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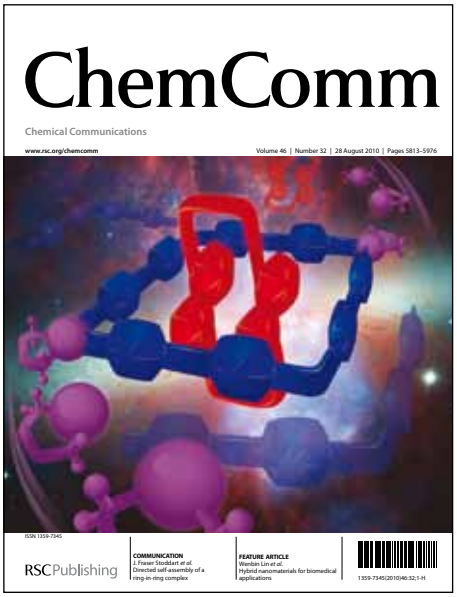


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ARTICLE TYPE

# Deep Cavitands Featuring Functional Acetal-Based Walls

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**The synthesis of deep cavitands with functionalized acetals as a fourth-wall is described. Recognition properties and stabilities of the complexes of two representative cavitands with aliphatic, aromatic, carbocyclic and adamantane guests were evaluated by NMR methods.**

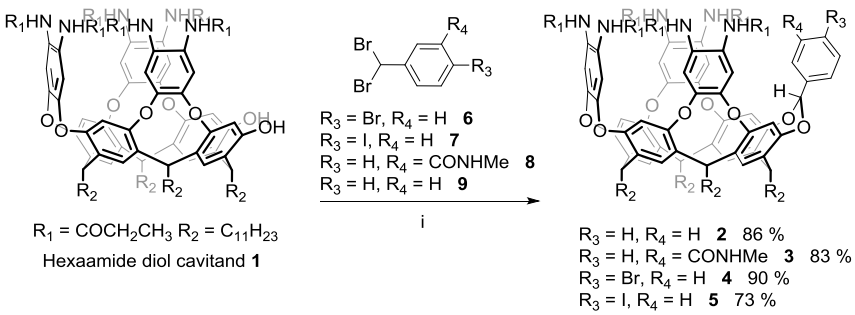
Self-folding cavitands are resorcinarene-based synthetic receptors providing a deep vase-like shape that can be stabilized by a seam of intramolecular hydrogen bonds.[1] Their cavities show molecular recognition properties and act as hydrophobic nano environments that can promote molecular interactions.[2] Reduced symmetry hosts formed by six amide groups and a functionalized panel were used for the isolation and characterization of elusive reaction intermediates and to accelerate, even catalyze, organic reactions within their cavities.[3] The hexaamide diol cavitand **1**[4] (Scheme 1) is the module for the introduction of new functions.[2b, 3b] However, the formation of deep cavitands via the stereoselective bridging of resorcinarenes with four benzal bromides was introduced by Gibb, and resulted in a new generation of container molecules.[5] We recently used an acetal to functionalize hexaamide diol **1** with a pyridyl group as a fourth wall.[6] Here we report the versatility of this approach to access a range of monofunctionalized cavitands with unique recognition properties.

The hexaamide diol cavitand **1** was outfitted with various phenyl acetal walls: unsubstituted, *meta*-methylamide, *para*-bromo and *para*-iodo, providing respectively cavitands **2**-**5** (Scheme 1). The requisite (noncommercial) benzal bromide derivatives **6** and **7** were prepared according to literature precedents,[5a, 5b] by treatment of suitable benzaldehyde derivatives with boron tribromide in dichloromethane, whereas **8** was synthesized from *m*-toluic acid through a radical bromination.[7]

