

Nanoscale Container Structures and Their Host–Guest Properties**

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Molecule-within-molecule complexes can be formed irreversibly, as in carcerands,^[1] or reversibly, as in self-assembled capsules.^[2] In between, hemicarcerands—covalently sealed container molecules with larger portals—offer a possibility for a guest to move more freely in and out.^[3] Open-ended hosts, cavitands, also show promise for molecular recognition,^[4] and recently we demonstrated that higher kinetic stability for their complexes, caviplexes, can be achieved when intramolecular hydrogen bonds control the cavity's size and shape.^[5]

Here we report that these cavitands can be fused together in a way that leads to novel molecule-within-molecule complexes. The hosts (**1**, see Figure 1) balance entropic advantages of unimolarity^[6] with dynamic qualities of hydrogen bonding. Above all, they accommodate guests of nanoscale dimensions.

The new structure **1** (Figure 1) consists of two deepened, resocinarene-based cavitands connected by an extended aromatic spacer. It is among the largest of synthetic unimolecular hosts, featuring cavity dimensions of about $23 \times 10 \text{ \AA}$ and an internal volume of approximately $800 \text{ \AA}^3$.^[7] The molecule may be thought of as a hemicarcerand, but the cavity is held in place by a seam of intramolecular hydrogen bonds rather than covalent bonds. Accordingly, access to the cavity is facile under ambient conditions, and the uptake and release of guests is reversible.

The synthesis of **1** draws on the regioselective functionalization of resocinarenes^[8] and the modular deepening of cavitands.^[9] Partial bridging of the hydroxyl groups in **2** with 1,2-difluoro-4,5-dinitrobenzene led to **3**, a cavitand with three extended walls (Scheme 1). The NO_2 groups were reduced (H_2 , Raney Ni, toluene) and then immediately acylated with propanoyl chloride. The remaining two resorcinol hydroxyl groups were also acylated under these conditions, but they were deprotected with NH_2NH_2 in toluene/EtOH to give hexaamide diol **4**. Reaction of **4** with another equivalent of 1,2-difluoro-4,5-dinitrobenzene followed by reduction with H_2

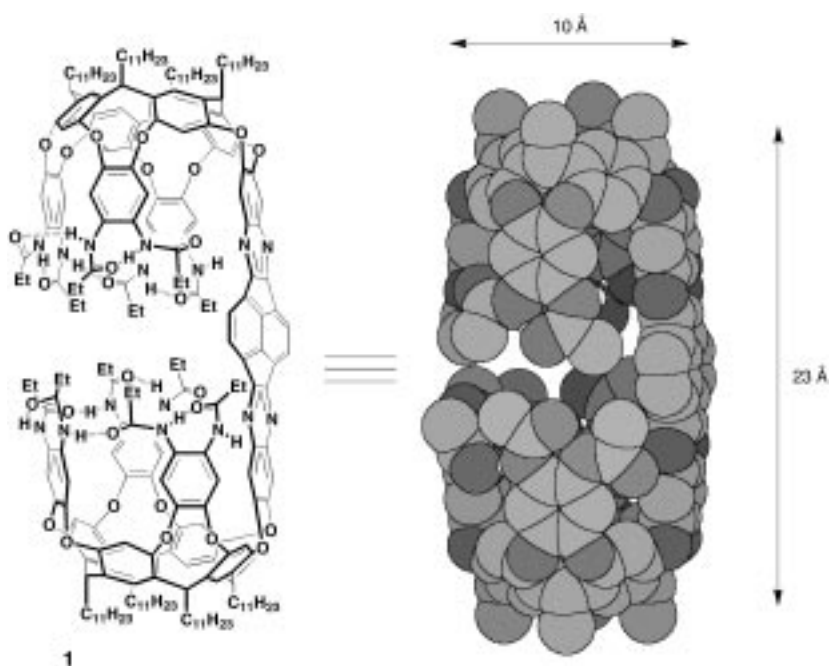


Figure 1. Molecular host **1** and its energy-minimized structure (Amber* force field, MacroModel 5.5 program). Long alkyl chains and CH bonds have been omitted for clarity.

and Raney Ni gave diamine **5**. Heterocyclization of **5** with 1,2,5,6-tetraoxopyracene gave the C-shaped **1** and its S-shaped isomer (not shown), which were separated by chromatography.^[10, 11]

