ENANTIOSELECTIVE AND DIASTEREOSELECTIVE CLEAVAGE OF AMINO ACID
ESTERS IN COAGGREGATES OF CONTROLLED SIZE

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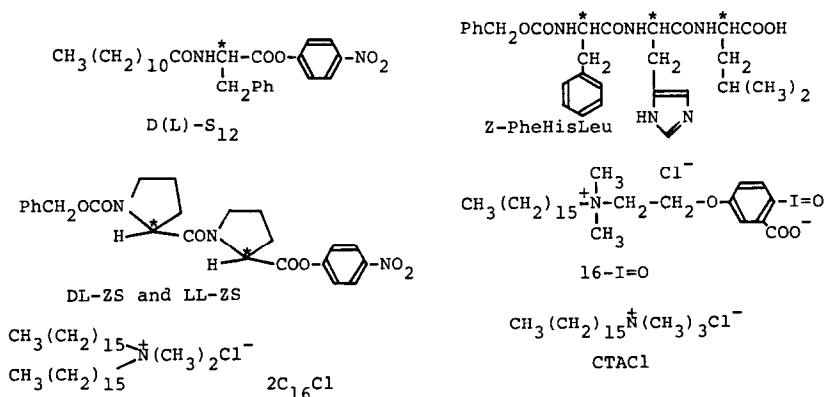Institute of Technology, Ikeda, Kumamoto 860, Japan

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Summary: The enantioselectivity of cleavage of $\underline{N}$-dodecanoyl-D(L)-phenylalaninates with
$\overline{LLL}$-$\underline{Z}$-PheHisLeu, and the diastereoselectivity of cleavage of $\underline{Z}$-D(L)-Pro-L-Pro-PNP by a
functional iodosobenzoate surfactant, were well correlated by the apparent hydrodynamic
diameters of coaggregates composed of double and single chain surfactants.

Stereoselective cleavages of $\underline{N}$-protected amino acid and peptide $\underline{p}$-nitrophenyl esters in
various surfactant aggregate systems have been used as models to probe the origins of
stereoselectivity in the proteolytic enzymes. Studies of enantioselectivity have emphasized
the roles of hydrophobic interaction between catalyst and substrate,[1] the structure of the
aggregates,[2-4] the effect of temperature,[5] and the amino acid sequence of the peptide
catalyst.[4] Studies of diastereoselectivity in the functional micellar cleavages of di-[6] and
tripeptide[7] substrates have generated molecular level models for substrate-surfactant
interaction and pointed to the importance of chirality-specific supramolecular micellar
effects.[8]

Most recently, an excellent correlation was observed between the enantioselectivity of
the hydrolytic cleavage of the long chain substrates [D(L)S_{12}] by the $\underline{LLL}$-tripeptide
$\underline{Z}$-PheHisLeu and the apparent mean hydrodynamic diameter (d_{hy}) of coaggregates formed from the
double chain surfactant ditetradecyldimethylammonium bromide ($2C_{14}Br$) and the single chain
surfactant cetyltrimethylammonium bromide (CTABr).[9] It was suggested that "correlated,
extended molecular alignment within coaggregates on the verge of phase separation may impose
ordered relative arrangements" on solubilized catalyst and substrate molecules, thus
engendering amplified stereoselectivities.[9] Now we extend the correlation between
stereoselectivity and coaggregate diameter to a different double/single chain surfactant
system. More importantly, we demonstrate that both amino acid ester enantioselectivity and

$CH_3(CH_2)_{10}CONH\overset{*}{C}H\text{-}COO\text{-}\langle\bigcirc\rangle\text{-}NO_2$
  $|$
  CH_2Ph

$D(L)\text{-}S_{12}$

$PhCH_2OCONH\overset{*}{C}HCONH\overset{*}{C}HCONH\overset{*}{C}HCOOH$
  $|$ $|$ $|$
  CH_2 CH_2 CH_2
  $|$ $|$ $|$
  $\langle\bigcirc\rangle$ $CH(CH_3)_2$

Z-PheHisLeu

$PhCH_2OCON$

H—C—CON

H—C—COO-$\langle\bigcirc\rangle$-NO_2

DL-ZS and LL-ZS

$CH_3(CH_2)_{15}\overset{+}{N}(CH_3)_2Cl^-$
$CH_3(CH_2)_{15}$ $2C_{16}Cl$

            CH_3 Cl^-
             $|$
$CH_3(CH_2)_{15}\overset{+}{N}\text{-}CH_2\text{-}CH_2\text{-}O\text{-}\langle\bigcirc\rangle\text{-}I\text{=}O$
             $|$ COO^-
            CH_3

16-I=O

$CH_3(CH_2)_{15}\overset{+}{N}(CH_3)_3Cl^-$

CTACl

dipeptide ester diastereoselectivity respond similarly to coaggregate size and composition.

