HETEROAROMATIC MOTIFS IN RESORCINARENE-DERIVED CAVITAND RECEPTORS: STRUCTURAL AND FUNCTIONAL ELEMENTS

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Abstract. *Cavitands are synthetic receptors typically based on resorcin[4]arenes, macrocyclic concave compounds that are readily available and can be easily transformed into deeper synthetic cavities by attachment of aromatic spacers or panels. The use of aromatic heterocycles is ubiquitous in these structures, either for synthetic convenience, to regulate the dynamic and self-assembling properties of these receptors, or to provide suitable coordination environments for metal-functionalized receptors.*

Contents

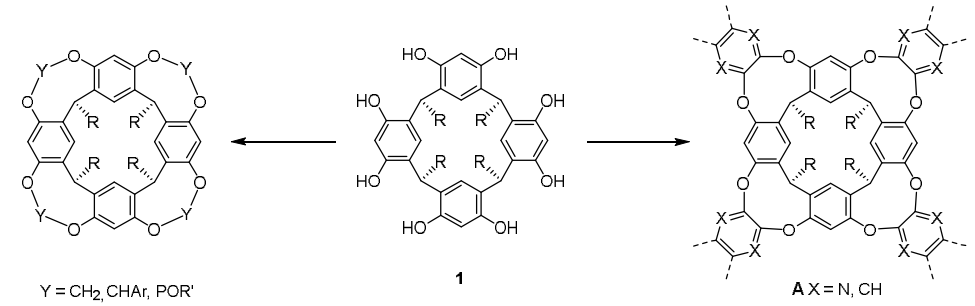
1. Introduction

The term *cavitand* was first coined by supramolecular chemistry pioneer Donald J. Cram to describe synthetic compounds that feature a permanent concavity where small molecules or ions can be bound.[1] Although this definition can be interpreted in a broad sense to include a variety of synthetic host molecules, it was originally applied to resorcin[4]arene derived hosts that surround the guest almost completely, isolating it from the external medium as in the active site of biological receptors (*i.e.* enzymes, proteins). This is in stark contrast with hosts with open portals that allow guest diffusion and/or contact with external media (solvent), such as crown ethers,[2] criptands[3] or metal-organic cages with large portals.[4] Regardless of its intended original use, a quick survey of the literature will reveal that the term cavitand refers mostly to structures in which the converging phenolic functions of a resorcin[4]arene **1** have been covalently bridged by organic spacers of different nature to provide a deep concavity. This account will focus on a specific subset of receptors prepared by extension with aromatic spacers, in particular those incorporating aromatic heterocycles as part of their structures **A** (Scheme 1). In some cases these heteroaromatic rings are merely structural elements of the host introduced for synthetic convenience, but in many others they are crucial for the conformational behavior of the receptors, their self-assembling abilities, or their ultimate intended function.

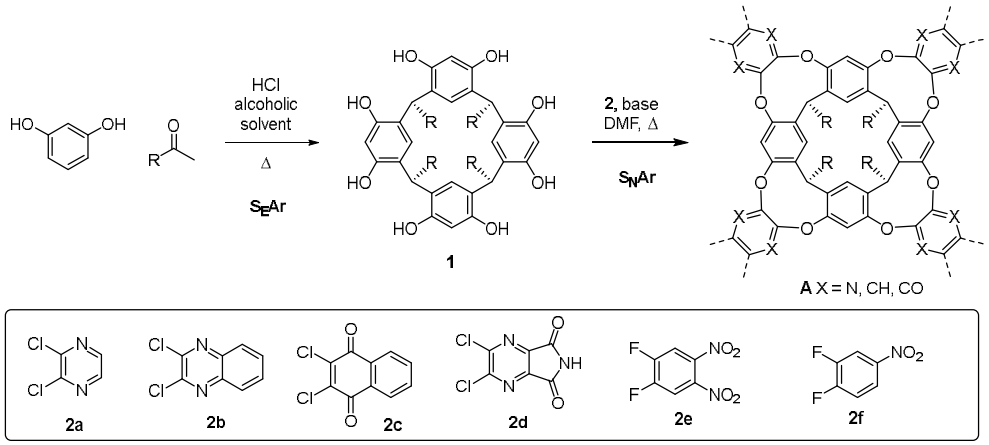
2. Synthesis of resorcin[4]arene derived cavitands

The chemistry of calixarenes unfolded in the 1940s within the field of phenolic resins and polymers, after researchers noticed that, under certain conditions, the polymerization of phenols and aldehydes

furnished discrete cyclic oligomers.[5] The condensation of resorcinol and various aldehydes under acidic conditions furnishes selectively resorcin[4]arenes, usually referred to as resorcinarenes **1** (Scheme 1). The tetrameric structure was first suggested by Niederl and Vogel in 1940,[5c] and later corroborated by X-ray diffraction studies.[6] Later on, Högberg reported an optimized and synthetically useful procedure.[7] The selectivity towards the tetramer of this transformation is astonishing in comparison to the phenol-formaldehyde cyclocondensation, which typically results in mixtures of different cyclooligomers.[8] In addition, the resorcinol-aldehyde condensation is stereoselective, and provides almost exclusively the so-called *rccc* isomer **1** (all *cis*, as shown in Scheme 2). In fact, multi-gram batches of pure **1** can be obtained starting from a range of aldehydes in a simple synthetic operation and without any chromatographic purification required.[9] The R groups, colloquially referred to as the *feet* of the cavitand, are a versatile point of variation in this reaction, allowing solubility tuning of resorcinarene derivatives in a facile manner. The ease of synthesis of **1** has certainly fostered their use in the development of new synthetic receptors, somewhat eclipsing other hosts and precursors. The most stable conformer of resorcin[4]arenes has a concave crown shape with molecular recognition properties on its own.[10] However, the true potential of these molecules comes from the realization that the phenolic functions of neighboring rings converge in space, and are ripe for condensation with a variety of aromatic electrophiles **2a-f**, providing not only a deeper cavity but also a more rigid and structured assembly (Scheme 2).[1]



Scheme 1. Extension of resorcin[4]arenes with different bridging units to obtain cavitand receptors.

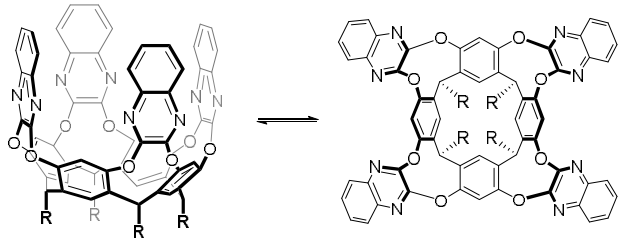


Scheme 2. Selective condensation of resorcinol and aldehydes to furnish resorcin[4]arenes, and further condensation with aromatic electrophiles to obtain deep cavity cavitands.

3. Cavitands with 1,3-diazine walls

3.1. Quinoxaline-type cavitands

The first cavitands, bearing a 1,3-diazine moiety as the upper panels, were reported by Cram and co-workers in the early 1980's.[1] The tall, vase-shaped receptor **3** was prepared from resorcin[4]arene **1a** (R=Me) upon treatment with 2,3-dichloroquinoxaline **2b** and base in dimethylformamide (DMF). CPK molecular modelling and a thorough structural analysis by NMR of the novel macrocycle led to the conclusion that it existed in solution as two slowly interconverting conformers (Scheme 3).[11] In the closed or *vase* conformer, the four benzene rings at the base of the cavitand form an enforced concave inner support for the attached quinoxaline walls, which provide a deep enclosure. This panels behave like mobile flaps, which can switch from *axial* to *equatorial* positions (ΔG of the conformational exchange ca 10 kcal mol^{-1}) to deliver the open or *kite* form. This flattened conformer exposes to the outer medium an extended π surface that is ripe for self-association through π-π stacking interactions, resulting in the so-called *velcrand* dimer. This dimer has no inner space available; therefore, the *kite* form is devoid of any molecular recognition capabilities for other molecules. VT-NMR analysis at temperatures between -62 °C (*kite* favored) and 45 °C (*vase* favored) permitted the characterization of the conformational equilibrium of the cavitand, and the description of the first temperature-dependent molecular encapsulation device.



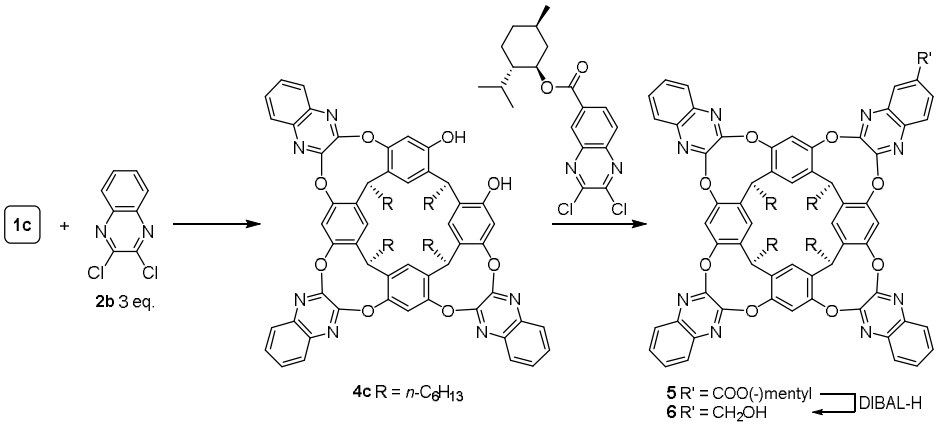
3a R = Me
3b R = *n*-C_5H_{11}
3c R = *n*-C_6H_{13}
3d R = *n*-C_7H_{15}
3e R = *n*-$C_{11}H_{23}$

Scheme 3. Interconverting ***vase*** and *kite* conformers of a 2,3-quinoxaline walled cavitand.

