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Extraordinary Diastereoselectivity Coupled to Altered Structure of Dipeptide Esters

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The diastereoselectivity for the hydrolysis of Z-D(L)-Phe-L-Phe p-methoxycarbonylphenyl ester was maximized ($k_s^{DL}/k_s^{LL} = 34$) at the optimum temperature (30 ℃). This could be attributed to the conformational change in the DL isomer, which was supported by the circular dichroism measurements.

Stereoselective cleavages of N-protected amino acid and peptide p-nitrophenyl esters in various surfactant aggregates systems have been used as models to prove the origins of stereoselectivity in the proteolytic enzymes.[1-4] Most recently, a remarkably high diastereoselectivity was observed for the deacylation of dipeptide esters catalyzed by unmodified cyclodextrins (CyD).[5] The CyD-dipeptide substrate complex could be referred to one of the typical examples of the so-called "supramolecular assemblies" which demonstrated novel functions only after association of individual molecular components. However, there have been few reports concerning the diastereoselective hydrolysis of dipeptide esters without a catalyst and the stereoselectivity observed was not so attractive.[1-3]

In this study, we report on the remarkable temperature effect on the diastereoselective hydrolysis of dipeptide esters related to the conformational change on the basis of circular dichroism (CD) measurements.

For exploring the correlation between the diastereoselective specificity and the conformation of dipeptide esters, we examined the hydrolytic cleavages of Z-D(L)-Phe-L-Phe p-methoxycarbonylphenyl ester (Z-D(L)-Phe-L-Phe-PMCP: 5×10^{-6} mol dm^{-3}) having the bulky and hydrophobic Phe-Phe unit[6] in pH 9.5, 0.02 M carbonate buffer over the temperature ranges of 22.5-40.0 ℃ as shown in Fig. 1. The diastereomeric substrates were synthesized by the mixed anhydride coupling of Z-phenylalanine and phenylalanine p-methoxycarbonylphenyl ester.[5] These isomers were fully characterized. The first-order rate constants (k_s) were evaluated by monitoring the release of p-methoxycarnonylphenolate ion at 297 nm. The temperature dependence of diastereoselectivity is shown in Fig. 2. The noteworthy aspects are as follows: (a) the rate enhancement of Z-D-Phe-L-Phe-PMCP sharply increased at 30 ℃. On the other hand, such an enhancement was not observed for the hydrolysis of Z-L-Phe-L-Phe-PMCP around the same temperature. As a result, (b) the diastereoselectivity was maximized at 30 ℃ (DL/LL=34), though small diastereoselectivities (DL/LL =1.1-2.5) were observed below 27.5 ℃.

It is already known that the specific CD spectra at 235 nm in the diastereomeric substrates may occur through the intramolecular interaction between L(D)-Phe and L-Phe residues.[4, 7] The authors examined the temperature dependence of the CD intensity at 235 nm ($[\theta]_{235}$) as shown in Fig. 1. Interestingly, the CD intensity of Z-D-Phe-L-Phe-PMCP changes sharply at 30 ℃ and this is in good harmony with the large rate enhancement for the hydrolysis of Z-D-Phe-L-Phe-PMCP and the maximized diastereoselectivity (DL/LL = 34) at

