Stereoselective Micellar Catalysis. Reactions of Amino-acid Ester Derivatives with N-Acyl-L-histidine in Micelles

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Mixed micelles of the N-acyl-L-histidines (I) and cetyltrimethylammonium bromide (CTABr) are effective stereo-selective catalysts for cleavage of the enantiomeric amino-acid ester derivatives (II). The rate enhancements and stereoselective effects depend on the hydrophobicity of (I) in micelles, and an increase in the chain length of the acyl part of (I) increases both the reaction rates and the enantiomer rate ratio. Mixed micelles with anionic and nonionic surfactants are relatively less effective stereoselective catalysts. Kinetic analysis indicates that the stereoselectivity in mixed micelles is mainly determined by catalytic acyl transfer to the optically active imidazole group of (I).

THE stereospecificity of enzymic reactions is one of their most specific properties. In order to gain further insight of stereoselective properties in enzymic reactions, various types of optically active micellar [1-4] and polymer [1,5] catalysed reactions have been investigated as model systems.

Optically active surfactant micelles derived from (—)-D-ephedrine showed slightly different catalytic efficiencies in hydrolyses of enantiomeric p-nitrophenyl α-methoxyphenylacetate [2a] and p-nitrophenyl N-benzyl-oxycarbonylamino-acid esters.[2f] But no appreciable specificity was observed in the presence of simple optically active surfactants [2c] and functionalized surfactants containing amino-acid residue at the polar head.[2d,e] Significant stereoselectivity resulted in the decomposition of enantiomeric p-nitrophenyl N-acetyl-phenylalanates in the presence of optically active functional micelles derived from coupling L-histidine methyl ester to (5-carboxyheptadecyl)trimethylammonium chloride.[2b] Recently Moss et al.[3] found comparable stereoselectivity for the cleavage of diastereoisomeric substrates by functional surfactant micelles. These

This paper describes the detailed results and additional studies which establish the stereoselective requirements for the cleavage of amino-acid ester derivatives (II) in functionalized mixed micellar systems formed from N-acyl-L-histidines (I) and cationic micelles of CTABr. The results are compared with those observed in the presence of anionic and nonionic surfactants. The stereoselective properties are also rationalized in terms of rate constants and the structural effects of catalysts and substrates in micelles.
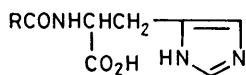
EXPERIMENTAL

Materials.—The surfactants, cetyltrimethylammonium bromide (CTABr) and sodium dodecyl sulphate (NaLS), were purified by established methods.[8] Polyoxyethylene(11)-nonylphenol (C_9EO_{11}; Kao Soap Co. Ltd.) was used without further purification. N-Acetyl- and N-benzoyl-L-histidines (Sigma Chemical Co.) were used without further purification. N-Decanoyl- and N-stearyl-L-histidines were prepared and purified by standard methods.[9]

The substrates, p-nitrophenyl esters of N-benzyloxycar-bonyl-D- and -L-phenylalanines, N-benzyloxycarbonyl-L-alanine, and N-benzyloxycarbonylglycine were purchased from Sigma Chemical Co. and were used without further purification. N-Benzyloxycarbonyl-D-alanine, and N-methoxycarbonyl-D- and -L-phenylalanine p-nitrophenyl esters were prepared by standard methods.[10] The esters were characterized by their m.p.s and specific rotatory powers. The experimental data were generally in good agreement with those from the literature. The purity of these esters was confirmed by kinetic analysis.

