Self-Assembly

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Deconstruction of Capsules Using Chiral Spacers**

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Since their introduction, the shallow bowl-like resorcinarenes have been elaborated into deeper cavitands through covalent attachment of various aromatic panels.[1,2] The deeper cavitands are useful in a number of applications including recognition,[3] catalysis,[4] sensing,[5] and switching.[6] They also provide realistic analogs of enzyme active sites: they fold around their target guests, isolate them from bulk solvent, provide a hydrophobic pocket in a framework maintained by secondary amide bonds and present the guests with reactive functional groups.[7] A depth of approximately 1 nm is easily achieved for cavitands,[8] but attempts to further deepen the binding sites have been thwarted by conformational changes that lead to solvophobic collapse[9] and the formation of alternative structures that have no cavities.[10] We have now used self-assembly to deepen cavitands as an alternative to covalent synthesis and describe here the new container structures. These arise from the application of a chiral glycoluril as a spacer module that results in the expected deeper cavitands but also causes the unexpected formation of expanded, reversibly formed capsules.

Earlier, we reported that the cylindrical capsule **1·1**[11] can be expanded with glycolurils **2** when suitable guests are present (Figure 1).[12] The hydrogen bonding possibilities offered by glycolurils lead to a twisted "belt" of four spacer elements inserted between the two cavitands of **1·1**. The extended complex **1·2$_4$·1** is held together through a network of hydrogen bonds and each hydrogen bond donor and acceptor site on the glycoluril finds a complement in the complex.[13] Longer guests such as normal alkanes (from *n*-$C_{19}H_{40}$ to $C_{26}H_{54}$) drive the assembly of hyperextended capsules.[14] Undoubtedly, the hydrogen bonding is one of the driving forces for the self-assembly. We considered "short circuiting" the network by applying a *N*-monosubstituted glycoluril such as **3**. This was expected to dismember **1·1**, stabilize[15] the deep cavitand and, as a dividend, provide an asymmetric microenvironment on its rim.

Addition of *N*-methylated glycoluril **3** (see Experimental Section) to a solution of the normal alkanes, from *n*-$C_{10}H_{22}$ to $C_{14}H_{30}$, encapsulated in **1·1** results in the new cavitand host **1·3$_4$** (Figure 2) with alkanes partially inside. As *n*-$C_{11}H_{24}$ is one of the optimal alkane guests[16] for **1·1**, a small amount of the original complex persists, but with longer alkanes only the new, open ended assemblies were observed. In these assemblies, only the first four carbons of the alkanes experience the aromatic envelope of the cavitand and their proton signals shift upfield by as much as $\Delta\delta = -5$ ppm. The CH_2 groups of the guests experience a chiral magnetic environment and show diastereotopic signals. Several lines of evidence were followed to confirm the details of the structure. The integration of signals showed four *N*-methylated glycolurils insert into the bifurcated hydrogen bonds of **1·1**. The singlet at $\delta \approx 13.5$ ppm indicates that all the imide N–H's (H_a) are equivalent; the array of glycolurils is highly symmetric and diastereoselective assembly occurs; **1·(*R*)-3$_4$** and **1·(*S*)-3$_4$** were selectively formed whereas **1·(*R*)-3$_x$·(*S*)-3$_{4-x}$** ($x = 1$–3) were not formed. The four methyl groups on **3$_4$** are oriented in the same direction, represented as an up–up–up–up arrangement. The belt of **3** apparently attracts normal alkanes, since these flexible molecules are generally not good guests for open-ended container hosts: indeed, this is our first observation of *n*-alkanes in a cavitand competing with an organic solvent.[17] A solution of **1** and **3** without the *n*-alkane present does not lead to **1·3$_4$** even though **1** bears C_{11}-alkyl feet as potential

