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Complementary Binding in Urea-Based Self-Folding Cavitands

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Supporting Information

ABSTRACT: A new family of cavitands bearing urea groups has been prepared. The hosts display a fluxional behavior akin to that of amide analogues. The ureido functions serve a dual role, stabilizing the folded conformer of the receptor and providing stabilization to guests present in the cavity.

Self-folding cavitands are a unique type of artificial receptors that are stabilized in their closed, concave conformation by means of a hydrogen bond network of secondary amides, very much like the one stabilizing secondary structure in proteins (Figure 1).[1] As a result, these receptors present a rich and

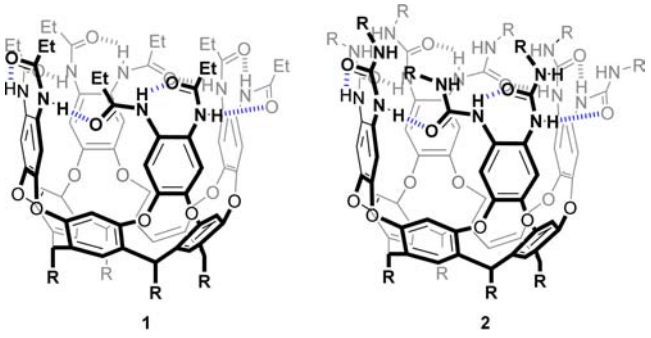


Figure 1. Amide (**1**) vs urea (**2**) stabilized cavitands.

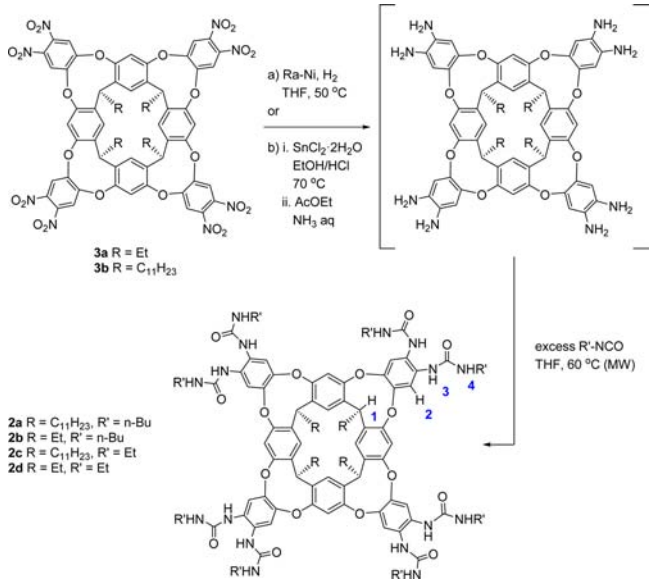
useful fluxional behavior not found in systems locked by covalent or dative bonds (carcerands and coordination cages, respectively). Self-folding cavitands have been used to stabilize and isolate elusive reaction intermediates and, to a much lesser extent, to replicate the mechanisms of biocatalysis.[2]

In the context of a nascent research program devoted to the development of supramolecular biomimetic catalysis, the preparation of self-folding structures with enhanced functions was envisaged. Rather than seeking selectivity for a particular type of guest, the focus was put on developing a multipurpose receptor, able to recognize intermediates with disparate electronic profiles which may occur, for instance, in carbocationic cyclizations. Presented herein are a new family of urea stabilized cavitands (**2**) and their molecular recognition properties.

Functional cavitands are typically nonsymmetric molecules requiring extensive synthetic effort. At the onset of this work, it was hypothesized whether structural elements and functional groups could be integrated in a symmetric, minimalistic design of straightforward access. Ureido groups seemed suitable to exert this dual function, maintaining the stabilizing hydrogen bond seam along the cavitand's rim while serving as eventual anchors for properly positioned guests through rotation about the *N*-aryl linkage. *N*,*N*′-Disubstituted ureas are well-known receptors for anions and neutral electrophiles.[3,4]

Cavitands **2a**−**d** were prepared in two steps from known octanitroderivatives **3a**,**b**[5] as depicted in Scheme 1. Following reduction with tin(II) chloride or Raney-Nickel under a

Scheme 1. Synthesis of Cavitands 2a−d



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hydrogen atmosphere, the isolated crude octaamine was reacted immediately with the required isocyanate under microwave heating. Different R and R′ aliphatic chains were appended to the cavitand to regulate solubility in organic solvents, which was found to be governed chiefly by the R′ groups at the highly polar upper rim of the cavitand. The more lipophilic derivative **2a** is soluble in common polar organic solvents such as acetone, chloroform, or THF but poorly soluble in hydrocarbons such as toluene. At the other extreme, cavitand **2d** was only solubilized in THF or mixtures thereof.

