Structure and binding properties of water-soluble cavitands and capsules

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Received 1st June 2006
First published as an Advance Article on the web 21st July 2006
DOI: 10.1039/b508530f

Synthetic receptors are modern tools for investigations into the forces involved in recognition. A widely exploited class of receptors are the resorcin[4]arene-based cavitands and capsules. This *critical review* (71 references) describes the evolution of water-soluble versions of these structures, along with insights the resulting host–ndash complexes have provided with regard to complexation driving forces in water. An emphasis has been placed on the influence of host structure on guest affinity and dynamics.

1. Introduction

The development of host–ndash systems that operate in water is a desirable but challenging goal for researchers working in the field of molecular recognition. While organic-soluble systems have offered insight into the forces involved in binding, particularly those affecting selectivity, they do not account for the strong desolvation and entropic benefits experienced in water. As many research groups have discovered, working in water presents many problems that are either not an issue in organic solvents or simply easier to manage. A common problem is solubility: often each piece of a multicomponent system is water-soluble, yet the resulting complex is not. Obtaining the desired protonation state of each functional group can also be troublesome. Buffers are required to maintain the appropriate pH, but depending on the buffer's identity, they can lead to more solubility problems and often change the binding properties of the host.

One of the earliest accounts of molecular recognition in water involved the formation of a non-stoichiometric complex between deoxycholic acid and hydrolyzed fatty acids.[1] On a historical note, this represented the first time that the terms "host" and "guest" were used to describe their roles in chemical complexation. It was not long before a series of synthetic, macrocyclic receptors with stoichiometric complexation properties followed: Pedersen's crown ethers,[2,3] cyclodextrins,[4] cyclophanes,[5,6] calix[*n*]arenes[7] and the glycoluril-derived cucurbiturils (Fig. 1).[8] These host structures offer a significant interior concave surface available for contact with convex guests, but their large openings provided rapid on/off rates and precluded the formation of long-lived complexes. At the other end of the spectrum lie the reversibly formed metal–ndash encapsulation assemblies. The reversible interactions between metal and ligand can approach the stability of a covalent bond while still allowing the system to find a thermodynamic minimum. There have been many examples

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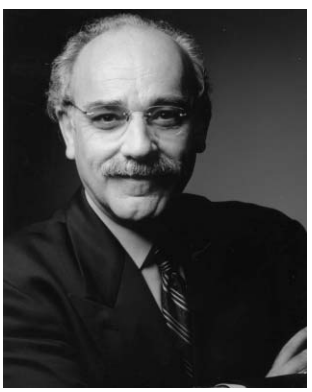


Julius Rebek, Jr.

Julius Rebek, Jr. was born in Hungary in 1944 and lived in Austria from 1945–49. He and his family then settled in the USA in Kansas. He received his undergraduate education at the University of Kansas in 1966, and obtained the PhD 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 molecular recognition and self-assembling systems.

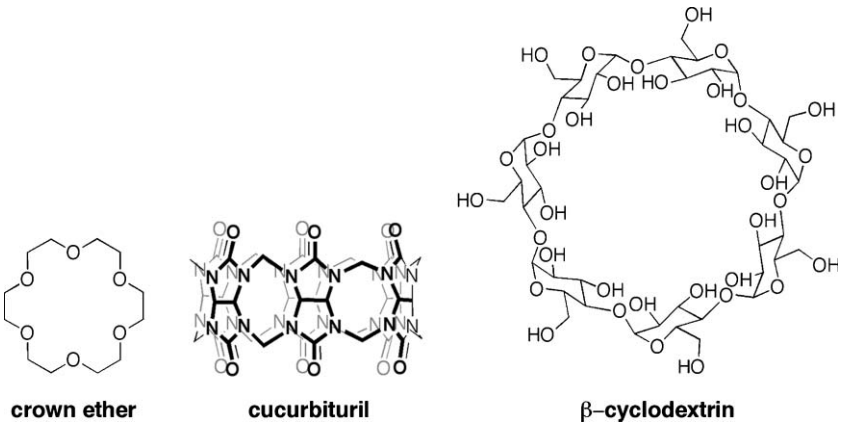


Fig. 1 Structures of other water-soluble macrocyclic hosts: (from left to right) [18]crown-6, cucurbit[6]uril and β-cyclodextrin.

of these complexes in the literature over the past decade; these structures fall outside the scope of this review but have been discussed elsewhere.[9–15]

The resorcin[*n*]arene based cavitands and capsules show behavior somewhere in between the hosts described above. The initial structures were quite flexible and consequently existed as short-lived complexes. As researchers decorated them with more and more recognition features, they observed increased binding selectivity as well as stronger host–ndash associations with slower dissociation rates. This review surveys recent developments concerning receptors that more or less completely surround their guests in water but have one open end. We have not been exhaustive in this literature survey, but in the neglected cases an effort has been made to direct the reader to the most informative publications and leading references.

2. Water-soluble cavitands

2.1 Simple cavitands

The condensation of resorcinol **1** with a wide range of aldehydes provides resorcin[4]arenes **3** (Fig. 2). A few specific