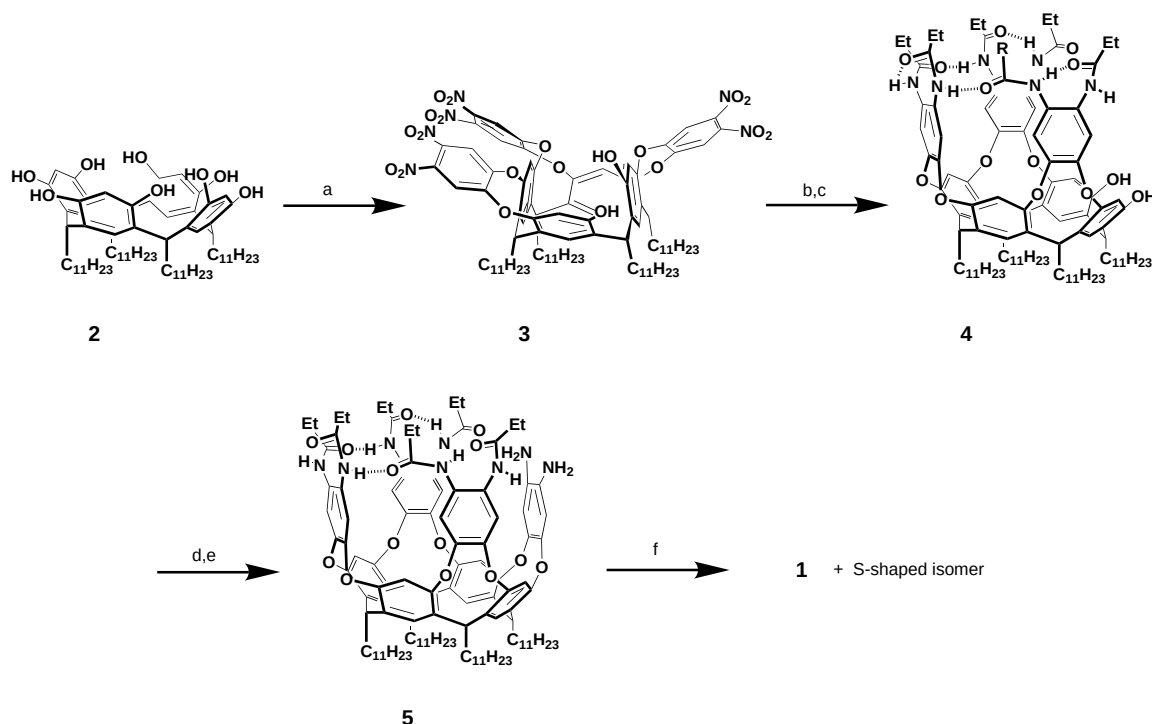
The ^1H NMR spectra of **1** are sharp in $[\text{D}_6]\text{benzene}$ and $[\text{D}_8]\text{toluene}$, but broad in $[\text{D}_{10}]\text{p-xylene}$ at room temperature (Figure 2), suggesting that rates for guest exchange are sensitive to solvent size. The NH resonances are observed far downfield at $\delta = 8$ to 11 in the spectra, and the corresponding FT-IR spectra show stretching absorptions for hydrogen-bonded NH at $\tilde{\nu} = 3244 \text{ cm}^{-1}$ ($[\text{D}_8]\text{toluene}$). Accordingly, the secondary amides of each cavitand form a seam of five intramolecular hydrogen bonds, and modeling implicates an additional interaction of this type between one NH group and its neighboring quinoxaline nitrogen atom. These hydrogen bonds help to maintain the vase-like shape shown in Figure 1. Each cycloenantiomeric cavitand in **1** can possess either clockwise or counterclockwise arrangements of the head-to-tail amides (Figure 2). The presence of two seams in **1** results in diastereomeric relationships, and multiple NH resonances appear in the ^1H NMR spectra: In $[\text{D}_6]\text{benzene}$ and $[\text{D}_8]\text{toluene}$ at least ten singlets are seen downfield of $\delta = 8$, while twelve are expected for two diastereomers undergoing slow exchange. Since two NH protons do not participate in the cyclic arrays they appear more upfield, in the aromatic region of the spectra.

