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REMARKABLE SUBSTITUENT EFFECTS ON THE MICELLAR ENANTIOSELECTIVE HYDROLYSIS OF AMINO ACID ESTERS

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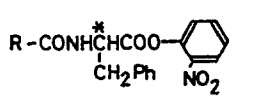
Summary: The remarkable substituent effects were observed for the enantioselective hydrolysis of the long-chained and nitro-substituted phenyl esters; With respect to the enantioselectivity, p-isomers (k_ψ^L/k_ψ^D = 40.2) > o-isomers (20.1) > m-isomers (10.8) and with respect to the rate-enhancement, o-isomers > p-isomers >> m-isomers, respectively.

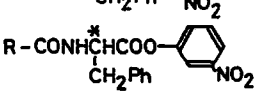
The functional molecular assemblies composed of surfactants and active peptides have attracted the attention of many researchers in Biomimetic Chemistry as one of the efficient enzyme models for clarifying the catalytic specificity of native enzymes.[1,2]

In the course of our study on enantioselective hydrolysis of amino acid esters, it has been emphasized that the efficient hydrophobic interaction of amino acid residues and long acyl-chains in nucleophiles and substrates is important in enhancing the catalytic efficiency and stereoselectivity in micellar,[3,4] vesicular,[5,6] and co-aggregates[7,8] systems. However, all of the enantiomeric substrates employed in the previous papers are isomers having a p-nitro group and there has been no report of the substituent effect of nitro groups in amino acid esters on the stereoselective hydrolysis in micellar systems.

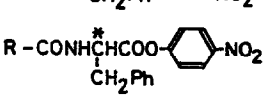
In the present study, we investigated the substituent (ortho, meta, and para) effects of nitro groups on the enantioselective hydrolysis. The substrates, catalysts, and surfactants employed in this study are as follows:



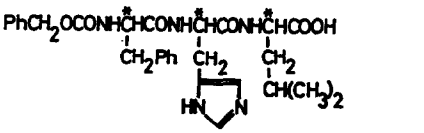
Z-L(D)-Phe-ONP (R=$PhCH_2O$)
C_{12}-L(D)-Phe-ONP (R=$CH_3(CH_2)_{10}$)



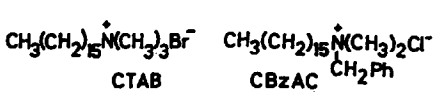
Z-L(D)-Phe-MNP (R=$PhCH_2O$)
C_{12}-L(D)-Phe-MNP (R=$CH_3(CH_2)_{10}$)



Z-L(D)-Phe-PNP (R=$PhCH_2O$)
C_{12}-L(D)-Phe-PNP (R=$CH_3(CH_2)_{10}$)



Z-L-Phe-L-His-L-Leu



First, we examined the hydrolytic cleavages of the enantiomeric substrates (C_{12}-D(L)-Phe-ONP, C_{12}-D(L)-Phe-MNP, C_{12}-D(L)-Phe PNP, Z-D(L) Phe-ONP, Z-D(L)-Phe-MNP, and Z-D(L)-Phe-PNP)[9] catalyzed by Z-L-Phe-L-His-L-Leu in the CBzAC micellar systems. The kinetic results are summarized in Table I. The noteworthy aspects are: With respect to the long-chained enantiomers, (a) the order of the catalytic-cleavage rate (k_ψ) was o-isomers > p-isomers >> m-isomers for each L- and D-substrates, though the order of the spontaneous hydrolytic-cleavage rate (k_s) was p-isomers > o-isomers >> m-isomers. Especially, it is attractive that the extremely larger rate-enhancement in the presence of catalyst (k_ψ)as compared with the rate in the absence of catalyst (k_s) was observed for the hydrolysis of C_{12}-L-Phe-ONP having a nitro group in the ortho position; On the other hand, (b) the C_{12}-D(L)-Phe-PNP substrates having a nitro group in the para position was the most efficient for the enhancement of enantioselectivity (k_ψ^L/k_ψ^D = 40) among all the long-chained enantiomeric-substrates employed in this study; With respect to the enantiomers having a benzyloxycarbonyl(Z) group, (c) both the orders of k_s and k_ψ were analogous to the case of the long-chained enantiomers, although the k_ψ/k_s value (ca. 600) for the hydrolysis of Z-L-Phe-ONP having a ortho nitro group was most attractive; Furthermore, (d) the Z-D(L)-Phe-ONP having a nitro group in the ortho position was more efficient for the enhancement of enantioselectivity (k_ψ^L/k_ψ^D = 4.9) as compared with the para- and meta-isomers (k_ψ^L/k_ψ^D = 4.5 and 2.0, respectively). Here, we can emphasize that the striking enhancement for the o-isomer hydrolysis (especially the L-form substrate) in the presence of catalyst might be attributed to a more effective electrostatic interaction (that is, intermolecular interaction) between the positive charge of micelles and the negative charge of the leaving phenoxy group of o-isomers than in the case of p-isomers in being able to stabilize the transition state for the imidazole acylation.[10-12]

