

# Alkyl Groups Fold to Fit within a Water-Soluble Cavitaand

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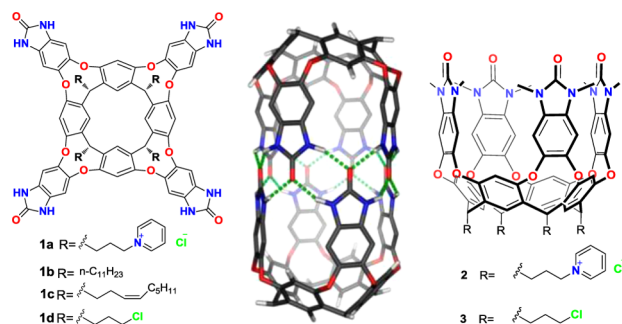
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**S** Supporting Information

**ABSTRACT:** We report here a widened, deep cavitaand host that binds hydrophobic and amphiphilic guests in D<sub>2</sub>O. Small alkanes (C<sub>6</sub> to C<sub>11</sub>) are bound in compressed conformations and tumble rapidly within the space. Longer *n*-alkanes (C<sub>13</sub> to C<sub>14</sub>), *n*-alcohols, and  $\alpha,\omega$ -diols are taken up in folded conformations. The guests' termini are exposed to solvent while atoms near the alkane's center are buried and protected. The cavitaand acts as a concave template that pushes terminal atoms of the guest closer together. The unexpected binding modes are interpreted in terms of the size and shape of the space accessible in the new cavitaand.

We recently revisited<sup>1</sup> the deep cavitaands **1** (Figure 1) introduced by de Mendoza<sup>2</sup> a decade ago. The



**Figure 1.** Structures of cavitaands **1** and a modeled capsule showing hydrogen bonds. Cavitaand **2** is water-soluble over a range of pH values but does not form a capsule.

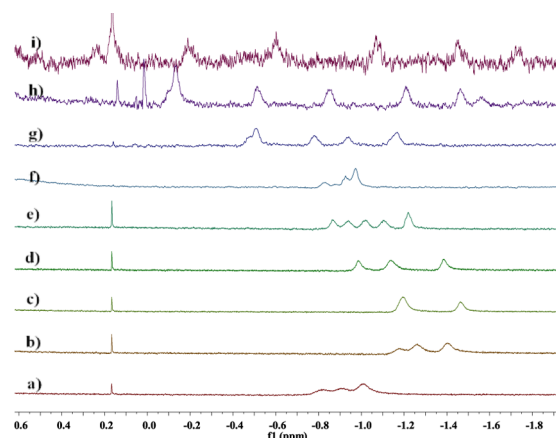
hydrophobic “feet” of **1b** and **1c** allow solubility in organic solvents. The hydrogen bond donors and acceptors on the upper rim are self-complementary, and dimerization into host capsules **1.1** occurs when appropriate guests are present.<sup>2–4</sup> The pyridinium ions of **1a** were effective in imparting water solubility for applications in aqueous media, and small guests are taken up within monomeric **1a** alone in D<sub>2</sub>O.<sup>5</sup> But when large hydrophobic guests are introduced, dimeric capsule formation occurs even in this competitive solvent.<sup>1</sup> In order to suppress dimer formation, we exhaustively *N*-methylated the benzimidazolones at the upper rim and prepared **2**. We report here the new cavitaand's ability to take up hydrophobic species in water (D<sub>2</sub>O). Unexpectedly, long chain hydrocarbons adopt *folded* conformations in order to fill the available space in **2**.

Amphiphilic species such as  $\alpha,\omega$  diols of appropriate length also fold to bury their hydrophobic parts.

Treatment of **1d** with MeI and Cs<sub>2</sub>CO<sub>3</sub> gave the octamethyl **3** in good yield after chromatography. On heating a pyridine solution of **3**, **2** precipitated from the solution. The compound **2** exhibited solubility in water (D<sub>2</sub>O) at concentrations up to 10 mM, in which it shows the NMR earmarks of a “kite” (vs “vase”) conformation:<sup>6</sup> the methine C–H appears at 4.2 ppm and the aryl C–H signals are those of a structure with an overall D<sub>2d</sub> symmetry (see Supporting Information (SI)). The kite is expected to exist as a dimeric velcraand in water to minimize exposure of hydrophobic surfaces.

While the vase conformation of **1a** is stabilized and rigidified by hydrogen bond bridges between adjacent walls provided by water, the *N*-methyl groups of **2** prevent such bridging and allow more wall motion. Brief sonication and/or heating of **2** with excess (insoluble) guests in water (D<sub>2</sub>O) gave the characteristic spectra of discrete, stoichiometric cavitaand complexes. The NMR spectra obtained with a series of alkanes (C<sub>6</sub> to C<sub>14</sub>) are shown in Figure 2.

