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STEREOSELECTIVITY IN MICELLAR AND VESICULAR REACTIONS

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Summary. The diastereoselectivity of esterolytic cleavage of certain dipeptide and tripeptide activated esters is lower in thiol-functionalized vesicles than in comparable micelles. This is thought to be a mechanism-specific effect related to the greater molecular ordering in vesicular systems.

Efforts to realize stereoselective reactions in micelles have centered upon enantioselective reactions between chiral nucleophiles and chiral substrates (e.g., amino acid esters)[1] or diastereoselective reactions between nucleophilic surfactants and di or tripeptide esters.[2] The 12.2 enantioselectivity attending the cleavage of D or L-methoxycarbonylphenylalanine p-nitrophenyl (PNP) esters by N-(Z)-(L)-Leu-(L)-His in micellar cetyltrimethylammonium (CTA) bromide[3] and the 32-fold LL/DL stereoselectivity for micellar cleavage of Z-Val-Pro-PNP diastereomers by a functional thiocholine surfactant, relative to esterolysis in CTACl solution,[2c] represent the present records in these endeavors.

The current emphasis on reactions in surfactant vesicles,[4] coupled with the greater molecular order in vesicles, relative to micelles,[5] make inevitable the study of reactions of chiral substrates with chiral vesicular surfactants or chiral nucleophiles in "achiral" vesicles.[6,7] Indeed, enhanced enantioselectivities are reported for cleavage of Z-Phe-PNP substrates by vesicular (vs micellar) surfactant histidine derivatives,[7a] and for cleavage of (e.g.) N-hexadecanoyl-Phe-PNP substrates by (L)-α-N-hexadecanoyl-His in nonfunctional vesicles (vs. micelles).[7b] However, because the origins of micellar or vesicular stereoselectivity are mechanism-dependent, the enhanced molecular restriction obtainable in vesicular systems may not necessarily induce greater stereoselectivity. In fact, we now report that diastereoselectivities for the cleavages of certain dipeptide and tripeptide PNP esters are substantially lower in functional vesicular environments, relative to comparable micellar systems.

The surfactants employed included CTACl, dicetyldimethylammonium bromide, 1 (16_2),[8] monocetylthiol surfactant 2 (16-SH),[9] and dicetylthiol surfactant 3 (16_2SH).[10] Micellar solutions were prepared from CTACl or 16-SH, and vesicular solutions were generated from 16_2 or 16_2SH by

$(n\text{-}C_{16}H_{33})_2\overset{+}{N}Me_2$, Br^- — 1 (16_2)

$n\text{-}C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2SH$, Cl^- — 2 (16-SH)

$(n\text{-}C_{16}H_{33})_2\overset{+}{N}MeCH_2CH_2SH$, Cl^- — 3 (16_2SH)

injection methods.[10] Substrates included the diastereomeric dipeptide esters N-carbobenzyloxy (Z)-(D or L)-Trp-(L)-Pro-PNP (4), available from a previous study,[2c] and the four diastereomeric tripeptide esters, Z-(D or L)-Trp-(D or L)-Trp-(L)-Pro-PNP (5). The latter were prepared

by first coupling Z-(D or L)-Trp to (D or L)-Trp-OMe (i-BuO_2CCl, N-methylmorpholine, THF, 2h, 0°, 4h, 25°), followed by saponification (0.18 M NaOH in 2.2:2 2:1 dioxane-CH_3OH-H_2O, 25°, tlc monitoring), acidification (0.5 M aq. citric acid, 0°), extraction (EtOAc), and crystallization (Et_2O/pet. ether, recryst. from EtOAc-MeOH-pet. ether) to give the four Z-Trp-Trp(COOH) diastereomeric dipeptide acids, 6, which were characterized by nmr and elemental analysis.[11] Mixed anhydride coupling (reagents and conditions above, initial activation of 6 at -15°, 5 min.) then gave the four tripeptide esters, 5, as pale yellow solids after filtration, evaporation of THF, and trituration (3x, dry Et_2O) to remove p-nitrophenol. Further purification could not be effected without significant decomposition of the active esters.[12]

