Recent Advances in the Applications of Water-soluble Resorcinarene-based Deep Cavitands

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We review here the use of container molecules known as cavitands for performing organic reactions in water. Central to these endeavors are binding forces found in water, and among the strongest of these is the hydrophobic effect. We describe how the hydrophobic effect can be used to drive organic molecule guests into the confined space of cavitand hosts. Other forces participating in guest binding include cation–π interactions, chalcogen bonding and even hydrogen bonding to water involved in the host structure. The reactions of guests take advantage of their contortions in the limited space of the cavitands which enhance macrocyclic and site-selective processes. The cavitands are applied to the removal of organic pollutants from water and to the separation of isomeric guests. Progress is described on maneuvering the containers from stoichiometric participation to roles as catalysts.

1. Introduction

Heightened awareness of the environmental problems presented by the continued consumption of fossil fuels has stimulated the search for alternatives.[1] In organic chemistry, much of the use is in solvents and nothing is more attractive and more obvious than replacing organic reaction media with water.[2] But problems with accessible acids and bases, diminished polar binding forces and general insolubility of many organic compounds in water make direct substitution of solvent with water unworkable. Moreover, many catalysts “drown” in water, one reason why enzymes hide their catalytic sites in “dry” environments in Nature.[3] Synthetic container molecules such as capsules provide a haven for small guests by providing a physical barrier between the cavities inside and the solvent outside.[4] The containers come with built-in hydrophobic interiors, as a result of the aromatic panels used for their construction. While convenient for synthetic purposes, aromatics provide little in the way of functional groups that can bear directly on the guest inside.[5] This is an unintended consequence of the encapsulation process. Cavitands, by way of their open ends, provide access of reagents in solution to exposed parts of their guests,[6] and water-soluble cavitands direct which parts of their guests are exposed.[7] Earlier, we described how this works for macrocycle synthesis chaperoned by cavitands,[8] here we develop these notions to subtle applications in guest recognition and reaction selectivity.

2. Binding Selectivity in Water-soluble Cavitands

2.1. Orientations of α, ω-Difunctional Alkanes

Water-soluble synthetic deep cavitands, tetra-urea cavitand H1[9] and its exhaustively methylated version, cavitand H2, unable to dimerize into a capsule (Figure 1),[10] have been extensively studied in molecular recognition and as confined spaces for reactions.[11] These two deep cavitands possess a highly preorganized, nonpolar hydrophobic interior, as a result of the aromatic panels used for their construction. While convenient for synthetic purposes, aromatics provide little in the way of functional groups that can bear directly on the guest inside.[12] This is an unintended consequence of the encapsulation process. Cavitands, by way of their open ends, provide access of reagents in solution to exposed parts of their guests,[13] and water-soluble cavitands direct which parts of their guests are exposed.[14] Earlier, we described how this works for macrocycle synthesis chaperoned by cavitands,[15] here we develop these notions to subtle applications in guest recognition and reaction selectivity.

Figure 1. Chemical structures of cavitands H1 and H2, and the cartoon used for cavitand H2.
Formamides exist as a mixture of both cis and trans isomers and cannot be separated under ordinary conditions owing to their rapid interconversion on the human timescale. Recently, we determined the relative hydrophilic differences between isomeric formamides by binding in the synthetic cavitand H2 through direct competition experiments. Long-chain mono- and bis-formamides were sequestered in the deep cavitand, driven by hydrophobic forces. The complexes show two sets of NMR signals in the upfield regions corresponding to the trans- and cis-isomers (Figure 2). However, the caviplexes of diformamides showed starkly different signal patterns to that of the monoformamides. The major trans,trans-bis-formamide isomers presented simplified spectra indicating a time-averaged symmetrical arrangement in the cavity, and the minor trans,cis-bis-formamide isomers presented a superimposed set of signals featuring an unsymmetrical arrangement, in which one end spends more time inside the cavitand than the other (Figure 2B). The biased arrangement of the unsymmetrical trans,cis guest arises from the differences in relative hydrophilicity and hydrophobicity of the two ends. According to the NMR spectroscopic assignments of both mono- and bis-formamides, the terminal trans-formamides spend more time outside the cavitand than the cis-isomers, revealing that cis-formamides are more hydrophobic than the corresponding trans-counterparts.