The ^{1}H NMR spectra of **2a**−**d** are consistent with a structure of C_{4v}-averaged symmetry and display a triplet at δ 5.7−5.8 ppm for the methine proton of the resorcinarene core (H1), diagnostic for the cavitand adopting a closed "vase" conformation (Figure 2).[6] At 298 K, broad resonances are

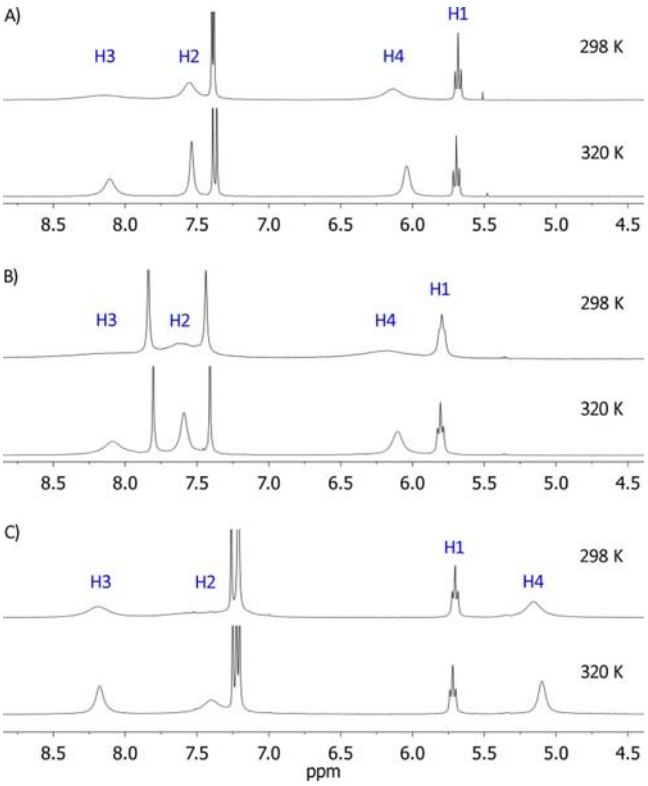

Figure 2. Downfield regions of the ^{1}H NMR spectra of (A) **2d** in THF-d_8, (B) **2a** in acetone-d_6, and (C) **2a** in $CDCl_3$.

observed for both H2, H3, and H4 (see numbering in Scheme 1), suggesting that a fluxional process involving the urea moieties is taking place at a slow rate relative to the NMR time frame. These resonances sharpen up upon heating; at low temperature, the symmetry is lost and the signals split into a complex pattern (see the Supporting Information). Rather than simple concerted rotation about the N−C_{Ar} bond observed in amide derived cavitands, a more complex process must be invoked for cavitands **2a**−**d**, involving *cis-trans* isomery of the ureido groups.[7] The small temperature coefficients observed, especially for H3, suggest the formation of a cooperative cyclic array of hydrogen bonds along the rim. This is corroborated by a molecular model of **2** computed at the DFT level of theory (see the Supporting Information). The model shows that H4 is not engaging effectively in hydrogen bonding (CO···HN distance ∼3 Å) and must be more exposed to solvent. This is well corroborated by the downfield shift experienced by H4 when changing from $CDCl_3$ to solvents with hydrogen-bond-accepting abilities (acetone-d_6, THF-d_8, $\Delta\delta \sim 1$, Figure 2).

Despite the propensity of other urea-decorated macrocycles to form self-assembled aggregates,[8] the cavitands exist solely in monomeric form in solution, as ascertained by ^{1}H NMR diffusion experiments.[9] Cavitand **2d** has a diffusion coefficient (D) of 4.4 × 10^{-6} cm^2 s^{-1} in THF-d_8 ([**2d**] = 4.5 mM, T = 298 K), which is in good agreement with the value found for **1a** (R = Et, D = 4.9 × 10^{-6} cm^2 s^{-1}) at the same concentration and temperature. The monomeric species is also observed preferentially in the gas phase, even if guests are absent (see the Supporting Information).

