Stereoselective Micellar Catalysis. Part 4.[1] Catalytic Hydrolyses of Enantiomeric Esters by Dipeptide Derivatives containing a Histidyl Residue

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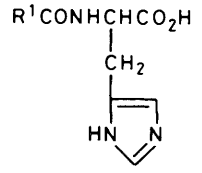
The rate constants for hydrolyses of the enantiomers of various amino acid *p*-nitrophenyl esters catalysed by optically active dipeptide catalysts containing a histidyl residue have been determined at pH 7.30, 0.02M-phosphate buffer, and 25 °C in the presence of cetyltrimethylammonium bromide micelles. The dipeptide catalysts demonstrate greater stereoselectivity than simple optically active catalysts. The structural effects of catalysts and substrates are examined by investigation of the rate constants and stereoselectivities. The role of their hydrophobicity and their stereoselective reaction mechanism are discussed.

Stereospecificity and high catalytic reactivity are among the most interesting properties of enzyme action.[2] Several model studies on micellar,[3-10] polymer,[3,11-15] and macrocyclic [3,16-19] catalysed reactions have been investigated in order to gain further insight into the stereoselective nature of enzyme reactions. In the course of our study on stereoselective micellar catalysis,[1,20] we found that mixed micelles of optically active *N*-acylhistidines (Ia—d) and cationic surfactants are effective stereoselective catalysts for the hydrolyses of enantiomeric esters. A mechanism was suggested for the stereoselective catalysis involving the acylation of the optically active histidine residue. Recently, a high stereoselectivity was observed in the hydrolyses of long-chain *p*-nitrophenyl *N*-acylphenylalanates catalysed by *N*-(*N*-dodecanoyl-L-histidyl)-L-leucine and a cationic chiral surfactant.[21] An exceptional micellar stereoselectivity was observed in the cleavage of diastereomeric dipeptide *p*-nitrophenyl esters by functional surfactant micelles.[22] These observations indicate the possibility of designing optically active catalysts with enhanced stereoselectivity.

It has been suggested that the stereospecificity of enzyme catalysis is based on the steric configuration of the constituent amino acids; therefore, the introduction of two asymmetric centres into the catalyst would lead to decreased flexibility and allow for a more stereospecific interaction between the catalyst and the substrates. Thus, we offered a preliminary report [23] of stereoselective effects in the hydrolyses of enantiomeric substrates by a series of dipeptide catalysts containing a histidyl residue, in the presence of cetyltrimethylammonium bromide (CTABr) micelles. Very recently, however, Ohkubo *et al.*[24] demonstrated very large stereoselective effects in the hydrolysis of *p*-nitrophenyl *N*-acylphenylalanates catalysed by vesicular systems, which include the same dipeptide catalysts. In this report, we provide full details of the previous work, and discuss the structural effects of catalysts and substrates on stereoselectivity.

Results and Discussion

Micellar Catalysis and Stereoselectivity.—Kinetic studies were performed at pH 7.30, 0.02M-phosphate buffer, and 25 °C. Pseudo-first-order rate constants (k_ψ) were evaluated by monitoring the release of *p*-nitrophenoxide ion spectrophotometrically at 400 nm under the conditions [CTABr] > [catalyst] > [substrate]. The catalytic hydrolyses of (IIa and b) by various dipeptide catalysts (IIIa—g) were first examined in the presence of a fixed CTABr concentration (6.00×10^{-3}M), and a typical k_ψ–catalyst concentration profile is shown in Figure 1, which shows that in all cases a linear relationship exists between the rate constant and the catalyst concentration. From the slopes of the straight lines, the apparent catalytic rate constants (k_c) in Table 1 were evaluated, together with analogous results for the catalysts (Ic and e) and *N*-(benzyloxycarbonyl-L-histidyl)-L-leucine.



(I)

a; R^1 = Me
b; R^1 = Ph
c; R^1 = $Me[CH_2]_8$ (Dec-His)
d; R^1 = $Me[CH_2]_{16}$
e; R^1 = $PhCH_2O$ (Z-His)

From Table 1, it is apparent that the catalysts containing an L-histidyl residue (or D-histidyl residue) stereoselectively hydrolyse the L-enantiomers (or D-enantiomers) of the substrates, (IIa or b), in all cases. This indicates that the stereoselective control is mainly determined by catalytic acyl transfer to the imidazole function at the active site of the optically active catalyst. However, the variation in the stereoselectivity of the catalysts is fairly large (1.2—12.2), indicating that the selectivity is affected by the amino acid side chains (R^2 group) of the dipeptide catalysts. In general, the dipeptide catalysts (IIIa—g) are more stereoselective than Z-L-His (Ie).

