J. Am. Chem. Soc. **2001,** *123,* 5849−5850

C-H···X−R (X = Cl, Br, and I) Hydrogen Bonds Drive the Complexation Properties of a Nanoscale Molecular Basket

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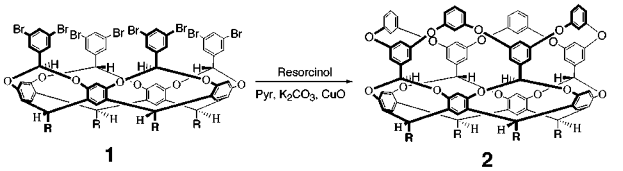
Received December 29, 2000
Revised Manuscript Received April 11, 2001

In the design of synthetic molecular cavities several important parameters warrant consideration. In the first instance the size of the cavity must be borne in mind, for its inner surface must contain all of the necessary information to bind the anticipated guest. Furthermore, the symmetry of the cavity must also be considered, with perhaps chiral cavities for enantioselective recognition being the ultimate long-term goal. In addition, the cavity volume-to-portal size ratio must also be factored in to bestow the host with the desired physicochemical properties. Add to these criteria the necessity that the cavity ought to possess sufficient rigidity to prevent collapse, and it is apparent that the emulation of Nature's cavities in, for example, enzymes is a considerable undertaking.

The burgeoning calixarene field has provided rich pickings for those interested in cavity design and host−guest properties.[1−3] However, progress has been slower as the field moves toward the nanoscale, a necessity when designing converging binding sites capable of binding molecules with 10 or more non-hydrogen atoms. Thus, there have been relatively few reports concerning the development of large molecular cavities of an integral[4] or dynamic nature.[5] Here we report the synthesis, characterization, and host properties of a new molecular basket. Its structural features bestow the host with unique complexation properties which shed light on the debate concerning C−H···X−R hydrogen bonds.

We recently reported the synthesis of deep-cavity cavitands (DCCs) by the stereoselective bridging of resorcinarenes with benzal bromides.[6] Although involving the irreversible formation of eight covalent bonds and the generation of four stereogenic centers, yields as high as 65% for the overall process have been observed. Consequently, access to multigram quantities of bowl-shaped DCCs such as **1** (Scheme 1) is straightforward. We have investigated the binding properties of a number of DCC derivatives similar to **1** (R = $\mathrm{CH_2CH_2Ph}$) but have observed nothing but perhaps the weakest of interactions with potential guests. Evidently, the free rotation of the second row of aromatic rings prevents guests from binding. With this in mind we set out to inhibit this rotation by bridging between the second row of aromatic rings. An integral cavity design was our primary consideration; thus, we chose to investigate the formation of DCC **2** (R = $\mathrm{CH_2CH_2Ph}$) by the application of an eight-fold Ullmann ether synthesis. Recently efficient catalytic processes for the formation of aryl−aryl ether bonds have been devised;[7] however, these approaches failed when applied to DCC **1**. In actuality the more traditional approach of using pyridine, $\mathrm{K_2CO_3}$, and CuO give the desired basket **2** in an outstanding 88% yield. Each of the eight ether bonds is formed with greater than 98% efficiency.

Scheme 1



1 **2**

Basket **2** can potentially adopt two C_{4v} conformations with radically different portal sizes (Figure 1). Initial computational considerations indicate that an outward curving third row of aromatic rings, giving the cavity an overall brandy glass shape, is the most stable conformation. However, barring the "roof", both conformations possess almost identically shaped cavities approximately 1 nm in diameter and depth.

A ^{1}H NMR spectrum (Supporting Information) of a 1:1 mixture of **2** and 1-iodoadamantane demonstrated the inclusion of the guest within **2**, and a slow exchange rate (298 K, 500 MHz) between free and bound guest. For the host the largest chemical-induced shift (CIS) was $\Delta\delta = +\ 0.67$ ppm for the benzal proton which protrudes into the southern "hemisphere" of the cavity. As expected the signals for the guest moved to higher field because of shielding by the π-rich cavity walls.

Following this observation we carried out a series of titration studies in $\mathrm{CDCl_3}$ and toluene-d_8. The resulting binding constants for a number of adamantanes are shown in Table 1.[8] With stronger binding for the Cl/Br/I derivatives it seemed reasonable to conclude that these halogen atoms were interacting with the host, that is, that the guests bind "halogen down". Indeed, strong evidence for the selective orientation of these guests (so-called carceroisomerism[9]) was provided by EXSY experiments which allowed the guest protons in both the free and the bound state to be identified, while showing that the protons α to the halogen underwent the expected larger CIS upon complexation because they are positioned deeper in the cavity (Supporting Information). The binding studies also showed that because of the rigid nature of the host, guest topology is crucial in determining binding. A comparison of 2-bromoadamantane (C_s) verses 1-bromoadamantane (C_{3v}) is illustrative. Without a C_3 axis to align with the C_4 axis of the host, the former guest experiences significant negative interactions with the cavity walls upon binding.