Kinetic Measurements.—The reactions were carried out by following the appearance of p-nitrophenol spectrophoto-metrically at 400 (pH > 6) and 317 nm (pH < 6) using a Hitachi 200 spectrophotometer or a Shimazu 140 spectro-photometer with a thermostatted cell holder at 25 °C. In the general procedure a solution (25 µl) of ester in acetonitrile was added to a buffer solution (3.00 ml) containing the catalysts and surfactants at the desired concentrations unless specified otherwise. Pseudo-first-order rate constants were obtained from plots of $(A_\infty - A_t)$ versus time(t) and calculated by the least-squares method using data for up to four half-lives. Correlation cofficients were >0.999.
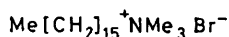

$$RCONHCHCH_2 \overline{\quad\quad} \atop \underset{CO_2H}{|} \quad \underset{HN\diagdown N}{}$$

$$R^1OCONHCHCO_2C_6H_4NO_2-p \atop \underset{R^2}{|}$$

(I)
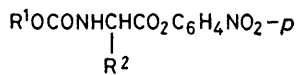
(II)

a; R = Me

b; R = Ph

c; R = Me[CH₂]₈

d; R = Me[CH₂]₁₆

a; R¹ = PhCH₂, R² = PhCH₂

b; R¹ = PhCH₂, R² = Me

c; R¹ = PhCH₂, R² = H

d; R¹ = Me, R² = PhCH₂

$$Me[CH_2]_{15}\overset{+}{N}Me_3 \ Br^-$$

CTABr

observations suggest that micellar stereoselectivity probably depends on the presence of a functional group in the optically active surfactant.

In a communication,[6] it was reported that mixed micelles of optically active N-acylhistidines and cationic surfactants are very effective stereoselective catalysts for cleavage of enantiomeric p-nitrophenyl N-acylphenyl-alanates.[7]

RESULTS AND DISCUSSION

Hydrolysis of (II) *in Water and Surfactants.*—The first-order rate constants k_0, for hydrolysis of (II) in

0.02M-phosphate buffer at pH 7.30 are given in Table 1. The rate of hydrolysis of (IIa) was difficult to measure due to the insolubility in water. The measurements,

TABLE 1

Pseudo-first-order rate constants for the hydrolysis of (II) in water [a]

Substrate	$10^5 k_0/\text{s}^{-1}$	
	L	D
(IIa)	1.95 [b]	1.90 [b]
(IIb)	5.61 ± 0.15	5.50 ± 0.14
(IIc)		11.2 ± 0.3
(IId)	6.50 ± 0.12	6.60 ± 0.14
	4.44 [b]	4.23 [b]

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C. [(II)] 1.0 × 10⁻⁵M. [b] Single run in 2.00 × 10⁻³M-C_9EO_{11}.

therefore, were made in a non-ionic surfactant (C_9EO_{11}). Addition of C_9EO_{11} results in rates of hydrolysis slightly below those of the buffer alone [(IId)]. In water there is no difference between the rates of hydrolysis of the two enantiomeric substrates within experimental error.

TABLE 2

Pseudo-first-order rate constants for the hydrolysis of (II) in CTABr [a]

Compound	$10^3[\text{CTABr}]/$ M	$10^3 k_\psi/\text{s}^{-1}$		k_{rel} [b]
		L	D	
(IIa)	1.00	6.22 ± 0.14	6.22 ± 0.24	320 [c]
	2.00	6.81 ± 0.15	6.86 ± 0.12	350 [c]
	4.00	5.24 ± 0.23	5.40 ± 0.12	280 [c]
	6.00	4.97 ± 0.25	5.16 ± 0.20	260 [c]
(IIb)	2.00	3.48 ± 0.10	3.47 ± 0.20	63
(IIc)	2.00	6.68 ± 0.09		60
(IId)	1.00	3.12 ± 0.09	3.06 ± 0.08	47
	2.00	3.38 ± 0.06	3.41 ± 0.08	52
	4.00	2.96 ± 0.10	3.01 ± 0.09	46
	6.00	2.63 ± 0.12	2.58 ± 0.10	40

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C. [(II)] 1.0 × 10⁻⁵M. [b] Calculated using average rate constants of D- and L- substrates at pH 7.30 in water and CTABr. [c] Based on nonionic surfactant (C_9EO_{11}).

