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Water-Stabilized Cavitands

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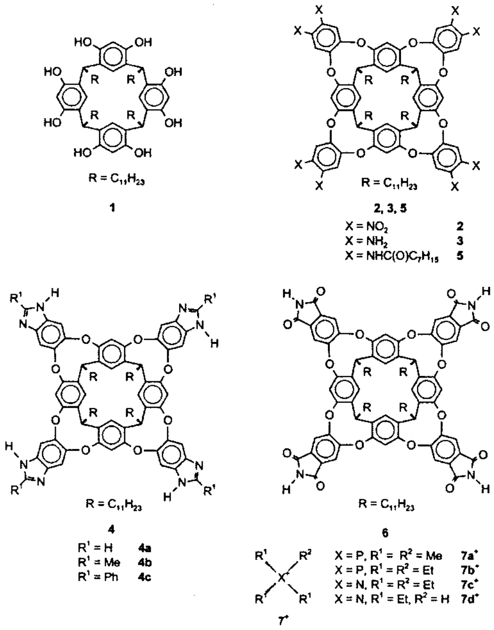
Cavitands are open-ended host molecules possessing enforced cavities in which complementary guest molecules can be accommodated and detained.[1] The inclusion complexes (caviplexes) of the resorcinarene-based cavitands have typically been characterized in the crystalline state by single-crystal X-ray analysis.[2] At ambient temperatures in solution the caviplexes are short-lived on the NMR time scale.[3] The upper rims of the cavitands can be extended through synthesis, but such changes can also result in conformations that no longer possess well-defined cavities.[4] Additional features that favor a vaselike shape must be incorporated, such as a cyclic array of intramolecular hydrogen bonds.[5] These constructs allow the formation of kinetically stable caviplexes with sizable guests, such as adamantane derivatives and ammonium cations. We report here that the cyclic array of hydrogen bonds can be provided in an intermolecular sense, from interacting water molecules.[6] The result is novel molecular containers of tetrabenzimidazoles that form kinetically stable inclusion complexes on the NMR time scale.

Scheme 1



Alkylation of resorcinarene **1** with 4 equiv of 1,2-dinitro-4,5-difluorobenzene resulted in octanitrocavitand **2**. Complete reduction of **2** by $SnCl_2$ in EtOH/ HCl led to octaamine **3** in hydrochloride form. The treatment of this amine salt with excess ortho esters[7] in 1:3 DMF:CH_2Cl_2 at room temperature afforded the corresponding benzimidazole derivatives **4** in 52−82% yield. Compounds **4** were characterized by NMR and IR spectroscopy and mass spectrometry.

The energy-minimized[8] structure of **4** in the vase conformation shows that *no intramolecular hydrogen bonds* are possible between the NH and N atoms of the neighboring benzimidazole fragments (Figure 1). On the other hand, structure A provides four excellent binding sites for hydroxyl-containing molecules such as alcohols and water, which would stabilize the vase shape to give structure B. This prediction and the experimental results below strongly suggest that cavitands **4** can exist in water-saturated $CDCl_3$ in the form of hydrogen-bonded complexe(s) resembling structure B.

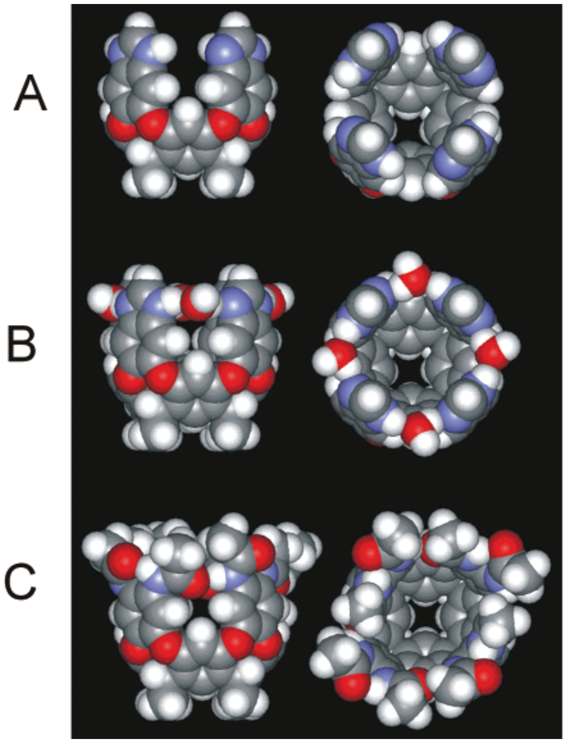


Figure 1. Energy-minimized structures of **4a** (A) and **4a**·$4H_2O$ (B) and self-folding cavitand **5** (C) in space-filling representations (AMBER force field). Long pendant chains are replaced by methyls for clarity.

