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Adaptive Dendron: A Bile Acid Oligomer Behaving as *Both* Normal and Inverse Micellar Mimic

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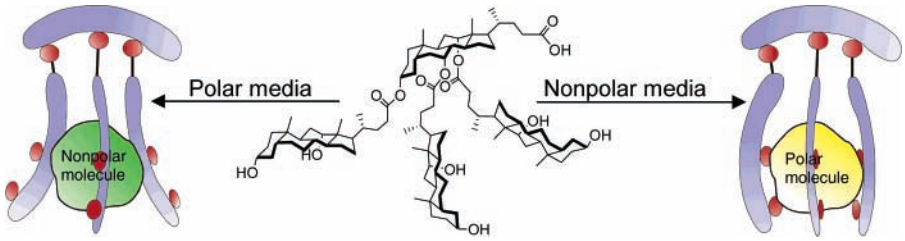
ABSTRACT



The normal and inverse micellar property of a bile-acid-based dendritic structure was established through dye solubilization studies in both polar and nonpolar media.

During the past two decades, dendritic structures and dendrimers have been utilized in a variety of applications including host−guest chemistry, catalysis, metaloorganic chemistry, light harvesting, and drug delivery.[1] An important structural feature of the dendritic architecture is their resemblance to micellar structures and hence they are often described as covalently linked micelles.[2] Micellar structures, which can solubilize guest molecules in their core,[3] do so only above the critical micellar concentration (CMC) of the detergents, and this technique (dye solubilization) has routinely been used to determine the CMC values. With dendrimers, the "micellar structures" are maintained at all concentration ranges and thus the guest solubilization increases *linearly* with concentration. Newkome et al. have described such structures as "unimolecular micelles".[4] Depending upon the nature of the interior, they have the ability to either solubilize[5] a polar guest molecule in a relatively nonpolar solvent or vice versa. Regen et al. have described a bile-acid-based "molecular umbrella"[6] that can change its conformation as a function of solvent polarity. Also, Kobuke

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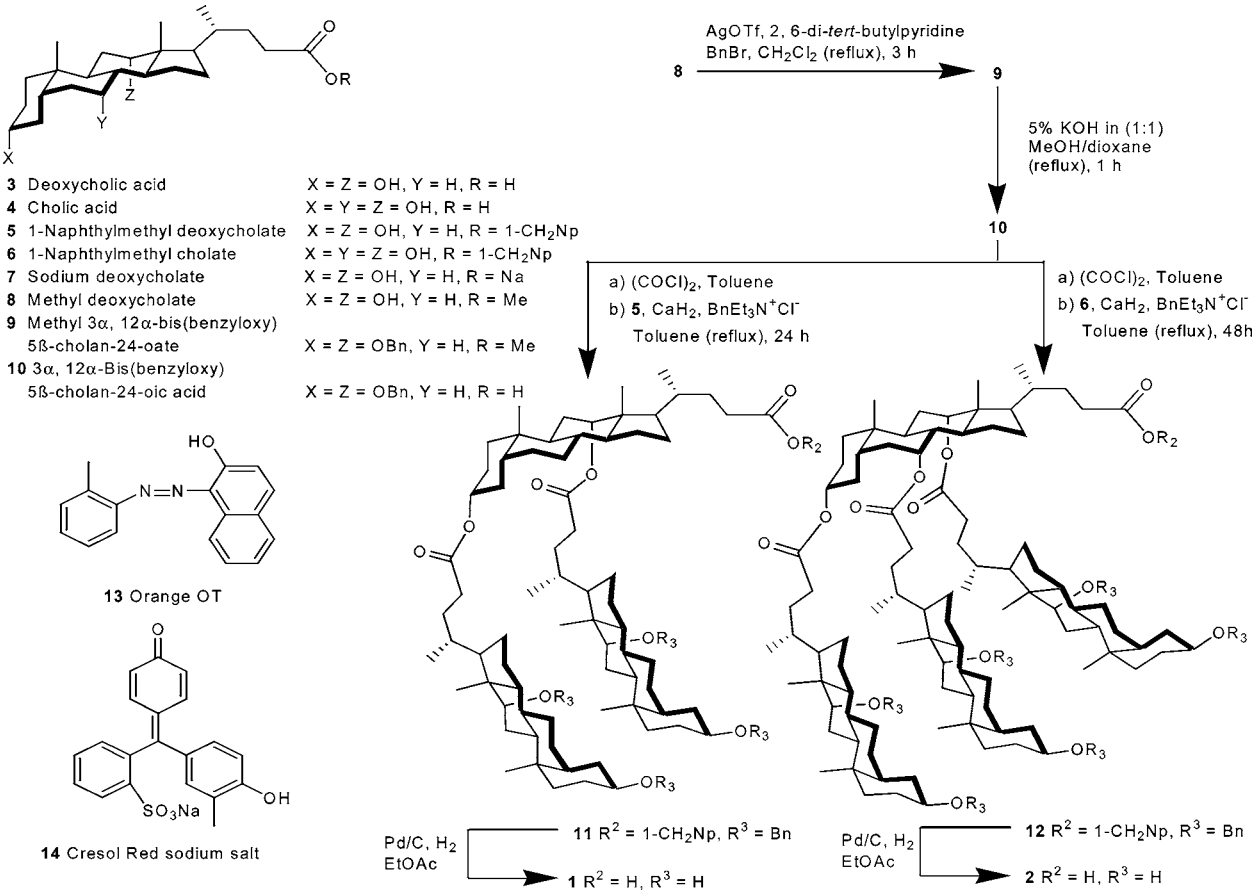
Scheme 1



