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STEREOSELECTIVE MICELLAR CATALYSIS IN THE HYDROLYSIS OF ENANTIOMERIC ESTERS BY DIPEPTIDE DERIVATIVES CONTAINING HISTIDINE RESIDUE

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The catalytic hydrolysis of enantiomeric substrates is examined using optically active dipeptide derivatives containing histidine residue in the presence of CTABr micelles. A very high stereoselectivity, $k_c(L)/k_c(D)$, of 12.2 is observed in the reaction with the enantiomers of p-nitrophenyl N-methoxycarbonylphenylalanate (MocPheONp) and N-(benzyloxycarbonyl-L-leucyl)-L-histidine (ZLeuHis).

Micellar catalysis as the model of enzymic catalysis has been extensively investigated[1] and particularly micelles derived from optically active surfactants have been used as catalysts for a number of hydrolysis reactions of enantiomeric esters.[2-6]

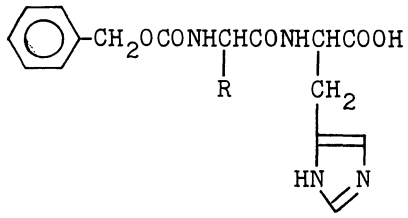
In the course of our study on the stereoselective micellar catalysis, we have found that mixed micelles of optically active N-acylhistidines and cetyltrimethylammonium bromide (CTABr) are very effective stereoselective catalysts for hydrolysis of enantiomeric p-nitrophenyl esters, and a mechanism was suggested for the stereoselective catalysis involving acylation of optically active histidine residue.[7]

Recently, a high degree of stereoselectivity (5.5-5.7) was observed in the deacylation of long chain p-nitrophenyl N-acylphenylalanates by N-(N-dodecanoyl-L-histidyl)-L-leucine and a cationic chiral surfactant.[8] Moreover, an exceptional micellar stereoselectivity was also observed in the cleavage of diastereomeric dipeptide p-nitrophenyl esters by functional surfactants.[9] These observations indicate the possibility of designing optically active catalysts with enhanced stereoselectivity.

It has been suggested that the stereospecificity of enzymes is based on the steric configuration of the constituent amino acids, therefore, the introduction of two asymmetric centers into the catalyst would lead to decreased flexibility and allow for a more stereospecific interaction between catalyst and substrate. This communication describes a very high stereoselective effect in the hydrolysis of the enantiomeric substrates by a series of dipeptide catalysts containing histidine residue in the presence of surfactant micelles.

Kinetic studies were performed at pH 7.30, 0.02 M phosphate buffer, and

Catalyst



ZAlaHis, R = CH_3

ZValHis, R = $CH(CH_3)_2$

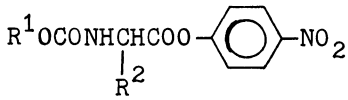
ZLeuHis, R = $CH_2CH(CH_3)_2$

ZPheHis, R = $CH_2C_6H_5$

ZTryHis, R = CH_2-(3-indolyl)

ZLys(Z)His, R = $(CH_2)_4NHCOOCH_2C_6H_5$

Substrate



ZPheONp, $R^1 = R^2 = CH_2C_6H_5$

MocPheONp, $R^1 = CH_3$, $R^2 = CH_2C_6H_5$

Surfactant

$CH_3(CH_2)_{15}\overset{+}{N}(CH_3)_3$, Br^-

CTABr

25°C. Pseudo-first-order rate constants (k_ψ) were evaluated by monitoring the release of p-nitrophenoxide ion spectrophotometrically at 400 nm under conditions [CTABr]>[catalyst]>[substrate] . The catalytic second-order rate constants (k_c) were obtained from the liner slope of k_ψ against catalyst concentration in the absence or presence of CTABr. Table 1 summarizes the result in the presence of 6.00×10^{-3} M CTABr.