We examined the cleavages of the enantiomeric substrates [D(L)-S$_{12}$] and the diastereomeric Pro-Pro substrates [DL(LL)-ZS][10] catalyzed, respectively, by Z-PheHisLeu or 16-I=O[11] in coaggregates composed of dihexadecyldimethylammonium chloride (2C$_{16}$Cl) and hexadecyltrimethylammonium chloride (CTACl) at 25°C. The kinetic results are summarized in Table I. In Figure 1, we plot the reaction stereoselectivity (either enantioselectivity, $\underline{k}_\psi^L/\underline{k}_\psi^D$, or diastereoselectivity, $\underline{k}_\psi^{LL}/\underline{k}_\psi^{DL}$) on the left-hand ordinate and the apparent mean hydrodynamic diameter (d_{hy}, Å) from dynamic light scattering (dls) measurements,[12] on the right-hand ordinate, both versus the coaggregate composition on the abscissa.

In the previously studied 2C$_{14}$Br/CTABr coaggregates, the enantioselectivity of D(L)-S$_{12}$ cleavage by Z-PheHisLeu peaked in large, rod-shaped micelles formed at a composition of 33% 2C$_{14}$Br/67% CTABr.[9] Here, in 2C$_{16}$Cl/CTACl, enantioselectivity is maximized in vesicular coaggregates[13] of composition 77% 2C$_{16}$Cl/23% CTACl. Most remarkably, the diastereoselectivity of the LL(DL)-ZS/16-I=O reaction shows an identical dependence on apparent d_{hy}, and peaks at the same coaggregate composition. The intraaggregate effects that optimize enantioselectivity at 77% 2C$_{16}$Cl/23% CTACl in the first reaction similarly elicit optimal (albeit smaller) diastereoselectivity in the second reaction!

In the present case, maximal steroselectivity does not appear adjacent to a patent phase boundary of the coaggregate system as it did with 2C$_{14}$Br/CTABr.[9] However, dls indicates very large (8500-10,000 Å), unstable ("growing") micellar aggregates in the 25-40 mol-% 2C$_{16}$Cl region (i.e., to the left of the maximum in Figure 1), so that the maxima in d_{hy} and stereoselectivity do lie reasonably close to coaggregate compositions in which correlated and extended molecular ordering obtains.

In conclusion, both the enantioselectivity and diastereoselectivity of reactions occurring in micelles or vesicles can be augmented in identical coaggregates of double and single chain surfactants, and the magnitudes of the expressed stereoselectivities correlate with the hydrodynamic diameters of the coaggregates.

Table I. Enantioselectivity ($\underline{k}_\psi{}^L/\underline{k}_\psi{}^D$) and Diastereoselectivity ($\underline{k}_\psi{}^{LL}/\underline{k}_\psi{}^{DL}$) in the Coaggregate Systems Composed of (2C$_{16}$Cl) and (CTACl) Surfactants[a]

$\dfrac{[2C_{16}Cl]}{[2C_{16}Cl] + [CTACl]}$ (mol%)	$\underline{k}_\psi$ (s^{-1}) for enantiomers[b]		$\underline{k}_\psi{}^L/\underline{k}_\psi{}^D$	$\underline{k}_\psi$ (s^{-1}) for diastereomers[c]		$\underline{k}_\psi{}^{LL}/\underline{k}_\psi{}^{DL}$
	L-S$_{12}$	D-S$_{12}$		LL-ZS	DL-ZS	
0	0.0202	0.00255	7.9	0.810	0.107	7.6
33	0.0580	0.00410	14	0.697	0.0807	8.7
50	0.0869	0.00483	18	1.05	0.113	9.3
64	0.146	0.00644	23	1.23	0.119	10
77	0.196	0.00603	33	1.07	0.0915	12
90	0.120	0.00433	28	–	–	–
100[d]	0.103	0.00400	26	0.733	0.0750	9.8

