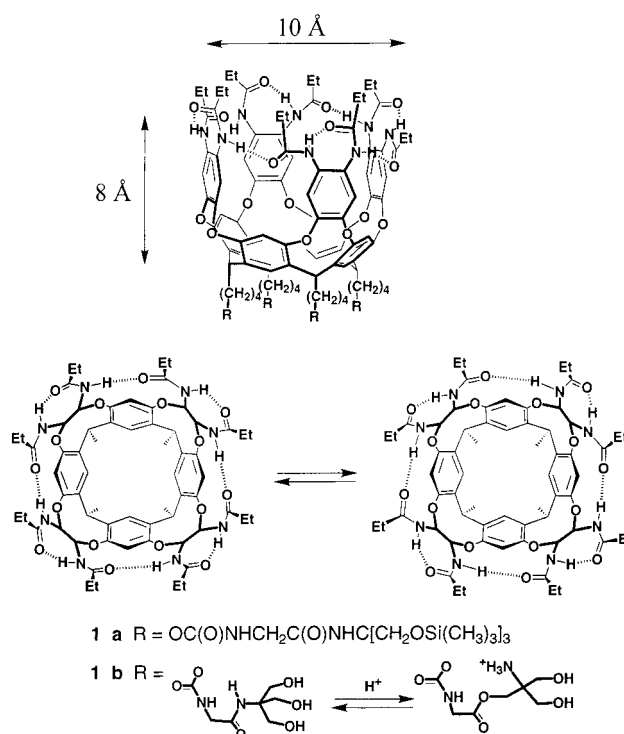# Kinetically Stable Caviplexes in Water

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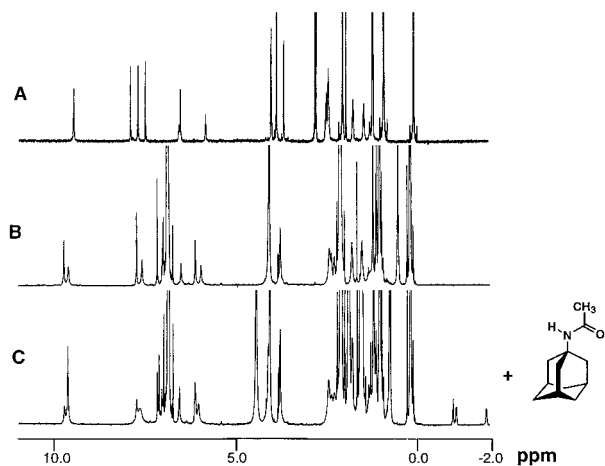10550 North Torrey Pines Road, La Jolla, California 92037*

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In the extensive literature involving synthetic hosts in aqueous solution, slow exchange of guests is rarely encountered. Cyclophanes,[1] cyclodextrins,[2] and calixarenes[3,4] generally show rapid exchange, at least on the NMR time scale, of their binding partners. This research was undertaken to explore the behavior of deep cavitands in water. We have found that gross conformational changes take place during complexation and, as a result, the complexes, caviplexes, show slow exchange and high kinetic stability in water.

Cavitands are open-ended molecular vessels that act as hosts for complementary guests.[5] Octaamido cavitands **1** (Figure 1) show moderate affinity for adamantane and cyclohexane derivatives in nonpolar solvents,[6] but their caviplexes exhibit high kinetic stability. Guest uptake and release rates ($k \sim 2$ $s^{-1}$) are indirectly controlled by the seam of intramolecular hydrogen bonds along the rim of the vase-like receptor. These bonds resist the conformational changes to the more open shapes required to exchange the guest molecules. For example, the persilylated **1a**[7] shows excellent solubility in organic media and binds guests in *p*-xylene-$d_{10}$. The NMR spectrum of guest-free **1a** shows two NH singlets downfield of 10 ppm and two singlets for the ortho-aromatic CH

