Intramolecular Hydrogen Bonding in Calixarenes

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Abstract: The construction of a molecular cavity for recognition and catalysis requires either covalent synthesis or intermolecular self-assembly of complementary units. Intramolecular hydrogen bonding is another tool to control the cavity-forming process. When properly positioned within the same molecular structure, hydrogen bonding sites are responsible for the formation, preorganization, and binding ability of the host. The most typical examples from the supramolecular chemistry of calixarenes, the key cavity-containing building blocks, and derived from them receptor molecules are discussed.

Keywords: calixarenes · hydrogen bonds · molecular recognition · supramolecular chemistry

Introduction

"Molecule-within-molecule" complexes are an extreme form of molecular recognition[1] and within the last decade, a sizable number of supramolecular complexes have been prepared: open-ended cavitands,[2] covalently sealed carcerands[3] and self-assembled hydrogen-bonded capsules.[4] All of these hosts are able to capture smaller organic molecule guests within their interiors. Calixarenes, in particular, have had a great impact in the history of supramolecular cavities. Their three-dimensional, concave surface, commercial availability, and relatively rigid structure make them convenient platforms for elaboration.[5]

Though *covalent* bond formation still dominates the design of molecular hosts,[6] noncovalent assembly appears with increasing frequency. *Intermolecular* forces, especially hydrogen bonding, are capable of effectively organizing multicomponent supramolecular assemblies (e. g. cavities, surfaces, receptor sites) in a reversible and accurate fashion using error-correcting mechanisms. While this topic has been widely discussed in the literature and has inspired a number of excellent reviews,[7] the role of *intramolecular* hydrogen bonding in the cavity-forming processes has been largely ignored. Nonetheless, a steadily growing number of publications clearly demonstrate that much control over the size and shape, and therefore the complexing ability of host molecules can effectively be achieved through intramolecular hydrogen bonding. We address these issues here, taking the most striking examples from calixarene chemistry.

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Discussion

Cavity shaping: Intramolecular hydrogen bonding is largely responsible for the three-dimensional shape of calixarenes and the deeper/larger cavities derived from them. Already at the earliest stages of calixarene research, it became clear that the unsubstituted hydroxy groups at the lower rim are involved in strong intramolecular hydrogen bonding, both in solution (IR and NMR spectroscopy) and in the solid state (X-ray analysis). Gutsche proposed circular arrays of O–H···O bonds for calixarenes **1** (Figure 1) almost twenty years ago, using as analogy the cyclic intramolecular ("flip-flop") hydrogen bonding in cyclodextrins.[8]

Today, this is accepted as a general property of unsubstituted and partially substituted calixarenes, and is responsible for the conformational features of their macrocyclic skeletons.[5] For example, solid-state (X-ray) structures of calix[4]- and calix[5]arenes with free hydroxy groups adopt the cone conformations exclusively. [9] Unsubstituted calix[6]arenes also possess a maximum number of hydrogen bonds. In chloroform, the IR frequency of the OH is always situated below $\tilde{\nu} = 3300\ \mathrm{cm}^{-1}$ and the corresponding ^{1}H NMR shifts are generally downfield of $\delta = 9$. The hydrogen bonds are arranged in a cycloenantiomeric fashion: the cyclic array may be either clockwise or counterclockwise.[10] Computational studies with calix[4]arenes suggested that the hydrogen bonds are rather permanently oriented and not of a "flip-flop" character.[11] The hydrogen bond reversal may occur either via sequential breaking or in a concerted fashion by a proton-tunneling mechanism.[12] In the absence of the hydrogen bonding, for example in the lower rim per-methylated calixarenes, significant conformational flexibility of the macrocyclic skeleton results.[13]

A cooperative network of intramolecular hydrogen bonds also accounts for the crownlike conformation of unsubstituted