(a) The $\underline{k}_\psi$ value was evaluated from [$\underline{k}_t$ - $\underline{k}_s$], where $\underline{k}_t$ and $\underline{k}_s$ denote the first-order rate constants with and without catalyst, respectively. The rate constants are reproducible within ± 2.8%. [2C$_{16}$Cl]=1x10^{-3} M. (b) Conditions: pH 7.6, 0.02 M Tris buffer, μ=0.02, 25°C, 3% (v/v) CH$_3$CN-H$_2$O, [substrate]=1x10^{-5} M, [Z-PheHisLeu]=1x10^{-4} M. Sonication was carried out with a Bransonic 12 unit at 80 W, 50°C, 1 h. (c) Conditions: pH 8.2, 0.02 M Tris buffer, μ=0.02 M, 25°C, 0.1% v/v dioxane-H$_2$O, [substrate]=2x10^{-5} M, [16-I=O]=2x10^{-4} M. Sonication was carried out with a Braun-sonic 1510 unit at 80 W, 55°C, 30 min. (d) [CTACl]=2x10^{-3} M.
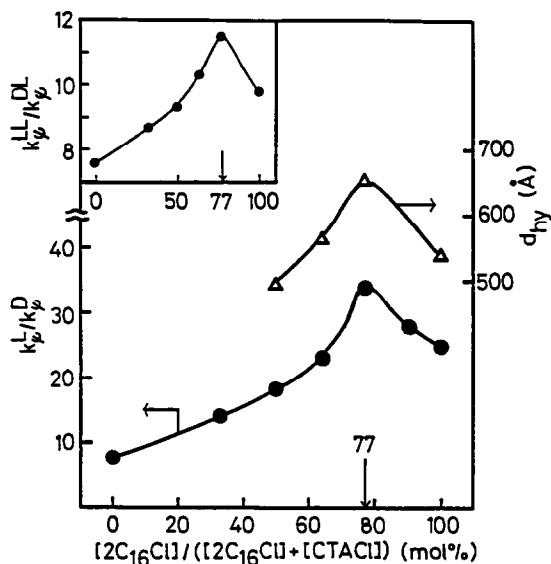

Figure 1. Enantioselectivity ($\underline{k}_\psi{}^L/\underline{k}_\psi{}^D$) or diastereoselectivity ($\underline{k}_\psi{}^{LL}/\underline{k}_\psi{}^{DL}$) on the left-hand ordinate, and d$_{hy}$, on the right-hand ordinate, versus coaggregate composition on the abscissa.

References and Notes

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(10) The Pro-Pro substrates were prepared analogously to the Z-Trp-Pro-PNP diastereomers described in ref. 8. Satisfactory C,H,N microanalyses were obtained for LL-ZS $[\alpha]_D^{23}$ -126.9° (c = 1, MeOH) and for DL-ZS, $[\alpha]_D^{23}$ -35.7° (c = 1, MeOH).

(11) The iodosobenzoate actually exists in its catalytically active, heterocyclic, valence tautomeric 1-oxido-1,2-benziodoxolin-3-one form; cf., R.A. Moss, K.Y. Kim, and S. Swarup, J. Am. Chem. Soc., in press; R.A. Moss, K.W. Alwis, and J-S. Shin, ibid., 106, 2651 (1984).

(12) See reference 8 for a description of the apparatus and technique. Aggregates were assumed to be spherical, and the reproducibility of d_{hy} was better than ± 7.6% in duplicate preparations.

(13) Conductivity measurements gave T_c = 20.0-21.7°C for $2C_{16}Cl$/CTACl coaggregates of 50-90 mol-% $2C_{16}Cl$, suggesting continuity of the vesicular form for these coaggregates (T_c = 21.0°C for 100% vesicular $2C_{16}Cl$). It was separately demonstrated that the conductivity method gave values of T_c for vesicular dialkyldimethylammonium surfactants that were in good agreement with those determined by differential scanning calorimetry; cf., reference 3.

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