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Guest-Induced, Selective Formation of Isomeric Capsules with Imperfect Walls

Wei Jiang and Julius Rebek, Jr.*

The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: The majority of building blocks in self-assembled capsules feature high symmetry. Reducing this symmetry inevitably leads to expanded possibilities for isomerism. Here, we report a deep cavitand host with one short and three long walls. Its dimerization to hydrogen-bonded capsules in the presence of suitable guest molecules can lead to two constitutional isomers. A given guest induces the predominant formation of only one isomer. The unexpected selectivity is interpreted in terms of the different hydrogen-bonding patterns of the capsules and their effects on the size, shape, and dynamics of the capsules' spaces.

Reversibly formed capsules are synthetic receptors that self-assemble around their targets, isolate them from the bulk medium, place them in a hydrophobic environment, and present them with reaction partners at very close range.[1] Like enzymes, they act as molecular flasks and are catalysts for reactions that fit the shape of the confined space.[2] Capsules also amplify intermolecular interactions and stabilize reactive intermediates or species.[3] Self-assembled superstructures generally, and capsules specifically, use multiple identical modules with high symmetry to create correspondingly symmetrical structures. This is the desired result of synthetic economy and limits the isomeric products to a manageable number. On the other hand, high symmetry makes tailoring the space or introducing functional groups at specific locations difficult. There are only a few self-assembled capsules constructed from building blocks with low symmetry.[4] Here, we introduce systems that assemble into capsular structures with "holes" on their surfaces and report their unexpected molecular recognition properties.

Deep cavitands such as **1** (Figure 1a) feature a C_{4v}-symmetry in the vase conformation and are readily prepared from resorcinarenes. Dimerization through a seam of 8 bifurcated hydrogen bonds gives a cylindrical capsule **1.1**[5] of S_8 symmetry. The capsule provides a host environment for elongated guests or guest combinations, and the shape of the space gives rise to spatial arrangements of guests and new stereochemistry that have no counterparts in solution chemistry.[6] Cavitand **2** with a single plane of symmetry was prepared from a monofunctionalized resorcinarene **3** (Figure 1b). It proved soluble in mesitylene-d_{12} and, in the absence of other guests, the ^{1}H NMR spectrum of cavitand **2** is well-resolved although slightly broadened (Figure 2a). This is in contrast to the spectrum of cavitand **1** where no aromatic peaks are detectable (Figure S7), presumably resulting from dynamic processes involving aggregates of unknown hydrogen-bonded networks. Apparently, introduction of one shortened wall without an imide group discourages the aggregation, affording a discrete structure in this solvent. The methine signals of **2** are downfield (5.7−6.2 ppm) and split into three peaks in 1:1:2 ratio, indicating vase-conformation with a plane of symmetry. No signals in the region of 9−11 ppm (usually seen for hydrogen-bonded imide N−H protons of capsules **1.1**) indicate that cavitand **2** does not dimerize in the mesitylene solvent. Yet the vase-conformation defines a cavity that is unlikely to be empty; rather, the short wall allows one mesitylene solvent molecule to occupy this space (Figure 2a), and the resident solvent undergoes exchange with other mesitylenes at a rate that slightly broadens the methine signals.[7]