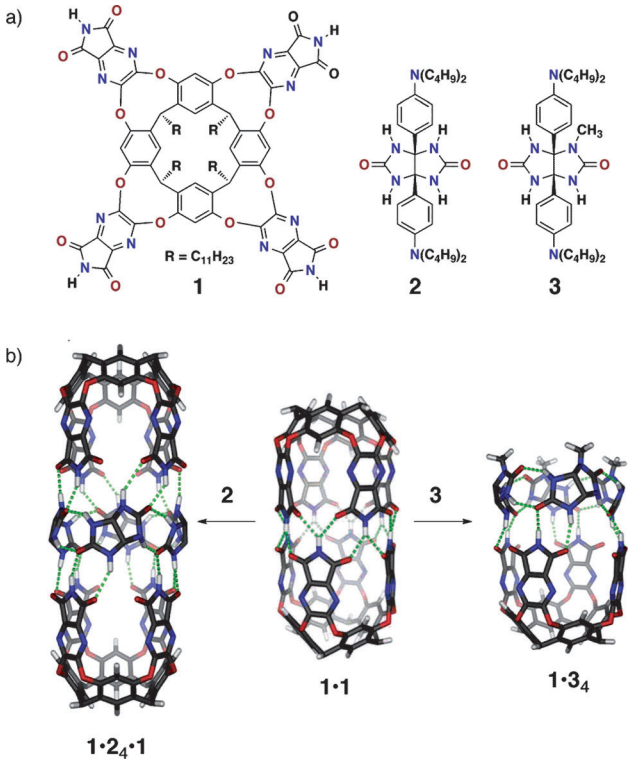

Figure 1. a) Chemical structure of cavitand **1**, glycoluril **2**, and *N*-methylated glycoluril **3**. b) Modeled structures of the cylindrical capsule **1·1**, extended capsule[9] **1·2$_4$·1**, and new cavitand **1·3$_4$**.

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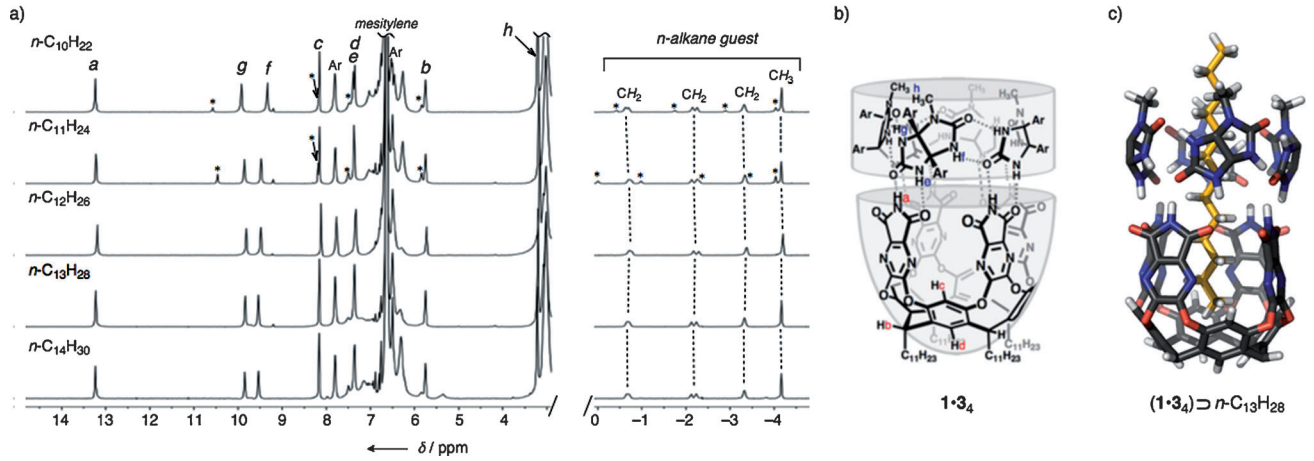

Figure 2. a) ^{1}H NMR spectra (600 MHz, 280 K, [D_{12}]mesitylene) of the **1·3$_4$** complex with normal alkanes (*n*-$C_{10}H_{22}$ to *n*-$C_{14}H_{30}$) (2 mM). b) Chemical structure of the **1·3$_4$** complex. c) Proposed model of the extended capsule (**1·3$_4$**)⊃*n*-$C_{13}H_{28}$ (the peripheral groups are removed for clarity). Asterisks represent the signals of encapsulated *n*-alkane within **1·1**.

guests. Both DOSY spectroscopy and 2D NOESY are consistent with the proposed model of the chiral cavitand **1·3$_4$** shown.