From that work, the interest in shape-shifting capsules and the recognition abilities of the inner space of 1,4-diazine-based cavitands increased, while novel and attractive features of this tunable scaffold were discovered. The groups of Dalcanale and Soncini carried out pioneering molecular recognition studies in 1989, reporting the selective binding of neutral aromatic compounds in organic solvents.[12] Early X-ray analysis of **3d** (R=*n*-C_7H_{15}) crystallized from acetone confirmed the presence of three acetone molecules bound: one enclosed in the interior of the cavity, a second one in between the lower-rim aliphatic chains, and the third in the void space created on top of the cavity. The deeper and non-disordered acetone molecule, places the carbonyl C=O double bond parallel-oriented to the quinoxaline walls, while the hydrogen atoms of the methyl groups point towards the quinoxaline ring engaging in a key CH-π interaction. Further NMR recognition studies carried out in acetone showed that cavitand **3** exhibits a 1:1 binding stoichiometry with benzene, toluene, chlorobenzene, fluorobenzene, and benzonitrile, while no complexation was observed with benzaldehyde, anisole, benzoic acid, and phenol.

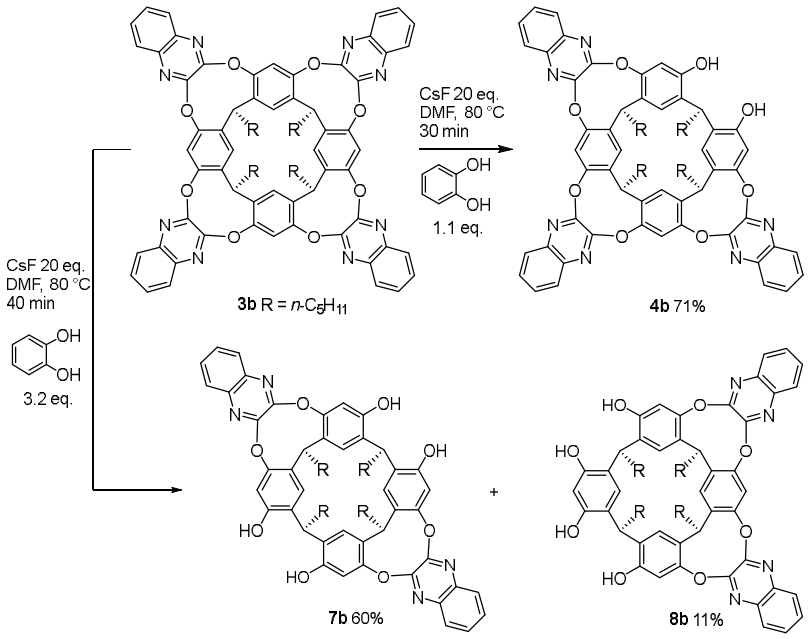
Capitalizing on the initial binding events observed with resorcin[4]arenes-based cavitands, the idea to selectively tune the properties of the cavity arose, mainly carrying out chemical modifications of the quinoxaline panels.[13] Thus, the synthesis of the tri-quinoxaline cavitand was reported by Dalcanale and co-workers, affording **4c** in a 53% yield in a statistical condensation of resorci[4]arene **1c** (R=*n*-C_6H_{13}) with 3 equivalents of 2,3-dichloroquinoxaline **2b**. Furthermore, the group could achieve the preparation of optically pure chiral derivatives starting from tri-quinoxaline cavitand **4c**, and study its molecular recognition features (Scheme 4). The incorporation of a fourth quinoxaline panel bearing a chiral auxiliary led to a mixture of diastereoisomeric cavitands **5** separable by silica gel chromatography, which could then

be reduced with DIBAL-H to provide the corresponding hydroxymethyl derivatives **6**. These are intrinsically chiral by virtue of the positioning of the unique hydroxymethyl substituent. The novel cavitands showed low association constants (K_a<200 M^{-1}) for aromatic guests like 4-(dimethylamino)-benzonitrile and 4-(dimethylamino)-nitrobenzene, directly comparable with those obtained with non-chiral quinoxaline-based derivatives.



Scheme 4. Synthesis of non-symmetric and intrinsically chiral quinoxaline-type cavitands.

Despite the above-mentioned examples, high yield desymmetrization of cavitands remained challenging until the group of Gutiérrez-Tunstad optimized in 2004 the synthesis of quinoxaline cavitands with non-uniform quinoxaline walls, relying on the reversibility of the S_NAr reaction employing heteroaromatic electrophiles (Scheme 5).



Scheme 5. Selective synthesis of partially bridged resorcin[4]arenes.

The group reported a reliable method to deliberately excise one or two quinoxaline walls from tetra-quinoxaline-spanned cavitand **3b**.[14] By screening the equivalents used of a nucleophile such as catechol, in presence of CsF in DMF, they could selectively promote the formation of tri- **4b** or di-quinoxaline-spanned cavitands **7b/8b**. The best results were found using 1.1 equiv. of catechol and 20 equiv. of CsF, providing tri-quinoxaline cavitand **4b** in up to 71% yield. Using 3.2 equiv. of catechol in the same reaction conditions, a 6:1 mixture of **7b**+**8b** di-quinoxaline-spanned cavitands (separable by chromatography) was obtained in 71% yield.

This work from Gutiérrez-Tunstad group provided the required toolkit to explore the supramolecular properties of partially bridged cavitands and non-uniform walled derivatives (see also section 5.1). Diederich and co-workers published the binding properties of an anti-di-quinoxaline resorcin[4]arene cavitand **7e** (R=*n*-$C_{11}H_{23}$) acting as receptor for steroids (Figure 1).[15] The group performed a comprehensive complexation study based on ^{1}H-NMR titrations of 14 steroidal substrates at 298K in $CDCl_3$, showing in all cases a 1:1 binding stoichiometry, verified by Job plot analysis. The binding constants of the study are in the range of 30-740 M^{-1}, showing a considerable selectivity of the cleft-shaped cavitand **7e** for steroids. The authors performed structure-activity relationships by docking analysis of the complexes to determine the key interactions between the host and the guest, concluding that a flat A-ring, a carbonyl group at position Y, and additional H-bonding groups at positions R^1, R^2, R^3, R^4 clearly enhance the strength of the binding.

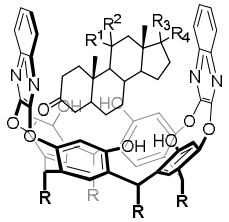
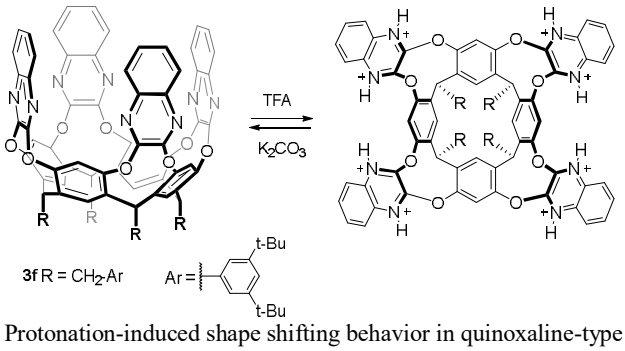


Figure 1. Anti-di-quinoxaline cavitand receptor for steroids.

3.2. Stimuli-responsive cavitands

Several studies have taken advantage of the conformational fluxionality of the resorcin[4]arene-based cavitands since the seminal report by Cram and co-workers on their temperature-dependent behavior.[11] Diederich and co-workers reported in 2001 that the change in the molecular geometry of the known cavitand **3** can also be promoted by a change in pH (Scheme 6).[16]



Scheme 6. Protonation-induced shape shifting behavior in quinoxaline-type cavitands.

Trifluoroacetic acid aliquots were added to a solution of **3f** in $CHCl_3$ and the variations in the cavitand's conformation were followed by UV/Vis spectroscopy. The changes in the spectra were similar to those observed with temperature decrease, and were unambiguously confirmed by ^{1}H-NMR spectroscopy, following the pH-induced shift of the methine signals. The structural variation was attributed to protonation

of the mildly basic nitrogen atoms of the quinoxaline moieties, and consequent electrostatic repulsion of the resulting cationic walls in the vase conformation (N-N distance: 4.54 Å). The reverse process was achieved by neutralization with K_2CO_3.

Combining the methodologies described in section 3.1 with an Cu-acetylenic oxidative coupling, the Diederich group developed a new series of enclosed cavitands **9** and **10**, based on anti-di-quinoxaline intermediate **7** (Figure 2). The switchable nature of these receptors allowed the complexation or release of neutral aliphatic guests dependent on pH.[17] At room temperature, the containers are found in the closed form evidenced by the characteristic methine signal in ^{1}H-NMR (acetone-d_6, $CDCl_3$, mesitylene-d_{12}). Upon addition of CF_3COOD the cavitand evolves towards the opened conformation due to Coulombic repulsion forces promoted by protonated quinoxaline rings. The closed conformation could be fully recovered upon addition of triethylamine. Cavitands **9** and **10** show complexation of cycloalkanes (cyclopentane, cyclohexane, and cycloheptane) in mesitylene-d_{12} at K_a 10^2-10^3 M^{-1}, as ascertained by ^{1}H-NMR (298K). It is worth mentioning here that, unlike other more commonly used deuterated solvents, mesitylene is a non-competitive solvent for resorcin[4]arene cavitands because of its larger size. The resonances of the neutral aliphatic guests are strongly shifted upfield, showing clearly 1:2 or 1:1 or binding stoichiometries in cavitands **9** and **10**, respectively. Interestingly, the addition of CF_3COOD turns off the binding ability of the cavitands inducing the decline of the NMR signals of the bound guests, until total release is complete at [CF_3COOD]=1.4 M. Remarkably, the switching mechanism of these cavitands is fully reversible, and upon addition of triehylamine the quinoxaline moieties are neutralized, allowing both containers to instantly recover the closed vase conformation and its binding abilities.

