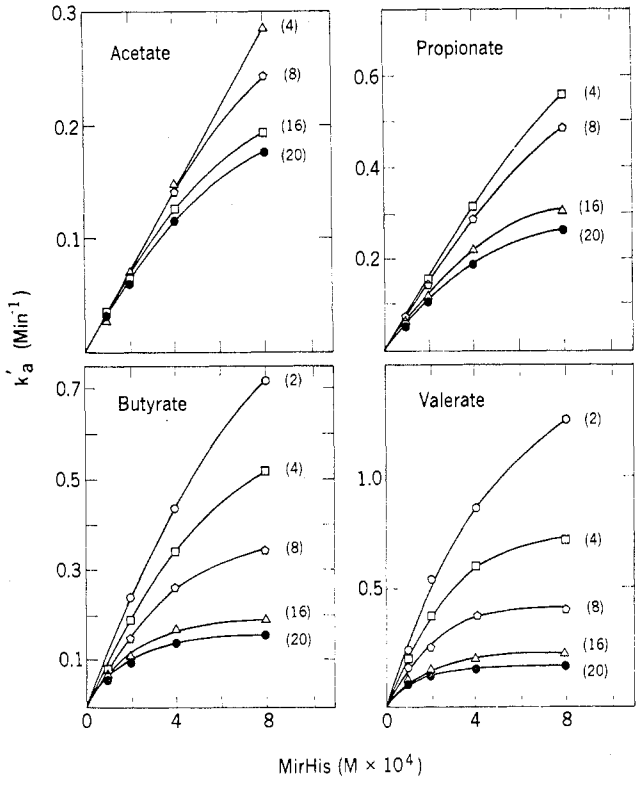


Figure 2. Pseudo-first-order rate constants for the liberation of *p*-nitrophenol in the reaction of mixed micelles of N$^{\alpha}$-myristoylhistidine and cetyltrimethylammonium bromide (at the ratio indicated in parentheses) with *p*-nitrophenyl acetate (PNPA), propionate (PNPP), butyrate (PNPB), and valerate (PNPV).

N$^{\alpha}$-myristoyl-L-histidine (MirHis) and hexadecyltrimethylammonium bromide.[19] In this system, the MirHis is acylated by the substrates and the cationic surfactant serves to solubilize the reactants and products. In Figure 2, first-order rate constants for the liberation of *p*-nitrophenol from several *p*-nitrophenyl esters are plotted as a function of the concentration of MirHis and as a function of the ratio of the concentration of MirHis to that of the cationic surfactant in the mixed micelles. Clearly, the reaction is linearly dependent on MirHis concentration only provided that there is relatively little cationic surfactant in the system and that the presence of the latter species inhibits the reaction. This can be understood in terms of a nonproductive binding of the substrates to the mixed micelles as a factor additional to those previously mentioned. The minimal kinetic scheme must take the form

$$S + Mi \overset{K_i}{\rightleftharpoons} S\cdot Mi$$

$$S + Ma \xrightarrow{k_2} X\text{-}Ma + P_1$$

$$X\text{-}Ma + H_2O \xrightarrow{k_3} Ma + P_2$$

in which S is the substrate, Mi and Ma, respectively, are the inactive and active positions within the mixed micelle, S·Mi is a rapidly formed nonproductive complex, X–Ma is acylated MirHis in the mixed micelle, and P_1 and P_2 are *p*-nitrophenol and the acid corresponding to the ester employed, respectively. Analysis

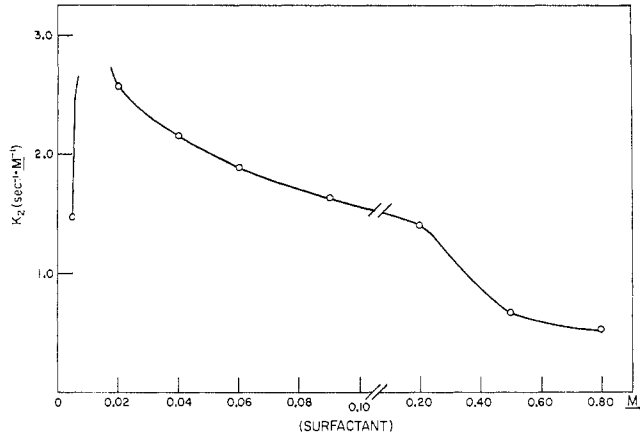
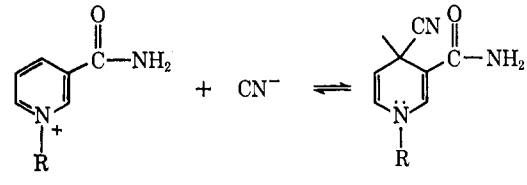