Both the rate constants and the stereoselectivity (L/D) for the reactions of (IIa and b) with the dipeptide catalysts (IIIa, c, d, f, and g) which have L,L configurations (cases 3, 5, 6, 10, and 12), increase to a maximum and then decrease as the R^2 groups of the catalysts become larger and more hydrophobic. Thus, the largest stereoselectivities we observed are 12.2 (Moc-Phe-ONp) and 6.32 (Z-Phe-ONp) with Z-L-Leu-L-His (IIId, case 6).

Comparisons of the diastereomeric dipeptide catalysts, Z-Leu-His (IIId) and Z-Phe-His (IIIf), show that Z-L-Leu-L-His and Z-L-Phe-L-His give increased rates for one of each pair of enantiomeric substrates and thus result in larger stereoselectivities than their diastereomers (cases 6 and 7,

$R^4OCONHCHCO_2C_6H_4NO_2-p$
R^5

(II)

a; R^4 = Me, R^5 = $PhCH_2$ (Moc-Phe-ONp)
b; $R^4 = R^5 = PhCH_2$ (Z-Phe-ONp)

$PhCH_2OCONHCHCONHCHCO_2R^3$
R^2 CH_2

(III)

a; R^2 = Me, R^3 = H (Z-Ala-His)
b; R^2 = Me, R^3 = Me (Z-Ala-His-OMe)
c; R^2 = Me_2CH, R^3 = H (Z-Val-His)
d; R^2 = Me_2CHCH_2, R^3 = H (Z-Leu-His)
e; R^2 = Me_2CHCH_2, R^3 = Me (Z-Leu-His-OMe)
f; R^2 = $PhCH_2$, R^3 = H (Z-Phe-His)
g; R^2 = 3-Indolyl-CH_2, R^3 = H (Z-Trp-His)

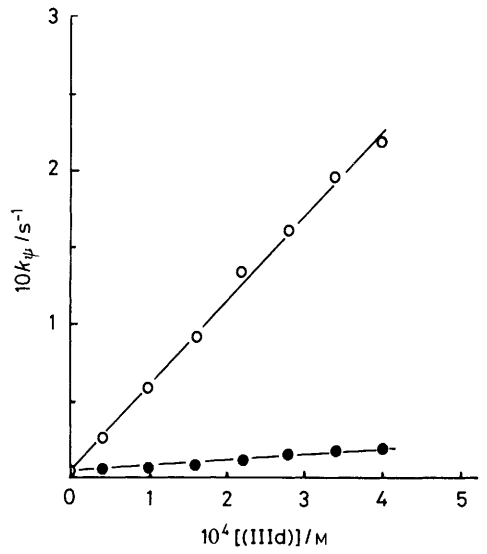


Figure 1. Pseudo-first-order rate constants (k_ψ) for the hydrolysis of Moc-Phe-ONp (IIa) as a function of the concentration of catalyst, Z-L-Leu-L-His (IIId), in the presence of CTABr micelles at pH 7.30, 0.02M-phosphate buffer, and 25 °C, [CTABr] 6.00 × 10^{-3}M, [(IIa)] 1.0 × 10^{-5}M. ● D-(IIa), ○ L-(IIa)

10 and 11). The chirality of the amino acid residue next to the histidine contributes to an increase in the stereoselectivity by increasing the rate of hydrolysis of one enantiomer. Recently, Brown *et al.*[25] prepared diastereomeric functional surfactants, and offered a preliminary report on their stereoselective catalytic properties. They found that the diastereomeric catalysts showed opposite selectivities for the hydrolyses of enantiomeric *p*-nitrophenyl *N*-acetylphenylalanates. This shows that structural differences between catalysts result in different selectivities; however, these selectivities were much less than those observed in our comicellar systems.

Interestingly, Z-L-His-L-Leu, which has the reverse sequence of amino acid residues, is much less stereoselective than Z-L-Leu-L-His (cases 6 and 9). This indicates the importance of the position of the imidazole group in the catalyst. These results suggest, therefore, that the catalytic reactions could be accelerated and the stereoselectivities increased when specific interactions exist between the catalyst and substrate, and the orientation of the active site in the catalyst is fixed in a particular conformation in the micellar phase. Moreover, Z-L-Ala-L-His-OMe and Z-L-Leu-L-His-OMe are less reactive and stereoselective than Z-L-Ala-L-His and Z-L-Leu-L-His, respectively (cases 3 and 4, 6 and 8). These results also indicate the importance of the existence of a free carboxyl group in the active site. We suggested previously [1,20d] that the carboxylate ion of the catalyst enhanced the reactivity of the imidazole group and produced an increase in the stereoselectivity.

