

MICELLAR CATALYSIS AND INHIBITION

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Abstract - Micelles of non-functional surfactants (detergents) can catalyze bimolecular reactions by bringing reactants together in an environment conducive to reaction and they inhibit reactions by keeping reactants apart but they affect rates of unimolecular reactions by providing a submicroscopic medium. The relation between rate and surfactant concentration can be explained in terms of the distribution of reactants between the aqueous and micellar pseudophases which can also be perturbed by added solutes. Catalysis depends upon the charge type of the reaction and reactant hydrophobicity. Functional micelles are often highly effective as nucleophilic or general base catalysts and can give chiral recognition. Substrate micellization can control reaction stereochemistry.

INTRODUCTION

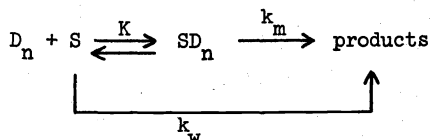
Micelles are submicroscopic aggregates of surfactants (detergents, amphiphiles) which have a hydrophobic residue and an ionic, zwitterionic or polar head group (Ref. 1). Typical ionic surfactants are: cationic, hexadecyltrimethylammonium bromide (CTABr), $n\text{-C}_{16}\text{H}_{33}\text{NMe}_3\text{Br}$; and anionic, sodium dodecylsulfate (NaLS, SDDS), $n\text{-C}_{12}\text{H}_{25}\text{OSO}_3\text{Na}$. Many commercial nonionic surfactants, e.g., Brij, Igepal and Triton are polyethylene oxides with a hydrophobic end group. In dilute aqueous solution ionic surfactants are strong electrolytes, but at the critical micelle concentration (cmc) there are sharp changes in such bulk properties as conductivity and surface tension, and light scattering shows that aggregates form. The cmc decreases with increasing length of the *n*-alkyl group, e.g., from 7×10^{-2} M for $\text{C}_{10}\text{H}_{21}\text{NMe}_3\text{Br}$ to 9×10^{-4} M for $\text{C}_{16}\text{H}_{33}\text{NMe}_3\text{Br}$ (Ref. 2), and is consistently lower for nonionic than for ionic surfactants, but for ionic surfactants it is relatively insensitive to the sign of the charge on the head group. In water micelles generally contain more than 50 monomer units and the aggregation numbers are larger for nonionic than for ionic micelles where coulombic repulsions oppose the hydrophobic and van der Waals interactions which hold the micelles together. Addition of salts and nonionic hydrophobic solutes increases micellar size and reduces the cmc by reducing interionic head group repulsions and introducing favorable hydrophobic interactions.

At relatively low surfactant concentration micelles are spheroidal, but they grow and elongate at higher surfactant concentration, especially in the presence of hydrophobic solutes (Ref. 1 & 3). Most kinetic studies have used conditions in which the micelles are approximately spheroidal and increase in micellar size, of itself, does not seem to affect the reaction rates (Ref. 4), although they are affected by added salts which change the surface charge of the micelle.

An idealized model of a (spherical) ionic micelle has a hydrocarbon-like interior which is surrounded by the so-called Stern layer containing the ionic head groups and bound counterions. There is then the broader Gouy-Chapman layer into which counterions are attracted (Ref. 1). It is generally assumed that counterions in the Stern layer are closely associated with the micelle, but there is generally a rapid exchange between solutes in the micelle and in bulk solvent and between monomeric and micellized surfactant, so that our definition of the micellar boundary is an arbitrary one, and it has been suggested that the micellar boundary should be defined in terms of the region of electric neutrality between micelle and bulk solvent rather than in terms of the boundary of the Stern layer (Ref. 5). Although the present discussion is concerned only with the normal micelles which form in water and in some other highly associated solvents (Ref. 6), reversed micelles, with the ionic or polar head group in the micellar interior, form in many nonpolar solvents. These micelles are often very effective catalysts and their chemical and physical properties are exciting considerable interest (Ref. 7). With both these systems, as with polyelectrolytes, we are studying reactions at the surfaces of submicroscopic aggregates, which in some respects model interfaces in biological systems.

Hydrophobic solutes and counterions will be attracted to the micelle so that a cationic micelle should assist reaction between neutral molecules and anions, whereas an anionic micelle will inhibit such a reaction (Ref. 8 - 11). Micelles may affect the rates of spontaneous, unimolecular reactions by attracting the substrate and providing an environment which is more or less favorable to reaction than the bulk solvent. Micellar effects on ionic equilibria were initially interpreted by Hartley (Ref. 12) in terms of micellar charge and reaction charge type, and his concepts have been successfully applied to rates, with the prediction that cationic micelles will catalyze, and anionic micelles inhibit, reaction between a neutral substrate and an anion. This coulombic role tells us nothing about the effects of non-ionic micelles, but they sometimes inhibit reactions of hydrophobic substrates which enter the micellar interior where they are protected from hydrophobic reagents (Ref. 13). There are also many examples of reactions of sparingly water soluble compounds being run effectively on a preparative scale using such adducts as quaternary ammonium ions or cationic or non-ionic surfactants (Ref. 14 & 15), but in many of these systems the important factors are phase transfer (Ref. 15), or dispersion of the insoluble reactant (Ref. 16).

