Functional cavitands: Chemical reactivity in structured environments

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Container-shaped molecules provide structured environments that impart geometric bounds on the motions and conformations of smaller molecular occupants. Moreover, they provide "solvation" that is constrained in time and space. When inwardly directed functional groups are present, they can interact chemically with the occupants. Additionally, the potential for reactivity and catalysis is greatly enhanced. Deep cavitands, derived from resorcinarenes, nearly surround smaller molecules and have been one of the most successful platforms for elaboration with functional groups. Derivatives bearing organic and metal-binding functional groups have been shown to affect recognition properties and selectively accelerate diverse reactions. In this review, we examine recent examples of these systems with an emphasis on how and why ordered nanoenvironments impart changes in the properties and reactivity of their occupants.

nanoenvironments | supramolecular

Molecular recognition became a popular theme in physical organic chemistry during the late 1980s, and many of those studies evaluated intermolecular forces as models for biochemical phenomena. Synthetic receptors of increasing sophistication such as clefts (1), armatures (2), tweezers (3), bowls (4), and other vehicles (5, 6) were devised for the study of reversible interactions, both in aqueous and nonaqueous media. The emergence of site-directed mutagenesis replaced much of this activity. The strength of a hydrogen bond inside, say, an enzyme can be determined *in situ* through substitution of an unnatural amino acid (7) with the appropriate functional groups. In addition, enzymes, aptamers, ribozymes, and catalytic antibodies can fold more or less completely around a target molecule. This creates a structured environment for the functional group interactions in question, a feature missing in the various concave structures invented by synthetic chemists. A receptor that completely and reversibly encapsulated sizable molecules was prepared in 1995 (8), but it lacked any appropriately positioned functionality. It took us another 5 years to synthesize a receptor that could, more or less, surround a target molecule *and* present it with a reactive functional group. This led to changes in reactivity of the sort encountered in the macromolecular complexes of biology. We do not intend here to promote these as model systems. Instead, this review is concerned with effects of physical restraints on a molecule surrounded by another; the physical organic chemistry of structured environments. More specifically, the structures are specially modified cavitands, macrocyclic compounds featuring a cavity that is sealed at one end and functionalized at the other. Cavitands have a long history in studies of molecular recognition, and several reviews are available that cover the literature up to 2002 (9–13). With rare exceptions, these cavitands offer only spaces to be filled by smaller molecules. Our departure was their functionalization with groups that are directed at the molecules held temporarily inside.

Synthesis

The condensation reaction of phenols with aldehydes has been known for more than a century and was once an important

source of polymers such as Bakelite. The reaction course can be controlled (14, 15), and good yields of cyclic tetramers **1** (resorcinarenes; Fig. 1) are obtained from resorcinol and various aldehydes. The resorcinarenes offer concave surfaces that alone are too shallow to surround other molecules. (Resorcinarenes do, however, self-assemble to form a hexameric capsule that completely surrounds suitable guests under appropriate conditions; see, for example, ref. 16 and references therein.) But when the phenolic oxygens are modified to deepen the concavity, the resorcinarenes are the source of a rich cavitand chemistry, and all of the compounds we describe here are derived from such structures.

We used the known octanitro compound **2** to create a deep cavitand **4** by re-enforcing a vase-like shape through hydrogen bonds along its upper rim. This was accomplished by reduction of the nitro groups to the octamine **3**, followed by modifications of the amino groups. For example, acylation with acid chlorides (17) gave the secondary amides that provided a cyclic, head-to-tail seam of intramolecular hydrogen bonds that help maintain the conformation of the deep cavitands **4**. The alkyl groups R on the acid chlorides or on the "feet" of the resorcinarene were chosen to control solubility in organic or aqueous media. Another functionalization reaction of the octamines leads to benzimidazoles **5**. They are obtained by condensations with ortho esters (18), imidates, (19), or aldehydes in the presence of oxidizing agents (20). These benzimidazoles can be stabilized in their vase shapes by small molecules such as water or methanol that offer both hydrogen bond donors and acceptors that are necessary to complete the cyclic seam of hydrogen bonds. Even the parent octamines **3** have recognition properties when solvents with strong hydrogen bond acceptors [DMSO and dimethylformamide (DMF)] are present to complete the hydrogen-bonding seam (21).