The cation–π interaction and the hydrophobic effect are important intermolecular forces for complex formation in water and play major roles in controlling recognition properties in biological systems. One question that arises in given situations concerns which driving force is stronger; the cation–π or the hydrophobic effect. The cation–π interaction is attractive in the gas phase and nonpolar organic solvents, nevertheless, the situation in water is more complicated. Molecular recognition in water involves competition with solvent interactions and the particularly significant desolvation. Many biomolecular complexation experiments suggest that, in water, the complex involving the ammonium-aromatic interaction is more stable than that featuring the t-butyl-aromatic interaction; however, most often the charged residues of biomolecules can compromise the experimental results. Synthetic host systems inspired by natural receptors provide an opportunity to elucidate the fundamental properties of noncovalent interactions in a stripped-down context that

Figure 2. A: Partial 1H NMR spectrum for a monoformamide and cartoons of its behavior in cavitand H2. B: Partial 1H NMR spectrum for a diformamide and cartoons of its behavior in cavitand H2.

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removes the complexity associated with the functional group diversity and conformational dynamics existing in biomolecules.

Very recently, we synthesized eight different deep cavitand hosts with the same binding pocket but differing in the polarity of the functional groups that line the entrance to the binding site and bearing different charges on the peripheral watersolubilizing groups (Figure 3). Direct intramolecular competition experiments using dumbbell guests – having a trimethylammonium group at one end and a tert-butyl group at the other – were devised to measure the relative contributions of cation–π interactions and hydrophobic effects to the complexation (Figure 4).[19] Unexpectedly, the container molecules consistently preferred binding to the uncharged tert-butyl group of the dumbbell guest with the longest linker G1. This occurred regardless of the charge on the host or the polarity of the functional groups that line the entrance to the binding pocket. This overwhelming preference is determined by the solvation of the polar trimethylammonium group in water, which outcompetes the attraction between the positive charge and the π-surfaces in the container. The cavitand complexes provide a direct measure of the relative strengths of cation–π interactions and desolvation in water, in which interactions with the uncharged tert-butyl group are more than 12 kJ mol\(^{-1}\) more favorable than the cation–π interactions with the trimethylammonium group.

Shorter dumbbell guests G2 and G3 showed more complicated behavior. The \(^1\)H NMR spectra of their complexes with cavitands H1, H4, and H5 indicate that the tert-butyl end of the guest is preferentially bound in the cavitand pocket, and the trimethylammonium group is exposed to water, resembling those shown for G1. In contrast, the complexation with cavitand H3, there are two sets of signals corresponding to the tert-butyl end bound and the trimethylammonium end bound: both of the isomeric complexes are present. Molecular modeling was used to provide some insight into the difference in binding behavior observed for these complexes. It revealed that when the length of the linker is shorter, the attractive interactions between polar trimethylammonium group and the rim of cavitands H1 increases the stability of this isomer. The hydrophobic interactions between the nonpolar tert-butyl group and the rim of the cavitands H3 favor the cation–π isomer (Figure 4). These additional interactions between the cavitand and the head groups perturb the equilibrium between the two isomeric complexes.

2.2. Binding Selectivity with Aromatics and Others

The energy-efficient separation of alkylaromatic compounds is a major industrial sustainability challenge, and separations of p-xylene from its o- and m-isomers was classified as one of the “seven chemical separations to change the world”.[20] During the past decade, many energy-efficient adsorption materials have been developed to meet the separation challenge, including zeolites,[21] carbon molecular sieves,[22] metal-organic frameworks (MOFs),[23] and solid-state pillar[n]arenes.[24] Nevertheless, approaches based on molecular recognition are scarce, and there seems to be no example of liquid–liquid phase separation for p-xylene and related positional isomers. Recently, we
reported a water-soluble cavitand H6\(^{[25]}\) and its palladium(II) derivative H6–2Pd (Figure 5).\(^{[26]}\) The coordination rigidifies the cavity and stabilizes the receptive vase shape,\(^{[27,28]}\) which imparts a welcome selectivity in guest binding. We applied the restricted volume of metallo-cavitand H6–2Pd and its dynamics to separate p-functionalized toluenes from their isomers in liquid–liquid extraction processes (Figure 5).\(^{[29]}\) All the functionalized toluene p-isomers showed the methyl group was bound deep in the cavity with a 1:1 stoichiometry of the host and guest. Competitive binding experiments indicate that the selectivity was exclusive and the p-isomer can be separated efficiently from a mixture using cavitand H6–2Pd.

