$C_{14}H_{22}O$ 206.1671, found 206.1661.

(±)-$\Delta^{9(12)}$-Capnellene (12). This compound was prepared as described previously:[17a] IR ($CDCl_3$) 2950, 2930, 2860, 1650, 1460 cm^{-1}; ^1H NMR δ 0.97 (s, 3 H), 1.05 (s, 3 H), 1.14 (s, 3 H), 1.50-2.70 (m, 13 H), 4.77 (s, 1 H), 4.88 (s, 1 H); ^{13}C NMR δ 26.1, 29.2, 31.7, 31.8, 40.6, 41.7, 42.4, 46.1, 48.1, 52.4, 53.4, 69.2, 105.0, 158.9; HRMS calcd for $C_{15}H_{24}$ 204.1882, found 204.1874.

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Registry No. 1, 77412-96-5; **3**, 92622-56-5; **6**, 32363-21-6; **8**, 92622-57-6; **9**, 92622-58-7; **11**, 92622-59-8; (±)-**12**, 81370-78-7; (±)-**13**, 92622-67-8; **14**, 91158-82-6; **16**, 92622-68-9; **17**, 92622-66-7; (±)-**18**, 85544-98-5; (±)-**19**, 92622-69-0; (±)-**20**, 92622-70-3; (±)-**21**, 81332-28-7; (±)-**22**, 81331-89-7; $Me_3SNCH{=}CH_2$, 754-06-3; (*E*)-$Me_3SnCH{=}CHCH_3$, 4964-07-2; (*Z*)-$Me_3SnCH{=}CHCH_3$, 4964-06-1; $Me_3SnCH_2CH{=}CH_2$, 762-73-2; $Me_3SnC{\equiv}CSiMe_3$, 16035-50-0; (*E*)-$Me_3SnCH{=}CHSiMe_3$, 65801-56-1; Me_4Sn, 594-27-4; Me_3SnPh, 934-56-5; *m*-$CF_3C_6H_4SnBu_3$, 53566-38-4; *p*-$CH_3OC_6H_4SnBu_3$, 70744-47-7; $Pd(PPh_3)_4$, 14221-01-3; CO, 630-08-0; 1-(6-methylcyclohex-1-en-1-yl)-prop-2-en-1-one, 92622-61-2; 1-(2-methylcyclohex-1-en-1-yl)prop-2-en-1-one, 92622-62-3; 1-(5,5-dimethylcyclohex-1-en-1-yl)prop-2-en-1-one, 92622-63-4; 1-(trimethylsilyl)-4-butylpenta-1,4-dien-3-one, 92622-64-5; 1-acetyl-4-*tert*-butylcyclohex-1-ene, 37881-09-7; 1-benzoyl-4-*tert*-butylcyclohex-1-ene, 33809-30-2; 1-(3-(trifluoromethyl)benzoyl)-4-*tert*-butylcyclohex-1-ene, 92622-65-6; 1-(4-methoxybenzoyl)-4-*tert*-butylcyclohex-1-ene, 33809-31-3; 6-methylcyclohex-1-en-1-yl triflate, 76605-82-8; 5,5-dimethylcyclohex-1-en-1-yl triflate, 91158-80-4; hex-1-en-2-yl triflate, 37555-23-0; 5,5-dimethylcyclohex-2-en-1-one, 4694-17-1; 2-methylcyclohexanone, 583-60-8; *N*-phenyltriflimide, 456-64-4; 1-(4-*tert*-butylcyclohex-1-en-1-yl)-3-(trimethylsilyl)propyn-1-one, 92622-60-1.

Origins of Micellar Diastereoselectivity

Robert A. Moss,* Yuan-Ching P. Chiang, and Yongzheng Hui

Contribution from the Wright and Rieman Laboratories, Department of Chemistry, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903. *Received May 21, 1984*

Abstract: Thiol-functionalized surfactant micelles (*n*-$C_{12}H_{25}N^+Me_2CH_2CH_2SH,Cl^-$) were used to cleave Z-Trp-Pro *p*-nitrophenyl dipeptide esters. Marked kinetic diastereoselectivity was observed in these reactions. For example at pH 8 and concentrations ($\sim$6-7) $\times 10^{-3}$ M, the micellar thiol cleaved the LL substrate 5-6 times more rapidly than its DL diastereomer. This kinetic diastereoselectivity was shown to develop at surfactant concentrations $\sim 5 \times 10^{-3}$ M, considerably above the cmc ($\sim 1 \times 10^{-3}$ M), i.e., at a second "critical concentration". Dynamic light-scattering measurements showed that micelles which had reacted with the LL (but not the DL) substrate underwent a marked increase in apparent hydrodynamic diameter (from $\sim$15 to 26 nm) near this second critical concentration. Similar phenomena could be induced upon addition of 2×10^{-5} M LL dipeptide surfactant *reaction product* to the thiol micelles. Micelles of *n*-$C_{12}H_{25}N^+Me_2CH_2CH_2OH,Cl^-$ or *n*-$C_{12}H_{25}N^+Me_3,Cl^-$ were unresponsive to such additions (light scattering). The results are discussed in terms of molecular and supramolecular interactions between surfactant and solubilizate molecules.

In order to expand the analogy between micelles and enzymes, many investigators sought to develop micellar reagents that would react with substrates rapidly and stereoselectively.[1] Following the original work of Bunton[2] and Brown,[3] most studies were devoted to enantioselective reactions between chiral nucleophiles and chiral substrates, usually activated amino acid esters.[4] Frequently, the nucleophiles were imidazole moieties, derived from hydrophobic histidine derivatives and solubilized in micellar surfactant carriers such as cetyltrimethylammonium (CTA) halides.[4a,c,e-h] Occasionally, fully functionalized histidine surfactant micelles,[3,5] micellar histidine dipeptide nucleophiles,[6] or other amino acid derived nucleophiles[7] were studied. Most recently, histidine and histidine dipeptide reagents were tested against activated esters of phenylalanine in vesicular or membrane aggregates.[8]

Impressive enantioselectivities have sometimes been observed. For example, *N*-Z-L-Leu-L-His cleaved L-methoxycarbonylphenylalanine *p*-nitrophenyl (PNP) ester 12.2 times more rapidly than its D enantiomer in micellar CTABr,[6b] whereas *N*-Z-L-Phe-L-His displayed an entioselectivity of 30 toward the *N*-decanoylphenylalanine PNP esters in vesicular (*n*-$C_{12}H_{25})_2N^+Me_2,Br^-$.[8a]

However, little is known about either the molecular level origins of these observed enantioselectivities or of the ways in which the micelles or vesicles elicit them. Ono et al. generalized that micellar stereoselectivity requires proximity of the nucleophile's chiral center and the active site, strong molecular interaction between the nucleophile and the substrate, and a reaction locus in the "hydrophobic field" of the micelle.[6a] Brown and Bunton offered a specific molecular model for an entioselective cleavage of *N*-acetylphenylalanine PNP by a micellar histidine reagent.[3,5] However, these examples are exceptions to the general lack of

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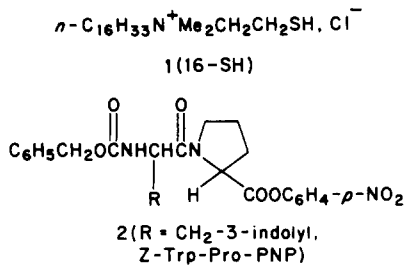
molecular detail in micellar enantioselectivity.

Our own studies have focused on the diastereoselective micellar cleavages of dipeptide and tripeptide PNP esters by functional micellar surfactants such as **1**.[9] For example, at pH 8, Z-L-



Trp-L-Pro-PNP, **2**, was cleaved 21 000 times more rapidly by 4×10^{-3} M micellar **1** than by OH^- in pH 8 micellar CTACl. The kinetic diastereoselectivity between LL-**2** and DL-**2** was 5.0 with **1** vs. 0.28 in CTACl.[9d] In the micellar **1**, cleavage occurred by thiolate anion attack on the substrate's scissile carbonyl group, whereas in OH^-/CTACl or buffer alone, cleavage was mainly the result of DL diastereoselective, intramolecularly assisted cyclization to a diketopiperazine.[9b]

LL diastereoselectivities with micellar **1** were also observed with four other sets of Z-D- or (*Z*)-L-AA-L-Pro-PNP dipeptides,[9d] and a mechanistic rationale was offered based on molecular modeling.[9d,e] CPK models of the LL substrate, arranged in extended peptide conformations, exhibit "clefts" defined by their Pro and PNP moieties and by the R groups of their variable amino acids. The CH_2 chain of **1** neatly fits into these clefts, poising the $CH_2CH_2S^-$ functionality slightly above and to the rear of the substrate's scissile carbonyl carbon. Thus, when (e.g.) LL-**2** is optimally arranged for hydrophobic bonding to **1**, the latter's thiolate moiety[10,11] is optimally positioned for attack. In contrast, extended conformers of the DL dipeptide substrates possess poorer binding sites for **1** because their R groups project away from their hydrophobic clefts. Binding of the DL substrates to **1** should not orient them for optimal thiolate–carbonyl interaction; their cleavage by **1** should be less facile than cleavage of their LL isomers.[9c,d]

