Tetrahedron Letters,Vol.24,No.26,pp 2615-2618,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A CRITICAL CONCENTRATION FOR MICELLAR DIASTEREOSELECTIVITY

Robert A. Moss* and Yuan-Ching P. Chiang

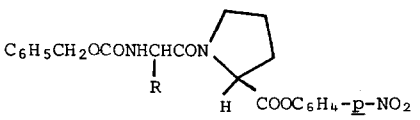
Department of Chemistry, Rutgers, The State University of New Jersey,
New Brunswick, New Jersey 08903

Summary. The onset of diastereoselectivity in the esterolyses of LL and DL-Z-Trp-Pro-PNP by a thiocholine surfactant is associated with a "critical" surfactant concentration which appears to lie above the apparent kinetic critical micelle concentration.

Stereoselective micellar or vesicular reagents continue to attract attention.[1,2] Efforts have mostly been devoted to enantioselective reactions between chiral nucleophiles and chiral substrates, particularly activated amino acid esters. Although impressive enantioselectivities have sometimes been observed,[2c] with few exceptions,[2d] little is known about their molecular-level origins.

We studied the stereoselective micellar cleavage of diastereomeric dipeptide[3a-e] and tripeptide[3f] esters by functional surfactants such as 16-SH, 1a. For example, at pH 8, Z-(L)-Trp-(L)-Pro-PNP, 2, was cleaved 21,000 times more rapidly by 4 x 10^{-3} M micellar 16-SH than by OH^- in micellar cetyltrimethylammonium (CTA) chloride, and the kinetic LL/DL substrate diastereoselectivity was 5.0 with 16-SH (vs. 0.28 in CTACl).[3c,d,4] LL diastereoselectivities were observed with

$R\overset{+}{N}(CH_3)_2CH_2CH_2SH$, Cl^-



1a, R = n-$C_{16}H_{33}$ (16-SH)
1b, R = n-$C_{12}H_{25}$ (12-SH)
1c, R = CH_3 (1-SH, counterion = Br^-)

2, R = CH_2-(3-indolyl) (Z-Trp-Pro-PNP)

4 other sets of Z-AA-(L)-Pro-PNP dipeptides,[3c] and, based on molecular model studies, a mechanistic rationale was offered.[3a,c]

Although our rationale satisfactorily accounted for the observations, and could be successfully extended to tripeptide substrates,[3f] it was based on specific, favorable 1:1 hydrophobic interactions of the surfactant's hydrocarbon chain with "clefts" defined by the Pro, PNP, and R moieties of the LL substrates in extended peptide conformations.[3a,c] Did micellization of the surfactant play any role in the diastereoselectivity? Here, we not only answer this question in the affirmative, but show that the onset of diastereoselectivity is associated with a critical surfactant concentration which appears to lie above the critical micelle concentration (cmc).

Thiol surfactant 12-SH (1b) was prepared by a reaction sequence identical to that employed in the synthesis of 16-SH.[5] The thioacetate precursor of 12-SH was characterized by nmr spec-

troscopy and elemental analysis, whereas 12-SH itself (mp 131-133° from CH_2Cl_2/Et_2O) was characterized by nmr spectroscopy and Ellman's assay (93% free SH). A standard rate constant/[surfactant] profile[5] was determined for the cleavage of p-nitrophenyl acetate (PNPA) using 12 concentrations of 12-SH between 0.677×10^{-3} and 6.80×10^{-3} M.[6] We observed an apparent cmc of ~1.1×10^{-3} M for 12-SH.

Next, we measured pseudo-first-order rate constants for the 12-SH cleavage of LL or DL-2[6] by stopped-flow spectroscopy, monitoring the release of p-nitrophenoxide ion at 400 nm. Least-squares values for k_ψ were determined in duplicate or triplicate (reproducibility, ±5%), and mean values appear in Figure 1 as a function of [12-SH]. Additionally, in Table I, are kinetic results at 3 surfactant concentrations (selected from the 8 concentrations of Figure 1), which permit comparisons of the rate constants and diastereoselectivities observed with micellar 12-SH or nonmicellar thiocholine bromide,[5] 1-SH (1c).

Together, the Figure and Table reveal three differing catalytic "regimes" for reactions of 12-SH with LL or DL-2: (a) Under Regime I ($2 \times 10^{-3} <$ [12-SH] $< 5 \times 10^{-3}$ M), esterolysis by 12-SH is strongly accelerated, relative to thiocholine (a factor of ~1800 at [SH] = 2.7×10^{-3} M), but no diastereoselectivity is observed. (b) Under Regime II (~$5 \times 10^{-3} <$ [12-SH] $<$ ~5.5×10^{-3} M), esterolytic rate enhancements increase (~5000 at [SH] = 4.55×10^{-3} M) and diastereoselectivity develops sharply over a very narrow range of surfactant concentrations. (c) Under Regime III (~5.5×10^{-3} M < [12-SH]), rate constant enhancements reach ~35,000, relative to 1-SH, and diastereoselectivity (k_ψ^{LL}/k_ψ^{DL}) appears to level off at ~5.7.

