J|A|C|S
COMMUNICATIONS

Exposure of Self-Assembly Interiors to External Elements. A Kinetic Approach

Fredric M. Menger* and Lei Shi

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received April 21, 2006; E-mail: menger@emory.edu

As with many seeds and larvae, partially solved problems in science tend to lie dormant for years, poised to emerge abruptly when conditions become more favorable. Such is the case for micelle structure. At one time, there was concern by many chemists,[1−5] including ourselves,[6−8] over the degree of chain exposure to the external medium (either by water entering the micelles or by chains looping into the bulk water). Despite all the attention, the issue of chain disorder and hydration was never fully resolved,[9] and it quietly vanished from the scene. We now interrupt our “hibernation” by describing a new kinetic approach for investigating chain exposure that can be applied not only to micelles but also to self-assemblies in general. The presence or absence of chain/water contact is important; no description of a self-assembly is complete without it.

A key feature of our approach entailed replacing a methylene by a sulfur in the thio-surfactants of Table 1 as synthesized in Scheme 1 (see details in Supporting Information). However, the synthesis began only after satisfying ourselves that the thioether unit is hydrophobic and (like the methylene it replaces) not prone to abnormally seek out an aqueous environment. Evidence for this assertion comes in part from protein chemists who consider methionine a hydrophobic residue. For example, O’Neil and DeGrado reported that eight exposed methionine side chains of calmodulin bind diverse nonpolar surfaces on associative partners.[10] Gellman commented that the unusually large polarizability of the sulfur atom generates binding sites that are tailored for strong dispersive interactions with nonpolar surfaces.[11] The Hansch partition constant between octanol and water for $-SCH_3$ favors octanol ($\pi = 0.45$), whereas the constant for $-OCH_3$ favors water ($\pi = -0.47$).[12] Affinity toward water of the “soft” sulfur atom is unfavorable owing to its poor H-bond acceptor properties.[13] Thus, a sulfur serves as a reasonably innocuous entity[14] in contrast to fluorescence, spin label, and other probes common in the literature.[15]

Table 2 gives surface-tension-based critical micelle concentrations (CMC) and steady-state-fluorescence-based aggregation numbers (N_{agg}) for six thio-surfactants and four conventional surfactants. Sulfur perturbations on the CMC and N_{agg} parameters are seen to be of little import. For example, the CMC for **2−10** with 12 chain-carbons is 14 mM, compared to 13 mM for DTAB also with 12 chain-carbons. Thio-surfactants **6−8** and **8−6** have CMCs of 6.5 and 6.6 mM, compared to 3.3 mM for TTAB (all with 14 carbons). Significant differences relative to an all-carbon analogue, OTAB, were found only for the two-sulfur surfactant, **6−6−6**. Intramolecular S/S interactions are a possible cause for this deviation. In any event, the data of Table 2 support the notion that micelles composed solely of mono-thio-surfactant are not dramatically altered by their sulfur content.

Table 1. Structure of the Thio-surfactants[a]

	$CH_3(CH_2)_nS(CH_2)_mN(CH_3)_3{}^+Br^-$	
thio-surfactant	*n*	*m*
3-3	2	3
2-10	1	10
6-6	5	6
6-8	5	8
8-6	7	6
8-8	7	8

[a] In addition, a two-sulfur thio-surfactant, **6-6-6**, was prepared with the structure $CH_3(CH_2)_5S(CH_2)_6S(CH_2)_6N(CH_3)_3{}^+Br^-$.

Scheme 1. Synthetic Route to Thio-surfactants in Table 1

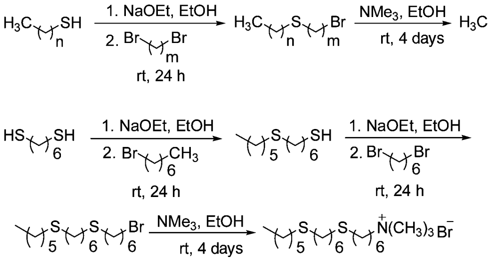

Table 2. Critical Micelle Concentrations and Aggregation Numbers of Thio-surfactants and Conventional Surfactants

surfactant	CMC, mM[d]	N_{agg}[b,d]
2-10	14	78
6-6	22	60
6-8	6.5	54
8-6	6.6	51
8-8	2.7	46
6-6-6	1.9	29
DTAB[a]	13	63
TTAB[a]	3.3	82
CTAB[a]	0.82	108
OTAB[a]	0.29	230[c]

[a] Refers to dodecyl-, tetradecyl-, cetyl-, and octadecyltrimethylammonium bromide. See ref 16. [b] Measured at thio-surfactant concentrations 5−8 times their CMCs. [c] At 40 °C. [d] CMC and N_{agg} values had uncertainties of ±5% and ±10%, respectively.