The rates of hydrolysis of (II) in the presence of CTABr are given in Table 2. The hydrolysis of (II) is strongly catalysed by cationic micelles. The rates of

but the rate augmentations were only 3—5 fold. The large rate enhancements of the hydrolysis of (II) are apparently due to the formation of a hydrophobically bonded complex between the substrates and CTABr. It was also found that there is no significant rate difference between D- and L-enantiomers in CTABr.

Effect of Acyl Functions in (I).—Micellar catalysis of a bimolecular reaction requires that both catalysts and substrates are incorporated into the micelles and the rate
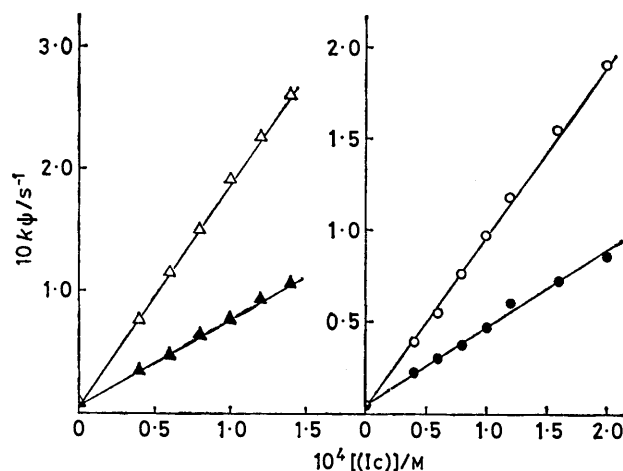

FIGURE 1 Pseudo-first-order rate constants for reactions of (IIa and d) with (Ic) in the presence of CTABr: ▲, D-(IIa); △, L-(IIa); ●, D-(IId); ○, L-(IId); pH 7.30; 0.02M-phosphate buffer; 25 °C; [CTABr] 2.00 × 10⁻³M; [(II)] 1.0 × 10⁻⁵M

of the micellar catalysed reaction depends on the catalyst concentrations.

The reactions of (II) with a variety of N-acyl-L-histidines (I) with increasing chain length of the acyl function were examined in the presence of CTABr and typical rate–catalyst concentration profiles are shown in Figure 1. The concentration of CTABr is kept constant at 2.00 × 10⁻³M (and 6.00 × 10⁻³M). In all cases there exists the expected linear relation between the rate and the concentration of (I) as shown in Figure 1. From the slope of the plot of observed rate constants against the

TABLE 3

Apparent second-order rate constants for reactions of (II) with (I) in the presence of CTABr [a]

$k_c/\text{l mol}^{-1} \text{s}^{-1}$

Catalyst	(IIa)			(IIb)			(IIc)	(IId)		
	L	D	(L/D)	L	D	(L/D)		L	D	(L/D)
(Ia)	2.75	1.96	1.40	3.07	2.25	1.36	1.90	3.64	2.64	1.38
(Ib)	174	101	1.72	83.5	61.5	1.36	71.3	119	83.5	1.43
(Ic)	1 730	690	2.51	783	358	2.03	469	877	403	2.16
	(572)	(231)	(2.51)	(281)	(140)	(2.01)	(162)	(314)	(145)	(2.17)
(Id)	2 740	985	2.78	1 150	544	2.11	649	1 370	622	2.20

[a] In 2.00 × 10⁻³M-CTABr at pH 7.30, 0.02M-phosphate buffer, and 25 °C. [(II)] 1.0 × 10⁻⁵M, [(Ia)] 2.0—20 × 10⁻⁴M, [(Ib)] 0.4—6.0 × 10⁻⁴M, [(Ic)] 0.4—2.0 × 10⁻⁴M, [(Id)] 0.4—1.0 × 10⁻⁴M. Values in parentheses are for 6.00 × 10⁻³M-CTABr. The k_c values are calculated by least-squares and generally have correlation coefficients > 0.98.

hydrolysis of *p*-nitrophenyl esters, such as *p*-nitrophenyl acetate, propionate, butyrate, valerate, and hexanoate, catalysed by Tris buffer at pH 7.2 decreased markedly in the presence of CTABr.[9a, 11] CTABr increased the rate of hydrolysis of *p*-nitrophenyl acetate under our conditions,

concentration of (I), the apparent second-order rate constants k_c in Table 3 are evaluated. The k_c values are calculated from the data by using a least-squares program.

