Deepening Cavitands

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The review describes the synthesis of deep open-ended cavities, based on calixarene and resorcinarene modules, and the host-guest properties that arise from their unique structures.

Introduction

How molecules fit together defines the science of molecular recognition, and cavities hold a special place in that science. The congruence of a concave and a convex surface is the easiest imaginable fit, probably predating complementarity of function. *Why* molecules fit together is related to stability: Molecular surfaces that are in contact with each other are hidden from solvent and are protected from exposure to solvolysis or harmful reagents. Recognition was likely an early step in prebiotic chemistry because molecules had survival as the first order of business.

Only when molecules large enough for sophisticated recognition are assembled could information be embedded within them and functions such as replication develop. In some ways the ultimate fit occurs when one molecule completely surrounds another, in a molecule-within-molecule complex, and cavitand structures are milestones along that road.

The interest of organic chemists in three-dimensional, cavity-containing hosts probably dates to the research of Cramer, who characterized the inclusion complexes of cyclodextrins.[1] The desirability of controlling the size and shape of the cavity led to the synthesis of cyclophanes in the mid 1950s. The discovery of crown ethers a decade later spurred a fascination with macrocyclic compounds that

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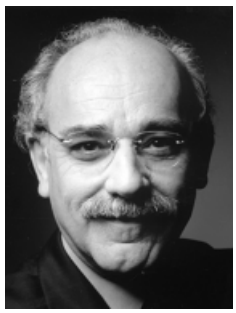
Dmitry M. Rudkevich was born in the country of Ukraine in 1963. He studied chemistry at the Institute of Organic Chemistry, National Academy of Sciences of the Ukraine, with the late Professor Leonid N. Markovsky. In 1992−1995 he worked with Professor David N. Reinhoudt at the University of Twente in Holland. He holds a Ph. D. in Organic Chemistry (University of Twente, 1995). In 1996 Dr. D. M. Rudkevich moved to the United States to work with Professor Julius Rebek, Jr., first at the Massachusetts Institute of Technology and later at The Scripps Research Institute in La Jolla, California. Currently he is an Assistant Professor of the Skaggs Institute for Chemical Biology at Scripps. His research interests deal with Supramolecular Chemistry and Molecular Recognition. Dmitry M. Rudkevich is a co-author of 70 scientific papers on the design and synthesis of macrocycles and clefts, calixarenes and related compounds, superstructured porphyrins; complexation studies with anions, cations and neutral guest molecules; hydrogen bonding, self-assembly and self-replication.



Julius Rebek, Jr. was born in Hungary in 1944 and lived in Austria from 1945−1949. He and his family then settled in the U.S.A. in Kansas. He received his undergraduate education at the University of Kansas in 1966, and obtained the Ph.D. degree from the Massachusetts Institute of Technology (1970) for studies in peptide chemistry with Professor D. S. Kemp. As an Assistant Professor at the University of California at Los Angeles (1970−1976) he developed the "three-phase test" for reactive intermediates. In 1976 he moved to the University of Pittsburgh where he rose to the rank of Professor of Chemistry and developed cleft-like structures for studies in molecular recognition. In 1989 he returned to the Massachusetts Institute of Technology, where he was the Camille Dreyfus Professor of Chemistry and devised synthetic, self-replicating molecules. In July of 1996, he moved his research group to The Scripps Research Institute to become the Director of The Skaggs Institute for Chemical Biology, where he continues to work in combinatorial chemistry and self-assembling systems. Julius Rebek, Jr. is an author of more than 250 journal articles, 6 book chapters and 4 patents.

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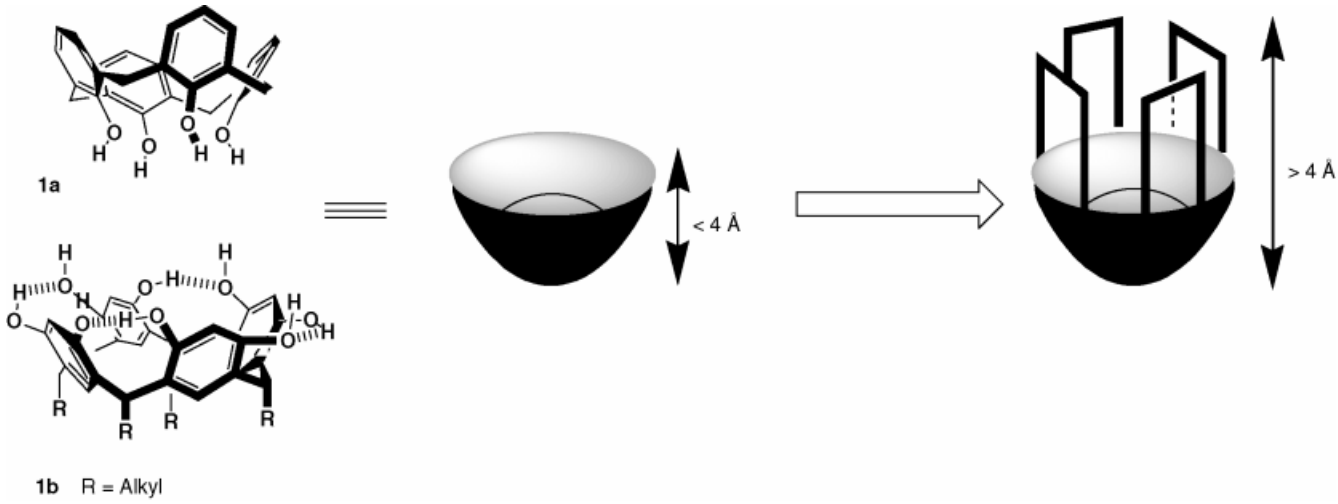


Figure 1. Calix[4]arene **1a** and resorcinarene **1b** as bowl-shaped modules for construction of deep cavitands

persists to this day. Cyclodextrins and the early synthetic cavities are open on two sides, and the notion of a cavitand, e.g. a cavity with one open end, had to await the availability of appropriate modules.[2] Apart from bowl-shaped curvature, large, extended surfaces for intermolecular interactions and functional groups for further elaboration were needed. Calixarenes and resorcinarenes **1a,b** (Figure 1) provided these features for cavitand construction,[3−6] and the first examples were produced by Cram in the early 1980s.[2] Subsequently, cavitands were elaborated into carcerands, the closed-surface container molecules, with enforced interiors of sufficient size to embrace simple organic molecules, inorganic ions and gases.[3] The difference, then, between cavitands and carcerands is in their ease of guest uptake and release − the exchange rates. The carcerands lack a sizeable opening and can hold guests indefinitely; in fact, most guests are present during the synthesis of the carcerand and often help template the synthetic process. Hemicarcerands have small openings capable of permitting guest passage at high temperatures, while cavitands have larger openings − an open end − allowing guest access at ambient temperatures.[3]

First generation cavitands **2** (Figure 2) were prepared by Cram from Högberg's resorcinarenes **1b** through alkylenedioxy- and dialkylsilicon bridging.[7][8] Their complexation properties have been studied in detail, but their depth of just 3.3−4.2 Å limited the types of molecules they could bind. For example, in solution, only weak affinity towards small organic molecules (CD_2Cl_2, CD_3CN, CS_2, CD_3NO_2 and $C_6D_5CD_3$, etc.) was detected. The complexation processes were fast on the NMR timescale, and only time-averaged signals were seen when binding occurred. Two hemispherical cavitands, when covalently connected rim-to-rim, gave the first carcerands − and the first molecules-within-molecules.[3]

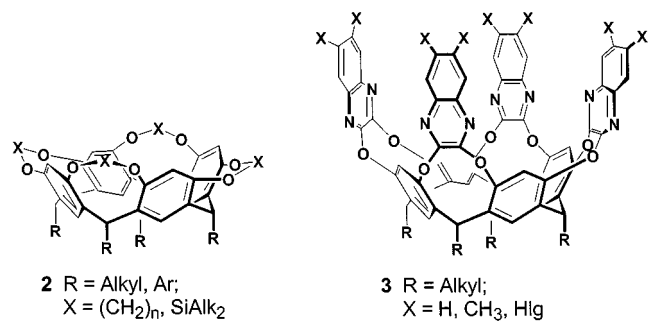


Figure 2. First-generation cavitands **2** and **3**

Condensation of resorcinarenes with 2,3-dichloropyrazines or 2,3-dichloroquinoxalines built deeper cavitands **3** (Figure 2). These molecules are conformationally flexible and flutter between C_{4v} and C_{2v} symmetries.[9] The former is preferred at higher temperatures and has all four "walls" up; it features a well-defined, vase-like shape. The latter has these walls flipped outward in a kite-like shape and is the dominant conformation below room temperature. The barrier to interconversion is typically 10−12 kcal/mol for cavitands with unsubstituted resorcinol units. Cavitands **3** (X = H) possess a lipophilic cavity 7.2 Å wide and 8.3 Å deep, large enough to accommodate sizeable guests. As expected, they show affinity towards aromatic molecules in solution and in the gas phase.[10] The guests inside cavitand **3** were located in the solid state by X-ray crystallography. Because of the open-ended structure, the complexation−decomplexation process in solution was fast on the NMR timescale, and the averaged chemical shift changes were not always easily interpreted.