Figure 3. Second-order rate constants for the addition of cyanide ion to N-dodecyl-3-carbamoylpyridinium bromide as a function of the concentration of tetradecyltrimethylammonium bromide at 25°.

of the rate laws derived from this formulation yields values for the associated rate and equilibrium constants. Acylation of the mixed micelle is very much more rapid then subsequent deacylation just as is the case with the reactions of these same esters with enzymes such as chymotrypsin and glyceraldehyde 3-phosphate dehydrogenase.[31,32]

In isolated cases, reaction kinetics have been studied in concentrated solutions of ionic surfactants. One example is provided by the addition of cyanide ion to N-dodecyl-3-carbamoylpyridinium bromide in a solution of *n*-tetradecyltrimethylammonium bromide.[24] Ob-



served rate constants for this reaction are illustrated in Figure 3 as a function of surfactant concentration. At low concentrations the profile is typical; at higher concentrations, the rates fall off. This must be partially the consequence of salt effects but part of the effect may be due to changes in micellar structure. Over this concentration range, two transitions in structure do occur: a transition from spherical to rod-shaped micelles and one to an essentially liquid crystalline phase. While these transitions perhaps affect the reaction rate, the effects are not sharp at the positions where the transitions occur.

Substrate Concentration–Rate Profiles. By analogy with other systems, including enzymatic ones, in which a complex is formed between reactants prior to bond-changing reactions, one might expect that saturation of the micellar phase with increasing substrate concentrations would be observed. In certain cases at least, such

(31) F. J. Kèzdy and M. L. Bender, *Biochemistry*, 1, 1097 (1962).
(32) M. T. A. Behme and E. H. Cordes, *J. Biol. Chem.*, **242**, 5500 (1967).

Table I

Temperature Dependence of the Maximal Rate Increases Elicited by a Series of Sodium Alkyl Sulfates for Methyl Orthobenzoate Hydrolysis in Aqueous Solution

Sodium alkyl sulfate	Temp, °C	$k_2^0 \times 10^{-6}$,[a] M^{-1} min^{-1}	$k_2 \times 10^{-6}$,[b] M^{-1} min^{-1}	Max rate increase
Octyl	25.0	0.00502	0.0351 at 0.20 M	7.0
Decyl	40.0	0.0191	0.296 at 0.075 M	15.5
	32.5	0.0094	0.211 at 0.075 M	22.4
	25.0	0.00452	0.121 at 0.075 M	26.8
Dodecyl	40.0	0.0188	0.774 at 0.024 M	41.2
	32.5	0.0094	0.584 at 0.036 M	62.1
	25.0	0.00452	0.357 at 0.048 M	79.0
Tetradecyl	40.0	0.0168	1.37 at 0.030 M	81.5
	35.0	0.0122	1.06 at 0.015 M	86.9
	30.0	0.00864	0.793 at 0.020 M	91.8
Hexadecyl	45.0	0.0298	2.56 at 0.006 M	86

[a] Second-order rate constants in the absence of surfactant. [b] Second-order rate constants for the reaction in the presence of the indicated concentrations of surfactants at which values maximum catalysis occurs.

behavior is found. In Figure 4, the first-order rate constants for hydrolysis of methyl orthobenzoate in the presence of 0.001 M sodium dodecyl sulfate are plotted as a function of the concentration of the ortho ester.[16] The decreasing rate with increasing substrate concentration most likely represents saturation of the micellar phase with substrate. Thus, as substrate concentration increases beyond the saturation point, an increasing fraction of the substrate must exist free in the solution. As this fraction approaches unity, the rate constant for the reaction must approach that for the reaction in purely aqueous solution, as indeed it does.

Effect of Surfactant Structure. Perhaps the most dramatic change in surfactant structure, and the easiest to interpret, in terms of influence on the kinetics of reactions in micellar phases, is change in the charge type of the head group. As developed briefly above, those reactions which are catalyzed by anionic surfactants are generally unaffected by nonionic ones and inhibited by those which are cationic, and so on.

