Micellar Catalysis of Ester Hydrolysis. The Influence of Chirality and Head Group Structure in "Simple" Surfactants

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d-, *l*-, and *dl*-*p*-nitrophenyl α-methoxyphenylacetates (I) were hydrolyzed at pH 7.0, 8.0, and 9.0 in aqueous micellar solutions of cetyltrimethylammonium bromide, *N*-benzyl-*N*-cetyldimethylammonium bromide, *d*-, *l*-, and *dl*-*N*-α-methylbenzyl-*N,N*-dimethylcetylammonium bromide, and *d*-, *l*-, and *dl*-*N*-α-methyl-*p*-methoxybenzyl-*N,N*-dimethylcetylammonium bromide. Rate constants for the pseudo-first-order hydrolyses reveal significant micellar catalysis, but limited dependence on head group structure, and no substantial stereoselectivity. Similar results were obtained in hydrolyses of I catalyzed by inverse (*n*-hexyl alcohol–water) micellar solutions of the same surfactants. The uv spectra of *N*-*n*-tetradecyl-2,4-dinitroaniline, solubilized in the various surfactant solutions, afforded a measure of the "polarity" of the micellar Stern layers.

The catalysis of organic reactions by surfactant micelles is an area of great endeavor.[3] Many organic reactions have now been examined, and attention is turning toward the influence of surfactant structure on catalytic efficiency. Particularly because of the often-cited enzyme–micelle analogy,[3,4] the question of chirality has become topical.

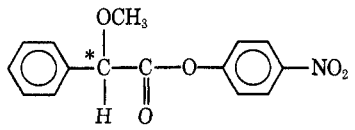
There has been little study of stereochemical effects in micelle-catalyzed reactions, and our demonstration of micellar control of stereochemistry in the nitrous acid deamination reaction appears to have been the first such report.[5,6] More recently, catalysis of the mutarotation of 2,3,4,6-tetramethyl-α-D-glucose by inverse micelles has been reported.[7]

Of very direct concern to us was the communication by Bunton, Robinson, and Stam of the stereoselective hydrolysis of *d*- or *l*-*p*-nitrophenyl α-methoxyphenylacetate catalyzed by surfactants derived from D-(−)-ephedrine.[8] This was the first report of catalytic interaction between chiral micellar reagents and chiral substrates,[9] and coincided with our own developing interests.[10]

Here, we present a full report of some micelle-catalyzed hydrolyses of optically active and racemic *p*-nitrophenyl α-methoxyphenylacetate. We employed rather simple surfactants in this initial study, and considered the effects of structural variation of the surfactant head group and of the introduction of a *single* center of chirality. The micellar catalysts were examined under normal (aqueous) conditions, and, briefly, under nonaqueous (inverse micelle) conditions.

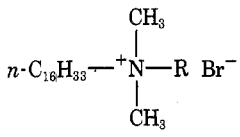
Results

Synthesis. The substrates were *d*-, *l*-, and *dl*-*p*-nitrophenyl α-methoxyphenylacetate (I). Racemic or optically active mandelic acids were O-methylated with dimethyl sulfate in aqueous sodium hydroxide solution; the methoxy acids were converted to the acid chlorides with oxalyl chloride, whereupon treatment with *p*-nitrophenol in toluene and pyridine afforded I. The *d*- and *l*-α-methoxyphenylacetic acids, from which the esters were obtained, were >99% optically pure, and subsequent hydrolysis of *d*-I, followed by reisolation of the *d*-α-methoxyphenylacetic acid, demonstrated that optical purity had been preserved to >96% in the acid → ester sequence.[11]



I

The surfactants were all of the general form II, and are described in Table I.



II

Surfactant IIb was prepared from *N,N*-dimethylbenzylamine and cetyl bromide in refluxing acetone. The catalysts of the *N*-α-methylbenzyl-*N,N*-dimethylcetylammonium bromide series (IIc) were prepared from the appropriate *d*-, *l*-, or *dl*-α-methylbenzylamine by dimethylation,[12] followed by reaction with cetyl bromide in refluxing ethanol. The active amines were >97% optically pure, and it is assumed that this holds for the resulting surfactants. The catalysts of the MeO-16 (IId) series were prepared from cetyl bromide and *N,N*-dimethyl-α-methyl-*p*-methoxybenzylamine, which was obtained from *p*-methoxyacetophenone by a Leuckart reaction, followed by dimethylation.[12] *d*- or *l*-α-methyl-*p*-methoxybenzylamines were derived from the racemate by fractional crystallization (respectively) of the *d*- or *l*-tartrate salts. The amines, and hence *l*-IId and *d*-IId, were at least 85% optically pure.[11]

All of the surfactants were purified by repetitive crystallizations, and log [surfactant] *vs.* surface tension graphs did not display minima.

Table I
Surfactants and Their Critical Micelle Concentrations

Compd	R	Abbreviation	Cmc, $M \times 10^4$ [a]
IIa	CH_3	CTA-Br	8.6[b]
IIb	$CH_2C_6H_5$	CBzDA-Br	2.73 ± 0.15[c]
dl-IIc	$CH(CH_3)C_6H_5$	*dl*-16	2.73 ± 0.11
l-IIc	$CH(CH_3)C_6H_5$	*l*-16	2.08 ± 0.06
d-IIc	$CH(CH_3)C_6H_5$	*d*-16	2.29 ± 0.11
dl-IId	$CH(CH_3)$-*p*-$CH_3OC_6H_4$	*dl*-MeO-16	1.56 ± 0.07
l-IId	$CH(CH_3)$-*p*-$CH_3OC_6H_4$	*l*-MeO-16	1.43 ± 0.10
d-IId	$CH(CH_3)$-*p*-$CH_3OC_6H_4$	*d*-MeO-16	1.46 ± 0.09

[a] Determined in distilled water, resistivity >1.5 × 10^6 ohm cm from graphs of surface tension *vs.* log [surfactant]. Measurements were made with a Fisher automatic surface Tensiomat on solutions maintained at 31.0°. The results are mean values of three runs on separately prepared stock solutions, unless otherwise noted. Errors are average deviations from the means. Details of the experimental method appear in ref 5 (Moss, Talkowski, Reger, and Powell) and 10. [b] Single run. Literature values are 8 × 10^{-4} *M* [C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969)] and 9.2 × 10^{-4} *M* (ref 3b). [c] Two determinations.