Rate constants for thioether oxidation to sulfoxide were determined by proton NMR (D_2O, 20 °C) under the following conditions: thio-surfactant (8 mM) was admixed with a 10-fold molar excess of a conventional anionic surfactant, sodium dodecyl sulfate (SDS). The 80 mM SDS concentration was also 10-fold higher than its own CMC. These conditions were deliberately chosen because a low thio-surfactant concentration minimized any (inherently minor) perturbation by the sulfur to the overall SDS micelle structure. Adding 8 mM thio-surfactant **8−6** to 80 mM SDS had only a small effect on N_{agg} (increasing it from 81 to 88).

The percentage of thio-surfactant residing in the free solution was considered kinetically insignificant. This implies that rate constants reflect only micelle-bound substrates. Three factors favor total binding of the thio-surfactants to the excess SDS: (a) Association constants between SDS and even mildly “hydrophobic” cations are large (e.g., $K_{assoc} = 1.6 \times 10^4$ for Bu_4N^+).[17] Similarly, a “very large synergetic effect” was noted between cationic and anionic surfactants.[18] (b) Cooperative hydrophobic and electrostatic

10.1021/ja062807i CCC: $33.50

Table 3. Oxidation Rates of Thio-surfactants, Co-micellized into SDS Micelles, by IO_4^- or H_2O_2 at 20 °C in D_2O

thio-surfactant	IO_4^- k_2[a,c] 10^{-3} s^{-1} M^{-1}	rel. k_2	H_2O_2, k_2[b,c] 10^{-3} s^{-1} M^{-1}	rel. k_2
3-3	2300	190	5.0	3.8
2-10	26	2.2	2.4	1.8
6-6	28	2.3	2.2	1.7
6-8	18	1.5	1.9	1.5
8-6	16	1.3	1.4	1.1
8-8	12	1.0	1.3	1.0
6-6-6	23, 31[d]	1.9, 2.6	1.6, 2.9	1.2, 2.2

[a] **3-3** was studied without SDS and served as a control. All thio-surfactants (8 mM) were studied with SDS (80 mM) and at five IO_4^- concentrations (80−240 mM). [b] Thio-surfactants (8 mM) were studied with SDS (80 mM) and at five H_2O_2 concentrations (800−2400 mM). [c] Plots of k_{obs} versus [oxidant] were linear ($R^2 = 0.97$); their slopes gave k_2 values with uncertainties of <10%. [d] The two numbers represent oxidation rates of the two sulfurs in **6-6-6**.

attraction between comparable quantities of cationic and anionic surfactants leads to huge micellar growth, vesicular association, or outright precipitation.[19,20] (c) Most convincingly, our rate constants are independent of the excess SDS concentration, an observation consistent with an absence of external monomeric substrate and subsequent nonmicellar reactivity.

After adding periodate (80−240 mM) to the above micellar system, we quantitatively monitored the ensuing appearance of sulfoxide α-methylenes in the NMR for more than two half-lives. (After several days, sulfone was formed, but it was not followed.) Data from linear pseudo-first-order plots gave the second-order rate constants (k_2) recorded in Table 3.[21] One sees from columns 2 and 3 that monomeric **3−3**, with no SDS present, is oxidized 2 orders of magnitude faster than any of the micellized thio-surfactants. By way of comparison, SDS micelles inhibit hydroxide-catalyzed hydrolysis of a hydrophobic ester by a factor of 15.[22]

Importantly, all the thio-surfactants reacted at roughly the same rates, indicating that oxidation rates are largely independent of the sulfur position within the chains. The simplest explanation is that the anionic SDS micelle surface electrostatically repels anions, and that all the chain loci access this periodate-depleted surface at about the same frequency. Alternatively, oxidation may originate in part from low levels of IO_4^- entering concavities within a porous self-assembly. Either way, the kinetics provide strong evidence for chain disorder within SDS micelles, a point that we have previously touted.[6−8]

A quite different behavior emerges when H_2O_2, a nonionic oxidant, was used instead of anionic IO_4^- (Table 3, columns 4 and 5). In this case, all six thio-surfactants were oxidized at a rate only slightly smaller than that of monomeric **3−3** in the free solution. We interpret this result as indicating that H_2O_2 (which would be excluded from the hydrocarbon regions of the micelle interior)[23] is not electrostatically repulsed from the SDS micelle surface. Our kinetic data also indicate that the H_2O_2 at the micelle surface, or possibly in aqueous micellar concavities, has roughly equal access to the sulfurs independent of their positions on the surfactant chains. Oxidation of "interior" sulfur groups manifests itself not only in anionic SDS micelles but also in cationic TTAB micelles, as well (see Supporting Information).