We believe that the rate constant enhancements observed under regime I are micellar. The kinetic cmc of 12-SH measured for cleavage of PNPA (~1.1×10^{-3} M) should be lowered upon solubilization of the more hydrophobic substrates LL or DL-2. Reactions of these substrates at [12-SH] $\geq 2 \times 10^{-3}$ M should be micellar. Accepting this, however, implies that the abrupt onset of diastereoselectivity at ~5×10^{-3} M 12-SH corresponds to a transition to a second kind of 12-SH micelle, one which is stereoselective for LL-2.[7]

Tentatively, we propose that the 12-SH micelles of regime I are small and loosely packed. They bind LL or DL-2 and induce significant esterolytic rate enhancements, but they are not stereoselective. At [12-SH] ~5×10^{-3} M, transition occurs to a more densely packed micelle, which selectively enforces the specific 12-SH/LL-2 interactions[3c] responsible for diastereoselectivity.[8] One might attribute the non-stereoselective rate enhancements of regime I to premicellar association of 12-SH and 2, in which case micellization would occur at ~5×10^{-3} M 12-SH. (Even under this interpretation, diastereoselectivity is clearly a micelle-induced phenomenon.) However, in view of the kinetic results with PNPA and Z-Ala-Pro-PNP,[8] we consider 5×10^{-3} M 12-SH too high a concentration to represent the cmc. Accordingly, we prefer the two-micelle model. Appropriate light scattering experiments are planned to further test this explanation.

Acknowledgments. We thank the donors of the Petroleum Research Fund (American Chemical Society) and the U.S. Army Research Office for financial support.

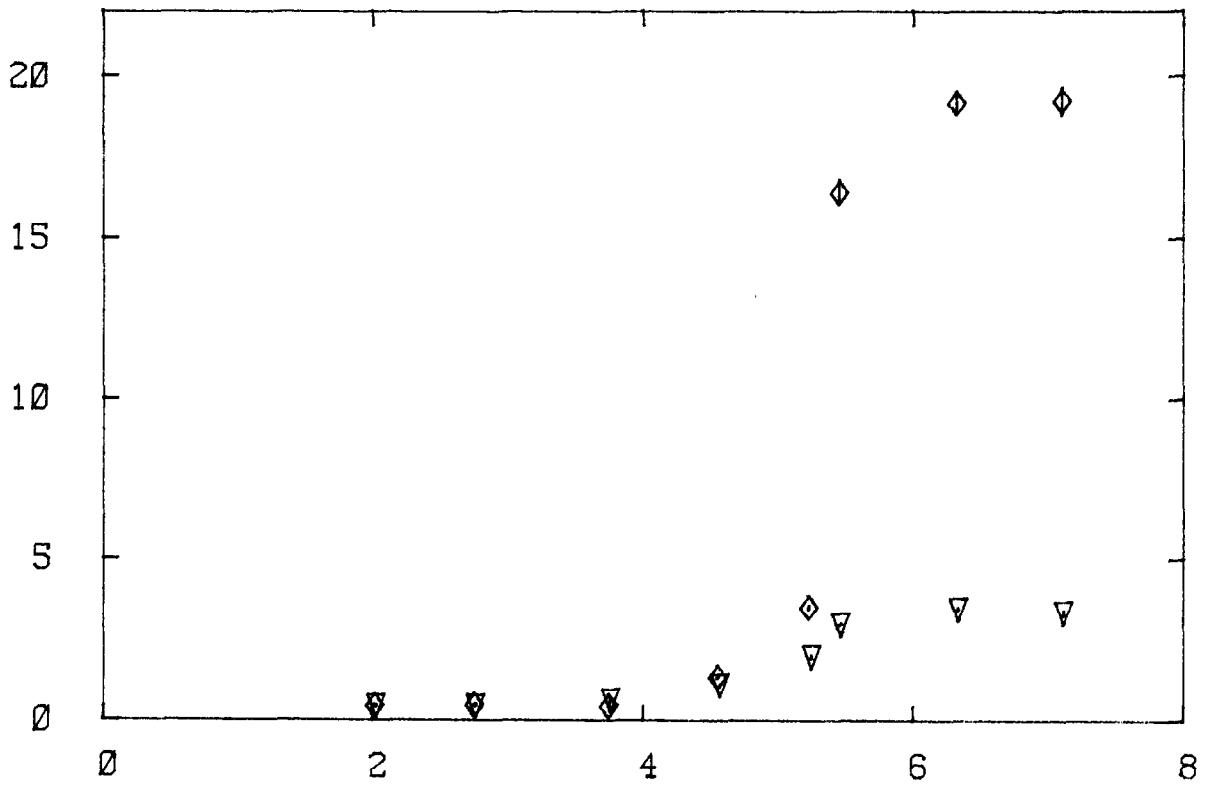


Figure 1. k_{ψ} (sec^{-1}), ordinate, vs. 10^3x[12-SH] (M), abscissa, for the cleavages of LL-2 (diamonds) or DL-2 (triangles) by 12-SH (1b).