Table II
Maximum Pseudo-First-Order Rate Constants (sec^{-1}) for Micellar Hydrolysis of Ester I[a]

Case	Substrate	Surfactant[b]	$10^2 k_\psi^{max}$ at pH 9.0	8.0	7.0	8.0 − 7.0[c]
1	*dl*-I	CTA-Br	2.94[d]	0.332	0.147	0.185
2	*dl*-I	CBzDA-Br	2.92[e]	0.330[e]	0.152[e]	0.178
3	*dl*-I	*dl*-16	2.24	0.265	0.121	0.153
4	*dl*-I	*dl*-MeO-16	2.02	0.252	0.118	0.134
5	*dl*-I	*l*-16	*f*	0.271	0.133	0.138
6	*l*-I	*dl*-16	2.70	0.252	0.136	0.116
7	*l*-I	*l*-16	2.49	0.271	0.135	0.136
8	*l*-I[g]	*d*-16	2.47	0.267	0.139	0.128
9	*dl*-I	*l*-MeO-16	*h*	0.233	0.115	0.118
10	*l*-I	*dl*-MeO-16	2.10	0.221	0.113	0.108
11	*l*-I	*l*-MeO-16	2.04	0.223	0.108	0.115
12	*l*-I	*d*-MeO-16	2.07	0.236	0.109	0.127

[a] See the text and the Experimental Section for details of the measurements. From duplicate runs, and from the scatter of the k values in the plateau region, we estimate that the rate constants are reproducible to ±3%. [b] See Table I for surfactant abbreviations. [c] The difference in rate constants at pH 8.0 and 7.0 is recorded as a reflection of the *base-catalyzed* process at pH 8.0. [d] Reference 8 gives ~4.9×10^{-2} sec^{-1} in 0.01 *M* sodium borate buffer. The discrepancy may have to do with differing buffer concentration *and* quality; this is amplified in the Discussion. All of the rate constants of Table II were determined with a single lot of Fisher Certified buffer, and within several weeks. [e] The plateau rate constant could not be determined owing to limited surfactant solubility. The quoted value is therefore not necessarily a maximum. [f] See text. [g] The following additional k_ψ^{max} values were determined at pH 9: *d*-I in *d*-16, 0.0240 sec^{-1}; *d*-I in *l*-16, 0.0235 sec^{-1}. [h] Not determined.

Kinetic Results, Normal Micelles. Pseudo-first-order hydrolysis of I was followed spectrophotometrically by monitoring the appearance of *p*-nitrophenoxide at 400 nm. Runs were carried out at 25.0 ± 0.2°, in buffered aqueous solutions which contained 2.0×10^{-5} *M* substrate and 0.5% (volume) of purified dioxane. Hydrolysis studies were conducted at pH 9.0 (0.005 *M* borate buffer) and at pH 8.0 and 7.0 (0.01 *M* phosphate buffers).

At pH 8.0 and 9.0, runs were done at several surfactant concentrations, so as to derive a rate constant *vs.* [surfactant] profile. The profiles were of the expected form;[3b] *viz.*, the rate constant increased sharply as [surfactant] exceeded the cmc, and then reached a maximum at higher surfactant concentrations (~10 cmc). At still higher [surfactant], inhibition was observed. Plateau values of k_ψ were generally encountered at $1.5\text{–}3.0 \times 10^{-3}$ *M* surfactant, and are taken as $\sim k_m$, the hydrolytic rate constants in the micellar phase. pH 7.0 rate constants were determined only at the [surfactant] corresponding to k_ψ^{max} at pH 8.0. Table II contains the data.

Base values for *noncatalyzed* hydrolyses of I (k_o) were determined from runs carried out in the appropriate buffer solution but *without* added surfactant. We found $k_o = 2.76 \times 10^{-3}$ and 4.06×10^{-4} sec^{-1} for hydrolyses of *dl*-I at pH 9.0 and 8.0, respectively. The former value is to be compared with 4.8×10^{-3}, which can be measured from Figure I of ref 8. (See footnote *d*, Table II.) The catalytic effectiveness (k^{max}/k_o) of the various micellar systems is given in Table III.

Kinetic Results, Inverse Micelles. Friberg and coworkers reported that certain compositions of CTA-Br, *n*-hexyl alcohol, and water yielded inverse CTA-Br micelles which catalyzed the basic hydrolysis of *p*-nitrophenyl esters.[13] These ternary catalytic systems are complicated, and the microenvironment of the components strongly depends on their relative proportions.[14] For example, in 1:4.5 mixtures of CTA-Br:H_2O, in *n*-hexyl alcohol, the *n*-hexyl alcohol serves as an intermicellar liquid for inverse CTA-Br micelles with hydrated polar cores.

We carried out a brief study of the hydrolysis of I in several *n*-hexyl alcohol–water–surfactant systems. However, in the absence of a complete phase-diagram study of the new ternary systems, the exact state of the catalytic species present in our apparently homogeneous solutions (*i.e.*, inverse micelles, smaller hydrated ionic aggregates, or hydrated ion pairs) remains uncertain.

Table III
Effectiveness of the Micellar Catalysts. Hydrolysis of *dl*-I[a]

Surfactant	k_ψ^{max}/k_o pH 9.0	pH 8.0
CTA-Br	10.7	8.17
CBzDA-Br	10.6[b]	8.12[b]
dl-16	8.11	6.52
dl-MeO-16	7.32	6.20

[a] k_ψ^{max} values are from Table II. For surfactant abbreviations, see Table I. [b] See footnote *e*, Table II.

Table IV
Hydrolysis of *dl*-I in Inverse Micelles[a]

Surfactant	$10^2 k_{obsd}$, sec^{-1}
CTA-Br	2.67
CBzDA-Br	2.59
l-16	1.78
l-MeO-16	1.92

[a] Results of single determinations; see the text for details. Surfactant abbreviations are defined in Table I.