To our surprise, the presence of higher alkanes (from *n*-$C_{15}H_{32}$ to *n*-$C_{19}H_{40}$) resulted in the formation of a new, extended but once again capsular assembly, where the methyl groups of **3** adopt an up–down–up–down orientation. The NMR spectra (Figure 3) indicate that the alkanes compress to fit into the new capsule as both the number of upfield-shifted CH_2 signals and $\Delta\delta$ value increase. Integration of the signals indicates the presence of four glycolurils, two cavitands, and one guest in the assembly. The imide N–H signals (H_a, $H_{a'}$) are the furthest downfield resonances (13–14 ppm) and they are separated as capsule's symmetry is reduced from fourfold to twofold. Two of the ureido N–H's (H_e, H_f) form weaker hydrogen bonds with imide carbonyls of the cavitands; the remaining ureido N–H's (H_g) hydrogen-bond to the carbonyl of the adjacent glycoluril. The NOESY spectrum (see Supporting Information) of this assembly shows cross-peaks between the *N*-methyl signal (H_h) and the imide N–H signals ($H_{a'}$). This is not reasonable for cavitand **1·3$_4$**, but quite appropriate if two of these are brought together as a capsule that sheds four glycolurils. These aspects are all consistent with a capsule with formulation of **1·3$_2$·3$_2$·1** as shown in Figure 3.

An alternative structure **1·3$_4$·1** in which the *N*-methylated glycolurils adopt a twisted orientation[18] in the middle of the capsule (similar to **1·2$_4$·1**, where each glycoluril is rotated clockwise or anticlockwise some 30° from **1·3$_2$·3$_2$·1**) was also considered. Calculations (DFT; see Supporting Information) of the host frameworks indicated that this arrangement is considerably (13.6 kcal mol^{-1}) less stable than that of **1·3$_2$·3$_2$·1** proposed. Also, 2D NOESY spectroscopy is consistent only with structure **1·3$_2$·3$_2$·1**. A comparison of the pattern of the upfield-shifted signals of encapsulated *n*-$C_{17}H_{36}$ in **1·3$_2$·3$_2$·1** versus **1·2$_4$·1** indicated that the **1·3$_2$·3$_2$·1** is slightly longer than