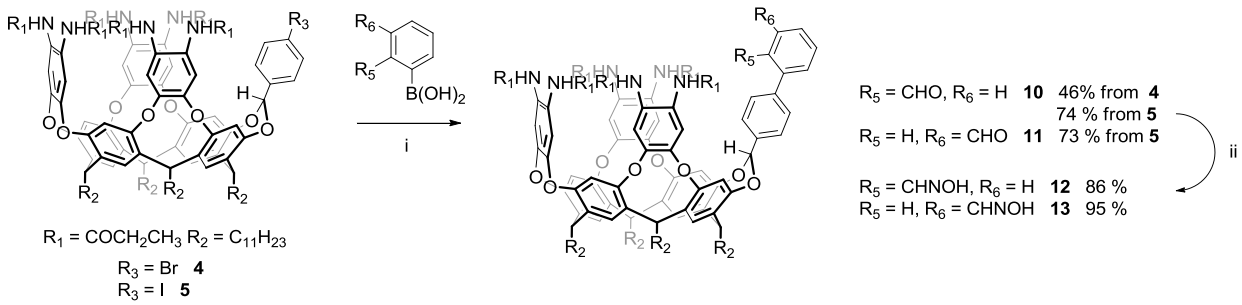
The α,α-dibromotoluene **9** and benzal bromide derivatives **6**-**8** were installed on the hexaamide diol cavitand **1** featuring $C_{11}$ feet by treatment for 3 days at 60°C in *N*,*N*-dimethylacetamide in the presence of DBU as an homogeneous base.[5b] Hexaamide acetal cavitand **2**, heptaamide acetal cavitand **3** and halogenated cavitands **4** and **5** were obtained in 86 %, 83 %, 90 % and 73 % yields, respectively, after purification (Scheme 1).

Although two diastereoisomers (inward and outward orientation of the benzal hydrogen) might have been formed during the reaction, TLC and crude $^1$H NMR spectra showed the exclusive formation of only one isomer, the one with the inwardly-directed hydrogen. The chemical shifts of the benzal hydrogens of cavitands **2**-**5** (δ = 5.38 ppm, 5.32 ppm, 5.30 ppm and 5.30 ppm, respectively, in chloroform-$d_1$) are in accordance with the literature in a similar solvent (δ = 5.38 ppm in dichloromethane-$d_2$) confirming their inward orientations.[6, 8]

We used halogenated acetal cavitands **4** and **5** as substrates for Suzuki-Miyaura couplings (Scheme 2). Treatment of **4** with $PdCl_2(PPh_3)_2$ in aqueous sodium carbonate (1M) and THF for 24 hours at 70°C led to the *ortho*-formylated cavitand **10** in 46 % yield after purification. The same conditions were applied to the iodo derivative cavitand **5** and improved the isolated yield to 74 %. The *meta*-formylated derivative **11** was obtained in the same way by coupling 3-formylphenylboronic acid with **5** in 73 % yield. Formylated cavitands **10** and **11** were also derivatized by




**Scheme 1** Installation of various acetal walls on the hexaamide diol cavitand **1** providing acetal cavitands **2** - **5**. Reagents and conditions: (i) **1** (1 equiv), benzal bromide derivative **6**-**9** (4-4.6 equiv), DBU (4-4.8 equiv), DMA, 60°C, 3 days.




**Scheme 2** Functionalization of acetal cavitands by Suzuki-Miyaura couplings on halogenated precursor cavitands **4-5** and derivatization to oximes **12-13**. Reagents and conditions: (i) $PdCl_2(PPh)_3$, aq $Na_2CO_3$ 1M/THF 30/70 (v/v), 70°C, 24 h ; (ii) $NH_2OH$ • HCl, aq NaOH 1M/THF 50/50 (v/v), RT, 24 h.

condensation of hydroxylamine hydrochloride in THF at room temperature in presence of aqueous 1M NaOH. Oxime cavitands **12** and **13** were obtained in 86 % and 95 % yields, respectively.

Accordingly, cavitand **5** represents a versatile platform for the introduction of numerous functionalities, thanks to the impressive number of boronic acid derivatives available commercially or through synthesis. All new compounds were fully characterized by $^1H$, $^{13}C$ NMR spectroscopy and MALDI-TOF or ESI mass spectroscopy.