This model satisfactorily accounted for our experimental observations[9d,e] and was successfully extended to the four Z-D- or Z-L-Phe-D- or -L-Phe-L-Pro-PNP diastereomeric tripeptide ester substrates.[9c] Photographs of various dipeptide and tripeptide substrates and reaction transition states have been published.[9f]

Our rationale seemed satisfactory as far as it went, but it was based on specific 1:1 hydrophobic interactions between the surfactant and the substrate. Was micellization of the surfactant essential or would similar stereoselectivity be observed at submicellar concentrations? To answer this question, we prepared the shorter thiol surfactant **3** (12-SH) so that we could conven-

$$n\text{-}C_{12}H_{25}N^+Me_2CH_2CH_2SH,Cl^-$$
3 (12-SH)

iently study its reactions with DL- and LL-**2** above and below the surfactant's critical micelle concentration (CMC).[12] We found the onset of LL diastereoselectivity to be associated with an apparent critical concentration lying substantially *above* the CMC of 12-SH.[12]

Here, we present full details of this work and show that kinetic selectivity for LL-**2** is associated with a sharply defined, concentration-dependent physical transition of micellar 12-SH, observable by dynamic light scattering. Moreover, this phenomenon is chirality dependent, occurring with solubilized LL-**2**, but not with its DL isomer. To our knowledge, this is the first instance in which the occurrence of kinetic micellar stereoselectivity has been linked to a specific form of a micellar aggregate by direct observation.

Results

Synthesis of Surfactants. The three principal surfactants used in this study were **3**, **4** (12-OH), and **5** (12-Me_3). Thiol surfactant

$$n\text{-}C_{12}H_{25}N^+Me_2CH_2CH_2OH,Cl^- \quad n\text{-}C_{12}H_{25}N^+Me_3,Cl^-$$
4 (12-OH) **5** (12-Me_3)

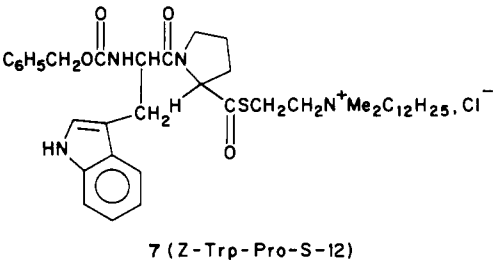
3 was prepared by a sequence analogous to that used to prepare **1**.[11] *N,N*-Dimethylethanolamine was quaternized with 1-bromododecane to give **4**(Br^-). The latter was converted to its triflate (Tf_2O, pyridine, CH_2Cl_2), which underwent self-phase-transfer conversion[13] to thioacetate surfactant **6** upon reaction with

$$n\text{-}C_{12}H_{25}N^+Me_2CH_2CH_2SCOCH_3,CF_3SO_3^-$$
6

aqueous sodium thioacetate. Ion exchange converted **6** to its water-soluble Cl^- form, and subsequent deprotection with deoxygenated 3 N aqueous HCl gave 12-SH, after lyophilization and recrystallization from CH_2Cl_2/Et_2O. Surfactant **6**(Cl^-) was fully characterized, whereas hygroscopic, air-sensitive 12-SH was characterized by NMR spectroscopy and Ellman's assay[14] (93% free SH). Surfactants **4** (12-OH) and **5** (12-Me_3) were easily prepared by quaternizations of *N,N*-dimethylethanolamine or trimethylamine, respectively, with 1-chlorododecane. These products were fully characterized.

Synthesis of Peptides. DL- and LL-**2** were prepared by the mixed anhydride method, condensing Z-L-Trp or Z-D-Trp with L-Pro-PNP (ethyl chloroformate, Et_3N, CH_2Cl_2). The peptide esters were purified by preparative TLC and fully characterized. The free carboxylic acids corresponding to **2**, Z-L- or Z-D-Trp-L-Pro(COOH) were obtained by aqueous methanolic NaOH hydrolysis of the corresponding methyl esters, themselves available by dicyclohexylcarbodiimide-mediated coupling of Z-D- or (*Z*)-L-Trp to L-Pro(COOMe). NMR and TLC studies indicate <5% cross-contamination of diastereomers.

The diastereomeric surfactant dipeptide reaction products of 12-SH and Z-Trp-Pro-PNP were synthesized by reacting 100-mg samples of DL- or LL-**2** with 12-SH in buffered aqueous dioxane. The products **7** (Z-Trp-Pro-S-12) were ion exchanged to the Cl^- form, lyophilized, purified by preparative TLC, and crystallized from CH_2Cl_2/Et_2O. Each diastereomer was characterized by 200-MHz proton NMR and (as the hemihydrate) by elemental analysis.



7 (Z-Trp-Pro-S-12)

Critical Micelle Concentrations. The cmc's of surfactants **4** and **5** were determined by the surface tension method[15] in 0.02 M phosphate buffer, pH 8.0 (μ = 0.05, KCl), at 25 °C using a Fisher "Tensiomat" instrument. Determinations were made in the presence of a constant concentration (2×10^{-5} M) of DL-**7** (for reasons described below), and surfactant concentrations were

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(10) The pK_a of micellar **1** is 7.3,[11] and so micellar **1** will be largely converted to the thiolate form at pH 8.

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Table I. Cleavage of PNPA by 12-SH[a]

10^3[12-SH], M	min free, SH,[b] %	k_ψ,[c] s^{-1}
6.80	87	0.313 ± 0.003
6.36	83	0.358 ± 0.001
5.55	84	0.272 ± 0.002
5.22	82	0.255 ± 0.002
4.77	84	0.239 ± 0.003
3.77	86	0.152 ± 0.001
3.06	85	0.0919 ± 0.0005
1.94	83	0.0447 ± 0.0002
1.64	82	0.0296 ± 0.0002
1.25	80	0.0166
1.05	73	0.00778
0.677	73	0.00848

[a] Standard conditions, see text. [b] Analysis by Ellman's assay.[14] [c] Errors are average deviations from the mean of two runs.

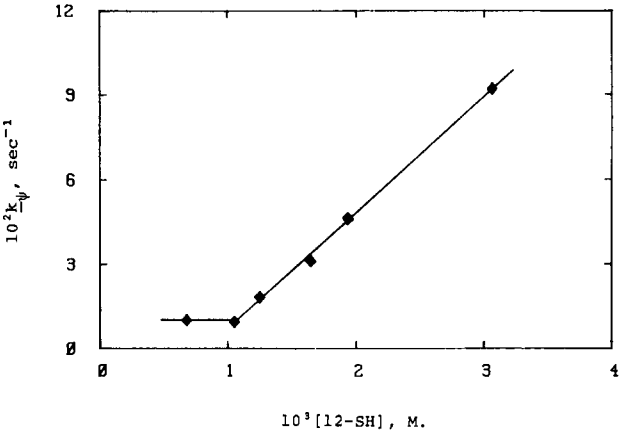

Figure 1. Pseudo-first-order rate constants for the pH 8 cleavage of PNPA by 12-SH vs. [12-SH].

varied from 0.01 or 0.1 M to 5.0×10^{-5} M with seven or eight surface tension readings (±0.1 dyn/cm) taken within these concentration ranges. Cmc's taken from the "break points" of surface tension vs. log (concentration) correlations were 4.5×10^{-4} M for 12-OH and 2.8×10^{-3} M for 12-Me_3. The cmc of 12-SH was determined from a rate constant/[surfactant] profile, as described below.

Kinetic Studies. Initial studies were carried out with *p*-nitrophenyl acetate (PNPA) as the substrate in order to establish an operational cmc for 12-SH. Pseudo-first-order rate constants were evaluated by spectroscopically monitoring the time dependent concentration of released *p*-nitrophenoxide ion at 400 nm. *Standard conditions*, employed throughout, were 0.02 M aqueous phosphate buffer [pH 8.0 μ = 0.05 (KCl), 25 °C, [substrate] = 2.0×10^{-5} M]. Rapid reactions, $k_\psi > 0.03$ s^{-1}) were followed by stopped-flow spectroscopy, whereas slower processes were monitored on a conventional (Gilford) spectrophotometer.

Pseudo-first-order rate constants for the pH 8 reactions of 12-SH and PNPA were obtained at 12 different surfactant concentrations. The data appear in Table I and a graphical correlation of the data for the six *lowest* [12-SH] appear in Figure 1. In previous work,[11] we found that the micellar kinetic properties of 16-SH toward PNPA remained essentially constant as long as its free SH titer exceeded 55%. We assume here that 12-SH is at least as sensitive to air oxidation.

From the rate constant/[12-SH] profile, we take $\sim 1.1 \times 10^{-3}$ M as the cmc of 12-SH under "standard" kinetic conditions. Because of the serious instability to air oxidation of dilute pH 8 solutions of 12-SH, we could obtain only limited data below 10^{-3} M. Nevertheless, it is clear from Figure 1 that the cmc of 12-SH *cannot be greater* than $\sim 1.1 \times 10^{-3}$ M. This is an important point for our subsequent discussions.

