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Remarkable Steric Control for the Enantioselective Cleavage of Amino Acid Esters

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The perfect enantioselective catalysis was observed for the hydrolytic cleavage of p-nitrophenyl N-dodecanoyl-D(L)-phenylalaninates by N-benzyloxycarbonyl-L-phenylalanyl-L-histidyl-L-leucine in specific co-aggregates composed of a cationic double-chain surfactant and a cationic, an anionic, or a nonionic single-chain surfactant.

The stereoselective cleavages of p-nitrophenyl esters derived from N-protected amino acids1) and oligopeptides2) in various surfactant aggregates have been examined to probe the physico-chemical origins of stereoselectivity demonstrated by proteolytic enzymes. From the viewpoint of enantioselectivity, reaction sites porvided by bilayer membranes are subjected to modification by added cholesterol3,4) and micellar surfactants3,5) and by temperature regulation6) as well as by the amino acid sequence of peptide catalysts.5) Very recently, a remarkable correlation was observed between enantioselectivity or diastereoselectivity and the apparent mean hydrodynamic diameter of co-aggregates formed with a cationic double-chain surfactant and a cationic single-chain surfactant, and fairly high stereoselectivity was attained by adjusting the composition of co-aggregates.7,8)

We have clarified previously the microenvironmental effect of cationic co-aggregates formed with a double-chain surfactant, ditetradecyldimethylammonium bromide ($2C_{14}Br$), and a single-chain one, hexadecyltrimethylammonium bromide (CTABr), on the enantioselective cleavage of p-nitrophenyl N-dodecanoyl-D(L)-phenylalaninates [$D(L)-S_{12}$] as catalysed by N-benzyloxycarbonyl-L-phenylalanyl-L-histidyl-L-leucine (Z-PheHisLeu). The enantioselectivity ($e_{L/D} = k^{L}_{a,obsd}/k^{D}_{a,obsd}$)9) reached a maximum value ($e_{L/D}$ = 71) in large rod-shaped aggregates formed at the composition of 33 mol% $2C_{14}Br$/67 mol% CTABr in 0.08 M (1 M=1 mol dm^{-3}) Tris buffer (μ = 0.08),5,7) and a smaller but still large enantioselectivity ($e_{L/D}$ = 52) was observed in large vesicular aggregates formed at the composition of 59 mol% $2C_{14}Br$/41 mol% CTABr under the same medium conditions. However, the $e_{L/D}$ value was dramatically raised to 1000 by

Table 1. Rate Constants ($k_{a,obsd}/M^{-1}s^{-1}$) for the Cleavage of L- and D-S_{12} in Co-aggregates Composed of $2C_{14}Br$ and CTABr as Catalysed by Z-PheHisLeu[a)]

$\frac{[CTABr]}{[CTABr]+[2C_{14}Br]}$ (mol%)	$k^{L}_{a,obsd}$	$k^{D}_{a,obsd}$
0	1300	48
23	1900	84
41	1000	1
50	1100	0
67	840	0
75	670	12
100[b)]	350	56

a) 25 °C, pH 7.6, 0.02 M Tris buffer(0.02 M KCl), 3% (v/v) CH_3CN-H_2O, [sub]=$1x10^{-5}$ M, [cat]=$5x10^{-5}$ M, [$2C_{14}Br$]=$1x10^{-3}$ M. The rate constants were reproducible within an accuracy of ±3%.

b) [CTABr]=$3x10^{-3}$ M.

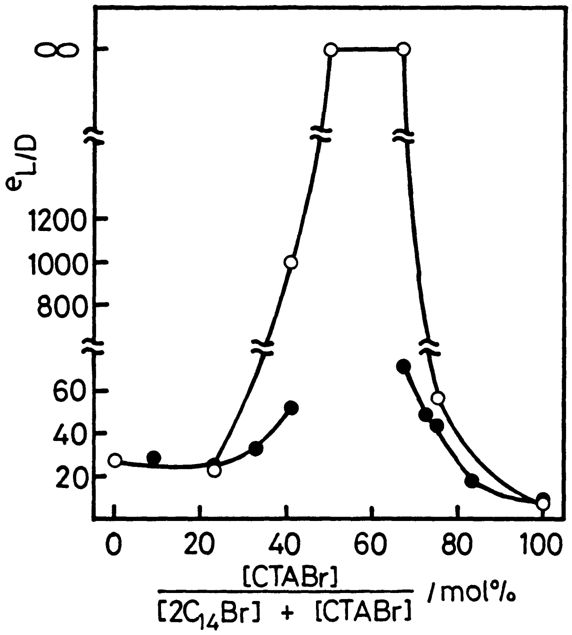
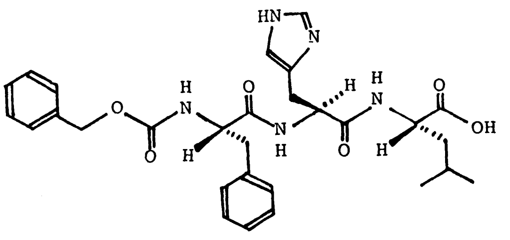
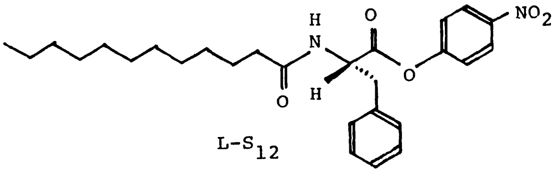