The simplest model for micellar catalysis or inhibition is:



where S is the substrate and D the surfactant (detergent), and D_n the micelle. Provided that we assume that only one substrate molecule is incorporated into D_n each micelle, that the reactants do not change the micellar properties, and that k_w is unaffected by added surfactant we can write (Ref. 9 & 10):

$$k_{\psi} = (k_w + k_m K C_m) / (1 + K C_m) \quad (1)$$

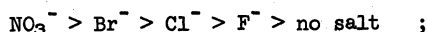
where the concentration of micelles, $C_m = (C_D - cmc)/N$, and N is the aggregation number of the micelles. These assumptions require that the surfactant be in large excess over the substrate, and most experiments have been done under these conditions. For this reason most workers use substrates whose reactions can be followed by a sensitive analytical technique, e.g., spectrophotometry, so that nitrophenyl derivatives are very popular substrates.

Equation 1 is akin to the well known Michaelis Menten equation and is usually rearranged into the reciprocal form (Ref. 17), which is analogous to the Lineweaver-Burk equation as applied to enzymic reactions:

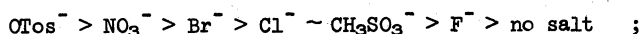
$$\frac{1}{k_{\psi}} = \frac{1}{k_w - k_m} + \frac{1}{(k_w - k_m)} \frac{N}{K(C_D - cmc)} \quad (2)$$

Equations 1 and 2 are successful in treating micellar inhibition and micellar catalysis of unimolecular reactions where rate constants increase with increasing surfactant concentration above the cmc to plateau values when all the substrate is in the micelles (Ref. 4,9,10 & 17). But many bimolecular reactions give rate maxima because equations 1 and 2 do not take into account the distribution of both reagents (Ref. 8 - 10, 18 & 19). Qualitatively we can assume that the rate will increase as both reactants are brought together in the micelle, but once one of the reactants is almost wholly in the micelles a further increase in surfactant concentration will "dilute" the reactants in the micellar pseudophase. There are, however, some bimolecular reactions which give rate-surfactant plateaux, and they appear to involve hydrophobic reactants of structures such that incorporation of one reactant into the micelle assists incorporation of the other. Some examples are: aromatic nucleophilic substitution by PhS^- and reactions of triarylmethyl carbocations with OH^- or BH_4^- catalyzed by cationic micelles. Association constants, K, have been determined directly, e.g., by gel filtration or solubility, and by kinetic analysis. They are as large as 10^8 for hydrophobic substrates.

Before considering further the failure of the quantitative treatment as applied to many bimolecular reactions it will be useful to consider qualitatively the decrease of micellar catalysis brought about by added salts, as shown below by the following sequences of inhibition. For the reaction of OH^- with carboxylic esters in cationic micelles the inhibition follows the anion order:

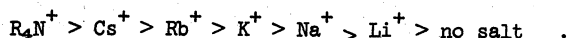


and for the corresponding reactions of halonitrobenzenes and triaryl phosphates it is:



but for the acid hydrolysis of trimethylorthobenzoate in anionic micelles inhibition follows

the cation order:



The salt inhibition clearly depends on the nature of the added ion of opposite charge to the micelle. For univalent ions the large effects are given by low charge density, hydrophobic, ions which interact strongly with the micelle and compete for it with ionic reagents (Ref. 20). The salt orders of inhibition depend little upon the nature of reactions of the same charge type, except for a few unimolecular reactions where the salt effects are anomalous (Ref. 21). These anomalies can be understood in terms of changes in the structure of the micelle, and in general counterions reduce micellar catalysis by excluding ionic reagents from the micelle. These negative salt effects show very clearly that reaction actually occurs on the micelles and that one ion can displace another at the micellar surface so that even in the absence of added electrolyte we must consider the distribution of reagents between micelles and bulk solvent.

This problem of the distribution of more than one reagent between micelles and bulk solvent, which complicates the simple quantitative treatment, has been treated by several groups. (a) One approach is to use electrochemical methods to determine the distribution of an ionic reagent between water and the micelles. (The distribution of nonionic reagents can often be determined directly.) For example we can assume that pH will measure only the concentration of hydrogen ions in water, and for a specific hydrogen ion catalyzed reaction in the presence of anionic micelles we can calculate the number of hydrogen ions bound to the micelle, and therefore the second order rate constant with respect to the concentration of both reagents in the micelles. This approach has been applied to acetal hydrolysis in NaIS, and the corrected second order rate constants do not vary appreciably over a range of concentrations of acid and surfactant (Ref. 19). (b) A somewhat similar approach has been to use relatively hydrophobic reagents whose concentrations in the micelle can be determined directly (Ref. 22). This method has been applied to a number of nucleophilic additions and substitutions by Berezin and his coworkers who used solubility to determine the distribution of hydrophobic reagents between micelles and bulk solvent, for such reactions as ester deacylation by aldoximes, and aromatic nucleophilic substitution (Ref. 18 & 23). (c) A third approach is to treat distribution constants between water and the micelle as disposable parameters, and so evaluate rate constant-surfactant profiles which fit the observed profiles (Ref. 24). This approach also treats negative salt effects in terms of a competition for the micelle between a reacting ion and an inhibiting ion.