Host-guest properties of cavitands are clearly dependent on the dimensions of their cavities. In this review, we will concentrate our discussion on the recent efforts that lead to the next generation of these molecules − *deeper cavitands.* We also address the special consequences a deep cavity holds for complexation and physical-chemical properties of the encapsulated guest. Another recent development is the functionalization of these cavitands that make them more attractive to guests, and even available for the catalysis of chemical reactions of the guests. First, synthetic approaches towards extended molecular surfaces and deeper cavities will be reviewed. Second, the use of noncovalent forces (hy-

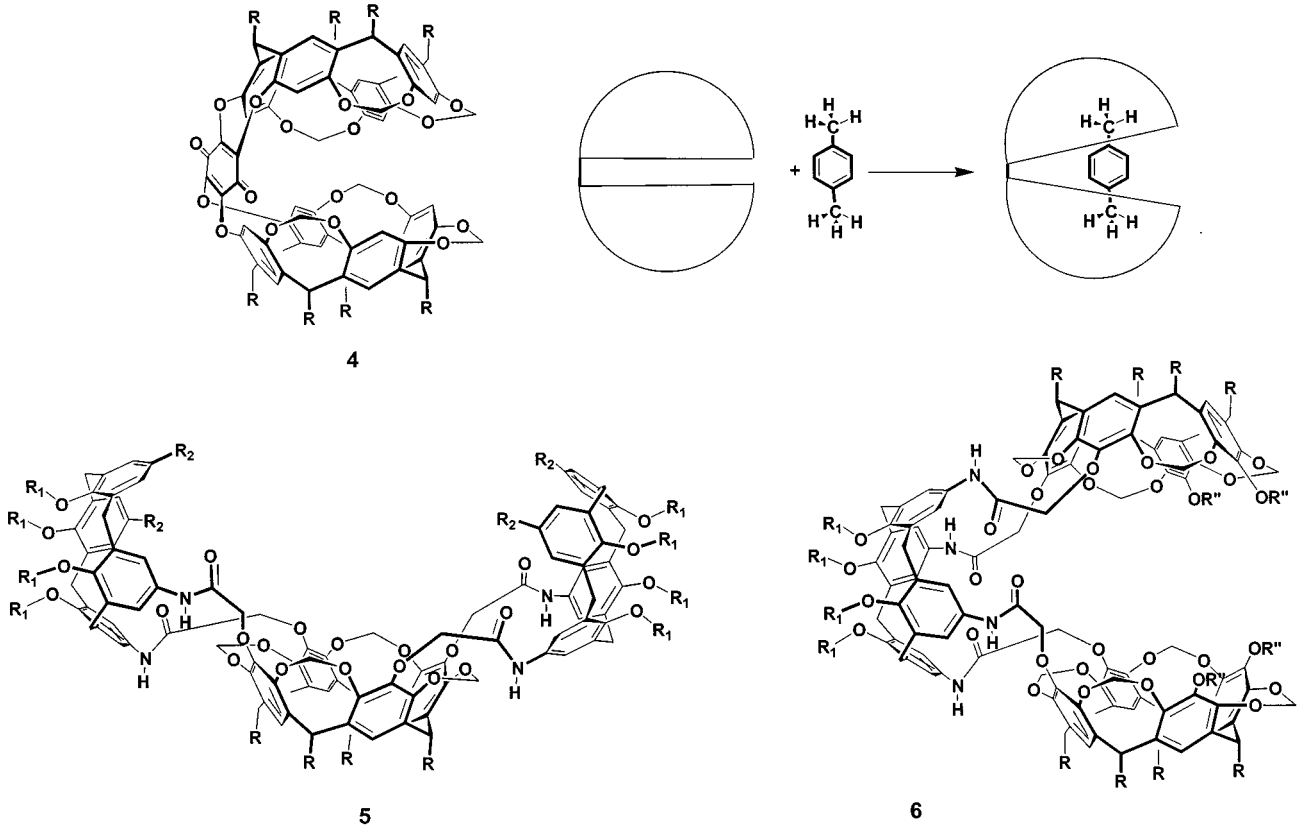


Figure 3. C-shaped bis(cavitand)[11] **4**, a schematic representation of its complex with *p*-xylene (top); Reinhoudt's[12] extended surfaces **5** and **6**

drogen bonding, solvent effects, etc.) in the cavity-forming processes will be discussed using examples from calixarene and resorcinarene chemistry. The host-guest properties of cyclodextrins have been thoroughly treated in recent reviews and they will not be included here.[5]

Extended Surfaces

The first extended cavitand surfaces were made by Cram, who covalently linked two modules. The result was a C-shaped structure **4**, bridged by fluoranil (Figure 3).[11] Even so, only very weak complexation of solvent molecules ($C_6D_5NO_2$, $C_6D_5CD_3$, *p*-$CD_3C_6D_4CD_3$, $CH_3COCH_2CH_3$), with $K_a = 0.6-1.8\ M^{-1}$ in CD_2Cl_2, was detected. The total number of guest equivalents added per equivalent of host **4** was large and ranged from 154 to 500. These numbers were lower than the 685 to 1466 equivalents needed for the titration of the corresponding Z-shaped isomer, where the cavities are remote. The cooperativity of the two concave hemispheric binding sites in **4** was, therefore, revealed.

Reinhoudt et al. reported the synthesis of large U-shaped hydrophobic surfaces **5,6** by combination of either two calix[4]arenes and one resorcinarene or one calix[4]arene and two resorcinarenes (Figure 3).[12] Compounds **5,6** selectively bind certain corticosteroids, sugars and alkaloids ($-\Delta G_{298} = 13-17$ kJ mol^{-1} for 1:1 complexation) in $CDCl_3$. Hydrogen bonding and CH-π interactions are the main driving forces for complexation. The structure of some steroid complexes was deduced by systematic ^{1}H-NMR studies. Doubtless, such enormously extended lipophilic surfaces would be even more effective in aqueous media.

Recently, a water-soluble, extended macrocyclic sugar cluster **7** was prepared, which could be adsorbed on a silica (quartz) surface.[13] Cavitand **7** is 20 Å in diameter and forms a strong 1:1 complex with 8-anilinonaphthalene-1-sulfonate (ANS) in aqueous solution (Figure 4). The K_a value of $2.2 \times 10^5\ M^{-1}$ was determined from fluorimetric titration; this value is some 3 orders of magnitude larger than that for β-cyclodextrin and ANS. In water, ANS alone is not adsorbed on a quartz plate, but it is in the presence of **7**. This remarkable behavior could lead to novel solution-to-surface molecular transport devices or delivery systems.

Deeper Cavitands

Within the last few years, numerous synthetic attempts were made to deepen the cavity, rigidify the structure, and functionalize the cavitand surface for further applications.

Bridged Cavitands

Starting from the phosphonite-bridged molecules, bowl-shaped tetragold(I), tetracopper(I) and tetrasilver(I) met-

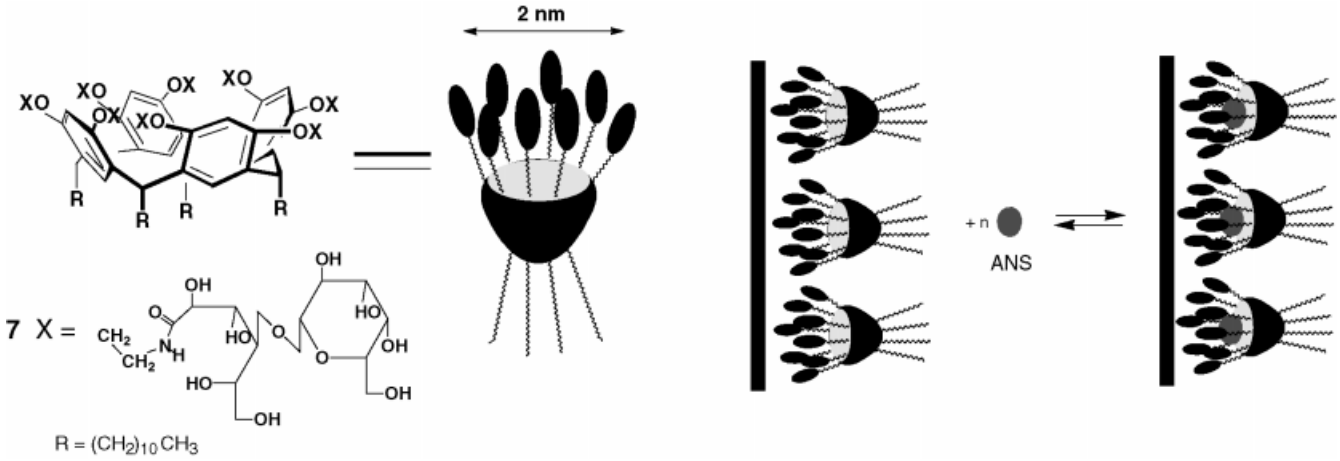


Figure 4. Aoyama's[13] solution-to-surface molecular delivery system based on sugar cluster **7**, and schematic representation of sugar-directed adsorption of ANS in water on a polar solid surface

allo-cavitands **8** were prepared (Figure 5).[14] Their Lewis-acidic character permitted complexes of alkylamines through (Au)···NH_2Alk interactions, and ^{1}H-NMR spectroscopy detected the alkyl chains inside the cavity. Cavitands **8** also showed size selectivity for halide anions with the highest preference for I^-. In case of the tetrasilver(I) complex, an encapsulated Cl^- anion behaved as a nucleophile and reacted with RI to give RCl and I^-. The conversion occurred in high yield; however, not the expected S_N2 but S_N1 mechanism was revealed by relative reaction rates: *t*BuI > *i*PrI > MeI. The retention of stereochemistry in the reaction with (*S*)-(+)-2-ioodooctane was also observed, suggesting that the displacement took place *within* the cavity. This was the first example of chemical reaction inside a deep open-ended cavitand (Figure 5).

The cavity expansion can be achieved without metals. For example, octol **1b** reacted with benzal bromide ($PhCHBr_2$), and diastereoselective bridging with the formation of cavitands **9** (Figure 5) resulted.[15] The fourfold symmetry of **9** was evident from the ^{1}H-NMR spectra and X-ray analysis; the protons of the bridging carbon atom − and not the phenyl rings − were directed into the cavity. This remarkable stereoselectivity in the bridging reaction, if proven to be general, could lead to a new family of deep and noncollapsing cavities.

