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SYNTHESIS AND PROPERTIES OF A SURFACTANT-CYCLODEXTRIN CONJUGATE

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Summary: A surfactant-cyclodextrin conjugate, in which an ion-terminated chain is attached to each of the seven cyclodextrin sugars, has been synthesized and examined by a variety of physical methods.

Micelles are spherical aggregates of roughly 50-100 surfactant molecules each comprised of a polar head-group and a long hydrocarbon chain. A vast literature has been devoted to reactions inside micelles owing, in part, to their superficial resemblance to enzyme-catalyzed processes. Micelles can bind guest molecules, for example, with association constants rivaling those for many enzymes and substrates.[1] Binding to micelles often leads to catalyzed reactions obeying Michaelis-Menten kinetics.[2] Stereoselectivity is possible with micelles composed of chiral surfactants.[3] Yet there is a rather serious disadvantage of micellar systems: To observe micellar effects, the surfactant concentration must exceed a critical micelle concentration. Otherwise, the surfactant exists entirely in the monomeric state. Thus, it is natural to consider tying several chains together covalently in order to prevent them from dissociating. Such a multi-armed or "tentacle" compound could behave like a micelle at all concentrations. Our first example of such a system, "hexapus",[4] does indeed manifest micellar properties. We now report a second example in which an ion-terminated chain is attached to each of the seven sugar moities of a ß-cyclodextrin (partial structure 5 in Figure 1). The "conjugate" possesses a two-part cavity: a rigid space within the cyclodextrin ring adjacent to a flexible region among the seven chains that project from the cyclodextrin periphery.

Synthesis of 5 was accomplished according to Figure 1 using the ensuing conditions. 2: literature procedure,[5] 54%. 3: reflux 27 hr in benzene DMF (9:1) with periodic replenishment of NaH and DMF, 36%.[6] 4: 0° for 20 min and 4 hr at 24° with excess borane complex in THF followed by overnight refluxing after addition of ethanol, 3N NaOH, and 30% H_2O_2, 89%.[7]