Confirmation of the mode of binding came from X-ray crystallography. The resulting ORTEP diagram of the 1:1 complex of **2** and 1-iodoadamantane is shown in Figure 2. As anticipated the C_3 axis of the guest is aligned with the C_4 axis of the host, and the iodine atom is directed toward, although not at, the bottom

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(8) Only weak binding of 1-adamantamine, 1-adamantanecarboxylic acid, 1-adamantol, 1-adamantanemethanol, and 1-adamantaneethanol was noted

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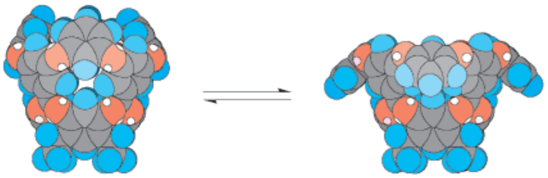

Figure 1. Space-filling models of the closed and open C_{4v} conformers of basket molecule **2**.

Table 1. Association Constants for Various Adamantyl Derivatives Binding to Host Basket **2**[a]

guest	K_a (M^{-1}) in $CDCl_3$[b]	K_a (M^{-1}) in $CD_3C_6D_5$[b]
adamantane	<5	15
1-cyanoadamantane	<5	36
1-fluoroadamantane	<5	<5
1-chloroadamantane	53	311
1-bromoadamantane	287	1628
2-bromoadamantane	78	380
1-iodoadamantane	670	4393

[a] $T = 298$ K, host concentrations were 1−5 mM. [b] Average values for at least three titrations. All associated errors are less than ± 8%.

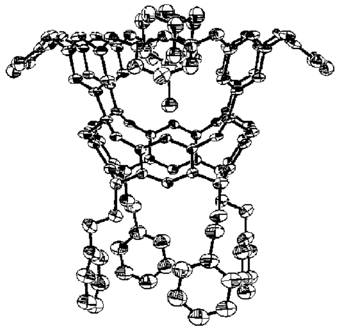

Figure 2. ORTEP view of the molecular basket **2** binding 1-iodoadamantane. Thermal ellipsoids are plotted at the 50% probability level. Only one orientation of the adamantyl guest, which is disordered around its C_3 axis due to a coincident crystallographic C_4 axis, is plotted.

of the cavity. Instead the guest "hovers" over a small cavity which upon inspection of CPK models looks ideal for packing a large atom such as a halogen. Why the "inefficient" packing? The reason is perhaps best explained by considering the 3.077 Å distance between the iodine atom and each benzal hydrogen. These distances are considerably shorter than the sum of the van der Waals radii for I and H (3.35 Å). In addition the benzal C−H bonds are pointing directly at the mid-section of the iodine atom, the belt of strongest negative potential observed in electrostatic calculations of halomethanes.[10] These interatomic distances, the observed "hovering" of the guest, and the downfield shift of the benzal proton—a phenomenon observed in hydrogen bonding—strongly suggest that a significant contributor to the stability of these complexes are C−H···X−R hydrogen bonds. This hypothesis is further supported by the weak binding of highly polar 1-cyanoadamantane[11] (Table 1), which indicates that a dipole/dipole interaction is not a major contributing factor to overall complex stability.

While halide ions are strong hydrogen bond acceptors, evidence for hydrogen bonds to halogens is weak.[12] For example, only a few possible C−H···X−R hydrogen bonds have been observed in the solid state,[13] and to our knowledge there has been no prior confirmation that the observed close proximity of H and X in these solid-state structures actually arises through attractive forces. Consequently, host **2** is unique in its modus operandi.[14]

Polarizability upon formation of the hydrogen bonds undoubtedly plays a role in the observed trend in association constants, but the number of hydrogen bonds that each halogen can form is tied directly to the size of the atom. The iodine atom, for example, can interact with all four C−H's at the same time, but as the atom decreases in size (Br, Cl, F), the number of simultaneous hydrogen bonds it can form with the host decreases also (three, two, and one, respectively, according to CPK models). At the lower limit, fluoroadamantane demonstrates weaker binding even than adamantane because its one potential C−H···X−R interaction cannot compensate for its reduced ability to tumble in the cavity as freely as adamantane undoubtedly does.

In summary, C−H···X−R (X = Cl, Br and I) hydrogen bonds can be added to the range of tools available to the supramolecular chemist. Given a ring of suitably preorganized acidic C−H moieties, it is possible to engender considerable interactions between host and halogenated guest. Further studies into the binding and conformational properties of **2**, as well as other related molecular baskets, are currently underway.

Acknowledgment. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Supporting Information Available: Experimental procedures and characterization data of **2**, 1D and EXSY ^1H NMR spectra of a typical complex, titration procedures, and X-ray structural information of the complex of **2** with 1-iodoadamantane (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Interestingly binding of chloroform in the solid state has been noted for ordinary cavitands; for example, see; Fox, O. D.; Leung, J. F. Y.; Hunter, J. M.; Dalley, N. K.; Harrison, R. G. *Inorg. Chem.* **2000**, *39*, 783−790. For deep-cavity cavitands, see ref 6a. In contrast, similar systems devoid of acidic C−H's, such as calix[4]arenes, show an aversion to "halogen down" binding; Brouwer, E. B.; Udachin, K. A.; Enright, G. D.; Ratcliffe, C. I.; Ripmeester J. A. *Chem. Commun.* **1998**, 587−588.