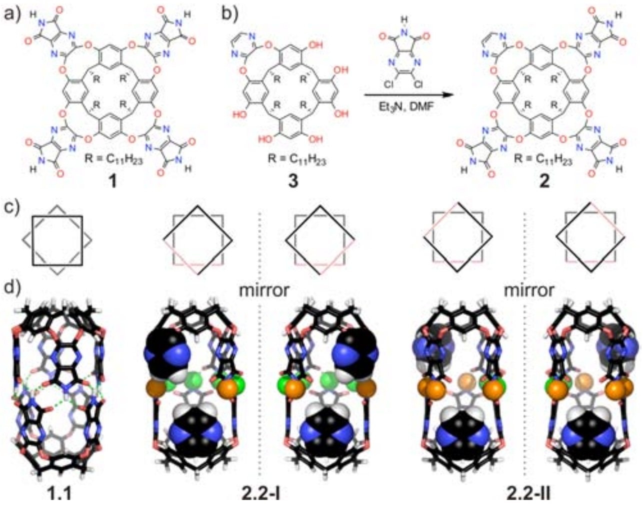

Figure 1. (a) Chemical structure of cavitand **1**, (b) synthesis of cavitand **2**, (c) top view cartoons of the space in the various capsules with the short walls in red, and (d) models of the dimeric capsule **1.1** and the four isomers of the capsule **2.2**. The short walls are rendered as space-filling models and the imide N−H hydrogens of **2.2** are shown as colored balls to represent different hydrogen bonding types: green, bifurcated hydrogen bonds; orange, two-center hydrogen bonds. Peripheral groups are omitted for viewing clarity.

We examined a number of potential guests and found that compared to **1.1**, a much narrower range of molecules is

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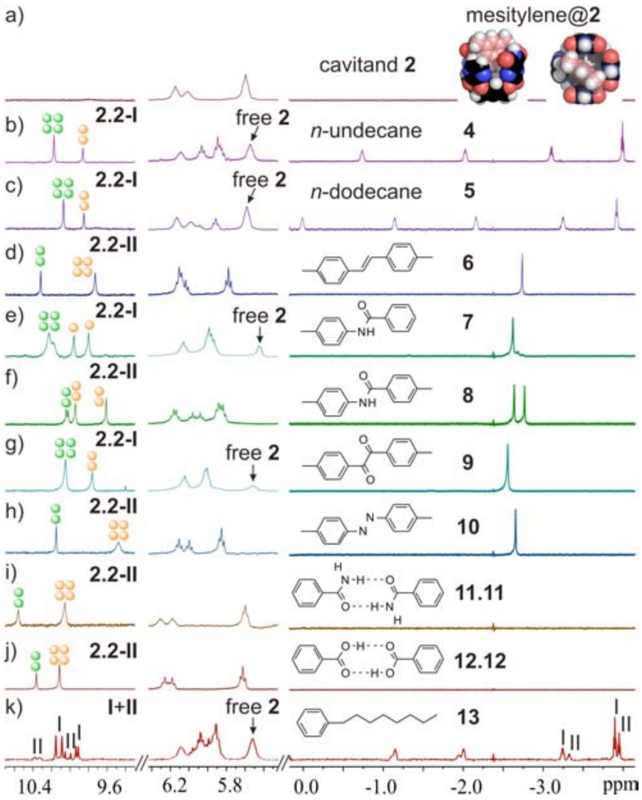

Figure 2. Partial ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of the solution of cavitand **2** in the absence (a) and the presence of guests (b) *n*-undecane (**4**), (c) *n*-dodecane (**5**), (d) 4,4′-dimethylstilbene (**6**), (e) *p*-[*N*-(*p*-tolyl)]benzamide (**7**), (f) *p*-[*N*-(*p*-tolyl)]-toluamide (**8**), (g) 4,4′-dimethylbenzil (**9**), (h) 4,4′-dimethylazobenzene (**10**), (i) benzamide (**11**), (j) benzoic acid (**12**), or (k) *n*-octylbenzene (**13**). The imide N−H signals of **2.2** are labeled with colored balls: green, bifurcated hydrogen bonds; orange, two-center hydrogen bonds.