For a comparison of micellar effectiveness as a function of head groups, arbitrary solutions of surfactant–*n*-hexyl alcohol–0.05 *M* pH 9 borate buffer were prepared in the mole ratios 0.04:0.71:0.25, respectively.[15] The substrate (*dl*-I) concentration was 2.0×10^{-5} *M*. The results appear in Table IV; note that with an alternative ternary catalyst composition, the effectiveness order could be different.

It was not possible to determine a meaningful k_o value. Thus 10 ml of *n*-hexyl alcohol and 0.6 ml of 0.05 *M* pH 9 buffer were shaken for several hours and then centrifuged for 1 hr. Use of the resulting supernatant (*n*-hexyl alcohol saturated with buffer) as the hydrolytic medium led to very slow, non-first-order hydrolysis. Since this process was on the time scale of hours, whereas the inverse micelle catalyzed process was completed within several minutes, buffer *not* solubilized by the micelles makes a negligible contribution to the hydrolyses of Table IV. Alternatively, one might take k_o as the rate constant for hydrolysis of *dl*-I in 0.05 *M* pH 9 buffer. This was found to be 0.0450 sec^{-1}.

Chirality studies were carried out with *dl*-, *d*-, and *l*-16, using approximately optimized catalytic systems. Solutions of 1, 2, 3, or 4 g of *d*-16 in 10 ml of *n*-hexyl alcohol

Table V
Hydrolysis of Ester I in Inverse Micelles of *dl*-, *d*-, and *l*-16[a]

Substrate	Surfactant	$10^2 k\psi$, sec^{-1}
dl-I	*dl*-16	4.16
dl-I	*d*-16	4.47
d-I	*d*-16	4.77[b]
l-I	*d*-16	5.06
l-I	*l*-16	6.00
d-I	*l*-16	4.44

[a] The substrate concentration was 2×10^{-5} *M*. These are mainly results for single runs. See the text for details and Table I for surfactant abbreviations. [b] Average of two runs, 4.44 and 5.10 $\times 10^{-2}$ sec^{-1}.

Table VI
Uv Maxima (Å) of the Long-Wavelength Absorption Band of III in Various Solvents[a]

Solvent	λ_{max}	$E_T(30)$[b]	Z[c]
Cyclohexane	3320	30.9[d]	
Benzene	3481	34.5	54
1,2-Dimethoxyethane	3497	38.2	62.1
Acetone	3522	42.2	65.7
Acetonitrile	3536	46.0	71.3
Dimethylformamide	3593	43.8	68.5
Water	3641[e]	63.1	94.6

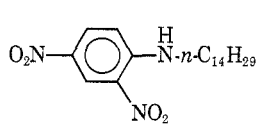
[a] The solutions were 3–6 $\times 10^{-5}$ *M* in III; ϵ for the band of interest was 1–2 $\times 10^4$. All organic solvents were of spectral grade, and were dried before use by distillation from Na, Na, $LiAlH_4$, K_2CO_3, CaH_2, and BaO, respectively. Water was distilled from $KMnO_4$. [b] A solvent polarity parameter based on the transition energy (kcal/mol) of the intramolecular charge-transfer band of a pyridinium phenol betaine; see ref 21. [c] Energy (kcal/mol) of the longest wavelength charge-transfer band of 1-ethyl-4-carbomethoxypyridinium iodide; see ref 22. [d] *n*-Hexane was used. [e] Probe III is insoluble (uv) in water. The cited λ_{max} is that of *N*-*n*-butyl-2,4-dinitroaniline, prepared by the procedure of ref 20.

were prepared. The rate constant for hydrolysis of *dl*-I was determined for each solution as a function of the amount of added 0.05 *M* pH 9 buffer (0.2–0.8 ml). Optimum catalysis was observed with *n*-hexyl alcohol–surfactant–buffer = 10 ml:3 g:0.4 ml (81:8:22 mmol ratio). Kinetic results with this catalytic system are collected in Table V.

Uv Studies. The uv spectra of micelle-solubilized molecules have provided details of the local environment of the solubilized species.[16-18] A broad summary of this work is that "molecules of appreciable polarity occupy the micellar surface, not the micellar interior."[19] Molecules of hydrolytic interest, such as esters, fall into this class.[3a]

We carried out two sets of uv experiments, the first to probe the nature of the Stern layers of our surfactant micelles, and the second to characterize the solubilization site of ester I.

The probe solubilizate *N*-*n*-tetradecyl-2,4-dinitroaniline (III) was readily prepared,[20] and its uv spectrum was



III

measured in several solvents; *cf.* Table VI. The behavior of the long-wavelength absorption band of III, as a function of solvent, is consistent with that of a $\pi \rightarrow \pi^*$ transition. Note, especially, the bathochromic shift of λ_{max}, which accompanies increasing solvent polarity, as well as the general parallel of λ_{max} with $E_T(30)$[21] and Z[22] parameters.[23]

Table VII
Absorption Maxima (Å) for III in Micellar Environments[a]

Surfactant micelle[b]	λ_{max}
CTA-Br	3586
d-16[c]	3566
dl-MeO-16[d]	3560
CBzDA-Br[e]	3540

[a] 0.56 *M* surfactant and 3 $\times 10^{-4}$ *M* III in 99:1. water–dioxane (by volume). [b] See Table I for surfactant abbreviations. [c] An identical maximum was observed with *l*-16.[26] [d] We thank Mr. C. E. Powell for this experiment. [e] 0.0015 *M* surfactant was used. The concentration is limited by solubility.

Table VIII
Uv Maxima of Ester I

Solvent	λ_{max}, Å	ϵ
Cyclohexane	2668	9100
Aqueous *dl*-16	2705	5900[a]
Water	2707	7600

[a] This solution corresponds to the medium of a kinetic run which gave $k\psi^{max}$: 2 $\times 10^{-3}$ *M* *dl*-16, 2 $\times 10^{-5}$ *M* *dl*-I, and 0.5 vol. % dioxane. Base was omitted. It is believed that I is completely solubilized by the micelles under these conditions.

Probe III appears to be a sensitive mirror of solvent polarity.[23] Moreover, its long hydrophobic tail and polar chromophore make it likely that, when solubilized by a micelle, the tail will anchor in the micelle's hydrocarbon core, while the chromophore will reside in the Stern layer or near the surface of the micelle.[17,24,25] Similarly, an "anchored" (spin label) micellar probe, *N*-4-(2,2,6,6-tetramethylpiperidine-1-oxyl)-*N*,*N*-dimethyl-*n*-dodecylammonium ion, has been used to study sodium dodecyl sulfate micelles.[18]

Table VII gathers the λ_{max} values observed for probe III solubilized in the various surfactant micelles.