The in/out exchange of guests is relatively slow on the NMR time scale, and guest signals are shifted upfield by the shielding provided by the eight surrounding aromatic panels. The range of signals for bound guests is considerably compressed; from C<sub>6</sub>



**Figure 2.** Partial <sup>1</sup>H NMR (600 MHz, D<sub>2</sub>O, 298 K) spectra of the complexes formed between host **2** (0.5 mM) and (a) *n*-hexane; (b) *n*-heptane; (c) *n*-octane; (d) *n*-nonane; (e) *n*-decane; (f) *n*-undecane; (g) *n*-dodecane; (h) *n*-tridecane; and (i) *n*-tetradecane.

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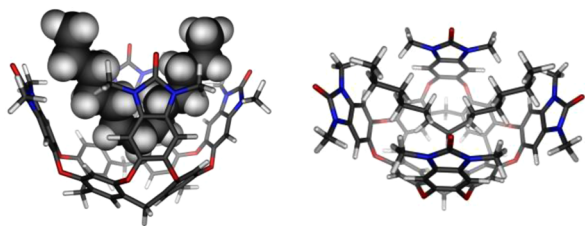
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to C<sub>12</sub> the resonances span only about 0.6 ppm, while those of C<sub>13</sub> and C<sub>14</sub> are spread over 2 ppm. In contrast, other deep cavitands show much broader ranges and different patterns for guest alkane signals.<sup>7</sup>

The small number of upfield resonances—three signals for C<sub>6</sub>, five for C<sub>10</sub>, seven for C<sub>13</sub>—indicate time-averaged, symmetric environments for the alkanes. For the shorter alkanes (C<sub>6</sub> to C<sub>10</sub>), the furthest upfield signals are those of the methyl groups. In its resting state, one methyl of the alkane is directed toward the resorcinarene floor where the greatest shielding occurs and the other methyl is directed toward the open end of the cavitand. Tumbling exchanges the magnetic environments of the guest's two ends. This is a dynamic process that is fast on the NMR time scale, and the signals represent the average environment of a given CH<sub>2</sub> or CH<sub>3</sub> group.<sup>8</sup>

The longer alkanes (C<sub>12</sub> to C<sub>14</sub>) show different behavior within **2**. The furthest upfield signals (−1.5 to −1.7 ppm) are those of the central CH<sub>2</sub> groups and place them near the resorcinarene floor. The furthest downfield signals (−0.5 to 0 ppm) are those of the CH<sub>3</sub> groups, placing them near the open end of **2**, where the least shielding occurs. These assignments were established by 2D spectra (see SI). The patterns of signals for C<sub>13</sub> and C<sub>14</sub> indicate they are *folded* inside **2**.

Such folds are observed rarely and then only in larger capsules.<sup>9</sup> In the cavitand **2**, they reveal a widened open end with sufficient flexibility to accommodate the folded alkanes. Both features are reasonable, as the eight methyl groups splay the cavitand walls outward. The resorcinarene also appears widened; Figure 3 shows semiempirical (AM1) energy-minimized structures proposed for the C<sub>13</sub> complex.

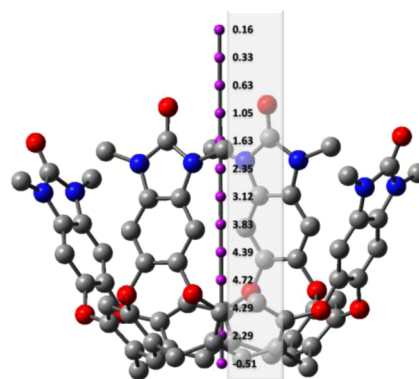


**Figure 3.** Two views of C<sub>13</sub> inside the octamethyl cavitand **2**, energy minimized at a semiempirical (AM1) level. Peripheral solubilizing groups have been removed.

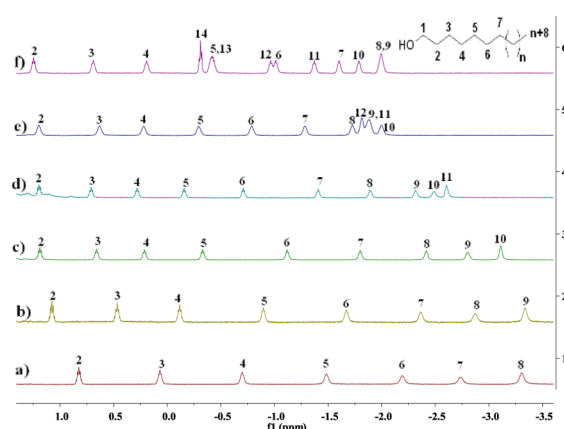
The vase conformation of the cavitand **2** was used in Nucleus Independent Chemical Shift (NICS) calculations<sup>10</sup> (Figure 4). These indicate that the maximum upfield shift for a nucleus in the (idealized) C<sub>4</sub> symmetrical structure is −4.72 ppm, a value less than that of **1a** (−4.9 ppm; see SI)

The complexes with the alkanes are, however, dynamic; a frozen alkane conformation would give a much broader range of signals in the NMR spectra. Instead, the alkane surely writhes in the space through many different low-energy conformations in which few of its hydrogens rest along the central axis. In fact, for reasons of symmetry, a maximum of two hydrogens (at the resorcinarene floor) of an odd-numbered, folded alkane can be near the axis in a resting state. The remaining hydrogens are off-axis. The cavitand is also expected to respond by changing shape to maintain attractive contacts with the moving alkyl groups inside.