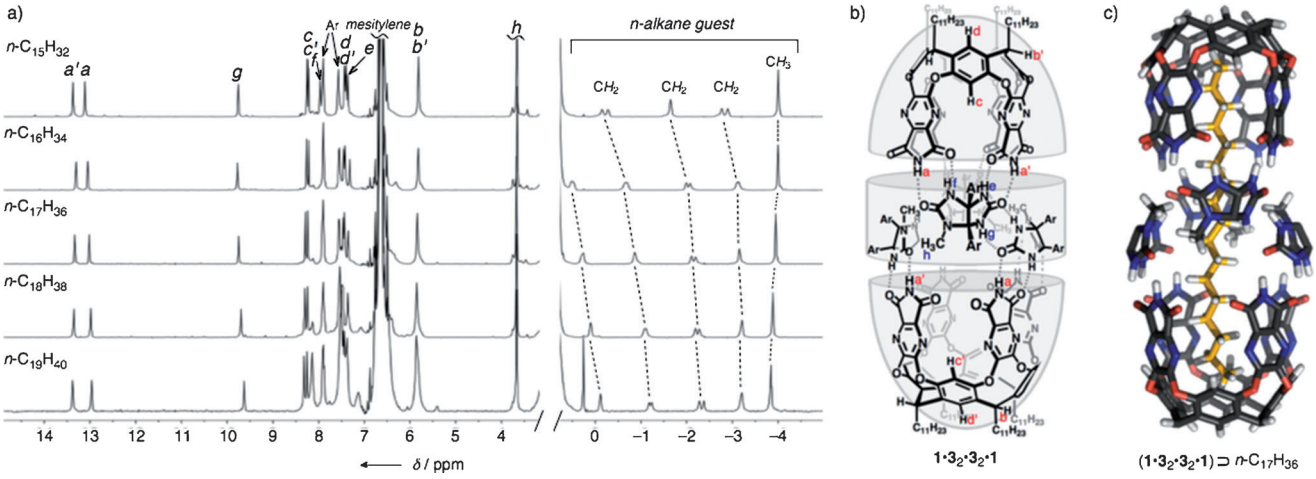

Figure 3. a) ^{1}H NMR spectra (600 MHz, 300 K, [D_{12}]mesitylene) of **1·3$_2$·3$_2$·1** complex with normal alkanes (*n*-$C_{15}H_{32}$ to *n*-$C_{19}H_{30}$). b) Chemical structure of **1·3$_2$·3$_2$·1** complex. c) Proposed model of the encapsulation complex (**1·3$_2$·3$_2$·1**)⊃*n*-$C_{17}H_{36}$ (the peripheral groups were removed for clarity).

1·2$_4$·1 (see Supporting Information). The DOSY spectrum of a mixture of **1·3$_2$·3$_2$·1** and **1·1** shows a smaller diffusion coefficient for the former (see Supporting Information). Likewise, a pairwise DOSY experiment shows nearly the same diffusion coefficient for **1·1** and **1·3$_4$** (see Supporting Information).

Normal alkanes longer than $C_{19}H_{40}$ do not fit into the inner space of extended capsule **1·2$_4$·1**.[18] Instead, the capsular assembly elongates by recruiting two, three, or four belts of (unsubstituted) glycoluril spacers in response to the increasing length of the guest, represented as **1**·(**2**$_n$)·**1** (n = 2–4).[14] This is not possible for the *N*-methyl glycouril **3** as there are no optimal arrangements to extend the dimensions of a capsule while maximizing the number of hydrogen bonds. Consequently, *n*-$C_{20}H_{42}$ and longer alkanes are not guests for extended capsule **1·3$_2$·3$_2$·1**. But *n*-$C_{20}H_{42}$ appears to be a good guest for extended cavitand **1·3$_4$**, since ^{1}H NMR spectra of the solution (see Supporting Information) is similar to that shown in Figure 2a.

As mentioned above, the new assemblies emerge with complete diastereoselectivity. This was confirmed by resolving the racemic glycoluril **3** on a chiral HPLC column and repeating the alkane binding experiments using the single enantiomer. The NMR spectra of the optically active complexes were identical to those of their racemic counterparts (see Supporting Information). Accordingly, each extended cavitand (**1·3$_4$**) and capsule (**1·3$_2$·3$_2$·1**) in the spectrum of Figure 2a and Figure 3b, contains only one enantiomer of the glycoluril shown as Figure 2c and 3c, respectively. The CD spectra of the optically active assembly with *n*-$C_{13}H_{28}$ and *n*-$C_{17}H_{36}$ guest were characteristic of their structures (Figure 4); the CD signals of chiral assembly were distinct from that of chiral **3**. At 25 °C, (**1·3$_4$**)⊃*n*-$C_{13}H_{28}$ showed weaker Cotton effects than (**1·3$_2$·3$_2$·1**)⊃*n*-$C_{17}H_{36}$, indicating the former has a less stable interaction between assembly components than the latter. This was also supported by ^{1}H NMR spectra at 27 °C, in which the extended cavitand (**1·3$_4$**)⊃*n*-$C_{13}H_{28}$, gave rise to slightly broadened signals of the ureido N-H groups (H_e, H_f, H_g, see Supporting Information), implying intermediate exchange of bound and free states. The exchange was slowed by cooling (**1·3$_4$**)⊃*n*-$C_{13}H_{28}$ in the mesitylene medium, and the CD intensity became stronger.

