methyl-2-cyclohexenone semicarbazone, 54352-37-3; (−)-5-methyl-2-cyclohexenone 2,4-DNP, 54307-77-6; *trans*-3(*R*),5(*R*)-dimethylcyclohexanone semicarbazone, 54307-78-7; 3,3,5(*R*)-trimethylcyclohexanone, 33496-82-1; *dl-cis*-3,3,5-trimethylcyclohexanol, 54307-79-8; *p*-nitrobenzoic acid, 62-23-7; *dl-cis*-3,3,5-trimethylcyclohexanyl *p*-nitrobenzoate, 54307-80-1; *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate, 54307-81-2; phthalic anhydride, 85-44-9; *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate cinchonine salt, 54307-82-3; cinchonine, 24831-03-6; (−)-*cis*-3,3,5-trimethylcyclohexanyl acid phthalate, 54352-38-4; (−)-*cis*-3,3,5-trimethylcyclohexanol, 54352-39-5; (−)-3,5-dimethyl-2-cyclohexenone, 54307-83-4; 3,3,5(*S*)-trimethylcyclohexanone, 33496-83-2; brucine, 357-57-3; *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate brucine salt, 54307-84-5; (+)-*cis*-3,3,5-trimethylcyclohexanyl acid phthalate, 54352-40-8; (+)-*cis*-3,3,5-trimethylcyclohexanol, 54352-41-9; 3,3,5(*S*)-trimethylcyclohexanone semicarbazone, 54307-85-6.

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Effect of Changes in Surfactant Structure on Micellarly Catalyzed Spontaneous Decarboxylations and Phosphate Ester Hydrolysis[1]

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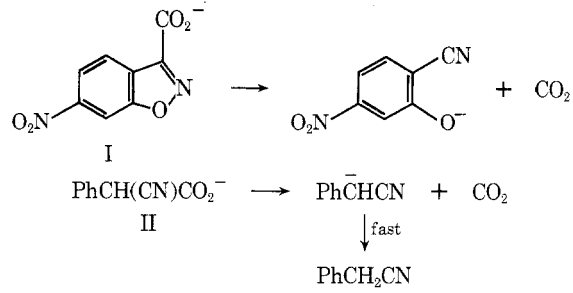
Micelles of the zwitterionic surfactant, *N,N*-dimethyl-*N*-dodecylglycine, catalyze the spontaneous decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion 170-fold and that of cyanophenyl acetate ion 690-fold, and they, and micelles of the corresponding alanine surfactant, are better catalysts than dodecyltrimethylammonium bromide by factors of almost 3-fold. The catalytic efficiency of cationic micelles of *N,N*-dimethyl-*N*-hydroxylethyl-2-hexadecylammonium bromide is also increased 2-fold by conversion of this surfactant into a zwitterion at high pH. Lecithin and lysolecithin are very poor catalysts, showing that the arrangement of charge in the zwitterionic head group is of key importance. Catalysis by micelles of *N,N*-dimethyl-*N*-dodecylglycine is subject to large salt effects which depend upon the anion, but differ from those typical of micellar catalysis. Salts having hydrophilic anions tend to increase catalysis and those having hydrophobic anions decrease it. Chemically inert solutes such as phenols and aliphatic amines change the catalytic effectiveness of micelles of cetyltrimethylammonium bromide, but these micelles in aqueous ethylene glycol, or the reverse micelles in hexanol–water, are poor catalysts both for decarboxylation and for the spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion.

The spontaneous decarboxylations of 6-nitrobenzisoxazole-3-carboxylate ion (I)[3] and 2-phenylcyanoacetate ion (II)[4] are catalyzed strongly by cationic micelles[5,6] and by cyclodextrins.[7] The micellar catalysis is enhanced by some electrolytes, which is an unusual feature because micellar catalysis is generally decreased by added electrolytes.[8]

These decarboxylations are much faster in organic or aqueous organic solvents than in water,[3,4] and these observations together with the unusual electrolyte effect on micellar catalysis suggest that these reactions may provide a useful probe of the nature of the micellar surface.[5,6] The enhancement of the rate of decarboxylation of I in cationic micelles of cetyltrimethylammonium bromide (CTABr) containing less than 1 equiv of sodium tosylate was explained in part in terms of an initial state electrostatic re-



pulsion between the carboxylate moiety of the substrate and tosylate ion occupying neighboring sites in the micelle, and it seemed probable that micelles of zwitterionic surfactants might be effective catalysts.[11,12] Micelles of synthetic zwitterionic surfactants and liposomes of phospholipids have been shown to be effective catalysts of the addition of cyanide ion to *N*-alkylpyridinium ions,[13] but our interest was in a micellarly catalyzed unimolecular reaction, where the factors affecting the catalysis are more easily analyzed.[5]

Reverse micelles have been found to be powerful catalysts for many bimolecular reactions,[14] and therefore we examined their effect upon the unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion and also upon the spontaneous hydrolysis of the 2,4-dinitrophenyl phosphate dianion, because this reaction is similar to the spontaneous decarboxylations of I and II in its solvent[15] and micellar effects.[16] The spontaneous decomposition of 2,4-dinitrophenyl sulfate is catalyzed strongly by reverse micelles of alkylammonium carboxylates in benzene.[17]

The dependence of catalysis upon micellar charge is well understood, and for bimolecular reactions catalysis is decreased by screening the micelle with counterion or by going from ionic to zwitterionic head groups.[9-12] The aim of the present work was to examine the extent to which catalysis of unimolecular reactions could be controlled by changing the charge arrangement of the head group, or by incorporation of inert solutes into the Stern layer.