Excepting the DMF results, which correlate very poorly, the data of Table VI afford a reasonable linear correlation of λ_{max} (III) and Z. According to the correlation, Z values of about 82, 77, and 70 can be determined for the average micellar environments scrutinized by the polar chromophore of probe III in CTA-Br, *d*-16, or CBzDA-Br, respectively. The first value compares reasonably well with Z = 85.5, derived from the fluorescence emission maximum of CTA-Br-solubilized 1-aminonaphthalene 7-sulfonate,[27] especially if it is granted that this probe, lacking a hydrophobic tail to anchor it, may observe a more aqueous region of the micelle's Stern layer (*i.e.*, may enjoy a time-averaged residence closer to the micelle surface).

The present results also agree with those of Gitler in suggesting that the polarity of the Stern layer of CTA-Br micelles is definitely lower than that of water.[27] The observed Z value is similar to that of ethanol (79.6). Note, too, the still lower Z values for *d*-16 and CBzDA-Br micelles, which may indicate a lower effective polarity in the Stern layers, owing to the increased hydrocarbon content of the aromatic head groups. The similarity of λ_{max} for III solubilized in either *d*-16 or *dl*-MeO-16 rules out important charge-transfer interactions between the *p*-methoxyphenyl micellar head groups and the 2,4-dinitroaniline chromophores of III.

The lower Z value of micellar CBzDA-Br, compared to those of micellar *d*-16 or *dl*-MeO-16, is somewhat puzzling. Perhaps the Stern layer of the former features tighter packing of head groups and closer average approach of head group and probe. Close packing and approach may

be somewhat inhibited in the latter micelles because of steric problems associated with the α-methyl substituent at the benzylic carbon. This could lead to more "open" and aqueous Stern layers.[28]

Finally, we determined uv spectra of substrate *dl*-I under several conditions, in order to examine its solubilization environment (Table VIII). Unfortunately, λ_{max} is not very solvent sensitive. However, the near identity of λ_{max} for aqueous and micellar solutions suggest that I is solubilized at or close to the micelle–water interface (micellar surface). A similar conclusion was reached in a study of dimethyl phthalate solubilization in dodecylammonium chloride micelles.[17] We speculate that the *p*-nitrophenyl moiety of solubilized I is closer to the micellar surface than the 2,4-dinitrophenyl chromophore of probe III. Whether this is also true of the ester linkage of I is not known.

Discussion

In their important implications, the Results are clear, and this Discussion can be limited to a brief exposition followed by a prognosis of the future course of stereoselective micellar catalysis.

Table I reveals no significant differences between the cmc's of optically active and racemic MeO-16 surfactants. This is in accord with analogous comparisons of racemic and active *N*-methyl-*N*-*n*-dodecylephedrinium bromide,[8] 2-octylammonium and 2-octyltrimethylammonium ions,[10] and *N*-alkyl-*N,N*-dimethylalanine hydrobromides.[29] In contrast, the cmc's recorded for *d*-16 and *l*-16 are significantly lower than that of *dl*-16. However, the large Δcmc between the *d* and *l* surfactants suggests caution in accepting these results as an initial instance of stereochemical differentiation in micellization. Traces of homologous impurities can alter cmc's without being detected by microanalysis. Indeed, the analogous tetradecyl surfactants, *d*-14, *l*-14, and *dl*-14, exhibit no significant cmc differences.[30]

Table III reveals that surfactants IIb–d cause substantial catalysis of the basic hydrolysis of I. The magnitude of catalysis (k_ψ^{max}/k_o) is larger than that observed in studies of the basic hydrolyses of *p*-nitrophenyl hexanoate, octanoate, and dodecanoate in *n*-tetradecyl, *n*-dodecyl, and *n*-tetradecylammonium ion micelles, respectively.[31-33] Note, however, that *dl*-16 and *dl*-MeO-16 are rather less effective catalysts than CTA-Br toward the more complicated substrate, I.

The data of Table III are based on k_ψ^{max} (plateau) values and should reflect conditions in which the substrate is essentially all solubilized (*i.e.*, in which $k_\psi^{max} \cong k_m$, the rate constant for hydrolysis in the micellar phase). One can then note that the catalytic trend suggests poorer catalysis by the surfactants with the more highly *branched* head groups. Current attribution[3] of cationic micellar catalysis of basic ester hydrolysis, in part, to electrostatic stabilization of the anionic transition state, and to enhancement of hydroxide ion activity by its desolvation at the cationic micellar surface,[34] provides a simple rationalization of the trend: the more effective the hydrocarbon screening of the head group's cationic centers,[28] the lower the catalytic efficiency of the micelles.

Possibly, a similar argument can explain the decreasing catalytic efficiencies of isomeric hexadecyl sodium sulfates (in the acidic hydrolysis of methyl orthobenzoate) as the head group is moved in from the terminus of the alkyl chain.[35] Other explanations are possible, however,[35] and, lest ours be accepted too readily, we note that Bunton has reported an opposite structure *vs.* catalytic efficiency sequence: phenyl- and 2,4-dimethoxyphenylcetyldimethylammonium bromides are more effective than CTA-Br in catalyzing reactions of OH^- and F^- with *p*-nitrophenyl diphenyl phosphate, and of OH^- with 2,4-dinitrochlorobenzene.[36] The sequence was mainly due to better substrate *binding* by the aryl-substituted surfactants,[36] but a small catalytic advantage persisted, even at k_ψ^{max}, in the latter reaction. Further work is clearly required to elucidate the relation between head-group structure and catalytic efficacy.