We briefly examined the reactions in the absence of CTABr. The reactions were difficult to study owing to the insolubility of the catalyst and/or substrate in the absence of surfactant. The measurements were therefore made in 20% ethanol solution. The results appear in Table 2, wherein it appears that the reaction rates in the absence of surfactant are about two orders of magnitude slower than those in the presence of surfactant. The kinetic stereoselectivities are also small (1.04—2.03). These results show that rate enhancements and stereoselectivity are strongly associated with incorporation of the catalyst and substrate into micelles by hydrophobic interaction, leading to an effective orientation between the reactants. In previous papers [20a,b] we have shown that improved stereoselectivity results from increasing hydrophobic interaction between the catalyst and substrate in the micelles. In the present study, hydrophobic interaction is again one of the important factors in producing the high degree of stereochemical control of the esterolyses of enantiomeric substrates.

The catalytic hydrolyses of non-specific substrates, such as *p*-nitrophenyl acetate (PNPA), hexanoate (PNPH), and laurate (PNPL) by dipeptide catalysts were also examined at pH 7.30, 0.02M-phosphate buffer, and 25 °C in the presence of CTABr micelles. The results of these experiments appear in Table 3. The catalysts employed here do not seem to affect the reaction rates significantly, and diasteromeric pairs of Z-Leu-His and Z-Phe-His show no significant rate differences in the hydrolyses of non-specific substrates. These results suggest that the formation of a hydrogen-bonding interaction between the amide bonds of the amino acid substrate and the catalyst is another important factor that brings about high stereoselectivity.

Catalytic Efficiency of Comicellar Systems.—In order to investigate further the stereoselective properties of these comicellar systems, kinetic treatments were carried out in terms of a micellar pseudophase model [equation (1)], where M is the comicelle (catalyst + CTABr), S is the substrate,

$$\begin{array}{ccccc} M + S & \overset{K}{\rightleftharpoons} & MS & \xrightarrow{k_m} & \text{Products} \\ & \searrow^{k_o} & & & \\ & & \text{Products} & & \end{array} \qquad (1)$$

MS is the micelle–substrate complex, K is the dissociation constant, and k_o and k_m are the rate constants for product formation in bulk solvent and in the micellar phase, respectively. The k_m and K values were obtained according to previous techniques.[3a,20a] Table 4 shows that the k_m values are quite different but that the K values are not very different for enantiomeric D and L substrates. These results indicate that

Table 1. Apparent catalytic rate constants (k_c) in the presence of CTABr micelles [a]

Case	Catalyst	k_c/l mol^{-1} s^{-1} Moc-Phe-ONp (IIa) L	D	L/D	Z-Phe-ONp (IIb) L	D	L/D
1	Dec-L-His (Ic)	314	145	2.17	572	231	2.52
2	Z-L-His (Ie)	80.7	66.0	1.22	111	92.3	1.20
3	Z-L-Ala-L-His (IIIa)	139	32.1	4.33	98.9	37.9	2.61
4	Z-L-Ala-L-His-OMe (IIIb)	32.6	15.4	2.12	33.0	18.9	1.75
5	Z-L-Val-L-His (IIIc)	309	44.7	6.91	225	56.7	3.97
6	Z-L-Leu-L-His (IIId)	645	52.7	12.2	473	74.9	6.32
7	Z-L-Leu-D-His (IIId)	60.9	146	2.40 [b]	78.4	176	2.24 [b]
8	Z-L-Leu-L-His-OMe (IIIe)	291	46.2	6.30	210	56.4	3.72
9	Z-L-His-L-Leu [c]	54.5	47.0	1.16	70.5	54.0	1.31
10	Z-L-Phe-L-His (IIIf)	541	74.5	7.26	439	110	4.48
11	Z-D-Phe-L-His (IIIf)	172	74.2	2.32	202	98.1	2.06
12	Z-L-Trp-L-His (IIIg)	85.9	47.2	1.82	103	67.5	1.53

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C in the presence of 6.00×10^{-3}M-CTABr, [catalyst] $0.50—6.0 \times 10^{-4}$M, [substrate] 1.0×10^{-5}M. The k_c values are calculated by least-squares and generally have correlation coefficients >0.99. [b] The rate constant ratios are D/L. [c] *N*-(Benzyloxycarbonyl-L-histidyl)-L-leucine.