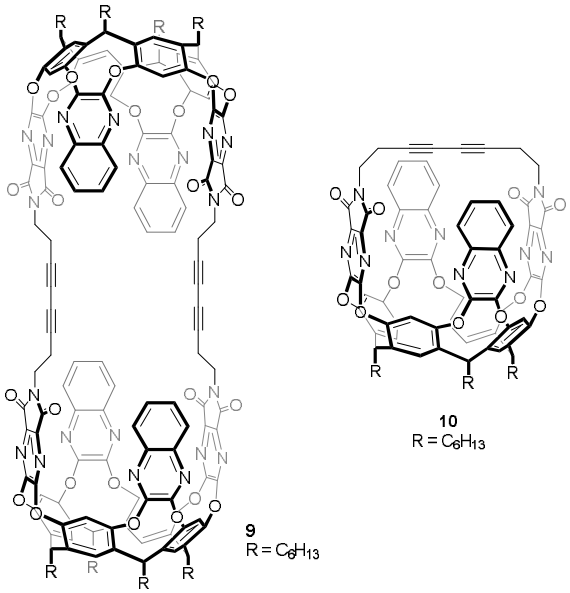
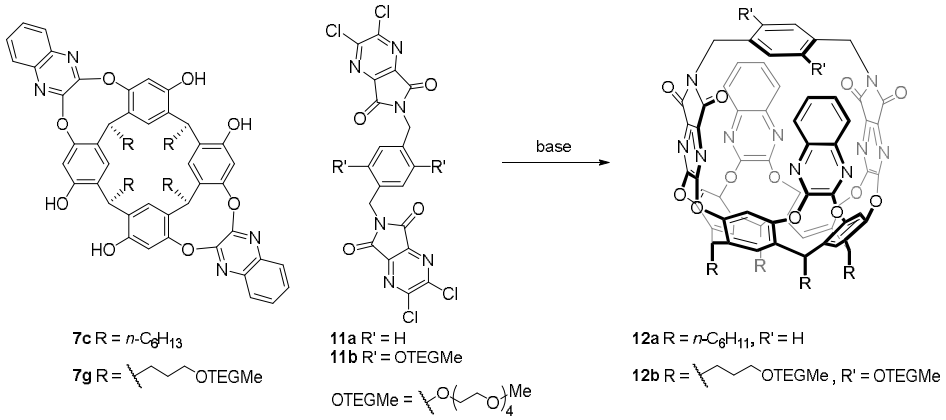


Figure 2. Covalently assembled capsules based on quinoxaline-type cavitands.

In a similar fashion, the same research group reported an enclosed basket **12a** employing an aromatic *para*-phenylene capping moitety rigidly bridged to the heterocyclic walls of the resorcin[4]arene cavitand (Scheme 7).[18] This linker provides stiffness to the system and disfavors the kite conformation. The system was studied to bind a large library of (hetero)cyclic aliphatic and aromatic molecules in mesitylene-d_{12}, employing ^{1}H-NMR spectroscopy and Isothermal Titration Calorimetry (ITC). The K_a values found at 303 K were in the range of 10^2 M^{-1}-10^7 M^{-1}. A preference for 6-membered heterocycles was observed mostly to enthalpic effects, which can be understood in simple terms as the result of a better size and shape complementarity. The aromatic *para*-xylene ceiling was found to play a key role in binding events,

providing additional stabilizing N-H···π or S···π interactions. Despite this favorable binding events with the vase form, addition of CF_3COOD to a certain concentration swaps the conformational equilibrium of the quinoxaline-walled cavitand as previously observed, allowing controlled release of guests to the outer solution.



Scheme 7. *p*-Phenylene capped molecular baskets.

A few years after this thorough study, a water soluble version of this receptor **12b** was prepared by appending poly(ethyleneglycol) (PEG) chains at the lower and upper ends of the cage.[19] Analysis by ^{1}H-NMR confirmed the prevalence of the vase conformation of the capsule in D_2O/CD_3CN (2:1), and subsequent binding studies of cavitand **12b** in aqueous media were performed using barely soluble guests, such as cyclohexane or heterocyclic molecules. Maximum K_a values were detected on complexation of 1,4-dithiane (3724 M^{-1}), which was rationalized on the basis of its higher hydrophobicity with respect to similar guests (1,4-thioxane, 1,4-dioxane), and the positive effect of the aforementioned S···π interactions with the capping aromatic panel.

The Diederich group has lead the development of sophisticated stimuli-responsive hosts based on the resorcin[4]arene scaffold. A remarkable example comprises a series of rigid resorcin[4]arene cavitands bearing donor-acceptor BODIPY dye pairs, which enable the study of the conformational switching process by Förster Resonance Energy Transfer (FRET).[20] Two BODIPY moieties were carefully selected to behave unidirectonally as a FRET donor and acceptor, and showing a low sensitivity to changes in pH. This chromophores were installed sequentially through key Sonogashira coupling reactions, following synthetic schemes analogous to those previously delineated (Figure 3).

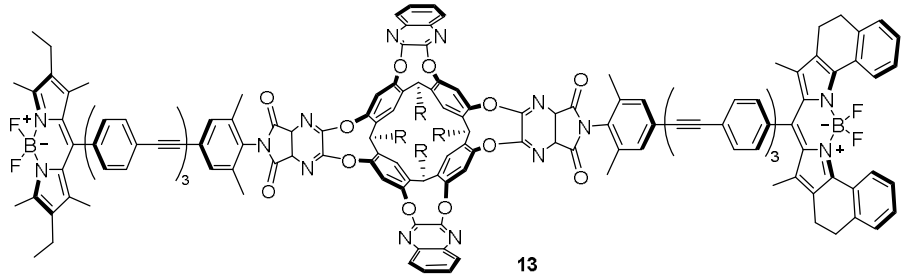
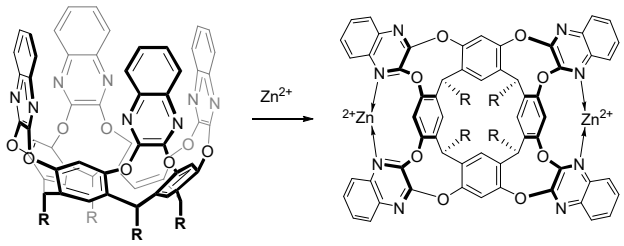


Figure 3. BODIPY dye functionalized cavitand receptor. The two chomophores are within FRET distance In the *vase* conformation (shown), but to far away when the cavitand opens to the kite form.

Again, ^{1}H-NMR studies confirmed the existence of cavitand **13** in the concave vase conformation, which places the two BODIPY chromophores at a distance of ca 7 Å according to modelling studies. The emission spectra of compound **13** in $CHCl_3$ showed two strong peaks at 542 nm (donor dye) and 630 nm (acceptor dye), revealing a moderate FRET effect. The low FRET efficiency was rationalized on the basis of the receptor's flexibility. Interestingly, upon addition of TFA (favoring the *kite* conformation) the acceptor fluorescence vanishes nearly to completion whereas the donor fluorescence doubles its intensity, thus noticeably reducing the FRET efficiency between the two dye stations, which are about 70 Å apart in the open *kite* conformer according to molecular models. The spectral changes described can be reversed upon neutralization with $Et(i\text{-}Pr)_2N$.

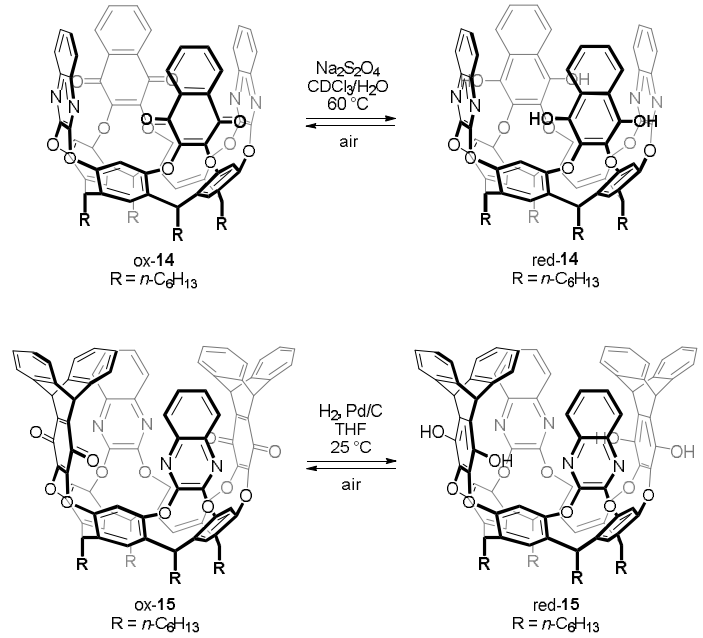
The *vase* to *kite* switch of resorcin[4]arene derived cavitands can be triggered by mechanisms other than protonation/deprotonation. In 2004, the Diederich group reported the shift of the conformational equilibrium induced by metal cation complexation.[21] The aim of this study was the production of a Langmuir monolayer of the amphiphilic cavitand **3h** (Scheme 8), which was hypothesized to create a film between $CHCl_3$ and a water sub-phase, with the methyl ester groups pointing towards the polar surface and the quinoxaline panels acting as hydrophobic groups. In the course of this investigations cavitand **3h** showed conformational sensitivity to concentration of Zn(II) salts in the aqueous phase. This effect was analyzed by ^{1}H-NMR with analogue **3c** (R=*n*-C_6H_{13}). Upon treatment of **3c** with ZnI_2 in CD_2Cl_2/CD_3OD (3:1), the diagnostic shift of the methine protons was clearly observed (triplet moving from 5.54 ppm in the *vase* to 3.90 ppm in the *kite*). The authors suggested a coordination of two Zn(II) ions on two neighboring nitrogen atoms of the expanded quinoxaline walls.



