Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis, Guest Binding, and Metal Coordination of Functionalized Self-Folding Deep Cavitands

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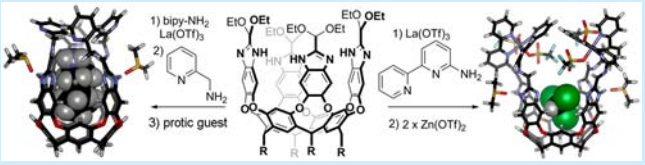
Supporting Information

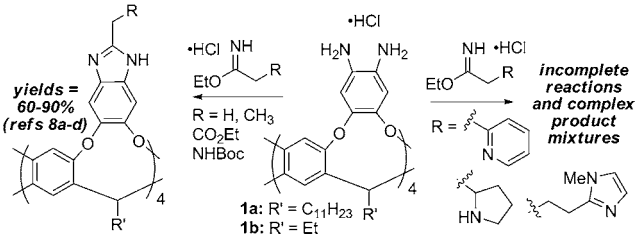
ABSTRACT: A simple method to introduce donor functions to the upper rim of self-folding benzimidazole-based deep cavitands is described. The upper rim donors allow controlled noncovalent binding of suitably sized guest species via both self-complementary hydrogen bonding and space-filling interactions, and metal-mediated self-folding is possible if bidentate coordinators are incorporated.



Deep cavitands are synthetic receptor molecules that show great potential as protein and enzyme mimics, and have applications in sensing, molecular recognition, and biomimetic catalysis.[1] Self-folding is key to the kinetic stability of these cavities: by incorporating self-complementary hydrogen bonding motifs such as secondary amides to the rim of the cavitands,[2] single conformations can be accessed that maximize target binding. Enzyme mimicry requires functions beyond host:guest binding, but conferring active functional groups to self-folded deep cavity hosts is challenging. Single functions such as carboxylic acids or aldehydes[1] can be incorporated, as can planar metal-containing species such as salen[3a] or porphyrins.[3b] These hosts are typically monofunctionalized and unsymmetrical and rely on hydrogen-bonding for self-folding. While cavitand-based capsules formed by metal coordination are well-known,[4] macrocycles that self-fold via this method are far less common.[5] Metal binding arms can be attached to rigid macrocycles and shallow bowls,[6] but the combination of hydrogen-bonding groups and metal donors in flexible deep cavities is rare.[7]

To expose any bound guest to an incorporated metal species, the donor functionalities must point *toward* the cavity. This is not possible with many known cavitand scaffolds, as appended groups are forced away from the cavity.[2] The exception are the self-folding benzimidazole cavitands[8] shown in Scheme 1, but the attachment of donor functional groups to these species has been limited due to the challenges in benzimidazole formation and the solubility of the cavitand products. Tetrabenzimidazole deep cavitands with complex functions are often challenging to synthesize due to the formation of highly insoluble velcrands.[9] Self-folding (and solubility) requires additives that contain both hydrogen-bond donors and acceptors, such as water or methanol, providing a seam of intermolecular hydrogen bonds at the cavity rim. Known methods for accessing these hosts involve treating the octaamine precursors **1** with a corresponding orthoester,[8a] alkoxyimidate,[8b,c] or aldehyde in the presence of oxidizing agents.[8d] Inert substituents such as alkyl groups or esters are tolerated, but species such as amines, heterocycles, and other functions are poorly tolerated, leading to low yields of the target or limited scope of rim functionality. Here we describe the synthesis of benzimidazole deep cavitands that display a variety of nitrogen containing groups at the rim and study their metal coordination and host:guest properties.