The internal dimensions of **1** were estimated using a series of molecular rulers **6–10**,^[12] guest molecules of well-defined length (Scheme 2). The cavities in **1** are similar to those in self-folding octaamido cavitands **11**,^[5] which showed high affinity to adamantanes as guests. Therefore, we acylated 1-adamantanamine with acyl chlorides of varying length.

The rigid, long (ca. $18 \text{ \AA}$) guests **6** and **7** form kinetically stable complexes. Admittedly, the criteria for kinetic stabil-

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Scheme 1. Synthesis of **1** and its precursors **3–5**: a) 1,2-difluoro-4,5-dinitrobenzene (3 equiv), Et₃N (16 equiv), DMF, 70 °C, 16 h, 57 %; b) Raney Ni, H₂, toluene/MeOH (3/1), 40 °C, 12 h, > 90 %; c) C₂H₅C(O)Cl (ca. 10 equiv), pyridine (18 equiv), CH₂Cl₂, –78 °C, 1 h; then NH₂NH₂/H₂O (10 equiv), toluene/EtOH (1/1), 85 °C, 4.5 h, 13 %; d) 1,2-difluoro-4,5-dinitrobenzene (2 equiv), Et₃N (10 equiv), DMF, 70 °C, 15 h, 65 %; then Raney Ni, H₂, toluene, 40 °C, 3 h, 65 %; e) 1,2,5,6-tetraoxopyracene (0.5 equiv), AcOH_{glacial}/THF (1/100), reflux, 15 h, 55 % C-shaped and S-shaped isomers (ca. 1:1 ratio).