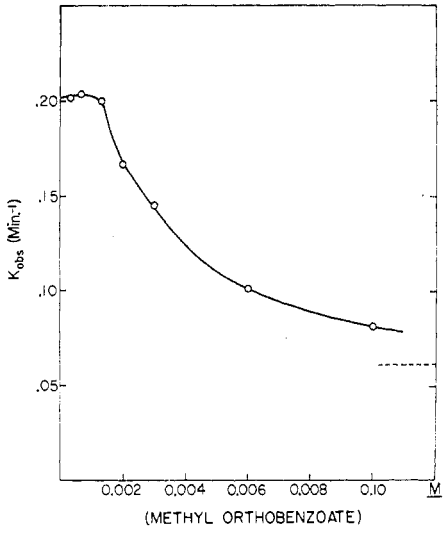


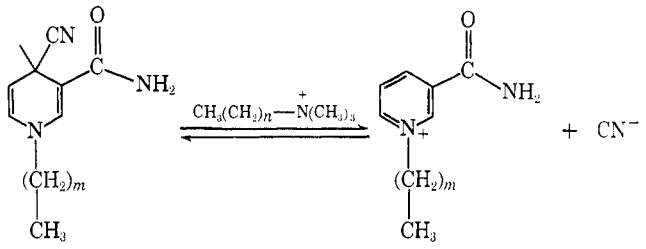
Figure 4. First-order rate constants for the hydrolysis of methyl orthobenzoate in the presence of 0.001 M sodium dodecyl sulfate at 25° and pH 4.95 plotted as a function of the substrate concentration. The dotted line indicates the rate constant under these conditions in the absence of surfactant.

Maintaining the charge type of the surfactant constant there are two means of varying the surfactant structure: by changing the length of the hydrocarbon chain and by changing the nature of the head group. Some information is available concerning both of these points. Quite generally, increasing the hydrophobic character of the surfactant increases its efficiency as a catalyst. Here we must distinguish two cases. In the first place, at equal concentrations of two surfactants, the more hydrophobic may appear to be the better catalyst (or inhibitor) simply because it has the greater affinity for the substrate. In the second place, differences in catalytic ability between related surfactants may persist even under conditions in which they are present at concentrations sufficiently high so that substantially all of the substrate is incorporated into the micellar phase in both cases.

While there are several examples of both types of behavior more interesting observations relate to the latter point. Several examples in the literature indicate that the more hydrophobic surfactants are also the better catalysts under conditions of saturation with surfactant. For the case of methyl orthobenzoate hydrolysis in the presence of sodium alkyl sulfates maximal rate increases as a function of surfactant structure are collected in Table I. Clearly, the longer the hydrocarbon chain of the surfactant, the better catalyst it becomes. Similar results are obtained in other systems, *e.g.*, the rate and equilibrium constants for addition of cyanide ion to N-alkylpyridinium ions in the presence of *n*-alkyltrimethylammonium salts increase with increasing hydrophobicity of the surfactant.[24] There are several reasons why increasing the hydrophobic character of the surfactant might tend to make it a better catalyst for organic reactions under saturating conditions. The charge density of ionic groups at the surface may increase with increasing chain length, thus increasing the electric field at the reaction site. There is substantial evidence to indicate that this is in fact the case, although it is difficult to know if the increased field is large enough to account for the observed differences in rate. There is the difficult question of the exact posi-

Table II

Equilibrium Constants and Rate Constants for Dissociation of 1,4-Cyanide Adducts of a Series of N-Alkylpyridinium Ions in Aqueous Solutions of 0.02 *M* Alkyltrimethylammonium Ions at 25°



m	*n* = 9	11	13	15
		Equilibrium Constants, *M*		
7				7.4×10^{-3}
9			1.9×10^{-3}	1.4×10^{-3}
11		5.5×10^{-4}		2.9×10^{-4}
13	3.1×10^{-3}	3.4×10^{-4}	2.8×10^{-4}	2.6×10^{-4}
15		2.2×10^{-4}		2.1×10^{-4}
		Rate Constants, M^{-1} sec^{-1}		
7				0.21
9			1.08	1.35
11		2.46		5.77
13	0.28	5.84	6.57	10.4
15		6.38		13.3

tioning of the substrate with respect to the micellar surface and its dependence on the hydrocarbon moiety of the surfactant. Also the binding forces between the hydrophobic parts of the substrate and micelle may be employed to reduce the over-all activation energy for the reaction.[19]

In terms of changing the nature of the head group without changing the charge type, only one thorough study has been carried out.[15] Examination of some 30 anionic surfactants as catalysts for methyl orthobenzoate hydrolysis reveals marked differences between them, although all are active. Some of the most active appear to be exceptionally good catalysts.