An alternative structural motif that also depends on intramolecular hydrogen bonding for stability is presented in structure **6** (Fig. 2). The synthesis involves the condensation of dichloroimides **7** with the resorcinarene, followed by deprotection. The imides of various amino alcohols, including those that are optically active, were used (22). The intramolecular hydrogen bonds provided by the alcohols temporarily hold the walls in place, and modeling suggests that the inward folding of the walls reduces the symmetry and that two C₄ symmetric cycloenantiomers exist. A recent innovation by Atwood produced a sealed cavitand **8** capable of encapsulating both components of an ion pair (Fig. 3) (23).

The selective functionalization of these deepened cavitands followed from the hexanitro **9** (Fig. 4), first encountered as a side-product of the octanitro preparation. Reduction and acylation gave the hexaamide **10** (24) that, despite its open side, showed a recognition chemistry of its own. The addition of the fourth wall and reduction to the diamine gave the common precursor to the monofunctionalized cavitands. These include

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Fig. 1. The synthesis of deep cavitands from a resorcinarene platform. 1, 1,2-difluoro-4,5-dinitrobenzene, Et₃N, DMF, Δ; 2, SnCl₂, HCl, EtOH, Δ; or H₂, Raney Ni, toluene; 3, acyl chloride, K₂CO₃, EtOAc, H₂O; or acyl chloride, Et₃N, toluene; 4, ortho ester, DMF/CH₂Cl₂; or imidate, EtOH; or aldehyde, C₆H₅NO₂. The model structure of 5 has been minimized by using the AMBER force field, whereas that of 4 is truncated from the crystal structure (51). The R groups have been removed or truncated for viewing clarity.

the self-complementary structure **11**, (25) the introverted acid **12** (26), the dipyrrole **13** (27), the porphyrin **14** (28, 29), the biscavitand **15** (30), the phenanthroline **16** (20), salen **17** (31), and the pyridone **18** (Fig. 5) (32).

The Inner Space

The interior of the cavitand is lined with sp²-hybridized atoms with π bonds coating the surface and may be thought of as an envelope featuring a thin layer of negative charge. Little space exists for guests at the tapered end of the cavity made up by the resorcinarene aromatics; instead, the larger cavity consists of four benzene molecules (“solvents”) that are fixed in a box-like shape. *The solvent is structured.* Higher on the rim of the vase-like shape the cyclic seam of eight secondary amides provides, in addition to the π surfaces, both hydrogen bond donors and acceptors. This nanoenvironment is a polar one and, at any given time, it is chiral. The shape of the cavity is not sterically asymmetric, but its electronic or magnetic environment is sterically asymmetric. The clockwise or counterclockwise array of amides involves two chemical environments for the hydrogen bond donors, one centered above each wall and the other

Fig. 3. Atwood's anion-capped cavitand **8** shown as a line drawing, and a rendition of the crystal structure of the encapsulated ion pair.

between two walls (see the crystal structure in Fig. 1). These hydrogens showed different ¹H NMR signals at room temperature that coalesced upon heating. The activation energy for the process was 17 kcal/mol and represents the barrier to interconversion of the clockwise and counterclockwise (enantiomeric) arrangements of the secondary amides. Accordingly, the octa-amide cavitands racemize at room temperature and show lifetimes on the order of 1 sec. These amide “solvents” are structured inasmuch as they cannot dissociate from the cavitand but can rotate and present either end of their amide dipoles to whatever is inside the cavity. The benzimidazoles (e.g., of **5**) also undergo a related racemization, but the interconversion requires proton transfers. For the introverted acid **12**, the array of the six amides is fixed, because the acyl group on the benzimidazole is the best hydrogen bond acceptor and establishes the directional arrangement of the rim. The x-ray structure shows this structure to be racemic (P. Ballester and J.R., unpublished work), and it features additional interactions of the Kemp triacid carboxyl with the neighboring amides. This introverted acid cavitand has been resolved on a chiral HPLC column.

Although the imides **6** can also racemize by rearrangement of the cyclic seam of 4 alcohols, those derived from optically active amino alcohols show a single cycloenantiomeric structure on the NMR time scale. This structure results in a cavity with a chiral lining that, as we shall soon relate, has consequences for guests held inside. The NMR reports the interior magnetic environ-

Fig. 2. Chiral cavitand **6** and its complex with norbornene. The ¹H NMR spectrum shows that norbornene is desymmetrized in this chiral environment. For example, normally equivalent hydrogens 1 and 4 appear as separate resonances.