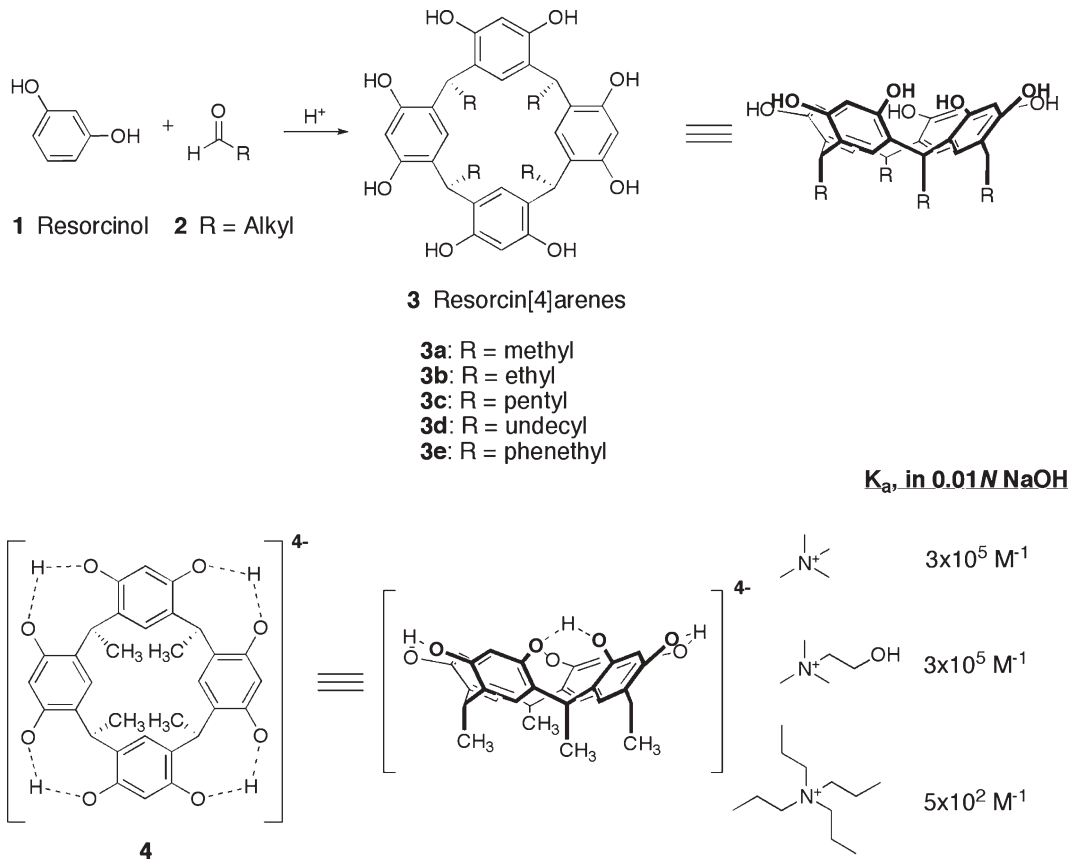


Fig. 2 Top: synthesis of resorcin[4]arenes bearing a variety of pendant R groups; bottom: structure of tetraanionic resorcin[4]arene host **4** and some suitable guests.

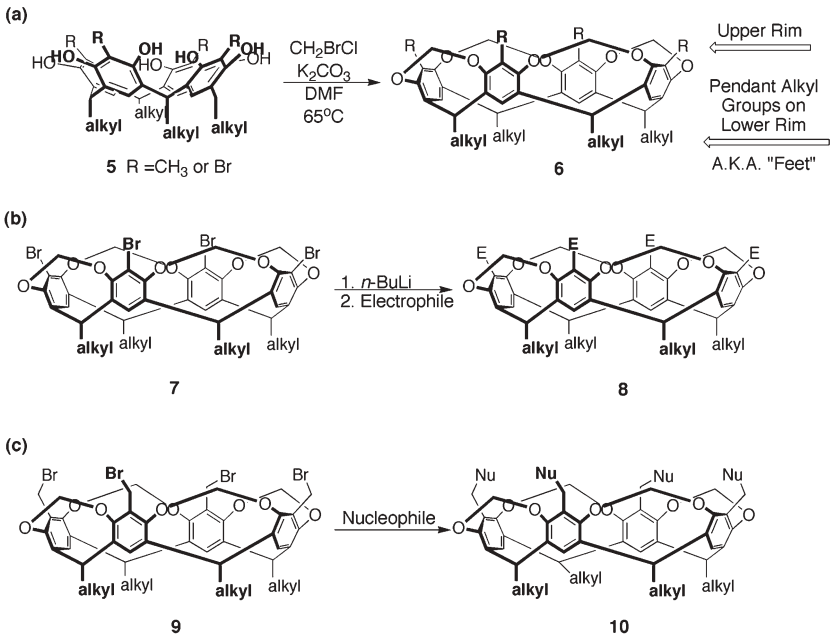


Fig. 3 Synthesis of (a) methylene bridged cavitands and methods to derivatize the upper rim by (b) halogenation/lithiation and (c) nucleophillic substitution.

resorcin[4]arenes are shown as **3a–e** bearing varied pendant alkyl groups on their lower rim (a.k.a. "feet"). The earliest reports of this reaction date back to the 1880's, although the product(s) could not be characterized.[16–22] In 1940 Niederl and Vogel[23] determined the tetrameric structure and 40 years later Högberg[24–26] developed the efficient synthetic procedure still in use today.

Exposure of the simple resorcin[4]arene **3a** with pendant methyl groups to excess NaOH produces the tetraanionic structure **4**—where only one hydroxyl group on each aromatic ring is deprotonated.[27] The resulting structure is surprisingly stable due to the formation of four strong intramolecular hydrogen bonds and the efficient delocalization of charge. This shallow bowl-shaped host binds small tetraalkylammonium salts, such as the tetramethylammonium ion and acetylcholine chloride, with association constants in the 10^4–10^5 M^{-1} range. Such strong binding has been attributed to favorable electrostatic interactions between host and guest; the neutral molecule *tert*-butyl alcohol has almost no affinity for the cavity ($\sim$10 M^{-1}). NICS calculations (HF/6-31G$^+$) performed on the complex of host **4** with tetramethylammonium ion show that one methyl group is interacting with the aromatic rings of the resorcin[4]arene. This allows the thin layer of positive charge around the ammonium center to make favorable contacts with the tetraanionic upper rim. Guest exchange in this system is fast on the NMR time scale.

In order to create hosts with larger and less flexible cavities, these bowl-shaped resorcin[4]arenes were rigidified by reaction with four equivalents of bromochloromethane (Fig. 3a).[28] The neighboring hydroxyl groups become bridged with a methylene spacer to give "simple cavitands". Further modifications (*i.e.* attachment of solubilizing groups) can be carried out on either the pendant alkyl groups on the lower rim or by additional substitutions to the upper rim (Fig. 3b,c)[29–31]

2.1.1 Cavitands with solubilizing groups on the upper rim. Perhaps the simplest of all cavitands, **11** and **12**, can be prepared by deprotonation of methylene bridged cavitands **8** (where E = OH) using sodium methoxide in methanol (Fig. 4).[32] These compounds are soluble in water, however structure **11** bearing pendant phenethyl groups on its lower rim

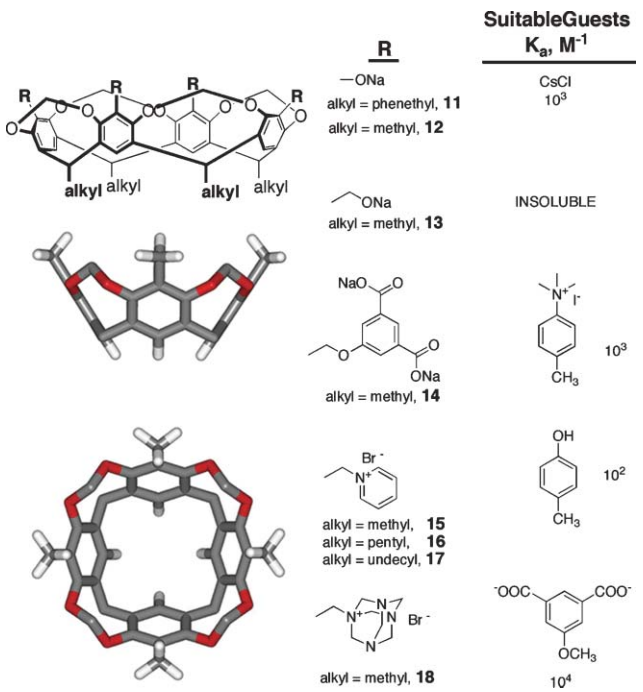


Fig. 4 Left column: depiction of general methylene-bridged resorcin[4]arene cavitands where R = methyl (some protons and the pendant alkyl feet have been omitted for clarity); Right columns: Solubilizing groups appended to the upper rim of simple cavitands and examples of a suitable guest.

