Stereoselective Micellar Catalysis. Part 5.[1] Deacylation Behaviour in the Cleavage of Enantiomeric Esters by Optically Active Catalysts containing the Imidazolyl Group

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The rate constants of both acylation and deacylation in the cleavage of the enantiomers of amino acid *p*-nitrophenyl esters catalysed by optically active catalysts containing the imidazolyl group have been determined in the presence of surfactant micelles at pH 7.30 in 0.02M-phosphate buffer and 25 °C. The kinetic analysis suggests a nucleophilic mechanism which involves acylation followed by deacylation at the imidazolyl group. Micellar catalysis in deacylation as well as acylation is examined in terms of the rate constants and stereoselectivity. The structural effects of catalysts and substrates and the stereoselective reaction mechanism are discussed.

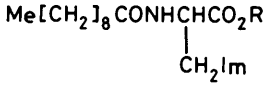
Stereospecificity is one of the most interesting properties of enzyme reactions. Optically active surfactant micelles have been extensively studied as models to gain further insight into the stereospecific properties of enzyme reactions.[2-9] In previous papers,[10,11] we have shown that co-micelles consisting of optically active *N*-acylhistidine or dipeptide derivatives and a cationic surfactant are effective stereoselective catalysts for the cleavage of enantiomeric esters. A mechanism was suggested for stereoselective catalysis involving the acylation of the optically active histidyl residue.

Although only acylation was followed in our previous work, we can clearly observe the formation and decay of an acylimidazole intermediate spectrophotometrically at 245 nm. Recently, we demonstrated stereoselective deacylation in the cleavage of enantiomeric esters by optically active catalysts in the presence of cetyltrimethylammonium bromide (CTAB) micelles.[12] Thus, deacylation of the acylated intermediates can be observed in the esterolytic reactions described above. In this study, we report the details of micellar catalysis and the stereoselectivity for deacylation as well as in acylation during the cleavage of enantiomeric esters by optically active catalysts in the presence of surfactant micelles.

Experimental

Materials.—*N*-Benzyloxycarbonyl-D-phenylalanyl-D-histidine (**IId**) was prepared by standard methods.[13] Brij 35 [polyoxyethylene(23)-lauryl alcohol ether] was a specially prepared reagent purchased from Nakarai Chemicals Ltd. and was used without further purification. Other materials have been described elsewhere.[10,11]

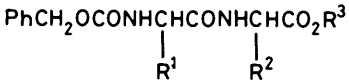
Kinetic Measurements.—Reactions were generally monitored on Hitachi 200 or Shimadzu 140 spectrophotometers with a thermostatted cell holder at 25 °C. In the general procedure, a solution (25 μl) of esters in acetonitrile was added to a buffer solution (3.00 ml) containing the catalyst and surfactant at the desired concentrations. The hydrolyses of the substrates were examined under single turnover conditions, [surfactant] > [catalyst] > [substrate], at pH 7.30 and 0.02M-phosphate buffer. The pseudo-first-order rate constant k_ψ was determined by monitoring the release of the *p*-nitrophenolate ion at 410 nm. The acylation rate constant k_a was calculated from the equation $k_a = k_\psi - k_{CTAB}$, where k_{CTAB} refers to spontaneous hydrolysis in the presence of CTAB. The deacylation rate constant k_d was measured spectrophotometrically by



(I)

a ; R = H (Dec-His)

b ; R = Me (Dec-His-OMe)



(II)

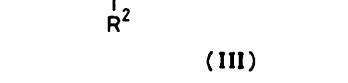
a ; R^1 = Me , R^2 = CH_2Im , R^3 = H (Z-Ala-His)

b ; R^1 = Me_2CHCH_2 , R^2 = CH_2Im , R^3 = H (Z-Leu-His)

c ; R^1 = CH_2Im , R^2 = Me_2CHCH_2 , R^3 = H (Z-His-Leu)

d ; R^1 = $PhCH_2$, R^2 = CH_2Im , R^3 = H (Z-Phe-His)