Another surprising feature of this system is the coexistence of the two new assemblies **1·3$_4$** and **1·3$_2$·3$_2$·1** in the presence of certain alkane guests. Figure 5 shows the distribution of the assemblies as a function of glycoluril concentration and temperature, where *n*-$C_{14}H_{30}$, *n*-$C_{17}H_{36}$, and *n*-$C_{18}H_{40}$ were used as a guest, respectively. The overall process is represented by the equilibrium (1):

$$(\mathbf{1}\cdot\mathbf{3_2}\cdot\mathbf{3_2}\cdot\mathbf{1})\supset G + G_{\text{free}} + 4\,\mathbf{3} \rightleftharpoons 2\,(\mathbf{1}\cdot\mathbf{3_4})\supset G \qquad (1)$$

While the trends are consistent with the expectations based on mass action (the excess **3** leads to more cavitands) and entropy (higher temperatures favor more particles), there are apparently some limits to these simple interpretations. For example, since the *n*-$C_{17}H_{36}$ is the best fit for the capsular assembly, the resulting complex (**1·3$_2$·3$_2$·1**)⊃*n*-$C_{17}H_{36}$ will tolerate an excess of **3**. The degree of attraction between host and guest is also an important factor in governing the equilibrium.

In conclusion, we described formation of extended chiral cavitand **1·3$_4$** as well as extended chiral capsule **1·3$_2$·3$_2$·1** through diastereoselective assembly of *N*-methylated glycoluril spacer **3** with the tetraimide cavitand **1**. These host structures were selectively constructed depending on the length of guest molecules, component ratio, and temperature; moreover they interconvert. The dimensions and conformations of normal alkane guests can be manipulated in these hosts with changes in external stimuli. The reversible encapsulation reveals molecular behavior in confined spaces and there is much evidence that encapsulated molecules behave quite differently than those in dilute solution.[19] The cavitands and capsules provide a convenient method of isolating molecules and observing them in very small spaces. There is also a broader perspective in biology since the majority of medicines are synthetic molecules that exert their effects when they fit into the small cavities of proteins and nucleic acids.

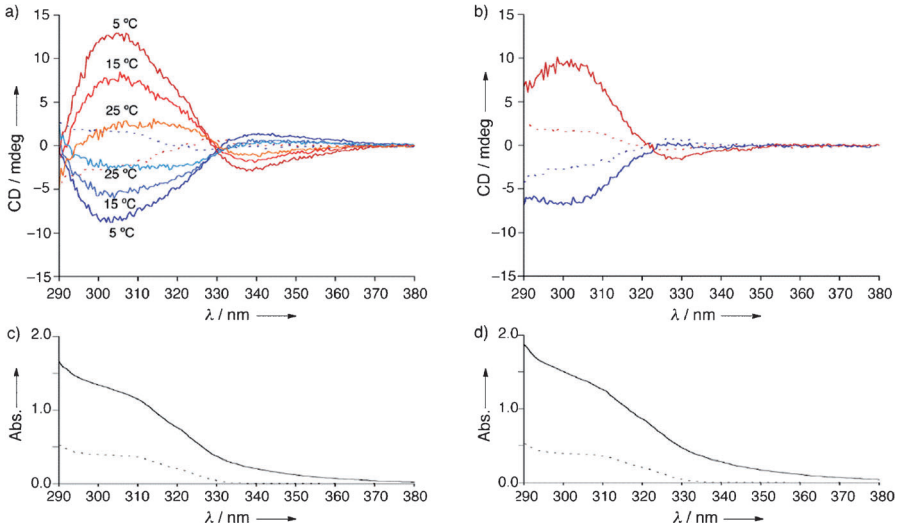

Figure 4. CD spectra in mesitylene of **3** (5.0×10^{-4} M, dotted lines) at 25 °C; the blue and red colors correspond to the first and second fractions in the chiral HPLC separation, respectively. The solid lines indicate the CD spectra of a) (**1·3$_4$**)⊃*n*-$C_{13}H_{28}$ and b) (**1·3$_2$·3$_2$·1**)⊃*n*-$C_{17}H_{36}$ under the same conditions as **3**, where the concentration of **3** is 5.0×10^{-4} M. Absorption spectra of the corresponding solution for c) (**1·3$_4$**)⊃*n*-$C_{13}H_{28}$, d) (**1·3$_2$·3$_2$·1**)⊃*n*-$C_{17}H_{36}$, respectively.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-600 spectrometer with a 5 mm QNP probe, where chemical shifts were determined with respect to non-deuterated residue DMSO (δ = 2.50 ppm) and non-deuterated mesitylene (δ = 6.63 ppm) for ^{1}H NMR spectroscopy and DMSO (δ = 39.52 ppm) for ^{13}C NMR