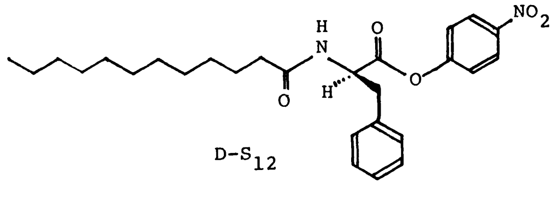
Fig. 1. Enantioselectivity vs. co-aggregate composition: ○, μ = 0.02; ●, μ = 0.08.



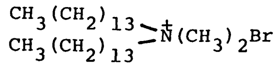
Z-PheHisLeu



L-S_{12}



D-S_{12}

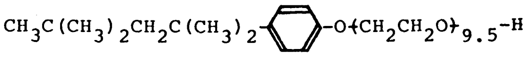


$$\begin{matrix} CH_3(CH_2)_{13} \\ CH_3(CH_2)_{13} \end{matrix} \overset{+}{N}(CH_3)_2Br^-$$

$2C_{14}Br$

$CH_3(CH_2)_{15}\overset{+}{N}(CH_3)_3Br^-$ CTABr

$CH_3(CH_2)_{11}SO_4^-Na^+$ SDS



Triton X-100

decreasing the ionic strength from 0.08 to 0.02 at pH 7.6 and 25 °C with the latter surfactant composition.[10)] Now, our work is directed toward attainment of perfectly enantioselective catalysis in various co-aggregate systems.

In the present work, we firstly carried out systematic experiments on the Z-PheHisLeu-catalysed cleavage of D- and L-S_{12} by varying the composition of $2C_{14}Br$

Table 2. Rate Constants ($k_{a,obsd}$/$M^{-1}s^{-1}$) for the Cleavage of L- and D-S_{12} in Co-aggregates Composed of $2C_{14}Br$ and SDS, or Triton X-100 as Catalysed by Z-PheHisLeu[a)]

$\frac{[SDS]}{[SDS]+[2C_{14}Br]}$ (mol%)	$k^L_{a,obsd}$	$k^D_{a,obsd}$	$\frac{[Triton\ X\text{-}100]}{[Triton\ X\text{-}100]+[2C_{14}Br]}$ (mol%)	$k^L_{a,obsd}$	$k^D_{a,obsd}$
0	1300	48	0	1300	48
7	1900	0	20	1300	17
15	1600	0	30	1000	6.4
20	1400	0	40	840	0
25	940	6.2	50	720	0
90	2.6	0.6	60	630	6.8
100[b)]	2.7	1.5	80	370	9.3
			100[c)]	19	2.2

a) 25 °C, pH 7.6, 0.02 M Tris buffer (0.02 M KCl), 3% (v/v) CH_3CN-H_2O, [sub]= 1×10^{-5} M, [cat]=5×10^{-5} M, $[2C_{14}Br]=1\times10^{-3}$ M. The rate constants were reproducible within an accuracy of ±2%.

b) [SDS]=1×10^{-2} M.

c) [Triton X-100]=3×10^{-2} M.

and CTABr in 0.02 M Tris buffer (μ = 0.02 with KCl) at pH 7.6 and 25 °C. Sonication of co-aggregates was performed before each kinetic run with a Bransonic 12 apparatus for 1 h at 80 W and 50 °C. The kinetic results were summarized in Table 1. Remarkably enantioselective catalysis was observed at compositions of 50 mol% $2C_{14}Br$/50 mol% CTABr and 33 mol% $2C_{14}Br$/67 mol% CTABr, although the general correlation of enantioselectivity with the surfactant composition is common to both reactions carried out at different ionic strength, 0.02 and 0.08[7)] (Fig. 1).

