Host–Guest Compounds

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Supramolecular Architecture with a Cavitand–Capsule Chimera**

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Signaling events in biological systems often make use of macromolecules featuring separated binding compartments and some means of communication between the sites. In synthetic, self-assembled systems, early attempts to arrange confinement in two very different capsules were thwarted by the formation of hybrid capsule structures.[1] The hybridization was unexpected, given the self- and non-self-sorting generally at work in such molecular assemblies.[2] We report here the preparation and molecular recognition properties of a molecule, **1**, featuring covalently linked binding sites that do not hybridize yet provide unambiguous self-assembly. The compartments (a deep cavitand and a dimeric capsule) are orthogonal in binding behavior and allow the simultaneous molecular recognition and exchanges of their respective guests (Figure 1).

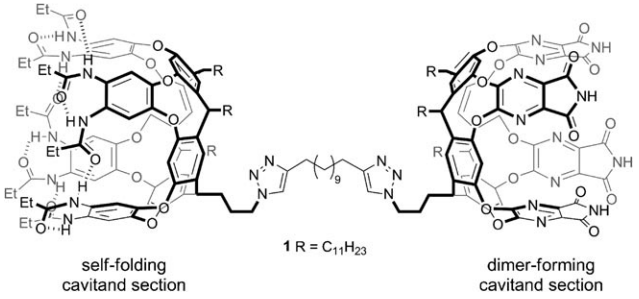
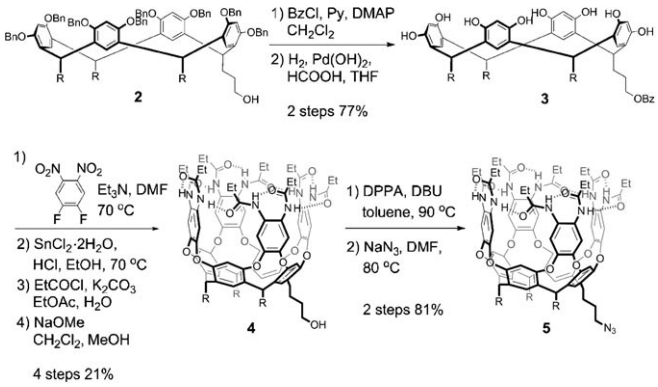


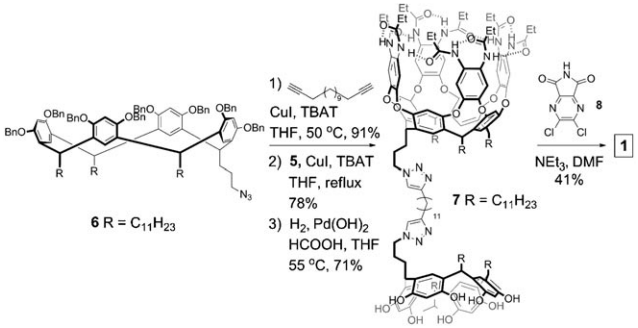
Figure 1. Chimeric host **1**.

Chimeric host **1** was accessed through a convergent sequence, in which copper-catalyzed azide–alkyne cycloadditions (Click reactions)[3] played a key role in the final stage of the synthesis. The octaamide cavitand portion was prepared in eight steps starting from the previously reported monofunctionalized resorcinarene **2** (Scheme 1).[2e] After protection of the hydroxy anchor on the "feet" as the benzoate ester and debenzylation of the phenolic functions, the "walls" of the cavitand were incorporated using the standard condensation with 3,4-difluoro-1,2-dinitrobenzene. The resulting octanitro compound was reduced, acylated, and deprotected at the hydroxy terminus to yield **4**. Functional group interconversion was easily accomplished to yield the key azide building block **5**.



Scheme 1. Synthesis of azide-functionalized cavitand module **5**. Bn = benzyl; Bz = benzoyl; DMAP = dimethylaminopyridine; DPPA = diphenylphosphoryl azide.

The sequential click coupling sequence between **5**, azide-functionalized resorcinarene **6**, and pentadeca-1,14-diyne allowed an efficient assembly of the two main building blocks. After debenzylation, the final build-up of the imide capsule-forming skeleton was accomplished by condensation of **7** with dichloropyrazine **8** following an optimized protocol (Scheme 2).[4]



Scheme 2. Completion of the synthesis. TBAT = tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.