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(2) Several excellent reviews on the host−guest chemistry of cyclodextrins may be found in: *Chem. Rev.* **1998**, *98*, pp 1741−2076.
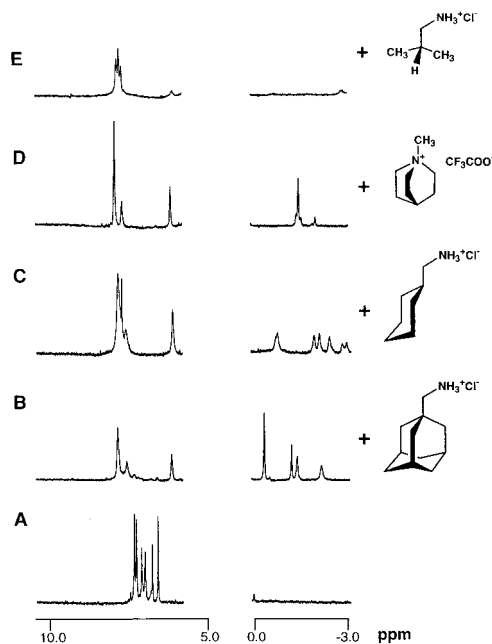
(3) Leading references on water-soluble calixarene-based receptors and cavitands for organic guests: (a) Manabe, O.; Asakura, K.; Nishi, T.; Shinkai, S. *Chem. Lett.* **1990**, 1219−1222. (b) Shinkai, S.; Araki, K.; Matsuda, T.; Nishiyama, N.; Ikeda, H.; Takasu, I.; Iwamoto, M. *J. Am. Chem. Soc.* **1990**, *112*, 9053−9058. (c) Grote Gansey, M. H. B.; Bakker, F. K. G.; Feiters, M. C.; Geurts, H. P. M.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1998**, *39*, 5447−5450. (d) Arena, G.; Casnati, A.; Contino, A.; Lombardo, G. G.; Sciotto, D.; Ungaro, R. *Chem. Eur. J.* **1999**, *5*, 738−744 and references therein. (e) Bügler, J.; Sommerdijk, N. A. J. M.; Visser, A. J. W. G.; van Hoek, A.; Nolte, R. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1999**, *121*, 28−33. (f) Mezo, A. R.; Sherman, J. C. *J. Am. Chem. Soc.* **1999**, *121*, 8983−8994. Review: Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon: Tarrytown, NY, 1996; Vol. 2, pp 103−142.

(4) In cryptophanes and hemicarcerands, high kinetic stability of the complexes was achieved in aqueous solution: (a) Collett, A. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon: Tarrytown, NY, 1996; Vol. 2, pp 352−355. (b) Yoon, J.; Cram, D. J. *Chem. Commun.* **1997**, 497−498.

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(7) Detailed experimental procedures will be published elsewhere. See Supporting Information for selected spectral data. Tris(hydroxymethyl)-aminomethane was used in the syntheses of water-soluble calix[4]arenes, see: (a) Grote Gansey, M. H. B.; Steemers, F. J.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1997**, 643. (b) Steemers, F. J.; Meuris, H. G.; Verboom, W.; Reinhoudt, D. N.; van der Tol, E. B.; Verhoeven, J. W. *J. Org. Chem.* **1997**, *62*, 4229−4235.



**Figure 1.** Cavitands **1a,b** and schematic depiction of the cycloenantiomerism resulting from the head-to-tail cyclic array of hydrogen-bonded amides.



**Figure 2.** ¹H NMR spectra (600 MHz, 295 K, ∼1 mM) of (A) cavitand **1a** in acetone-$d_6$, (B) cavitand **1a** in *p*-xylene-$d_{10}$, and (C) complex **1a·** *N*-(1-adamantyl)acetamide in *p*-xylene-$d_{10}$; guest-free cavitand **1a** is also present due to the low binding affinity.

resonances. The structure exists as two cycloenantiomers with clockwise and counterclockwise orientation of the C(O)−NH···O=C−NH groups and overall $C_4$ symmetry (Figure 1). Upon addition of *N*-(1-adamantyl)acetamide, four characteristic resonances of the bound adamantyl fragment emerged between 0 and −2 ppm, and guest exchange was slow on the NMR time scale (Figure 2). The NMR spectrum of **1a** in more polar acetone-$d_6$ is still a vase-like but now is $C_{4v}$ symmetrical: the NH and ortho CH resonances are each singlets. The cycloenantiomers interconvert rapidly since this solvent competes for the intramolecular hydrogen bonds.[8] This host is the immediate precursor of water-soluble cavitand **1b**.

**Figure 3.** Downfield and upfield regions of the ¹H NMR spectra (D₂O, 600 MHz, 295 K) of cavitand **1b** and its complexes. (A) Guest-free cavitand **1b** alone and (B) with 1-Ad-CH₂NH₃⁺Cl⁻, (C) *cyclo*-C₆H₁₁-CH₂NH₃⁺Cl⁻, and (D) *N*-methylquinoclidinium trifluoroacetate. With *N*-CD₃-quinuclidinium as guest, the spectrum was essentially that of D, indicating that the *N*-methyl group is directed at the open ends of the cavitand in the complexes. (E) Cavitand **1b** with (CH₃)₂CH-CH₂-NH₃⁺Cl⁻. The furthest upfield signals (0 to −3 ppm) are due to the encapsulated species. The host and guest concentrations are 0.5 and ≥50 mM, respectively.