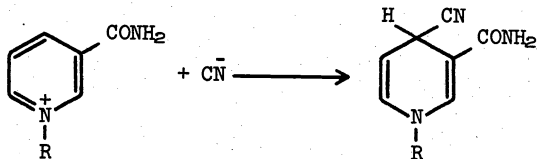
All these methods show that in bimolecular micellar catalyzed reactions we must consider the distribution of both reagents between the micelles and bulk solvent. Each method introduces its own uncertainties, for example added surfactants may alter the properties of a glass electrode or liquid junction (Ref. 19), and the distribution constants of two hydrophobic solutes between water and micelles may not be mutually independent, because either may alter the micellar properties and so affect the incorporation of the other. (The effect of added thiophenoxide ion on the interaction of CTABr with a fatty acid is discussed in Ref. 25.) However in principle these methods allow us to measure rate constants in the micellar phase. Unfortunately different investigators have measured the concentrations in different ways. The concentration of aqueous solutes is generally measured in molarities, and for dilute solution this measure gives the relative numbers of solute and solvent molecules or ions. The concentration of solutes in the micellar pseudophase can also be measured in terms of moles per unit volume, but then we have to choose our volume element. If we use the total volume of the micelle we have the problem that the solute is not distributed uniformly throughout the micelle (Ref. 18 & 23), because polar or ionic solutes will be located in the Stern layer at the micellar surface, and alternatively we can estimate the volume of the Stern layer and use this as our volume element (Ref. 24). Another approach is to ignore micellar volumes and to calculate concentrations in terms of mole fractions, and to compare the number of solute molecules per micellar head group with the number per solvent molecule (Ref. 19).

Thus our comparison of second order rate constants in water and in the micelle depends on our arbitrary choice of volume element, but despite this problem the results suggest that for many bimolecular reactions the second order rate constants are little larger, and may even be smaller, than in water, showing that micellar catalysis is often due largely to the increased reagent concentrations in the micelles as compared with bulk solvent (Ref. 18, 19, 23 & 24). It has been pointed out by a number of workers that the formation of bimolecular transition states involves considerable loss of translational, and sometimes, rotational entropy, and bringing reagents into a small volume element, prior to transition state formation, is a powerful mode of catalysis. This is the principle of the so-called intramolecular catalysis (Ref. 26), and it can also apply to catalysis at other submicroscopic surfaces e.g., enzymes or polyelectrolytes, where we should also consider the distribution of reagents, e.g., hydrogen ions, between reaction site and bulk solvent.

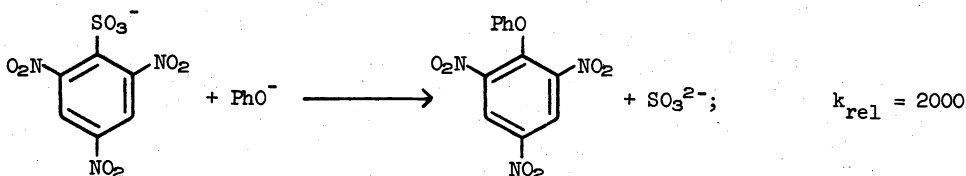
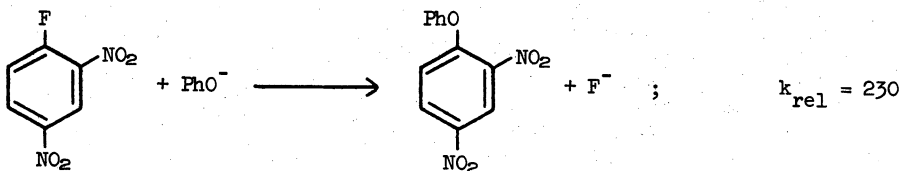
We should not assume that only this concentration effect is important in micellar catalysis. It plays no part in the catalysis of unimolecular reactions, for example cationic micelles effectively catalyze unimolecular anionic decarboxylations (Ref. 21), and the unimolecular elimination of PO_3^- from dinitrophenyl phosphate dianions (Ref. 4 & 17), and typically S_N1

reactions are inhibited by micelles (Ref. 21b and 27). In these reactions the micelle behaves as a submicroscopic solvent which can either assist or inhibit reaction.