The results in Table 3 show that the mixed micelle of

(I) and CTABr catalyses stereoselective deacylation of the enantiomeric substrates (II), and L-(II) is consistently more reactive than D-(II). An increase in the chain length of the acyl group of (I) increases both the reaction rates and the enantiomer rate ratios. The hydrophobicity of the acyl function is an important factor in the high degree of stereochemical control of the enantiomeric substrates. Thus this result indicates that stereoselectivity in mixed micelles is associated with incorporation of (I) onto the surface of the micelle leading to an effective interaction between catalyst and substrate. Similar kinetic behaviour is observed upon comparison of the N-protected groups of (IIa and d), and the amino-acid side groups of (IIa and b). The larger stereoselective effect of (11a) accords with the larger rate enhancement of the reaction. This parallels the improved stereoselectivity resulting from increasing the hydrophobic interaction between the substrate and the hydrophobic group at the active site.

Effects of Anionic and Non-ionic Surfactants.—Table 4

TABLE 4

Apparent second-order rate constants for reactions of (IIa and d) with (Ic) in the presence of anionic and non-ionic surfactants [a]

| Surfactant | 10^3 [Surfactant]/ M | k_c/l mol^{-1} s^{-1} | | |
		L	D	L/D
None		(1.02)	(0.805)	(1.27)
NaLS	2.00	0.898 (0.996)	0.668 (0.802)	1.34 (1.24)
	20.0	0.842	0.629	1.34
C_9EO_{11}	2.00	2.51 (3.27)	1.64 (2.44)	1.53 (1.34)

[a] At pH 7.30, phosphate buffer, and 25 °C. [(IIa)] 1.0 × 10^{-5}M. [(Ic)] 2.66—13.3 × 10^{-4}M. The values in parentheses are for (IId).

shows the apparent second-order rate constants for the reactions of (IIa and d) with (Ic) in the presence of anionic and nonionic surfactants. Addition of anionic surfactant (NaLS) to (Ic) solutions results in rates of reactions slightly below those of (Ic) alone. In the presence of non-ionic surfactant (C_9EO_{11}), the rates and the stereoselectivity increase slightly but the effects are relatively small.

Effect of CTABr Concentration.—Figure 2 show the rates of reaction of (IId) with (Ic) as a function of CTABr concentrations. The rate constants for reactions of both D- and L-(IId) increase sharply as the CTABr concentration exceeded the c.m.c.,* and then reach a maximum. At higher concentrations inhibition is observed. This behaviour is common for bimolecular micellar catalysed reactions. The stereoselectivity, however, increases with increasing CTABr at low surfactant concentration when micelles begin to form and then almost reach a constant value when (Ic) is diluted with CTABr. Table 5 shows the rates of reaction of (IIa) with (Ic) with various concentrations of CTABr. At higher ratios the rates decrease but the enantiomer rate ratio is almost unchanged when (Ic) is diluted with CTABr. These

* The critical micelle concentration (c.m.c.) of CTABr is 1.45 × 10^{-4}M in 0.02M-phosphate buffer at pH 7.30 and 25 ± 0.5 °C (measured by the surface tension method).