Acetal cavitands **2-5** differ from the other well-known deep resorcinarene-based hexaamide cavitands. The inwardly-oriented benzal hydrogen modifies the inner space at the bottom of the cavity, by decreasing its symmetry,[7] and the free rotation of the phenyl group can decrease the shielding effect experienced by complexed guests. First, binding studies were conducted to compare the recognition properties and to ascertain these influences between host **2** and the reference octaamide.[7]

A series of ten guests (Fig. 1) were screened with cavitand **2** at 300 K and 270 K in mesitylene-$d_{12}$, a non-competitive solvent. To build a binding profile of the cavity shape, we chose a list of guests composed of aliphatic chains, aromatic, alicyclic derivatives and the bulky 2,2'-paracyclophane.

No kinetically stable inclusion complex with host **2** could be detected at either 300 K or 270 K with toluene derivatives **G1, G2** or 2,2'-paracyclophane **G3** which is one of the largest guests known for resorcinarene-based cavitands.[9] Adamantane derivatives are particularly good complements for the cavity of the octaamide cavitands.[1a, 10] Guests 2-adamantanone **G4** and 1-adamantane carbonitrile **G5** both bound **2** at 270 K with respective $K_a$ values of 170 $M^{-1}$ and 50 $M^{-1}$ (Table 1). The most upfield signals of bound **G4** and **G5** show chemical shifts respectively of δ = -0.6 ppm and δ = -1 ppm while **G5** gave a value of δ = -2 ppm with reference octaamide cavitand.[11] The chemical shifts of the guest signals are directly related to their positions inside the cavity; in particular, the deeper a nucleus resides, the more it is magnetically shielded. It appears that the adamantane anchors of both guests **G4** and **G5** float higher in the cavity of host **2** than in the octaamide cavitand; the benzal hydrogen at the bottom of the cavity apparently prevents deeper sinking of the adamantane into the cavity. Also, the divergent orientation of the phenyl acetal wall likely reduces the magnetic shielding.

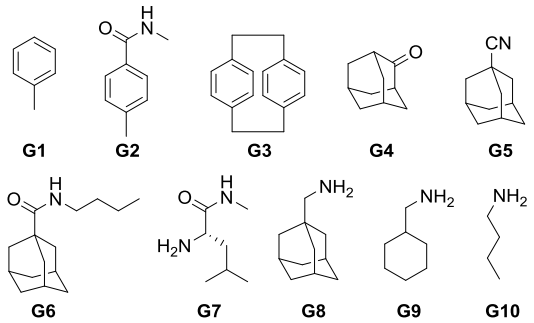



**Fig. 1** Guests screened with cavitands **2** and **3** in this study.

**Table 1** Thermodynamic parameters $K_a$ for host **2** and **3** (2 mM) with guests **G4** – **G6** determined by $^1H$ NMR in mesitylene-$d_{12}$ at 300 K and 270 K.

| | $K_a$ ($M^{-1}$) [a] Hexaamide **2** | | $K_a$ ($M^{-1}$) [a] Heptaamide **3** | |
|---|---|---|---|---|
| | 300 K | 270 K | 300 K | 270 K |
| **G4** | - | 170 | broad | 440 |
| **G5** | - | 50 | 40 | 200 |
| **G6** | broad | 435 | broad | 740 |

The symbol "-" denotes that no binding was observed; [a] Errors are within 10 % from an average of at least three experiments.