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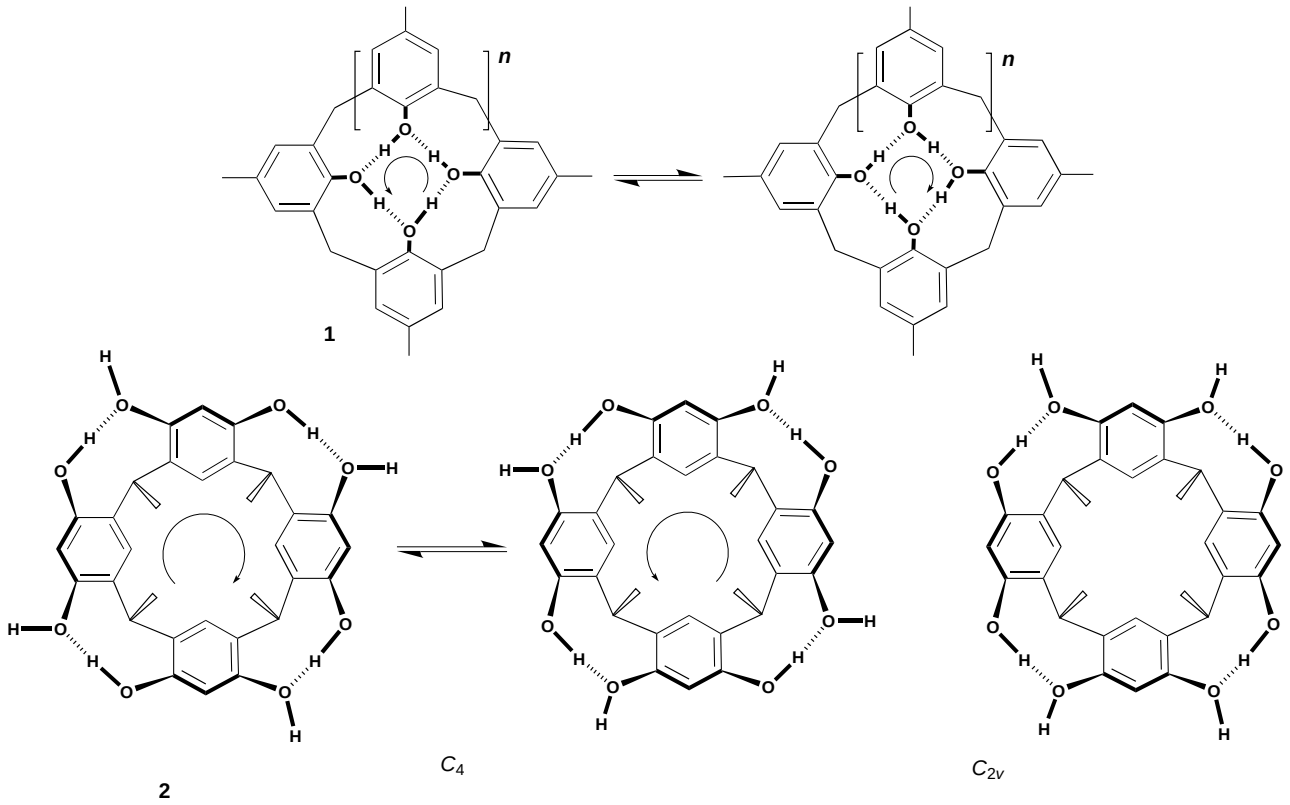

Figure 1. Arrays of intramolecular hydrogen bonds in unsubstituted calixarenes **1** and resorcinarenes **2**.

resorcinarenes **2** (Figure 1), both in solution and in the solid state,[14] and it essentially defines the structure of larger, intermolecular hydrogen-bonding assemblies of resorcinarenes. For example, six molecules of **2** may assemble to form a spectacular spherical cavity with a diameter of 17.7 Å and an internal volume of about 1375 Å^3. [15] This is the biggest cavity synthesized to date from organic materials. Complete acylation of resorcinarene **2** transforms the skeleton into the corresponding C_{2v} boatlike structure, as the circle of hydrogen bonds is broken. [16]

Properly attached hydrogen bonding sites can effectively control the conformation and binding properties of calixarene-based receptors. For example, an intramolecular C=O $\cdots$ H–N bridge keeps calix[4]arene bis-urea **3** in a pinched-cone conformation (Figure 2), and prevents its complexation of anions; no Cl^- or Br^- binding was detected in $CDCl_3$ solution.[17, 18] Addition of a Na^+ source breaks the intramolecular "lock" at the upper rim, and the **3** $\cdot$ Na^+ complex readily exhibits effective anion binding and extraction in chloroform. An impressive (100%!) solubilization of NaX (X = Cl^-, Br^-, I^-) salts was thus achieved.

In another example, sodium-free diamidopyridine-containing calixarene **4** is surprisingly inert towards base-pairing (Figure 2), while its Na^+ complex binds complementary thymines; the K_{ass} values as high as 1.7×10^3 M^{-1} were calculated in [D_8]toluene.[19] Addition of Na^+ disrupted the intramolecular hydrogen bonding; the calixarene C=O groups now turn around to coordinate the cation, thus exposing the diamidopyridine for intermolecular binding.

Sherman's "bis-bowl" **5**, in which two cavitand molecules are bridged with two methylene units, forms kinetically stable host–guest complexes with neutral molecules (e.g. pyrazine, dioxane, etc.).[20] Upon addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), deprotonation of two phenolic hydroxyl groups occurs and two charged hydrogen bonds (CHBs) form (Figure 3). At room temperature in $CDCl_3$, neutral complex **5** $\cdot$ $CHCl_3$ releases $CHCl_3$ within a few minutes, while doubly charged **5** $\cdot$ $CHCl_3$ is relatively stable within four days.