Im = 4-imidazolyl, Z = benzyloxycarbonyl



(III)

a ; R^1 = Me , R^2 = $PhCH_2$ (Moc-Phe-ONp)

b ; R^1 = $PhCH_2$, R^2 = H (Z-Gly-ONp)

c ; R^1 = $PhCH_2$, R^2 = Me (Z-Ala-ONp)

d ; R^1 = $PhCH_2$, R^2 = $(Me)_2CH$ (Z-Val-ONp)

e ; R^1 = $PhCH_2$, R^2 = $(Me)_2CHCH_2$ (Z-Leu-ONp)

f ; R^1 = $PhCH_2$, R^2 = $MeCH_2CH(Me)$ (Z-Ile-ONp)

g ; R^1 = R^2 = $PhCH_2$ (Z-Phe-ONp)

h ; R^1 = $PhCH_2$, R^2 = p-$HOC_6H_4CH_2$ (Z-Tyr-ONp)

i ; R^1 = $PhCH_2$, R^2 = 3-Indolyl-CH_2 (Z-Trp-ONp)

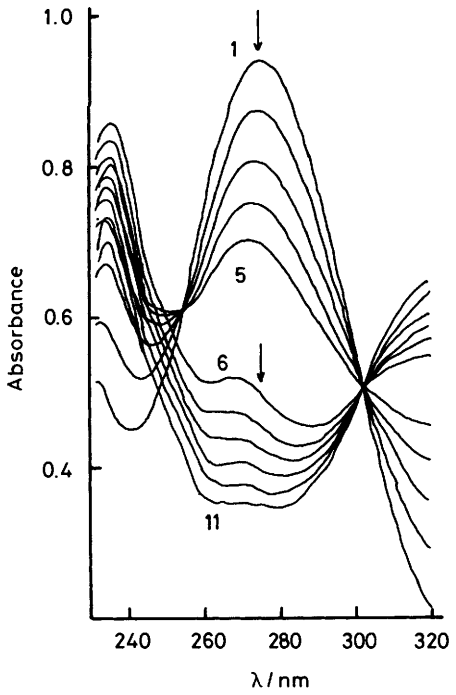


Figure 1. Spectral time study for the reaction of (**IIIa**) with (**Ia**) in the presence of CTAB at pH 7.30, 0.02M-phosphate buffer (0.4M-KCl), and 10 °C. [(**IIIa**)] 1.6×10^{-4}M, [(**Ia**)] 1.00×10^{-3}M, [CTAB] 1.00×10^{-2}M. Spectra curves 1—5 and 6—11 show repeated scans and scans after a 10 min interval, at 480 nm min^{-1}, respectively

following the decomposition of acylimidazole intermediate at 245 nm or near the isosbestic points (250—260 nm) for the acylation reactions. Details of the kinetic techniques and conditions may be found in the Results and Discussion section. The spectra–time study of the reactions was monitored on a Hitachi 200 spectrophotometer with a wavelength program attachment.

Results and Discussion

Reaction Traces and Acyl Intermediates.—The spectra–time study of the reaction of (**IIIa**) with (**Ia**) in the presence of CTAB was followed in the wavelength range 240—320 nm as shown in Figure 1. The spectra in Figure 1 consists of two phases with a fast reaction (acylation) followed by a much slower reaction (deacylation). We also observe a good isosbestic point at 255 nm during the course of the acylation reaction. The reaction trace at fixed wavelengths (245 and 255 nm) is shown in Figure 2. We can observe build-up of acylated intermediates during the reaction. The Figures clearly show that two steps are involved in the total catalytic mechanism. The first step involves an acyl transfer from the substrate to an imidazole group in the catalyst; the second step is the deacylation of the intermediate to regenerate the catalyst.

An attempt was made to prepare the acylated intermediate under anhydrous conditions. Thus, (**Ia**) in *NN*-dimethylformamide was treated with the *N*-hydroxysuccinimide ester of *N*-benzoyloxycarbonyl-L-phenylalanine and two equivalents of triethylamine. The resulting solution was syringed into a buffered micellar solution at pH 7.3 and the u.v. spectrum was recorded immediately. The acyl intermediate was observed at $\lambda_{max.}$ 260 nm, using the previous hydrolysed solution as a reference.

