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Cucurbit[10]uril

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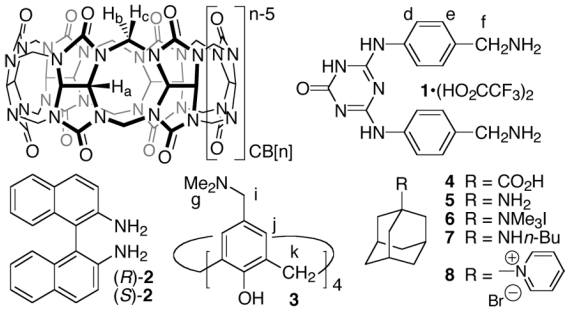
Abstract

Melamine diamine **1** is able to displace CB[5] from the CB[10]•CB[5] complex resulting in CB[10]•$\mathbf{1}_2$ and precipitated CB[5]•**1**. We were able to isolate free CB[10] by treatment of CB[10]•**1** with acetic anhydride followed by washing with MeOH, DMSO, and water. The spacious cavity of CB[10] is able to complex large guests including a cationic calix[4]arene derivative in its 1,3-alternate form (CB[10]•1,3-*alt*-**3**). The addition of adamantane carboxylic acid (**4**) to CB[10]•**3** triggers a conformational change during the formation of termolecular complex CB[10]•*cone*-**3**•**4**.

In 1981, Mock disclosed the structure of cucurbit[6]uril (CB[6]) and subsequently delineated its outstanding binding properties toward ammonium ions in a series of elegant papers.[1] Nearly 20 years later, the groups of Kim and Day reported the preparation and isolation of the CB[n] homologues CB[5], CB[7], CB[8] and CB[10] as its CB[10]•CB[5] inclusion complex.[2] With their enhanced cavity size, the new members of the CB[n] family[3] display a range of novel properties and applications including gas encapsulation, polarizability enhancement, and supramolecular dendrimer chemistry.[4] Most notable, however, is the ability of CB[8] to simultaneously bind two aromatic guests which function as molecular machines in response to external stimuli.[3b,5] In this paper we report the isolation of free CB[10] and disclose its unusual recognition properties. These results suggest that CB[10] will rival CB[8] for use as an advanced component for molecular machines and biomimetic systems.[3,6]



We isolated CB[10]•CB[5] in good quantities using a modification of the procedure reported by Day.[2b,2c] After much experimentation we discovered that treating a solution of CB[10]•CB[5] (Figure 1a) with a five equivalents of **1** results in the precipitation of the (CB[5]•**1**)$_n$ exclusion complex and the formation of the CB[10]•$\mathbf{1}_2$ inclusion complex (Figure 1b). ^{1}H NMR and x-ray crystallography indicates that **1** adopts a U-shape[6] within the cavity of CB[10] (Figure 2); the two equivalents of **1** are arranged in a head-to-tail manner which results in a single set of resonances for H_b and H_c within CB[10]•$\mathbf{1}_2$. The second equivalent of **1** is relatively weakly bound to CB[10] and can be removed by washing with MeOH to yield CB[10]•**1** (Figure 1c). Once again, **1** adopts a U-shape within the CB[10]•**1** complex; in this

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instance the top and bottom of CB[10] are differentiated and two sets of resonances are observed for H_b and H_c. Free CB[10] was obtained by heating CB[10]•**1** in Ac_2O followed by washing with $(CH_3)_2SO$, MeOH, and H_2O (Figure 1d). CB[10] is quite stable in acidic solution (>1 month in 20% D_2O/DCl at room temperature) which enabled our investigations of its molecular recognition properties.

CB[10] is insoluble in D_2O (< 50 μM) but its inclusion complexes often are nicely soluble which allows their characterization by NMR. Alternatively, CB[10] can be dissolved in 20% DCl / D_2O for binding studies. An initial screen of many guests revealed that CB[10] – with its cavity volume of ≈ 870 $Å^3$ – undergoes complexation with several chemically and biologically important substances (e.g. dyes, fluorophores, pharmaceuticals, and peptides) although some of these complexes occur as insoluble precipitates (Supporting Information). A soluble, kinetically stable complex was obtained with the more sizable and cationic guest (*R*)-**2** which gave exclusively the termolecular complex CB[10]•(*R*)-$\mathbf{2}_2$. Interestingly, when racemic (±)-**2** was used, the racemic mixture of homochiral complexes (CB[10]•(*R*)-$\mathbf{2}_2$ and CB [10]•(*S*)-$\mathbf{2}_2$) was preferred relative to the heterochiral *meso*- complex (CB[10]•(*R*)-**2**•(*S*)-2) by a factor of three (Supporting Information). In combination, these results suggest that CB[10] may find application in drug delivery, for peptide sensing, and even to modulate the behavior of catalysts based on binaphthalene derived ligands.