was found to aggregate in D_2O to achieve this solubility. Since these structures have limited space and functionality to offer potential guests, only the binding of caesium cations has been reported.[33] Addition of one methylene group to cavitand **11** between the aromatic rings and the hydroxyl groups produces cavitand **13**—which is completely insoluble in water, even at pHs greater than 12.[33]

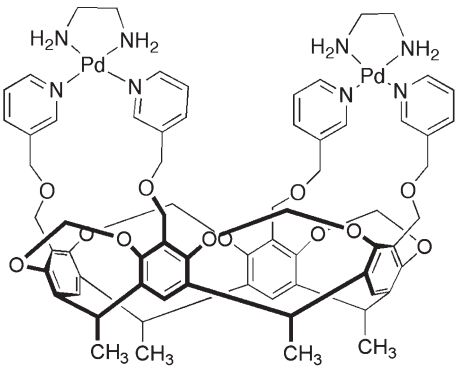
Hong and co-workers produced cavitand **14** by alkylation of these hydroxymethyl groups with isophthalates.[34] Under basic conditions, this presumably octa-anionic cavitand binds cationic guests such as *N*-methylpyridinium, acetylcholine and *N*,*N*,*N*,4-tetramethylbenzenaminium with association constants ranging from 10^1 to 10^3 M^{-1}. An anionic guest, sodium 4-methylbenzoate, was found to have no affinity for this host, most likely due to unfavorable electrostatic interactions.

Tetra(bromomethyl)cavitand **9**[35,36] bearing methyl, pentyl or undecyl pendant groups was alkylated with pyridine to give cavitands **15–17** (Fig. 4).[37] These tetracationic hosts presenting sp^2 ammonium centers were all soluble in water, but **16** and **17** were found to aggregate. Derivative **15** with pendant methyl groups was exposed to *p*-cresol and *p*-toluenesulfonate to produce 1 : 1 complexes with association constants of 1.1×10^2 and 5.2×10^2 M^{-1}, respectively. The authors attempted 2D NMR experiments to determine the exact orientation of the guests in the resorcin[4]arene cavity, but unfortunately in–out exchange was too fast on the ^1H NMR time scale.

Similar in structure to this cavitand, but presenting an sp^3 ammonium center, is the tetra-hexamethylenetetramine cavitand **18**.[38] Extensive guest-binding studies revealed strong electrostatic contributions to guest binding with mono-anionic guests such as the sodium salt of 4-methylbenzoate. It shows an association constant of $\sim 10^2$ M^{-1}, while introduction of a second anionic center (4-methoxyisophthalate) increases the binding constant by up to two orders of magnitude. Cationic compounds, such as anilinium derivatives, have no affinity for the cavity—again due to repulsive electrostatic effects.

In order to achieve larger association constants, Lim and Hong prepared the Pd(II) complexed cavitand **19** shown in Fig. 5.[39] Although the extended "walls" were not enough to induce slow in–out guest exchange on the NMR time scale (kinetic stability), the observed association constants were an order of magnitude greater than that for previous systems. The sodium salt of *p*-anisic acid bound with a K_a of 10^5 M^{-1}. Other research groups have used large, neutral polyethyleneglycol dendrimers to solubilize the cavitand macrocycle (**20**).[40] These structures bind neutral aromatics such as *p*-cresol, toluene and phenol with binding constants in the 10^4 M^{-1} range. Again, this increased binding affinity is attributed to the host's larger (aromatic) surface area available for contact with the guest.

2.1.2 Cavitands with solubilizing groups on the lower rim ("feet"). Sebo and Diederich prepared three ethylene bridged cavitands presenting four amidinium groups on their upper rim (Fig. 6).[41] Solubility in water was only achieved when the pendant alkyl groups were modified to contain polyethyleneglycol chains. Since this cavitand (**21**) presented a larger cavity than those mentioned earlier, 1 : 2 host–ndash complexes were formed with 5-methoxy- and 5-nitroisophthalate at room temperature. The binding constants for these associations were



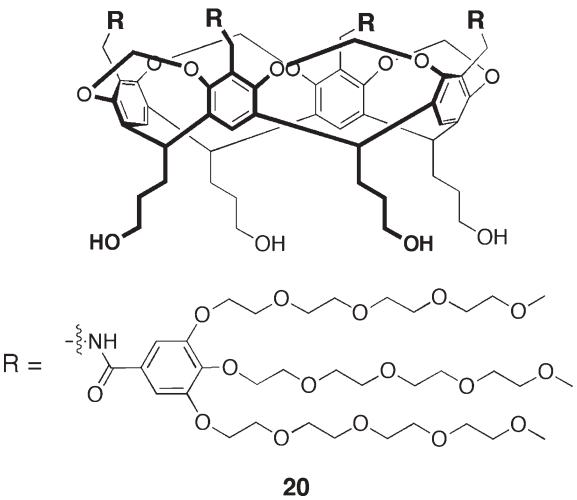


Fig. 5 (left) Structure of Pd(II)-pyridine complexed cavitand **19**; (right) water-soluble cavitand **20** bearing polyethylene glycol solubilizing groups.

found to be $\sim 10^4$ M^{-1} (K_{a1}) and $\sim 10^3$ M^{-1} (K_{a2}), with the methoxyisophthalate having slightly more affinity for the cavity than the nitro-derivative.

In D_2O, the 1 : 2 host–ndash complex is likely composed of one isophthalate guest occupying the hydrophobic cavity of the cavitand while the second guest is present outside the cavity—perhaps associated by electrostatic and/or non-specific hydrophobic contacts. This binding mode allows both guest molecules to make favorable electrostatic contacts with the amidinium groups on the upper rim of the host. Molecular modeling by the authors support this hypothesis (Fig. 6). Additional binding experiments carried out in borate buffered aqueous solutions (5 mM $Na_2B_4O_7$, pH 9.2) show the formation of only 1 : 1 host–ndash complexes. The borate ions interact strongly with the amidinium groups of the host and effectively block any external binding sites. The K_{a1} for methoxyisophthalate remained the same (within experimental error) as in unbuffered D_2O, while the first association constant for nitroisophthalate was reduced by a factor of four.