Table IV indicates a similar catalytic order, CTA-Br ~ CBzDA-Br > *l*-MeO-16 ~ *l*-16, in the inverse micellar hydrolyses of ester I. However, as these k_ψ values were not necessarily maxima, the order may not truly reflect catalytic efficiency. In comparison to the hydrolysis of *dl*-I in 0.05 *M* pH 9 buffer ($k_o = 4.50 \times 10^{-3}$ sec^{-1}), *optimal* catalysis by *dl*-16 inverse micelles (Table V), for which $k_\psi = 4.16 \times 10^{-2}$ sec^{-1}, leads to $k_\psi/k_o \cong 9.3$. This is similar to the ratio for *normal* *dl*-16 micelles (8.11, Table III), and parallels the results of Friberg and Ahmad,[13] who found similar magnitudes of catalysis for the basic hydrolysis of *p*-nitrophenyl laurate in either normal (aqueous) or inverse (hexanol–water) CTA-Br micelles.

The main purpose of our study was to search for stereoselective hydrolysis of *active* ester I, solubilized by *active* surfactants IIc or IId. Cases 7 and 8[37] and 10–12 of Table II reveal no substantial stereoselectivity. Bunton[8] reported $10^2 k_\psi^{max} = 7.86$ and 7.07[38] for the hydrolyses of *l*-I and *d*-I in *l*-*N*-*n*-dodecyl-*N*-methylephedrinium bromide micelles. Expressed as $100(k_d^{max} - k_l^{max})/k_l^{max}$, the maximum stereoselectivity was about 11.5%. The parallel experiments of Table II exhibit no such selectivity; *e.g.*, from case 7 and footnote *f*, a stereoselectivity of 6% can be calculated, but it is not significantly beyond the combined uncertainties of the determinations (±3%). The ephedrinium micelles[8] appear to be more stereoselective than our own (see below).

There is an additional complicating feature, however. Bunton[8] also noted that *dl*-I was less reactive ($k_\psi^{max} = 4.28 \times 10^{-2}$ sec^{-1})[38] than either enantiomer (see above) in *l*-ephedrinium micelles, and also that, in CTA-Br micelles, *dl*-I was slightly more reactive (factor of 1.2[38]) than either enantiomer. It was therefore suggested that "more than one ester molecule is incorporated into each micelle, and that an enantiomeric substrate molecule perturbs the micellar structure, in such a way that the perturbed micelle then exhibits different activities towards the two enantiomers."[8,39] The CTA-Br observations have been questioned by Hindman and Jacobus,[40] who report no significant rate differences for the CTA-Br- or CTA-Cl-catalyzed hydrolyses of active or racemic I.

We find $k_\psi^{max} = 0.0294$ and 0.0298 sec^{-1}, respectively, for hydrolysis of *dl*-I and *d*-I at pH 9, in CTA-Br micelles, and 0.005 *M* Fisher sodium borate buffer (H_3BO_3 and NaOH). With 0.01 *M* $Na_2B_4O_7$ buffer at pH 9, corresponding values of 0.0376 and 0.0384 sec^{-1} were measured. Although all of the values are lower than the 0.049–0.039 sec^{-1} reported in ref 8 (see Table II, footnote *d*), there is no indication of stereoselectivity.

Jacobus[40] indicates that, as 0.01 *M* pH 9 sodium borate buffer ages, it yields gradually decreasing rate constants for hydrolysis of I. We have also observed this effect. The data of Table II, repeated with older buffer, gave 20–30% lower rate constants. The rate data *within* Tables II, IV, and V were collected within a period of several weeks, and should be free of the "aging" effect. Comparison with data determined with other lots of buffer, and in *other* laboratories, however, is probably dangerous, especially when small rate differences are involved.

Another chance to investigate the effect in question arises in comparison of k_ψ^{max} for hydrolyses of *dl*-I and *l*-I in *l*-16 micelles. (We studied these cases with a new lot of

buffer and found somewhat higher values than those of Table II, cases 7 and 8.) The k values were 3.08×10^{-2} and 3.22×10^{-2} sec^{-1}, respectively; again we found no significant rate differences for the hydrolysis of active or racemic I, catalyzed by a chiral surfactant micelle. The observational differences of Bunton,[8] Jacobus,[40] and those of our laboratory merit further study.

Table V reveals no experimentally significant stereoselectivity in basic hydrolyses of I catalyzed by *inverse d-* or *l*-16 micelles in aqueous *n*-hexyl alcohol. We hoped that the surfactant head groups might pack more tightly in the inverse mode, and that the solubilized substrate would be more sensitive to the chirality information carried by the head groups. However, consideration of the kinetic results for all "enantiomeric" and "diastereomeric" substrate–surfactant pairs indicates the absence of stereoselectivity in excess of the scatter in the data.

In these initial studies of stereoselectivity in micellar catalysis, we employed "simple" or nonfunctionalized surfactants. We questioned whether chirality in the head group could be translated into a kind of "net chirality" throughout the micelle's Stern layer, such that the activation energies for hydrolyses of solubilized enantiomeric substrates would be differentiated. The negative results show that simple chirality does not suffice; more profound interactions between substrate and micelle and, perhaps, between the micellar head groups themselves, are required to amplify the chirality differences to a chemically significant level. Such interactions could take the form of hydrogen bonding or other complexation. The weak charge-transfer interaction possible between the *p*-nitrophenylate leaving group of I and the *p*-anisyl group of the MeO-16 surfactants does not make the latter more stereoselective than the simple "16" surfactants. *Functionalized* chiral surfactants appear to be required for substantial stereoselectivity.

Whereas our (nonstereoselective) chiral surfactants are slightly poorer catalysts than CTA-Br for hydrolysis of I, the stereoselective *l*-ephedrinium surfactant is about twice as effective as CTA-Br.[8] Bunton has suggested that the hydroxyl function of the ephedrinium head group is responsible for the augmented catalysis.[8,39] It could assist ester hydrolysis either by H bonding to the ester's carbonyl oxygen, thus aiding the attack of hydroxide ion at the carbonyl carbon, or by itself acting as a nucleophile, especially if it were first deprotonated by the external base.

The latter mode of catalysis is apparently involved in the micellar hydrolysis of phosphates at high pH (~12).[39,41] The former mode is likely to be involved in the catalytic action of choline-type surfactants in the pH range 7–10. For the basic hydrolysis of simple esters, these surfactants are superior to CTA-Br by 1–2 orders of magnitude.[42]

It seems reasonable that the stereoselectivity elicited by chiral surfactant micelle catalysts will increase as the micelles become better catalysts. Thus the *l*-ephedrinium surfactant,[8] which is two to three times as effective as our own chiral surfactants, appears to exhibit some catalytic stereoselectivity. The implication is that chiral surfactants, functionalized with β-hydroxyethyl or 4-methylimidazole[43] substituents, may show greater stereoselectivity than the chiral surfactants studied thus far. We are exploring this possibility.