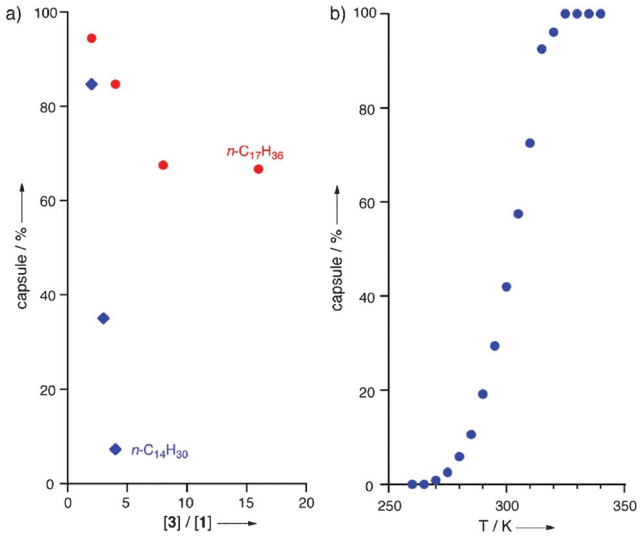

Figure 5. Equilibria between capsules and cavitands: the concentration of $\mathbf{1}\cdot\mathbf{3}_2\cdot\mathbf{3}_2\cdot\mathbf{1}$ (initially 2 mM) decreases as a) a function of added **3** (n-$C_{14}H_{30}$ and n-$C_{17}H_{36}$ are guests) or b) the temperature is lowered (n-$C_{18}H_{38}$ as guest).

spectroscopy as internal standards. Deuterated DMSO and mesitylene were obtained from Cambridge Isotope Laboratories, Inc. High-resolution mass spectra (HRMS) was recorded on an agilent ESI-TOF mass spectrometer. Preparative chiral HPLC was performed at room temperature using ethanol/hexane (1:9) as an eluent on a CHIRAL TECHNOLOGIES INC CHIRALCELL OD column (2 cm-$\phi\times$25 cm) using a SHIMADZU type liquid chromatograph LC-6AD HPLC pump, equipped with SHIMADZU type SPD-10A variable-wavelength UV/vis detector. CD and UV/vis spectra were recorded on Aviv Model 202 Circular Dichroism Spectrometer and Cary 50 UV-Visible Spectrophotometer, respectively. All the CD and UV/vis spectra were measured in a 2 mm cell.

All reagents were obtained from commercial suppliers and used without further purification. Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, and used without further purification.

Synthesis of compound **3**: To a dry THF solution (275 mL) of the glycoluril derivative **2** (3.15 g, 5.74 mmol) was added NaH (275 mg, 11.6 mmol) and methyliodide (1.63 g, 11.5 mmol). The resultant solution was stirred at room temperature for 12 h. The solvent was evaporated in vacuo, and the residue was resolved in ethylacetate. The ethylacetate layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (gradient elution from hexane/ethyl acetate = 1:1 to ethyl acetate) to give **3** as a white powder (1.18 g, 2.09 mmol) in 36 % yield. ^{1}H NMR (600 MHz, 330 K, [D$_6$]DMSO): δ = 7.64 (s, 1H, NH), 7.30 (s, 1H, NH), 7.18 (s, 1H, NH), 6.82 (d, 2H, J = 8.4 Hz, ArH), 6.68 (d, 2H, J = 8.4 Hz, ArH), 6.34 (d, 2H, J = 8.4 Hz, ArH), 6.31 (d, 2H, J = 8.4 Hz, ArH), 3.13 (br, 8H, CH_2), 2.53 (br, 3H, CH_3), 1.39 (m, 8H, CH_2), 1.26 (m, 8H, CH_2), 0.88 ppm (m, 12H, CH_3); ^{13}C NMR (150 MHz, 300 K, [D$_6$]DMSO): δ = 160.50, 159.62, 147.20, 147.13, 128.02, 127.91, 124.05, 121.39, 110.52, 110.27, 85.18, 79.99, 49.71, 49.68, 28.77, 25.86, 19.58, 13.82 ppm, HRMS (ESI+); m/z calcd for $[M+H]^+$: 563.4068; found 563.4075.