Scheme 1. Challenges in Functionalized Cavitand Synthesis[8]



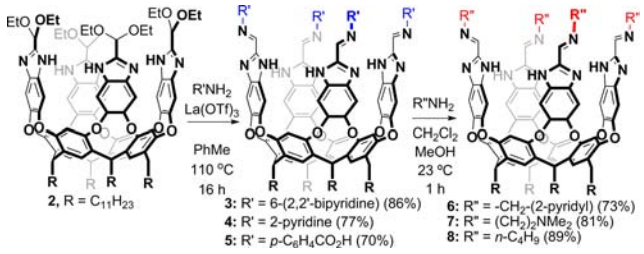
The roadblock in the synthesis is often the requirement for acid-catalyzed heterocycle formation (Scheme 1). While simple hydrocarbon or ester groups can be easily added to the known cavitand precursor scaffolds **1** via condensation with the corresponding imidate HCl salt in anhydrous ethanol, introduction of *N*-donor groups is far more challenging. For example, *N*-methylimidazole-based imidate HCl salts can be synthesized relatively simply (see the Supporting Information) but are extremely sensitive to moisture and form complex mixtures when reacted with **1**, even in vast excesses of imidate. To determine a reliable synthetic method for the introduction of complex *N*-donor functions to benzimidazole scaffolds, we focused on an alternate synthetic route from the recently reported octaethylacetal cavitand **2**.[10] The acetal imidate required for synthesis of **2** is stable and reacts well with **1**, with none of the drawbacks associated with more complex imidate incorporation. Previously, cavitand **2** was applied to covalent cage formation via acid-catalyzed reaction with *p*-phenylenediamine,[10] and a similar acetal to imine conversion to introduce donor substituents to a cavitand rim seemed plausible. In our

Received: February 5, 2015
Published: March 11, 2015

DOI: 10.1021/acs.orglett.5b00383
Org. Lett. 2015, 17, 1497−1500

hands, however, treatment of **2** with 2-pyridylamine and trifluoroacetic acid under the previously described conditions gave poor conversions to the desired pyridyl imine cavitand **4**. An alternate method of converting dialkyl acetals to substituted imines is to use anhydrous Lewis acid catalysts for the condensation. Strong Lewis acids such as $Ti(O^iPr)_4$ and $AlCl_3$ were unsuccessful in this case, but the application of $La(OTf)_3$ proved effective.[11] To test the scope of the rim functionalization process, we exposed acetal cavitand **2** to a variety of different amine nucleophiles in the presence of catalytic $La(OTf)_3$. The more basic amines such as primary alkylamines (*n*-butylamine, *unsym*-dimethylethylenediamine, and 2-picolylamine) were not amenable to the reaction, giving a mixture of starting materials and partially reacted cavitands that were challenging to purify. On the other hand, less basic nucleophiles such as aniline derivatives were excellent partners for the reaction. Imine-based cavitands **3**–**5** were synthesized in good to excellent yield (Scheme 2) with minimal purification required. The reaction was

Scheme 2. New Strategy for Coordinating Cavitand Scaffolds



tolerant to functional groups on the arylamine such as carboxylic acids, as well as donor nitrogen atoms in pyridine groups (**3**, **4**).

While the scope of direct functionalization by this method is limited to arylamines, the more basic nucleophiles can be simply introduced by transimination. While the arylimine cavitands **3**–**5** are stable to water and other alcoholic nucleophiles under the conditions used to obtain NMR data, they are susceptible to reaction with stronger nucleophiles such as primary amines. Simple sonication of the bipyridyl derivative **3** with primary alkylamines such as 2-picolyamine or *unsym*-*N*,*N*-dimethylethylenediamine in a mixture of CH_2Cl_2/MeOH for 1 h smoothly gave the corresponding alkylimine cavitands **6** and **7** in good yields. The nucleophiles need not contain extra coordinating nitrogens: cyclohexylamine was also a suitable substrate, although reaction with more hindered primary alkylamines such as adamantanamine was unsuccessful. This combination of synthetic strategies allows access to a wide range of functionalities at the cavitand rim, either directly from **2** or via subsequent transimination of **3** or **4**.

