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# Dendronized Supramolecular Nano-Capsules:

## pH Independent, Water-Soluble, Deep-Cavity Cavitands Assemble via the Hydrophobic Effect

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## Abstract

At neutral pH, dendronized deep-cavity cavitands were shown to form supramolecular nano-capsules via assembly around a range of guest molecules.

The majority of synthetic supramolecular assemblies rely on enthalpically powerful hydrogen-bonding[1-5] and metal coordination to drive assembly;[6-10] motifs that are most powerful in non-aqueous media. In contrast, Nature often relies on entropy - in the guise of the hydrophobic effect - to bring about assembly. Inspired by this point, one of our laboratories has reported on a supramolecular capsule formed by the dimerization of **1a** around a guest(s) (Scheme 1 and 2).[11-15] This capsule, soluble in aqueous base by virtue of a coat of sixteen carboxylates, has been shown to affect the separation of hydrocarbon gases,[16] and act as a nano-scale 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** (Scheme 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 analogs,[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, whilst 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 firstgeneration (G-1) dendronized cavitand bearing 16 OH groups, Cav-([G-1]-$OH_2$)$_8$ was then subjected to a second repetition of coupling and

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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 soluble in alcohols and mixtures of water and methanol up to 80% water by volume, while the G-3 cavitand **2** was freely soluble in pure water.

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. In all probability, the large size of **2** ($C_{376}H_{528}O_{192}$, avg. mw = 8120.10 amu) and a restricted mobility of the dendrons 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 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, non-amphiphilic 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 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 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.

Even though more non-covalent contacts are possible between two molecules of **2**, initial experiments (SI) suggest that **1a** binds guests more strongly. Thus, in the presence of one equivalent 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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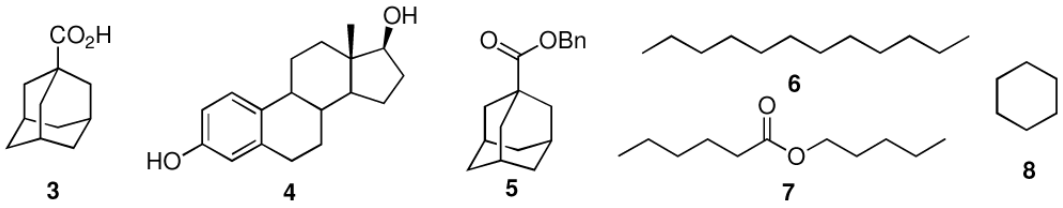



**Figure 1.**
Guests investigated in this study.

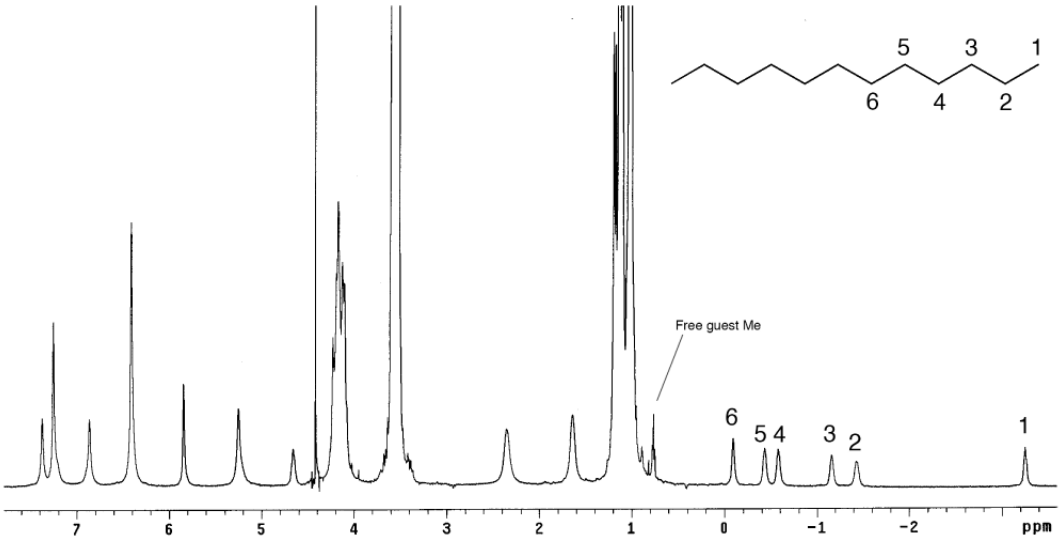
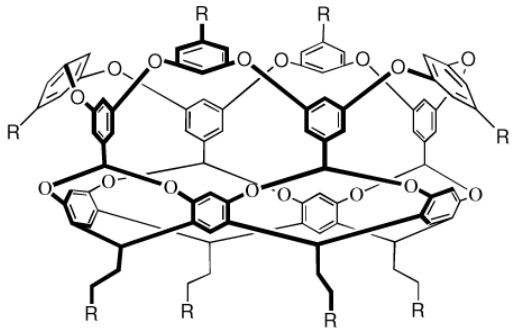
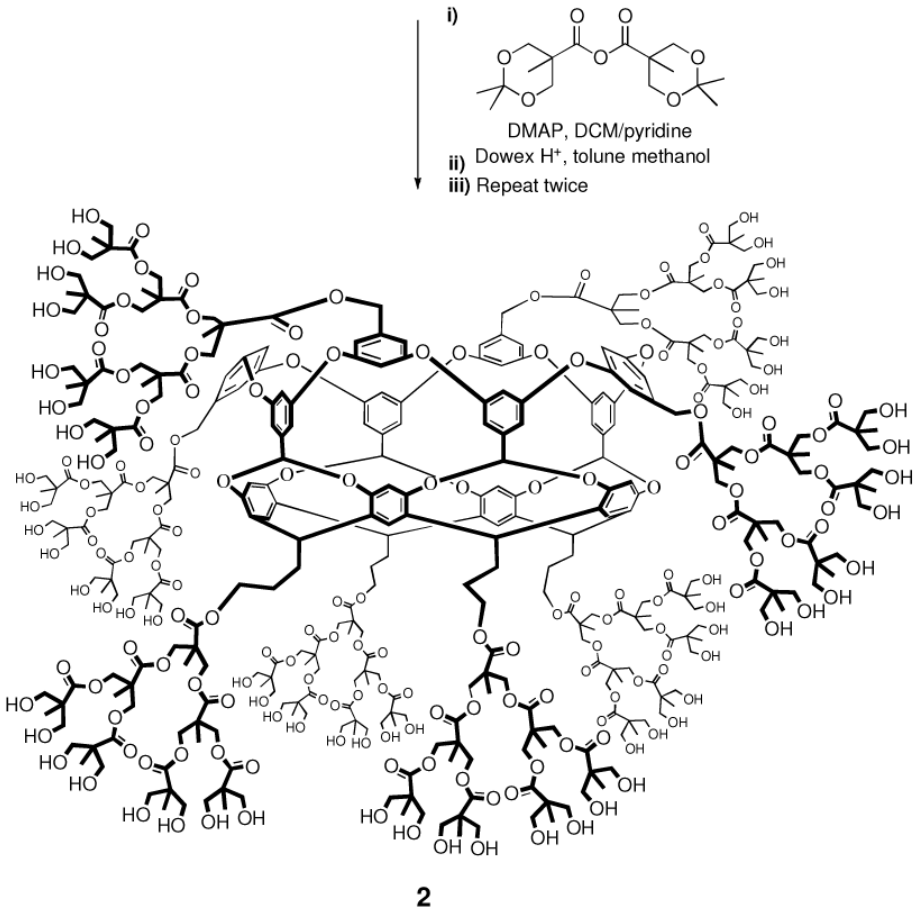