Upon addition of *trans*-4,4′-dimethylstilbene (**9a**) to a solution of **1** in [D_{12}]mesitylene (a noncompeting solvent) a singlet corresponding to the methyl groups of **9a** appears at $\delta = -2.80$ ppm, indicating the formation of a 1:1 capsule with two molecules of **1** (Figure 2). There are two ways to form this capsule and while both diastereomers are doubtlessly formed, the guest inside is oblivious to the differences of the assemblies as revealed by the sharp signal for its methyl groups. Addition of 1-adamantylcarbonitrile (**10a**) to this solution brings about three more resonances in the upfield

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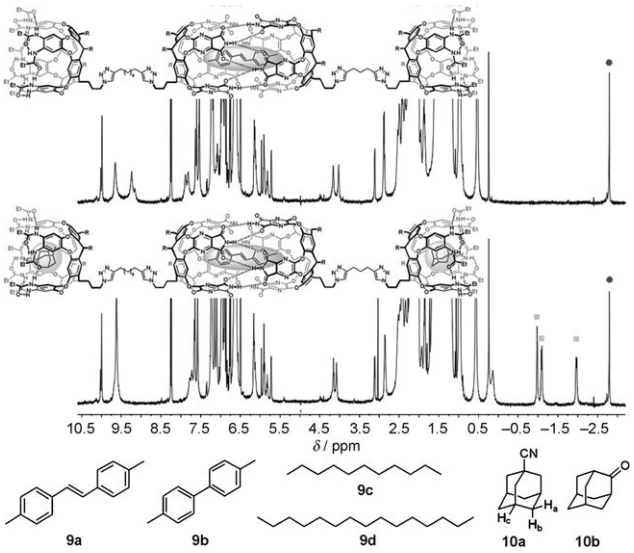

Figure 2. The NMR spectra of host **1** ([D_{12}]mesitylene, 320 K, [**1**] = 1.8 mM) upon addition of guests **9a** (top) and **10a** (bottom) are shown. Circles indicate the methyl resonance of bound **9a** and squares correspond to the buried 1-adamantylcarbonitile protons.

region which are assigned to the adamantyl protons bound to the cavitand region of **1**. The adamantyl guest binds to its complementary binding site without disruption of the initial capsular assembly. With excess **10a** (twofold per binding site) present in solution, integration reveals a 2:2:1 stoichiometry of assembly components as all cavities are saturated.

The formation of a unique and discrete supramolecular assembly of formula $\mathbf{1}_2\cdot\mathbf{9a}\cdot\mathbf{10a}_2$ is confirmed by diffusion ordered spectroscopy (DOSY)[5] experiments (Figure 3). The

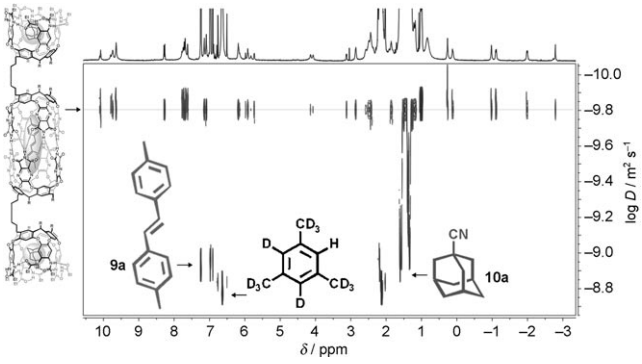

Figure 3. ^{1}H DOSY NMR spectrum ([D_{12}]mesitylene, 300 K, [**1**] = 1.8 mM) showing distinct diffusion coefficients (*D*) for assembly $\mathbf{12}\cdot\mathbf{9a}\cdot\mathbf{10a}_2$ and small, faster diffusing molecules.

rigidity and kinetic stability of this assembly provides an unambiguous and graphical result: all the resonances corresponding to the cavitand–capsule hybrid and their guests lie in a narrow trace in the diffusion dimension ($D = 1.7\times10^{-6}\,cm^2s^{-1}$) which is clearly distinguished from the much faster diffusing small molecules present in solution ([D_{11}]mesitylene $D = 1.6\times10^{-5}\,cm^2s^{-1}$, **9a** $D = 1.2\times10^{-5}\,cm^2s^{-1}$, **10a** $D = 1.6\times10^{-5}\,cm^2s^{-1}$). The same diffusion values are obtained (within experimental error) at either long ($\Delta = 100$ ms) or short ($\Delta = 50$ ms) diffusion times.