Scheme 8. Zn(II)-induced shape shifting of quinoxaline-based cavitands.

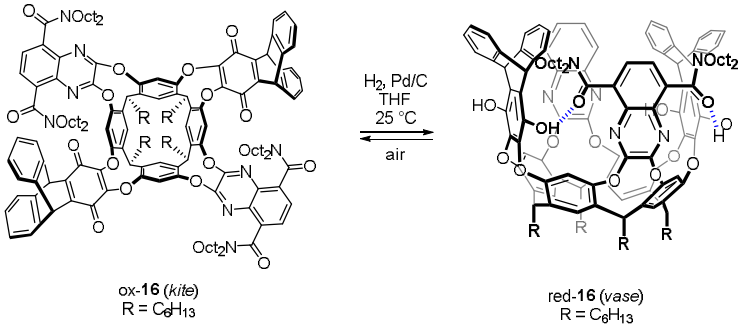
Until 2010, most of the cavitands based on the resorcin[4]arene core were elaborated from a reduced set of wall component units, namely 2,3-dichloroquinoxaline, 2,3-dichloropyrazine, and 1,2-difluoro-4,5-dinitrobenzene. The search for novel architectures that could bring on emerging applications in host-guest chemistry was hampered by the synthetic difficulties in accessing heterocyclic fragments with two *ortho* leaving groups. The Diederich group opened new avenues in this directions by introducing redox-active moieties to the walls of cavitand receptors, which allowed the control of the conformational equilibrium (and therefore binding) by redox stimuli. Inspired by previous work of Cram and co-workers,[22] in which tetrafluoro-1,4-benzoquinone was used as a bridging reagent, the group studied the features of di- and tetra-quinoid based resorcin[4]arene cavitands **14** and **15** (Scheme 9).[23] Di-quinoid-di-quinoxaline cavitands **14/15** were synthesized using 2,3-dichloronaphthoquinone **2c** and the analogue triptycene derivative in a similar fashion as other aforementioned examples, and their conformational and binding behavior was tested under reducing and oxidative conditions.

The redox state of the cavitand has a marked influence on the relative stabilities of the open and closed conformers, which can be exploited to exert external control onto host-guest systems. The enclosed triptycene derivative **15** provides kinetically stable complexes (in the NMR time scale) with cyclopentane, cyclohexane, and cycloheptane, in mesitylene-d_{12}. The binding constants are up to an order of magnitude higher in the oxidized form ox-**15** (K_a 19.2 vs 3.1 M^{-1} for cyclohexane), which was reasoned on the observation that the open, non-binding kite conformation is stabilized in the reduced form red-**15**.



Scheme 9. Redox-active cavitands bearing quinoid panels.

Based on this proof-of-concept system, the same authors further refined the structures of these receptors to allow a complete shape shifting mechanism triggered by redox stimuli (Scheme 10).[24] By appending hydrogen-bond acceptors to the quinoxaline panels, the oxidized form of the cavitand **16** is stabilized in the *vase* conformation thanks to hydrogen bonding to the hydroquinone panels, whereas the reduced form favors the *kite* conformer due to steric crowding between adjacent aromatic panels. As a result, controlled binding and release of aliphatic guests (cyclopentane, cyclohexane, cycloheptane, cyclooctane, 1,4-cyclohexenedione) can be effected by external redox stimuli.



Scheme 10. Shape-shifting of a cavitand receptor induxed by redox stimuli.

3.3. Self-assembling pyrazine-based cavitands

In 1998, Rebek and co-workers opened a whole new direction of research in the area of cavitands when they reported the first self-assembled *containers*.[25] Condensation of resorcin[4]arenes with dichloropyrazine imide **2d** furnishes a cavitand receptor bearing a hydrogen bond motif at the rim that is self-complementary **17**, and therefore triggers the formation of a dimeric elongated assembly with a

completely enclosed inner cavity, the so-called "Heinz capsule" **17**·**17** (Figure 4).[26] Extended versions of this assembly can be elaborated with additional hydrogen-bonding spacers.[27]

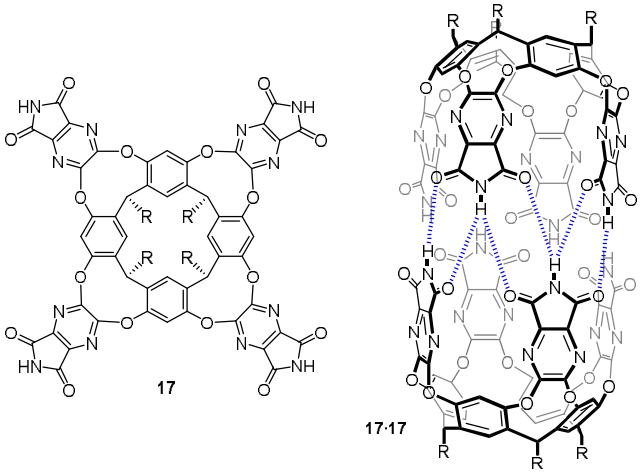
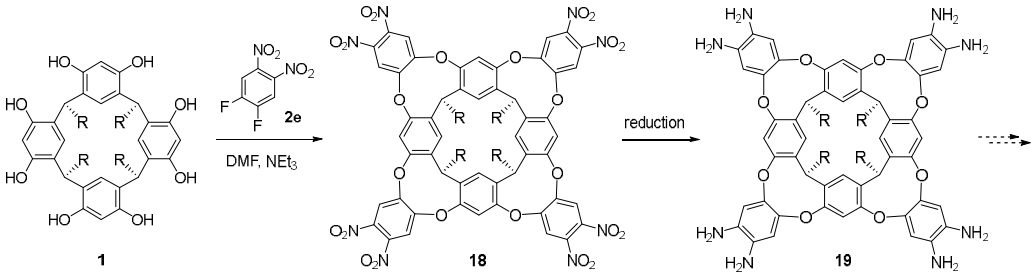


Figure 4. Self-assembled capsule based on a pyrazine-type cavitand.

The confined space of the Heinz capsule has remarkable molecular recognition properties and enables, for instance, the co-encapsulation of multiple guests that properly fill the space when combined.[28] This property also gives rise to the emergence of "social isomerism".[29] When two guests present in the cavity fill the space to the limit of its capacity, the inner motions of the guests are restricted in a way that interconversion between different relative orientations is slowed down significantly.[30] The resulting "social isomers" can be observed as separate species by NMR. Another interesting property of the Heinz capsule is the ability to compress the guests within. Multiple cyclopropane molecules can be encapsulated in the Heinz capsule and related assemblies. The packing coefficient of the bound cyclopropane molecules is that of a liquid, and not a gas as it would be under normal conditions. Similarly, *n*-alkanes are compressed into compact helicoidal conformations if they are too large to fit in the cavity as the all-alternated conformer.[31] The energetic penalty of multiple gauche conformations is compensated by a better filling of the available spaces, which maximizes attractive CH-π interactions with the aromatic panels of the cavity.

4. Cavitands with benzo-fused heterocyclic walls

The second big family of resorcinarene-derived receptors stems from the condensation of resorcin[4]arene with difluorodinitrobenzene **2e**, providing structures with benzene bridges that can be further derivatized into a variety of heteroaromatic panels.



Scheme 11. Condensation of resorcin[4]arenes with **2e** provides octanitro cavitands. Upon reduction, the corresponding octaaminocavitands are obtained, which are the basis of many receptors.

4.1. 1,3-Dihydro-2*H*-benzo[*d*]imidazol-2-one walls

The preparation of cavitands with benzimidazolone panels **20** (Figure 5) was first reported by the group of de Mendoza.[32] Very much like in cavitand **17**, this motif is self-complementary and promotes auto-association, providing a dimeric assembly akin to **17**·**17** (section 3.3.). Water soluble versions of this receptor **20e-f** were subsequently developed by Rebek and collaborators.[33] In water, the cavitand can either dimerize or exist in its monomeric form depending on the available guest. Linear aliphatic guests such as fatty acid derivatives are encapsulated in the monomeric cavity in contorted conformations, with the polar functionality exposed to the surrounding aqueous medium. In this fashion, the cavitand templates the macrocyclization of difunctional substrates (*e.g.* long chain aminoacids cylize to macrolactams).[33a] An interesting modification of the benzimidazolone scaffold was introduced by the group of Rebek more recently. Permethylation of the structure provides a structure without self-assembling behavior **21a-b**, but the spatial proximity of the *N*-methyl groups results in a slightly widened receptor by virtue of the steric repulsion.[34] A similar widening effect of the cavity is obtained by replacing oxygen by sulfur in the original benzoimidazolone cavitand **20g**.[35] Having access to varied shapes (a feature that is hard to implement in resorcinarene-derived cavitands) is highly desirable for molecular recognition studies.