Table 2. Catalytic effects in the absence of surfactant [a]

Catalyst	k_c/l mol^{-1} s^{-1} Moc-Phe-ONp (IIa) L	D	L/D	Z-Phe-ONp (IIb) L	D	L/D
Z-L-His (Ie)	0.852	0.818	1.04	1.27	1.12	1.14
Z-L-Leu-L-His (IIId)	1.03	0.722	1.43	1.79	0.930	1.92
Z-L-Phe-L-His (IIIf)	1.62	0.828	1.96	3.07	1.51	2.03
Z-D-Phe-L-His (IIIf)	0.808	0.642	1.26	1.41	0.859	1.64

[a] At pH 7.30, 0.02M-phosphate buffer, 20% v/v ethanol, and 25 °C.

Table 3. Catalytic hydrolysis of non-specific substrates in the presence of CTABr micelles [a]

Catalyst	k_c/l mol^{-1} s^{-1} PNPA	PNPH	PNPL
Z-L-His (Ie)	4.2	7.7	7.8
Z-L-Leu-L-His (IIId)	4.8	5.8	6.2
Z-L-Leu-D-His (IIId)	4.8	7.9	8.4
Z-L-His-L-Leu	4.2	4.4	4.2
Z-L-Phe-L-His (IIIf)	5.1	6.3	6.2
Z-D-Phe-L-His (IIIf)	4.8	7.6	7.8

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C in the presence of 6.00×10^{-3}M-CTABr, [CTABr] $0.50 \times 10^{-4}—6.0 \times 10^{-4}$M, [substrates] 1.0×10^{-5}M.

D and L substrates may bind equally well in the hydrophobic region of the micelles near the active site of the catalyst, but that the binding of the D substrate leads to the wrong orientation between the reactive group of the catalyst and the carbonyl group of the substrate.

Structural Effects of Catalysts and Substrates.—Brown and Bunton [4b] suggested that hydrogen-bonding interactions make an important contribution to the high stereoselectivity observed in the hydrolysis of enantiomeric *N*-acylphenylalanine *p*-nitrophenyl esters, catalysed by an optically active functionalized surfactant. Our data in Table 1 shows that the observed stereoselectivity gaves a maximum at Z-L-Leu-L-His (IIId) for both substrates, (IIa and b). This behaviour results when a hydrogen-bonding interaction can exist between the amide bonds of the catalyst and the substrate in addition to the hydrophobic interaction.

Analogous kinetic studies were carried out with various amino acid ester substrates and two different micellar catalytic systems, Dec-D and L-His, and Z-L-Leu-D and L-His (Table 5). Table 5 shows the stereoselectivity, with a maximum for Z-L-Leu-ONp in each catalytic system. Similar behaviour was observed in the hydrolysis of amino acid esters catalysed by optically active *N*-lauroylhistidine and CTABr systems.[7b] These results also suggest that hydrogen-bonding and hydrophobic interactions are important in the designing of systems to realize maximum micellar stereoselectivity.

The present study presents evidence that optically active dipeptide derivatives are effective stereoselective catalysts for reactions of enantiomeric substrates in the presence of surfactant micelles. The micellar stereoselectivity depends upon both the hydrogen-bonding and hydrophobic interactions between the substrates and catalysts. These interactions lead to enhanced reactivity for one enantiomer and result in high stereoselectivity.

Experimental

Materials.—The dipeptide catalysts (IIIa—g) were prepared by reactions of corresponding *N*-hydroxysuccinimide esters of *N*-benzyloxycarbonylamino acids with histidine or histidine methyl ester according to a modification of the literature methods.[26,27] *N*-(Benzyloxycarbonyl-L-ananyl)-L-histidine (IIIa), m.p. 131—132 °C (lit.,[28] 131 °C), $[\alpha]_D^{20}$ +23.3° (*c* 0.6 in 80% EtOH). *N*-(Benzyloxycarbonyl-L-ananyl)-L-histidine methyl ester (IIIb), m.p. 164—165 °C (lit.,[27b] 164—165 °C), $[\alpha]_D^{20}$ −18.7° (*c* 2 in MeOH + 1 equiv. HCl) [lit.,[27b] −19.2° (*c* 2, MeOH + 1 equiv. HCl)]. *N*-(Benzyloxycarbonyl-L-valyl)-L-histidine (IIIc), m.p. 122—124 °C (lit.,[29] 120—121 °C),

Table 4. Kinetic parameters for reactions of comicellar systems [a]

Catalyst	Substrate	$10^2k_m/s^{-1}$			$10^4K/l\ mol^{-1}$	
		L	D	L/D	L	D
Z-L-Leu-L-His (IIId)	Moc-Phe-ONp (IIa)	72.8	5.35	13.6	12.5	8.12
	Z-Phe-ONp (IIb)	35.4	6.91	5.13	2.39	1.92
Z-L-His-L-Leu	Moc-Phe-ONp (IIa)	4.98	4.16	1.20	7.58	7.09
Z-L-Phe-L-His (IIIf)	Moc-Phe-ONp (IIa)	26.1	3.58	7.29	5.50	3.67
	Z-Phe-ONp (IIb)	23.6	5.82	4.05	0.797	0.606

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C. The molar ratios of catalyst to CTABr are 1 : 10, [substrate] 1.0×10^{-5}M.