Based on the binding selectivity, liquid–liquid extraction experiments\(^{[30]}\) were carried out for the separation of a typical mixture of xylene isomers obtained from crude oil distillation (1:3:1 for o:m:p-isomers) (Figure 6), and also p-nitrotoluene from its isomers. The binding and liquid–liquid extraction of the xylene mixture was quantified and the recyclability of this metal cavitand system was also confirmed.

Alkanes are also important industrial feedstocks obtained from fossil fuels and traditionally separated by energy-intensive fractional distillation. Very recently, we showed that metallo-cavitand H6–2Pd can also be applied to the selective sensing and separation of straight and branched chain alkanes in energy-efficient processes, which involves gas–liquid adsorption and liquid–liquid extraction.\(^{[13]}\) Competitive binding experiments and NMR spectroscopy showed the overwhelming preference of this synthetic water-soluble cavitand host for the hydrophobic guests that possess narrow or flat shapes (Figure 7).\(^{[31]}\) For additional separation applications, interphase adsorption and liquid–liquid phase extraction were performed, and the alkane mixtures were efficiently separated. In addition, cavitand H6–2Pd can also be used as a recyclable synthetic cavitand host for selective separation of n-alkanes from isooctane in an energy-efficient manner.

Many structural variants of cavitands have been reported that are based on the resorcinarene platform, with additional functional groups on the upper rim for further possibilities in selective guest recognition.\(^{[23]}\) We recently expanded the applications of metal complexation by using 2-aminobenzimidazoles for the walls of the cavitand (Figure 8A).\(^{[32]}\) The reorganized shape of the space in metallo-cavitand H7–2Pd showed a good shape and size selectivity for o-difluorobenzene over its isomers. Competitive experiments concerning the binding of difluorobenzene isomers to cavitand H7–2Pd used \(^{19}\)F NMR spectroscopy and revealed their stabilities decreased in the following order: o-difluorobenzene > p-difluorobenzene > m-difluorobenzene (Figures 8B, 8C). Furthermore, based on the recognition selectivity, o-difluorobenzene was also effectively separated from its regioisomers in liquid–liquid extraction process. The aqueous solution of cavitand H7–2Pd was reused to perform another extraction cycle.

It has been generally accepted that cavitands with more rigidified walls in their receptive vase shapes often show slower dynamics of guest exchange and a better selectivity in guest binding. Such is the case with Gibb’s deep cavitand having...
covalent and rigid walls that pre-organize its shape. To control the shape and size of the container’s cavity and suppress the kite conformers, a new water-soluble dynamic cavitand $H_8$ with covalently bridged benzimidazolones at the upper rim was prepared (Figure 9).

In contrast to dynamic cavitands $H_1$ and $H_2$, the flexible spacers of cavitand $H_8$ cannot fold to the unreceptive kite shape. The motions of the walls are somewhat reduced, resulting in altered recognition properties. In $D_2O$, cavitand $H_8$ can form stoichiometric complexes with any $o$- and $m$-xylene isomers, and competitive binding experiments showed the stability order was $o$-xylene $> m$-xylene. Surprisingly, the $p$-xylene isomer showed no binding (Figure 9), which is in contrast to the narrower metallo-cavitand $H_6 2Pd$ that shows high selectivity for this isomer. Based on the unexpected selectivity for the $o$-xylene isomer, cavitand $H_8$ was applied to the separation of a typical mixture of xylene isomers obtained from crude oil distillation with a liquid-liquid extraction process.

In recent years, a greater awareness concerning the hazardous nature of halogen-containing organic compounds and their roles in several human and animal diseases has grown. Meanwhile, interest in reducing toxic chemicals released into aqueous environments by sequestration is also growing. We used octamethyl-urea cavitand $H_2$ as a sensor for monitoring cycloalkyl halides and 2-methylisoborneol, a common drinking water pollutant. Cycloalkyl halides with different halogen atoms (chloro, bromo or iodo) can qualitatively form the corresponding host–guest complexes with cavitand $H_2$, which significantly reduces their characteristic smells. The presence of halogen atoms leads to preferred orientations in the cavity and completely different $^1H$ NMR spectra of the host–guest complexes (Figure 10).