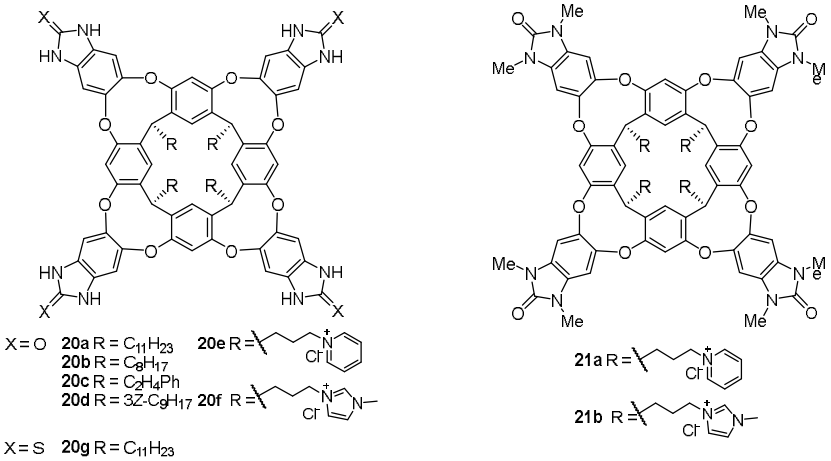
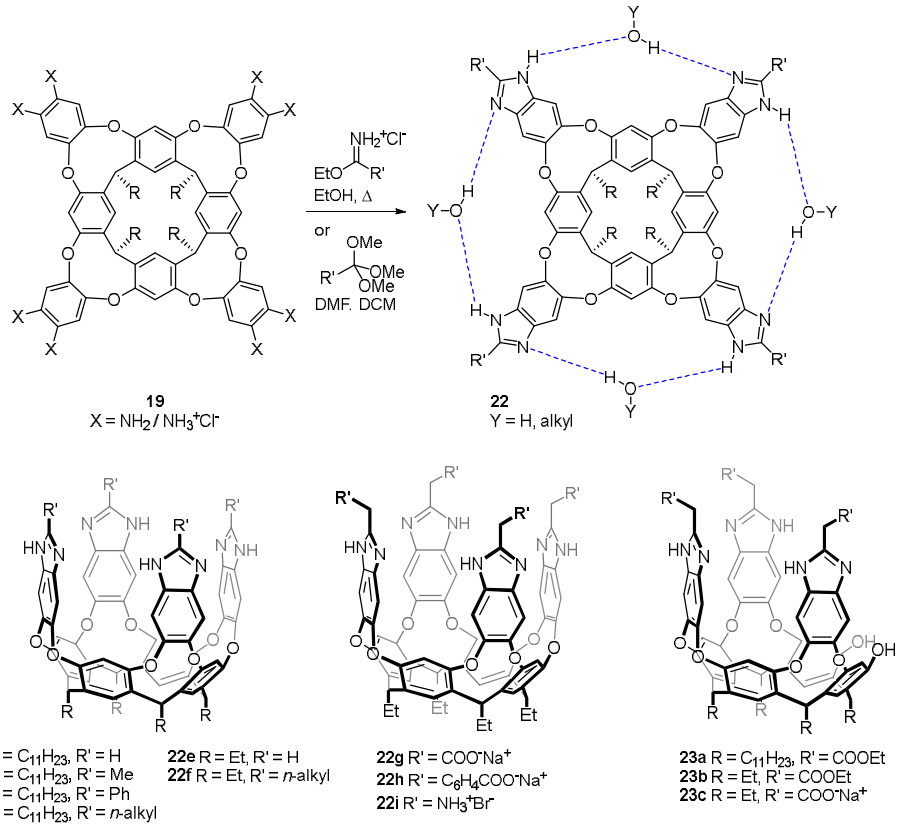


Figure 5. Structures of cavitand receptors bearing benzimidazolone panels, with (left) and without (right) self-assembling properties.

4.2. 1*H*-Benzo[*d*]imidazole walls

Cavitands with 1*H*-benzo[*d*]imidazole walls (another original contribution of the Rebek lab.) are obtained by condensation of the key octaamino intermediate **19** with ortho-esters or imidates (Scheme 12).[36] The resulting cavitands **22** do not have self-assembling abilities. Instead, the benzimidazole rings allow the stabilization of monomeric cavitands in the *vase* form through an array of hydrogen bonds established with external donor/acceptor molecules, such as alcohols or water. This is a unique feature of these receptors that allows stabilization in aqueous or protic media, which is usually detrimental for folding of other structures such as amide stabilized cavitands (sections 5.2. to 5.4.). Indeed, this scaffold provided the first resorcinarene-derived water-soluble cavitands **22g-i**, a system that enabled the exploitation of the hydrophobic effect to drive the formation of host-guest complexes.[37] This is a powerful approach, as illustrated by the binding of long alkyl chains from organic surfactants in compact, intrinsically disfavored helical conformations containing no less than 5 destabilizing gauche interactions.[38]

Partially bridged benzimidazole cavitands can also be accessed from the corresponding hexanitro derivatives, which can be isolated in moderate yields from a statistical condensation akin to that in Scheme 4 but employing **2e** as the limiting reagent (see section 5.2.).[39] Benzimidazole cavitands with only three walls **23** retain most of the molecular recognition properties of their symmetrical couterparts.

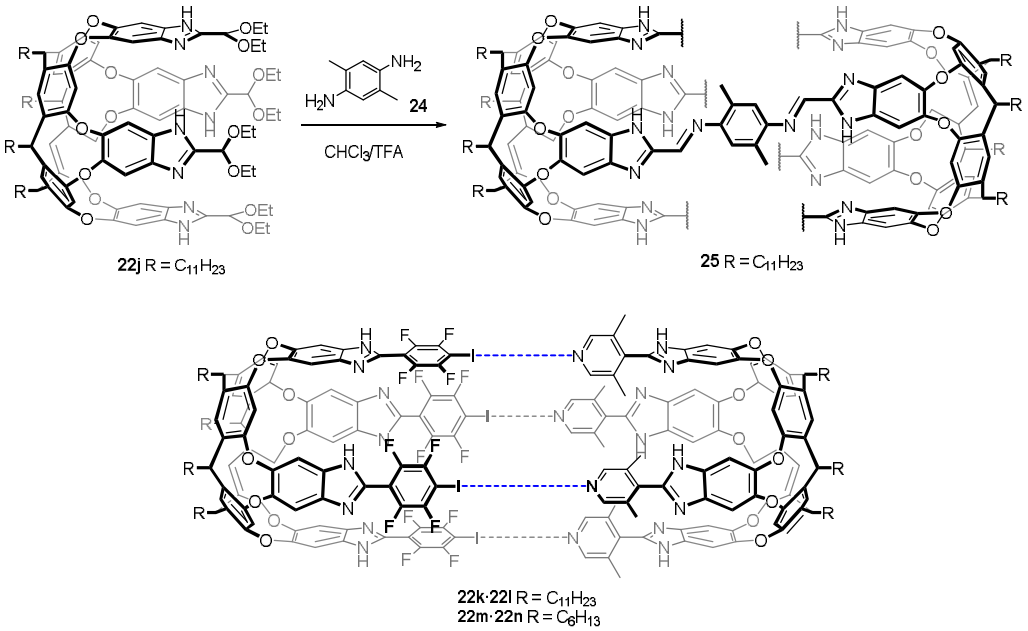


Scheme 12. Synthesis of benzimidazole-type cavitands and different variants reported in the literature. The *vase* conformation is stabilized by hydrogen-bonding with external donor-acceptor molecules.

The benzimdidazole connector has also proven synthetically useful in the ellaboration of larger and more complex assemblies (Scheme 13). Tetraacetal cavitand **22j** can be condensed under acidic conditions with a difuncional aniline spacer **24** to provide a covalently assembled capsule **25**, composed of two cavitands and 4 aromatic tethers.[40] The benzimidazole spacer has also been utilized by the Diederich group to assemble capsules through halogen bonding, by derivatization of two cavitand moieties with: a) an electron-deficient haloaryl moitety **22k**/**22m** (XB donor) and b) a pyridine ring **22l**/**22n** (XB acceptor). The two halves of the capsule assemble through four halogen bonding interactions, which act cooperatively to deliver a strong assembly.[41]

5. Functionalized cavitands

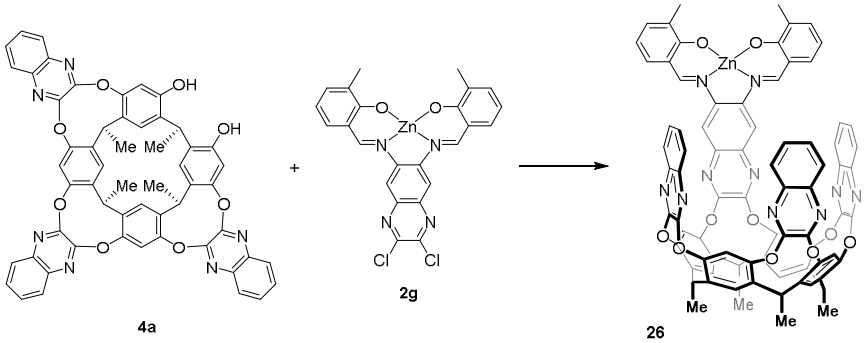
The beginnings of synthetic supramolecular chemistry focused on constructing confined spaces inspired by the active site of enzymes and proteinogenic receptors, a paradigm which is nowadays very mature. Obtaining functionalized cavities that impart functions to these confined spaces is the next level in mimicking biological host-guest systems. The synthetic versatility of the resorcin[4]arene-based cavitand structure, in particular the ability to access desymmetrized variants, makes it a very appealing starting point for obtaining functionalized receptors with potential applications in sensing, catalysis or other bioinspired applications. Aromatic heterocycles are useful motifs in this regard. Apart from being structural constituents of the receptors as seen in previous sections, heteroaromatics can either act as tethers that facilitate the introduction of the required functionality, or be an integral part of the added function. In the latter case heterocyclic rings will be mostly employed as ligands to elaborate transition-metal functionalized receptors.



Scheme 13. Covalently assembled (top) and halogen-bonded (bottom) capsules based on benzimidazole cavitands.