A guest screening was next performed to probe the molecular recognition properties of the newly prepared cavitands (Figure 3). Similar to host−guest complexes based on **1**, urea-based

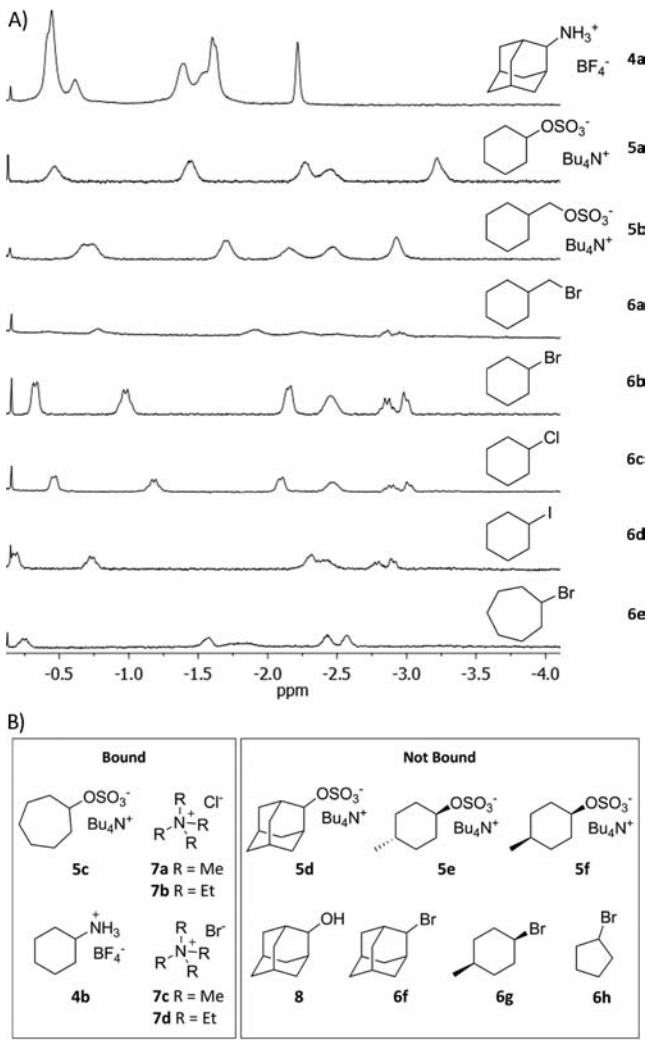

Figure 3. (A) Upfield region of ^{1}H NMR spectra for various complexes of **2a**. (B) Other guests used in this study.

cavitands provide complexes which are kinetically stable in the NMR time scale. Molecules buried in the deep cavity experience strong upfield shifts in the ^{1}H NMR spectra caused by the anisotropic shielding of multiple aromatic rings; the deeper an atom is positioned the stronger the shift is.[10] Primary ammonium cations with an alicyclic fragment which properly fills the space (**4a**,**b**) are bound effectively in $CDCl_3$ and acetone-d_6.[11] In addition to attractive CH−π interactions

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occurring in the aromatic cavity, additional electrostatic interactions with the carbonyl groups at the rim are necessary for effective binding (compare guests **4a**/**8**). This secondary interaction is evidenced when looking at the upfield shifts ($\Delta\delta$) of the bound guest (Figure 4). The pattern observed indicates

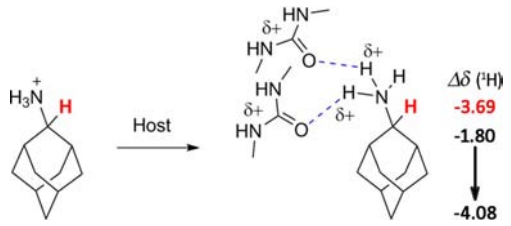

Figure 4. Effect of hydrogen bonding on upfield shifts of **4a**.