For comparisons with micellar 16-SH,[11] a complete PNPA k_ψ/[12-SH] profile (14 points at [12-SH] ranging from 4.0×10^{-4} to 0.32×10^{-2} M) was also carried out at pH 7 under otherwise standard conditions. The data (not shown) gave a cmc of $\sim 6 \times 10^{-4}$ M for 12-SH at pH 7 and a maximum observed $k_\psi = 0.93$ s^{-1} at [12-SH] = 0.032 M. Comparable data for micellar 16-SH are cmc $\sim 4.2 \times 10^{-4}$ M and $k_\psi = 2.2$ s^{-1} at 0.03 M.[11] The basic micellar kinetic properties of 12-SH and 16-SH are therefore similar.

Table II. Cleavage of Z-L or Z-D-Trp-L-Pro-PNP by 12-SH[a]

10^3[12-SH], M	k_ψ^{LL}, s^{-1}	k_ψ^{DL}, s^{-1}	k_ψ^{LL}/k_ψ^{DL}
7.10	19.2 ± 0.8	3.35 ± 0.15	5.73
6.32	19.1 ± 0.5	3.46 ± 0.04	5.52
5.45	16.4 ± 0.6	2.99 ± 0.01	5.48
5.23	3.5 ± 0.1	2.00 ± 0.07	1.75
4.55	1.36 ± 0.03	1.11 ± 0.05	1.22
3.74	0.455 ± 0.007	0.63 ± 0.09	0.72
2.74	0.49 ± 0.02	0.47 ± 0.02	1.04
2.00	0.46 ± 0.01	0.47 ± 0.01	0.98

[a] Standard reaction conditions at pH 8. Ellman's titers were determined after each dilution of the 12-SH stock solution (at each [12-SH]). Values of min free SH ranged from 83 to 90%. Reproducibilities are average deviations of two or three runs.

Table III. Cleavage of Z-L or Z-D-Trp-L-Pro-PNP by 1-SH[a]

10^3[1-SH], M	$10^4 k_\psi^{LL}$, s^{-1}	$10^4 k_\psi^{DL}$, s^{-1}	k_ψ^{LL}/k_ψ^{DL}	$(k_\psi^{LL})_{12\text{-SH}}/(k_\psi^{DL})_{1\text{-SH}}$[b]
7.10	5.46	6.89	0.79	35200
4.55	2.70	3.61	0.75	5040
2.74	2.65	3.22	0.82	1840
0.00[c]	0.93	2.2	0.42	

[a] Standard reaction conditions at pH 8. Ellman's activity of 1-SH was >95%. Rate constants were determined on the Gilford spectrophotometer. [b] $(k_\psi^{LL})_{12\text{-SH}}$ values are taken from Table II at appropriate [12-SH]. [c] In 0.02 M, pH 8, aqueous phosphate buffer, μ = 0.05 (KCl). Because of the low solubility of **2** in water, values are extrapolated to pure buffer from three runs in 20–40% dioxane buffer.

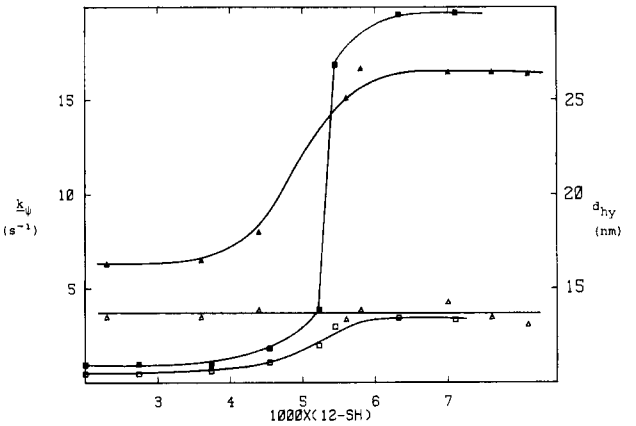

Figure 2. (a) k_ψ(s^{-1}) (left-hand ordinate) vs. 10^3[12-SH] (M) for the cleavages of LL-**2** (■) or DL-**2** (□) by micellar 12-SH; cf. Table II. For clarity, k_ψ^{LL} has been arbitrarily increased by 0.5 s^{-1} at each point. (b) Apparent hydrodynamic diameters (nm) (right-hand ordinate) of 12-SH micelles vs. 10^3[12-SH] (M) after reactions at pH 8 with 2.0×10^{-5} M LL-**2** (▲) or DL-**2** (△); cf. Table V, run 1.

Next, we determined k_ψ for the pH 8 12-SH cleavages of LL- or DL-**2**, monitoring *p*-nitrophenoxide ion release by stopped-flow spectroscopy under standard conditions. The k_ψ data appear in Table II as a function of [12-SH], together with the kinetic diastereoselectivity, k_ψ^{LL}/k_ψ^{DL}. The data are also plotted in Figure 2 as a function of [12-SH]; cf. left-hand ordinate vs. abscissa.

As a reference, we measured k_ψ for cleavage of LL- and DL-**2** by thiocholine bromide **8** (1-SH),[11] a nonmicellar model for 12-SH. These data appear in Table III, together with $(k_\psi^{LL})_{12\text{-SH}}/(k_\psi^{LL})_{1\text{-SH}}$ which reflects the maximum micellar rate enhancement at a given [thiol].

$Me_3N^+CH_2CH_2SH,Br^-$
8 (1-SH)

Table IV. Apparent Micellar Diameters of 12-SH[a]

10^3[12-SH], M	d_{hy},[b] nm	10^3[12-SH], M	d_{hy},[b] nm
4.1	11.0	6.4	11.8
5.0	10.7	6.8	11.5
5.7	11.7		

[a] Conditions: 0.02 M pH 8.0 phosphate buffer, μ = 0.05 (KCl), 25 °C, 81% free SH by Ellman's assay. For other conditions, see text. [b] Uncertainty ±1 nm.

Taken together, the data of Tables II and III and Figure 2 indicate the existence of three different catalytic "regimes" for reactions of 12-SH with LL- or DL-**2**. (a) Under regime I ($2 \times 10^{-3} < [12\text{-SH}] < 5 \times 10^{-3}$ 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 ($\sim 5 \times 10^{-3} < [12\text{-SH}] \lesssim 5.5 \times 10^{-3}$ 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 ($\sim 5.5 \times 10^{-3}$ 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.[12]

We argued[12] that the k_ψ enhancements of regime I were micellar because the cmc of 12-SH kinetically determined in the cleavage of PNPA (~1.1×10^{-3} M, above) would, if anything, be *lowered* upon solubilization of the more hydrophobic LL- or DL-**2** substrates. Reactions of these substrates at [12-SH] ≥ 2×10^{-3} M would therefore be micellar.[16] This implied, however, that the abrupt onset of diastereoselectivity at ~5×10^{-3} M 12-SH (Table II) corresponded to formation of a second kind of 12-SH micelle, stereoselective for the cleavage of LL-**2**. To obtain confirmation of this proposal, we examined micellar **3**, **4**, and **5** by dynamic (quasi-elastic) light scattering under various experimental conditions.

Light Scattering Studies. Fairly extensive dynamic light scattering studies have been made of sodium dodecyl sulfate (SDS) micelles.[17] These measurements afford mean translational diffusion coefficients for the micelles and mean micellar hydrodynamic radii via the Stokes–Einstein equation (assuming the micelles to be spherical). The temperature dependence of the light scattering data also permits conclusions to be made about micellar shape and aggregation number.[17] However, analysis is complicated because the micellar diffusion coefficients are affected by surfactant identity, concentration, temperature, and (especially) the concentration of added electrolytes.[17] Moreover, the hydrodynamic radius derived from light scattering studies at ambient temperatures cannot be directly equated with the micelle's "theoretical radius" based on the surfactant's molecular dimensions. This is because interactions between the micellar Gouy–Chapman double layer and the aqueous electrolyte solutions, which contain the micelles, contribute to the translational diffusion coefficient and hence to the derived hydrodynamic radius.[17]

Accordingly, we have used dynamic light scattering information as a probe of abrupt changes in micellar properties as signaled by alteration of their size or shape and hence in their apparent hydrodynamic radius or diameter. We do not take the data as a literal indication of micellar size.

Our dynamic light scattering measurements employed a Nicomp Model TC-100 computing autocorrelator, an argon laser light source (488 nm), and a Hazeltine microcomputer that used the cumulant program and directly afforded d_{hy}, the mean hydrodynamic diameter of the micelle. Data were collected at 25 °C and a 90° scattering angle. For all experiments, the channel width (the value in seconds of the time interval of each contiguous channel of the light scattering autocorrelation function) was 0.6–1.2 μs; the resultant correlation functions exhibited 1.5–2.0 decay times over 56 channels. These are optimal parameters for particles nominally in the 10-nm diameter range.[18] Reproducibilities are not shown in the tables of light scattering data, but repeat runs have indicated ±1 nm to be an appropriate uncertainty in d_{hy}.