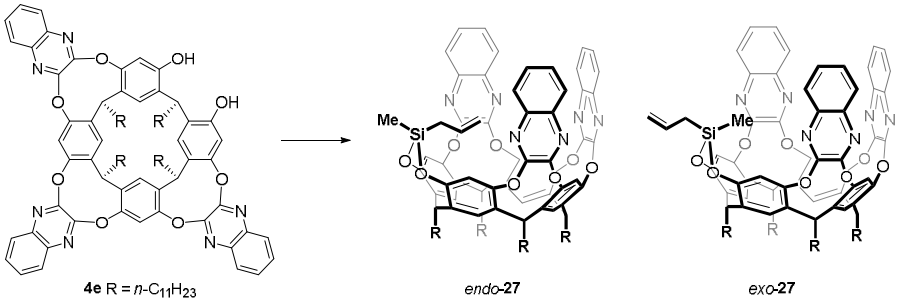
5.1. Functionalized cavitands with 1,3-diazine walls

Access to efficient protocols for obtaining di- and tri- quinoxaline-walled resorcin[4]arene cavitands (section 3.1) fostered further developments in the derivatization of quinoxaline-based cavitands with diverse functional groups. As an example, de group of Harrison reported in 2014 a straightforward synthesis for the incorporation of a Zn-salen moiety into one of the quinoxaline walls of cavitand **26** (Scheme 14).[42] The fluorescence of Zn-salen derivatives is potentially useful for applications in sensing. In this study, the authors tested the fluorescence quenching of the Zn-salen fragment by nitro compounds, such as 4-nitrotoluene, 2,4-dinitrotoluene, or 2,3-dimethyl-2,3-dinitrobutane. Unfortunately the quenching effect was no different with **26** than with model compound **2g**, ruling out a host-guest effect that could provide the basis for developing more efficient fluorescent sensors.



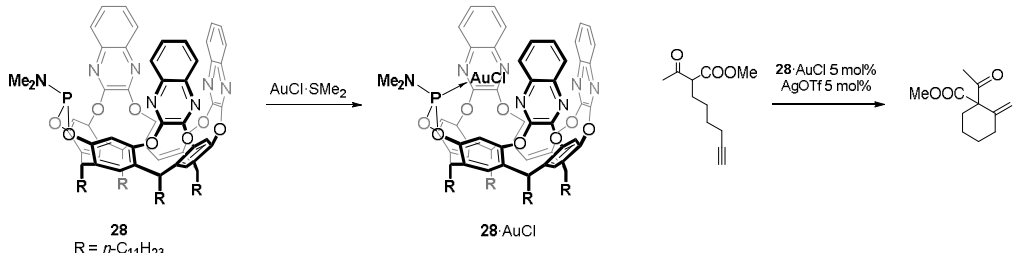
Scheme 14. Synthesis of a salen-functionalized quinoxaine-type cavitand.

The group of Iwasawa has pioneered in recent years studies on the functionalization cavitands with quinoxaline panels. In an initial communication, the group reported the incorporation of an allyl(methyl)silane moiety by reaction of allyl(dichloro)methylsilane with the tri-quinoxaline cavitand **4e** (Scheme 15).[43] An isomeric 1:1 mixture of the introverted allyl cavitand *endo*-**27** and its *exo* isomer was obtained and separated by silica column chromatography. The authors tested the influence of the concavity surrounding the allyl group on the epoxidation of the olefin with *m*CPBA. Competitive reactions were tested between the inwardly and outwardly located double bonds in order to demonstrate the influence of the cavity, showing an increase of reactivity of the allyl group pointing inward towards the quinoxaline walls.



Scheme 15. Tri-quinoxaline-walled cavitand with an introverted allyl group.

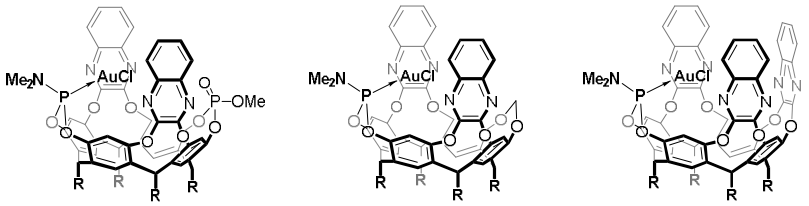
This prominent feature encouraged the authors to investigate the influence of the confined environment formed by the quinoxaline panels to different types of chemical transformations. In this regard, Iwasawa and co-workers reported a few years later a phosphoramidite derivative of tri-quinoxaline-walled cavitand **4e**, which permitted access to an Au metallo-cavitand **28**·AuCl upon reaction with AuCl·SMe_2 (Scheme 16).[44] The desired inward arrangement of the metallic atom was confirmed by X-ray diffraction analysis. The novel metalo-cavitand was used as a catalyst in a series of known Au-catalyzed transformations, such as the hydration of terminal alkynes and the Conia-ene reaction of β-ketoesters, in order to prove that metal catalysis and confinement effects could work synergistically to achieve complex reaction transformations. Catalytic hydration of terminal aromatic and aliphatic alkynes were successfully accomplished. Unfortunately, only moderate yields were achieved in Conia-ene reactions catalyzed by **28**·AuCl as catalyst, showing a poor overall performance of the metallic capsule in comparison with known catalytic systems for this transformation.



Scheme 16. Preparation of a quinoxaline-type Au metallo-cavitand, and catalytic application in the Conia-ene reaction.

Along these lines, the Iwasawa group reported a variation of cavitand **28** including modifications to the catalyst architecture aiming at an enhancement of the catalytic performance of the receptor (Scheme 17).[45] In a work published in 2018, the authors reported an exploration of the catalytic hydration of dissymmetric internal alkynes promoted by metallo-cavitands **29-31**, with the aim of evaluating the influence of confinement effects on the regioselectivity of the transformation. A systematic study was carried out

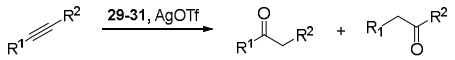
incorporating different groups facing the cationic Au catalytic center: a phosphine oxide group, a methylene, or a quinoxaline panel. The best performance was achieved with metallo-cavitand **29** bearing the phosphine oxide group. The authors hypothesized that the P=O group facing the concave section of the cavitand assists the addition of water to the C-C triple bond through hydrogen-bonding, enhancing the nucleophilicity of the water molecule and stabilizing the orientation that facilitates nucleophilic attack to the Au-activated triple bond. This study illustrates the importance of the interactions within the boundaries of quinoxaline-based cavitand, and how this space can be tuned to govern the phenomena occurring inside.



29
R = *n*-$C_{11}H_{23}$

30
R = *n*-$C_{11}H_{23}$

31
R = *n*-$C_{11}H_{23}$

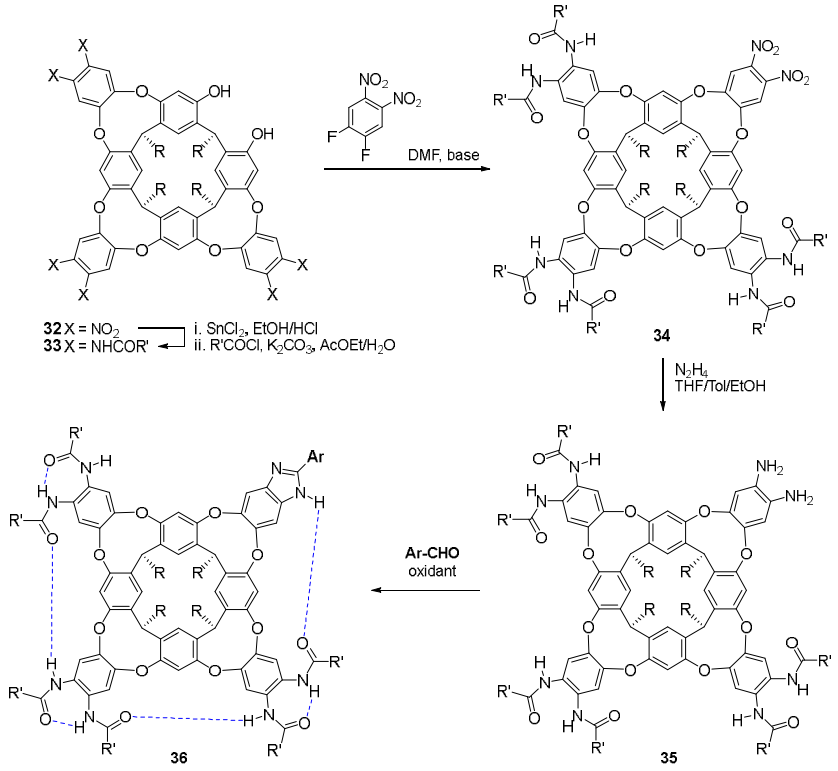


Scheme 17. Alternate desings of Au metallo-cavitands. Application to regiosective akyne hydration.

5.2. Dissymmetric cavitands with singular 1*H*-benzo[*d*]imidazole walls

As previously discussed in section 3, accessing desymmetrized intermediates in high yield is one the major synthetic hurdles in the preparation of resorcinarene derived cavitands. However, such intermediates are extremely valuable for the preparation of monofunctional compounds that retain the molecular recognition features of their symmetrical counterparts. In particuar, hexaamide diol derivative **33** constitutes a unique platform for developing functionalized receptors that preserve the self-folding characteristics of octaamide cavitands.[46] This type of receptors are stabilized, both thermodynamically and kinetically, in the binding competent *vase* conformation thanks to a cyclic array of secondary amides that establishes a circular hydrogen bond network akin to the one stabilizing secondary structure in proteins (Scheme 18). The required hexanitro precursor **32** is accessed by a statistical S_NAr condensation of resorcin[4]arenes **1** with **2e** as the limiting reagent. The desired three-fold condensation product can be isolated in respectable yields from the reaction mixture. Hexanitro derivative **32** is then further reduced and acylated to deliver key intermediate **33** (Scheme 18). The majority of hexaamide-type functionalized cavitands are elaborated from **33** by condensation with an additional molecule of the difluorodinitrobenzene building block **2e**, reduced, and condensed with an aromatic aldehyde carrying the desired functionality under oxidative conditions to provide a cavitand **36** bearing one benzo[*d*]imidazole panel. This layout is not only synthetically convenient (the benzimidazole formation reaction tolerates a range of functional groups), but also provides a structured microenvironment by extending the amide hydrogen bond seam to the neighboring benzimidazole NH (Scheme 18).

