Straight-chain alkanes template the assembly of water-soluble nano-capsules†

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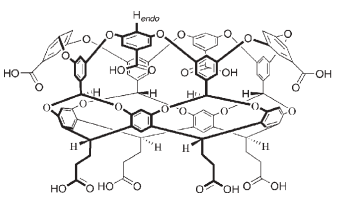
Cavitand 1 is sufficiently predisposed to form nano-scale capsules in the presence of templating straight-chain hydrocarbons; quaternary complexes are formed when two copies of smaller guests are encapsulated, whilst larger guests form ternary entities.

The self-assembly of molecules into well-defined supramolecular containers can bring about a plethora of unusual chemical phenomena. Direct effects include how a container can template distinct conformations of the guest residing within the nano-space,[1–3] how it can engender unusual supramolecular stereochemistry built on the position or orientation[4] of multiple guests,[5] or how it can accelerate or catalyze[6,7] or some way redirect a reaction.[8] Furthermore, encapsulation of a guest can also influence the external environment, for example in such cases as when the guest is part of a solution-based reaction scheme.[9] To date, dynamic containers have primarily been formed *via* highly directional non-covalent forces such as metal coordination or hydrogen bonding.[1,5,7,9–17] Recently however, we have shown that in water cavitand **1** can assemble into nano-capsules.[18] Although "only" held together by non-directional π–π stacking interactions, the wide hydrophobic rim of the cavitand is preorganized enough that a discrete dimeric capsule is formed in the presence of hydrophobic guests. Initial guests investigated included highly complementary and rigid steroids,[18] but more recently it was demonstrated that even small guests can template assembly.[19] Indeed, this wide range of possible guests has allowed us to examine unusual photochemical and photophysical processes carried out within the capsule.[8,20,21] Here we investigate the assembly of cavitand **1** in the presence of straight-chain hydrocarbons. This series of guests demonstrates that the combination of the hydrophobic effect[22,23] and a suitably predisposed subunit[24] are powerful inducers of assembly.



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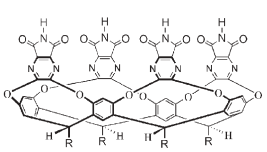

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The synthesis of host **1** has been previously reported.[18] Its ^{1}H NMR spectrum (1 mM in 10 mM sodium tetraborate) shows sharp signals, and that the host is monomeric at this concentration was confirmed by a pulse-gradient stimulated spin-echo (PGSE) NMR experiment; the diffusion constant of the host under these conditions (D = 1.82 × 10^{-6} cm^2 s^{-1}) corresponding to a hydrodynamic volume of 7.2 nm^3.[19] We examined the encapsulation of a series of hydrocarbon guests, from pentane (C_5H_{12}) through octadecane ($C_{18}H_{38}$). For encapsulation, a slight excess of the guest was added neat to the aqueous solution of the host. For the small alkanes that possess a modicum of solubility in water, uptake was rapid. For the larger guests, it was necessary to heat/sonicate the mixture (ESI†).

Octadecane was the largest guest examined (V = 385 Å^3), and although it was solubilized by the host solution, broad NMR signals indicated that the guest was too large for the capsule (V = ~500 Å^3). In contrast, the guests pentane through heptadecane formed kinetically stable complexes with assembly and disassembly rates slower than the (500 MHz) NMR timescale. Fig. 1 shows the full ^{1}H NMR of the dodecane complex. Typical of these types of encapsulations, the signals of the guest are moved considerably upfield from their free positions, and with slow exchange, integration of the host and guest peaks gave the stoichiometry of each complex; the smaller guests pentane through heptane formed well-defined 2 : 2 quaternary complexes, while guests larger than octane formed distinct 2 : 1 tertiary complexes. That the former were indeed quaternary complexes rather than 1 : 1 species was confirmed by diffusion studies. The diffusion constant of the hexane complex, D = 1.45 × 10^{-6} cm^2 s^{-1}, was similar to that determined for the decane containing capsule (D = 1.36 × 10^{-6} cm^2 s^{-1}), and much smaller than that of the free host.