Table V. Apparent Micellar Diameters of 12-SH + Z-Trp-Pro-PNP[a]

10^3[12-SH], M	d_{hy}, nm (1) LL	(1) DL	(2) LL	(2) DL	(3)[b] LL	(3)[b] DL
2.3	16.3	13.5				
3.6	16.5	13.5	14.6	15.7		
4.1					14.8	14.9
4.4	18.0	13.9				
4.5			14.9	15.8		
5.0					14.9	15.6
5.3			16.9	15.6		
5.6	25.1	13.4				
5.8	26.7	13.9			25.0	15.0
6.0			25.0	14.6		
6.3					24.6	15.2
7.0	26.5	14.3	25.6	15.4		
7.4					26.0	15.2
7.6	26.5	13.5				
8.1	26.4	13.1				

[a] Conditions as in Table IV; 2.0×10^{-5} M DL- or LL-**2** was added to each sample of 12-SH before measurement. [b] This stock solution of 12-SH had 88% free SH by Ellman's assay.

Table VI. Apparent Micellar Diameters of 12-SH + Z-Trp-Pro-S-12[a]

10^3[12-SH], M	d_{hy}, nm (1)[b] LL	(1)[b] DL	(2)[c] LL	(2)[c] DL	(3) LL	(3) DL
4.0	12.6	12.4	13.2	12.9	13.1	11.7
5.0	13.7	13.4	13.3	13.0	12.6	12.4
5.6	19.0	13.6	19.4	12.3	18.1	13.6
6.4	19.6	14.6	19.5	12.8		
6.8			18.6	12.3	18.5	13.6
7.1	18.6	13.0			19.4	14.0

[a] Conditions as in Table IV; 2.0×10^{-5} M DL- or LL-**7** was added to each sample of 12-SH before measurement. [b] Ellman's assay, 86% free SH. [c] Ellman's assay, 78% free SH.

All micellar solutions were prepared in aqueous solutions identical with those used in the kinetic studies and were filtered through a 0.45 μm Bio-Rad polycarbonate filter before the measurement. Table IV records apparent d_{hy} in nm of 12-SH micelles in our standard kinetic medium. There is no noticeable dependence of the apparent diameter on [12-SH] over the indicated concentration range.

Next, we measured d_{hy} of 12-SH micelles that had *reacted with Z-Trp-Pro-PNP*. These solutions therefore correspond to spent solutions of the kinetic runs. The micelles initially contained 2×10^{-5} M **2** and, assuming 100% conversion, finally contained 2×10^{-5} M **7**. Data appear in Table V. Three independent sets of determinations were made. In each set, d_{hy} was measured after additions of LL-**2** or DL-**2** to an appropriately diluted aliquot of micellar 12-SH stock solution. Fresh stock solution was used for each set of measurements. We determined an Ellman's titer[14] for the 12-SH used in data set three (88% SH) and used freshly deprotected 12-SH (from 12-SAc) for each set.

Within each data set, the trends are clear and in mutual agreement. Micellar diameters of 12-SH to which LL-**2** was added, increase from ~15–16 to ~25–26 nm as a function of [12-SH] over the indicated concentration range. The growth in apparent d_{hy} occurs abruptly over a narrow concentration range (4–6) × 10^{-3} M. In contrast, addition of DL-**2** to micellar 12-SH has *no* apparent effect on d_{hy} under the same conditions.

(16) This conclusion is supported by the light scattering studies of 12-SH discussed below.

(17) For leading references, see ref 2, pp 16–18. See particularly: Corti, M.; Degiorgio, V. *Chem. Phys. Lett.* **1978**, *53*, 237; *J. Phys. Chem.* **1981**, *85*, 711. Briggs, J.; Nicoli, D. F.; Ciccolello, R. *Chem. Phys. Lett.* **1980**, *73*, 149. Mazer, N. A.; Benedek, G. B.; Carey, M. C. *J. Phys. Chem.* **1976**, *80*, 1075.

(18) Instruction Manual for Nicomp Model TC-100 Autocorrelator, Nicomp Instruments, Inc., Santa Barbara, CA.

Table VII. Apparent Micellar Diameters of 12-SH + Z-Trp-Pro-S-12 at pH 4[a]

10^3[12-SH], M	d_{hy}, nm	
	LL	DL
4.0	8.18	8.79
5.0	7.85	8.15
5.7	8.32	8.56
6.3	8.56	8.62
7.1	8.06	7.92

[a] Conditions: 0.01 M acetate buffer, pH 4.0, μ = 0.01, 25 °C, 2.0 × 10^{-5} M added LL- or DL-**7**. The 12-SH had 86% free SH by Ellman's assay.

Table VIII. Apparent Micellar Diameters of 12-SH + Z-Trp-Pro(COO^-)[a]

10^3[12-SH], M	d_{hy}, nm	
	LL	DL
4.1	12.6	12.8
5.0	12.7	12.9
5.7	13.0	12.0
6.4	13.9	13.2
6.8	13.1	12.4

[a] Conditions as in Table IV; 2.0 × 10^{-5} M DL- or LL-(*Z*)-Trp-Pro-(COOH) was added to each sample of 12-SH before measurement. The Ellman's titer indicated 82% free SH.

The data of Table V, set 1, is plotted in Figure 2 (right-hand ordinate). The contrasting behavior of d_{hy} for LL-**2**/12-SH and DL-2/12-SH micellar systems *occurs over the same narrow concentration range where 12-SH develops its LL stereoselectivity.*

Table VI indicates that similar diastereomer and concentration dependent effects upon d_{hy} could be elicited by doping the 12-SH micelles with LL- or DL-**7**, the products of the (12-SH + **2**) reactions. Although the increase in d_{hy} is not as large as that recorded in Table V, the results are unequivocal; a discontinuity in d_{hy} was evoked by solubilized LL-**7** but *not* by DL-**7**, and the discontinuity occurred abruptly at [12-SH] ≈ (5–6) × 10^{-3} M.

In one set of (untabulated) measurements, no change in d_{hy} was elicited by either diastereomer of **7**; d_{hy} remained at 15 ± 1 nm over 4.0 × 10^{-3} ≤ [12-SH] ≤ 6.9 × 10^{-3} M. However, Ellman's assay revealed that the 12-SH contained only 65% free SH. As indicated above, the properties of 16-SH toward PNPA also change markedly at low SH titers. Presumably, partial air oxidation of 12-SH to 12-S–S-12 significantly alters the properties of the resulting comicelle, relative to those of more nearly pure micellar 12-SH.

At pH 8, micellar 12-SH must be largely in its zwitterionic 12-S^- form. (The pK_a of micellar 16-SH is 7.3 under similar conditions.[11]) Therefore, it is interesting to observe that fully protonated 12-SH at pH 4 does not respond to added **7**; compare Table VII with Table VI. Note also the marked decrease in d_{hy} of 12-SH, at pH 4. Without overinterpreting this behavior,[19] it seems that fully protonated, cationic 12-SH shows no variation of d_{hy} upon solubilization of either LL-**7** or DL-**7** over the usual [12-SH] range. We caution, however, that the cmc of cationic 12-SH at pH 4 may be significantly higher than that of the (largely) zwitterionic 12-SH at pH 8. Therefore, this conclusion must be considered provisional until the study can be extended to higher [12-SH].

Some further "negative" results are of interest. Although surfactant dipeptide LL-**7** provokes a discontinuity in d_{hy} of micellar 12-SH at pH 8 (Table VI), this is not true of the corresponding free dipeptide carboxylate anion, Z-Trp-Pro(COO^-); cf. Table VIII. Neither diastereomeric peptide carboxylate markedly affects d_{hy} of micellar 12-SH over the usual concentration range.

(19) For example, the general decrease in d_{hy} noted upon comparison of Tables V and IV with VII is more likely due to the associated decrease in ionic strength[17] (μ = 0.05 vs. μ = 0.01), rather than to the change from zwitterionic 12-S^- to cationic 12-SH. This interpretation is supported by the similarity in size of fully cationic micellar 12-OH and 12-Me_3 and zwitterionic 12-S^- at pH 8, μ = 0.05; cf., Table IX, below.

Table IX. Apparent Micellar Diameters of 12-OH or 12-Me_3 + Z-Trp-Pro-S-12[a]

10^3[surf], M	d_{hy}, nm					
	12-OH				12-Me_3	
	LL	DL	LL	DL	LL	DL
4.0	11.9	12.4	12.4	12.7	12.9	11.6
5.0	11.5	11.4	11.5	12.6	12.6	12.7
6.0	13.5	11.6	11.7	11.6	12.6	12.0
7.0	12.8	11.9	11.7	11.9	13.1	11.7
8.0	13.6	12.5	12.2	12.5	13.0	13.0

[a] Conditions as in Table IV; 2.0 × 10^{-5} M DL- or LL-**7** was added to each surfactant before measurement.

Finally, as shown in Table IX, micelles of 12-OH or 12-Me_3 exhibit no marked discontinuities in d_{hy} upon solubilization of LL-**7** or DL-**7**.

Discussion

The data of Table I and Figure 1 establish the cmc of 12-SH as ≤1.1 × 10^{-3} M under our reaction conditions. In this light, the kinetic data for the cleavages of Z-Trp-Pro-PNP by 12-SH and 1-SH (Tables II and III) take on particular significance. Reactions of Z-Trp-Pro-PNP and 12-SH at surfactant concentrations between 2.0 and 4.5 × 10^{-3} M are clearly micellar: [12-SH] exceeds the cmc, and there is strong acceleration (2000–5000 times) relative to reactions with the nonmicellar thiocholine **8** at comparable concentrations (cf. Table III). Nevertheless, these micellar reactions manifest little or no stereoselectivity (Table II, Figure 2). Only when [12-SH] > 5 × 10^{-3} M does diastereoselectivity develop, rising rapidly over a narrow 12-SH concentration range to a 5–6-fold kinetic selectivity in favor of LL-**2** with an overall micellar kinetic advantage of 35 000, relative to **8**.