Modular Approach

Most often, the resorcinarene-based cavitands are prepared by coupling resorcinarene **1b** with an appropriate bridging module. The yields of these reactions are not uniformly high, especially for more elongated (hetero)aromatic walls.[16] For such cases, a different synthetic strategy was pursued. The bridging of the resorcinarene **1b** hydroxyls was achieved with a simpler, reliable unit and then the wall was extended by heterocyclic synthesis. Cavitand **10** possessing eight NO_2 groups was employed in this way.[16] First, **1b** was coupled with 1,2-difluoro-4,5-dinitrobenzene in DMF in the presence of Et_3N at 70°C and gave **10** in 80% yield. Subsequent reduction followed by condensation with α-diketones gave compounds **11,12** with the extended heteroaromatic walls and deeper cavities (Figure 6).[16]

Cavitands **11,12** are relatively rigid and exist as C_{4v} vase-like structures at > 320 K. Octaester **11** was easily converted into the corresponding octaacid with LiOH, and the corresponding octaamides were also formed through reaction with methyl- or *n*-butylamine in alcohol. Other acylations that raise the walls appear routine. Cavitand **12** already is ca. 14 Å deep and 12 Å wide, and, according to molecular modeling, is able to accommodate at least three benzene or toluene molecules within its internal cavity. To our knowledge, molecule **12** represents the deepest cavitands synthesized to date. The cavities reported here feature wide openings with guest/solvent exchange which is fast on the NMR timescale. The uptake and release of guests involves the folding and unfolding of the host walls, motions that are influenced by solvent size and polarity. Modeling suggested that **12** can accommodate C_{60} (Figure 6). The electron-rich walls of **12** and their considerable contact with C_{60} resulted in the complexation of C_{60}. Addition of **12** to a toluene solution of C_{60} ($1.0-2.0 \times 10^{-5}$ M) led to a increase in the UV/Vis absorption of the band at 430 nm, characteristic of complexation (Figure 6). The association constant $K_a = 900 \pm 250$ M^{-1} at 293 ± 1 K ($\Delta G = -4.0 \pm 0.2$ kcal/mol) was calculated; the binding isotherm provides a good fit to a 1:1 stoichiometry. Unexpectedly, the UV/Vis spectra showed no apparent binding of the slightly larger C_{70} in **12**. Accordingly, this example of selective complexation of fullerenes by resorcinarene-based compounds is one of the first reported.

C-Arylation of Calixarenes and Cavitands

Direct arylation of the aromatic rings in calixarenes and related structures provides another attractive route towards rigid and large hydrophobic cavities. "Deep-cavity" calix[4]-

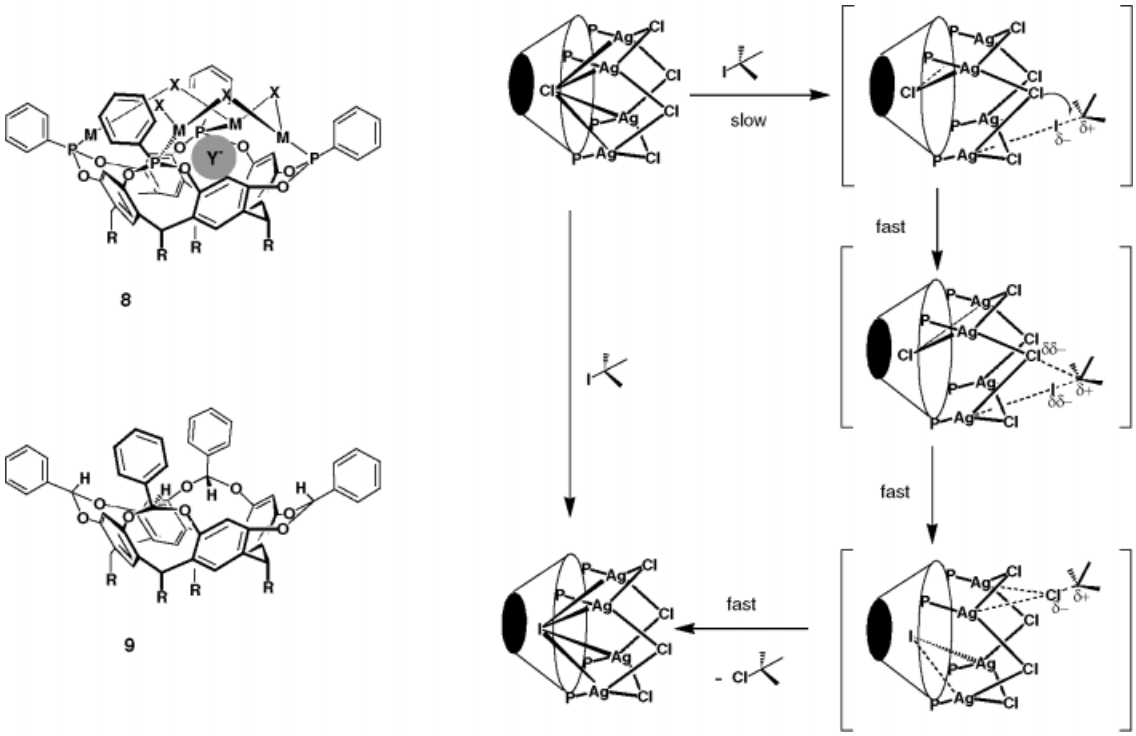
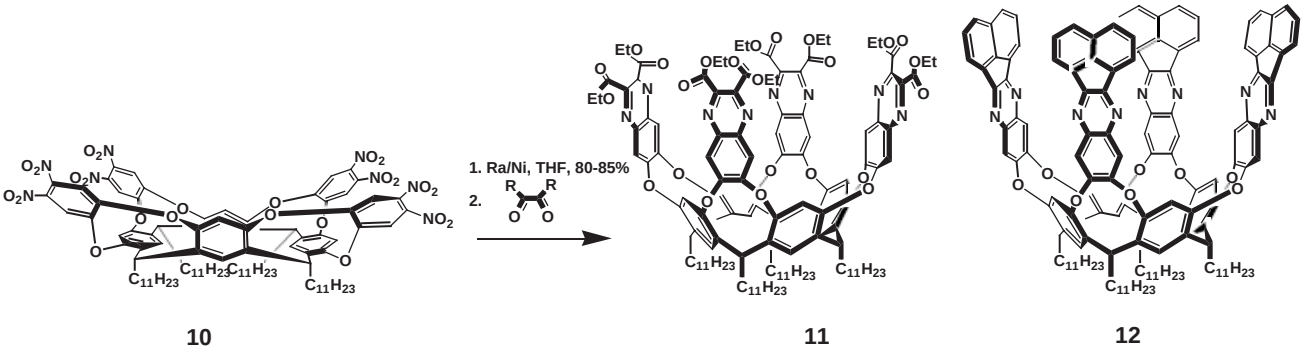


Figure 5. Caviplex **8** and proposed[14] mechanism for the nucleophilic substitution within tetrasilver cavitand **8**; deep-cavity structure[15] **9**



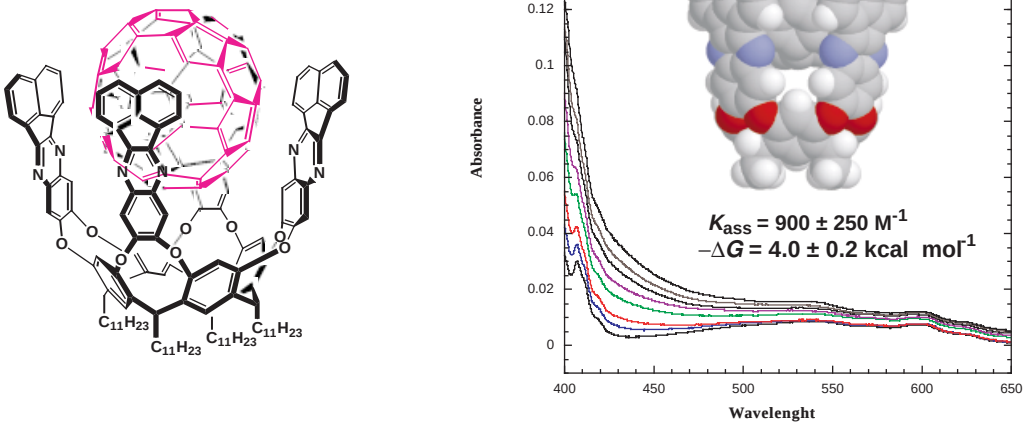


Figure 6. Top: synthetic route to deep cavitands[16] **11** and **12**; bottom: complexation of C_{60} in toluene (UV/Vis spectra) and energy-minimized representation (MacroModel 5.5, Amber* force field) of the 1:1 complex **12**·C_{60}; long alkyl chains are deleted for clarity

arene was initially prepared by Gutsche more than a decade ago by stepwise condensation of *p*-phenylphenol and formaldehyde, but the yield was very low.[17] Subsequently, the aryl walls were attached to calix[4]arenes (see **13**, Figure 7) by thallium- and mercury-mediated coupling, and more recently by Suzuki arylboronic syntheses.[18] Calixarenes functionalized with bulky adamantane units on the upper rim were also prepared.[19] However, it is difficult to keep the cavity open; calixarenes accessible like the heteroarylene-based cavitands (vide supra), are flexible and the "perfect" cone (C_{4v}) easily collapses to the "pinched" C_{2v} conformation.[20]

This is not a problem with rigid (C_{4v}) bowl-shaped cavitands **14**, based on resorcinarenes. The depth of the cavity is increased by building up the sides with boronic acid derivatives in the Suzuki and Stille reactions (Figure 7).[21][22] The *p*-substituents in cavitands **14** (e.g. CO_2Me, OH, NO_2) can then be used for further derivatization. For example, the NO_2 groups in **14** were readily reduced to the corresponding amine, which were subsequently acylated with acyl chlorides and isocyanates.[22] The Suzuki coupling was also performed on the lower rim of resorcinarene.[23] However, the resulting cavities appear to be too narrow for complexation.

Deepened Calixarenes

"Stapled" calix[6]arene **15**, possessing three electron-rich *m*-phenylenediamine walls, is deep and wide enough to capture C_{60} in organic media.[24] The association constant is 1.1×10^2 м$^{-1}$ in toluene and is due to both charge transfer between the electron-rich walls and C_{60} and the preorganization of **15** (Figure 8).