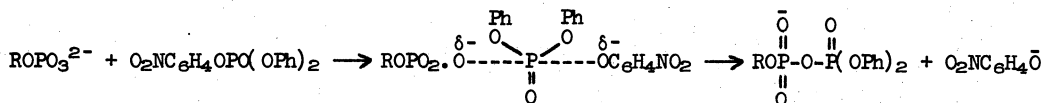
For some bimolecular reactions the variation of overall reaction rate with substrate seems to depend upon both the second order rate constants and reactant concentration in the micellar pseudophase. The cationic micellar catalysis of addition of cyanide ions to N-alkyl pyridinium ions increases with increasing length of the alkyl group (Ref. 28), possibly because this group draws the reaction center more deeply into the Stern layer of the cationic micelle and creates an unfavorable initial state coulombic interaction which is lost in forming the transition state:



A similar pattern is shown by the reactions of phenoxide ion with 2,4-dinitrofluorobenzene and 2,4,6-trinitrobenzenesulfonate in CTABr, because all the reagents should interact strongly with the micelle.

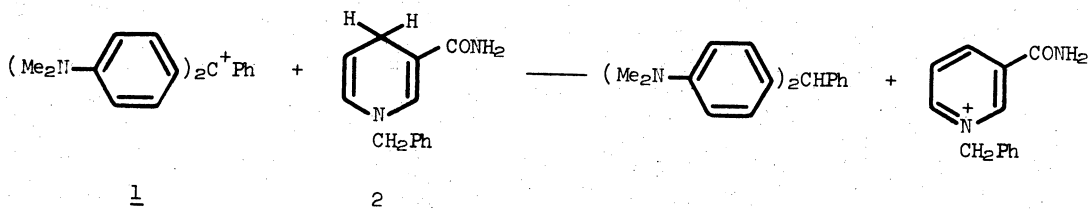


Another example of the micelle apparently acting as a submicroscopic medium in a bimolecular reaction comes from phosphorylation:



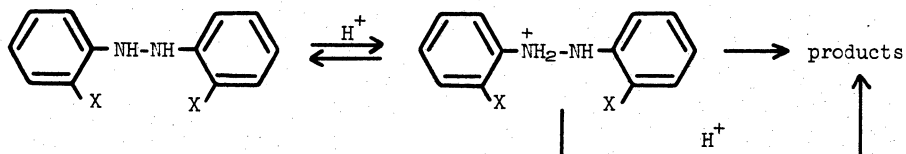
This reaction is catalyzed by cationic micelles, for example with R=H-; C₆H₅-; n-C₁₀H₂₁-; n-C₁₂H₂₅-, and the catalysis increases with increasing hydrophobicity of R (Ref. 29 & 30). Instead of using a cationic micelle we can make R sufficiently hydrophobic for the alkyl phosphate dianion itself to micellize, but although these anionic micelles should take up the hydrophobic substrate and bring it into close proximity with the nucleophile, they are poor catalysts, suggesting that the anionic transition state is best stabilized by cationic centers.

Micellar effects upon reactions of carbocations with nucleophiles have been extensively studied (Ref. 31 & 32), and provide other examples in which micellar catalysis depends not merely upon the bringing together of the reagents but upon the interaction between the head groups and the reactive centers. Reactions of triarylmethyl dye cations, e.g., Malachite Green (1) with hydroxide and borohydride ions are catalyzed by cationic and inhibited by anionic micelles (Ref. 31 & 33). The reaction with 1-benzylidihydronicotinamide (2) is catalyzed by anionic micelles but cationic micelles have almost no effect, even though they should take up both reactants, probably because of unfavorable interactions between the cationic head groups and the developing pyridinium ions.



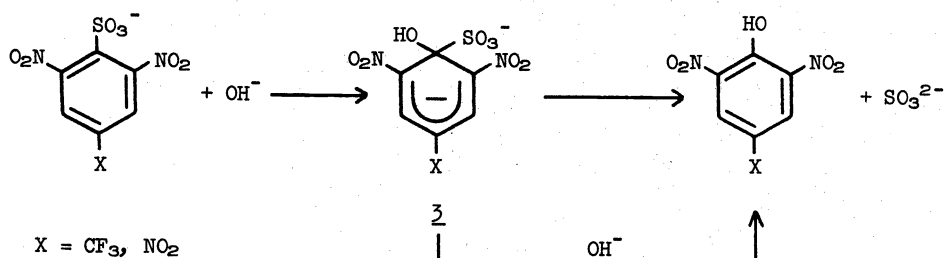
The catalysis of the reaction of borohydride ion (300-fold) is much greater than that of hydroxide ion (15-fold), illustrating the importance of hydrophobicity of an ionic reagent.

The conclusion that concentration of the reagents into the Stern layer of a micelle is one of the key ingredients in catalysis suggests that for similar substrates the catalysis should increase with increasing reaction order. The benzidine rearrangement is a good candidate for this test, because both one and two proton rearrangements can be observed using structurally similar substrates; e.g.,



When X = H, Me, OMe, the products are diaminobiphenyls, and the two proton rearrangements are powerfully catalyzed by anionic micelles of NaLS by up to 5000-fold, but for a one proton rearrangement (X = OMe), the catalysis is only ca. 50-fold (Ref. 34).