encapsulated in **2.2**. This is due to the lowered stability of the capsules and the more favorable (competitive) solvation of the free cavitand **2** by mesitylene. Only the best guests for **1.1** can coax the formation of the capsule **2.2**. Among the *n*-alkane guests, only *n*-undecane (**4**) and *n*-dodecane (**5**) templated the formation of **2.2** (Figure 2). The aromatic guests with appropriate length and width, such as 4,4′-dimethylstilbene (**6**), *p*-[*N*-(*p*-tolyl)]benzamide (**7**), *p*-[*N*-(*p*-tolyl)]toluamide (**8**), 4,4′-dimethylbenzil (**9**), 4,4′-dimethylazobenzene (**10**), and *n*-octylbenzene (**13**) are also good guests. Neither shorter nor longer guests such as azobenzene, 4,4′-dimethylbiphenyl, stilbene, benzil, *N*,*N*′-dicyclohexylcarbodiimide, and 4,4′-dimethoxybenzil are taken up by the capsule **2.2**. Dimeric guests such as the hydrogen-bonded benzamide homodimer (**11.11**) and benzoic acid homodimer (**12.12**) are good guests, but other multiple guests—chloroform, toluene, picoline and co-guest combinations such as [2,2]paracyclophane with chloroform or dichloromethane—are not accommodated by the capsule **2.2**. Apparently, a stricter template effect[8] is required for the formation of the capsule **2.2**. Integration (Figure S8−S10) and DOSY[9] (Figure S11) experiments confirm the encapsulation of the guests of Figure 2.

As is the case for cavitand **1** and its capsule **1.1**, the four heterocyclic walls of cavitand **2** define a square prismatic space in the vase-conformation. Two of these can come together to form capsule **2.2** with the prisms rotated 45° along the capsule's long axis. There are two constitutionally isomeric arrangements of the cavitands: the two short walls can be proximal (**2.2-I**) or distal (**2.2-II**) to each other, and as both of these two isomers are chiral, their mirror images are also present. Moreover, the two isomers have different hydrogen-bonding patterns. Both have two kinds of hydrogen bonds: bifurcated (green balls, Figure 1) and "normal" two-center ones (orange balls, Figure 1). The bifurcated hydrogen bonds have two carbonyl acceptors to each hydrogen bond donor (imide N−H). Accordingly, the bifurcated N−H protons are shifted further downfield than the two-centered ones with only one acceptor per donor in the same capsule.[10] The numbers of bifurcated and two-centered hydrogen bonds are different for the two isomers **2.2-I** and **2.2-II**: 4 bifurcated and 2 normal for isomer **I**; 2 bifurcated and 4 normal for isomer **II**. Consequently, the chemical shifts of the N−H signals and their ratios allow NMR assignments of the two isomeric capsules.

At first glance, a guest might see little difference between the two potential hosts, but the encapsulation experiments proved otherwise: apparently, guests take a long hard look at the accommodations and choose carefully. For example, *n*-undecane (**4**) and *n*-dodecane (**5**), which fit comfortably into the parent capsule **1.1** and have no obvious means of discriminating the subtle hydrogen-bonding patterns detailed above, nonetheless select capsule **2.2-I**—exclusively![11] As seen in Figure 2b,c, we observed the appropriate N−H signals for these symmetrical guests, with the ratio of the downfield (bifurcated) and upfield (normal) of 2:1. In contrast, the stilbene **6**, another guest without hydrogen bonding capabilities, was found only in capsule **2.2-II** (Figure 2d). As seen from the other spectra of Figure 2, almost all guests prefer one or the other arrangement of host. Comparison of the results for benzanilides **7** (Figure 2e) and **8** (Figure 2f) provides the starkest contrast; a single methyl group, far from the center of the capsule, makes all the difference in the choice between **2.2-I** and **2.2-II**. 4,4′-Dimethylbenzil **9** prefers isomer **I**, while 4,4′-dimethylazobenzene (**10**), benzamide homodimer (**11.11**), and benzoic acid homodimer (**12.12**) exclusively template isomer **II**. It was difficult to find a guest that did not discriminate; only *n*-octylbenzene **13** could be seen in both capsules, but even so, favored isomer **I**.