We used a series of *n*-alcohols to follow alkyl bending as a function of length, and the spectra of C8 to C14 in **2** are shown in Figure 5. The position of the CH<sub>2</sub>–OH is near the rim of the



**Figure 4.** Calculated (HF/6-31G\*) NICS values for **2** along the central axis at 1 Å intervals. The numbers indicate upfield shifts (negative  $\Delta\delta$  in ppm).

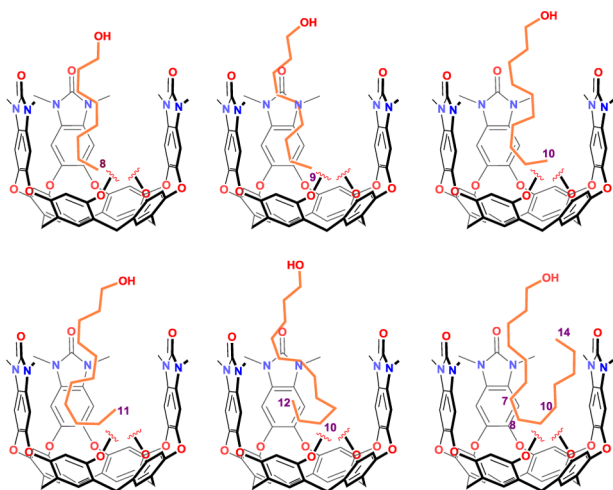


**Figure 5.** <sup>1</sup>H NMR spectra (600 MHz, D<sub>2</sub>O, 298 K) of complexes of **2** with *n*-alcohols: (a) octanol; (b) nonanol; (c) decanol; (d) undecanol; (e) dodecanol; (f) tetradecanol. The assignments for tetradecanol are from the 2D spectra (see SI).

cavitand, and while that signal is hardly shifted, the signal for the CH<sub>2</sub>CH<sub>2</sub>–OH moves *downfield* from octyl (0.75 ppm) to nonyl (1.0 ppm) to decyl (1.25 ppm) where it remains for the longer alcohols. In other words, the position of this carbon remains fixed and near the cavitand's rim for C10–C14. Any changes in cavitand “depth” must take place at the other (methyl) end of the alcohols.

The methyl groups of both 1-octanol and 1-nonanol are at the maximum depth in the cavitand, as their resonances appear at −3.4 ppm. This corresponds to a  $\Delta\delta$  of −4.2 ppm and represents the limit of penetration for a methyl group in the tapered end of the cavitand. With C10 and C11 the methyl signals are still the furthest upfield, but at −3.1 and −2.6 ppm, respectively. They (and all the other signals) have shifted significantly *downfield*. Clearly the CH<sub>3</sub>'s have moved out of the cavitand's end to a higher, wider space to accommodate folding. The folding continues with C12, and with C14 the methyl emerges at −0.3 ppm. Complete COSY spectra for C12 and C14 (see SI) gave the assignments shown. A cartoon of the folding sequence, consistent with the chemical shift changes, is proposed in Figure 6. In contrast, these alcohols in the narrower **1a** show coiled conformations with the methyl groups deep in the cavitand (see SI).

Among other guests, long  $\alpha,\omega$  diols were bound in **2** (see SI), and their NMR spectra all indicate folded conformations. The *N*-methyl groups on the new cavitand **2** widen the open



**Figure 6.** Cartoons of the complexes of *n*-alcohols. The relative positions of the C atoms in the cavitan correspond to the NMR spectra and the NICS calculations. Adapting changes in the shape of the cavitan (as in Figure 3) are expected but are not shown.

end and loosen the walls enough to accommodate folded alkanes. This is in contrast to their behavior with **1**, where longer alkanes induce the formation of dimeric capsules. The folded over conformation within **2** fixes the guests' termini at relatively close range and exposed to reagents in the bulk solution. This propinquity hints at applications in remote functionalization and macrocyclization processes. The cavitan is a concave template that pushes atoms of the guest closer together; metal ion templates, on the other hand, are convex and pull atoms closer together.<sup>11</sup> Accordingly, these cavitan promise intriguing supramolecular departures from existing cyclization and protection protocols.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Synthetic procedures, <sup>1</sup>H, <sup>13</sup>C, COSY, and mass spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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