Experimental Section

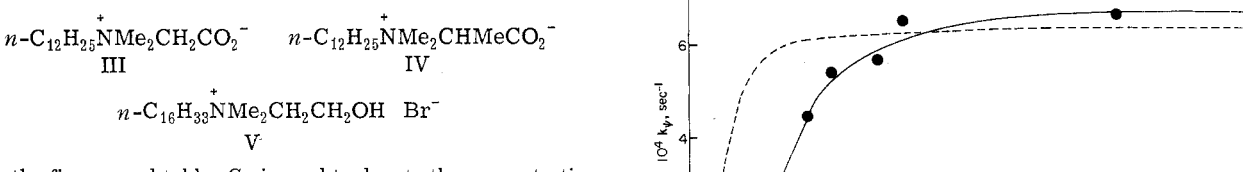
Materials. The preparation and purification of the substrates and most of the surfactants have been described.[5,6,16,18]

The *N,N*-dimethyl glycine and alanines were prepared by reductive methylation,[19] and were purified by recrystallization from MeOH–Me_2CO or EtOH–Et_2O at 0°. Their melting points and optical rotation agreed well with literature values. These amines were quaternized with bromododecane, usually in 2-propanol, and the glycine derivative (III) and the alanine derivative (IV)[20] were crystallized from acetone. The rotation of the hydrobromide of *N*-dodecyl-*N,N*-dimethyl-L-alanine was $[\alpha]^{25}_D$ −9.58° (lit.[20a] $[\alpha]^{20}_D$ −9.50°).

Sodium salts were generally reagent grade or were prepared in solution by neutralization of the acids, although the sodium arenesulfonates were recrystallized from EtOH, as were the mandelic acids (Aldrich). The phenols and amines were redistilled, generally under reduced pressure.

Kinetics. The reactions were followed spectrophotometrically at 25.0° using Gilford or Cary spectrophotometers with water-jacketed cell compartments.[5,6,16] The first-order rate constants, k_ψ, are in reciprocal seconds. The concentration of 6-nitrobenzisoxazole-3-carboxylate ion was generally 7×10^{-5} *M*, but because of the relatively small absorbance change during reaction that of 2-cyano-2-phenylacetate ion had to be in the range $7–10 \times 10^{-4}$ *M*.[6]

The surfactants were dodecyl- and hexadecyltrimethylammonium bromide (DDTBr and CTABr), *N,N*-dimethyl-*N*-dodecylglycine and -alanine (III and IV), and *N,N*-dimethyl-*N*-2-hydroxyethyl hexadecyl ammonium bromide (V).



III IV

V

In the figures and tables C_D is used to denote the concentration of surfactant (detergent).

Effect of Phospholipids. We examined the effect of α-lecithin upon the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion using sonicated α-lecithin (Schwarz Mann, egg white, sonicated at 0° for 5-min periods until clear). However although the solutions were initially clear, they gradually became cloudy during the reaction so that we could not get good rate data. From the initial rate of formation of the phenoxide ion product we estimated that 2×10^{-3} *M* sonicated α-lecithin in 2×10^{-3} *M* ammonia buffer at pH 9.2 increased the reaction rate by a factor of less than threefold. Cordes and his coworkers noted that it was difficult to get good rate data for the reaction of cyanide ion with *N*-alkylpyridinium ions using liposomes of sonicated phospholipids.[13]

Table I
Salt Effects on the Decarboxylation of 6-Nitrobenzisoxazole-3-Carboxylate Ion in the Presence of Lysolecithin[a]

Added salt, m*M*	$10^6 k_\psi$, sec^{-1}	Added salt, m*M*	$10^6 k_\psi$, sec^{-1}
	3.7	27 $MgCl_2$	3.9
5.1 NaCl	6.6	0.26 $CaCl_2$	4.4
6.0 NaBr	4.8	0.51 $CaCl_2$	4.5
30 NaBr	2.9	1.3 $CaCl_2$	5.5
13 $NaNO_3$	2.5	5.1 $CaCl_2$	8.3
13 $MgCl_2$	4.6	13 $CaCl_2$	8.7

[a] With 6.3×10^{-4} *M* lysolecithin at 25.0° at pH 9.5 in 5×10^{-3} *M* NH_4Cl buffer: in the absence of lysolecithin $10^6 k = 2.8$ sec^{-1}.

Because of these problems with sonicated α-lecithin we also used lysolecithin (Sigma) because it forms normal micelles rather than liposomes.[21] Solutions of lysolecithin became cloudy during reaction of I, but this cloudiness was removed by centrifugation. Our first-order rate constants were determined by following the formation of the nitrophenoxide ion for approximately 1 half-life of reaction, and determining the absorbance of nitrophenoxide ion at complete reaction after centrifugation. By this method we could obtain reasonable first-order rate constants for up to 50% reaction. These normal micelles of lysolecithin are also poor catalysts (Table I), and only a low concentration of lysolecithin was used because of turbidity at higher concentrations. We ascribe this low catalytic efficiency of both α-lecithin and lysolecithin to the nature of the zwitterionic head group with its terminal quaternary ammonium ion.