The two capsule isomers show different thermal stabilities. For example, all the complexes of isomer **I** show the presence of cavitand **2** even when a large excess of guest is present (Figure 2). At 360 K, isomer **I** with **4** or **9** as a guest completely dissociates (Figures S12 and S13) to give the cavitand. In contrast, no free cavitand was detected with any of the complexes **II** and no dissociation was detected on heating up to 360 K for the stilbene **6** occupied capsule (Figure S14).

What gives rise to these guest choices? In the capsule **2.2-I** with proximal short walls, a large gap in the seam of hydrogen bonds exists and a sizable hole in the structure is created. The opening is expected to permit the overall structure to bend more easily than the more rigid **2.2-II** with more evenly distributed hydrogen bonds along the seam. These features result in a smaller and more dynamic space in **2.2-I**, and are expected to affect the guest exchange dynamics.[12,13] This mobility is proposed to account for its preferred encapsulation of the flexible alkanes, the shorter benzanilide **7**, the (preferably) bent[14] benzil **9** and its indifference to the part-rigid, part-flexible **13**. In contrast, the more evenly distributed hydrogen bonds in isomer **II** result in greater cooperativity and more rigid capsule structures with less bending ability. Isomer **II** prefers longer and more rigid guests.

A closer look at guest **13** provides comparative information on the thermal stabilities of the two isomeric capsules. With increasing temperature, the ratio of isomer **I** to **II** gradually increases (Figures 3a and S15). At 340 K, the capsule and guest signals are significantly broadened and the interconversion between the two isomers is at an intermediate rate (Figure S15). The equilibrium constants between these two isomers were determined by integration of the methyl signals (Figure S16), and the thermodynamic data for this equilibrium were calculated according to the van't Hoff equation (Figure 3b,c). Isomer **I** emerges as entropically more favorable than isomer **II**, as suggested above: the sizable hole in the structure permits greater mobility, while isomer **II** has more evenly distributed hydrogen bonds that do not allow as much bending. Surprisingly, isomer **II** is enthalpically preferred over isomer **I**. This seems to be inconsistent with the facts: isomer **I** possesses four bifurcated hydrogen bonds and two normal hydrogen bonds, while isomer **II** has only two bifurcated hydrogen bonds and four normal hydrogen bonds. However, the chemical shifts of N−H protons of the two isomers with **13** as guests (Figure 2k) support this result. The N−H signals of isomer **II** are shifted further downfield than those of isomer **I** for the corresponding types, suggesting stronger hydrogen bonds are involved in isomer **II**.[15] In short, isomer **I** has more freedom and weaker hydrogen bonds, and isomer **II** has stronger hydrogen bonds and less mobility, another, if unconventional, example of the enthalpy−entropy compensation.[16]

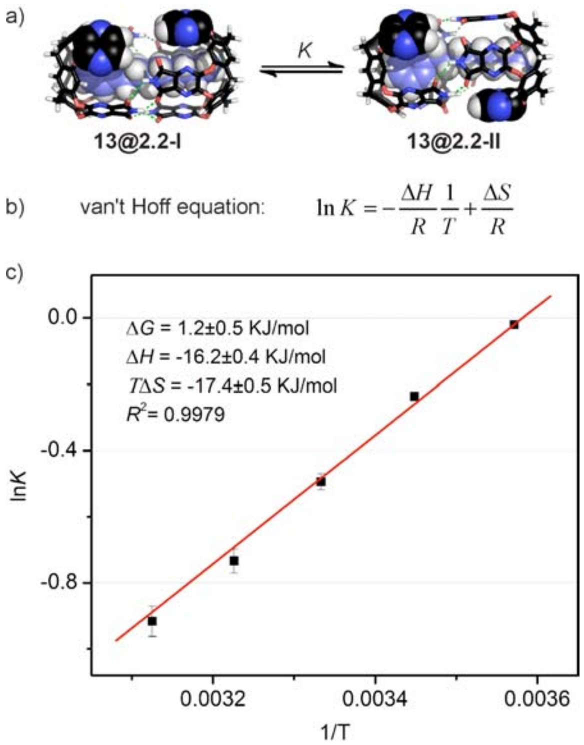

Figure 3. (a) The equilibrium between the two capsule isomers with **13** as the guest, (b) van't Hoff equation, and (c) van't Hoff plot of the equilibrium between the two capsule isomers with **13** as the guest and the obtained thermodynamic parameters. Error bars were estimated as ±5%.