The hybridization of a calix[8]arene and a calix[4]arene afforded a remarkable "macrocavitand" **16** (Figure 9).[25] This is the first example of a lower-rim-capped calix[8]arene. The deep cavity in **16** is not well defined; the flipping of the four-bridged aromatic rings in the calix[8]arene rim is restricted, but the unsubstituted aromatics are conformationally mobile. In addition, there is residual mobility of the calix[4]arene units between two pinched cone conformations[20] which results in an elliptical shape of the cavity. At 330 K in $C_2D_2Cl_4$ only the C_{2v} conformation was seen, and at 370 K in [D_6]DMSO, an averaged C_{4v} symmetry was observed through the fast exchange between two elliptical structures. This reduces the complexation capacity of **16**, and no interaction with several aromatic guests could be detected. The alkylation of free OH groups was proposed

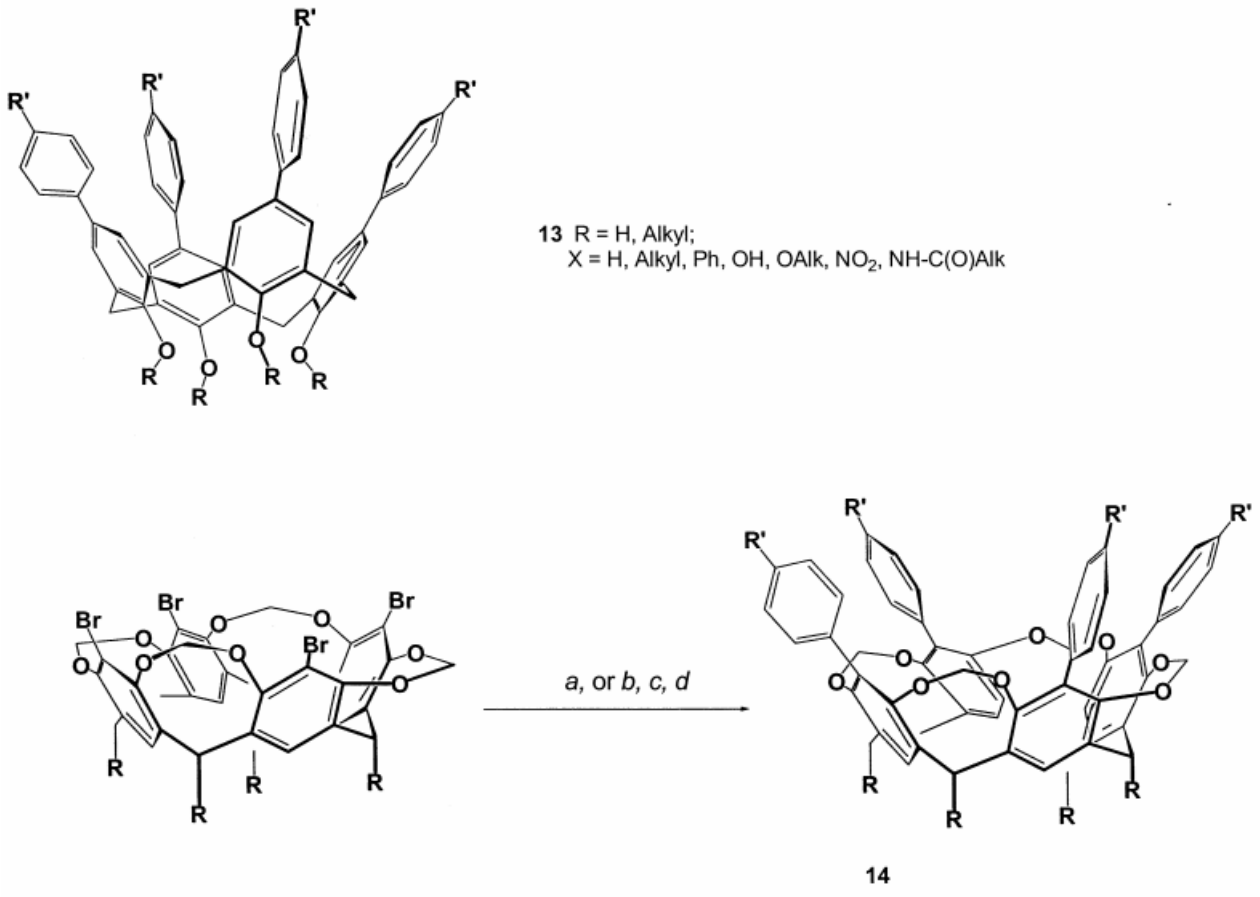


Figure 7. Deep calix[4]arenes **13** and synthesis[22] of deep cavitands **14**; for R = $C_{11}H_{23}$: a) $Pd(PPh_3)_4$, *p*-$Bu_3Sn-C_6H_4-C(O)NH-(CH_2)_nCH_3$, toluene, 110°C, 1−3 d, 10−12%, or b) $Pd(PPh_3)_4$, *p*-$O_2N-C_6H_4-B(OH)_2$, Na_2CO_3, toluene, 110°C, 26 h, 71%; b) Raney Ni/H_2, 45°C, toluene, 16 h, 95%; c) Alk−COCl, EtOAc/H_2O, 1:1, K_2CO_3, room temp. 2 h, > 90°C, or Alk−N=C=O, CH_2Cl_2, room temp. 2−3 h, > 90°C

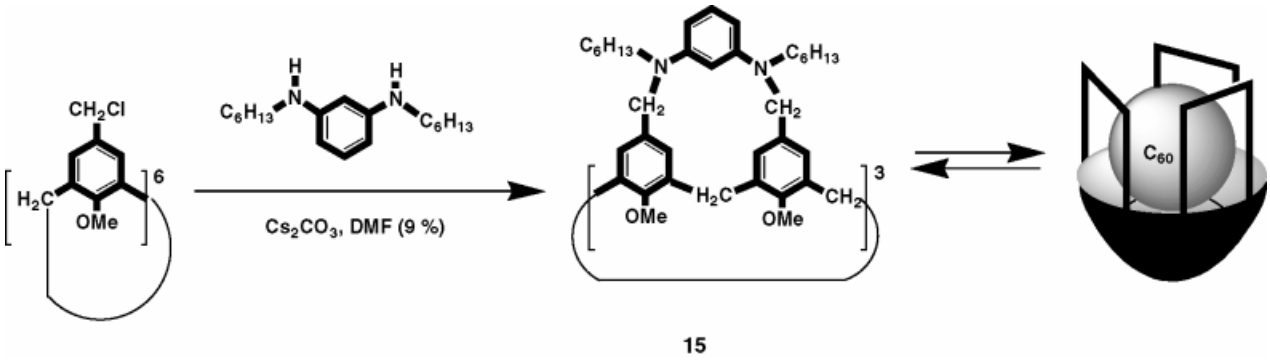


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Figure 8. "Stapled" calix[6]arene cavitand **15** and a proposed structure of its complex with C_{60}, including the cooperative action of donor walls[24a]

to rigidify the cavitand structure,[25] but a complementary guest might also preorganize the cavity for complexation.

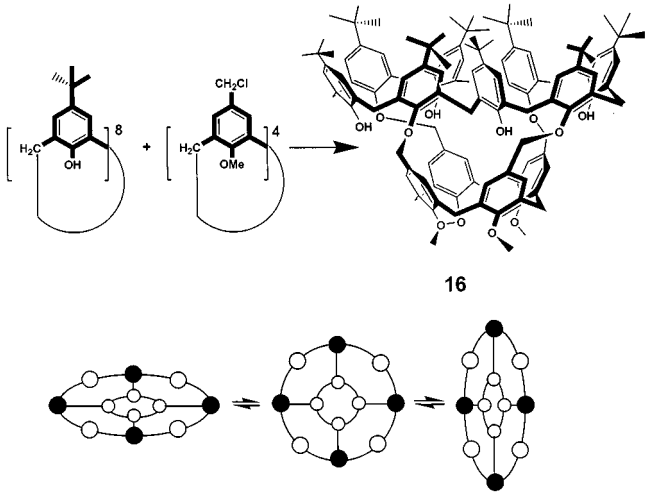

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Figure 9. Top: macrocavitand **16**, based on the combination of a calix[4]arene and a calix[8]arene; bottom: the conformational dynamics of this structure[25] (depicted schematically)

Self-Folding Cavitands

In Högberg's resorcinarenes **1b**, the eight hydroxy groups form a seam of intramolecular hydrogen bonds, and these rigidify the structure by stabilizing the C_{4v} cone conformation.[26] When the OH hydrogen atoms are substituted, the flexibility of the resorcinarene skeleton increases, and other conformations become preferred.[7] To control the size and shape of the cavities – their folding and defolding behavior – and their binding properties, reversible noncovalent forces have been employed, such as *intramolecular* hydrogen bonding and solvent effects. We call these molecules self-folding cavitands (Figure 10).

Böhmer et al. discovered that the reaction of resorcinarene with primary amines and formaldehyde gave the C_4-symmetrical tetrabenzoxazine cavitand **17** in high yield (up to 90%).[27] The conformation, most probably, is stabilized by the four intramolecular hydrogen bonds O–H···O (Figure 10).[27] The X-ray studies show the nitrogen atoms of all the benzoxazine rings near the cavity, and the hydrogen bonds are within a 2.8–2.9 Å range (O···O distances). The volume of the internal cavity is estimated at 250 $Å^3$; one acetone or one CH_2Cl_2 molecule were found inside.

Calixarenes functionalized with two 1,3-distal amide or urea moieties on the upper rim are known to undergo either dimerization or pinching.[20b] In contrast, ureas based on tetrakis(aminomethyl) cavitands **18** do not have a strong tendency to dimerize, and they are also too rigid to collapse. Instead, they form a seam of intramolecular hydrogen bonds (Figure 10).[28] In the IR spectra in chloroform, two bands were observed at $\tilde{\nu}$ = 3381 and 3323 cm^{-1} for the intramolecularly bonded NH urea protons. The MM2 calculations supported the structure **18**, although quite long C=O···N distances (e.g. 3 Å, upper NH, and 3.7 Å, lower NH) were computed, suggesting that the intramolecular hydrogen bonding is weak. In addition, the presence of both free and bonded NH bands in the IR spectra suggests that the seam of hydrogen bonds has gaps and is in a dynamic equilibrium with partially bonded species. Cavitand **18** binds halide anions,[28] and does so by presenting N–H bonds that converge on the guest.

Recently, Sherman et al. described so-called *caviteins*, a new family of de novo proteins, based on rigid cavitand templates.[29] Those are hybrids of cavitands and proteins. Four units – amino acids, dipeptides and even peptides – were attached to the upper rim of the cavitands. The methylenedioxy-bridged cavitand (e.g. **2**) offered an almost ideal interhelical distance (ca 8 Å) for positioning four-helix bundles. For several model caviteins, strong intramolecular hydrogen bonding/folding was detected by IR and ^{1}H-NMR spectroscopy. The hydrophobic cavity in caviteins may be useful as a binding site for drugs and substrates in water, but this has not yet been achieved.

