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STEREOSPECIFIC MICELLAR CATALYZED ESTER HYDROLYSIS

C. A. Bunton, L. Robinson and M. F. Stam

Department of Chemistry, University of California

Santa Barbara, California, 93106

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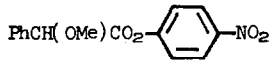
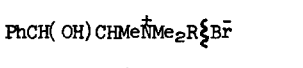
In an attempt to observe a stereospecific micellar catalysis we examined the hydrolysis of (I), followed by formation of nitrophenoxide ion, in the presence of micelles of the optically active detergents (II) (For reviews of kinetic micellar effects see ref. 1-3). These detergents have the same configuration as D (-) ephedrine, from which they were prepared by methylation with formaldehyde[4] followed by quarternization using decyl or dodecyl bromide and purified by recrystallization. Because of the possibility that a small amount of impurities might affect the stereospecificity a portion of D (-) IIb was recrystallized without affecting the rate constant. The esters were prepared from mandelic acid by standard methods,[5,6] and had mp. 49-50° D (-); 48.5-49.5°, L (+); 46-48°, DL. Satisfactory elementary analyses were obtained for I and II.



I



II

IIa R = $C_{10}H_{21}$

IIb R = $C_{12}H_{25}$

Hydrolysis was followed spectrophotometrically at 25.0°, pH 9.0 in 0.01 M sodium borate buffer with 10^{-5} M substrate in the presence of 0.5 vol.% purified dioxane.

The results in Figure I show that with D (-) IIb the D (-) ester is more reactive than the L (+), and the differing steepness of the plots of k_ψ (the first order rate constant) against detergent concentration, C_D, suggests differential binding of the enantiomers with the optically active detergent. Stereospecific interactions have been observed between optically active amino acids and optically active micelles,[7] and between mandelic acids and esters and optically active polymers.[8]

Unexpectedly the DL-ester is less reactive than its enantiomers with D (-) IIb, suggesting 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 markedly different activities towards the two enantiomers. Another example of this effect is the hydrolysis catalyzed by micelles of cetyltrimethylammonium bromide (CTABr).

With this detergent the two enantiomers of I give identical rate profiles (Figure I), but a different profile with racemic ester. However in this case the racemic is more reactive than the optically active esters. In order to exclude the possibility that impurities in the optically active esters were responsible for these reactivity differences we used samples of DL-esters prepared from DL-mandelic acid, and by mixing D- and L-ester, and found the rates to be the same within experimental error.