Kinetics.—The catalytic process for the cleavage of the substrates is described by equation (1), where C_{Im} is the

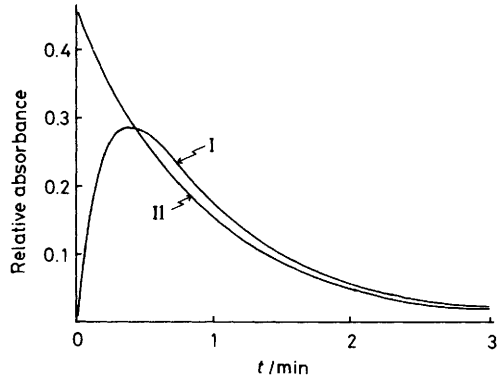


Figure 2. Relative absorbances during the reaction of (**IIIa**) with (**Ia**) in the presence of CTAB (curve **I**, at 245 nm; curve **II**, at 255 nm). Conditions; pH 7.30, 0.02M-phosphate buffer, and 25 °C. [(**IIIa**)] 1.6×10^{-4}M, [(**Ia**)] 1.00×10^{-3}M, [CTAB] 1.00×10^{-2}M

imidazolyl catalyst, AcONp is the substrate, Ac–C_{Im} is the acylated intermediate, and AcOH is the product acid, and k_a and k_d are the rate constants for acylation and deacylation respectively.

$$C_{Im} + AcONp \xrightarrow{k_a} Ac\text{–}C_{Im} \xrightarrow{k_d} C_{Im} + AcOH \quad (1)$$
$$+$$
$$p\text{-nitrophenol}$$

The kinetics were studied under single turnover conditions, [surfactant] > [catalyst] > [substrate], at pH 7.30, 0.02M-phosphate buffer, and 25 °C. The acylation rate constants (k_a) were followed by monitoring the release of *p*-nitrophenolate ion spectrophotometrically at 410 nm. The deacylation rate constants (k_d) were measured by the following kinetic techniques. (1) In the case of $k_a > k_d$, the rate constants were directly measured spectrophotometrically by following the slow decrease in absorption at 245 nm (Figure 1, curve I) or near the isosbestic point (Figure 1, curve II) for acylation. In both cases, the kinetics were first order and good least-squares rate constants were obtained ($r > 0.999$). (2) In the case of $k_a < k_d$, the observed absorption spectrum at 245 nm, which shows the formation and decay of an acylimidazole intermediate, was analysed to obtain the deacylation rate constants from consecutive first-order reaction kinetics [equation (2)].[14]

$$[Ac\text{–}C_{Im}] = \frac{[AcONp]_o k_a}{k_d - k_a}(e^{-k_a t} - e^{-k_d t}) \quad (2)$$

A nonlinear least-squares program was used to fit the data. In the case of $k_a > k_d$, the deacylation rate constants, calculated from the decrease of absorbances at 245 nm or at near the isosbestic point and from nonlinear least-squares fitting, agree within experimental error.

Effects of Catalyst and Surfactant Concentrations.—First, we briefly examined the reactions at varying substrate concentrations ($1.0—30 \times 10^{-5}$M) at fixed concentrations of (**Ia**) (1.00×10^{-3}M) and CTAB (1.00×10^{-2}M) in order to clarify the association effects of substrate on the reaction rate. In these conditions, first-order plots on the basis of absorption due to dissociated *p*-nitrophenolate ion are linear and the rate constants are independent for the substrate concentrations studied within experimental error.

The catalytic hydrolyses of (**IIIa**) by (**Ia**) were carried out with varying catalyst concentrations at a fixed surfactant concentration at pH 7.30, 0.02M-phosphate buffer, and 25 °C. Typical