Table 5. Rate constants for the catalytic hydrolyses of substrates in the presence of CTABr micelles [a]

Substrate [b]	$k_c/l\ mol^{-1}\ s^{-1}$					
	Dec-His (Ic)			Z-Leu-His (IIId)		
	L	D	L/D	L,L	L,D	L,L/L,D
Z-Gly-ONp	162	161	1.01	72.0	64.6	1.11
Z-L-Ala-ONp	280	141	1.99	202	52.8	3.83
Z-L-Val-ONp	58.1	20.5	2.84	51.9	9.03	5.75
Z-L-Leu-ONp	415	134	3.10	360	52.3	6.88
Z-L-Ile-ONp	36.1	13.1	2.76			
Z-L-Phe-ONp (IIb)	572	228	2.51	473	78.4	6.03
Z-L-Trp-ONp	42.3	36.5	1.16	19.0	11.6	1.64

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C in the presence of 6.00×10^{-3}M-CTABr micelles, [catalyst] 0.5×10^{-4}—6.0×10^{-4}M, [substrate] 1.0×10^{-5}M. [b] *N*-(Benzyloxycarbonyl)-amino acid *p*-nitrophenyl esters; abbreviations follow the rules in I.U.P.C. (Information Bulletin No. 26).

$[\alpha]_D^{20}$ +27.5° (*c* 1 in MeOH) [lit.,[29] +26.8° (*c* 1.5 in MeOH)]. *N*-(Benzyloxycarbonyl-L-leucyl)-L-histidine (IIId), m.p. 121—122 °C (lit., [29] 120—121 °C), $[\alpha]_D^{20}$ +7.30° (*c* 2 in 80% EtOH). *N*-(Benzyloxycarbonyl-L-leucyl)-D-histidine (IIId), m.p. 126—128 °C, $[\alpha]_D^{20}$ −46.3° (*c* 1 in 80% EtOH). *N*-(Benzyloxycarbonyl-L-leucyl)-L-histidine methyl ester (IIIe), m.p. 130—132 °C (lit.,[30] 131—132 °C), $[\alpha]_D^{20}$ −15.5° (*c* 1 in MeOH) [lit.,[30] −16.5° (*c* 1.5 in MeOH)]. *N*-(Benzyloxycarbonyl-L-phenylalanyl)-L-histidine (IIIf), m.p. 215—217 °C (lit.,[31] 210—211 °C), $[\alpha]_D^{20}$ −5.0° (*c* 1 in DMF) [lit.,[31] −5.1° (*c* 1 in DMF)]. *N*-(Benzyloxycarbonyl-D-phenylalanyl)-L-histidine (IIIf), m.p. 167—168 °C (lit.,[31] 165—168 °C), $[\alpha]_D^{20}$ +36.4° (*c* 1 in MeOH) [lit.,[31] +38° (*c* 1 in MeOH)]. *N*-(Benzyloxycarbonyl-L-tryptophyl)-L-histidine (IIIg), m.p. 140—142 °C, $[\alpha]_D^{20}$ −8.5° (*c* 1 in DMF). The dipeptide derivatives were identified by elemental analyses.

N-Benzyloxycarbonyl-L-histidine (Ie) and *N*-(benzyloxycarbonyl-L-histidyl)-L-leucine were purchased from Tokyo Chemical Industry Co. and Kokusan Chemical Works, respectively. Other materials have been described elsewhere.[20b]

Kinetic Measurements.—Reactions were generally monitored on a Hitachi 200 spectrophotometer or a Shimazu 140 spectrophotometer with a thermostatted cell holder at 25 °C. In the general procedure, a solution (25 μl) of substrate in acetonitrile was added to a buffer solution (3.00 ml) containing the catalyst and surfactant at the desired concentrations.

Pseudo-first-order rate constants were obtained from plots of log $(A_\infty - A_t)$ *versus* time (t) by use of the least-squares method. Correlation coefficients were >0.999. Details of the kinetic conditions may be found in the Results and Discussion section.

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