results suggest that the stereoselective control mainly depends on the catalytic site of the optically active imidazole group of (I). Gitler *et al.*[9a,11] found that hydrolysis of *p*-nitrophenyl esters catalysed by mixed micelles of N-myristoyl-L-histidine (I; R = $C_{13}H_{27}$) and CTABr involves nucleophilic transacylation and rate-determining formation of an acylimidazole. Moss *et al.*[2c]
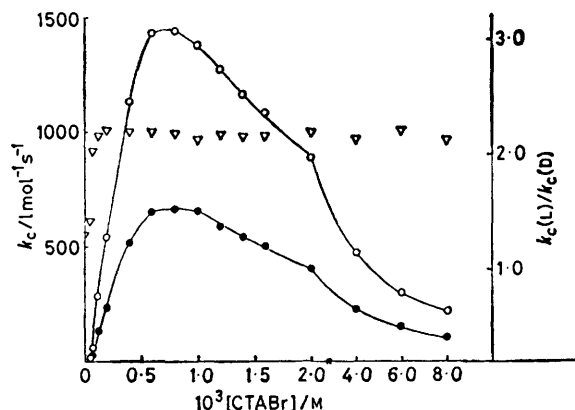

FIGURE 2 Apparent catalytic rate constants for reaction of (IId) with (Ic) on variation of CTABr concentrations: ●, D-(IId); ○, L-(IId); ▽, k_c(L)/k_c(D); pH 7.30, 0.02M-phosphate buffer; 25 °C; [(Ic)] 1.00 × 10^{-4}M; [(IId)] 1.0 × 10^{-5}M

observed no appreciable stereoselectivity for the hydrolysis of enantiometic *p*-nitrophenyl 2-methoxyphenylacetate in the presence of simple optically active surfactants. There is probably no stereoselective discrimination due to interactions requiring micellar chirality of simple optically active surfactants.

Effect of pH.—The effect of pH on the rates of reactions of (IIa and d) with (Ic) in CTABr was investigated over the pH range 4.0—8.0. The results indicated that the k_c values of both D- and L-enantiomers increased on the manner shown in Figure 3. The sigmoidal nature of the curve indicates that the reactivity in this mixed micellar system is derived from the dissociated form of imidazole. The kinetic pK_a values observed for pH–rate profiles

TABLE 5

Rate constants for reaction of (IIa) and (Ic) on variation of CTABr concentrations [a]

| 10^3[CTABr]/M | k/l mol^{-1} s^{-1} | | |
	L	D	L/D
1.00	3 220	1 380	2.33
2.00	1 730	690	2.51
4.00	875	350	2.50
6.00	572	231	2.51
8.00	408	174	2.34

[a] At PH 7.30, 0.02M-phosphate buffer, and 25 °C. [(IIa)] 1.0 × 10^{-5}M. [(Ic)] 0.4—2.0 × 10^{-4}M.

with each two enantiomeric substrates appears to be 6.4—6.6.† The stereoselective effects are slightly dependent of pH, thus the values of k_c(L)/k_c(D) slightly increase with increasing pH and then slightly decrease at

† The kinetic pK_a values of N-myristoyl- and N-lauroyl-L-histidine in CTABr have been determined as 6.2[9a] and 6.0,[9b] respectively (pH–rate profile for *p*-nitrophenyl acetate).

higher pH. These phenomena may be explained by a reduction in the number of dissociated forms of imidazole or the carboxy-group of (Ic) at lower pH, and structural changes in complex formation of mixed micelles at higher
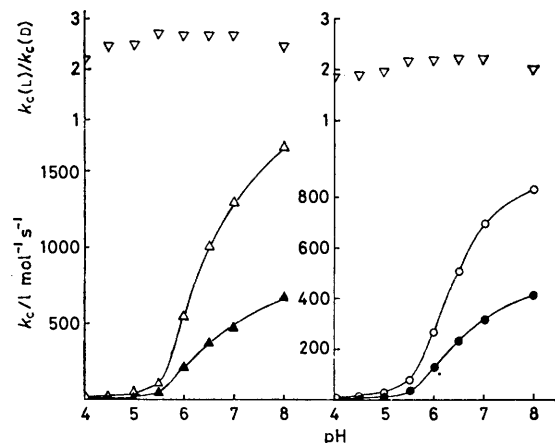