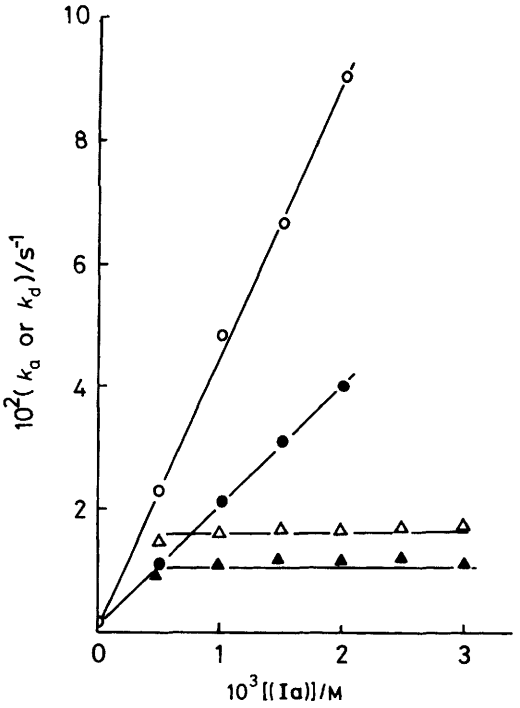


Figure 3. Effect of catalyst (**Ia**) concentration on the rate in the presence of CTAB at pH 7.30, 0.02M-phosphate buffer, and 25 °C. [(**IIIa**)] 1.0×10^{-4}M, [CTAB] 3.00×10^{-2}M, (●, ○) acylation rate constants, ● with D-(**IIIa**), ○ with L-(**IIIa**); (▲, △) deacylation rate constants, ▲ with D-(**IIIa**), △ with L-(**IIIa**)

rate–catalyst concentration profiles are shown in Figure 3. Although the kinetics of the acylation process were obviously first order in catalyst, those of the deacylation process did not depend on the catalyst concentration over the range of concentrations followed. This indicates that the deacylation is a hydroxide ion-mediated process and zero-order in the catalyst.

The catalytic rates were also measured at different surfactant concentrations (2.0—30 $\times 10^{-3}$M) and are shown in Table 1. The k_a values are sensitive to the surfactant concentration and decrease as the concentration of surfactant increases. On the other hand, k_d values first reach a plateau and then slightly decrease as the concentration of surfactant increases. Therefore k_a/k_d values decrease with increasing surfactant concentration; however, the stereoselectivities are almost unchanged.

Catalytic Efficiency and Stereoselectivity.—The catalytic hydrolyses of (**IIIa** and **g**) by (**Ia**) were examined at pH 7.30 and 0.02M-phosphate buffer at a fixed [surfactant] of 1.00×10^{-2}M with various surfactant micelles and the results are summarized in Table 2. In the presence of nonionic surfactant (Brij 35) or addition of salt (0.4M-KCl) to the reaction media there is a marked decrease in both the acylation and deacylation rates, based on CTAB, but both stereoselectivities are almost the same or slightly increased. In the presence of anionic surfactant (SDS), acylation is very slow and the stereoselectivity are also relatively small. We do not find a clear acyl intermediate in this system since the rates are very slow.

Results of catalytic hydrolyses of (**IIIa**) with various catalysts in the presence of CTAB micelles are summarized in Table 3. Deacylation is slower than acylation in all cases. This indicates that the acyl intermediate accumulates and the deacylation step becomes rate determining. Both k_a and k_d depend on the structure of the catalysts. Moreover, in acylation, the catalysts containing an L-histidyl residue stereoselectively hydrolyse the L enantiomers of the substrate in all cases. This clearly indicates

Table 1. Variation of both acylation and deacylation rate constants for cleavage of (**IIIa**) by (**Ia**) with CTAB concentrations[a]

10^3[cTAB]/M		$10^2k_a/s^{-1}$	$10^2k_d/s^{-1}$	k_a/k_d
2.00	L	47.0	2.99	15.7
	D	21.9	2.07	10.6
	(L/D)	(2.15)	(1.44)	
5.00	L	30.4	3.07	9.90
	D	14.6	2.24	6.52
	(L/D)	(2.08)	(1.37)	
10.0	L	16.8	2.62	6.41
	D	8.03	1.95	4.12
	(L/D)	(2.09)	(1.34)	
20.0	L	6.84	2.06	3.32
	D	3.35	1.44	2.33
	(L/D)	(2.04)	(1.43)	
30.0	L	4.74	1.65	2.87
	D	2.41	1.14	2.11
	(L/D)	(1.97)	(1.45)	

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C. [(**IIIa**)] 1.0×10^{-4}M, [(**Ia**)] 1.00×10^{-3}M.