In unimolecular capsule **6**, two calix[4]arene tetraureas are covalently connected through their upper rims.[21] Upon dimerization—through a cyclic array of complementary hydrogen bond donors and acceptors[4a–c]—all the hydrogen bonds involved become intramolecular (Figure 3). When the linker is short enough to minimize the loss of entropy due to restriction of freely rotating single bonds, stronger dimerization is expected. With the hexamethylene -$(CH_2)_6$- spacer, only the intramolecularly folded capsule **6** was detected by electrospray mass spectrometry. For detection, the *N*-methyl quinuclidinium cation (of a tetrafluoroborate salt) was encapsulated and provided a charge for the whole complex in the gas phase. In $CDCl_3$ solution, signals for the encapsulated quinuclidinium CH protons appeared upfield at $\delta = -0.2$ to -0.4 in the ^{1}H NMR spectra.[21]

A cyclic array of eight intramolecular secondary amide hydrogen bonds was found in self-folding cavitands **7** (Figure 4).[22] The result is a deepened C_4 symmetrical vase possessing a unique property in solution: exchange between complexed and free guest species is slow on the NMR time scale. Most probably, the circle of hydrogen bonds slows this process by resisting the opening of the cavity required for guest exchange. Upon complexation with adamantanes, cyclohexanes, and lactams, the ^{1}H NMR spectra exhibit two sets of

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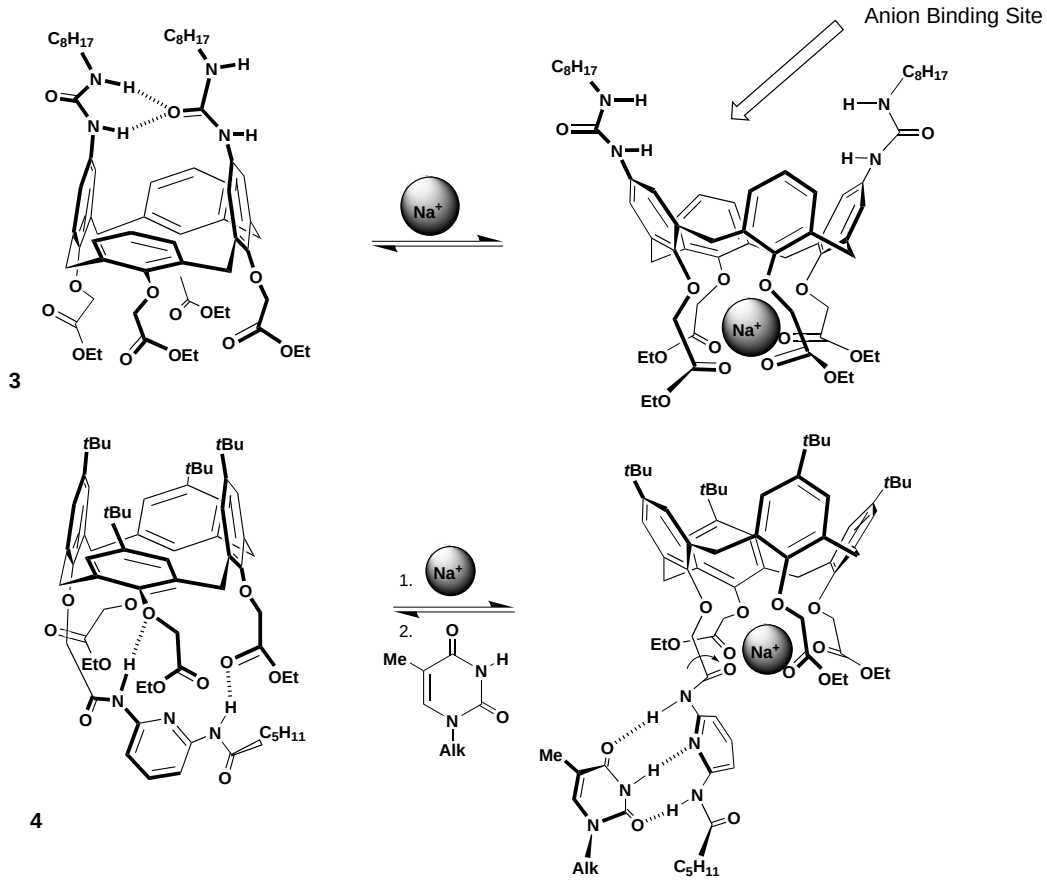

Figure 2. Intramolecular hydrogen bonding at the upper or lower rims in calix[4]arene based receptors **3**[17] and **4**[19a] prevents recognition processes but can be broken by Na^+ complexation.