Fig. 4. Structures of the octanitro and octaamide cavitands **9** and **10**.

ment: Hydrogens near the tapered ends show the shielding effects of the eight aromatics that surround them and feature large up-field shifts, up to $\Delta\delta$ of 5 ppm. For typical aliphatic protons this shift places their resonances far up-field of tetramethylsilane (TMS), at -2 to -3 ppm, where they are easily identified and integrated. The anisotropic shielding diminishes gradually and disappears above the rim of the cavitand (see the NMR of SDS in Fig. 6).

Guests

Affinities. The guests were selected to complement the host cavity's size, shape, and chemical surfaces, and as we have reported in reviews (12) adamantanes fill the space well. Their C–H bonds can touch the π lining of the cavity, and this CH– π attraction is among the weakest of intermolecular forces (33). Accordingly, it was surprising that guests would contort them-

selves, assume otherwise unfavored shapes, to properly fill the cavitand's space (as in the case of SDS). Initially, we amplified the attraction using guests that had increased positive charge on their surface hydrogens—guests that had a thin layer of positive charge on their surfaces, alkyl ammonium ions. This approach “promoted” the intermolecular force to cation– π interactions, a significant force in biological systems (34, 35). A trimethylammonium knob proved an ideal fit in size and shape for the interior of the cavitand, and the association constants were 10^3 to 10^4 M^{-1} (4–5 kcal/mol) in organic media. A water-soluble version **19** that bound choline and its derivatives (19, 36) was synthesized by placing carboxyl groups that bore negative charges at neutral pH along the rim. Choline and acetylcholine were bound with high affinities (Table 1); other larger alkyl ammonium groups showed much weaker binding. In contrast to the behavior of cavitands soluble in organic solvents, tetraethylammonium was bound more strongly than tetramethylammonium. This hydrophobic effect is not a change in the host's intrinsic preferences but illustrates the importance of the solvent as an environment that competes for interactions with the guest. The cavitand's carboxylates enhanced the selectivity: Carnitine showed $\approx 1/100$ the affinity for this cavity, a reflection of the charge–charge repulsion that takes place between the carboxylates of the host and guest.

Another surprise came with phosphatidylcholine as the guest. This molecule resembles carnitine in that the distance between the positive charge (trimethylammonium knob) and the phosphate anion was nearly the same as that to the carboxylate of carnitine. So, although we expected weakened

Fig. 5. Functionalized cavitands. Parts of structures **12**, **17**, and **18** have been removed to show the positioning of the functional groups.

Fig. 6. SDS complexed by water-soluble tetracarboxylic acid cavitaand **19**. The hydrocarbon tail of SDS coils to fill the space defined by the cavity, with hydrogen atoms deepest in the cavity shifted farthest up-field in the NMR spectrum.

binding, we did not at all expect that the dodecyl group would insert into the cavitaand (37). From the up-field shifts in the NMR spectra, no less than eight carbons were accommodated in this cavitaand in its deshielding region, and this can occur only if the alkyl group assumes a coiled, *helical* shape. This shape appropriately fills the space and allows the CH- π contacts even though each gauche interaction costs some 0.5 kcal/mol in solution. This behavior is similar to that observed when SDS is the guest (Fig. 6). Lacking an ammonium knob, SDS has no choice but to occupy the cavity through the coiling of its alkyl chain, resulting in the resolution of the terminal methyl group and all 11 methylenes in the ^1H spectrum. Hydrocarbons have long been known to occupy the cylindrical cavities of solid-state urea clathrates (38). In these crystals, urea molecules are arranged in a double-helix that defines parallel channels 5.5 Å wide spanning the length of the crystal. Simple alkanes are present in a disordered state in the channels, which must be occupied by a guest to be stable. In striking contrast to these structures, it is the hydrocarbon guests of cavitaand **19** that adopt a helical conformation to complement the greater diameter of 6.5 Å of the cylindrical cavity of this host.

Host **6** (Fig. 2), a structural analog to **19**, was prepared by using optically active amino alcohols. We were able to show by CD spectroscopy that exciton coupling exists between the asymmetric centers and the walls of the cavitaand. This coupling is lost in solvents that compete for the hydrogen bonds; the host does not fold around the guest. It appears that the asymmetric centers on the periphery of the cavitaand impart some asymmetry to the folded cavity itself. The binding of norbornene, for example, shows that the asymmetry affects the NMR spectrum: Each of the guest hydrogens is seen shifted up-field, and the plane of symmetry is lost. With a racemic cyclohexane diol, a 33% diastereomeric excess of the complex was observed and this is

Table 1. Association constants of several quaternary ammonium salts and water-soluble cavitaand **19**

Guest	K, M^{-1}
Me_4NBr	$3,800 \pm 600$
Et_4NBr	$12,000 \pm 900$
EtMe_3NBr	$>10^4$
Choline chloride	$26,000 \pm 700$
Acetylcholine chloride	$15,000 \pm 1,200$
L-carnitine	150 ± 10

See ref. 36.

raised to 60% with larger asymmetric groups appended to the cavitaand.