Dry tetrabenzimidazoles **4** are not soluble in dry $CDCl_3$ but form gels upon heating. In commercial $CDCl_3$, these compounds are scarcely soluble, and the ^1H NMR spectra of such solutions contain incomprehensible sets of broad resonances, likely due to the formation of ill-defined aggregates. However, the addition of small amounts of alcohols (ca. 5%)[9] resulted in immediate solubilization in $CDCl_3$. The same was also observed upon saturation of the $CDCl_3$ solutions with water. The ^1H NMR spectrum of **4b** in water-saturated $CDCl_3$ is sharp and contains one triplet for the methine protons of the bridges at 5.68 ppm, two singlets for the protons of the resorcinol rings, and one singlet for the protons of methyl groups at the 2-position of the benzimidazole fragments of the cavitand walls (Figure 2a). This pattern is characteristic for a hollow C_{4v}-

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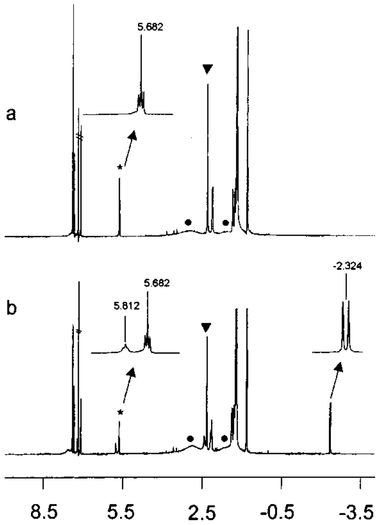

Figure 2. The ^{1}H NMR spectra in water-saturated $CDCl_3$ (600 MHz, 295 K): (a) **4b**; (b) 3 **4b** + **7a**$^+$ Br$^-$ water saturated $CDCl_3$. (●) water; (*) methine protons of the bridges; (▼) methyl protons of benzimidazole fragments.

symmetrical vase conformation of cavitands. A signal for water involved in hydrogen bonds to **4** was broad and centered at 2.70 ppm; free water molecules gave a broad signal at 1.6 ppm. The pattern for the cavitand protons did not significantly change with temperature between 233 and 323 K. The vase conformation is rigid.

The pattern of hydrogen bonds presented by the imidazoles is self-complementary and raised the possibility that the compounds exist as dimeric capsules, but the following experiments exclude such structures. The ^{1}H NMR spectra of 1:1 mixtures of **4a** + **4b**, **4a** + **4c**, and **4b** + **4c** in water-saturated $CDCl_3$ were the superimpositions of the spectra of the individual components and showed no sign of kinetically stable heterodimers. Moreover, cavitands **4** and monomeric self-folding cavitands **5** showed nearly the same kinetics of NOEs (1D GOESY) upon irradiation of the methine protons of the bridges, which reveals the comparable size of both molecules. This is in contrast to the same experiments with the tetraimide **6**.[10] This compound exists as a dimer and forms a cylindrical capsule approximately twice as large as the monomers **4** and **5**.[11] The capsule's negative NOEs are about 10 times stronger than those of the monomers **4** and **5**. The solubility and the NMR spectra of **5** in $CDCl_3$ show no dependence on the amount of water present in the solution.

Structure B has nearly the same size of cavity as **5** (structure C, Figure 2), and therefore similar inclusion properties were expected. The addition of tetramethylphosphonium bromide **7a**$^+$Br$^-$ to the solution of **4b** in water-saturated $CDCl_3$ resulted in a new set of cavitand signals which grew at the expense of the original set upon further addition of the salt (Figure 2b). A sharp doublet emerged at −2.32 ppm, corresponding to the methyl protons of the complexed cation. The large upfield shift for this resonance ($\Delta\delta = -4.4$ ppm) is consistent with the position of the cation **7a**$^+$ deep in the cavity of the host. The broad signal for water was found at 3.0 ppm in the caviplex.[12] Upon complexation, the ^{31}P resonance of **7a**$^+$ undergoes an upfield shift of 8.0 ppm. The complex has a 1:1 stoichiometry and is kinetically stable on the NMR time scale at 295 K. The low solubility of **7a**$^+$Br$^-$ in $CDCl_3$ and its strong complexation in the cavitand hampered the reliable evaluation of the stability constant.

A kinetically stable 1:1 complex between cavitands **4** and triethylammonium chloride **7d**$^+$Br$^-$ was observed in water-saturated $CDCl_3$ at 295 K, although the binding was rather weak ($K_{ass} < 10$ M^{-1}). Tetraethylphosphonium and ammonium bromides **7(b−c)**$^+$-Br$^-$, as well as adamantane and 1-hydroxyadamantane did not interact with cavitands **4** under the same conditions.

The octaamide **5** also forms a kinetically stable 1:1 complex with **7a**$^+$Br$^-$ either in dry or water-saturated $CDCl_3$. The induced upfield shifts for the ^{1}H and ^{31}P signals were considerably smaller ($\Delta\delta = -3.4$ and -5.8 ppm, respectively) than those for the complex with **4**. An analogous trend was found also for the complexes with triethylammonium chloride. Apparently the four imidazole rings in **4** contribute to the shielding effect of the cavity. The addition of 5% of methanol resulted in a complete destruction of the inclusion complexes of cavitands **4.** Whether this is due to better solvation of the guest, host or both is not yet known.

In summary, readily available tetrabenzimidazole cavitands **4** are new open-ended hosts with deep cavities. The crucial role of water in the hydrogen bonding with **4** is, to the best of our knowledge, the first example of such solvent effects on simple cavitands.[6,13]

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Supporting Information Available: Synthetic procedures and analytical data for compounds **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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