Stereoselective Micellar Catalysis. II. Kinetic Properties of Optically Active Micellar Catalysts for Cleavage of Amino Acid Ester Derivatives

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Synopsis. Stereoselective reactions of the enantiomers of *N*-acylamino acid *p*-nitrophenyl esters with *N*-decanoyl-(D or L)-histidine (DecHis) in an optically active surfactant (DMEBr) derived from (*l*)-ephedrine were studied at 25 °C and pH 7.30 in comparison with those of simple surfactant, hexadecyltrimethylammonium bromide (CTABr). The mixed micelles of DecHis and DMEBr are effective stereoselective catalysts and the catalytic effects are determined mainly by the nucleophilic reactivity of the optically active histidine residue of DecHis.

Surfactant micelles have been extensively investigated as favorable models for enzyme catalysis;[1] particularly, several esterolysis reactions have been performed with optically active micellar systems in order to gain further insight into stereoselective properties of enzymic reactions.[2]

In our previous papers,[3] we showed that functional mixed micelles of optically active catalysts containing a histidine residue and hexadecyltrimethylammonium bromide (CTABr) are very effective stereoselective catalysts for cleavage of enantiomeric substrates, and a mechanism was suggested for reaction in mixed micelles involving acylation of the optically active histidine residue.

In this paper, we describe kinetic results for cleavage of amino acid ester derivatives in a mixed micellar system formed from *N*-decanoly-(D or L)-histidine (DecHis) and an optically active cationic surfactant (DMEBr) having the hydroxyl function at the polar head, and results are compared with those observed in the mixed micelles with CTABr.

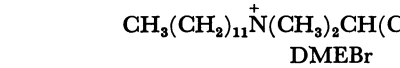
Catalyst

DecHis; $R=CH_3(CH_2)_8$
BzHis; $R=C_6H_5$

Substrate

ZPheONp; $R^1=R^2=C_6H_5CH_2$
ZAlaONp; $R^1=C_6H_5CH_2$, $R^2=CH_3$
ZGlyONp; $R^1=C_6H_5CH_2$, $R^2=H$
MocPheONp; $R^1=CH_3$, $R^2=C_6H_5CH_2$

Surfactant



DMEBr

Experimental

Materials. Hexadecyltrimethylammonium bromide (CTABr) was purified by established methods.[4] *N*-Dodecyl-*N*-methyl-*l*-ephedrinium bromide (DMEBr) and *N*-decanoyl-(D or L)-histidine (DecHis) were prepared and purified by standard methods.[5] *N*-Benzoyl-L-histidine (BzHis) was obtained from Sigma Chemical Co. The substrates, *p*-nitrophenyl esters of *N*-benzyloxycarbonyl-D-alanine, and *N*-methoxycarbonyl-D and L-phenylalanine were synthesized by the dicyclohexylcarbodiimide method.[6] Other *p*-nitrophenyl esters of *N*-benzyloxycarbonyl amino acids were purchased from Sigma Chemical Co., and were used without further purification. The purity of these esters was confirmed by kinetic analysis.

Kinetic Measurements. The cleavage of *p*-nitrophenyl esters was performed at pH 7.30, 0.02 mol dm^{-3} of phosphate buffer, and 25 °C in 0.83% CH_3CN–H_2O, and the formation of the *p*-nitrophenolate anion was followed spectrophotometrically at 400 nm. The pseudo-first-order rate constants were obtained from plots of $\log(A^{\infty}-A^{t})$ *vs.* time (t) by use of the least-squares method. Correlation coefficients were >0.999.

Results and Discussion

Optically active DMEBr micelles showed considerably different catalytic efficiencies for the hydrolysis of enantiomeric *p*-nitrophenyl α-methoxyphenylacetate.[7] However, no appreciable stereoselectivity was observed for the above esters in the presence of a simple optically active surfactant, hexadecyldimethyl-(α-methylbenzyl)ammonium bromide.[8]

In this study, substrates, ZPheONp, ZAlaONp, and MocPheONp, were hydrolyzed in the presence of

Table 1. Hydrolysis of enantiomeric substrates in the presence of DMEBr[a]

Substrate	$10^3(k_\psi-k_0)/s^{-1}$		D/L
	D	L	
ZPheONp	4.46±0.11	3.99±0.15	1.12
ZAlaONp	2.23±0.08	2.06±0.05	1.08
MocPheONp	1.87±0.08	1.78±0.05	1.05

a) In 6.00×10^{-3} mol dm^{-3} DMEBr, at pH 7.30, 0.02 mol dm^{-3} of phosphate buffer, and 25 °C. [Substrate] $=1.0\times10^{-5}$ mol dm^{-3}. k_ψ and k_0 denote the pseudo-first-order rate constants in the presence and absence of DMEBr.