Experimental Section[44]

***dl-p*-Nitrophenyl α-Methoxyphenylacetate (*dl*-I).** *dl*-Mandelic acid (25 g, 164 mmol) was converted to sodium α-methoxyphenylacetate by treatment with 7.57 *M* aqueous sodium hydroxide and excess dimethyl sulfate. The precipitated sodium salt was neutralized with dilute HCl; the liberated acid was isolated as an oil by ethereal extraction, and then crystallized from benzene–petroleum ether (bp 90–120°).[45] The pure acid (7.65 g, 28%), mp 69–70° (lit.[45] mp 70.5–71°), had ir ($CHCl_3$) 5.81 (carbonyl) and 9.01 μ (ether); nmr ($CDCl_3$) 7.44 (5 H, phenyl), 4.78 (1 H, benzylic), and 3.43 ppm (3 H, methoxy), all singlets.

The purified acid was converted to *dl*-I by stirring 2 g (12 mmol) with 1.5 equiv of oxalyl chloride at ambient temperature. After 2 hr, excess oxalyl chloride was removed under reduced pressure, and 1 equiv of *p*-nitrophenol, 15 ml of toluene, and 1 ml of pyridine was added. The mixture was refluxed (1 hr), cooled, and extracted with 0.1 *N* aqueous NaOH, followed by saturated aqueous $NaHCO_3$, until the aqueous extract was no longer yellow.[31,32] The toluene solution was washed with 0.1 *N* HCl and with water, and dried over $MgSO_4$. Removal of the toluene afforded an oil which was crystallized from methanol.[46] Recrystallization from methanol gave 1.05 g (29%) of white flakes, mp 50–51° (lit.[8] mp 46–48°). The ir spectrum (CCl_4) had 5.60 μ (carbonyl); nmr (CCl_4) 8.34, 8.20, 7.28, 7.14 (4 H, q, *p*-nitrophenyl), 7.46 (5 H, narrow m, phenyl), 4.93 (1 H, s, benzylic), and 3.50 ppm (3 H, s, methoxy).

Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.57; N, 4.88. Found: C, 62.55; H, 4.42; N, 4.71.[47]

***l-* or *d-p*-nitrophenyl α-methoxyphenylacetate (*l-* or *d*-I)** were prepared as above, starting with commercially available *l-* or *d*-mandelic acids (Aldrich). The intermediate *l*-α-methoxyphenylacetic acid had mp 65–66° (lit.[48] mp 65–66°) and $[\alpha]^{25}D$ −149.3° (*c* 0.574 g/dl, ethanol); the literature value, under the same conditions is $[\alpha]^{20}D$ −150.7°.[48,49] Similarly, *d*-α-methoxyphenylacetic acid had mp 64–65° (lit.[48] mp 65–66°) and $[\alpha]^{25}D$ +149.6° (*c* 0.494 g/dl, ethanol); the literature[48] value, under the same conditions, is $[\alpha]^{20}D$ +150.0°.

The *l*-methoxy acid was converted to white needles of *l*-I, which had mp 55–56° (lit.[8] mp 49–50°) and $[\alpha]^{25}D$ −112.56° (*c* 5 g/dl, methanol). Similarly, *d*-I was obtained as white needles, mp 53.5–54.5° (lit.[8] mp 48.5–49.5°), $[\alpha]^{25}D$ +109.64° (*c* 5 g/dl, methanol).

The following experiment was carried out to demonstrate that the enantiomers of I were of high optical purity. *d*-I (0.5 g) was hydrolyzed in 25 ml of 0.1 *N* NaOH (steam bath, 30 min). The resulting solution was acidified to pH 1 with 0.1 *N* HCl and extracted with 3 × 25 ml of ether. The ethereal extract was dried ($MgSO_4$) and stripped; the residue was chromatographed on Brinkmann, SilPlate P20F-22, 2-mm (F-254) silica gel plates. Elution with acetone afforded 0.12 g of *d*-α-methoxyphenylacetic acid (R_f ~0.1), which was recovered with ether, and had $[\alpha]^{28}D$ +0.720° (*c* 0.5 g/dl, ethanol) or $[\alpha]^{28}D$ +144°. The recovered acid had >96% of the rotation of the initial α-methoxyphenylacetic acid, which itself had been >99% optically pure (see above).

Cetyltrimethylammonium bromide (CTA-Br, IIa) was obtained from City Chemical Corp. and was purified by standard methods[50] to afford white crystals, mp 244–247° (lit.[50] mp 227–235° dec).

***N*-Benzyl-*N*-cetyldimethylammonium bromide (CBzDA-Br, IIb)** was prepared by refluxing 50 g (0.37 mol) of *N,N*-dimethylbenzylamine (MCB) and 113 g (1 equiv) of cetyl bromide in 50 ml of acetone for 24 hr. Cooling afforded 85 g (65%) of crystals which after three recrystallizations from acetone had mp 79–80°.

Anal. Calcd for $C_{25}H_{46}NBr$: C, 68.14; H, 10.54; N, 3.18; Br, 18.13. Found: C, 67.60; H, 10.67; N, 3.29; Br, 17.61.[51]

***dl-N*-α-Methylbenzyl-*N,N*-dimethylcetylammonium bromide (*dl*-16, *dl*-IIc)** was prepared from α-methylbenzylamine (MCB). Conversion of the latter to *N*-α-methylbenzyl-*N,N*-dimethylamine was accomplished by the procedure of Clarke.[12] The tertiary amine (bp 70–71°, 9.7 Torr) was produced in 73% yield and had ir, nmr, and mass (M^+) spectra in accord with expectations. Quaternization of 41.3 g (0.28 mol) of the amine was effected by refluxing with 107 g (1.25 equiv) of cetyl bromide (Eastman) in 50 ml of absolute ethanol for 48 hr. Ethanol was stripped and crystallization was induced with ether. Three recrystallizations from acetone gave 60 g (48%) of *dl*-16, mp 111–112.5°, as a white powder.