We next tested the orthogonality of the binding sites by way of the controlled release of guests (Figure 4). Capsule $\mathbf{1}_2$ was charged with 4,4′-dimethylbiphenyl (**9b**, Figure 4a) and then the cavitand sites were loaded with 2-adamantanone (**10b**, Figure 4b). Incremental addition of 1-adamantylcarbonitrile, a better fit for the cavitand binding pocket, displaces bound **10b** from the cavity without perturbing the capsule section (Figure 4c). Displacement of the biphenyl without disturbing the cavitands could be demonstrated as well: *n*-undecane (**9c**) smoothly replaces **9b**. Although both guests fill slightly less than half of the space inside the capsule, the flexible alkane can find a better fit.[6] The capsule can also be extended by means of a glycoluril spacer **11** in the presence of a slightly longer alkane (**9d**, *n*-pentadecane). Pentadecane fills the expanded space and displaces the undecane back into the solution.[1a] The formation of the new nine-component assembly is confirmed by the appearance of the signature resonances at $\delta = 13.3$ ppm of the imides' NH's in contact with glycoluril carbonyls.[7] The newly added hydrogen bonding spacer does not engage the cavitand section and leaves this binding site unaltered. When CD_3OD was added to the solution, cleavage of capsule occurred and the pentadecane guest was released. The presence of methanol disrupts the hydrogen bond network of the capsule and accelerates the rotation about the amide *N*-aryl bond of the cavitand (racemization of the cycloenantiomers), but the concentration of bound **10a** is unchanged. The deuteration by the solvent CD_3OD causes depletion of the NH resonances and the signal of the imide NH shifts upfield to $\delta = 8.2$ ppm (merges with the multiple aromatic resonances of the system, not shown) as the capsule is disrupted. The dehiscence provoked by the competing CD_3OD molecules can be reversed by the addition of **9a** (packing coefficient 48%), and the assembly of five molecules with encapsulated stilbene is restored.

Receptor molecules that self-assemble into oligomeric aggregates of respectable sizes are numerous: they can be constructed through repetitive accumulation of a single module,[2a,8] and two-component systems are even more plentiful.[9] Here we have shown that a self-assembled, ditopic host—a cavitand–capsule chimera—can engage guests at independent binding sites without interacting directly (hybridizing). The guests can be released selectively from either site by action of external chemical stimuli and the dimensions of the capsule compartment can be altered without effect on the cavitand. The orthogonality of the two sites extends to the dynamics of the system since exchange of guests occurs in well-separated time frames: cavitand-bound molecules have an encapsulated half-life of 1 to 25 s[10] whereas this value is as high as 32 h for some capsule-bound molecules.[11] We note that **7** is itself a chimera and not without its own possibilities for assembly.[12]

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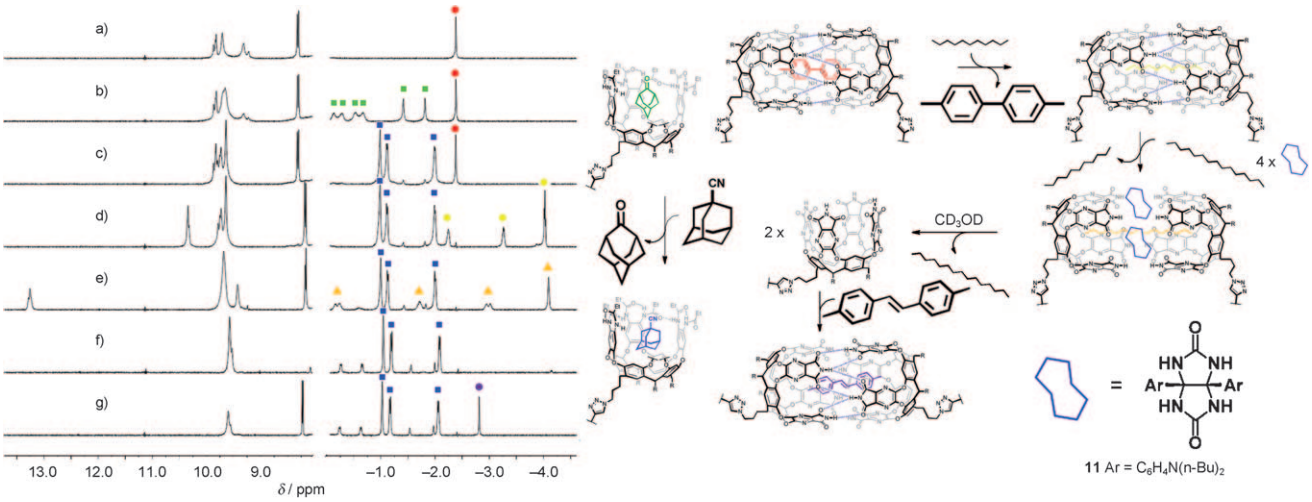

Figure 4. a) $\mathbf{1}_2$ charged with **9b** (red circles), b) the cavitand sites are charged with **10b** (green squares), c) addition of **10a** (blue squares) releases **10b** from the cavitand, d) **9c** (yellow circles) replaces **9b** in the capsule section, e) addition of glycoluril **11** triggers the formation of an extended capsule incorporating a longer alkane **9d** (orange triangles), f) addition of CD_3OD disrupts the dimer to release **9d**, and g) addition of **9a** (purple circle) restores the capsular assembly.

Keywords: cavitands · host–guest compounds · molecular capsules · molecular recognition · supramolecular chemistry

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