Table I. Cleavage of LL or DL-2 by 12-SH or 1-SH (1b or 1c).[a]

10^3 [SH]	Reagent	k_{ψ}^{LL}, s^{-1}	k_{ψ}^{DL}, s^{-1}	$k_{\psi}^{LL}/k_{\psi}^{DL}$	$(k_{\psi}^{LL})_{12\text{-SH}}/(k_{\psi}^{LL})_{1\text{-SH}}$
7.10	12-SH	19.2	3.35	5.73	35,200
7.10	1-SH[b]	0.000546	0.000689	0.79	
4.55	12-SH	1.36	1.11	1.22	5,040
4.55	1-SH	0.000270	0.000361	0.75	
2.74	12-SH	0.487	0.472	1.03	1,840
2.74	1-SH	0.000265	0.000322	0.82	
0.00	buffer[c]	0.000093	0.00022	0.42	

[a]See ref. 6 for conditions. [b]Rate constants for 1-SH cleavages were determined on a Gilford Model 250 spectrophotometer. [c]Values of k_{ψ} are extrapolated to pure buffer from 3 runs in 20-40% dioxane/buffer; cf., ref. 2c.

References and Notes

(1) Review: J. H. Fendler, "Membrane Mimetic Chemistry," John Wiley & Sons, New York, 1982, pp. 309-322.

(2) (a) K. Ogino, I. Tomita, K. Machiya, and W. Tagaki, Chem. Lett., 1875 (1982); (b) Y. Ihara, Y. Kimura, M. Nango, and N. Kuroki, Makromol. Chem. Rapid Commun., 3, 521 (1982); (c) K. Ohkubo, N. Matsumoto, and H. Ohta, Chem. Commun., 739 (1982); (d) J. M. Brown, R. L. Elliott, C. G. Griggs, G. Helmchen, and G. Nill, Angew. Chem. Int. Ed., 20, 890 (1981); (e) Y. Murakami, A. Nakano, A. Yoshimatsu, and K. Fukuya, J. Am. Chem. Soc., 103, 728 (1981); (f) R. Ueoka, Y. Matsumoto, Y. Ninomiya, Y. Nakagawa, K. Inoue, and K. Ohkubo, Chem. Lett., 785 (1981); (g) Y. Ihara, N. Kunikiyo, T. Kunimasa, M. Nango, and N. Kuroki, ibid., 667 (1981); (h) S. Ono, H. Shoshenji, and K. Yamada, Tetrahedron Lett., 2391 (1981); (i) K. Ohkubo, K. Sugahara, H. Ohta, K. Tokuda, and R. Ueoka, Bull. Chem. Soc. Jpn., 54, 576 (1981).

(3) (a) R. A. Moss and Y-S. Lee in "Chemical Approaches to Understanding Enzyme Catalysis," B. S. Green, Y. Ashani, and D. Chipman, Ed., Elsevier, New York, 1982, pp. 200 ff; (b) R. A. Moss, Y-S. Lee, and T. J. Lukas, J. Am. Chem. Soc., 101, 2499 (1979); (c) R. A. Moss, Y-S. Lee, and K. W. Alwis, ibid., 102, 6646 (1980); (d) R. A. Moss and Y-S. Lee, Tetrahedron Lett., 22, 2353 (1981); (e) R. A. Moss, T. Taguchi, and G. O. Bizzigotti, ibid., 23, 1985 (1982); (f) R. A. Moss, Y-S. Lee, and K. W. Alwis, ibid., 22, 283 (1981).

(4) In micellar 16-SH, cleavage occurs by 16-S^- attack on the substrate's scissile carbonyl group,[3a-c] but in OH^-/CTACl or buffer alone, cleavage results mainly from (DL-stereoselective) intramolecular cyclization to a diketopiperazine.[3d]

(5) R. A. Moss, G. O. Bizzigotti, and C-W. Huang, J. Am. Chem. Soc., 102, 754 (1980).

(6) Conditions: 0.02 M phosphate buffer, pH 8, μ = 0.05 (KCl), 25°C, [substrate] = 2.0×10^{-5} M.

(7) Concentration dependent "transitions" between different CTABr micelles are known: J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems," Academic Press, New York, 1975, pp. 32-35.

(8) Rate constant/[12-SH] profiles with LL and DL-Z-Ala-Trp-Pro-PNP substrates reveal similar phenomena, although the concentration limits are shifted downward. From ~$0.22-0.75 \times 10^{-3}$ M 12-SH, LL/DL diastereoselectivity ranges from 1.1-1.4, and $k_{\psi}^{12\text{-SH}}/k_{\psi}^{1\text{-SH}}$ varies from 3-30. Between ~$0.75-1.5 \times 10^{-3}$ M 12-SH diastereoselectivity rapidly rises to ~3.1 and remains nearly constant out to ~20×10^{-3} M 12-SH, even as the overall rate constant enhancement rises from ~180 (at [12-SH] = 1.5×10^{-3} M) to ~600 (at [12-SH] = 17×10^{-3} M).

(Received in USA 3 March 1983)