We were also surprised to find that the octamines **3** had a complexation chemistry of their own (21). Ordinarily, benzene rings with many electron-releasing substituents are unstable toward air oxidation, so we had used these molecules as rapidly as we had made them. Yet these cavitaands were reasonably stable in solution; there was no selectivity seen by **3** for choline versus carnitine but the branched acetylcarnitine was a very poor guest. The size at the ammonium nitrogen also matters; tetramethylammonium shows a 100-fold higher affinity than the larger tetraethylammonium.

Monofunctionalization of the upper rim of the self-folding cavitaand **4** with a porphyrin gave us a host **14** with two binding sites (28, 29). The cavitaand portion of the molecule retains its affinity for adamantyl groups, and the metalloporphyrin acts as an excellent coordination site for a pyridyl group linked to the adamantane. The length of an appropriate linker allows these modes of molecular recognition to operate in concert, affording binding affinities of up to 10 kcal/mol in toluene. The related salen cavitaand **17** is able to form host-guest complexes with *para*-nitrophenylcholine carbonate by inclusion of the quaternary ammonium deep in the cavitaand and coordination of the carbonyl group to a zinc atom bound by the salen (31). The mode of guest binding is the same as the porphyrin cavitaand, but the spatial separation between binding sites differs. Phenanthroline cavitaand **16**, when metallated with zinc, further reduces this separation; it forms tight complexes with quinuclidine and DABCO (20).

Dynamics. When molecules are held together by the electronic and shape complementarities of their surfaces, the lengths of the encounters often reflect the strengths of the forces that attract them to each other. The binding behavior of these stabilized cavitaands revealed surprises with guests like adamantane derivatives. The association constants are small; at 50 M^{-1} only 2 kcal/mol are involved, yet separate signals for free and bound adamantanes are observed in the ^1H NMR spectrum, implying a barrier to guest exchange of more than 13 kcal/mol.[†] The peculiarity was resolved by a study of the exchange rates of guests. These were determined by EXSY experiments and showed that the activation barrier for exchange was large, some 17 kcal/mol. The identical energetics of racemization of the cavitaand and guest exchange is no coincidence but reveal that the two processes are connected. The seam of hydrogen bonds must be broken for exchange to occur; an unfolding process occurs that allows one guest to displace another. Details are available in a recent review (39), and a video presentation of the exchange

[†]Whether a particular hydrogen that is in exchange with two or more environments is seen as separate signals in the ^1H NMR spectrum depends on the exchange rate (at a given temperature), the chemical shift difference $\Delta\delta$, and the frequency of the spectrometer. If the barrier to exchange is <10 kcal/mol, the signals are usually coalesced. A barrier of >15 kcal/mol typically results in separate signals.

process with a narrative can be found at www.scripps.edu/skaggs/rebek. Slow exchange on the NMR time scale is of great practical advantage, but much more revealing was the unprecedented, weak binding with *high activation barriers*. The slow dissociation rate did not match the low affinity; the encounter of the guest with host was much longer than expected.

Folding and unfolding allows for the orderly exchange of guests and is a general requirement of cavitand complexation (40). The alternatives are difficult to imagine: A cavity sealed at one end does not allow the entrance of one guest before the other has departed; removing the guest leaves an energetically expensive vacuum (unsolvated surfaces) as has been encountered in the mechanism of guest exchange for carcerands and capsules (41).

Reactivity

Merging recognition with catalysis is a time-honored goal in modern physical organic chemistry, but transition states are moving targets. Supramolecular chemists have been able to position catalytically active functional groups on synthetic host molecules in a manner predicted to be complementary to those transition states, leading to large increases in reaction rates. Open-ended macrocycles, such as modified cyclodextrins (42–45), are favorite scaffolds, and purely synthetic macrocycles (the open-sided calix[6]arenes) offer much promise in this regard (46, 47). Our earlier cleft-like structures offered placement of functional groups but lacked independent binding sites (48). The key to combining the appropriate surroundings for catalysis could be molecules that can fold around the targets in a way that results in their isolation from solvent with the proper orientations of catalytically useful acids and bases. Moreover, the role of solvent positioning is important. The motions along a reaction coordinate, although on a very short time scale, are intimately tied to the motions of the surrounding molecules that these reactants contact. The solvent molecules surrounding a reaction-in-progress must respond to changes in shape, volume, polarity, and charge distribution of those reacting molecules; doing this requires energy. The implication of controlled solvation for the selective acceleration of reactions deserved exploration; this paradigm of catalysis emerged in parallel with the technology to functionalize these deep cavitands. The effects of this structured environment, in which a box of four benzenes surround most of the guest and up to eight secondary amides are on the periphery, were seen in the following examples.