Of the thirteen successful guests, octane proved to be unique in so much as it formed both 2 : 2 and 2 : 1 complexes. Two lines of evidence demonstrate this. First, the guest signals of this complex were broadened somewhat (ESI†), and integration between the host and guest signals were temperature dependent. Thus, the 2 : 1 complex is expected to give a 1.33 : 1 ratio for the guest methyl signal and the H_{endo}[25] signal (Fig. 1) of the host. However, at 2 °C, this ratio was 0.93 : 1, whereas at 45 °C it was 1.22 : 1. As the relationship between integration and population is temperature independent, these values translate to an 40 : 60 ratio of the quaternary and ternary complexes at 2 °C, but a 83 : 17 ratio at 45 °C. The second line of evidence involves the host atoms most influenced by complexation, the *endo* protons, that find themselves going from a water-exposed environment in the host monomer to a dry[8] aromatic solvent-like environment in the capsule. Fig. 2(a) shows a plot of the shift in the NMR signal ($\Delta\delta$) for these atoms as

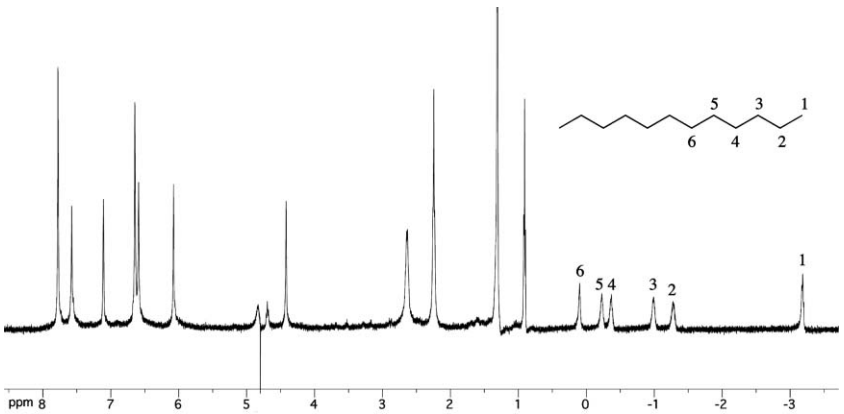

Fig. 1 ^{1}H NMR spectra of the 2 : 1 complex formed between host **1** and dodecane.

a function of the volume of the cavity contents (V). There are two trends to the data, a linear relationship between the $\Delta\delta$ values and V for the quaternary complexes (pentane through heptane), and a non-linear relationship for the ternary complexes (nonane through heptadecane). Points for ternary and the quaternary octane complexes are also plotted. It is apparent that awkward octane fits neither trend. Treated as a 2 : 2 complex, the shift is similar to the hexane quaternary complex; the guest appears smaller than expected. On the other hand, if treated as 2 : 1 quaternary complex