Given the vast size of the CB[10] cavity we envisioned the encapsulation of smaller host molecules like cyclodextrins, calixarenes, or even CB[6] that would merge the advantageous features of these host families. In the event, only cationic calix[4]arene derivative **3** formed a soluble stable complex (CB[10]•**3** Figure 3a). Based on the number and multiplicity of resonances observed for CB[10]•**3**, we conclude that **3** adopts a mixture of the D_{2d}-symmetric 1,3-alternate conformation and a rapidly equilibrating mixture of cone, 1,2-alternate and partial cone conformers within the CB[10] host. Intrigued by the possibility of using allosteric effects to control the conformation of the macromolecular complex[7] we studied the binding of small molecule guests to CB[10]•**3**. We found that substituted adamantanes (**4** – **8**) – which do not bind to **3** alone – induce a dramatic change in the conformer distribution during the formation of CB[10]•*cone*-**3**•adamantane complexes (Figure 3b).[8] Scheme 1 shows an MMFF minimized model of the CB[10]•*cone*-**3**•**4** complex.[9] One of the hallmarks of biological allostery is the reversible response of the system to activator concentration. For this purpose we added stoichiometric amounts of CB[7] which sequesters **4** as its CB[7]•**4** complex[3b,6d] and resets the system to its original CB[10]•**3** state (Figure 3c).

Just like the smaller CB[n] homologs, CB[10] retains the ability to bind a variety of chemically and biologically important cationic substances within its cavity. We have further demonstrated that CB[10] readily forms termolecular complexes (e.g. CB[10]•$\mathbf{2}_2$ and CB[10]•*cone*-**3**•**4**); the vast cavity volume of CB[10] (≈ 870 $Å^3$) suggests the potential formation of even higher molecularity complexes. The termolecular complexes already display a range of intriguing behavior including chiral recognition and efficient allosteric control of macromolecular geometry in response to a small molecule (e.g. **4**). Overall, these results suggest that CB[10] will find broad application as an advanced component of molecular machines and biomimetic systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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8. Addition of 1 equiv. **4** to a solution of CB[10]•**3** (500 μM) results in ≅ 90% formation of CB[10] • *cone*-**3**•**4** reflecting the strong binding of **4** to CB[10] •**3**. A larger number of equivalents of **5** – **8** are required to complete the conformation change presumably because of weaker binding interactions of tetracationic CB[10] •**3** with these cationic guests.
9. The ^{1}H NMR spectrum of CB[10]•*cone*-**3**•**4** does not show doubling of the H_g and H_j resonances as expected for the geometry shown in Scheme 1. We attribute this result to a dynamic process in which **4** reorients its CO_2H group between the two portals rapidly on the chemical shift timescale. The bulkier adamantanes **7** and **8** display two sets of resonances as expected.