In cavitands **19**, the vicinal secondary amides at the upper rim of the molecule form intramolecular, intraannular hydrogen bonds through a seven-membered ring and also bridge-adjacent rings. The result is a self-folded deepened vase.[30] The amide groups deepen the cavity to dimensions of ca. 8 × 10 Å (Figure 11). Although the size and shape of the cavity in **19** very much resembles those of known cavitand **3**, it is stabilized by the hydrogen bonds and exchange between complexed and free guest species becomes

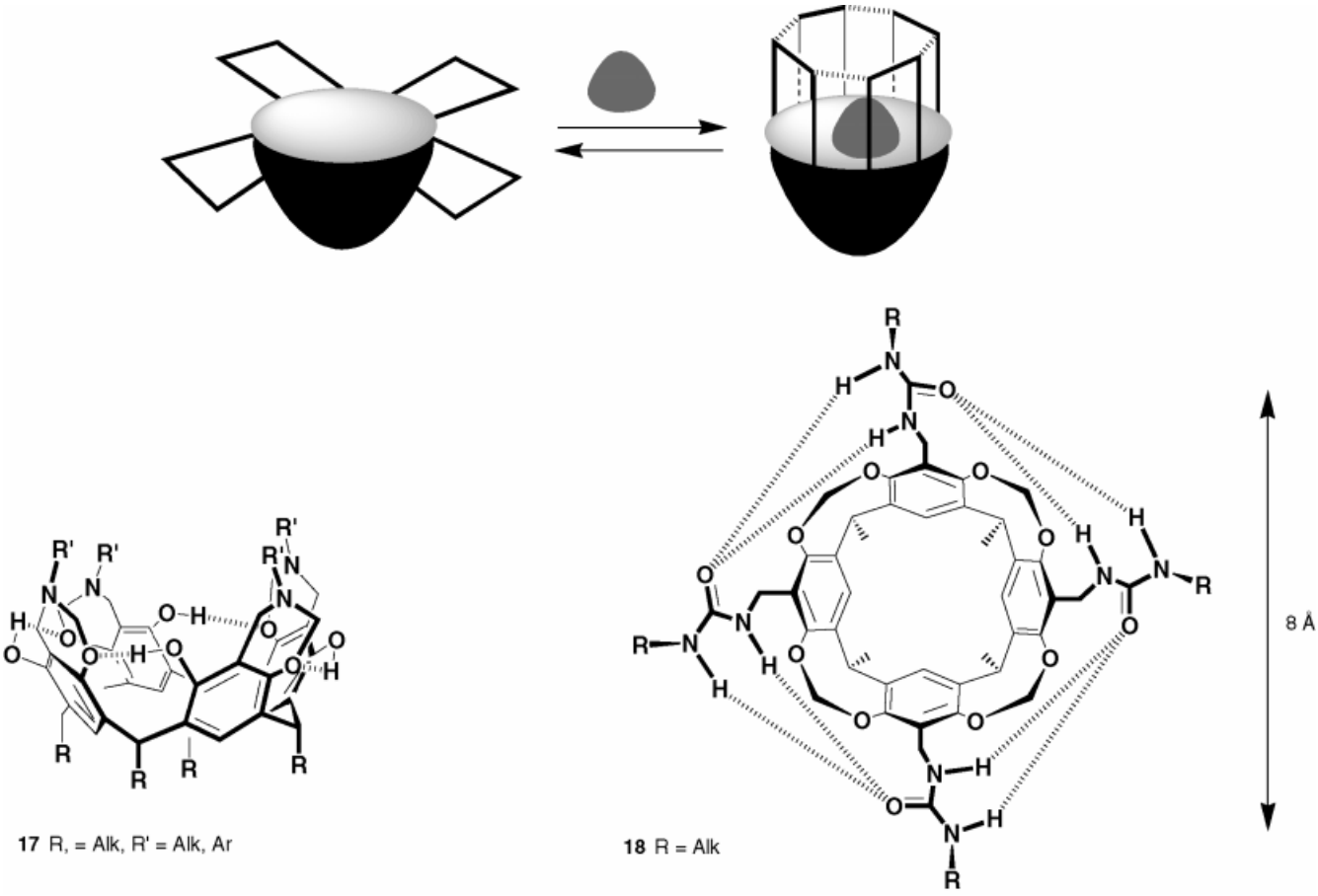


Figure 10. Top: schematic representation of the concept of reversibly self-folding cavitands; dashed lines indicate sites of intramolecular hydrogen bonds; bottom: cavitands **17**[27] and **18**,[28] stabilized by intramolecular hydrogen bonds

slow on the NMR timescale. The circle of hydrogen bonds is responsible for these features; it slows this exchange since it resists the opening to the kite conformation. In contrast, **3** shows rapid exchange, probably through the kite conformation as an intermediate. Upon complexation with adamantanes, cyclohexanes and lactams, the ^{1}H-NMR spectra exhibit two sets of 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 environment and reminiscent of the shifts observed in covalently bound carceplexes.[3]

This slow exchange implies that substantial energetic barriers exist between free and bound species, a behavior for open-cavity receptors that is unprecedented.[31] At higher temperatures (60°C), the signals for complexed and free species become broad, and the guest signals eventually disappear into the baseline. 1-[*N*-(1-Adamantyl)]adamantanecarboxamide, taken in ca. 50-fold excess, gave two *diastereomeric* 1:1 complexes with **19** in [D_{10}]*p*-xylene solution; two sets of characteristically upfield adamantane signals can be seen (Figure 11). The adamantane guest can spin about the long axis of the cavity but is too large to tumble within it. The resulting diastereomerism has precedent in carceplexes,[32] but was undetectable in open-ended cavities.

It was unexpected to find that an open-ended vessel could so effectively desolvate and shield guest species from the environment of the bulk solution. Although the guest exchange process is quite slow on the NMR timescale ($k = 2 \pm 1\ s^{-1}$), it is still faster than that observed for the completely closed hydrogen-bonded calixarene-based capsule ($k = 0.47 \pm 0.1\ s^{-1}$),[33] or for covalently bound hemicarcerands ($k = 0.0093\ s^{-1}$).[34]

Assembling Deep Cavities

Multi-Component Assemblies

Another strategy to extend a cavity is by utilizing *intermolecular* hydrogen bonding. MacGillivray and Atwood constructed multicomponent host cavitands (see for example, **20**, Figure 12) in solid state from resorcinarene and four pyridine, 4,4′-bipyridine, 4-picoline or 1,10-phenantroline molecules.[35][36] The formation of the O−H···N hydrogen bonds between the upper rim of **1b** and four heterocycle molecules enlarged the cavity, and the fifth pyridine molecule or even other guest molecule (!) was clearly observed inside the structure determined by X-ray crystallography.

Capsules

Self-complementary molecules dimerize through solvophobic[9] or hydrogen-bonding[37] interactions in apolar me-