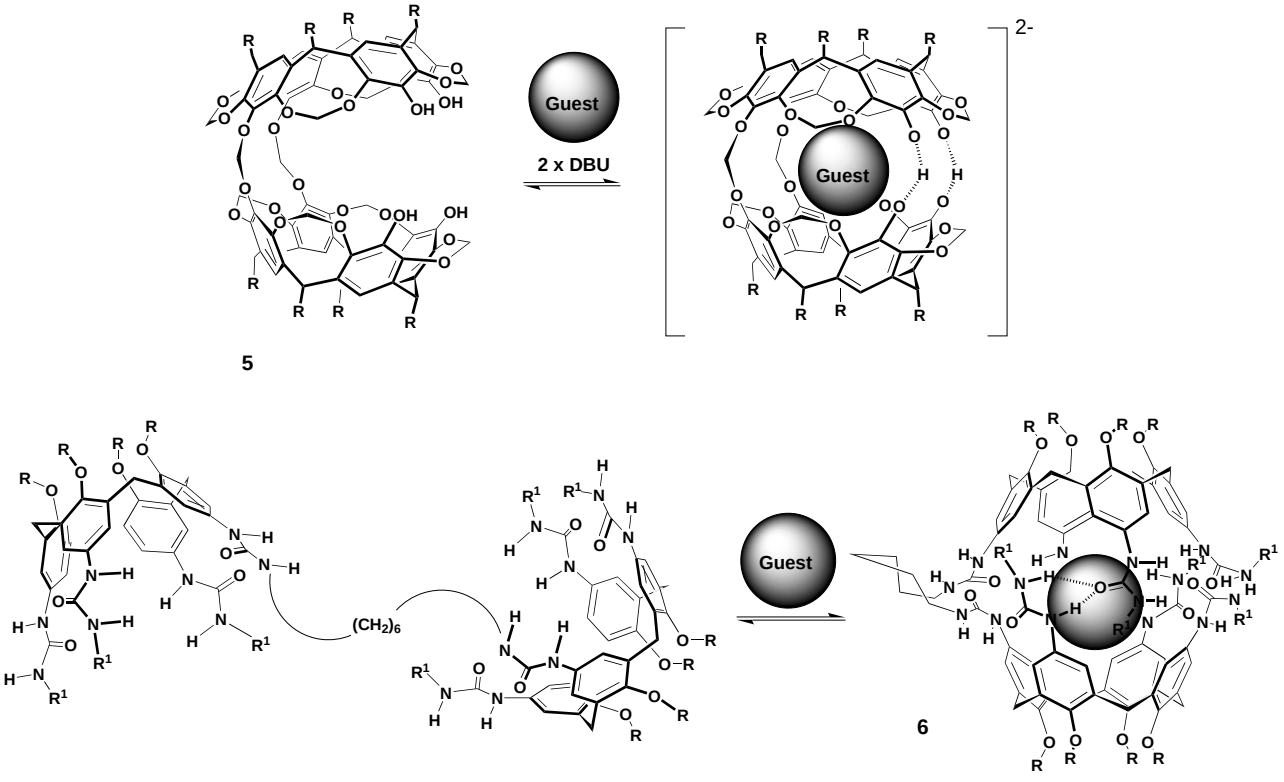

Figure 3. Unimolecular capsular structures **5**[20] and **6**[21] and their complexes.