Table 2. Rate constants on variation of surfactant concentration[a]

10^3[DMEBr] / mol dm^{-3}	$10^3(k_\psi-k_{surfact})/s^{-1}$		
	L	D	L/D
3.00	214(5.86)	90.6(4.06)	2.36(1.44)
4.00	164(5.32)	65.6(3.96)	2.50(1.34)
5.00	(5.20)	(3.64)	(1.43)
6.00	104(4.70)	41.6(3.44)	2.50(1.37)
8.00	64.0	26.8	2.39

a) In 2.00×10^{-4} mol dm^{-3} L-DecHis at pH 7.30, 0.02 mol dm^{-3} of phosphate buffer, 25 °C, and [ZPheONp] $=1.0\times10^{-5}$ mol dm^{-3}. The values in parentheses are for L-BzHis.

Table 3. Apparent catalytic rate constants in optically active mixed micellar systems[a]

Substrate	Surfactant	k_c/mol^{-1} dm^3 s^{-1}		L/D (D/L)
		L-DecHis	D-DecHis	
PNPA[b]	DMEBr[b]	5.97	5.77	1.03
PNPH[b]	DMEBr[b]	15.4	15.2	1.01
ZGlyONp	DMEBr	121	116	1.04
	CTABr	162	161	1.01
L-ZAlaONp	DMEBr	139 (85.4)	85.5 (121)	1.63 (1.42)
	CTABr	280 (140)	141 (283)	1.99 (2.02)
L-ZPheONp	DMEBr	522 (208)	192 (462)	2.72 (2.22)
	CTABr	572 (231)	228 (569)	2.51 (2.46)
L-MocPheONp	DMEBr	229 (127)	114 (229)	2.01 (1.80)
	CTABr	314 (141)	145 (315)	2.17 (2.23)

a) In 6.00×10^{-3} mol dm^{-3} DMEBr or CTABr, at pH 7.30, 0.02 mol dm^{-3} of phosphate buffer, and 25 °C. [DecHis] = 0.40—5.33×10^{-4} mol dm^{-3} and [substrate] = 1.0×10^{-5} mol dm^{-3}, unless otherwise specified. Values in parentheses are for D-substrates. The k_c values are calculated by the least-squares method and generally have correlation coefficients of over 0.99. b) [PNPA or PNPH] = 1.0×10^{-4} mol dm^{-3} and [DMEBr] = 5.00×10^{-3} mol dm^{-3}.

6.00×10^{-3} mol dm^{-3} DMEBr at pH 7.30 and 25 °C (Table 1). DMEBr micelles show slightly different catalytic efficiencies in the hydrolysis of the enantiomeric substrates; D substrates are more reactive than L enantiomers. In CTABr micelles there was no difference between the rates of hydrolysis of the enantiomeric substrates within experimental error.[3]

The catalytic effects of L-DecHis and L-BzHis for ZPheONp hydrolysis were first examined by varing the DMEBr concentration at pH 7.30 and 25 °C (Table 2). At higher ratios the rates decrease but the stereoselective effect is almost unchanged when L-DecHis is diluted with DMEBr. A similar effect is observed in the mixed micelles of L-BzHis and DMEBr. Therefore, the stereoselective kinetic analysis was carried out at a fixed surfactant concentration (6.00×10^{-3} mol dm^{-3}). The catalytic second-order rate constants (k_c) were obtained from the linear slope of a plot of the observed pseudo-first order rate constants (k_ψ) against catalyst concentration under the condition: [surfactant] > [catalyst] > [substrate]. Table 3 summarizes results for the cleavage of the substrates by (D or L)-DecHis in the presence of DMEBr. For comparison, (D or L)-DecHis–CTABr catalyzed rates also are determined and listed in Table 3.

From Table 3, it is apparent that there is no rate difference between D- and L-DecHis for cleavage of nonspecific substrates, such as *p*-nitrophenyl acetate (PNPA) and hexanoate (PNPH), and optically inactive substrate (ZGlyONp). On the other hand, it is found that L-DecHis reacts more selectively than D-DecHis with L substrates, and D-DecHis with D substrates. The pattern of stereoselective effects for the optically active substrates in the mixed (D or L)-DecHis–DMEBr micelle is similar to that found in the mixed (D or L)-DecHis–CTABr. These results show that the stereoselectivity is determined mainly by the nucleophilic reactivity of the optically active histidyl residue of DecHis. It is well known that the imidazolyl and hydroxyl groups act as nucleophiles giving acylated products, and that the imidazolyl group is more reactive than the hydroxyl group under neutral conditions. Thus, reaction rates with the mixed DecHis–DMEBr micelle are two orders of magnitude higher than those with the DMEBr micelle alone at pH 7.30.

A comparison of the rate constants between mixed micelles with DMEBr and CTABr indicates that both the reactivity and stereoselectivity of ZPheONp are essentially the same, but that the rates of less hydrophobic substrates such as ZAlaONp bring about 2-fold decreases with the extent of stereoselectivity also decreasing from 2.0 to 1.4—1.6. Although the reactions with mixed D-DecHis–CTABr and L-DecHis–CTABr micelles produced the same differences between D and L substrates in the opposit direction within experimental error, the D-DecHis–DMEBr and L-DecHis–DMEBr micelles show slightly different catalytic efficiencies in the reactions with D and L enantiomers.

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