We further examined the enantioselective cleavage of D- and L-S_{12} by Z-PheHis-Leu in the co-aggregates composed of $2C_{14}Br$ and an anionic micellar surfactant, sodium dodecyl sulfate (SDS) and those of $2C_{14}Br$ and a nonionic micellar surfactant, α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxypolyoxyethylene (Triton X-100), as shown in Table 2 and Fig. 2. The noteworthy aspects with respect to the $2C_{14}Br$/SDS co-aggregate systems are as follows: (i) the perfect enantioselective catalysis was observed in the co-aggregate systems composed of 7-20 mol% SDS. In particular,

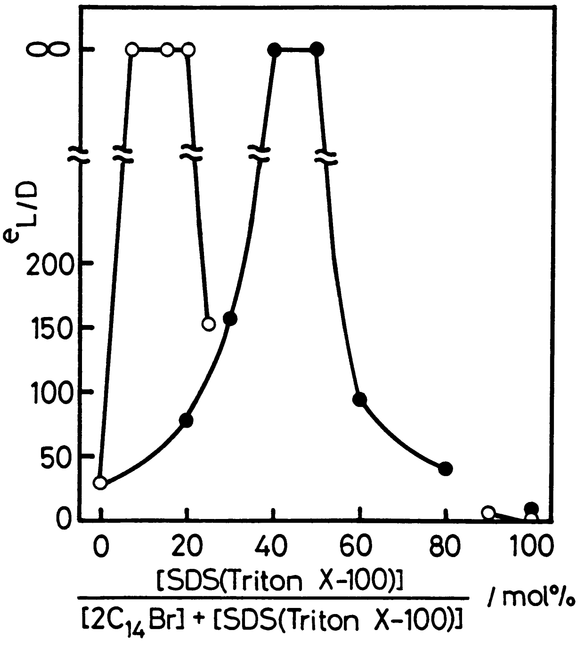


Fig. 2. Enantioselectivity vs. co-aggregate composition:
○, $2C_{14}Br$ and SDS;
●, $2C_{14}Br$ and Triton X-100.

the highest rate enhancement ($k^{L}_{a,obsd}$ = 1900 $M^{-1}s^{-1}$) for the cleavage of L-S_{12} and no cleavage of D-S_{12} were observed in the co-aggregate system of 93 mol% $2C_{14}Br$/7 mol% SDS; (ii) both catalytic activity and enantioselectivity were much reduced in the anionic micellar systems (100 mol% SDS and 10 mol% $2C_{14}Br$/90 mol% SDS); (iii) clear solutions were not obtained in a wide composition range from 26 to 89 mol% with respect to SDS. As for the $2C_{14}Br$/Triton X-100 co-aggregate system, the following facts need to be pointed out: (i) clear solutions were obtained in a wide composition range except for a limited range, 81-99 mol% with respect to Triton X-100; (ii) the exclusively preferential cleavage of the L-isomer, $k^{L}_{a,obsd}$ = 840 and 720 $M^{-1}s^{-1}$, without detectable cleavage of the D-isomer was observed in the co-aggregate compositions of 40 and 50 mol% with respect to Triton X-100. It is of interest that the correlation between enantioselectivity and composition of co-aggregates in the $2C_{14}Br$/Triton X-100 system (Fig. 2(●)) was very similar to that in the $2C_{14}Br$/CTABr system (Fig. 1(○)) and was fairly different from that in the $2C_{14}Br$/SDS system (Fig. 2(○)) under the same reaction conditions of pH 7.6 (0.02 M Tris-KCl buffer) and 25 °C.

In conclusion, it needs to be noted that the perfect enantioselective catalysis by the tripeptide catalyst, Z-PheHisLeu, was observed for the hydrolytic cleavage of the long-chained enantiomers, D- and L-S_{12}, in the specific co-aggregate systems composed of $2C_{14}Br$ (cationic vesicular surfactant) and one of the micellar surfactants; cationic CTABr, anionic SDS, and nonionic Triton X-100. The perfectly steric controlled catalysis in this study is one of beautiful enzyme models from the point of view of the optimum regulation of hydrophobic reaction fields in order to discriminate the hydrophobic L-form substrate from the D-isomer.

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