However generalizations are dangerous, because a different pattern is followed for the reaction of hydroxide ion with activated arenesulfonates, which involves addition followed by spontaneous and base catalyzed decomposition of an addition complex.

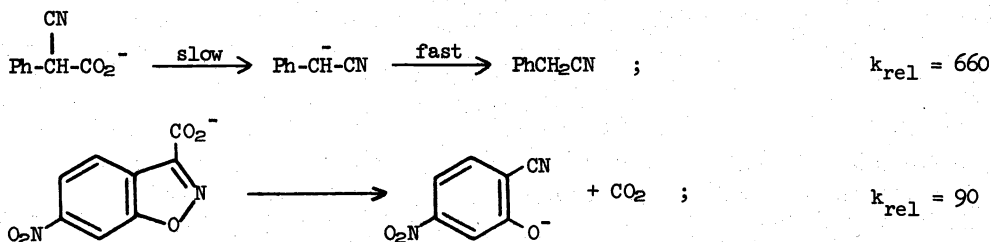


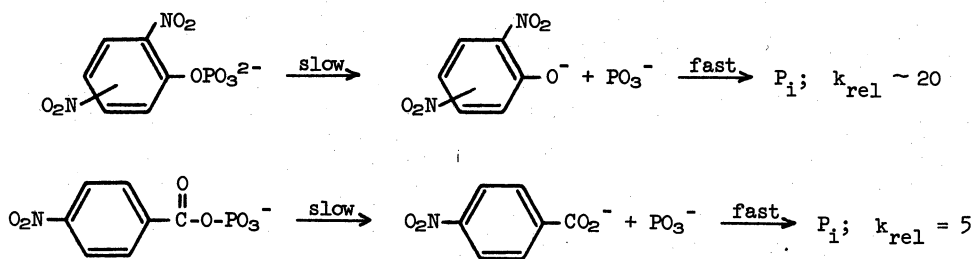
In dilute hydroxide ion the reaction is catalyzed by cationic micelles of CTABr (Ref. 35), as is typical of aromatic nucleophilic substitutions (Ref. 36), but the micellar catalysis decreases with increasing hydroxide ion concentration, showing that the micelle provides an environment which is unfavorable to the hydroxide ion catalyzed decomposition of the intermediate (3).

RELATION BETWEEN MICELLAR CATALYSIS AND SUBSTRATE STRUCTURE

Incorporation of reactants into the micelle is essential and increases with increasing reactant hydrophobicity. Its importance can be seen very clearly by comparing micellar catalysis for a series of similar reactions involving different nucleophiles, for example in nucleophilic aromatic substitution the maximum catalysis by CTABr of reactions of 2,4-dinitrofluorobenzene with hydroxide, phenoxide and thiophenoxide are 60, 230 and 1100 respectively (Ref. 36). It appears that reactant structure influences not only distribution of reactants between solvent and micelles, but also the relative free energies of reactants and transition state in the micelles, i.e., the specific reaction rate in the micelles.

Pearson's concept of hard and soft reagents (Ref. 37), provides a useful rationalization of micellar catalysis. For example a quaternary ammonium ion is a very soft reagent, which should interact more readily with a soft low charge density anion than with a hard anion. For unimolecular reactions having anionic transition states micellar catalysis should be greatest when a hard anion in the initial state is converted with a soft, low charge density, transition state; and this generalization is shown very clearly by considering some spontaneous unimolecular decarboxylations (Ref. 21), and dephosphorylations (Ref. 17 & 38):





In the decarboxylations transition states have considerable carbanionic character, and the catalyses are large. In reactions of the dinitrophenyl phosphate dianions the transition state is akin to a phenoxide ion, with much of the negative charge on oxygen, and the micellar catalysis is smaller, and in reaction of an acyl phosphate dianion the leaving carboxylate ion has all its charge on oxygen, and the micellar catalysis is even smaller (Ref. 38). In these unimolecular reactions there is a clear relation between the rate enhancements by a cationic micelle and the dispersion of negative charge in the transition state, i.e., the softness of the transition state.