In TRIS/HCl-buffered D_2O, cavitand **21** also forms 1 : 1 complexes with a variety of nucleotides. Complexation strength was correlated strongly with guest charge: cAMP < AMP < ADP < ATP. This series showed association

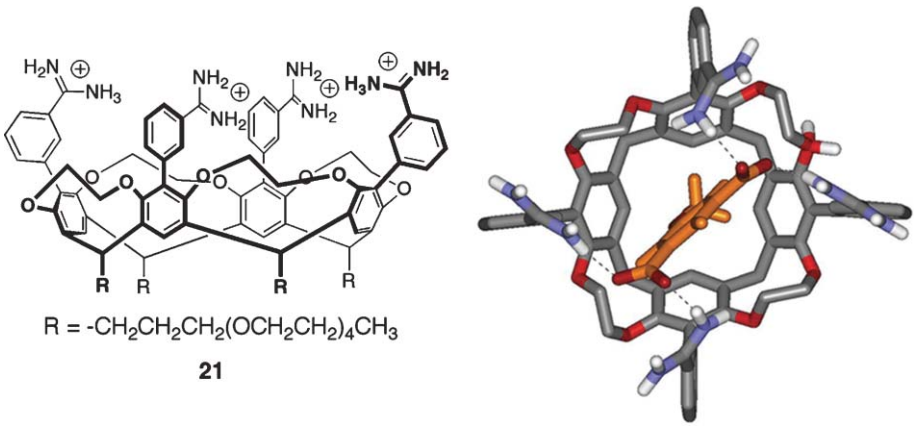


Fig. 6 Left: Structure of Diederich's ethylene bridged cavitand **21** bearing PEG groups on the lower rim; Right: top view of energy-minimized model of cavitand **21**–methoxyisophthalate complex showing hydrogen bonds between host and guest (dashed lines, some protons and the pendant chains have been omitted for clarity).

constants ranging from 10^3 M^{-1} to 10^5 M^{-1}. Other nucleotide monophosphates were bound (GMP, CMP, TMP, UMP), but with less affinity than the adenine derivatives. ^{1}H NMR data revealed that the nucleotides were oriented with their aromatic ring near the cavity of host **21**, allowing the phosphate(s) to interact with the amidinium groups of the upper rim.

Thermodynamic analysis of complex formation revealed that binding of both the isophthalates and nucleotides was enthalpically driven. This type of complexation was also observed by Sherman and co-workers with a simple cavitand bearing phosphate groups on the pendant alkyl chains.[42,43] While the entropically favorable hydrophobic effect is contributing to complexation, the process of "creating order" among the host and guest is very unfavorable. Enthalpically speaking, there are many favorable polar and non-polar interactions between host and guest contributing to overall complex stability.

2.2 Deep cavitands

In order to create hosts with larger cavities, resorcin[4]arene **3** was condensed with electron-poor aromatic rings to give "deep cavitands", like those shown in Fig. 7. Two water-soluble versions, **24** and **25**, were synthesized by our group. Each bears an octa-amide upper rim and four ammonium centers on the pendant alkyl chains as solublilizing groups. Upon dissolution in water, these structures exist in the kite conformation as D_{2d} velcraplex dimers[44]—most likely to maximize burial of lipophilic surfaces from aqueous solvent.[45,46] Upon exposure to guests of suitable size and shape, the cavitands rearrange to the C_{4v} vase conformation and form complexes where in–out *guest exchange is slow on the NMR time scale*. The consequences of this property in the ^{1}H NMR spectrum are the observation of large $\Delta\delta$'s ($\geqslant$3 ppm) for both host and guest proton resonances in the free and bound states. A significant energetic barrier between free and bound conformations results in the kinetic stability of these complexes.

A variety of suitable guests were found, most of them exhibiting a hydrophobic center bearing one polar functional group (*i.e.* ammonium, hydroxyl). The only guest reported to undergo fast in-out exchange on the NMR time scale was isopropyl ammonium chloride. Interestingly, this guest induced the conformational change in the host to the C_{4v} vase shape, but was not bound tightly enough to show slow guest exchange in and out of the cavity on the NMR time scale. Guest binding affinities were modest—the maximum observed was 1.4×10^2 M^{-1} for the neutral cyclohexanone.

Further modification of the intermediate octaamine cavitand **23** with four carboxylate-substituted benzimidazoles gave a second water-soluble cavitand **26** (Fig. 8).[47] In contrast to the previous case, this cavitand exists in the C_{4v} symmetric vase conformation in water. The stability of this structure stems from (a) the rim of hydrogen bonds formed structure stems from (a) the rim of hydrogen bonds formed between four solvent water molecules and the nitrogen atoms of the benzimidazole rings and (b) an adventitious molecule of THF bound inside the host cavity as a remnant from the final saponification step in the preparation.

Some unexpected results were obtained when this cavitand was studied in solutions containing sub-micellar concentrations of sodium dodecylsulfate (SDS) or dodecyl phosphatidylcholine (DPC). Exposure of cavitand **26** to one equivalent of SDS or DPC produces a stunning host–ndash complex where *the long alkyl chain appears in the host's hydrophobic cavity, and is coiled into a helix*.[48] This conformation fills the cavity's space with eight carbons and leaves the polar sulfate head group exposed to solvent (Fig. 9). This coiled structure was supported by the observation of NOE's between the terminal methyl group and the methylene at C-4.

This system offers a qualitative measure of the magnitude of the hydrophobic effect. Long alkyltrimethylammonium salts present two binding sites that are known to be complementary to the host's cavity: a long alkyl chain and a trimethylammonium "knob" (choline, for example, shows a binding constant of $>10^4$ M^{-1} in **26** in D_2O[49]). When dodecyltrimethylammonium bromide is added to a solution of **26** in D_2O, *binding of the (helical) alkyl chain, and not the trimethylammonium group is observed*. The association constant is again $>10^4$ M^{-1}. Each gauche interaction that propagates the helix conformation destabilizes the system by 0.55–0.65 kcal mol^{-1}.[50] In addition to the favorable electrostatic interactions between the