From Table 1, it is apparent that the catalysts containing L-histidine residue (or D-histidine residue) stereoselectively hydrolyze the L enantiomers (or D enantiomers) of the substrates, ZPheONp or MocPheONp, in all cases. This indicates that the stereoselective control is mainly determined by catalytic acyl transfer to the optically active imidazole group of the catalyst.[7] On the other hand, the variation in stereoselectivity among the catalysts is fairly large (1.2-12.2), indicating the stereoselectivity is affected by amino acid side chains of the catalysts. The rate constants for reactions of L substrates with dipeptide catalysts having L-L configuration increase with the increasing hydrophobicity of amino acid side chains, and rate maxima result at ZPheHis (ZPheONp) and ZLeuHis (MocPheONp). Rate constants for reactions of D substrates show similar patterns but the magnitude of the effects is much less for D substrates. Therefore, the stereoselectivity, $k_c(L)/k_c(D)$, thus observed gives a bell shaped behavior with a maxium at ZLeuHis for ZPheONp and MocPheONp, respectively. We observe the stereoselectivities of 12.2 (MocPheONp) and 6.32 (ZPheONp) with ZLeuHis(L-L).

In the previous papers,[7] we have proven that the improved stereoselectivity resulted from increasing hydrophobic interaction between the hydrophobic groups of catalysts and substrates. In the present study, the hydrophobic interaction is also an important factor in the high degree of stereochemical control of the enantiomeric substrates since the larger stereoselective effects accord with the larger rate enhancement of the reactions in micellar phase. Indeed, the reaction rates with ZPheHis(L-L) in the absence of CTABr[10] were about two orders of

Table 1. Apparent Catalytic Rate Constants (k_c) in the Presence of CTABr Micelles[a)]

Catalyst	(Confi.)	k_c, $M^{-1}sec^{-1}$ ZPheONp L	ZPheONp D	ZPheONp L/D	MocPheONp L	MocPheONp D	MocPheONp L/D
ZHis[b)]	(L)	111	92.3	1.20	80.7	66.0	1.22
ZAlaHis	(L-L)	98.9	37.9	2.61	139	32.1	4.33
ZValHis	(L-L)	225	56.7	3.97	309	44.7	6.91
ZLeuHis	(L-L)	473	74.9	6.32	645	52.7	12.2
	(L-D)	78.4	176	2.24[c)]	60.9	146	2.40[c)]
ZPheHis	(L-L)	493	110	4.48	541	74.5	7.26
	(D-L)	202	98.1	2.06	172	74.2	2.32
ZTryHis	(L-L)	103	67.5	1.53	85.9	47.2	1.82
ZLys(Z)His	(L-L)	84.3	40.2	2.10	78.3	32.1	2.44

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

magnitude slower than those in the presence of CTABr, and kinetic stereoselectivities were also small (about 2.0).

The bell shaped behaviors observed for reactivity and stereoselectivity in Table 1 are thus seen to result when the hydrogen bonding interaction can exist between catalyst and substrate in the micellar phase as Brown and Bunton[2b)] have mentioned in the stereoselective catalyzed reaction of enantiomeric N-acetylphenylalanine p-nitrophenyl esters with an optically active functional surfactant. Further evidence is obtained from comparisons of the diastereomeric dipeptide catalysts of ZLeuHis and ZPheHis. ZLeuHis(L-D) and ZPheHis(D-L) give reduced rates for one of the enantiomeric substrates and result in decreased stereoselectivities. The diastereomeric rate ratios, k_c(L-L)/k_c(D-L), of ZPheHis for L substrates are 2.4-3.2. However, the hydrolysis of nonspecific substrates, such as p-nitrophenyl acetate, hexanoate, and laurate catalyzed by the diastereomeric pair of ZPheHis shows almost no significant rate difference. These facts thus suggest that the steric effects induced by hydrogen bonding interaction between the amide bonds of these specific substrates and catalysts are very important for the enhanced stereoselectivity.

In conclusion, the results reported here suggest that the micellar stereoselectivity is dependent on both the hydrophobic and hydrogen bonding interactions between the substrate and the catalyst. These interactions lead to the enhanced reactivity for one of the enantiomeric substrates and result in high stereoselectivity. A detailed study of stereoselective catalysis in these micellar systems

is now in progress.

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10) The reactions of ZPheONp and MocPheONp with ZPheHis(L-L) gave values of k_c(L) of 3.07 and 1.62, k_c(D) of 1.51 and 0.828, and k_c(L)/k_c(D) of 2.03 and 1.96, respectively, in 0.02 M phosphate buffer at pH 7.30, containing 20 % v/v ethanol.

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