FIGURE 3 Apparent catalytic rate constants for reactions of (IIa and d) with (Ic) as a function of pH. ▲, D-(IIa); △, L-(IIa); ●, D-(IId); ○, L-(IId); ▽, $k_c(L)/k_c(D)$; 25 °C; μ 0.05 (KCl); buffer, 0.04M-acetate (pH <6), 0.02M-phosphate (pH >6); [CTABr] 2.00 × 10⁻³M; [(Ic)] 0.6—2.0 × 10⁻⁴M; [(II)] 1.0 × 10⁻⁵M

pH. The results also demonstrate that stereoselectivity in mixed micelles is mainly determined by nucleophilic attack of the dissociated form of the optically active imidazole group.*

Kinetic Analysis of Reactions in Mixed Micelles.—In order to investigate further the stereoselective properties in mixed micelles, experiments were carried out with [CTABr] > [(I)] > [(II)] and a constant [CTABr] : [(I)] ratio. In these experiments, normal saturation type kinetics were observed on variation of the mixed micelle concentration above the c.m.c. at constant [CTABr] : [(I)] as shown in Figure 4. The data were treated in a manner analogous to that used for enzymatic catalysis which has previously been shown to be useful for investigating reactions involving micellar complex formation [1a],† {reaction (1) where M is the total mixed micelle

$$M + S \underset{K}{\overset{K}{\rightleftharpoons}} MS \xrightarrow{k_m} \text{Products} \qquad (1)$$

$$\downarrow k_0$$
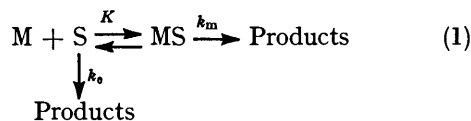
Products

[(I) + CTABr], S is the substrate (II), MS is the micelle–substrate complex, K is the dissociation constant, and k_0 and k_m are the rate constants for product formation in bulk solvent and in the micellar phase, respectively}. The pseudo-first-order rate constants k_ψ with the condition [CTABr] > [(I)] > [(II)], is given by equation (2) which can be written in the form (3). Thus the values of

* However, it is found that the rates increase remarkably above pH 9. This enhanced reactivity is apparently due to the presence of an anionic imidazole production and results in a decrease in the stereoselectivity. For example, the reaction of (IIa) with (Ic) in CTABr gives values of k_c (L) of 2 870 l mol⁻¹ s⁻¹, k_c (D) of 1 850 l mol⁻¹ s⁻¹, and k_c (L)/k_c (D) of 1.55 at pH 9.55 (μ 0.05 with KCl, 0.02M-carbonate buffer).

k_m and K could be derived from reciprocal plots of equation (3), where the kinetic c.m.c. were taken from the plots of k_ψ *versus* total micelle concentration so as to obtain a better fit of the data.

$$k_\psi = \frac{k_0 + k_m[\text{M}]/K}{1 + [\text{M}]/K} \qquad (2)$$

$$\frac{1}{k_\psi - k_0} = \frac{K}{(k_m - k_0)[\text{M}]} + \frac{1}{k_m - k_0} \qquad (3)$$

The k_m and K values were calculated from the data by a least-squares program and are summarized in Table 6 with the correlation coefficients. The results show that the k_m values are quite different for the two enantiomeric substrates. Thus the values of $k_m(L)/k_m(D)$ in Table 6 are almost comparable with those of $k_c(L)/k_c(D)$ in Table 3, while there is little or no difference in the K values for D- and L-enantiomers. This observation indicates that the stereoselectivity depends on the micellar rate constant (k_m) for nucleophilic reaction rather than dis-