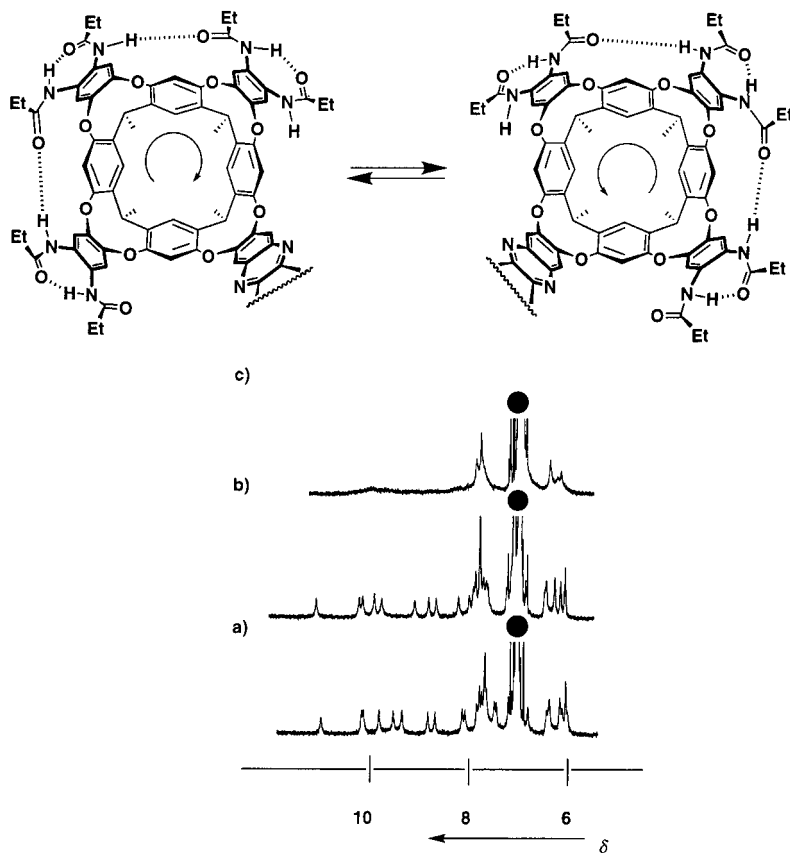
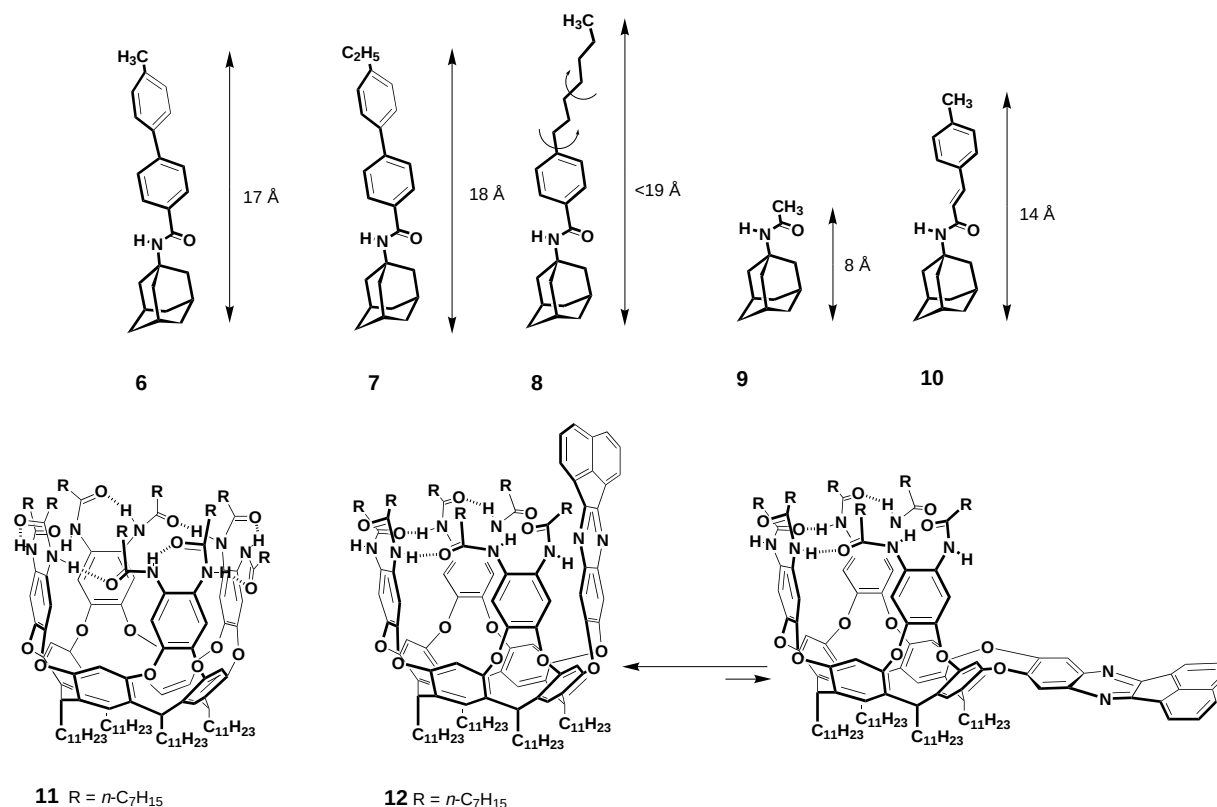


Figure 2. Top: Schematic representation of two cycloenantiomeric cavities in **1**. Bottom: Portion of the ¹H NMR spectra (600 MHz, 295 K) of **1** in a) [D₆]benzene, b) [D₈]toluene, and c) [D₁₀]p-xylene. The amide C(O)-NH signals are shown in the region $\delta = 8$ –11. The solvent signals are marked with ●.

ity—slow exchange on the NMR time scale at room temperature for measurement with a 600-MHz spectrometer—are arbitrary, but the behavior of **1** is unprecedented for unimolecular cavities of such dimensions.^[7] Specifically, four adamantyl signals and resonances for the CH₃ or C₂H₅ groups of complexed **6** and **7** were clearly observed *upfield* of $\delta = 0$ (Figure 3). This feature is characteristic of guests in a highly shielded environment.^[1–3]

Through integration, association constants K_a of $500 \pm 50 \text{ M}^{-1}$ ($-\Delta G^{295} = 3.6 \pm 0.1 \text{ kcal mol}^{-1}$) and $270 \pm 100 \text{ M}^{-1}$ ($-\Delta G^{295} = 3.2 \pm 0.2 \text{ kcal mol}^{-1}$) were calculated for the 1:1 complexes **1·6** and **1·7**, respectively. With the more flexible guest **8** and/or shorter (<14 Å) adamantanes **9** and **10** (Scheme 2), slow exchange between the free and complexed guest species was the case only at lower temperatures (<280 K in [D₈]toluene). Moreover, two equivalents of the smallest guest **9** were bound.