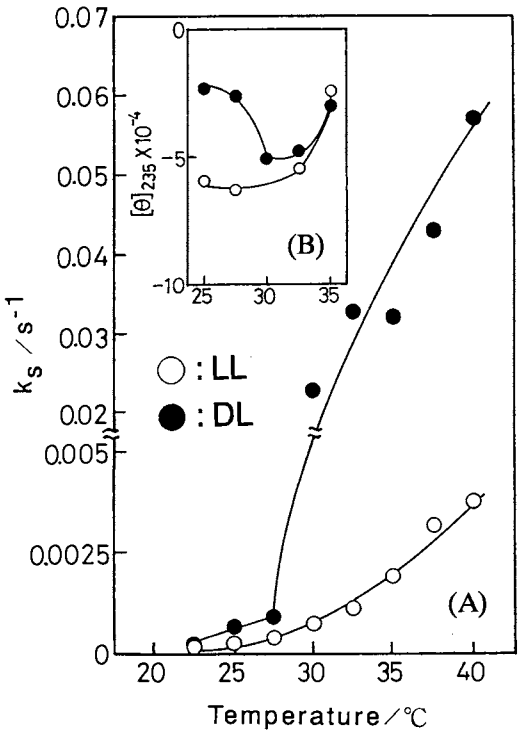
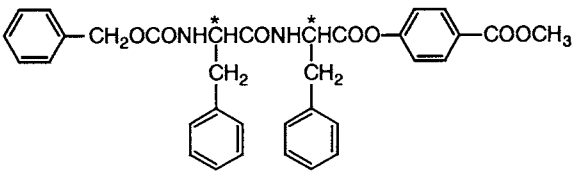


Fig. 1. Temperature dependence of k_s for the hydrolysis of Z-D(L)-Phe-L-Phe-PMCP (A) and CD intensity of substrates (B) in the buffer solution.



Z-D(L)-Phe-L-Phe-PMCP

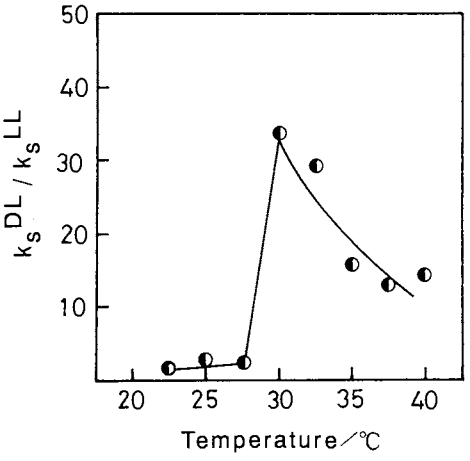


Fig. 2. Temperature dependence of k_s^{DL}/k_s^{LL} for the hydrolysis of Z-D(L)-Phe-L-Phe-PMCP in the buffer solution.

the same temperature. This result suggests that the conformation of Z-D-Phe-L-Phe-PMCP should be changed around 30 ℃ and the fluctuation between stable and unstable states of the diastereomeric substrates may be very important for the production of the largest diastereoselectivity.

In conclusion, the most striking feature of this study was that an extraordinary large DL diastereoselectivity was produced due to the abrupt conformational change in the DL-isomer and this may be attributed to the more facile OH^- attack toward the carbonyl of DL-isomer than that which occurs in the case of LL-isomer.

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References

1) R. A. Moss, Y-S. Lee, and K. W. Alwis, *J. Am. Chem. Soc.*, **102**, 6646 (1980).
2) R. Ueoka, Y. Matsumoto, T. Yoshino, T. Hirose, R. A. Moss, K. Y. Kim, and S. Swarup, *Tetrahedron Lett.*, **1986**, 1183.
3) R. A. Moss, T. F. Hendrickson, R. Ueoka, K. Y. Kim, and P. K. Weiner, *J. Am. Chem. Soc.*, **109**, 4363 (1987).
4) R. Ueoka, Y. Matsumoto, R. A. Moss, S. Swarup, A.Sugii, K. Harada, J. Kikuchi, and Y. Murakami, *J. Am. Chem. Soc.*, **110**, 1588 (1988).
5) R. Ueoka, Y. Matsumoto, K. Harada, H. Akahoshi, Y. Ihara, and Y. Kato, *J. Am. Chem. Soc.*, **114**, 8339 (1992).
6) The altered structure of these diastereomeric substrates was predicted on the basis of the CPK models.
7) N. Harada and K. Nakanishi, Circular Dichroic Spectroscopy Excition Coupling in Organic and Bioorganic Chemistry, University Science Books, Mill Valey, CA, 1983.

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