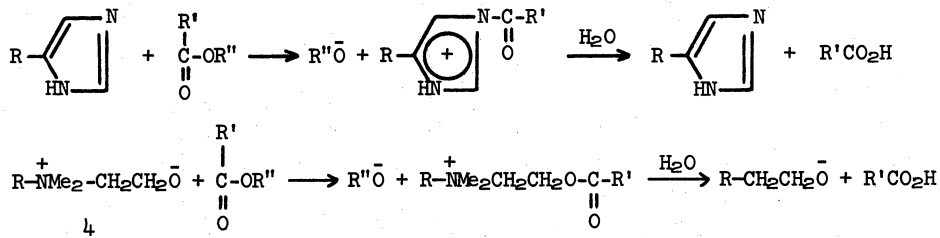
It is not so simple to test this hypothesis for bimolecular reactions where more than one reactant is taken up by the micelles, but for reactions involving hydroxide ion as a nucleophile micellar catalyses appear to be larger for nucleophilic aromatic substitution where the transition state is carbanion like than for deacylations of esters and related compounds where the negative charges in the transition state are on oxygen. These differences should not be due to differences in the hydrophobicities of the substrate, for example 2,4-dinitrochlorobenzene with a 60-fold catalysis in CTABr (Ref. 36a) should be no more hydrophobic than *p*-nitrophenyldiphenyl phosphate with an 11-fold catalysis (Ref. 13), and for some deacylations, e.g., that of *p*-nitrobenzoyl phosphate dianion by hydroxide ion (Ref. 38), the catalysis is only by a factor of 9 in CTABr, even though the cationic micelle should bring two anions together by coulombic attraction.

In this context I note that there are strong interactions between aromatic moieties and quaternary ammonium ions in both micellar and nonmicellar systems (Ref. 39), so that reactions in which negative charge is delocalized into an aryl group are generally effectively catalyzed by cationic micelles.

CATALYSIS BY FUNCTIONAL MICELLES

The phenomenon of "intramolecular catalysis" or "neighboring group participation" is well recognized in physical organic chemistry (Ref. 26), and analogies between it and micellar catalysis of a bimolecular reaction become even closer if one of the reactants is chemically bound to the micelle. There are now many examples of reactions in which a micelle of a functional surfactant is a very effective reagent (Ref. 40). Typically the functional group is a nucleophile or a general base, for example amino, thio or hydroxy, and because of the role of imidazole at the active site of many proteolytic enzymes many workers have used imidazole derivatives. The substrates have usually been carboxylic esters, although aryl carbonates and phosphates and activated aryl halides have also been used.

In most of these reactions the nucleophilic functional group attacks the reaction center giving a covalent intermediate, e.g., an acyl imidazole, and in a few cases formation of a covalent intermediate has been detected kinetically or spectrophotometrically (Ref. 41).



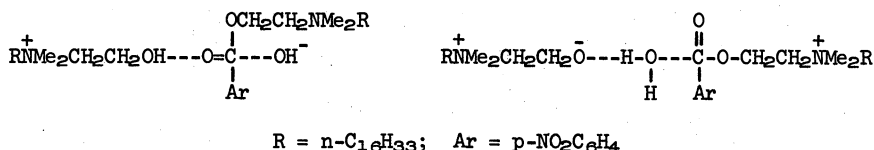
If the functional group acts as a base, e.g., if it activates a water molecule, it will not become bound in a covalent intermediate, so that detection of such an intermediate immediately demonstrates the mode of catalysis. This test is similar to the "burst" experiments often used to study the initial steps in enzymic reactions (Ref. 42), and it has been used to demonstrate initial acylation in reactions of carboxylic esters catalyzed by both imidazole (Ref. 41) and hydroxyethyl (Ref. 43) derived surfactants, where there is an initial

"burst" of p-nitrophenoxide ion, followed by a slower deacylation turnover step. A problem is that these experiments require the substrate to be in large excess over the functional surfactant, so that the micelles may be drastically affected by the substrate, e.g., their structures may be those of micellized substrate containing small amounts of the functional surfactant.

Another approach is to use the typical conditions of micellar catalysis, where the concentration of substrate is much less than that of surfactant, and to detect the covalent intermediate physically, e.g., spectrophotometrically. This method has been applied to the hydrolysis of 2,4-dinitrohalobenzenes catalyzed by the hydroxyethyl derived surfactant (4, R = C₁₂H₂₅).

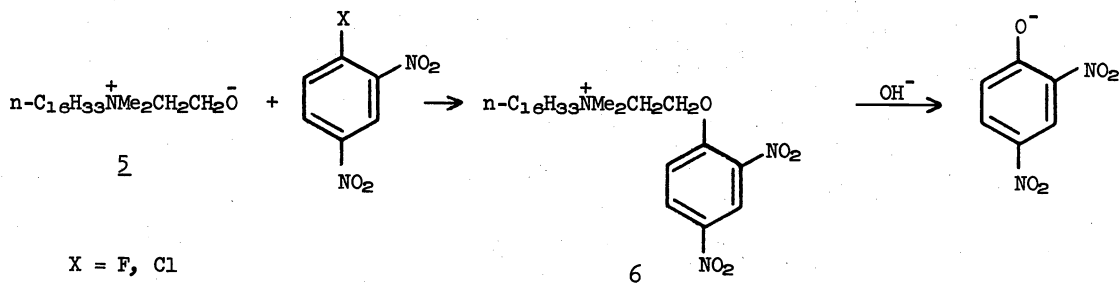
Evidence can also be obtained by choosing a system in which intermediate formation gives no chemical change. Micelles of hydroxyethyl derived surfactants (4) are effective catalysts of deacylation and of the hydrolysis of di- and trisubstituted aryl phosphates, and of S_N reactions of alkyl halides and addition of triarylmethyl carbocations (Ref. 44 - 46). For the dephosphorylations there is evidence that the first step is attack upon the phosphoryl group by the alkoxide moiety, and from the variation of reaction rate with pH a pK_a value of 12.4 (Ref. 44) has been estimated for micellized 4. (This value is lower than that of choline, pK_a = 13.9 (Ref. 47), because micellization increases acid strength.)