The derivatized tetraimine cavitands displayed unusual folding properties. When bipyridyl cavitand **3** was dissolved in anhydrous $CDCl_3$, the ^{1}H NMR spectrum showed broad and undefined peaks for the cavitand and resorcinarene protons that are attributed to the cavitand "flexing" between the vase- and kitelike conformations, as expected (Figure 1b).[2] While most benzimidazole cavitands form kinetically stable vase conformations upon the addition of small amounts of water due to the hydrogen bonds provided to the benzimidazole walls,[8a] this was not the case for **3** and **4**. In either $CDCl_3$ (Figure 1b) or $CDCl_3$ + small amounts of water/MeOH, the ^{1}H NMR spectrum was broad, indicating that the cavitand is flexible in solution. The methine peak at δ 5.6 ppm suggests the vase form is present, but the cavitand flexes between conformations at ambient temperature. Addition of 1–5% DMSO-d_6 to a $CDCl_3$ solution of **3** provided a well-defined ^{1}H NMR spectrum (Figures 1c,d), suggesting that the cavitand is rigid and exists in the vase-like conformation in this environment due to intermolecular hydrogen bonding. Presumably, the strongly donating nitrogen atoms of the functional groups at the rim outcompete the benzimidazoles for H-bond donors, whereas hydrogen bond *acceptors* such as sulfoxides are unaffected. As DMSO does not provide both H-bond donor and acceptor groups, it is likely that two DMSO molecules are incorporated between two benzimidazole NH groups at the rim (Figure 1), as opposed to the more usual four water molecules.[12] This method of folding is unusual among benzimidazole cavitands,[13] and the folded vase conformation of bipyridyl cavitand **3** stabilized by DMSO is less robust than the unfunctionalized cavitands (e.g., **2**) that employ methanol or water. The ^{1}H NMR spectrum appears symmetrical at room temperature, but the DMSO molecules are in a state of rapid exchange between the benzimidazoles, causing rapid equilibration between the two states. When the system is cooled to −40 °C, significant broadening of the cavitand resonances occurs, indicating intermediate exchange rates of the DMSO molecules (see the Supporting Information for spectra).

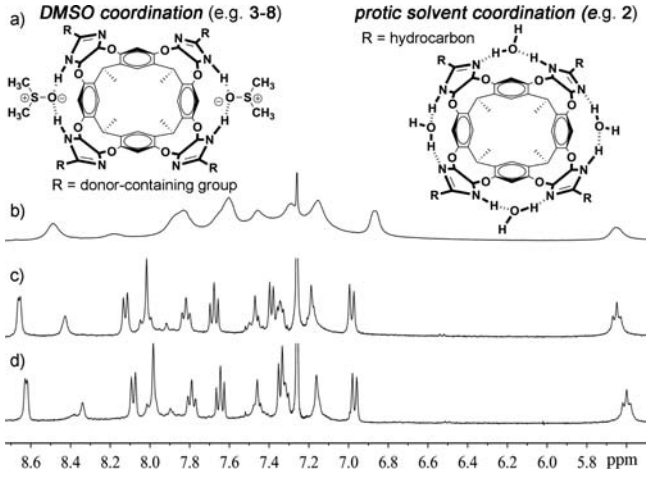


Figure 1. Self-folding patterns of benzimidazole cavitands: (a) possible coordination modes; downfield regions of the ^{1}H NMR spectra (400 MHz, 298 K) of (b) 4 mM **3**, $CDCl_3$; (c) 4 mM **3**, 2% DMSO-d_6 in $CDCl_3$; (d) 4 mM **3**, 5% DMSO-d_6 in $CDCl_3$.