As previously mentioned, the benzimidazole linkage has proven invaluable to attach functionalities that can interact with guests present in the cavity. Employing an anthracene spacer, Rebek and collaborators managed to introduce a variety of functions pointing inwards the aromatic pocket, allowing the stabilization and detection of elusive reaction intermediates such as hemiaminals, hemiketals or isoimides (Scheme 19).[47] Free rotation about the anthracenyl-imidazolyl linkage provides two extreme skewed conformations with the group at the C1 position either inside or outside the cavity. When a suitable guest is present in the cavity, the anthracenyl rotor can point inwards reacting with the guest. Non-covalent interactions stabilize reactive intermediates that may appear along the way, *e.g.* hemiaminals formed in an imine condensation. As a consequence, these species are long lived enough to be detected by ^{1}H-NMR spectroscopy (Scheme 19).



Scheme 18. Synthetic sequence for non-symmetrical amide-stabilized cavitands with a fourth benzimidazole wall. The hydrogen bond stabilization scheme extending to the benzimidazole ring is highlighted.

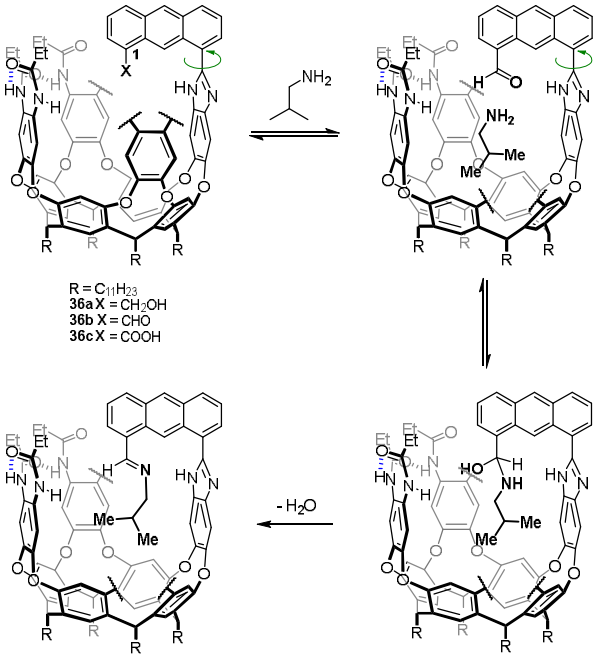
Following this idea, an endless number of functionalities can be attached to the amide-stabilized cavitand platform. Our group has contributed in this area with a thiourea-functionalized cavitand that provides a cooperative binding motif for ions pairs, with large enhancements in the binding affinities in comparison to non-cooperative receptors.[48] An interesting application of these functionalized receptors is their use in bioinspired supramolecular catalysis.[49]

5.3. The introverted acid cavitand

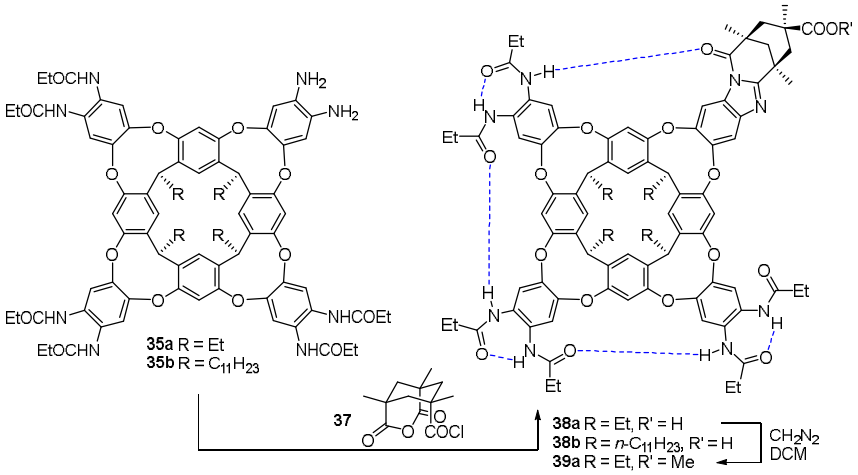
The so-called *introverted acid cavitand* (**38**) results from the fusion of the benzo[*d*]imidazole connector to a Kemp's triacid derivative,[50] and provides an elegant example of functionalized synthetic confined space (Scheme 20).[51] This structure is obtained by condensation of intermediate diamino cavitand **35** and Kemp's triacid anhydride chloride **37**.[52]

In contrast to previous examples exploiting the anthracenyl rotor, the functionalized cavitand is obtained here as a non-interconverting mixture of isomers, the desired *endo* isomer and the *exo* isomer, which is devoid of any interesting properties for the problem at hand (Figure 6). While this is inconvenient from the synthetic point of view (not one of the major concerns in the area of synthetic supramolecular chemistry), the rigidification of the structure has dramatic consequences for the reactivity of the inwardly functionalized *endo* isomer. For instance the formation of an acid/base pair with a tertiary amine that is a snug fit for the cavity slows down dramatically nitrogen inversion.[53] As a result, diastereomeric complexes arising from different configurations at a chiral nitrogen atom can be observed as separate species by NMR spectroscopy. Even more interesting is the effect of confinement in the reactivity of the buried functionality. The introverted methyl ester derivative **39a** accelerates amine methylation of substrates that fit within the cavity up to $2x10^4$ times with respect to a conventional ester, a dramatic acceleration effect that originates

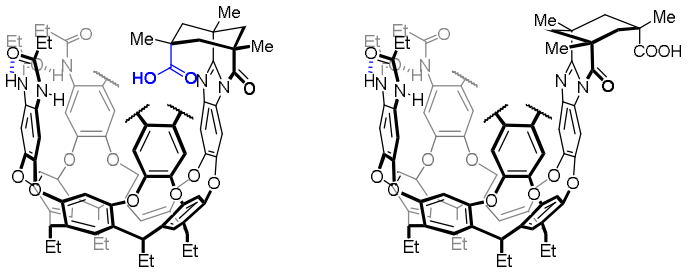
from both the concentration effect and the polarized microenvironment in the confined space surrounding the introverted ester function.[54] The ultimate application of cavitands with introverted functions is their use as enzyme mimics. Introverted acid **38b** functions as a catalyst for an epoxide ring opening cascade reaction of biological relevance.[55] This process displays the main features of an enzymatic reaction, namely, substrate molecular recognition, competitive and allosteric inhibition, acceleration, and selectivity.



Scheme 19. Stabilization of a hemiaminal intermediate in the cavity of an aldehyde functionalized self-folding cavitand.



Scheme 20. Preparation of the introverted acid cavitand **38** and ester **39** from diamino precursor **35**. The hydrogen-bond stabilizing scheme is highlighted for **38**/**39**.

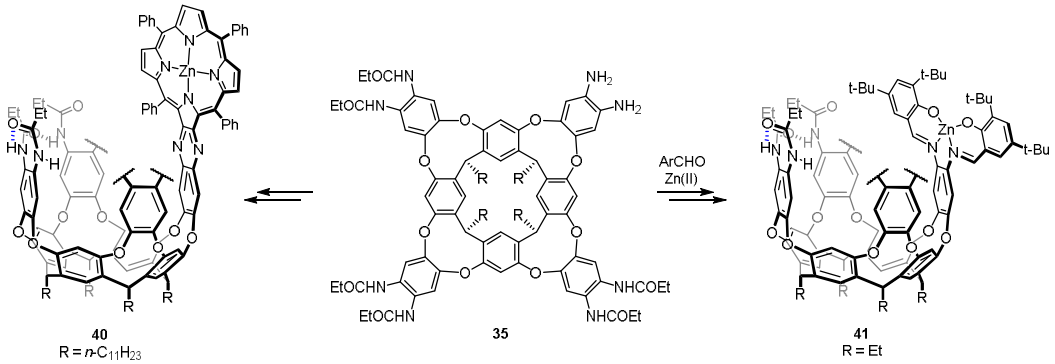


endo-**38a** *exo*-**38a**

Figure 6. *Exo* and *endo* isomers of the condensation of diamino cavitand **35** with Kemp's triacid anhydride chloride.

5.4. Metal-functionalized cavitands with heterocyclic coordination motifs

A distinct family of functionalized receptors based on the hexaamido cavitand scaffold comprises hosts functionalized with transition metal centers. To this end, a variety of heterocyclic motifs have been incorporated into the cavitand structure in order to provide an efficient coordination environment for the desired metal. The condensation of diamino derivative **35** with a porphyrin diketone provides a cavitand-porphyrin hybrid with the porphyrin functioning as the 4th panel to complete the enclosure of the receptor (Scheme 21). Single cavitands **40** or capsular assemblies containing a Zn(II)-porphyrin can be elaborated in this vein, and the resulting structures provide unusual properties and high binding constants for aliphatic guests that can also coordinate to the Zn(II) center. Cavitands with Zn centers can be constructed alternatively employing a salophen ligand system **41**.[56] This is easily accomplished by condensation of the ortho-diamino benzene intermediate **35** with two equivalents of an aromatic aldehyde (Scheme 21). The resulting Zn-salophen functionalized cavitand was found to function as a catalyst for both the hydrolysis[56b] and synthesis[56a] of choline derivatives, providing significant acceleration effects originating from the encapsulation phenomena.