The capsules **2.2** inherit most of the structural elements of **1.1** with only two hydrogen-bonding walls missing. We tested whether cavitands **1** and **2** can form a hybrid capsule **1.2**. With guest **9**, we observed predominant self-sorting[17] (Figure 4a). The peaks labeled with the asterisks are assigned to the hybrid capsule, which accounts for less than 3% of the capsule population. However, with guest **6**, ca. 20% of the capsule population is the hybrid species. This result is further consolidated by self-sorting experiments with guests **4** and **10** (Figure S17). This was surprising because isomer **II** is generally more stable than isomer **I**. However, structurally and energetically, isomer **II** is closer to the parent capsule **1.1** than isomer **I**, and more readily forms the hybrid capsule with the guests appropriate for **II**.

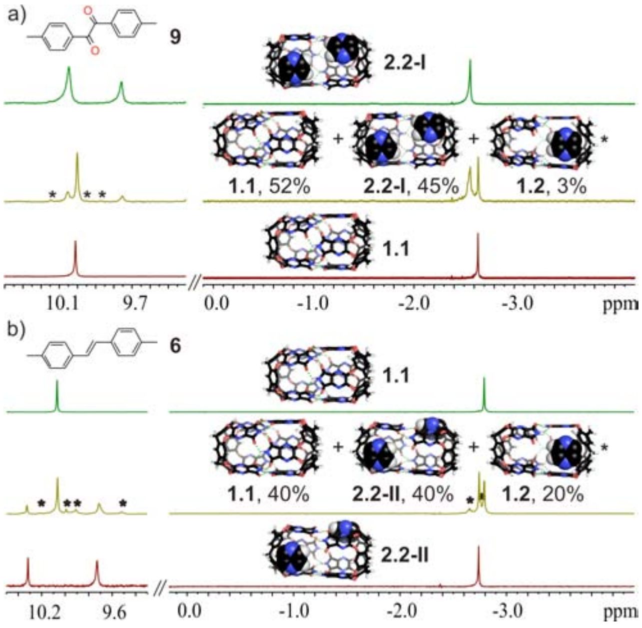

Figure 4. Partial ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of guests (a) 4,4′-dimethylbenzil (**9**) and (b) 4,4′-dimethylstilbene (**6**) in the solutions of the cavitands **1**, **2**, or their 1:1 mixtures. The relative populations of the capsules were determined by the integrals of the N−H signals in the region of 9.4−10.4 ppm. The asterisks indicate the signals arising from the hybrid capsule **1.2**.

In summary, we have synthesized an abbreviated cavitand that lacks a full set of hydrogen bonds for self-complementarity. Yet, the cavitand still assembles with appropriate guests to form dimeric capsules. Two constitutionally isomeric capsules are observed and almost all the guests show an exclusive selection of one capsule or the other. The results underscore the large differences in selectivity that can arise from seemingly small differences in structure in complexes where a host more or less completely surrounds a target guest.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section, ^{1}H NMR and DOSY NMR spectra, variable-temperature experiments, and self-sorting experiments. 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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(10) This assignment is supported by line-shape change of the corresponding NMR peaks at lower temperatures. In the case of isomer **I**, the four N−H protons involved in bifurcated hydrogen bonds are in two different chemical environments. However, the signals coalesce at 300 K. When the temperature is decreased to 280 K, this signal broadens while the other N−H peak remains sharp (Figure S13). The same phenomenon was also observed for the N−H protons of isomer **II** involved in two-centered hydrogen bonds (Figure S14). This supports the assignments for the two types of hydrogen bonds.

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