The energetics of the exchange process depend on the seam of hydrogen bonds that encircle the host structure. For example, addition of [D₇]DMF to solutions of the complexes in [D₈]toluene causes the upfield guest signals to disappear. [D₇]DMF competes for hydrogen bonds that stabilize the complex and may also compete for the cavity. At temperatures of 320 K or higher, exchange rates become fast on the



Scheme 2. Guests **6–10** and model cavitands **11** and **12**. The proposed conformational mobility in cavitand **12** is depicted.

NMR time scale. A model structure representing half of the cavity in **1** was found in **12** (Scheme 2), which is prepared by reaction between **5** and 1,2-acenaphthenequinone. Compound **12** does not form kinetically stable complexes with adamantanes **6–10** at room temperature.

Conformational changes in the host seem unavoidable during the process of guest exchange, as openings must be created that allow for guest substitution. The fast exchange of smaller guests from **1** and **12** may result from their “odd” walls. These can flip open and expose the resident guest to displacement (Scheme 2). This conformational mobility may be contrasted with octaamide **11**.^[5] This cavitand features a complete seam of hydrogen bonds and forms kinetically stable complexes with small guests, even at higher temperatures (up to 330 K). For exchange of the longer, more rigid guests, one opening is not enough: A second wall must also open, and the increased energy required slows the process.

The ROESY spectrum of complex **1·6** yielded the exchange rate constant of $k \approx 0.5 \text{ s}^{-1}$ (at 295 K). The reaction is faster than for Cram’s hemicarceplexes with sizeable guests ($k = 1 \times 10^{-2} \text{ s}^{-1}$, $T \geq 373 \text{ K}$),^[3] but slower than that of the open-ended cavitand **11** ($k \approx 2 \text{ s}^{-1}$ at 295 K).^[5, 13]

Carcerands and cryptophanes produced the earliest molecule-within-molecule complexes.^[1] Their kinetic stability allowed the direct observation of reactive intermediates,^[14] while their cramped quarters permitted trapped guests to show isomeric orientations.^[15] Self-assembled capsules allow the encapsulation of more than one guest^[12, 16] and they are useful as reversibly formed chambers for bimolecular reactions.^[17] The features described above for molecule **1** fulfill

the promise of hybrid properties expected, and place **1** in a unique position among the cavity-forming structures.

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- [1] a) J. A. Bryant, M. T. Blanda, M. Vincenti, D. J. Cram, *J. Am. Chem. Soc.* **1991**, *113*, 2167–2172; b) J. C. Sherman, C. B. Knobler, D. J. Cram, *J. Am. Chem. Soc.* **1991**, *113*, 2194–2204; reviews: c) D. J. Cram, J. M. Cram, *Container Molecules and their Guests*, Royal Society of Chemistry, Cambridge, **1994**, pp. 131–148; d) A. Collet, J.-P. Dutasta, B. Lozach, J. Canceill, *Top. Curr. Chem.* **1993**, *165*, 103–129; e) A. Jasat, J. C. Sherman, *Chem. Rev.* **1999**, *99*, 931–967.
- [2] a) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668; b) J. de Mendoza, *Chem. Eur. J.* **1998**, *4*, 1373–1377; c) D. L. Caulder, K. N. Raymond, *J. Chem. Soc. Dalton Trans.* **1999**, 1185–1200; d) T. Kusakawa, M. Fujita, *Angew. Chem.* **1998**, *110*, 3327–3329; *Angew. Chem. Int. Ed.* **1998**, *37*, 3142–3144; e) T. Kusakawa, M. Fujita, *J. Am. Chem. Soc.* **1999**, *121*, 1397–1398.
- [3] a) D. J. Cram, M. E. Tanner, C. B. Knobler, *J. Am. Chem. Soc.* **1991**, *113*, 7717–7727; b) D. J. Cram, M. T. Blanda, K. Paek, C. B. Knobler, *J. Am. Chem. Soc.* **1992**, *114*, 7765–7773; c) T. A. Robbins, C. B. Knobler, D. R. Bellew, D. J. Cram, *J. Am. Chem. Soc.* **1994**, *116*, 111–122; slow decomplexation at 295 K: d) D. J. Cram, R. Jaeger, K. Deshayes, *J. Am. Chem. Soc.* **1993**, *115*, 10111–10116.
- [4] Reviews: a) D. J. Cram, *Science* **1983**, *219*, 1177–1183; b) D. M. Rudkevich, J. Rebek, Jr., *Eur. J. Org. Chem.* **1999**, 1991–2005.
- [5] a) D. M. Rudkevich, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 12216–12225; b) D. M. Rudkevich, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 9911–9912; c) S. Ma, D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **1999**, *111*, 2761–2764; *Angew. Chem. Int. Ed.* **1999**, *38*, 2600–2602.
- [6] Earlier examples of unimolecular capsules: a) R. G. Chapman, J. C. Sherman, *J. Am. Chem. Soc.* **1998**, *120*, 9818–9826; b) M. S. Brody,