This abrupt onset of diastereoselectivity suggests a transition to a second kind of 12-SH micelle,[20] in which the specific 12-SH/LL-**2** interactions[9d-f] responsible for the diastereoselectivity are "turned on" or enforced. The light scattering results provide direct evidence for this hypothesis.

Table V demonstrates that 12-SH micelles which have reacted with LL-**2** undergo an apparent increase in d_{hy} commencing at [12-SH] ≈ 4–5 × 10^{-3} M and rising rapidly to an apparent maximum at ~6 × 10^{-3} M. The overall increase is 60%. In Figure 2, a plot of d_{hy} vs. [12-SH] for run 1 of Table V is superimposed on comparable kinetic data (k_ψ vs. [12-SH]) from Table II. The similarities in light scattering and kinetic behavior for the 12-SH/LL-**2** system and the contrasting results for the 12-SH/DL-**2** system are striking and suggest that the phenomena are linked: LL diastereoselectivity originates in a second type of 12-SH micelle formed in the presence of certain solubilizates at [12-SH] ≈ 5 times above the cmc.

Perhaps the most remarkable feature of the light scattering results is the apparent stereoselectivity of the 12-SH micellar transition; only the micelles doped with the LL substrate respond. The DL-**2**-doped micelles, although "larger" than native 12-SH micelles (compare Tables IV and V), show no 12-SH concentration dependence of d_{hy}.[21]

Analysis of Tables VI–IX gives a more detailed picture of the factors that are involved. (a) Table VI indicates that the 12-SH micellar transition can be induced by solubilized LL-**7**, the product of the reaction of LL-**2** and 12-SH. However, neither the diastereomeric product DL-**7** nor the free dipeptide carboxylates, Z-D- or (*Z*)-L-Trp-L-Pro(COO^-), are active (Tables VI and VIII). (b)

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

(21) There is, however, a significant increase in K_ψ^{DL} for 12-SH cleavage of DL-**2**, which is apparent at [12-SH] ~(5–6) × 10^{-3} M (Table II, Figure 2). This increase, of course, is much smaller than the one manifested by k_ψ^{LL}. If there is a transition in the DL-doped 12-SH micelles, therefore, it goes undetected by light-scattering measurements under our experimental conditions.

At pH 4, where 12-SH is fully protonated, d_{hy} of the 12-SH micelles shows no response to either LL-**7** or DL-**7** (Table VII). (c) The apparent d_{hy} of micellar 12-OH or 12-Me_3 are unresponsive to either LL- or DL-**7** solubilizates at concentrations similar to those employed with 12-SH and above their respective cmc's (Table IX).

Taken together, the new observations permit refinement of our model[9,12] for micellar diastereoselectivity by 12-SH or 16-SH. At concentrations at or just above its cmc, 12-SH probably forms loosely packed spherical or nearly spherical micelles in which the favorable 1:1 interaction between 12-SH and LL-**2** are not enforced. Both DL- and LL-**2** are bound, however; significant micellar esterolytic rate enhancements are observed (Table III), but no diastereoselectivity (Table II). At higher [12-SH], a relatively low loading of an appropriate hydrophobic solubilizate (LL-**2** or LL-**7**) induces a transition to an apparently larger, perhaps ellipsoidal or cylindrical[20] form of the micelle, in which LL stereoselective surfactant/substrate interactions are buttressed and strongly expressed in kinetic terms. Chirality dependent kinetic and light scattering micellar phenomena are much weaker upon solubilization of DL-**2** or DL-**7**.

The concentration of **2** or **7** employed throughout our work was 2×10^{-5} M. Assuming complete binding by micellar 12-SH and an aggregation number (N) of about 500 at [12-SH] $\approx 5 \times 10^{-3}$ M,[22] there would be about two solubilizate molecules per micelle. The chirality dependent phenomena must therefore be induced by a small proportion of chiral solubilizate molecules in a micelle constructed of many achiral surfactant molecules. This represents an *amplification* of the chirality information contained in the LL solubilizates. The amplification is expressed on the *supramolecular* level; the entire micelle responds to the presence of LL solubilizate much more strongly than it responds to DL solubilizate.

Micellization is a dynamic process that normally operates on the μsec to msec time scale.[23] If the micellar transition of 12-SH also occurs with this rapidity, then it is possible that the transition already occurs upon solubilization of LL-**2**, before or during its conversion to LL-**7**. (The half-life of the 12-SH + LL-**2** $\rightarrow$ LL-**7** reaction is $\sim$36 ms[24] at [12-SH] = 7.1×10^{-3} M, well above [12-SH] needed for the transition.) If the 12-SH micelles are not converted to their stereochemically active form upon solubilization of LL-**2**, then the initial stages of the ensuing reaction must provide enough LL-**7** to induce the transition. The latter idea requires the overall observed LL-**2** kinetic stereoselectivity to be a minimum, because some of the substrate would be initially needed to generate LL-**7**, and this "primer" substrate would not be cleaved stereoselectively.

In principle, the matter is subject to test by redetermining the data of Table II at varying [substrate]. What is clear, however, is that the micellar 12-SH transition requires an hydrophobic LL-Trp-Pro derivative such as **7** or (perhaps) **2**. The ionic Z-Trp-Pro(COO^-) diastereomers are ineffective at comparable concentrations (Table VIII). This suggests that an effective LL solubilizate must be appropriately *oriented* within the 12-SH micelles. The dipeptide carboxylates, in contrast, may be bound closer to the surface of the micelle, where the effect of their chirality may be mitigated.

It also appears that in order to respond to the solubilizate's chirality, the surfactant micelle requires an additional type of supramolecular integrity or cohesiveness. In 12-SH micelles at pH 8, this property might be afforded by peripheral "stitching" due to S^-/SH hydrogen bonding of the functional head groups. At pH 4, where no ionized SH groups are present, cationic head group repulsions may diminish this "stitching" and responsiveness to the solubilization of LL-**7** is lost (Table VII). Similarly, neither micellar 12-OH (very largely unionized at OH at pH 8[25]) nor micellar 12-Me_3 respond to LL-**7** (Table IX).

The newly refined model for micellar diastereoselectivity can be summarized as follows: a small quantity of chiral solubilizate can induce a structure-dependent, chirality-dependent, supramolecular effect in a micelle constructed of achiral surfactant molecules if (a) the particular additive is appropriately oriented and strongly bound in the micelle, (b) the additive properly approximates to the surfactant on a 1:1 molecular level, and (c) the micellar head groups are capable of strong interactions. The resultant effect, which is a micellar amplification of the chirality information contained in the additive, can find kinetic expression in the reactions of diastereomeric substrates, occurring within the "altered" micelles, as well as physical consequences in such colligative micellar properties as light scattering. Various components of this model will be subjected to further experimental tests and elaboration.

It is known, for example, that the viscosity, light scattering properties, diffusion coefficient, shape, and d_{hy} of tetradecyldimethylammonium bromide micelles are strongly affected by the solubilization of alcohols (e.g., pentanol).[26] What is unique about the present results, however, is the strong *chirality dependence* manifested by the micelles in both physical and kinetic phenomena upon solubilization of certain chiral solubilizates. There is some resemblance here to the alteration of the stereochemical course of the deamination of cationic micellar 2-aminooctane, which is only evoked by certain tightly bound hydrophobic counterions.[27] In this case, it was suggested that these counterions (e.g., ClO_4^-, BF_4^-) afforded "larger, more effectively charge-neutralized, denser, and less aqueous micelles".[27] However, physical evidence was not provided for the specific systems under examination. The present results are also reminiscent of the chiral recognition exhibited by certain hydrophobic amides diluted in monolayers of dipalmitoylphosphatidylcholine,[28] where it has been suggested that stereospecific interactions between the chiral solubilizate molecules are transmitted in a behaviorally achiral medium even at low solubilizate concentrations. The chirality of the amide molecules thus appears to be propagated through at least several intervening molecules in the oriented, compressed monolayer.[28] Conceivably, the chiral micellar effects revealed in the present work could be transposed, perhaps with enhancement, to appropriately constituted monolayers. Monolayers, subject to externally imposed controls and greater enforcement of monomer orientation, should prove superior to micelles as chirality transducers.

The present results may also have implications for the design of asymmetric syntheses or for prebiotic chemistry. Thus, reactions of prochiral reagents bound to micelles rendered "chiral" on a supramolecular scale by the solubilization of chiral "impurities" would not (at least in theory) have to form equal quantities of enantiomeric products. We intend to vigorously pursue these and other lines of investigation suggested by the present findings.

