Communication

Cucurbit[10]uril

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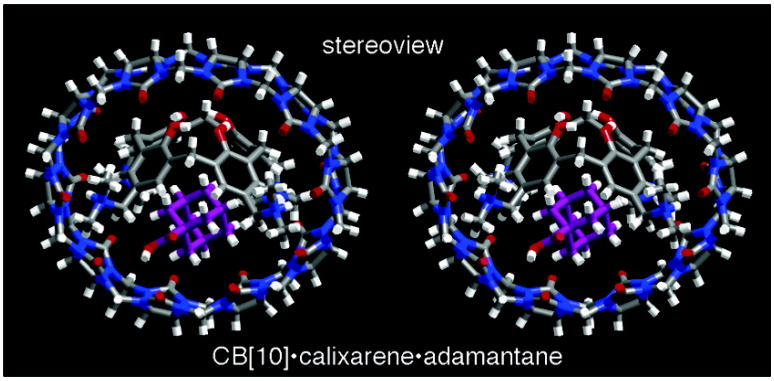

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Cucurbit[10]uril

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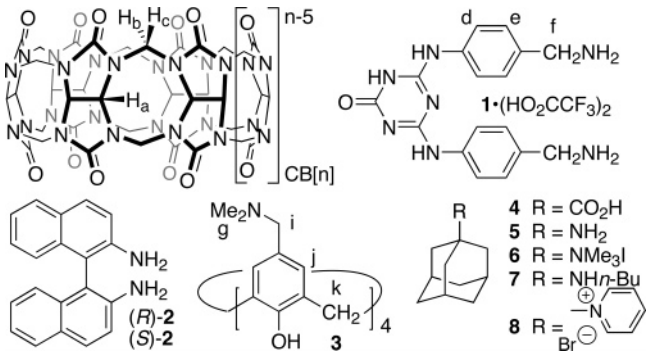
In 1981, Mock disclosed the structure of cucurbit[6]uril (CB[6]) and subsequently delineated its outstanding binding properties toward ammonium ions in a series of elegant papers.[1] Nearly 20 years later, the groups of Kim and Day reported the preparation and isolation of the CB[*n*] homologues CB[5], 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,c] After much experimentation, we discovered that treating a solution of CB[10]·CB[5] (Figure 1a) with a 5 equiv of **1** results in the precipitation of the (CB[5]·**1**)$_n$ exclusion complex and the formation of the CB[10]·**1**$_2$ inclusion complex (Figure 1b). ^{1}H NMR and X-ray crystallography indicate that **1** adopts a U-shape[6] within the cavity of CB[10] (Figure 2); the 2 equiv of **1** is arranged in a head-to-tail manner, which results in a single set of resonances for H_b and H_c within CB[10]·**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 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

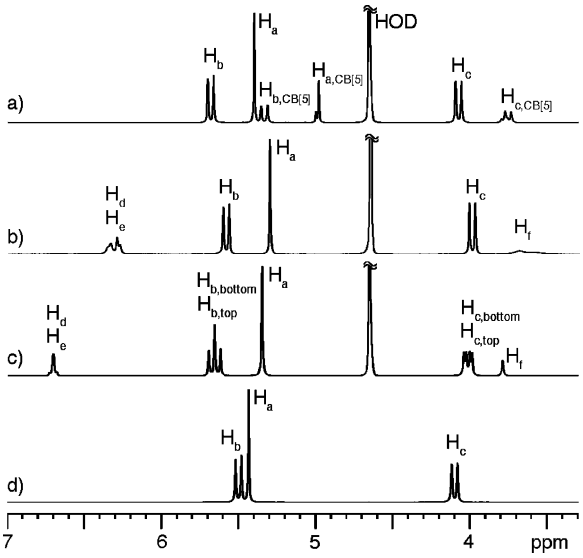


Figure 1. ^{1}H NMR spectra (400 MHz, D_2O, 298 K) for (a) CB[10]·CB[5], (b) CB[10]·**1**$_2$, (c) CB[10]·**1**, and (d) CB[10] (20% D_2O/DCl).

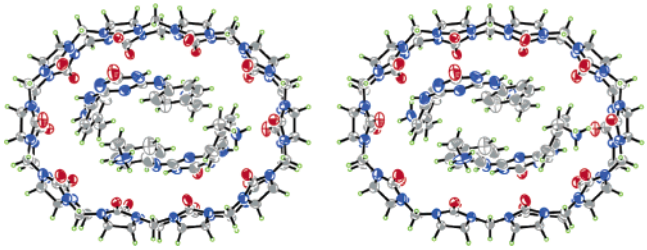


Figure 2. Cross-eyed stereoview of the structure of CB[10]·**1**$_2$ in the crystal. Solvating water has been removed for clarity.