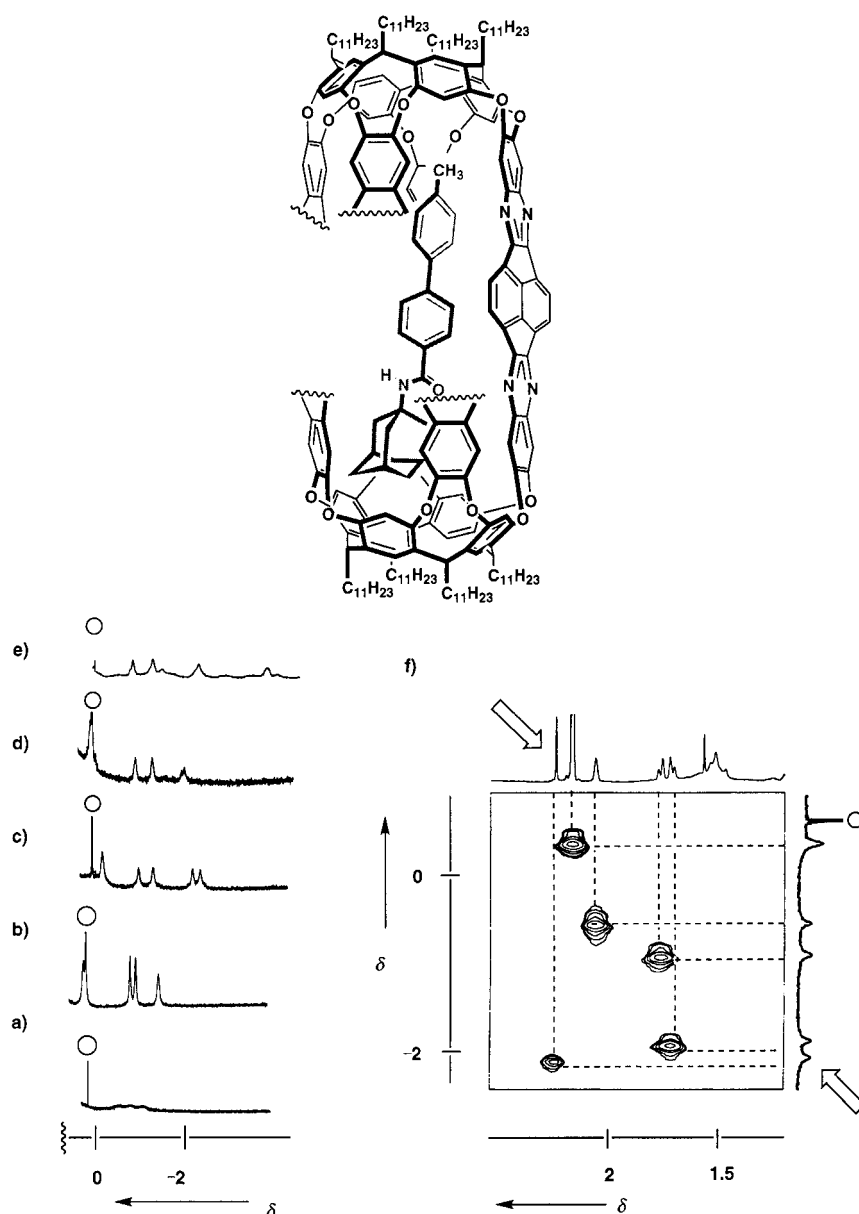


Figure 3. Upfield portions of the ^1H NMR spectra of the complexes (600 MHz, $[\text{D}_8]\text{toluene}$): a) **12**·**10** at 295 K. b) **12**·**10** at 220 K. In the downfield region, all six NH singlets of cavitant **12** are clearly seen now at $\delta = 8.5$ –11, as expected for the cyclic arrangement of the hydrogen bonds. c) The C-shaped **1**·**6** at 295 K. d) The S-shaped **1**·**6** at 280 K. No upfield signals were observed at 295 K. e) The C-shaped **1**·**7** at 295 K. f) Fragment of the ROESY spectrum of the **1**·**6** complex (295 K). The resonances for exchangeable CH_3 groups of free and encapsulated **6** are indicated. The internal standard singlet is marked with $\circ$.

- [10] The assignment of the C- and S-shaped diastereomers **1** was performed through ^1H NMR spectroscopy by the encapsulation of guests **6** and **8**. Thus, four adamantyl signals and resonances for the biphenyl CH_3 group of the complexed **6** were observed upfield of $\delta = 0$ for the complex C-**1**·**6**, while only the adamantyl signals were seen for the complex S-**1**·**6** and the model complex **12**·**6**. The upfield signals of the complexes were assigned by ROESY experiments. Moreover, for the complex C-**1**·**8**—but not for S-**1**·**8**—the signals for encapsulated $n\text{-(CH}_2)_6\text{CH}_3$ were detected at temperatures of 240 K or lower in $[\text{D}_8]\text{toluene}$. Complete experimental details will be published in a full paper.
- [11] Topologically similar bis-cavitands have been reported: D. J. Cram, L. M. Tunstad, C. B. Knobler, *J. Org. Chem.* **1992**, 57, 528–535.
- [12] For the concept of molecular rulers, see S. K. Körner, F. C. Tucci, D. M. Rudkevich, T. Heinz, J. Rebek, Jr., *Chem. Eur. J.* **2000**, 6, 187–195.