Cavitands **3**, **4**, **6**, and **7** provide the opportunity to coordinate metal ions at the cavitand rim. The synthetic route allows simple introduction of a variable number of *N*-donors at each wall, including the imine nitrogen that is present in all cases. The cavitands can be separated into three distinct types: 4 × 2, 4 × 2/1, and 4 × 1 donors, referring to the number of accessible N donors on each wall. Bipyridyl cavitand **3** displays two donor nitrogens from each of the four bipyridyl groups, and the imine nitrogen is unlikely to participate due to angle strain, hence 4 × 2. Cavitands **6** and **7** provide one donor nitrogen from each wall, but in these cases participation of the imine nitrogen is more likely, leading to two possible coordination types 4 × 2/1. Cavitand **4** can only use its pyridyl nitrogen for coordination and is described as 4 × 1.

As might be expected, bipyridyl cavitand **3** was the most strongly coordinating host. While **3** showed complexation with both Fe^{2+} and Cu^{2+} ions, the paramagnetic nature of the complexes between these metals and **3** led to broadened ^{1}H NMR spectra and limited the possible structural analysis.

DOI: 10.1021/acs.orglett.5b00383
Org. Lett. 2015, 17, 1497–1500

Attempts to obtain X-ray quality crystals of the highly lipophilic and flexible metal−cavitand complexes were unsuccessful, and so $Zn(OTf)_2$ was used to study metal coordination with cavitand **3** by ^{1}H NMR. The partially assigned ^{1}H NMR spectra are shown in Figure 2, and they indicate reversible binding of Zn^{2+}. The

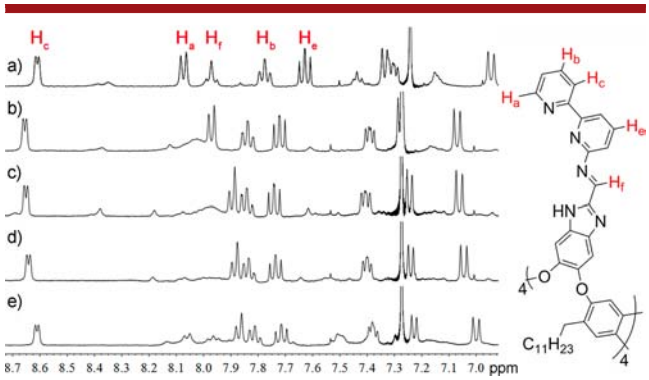


Figure 2. Metal binding properties of **3**: Downfield regions of the ^{1}H NMR spectra (400 MHz, 298 K, 5% DMSO-d_6 in $CDCl_3$, 4 mM **3**) of the addition of 0, 1, 2, 3, or 5 equiv of $Zn(OTf)_2$ to **3** (a−e, respectively).

most shifted resonances belong to the *ortho* proton H_a as well as the protons *para* to the bipy nitrogens (H_b and H_e). The imine CH proton H_f is relatively unaffected, suggesting that **3** is capable of binding Zn^{2+} only through the bipyridine nitrogens. Upon addition of 2 equiv of Zn^{2+}, a single complex was formed, and no further changes to the ^{1}H NMR spectrum occurred if further Zn^{2+} was added. The most favorable coordination mode is evidently that shown in Figure 3a, whereby each Zn^{2+} ion is

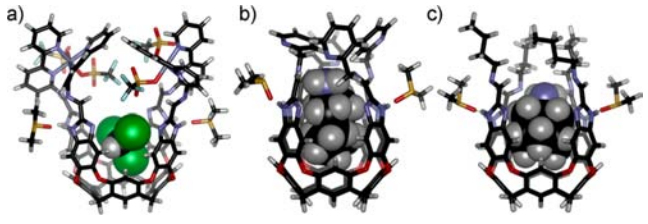


Figure 3. Metal coordination and guest binding. Minimized structures (SPARTAN, AM1 force field) of (a) self-folded metal cavitand complex **3**·$Zn_2(OTf)_4$; (b) host:guest complex **6**·cyclooctylamine; (c) host:guest complex **8**·adamantanamine.