Some added salts increase the rate of decarboxylation in the presence of lysolecithin (Table I). Calcium chloride is the most effective salt which we examined, probably because interactions between the phosphate moiety and calcium ions tend to convert the zwitterionic micelle of lysolecithin into a normal cationic micelle, although these interactions should also change the micellar structure. Sodium salts having relatively large anions, bromide or nitrate, have little effect or slightly inhibit the reaction (Table I).

Results

Decarboxylation of 2-Cyano-2-phenylacetate Ion (II). This substrate was not used extensively because its decarboxylation was followed at 235 nm, where many solutes absorb, and the overall absorbance change during reaction is small.[6]

The cationic surfactant dodecyltrimethylammonium bromide (DDTBr) is not as effective a catalyst as is CTABr (Figure 1). For CTABr the rate enhancement is by a factor of 660-fold at 25.0°, whereas for DDTBr it is 280-fold. (The broken line in Figure 1 relates to CTABr.[6]) As is generally found, the amount of surfactant required for catalysis de-

Figure 1. Decarboxylation of 2-phenylcyanoacetate ion at 25.0° in trisbuffer at pH 8: ■, DDTBr; ●, *N,N*-dimethyl-*N*-dodecylglycine. (The broken line is for CTABr, ref 6.)

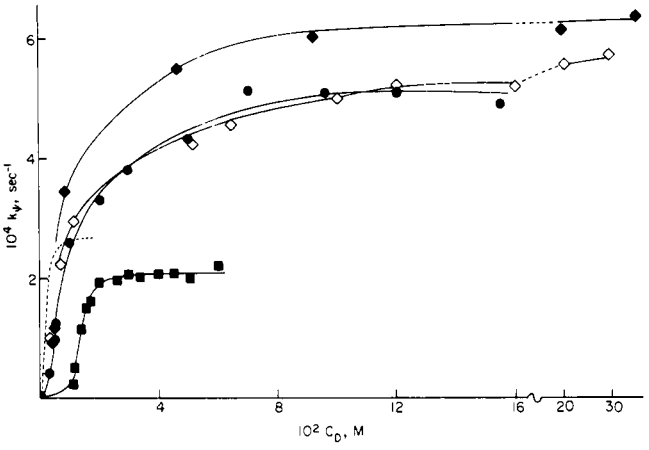


Figure 2. Decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion at 25.0° in ammonia buffer, pH 9.2: ■, DDTBr; ●, *N,N*-dimethyl-*N*-dodecylglycine; ◊ and ♦, L- and DL-*N,N*-dimethyl-*N*-dodecylalanine, respectively. (The broken line is for CTABr, ref 5.)

creases with increasing length of the *n*-alkyl group, e.g., the amount of surfactant required for 50% of the maximum rate is 1.8×10^{-2} *M* for DDTBr and ca. 0.5×10^{-2} *M* for CTABr. This difference comes in part from the lower cmc of CTABr as compared with the other surfactants,[20b] but probably the substrate is drawn more deeply into the Stern layer of the larger micelles formed by CTABr.

Micelles of the zwitterionic surfactant *N,N*-dimethyl-*N*-dodecylglycine (III) give greater rate enhancements for the reaction of II than does DDTBr, and despite the shorter chain length are slightly more effective than micelles of CTABr. In the absence of surfactant[6] $k_\psi = 9 \times 10^{-7}$ sec^{-1}.

Decarboxylation of 6-Nitrobenzisoxazole Carboxylate Ion in the Presence of Synthetic Surfactants. The overall pattern for micellar effects upon this reaction are qualitatively very similar to those described earlier for reaction of 2-cyano-2-phenylacetate ion (II). Micelles of the cationic dodecyl surfactant, DDTBr, are not as catalytically effective as those of CTABr; the respective rate enhancements are 70- and 95-fold; the surfactant concentrations for 50% rate enhancement are respectively 1.2×10^{-2} and 1.6×10^{-3} *M* (Figure 2).

Micelles of the zwitterionic dodecyl surfactants III, L-IV, and DL-IV derived from glycine and alanine are better catalysts than the cationic micelles, DDTBr and CTABr, even though their hydrophobic *n*-alkyl groups are shorter than that of the hexadecyl surfactant, CTABr.

Effect of Micelles of 1-Hydroxyethyl-2-hexadecyldimethylammonium Bromide. Micelles of the hydroxyethyl surfactant V are effective catalysts for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion (Table II).

The rate enhancement (90-fold) is very similar to that given by CTABr, but if the hydroxide ion concentration is increased so that V is converted into the zwitterion VI, the catalysis increases (Table II), as expected for a zwitterionic micelle. The pK_a of V estimated kinetically is 12.4,[18] which,

$$n\text{-}C_{16}H_{33}NMe_2CH_2CH_2OH + OH^- \rightleftharpoons n\text{-}C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2O^-$$

V VI

despite some dubious assumptions,[22] is in reasonable agreement with pK_a = 13.9[23] for choline, because micellization should increase acidity.

There is no evidence that the decarboxylation of I is affected by added strong bases of nucleophiles,[3] so the increasing catalysis by micelles of zwitterionic surfactant VI must be a medium effect due to the changing charge of the head group. [In high concentration (>1 *M*) sodium hydroxide increases the rate of decarboxylation catalyzed by dimethyldodecylglycine (III), and this increase is considered in the discussion of electrolyte effects, but this rate enhancement was observed only at hydroxide ion concentrations very much greater than those used with the hydroxyethyl surfactant.]