- [13] The self-assembled dimeric capsules of calix[4]arene with benzene guest show $k = 0.47\text{ s}^{-1}$ (298 K): O. Mogck, M. Pons, V. Böhmer, W. Vogt, *J. Am. Chem. Soc.* **1997**, 119, 5706–5712; the “tennis ball” with ethane and methane shows $k \approx 0.5$ – 1.1 s^{-1} (295 K): T. Szabo, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, 120, 6193–6194.
- [14] a) D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem.* **1991**, 103, 1048; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1024–1027; b) R. Warmuth, *Angew. Chem.* **1997**, 109, 1406–1409; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1347–1350.
- [15] P. Timmerman, W. Verboom, F. C. J. M. van Veggel, J. P. M. van Duynhoven, D. N. Reinhoudt, *Angew. Chem.* **1994**, 106, 2437; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2345–2348.
- [16] a) T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Nature* **1998**, 394, 764–766; b) T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **1999**, 111, 1206–1209; *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 1136–1139; c) F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, 121, 4928–4929.
- [17] J. Kang, J. Rebek, Jr., *Nature* **1997**, 385, 50–52.

C. A. Schalley, D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **1999**, 111, 1738–1742; *Angew. Chem., Int. Ed.* **1999**, 38, 1640–1644.

- [7] For other approaches towards nanosize host-molecules, see a) P. Timmerman, K. G. A. Nierop, E. A. Brinks, W. Verboom, F. C. J. M. van Veggel, W. P. van Hoorn, D. N. Reinhoudt, *Chem. Eur. J.* **1995**, 1, 132–143; b) I. Higler, P. Timmerman, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1996**, 61, 5920–5931; c) I. Higler, W. Verboom, F. C. J. M. van Veggel, F. de Jong, D. N. Reinhoudt, *Liebigs Ann. Chem.* **1997**, 1577–1586; d) N. Chopra, J. C. Sherman, *Angew. Chem.* **1999**, 111, 2109–2111; *Angew. Chem. Int. Ed.* **1999**, 38, 1955–1957.
- [8] A. R. Renslo, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, 121, 7459–7460.
- [9] F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *J. Org. Chem.* **1999**, 64, 4555–4559.