et al. have used an amphiphilic bile acid unit for the construction of a supramolecular transmembrane ion channel.[7] In this communication we report the synthesis of small dendritic bile acid oligomer with a remarkable ability to act as *both* normal and inverse micelles owing to the *facially amphiphilic* nature of the bile acid backbone.

Bile acids are naturally occurring rigid, chiral molecules with unique facial amphiphilicity.[8] A few years ago we initiated a long-term research program to design bile-acid-based dendritic structures for a variety of applications. We[9] and others[10] have reported the synthesis of bile-acid-based chiral dendritic species. Our earlier work resulted in dendrons in which the hydroxy groups located on the peripheral bile acid units were protected as acetates, in which the facial amphiphilicity was lost. We reasoned that dendritic species with bile acid fragments bearing free hydroxy groups on the periphery are likely to adopt different conformations ("foldamers")[11] in solvents of different polarities, through different modes of intramolecular association of the peripheral bile acid units depending upon the media, enabling them to act as both intramolecular normal and inverse micelles (Figure 1).[12,13] To synthesize the dendritic species, orthogonally protected bile acid components **5**, **6**, and **10**[14] were synthesized. Compound **10** was combined[15] with **5** and **6** to get **11** and **12**, respectively (Scheme 1). Finally, the protecting groups were removed by hydrogenolysis, and the dendritic structures (trimer **1**[16] and tetramer **2**[17]) with free peripheral hydroxyl and carboxyl groups were obtained.

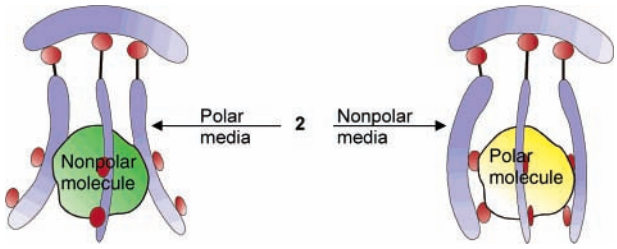


Figure 1. Cartoon representation of possible folding and guest solubilization ability of an "adaptive dendron" serving as both micellar and inverse micellar mimics.