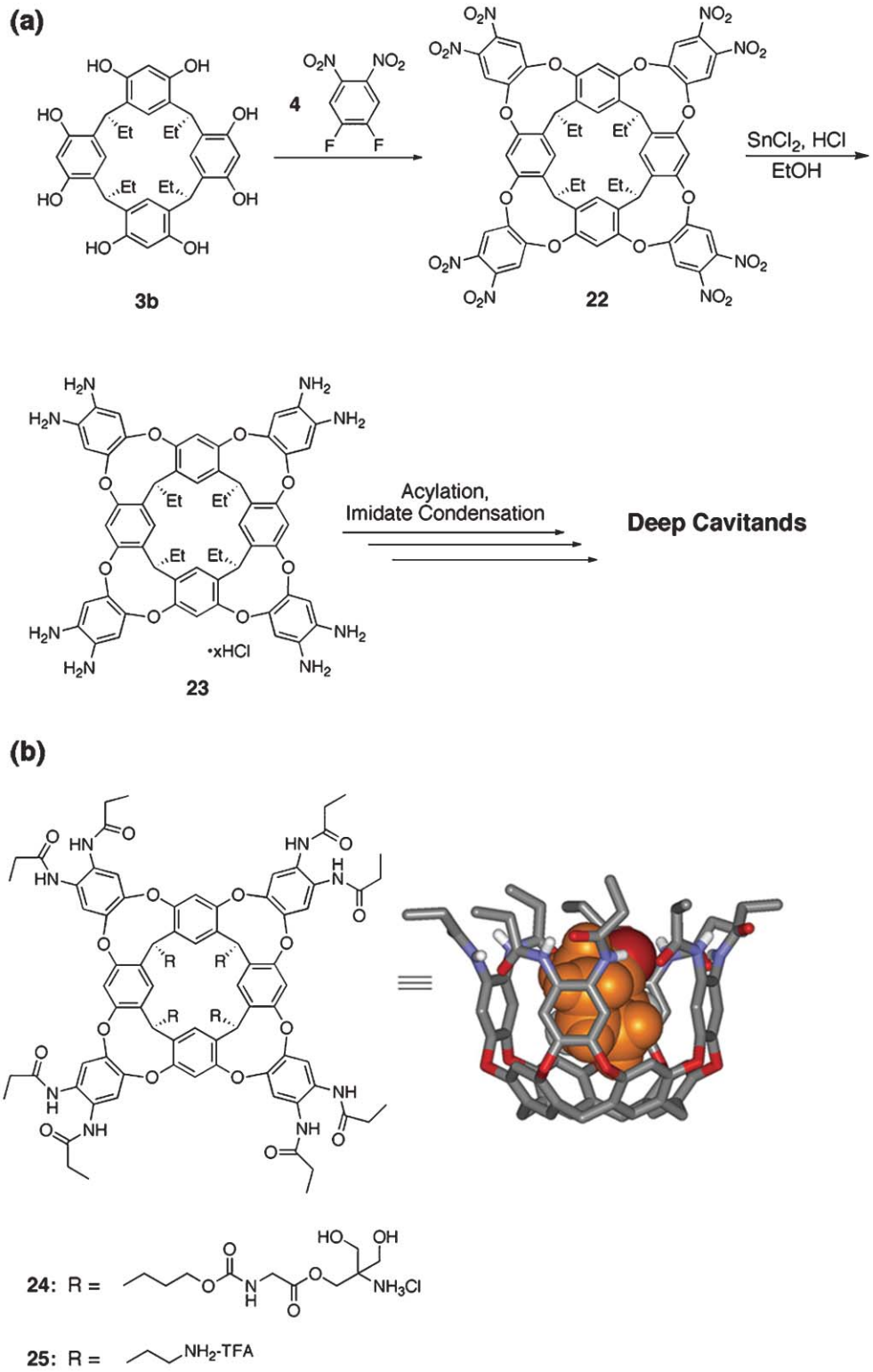


Fig. 7 (a) General synthesis of ''deep cavitands''; (b) Left: Structure of water-soluble, octaamide cavitands **24** and **25**; Right: energy-minimized structure of a deep cavitand with bound cyclohexanone (some protons and the pendant alkyl groups have been omitted for clarity).

tetracarboxylate upper rim and the tetraalkylammonium center, the large driving force of burying the hydrocarbon chain from water dominates the attraction.

When SDS is present in solution above its critical micellar concentration, the roles of ''host'' and ''guest'' are reversed: cavitand **26** becomes a guest inside a host structure.[51] These micelles are also capable of solubilizing the cavitand in aqueous solutions when the salt concentration is too high (*i.e.* phosphate buffered saline).[49] Cavitand **26** is still capable of binding guests under both conditions, although the resulting

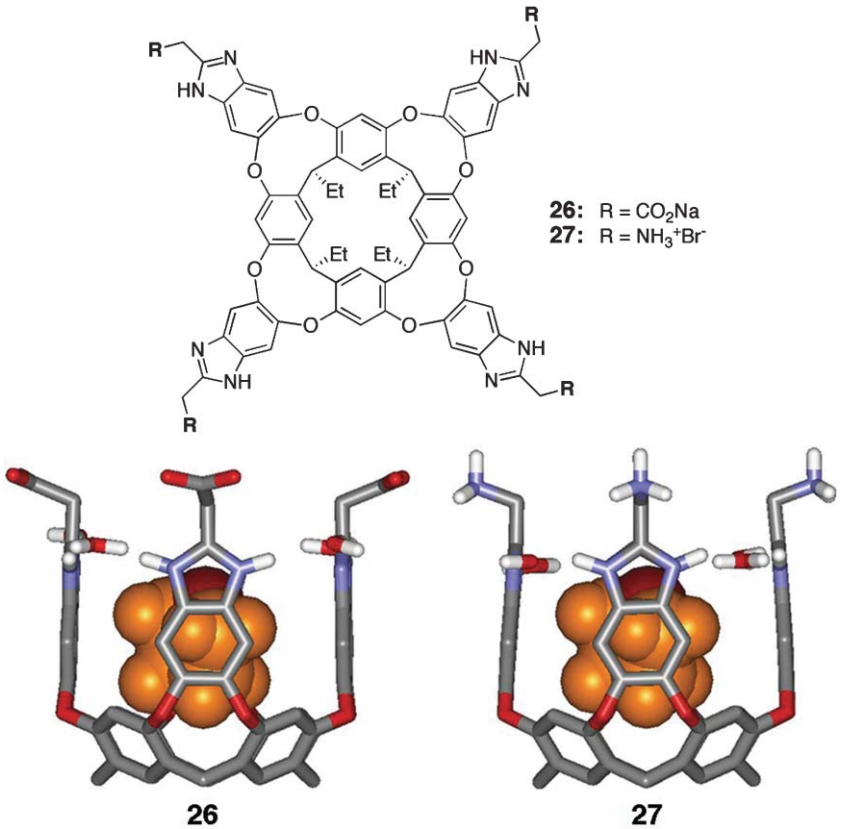


Fig. 8 Structure of deep, tetraanionic cavitands **26** and **27** binding one molecule of THF.

association constants are approximately an order of magnitude lower than in pure D_2O.

This host also extracts water-insoluble species into aqueous solution. We found that *n*-alkanes were extracted into D_2O and bound again in a helical fashion inside the cavity—just like the hydrocarbon tail of SDS. The difference in this situation is that with no polar head group present to "anchor" the orientation of the guest, the alkane tumbles rapidly on the NMR time scale *inside the host's cavity*.[52] The protons on carbons 1 and 8 (of *n*-octane) experience two environments within the window of the NMR timescale. The result of this motion is an averaging of the guest proton resonances in the NMR spectra (Fig. 10).

