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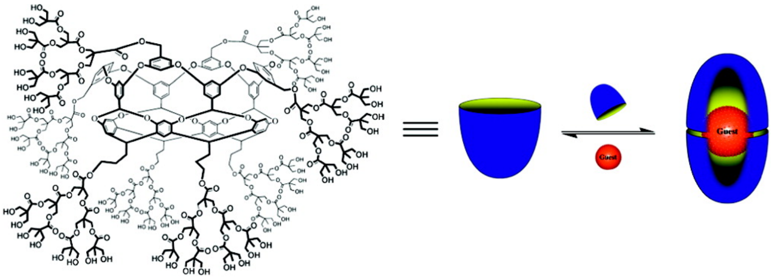

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Dendronized Supramolecular Nanocapsules: pH Independent, Water-Soluble, Deep-Cavity Cavitands Assemble via the Hydrophobic Effect

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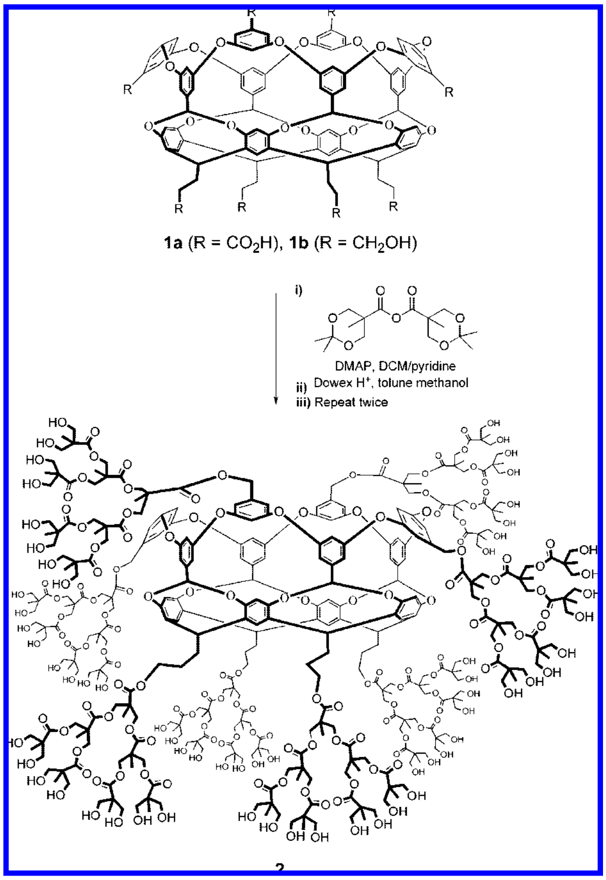
The majority of synthetic supramolecular assemblies rely on enthalpically powerful H-bonding[1−5] and metal coordination to drive assembly,[6−10] motifs that are most powerful in nonaqueous media. In contrast, Nature often relies on entropy, in the guise of the hydrophobic effect, to bring about assembly. One of our laboratories has reported on a supramolecular capsule formed by the dimerization of **1a** around a guest(s) (Schemes 1 and 2).[11−15] This capsule, soluble in aqueous base by virtue of a coat of 16 carboxylates, has been shown to affect the separation of hydrocarbon gases[16] and act as a nanoscale reaction vessel for photochemical reactions.[17−19] This type of encapsulation also offers an attractive route to modulating the physical properties of a drug without covalent modification; however, for this, water solubility close to neutral pH is required. Herein we report on the synthesis and assembly of dendronized cavitand **2** (Schemes 1 and 2). Coated with 128 hydroxy groups, the dimeric capsule formed by **2** encapsulates a range of guests at physiological pH.

The attachment of hydroxyl-terminated aliphatic polyester dendrons onto the cavitand core was pursued to impart both pH-independent water solubility and high biocompatibility. The dendritic structure[20] imparts an improved solubility over linear analogues,[21] while the hydroxylated periphery affords a highly biocompatible surface.[22] Similar biocompatible dendritic coats have been applied to small molecule cores,[23] linear polymers,[24] and solid surfaces.[25]

While a variety of protecting groups could be used for the diol monomer required for dendronization, the acid sensitive acetonide protecting group proved to be the most compatible with **1b**. Thus, **1b** treated with 1.5 equiv per hydroxyl of acetonide-protected bis(hydroxymethyl)propanoic anhydride (DMAP catalyst) gave the resulting ester after precipitation from methanol in >90% yield, while subsequent deprotection (Dowex acid resin) cleanly affected the removal of the acetonide acetals in quantitative yield. Both the esterification and the deprotection reactions could be monitored by MALDI-TOF MS (Supporting Information, SI). The resulting first generation (G-1) dendronized cavitand bearing 16 OH groups, Cav-([G-1]-OH_2)$_8$, was then subjected to a second repetition of coupling and deprotection to yield the G-2 cavitand Cav-([G-2]-OH_4)$_8$ and finally a third repetition of these steps to afford cavitand **2** Cav-([G-3]-OH_8)$_8$.