The catalyzed hydrolysis of carboxylic esters could, in principle, follow two routes: (i) nucleophilic attack giving an acyl intermediate (Ref. 43), or (ii) the hydroxy group of 4 could hydrogen bond to the ester, and activate it towards nucleophilic attack by hydroxide ion, or (iii) the alkoxide moiety could act as a general base and activate a water molecule. Transition state models for these general or acid base catalyzed reactions are shown for an ester in which nucleophilic attack would lead to no chemical change.



Thus if the hydroxyethyl-derived surfactant acted as a general acid or base it would always be a better catalyst than an otherwise similar nonfunctional micelle of, for example, CTABr. But if it acted as a nucleophilic catalyst it would, as it does, speed the hydrolysis of p-nitrophenyl esters, but not the reactions shown above. For these reactions it is an ineffective catalyst, suggesting that it always acts as a nucleophilic and never as a general acid-base (Ref. 48).

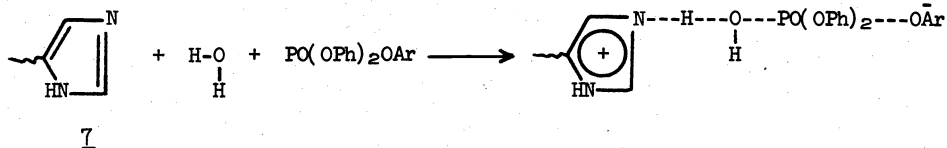
I noted earlier that for both uni- and bimolecular reactions catalysis by cationic micelles increases as we go to reactions in which there is extensive delocalization of charge in the transition state. The same pattern is shown for reactions in micelles of the hydroxyethyl surfactant (4) which involve the zwitterion (5). The first step of hydrolysis of fluoro- and chloro-2,4-dinitrobenzene catalyzed by 4 is formation of the ether (6) which then decomposes to products (Ref. 49).



The rate enhancements can be illustrated by considering the (hypothetical) molarity of hydroxide ion in water which would be required to give the same rate as 1M micellized zwitterion (5). This comparison is often used to illustrate the magnitude of intramolecular catalysis (Ref. 26). The molarities are: for 2,4-dinitrochlorobenzene, 410 M; for 2,4-dinitrofluorobenzene, 170 M; for p-nitrophenyldiphenyl phosphate, 8 M; for ethyl p-nitrophenyl phosphate monoanion, 3.5 M; and for p-nitrobenzoyl phosphate dianion, 4 M. We cannot make a direct comparison with reactions of carboxylic esters because of the different experimental conditions (Ref. 45 & 50), but here the rate enhancements seem to be of the same order of magnitude as those for the aryl and acyl phosphates and much lower than for aromatic nucleophilic substitution.

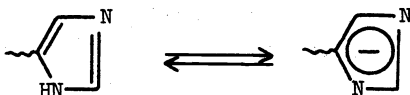
There are a few examples of general base catalysis by a functional micelle. The chiral surfactant (7) is a stereospecific catalyst in carboxylic ester hydrolysis, where reaction

almost certainly involves initial acylation of the imidazole moiety (Ref. 51). But γ is also an effective catalyst for the hydrolysis of *p*-nitrophenyldiphenyl phosphate (Ref. 52), and the kinetic deuterium solvent isotope effects ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 2.5-2.8$) are in the range typical of general base catalysis. (The isotope effects for reactions of carboxylic esters are $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} \sim 1.4$ in the range typical of nucleophilic catalysis). In addition there is no evidence for build-up of a covalent intermediate, e.g., a phosphorylated imidazole, when reaction is done using a micelle of γ and the nonionic surfactant, Brij, and an excess of *p*-nitrophenyldiphenyl phosphate over γ .



I know of no evidence for general base catalysis of carboxylic ester hydrolysis by a functional micelle, for example Moss and his coworkers have prepared micelles of functional surfactants which contain imidazole and hydroxyethyl moieties, and are effective catalysts, but less so than the imidazole derivatives, but they see no evidence for any reaction other than acylation of the imidazole (Ref. 53).

Rates of deacylation in the presence of functional surfactants containing an imidazole moiety generally increase with increasing pH above 8, because of deprotonation of the imidazole moiety to the highly reactive anion (Ref. 40 & 54).