Effect of Substrate Structure. There are two aspects of substrate structure which have proved interesting in terms of reaction kinetics in micellar systems: substrate hydrophobicity and polar substituents. Generally, increasing the hydrophobic character of the substrate increases the influence of the micellar phase on the velocity of the reaction just as increasing the hydrophobicity of the surfactant tends to accentuate these effects. Typical examples are provided by surfactant-dependent ester hydrolysis,[17,19,20,23] sulfate ester hydrolysis,[12] ortho ester hydrolysis,[17] and addition of cyanide ion to pyridinium ions.[24] In some respects, studies in the last of these systems may be the most revealing: in Table II rate and equilibrium constants for the addition of cyanide to a series of N-alkyl-3-carbamoylpyridinium ions in the presence of a series of alkyltrimethylammonium ions are collected. With respect to both substrate and surfactant, increasing hydrophobic properties increases the reactivity and affinity of cyanide ion for the substrates. This system perhaps provides the best evidence for a point raised above: that hydrophobic interactions may be employed to reduce the activation energy.[19] At the concentrations employed in these studies, 0.02 *M* surfactant, the rate and equilibrium constants are nearly maximal. Thus, the substrates are associated substantially completely with the micellar phase. Furthermore, the properties of the micelles themselves should not be markedly dependent on the nature of the substrate, even following incorporation of the substrate into the micelles, since surfactant molecules outnumber substrate molecules about 200:1. One possible model within the framework of hydrophobic interaction contributions to activation energy is the following. In the course of the reaction process, a substrate possessing a polar head group is converted into a product in which this polar character is largely lost. As a result, the product molecule may occupy a somewhat different position with respect to the micellar structure than the reactant. The increasing hydrophobic interactions may drag the polar head group into the less agreeable environment that, in the product, will be occupied by an uncharged species. The hydrophobic interactions thus destabilize the reactant state with respect to the product state and contribute to the activation energy for the over-all process. It is interesting to note that the rate and equilibrium constants for these reactions are 1000 to 10,000 times greater than for the same reactions in the absence of surfactants.

The effect of polar substituents on the rates of organic reaction in micellar phases appears to differ substantially from such effects in aqueous solution. In Figure 5 Hammett plots for the hydrolysis of a series of acetals in water and in dilute solutions of sodium dodecyl sulfate are provided.[30] Clearly, the reactions in the micellar phase are the more susceptible to polar effects. This finding suggests that the transition states

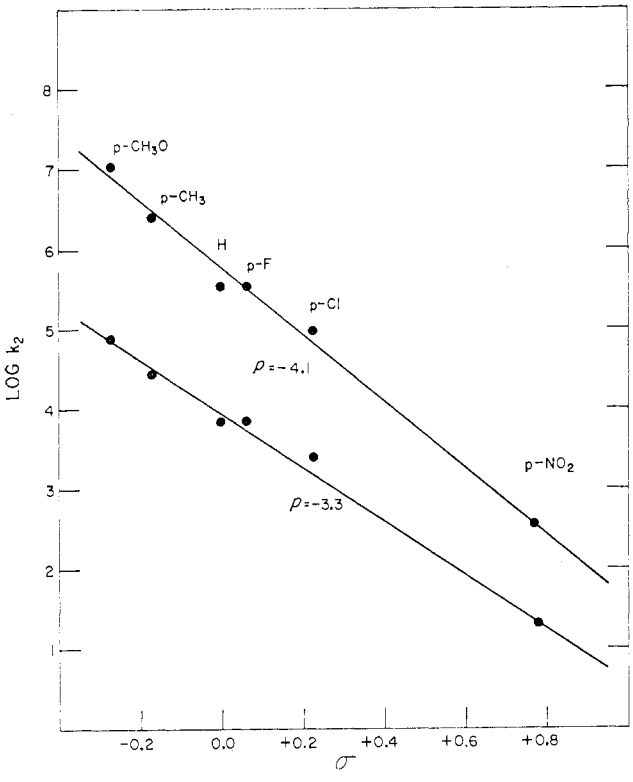


Figure 5. Logarithms of second-order rate constants (in units of M^{-1} min^{-1}) for the hydrolysis of a series of *para*-substituted benzaldehyde diethyl acetals in aqueous solution (lower line) and in the presence of sodium dodecyl sulfate (upper line) plotted against the Hammett substituent constants.