Table II
Effect of Hydroxide Ion on the Catalysis of the Decarboxylation of 6-Nitrobenzisoxazole Carboxylate Ion by Micelles of V[a]

	$10^2 C_D$, *M*						
C_{OH^-}, *M*	0.04	0.4	0.8	1.0	1.2	4.0	5.0
pH 9[b]							2.55
pH 10[b]						2.35	
0.002							2.72
0.005							2.71
0.008							2.89
0.01	2.41	3.24	3.26		3.01	3.40	
0.02							3.38
0.04							4.15
0.10				5.16			
0.12							4.94
0.18				5.47			
0.20				5.26		5.39	5.41
0.30				5.77			
0.50				6.14			5.75
0.90				6.35			6.40

[a] Values of $10^4 k_\psi$, sec^{-1}, at 25.0°. [b] 10^{-3} *M* ammonia buffer.

Effect of Added Solutes on Decarboxylation Catalyzed by Zwitterionic Micelles. The salt effect upon the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion catalyzed by micelles of CTABr was unusual in that salts having hydrophilic anions increased the reaction rate, and salts of some aromatic acids which increased reaction rate in low concentration decreased it at high. Salts having nonaromatic hydrophobic anions decreased the reaction rate at all concentrations, as did thiocyanate ion, which can interact strongly with a cationic micelle.[5] Salts generally decrease micellar catalysis,[9-11] and the behavior of the nonaromatic hydrophobic anions was typical, in that such ions generally retard reaction by competing with ionic reagents for the micelle. The effects of the hydrophilic anions were explained in terms of a reduction in the charge density of the micelle when relatively hydrophilic ions cluster around it. The unusual effects of aromatic anions were considered to be caused by changes in micellar structure by insertion of anions such as tosylate.[5]

The salt effects upon decarboxylation catalyzed by zwitterionic micelles are also unusual, and brook no simple explanation. For simplicity we consider salts of organic and inorganic acids separately.

The pattern for the effects of sodium salts of organic acids is straightforward (Figure 3). Sodium formate, acetate, and oxalate have relatively little effect, but the other more hydrophobic salts inhibit reaction, and the retardation parallels anion hydrophobicity, at least qualitatively. Because micelles of zwitterionic surfactants catalyze decarboxylation of the carboxylate ions I and II we assume that they also take up relatively hydrophobic carboxylate or sulfonate anions, and the micelle then goes from being formally uncharged to anionic, and should become ineffective as a catalyst. This explanation is consistent with the absence of

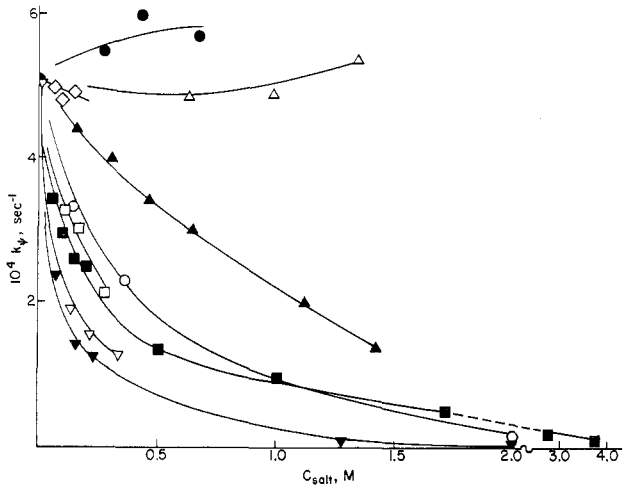


Figure 3. Effect of sodium salts of organic acids on the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion in micelles of *N,N*-dimethyl-*N*-dodecylglycine at 25.0° in ammonia buffer, pH 9.2: ●, AcO^-; ▲, $Me_3CCO_2^-$; ■, $CF_3CO_2^-$; ▼, $CCl_3CO_2^-$; ◇, $(CO_2^-)_2$; ○, n-$C_6H_{13}CO_2^-$; △, HCO_2^-; □, $PhCO_2^-$; ▽, p-$MeC_6H_4SO_3^-$.

the rate maxima in plots of k_ψ against salt concentration which we observed in CTABr-catalyzed decarboxylation in the presence of, for example, sodium tosylate.[5]

The pattern for the effect of inorganic salts (Figure 4) is also straightforward. The effects appear to depend upon the anion; for example, the chlorides of Li^+, Na^+, K^+, and NH_4^+ have little effect on the rate, or depress it slightly, and potassium nitrate retards the reaction. However, fluorides, sulfates, carbonates, and phosphate and sodium hydroxide increase the reaction rate, although relatively high concentrations (>2 *M*) are required for large rate increases. The anions which give these rate enhancements have high charge densities and they tend to organize water molecules about them, i.e., they are structure-making ions,[24] and we note that formate and acetate ions, which behave differently from the other organic anions (Figure 3), are also "structure makers".