Table 2. Rate constants of both acylation and deacylation in the presence of surfactant micelles[a]

		Moc-Phe-ONp (**IIIa**)		Z-Phe-ONp (**IIIg**)	
Surfactant		$10^2k_a/s^{-1}$	$10^2k_d/s^{-1}$	$10^2k_a/s^{-1}$	$10^2k_d/s^{-1}$
CTAB	L	16.8	2.62	30.1	4.81
	D	8.03	1.95	12.0	3.17
	(L/D)	(2.09)	(1.34)	(2.51)	(1.51)
CTAB[b]	L	5.90	0.404	7.50	0.672
	D	2.70	0.275	2.87	0.443
	(L/D)	(2.19)	(1.47)	(2.61)	(1.52)
Brij 35[c]	L	0.898	0.157	1.08	0.187
	D	0.434	0.104	0.535	0.134
	(L/D)	(2.07)	(1.51)	(2.02)	(1.40)
SDS[d]	L	0.0206			
	D	0.0152			
	(L/D)	(1.36)			

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C in the presence of 1.00×10^{-2}M-surfactant. [(**Ia**)] 1.00×10^{-3}M, [Substrate] 1.0×10^{-4}M. From three or more reactions, we estimated that rate constants are reproducible to ±4%. [b] In 0.4M-KCl. [c] Polyoxyethylene(23)-lauryl alcohol ether. [d] Sodium dodecyl sulphate.

that stereoselective control is mainly determined by catalytic transfer to the imidazolyl function at the active site. The acylation effects and stereoselectivities with these catalytic systems were widely discussed previously.[1] On the other hand, in deacylation the stereoselectivities show that the acyl intermediates from L substrates decompose more rapidly than those of D enantiomers although larger stereoselectivities are observed for acylation than for deacylation. Comparisons of stereoselectivity in four catalytic systems, Dec-L-His (**Ia**), and the dipeptides which have L,L configurations, Z-L-Ala-L-His (**IIa**), Z-L-Leu-L-His (**IIb**), and Z-L-Phe-L-His (**IId**) gives the following order of the rate-constant ratio for both acylation and deacylation: (**IIb**) > (**IId**) > (**IIa**) > (**Ia**). The dipeptide catalysts are more stereoselective than (**Ia**). The larger stereoselectivities observed with dipeptide catalysts suggest that steric factors could be dominant in both processes. Moreover, Z-L-His-L-Leu (**IIc**), which has the reverse sequence of amino acid residues, is much less stereoselective than Z-L-Leu-L-His (**IIb**) in both processes. This indicates the importance of the position of the imidazole group in the catalyst. In acylation, thus, the catalyst must have a suitable orientation of the functional group and a stereochemical fit with the substrate. On

the other hand, deacylation is a hydroxide ion-mediated process and the observed stereoselectivity is primarily due to the structural differences between the diastereoisomeric acyl intermediates. The reaction of (**IIb**) and (**IIIa**) gives the highest stereoselectivities: the enantiomer rate constant ratios (L/D) are 12.0 and 3.18 for acylation and deacylation, respectively.

Structural Effects of Catalysts and Substrates.—More kinetic studies were carried out with various amino acid ester substrates and three different micellar catalytic systems, Dec-L-His (**Ia**), Dec-L-His-OMe (**Ib**), and Z-L-Phe-L-His and Z-D-Phe-D-His (**IId**).