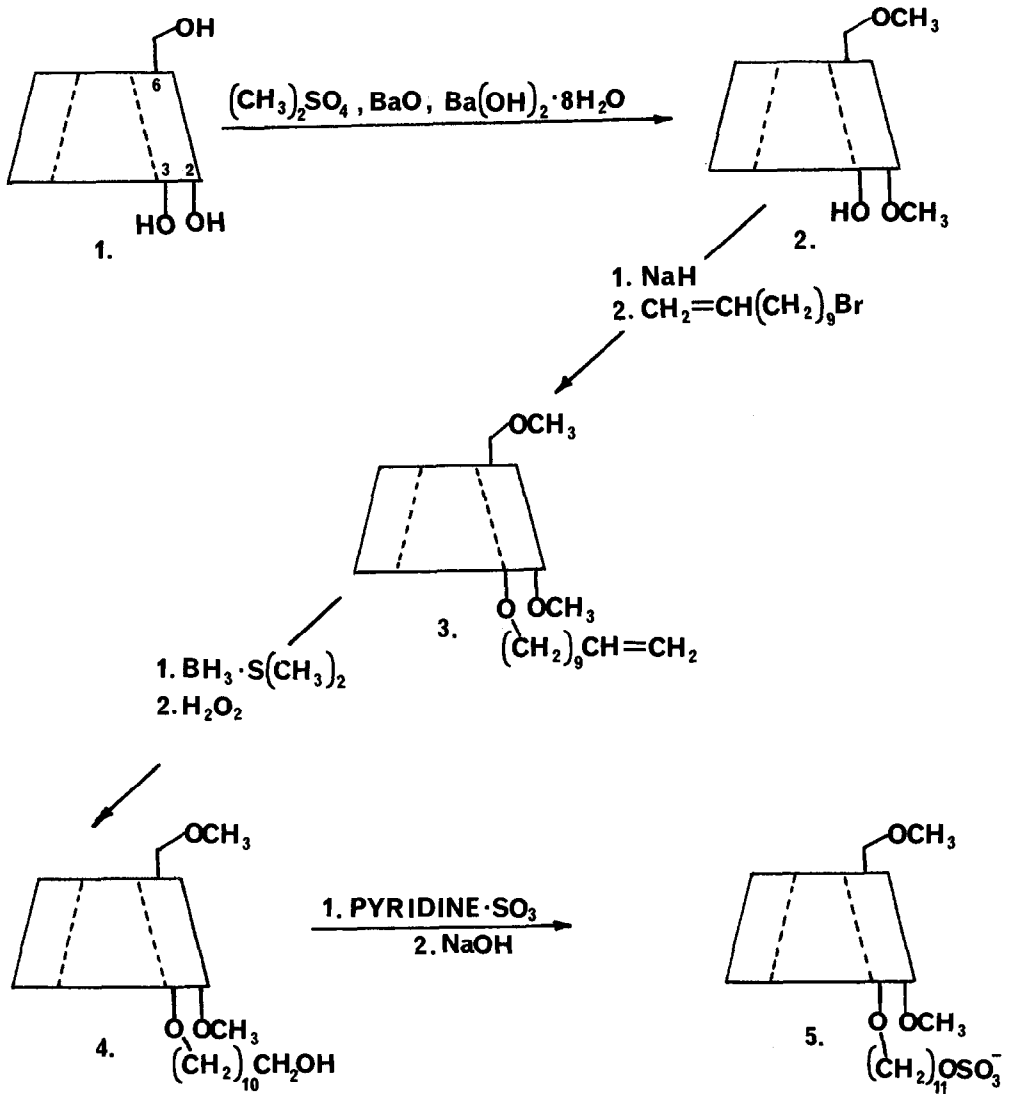

Figure 1. Synthesis of a surfactant-β-cyclodextrin conjugate. Note that for the sake of clarity only one cyclodextrin sugar is indicated, but in actual fact all seven sugars are identically derivatized except for 5 where 6 out of 7 hydroxyls are sulfonated.

5: 25 hr at 24° in pyridine, 76%.[8] Elemental analysis and spectroscopic characterization of the final product, namely the surfactant-cyclodextrin conjugate 5, indicated that only 6 out of 7 terminal hydroxyls were sulfonated. Since total sulfonation was neither feasible nor absolutely necessary, we performed our experiments with the material on hand.

A plot of surface tension vs. [5] in water shows that 5 is mildly surface active (S.T. = 50 dynes/cm at 8 mM) but devoid of a critical micelle concentration (i.e. there is no sharp break in the curve). Light scattering data, in which scattering ratios[9] are plotted vs. [5] down to 0.2 mM, display the linearity expected when a CMC is absent. Yet the light scattering experiments also reveal an unexpected behavior: the slopes of the linear plots increase dramatically with time as if 5 forms aggregates that progressively enlarge. For example, a scattering ratio vs. [5] plot has an 11-fold greater slope with a 5-day old solution (kept at 24°C) than with a fresh solution. The corresponding aggregation number (i.e. number of molecules per aggregate, A.N.) are 15 and 1.3, respectively. Slow growth to an A.N. = 3 was observed after 2 weeks of standing at 6°C. Sonication greatly accelerates the aggregation process. Thus, bath sonication of 0.34 mM 5 leads to a limiting A.N. value of 45 after 20 minutes. The situation is complicated, however, since the limiting A.N. is concentration-dependent: When [5] = 4.8 mM, the limiting A.N. is only about 4. In summary, the surfactant-cyclodextrin conjugate 5 differs from an ordinary single-chain surfactant in two ways: (a) the former possesses no critical micelle concentration and (b) it aggregates over hours or days as opposed to microseconds.

The ability of 5 to solubilize lipophilic materials in water was measured spectroscopically and compared with that of sodium dodecyl sulfate (SDS). For example, 0.10 M SDS solubilizes 61 mmoles naphthalene per mole of SDS; in contrast, 0.003 M 5 solubilizes 470 mmoles naphthalene per mole of 5. If one calculates the solubilization capacity on a "per arm" basis (i.e. divides 470 by 7), then it is seen that SDS micelles and 5 behave similarly. The same holds true for the two hosts toward several other solubilizates including 1-phenylhexane and nonyl phenyl ether. In one respect, however, 5 surpasses SDS in solubilization ability. The conjugate enhances solubility at low concentrations (e.g. 0.003 M) where SDS is monomeric and thus relatively ineffective.

There is no indication that the cyclodextrin and tentacle portions of 5 "cooperate"[10] in the binding of guests. Indeed, it appears that association to 5 occurs entirely among the seven arms with the cyclodextrin cavity contributing little. Dodecyl phenyl ether (which could conceivably place its aromatic ring inside the cyclodextrin cavity and its chain among the tentacles) shows no special affinity for 5. Fluorescence emission spectra of "naphthalene plus 5" are superimposable on "naphthalene plus SDS" but not "naphthalene plus β-cyclodextrin."[11] Apparently, the flexibility of the tentacles permits an "induced" or "custom" fit, an effect not possible with the rigid cyclodextrin. In competition between flexibility (and non-specificity) vs. rigidity (and specificity), the former wins out.

The cationic dye, pinacyanol chloride, binds to 5 with an association constant equal to $7.6 \times 10^3\ M^{-1}$ (measured by the Benesi-Hildebrand method at λ = 610 nm, 25.0°, pH = 9.0). No binding was observed between the dye and either β-cyclodextrin or 2,6-dimethyl-β-cyclodextrin. Interestingly, low levels of 5 are able to protect the dye against light-induced fading. Thus, a 1.0×10^{-5} M dye solution loses 75% of its original absorbance at 600 nm after 15 hr direct sunlight, whereas only 25% is lost in the presence of 2.3×10^{-4} M conjugate. The mechanism of protection is not understood.

The micropolarity of the binding site of 5 was probed using phenol blue (a dye which has a λ_{max} = 575, 605, 609, 668 nm in benzene, ethanol, methanol, and water, respectively). Since the complex between the dye and 5 has a λ_{max} of about 650 nm, the probe is obviously bathed in a highly aqueous environment (even more polar than when the dye resides in an SDS micelle where λ_{max} = 634 nm). Host-guest association must take place in a water-rich region among the tentacles.

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