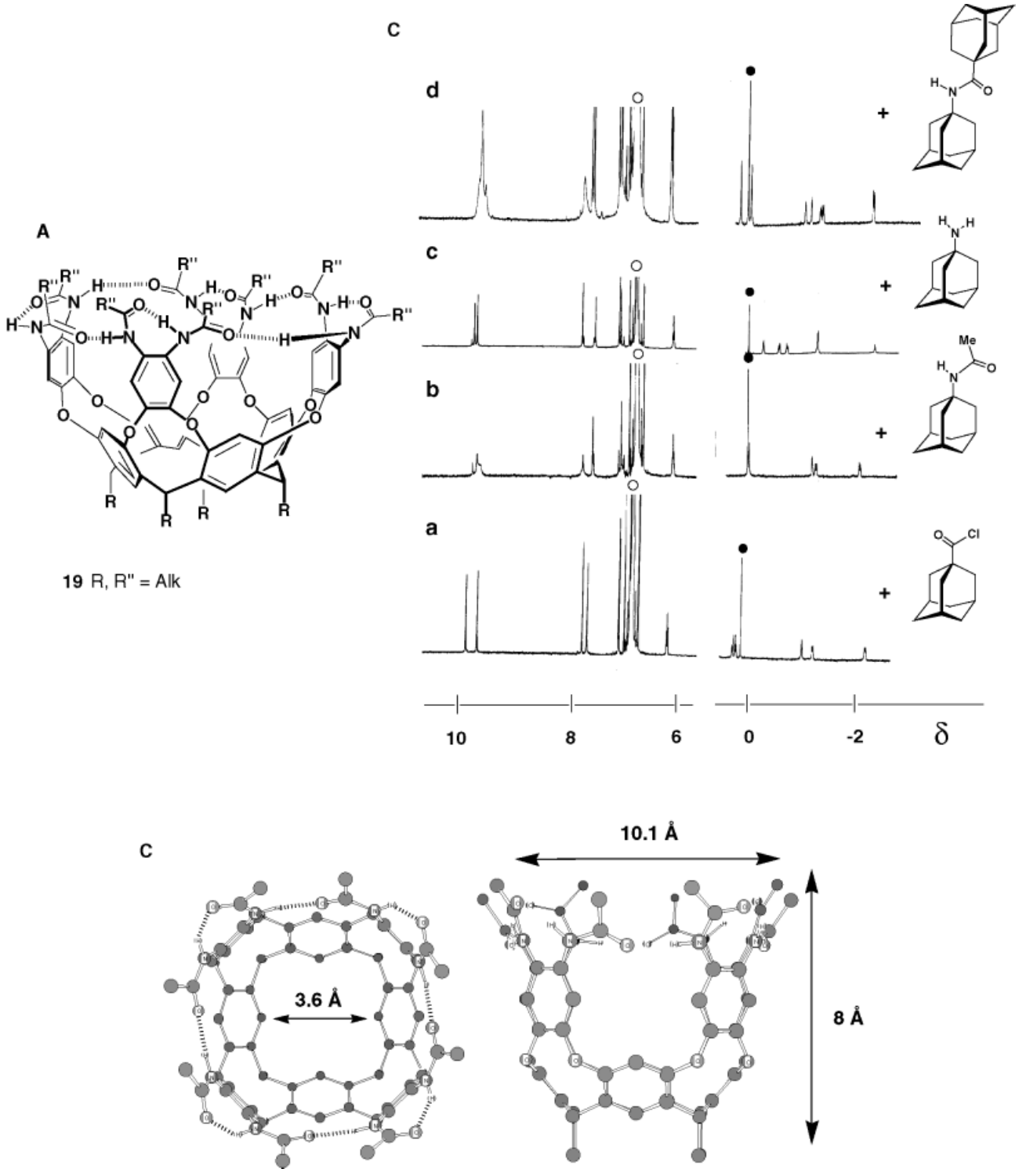


Figure 11. A: Intramolecular hydrogen bonding in vicinal diamides causes a self-folding in cavitands **19**; B: downfield and upfield regions of the ^{1}H-NMR spectra ([D_{10}]*p*-xylene, 600 MHz, 295 K) of cavitand **19** (R = $nC_{11}H_{23}$, R'' = nC_7H_{15}) during complexation with 1-substituted adamantanes;[30b] a: with 1-adamantanecarbonyl chloride; b:. with *N*-(1-adamantyl)acetamide; residual signals of guest-free cavitand **19** are also present due to weak complexation; c: with 1-adamantanamine; the furthest upfield signal ($\delta \approx -2$) is due to the NH_2 resonance; guest-free cavitand is also present due to weak complexation; d: with 1-[*N*-(1-adamantyl)]adamantanecarboxamide; two *different* complexes are present; the solvent signals with corresponding satellites and the internal standard singlet are marked "o" and "•", respectively; the host and guest concentrations are 5×10^{-4} and 2.5×10^{-2} M, respectively; for the complexed 1-substituted adamantanes, all four sets of the skeleton proton signals can be clearly seen; due to the effects of the nearby aromatic ring currents, the chemical shifts of the guest signals are directly related to their position inside the cavity; the functional group at the adamantane 1-position is generally not shifted upfield in the NMR spectra, indicating that the adamantane skeleton is oriented toward the bottom of the cavity and the functional group toward the top; C: two views of the energy-minimized[30a] structure of cavitand **19**; the long alkyl chains and CH hydrogen atoms are omitted for clarity

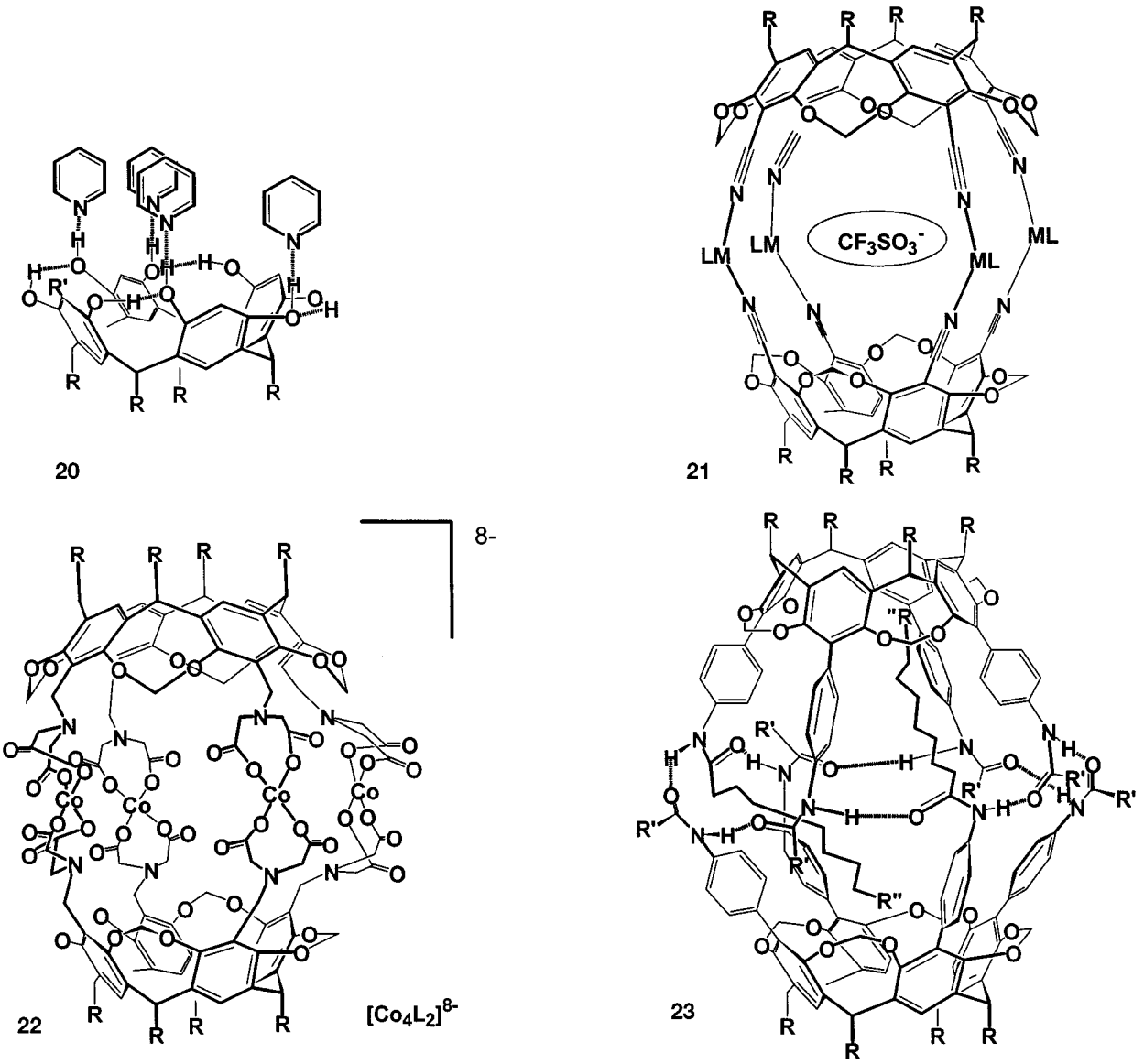
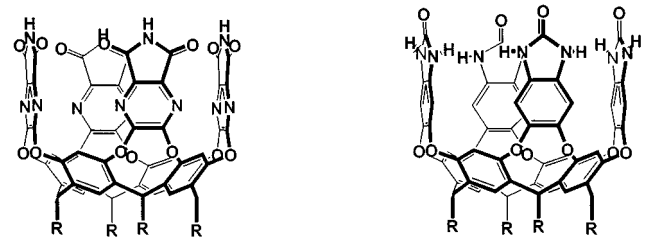


Figure 12. Multicomponent assembly[35] **20**, metallo-induced dimers[39][40] **21,22**, and capsule with self-inclusion[22] **23**

dia. With appropriate curvature, such self-assembling systems generate cavities and result in encapsulation of smaller guest molecules. Inside these, reactive intermediates can be stabilized, new forms of stereoisomerism are observed and even bimolecular reactions can take place.[38] Larger self-assembled cavities of nanoscale dimensions, capable of encapsulating more than one guest, are still rare.

Metal-induced self-assembly **21** of deep cavitands was first described by Jacopozzi and Dalcanale (Figure 13).[39] Two tetracyano cavitands were connected through four square-planar Pd^{II} or Pt^{II} complexes in CH_2Cl_2, $CHCl_3$ and acetone. Evidence of encapsulation of one triflate anion upon dimerization was obtained. The assembly process was shown to be reversible: Et_3N dissociated the capsule **21**, while the addition of trifluoroacetic acid restored it. Water-soluble Co^{II} resorcinarene-based cage **22** was also recently described (Figure 13),[40] but little is known about what is inside its cavity.



24 R = $C_{11}H_{23}$ **25** R = Alkyl

Figure 13. Cyclic imide[43] **24** and cyclic urea[44] **25**

"Deep cavity" tetraamides **14** [X = $NHC(O)(CH_2)_6CH_3$ and $NHC(O)(CH_2)_7CH_3$] dimerize by intermolecular hy-

drogen bonding in toluene in an unusual manner.[22] The dimers **23** possess egg-shaped cavities of dimensions 12 × 19 Å, the estimated volume of which is ca. 440 Å^3 (Figure 13). At the same time, one of the four amide alkyl chains from each cavitand is encapsulated in the cavity of the opposing dimer. The terminal CH_3 groups are situated in the deepest part of the cavity and their resonances are shifted upfield (up to $\delta = -1.8$) in the ^{1}H-NMR spectra in [D_8]toluene. Due to this self-inclusion, the solvent/guest molecules inside the cavity are replaced, which is apparently the entropically more preferred scenario. The residual internal volume thus becomes 190 Å^3. This means that ca. 57% of the cavity is already well filled by self-inclusion, and there is not enough room to accommodate any other molecules.[41] Self-inclusion of this sort has not been observed in the much smaller calix[4]arene dimers.[42] Neither the short-chain *n*-propionylamide derivative **14** [X = $NHC(O)CH_2CH_3$] nor the long-chain palmitoylamide derivative **14** [X = $NHC(O)(CH_2)_{14}CH_3$] show dimierization. Rather, both exist exclusively in the monomeric state in [D_8]toluene. While the same pattern of intermolecular hydrogen bonds are possible in their respective dimers, neither side chain is appropriate for self-inclusion. A delicate balance exists between the enthalpic and entropic contributions to this process.

Cyclic tetraimides **24**[43] and tetraureas **25**,[44] built on the resorcinarene platform, also dimerize through hydrogen bonding (Figure 13). The shape of monomers **24** and **25** is vase-like and the dimerization takes place in the rim-to-rim manner to give the large cylindrical capsules. They feature dimensions of ca 10 × 18 Å (Figure 14).