coordinated by two bipyridyl units. The affinity of **3** for Zn^{2+} ions is relatively strong, as two equivalents of Zn^{2+} is sufficient (at NMR concentrations) to fully saturate the cavitand. It should be noted that the addition of Zn^{2+} ions is not sufficient to self-fold the cavitand in the absence of an additional coordinator such as DMSO-d_6. If two equivalents $Zn(OTf)_2$ are added to a solution of **3** in anhydrous $CDCl_3$ (absent any coordinating DMSO-d_6), no discrete folded structure forms, and a broad NMR spectrum is observed. Only in the presence of *both* metal and H-bond coordinators is the structure shown in Figure 3 formed. Cavitand **3** was also capable of coordinating other metal ions, albeit more weakly: addition of $La(NO_3)_3$ gave similar results to $Zn(OTf)_2$ (see the Supporting Information for spectra).

The lack of involvement of the imine nitrogen in metal binding was corroborated by the other cavitands. Pyridyl cavitand **4**, which has a "4 × 1" donor mode, showed no metal binding at all: evidently, the enthalpic benefit of pyridine−Zn^{2+} coordination is not sufficient to overcome the entropic penalty of rigidifying the flexible cavitand. The more strongly donating cavitands **6** and **7** did show some affinity for Zn^{2+} salts, but only minor changes in the ^{1}H NMR spectra were observed, and no single end point was obtained even in the presence of excess metal. The donor groups evidently display weak coordination with Zn^{2+} ions, but no discrete complex is formed.

Benzimidazole cavitands are well-known to bind suitably sized guests, but the selectivity and guest binding scope varies wildly, dependent on the solvent used and the functionality at the rim. The widest scope and strongest binding occur in water when hydrophobic effects can be exploited.[8b] Addition of sterically bulky groups to the cavitand rim can restrict the opening, shrinking the effective cavity size and favoring smaller guests.[8e] In organic solution, solvent competition lowers guest affinity markedly, and flexible arms can self-complex, also providing competition.[8f] On the other hand, favorable charge or H-bonding interactions can be added by altering the rim functions,[14] so the scope of guest binding by either **3**−**7** or their metal complexes was not predictable.

Bipyridyl cavitand **3** was a very poor host in organic solvents: species such as cyclohexane, choline, and NMe_4Br that are strong guests for other, unfunctionalized cavitands[2,8] showed only minimal affinity for **3** (K_a < 10 mM). The addition of the large bipyridyl groups at the rim evidently blocks the cavity opening, and solvent competition from $CDCl_3$ dominates. Without any hydrophobic driving forces, guest binding is minimal. Larger guests such as cyclohexane and adamantane showed no affinity, even in large excess. The metal coordinated **3**·Zn_2 fared even worse: the rigidified arms provide a greater barrier to guest incorporation, and no binding of choline or NMe_4Br was seen. The bipyridyl arms are reversibly coordinated, so **3**·Zn_2 was heated for 4 h with both choline or NMe_4Br to establish whether the low affinity was due to a kinetic barrier to guest entry, but no affinity was seen under these conditions either. Most likely, the rotating bipyridyl arms provide a weak blocking effect,[8e] reducing the effective size of the cavity and favoring smaller guests; notably, the $CDCl_3$ solvent.

While cavitands **3** and **3**·Zn_2 were ineffective hosts, the cavitands with less obtrusive upper rim functionality showed interesting selectivity. Picolylimine cavitand **6** showed no affinity for unfunctionalized hydrocarbon guests that ostensibly fill the cavity. On the other hand, when substituted amine guests were added to a $CDCl_3$/5% DMSO-d_6 solution of **6**, host:guest complexation was observed that outcompeted solvent binding. Guest binding required both a protic group and suitable size: adamantanamine, cyclohexylamine, cyclooctylamine, and cyclohexanecarboxylic acid showed affinity for **6** (see Figure 4), whereas cyclohexane, sodium cyclohexane−carboxylate, and NMe_4Br were ineffective guests. Although some of these amine guests are able to effect transimination at higher concentrations, the binding experiments were performed at low concentration, and the NMR spectrum was taken immediately after addition. No transimination or cavitand decomposition was observed under these conditions.