Kinetic data for pH 8 micellar cleavage of tripeptide esters 4 by surfactants CTACl and 16-SH appear in Table I, together with analogous results for the previously studied Z-Phe-Phe-Pro-PNP diastereomers.[2b] All four Trp substrates are cleaved at similar rates by OH^-/CTACl, suggesting diastereomerically indiscriminate lyate ion esterolysis With 16-SH, however, micellar thiolysis is evident in the large rate enhancements (~1500-4000). More importantly, the rate constant order DLL>LLL>LDL or DDL, previously observed with Z-Phe-Phe-Pro-PNP substrates,[2b] persists with the Z-Trp-Trp-Pro-PNP analogues, supporting our suggested rationale for 16-SH diastereoselectivity (*see refs. 2b, 2c, and below*).

Key data appear in Table II, which compares diastereoselectivities for cleavages of Z-Trp-Pro-PNP or Z-Trp-Trp-Pro-PNP under micellar or vesicular conditions. Di or tripeptide esterolyses in nonfunctional micellar CTACl or vesicular 16_2 are quite comparable (cases 2 vs. 1), indicating that altering the aggregate pseudophase does not significantly alter the intermolecular (lyate) esterolysis or (for the dipeptides) the dominant DL-selective intramolecular diketopiperazine-forming esterolysis.[2a] Significantly, however, functional vesicular 16_2SH is substantially less diastereoselective than micellar 16-SH in cleavages of either di or tripeptide ester substrates (cases 3 vs. 4). This is not a simple function of the structural difference between 16_2SH (double chain) and 16-SH (single chain), as is shown by cases 6 and 7, in which either surfactant, comicellized in CTACl, exhibits similar diastereoselectivity. The reduced diastereoselectivity is therefore a vesicular effect, quite specific to 16_2SH holovesicles; 16-SH in vesicular 16_2 shows comparable diastereoselectivity to micellar 16-SH (cases 5 and 4) and even 16_2SH covesicallized in 16_2 shows only partially reduced diastereoselectivity (cases 8 vs 4-7 vs. 3).

We suggested[2b,c] that the CH_2 chain of micellar 16-SH approximated well to "clefts" of LL dipeptides (or XLL tripeptides) defined by the substrates' Pro and PNP moieties, and by the R group of the amino acid adjacent to Pro, thereby optimally orienting the surfactant's $CH_2CH_2S^-$ group for ester thiolysis. Approximation was thought to be less productive for DL dipeptides (or XDL tripeptides), where substrate R groups projected away from the hydrophobic clefts, affording less than optimal thiolate/carbonyl interaction between 16-SH and substrate.

We now further suggest that the imposed molecular ordering[5] of methylene chains in holovesicular 16_2SH inhibits the flexibility necessary for optimal "single chain" approximation between surfactant and LL or XLL substrate molecules which is needed for effective diastereoselectivity. This problem is absent with the more flexible chains of micellar 16-SH or comicell-

Table I. Kinetics of the Micellar Cleavage of Tripeptide Esters[a]

Tripeptide	Surfactant	k_ψ (sec^{-1}) for tripeptide diastereomers			
		LLL	DLL	LDL	DDL
Z-Trp-Trp-Pro-PNP	CTACl[b]	0.0018	0.0024	0.0023	0.0023
	16-SH[c,d]	7.1	9.3	3.2	3.6
Z-Phe-Phe-Pro-PNP	CTACl[e]	0.0038	0.0047	0.013	0.0076
	16-SH[e]	9.0	13.4	5 3	4.3

[a]Conditions: [surfactant] = 4.0×10^{-3} M; [substrate] = 2.0×10^{-5} M; pH 8.0, 0 02 M phosphate buffer, μ = 0.05-0.055 (KCl), 25°C. [b]Kinetics for triplicate runs, reproducibility $\leq$4%. [c]~100% free SH. [d]Kinetics for duplicate or triplicate runs, reproducibility $\leq$1.8%. [e]Data from reference 2b.

