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ENANTIOSELECTIVELY CATALYZED HYDROLYSIS OF p-NITROPHENYL ESTERS OF N-PROTECTED L OR D-AMINO ACIDS BY OPTICALLY ACTIVE HYDROXAMIC ACID AND DIPEPTIDES

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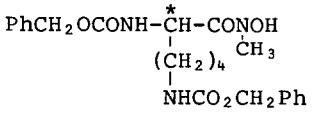
Summary: Catalyzed hydrolysis of p-nitrophenyl esters of N-protected L or D-phenylalanine by optically active hydroxamic acid or dipeptides in the presence of CTABr micelles showed high enantioselectivity (D/L = 5.68 for L-ZLysZ(MHX)), demonstrating control of the direction of the enantioselectivity based on the balance of the structures of the nucleophile and substituent.

Recently extensive studies have been published on the enantioselective ester hydrolysis in functionalized micelles,[1,2] as well as in mixed micellar systems with or without optically active surfactants.[3,4] Our previous papers have described marked enantioselectivities in ester hydrolyses catalyzed by N-lauroyl-L-histidine (L-LauHis), optically active hydroxamic acids and amines in the presence of cetyltrimethylammonium bromide (CTABr) micelles, emphasizing the importance of three requirements for the enantioselective enzyme model.[5-7] We have also demonstrated the dependency of the enantioselectivity on the steric factor of compounds[6,7]; hydroxamic acid of L-amino acids, for example, has a reversed D,L-preference of L-LauHis.[7]

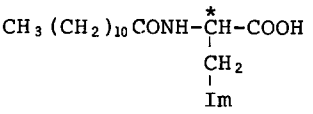
In this work we studied the hydrolysis of p-nitrophenyl esters of N-protected L or D-phenylalanine catalyzed by L-LauHis, N^{α},N^{ε}-bis(benzyloxycarbonyl)-L-lysine N-methylhydroxamic acid and dipeptides in the presence of CTABr micelles in order to investigate how the structures of the nucleophiles control the direction of the enantioselectivity.

The preparation of L-LauHis,[5,8] L-ZLysZ(MHX)[7] and p-nitrophenyl ester of N-benzyloxycarbonyl-L or D-phenylalanine (L or D-S_{ZP})[5,9] have been described else-

(Nucleophile)

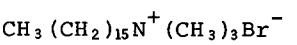


L-ZLysZ(MHX)



L-LauHis

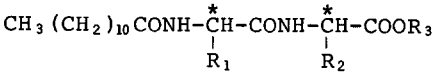
(Surfactant)



CTABr

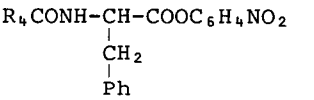
(Ph: Phenyl)

(Im: Imidazolyl)



R_1 = $-CH_2Im$	R_2 = $-CH_2Ph$	R_3 = $-C_2H_5$	L-LauHis-L-Phe(OEt)
$-CH_2Im$	$-CH_2Ph$	$-CH_2Ph$	L-LauHis-L-Phe(OBzl)
$-CH_2Ph$	$-CH_2Im$	$-CH_3$	L-LauPhe-L-His(OMe)
$-CH_2CO_2CH_2Ph$	$-CH_2Im$	$-CH_3$	L-LauAsp(β-OBzl)-α-L-His(OMe)

(substrate)



R_4 = $PhCH_2O-$		L or D-S_{ZP}
$CH_3(CH_2)_{10}-$		L or D-S_{LP}

where. The dipeptide nucleophiles were prepared by the coupling of N-Lauroyl-L-amino acids with esters of L-amino acids, N-lauroyl-L-histidyl-L-phenylalanine ethyl ester (L-LauHis-L-Phe(OEt)); mp 185.5-187.0 °C, N-lauroyl-L-histidyl-L-phenylalanine benzyl ester (L-LauHis-L-Phe(OBzl)); mp 79.5-81.0 °C, N-lauroyl-L-phenylalanyl-L-histidine methyl ester (L-LauPhe-L-His(OMe)); mp 134.0-135.0°C, β-benzyl ester of N-lauroyl-L-aspartic acid-α-L-histidine methyl ester (L-LauAsp(β-OBzl)-α-His(OMe)); mp 63.0-64.5 °C.

p-Nitrophenyl esters of N-lauroyl-L or D-phenylalanine (L or D-S_{LP}) were prepared in usual manners.[10] L-S_{LP}; mp 107.5-109.0 °C , D-S_{LP}; mp 106.5-108.0°C.

