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Hydrogen-Bonded Capsules in Water

Kang-Da Zhang,[‡] Dariush Ajami,[‡] and Julius Rebek*[,†,‡]

[†]Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China

[‡]The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Rd, La Jolla, California 92037, United States

S *Supporting Information*

ABSTRACT: Hydrogen-bonded capsules constrain molecules into small spaces, where they exhibit behavior that is inaccessible in bulk solution. Water competes with the formation of hydrogen bonds, and other forces for assembly, such as metal/ligand interactions or hydrophobic effects, have been applied. Here we report the reversible assembly of a water-soluble cavitand to a robust capsule host in the presence of suitable hydrophobic guests. The complexes are characterized by conventional NMR methods. Selectivity for guest length and fluorescence quenching of a stilbene guest are used as evidence for hydrogen bonding in the capsule.

The deep cavitands **1a** and **1b** (Figure 1), bearing four benzimidazolones on the upper "rim" were introduced by de Mendoza[1] more than a decade ago. Their self-complementary arrays of hydrogen-bonding sites allow dimerization to capsules **1**·**1** in noncompetitive solvents when suitable guests are present. The cavitand **1b** was subsequently used by Choi[2] to encapsulate guests in mesitylene or hot toluene, and our own experience with **1b** in more competitive media[3] suggested that the dimerization might even be possible in water, given a more hydrophilic cavitand. The 16 hydrogen bonds of **1**·**1** match strong donors with strong acceptors, and the rigidity of the system promises some cooperativity during assembly to a capsule. Here we describe a water-soluble version **1c** that encapsulates hydrophobic guests as a dimeric, hydrogen-bonded structure.

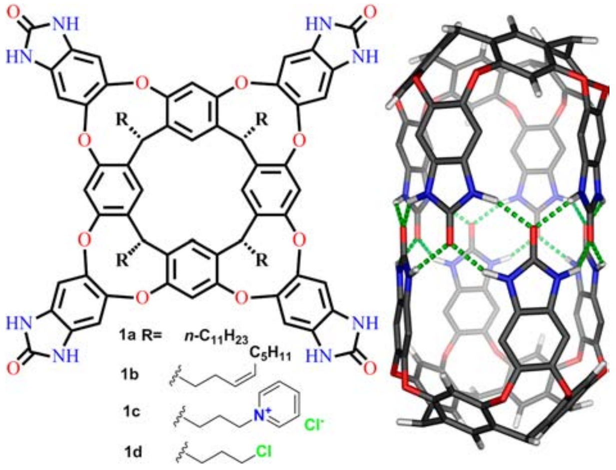

Figure 1. Structures of deep benzimidazolone cavitands and a modeled dimeric capsule highlighting the hydrogen bonds.

The resorcinarene with alcohol "feet" **2**[4] (Figure 2) was deepened with difluorodinitro benzene[5] **3** to give the octanitro tetrol **4a**. This was converted to the tetrachloride **4b** (see SI) then the tetra benzimidazolone rim of the cavitand was installed as described by Choi.[2] Reduction of the nitro groups gave the corresponding octamine which was treated with triphosgene to give the precursor tetrachloride **1d**. Excess pyridine converted the halides to the quaternary pyridinium compound **1c**.

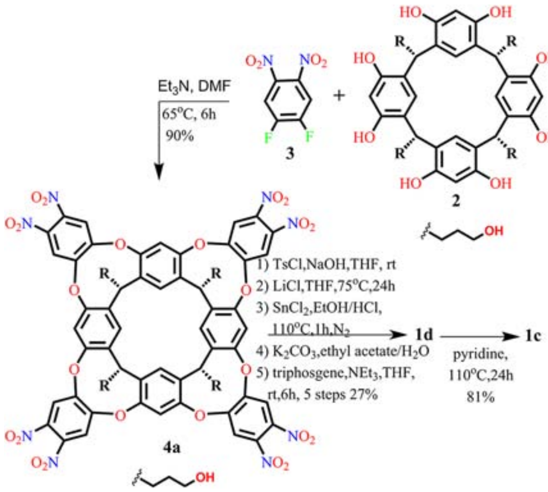

Figure 2. Synthesis of the water-soluble cavitand.

The cavitand **1c** exhibited solubility in water (D_2O) at concentrations up to 25 mM. At low concentrations, both vase and kite conformations are observed in the NMR spectra: in the former, the methine C−H signal appears at 5.5 ppm,[6] while in the latter the (broadened) aryl C−H signals are those consistent with D_{2d} symmetry[7] (see SI). Earlier studies with related capsules in organic media[8] indicated that *n*-undecane and longer alkanes (up to *n*-tetradecane) were likely to be good guests for the capsule **1c**·**1c**, and brief sonication with these normal alkanes in D_2O gave complexes. The characteristically upfield-shifted NMR signals of the alkane guests (Figure 3) leave no doubt about their encapsulation. The guest *n*-undecane fits the space comfortably in an extended

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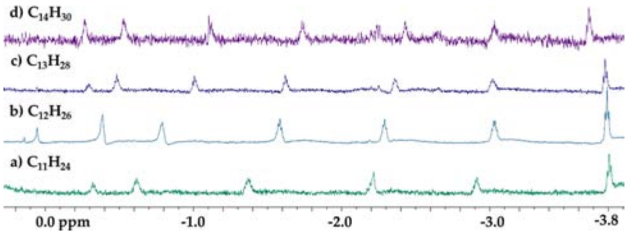

Figure 3. Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of the complexes formed between host **1c·1c** (0.25 mM) and (a) *n*-undecane; (b) *n*-dodecane; (c) *n*-tridecane; (d) *n*-tetradecane.

conformation and typically sharp, symmetrical signal patterns were observed. Longer alkanes must adopt *gauche* conformations to fit, and this is seen in the upfield shifts of the signals for protons on C2, C3, etc., as they are pushed toward the ends and walls of the capsule.[9] The longest alkane that was accommodated is *n*-tetradecane.[10] Accurate binding affinities for alkanes could not be measured due to their low solubilities in water. However, pairwise competition experiments showed the following order for encapsulation of alkanes: C11 > C12 > C13 > C14. This is similar to what has been observed for related capsules in mesitylene solvent and reflects the increased *gauche* interactions along the chains as the longer alkanes compress to be accommodated.