Table 3. Rate constants for reaction of (**IIIa**) in the presence of CTAB[a]

	10^2k_a			10^2k_d		
Catalyst	L	D	L/D	L	D	L/D
Dec-L-His (**Ia**)	16.8	8.03	2.09	2.62	1.95	1.34
Dec-L-His-OMe (**Ib**)	10.3	6.57	1.57	4.98	3.05	1.63
Z-L-Ala-L-His (**IIa**)	7.22	1.81	3.99	3.71	1.59	2.33
Z-L-Leu-L-His (**IIb**)	37.7	3.14	12.0	7.91	2.49	3.18
Z-L-His-L-Leu (**IIc**)	2.45	2.24	1.09	1.72	1.60	1.08
Z-L-Phe-L-His (**IId**)	27.3	3.72	7.34	7.50	2.65	2.83
Z-D-Phe-L-His (**IId**)	6.76	2.97	2.28	2.87	2.05	1.40

[a] At pH 7.30, 0.2M-phosphate buffer, and 25 °C in the presence of 1.00×10^{-2}M-CTAB, [Catalyst] 1.00×10^{-3}M, [(**IIIa**)] 1.0×10^{-4}M. From three or more reactions, we estimate that the rate constants are reproducible to ±4%.

The results shown in Table 4 indicate the effect of the amino acid side chain of the substrates on catalysis by (**Ia** and **b**) in the presence of CTAB. Both the rate constants depend on the structure of the substrates. Interestingly, in acylation, (**Ia**) is *ca.* 1.6—2.4 times as reactive as (**Ib**) for all substrates used. As claimed in previous papers,[11a,b] this is consistent with intermolecular assistance provided by the carboxy group to the imidazolyl group in (**Ia**). On the other hand, the deacylation rate constants with (**Ia**) are smaller than those with (**Ib**), in contrast to the opposite order of their acylation rate constants. The carboxylate anion of (**Ia**) may stabilize the acylimidazolium group of the intermediate. We have also demonstrated the examples of micellar catalysis with three catalytic groups for the cleavage of *p*-nitrophenyl esters in the presence of hydroxy-functionalized surfacant micelles.[15]

Table 5 summarizes the rate constants for acylation and deacylation, and the stereoselectivities (L,L/D,D) for cleavage of different substrates (**III**) by two dipeptide catalysts [D,D- and L,L-(**IId**)] in the presence of CTAB. The following observations derived from Table 5. (1) In acylation, the hydrolysis of various substrates shows a remarkable dependence of the rate constants and stereoselectivity on the size of the amino acid side chain of the substrates. The rate acceleration effect (k_a/k_{CTAB}) increases to a maximum and then decreases as the size of the amino acid side chain increases, but (**IIIh**) reacts more slowly than expected because of its hydrophobic side chain. Probably the reaction sites of (**IIIh**) incorporated into the micelles are too far apart from the catalytically active imidazole group of (**IId**). It is further found that the L,L catalyst reacts more selectively than the D,D

Table 4. Rate constants for reactions of (**III**) with (**Ia**) and (**Ib**) in the presence of CTAB[a]

	Dec-L-His (**Ia**)			Dec-L-His-OMe (**Ib**)		
Substrate	$10^2k_a/s^{-1}$	$10^2k_d/s^{-1}$	k_a/k_d	$10^2k_a/s^{-1}$	$10k_d/s^{-1}$	k_a/k_d
Z-Gly-ONp (**IIIb**)	8.39	0.830	10.1	4.74	1.66	2.86
Z-L-Ala-ONp (**IIIc**)	14.4	1.69	8.52	6.93	3.17	2.19
Z-L-Val-ONp (**IIId**)	3.29	0.515	6.39	1.40	0.864	1.62
Z-L-Leu-ONp (**IIIe**)	22.2	2.00	11.1	9.24	4.66	1.98
Z-L-Phe-ONp (**IIIg**)	30.1	4.81	6.26	12.7	8.10	1.57
Z-L-Tyr-ONp (**IIIh**)	4.43	0.711	6.23	2.77	1.60	1.73
Z-L-Trp-ONp (**IIIi**)	2.79	0.790	3.53	1.58	1.21	1.31

[a] At pH 7.30, 0.02M-phosphate buffer, and 25 °C in the presence of 1.00×10^{-2}M-CTAB, [Substrate] 1.0×10^{-4}M, [Catalyst] 1.00×10^{-3}M. From three or more reactions, we estimate that the rate constants are reproducible to ±4%.