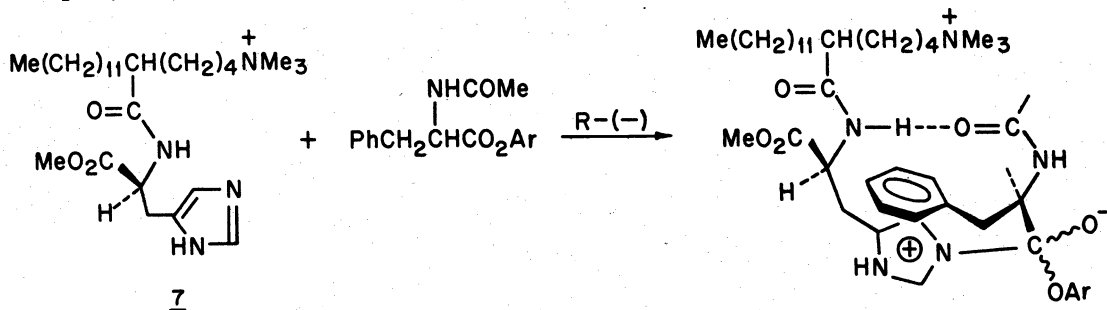


At pH < 6 the rate increases as protonated imidazole is deprotonated; there is then a plateau region at pH ~ 7 in which an imidazole moiety is the reagent, and the rate then increases with formation of the imidazole anion. For hydrolysis of *p*-nitrophenyldiphenyl phosphate in micelles of γ , which we believe to be general base catalyzed, the rate increases only slightly with increasing pH, suggesting that under these conditions the imidazole anion is not a particularly effective kinetic base although it is an excellent nucleophile.

STEREOCHEMICAL CONSEQUENCES OF MICELLIZATION

There have been a number of attempts to use micelles in chiral recognition, and to control the stereochemical course of reactions by micellization, and a limited degree of success has been obtained using both approaches.

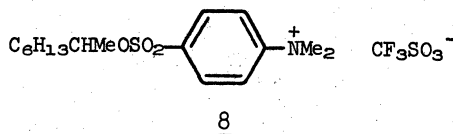
The use of micelles of nonfunctional chiral surfactants as catalysts leads to little or no chiral recognition (Ref. 55). But micelles of the chiral surfactant (γ) derived from L-histidine give a 3-fold specificity in the catalyzed hydrolyses of the enantiomers of *p*-nitrophenyl N-acetylphenylalanine (Ref. 51).



However only a small chiral recognition was found in the hydrolysis of *p*-nitrophenyl-2-phenylpropionate and it was suggested that chiral recognition depended on hydrogen bonding between amide moieties which leads to unfavorable phenyl-imidazole interactions in reaction of the R(-) ester but not of the S(+) ester. Formation of the tetrahedral intermediate from the R(-) ester forces an unfavorable interaction between the imidazole group and the phenyl group of the ester. There appears to be no chiral recognition in the binding of the enantiomeric substrates to the chiral micelle.

There are also several systems in which substrate micellization controls the stereochemical course of reactions. The nitrous acid deamination of chiral primary amines generally involves extensive racemization with partial inversion of the product alcohol. However if the alkyl group of the amine is sufficiently hydrophobic for substrate micellization the product has a partially retained configuration, because micellization causes the intermediate carbocation, or ion pair, to suffer predominantly front side attack by water molecules of the solvent (Ref. 56). The stereochemical course of the reaction is also very sensitive to added salts whose anions cluster around the micellized alkylammonium ion and so affect attack of water.

The other examples involve stereochemical control in S_N1 solvolyses. Comicellization of 8 with NaLS changes the stereochemical course of the reaction from complete inversion in water



to 56% inversion with approximately 1:1 substrate:surfactant (Ref. 57). However substrate micellization or comicellization with CTABr has little effect on either rate or stereochemistry. These results can be rationalized on the assumption that strong head group interactions between 8 and NaLS force water molecules away from the reaction center, but head group repulsions in the cationic micelles allow water molecules to enter the Stern layer and orient around the reaction center. Slightly different results were obtained for the S_N1 solvolysis of 1-methylheptyltrifluoromethane sulfonate which is strongly inhibited by micelles of either NaLS or CTABr and both anionic and cationic micelles change the stereochemical course of reaction from net inversion in aqueous solvents to net retention (Ref. 58).

PREPARATIVE APPLICATIONS

Mechanistic work on micellar effects is typically done using low reactant concentrations, much below those required for useful preparations. However surfactants are used in emulsion polymerization (Ref. 59), where the micelles control chain initiation and growth, and in some organic reactions (Ref. 16). The use of surfactants in phase transfer catalysis is well established (Ref. 14 & 15), although micellization may not be important here. Unfortunately surfactants often complicate product isolation, and therefore the use of immobilized reagents is attractive, cf. Ref. 60. We have found that the histidine derived surfactant 7 binds well to sulfonate ion resin and then effectively catalyzes hydrolysis of p-nitrophenyldiphenyl phosphate (Ref. 61), and in this system the catalyst can be reused after recovery by filtration with little loss of activity.

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