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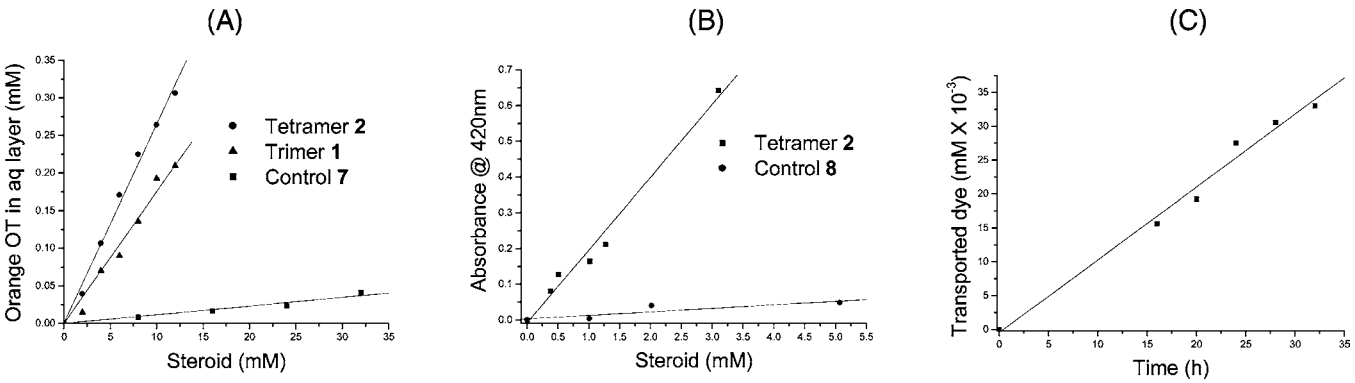

Figure 2. (A) Concentration dependence of Orange OT extraction from hexane to MeOH/H_2O (1:1) after 12 h, $r = 0.996$ for **2**, 0.991 for **1**, and 0.981 for **7**. (B) Concentration dependence of solubilization of **14** in chloroform following solid−liquid extraction protocol after 48 h, $r = 0.992$ for **2** and 0.874 for **8**. (C) Time course study of the transportation of **14** through organic media and release in water, $r = 0.993$. (r indicates coefficient of linearity.)

Preliminary screening revealed that the sodium salts of both **1** and **2** were able to solubilize Orange OT (**13**), a nonpolar dye, in 50% MeOH/H_2O. To study their dye solubization abilities, partitioning of the dye between hexane[18] and 50% MeOH/H_2O[19] was carried out. It was observed that the sodium salts of the dendritic species (**1** and **2**) were able to extract **13** from hexane to 50% MeOH/H_2O (Figure 3) and with increasing concentration of the dendritic component in aqueous layer, the amount of dye extracted from the organic layer increased linearly (Figure 2A). A control experiment carried out with an excess of **7** showed that only a small amount of dye was extracted in comparison with **1** and **2**. This clearly suggests that the amount of dye extracted from the organic layer does not depend merely on the *number* of steroid units present in the aqueous layer but on the dendritic architecture, where a micellelike organization develops once the facially amphiphilic units are appropriately arranged with the polar hydroxyl groups pointing "outward".[20] Thereby these amphiphilic dendrons create a hydrophobic patch for the accommodation of a apolar dye in the polar media.[21] In the absence of any carrier in the aqueous layer, no dye extraction was observed (Figure 3).

Figure 3. Orange OT partitioning experiment in hexane equilibrated with MeOH/H_2O (1:1) after 12 h. Vial 1 has no additive, vials 2 and 3 have NaDC **7** (48 mM) and tetramer **2** (12 mM), respectively.

These results prompted us to examine the solubilization ability of a polar dye in a nonpolar media with dendrons **1** and **2**. It was observed that *only* **2** was able to solubilize the sodium salt of cresol red (**14**) in chloroform.[22] With an increase in the concentration of the dendron, the amount of

(12) Zhao et al. have attached cholate fragments on a tetraaminocalixarene scaffold and have shown by NMR that the cholates can respond to environmental (polarity) changes by rotation (Ryu, E.-H.; Zhao, Y. *Org. Lett.* **2004**, *6*, 3187). This group has very recently shown phenyl β-D-glucopyranoside binding with a calixarene tetracholamide derivative in a CCl_4/MeOH mixture and pyrene binding with a *modified* cholamide calixarene derivative in water (Zhao, Y.; Ryu, E.-H. *J. Org. Chem.* **2005**, *70*, 7585).