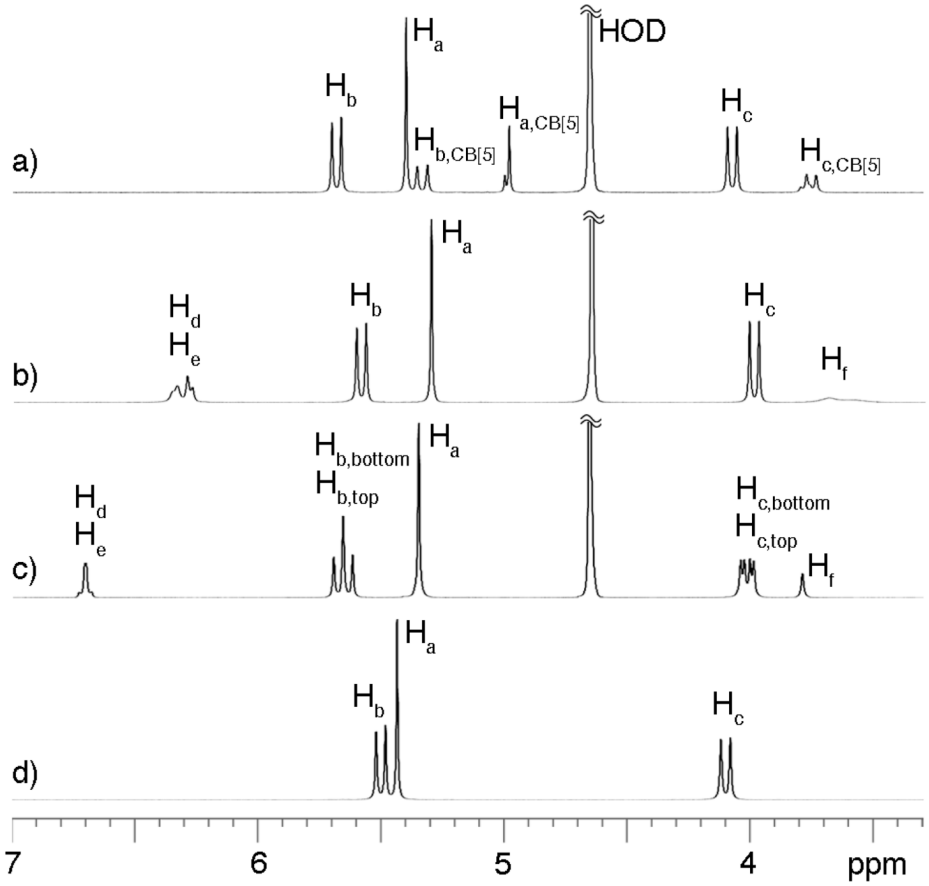


Figure 1.

^{1}H NMR spectra (400 MHz, D_2O, 298 K) for: a) CB[10]•CB[5], b) CB[10]•**1**$_2$, c) CB[10]•**1**, d) CB[10] (20% D_2O/DCl).

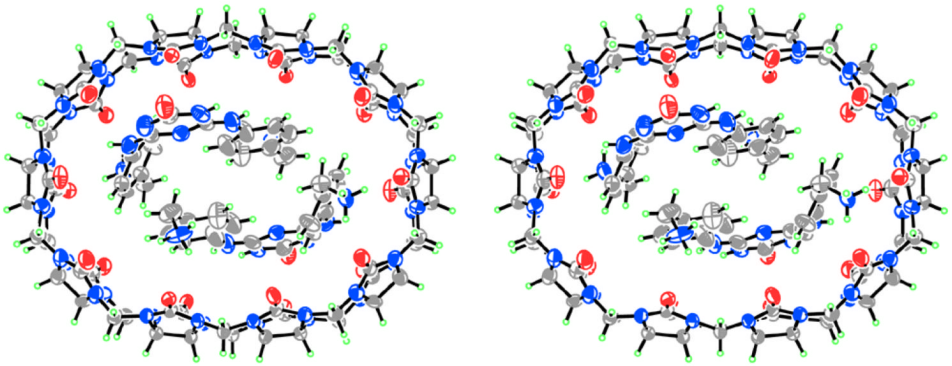


Figure 2.
Cross-eyed stereoview of the structure of CB[10]•$\mathbf{1}_2$ in the crystal. Solvating water has been removed for clarity.