40 R = *n*-$C_{11}H_{23}$ **35** **41** R = Et

Scheme 21. Synthesis of Zn(II) metallo-cavitands based on the hexaamide cavitand scaffold.

As developed in section 5.2, the benzimidazole motif constitutes a convenient way of attaching functionalities to amide-stabilized cavitands. A variety of metal containing cavitands have been prepared following this strategy (Figure 7). The incorporation of a phenanthroline unit enables de preparation of the corresponding Zn(II) metallo-cavitand **42**, with properties analogous to those of cavitands reported above.[57] Interestingly, the benzimidazole linker has proven valuable not only to embed metal containing functionalities, but also to impart complex functions upon the cavitand structure. A 2,2'-bipyridine unit, for instance, allowed the preparation of a cavitand with switching behavior, **43**.[58] The bipy arm was designed as to occupy the binding space of the cavitand with a bulky substituent, which is retracted upon Zn(II)

coordination, allowing binding of extraneous guests. In a different application, a Ru(II) complex was obtained by incorporation of a terpyridine unit to the cavitand scaffold.[59] The resulting Ru(II)-aqua complex **44** is catalytically active in olefin epoxidation reactions, although no supramolecular effects have been observed with this system.

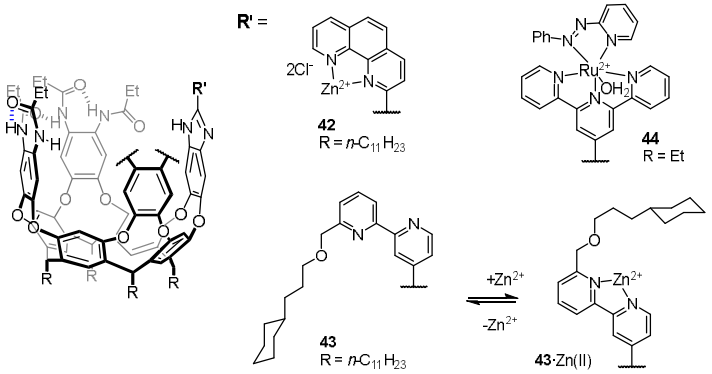
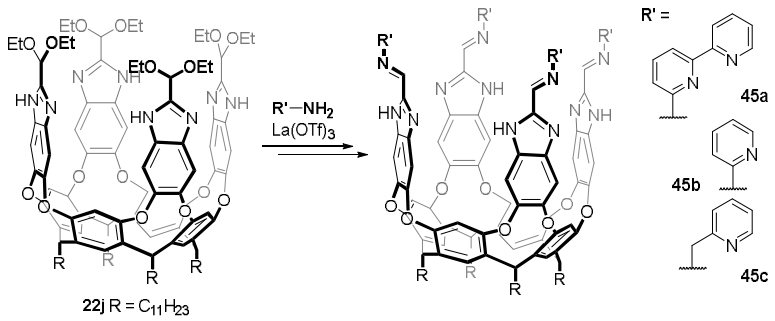


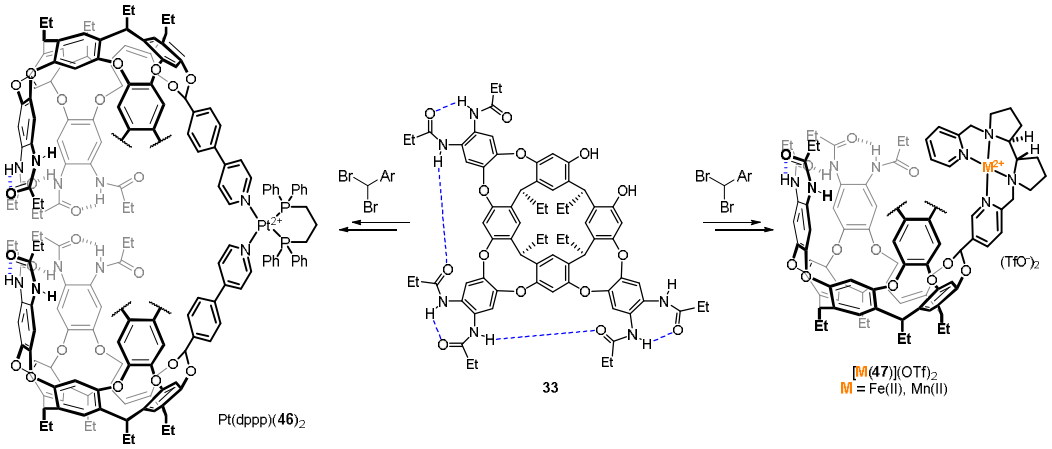
Figure 7. Benzimidazole appended hexaamido cavitands functionalized with diverse heteroaromatic coordination motifs.

The benzimidazole linkage has also been employed as a point of attachment for heterocyclic coordination motifs in completely symmetric cavitands analogous to those in section 4.2. Hooley and co-workers found that the condensation of tetraacetal cavitand **22j** and heteroaromatic amines under Lewis acid catalysis provided the corresponding tetraimines **45** in good yields (Scheme 22).[60] From **45**, the corresponding Zn(II) and La(III) complexes were obtained. In the Zn(II) complex [**45a**·Zn_2]$^{4+}$, two 2,2'-bipyridine units coordinate each Zn(II) atom in a chelated fashion.



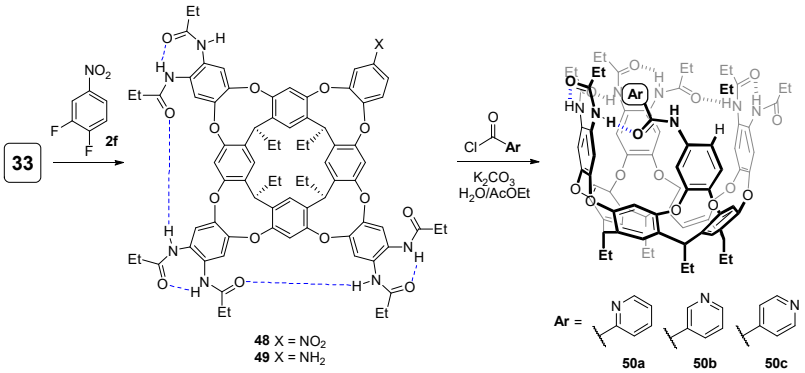
Scheme 22. Cavitand receptors functionalized with iminopyridine ligands through benzimidazole panels.

An alternative strategy to introduce metal coordinating units to the hexaamide cavitand base consists on attaching aromatic moieties through an acetal bridge between the phenolic functions of hexaamide-diol cavitand **33a**, by reaction with (dibromomethyl)-aryl derivatives (Scheme 23).[61] In this manner, a pyridyl-functionalized cavitand **46** has been obtained, which easily assembles into a ditopic container Pt(dppp)(**46**)$_2$ upon coordination to a Pt(II) metal precursor.[62] Our group has employed a similar strategy to prepare a cavitand embedded with a bis(pyridyl)dipyrrolidine unit, an excellent chelating unit for Fe and Mn (**47**).[63] The resulting Fe(II) and Mn(II) metallo-cavitands proved to be very active in bioinspired C-H and C=C oxidations employing H_2O_2 as terminal oxidant. Despite the fact that this structure is robust, and can support highly reactive high-valent metal-oxo intermediates, supramolecular or proximity driven effects have not been observed so far.



Scheme 23. Metal-assembled capsule and metallo-cavitand obtained by attaching pyridine coordination motifs to the hexaamido cavitand core through an acetal linkage.

Finally, functional cavitands can also be accessed from monoamino derivative **49**, which is obtained by condensation of difluoronitrobenzene **2f** and subsequent reduction (Scheme 24).[64] This monoamino derivative was acylated with pyridylcarboxyl chlorides to obtain pyridine functionalized heptaamido cavitands **50a-c**.[65] The coordination behavior of these receptors towards Rh(I)-norbornadiene was studied by the group of Ballester, and the resulting system was used in Rh(I)-catalyzed hydrogentation reactions. The overall aim was to develop hydrogenation reactions with unusual selectivity imparted by binding effects, which was not observed in this case.



Scheme 24. Preparation of pyridyl functionalized heptaamido cavitand receptors.

6. Conclusions

To sum up, heterocyclic motifs are ubiquitous in resorcin[4]arene derived deep cavity cavitands, for a number of reasons. In the first place, they are suitable units for bridging resorcinarenes through S_NAr reactions, the most utilized way to build up the panels that define the confined space of cavitand receptors. Secondly, the presence of heteroatoms in the panels of these synthetic cavities has profound implications for their characteristic conformational behavior. Acid-base or redox reactions can be used to bias the conformational equilibrium between open and closed states, eventually giving rise to molecular switching phenomena. The ability of heterocyclic motifs to establish hydrogen bonding and other non-covalent interactions is also important for tuning these dynamic features, and, most importantly, to trigger self-assembly of the cavitand units into multicomponent capsular assemblies. Finally, resorcin[4]arene derived

cavitands are suitable scaffolds for further functionalization with bespoke functional groups. Diverse strategies have been exploited to attach assorted heterocyclic ligands for different purposes, including bioinspired and supramolecular catalysis with transition-metal functionalized cavitands. Despite remarkable advances, the results obtained in this area showcase the challenges of imparting selectivity based on the confinement and proximity effects in synthetic host-guest systems.

Acknowledgements

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