Solubility studies revealed that the G-1 cavitand was sparingly soluble in methanol, the G-2 was soluble in alcohols and mixtures of water and methanol up to 80% water by volume, and the G-3 cavitand **2** was freely soluble in pure water.

Scheme 1. Synthesis of Dendronized Cavitand **2**



Binding studies began with an NMR analysis of free host **2** (SI). Whereas the spectrum of **2** in MeOH showed well-resolved peaks, in pure D_2O many signals were broad. This broadness was independent of concentration, but the peaks did sharpen upon capsule formation (*vide infra*) suggesting that free **2** undergoes some aggregation at mmol concentrations. The large size of **2** ($C_{376}H_{528}O_{192}$, av MW = 8120.10 amu) and a restricted mobility of the dendrons likely also contribute to peak broadening. The spectrum of **2** in D_2O also exhibited broad peaks in its guest region (<0 ppm). Titration with MeOH resulted in their disappearance but no free signals indicative of impurities being displaced. As

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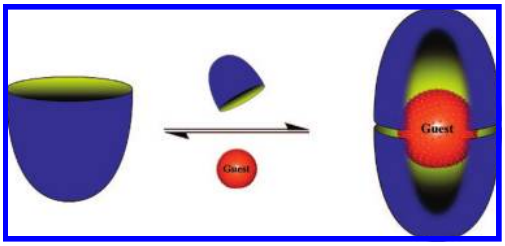
Scheme 2. Representation of the Dimerization of Deep-Cavity Cavitands **1a** and **2** around a Single Guest



models indicate it is possible for the third generation dendrons to bind into the pocket of **2**, we attribute these upfield signals to self-inclusion.

At neutral pH, **2** proved to be a consummate host with a broad range of complexation properties. In the presence of **3** (Figure 1) it formed a well-defined 1:1 complex.[26] NMR signal shifts for the guest demonstrated that it adopted an orientation such that the carboxylate group resides at the portal of the host. Consequently, the propensity of the complex to be capped by another cavitand is inhibited.

In contrast, nonamphiphilic guests formed capsular complexes. Thus, rigid estradiol **4** readily formed a 2:1 host−guest complex, although some degree of broadening prevented a detailed analysis of the guest binding region. Furthermore, 1D and 2D NMR (NOESY and COSY) experiments revealed that the more flexible **5** also led to capsule formation, as did highly flexible **6** and ester **7**. In most of the complexes, NOE interactions between host and guest, and between one host hemisphere and the next, were apparent. The symmetry of **6** led to a particularly well-defined NMR spectrum (Figure 2). In the free state, signals for **6** are found over a narrow range, but in the capsule they are spread over 3 ppm; "equatorially" located methylenes in the middle of the chain undergo small shifts, whereas the terminal methyls, deep within the "north/south polar" regions of the capsule, were shifted almost 4 ppm upfield. The NOESY NMR did not reveal any helical conformation of the guest. Finally, we wished to determine if small guests also formed kinetically stable complexes. Gratifyingly, the addition of excess **8** resulted in a slow exchanging 2:2 capsular complex, with free and bound guest signals at 1.25 and −0.75 ppm.

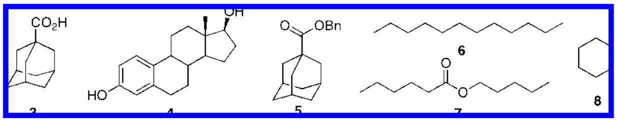


Figure 1. Guests investigated in this study.

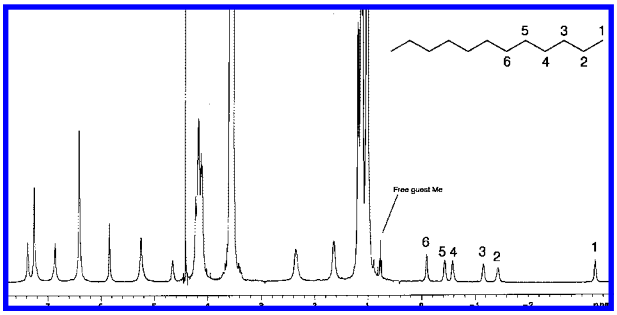


Figure 2. NMR spectrum of the complex **6@2**$_2$.

Even though more noncovalent contacts are possible between two molecules of **2**, initial experiments (SI) suggest that **1a** binds guests more strongly. Thus, in the presence of 1 equiv of **7**, a small amount of free guest is observed with **2** that was not observed with **1a**. We hypothesize two reasons for this. First, self-inclusion by **2** would reduce its affinity for guests. Second, because of the relatively thick dendritic coat, the hydrophobic rim of cavitand **2** may be less solvated by water than its more "naked" counterpart **1a**. Consequently, capsule formation would not result in the same degree of desolvation. We are currently studying the properties of host **2** further and synthesizing other dendritic cavitands to shed light on this potentially important structural consideration of assemblies driven by the hydrophobic effect. We will report on these findings in due course.

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Supporting Information Available: ^{1}H NMR, COSY, and NOESY spectra and MALDI-TOF data of intermediates, host **2**, and its complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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