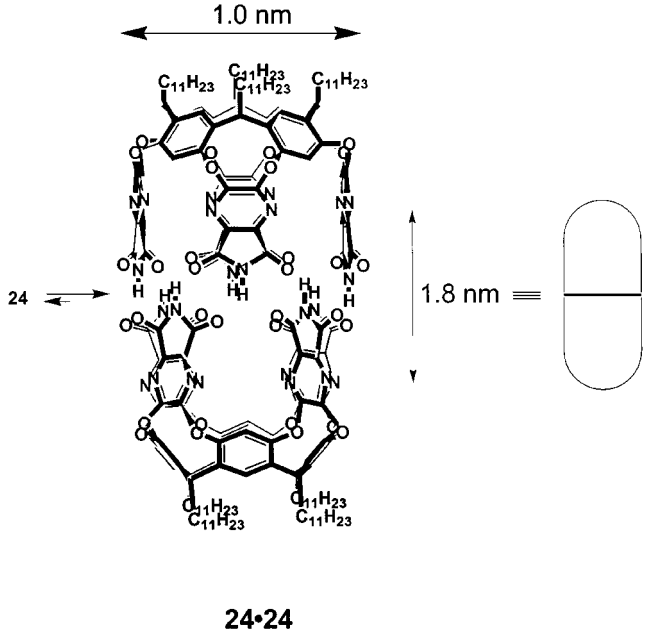


Figure 14. Two cavitands **24** self-assemble through hydrogen bonding into a cylindrical capsule **24 · 24**; the cartoon representation is used elsewhere in this review

The imides are stabilized by a seam of bifurcated hydrogen bonds, while the ureas enjoy conventional hydrogen bonds. When both benzene and *p*-xylene were added in a 1:1 ratio to the [D_{12}]mesitylene solution of **24**, an unsymmetrically filled capsule was the predominant species (Figure 15); a comfortable occupancy is reached with one of each guest in the capsule. The complex is unsymmetrical because the two guests cannot squeeze past each other to exchange positions in the capsule − at least not on the NMR timescale. Likewise, benzene paired with *p*-trifluoromethyltoluene, *p*-chlorotoluene, 2,5-lutidine, and *p*-methylbenzyl alcohol (Figure 15) to give new species with one of each guest inside.[43] Even in a competition experiment involving three different solvent guests, in which toluene, benzene and *p*-xylene were added in a 2:1:1 ratio to the [D_{12}]mesitylene solution of **24**, again, the capsule was filled preferentially (ca. 90%) with benzene and *p*-xylene, and only ca. 10% of the capsule with two toluene molecules inside was observed. The peculiarity is that neither the host nor either guest has a dipole moment but the assembly does. In another experiment, benzene and *p*-xylene in [D_{12}]mesitylene replaced encapsulated toluene molecules within a few minutes at room temperature (1:1:1 ratio of toluene, benzene and *p*-xylene was employed).

That "molecule-within-molecule" complexes, held together only by hydrogen bonds, can show such selectivity was unexpected − the overall length of two guests matches the dimensions of the cavity. Moreover, these are *tetramolecular* species in which entropic resistance to assembly is overcome by intermolecular forces and subtle, volume-filling effects.

Capsule **24 · 24** exhibits complexation of smaller hydrogen-bonded aggregates: 2-Pyridone/2-hydroxypyridine dimer, benzamide dimer and benzoic acid dimer are encapsulated.[45] Diastereomeric "complexes within a complex", using chiral guests, were observed. Two different species are observed in the presence of the racemic *trans*-1,2-cyclohexanediol[45] while one appears when only the single enantiomer is available (Figure 16). In either case, integration indicates there are two guests inside each capsule, but a comparison of the intensity of the signals for the enantiopure and the racemic guests indicates more of the latter − the capsule prefers to be filled with a guest and its mirror image rather than two identical molecules.

The chemical-shift differences between guests in the bulk solution and those in capsule **24 · 24** are related to their positions in the dimeric assembly. In [D_{12}]mesitylene solution, α-, β- and γ-picolines gave complexes with two identical guests per capsule − *homo* capsules.[46] When γ-picoline is encapsulated, the chemical shift of the methyl groups in the NMR spectrum places them near the ends of the cavity: at $\delta = -2.79$. The dipole involving the nitrogen atom, therefore, prefers the middle of the cavity, and at the methyl ends the change in shift is maximal: $\Delta\delta = 4.55$. For the encapsulated β-picoline, the methyl chemical shift is $\delta = -1.65$ ($\Delta\delta = 3.43$), whereas with α-picoline, the methyl group signal is seen at $\delta = 0.58$ ($\Delta\delta = 1.33$). These guests spin along the long axis of the capsule but apparently do not tumble about other axes. When equal amounts of two different picolines were added to a [D_{12}]mesitylene solution

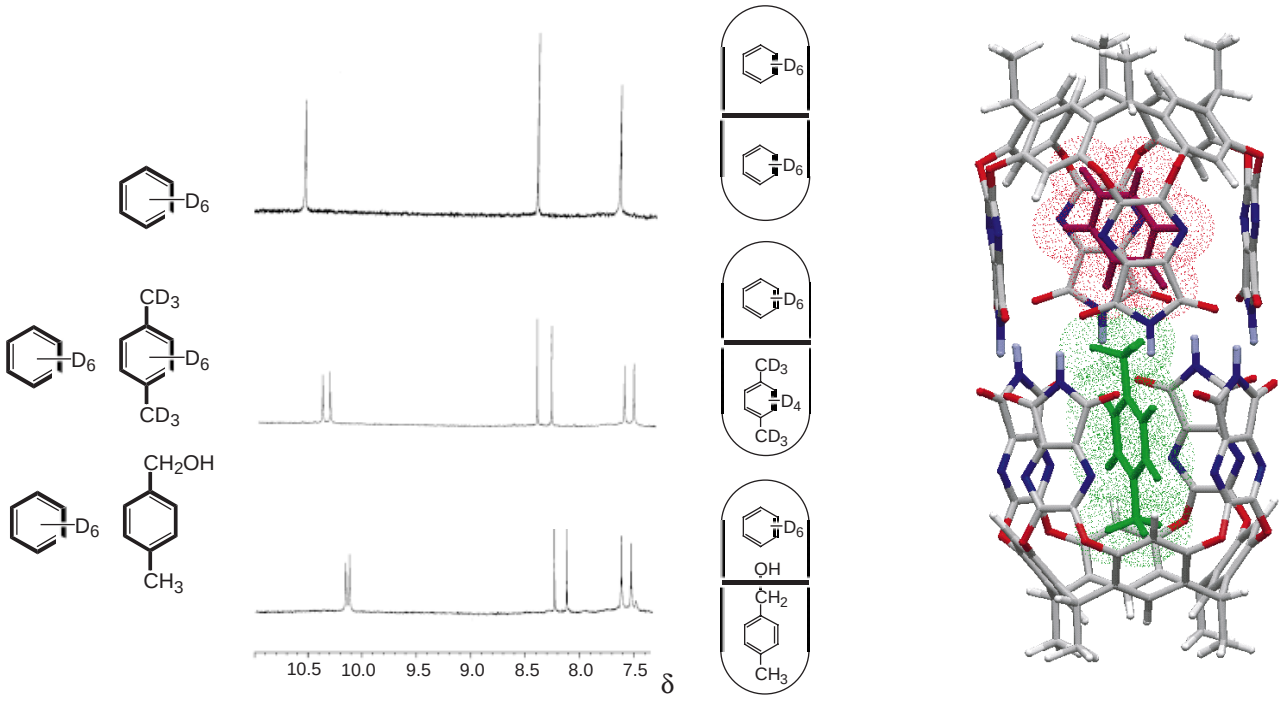


Figure 15. Left: downfield portions of the ^{1}H-NMR spectra (600 MHz, 295 K) of capsule **24 · 24** (total concentration of **24** ca. 1×10^{-3} M):[43] a) in [D_6]benzene; b) in [D_6]benzene/[D_{10}]*p*-xylene, 1:1; c) complex (**24** · [D_6]benzene−*p*-methylbenzyl alcohol · **24**) in [D_{12}]mesitylene; the capsule **24 · 24** imide N−H and aromatic signals are only shown; the CH_3 singlet of the complexed *p*-methylbenzyl alcohol is seen at $\delta = -2.77$; right: the energy-minimized (MacroModel 5.5, Amber* force field) structure **24 · 24** filled with benzene and *p*-xylene; the long alkyl chains and CH hydrogen atoms are omitted for clarity

of **24 · 24**, in addition to the corresponding homo capsules, nonsymmetric *hetero* capsules were also formed, which are filled with two different guests (Figure 17).[46] Again, these guests are too large to move past each other within the capsule, and they can exchange their positions only by exiting the capsule and reentering it − a process that is slow on the NMR timescale. Accordingly, the capsule shows two sets of signals (two different ends) when two different picoline molecules are inside. Moreover, when all three picolines were added to **24 · 24**, two homo capsules (γ-picoline- and β-picoline-filled) and three hetero capsules were clearly detected (Figure 17).[46] More of these peculiar stereochemical relationships are likely to emerge as the capsules become larger and able to accommodate more guest molecules. The control of guest orientations should lead to enhanced interactions, or even reactions inside these cylindrical capsules.

Larger Assemblies

Intermolecular assembly of six resorcinarenes into spectacular spherical cavity **26** with a diameter of 17.7 Å and an internal volume of ca. 1375 Å^3 was described by Atwood.[47] This is the biggest cavity synthesized from organic materials. Sixty hydrogen bonds hold the cavity together and eight water molecules also participate (Figure 18). The hydrogen atoms were not located; however, it was deduced that the assembly involves both C_{4v} and C_{2v} resorcinarene conformers in a ratio 4:2 (2:1). The ^{1}H-NMR spectroscopy indicates that the assembly persists in benzene solution as well. Although the presence of guest species may be deduced by electron-density maxima, they have not been identified from the X-ray experiment. At the same time, molecular modeling suggests that the assembly is large enough to accommodate mammoth guests such as fullerenes or porphyrins.