Next, we examined the temperature dependence of enantioselectivity for the hydrolysis of C_{12}-D(L)-Phe-PNP, C_{12}-D(L)-Phe-ONP, Z-D(L)-Phe-PNP, and Z-D(L)-Phe-ONP catalyzed by Z-L-Phe-L-His-L-Leu in the CTAB micellar systems as shown in Figure 1. It is worthy to note that (e) the enantioselectivity of the long-chained p-nitrophenylalaninates (C_{12}-D(L)-Phe-PNP) was superior to that of the long-chained o-nitrophenylalaninates (C_{12}-D(L)-Phe-ONP) and (f) the enantioselectivity of o-isomers having a Z unit (Z-D(L)-Phe-ONP) was higher than that of p-isomers (Z-D(L)-Phe-PNP) at each temperature in the range of 15-35 °C. Particularly, the difference in enantioselectivity between p- and o-isomers sharply increased at the lower temperatures (at 15-20 °C in the case of the long-chained enatiomeric substrates and 15 °C in the case of the substrates having a Z-unit).

Table I. Rate Constants (k_s and k_ψ) and Enantioseletivity (k_ψ^L/k_ψ^D) for the Hydrolysis of o-, m-, and p-Nitrophenyl Phenylalaninates Catalyzed by Z-L-Phe-L-His-L-Leu in the CBzAC Micellar Systems[a]

Substrate	k_s (s^{-1})	k_ψ (s^{-1})		k_ψ^L/k_ψ^D
		L	D	
C_{12}-Phe-ONP	0.0074	0.7739	0.0385	20.1
C_{12}-Phe-MNP	0.00182	0.01003	0.00093	10.8
C_{12}-Phe-PNP	0.0214	0.4821	0.0120	40.2
Z-Phe-ONP	0.00014	0.0844	0.0173	4.9
Z-Phe-MNP	0.00009	0.00131	0.00064	2.0
Z-Phe-PNP	0.00025	0.0631	0.0140	4.5

(a) The k_ψ value was evaluated from $[k_t - k_s]$, where k_t and k_s denote the first-order rate constants with and without catalyst, respectively. The rate constants are reproducible within ±3%. Conditions: pH 7.6, 0.08 M Tris buffer, μ=0.08, 25 °C, 3% (v/v) CH_3CN-H_2O, [substrate]=(1-2)x10^{-5} M, [Z-L-Phe-L-His-L-Leu]=2x10^{-4} M, [CBzAC]=1x10^{-3} M.

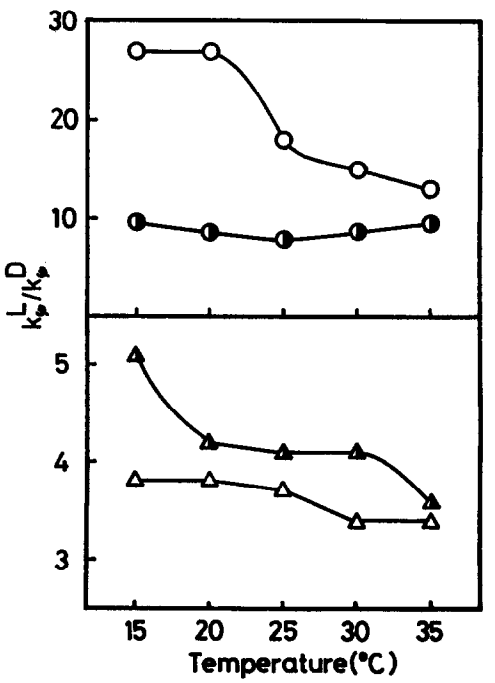


Figure 1. Temperature dependence of enantioselectivity (k_ψ^L/k_ψ^D) for the hydrolysis of o- and p-nitrophenylalaninates catalyzed by Z-L-Phe-L-His-L-Leu in the CTAB micellar systems. Conditions: pH 7.6, 0.2 M Tris buffer, μ=0.2, 3% (v/v) CH_3CN-H_2O.
○: C_{12}-Phe-PNP, ◐: C_{12}-Phe-ONP,
△: Z-Phe-PNP, ▲: Z-Phe-ONP

It is concluded that the remarkable substituent effects on the micellar enantioselective hydrolysis could be attributed to the framework in enantiomeric substrates and would not depend on the temperature or the species of micelles. Thus, we can presume that the orientation between the long-chained p-isomeric substrates (C_{12}-D(L)-Phe-PNP) and the active tripeptide (Z-L-Phe-L-His-L-Leu) might be the most favorable for the discrimination of the L-enantiomer from the D-enantiomer, though the rate-enhancement was most attractive for the o-isomeric substrates (C_{12}-D(L)-Phe-ONP).

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(9) Satisfactory results of elemental analyses were obtained for C_{12}-D-Phe-ONP $[\alpha]_D^{30}$ +29.12° (c2, $CHCl_3$), C_{12}-L-Phe-ONP $[\alpha]_D^{30}$ -29.90° (c2, $CHCl_3$), C_{12}-D-Phe-MNP $[\alpha]_D^{24}$ +5.95° (c2, $CHCl_3$), C_{12}-L-Phe-MNP $[\alpha]_D^{24}$ -5.45° (c2, $CHCl_3$), Z-D(L)-Phe-ONP, and Z-D(L)-Phe-MNP. See reference 8 for description of the elemental analyses obtained for C_{12}-D(L)-Phe-PNP and Z-D(L)-Phe-PNP.

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