Desilylation of **1a** with HClₐq gave a dodecahydroxy cavitand that quickly rearranged to the corresponding octahydroxy tetra-ammonium salt **1b** exhibiting excellent water solubility.[7,9]

The ¹H NMR spectrum of **1b** in D₂O is reproduced in Figure 3A. It is rather broad at >1 mM, but simplifies at lower concentrations.[10] The aromatic region contains six visible signals, clearly indicating the symmetry of the molecule is significantly reduced from that of **1a**. Most probably, the conformational equilibrium is now shifted toward the kite-shaped $C_{2v}$ structure that equilibrates with its $D_{2d}$ dimeric (velcrand)[11] form (Figure 4). Further evidence for the dimerization was obtained from electrospray mass spectrometry (ESI-MS). Only peaks for the dimer **1b·1b** were observed for millimolar aqueous solution of **1b**: at 4917 (negative ESI-MS, singly charged); at 2460 (positive ESI-MS, doubly charged); at 1640 (negative ESI-MS, triply charged); and at 1230 (negative ESI-MS, quadruply charged). This dimerization in water maximizes the burial of hydrophobic surfaces of the resorcinarene skeleton and the aromatic walls of **1b**.
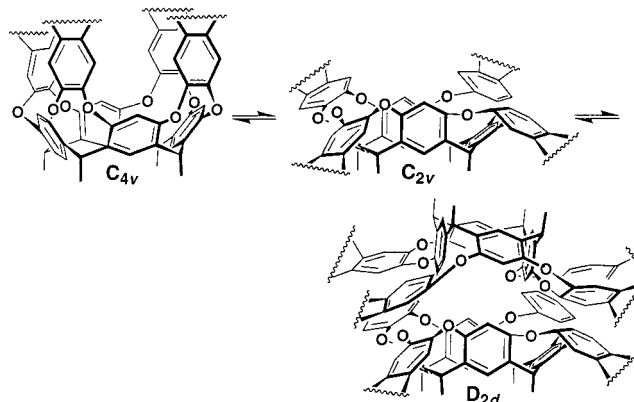
Addition of appropriate guests, such as aminomethyladamantane and aminomethylcyclohexane hydrochlorides and *N*-methyl quinuclidinium trifluoroacetate, resulted in dramatic changes in the NMR spectra (Figure 3B–D). The symmetry returns to $C_{4v}$



**Figure 4.** Proposed schematic representation of the $C_{4v}-C_{2v}-D_{2d}$ conformation equilibrium for water-soluble cavitand **1b**.

with one set of aromatic CH protons with a 2:1:1 ratio. In addition, new signals emerged between 0 and −3 ppm, characteristic of guests bound within the cavitand. The signals in this upfield window are widely separated from those of the free guest ($\Delta\delta \geq$ 3 ppm) and are relatively sharp: traits that speak for sizable energetic barriers between free and bound states.[12]

What causes the change from the structure of the host in water to the well-defined complex? Certainly the main part of the answer is hydrophobicity: the convex hydrocarbon surface of the guest finds its complement in the concave and π-bonded inner surface of the host. Cation−π interactions also contribute but not strongly: the smaller guest *iso*butylammonium hydrochloride also fixes the vase conformation of **1b** but does not show a kinetically stable complex at room temperature (Figure 3E). There is apparently not enough hydrophobic contact within the host−guest complex to slow the exchange. The energetic barriers for the conformational changes, e.g. from the kite ($C_{2v}$) and/or velcrand ($D_{2d}$) to the vase of $C_{4v}$ symmetry usually amount to 10−12 kcal mol⁻¹ in organic solvents.[11] Intramolecular hydrogen bonding may add to this energetic barrier even in D₂O, as intramolecular hydrogen bonds can participate in guest complexation even in polar media.[13]

Though the criteria for kinetic stability, slow exchange at ambient temperature and 600 MHz, are arbitrary, the behavior of the caviplexes presented here is unusual in that large and energetically costly conformational changes accompany binding. That the positive charges on the host do not prevent ammonium guests from binding suggests that complexation with these hosts will tolerate a range of polar characteristics in the guest. This brings closer the possibility of applying cavitands as reaction vessels and sensors for biologically relevant guests in aqueous solutions.

**Supporting Information Available:** Selected spectral data for cavitands **1a,b** and their synthetic precursors and characteristic ¹H NMR spectra of cavitand **1b** in D₂O at different concentrations and temperatures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(8) The C(O)−NH singlet for nonmacrocyclic 1,2-dimethoxy-4,5-bis(*n*-octanoylamido)benzene appears at 8.8 ppm in acetone-*d₆* (i.e., ∼0.7 ppm *upfield* of the corresponding signal of **1a** in the same solvent).

(9) Neutral dodecahydroxy isomer **1b** was obtained from **1a** by using TBAF, and it is not soluble in water (¹H NMR).

(10) Broadening in the ¹H NMR spectra observed at higher concentrations is most probably due to some nonspecific lipophilic aggregation in aqueous media. Hydrogen bonding amide sites on the periphery of the molecule may also be involved. In addition, some changes in the spectra of **1b** were detected upon varying the temperature (5−80 °C). See Supporting Information for the details.

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(12) The corresponding binding energy values are estimated to be −$\Delta G$ ≤ 3 kcal/mol (295 K), since significantly large excess (≥11 equiv for *N*-methylquinoclidinium trifluoroacetate and ≥50 equiv for the other guests) of the guest is needed to observe the complexes by ¹H NMR at millimolar concentrations.

(13) For typical examples see: (a) Schneider, H.-J.; Güttes, D.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6449−6454. (b) Alvarez, J.; Wang, Y.; Gomez-Kaifer, M.; Kaifer, A. *Chem. Commun.* **1998**, 1455−1456.