***l*-16 and *d*-16** were prepared similarly. *l*-α-Methylbenzylamine (Aldrich) was distilled from sodium (bp 68–69.5°, 9.5 Torr) and had $[\alpha]^{23}D$ −18.63° (neat, *l* 0.5),[52] ~97.5% optically pure. It gave *l*-*N*-α-methylbenzyl-*N,N*-dimethylamine, $[\alpha]^{21}D$ −31.52° (neat, *l* 0.5), from which *l*-16 was obtained by cetylation. Recrystallized *l*-16 had mp 111–113° and $[\alpha]^{21}D$ −19.34° (*c* 0.454 g/ml, methanol, *l* 0.5).

Anal. Calcd for $C_{26}H_{48}NBr$: C, 68.70; H, 10.64; N, 3.22; Br, 17.58. Found: C, 68.71; H, 10.64; N, 3.22; Br, 17.83.

From *d*-α-methylbenzylamine (Aldrich), $[\alpha]^{23}D$ +18.57° (neat, *l*

0.5), ~97% optically pure,[52] we obtained *d*-*N*-α-methylbenzyl-*N,N*-dimethylamine, $[\alpha]^{21}D$ +31.44° (neat, *l* 0.5). Quaternization afforded *d*-16 as white crystals, mp 111.5–113°, $[\alpha]^{21}D$ +19.82° (*c* 0.454 g/ml, methanol, *l* 0.5).

Anal. Found: C, 68.58; H, 10.74; N, 3.28; Br, 17.86.

***dl*-*N*-α-Methyl-*p*-methoxybenzyl-*N,N*-dimethylcetylammonium Bromide (*dl*-MeO-16, *dl*-IId).** *dl*-α-Methyl-*p*-methoxybenzylamine was prepared from *p*-methoxyacetophenone (Aldrich) in 50% overall yield by a modified Leuckart procedure.[53] The product was purified by distillation, bp 65.0–65.5° (0.22 Torr) [lit.[53] bp 126° (20 Torr)], and had nmr (CCl_4) 7.29, 7.13, 6.83, 6.68 (4 H, q, aryl), 4.03 (1 H, q, J = 7 Hz, benzylic), 3.77 (3 H, s, methoxy), 1.27 (3 H, d, J = 7 Hz, methyl), 1.15 ppm (2 H, s, amino).

The *N,N*-dimethyl derivative was prepared by Clarke's procedure,[12] and the product, *dl*-α-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine, was distilled from sodium, bp 65–65.5° (0.15 Torr). Nmr (CCl_4) showed essentially unchanged aryl, methoxy, and *C*-methyl resonances. The benzylic proton appeared at 3.15 (1 H, q, J = 7 Hz)) and the *N*-methyl resonance appeared at 2.14 ppm (6 H, s). The tertiary amine (25 g, 0.14 mol) and 53.2 g (1.25 equiv) of cetyl bromide in 50 ml of acetone were refluxed for 24 hr. Cooling afforded a solid, which was recrystallized four times from acetone to give 38.8 g (57%) of *dl*-MeO-16 as a white powder, mp 112–114°. Ir showed the absence of $^+$N–H stretching. Nmr (CCl_4) showed 7.84 and 6.94 (4 H, A_2B_2 "doublets," aryl), 5.56 (1 H, m, benzylic), 3.80 (3 H, s, methoxy), 3.37 (6 H, broad s, *N*-methyls), 1.90 (5 H, m, *C*-methyl + NCH_2), 1.23 (broad s,), and 0.87 ppm (crude t, cetyl group, 31 H).

Anal. Calcd for $C_{27}H_{50}NOBr$: C, 66.92; H, 10.39; N, 2.89; Br, 16.49. Found: C, 67.23; H, 10.54; N, 2.90; Br, 16.51.

***d*-MeO-16 and *l*-MeO-16.** *d*-α-Methyl-*p*-methoxybenzylamine was obtained by repeated recrystallization of the *d*-tartrate salt of the *dl* amine in methanol,[54] until constant melting point (181–183°) and rotation {$[\alpha]^{25}D$ +2.384° (*c* 13.25 g/dl, H_2O, *l* 1)} were obtained. A final recrystallization from water[55] and cleavage[54] afforded *d*-α-methyl-*p*-methoxybenzylamine, $[\alpha]^{20}D$ +24.4° (*c* 2 g/dl, methanol, *l* 1), 85.1% optically pure.[56] A parallel resolution using *l*-tartraric acid gave a salt with mp 181.5–184° and $[\alpha]^{25}D$ −0.440° (*c* 2.65 g/dl, H_2O, *l* 1), from which the *l* amine was obtained with $[\alpha]^{20}D$ −24.3°, 84.9% optically pure.[55,56]

Dimethylation of the active amines was accomplished as above: *d*-*N*-α-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine, $[\alpha]^{24}D$ +27.05° (neat, *l* 0.5); *l* enantiomer, −27.01° (neat, *l* 0.5). Ir and nmr spectra were identical with those of the racemic compound.

Cetylation as above afforded *d*-MeO-16, white flakes, mp 118–119°, $[\alpha]^{25}D$ +28.84° (*c* 5 g/dl, methanol, *l* 1), and *l*-MeO-16, white flakes, mp 116.5–118°, $[\alpha]^{25}D$ −28.76° (*c* 5 g/dl, methanol, *l* 1). Nmr and ir spectra were identical with those of *dl*-MeO-16.

***N*-*n*-Tetradecyl-2,4-dinitroaniline (III)** was prepared from 10.0 g (46.9 mmol) of *n*-tetradecylamine and 9.49 g (1 equiv) of 2,4-dinitrochlorobenzene by the procedure of Mustafa and Zahran.[20] Recrystallization from 98% ethanol, followed by two recrystallizations from petroleum ether (bp 37–49°), gave light yellow crystals, which were dried at 1 mm for 24 hr, mp 58–59° (lit.[20] mp 53°). Mass spectral analysis indicated M^+ at 379 and contamination by at least 4% of the C_{16} homolog (M^+ at 407). The nmr spectrum[57] appeared to integrate normally, however: nmr (CCl_4) 8.95 (1 H, d, J = 3 Hz), 8.20 (1 H, d of d, J = 3.9 Hz), and 6.88 (1 H, d, J = 9 Hz) (3, 5, and 6 aryl protons), 8.46 (1 H, NH), 3.38 (2 H, q, J = 6 Hz, NCH_2), 2.0–0.67 (27 H, other alkyl).