A tetracationic derivative **27** was also synthesized (Fig. 8).[53] In this case, at the acidic pHs needed to obtain significant solubility in water the cavitand existed in the C_{2v} kite conformation, without a cavity. A 25% DMSO in water solution was needed to induce the C_{4v} vase conformation, and under these conditions guest binding was observed. This host has no affinity for cations—even tetraalkylammonium salts

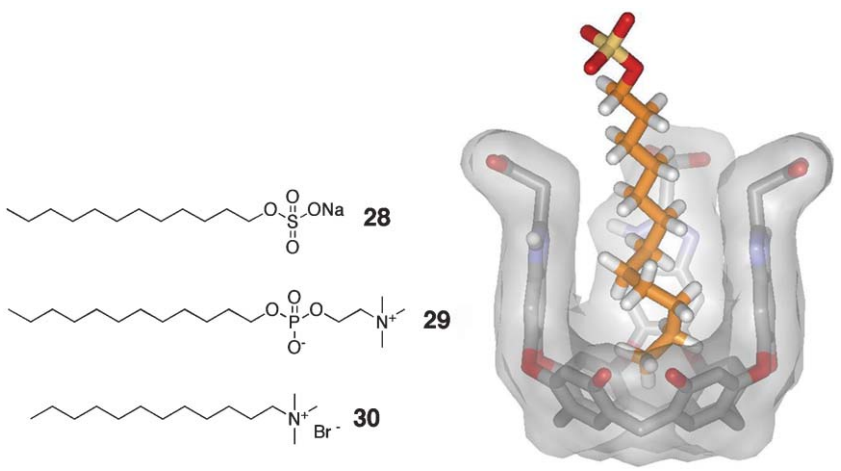


Fig. 9 Left: Structures of SDS (**28**), DPC (**29**) and dodecyltrimethylammonium bromide (**30**); Right: helical SDS–cavitand **26** complex in D_2O showing eight carbons in a coiled conformation.

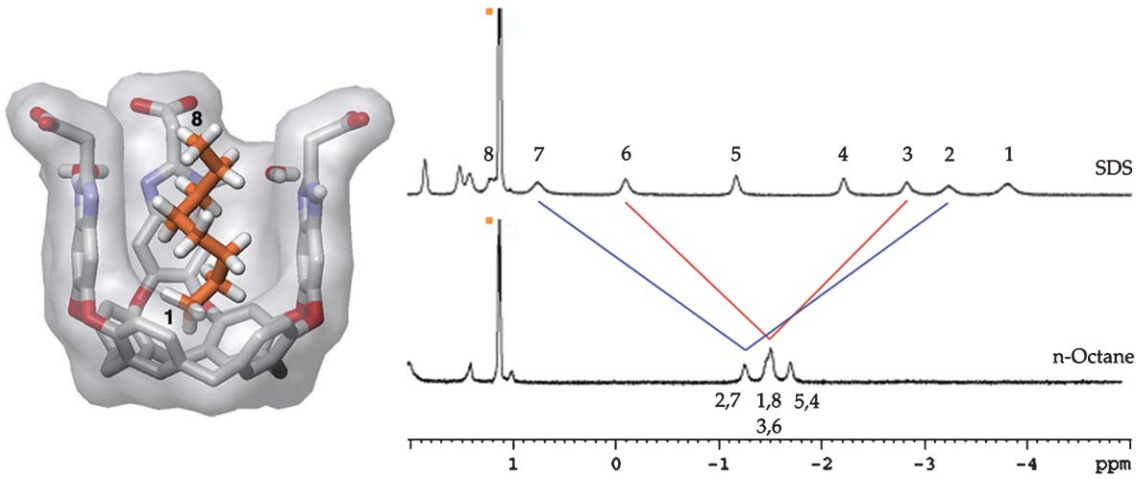


Fig. 10 Left: model of complex between host **26** and helical *n*-octane; Right: Upfield region of ^{1}H NMR spectra of SDS and *n*-octane in the presence of 1 mM cavitand **26**; red and blue lines show "averaging" of guest resonances by fast tumbling inside the cavity.

whose shape and size are complementary to the cavity are unable to penetrate the tetracationic upper rim of the cavitand. However, neutral and anionic adamantanes were bound in a kinetically stable fashion with association constants in the 10^2–10^3 M^{-1} range.

A fourth deep, water-soluble cavitand **31** bearing four benzoate groups along its upper rim is shown in Fig. 11.[54] These benzoates act as "revolving doors" allowing limited access to the host's cavity. The consequences of this motion in solution become apparent in the ^{1}H NMR spectrum of cavitand **31** in D_2O. The proton resonances representing the adventitious molecule of THF bound in the cavity are sharp, in contrast to the broad peaks observed for THF bound in tetracarboxylate cavitand **26**. This feature indicates the slowed in–out guest exchange rate by the rotating phenyl rings of cavitand **31**.

The guest binding preferences of this cavitand are quite different than those observed for the tetracarboxylate cavitand **26** due to the "restricted" cavity size. While host **26** binds a wide range of *n*-alkanes (pentane to dodecane), tetrabenzoate cavitand **31** will only bind pentane through octane. The longer alkanes are not bound by cavitand **31**. Apparently, the energy involved in disrupting the phenyl rings' positions around the rim of the cavity makes complex formation unfavorable.

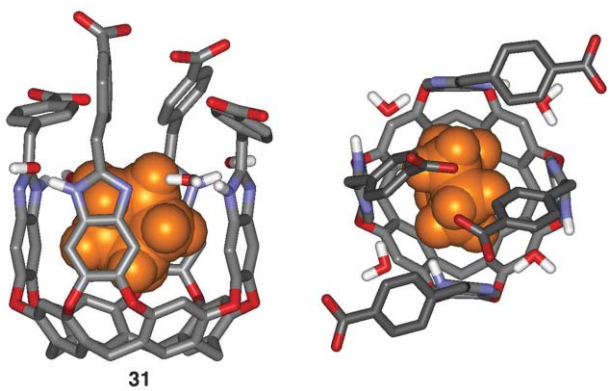


Fig. 11 Depiction of the tetrabenzoate cavitand **31**–cyclopentane complex featuring aromatic "revolving doors". On average, two doors are suspended above the open end of the cavity at any time.

3. Water-soluble molecular capsules

The creation of molecular capsules in organic solvents relies heavily on properly oriented hydrogen bonding functionalities to bring two (or more) species together in solution.[55] Unfortunately, hydrogen bonds are of limited use in aqueous solvents to drive multi-component assemblies—water competes too strongly for these recognition sites. Instead, researchers in this area have relied on electrostatic interactions and the hydrophobic effect. There are relatively few examples of water-soluble molecular capsules in the literature, and we have included those associated through non-covalent and metal–ndash interactions as well as some entirely covalent analogues.

3.1 Capsules assembled through non-covalent interactions

The Reinhoudt group described the preparation of calix[4]-arenes derivatized on their upper rims with either amidinium, sulfonate or carboxylate groups (Fig. 12). Initial studies involving monomers **32** and **33** resulted in the precipitation of the dimeric assembly from aqueous solution, even though both monomers were water-soluble.[56] (A similar result was obtained by Schrader and co-workers) with ammonium and phosphonate substituted calix[4]- and calix[6]arenes.[56–58] Dissolution of the complex in methanol reveals formation of a 1 : 1 heterodimeric molecular capsule containing one of the host propyl chains as a "guest". Addition of water (up to 35%) increases the upfield shift of these protons and NOE connectivities were observed between the methyl group of this chain and the aromatic rings of the host.