Concluding Remarks

Deep cavities represent unique species of molecular containers, distinct not only from the covalently sealed carcerands, but also from earlier open-cavity macrocycles. They are open-ended, but guest inclusion can be slow on the NMR timescale. In some cases, the significant ^{1}H-NMR upfield shifts of the complexed molecules offers the opportunity to deduce the structural details of the complexes "from inside", i.e. to determine the orientation of the guest and its interaction with the receptor's interior walls. The uptake and release of guests may, in some cases, involve the folding and unfolding of the host, achieved by either varying solvent polarity and/or temperature. As the constant flow of the substrate into and the product out of the cavity can be achieved, there is cause for optimism that these containers can be used as reaction vessels; even catalysis (turnover) may be possible. The introduction of additional func-

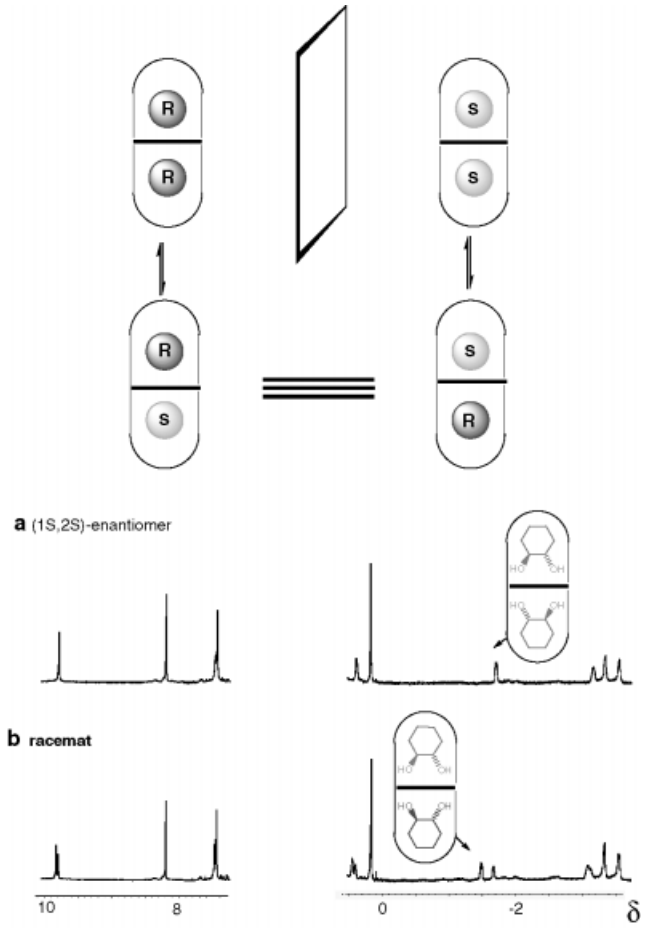


Figure 16. Top: cartoon representation of chirality expression upon encapsulation of two racemic molecules;[45] bottom: portions of the ^{1}H-NMR spectra in [D_{12}]mesitylene (600 MHz, 295 K): a) encapsulated (1*S*,2*S*)-*trans*-1,2-cyclohexanediol; b) encapsulated racemic *trans*-1,2-cyclohexanediol; downfield region: the capsule **24** · **24** imide N−H and aromatic signals are shown; upfield region: the guest cyclohexane CH proton signals are shown

tions for acid and base catalysis appears likely. Another application is in analysis and sensing. Extended lipophilic surfaces should strongly attract organic guests in aqueous solution. Cavitands **3** sense aromatic and other molecules in a gas phase. Cavitands **19** act as NMR-shift reagents for a number of alicyclic molecules: Substituted adamantanes, lactams, cyclohexane derivatives in mixtures can be readily detected in the upfield region of their ^{1}H-NMR spectra.

Both covalent bonds and noncovalent interactions can be utilized to control size and shape of the cavities. Dimers and also multicomponent systems have been prepared by means of hydrogen bonding. The pairwise selection of two different molecules by self-assembled deep capsules points directly to their use as selective reaction chambers for bimolecular processes, and suggests that orientations of the reacting partners can be controlled in the future.

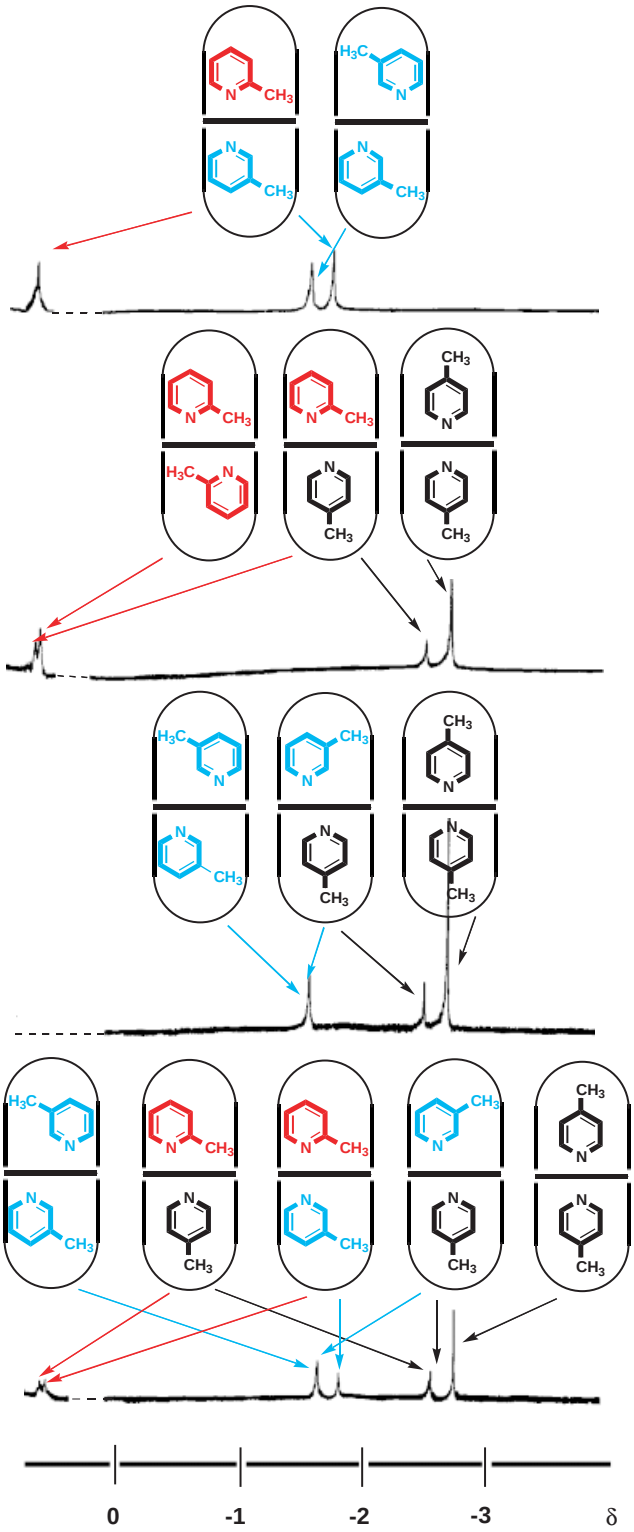


Figure 17. Upfield portion of the ^{1}H-NMR spectrum (600 MHz) of homo and hetero capsules, filled with picoline molecules;[46] the complexed picoline CH_3 proton signals are shown; in each experiment, equal amounts of the guests (ca. 30 equiv. each) were added to a 5×10^{-4} M solution of **1** · **1** in [D_{12}]mesitylene, at 295 ± 1 K; a) α- and β-picolines; b) α- and γ-picolines; c) β- and γ-picolines; d) α-, β-, and γ-picolines

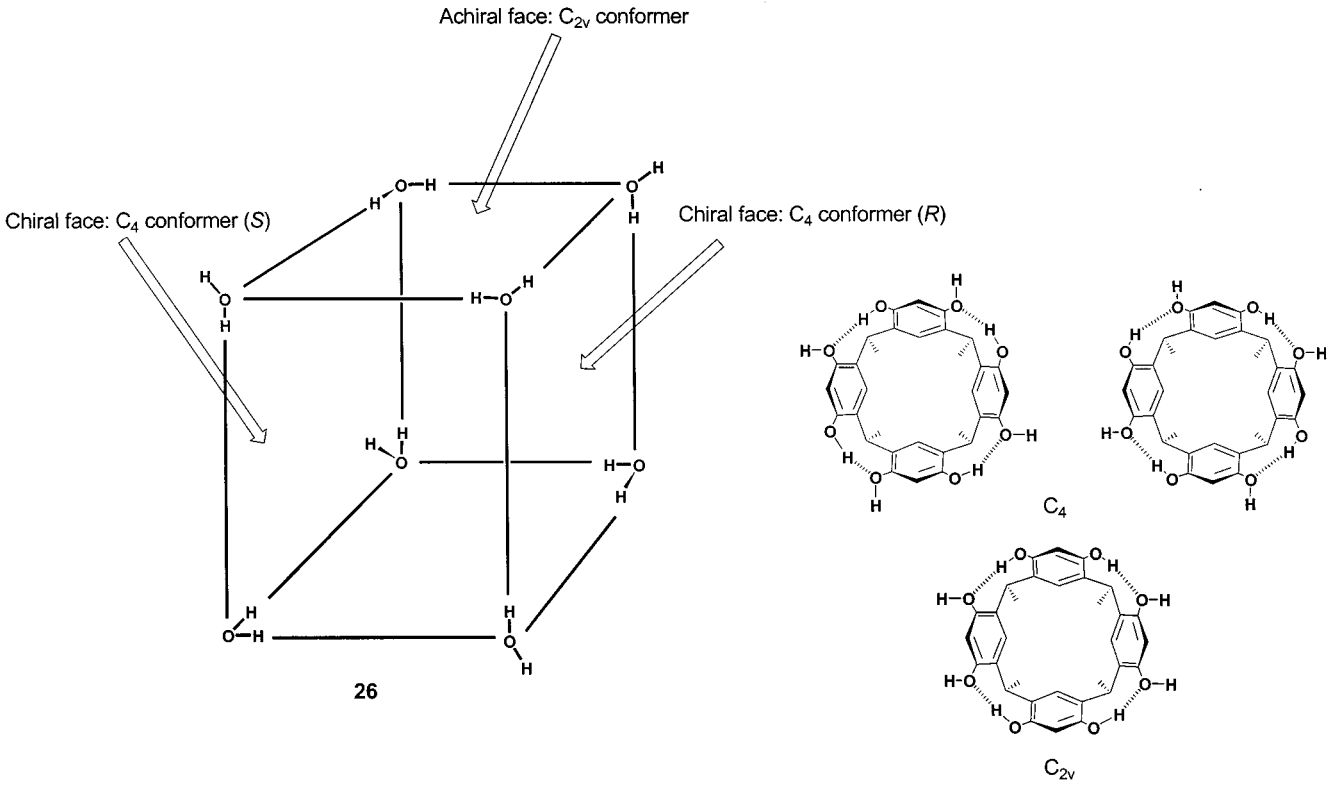


Figure 18. Schematic representation of multicomponent chiral spherical resorcinarene−water assembly **26** of D_{2d} symmetry; the three resorcinarene **1b** conformers are associated with the faces of the water cuboid **26**; the *R* and *S* enantiomers are assigned by looking along the fourfold axis of **1b** such that its wider rim is pointed away from the reader[47]

Acknowledgments

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