Experimental Section[29]

***N*-*n*-Dodecyl-*N*,*N*-dimethyl-*N*-(β-thioethyl)ammonium Chloride (3,[29] 12-SH).** 1-Bromododecane (26.5 g, 0.11 mol) and 10.7 g (0.12 mol) of *N*,*N*-dimethylethanolamine were refluxed in 150 mL of anhydrous MeOH for 24 h. Methanol was stripped on the rotary evaporator to afford a yellow solid that was recrystallized three times from MeOH/acetone affording 25.9 g (0.077 mol, 70%) of **4** (Br^- form): mp 193–196 °C; NMR (δ, $CDCl_3$) 0.90 (t, 3 H, term. CH_3), 1.28 (s, 20 H, $(CH_2)_{10}$), 3.40 (s, 6 H, $(CH_3)_2N^+$), 3.75 (m, 4 H, $CH_2N^+CH_2$), 4.10 (m, 2 H, CH_2OH), 5.0 (t, 1 H, OH).

Surfactant **4**, Br (6.27 g, 19 mmol) and 1.60 g (20 mmol) of pyridine in 80 mL of CH_2Cl_2 was added with stirring to 11.7 g (47 mmol) of triflic

(22) This seems a generous estimate. N is likely to be smaller; cf., ref 20, pp 20–21.
(23) Reference 1, pp 25–27.
(24) This value is calculated from the appropriate data of Table II.
(25) Bunton, C. A.; Robinson, L.; Stam, M. *J. Am. Chem. Soc.* **1970**, *92*, 7393. Martinek, K.; Levashov, A. A.; Berezin, I. V. *Tetrahedron Lett.* **1975**, 1275.
(26) Hirsch, E.; Candau, S.; Zana, R. *J. Colloid Interface Sci.* **1984**, *97*, 318 and references to earlier papers therein.
(27) Moss, R. A.; Talkowski, C. J.; Reger, D. W.; Powell, C. E. *J. Am. Chem. Soc.* **1973**, *95*, 5215.
(28) Arnett, E. M.; Gold, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 636. See also: Arnett, E. M.; Chao, J.; Kinzig, B. J.; Stewart, M. V.; Thompson, O.; Verbiar, R. J. *Ibid.* **1982**, *104*, 389. Arnett, E. M.; Chao, J.; Kinzig, B.; Stewart, M.; Thompson, O. *Ibid.* **1978**, *100*, 5575.
(29) Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 727B instrument. NMR spectra were determined on Varian T-60 or, when indicated, XL-200 instruments. Microanalyses were done by Robertson Laboratory, Florham Park, NJ.

anhydride in 60 mL of CH_2Cl_2 at 25 °C. After 30 min, the NMR spectrum of an aliquot revealed the disappearance of the CH_2OH signal of **4** (δ, $CDCl_3$) at 4.10, and the appearance of a new signal at δ 5.01 (CH_2OTf). To the CH_2Cl_2 solution of *4*-OTf was added a solution of 30.8 g (405 mmol) of *fresh* thioacetic acid in 20 mL of water (pH adjusted to 7.5 with 0.5 N NaOH). The resulting two-phase solution was stirred for 1.5 h at 25 °C. The CH_2Cl_2 layer and 2 × 40 mL of CH_2Cl_2 washes of the aqueous layer were combined and dried ($MgSO_4$). The CH_2Cl_2 was filtered and stripped on the rotary evaporator to afford a syrup (**6**), which was added to dry Dowex 1-X8 ion exchange beads (Cl^- form, 30 g, 126 mequiv) in 150 mL of H_2O. The mixture was heated with swirling to 85 °C for 15 min and cooled. The beads were filtered and washed with water. The total aqueous solution was then lyophilized to dryness, affording a powder which was dissolved in CH_2Cl_2, precipitated with ether, and centrifuged. The solid was recrystallized in the same way twice more, and the final **6** (Cl^- form) was dried under vacuum to afford 3.2 g (9.1 mmol, 48% yield based on **4**, Br) of thioacetate surfactant **6**(Cl): mp 86–88 °C. NMR (δ, $CDCl_3$) 0.90 (t, 3 H, term. CH_3), 1.30 (s, 20 H, $(CH_2)_{10}$), 2.34 (s, 3 H, $SCOCH_3$), 3.40 (br m, 12 H, $CH_2N^+(CH_3)_2CH_2CH_2S$).

Anal. Calcd for $C_{18}H_{38}ClNOS$: C, 61.4; H, 10.9; Cl, 10.1. Found: C, 61.2; H, 10.7; Cl, 10.4.

Surfactant **6**,Cl (1.60 g, 4.55 mmol) was dissolved in 60 mL of N_2-purged 3 N aqueous HCl. The solution was heated to 80 °C for 1.5 h; HCl was removed by aspiration; the solution was lyophilized to dryness. The solid residue was dissolved in a minimal amount of CH_2Cl_2 and precipitated with ether. This procedure was repeated twice more to give 1.30 g (4.20 mmol, 92%) of **3** (12-SH) after drying under high vacuum. Our best sample, mp 131–133 °C, had 93% SH activity by Ellman's assay:[14] NMR (δ, $CDCl_3$) 0.90 (t, 3 H, term. CH_3), 1.28 (s, 20 H $(CH_2)_{10}$), 3.20 (br m, 13 H, $CH_2N^+(CH_3)_2CH_2CH_2SH$).

N-n-Dodecyl-N,N-dimethyl-N-(β-hydroxyethyl)ammonium Chloride (4, 12-OH). 1-Chlorododecane (10.2 g, 49.8 mmol) and 4.9 g (56 mmol) of *N*,*N*-dimethylethanolamine were stirred and refluxed in 80 mL of dry methanol for 24 h. Solvent was removed under vacuum; the solid residue was recrystallized 4 times from acetone and dried under vacuum to give 9.1 g (31 mmol, 62%) of **4**,Cl as white crystals: mp 188–190 °C; NMR (δ, $CDCl_3$) 0.93 (t, 3 H term. CH_3), 1.28 (s, 20 H, $(CH_2)_{10}$), 3.36 (br "s", 8 H, $CH_2N^+(CH_3)_2$), 3.66 (m, 2 H, NCH_2CH_2OH), 4.06 (m, 2 H, $N^+CH_2CH_2OH$), 5.83 (t, 1 H, OH). Anal. Calcd for $C_{16}H_{36}ClNO$: C, 65.4; H, 12.4; N, 4.77. Found: C, 65.6; H, 12.2; N, 4.77.

N-n-Dodecyl-N,N,N-trimethylammonium Chloride (5, 12-Me$_3$). 1-Chlorododecane (10.2 g, 49.8 mmol) and 12.5 g of trimethylamine (33% in ethanol, 70 mmol) were stirred and refluxed in 100 mL of dry methanol for 24 h. Removal of solvent, 4 times recrystallization from EtOAc, and drying gave 6.5 g (24.6 mmol, 49%) of **5** as white hygroscopic crystals: mp 248–249.5 °C; NMR (δ, $CDCl_3$) 0.90 (t, 3 H, term. CH_3), 1.23 (s, 20 H, $(CH_2)_{10}$), 3.51 (s + m, 11 H, $CH_2N(CH_3)_3$). Anal. Calcd for $C_{15}H_{34}ClN$: C, 68.2; H, 13.0; Cl, 13.4; N, 5.31. Found: C, 68.0; H, 12.8; Cl, 13.4; N, 5.14.

Thiocholine Bromide (8, 1-SH). This material was prepared from commercially available *S*-acetylthiocholine bromide (Aldrich), using the procedure of ref 11.

N-Carbobenzyloxy-L-tryptophan-L-proline p-Nitrophenyl Ester (LL-2).[30] *N*-Carbobenzyloxy-L-proline *p*-nitrophenyl ester (Sigma) (1.40 g, 3.78 mmol) was deprotected in 5 mL of HBr-saturated dry acetic acid for 2 h at room temperature.[31] Dilution of the acidic mixture with 30 mL of dry ether gave a white fluffy solid that was collected and washed with dry ether several times. This product (L-proline *p*-nitrophenyl ester–hydrogen bromide) was dried and used in coupling reactions without further purification. The yield was 1.15 g (96%); mp 195–198 °C dec (lit.[32] mp 198–199 °C dec.).

N-Carbobenzyloxy-L-tryptophan (Sigma) (661 mg, 1.95 mmol) was dissolved in 20 mL of methylene chloride. The initial suspension became a solution after adding 0.274 mL (1.98 mmol) of triethylamine at −10 °C. Then, 212 mg (1.95 mmol) of ethyl chloroformate was added, and the solution was stirred for about 15 minutes under nitrogen. After 620 mg (1.95 mmol) of L-proline *p*-nitrophenyl ester hydrobromide was added, the reaction was started by adding 0.270 mL (1.95 mmol) of triethylamine to the reaction mixture over 5 min. The final yellow solution was stirred in the cold (0 °C) for 2 h and then for an additional 2 h at room temperature. The organic solution was washed with 4% aqueous $NaHCO_3$ (3 × 15 mL), water (3 × 15 mL), and 1 N HCl (3 × 15 mL) and dried over $MgSO_4$.