Simple synthetic alterations were made to each monomer resulting in an increased water-solubility of the complex. The ethylene glycol groups of the amidinium monomer **32** were lengthened and the sulfonates of **33** were exchanged for carboxylates. Combination of calix[4]arenes **34** and **35** in a 1 : 1 ratio gave the heterodimeric assembly **34·35**. This complex is

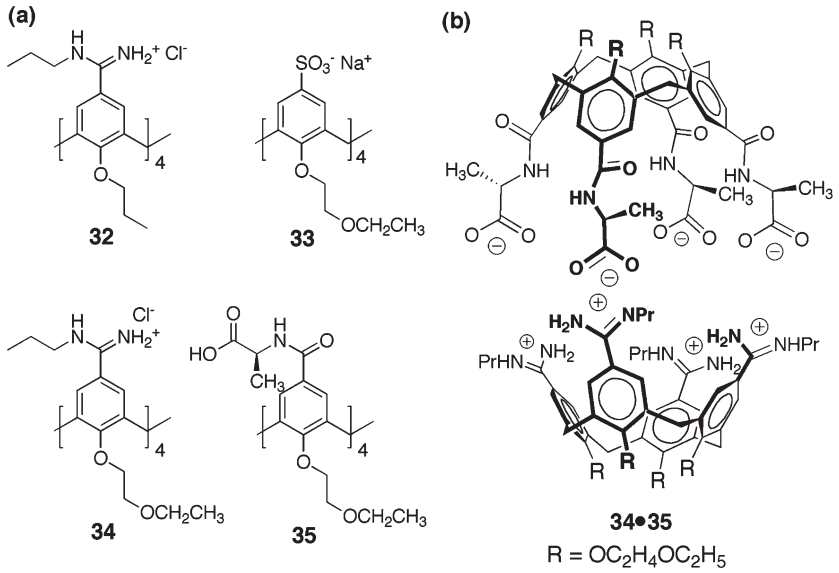


Fig. 12 Structure of (a) tetra-substituted calix[4]arene monomers; (b) depiction of a water-soluble dimeric capsule assembled through electrostatic interactions.

completely soluble in water buffered at pH 9 (Fig. 12).[59] One propyl substituent is again encapsulated in the hydrophobic cavity, along with the methyl groups of the alanine amino acidic moieties. These peaks are also broadened, indicating hindered rotation of the encapsulated side chains, or intermediate rates of assembly.

Further experiments with this complex in the presence of a variety of cationic guests offered promising results. Upon exposure of capsule **34·35** to 30 equivalents of *N*-methylquinuclidinium, the amidinium propyl side chain resonances were shifted downfield—indicating their displacement from the cavity.[60] Only one set of guest resonances was observed, suggesting fast exchange on the NMR time scale. A similar result was observed upon exposure of complex **34·35** to 10 equivalents 6-amino-2-methylquinoline: guest proton resonances were shifted upfield (max $\Delta\delta = 0.10$ ppm) although fast exchange was still observed.

A second (and most spectacular) molecular capsule, formed from two deep, water-soluble cavitands was assembled *via* the hydrophobic effect.[61] The monomers feature eight carboxylate groups which afford their solubility in water (Fig. 13). Upon exposure of this cylindrical monomer **36** to an appropriate steroidal guest, Gibb observed homodimerization to a capsule in the ^{1}H NMR spectrum. The best guest for this dimeric system was found to be (+)-dehydroisoandrosterone **37** due to its complementary size, shape and polarity. A remarkable apparent binding constant of 1×10^8 M^{-1} was reported, indicating the strong influence of the hydrophobic effect. The authors cite this as the main driving force for complex formation; this interpretation is also supported by the observation of complex destruction upon addition of methanol (up to 20%).

3.2 Cage complexes: hemicarcerands

Hemicarcerands are cage-like structures assembled from two rigid bowl-shaped units, most often resorcin[3]- or resorcin[4] arenes, connected by 3–4 ''bridges''.[62] These bridges can range from rigid (hetero)aromatics to flexible alkyl chains. While these structures are assembled through covalent bonds, the flexible bridges create portals that allow small guests to move in and out of the cavity. The resulting hemicarceplexes are generally quite stable, and many solid-state structures have been solved.[63] The most recent addition to this collection of molecules is an octahedral ''nanocontainer'' composed of six resorcin[4]arene units connected with ethylene diamine bridges.[64] A remarkable dynamic covalent strategy was employed to achieve the synthesis of this macrostructure in one pot.

The first water-soluble hemicarcerand **38** appeared in 1997 as work toward an efficient drug delivery system (Fig. 14).[65] These structures have affinity for small aromatic compounds much like aspirin and acetaminophen. A justification for the cost of preparation of these ''delivery agents'' *versus* the potential payload remains dubious. Initial studies by Yoon and Cram show that this macrostructure binds small organic

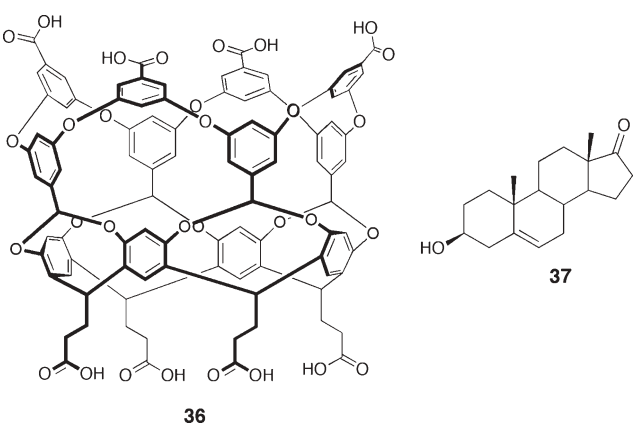


Fig. 13 Structure of cavitand monomer **36** which dimerizes *via* the hydrophobic effect and structure of the best guest, (+)-dehydroisoandrosterone **37**.