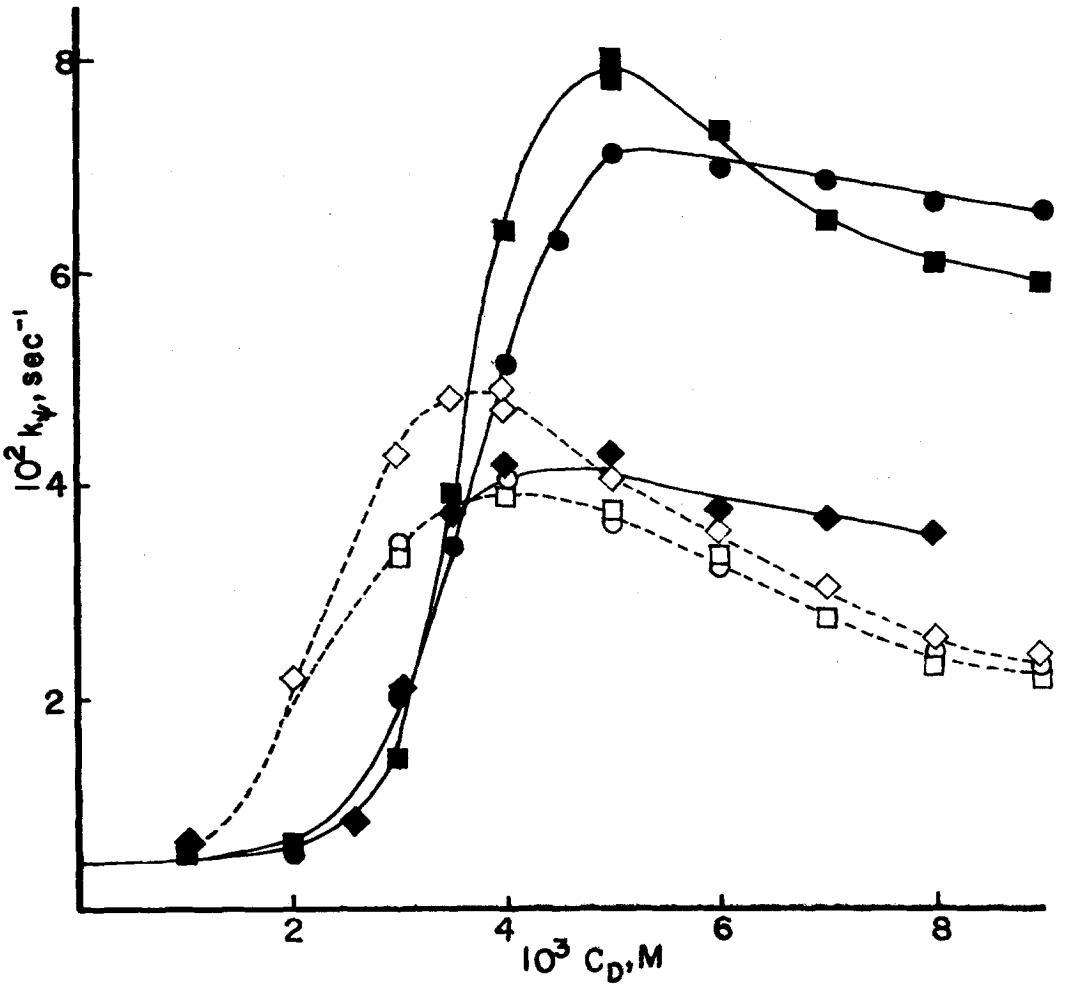


Figure I. Variation of k_ψ with detergent concentration at pH 9.0, 25.0° and 1.4 x 10^{-5} M substrate; solid line and points with D (-) IIb; open points and broken line with CTABr.
■ □ D (-) I; ● ○ L (+) I; ◆ ◇ DL I.

Micellar catalysis and inhibition have often been treated on the assumption that only one substrate molecule is bound to each micelle.[3,6] Our present results suggest that these treatments may not always be correct.

We attempted to use DL-IIb as a catalyst, but its solubility is too low (0.0035 M). However D-IIb is a slightly better catalyst than DL-IIb for the hydrolysis of p-nitrophenyl diphenyl phosphate.[9] (In this system catalysis is observed at very low detergent concentrations). Although we observe these physical differences between the optically active and racemic detergents the c.m.c. (critical micelle concentrations), measured by the dye method,[10] were the same within experimental error,[9] as has been observed with optically active octyl ammonium ion detergents.[11]

Shortening the length of the alkyl chain in a detergent molecule generally reduces micellar catalysis,[1-3] and we observe that effect here, with D (-) IIa $k_{\psi}(max) = 4.6 \times 10^{-2}$ sec^{-1} at $C_D = 0.025$ M with D (-) I and 3.5×10^{-2} sec^{-1} at $C_D = 0.030$ M with DL I, showing that the stereospecificity is maintained. With D (-) IIa the hydrolysis of the D (-) ester is speeded approximately tenfold as compared with the sixteenfold rate enhancement observed with D (-) IIb. The hydroxyl group of II may be involved in the catalysis, either as a chemical reagent, or in binding of the substrate, because despite the shorter length of the alkyl group IIb is a better catalyst than CTABr (Figure I). We have observed nucleophilic attack by the alkoxide group of IIa,b upon p-nitrophenyldiphenyl phosphate.[9]

Micellization of D (-) IIa enhances its molar ellipticity in the region of 2400-2800 A, without changing the shape of the CD curve. In so far as interactions between the OH dipole and the adjacent phenyl group are probably the most important factors in determining the CD spectra these qualitative results suggest that the conformation of the head group of II does not change markedly upon micellization, but that the OH-phenyl interaction is increased, possibly because water molecules are excluded from the region of the head group on micellization.

Our present studies extend existing evidence on stereospecific incorporation into micelles,[7] and the effect of micellization upon amine deamination.[11,12] They accord with the physical studies of amino acid-micelle binding as a model for drug action,[7] because in both cases the strongest binding is observed when the amino acid and the detergent have the same configuration.

Inhibition of micellar catalysis by counter ions has been observed in many systems.[2,3] The catalysis of the hydrolysis of D (-) I by micelles of D (-) IIb is stereospecifically inhibited by III.

$PhCH(OMe)CO_2Na$

III

In the presence of 0.005 M D (-) IIb $k_\psi = 7.95 \times 10^{-2}$ sec^{-1}, addition of 2.0×10^{-3} M D (-) III gives $k_\psi = 6.01 \times 10^{-2}$ sec^{-1}, whereas addition of L (+) III gives $k_\psi = 6.37 \times 10^{-2}$ sec^{-1}. Similar salt effects were observed with 0.008 M D (-) IIb, and with D (-) IIa. (From triplicate experiments we estimate the mean deviation to be 3%). In an examination of the enzymic hydrolysis of methyl mandelate stereospecific inhibition by mandelic acid was observed, the maximum being observed when the ester and the inhibiting acid had the same configuration.[13]

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