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*)-**2**$_2$. Interestingly, when racemic (±)-**2** was used, the racemic mixture of homochiral complexes (CB[10]·(*R*)-**2**$_2$ and CB[10]·(*S*)-**2**$_2$) was preferred relative to the heterochiral *meso*-complex (CB[10]·(*R*)-**2**·(*S*)-**2**) by a factor of 3 (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, such as 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**

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Scheme 1. Allosteric Control of the Conformations of CB[10]·**3** (MMFF minimized) with **4** (purple) and CB[7]

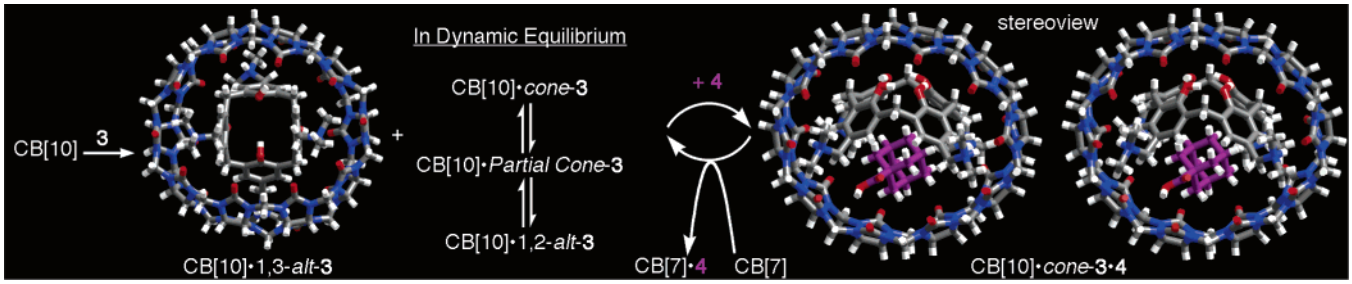

Figure 3a). On the basis of the number and multiplicity of resonances observed for CB[10]·**3**, we conclude that **3** adopts a mixture of the D_{2d}-symmetric 1,3-alternate conformation and a rapidly equilibrating mixture of cone, 1,2-alternate, and partial cone conformers within the CB[10] host. Intrigued 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*] homologues, 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

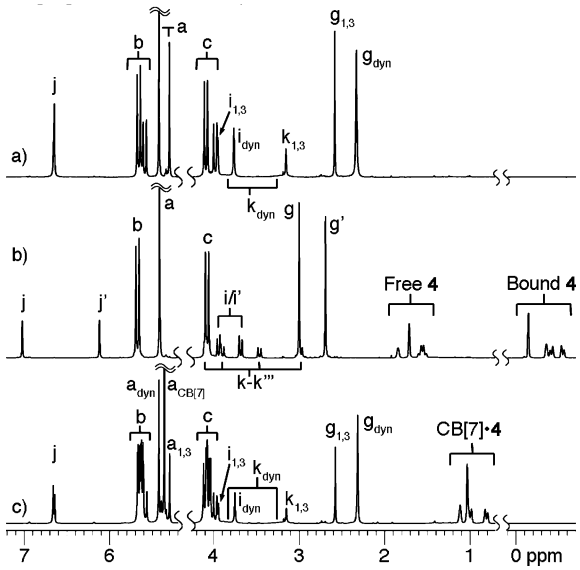

Figure 3. ^{1}H NMR spectra recorded (400 MHz, D_2O/DCl, RT) for (a) CB[10]·**3** (1,3-*alt* and dynamic equilibrium between cone, 1,2-*alt* and partial cone), (b) CB[10]·*cone*-**3**·**4** with excess **4** (0.8 equiv), and (c) CB[10]·**3** and CB[7]·**4**. Subscripts: 1,3 = 1,3-*alt*-**3**; dyn = dynamic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

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.

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Supporting Information Available: Synthetic procedures, characterization data for CB[10], and selected ^{1}H NMR spectra for CB[10]·guest complexes (.pdf), and details of the X-ray structure of CB[10]·$\mathbf{1}_2$ (.cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Addition of 1 equiv of **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 time scale. The bulkier adamantanes **7** and **8** display two sets of resonances as expected.

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