that the proton α to the NH_3^+ group should be positioned near the rim; the observed $\Delta\delta$ is however close to that of protons which are further inside the cavity. This can be explained by the fact the carbonyl groups are partially alleviating the charge in **4a** through hydrogen bonding. Therefore, the intrinsic chemical shifts of bound **4a** are closer to those of the free base, hence the apparently large, anisotropy induced $\Delta\delta$. In a complementary fashion, cycloalkyl halides and sulfates were also bound through attractive interactions with the ureas' NH's. Proper filling of the hydrophobic pocket and positioning of the polar function relative to the urea units is crucial for binding: subtle changes in the guest structure result in a complete loss of affinity (Figure 3B). Small tetraalkylammonium halides also bind cavitands **2a**−**d**, through stabilizing NH···X^- interactions at the rim in addition to cation−π interactions in the cavity. The involvement of both NH moieties in hydrogen bonding with the anionic portion of the guests can be inferred from the ^{1}H NMR spectra in $CDCl_3$ (see the Supporting Information). For H4, a significant downfield shift is observed upon binding of tetraalkylammonium salts or alkyl sulfates ($\Delta\delta_{H4}$ **7b** 1.13, **7d** 1.33, **5a** 0.53), indicating a transition from a non-hydrogen-bonded (vide supra) to a hydrogen-bonded NH. Conversely, H3 must partially disengage from the circular hydrogen bond seam to fulfill interactions with the guest in the middle of the cavity. Accordingly, smaller downfield shifts are observed ($\Delta\delta_{H3}$ **7b** 0.77, **7d** 0.87) because the net gain in hydrogen bonding is reduced. In the case of sulfate **5a**, a suboptimal hydrogen-bonding situation results, which is reflected on an upfield shift ($\Delta\delta_{H3}$ −0.73) with respect to the solvent-filled cavitand where the hydrogen bond seam is closed. It is worth noting that only two urea groups can interact at once with the anion according to modeling. The observed shifts thereby reflect a time averaged situation by virtue of the fast-exchange regime along the rim.

Integration of the ^{1}H NMR spectra allows a direct estimation of the apparent binding constants, which are in the 1−100 M^{-1} range (Table 1). The seemingly low magnitude of these constants is a consequence of the competition by the solvent molecules which are in large excess with respect to added guests (>4 × 10^3 fold).[12] While being detrimental for binding in absolute terms, this approach is useful for probing the recognition properties of these cavitands in detail, since only the guests presenting attractive interactions at both the hydrophobic cavity *and* the polar rim are bound.[13] For halogenated and anionic guests, very subtle variations in their spatial arrangement can prevent effective hydrogen bonding to both NHs of a ureido group, thereby diminishing the stabilizing effect.

Finally, the kinetics of guest exchange were investigated. A 2D-EXSY experiment[14] was carried out using complex **4a**⊂**2a** in acetone-d_6, revealing a barrier of 17.5 ± 0.1 kcal mol^{-1} for the efflux of **4a** from the host. This compares well with the values observed for analogous complexes with **1** (16−19 kcal mol^{-1}).[15] Guest-exchange kinetics in self-folding cavitands are governed by the breaking of the hydrogen bond seam along the rim. This result is therefore indicating that the ureido groups in **2a**−**d** provide a cyclic array of hydrogen bonds of at least equal strength to the one of amide-derived cavitands (Figure 5).

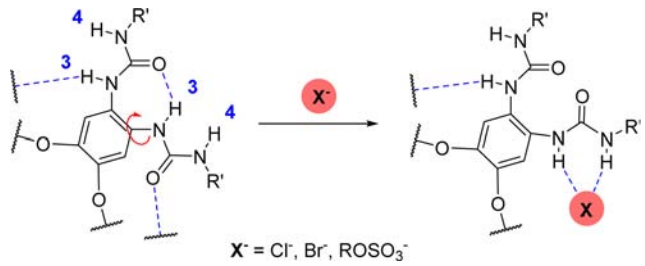

Figure 5. Hydrogen-bonding rearrangement upon binding of anions.

In conclusion, a new family of self-folding cavitands has been prepared featuring an array of eight ureido groups that stabilize the productive folded conformation. These functions, in turn, stabilize guest molecules with properly positioned functional groups of disparate electronic nature: cationic, anionic, or neutral. The guests explored herein can be seen as surrogates for reaction intermediates along a cationic cascade reaction (activated anionic precursor → carbocation/anion pair), making cavitand **2** a promising platform for the development of supramolecular anion binding catalysis.[16] Current efforts in this direction are underway.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization data for hosts **2a**−**d**, guests **4a**,**b** and **5a**−**f**, details for the DOSY and EXSY experiments, ESI-MS data for **2c**, VT ^{1}H NMR data for **2c**, and expansion of downfield regions for complexes with anionic guests (**5a**, **7b**, **7d**). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01747.

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Table 1. Binding Constants[a] with Cavitand 2a

guest	4a	4b	5a	5b	6b	6c	6d	6e	7a	7b	7c	7d
K_a (M^{-1})	165[b]	175[b]	32[c]	19[c]	6.5[c]	4.4[c]	4.2[c]	6.6[c]	84[d]	33[d]	68[d]	98[d]

[a]Estimated error ±10%, [**2a**] = 2.8−3.0 mM. [b]In acetone-d_6. [c]In $CDCl_3$. [d]In $CDCl_3/CD_3OD$ (7:3).

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Notes

The authors declare no competing financial interest.

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