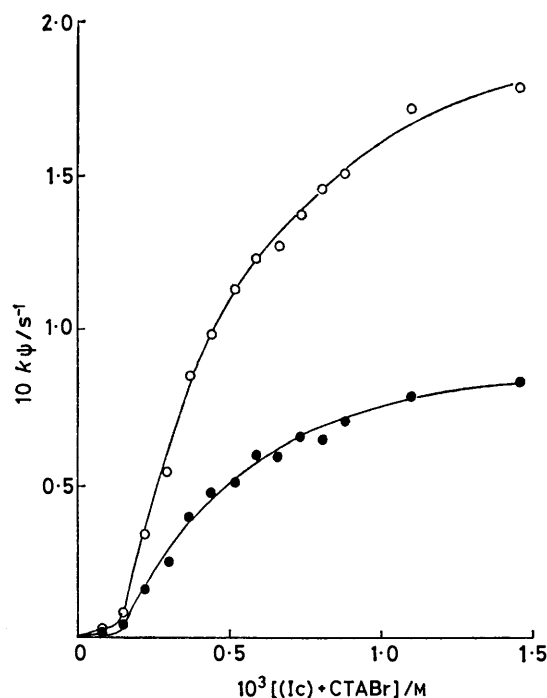

FIGURE 4 Pseudo-first-order rate constants for reaction of (IId) in the presence of mixed micelles of (Ic) and CTABr. The ratio [(Ic)] : [CTABr] is 1 : 10. ●, D-(IId); ○, L-(IId); pH 7.30, 0.02M-phosphate buffer; 25 °C, [(IId)] 1.0 × 10⁻⁵M

sociation constant (K) of complex formation. Similar phenomena have already been observed by Brown and Bunton [2b] for the stereoselective catalysed reaction of enantiomeric N-acetylphenylalanine p-nitrophenyl esters with an optically active functional surfactant. From kinetic analysis of the relation of the rate constant to surfactant concentration they suggested that the stereospecificity depended on transition-state rather than

† Reaction (1) differs from that proposed by Gitler *et al.*[9a] because the dissociation constants changed appreciably with the nature of (I). For an example see ref. 9b.

TABLE 6

Kinetic analysis of mixed miselles of (I) and CTABr [a]

Catalyst	Substrate	k_m/s^{-1}			$10^4\ K/l\ mol^{-1}$		Correlation coefficient
		L	D	L/D	L	D	
(Ic)	(IIa)	0.354	0.146	2.42			
	(IIb)	0.216	0.105	2.05	3.82	4.06	0.9928, 0.9936
	(IIc)	0.128			4.35		0.9979
	(IId)	0.232	0.116	2.00	4.77	5.59	0.9886, 0.9876
	(IIa) [b]	0.707	0.299	2.36	0.535	0.412	0.9764, 0.9681
	(IId) [b]	0.424	0.206	2.06	6.38	6.47	0.9849, 0.9947
(Ib)	(IIa) [b]	0.144	0.0834	1.73	19.4	16.4	0.9981, 0.9975

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C.   [(II)] 1.0×10^{-5}M.   The molar ratio of (I) to CTABr is 1 : 10 unless specified otherwise.   [b] Molar ratio of (I) to CTABr is 1 : 5.

initial-state interactions between substrates and micelles. Although the present mixed micellar system is somewhat different from the functional micellar system, the stereoselective reaction mechanisms are similar.

Conclusions.—The present study establishes that optically active functionalized mixed micelles are very effective stereoselective catalysts for reactions of the enantiomeric substrates. The stereoselective effects depend on the catalytic site of the optically active imidazole group and are associated with incorporation of the catalyst of (I) onto the surface of the micelles leading to an effective interaction between catalyst and substrate. Greater stereoselectivity may be obtained when the optically active reactive group is present on the surface of the micelles. The stereoselectivity is dependent on the degree of incorporation of reagent onto the micelles. This mixed micellar system is of interest in connection with studies on enzyme mechanisms. More effective stereochemical features may be obtained by different combinations of catalysts, substrates, and surfactants than those used in the present system.

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