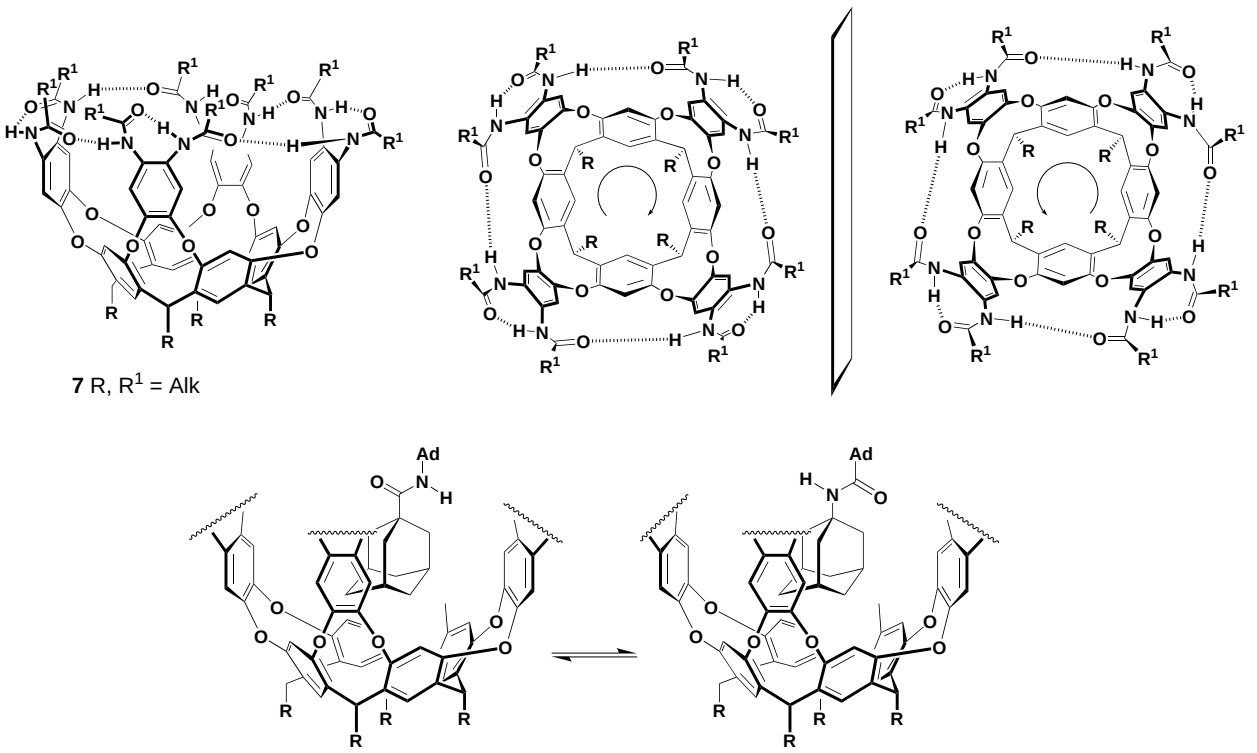

Figure 4. Top: intramolecular hydrogen bonding in self-folding cavitands **7**. Two cycloenantiomeric C_4 stuctures are presented. Bottom: diastereomerism in caviplexes of **7** with 1-[*N*-(1-adamantyl)]adamantanecarboxamide.[22, 23]

signals—both for the complexes (caviplexes) and the free guest. The complexed guest species are clearly observed upfield of $\delta = 0$, a feature characteristic of inclusion in a shielded magnetic environment. With guests containing both cyclohexyl and adamantyl groups in the same molecule, diastereomeric caviplexes were observed upon complexation with **7**.[23] The guest can spin about the long axis of the cavity but is too large to tumble within it (Figure 4). The high kinetic stability of the caviplexes was subsequently employed in the synthesis of self-complementary cavitands bearing covalent tethers to adamantane guests.[24] Self-complementarity results in noncovalent dimers and higher oligomers of both kinetic and thermodynamic stability in apolar solvents. In competitive solvents such as [D_7]DMF, no aggregation was observed.

Even in the context of large hydrophobic surfaces, secondary amide C=O···H–N hydrogen bonds can significantly rigidify molecular structure. For example, concave surface **8**, obtained by combination of one calix[4]arene and two resorcinarene cavitands,[25] possesses four such intramolecular hydrogen bonds—between the bridging acetamide $CH_2C(O)-NH$ and the oxygen atoms of the cavitand acetal bridges (Figure 5). The N–H chemical shift is seen downfield of $\delta = 9$ in $CDCl_3$. For their nanoscale dimensions, structures such as **8** are very rigid. Compounds **8** selectively bind certain steroids, carbohydrates and alkaloids ($-\Delta G_{298} = 13-15$ kJ mol^{-1} for 1:1 complexation) in $CDCl_3$; hydrogen bonding and CH-π interactions are the main driving forces for the complexation.[25]

Two self-folding cavitands (see structure **7**, Figure 4) were covalently attached to afford a rigid cylindrical host **9** of nanoscale dimensions (10 × 23 Å, ca. 800 Å^3 internal volume) (Figure 5).[26] The molecule ressembles a Cram's hemicarcerand but the internal cavity is held in place by a seam of intramolecular C=O···H–N hydrogen bonds rather than covalent bonds. Access to the cavity is facile under ambient conditions and the uptake and release of guests is reversible. High kinetic stability of the complexes was achieved for long (ca. 18 Å) and rigid adamantyl-containing guests. This behavior of **9** is unprecedented for unimolecular cavities of such dimensions.

Cavity syntheses: That intramolecular hydrogen bonding influences chemical reactivity has been known for decades.[27] Recently, such effects were detected in the syntheses of functionalized calixarenes, cavitands and carcerands.

One of the most striking examples is alkylation of calix[4]arene with alkyl tosylates or halides using a weak base, such as K_2CO_3, in MeCN.[28] Almost quantitative yields of the 1,3-dialkylated products **10** held in a cone conformation were obtained (Figure 6). The first step is undoubtedly the monoalkylation, then a second proton must be abstracted. Monoanion **11**, with the phenolate optimally stabilized by two (charged) intramolecular hydrogen bonds, is formed. This keeps the whole structure in a cone conformation, as the second electrophile attacks the distal oxygen atom. Similar alkylations and acylations using weak bases, where the phenolate anions are stabilized by the maximum number of hydrogen bonds, have also been reported for larger calixarenes.[28] The remarkable regioselectivity that results at the lower rim oxygens opens broad possibilities for selective transformations at the upper rim.