Table II. Diastereoselectivities of Micellar and Vesicular Cleavage Reactions[a]

Case	Surfactant	M or V	$k_\psi^{DLL}s^{-1}$[b]	$k_\psi^{DDL}s^{-1}$[b]	$k_\psi^{DLL}/k_\psi^{DDL}$[b]	$k_\psi^{LL}s^{-1}$[c]	$k_\psi^{DL}s^{-1}$[c]	k_ψ^{LL}/k_ψ^{DL}[c]
1	16_2[d]	V	0.00397	0.00475	0.836	0.00239	0.00932	0.256
2	CTACl[d]	M	0.00387	0.00430	0.900	0.00247	0.00647	0.382
3	16_2SH[d]	V	6.00	5.71	1.05	10.4	6.69	1.55[e]
4	16-SH[d]	M	8.20	3.23	2.57	18.7	3.90	4.80
5	16_2/16-SH[f]	V	1.12	0.411	2 73	2.23	0.492	4 53
6	CTACl/16-SH[f]	M				2.53	0.506	5.00
7	CTACl/16_2SH[f]	M				1.79	0.402	4.45
8	16_2/16_2SH[f]	V				2.51	0.786	3.19

[a]M = micellar, V = vesicular conditions, reproducibilities of rate constants were generally <5% for duplicate runs [b]Substrate Z-Trp-Trp-Pro-PNP. [c]Substrate Z-Trp-Pro-PNP. [d]Conditions pH 8.05, 0.01 M tris buffer, μ = 0.01, 25°, [surfactant] = 5×10^{-3} M, [substrate] = 2×10^{-5} M. [e]This value reproduced twice by T.T. and G.O.B., each with duplicate runs, error <5%. [f][nonfunctional surfactant] = 5×10^{-3} M, [functional surfactant] = 5×10^{-4} M, [substrate] = 2×10^{-5} M, other conditions as in d.

ized 16_2SH The lower diastereoselectivity is not specific to a "gel" vesicular phase, however, LL/DL diastereoselectivity for case 8 of Table II is 3.8 (15°), 3.2 (25°), and 2.6 (35°), showing only a reasonable temperature effect with no obvious discontinuity which might be associated with a gel to liquid crystalline vesicular transition [13] The notion of imposed chain ordering as the dominant cause of mitigated vesicular diastereoselectivity is supported by an experiment in which 50 mol-% of added cholesterol (known to rigidify vesicular structure[14]) completely destroys the residual diastereoselectivity observed with $16_2/16_2$SH covesicles (case 8, i e., LL/DL decreases to 1.0 for the doped covesicles)

It is thus clear that enhanced molecular ordering in vesicular aggregates does not inevitably translate into enhanced reaction stereoselectivity. The origins of stereoselectivity are specific to a given reaction mechanism, and it is the interplay of molecular ordering and reaction mechanism which determines the effect of increased order on stereoselectivity.

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12. Esters 5 were unstable to various chromatographic or recrystallization conditions. A satisfactory analysis was obtained for DLL-5·H_2O, but not for its diastereomers Apparent chemical purity was demonstrated by tlc (silica gel 60 (EM), 20% MeOH/80% $CHCl_3$) and by nmr, LLL-5, mp 112-116°, $[\alpha]_D^{22}$-14.8° (c=0 98, dioxane), R_f=0.72; DLL-5 mp 106-109°, $[\alpha]_D^{21}$-6 6° (c=1.0, dioxane), R_f=0.68, LDL-5, mp 88-94°, $[\alpha]_D^{22}$-38.1° (c=0.95, dioxane), R_f=0.73, DDL-5, mp 72-78°, $[\alpha]_D^{20}$-25.4° (c=0.98, dioxane), R_f=0.76

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