General procedure for formation of assemblies: To a solution of cavitand **1** (2.0 mg, 1.2 mmol) in [D$_{12}$]mesitylene (0.6 mL) in 5 mm NMR tube was added **3** ([2.8 mg, 5.0 mmol] for $\mathbf{1}\cdot\mathbf{3}_4$ or [1.4 mg, 2.5 mmol] for $\mathbf{1}\cdot\mathbf{3}_2\cdot\mathbf{3}_2\cdot\mathbf{1}$). The neat guest (20 equiv) was added into the solution and the tube was placed in an ultrasonic bath (230W) and sonicated for 5–10 min or briefly heated with heat gun to give a clear solution.

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[1] J. R. Moran, S. Karbach, D. J. Cram, *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828.
[2] E. Dalcanale, P. Soncini, G. Bacchilega, F. Ugozzoli, *J. Chem. Soc. Chem. Commun.* **1989**, 500–502.
[3] R. M. Yebeutchou, E. Dalcanale, *J. Am. Chem. Soc.* **2009**, *131*, 2452–2453.
[4] F. Pinacho Crisóstomo, A. Lledo, S. Shenoy, T. Iwasawa, J. Rebek, Jr., *J. Am. Chem. Soc.* **2009**, *131*, 7402–7410.
[5] L. Pirondini, E. Dalcanale, *Chem. Soc. Rev.* **2007**, *36*, 695–706.
[6] a) V. A. Azov, A. Schlegel, F. Diederich, *Angew. Chem.* **2005**, *117*, 4711–4715; *Angew. Chem. Int. Ed.* **2005**, *44*, 4635–4638; b) T. Gottschalk, B. Jaun, F. Diederich, *Angew. Chem.* **2007**, *119*, 264–268; *Angew. Chem. Int. Ed.* **2007**, *46*, 260–264.
[7] a) R. J. Hooley, J. Rebek, Jr., *Chem. Biol.* **2009**, *16*, 255–264; b) G. Gil-Ramírez, M. Chas, P. Ballester, *J. Am. Chem. Soc.* **2010**, *132*, 2520–2521.
[8] a) H. Gan, C. J. Benjamin, B. C. Gibb, *J. Am. Chem. Soc.* **2011**, *133*, 4770–4773; b) C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2011**, *133*, 7344–7347.
[9] D. J. Cram, H. J. Choi, J. A. Bryant, C. B. Knobler, *J. Am. Chem. Soc.* **1992**, *114*, 7748–7765.
[10] F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *Chem. Eur. J.* **2000**, *6*, 1007–1016.
[11] T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Nature* **1998**, *394*, 764–766.
[12] D. Ajami, J. Rebek, Jr., *J. Am. Chem. Soc.* **2006**, *128*, 5314–5315.
[13] D. Ajami, J. Rebek, Jr., *Proc. Nat. Acad. Sci. USA* **2007**, *104*, 16000–16003.
[14] D. Ajami, J. Rebek, Jr., *Angew. Chem.* **2007**, *119*, 9443–9446; *Angew. Chem. Int. Ed.* **2007**, *46*, 9283–9286.
[15] D. Ajami, J.-L. Hou, T. J. Dale, E. Barrett, J. Rebek, Jr., *Proc. Nat. Aca. Sci. USA* **2009**, *106*, 10430–10434.
[16] A. Scarso, L. Trembleau, J. Rebek, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 13512–13518.
[17] A. Scarso, L. Trembleau, J. Rebek, Jr., *Angew. Chem.* **2003**, *115*, 5657–5660; *Angew. Chem. Int. Ed.* **2003**, *42*, 5499–5502.
[18] D. Ajami, J. Rebek, Jr., *Nat. Chem.* **2009**, *1*, 87–90.
[19] a) J. Rebek, Jr., *Chem. Commun.* **2007**, 2777–2789; b) M. Yoshizawa, J. K. Klosterman, M. Fujita, *Angew. Chem.* **2009**, *121*, 3470–3490; *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438; c) D. Fiedler, D. H. Leung, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2005**, *38*, 351–360.