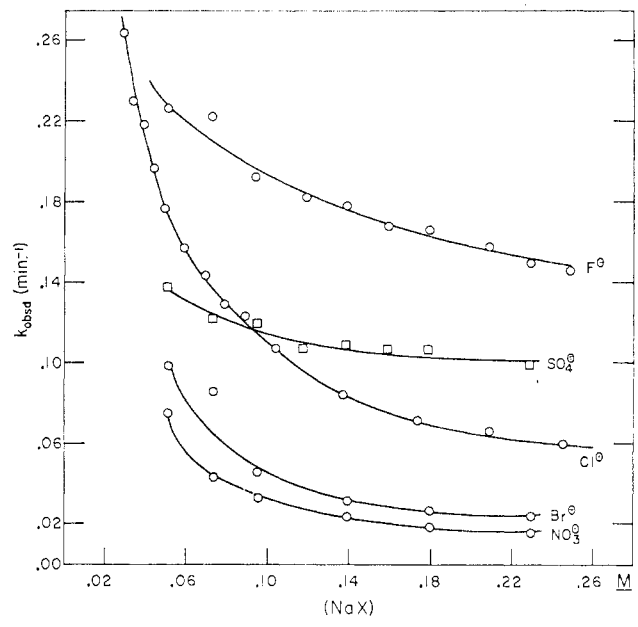


Figure 6. First-order rate constants for hydrolysis of *p*-nitrophenyl hexanoate in the presence of 0.009 M tetradecyltrimethylammonium chloride, pH 10.15, as a function of the concentration of several anions.

for these reactions are reached rather later along the reaction coordinate in the micellar phase than in the aqueous phase. At first glance at least, this is a surprising conclusion since, generally, those factors which facilitate reactions cause the transition state to be reached earlier along the reaction coordinate.[33,34] On the other hand, the observation can be rationalized on the basis of formation of a positively charged species early in the reaction process (the protonated substrates) and decreasing electrostatic stabilization as the positive charge is dispersed in the transition state.

Salt Effects. One of the striking aspects of the kinetics of organic reactions in micellar systems is their sensitivity to salt effects. Changes in the nature or concentration of electrolyte that would lead to barely detectable differences in rates of reactions in purely aqueous systems frequently cause differences of an order of magnitude or more for the same reactions in the presence of ionic surfactants. Two specific examples will suffice to indicate the principal feature of the inhibition. In Figure 6, first-order rate constants for hydrolysis of *p*-nitrophenyl hexanoate at pH 10.15 in the presence of tetradecyltrimethylammonium chloride are plotted as a function of the concentration of several monovalent anions.[17] All anions studied are inhibitors and 0.10 M concentrations of bromide and nitrate ions are sufficient to convert the surfactant-catalyzed reaction into a surfactant-inhibited one. As the hydrophobicity of the anion increases, and hence its tendency to associate with the micellar surface, the extent of inhibition is accentuated. Similar conclusions are evident from Figure 7 in which second-order rate constants for hydrolysis of methyl orthobenzoate in the presence of sodium dodecyl sulfate are plotted against the concentration of ammonium ions.[14] Again, marked inhibition is observed and the inhibition increases as the hydrophobic character of the salt increases. These observations can be readily understood in terms of increasing the extent of charge neutralization of the micellar surface. To the extent that catalysis is dependent on electrostatic stabilization of the transition state with respect to the ground state, such charge neutralization must reduce the catalytic effect. In other cases, the salt inhibition may derive principally from the displacement of one reactant from the micellar surface by the electrolyte.

Conclusion

At the outset of this short review, we pointed out that studies of the kinetics of organic reactions may prove relevant to the further understanding of enzymatic reactions and may prove of value for purely synthetic purposes. By way of conclusion, we should like to examine each of these points briefly.

There has been a great deal of loose discussion concerning "model systems" which purport to provide insight into the mechanism of enzymatic reactions. In this regard, it is important to distinguish those cases which merely mimic enzymatic reactions in one or more respects and those which actually provide insight into enzymatic reactions. While delicacy precludes ex-

(33) G. S. Hammond, *J. Am. Chem. Soc.*, 77, 334 (1955).
(34) J. E. Leffler, *Science*, 117, 340 (1953).