Böhmer and co-workers recently discovered that the reaction of resorcinarene **2** with primary amines and formaldehyde affords surprisingly high yields (up to 90%) of the

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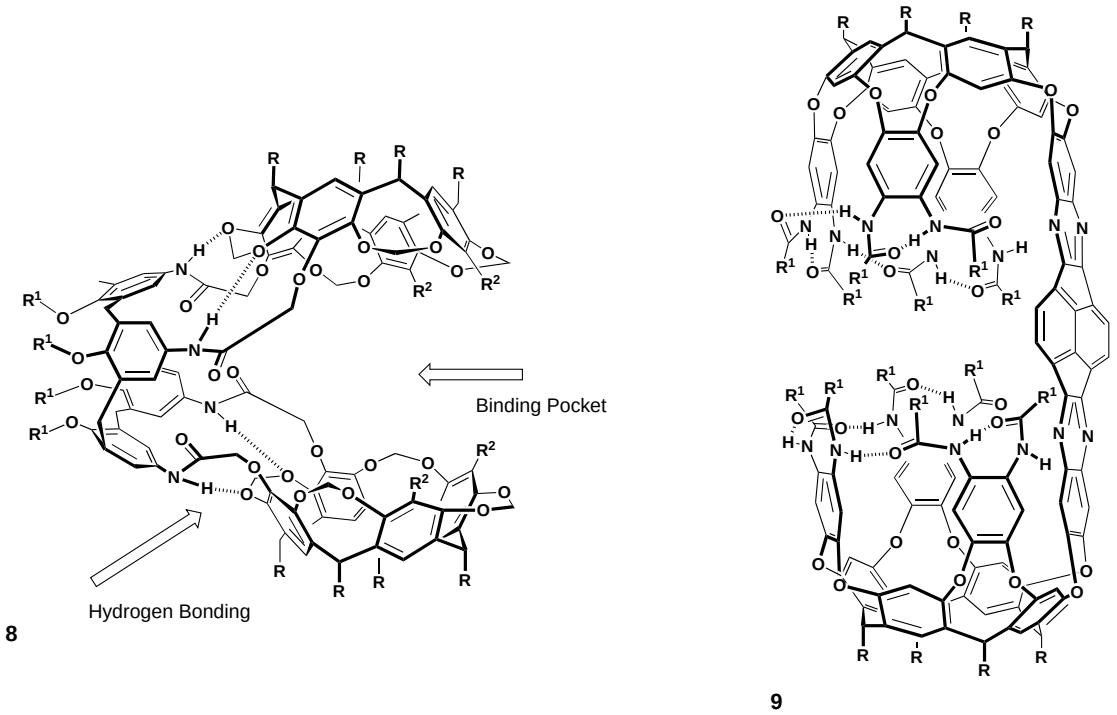

Figure 5. Intramolecular preorganization in the extended concave surface **8**[25] and nanoscale semi-capsular structure **9**.[26] The hydrogen bonds were detected by IR and NMR techniques and modeled by molecular mechanics calculations.

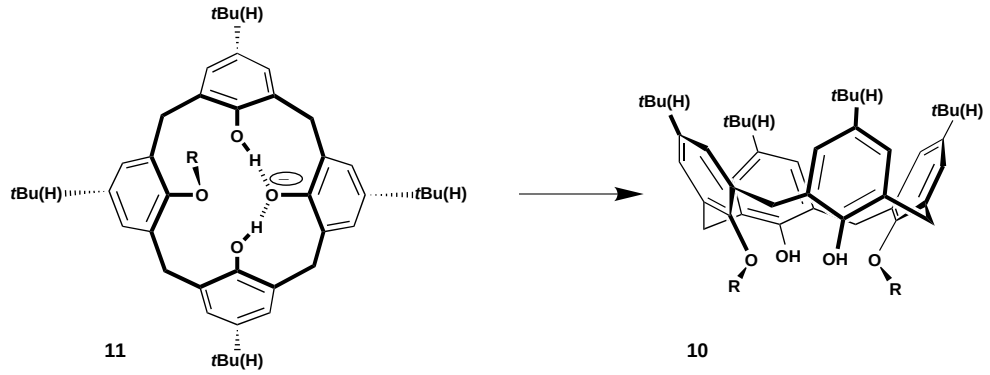

Figure 6. Regioselective alkylation of calix[4]arenes via the stabilized monoanion **11**.[28a]

C_4 symmetrical tetrabenzoxazine cavitands **12.**[29] It was proposed that the regioselectivity is due to the maximum number of intramolecular hydrogen bonds O–H···O formed (Figure 7). Their presence was indeed confirmed by semi-empirical calculations and the X-ray analysis: the hydrogen bonds were within a 2.8–2.9 Å range (O···O distances). Subsequently, this approach was utilized in the elegant synthesis of more extended supramolecular structures: C_2-symmetrical clefts **13** and even carcerand **14** (of D_4 or C_{4v} symmetry) were obtained in one (!) step by the reaction of resorcinarene **2** with formaldehyde and diamines.[30]