(13) Extensive study of hydrophilic dye solubilization by bile-acid-based dendrons having glycolate spacer have been performed by our group. See: *J. Org. Chem.* **2006**, *71*, posted ASAP (jo052173i).

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(16) Selected data for **1**. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ_H 5.12 (s, 1H, 12-β H), 4.70 (s, 1H, 3-β H), 4.15 (s, 2H, 12-β H's), 3.62 (m, 1H, 3-β H), 3.47 (m, 1H, 3-β H), 2.61−0.67 (m). MALDI-TOF: calcd for $C_{72}H_{116}O_{10}$ 1140.85, found 1163.1 (M + Na^+ 1163.8). Anal. Calcd for $C_{72}H_{116}O_{10}$ 0·3H_2O: C, 72.32; H, 10.28. Found: C, 72.08; H, 10.32. $[\alpha]^{25}_D$ +69.0 (*c* 2.0, $CHCl_3$).

(17) Selected data for **2**. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ_H 5.08 (s, 1H, 12-β H), 4.91 (s, 1H, 7-β H), 4.57 (m, 1H, 3-β H), 4.06 (s, 1H, 12-β H), 4.03 (s, 1H, 12-β H), 3.99 (s, 1H, 12-β H), 3.61 (m, 3H, 3-β H's), 2.37−0.65 (m). MALDI-TOF: calcd for $C_{96}H_{154}O_{14}$ 1531.13, found 1555.7 (M + Na^+ 1554.1). Anal. Calcd for $C_{96}H_{154}O_{14}$ 0·6H_2O: C, 70.29; H, 10.20; Found: C, 70.19; H, 9.85. $[\alpha]^{25}_D$ +45.0 (*c* 2.0, $CHCl_3$).

(18) Dendrons **1** and **2** were not soluble in hexane.

(19) Sodium salts of dendrons **1** and **2** were not soluble in pure water.

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(21) As a result of the solubilizing effect of MeOH, dendrons **1** and **2** are less likely to form aggregate in a MeOH/H_2O (1:1) system at low concentrations

(22) This dye solubilization was not due to an acid−base type of interaction because **1**, having a similar functional group, did not show dye extraction. Possibly the tripodal geometry of **2** assisted dye encapsulation better with additional functional groups. Compound **1**, on the other hand, has a tweezerlike geometry with fewer polar groups inside the cleft.

dye solubilized was again found to increase linearly (Figure 2B). A control experiment carried out with an excess of **8** showed only a small amount of dye extraction.[23] In a nonpolar solvent such as chloroform, **2** must adopt a different conformation where the polar hydroxyl groups point "inward" to accommodate a polar guest inside. The unique feature of **2** is that depending upon solvent polarity it can adopt different conformations and is thus able to act as both normal and inverse micelle mimics.[24]

To investigate the dye release in an aqueous system, a transport experiment in a U-tube (18.6 ± 0.3 °C) was carried out. Compound **14** dissolved in water (8.33 mM, pH 8.2) was found to be transported from one arm of the U-tube to another arm through a chloroform layer containing **2** (1.37 mM). A time course study (Figure 2C) revealed that with time the amount of released dye increased linearly. A control experiment carried out with an excess of **8** showed a negligible amount of transportation.

In conclusion, dendron **2** shows a remarkable ability of solubilizing both a polar dye in a nonpolar medium and a nonpolar dye in a predominantly aqueous medium, which is very rare.[25] Also this dendritic structure has an ability to transport and release a dye. As these dendrons are constructed *exclusively* from biocompatible bile acids, they are attractive motifs for drug delivery/release studies.

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Supporting Information Available: Synthetic details and experimental procedures for dye solubilization, extraction and transport. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) This observation is very similar to what was observed in the case of Orange OT extraction (Figure 2A). In a nonpolar solvent, a small portion of methyl deoxycholate possibly aggregates to form an inverse micelle type of structure.

(24) ^{1}H NMR spectra of **1** and **2** did not change with change in concentration, suggesting that self-aggregation was negligible.

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