In these solutions of high ionic strength, ions will be close to the micellar surface,[9-11] and may compete with the carboxylate groups of the micellized surfactant for water molecules, and therefore change micellar structure. Any effect which decreases the ability of water molecules at the micellar surface to hydrogen bond to carboxylate ions should assist reaction, first by decreasing the ability of water molecules to hydrate the substrate which is bound to the micelle, and second by reducing screening of the carboxylate head groups of the surfactant, and therefore increasing the initial-state charge repulsions which are responsible for the high catalytic effectiveness of the zwitterionic surfactants. It has been noted that ions can change the "dynamic basicity" of water,[25] although this conclusion was based on experiments involving proton loss from carbon acids, which does not proceed via a hydrogen-bonded species.

Some effects of uncharged solutes upon the decarboxylation of I catalyzed by zwitterionic micelles should be noted here. Ammonia has an appreciable effect on the reaction rate (Figure 4), and urea somewhat diminishes the micellar catalysis (by ca. 25% in 4 *M* urea). Urea disrupts water structure and modifies those of micelles and macromolecules, and its effects on reactions in micelles have been explained in these terms.[26] The effect of urea on decarboxylation of I in CTABr is similar to that found here.[5]

Decarboxylation in Zwitterionic Micelles of *N,N*-Dimethyl-*N*-dodecylalanine and the Effect of Sodium

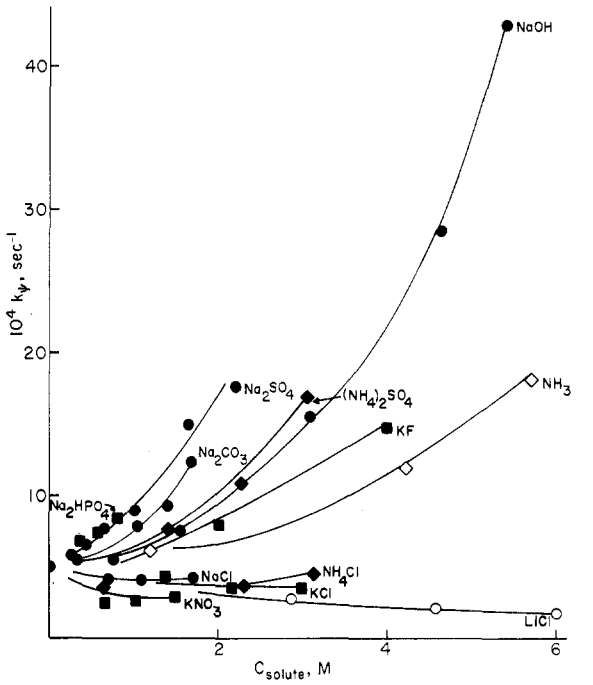


Figure 4. Effect of inorganic solutes on the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion in micelles of *N,N*-dimethyl-*N*-dodecylglycine.

Table III
Inhibition of Micellarly Catalyzed Decarboxylation by Mandelate Ions[a]

Na mandelate	Surfactant L-IV[b]	Surfactant DL-IV[c]
DL–	0.66	0.55
D(–)	0.63	0.64
L(+)	0.64	0.65

[a] Values of k_m^s/k_m^o for decarboxylation of I in micelles of 0.2 *M* L- and DL-IV at 25.0° in 2×10^{-3} *M* ammonia buffer, pH 9.2, and 7.7×10^{-5} *M* substrate. [b] Using 0.35 *M* salt; in the absence of added salt $10^4 k_\psi = 5.60$ sec^{-1}. [c] Using 0.32 *M* salt; in the absence of added salt $10^4 k_\psi = 6.12$ sec^{-1}.

Mandelate. The differences in the rates of reaction of 6-nitrobenzisoxazole-3-carboxylate ion in micelles of the zwitterionic L- and DL-dimethyldodecylalanines (Figure 2) suggest differences in the surface structures of the micelles of the optically active and racemic surfactants. The micellar catalysis is reduced by sodium mandelate, and the inhibition is similar to that found on the addition of relatively hydrophobic carboxylate ions to *N,N*-dimethyl-*N*-dodecylglycine (Figure 3). However, there are only small differences in the inhibitions shown by the various mandelates (Table III), and as expected D- and L-mandelates have the same effects on reaction rates catalyzed by the DL surfactant (DL-IV), but DL-mandelate ion behaves differently. However, the relative inhibitions by the various mandelate ions of decarboxylation catalyzed by micelles of the L surfactant are within experimental error, so that only the effects upon catalysis by the DL surfactant appear to be significant. Effects due to surfactant or inhibitor chirality which rely upon physical interactions seem to be small because micellization depends upon the sum of a large number of weak physical interactions. Moss and Sunshine have used micelles of optically active surfactants as catalysts for reactions of optically active substrates (generally carboxylic esters) and found essentially no stereoselectivity toward enantiomeric substrates.[27] However, appreciable stereo-