A slightly yellow solid (740 mg, 1.33 mmol, 68%) was obtained after the solvent was evaporated. This could be crystallized by tedious procedures involving bone dry ether: mp 125–127 °C (softening), 134–136 °C (melting); TLC (20:1 $CHCl_3$/methanol, silica gel) 1 spot, R_f 0.47; IR ($CHCl_3$): 1770, 1715, 1645 (all s), cm^{-1}; $[\alpha]^{23}_D$ −19.7° (*c* 1, CH_3OH).[30]

Alternatively, the crude product could be purified by preparative TLC on 1000 μm silica gel GF plates (5% MeOH in CH_2Cl_2, R_f 0.5): mp 124–126 °C; NMR (200 MHz, δ, $CDCl_3$)[33] 1.98 + 2.35 (m's, 3 H + 1 H, H_β + H_γ Pro), 3.10 (m, 1 H, H_δ Pro), 3.24 (m, 2 H, H_β Trp), 3.66 (m, 1 H, H_δ Pro), 4.68 ("q", spacing ~2 Hz, 1 H, H_α Pro), 4.90 ("q", $J \approx 3$ Hz, 1 H, H_α Trp), 5.12 (s, 2 H, OCH_2Ph), 5.58 (d, J = 4 Hz, 1 H, Z-N*H*), 7.10–7.50 (m, 11 H, 4 H from Trp C_6H_4 + 2 H from PNP + 5 H from OCH_2Ph), 7.72 (d, J = 4 Hz, 1 H, 2-indolyl H), 7.96 (s, 1 H, indole NH), 8.08 (d, J = 5 Hz, 2 H, PNP). Anal. Calcd for $C_{30}H_{28}N_4O_7$: C, 64.7; H, 5.08; N, 10.1. Found: C, 64.6; H, 5.13; N, 9.98.

N-Carbobenzyloxy-D-tryptophan-L-proline p-Nitrophenyl Ester (DL-2).[30] D-Tryptophan was carbobenzyloxylated by Smith's method.[34] D-Tryptophan (Sigma) (2.25 g, 12.5 mmol) in 12.5 mL of 1 N NaOH was chilled to 0 °C, and a total of 12.5 mL of 1 N NaOH and 2.25 g (12.6 mmol) of benzyl chloroformate (Aldrich, 95%) were added alternately over 20 min. One hour after the last addition, the solution was acidified to pH 4–5 with 5 N HCl. The precipitate was collected and recrystallized from ethyl acetate and petroleum ether. The yield was 3.1 g (9.2 mmol, 74%) of off-white solid, mp 121–122 °C (lit.[35] mp 127–129 °C). The specific rotation was $[\alpha]^{24}_D$ −2.4° (*c* 3, acetic acid).

N-Cbz-D-tryptophan was coupled to L-proline *p*-nitrophenyl ester in 82% yield, using the same procedure employed for the L,L diastereomer (see above). The final product was obtained in 62% yield as slightly yellow crystals from acetone/ether; mp 152–153 °C; TLC with chloroform/ethanol (20:1) on silica gel gave one spot, R_f 0.42; IR ($CHCl_3$ film) 1780 (s), 1715 (s), 1640 (s), 1614 (w), 1592 (w) cm^{-1}; $[\alpha]^{23}_D$ −50.4° (*c* 1, CH_3OH).

Alternatively, the crude product could be purified by preparative TLC, on 1000 μm silica gel GF plates (5% MeOH in CH_2Cl_2, R_f 0.45): mp 147–148 °C; NMR (200 MHz, δ, $CDCl_3$) 1.24 + 1.84 (m's, 1 H + 3 H, H_β + H_γ Pro), 2.62 (m, 1 H, H_δ Pro), 3.26 (m, 2 H, H_β Trp), 3.50 (m, 1 H, H_δ Pro), 4.32 ("q", spacing ~2 Hz, 1 H, H_α Pro), 4.80 ("q", $J \approx$ 4 Hz, 1 H, H_α Trp), 5.10 (s, 2 H, OCH_2Ph), 5.74 (d, J = 4 Hz, 1 H, Z-N*H*), 7.0–7.6 (m + s at 7.4, 11 H, 4 H from Trp C_6H_4 + 2 H from PNP + 5 H from OCH_2Ph), 7.64 (1 H, d, J = 3 Hz, 2-indolyl H), 8.06 (br s, 1 H, indole NH), 8.12 (d, J = 4 Hz, 2 H, PNP). Anal. Calcd for $C_{30}H_{28}N_4O_7$: C, 64.7; H, 5.08; N, 10.1. Found: C, 64.6; H, 5.12; N, 10.0.

N-Carbobenzyloxy-D-tryptophan-L-proline Methyl Ester.[30] L-Proline methyl ester hydrochloride (Sigma) (310 mg, 1.87 mmol) was neutralized with 0.206 mL (1.87 mmol) of *N*-methylmorpholine in 5 mL of dry THF and then added to a solution of *N*-carbobenzyloxy-D-tryptophan (Sigma) (633 mg, 1.87 mmol) in 15 mL of dry THF. After the addition of 280 mg (2.07 mmol) of hydroxybenztriazole (HOBT), the mixture was cooled to −5 °C, and 390 mg (1.90 mmol) of dicyclohexylcarbodiimide (DCC) in 5 mL of THF was added carefully. The final mixture was stirred for 1 h in an ice bath and then for 6 h at room temperature. After the white precipitate was filtered, the filtrate was stripped and the solvent was replaced by 20 mL of ethyl acetate. The solution was filtered again and washed with 5% aqueous $NaHCO_3$ (3 × 15 mL), water (15 mL), 1 N HCl (15 mL), and water (15 mL). After the organic solution had been dried ($MgSO_4$) and the solvent evaporated, the residue was triturated with dry ether several times to remove brown gummy residues. The final product was crystallized from acetone/ether. The yield was 500 mg of white crystals (60%): mp 141.5–142.5 °C; TLC with chloroform/ethanol (20:1) on silica gel gave a single spot, R_f 0.40; NMR (60 MHz, δ, $CDCl_3$) 1.3–2.24 (br, 4 H, H_β and H_γ Pro), 2.3–2.9 (br, 1 H, H_δ Pro), 3.0–3.95 (m + s at 3.7, 6 H, H_β Trp, H_δ Pro, and CH_3-OCO), 4.0–4.5 (br, 1 H, H_α Pro), 4.5–5.1 (m, 1 H, H_α Trp), 5.15 (s, 2 H, Ph-CH_2-O), 5.8 (br d, 1 H, Z-N*H*), 6.9–7.8 (m + s at 7.32, 10 H, *Ph*-CH_2 and indole), 8.4 (br s, 1 H, *NH* indole); the specific rotation was $[\alpha]^{22}_D$ −32.5° (*c* 1, dioxane).

N-Carbobenzyloxy-D-tryptophane-L-proline.[30] *N*-Cbz-D-tryptophan-L-proline methyl ester (395 mg, 0.88 mmol) was treated with 2 mL of methanol and 2 mL of 0.5 N NaOH for 6 h. After the addition of 5 mL of water, the solution was washed with ether (2 × 5 mL) and acidified

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to pH 1 with 4 N HCl. The resulting oil was extracted with methylene chloride and then dried over $MgSO_4$. After the solvent was removed, 375 mg of white solid was obtained. It was crystallized from chloroform/hexane, yielding 350 mg (91%) of (*Z*)-D-Trp-L-Pro: mp 100–105 °C (softening), 115–116.5 °C (melting); TLC with chloroform/ethanol (20:1) on silica gel gave R_f 0.15; IR ($CHCl_3$) 1710 (s), 1635 (s) cm^{-1}.

Alternatively, the Z-D-Trp-L-Pro was purified by preparative TLC, on 1000 μm silica gel GF plates (30% MeOH in CH_2Cl_2, R_f 0.5) and crystallized from a minimum amount of CH_2Cl_2 with precipitation by *n*-hexane (85% yield): mp 94–97 °C (softening), 112–114 °C (melting); $[\alpha]^{22}_D$ −39.0° (*c* 1, CH_3OH); NMR (200 MHz, δ, $CDCl_3$) 1.0–1.4 (m, 2 H, H_γ Pro), 1.66 (m, 1 H, H_β Pro), 2.1 (m, 1 H, H_β Pro), 2.40 ("q", $J \approx 4$ Hz, 1 H, H_δ Pro), 3.1–3.7 (m, 3 H, H_δ Pro + H_β Trp), 4.20 ("d", $J = 4$ Hz, H_α Pro), 4.78 (m, 1 H, H_α Trp), 5.10 (s, 2 H, OCH_2Ph), 5.74 (br s, 1 H, Z-*NH*), 7.0–7.40 (m + s at 7.25, 10 H, indole C_6H_4 + CH_2Ph + COOH), 7.57 (d, $J = 4$ Hz, 1 H, 2-indolyl H_2), 8.10 (s, 1 H, indole N*H*). Anal. Calcd for $C_{24}H_{25}N_3O_5$: C, 66.2; H, 5.78; N, 9.65. Found: C, 66.0; H, 5.80; N, 9.56.