Rigid molecules **5**−**10** (Figure 4) were used as rulers for the space of **1c·1c**. The longest **9** and shortest **7** were not encapsulated, while **5**, **6**, **8**, and **10** fit well inside the cavity (see SI). As shown on the potential surface for **5**, its methyl groups can form favorable CH−π interactions with aromatic surfaces at the tapered ends of the cylindrical space. For the pyridinium salts cation−π interactions are also on offer, but competition experiments between **5** and **8** resulted in exclusive encapsulation of dimethylstilbene **5**. The encapsulation of **5** could also be detected by mass spectrometry. The competition between **8** and **10** was more balanced with 60% **8** and 40% **10**, suggesting that the positioning of the positive charges is not critical.

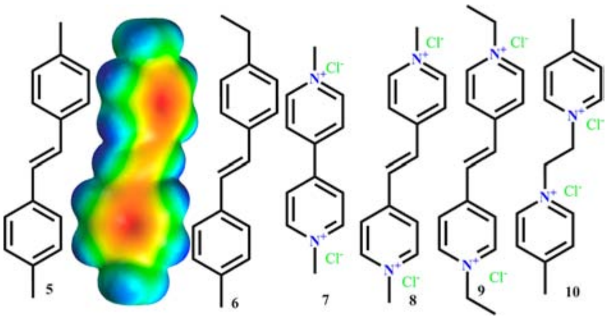

Figure 4. Structures of guests: 4,4′-dimethylstilbene **5**, 4-ethyl-4′-methylstilbene **6**, *N*,*N*′-dimethyl-4,4′-bipyridinium dichloride (paraquat) **7**, bis-*N*-methylpyridinium-4,4′-ethylene dichloride **8**, bis-*N*-ethylpyridinium-4,4′-ethylene dichloride **9**, and 1,2-bis 4-picolinium ethane dichloride **10**.

What is the nature of the interface between the two cavitands? The selectivity of the capsule for guest length speaks for a well-defined space, as would be expected with a cyclic seam of hydrogen bonds holding the two halves together. But there are many reports of molecular encapsulation in water driven only by hydrophobic forces,[11] using cavitands incapable of hydrogen bonding.[12]

We found indirect evidence concerning the capsule's structure in the photophysical behavior of an encapsulated stilbene derivative: its fluorescence was quenched (Figure 5), much as was the case for stilbene in a related octa-imide capsule in mesitylene.[13] A capsule with a dynamic, flexible, or ill-defined interface could accommodate a planar stilbene and allow its fluorescence. But the seam of hydrogen bonds fixes the shape of the space in either capsule—two square prisms twisted at 45° with respect to one another. A stilbene guest cannot be coplanar while inside and its fluorescence is quenched. This result indicates that the robust network of hydrogen bonds in **1c·1c** can resist disruption in water, at least when a hydrophobic guest is involved.

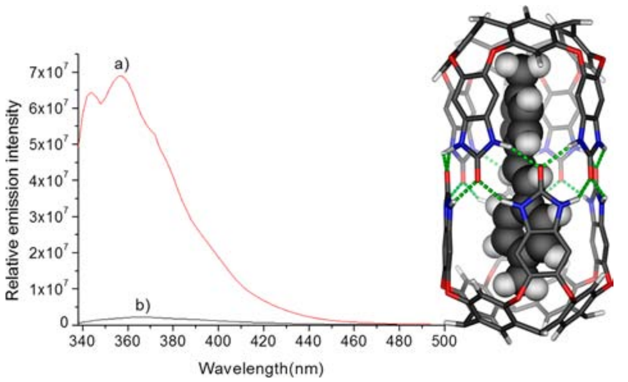

Figure 5. (Left) Room-temperature fluorescence spectra of (a) 4,4′-dimethylstilbene **5** (25 μM) in mesitylene; and (b) **1c·1c·5** (25 μM) in water at λ_{exc} = 318 nm. (Right) Semiempirically (AM1) minimized stilbene **5** in **1c·1c**.

The cavitand periphery must be solvated by water molecules making hydrogen bonds to the benzimidazolone donors and acceptors. Release of these waters to bulk solvent would help drive the capsule's formation. Presumably, capsule formation is entropy driven, as more of the hydrophobic surfaces of the guests are buried in the capsule, reducing the number of water molecules that are organized for guest solvation.

The interior of the cavitand is not a water-friendly space, so competition between solutes and solvent is not a factor. In earlier studies with organic media, mesitylene, a solvent too large to be encapsulated in this space, was required, which limited the types of solutes for host/guest studies. Molecules encapsulated in small spaces enjoy amplified concentrations and prearranged contacts that differ from their random encounters in bulk solution. As a result, interactions are prolonged and intensified at close range,[14] reactive species are stabilized,[15] and stereochemical effects are amplified by the confinement.[16] The water-soluble vessel described here provides a vehicles for a broadened range of small molecule payloads at neutral pH and provides new venues for molecular behavior in small places.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jrebek@scripps.edu

Notes

The authors declare no competing financial interest.

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