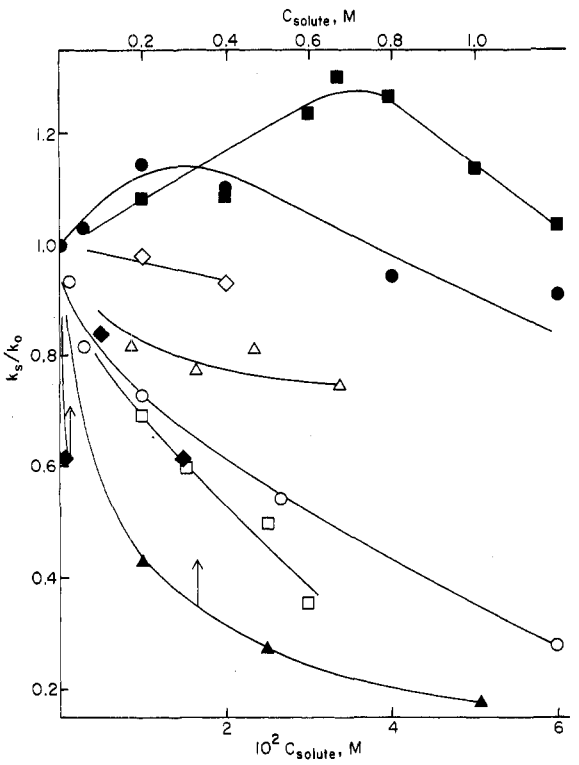


Figure 5. Effect of solutes on the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion in 2×10^{-2} *M* CTABr: ○ ●, phenol; □ ■, *p*-cresol; ◇, benzene; △, anisole; ▲, CF_3CO_2Na; ♦, n-$C_{10}H_{21}CO_2Na$. The open points represent runs at pH 7.5 and the solid points runs in 0.1 *M* NaOH except for ▲, which was at pH 9.2.

selectivity has been found using a functional micelle derived from L-histidine.[28]

Effect of Aromatic Solutes on Decarboxylation Catalyzed by CTABr. There is considerable spectral and other evidence that aromatic compounds interact strongly with both cationic micelles and unmicellized tetraalkylammonium ions,[5,29-33] and the enthalpies of transfer of a number of aromatic compounds from water to CTABr have been found to be much larger than for otherwise similar aliphatic compounds.[31] This favorable enthalpy change is indicative of a strong interaction between the cationic head groups and the aromatic residues. The unusual salt effects of arenesulfonate and similar anions upon the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion I in CTABr were explained in terms of an insertion of the phenyl group into the micelle and NMR and uv spectroscopic evidence,[5,32] and the effects of micelles on buffer equilibria of aromatic acids can be similarly explained.[30] Uncharged aromatic compounds having electron-releasing groups (OH or OMe) decrease the catalysis of the decarboxylation of I by CTABr (Figure 5), but in agreement with earlier work benzene has very little effect.[5] The aromatic solutes are in considerable excess over the substrate, whose concentration is $<10^{-4}$ *M*, and they can reduce the reaction rate both by inserting into the micelle and excluding substrate and by modifying the surface structure of the micelle. This insertion should be assisted by electron-releasing groups which should increase the interaction between the π-rich phenyl group and the quaternary ammonium head groups of the micelle. Paradoxically, the phenoxide ions increase the catalytic effectiveness of the cationic micelle, and behave similarly to arenesulfonate ions in this respect,[5] and this effect may be in part due to Coulombic initial state repulsions between the carboxylate ion of the substrate and the anionic oxygen of the phenoxide ion.[12]

For comparison purposes the inhibitions by sodium decanoate and trifluoroacetate are shown in Figure 5, and the uncharged benzenoid compounds are effective inhibitors by comparison with these relatively hydrophobic carboxylate ions. Decanoate is as expected a much better inhibitor than trifluoroacetate, and it probably interacts so strongly with CTABr that a catalytically ineffective anionic comicelle is formed. Examples of other inhibiting anions are given in ref 5 and trifluoroacetate ion is similar to trimethylacetate ion in its ability to reduce catalysis by CTABr.

Table IV
Effect of *n*-Alkylammonium Chlorides on Decarboxylation in CTABr[a]

Alkyl	10^4 k_ψ, sec^{-1}
	3.38[b]
n-Butyl	3.02
n-Octyl	2.84
n-Nonyl	2.77
n-Decyl	2.38
n-Dodecyl	1.34

[a] At 25.0° with 2×10^{-2} *M* alkylammonium chloride in 2×10^{-2} *M* CTABr and 0.022 Tris buffer, pH 7. [b] In the absence of added amine salt.

Table V
Effect of *n*-Alkylamine Decarboxylation in CTABr[a]

Alkyl	C_{RNH_2}, *M* 0.01	0.015	0.02
n-Butyl			3.55
n-Hexyl			3.05
n-Octyl	3.10		2.65
n-Nonyl	3.41	3.89	4.08
n-Decyl	3.80	4.43	5.26
n-Dodecyl	3.81	4.12	

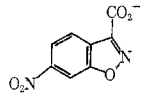
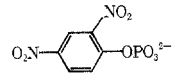
[a] Values of k_ψ, sec^{-1}, at 25.0°; in the absence of amine 10^4 k_ψ = 3.71 sec^{-1} in 2×10^{-2} CTABr and 0.1 *M* NaOH.

Effect of *n*-Alkylamines and Their Hydrochlorides on the Decarboxylation of I in CTABr. Decarboxylation is inhibited by solvents which strongly hydrogen bond to the carboxylate ion,[3] and we noted earlier that the substrate in a cationic micelle should be less strongly hydrogen bonded than in water. On this hypothesis incorporation of a primary alkylammonium ion into the cationic micelles should inhibit reaction, as is observed (Table IV), because a primary alkylammonium ion should be a good hydrogen-bonding donor. Increasing the length of the *n*-alkyl group should bind the ammonium ion more strongly to the micelle, and the inhibition is greatest with the most hydrophobic ammonium ion (Table IV).