In the Cram–Sherman syntheses of carcerands (e.g. **15**), mono-bridged "bis-bowl" **16** seems to be a key intermediate (Figure 8). Deprotonation of the phenolic hydroxyl groups at the initial reaction stage results in charged intramolecular hydrogen bonding which preorganizes two cavities for the shell closure.[31]

In the synthesis of the Reinhoudt's carcerand **17**, two hydrogen bonds between the N-H protons of the bridging acetamide groups and the oxygen atoms of the acetal bridges must be broken for the cavity closure event, and this process is facilitated by hydrogen bond accepting solvents (amides, sulfoxides).[32] Furthermore, once encapsulated the guest/solvent forms hydrogen bonds with the acetamide N-H protons, thus allowing the final covalent closure (Figure 8). In the ^{1}H NMR spectra of the carceplexes with DMF, dimethylamine (DMA), DMSO, the host N-H singlets were found downfield $\delta = 7.7$ indicating their involvement in the hydrogen bonding with the polar guest.[32]

Conclusion and Outlook

In Nature, intramolecular hydrogen bonds help proteins to fold and are responsible for the structures of enzyme's

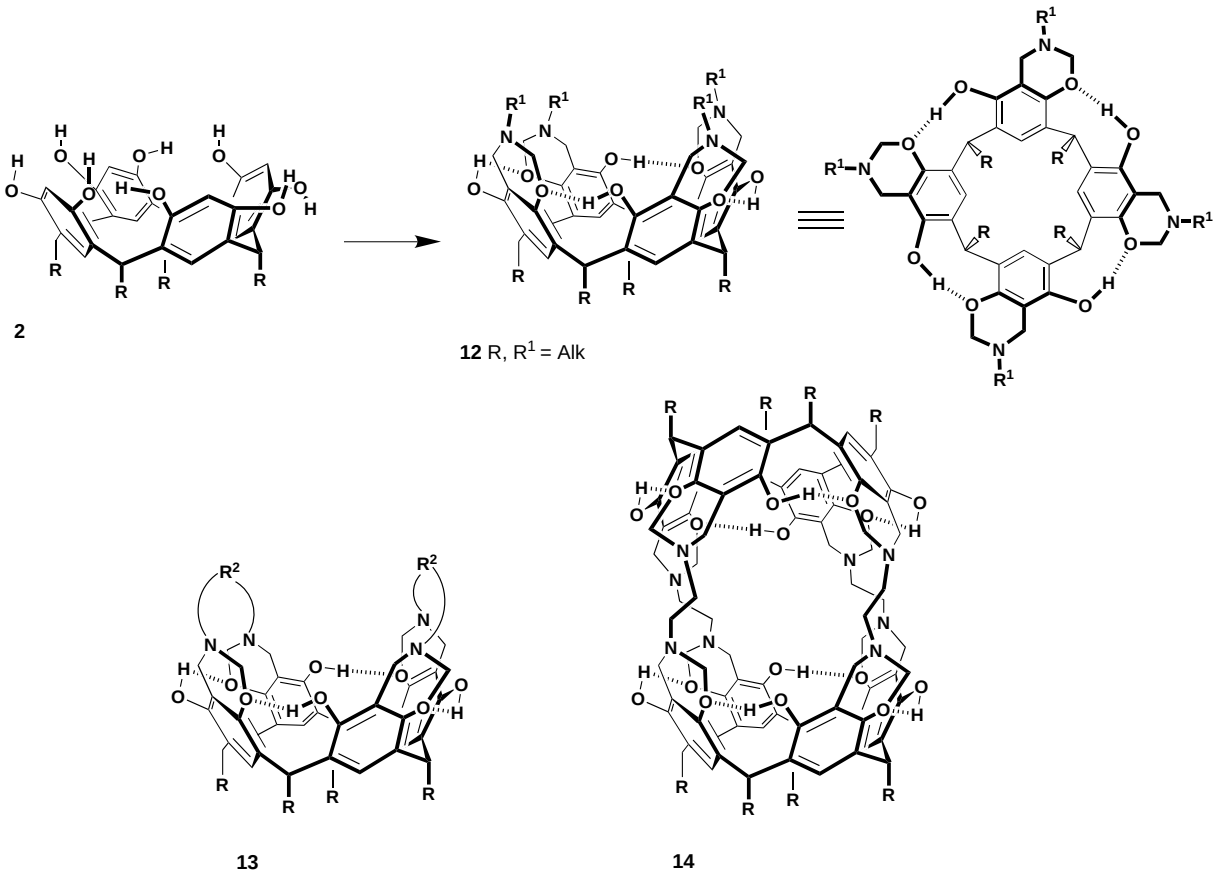

Figure 7. Syntheses of cavitands **12** and **13** and carcerand **14**.[29, 30]