N-Carbobenzyloxy-L-tryptophan-L-proline Methyl Ester.[30] *N*-Carbobenzyloxy-L-tryptophan (Sigma) (1.07 g, 3.17 mmol) was similarly coupled to 526 mg (3.17 mmol) of L-proline methyl ester hydrochloride using 440 mg (3.25 mmol) of HOBT and 654 mg (3.18 mmol) of DCC in dry THF. The brown gummy oil was obtained with the same workup used for the D,L ester. The residue was dissolved in ethyl acetate, and petroleum ether was added to remove a brown gummy residue. As a result, 800 mg of white solid was obtained after the solvent was removed (56%): mp 88–92 °C; TLC with chloroform/ethanol (20:1) on silica gel gave one spot, R_f 0.35; NMR (60 MHz, δ, $CDCl_3$) 1.3–2.7 (br, 5 H, H_β and H_γ Pro, H_δ Pro), 2.7–3.95 (m + s at 3.7, 6 H, H_β Trp, H_δ Pro, and CH_3-OCO), 4.0–5.0 (m, 2 H, H_α Pro and H_α Trp), 5.07 (s, 2 H, Ph-CH_2-O), 5.65 (br, 1 H, Z-N*H*), 7.0–7.9 (m + s at 7.33, 10 H, *Ph*-CH_2 and indole), 8.25 (br s, 1 H, N*H* indole). The specific rotation was $[\alpha]^{21}_D$ −25.3° (*c* 1, methanol).

N-Carbobenzyloxy-L-tryptophan-L-proline.[30] *N*-Cbz-L-tryptophan-L-proline methyl ester (300 mg, 0.67 mmol) was dissolved in 4 mL of methanol and 1 mL of dioxane and the mixture treated with 1 mL of 1 N NaOH for 2 h. After the addition of 10 mL of water to the solution, the organic solvent was removed from the reaction mixture under vacuum. The resulting emulsion was washed with ether (2 × 10 mL), and acidified to get an oil, which was taken up in methylene chloride, dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in ethyl acetate/ether and crystallized by adding mixed hexanes. The yield was 160 mg of off-white solid (55%): mp 138–140 °C (softening), 143–145 °C (melting); TLC on silica gel with chloroform/ethanol (20:1) gave a single spot, R_f 0.15; IR ($CHCl_3$ film) 1710 (s), 1640 (s) cm^{-1}; $[\alpha]^{23}_D$ −26.7° (*c* 1, CH_3OH).

Alternatively, the Z-L-Trp-L-Pro could be purified by preparative TLC (conditions as for the DL isomer, R_f 0.6) and crystallized from a minimum amount of CH_2Cl_2 with precipitation by *n*-hexane: 80% yield; mp 139–141 °C; NMR (200 MHz, δ, $CDCl_3$) 1.90 (AB q, 2 H, H_γ Pro), 2.10 (AB q, 2 H, H_β Pro), 3.24 (m, 3 H, H_δ Pro + H_β Trp), 3.66 ("q", $J = 4$ Hz, 1 H, H_δ Pro), 4.58 ("t", $J = 4$ Hz, 1 H, H_α Pro), 4.92 (m, 1 H, H_α Trp), 5.12 (AB q, 2 H, CH_2Ph), 5.70 (d, $J = 4$ Hz, Z-N*H*), 6.86–7.20 (m, 5 H, indole C_6H_4 + COO*H*), 7.38 (s, 5 H CH_2Ph), 7.58 (d, $J = 4$ Hz, 1 H, indole H_2), 8.88 (s, 1 H, indole N*H*). Anal. Calcd for $C_{24}H_{25}N_3O_5$: C, 66.2; H, 5.78; N, 9.65. Found: C, 65.9; H, 5.83; N, 9.59.

N-Carbobenzyloxy-L-tryptophan-L-proline Thioester with N-n-Dodecyl-N,N-dimethyl-N-(β-thioethyl)ammonium Chloride (LL-7). Z-L-Trp-L-Pro-PNP (LL-**2**) (100 mg, 0.180 mmol) was dissolved in 10 mL of dioxane, stirred, and mixed with a solution of 74.4 mg (0.240 mmol) of 12-SH (**3**) in 10 mL of H_2O. Then, 3 mL of aqueous 0.04 M phosphate buffer (pH 8) was added, and the reaction mixture was stirred at room temperature for 30 min. The mixture was lyophilized to dryness, and the yellow residue was purified by preparative TLC (1000 μm silica gel GF plates, 15% MeOH in CH_2Cl_2, R_f 0.4) to give 75 mg of crude **7** with mixed Cl^- and HPO_4^{2-} counterions. This material was dissolved in several milliliters of H_2O and washed through a column of 30 g (102 mequiv) of Dowex 1-X8 ion-exchange beads (Cl^- form). The eluted solution was lyophilized to dryness, and the residue was again purified by TLC (see above) to give LL-**7**, which was recrystallized from a minimum quantity of 1:10 CH_2Cl_2/Et_2O. We obtained 22 mg (17%) of white crystalline, hygroscopic LL-**7**: mp 93–95 °C. NMR (200 MHz, δ, $CDCl_3$) 0.88 (t, $J = 5$ Hz, 3 H, term. CH_3), 1.24 (s, 20 H, $(CH_2)_{10}$), 1.40–2.10 (m, "4 H", H_β + H_α Pro + H_2O peak at 1.84), 2.90–3.45 (m, 14 H, $CH_2N^+(CH_3)_2CH_2CH_2S$ + H_β Trp), 3.85 (m, 2 H, H_δ Pro), 4.57 ("d", $J = 4$ Hz, 1 H, H_α Pro), 5.10 (m, 3 H, CH_2Ph + H_α Trp), 5.75 (d, $J = 5$ Hz, 1 H, Z-N*H*), 7.1–7.8 (m, 11 H, CH_2Ph) + indole). Anal. Calcd for $C_{40}H_{59}ClN_4O_4S \cdot 0.5H_2O$: C, 65.2; H, 8.08; N, 7.61. Found: C, 65.1; H, 8.31; N, 7.66.

N-Carbobenzyloxy-D-tryptophan-L-proline Thioester with N-n-Dodecyl-N,N-dimethyl-N-(β-thioethyl)ammonium Chloride (DL-7). DL-**7** was prepared from 100 mg (0.18 mmol) of DL-**2** and 80 mg (0.26 mmol) of 12-SH (**3**) exactly as described above for the LL-**7** isomer. An identical purification sequence afforded 18 mg (14%) of white crystalline hygroscopic DL-**7**; mp 90–92 °C (softening), 98–100 °C (melting); NMR (200 MHz, δ, $CDCl_3$) 0.90 (t, $J = 4$ Hz, 3 H, term. CH_3), 1.25 (s, 20 H, $(CH_2)_{10}$), 1.40–2.10 (m, "4 H", H_β + H_γ Pro + H_2O peak at 1.65), 2.75–3.60 (m, 16 H, $CH_2N^+(CH_3)_2CH_2CH_2S$ + H_β Trp + H_δ Pro), 4.35 (m, 1 H, H_α Pro), 4.80 (m, 1 H, H_α Trp), 5.15 (m, 2 H, CH_2Ph), 5.92 (d, $J = 4$ Hz, 1 H, Z-N*H*), 7.0–7.65 (m, 10 H, CH_2Ph + indole), 8.9 ("s", 1 H, indole N*H*). Anal. Calcd for $C_{40}H_{59}ClN_4O_4S \cdot 0.5H_2O$: C, 65.2; H, 8.08; N, 7.61. Found: C, 65.1; H, 8.23; N, 7.48.

Quantitative Studies. *Critical micelle concentration* studies were carried out either by the surface tension method (**4** and **5**)[15] or by determining a rate constant/[surfactant] profile with PNPA (**3**). The surface tension results are summarized in the "Results".[36] The kinetic cmc determination of **3** is discussed in the "Results"; cf. Figure 1 and Table I. *Kinetic studies* are described in detail in "Results"; cf. Tables I–III and Figures 1 and 2. Conditions are described in the text and table notes. For a more extensive description, see the Experimental Section of ref 11. *Light scattering measurements* and apparatus are described in detail in the "Results", cf. Tables IV–IX and Figure 2.

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Registry No. D,L-**2**, 74992-65-7; L,L-**2**, 74992-61-3; **3** (12-SH), 87251-91-0; **4**·(Br^-), 7009-61-2; **4**·($^-$OTF), 92421-69-7; **4**·(Cl^-), 2271-92-3; **5** (12-Me_3), 112-00-5; **6**, 92421-71-1; **6**·(Cl^-), 92421-72-2; L,L-**7**, 92421-73-3; D,L-**7**, 92421-74-4; **8**, 50826-87-4; Z-D-Trp-L-Pro-OH, 79416-17-4; Z-L-Trp-L-Pro-OH, 79416-13-0; PNPA, 830-03-5; 1-bromododecane, 143-15-7; *N,N*-dimethylethanolamine, 108-01-0; triflic anhydride, 358-23-6; thioacetic acid, 507-09-5; 1-chlorododecane, 112-52-7; trimethylamine, 75-50-3; *N*-carbobenzyloxy-L-proline *p*-nitrophenyl ester, 3304-59-4; L-proline *p*-nitrophenyl ester hydrogen bromide, 2390-84-3; *N*-carbobenzyloxy-L-tryptophan, 7432-21-5; D-tryptophan, 153-94-6; *N*-Cbz-D-tryptophan, 2279-15-4; *N*-carbobenzyloxy-D-tryptophan-L-proline methyl ester, 92421-75-5; L-proline methyl ester hydrochloride, 2133-40-6; *N*-carbobenzyloxy-L-tryptophan-L-proline methyl ester, 55782-87-1.