Unprotonated *n*-alkylamines slightly change the micellar catalysis (Table V). The rate at first decreases as the length of the *n*-alkyl group increases, but then increases. Possibly the less hydrophilic amines merely interact with the micellar surface, whereas the more hydrophobic ones comicellize and increase reaction rate by decreasing charge density of the micelle, and we note that the nonionic surfactant Igepal increases the rate of decarboxylation of I by a similar mechanism.[5]

Micellar Effects in Aqueous Organic Solvents. With ionic surfactants in mixtures of relatively hydrophobic alcohols and water, normal ionic micelles form when the water content is high, but with decreasing water content the nature of the aggregate changes, and when the water content is low, reverse micelles form.[14,34] However, normal micelles form in ethylene glycol[35] and presumably also in its mixtures with water. The rates of some reactions are very sensitive to reverse micelles in nonpolar solvents, but

Table VI
Effect of Organic Solvents on the Decarboxylation of 6-Nitrobenzisoxazole and on Phosphate Ester Hydrolysis[a]

Solvent	Substrate: 	Substrate: 
H_2O	3×10^{-6}	0.8×10^{-5}
95% *n*-HexOH (w/w)	1.24×10^{-4}	2.2×10^{-4}
77.5% $(CH_2OH)_2$ (w/w)	3.2×10^{-5}	

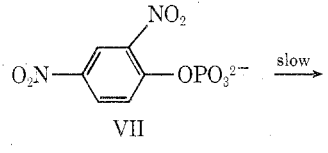
[a] Values of k_ψ, sec^{-1}, at 25.0°.

Table VII
Effect of CTABr in Organic Solvents on Decarboxylation of 6-Nitrobenzisoxazole Carboxylate Ion[a]

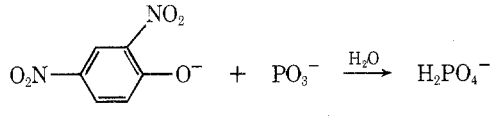
$10^3 C_D$[b]	$10^4 k_\psi$, sec^{-1}	$10^3 C_D$[b]	$10^4 k_\psi$, sec^{-1}
	1.24	11.2	2.63
0.06	1.34	21.0	3.76
0.52	1.59		0.32[c]
3.2	1.98	6.2	2.46[c]
7.0	2.14	11.0	2.83[c]
9.4	2.37	16.0	3.28[c]

[a] At 25.0° with 3×10^{-4} *M* KOH unless specified and 1-hexanol-water (95:5 w/w) unless specified. [b] As mole fraction. [c] In ethylene glycol–H_2O (77.5:22.5 w/w) and 3×10^{-3} *M* NaOH.

to date these have generally been bimolecular reactions involving acids or bases,[14,34] although the decomposition of 2,4-dinitrophenyl sulfate occurs readily in benzene containing *n*-alkylammonium carboxylates.[17] The rate of the SN1 bromodecarboxylation of 3-bromo-3-phenylpropionate ion to give mainly styrene was not especially sensitive to reverse micelles,[36] but it is also relatively insensitive to solvent effects,[37] and we also examined two reactions which are highly solvent sensitive. One was the decarboxylation of 6-nitrobenzisoxazole carboxylate ion (I),[3] and the other was the spontaneous hydrolysis of the 2,4-dinitrophenylphosphate dianion (VII).[15] Both these reactions are catalyzed by normal cationic micelles in water.[5,16]



VII



In agreement with earlier evidence the reaction rates in the absence of surfactant are increased by addition of organic solvents, and micellar effects on these reactions in both *n*-hexanol–water and ethylene glycol–water are small (Tables VI–VIII). In contrast to the small micellar catalysis of decarboxylation of I in these solvents by CTABr there is a 95-fold rate enhancement in water,[5] and for hydrolysis of the 2,4-dinitrophenylphosphate dianion in water the rate enhancement is 25-fold.[16] These results are understandable if we assume that decreased hydration of the substrate when it is incorporated into the micelle is important, because in going from initial- to transition-state electrons are transferred from the hydrophilic carboxylate or phosphate

Table VIII
Effect of Surfactants in 1-Hexanol–Water on Phosphate Ester Hydrolysis[a]

Surfactant	$10^3 C_D$[b]	$10^4 k_\psi$, sec^{-1}
		2.2
CTABr	7.2	1.05
CTABr	20	0.71
V[c]	1.3	1.87
V[c]	5.4	0.93
V[c]	8.8	0.84

[a] At 25.0° in 1-hexanol–water (95:5 w/w) and 5×10^{-3} *M* KOH. [b] Surfactant concentration as mole fraction. [c] *n*-$C_{16}H_{33}N^+Me_2$-$CH_2CH_2OHBr^-$.