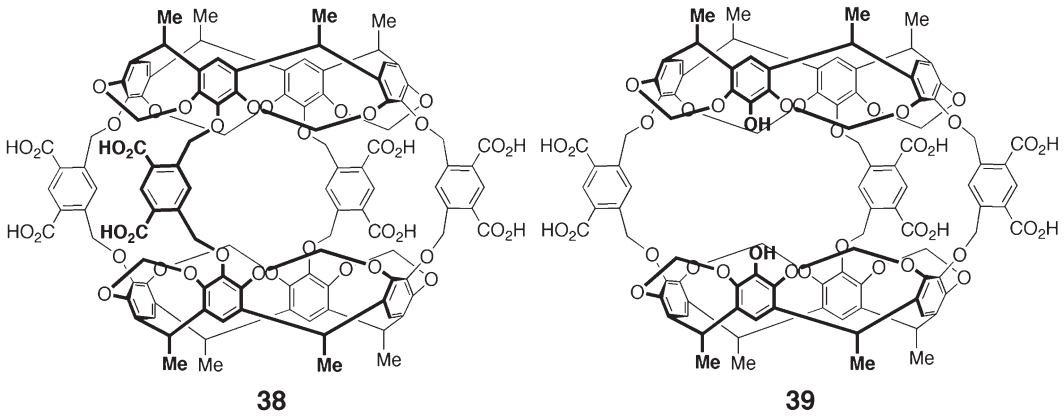


Fig. 14 Structure of hemicarcerands **38** and **39**.

molecules (DMSO, EtOAc), as well as substituted aromatics such as *p*-xylene and 1,4-dimethoxybenzene. Complexes were formed in a 1 : 1 fashion, with in–out guest exchange occurring slowly on the NMR time scale. Interestingly, tetraalkylammonium salts of suitable size were not bound by this hemicarcerand, even though they have been shown in previous systems to be complementary to the interior of a resorcin[4]arene cavity. Factors preventing this complexation could be the enthalpic desolvation costs incurred upon binding or simply size—the tetraalkylammonium salts may be too large to fit through the host's portals.

A closely related derivative, **39**, bearing only three bridging aromatic groups was synthesized and studied by DeShayes and co-workers (Fig. 14).[66] The large openings allow for in–out guest exchange to occur freely and the authors carried out an in-depth study of the complexation thermodynamics using ^{1}H NMR and isothermal titration calorimetry (ITC). These studies estimate that for hydrophobic aromatic guests such as naphthalene, ferrocene and *p*-xylene, association constants are greater than 10^8 M^{-1}. These complexes are stable in the solid state. Tri- and dimethoxy benzenes were all guests for the hemicarcerand, showing a strong influence of substitution pattern (guest shape) on binding affinity. Saturated cyclic structures containing hydrogen-bonding sites (*i.e.* camphor, norborneol) were relatively poor guests for the cavity ($K_a = 10^3$ and 10^4 M^{-1}), while compounds containing charge (hexamethylenetetramine, 1-naphthoic acid) showed no affinity for the cavity of host **39**. The binding properties of the deoxy-derivative were also examined and found to be identical to those of host **39**.

The authors examined the thermodynamic data highlighted in the preceding paragraph and found that complexation was driven by CH-π interactions between host and guest as well as the hydrophobic effect.[66] The macrocyclic effect also plays a large role in the thermodynamics of complex formation. This extensive host preorganization is the main source of the large association constants reported above. Any entropic penalties associated with organizing the host during complex formation have been paid for in covalent bonds using organic synthesis.

Analogous to the entirely covalent hemicarcerands described above, Harrison and co-workers have prepared a series of metal-bridged cage complexes able to bind small organic guests (Fig. 15).[67–69] This work has been discussed previously; for more details than the description that follows we refer the reader to an earlier review.[55] Functionalization of methylene-bridged resorcin[4]arene with four iminodiacetate

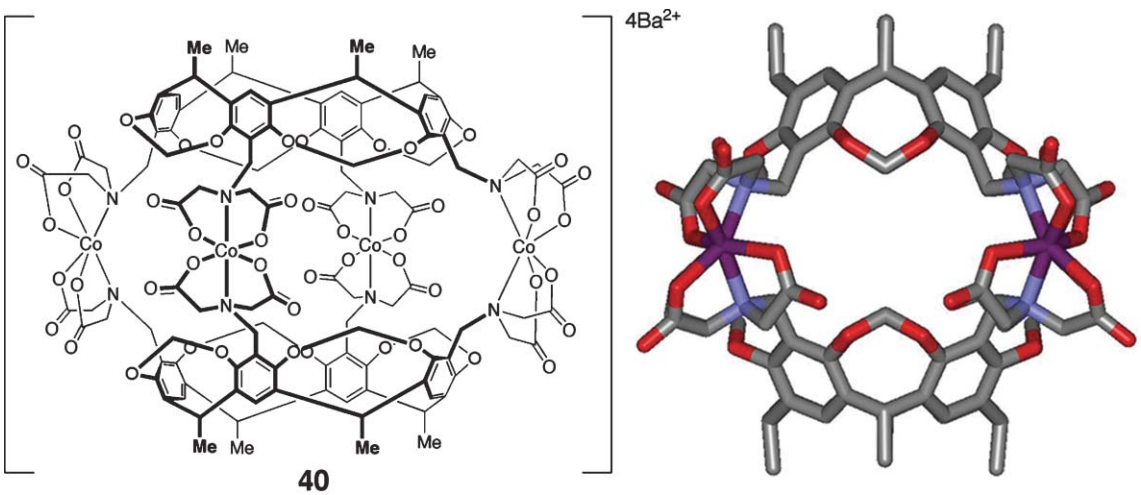


Fig. 15 Structure of metal-assembled dimeric resorcin[4]arene cage **40**.

ligands provides the scaffold for a dimeric molecular capsule, which is assembled in the presence of four metal ions [Co(II), Fe(II) or Cu(II)]. The openings are relatively small, and organic guests such as benzene and toluene cannot escape unless the capsule is disassembled.[68] A crystal structure was obtained of bromobenzene bound inside the Fe(II) coordinated cage and the authors found that this guest occupied two time-averaged positions in the cavity. Both show the bromine atom near the phenyl groups, not directed at the benzylic hydrogens. It is likely this position is the best steric fit for the cavity, as well as some complementary interactions between the bromine atoms and aromatic rings.

4. Summary and outlook

We have seen the effects of host structure on complex strength and stability through the examples described in this review. Hosts presenting multiple recognition features (ionic centers, hydrogen bonding sites) are capable of binding guests with relatively large association constants, however the in–out guest exchange rate is often fast on the NMR time scale. By rigidifying the host with intramolecular forces (hydrogen or covalent bonds) we observe a larger energetic barrier to guest exchange resulting in slower exchange rates.

These systems are not meant to act as direct mimics of protein active sites and binding clefts, but as tools to study the forces involved in the recognition of small, convex molecules by a larger, concave ones. There are, however, noteworthy similarities between the cavitands and some protein hydrophobic binding sites—both are pockets lined with aromatic surfaces and decorated with hydrogen bonding sites.[70,71] The capsules and cages are notional viral capsids; although there is much work to be done to create a molecular capsule made up of more than 2 subunits! At present, these structures show much promise as tools of physical organic chemistry.

Acknowledgements

We are grateful to the Skaggs Institute for Chemical Biology, the NIH and the ARCS Foundation (SMB) for funding. We also thank Dr Dariush Ajami for carrying out NICS calculations on host **4** and Janette Lundgren for assistance with manuscript preparation and helpful discussions. SMB is a Skaggs Predoctoral Fellow.

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