With *n*-butyl-1-carboxamide adamantane **G6**, two broad bound guest signals are observed at 300 K (δ = -0.74, -1.09 ppm). At 270 K, a $K_a$ value of 435 $M^{-1}$ was determined and the bound signals (δ = -0.82 and δ = -1.15 ppm) were sharper than for the two previous adamantane guests **G4** and **G5** showing a higher kinetic stability of the host-guest complex, as previously observed with octaamide cavitand.[12] The ability of **G6** to form hydrogen bonds with the amides at the host's rim improves its binding to **2** at 300 K. However, toluyl derivative (toluene methylamide **G2**), branched alkyl chain (leucine methylamide **G7**) and alicyclic derivatives (adamantane methylamine **G8** and cyclohexylmethylamine **G9**) – all able to form such hydrogen bonds – showed no kinetically stable complexes with **2** on the NMR timescale at 300 K. Only a broad signal was observed with **G7** and **G8** indicating little kinetic stability at the lowest temperature (270 K). With **G9**, a complex pattern displaying broad bound guest signals is observed in the upfield region at 270 K, this might be due to the chiral environment experienced by the

complexed guest.[12]

A fast-exchange complex (on the NMR timescale) was observed between **2** and **G10**. The use of 0.5 equivalent of guest allowed the observation of a set of three guest signals at 300 K which shift upfield when the temperature decreases.[7] With a higher amount of guest (1 equiv), no guest signal could be observed in the upfield area, showing a reduced stability. Free amine may interact with the seam of hydrogen bonds formed by the six amides of the rim of the cavitand and thereby destabilize the complexed state between the amine and **2**.

A **hepta**-amide acetal cavitand **3** was obtained by introducing an amide group at the *meta* position on the phenyl wall. The effect of the additional hydrogen-bonding site was apparent by comparing **2** and **3** in variable temperature NMR experiments[7] in chloroform-$d_1$ but the effect was modest.[13] These VT-NMR observations were supported by modelling studies.[7] The acetal amide can act as a hydrogen bond acceptor with good geometry (NH…O angle = 170°; length = 1.86 Å) or as an hydrogen bond donor (NH…O angle = 165°; length = 1.85 Å).

The thermodynamic parameters for complexation of well-behaved guests **G4**-**G6** with hosts **2** and **3** are compared in Table 1. Compounds **G4** and **G5** bind host **3** at 270 K with respective association constant values $K_a$ of 440 $M^{-1}$ and 200 $M^{-1}$, being higher than 170 $M^{-1}$ and 50 $M^{-1}$ for the same guests with **2**, indicating stabilization of the inclusion complexes with host **3** compared to **2**. With **G6**, a broad signal was observed at 300 K while, at 270 K, sharper signals were observed, showing a kinetically stable complex with a $K_a$ of 740 $M^{-1}$. In addition, the bound signals patterns with **2** and **3** denote slightly different positions and orientations of the guests inside their cavities (Fig. 2).

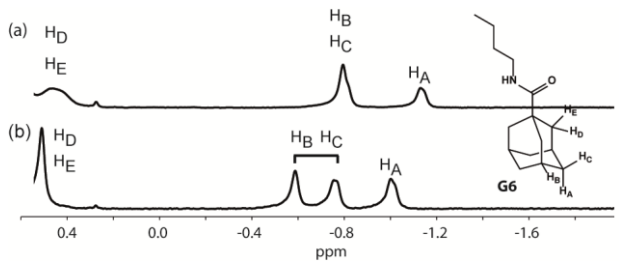



**Fig. 2** Partial $^1$H NMR spectra (600 MHz, mesitylene-$d_{12}$, 270 K) of guest **G6** with cavitands (a) **2** and (b) **3**. Hydrogen assignments were determined with 2D NOESY experiments.

In summary, acetal-bound walls were installed on a hexaamide diol cavitand to allow further functionalization through Suzuki-Miyaura coupling. A wide range of introverted functionalities could be introduced with this strategy. Host-guest complexes were observed with adamantane guests with binding constants ranging from 40 to 740 $M^{-1}$. The introduction of an additional hydrogen bonding site resulted in modest increases in the stability of the complexes. Applications of this new family of synthetic receptors bearing introverted functionalities will be reported in due course.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Synthetic procedures and characterization data for compounds **2**-**5**, **7**, **10**-**13**, NMR spectra of the studied host-guest systems, VT-NMR and NOESY experiments. See DOI: 10.1039/b000000x/

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