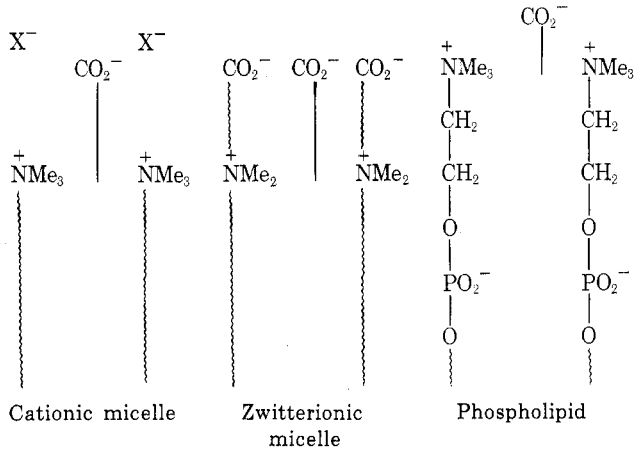
groups into the organic residue, where they are delocalized by resonance. Thus the role of a cationic micelle should be considerably reduced when initial-state hydration is decreased by addition of an organic solvent.

Discussion

Effects of Changes in Surfactant Structure. Decarboxylations of the anionic substrates I and II are strongly catalyzed by cationic micelles,[5,6] and replacing one methyl in the head group of CTABr by a 2-hydroxyethyl group does not affect the catalysis, but the rate of reaction in the micelle is approximately doubled when the pH is high enough to convert V into the zwitterion VI. Consistently, micelles of zwitterionic surfactants are better catalysts than the corresponding cationic micelles.

The charge distribution in zwitterionic micelles derived from an amino acid is similar to that of a cationic micelle surrounded by counterions (Scheme I). In both cases a substrate having its organic residue located between the ammonium head groups will be subject to Coulombic repulsions between its carboxylate ion and the negative charges on or adjacent to the micelle, but in the transition state the negative charge moves out of the carboxylate group and into the heterocyclic moiety, giving the transition state considerable carbanionoid character, as shown below for decarboxylation of I. Thus the negative charge will move

Scheme I



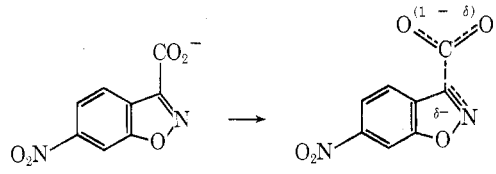
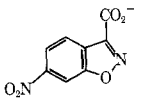


Table IX
Micellar Catalysis of Decarboxylation[a]

Surfactant	Substrate: $PhCH(CN)CO_2^-$	Substrate: 
n-$C_{12}H_{25}\overset{+}{N}Me_3Br^-$	280 (0.018)	70 (0.012)
n-$C_{16}H_{33}\overset{+}{N}Me_3Br^-$	660 (<0.005)[b]	95 (0.0016)[c]
n-$C_{12}H_{25}\overset{+}{N}Me_2CH_2CO_2^-$	690 (0.013)	170 (0.01)
DL-n-$C_{12}H_{25}\overset{+}{N}Me_2CHMeCO_2^-$		210 (0.006)
L-n-$C_{12}H_{25}\overset{+}{N}Me_2CHMeCO_2^-$		185 (0.008)
n-$C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2OH$		~90
n-$C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2O^-$		~200[d]

[a] Values of rate constants relative to those in water (k_m/k_o) at 25.0°; the values in parentheses are the molarities of surfactant required for 50% catalysis. [b] Reference 6. [c] Reference 5. [d] pH ~ 14.

closer to the quaternary ammonium center, with which it will interact beneficially.

The situation will be completely different with a micelle or liposome of a phospholipid,[10b] where the cationic ammonium ion moiety is at the head of the surfactant. The unfavorable initial-state interactions will be absent, and as the charge moves into the organic residue in the transition state it will interact unfavorably with the anionic phosphate group.

The zwitterionic micelles of III and IV are between two- and threefold more catalytically effective than the corresponding cationic micelles even though the micellar surface should be highly aqueous, which should decrease Coulombic interactions. Jencks has noted that unfavorable initial-state interactions, e.g., the introduction of steric strain in a substrate which is relieved in the transition state, may be important factors in enzymic catalysis.[38] Coulombic repulsions should be much greater in a hydrophobic cavity than at the surface of a micelle in water, where the dielectric constant is relatively high,[39] so that unfavorable initial-state Coulombic interactions which we observe in our aqueous systems could be playing a much more important role in enzymic catalysis.

In our system the hydrophobic interactions between the substrate and the micelle overcame the local Coulombic repulsions between anionic groups. The concentration of surfactant required for 50% of the total rate enhancement is an indication of the strength of micelle–substrate binding,[10] and it is not particularly affected by the nature of the micellar head group (Table IX). Table IX also summarizes the micellar rate enhancements of decarboxylation. There are examples in which bimolecular reactions are catalyzed by zwitterionic micelles,[9-11] but generally a zwitterionic micelle is a much poorer catalyst than the corresponding cationic micelle, as expected from electrostatic considerations.

As noted in the Results section, the effects of phenols and alkylamines are obtained with solute concentrations similar to that of the surfactant, suggesting a close interaction between the micelle and these chemically inert solutes which affects the micellar catalysis without changing the effective micellar charge.

Registry No.—I, 42540-91-0; II, 34220-42-3; III, 683-10-3; L-IV, 54385-46-5; DL-IV, 52665-42-6; V, 20317-32-2; VII, 18962-96-4; DDTBr, 1119-94-4; CTABr, 57-09-0; DL-Na mandelate, 34166-39-7; D(−)-Na mandelate, 54385-47-6; L(+)-Na mandelate, 19944-52-6; n-$C_{16}H_{33}N^+Me_2CH_2CH_2O^-$, 54385-45-4.

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