The 100-fold rate decrease with IO_4^- oxidation compared to no substantial decrease with H_2O_2 oxidation (Table 3) is basic to the understanding of our micellar systems. If the slow IO_4^- oxidation rates with SDS micelles were attributed (erroneously, as we have already argued) to low levels of rapidly reacting material in the free solution, then the corresponding H_2O_2 oxidation rates would have been similarly inhibited. Thus, there is only one explanation consistent with both sets of data: all sulfur loci have equal access to the SDS micelle surface, a surface that has a diminished IO_4^- concentration but a relatively normal H_2O_2 concentration. The picture that emerges, therefore, is a micelle in which disordered chains are rapidly rearranging to equalize chain exposure to water and the elements therein.

We have assumed, based on the properties of thioethers,[10−14] that the thio-surfactant chains buried within the SDS micelles possess conformational populations comparable to those of their SDS neighbors. Only if our assumption is correct can the results be extrapolated to conventional surfactants, but whether the thio-surfactants fold and twist anomalously or not, it is instructive that sulfur exposure at the micelle surfaces is independent of the sulfur atom position within the chains.

Oxidation rates of sulfur labels can be used to assess chain exposure to the external medium not only in micelles but also in a variety of other self-assemblies and polymeric systems wherever the NMR resolution so permits.

Acknowledgment. This work was supported by the Petroleum Research Foundation and the National Institutes of Health. We thank Dr. Syed Asad Rizvi of Georgia State University for his help in obtaining the aggregation number data. We also thank Dr. Dan Lundberg for useful discussions.

Supporting Information Available: Synthetic procedures, characterizations of new compounds, and detailed descriptions of experimental methods. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Wennerstroem, H.; Lindman, B. *J. Phys. Chem.* **1979**, *83*, 2931.
(2) Svens, B.; Rosenholm, B. *J. Colloid Interface Sci.* **1973**, *44*, 495.
(3) Dill, K. A.; Flory, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 676.
(4) Fromherz, P. *Chem. Phys. Lett.* **1981**, *77*, 460.
(5) Gruen, D. W. R. *J. Colloid Interface Sci.* **1981**, *84*, 281.
(6) Menger, F. M. *Acc. Chem. Res.* **1979**, *12*, 111.
(7) Menger, F. M.; Doll, D. W. *J. Am. Chem. Soc.* **1984**, *106*, 1109.
(8) Menger, F. M. *Nature* **1985**, *313*, 603.
(9) See: Menger, F. M.; Zana, R.; Lindman, B. *J. Chem. Educ.* **1998**, *75*, 115 for a brief discussion of the subject.
(10) O'Neil, K. T.; DeGrado, W. F. *Trends Biochem. Sci.* **1990**, *15*, 59.
(11) Gellman, S. H. *Biochemistry* **1991**, *30*, 6633.
(12) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525.
(13) Allen, F. H.; Bird, C. M.; Rowland, R. S.; Raithby, P. R. *Acta Crystallogr., Sect. B: Struct. Sci.* **1997**, *B53*, 696.
(14) Sokolowski, A. *J. Phys. Chem.* **1989**, *93*, 8223.
(15) Menger, F. M.; Jerkunica, J. M.; Johnston, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4676. See Table 2.
(16) (a) Barry, B. W.; Russell, G. F. J. *J. Colloid Interface Sci.* **1972**, *40*, 174. (b) Berr, S. S.; Caponetti, E.; Johnson, J. S., Jr.; Jones, R. R. M.; Magid, L. J. *J. Phys. Chem.* **1986**, *90*, 5766. (c) Swanson-Vethamuthu, M.; Almgren, M.; Karlsson, G.; Bahadur, P. *Langmuir* **1996**, *12*, 2173.
(17) Pradines, V.; Lavabre, D.; Micheau, J.-C.; Pimienta, V. *Langmuir* **2005**, *21*, 11167.
(18) Holmberg, K.; Jönsson, B.; Kronberg, B.; Lindman, B. *Surfactants and Polymers in Aqueous Solution*; John Wiley & Sons: Chichester, UK, 2002.
(19) Kaler, E. W.; Murthy, A. K.; Rodriguez, B. E.; Zasadzinski, J. A. *Science* **1989**, *245*, 1371.
(20) Li, G.-Z.; Li, F.; Zheng, L.-Q.; Wang, H.-L. *Colloids Surf., A* **1993**, *76*, 257.
(21) For a thorough kinetic analysis of micellar oxidations of aryl sulfides, see: Yao, H.; Richardson, D. E. *J. Am. Chem. Soc.* **2003**, *125*, 6211.
(22) Behme, M. T. A.; Fullington, J. G.; Noel, R.; Cordes, E. H. *J. Am. Chem. Soc.* **1965**, *87*, 266.
(23) Walton, J. H.; Lewis, H. A. *J. Am. Chem. Soc.* **1916**, *38*, 633.

JA062807I