Table 5. Rate constants for acylation and deacylation, and stereoselectivities (L,L/D,D) for the cleavage of different substrates by dipeptide catalysts in the presence of CTAB[a]

Substrate	$10^3k_{CTAB}/s^{-1}$	$10^3k_a/s^{-1}$	k_a/k_{CTAB}	$k_a(L,L)/k_a(D,D)$	$10^3k_d/s^{-1}$	$k_d(L,L)/k_d(D,D)$
Z-Gly-ONp (**IIIb**)	2.89	26.7	9.30	0.95	19.9	1.09
		(28.0)	(9.69)		(18.2)	
Z-L-Ala-ONp (**IIIc**)	1.53	46.5	30.4	2.27	30.2	1.48
		(20.5)	(13.4)		(20.4)	
Z-L-Val-ONp (**IIId**)	0.223	13.4	60.1	3.39	8.02	2.18
		(3.95)	(17.7)		(3.68)	
Z-L-Leu-ONp (**IIIe**)	0.933	74.4	79.7	3.82	45.5	2.34
		(19.5)	(20.9)		(19.4)	
Z-L-Ile-ONp (**IIIf**)	0.140	8.01	57.2	3.64	5.44	2.48
		(2.20)	(15.7)		(2.19)	
Z-L-Phe-ONp (**IIIg**)	2.36	165	69.9	4.73	93.3	2.51
		(34.9)	(14.8)		(34.7)	
Z-L-Tyr-ONp (**IIIh**)	1.38	8.22	5.96	1.28	43.9	1.99
		(6.41)	(4.64)		(22.1)	
Z-L-Trp-ONp (**IIIi**)	0.479	5.47	11.4	1.36	65.3[b]	1.72
		(4.01)	(8.37)		(38.0)[b]	

[a] At pH 7.30, 0.02M-phosphate buffer, 25 °C, [CTAB] 1.00×10^{-2}M, [(**IId**) (Z-L-Phe-L-His)] 1.00×10^{-3}M, [Substrate] 1.0×10^{-4}M. The values in parentheses are for (**IId**) (Z-D-Phe-D-His). From three or more reactions, we estimate that rate constants are reproducible to within ±6%. [b] ±10%.

catalyst with L substrates in all cases. The extent of stereoselectivity increases with increasing size of the amino acid side groups except for substrate (**IIIh**). This parallels the improved stereoselectivity resulting from an increase in the hydrophobic interaction between the amino acid side chain and the appropriate hydrophobic group at the active site. Substrate (**IIIg**) shows the highest stereoselectivity. (2) In deacylation, the deacylation rate constants are also remarkably affected by the structure of the substrates. Deacylation is a hydroxide ion-mediated process and the stereoselectivities show that the acyl intermediates of L,L-catalyst decompose more rapidly than those of D,D-catalyst. Interestingly, the substrates which give high stereoselective acylation effects also afford high deacylation stereoselectivities, although larger stereoselectivities are observed for acylations than for deacylations except for substrate (**IIIh**). These results indicate that the stereoselectivity observed in this process is primarily due to the structural differences between the diasteroisomeric acyl intermediates. Thus deacylation involves steric interaction of amino acid side groups and the larger stereoselectivity results from the larger steric strain release of the acyl intermediate.

In addition, the stereoselectivities of both acylation and deacylation with the dipeptide catalysts increase to a maximum and then decrease as the amino acid side groups of the substrates becomes larger and more hydrophobic. This suggests the importance of a combination of the specific interactions (steric, hydrophobic, hydrogen bonding) in both processes.

Conclusions.—The present study clearly shows that optically active functionalized micelles are effective stereoselective catalysts for cleavage of the enantiomeric substrates. The major course of catalysis is acylation followed by deacylation at the imidazolyl group. Stereoselective effects in catalysis are observed in acylation as well as deacylation. The kinetic results indicate that in acylation stereoselective control is mainly determined by catalytic acyl transfer to the imidazole function at the active site of the optically active catalyst. The catalyst must have a suitable orientation of the functional group and a stereochemical fit with a substrate. On the other hand, deacylation is a hydroxide ion-mediated process and the observed stereoselectivities are primarily due to structural differences between diastereoisomeric acyl intermediates. All the results suggest that a combination of specific interactions such as steric, hydrophobic, and hydrogen bonding is of importance for the extent of stereoselectivity in both processes.

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