The introverted acid cavitand **12** is reactive toward reagents small enough to fit the severely congested environment near the carboxylic acid group. Diazomethane meets this criterion and gave us the introverted methyl ester **20**. We first synthesized this molecule as a control for studies of the tumbling dynamics of DABCO in the introverted acid but unexpectedly found that this methyl ester was a highly active alkylating agent for suitable tertiary amines (49). Quinuclidine and DABCO were quaternized in <3 min at room temperature, a result of the nearly ideal organization of these amines in the cavitand. As Fig. 7 shows, the bound quinuclidine has its nitrogen oriented in an alignment predisposed for attack on the methyl carbon. The cavitand's surfaces can be viewed as preorganized solvent; once the quinuclidine is bound, many fewer motions are possible that are not along the reaction coordinate. Furthermore, the cavitand's upper-rim amide groups are polar and effectively solvate the charge build-up in the transition state, while the nonpolar recesses of the cavitand remain an excellent "solvent" for the hydrocarbon part of the nucleophile. Even bound triethylamine, which has much more freedom of motion than quinuclidine, is quaternized more than 2×10^5 times faster than in a comparable reaction in free solution. In a related investigation employing an oligomeric DMAP analogue, methylation rates with iodo-

Fig. 7. Quinuclidine bound by the introverted methyl ester cavitand **20**. One cavity wall has been removed, and ethyl groups are shown as methyl groups for clarity. Model structure of the pyridone cavitand **18** in complex with the tetrahedral intermediate that is the result of the attack of propylamine on PNPCC.

ane were increased >400-fold under conditions that promoted helical coiling of the oligomer (40). The inner space of the helix bound iodomethane.

We used the cavitand's affinity for alkylammonium ions to position reactive groups near catalytic sites on the cavitand's rim. The hydrolysis of *p*-nitrophenyl choline carbonate (PNPCC) was studied in the salen cavitand **17**, metallated with zinc(II) (Fig. 8) (31). The π -electron-rich cavity served to anchor the PNPCC by interacting with the quaternary ammonium group, while coordination of the carbonate group to the zinc provides further binding energy and activates the group toward nucleophilic attack. The net result is a modest 50-fold acceleration with a stoichiometric amount of catalyst, in which the reaction is first order. The efficacy of anchoring the substrate by its quaternary ammonium knob is demonstrated by comparing the catalytic efficiency of **Zn-17** with the corresponding zinc salen not attached to a cavitand. The former is 5-fold more efficient.

An organocatalytic approach to a related system makes use of pyridone-cavitand **18** (32). The reaction of interest is the aminolysis of PNPCC. In contrast to PNPCC hydrolysis in which the rate-limiting step is the attack of the nucleophile, attack by an amine is rapid in aprotic organic solvents. The collapse of the resulting tetrahedral intermediate is the slow step. Pyridone is a known catalyst for this step (50), and we appended it to a deep cavitand to yield a catalytic host for this substrate (Fig. 7). A modest rate enhancement was observed for the aminolysis reaction. Under the conditions of this reaction, only a small percentage of substrate was

Fig. 8. Model structure of the zinc-salen cavitand with bound PNPCC and experimental kinetics curves for the hydrolysis reaction with increasing mol % catalyst loading. The water was present as a 0.01% impurity in commercial CH_2Cl_2 .

bound to **18**. From this weak affinity, a rate acceleration of $\approx 6,000$ can be calculated in comparing the reaction catalyzed by **18** with the background rate. As expected by virtue of the geometric constraints of the catalyst, larger amines such as tritylamine failed to show an increased rate of aminolysis.

We propose that the solvent in these cases is the well positioned (or as well as we could position it and certainly better than others have) wall of the cavitand. By merely breaking one or two neighboring hydrogen bonds, the secondary amide can be po-

sitioned to solvate a reaction's transition state and the amides cannot drift away as they might in bulk solution. The cavitand's walls are a solvent cage, but one that persists. In this sense, the solvent is preorganized, fixed in time and space, to enhance reactivity in its structured environment.

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