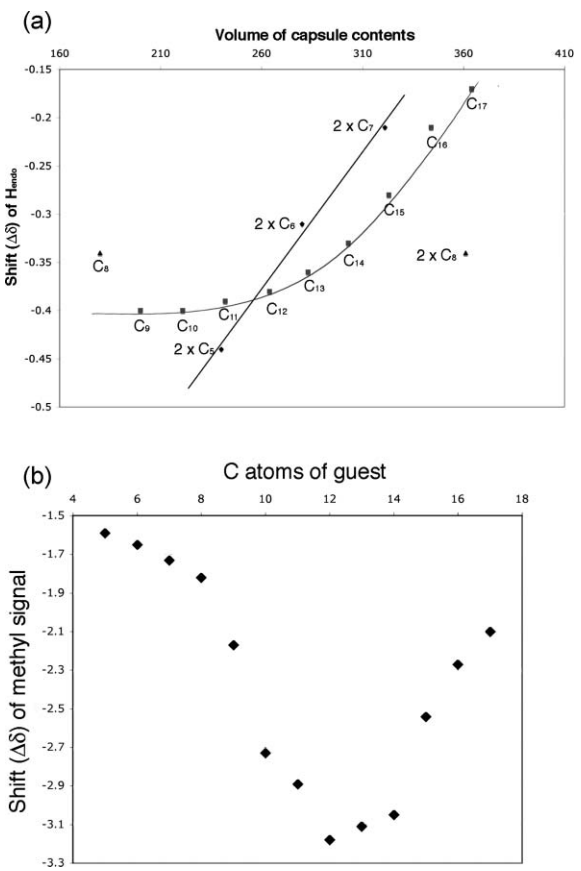

Fig. 2 (a) ^{1}H NMR shifts of the H_{endo} peak of the host as a function of the volume of the capsule contents. Lines shown are for visualization purposes. (b) ^{1}H NMR shifts ($\Delta\delta$) of the methyl-H atoms of the free and bound guests.

the shift is akin to tetradecane; the guest appears larger than expected. The most plausible explanation for this is a mixture of ternary and quaternary complexes that are hard to differentiate using NMR. It is interesting to note that this duel role for octane is in contrast to analogous hydrogen bonded capsules formed by cavitand **2**. In this case, guests too small to form 2 : 1 complexes and too big to form 2 : 2 complexes do not form stable entities.[2,5] We ascribe this lack of a "hole" in the binding profile of $\mathbf{1}_2$ to the power of the hydrophobic effect to drive complexation.

For all guests it is the methyl group signal that is the most shifted upon complexation, appearing between −1.60 and −3.15 ppm. Fig. 2(b) shows the $\Delta\delta$ shifts of the methyl group between the free and bound guest. We attribute the asymmetry of this curve (*e.g.*, the different shifts for heptane and tetradecane even though fourteen non-hydrogen atoms are encapsulated in both complexes) to the fact that there are twice as many methyl groups in the quaternary species. The methyl groups of dodecane undergo the most significant shifts upon complexation, indicating perhaps that the capsule is optimally packed (V = 263 Å^3, packing coefficient, PC ~53%), and that the methyl groups are anchored deeply in each cavitand. In contrast, the protons of the guest located mid-way along the alkane chain are minimally shifted (Fig. 1), indicating that they are located near the equator of the capsule.

To date, we have seen a wide range of PC values for stable complexes with $\mathbf{1}_2$, from ~31%[19] to ~85%.[20] The packing coefficients for the alkane complexes reported here fall within this range; two pentane molecules (V = 240 Å^3) corresponding to a PC of 48%, while one heptadecane (V = 364 Å^3) has a PC of 73%. However, the aforementioned 85% PC was noted for two rigid anthracene guests, and so the PC for heptadecane is remarkable considering its flexibility and reminiscent of the packing in a folded protein.

Models indicate that the guests decane through hexadecane must adopt folded conformations to fit within the confines of the capsule. We used NOESY and COSY NMR experiments to determine the preferred conformations of these guests (ESI†). These experiments revealed stronger NOE (C_i–C_{i+1} and C_i–C_{i+2}) interactions between the terminal methyl groups and proximal methylenes, than between methylenes near the center of the chain. C_i–C_{i+3} and C_i–C_{i+4} interactions indicative of helix formation[2,5] were also visible for the longer guests, but not to the exclusion of

other interactions. In other words, by and large the guests do not adopt one preferred conformation within the confines of $\mathbf{1}_2$.

We have shown that the assembly of cavitand **1** to form nano-scale capsules can be templated by straight-chain hydrocarbons. Although the guests are devoid of preorganization, and can only contribute at best weak C–H–π interactions with the host, a variety of ternary and even quaternary complexes are formed. For the larger guests, the packing coefficients are high and reminiscent of protein structure. With the intent of shedding light on the hydrophobic effect,[23,24] we are continuing to study the properties of these water-based nano-capsules.

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