Moreover, the rotation of the cyclohexyl halides is also slowed due to the steric hindrance of the halogen atoms. 2-Methylisoborneol was also captured quantitatively by cavitand $H_2$ at concentrations lower than 1 mM, a behavior that suggests the potential of cavitand $H_2$ in water purification.

Selective recognition of hydrophilic molecules in water is also a challenge for synthetic molecular receptors, and few supramolecular structures are up to this task. However, hydrophilic biomolecules, such as sugars, can be recognized by natural receptors, even with high selectivity, through cooperative action of hydrophobic effects and other non-covalent interactions, such as hydrogen bonds. There are few, if any, synthetic supramolecular systems that mimic this interaction, and very recently, we undertook the task to incorporate water-mediated hydrogen bonds for molecular recognition in host–guest chemistry. New 2-pyridylbenzimidazole-functionalized water-soluble cavitands $H_9$ possessing more extended aromatic...
walls and deeper hydrophobic spaces were synthesized (Figure 11A). The high affinity, water-mediated hydrogen bonds enhance the molecular recognition of neutral hydrophilic molecules, such as 1,3-dioxane, THP, oxepane, THF and 1,4-dioxane. All of these host–guest complexes generally show slow rates of in/out guest exchange on the NMR time scale. In addition, the signals in the upfield region suggest that the oxygen atoms of bound heterocycles prefer positions away from the walls and near the polar parts of the cavitand. Isothermal titration calorimetry (ITC) experiments showed high association constants ($K_a$) – up to $6.32 \times 10^4 \text{M}^{-1}$ for the complexation of THF and $1.09 \times 10^4 \text{M}^{-1}$ for 1,4-dioxane. All of these host–guest complexes generally show slow rates of in/out guest exchange on the NMR time scale.

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Similar work on the selective recognition of hydrophilic cyclic compounds, such as cyclohexyl alcohols, amines and acids in water by a new cavitand H10, has also been reported (Figure 12). The cavitand bears octa-amides on the upper rim and trimethylammonium groups on the feet. Interestingly, competitive binding experiments indicate that cavitand H10 shows higher binding affinity to hydrophilic cyclic molecules, compared to their hydrophobic counterparts of similar sizes and shapes (Figure 12). To some extent, this contradicts the usual experience that the hydrophobic effect is the main driving force attracting the guest into the cavity. The explanations for the selectivity can be attributed to the synergistic action of hydrogen bonding and the hydrophobic effect. Cavitand H10 has both a hydrogen bonding region on the upper rim and a hydrophobic region composed of four aromatic walls and the resorcinarene core. When molecules with both nonpolar parts and polar functions are encountered, cavitand H10 provides a hydrophobic environment to accommodate the hydrophobic surface of the guests, and the amides on the upper rim supply hydrogen bond donors and acceptors to complement the guests’ polar functional groups.

3. Reactivity in Water-soluble Deep Cavitands

In bulk solution, identical functional groups at the end of long chain substrates tend to behave independently: reactivity at one site is not affected by the remote site, showing essentially statistical reactivity and resulting in low selectivity. Therefore, the monofunctionalization of identical functional groups far away from each other is a true challenge and many efforts have...
been made to obtain selective processes for symmetric substrates. Encapsulation of a suitable guest in confined spaces forces orientations inaccessible in solution and can lead to unexpected reaction selectivity for the guest.\textsuperscript{44} Water-soluble synthetic host molecules offer a range of environments to their guests: polar functions of guests are exposed to the medium, while hydrophobic groups are generally buried deep in the containers and hidden from reagents in solution. We have reported the use of water-soluble cavitand H2 as reaction vessels and blocking groups.