N,N-Dimethylethylenediamine cavitand **7** showed similar binding properties: suitably sized protic guests were bound in the cavity. Short amines such as isobutylamine, *tert*-butylamine, and *n*-butylamine were not observed to bind inside the cavity. The fact that cyclooctane and adamantane showed no affinity for the host while their amine counterparts were successfully bound suggests that the amine plays a role in the binding of these guests inside **7**. The ^{1}H NMR spectra of the bound guests are remarkably similar to those in other deep cavitands where the

DOI: 10.1021/acs.orglett.5b00383
Org. Lett. 2015, 17, 1497−1500

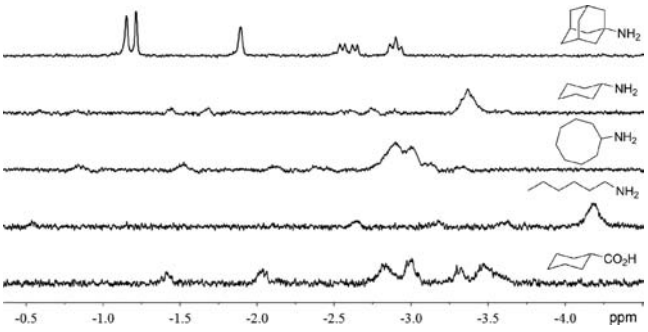


Figure 4. Upfield regions of the ^{1}H NMR spectra (400 MHz, 5% DMSO-d_6 in $CDCl_3$, 298 K, 4 mM **6**) obtained upon addition of excess protic guest to cavitand **6**.

hydrocarbon group fills the cavity,[14b] and the functionality points upward: minimized structures of the host:guest complexes are shown in Figure 3b,c. This orientation explains the guest selectivity: the donor N atoms in the rim groups provide favorable H-bonding with the guest, favoring the complexation process. The target must still fill the cavity for binding: small amines were not bound. Addition of metal salts to either **6** or **7** eliminated any host properties of these cavitands. It is unclear why this would limit guest affinity, but it is likely that the metal salts weakly coordinated the N-donor atoms in the nonpolar solvent system, either blocking the cavity (as in **3**·Zn_2) or removing any favorable H-bonding with the guests. Unfortunately, peaks for the NH protons in the bound guest are buried beneath free guest peaks, so direct ^{1}H NMR evidence for the interaction is not observable. Interestingly, multiple *N* donors are not necessary, and the imine nitrogens themselves are sufficient: butylimine cavitand **8** is also a suitable host. The free cavitand is not kinetically stable: the ^{1}H NMR spectrum is broad and ill-defined (see the Supporting Information), and addition of either water or DMSO to the $CDCl_3$ solution does not promote folding. Cavitand **8** can fold around a strong guest such as admantanamine, however. The range of guests was the same as for **6** and **7**, and unfunctionalized cyclic hydrocarbons were not bound.

In conclusion, we have shown a new, simple method for the introduction of donor functionality to the upper rim of flexible deep cavitands and analyzed the effect on self-folding, metal coordination, and guest binding. The upper rim imine species provide a handle for controlled noncovalent binding of suitably sized guest species via both self-complementary hydrogen bonding and space-filling interactions. Metal-mediated self-folding can be applied if a sufficiently strong coordinator is added to the upper rim: four bipyridyl groups coordinate two zinc(II) ions above the cavity, controlling the cavitand entrance and limiting target binding.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is sponsored by the National Science Foundation (CHE-1151773 to R.J.H. and a Bridge to the Doctorate Fellowship for M.M.). M.P.M. acknowledges support through a US Department of Education GAANN Award No. P200A120170. Prof. Julius Rebek, Jr. (The Scripps Research Institute, La Jolla) is thanked for initial discussion.

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DOI: 10.1021/acs.orglett.5b00383
Org. Lett. 2015, 17, 1497−1500