The structures and the purities of these compounds were determined by means of elemental analysis and IR and NMR spectroscopies. The hydrolysis was followed spectrophotometrically in 0.04 M Tris. buffer, 0.20 M KCl in the presence of CTABr.

Table I summarizes the result of the hydrolysis of L or D-S_{ZP} by dipeptide nucleophiles. L-LauHis-L-Phe(OEt), which is composed of L-LauHis and phenylalanine functions, showed an enantioselectivity as effective as L-LauHis in a marked contrast to little enhancement of the reaction rate by L-LauPhe-L-His(OMe), which has the same amino acid functions as those of L-LauHis-L-Phe(OEt), but in a

Table I Hydrolysis of L and D-S_{ZP}

Nuc	$k_{obs} \times 10^3$ (sec^{-1}) L-S_{ZP}	D-S_{ZP}	L/D
L-LauHis	13.43	5.91	2.27
L-LauHis-L-Phe(OEt)	17.32	7.95	2.18
L-LauHis-L-Phe(OBzl)	1.07	0.96	1.11
L-LauPhe-L-His(OMe)	0.01	0.01	—
L-LauAsp(β-OBzl)-α-L-His(OMe)	8.94	4.37	2.05
L-ZLysZ(MHX)*	21.42	47.29	D/L=2.21

25.0°C, pH 7.93(*7.40), 10.0-6.67 v/v% MeOH-MeCN-H_2O, [CTABr]= 4×10^{-3} M, [Nuc] = 1×10^{-4} M, [Sub] = 5×10^{-5} M.

Table II Hydrolysis of L and D-S_{LP}

Temp (°C)	$k_{obs} \times 10^3$ (sec^{-1}) L-S_{LP}	D-S_{LP}	D/L
35.0	20.86	97.80	4.69
25.0	10.86	54.14	4.99
15.0	4.74	24.19	5.19
10.0	2.60	14.78	5.68

pH 7.93, 10.0-6.67 v/v% MeOH-MeCN-H_2O, [CTABr] = 4×10^{-3} M, [L-ZLysZ(MHX)] = 1×10^{-4} M, [Sub] = 4×10^{-5} M.

reversed sequence. On the other hand, L-LauAsp(β-OBzl)-α-L-His(OMe) afforded the rate ratio (L/D) of 2.05. Here an interaction was presumably formed in the proximity of the active site between the long alkyl chain or ester moiety of the nucleophile and the hydrophobic moiety of the substrate. As we mentioned before[5-7], such an interaction is essential to rate enhancement and enantioselectivity.

As shown by Table I the L/D value decreases with increasing steric bulkiness or hydrophobicity of the amino acid function which is introduced on the carboxyl side of L-LauHis. A preference for D-substrate could be expected by introducing more bulky amino acid function. In other words, one can control the direction of the enantioselectivity by balancing the steric factor of the substituents on the amino and carboxyl groups of the nucleophile. In fact L-ZLysZ(MHX), which is obtained from N-protected L-amino acid by introducing a hydroxamic acid group on the carboxyl group, reacted preferentially with the D-substrate to the L-substrate.

Table II shows the rate constants of the hydrolyses of L and D-S_{LP} by L-ZLysZ(MHX). As in the case of S_{ZP} the nucleophile preferred D-substrate. It is noteworthy that the enantioselectivity observed for S_{LP} was much higher than that for S_{ZP}. The enhanced recognition by the nucleophile implies a tight interaction with the substrate due to the greater hydrophobicity of the acyl group with a

long alkyl chain in S_{LP} than that of the benzyloxycarbonyl group in S_{ZP}.

By lowering the reaction temperature to 10 °C , D/L value was incresed to 5.68. This is the highest enantioselectivity so far obtained without optically active surfactant.[11] Similar temperature dependencies have been observed for the hydrolysis of S_{ZP} by L-LauHis and L-ZLysZ(MHX).[6,7]

We have previously emphasized the importance of three requirements for the enantioselective enzyme model: (1) the asymmetric center and the active site must exist close to each other in the reaction system; (2) strong interactions must exist among reagents; (3) the catalyzed reaction must take place in a hydrophobic field in order to avoid the reaction with nonselective hydroxide ion.[5-7] The present system well substantiates these requirements by supplying the hydrophobic field even with optically inactive surfactant. In other words, the interaction between the nucleophile and the substrate plays more important role in the enantioselectivity. By balancing the substituents on these reagents higher enantioselectivity would be realized.

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11. The cleavage of diastereoisomeric ester gives L-L/D-L of 5.0,[2] and the ester hydrolysis in the presence of optically active surfactant micelles gives L/D of 5.7.[3]

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