Mono-functionalizations, such as the hydrolysis of long-chain diesters,\textsuperscript{45} synthesis of macrocyclic ureas,\textsuperscript{46} the Staudinger reactions of diazides,\textsuperscript{47} and the monohydrolysis of long chain α,ω-dibromides have been reported earlier.\textsuperscript{48} Recently, we again performed the mono epoxidation of α,ω-dienes in the presence cavitand H2, and excellent selectivity was obtained (Figure 13).\textsuperscript{49} Reaction of one end of a diene with NBS in water gives a bromohydrin intermediate that binds in the cavitand with the hydroxyl exposed and the remaining alkene buried assuming a J-shape orientation in the cavity. Treatment with base converts the bromohydrin to an epoxide, completing the mono-epoxidation process. With linear aliphatic dienes, the yield reached up to 84%, and for 1,4-diisopropenyl benzene, a nearly quantitative yield of the monoepoxide was obtained. The application should be general for converting long-chain, symmetrical hydrophobic guests to unsymmetrical, amphiphilic ones.

Free radicals are highly reactive species with fast kinetics and low discrimination. For such species, the selectivity of product distribution is usually a challenge, and only a few selective radical processes have been reported in supramolecular hosts.

The Ramamurthy group investigated radicals generated in capsular hosts\textsuperscript{44, 50–52} and showed that confinement plays an important role on product selectivity.\textsuperscript{52} Our recent studies revealed the effects of guest affinity on radical processes in dynamic cavitand H2 and metallo-cavitand H6–2Pd.\textsuperscript{53} Here, in order to give further information of the effects of confinement on fast radical reactions (k \textasciitilde 10^3 m^3 s^{-1}), the reduction of alkyl dihalide guests with trialkylsilanes (R3SiH) was performed in a water-soluble metallo-cavitand H6–2Pd (Figure 14).\textsuperscript{54} Excellent conversion (> 94%) and high selectivity (> 95%) for the mono-reduced products were obtained for both primary and secondary dihalides, even when 2 or 3 equivalents of the reducing agents were used. In bulk solution, only low selectivity could be observed. These results highlight the role of confinement for product selectivity in radical processes.

End-to-end intramolecular cyclization of long-chain linear precursors is generally hard to achieve and often unpredictable because of unfavorable entropic problems and competitive intermolecular reactions. Beyond the mono-functionalizations described above, template effects are also featured in complexes where intramolecular reactions can occur through control of guest conformation.\textsuperscript{55–57} Several reactions including macrolactonization chaperoned by the cavitand H2 have been reported,\textsuperscript{58–60} including a recent application in the intramolecular aldol/dehydration reaction of long-chain, linear dialdehydes in aqueous solution (Figure 15).\textsuperscript{61} Symmetric long chain α,ω-dialdehydes are bound in host cavitand H2 by hydrophobic forces. The NMR spectra show folded, J-shape conformations with “yo-yo motions” that favor macrocyclization reactions over intermolecular reactions observed in bulk solution. Linear dialdehydes, including heteroatomic dialdehydes, reacted smoothly, and 11- to 17-membered macrocyclic products were isolated in good yields (30–85%) and good selectivity. Unlike conventional templates with convex structures that become guests inside their assembled hosts, cavitands with concave surfaces reverse the roles and resemble the situation in biological catalysis – the templates are hosts for guests undergoing the assisted reaction processes.

**4. Conclusions**

In summary, this mini-review focuses on the most recent advances of resorcin[4]arene-derived water-soluble deep cavities. It includes their applications in molecular recognition, isomeric guest separations, sensing and removal of organic...
pollutants and their use as reaction vessels. Molecular recognition is the basis for distinguishing the subtle differences between isomers, determining the relative strength of cation—π and hydrophobic effects in water, sequestering small hydrophilic molecules and separating complex mixtures. Some fundamental principles of noncovalent interactions were also determined from the study of these synthetic host-guest systems, which enhanced our understanding of both chemical and biological molecular recognition phenomena. Guests confined in the limited spaces of synthetic containers can adopt unusual orientations, which leads to unexpected reactivity and changes in their chemical and physical properties. Monofunctionalization and macrocyclization were successfully reported, in which water-soluble cavitation hosts act as protecting groups, templates and reaction vessels. While these examples constitute encouraging applications of synthetic molecular containers, some problems still need more attention. Future cavitation research should address applications of these molecules as catalysts rather than as recyclable stoichiometric agents. Additionally, the development of resorcin[4]arene-based cavities as molecular sensors outside laboratory settings remains a challenge.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: confinement · deep cavitation · molecular container · molecular recognition · synthetic host

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