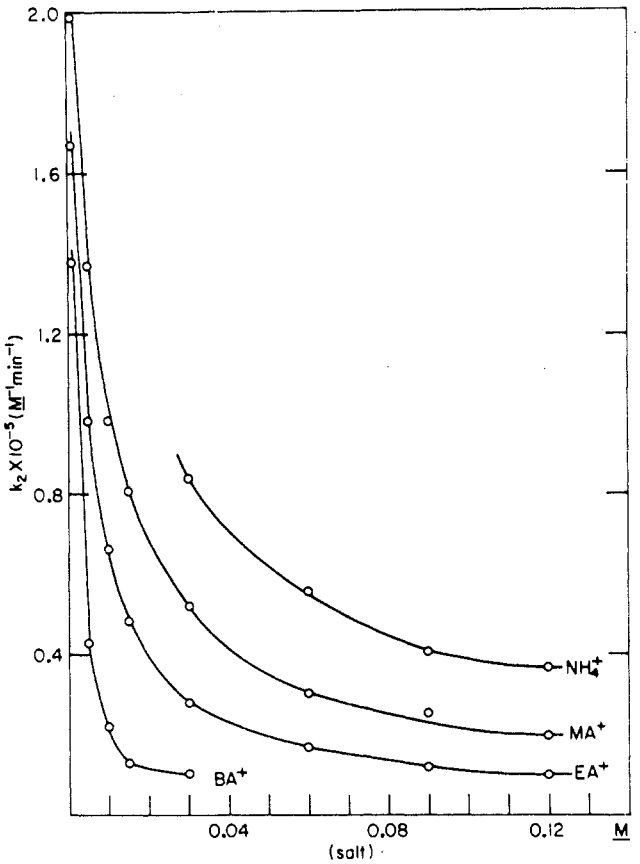


Figure 7. Second-order rate constants for methyl orthobenzoate hydrolysis in aqueous solutions containing 0.01 *M* sodium dodecyl sulfate plotted as a function of the concentration of unsubstituted, methyl-, ethyl,- and butylammonium ions.

amples which fall clearly into the former class, one might point out the important studies of Snell and Braunstein relevant to pyridoxal phosphate dependent reactions[35] and those of Bender, Bruice, Jencks, and others concerning the mechanism of acyl transfer reactions[36] as falling clearly into the latter one.

What can we hope to learn about enzymatic reactions from studies of reaction kinetics in micellar systems? Reasoning from the principle that reaction pathways and modes of catalysis for an enzymatic reaction and the corresponding nonenzymatic one will be closely related, it seems likely that one can gain some understanding concerning the extent to which particular types of interactions will contribute to reaction velocity and specificity for particular reaction types. Three examples of these points are: micellar systems provide a good means of examining proximity effects in systems in which weak interactions are employed to approximate the reactants; reactions in micellar systems probably maximize the influence of electrostatic interactions on reaction rates for certain types of reactions; micellar systems provide a reasonable opportunity to understand the extent to which hydrophobic interactions between substrate and catalyst contribute to enzymatic specificity. While studies in micellar systems are insufficiently developed to permit really firm conclusions to be drawn at the moment, the parallel between the catalysis observed for the hydrolysis of acetals by anionic surfactants[30] and that for related substrates by lysozyme lends credence to the proposal that an anionic group of the enzyme is active catalytically through electrostatic stabilization of the developing carbonium ion in the transition state.[37] Furthermore, on the basis of studies in micellar systems, it seems likely that this electrostatic catalysis contributes about 100-fold to the over-all catalytic effect.

The use of surfactant systems for the purpose of synthesis has only been probed in one case: emulsion polymerization. It seems reasonable that related systems will prove equally valuable for other syntheses as well. The basic point is a simple one. Taking advantage of the hydrophobic nteractions between the micellar interior and the substrate, one has the opportunity to carry out reactions in an essentially aqueous environment, the micellar surface, employing water-insoluble substrates. Such studies may prove particularly useful for those reactions which mimic biosynthetic processes, including the cyclization reactions of terpene and steroid precursors and those reactions involved in the assembly of alkaloids.

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(35) For a review see: A. E. Braunstein, "The Enzymes," Vol. II, P. D. Boyer, H. Lardy, and K. Myrback, Ed., Academic Press, New York, N. Y., 1960, p 113.

(36) For a review, see: T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966.

(37) C. C. F. Blake, L. N. Johnson, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Proc. Roy. Soc.* (London), **B167**, 378 (1967).