The uv behavior of III is, however, unaffected by the presence of the C_{16} impurity: λ_{max} 260 nm (ϵ 7.54 × 10^3), 349 (1.50 × 10^4), ~420 (shoulder). The *N*-ethyl analog of III has λ_{max} at 260 and 348 nm.[58]

Anal. Calcd for $C_{20}H_{33}N_3O_4$: C, 63.30; H, 8.76; N, 10.53. Found: C, 64.28; H, 8.93; N, 10.29.[59]

Cmc determinations are described in Table I and its footnotes. Full descriptions of the technique have appeared.[5,10]

Kinetic studies are described in the text and in Tables II–V. We used a Beckman DB spectrometer equipped with a Sargent Model SRL recorder to monitor the appearance of *p*-nitrophenoxide ion at 400 nm. A Haake constant-temperature circulating pump maintained the sample and reference solutions at 25.00 ± 0.02°. Aqueous samples were composed of 3.0 ml of a solution containing surfactant and buffer plus 15 μl of a purified[60] dioxane solution of I, introduced at zero time. The final [I] was 2.0 × 10^{-5} *M*. Buffers were Fisher Certified Ph 7.00 (phosphate), 8.00 (phosphate), and 9.00 (borate). The latter buffer was prepared from 50 ml of a mixture which was 0.1 *M* with respect to both KCl and H_3BO_3, to which was added 20.8 ml of 0.1 *M* NaOH; the whole was diluted to 100 ml.[61] This solution (0.05 *M*) was diluted 1:9 for use with aqueous micellar solutions, and not at all for use with inverse micellar solutions.

Rate constants were obtained from plots of $(A^\infty - A^t)$ *vs.* time (*t*), refined by a least-squares program on a Wang Model 700 calculator. Correlation coefficients were >0.999, and first-order kinetics were observed over >95% of reaction. Infinity values were taken at approximately 120, 16, and 13 half-lives for pH 7, 8, and 9 runs, respectively. A separate control experiment showed that Beer's law held for *p*-nitrophenoxide ion in 0.002 *M* *dl*-16 and 0.01 *M* pH 8 buffer.

The details of the inverse micellar kinetic studies are given in the text and in Tables IV and V.

Uv studies are described in the text and in Tables VI–VIII.

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Registry No.—*dl*-I, 31528-02-6; *l*-I, 31528-00-4; *d*-I, 31528-01-5; IIb, 3529-04-2; *dl*-IIc, 50640-90-9; *l*-IIc, 50640-91-0; *d*-IIc, 50640-92-1; *dl*-IId, 50640-93-2; *l*-IId, 50640-94-3; *d*-IId, 50640-95-4; III, 50641-10-6; *dl*-mandelic acid, 611-72-3; α-methoxyphenylacetic acid, 1701-77-5; *l*-mandelic acid, 17199-29-0; *d*-mandelic acid, 611-71-2; *N,N*-dimethylbenzylamine, 103-83-3; cetyl bromide, 112-82-3; *dl*-α-methylbenzylamine, 618-36-0; *l*-α-methylbenzylamine, 2627-86-3; *d*-α-methylbenzylamine, 3886-69-9; *dl*-α-methyl-*p*-methoxybenzylamine, 35600-82-9; *dl*-α-methyl-*p*-methoxy-*N,N*-dimethylamine, 50640-96-5; *d*-α-methyl-*p*-methoxybenzylamine, 22038-86-4; *l*-α-methyl-*p*-methoxybenzylamine, 41851-59-6; *d*-*N*-α-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine, 50640-97-6; *l*-α-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine, 50640-98-7.

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The Question of Amide Group Participation in Carbamate Hydrolysis

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Phenyl *N*-(*o*-carbamoylphenyl)carbamate is cyclized to 2,4(1*H*,3*H*)-quinazolinedione in the presence of basic catalysis. A mechanism suggested involving rate-determining E1cB type elimination of phenoxide ion followed by trapping of the isocyanate intermediate by the amide group is consistent with data for model compounds. Phenyl *N*-methyl-*N*-(*o*-carbamoylphenyl)carbamate also cyclizes, but at a much slower rate (since the elimination–addition pathway is blocked); in this case the amide anion participates in the expulsion of phenoxide ion. When the amide group is attached to the leaving phenoxide ion as in salicylanilide carbamate, large rate enhancements are observed in hydroxide-catalyzed hydrolysis, but these may be explained in terms of the electronic effect of the substituent, rather than by participation. No evidence was found for appreciable carbamate group tautomerism.

Although simple carbamates, such as urethanes (**1**, R^1 = Et) are hydrolyzed only with difficulty even in highly alkaline solution,[1] carbamates with good leaving groups (such as phenyl carbamates, **1**, R^1 = Ph) may undergo rapid base-catalyzed cleavage. This has been interpreted in terms of the existence of a facile elimination–addition pathway for hydrolysis with the intermediate formation of the isocyanate **3** (Scheme I).[2,3] The isocyanate **3** has been shown to lie on the reaction pathway, since it can be trapped by both internal and external nucleophiles;[4] the addition of amine nucleophiles was shown to result in appreciable urea formation (by reaction of **3** with the amine after the rate-determining step) without changing the rate of disappearance of the starting carbamate **1**.

The elimination–addition pathway is so attractive that some nucleophilic groups, even when approximated to the reactive group (for example, **1**, R = *o*-$NH_2C_6H_4$), preferentially react *via* this mechanism, rather than directly attacking the carbamate center. In contrast, the ionized carboxy (**1**, R = *o*-carboxyphenyl)[5] and hydroxy (**1**, R = *o*-hydroxyphenyl)[6] groups have been shown to form cyclic products (isatoic anhydride and benzoxazinone, respectively) by direct nucleophilic attack on the carbamate. Because of the duality of behavior shown by these diverse