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A Non-Steroidal Facial Amphiphile

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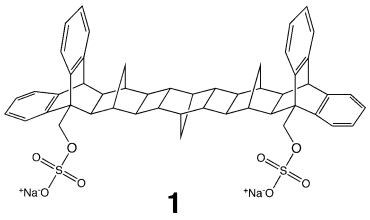
Synthetic amphiphiles most commonly consist of a polar group attached to a long hydrocarbon chain. Dissolving such amphiphiles in water produces micelles and other hydrophobically driven self-assemblies. Rigid hydrophobic surfaces, like the flexible linear chains, also induce association, a fact that Nature has exploited to great advantage. Bile salts (steroids with a hydrophobic α-side and a hydrophilic β-side)[1] and certain helical peptides with hydrophobic patches[2] are common examples. Attempts to synthesize nonpeptidal "facial amphiphiles" have centered mainly on steroidal systems. Thus, Kahne et al.[3] glycosylated the α-face of cholic acid, while Marcelis et al.[4] and Zhao et al.[5] placed three α-ammonium groups on the same steroid. Savage et al.[6] synthesized anionic facial amphiphiles from cholic acid. Elemans et al.[7] departed from the cholic acid motif with their glycouril-based facial amphiphiles. We have now synthesized non-steroidal facial amphiphile **1** that possesses two water-solubilizing sulfates on one face and a rigid wall of hydrophobicity on the other. As will be shown, the properties of **1** are markedly different from those of sodium dodecyl sulfate (SDS), a long-chain counterpart of **1**.

Scheme 1



1

Synthesis of **1** (Figure 1) followed in part the work of Feldman et al.[8] The Ni-catalyzed cycloaddition reaction of norbornadiene gave both dimer and trimer that were separated by fractional sublimation (65 and 127 °C). Diels−Alder reaction of the trimer with methyl 9-anthracenecarboxylate gave both syn and anti diesters that were separated by chromatography (see details in the Supporting Information). Proof of isomer structure relied on an X-ray analysis of the syn diester (Figure 2). Compound **1** had the expected ^{1}H and ^{13}C NMRs and an HRMS molecular weight calcd for $C_{51}H_{47}O_8Na_2S_2$ of 897.24997 $(M + H)^+$, found 897.25023. The anti isomer of **1** was also prepared, but it was too water-insoluble to warrant further study.

Evidence supporting an affinity of **1** for a hydrocarbon interface came from the following experiment: 3 mg of **1** was dissolved in 2.5 mL of water and vortexed for 10 min with 2.5 mL of toluene. This resulted in an o/w emulsion whose photomicrograph (20X) is given in Figure 3. No change in the size distribution of the droplets was observed after more than 6 months.

A 40.1 mM aqueous solution of **1** is noticeably viscous, suggesting solute aggregation. Microrheology measurements (obtained by analyzing the Brownian motion of suspended carboxylate-modified polystyrene particles bearing a fluorescent tag) on a freshly made solution gave a value of 170 ± 10 mPa·s. Since this value

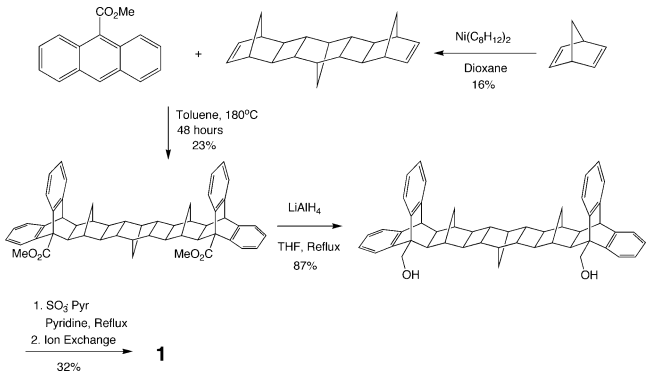


Figure 1. Synthesis of **1**.

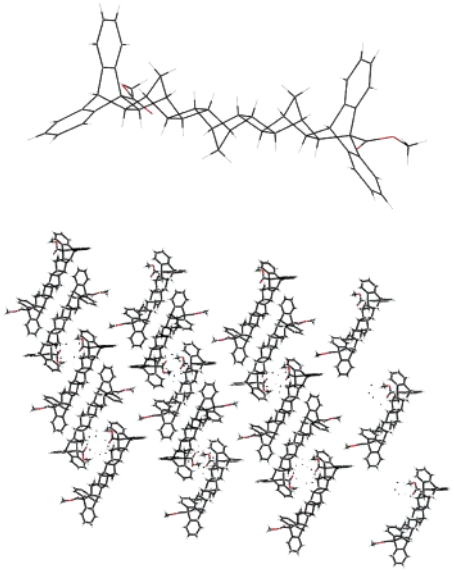


Figure 2. X-ray crystal structure of the syn trimer diester in Scheme 1.

reached 1100 ± 100 mPa·s after 6 days of aging, aggregation does not reach full equilibrium instantly as it does with SDS. Aggregation was further indicated by a ^{1}H NMR spectrum in D_2O where, in contrast to a normal sharp spectrum in CD_3OD, the peaks were obliterated owing to slow intra-aggregate tumbling. Defining aggregate size by dynamic light scattering was not possible because of a high polydispersity.