**Figure 2.**
NMR spectrum of the complex **6**@$\mathbf{2}_2$

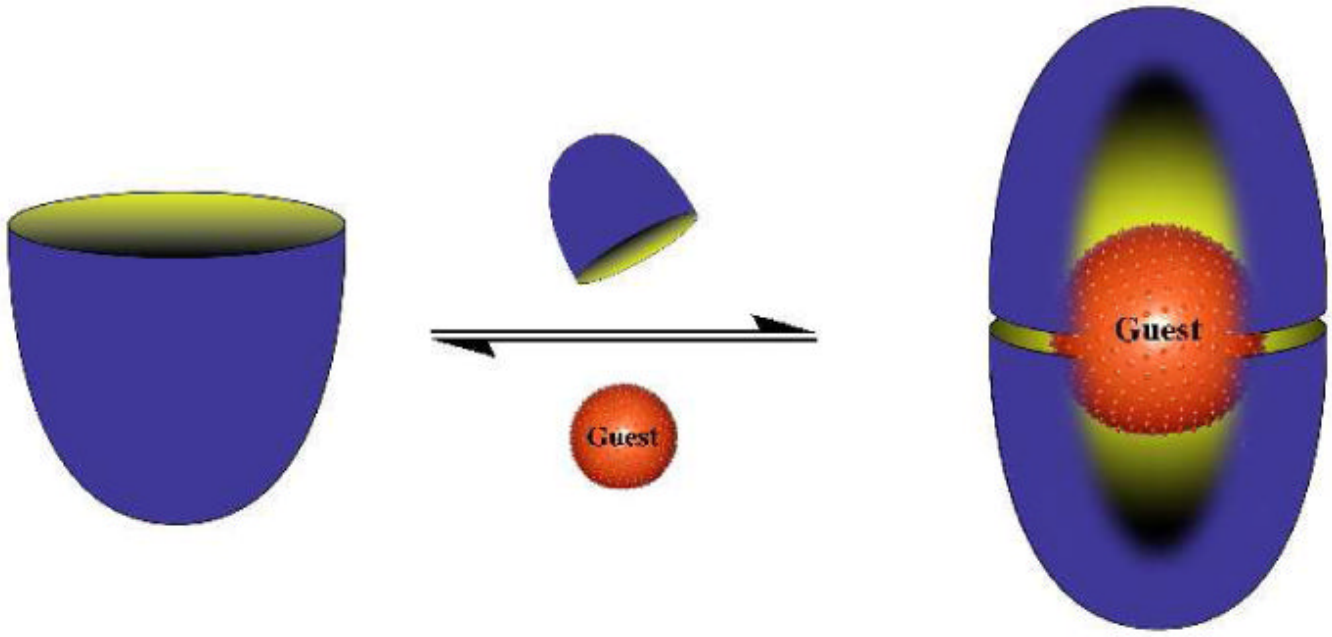


**1a** (R = $CO_2H$), **1b** (R = $CH_2OH$)




**2**

**Scheme 1.**
Synthesis of dendronized cavitand **2**.




**Scheme 2.**
Representation of the dimerization of deep-cavity cavitands **1a** and **2** around a single guest.