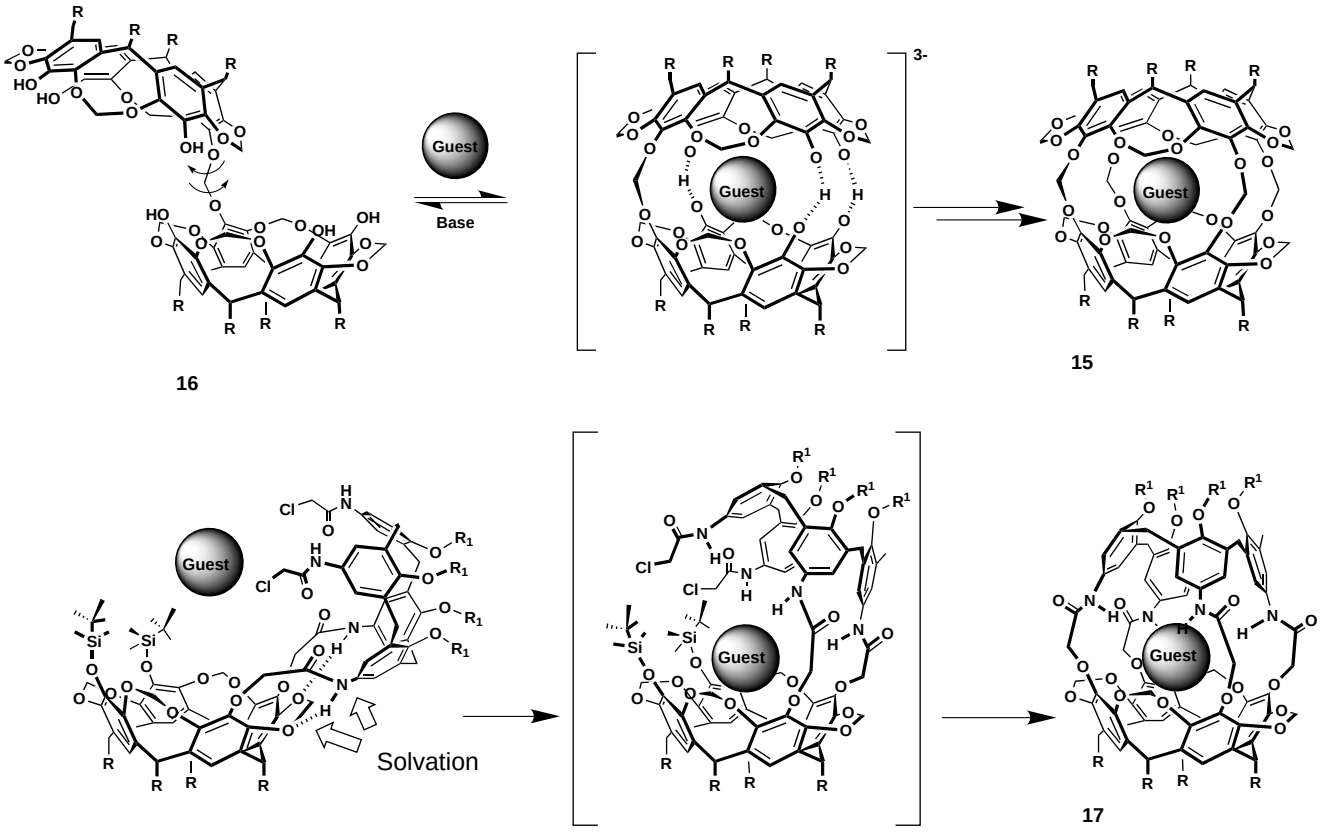

Figure 8. Hydrogen bonding is involved in the shell closure step in the syntheses of carcerands **15**[31] and **17**.[32]

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catalytic pockets. We have shown that in the cavity-forming processes, intramolecular hydrogen bonds are just as important as the intermolecular ones. Their formation and dissipation can reversibly change the host conformation, shape and therefore its binding ability. Cooperative (cyclic) arrays of hydrogen bonds seem to be an important feature here, that controls even more extended, nanoscale frameworks.

In contrast to the synthetic intermolecular assemblies, where the hydrogen bonding sites are placed in a self-complementary fashion and exposed to another approaching molecule, intramolecular hydrogen bonding is usually self-sufficient and frequently takes place inside the host molecule. This often requires different strategy to the syntheses. Intramolecular hydrogen bonds are fully expected to work in more polar media, even in aqueous solution since they are shielded within the receptor/host hydrophobic environment.

The entropic cost for an intramolecular hydrogen bond is usually low, so intramolecular geometrical organization of the molecular surface or cavity is thermodynamically reasonable. Unimolecular capsules provide the early examples in this direction.

The influence of intramolecular hydrogen bonding on the synthesis of cavitands and carcerands has only recently been uncovered, and some supramolecular control over reactivity has been established. Further exploration of intramolecular hydrogen bonding in host-guest chemistry is likely as its effects in covalent synthesis and self-assembly.

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