Surface tension versus log [conc] plots of **1** bear little resemblance to those of SDS (Figure 4A). Although SDS has a sharp break corresponding to its critical micelle concentration, **1** displays no such behavior; aggregation must be stepwise rather than cooperative. Moreover, **1** is less surface active than SDS (e.g., 63 vs 38 mN/m, respectively, at 15 mM). Consistent with previous work,[9] the larger area/molecule of **1** tends to adversely affect its surface activity. Additionally, the rigidity of the structure might impair the packing density at the air/water interface.

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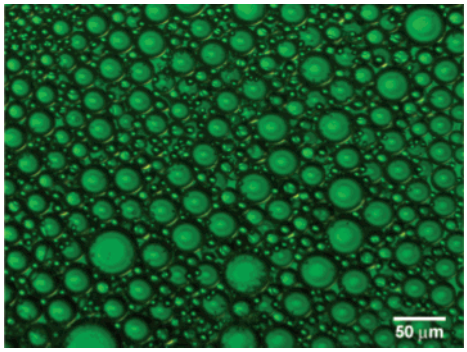

Figure 3. Photomicrograph (phase contrast, green filter) of an o/w emulsion stabilized by **1** in which toluene droplets are suspended in water. The emulsion is stable for many months.

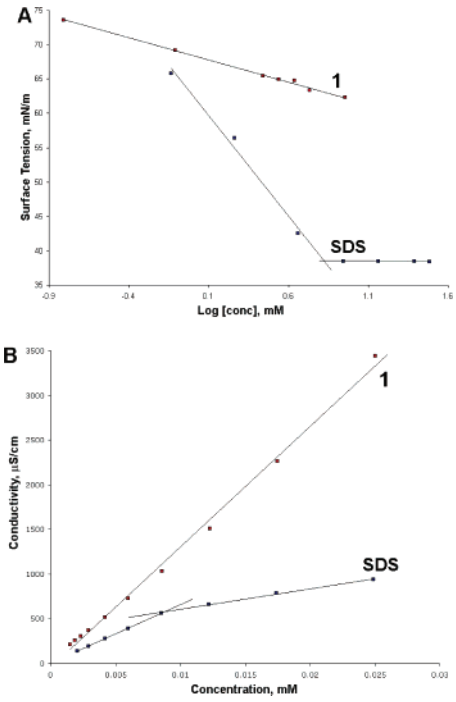

Figure 4. (A) Surface tension versus log [conc]. (B) Conductivity versus [conc] for **1** in water at room temperature.

Conductivity versus [conc] plots for **1** likewise do not show the abrupt change in slope accompanying micellization as seen with SDS (Figure 4B). The slope decrease at the CMC of SDS has been attributed to 63% of the sodium counterions binding tightly to the micelles.[10] Linearity with **1**'s conductivity plot thus indicates full sodium ion dissociation from the aggregates. Wide spacing of the sulfate groups in **1** must lead to a less compact anionic surface, relative to that in spherical SDS micelles, and therefore to a diminished electrostatic attraction toward the cationic counterions.

Cryo-high-resolution scanning electron microscopy[11] of a 6-day-aged sample of 32 mM **1** (10^4X instrumental magnification) showed a thick-walled (0.2 μm) network (Figure 5). As with X-ray

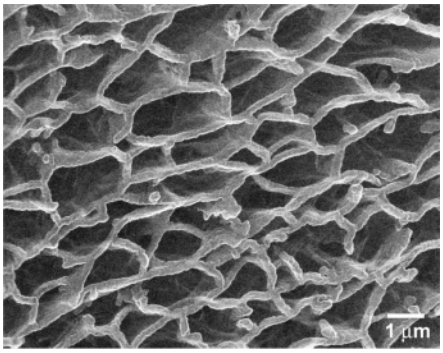

Figure 5. Cryo-HRSEM at 10^4X instrumental magnification; bar = 1 μm.

spectroscopy, caution must be exercised before extrapolating cryo-HRSEM to the solution state with which we have been primarily concerned.[12] Nonetheless, Figures 2 and 4, plus an observed birefringence under cross polarizers, are all consistent with a propensity of **1** to form lamellar sheets that grow in a noncooperative manner while enhancing the solution viscosity.

Until just recently, **1** was merely a virgin molecule unaddled by investigation. Future synthetic organic chemistry will no doubt bestow upon us additional facial amphiphiles whose solution properties presently defy prediction and thus pique curiosity.

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Note Added after ASAP Publication. After this paper was published ASAP on March 28, 2006, a production error in the text of the third sentence of the first paragraph was corrected to restore the authors' intended meaning. The corrected version was published ASAP on March 30, 2006.

Supporting Information Available: Analytical and synthetic procedures including spectroscopic data and instrumentation. This material is available free of charge via the Internet at http://pubs.acs.org.

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