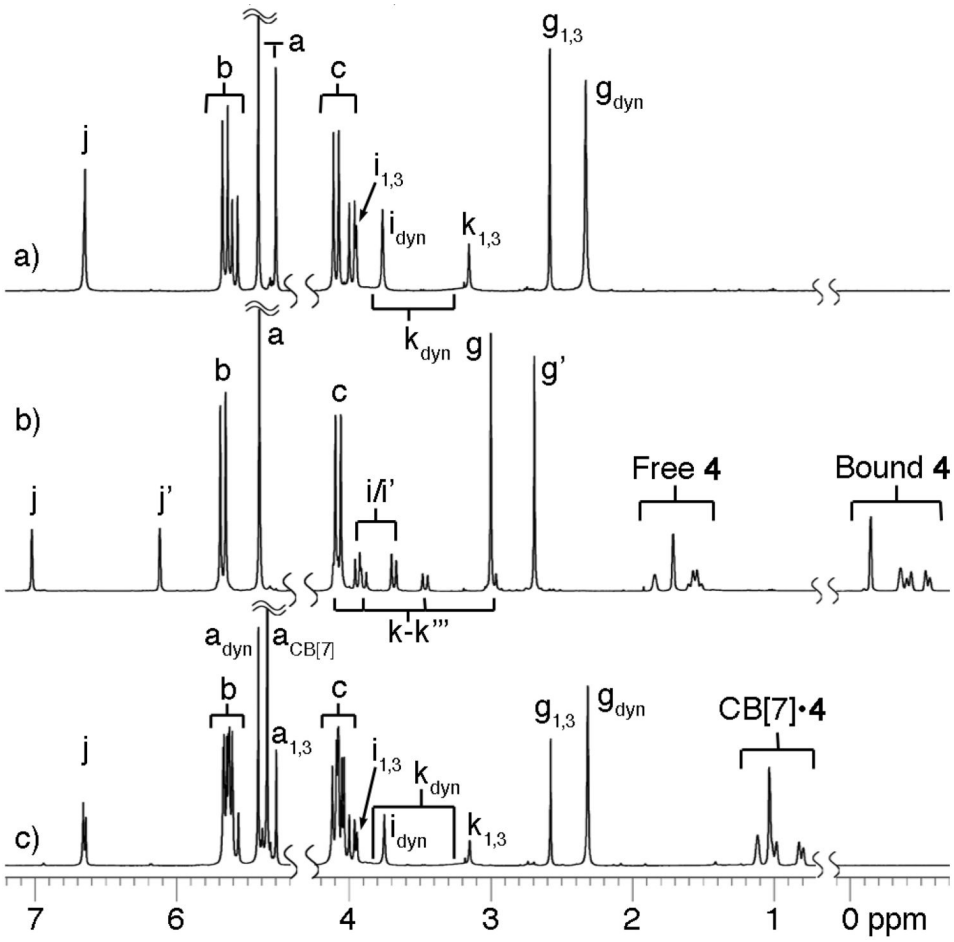
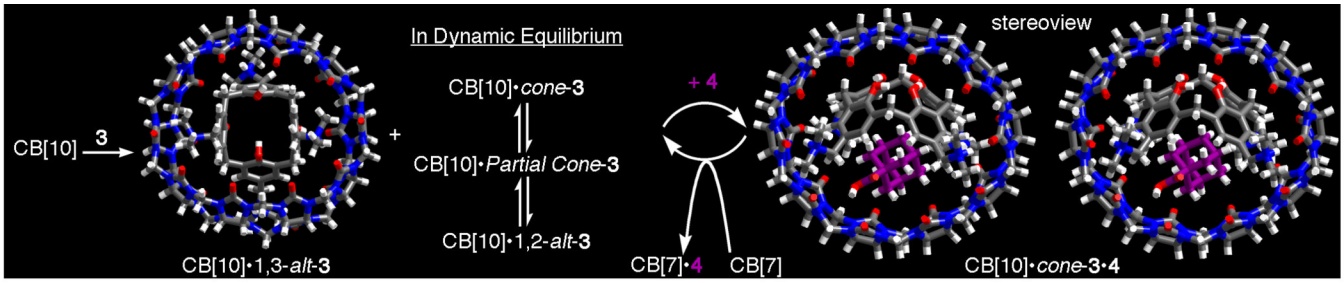


Figure 3.

^{1}H NMR spectra recorded (400 MHz, D_2O / DCl, RT) for: a) CB[10]•**3** (1,3-*alt* and dynamic equilibrium beween cone, 1,2-*alt* and partial cone), b) CB[10]•*cone*-**3**•**4** with excess **4** (0.8 equiv.), and c) CB[10]•**3** and CB[7]•**4**. Subscripts: 1,3 = 1,3-*alt*-**3**; dyn = dynamic equilibrium of **3**.



Scheme 1.
Allosteric control of the conformations of CB[10]•**3** (MMFF minimized) with **4** (purple) and CB[7].