Synthesis and Characterization of a Disulfide-Linked C_5-Symmetric [5]Carceplex
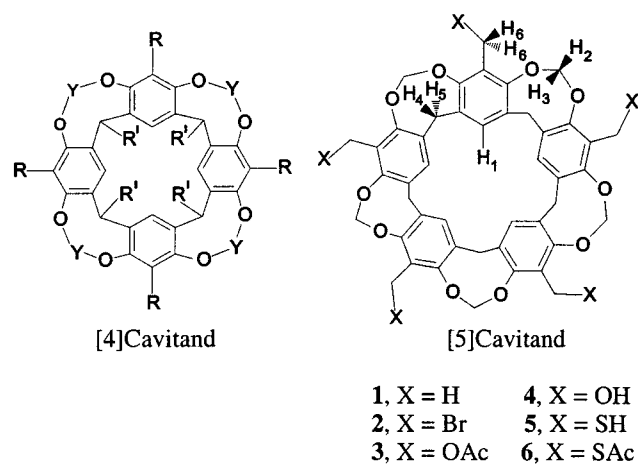
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Cavitands are rigid bowl-shaped molecules that manifest enforced cavities capable of binding neutral guests.[1] [4]Cavitands have been used extensively as receptors and as components for the preparation of carceplexes, which are closed-surface molecules that contain entrapped molecules.[1a,2,3] In recent years, efforts have been made to use [4]cavitands to create novel host molecules with larger cavities. One approach is to link three or more [4]cavitands,[4] while another route is to extend the walls via the bridging unit (Y).[1] A third approach is to increase the number of resorcinol units per cavitand, as we have described recently with a series of [n]cavitands (X = H), where $n > 4$.[5] We report here the use of [5]cavitands to create a disulfide-linked [5]carceplex, $7 \cdot (guests)_2$, that possesses C_5-symmetry.

Radical bromination of [5]cavitand **1** led to benzyl bromide **2**, a compound that was very insoluble in common organic solvents, and was not purified.[6] Crude [5]benzyl bromide **2** was reacted with thioacetic acid, and the resulting thioacetate **6** was hydrolyzed under acidic conditions to benzyl thiol **5** (25% yield for two steps).[7,8] Disulfide [5]carceplex $7 \cdot (DMF)_2$ was obtained in 25% yield by air-oxidation of benzyl thiol [5]cavitand **5** in the presence of Cs_2CO_3 in DMF (Figure 1).[9,10] MALDI-TOF mass spectroscopy in the presence of AgOTf gave $7 \cdot (DMF)_2 \cdot Ag^+$ as the predominant species.
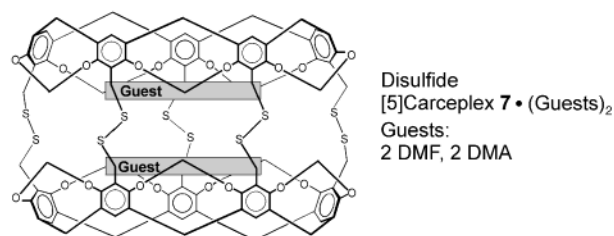

Figure 1. Schematic drawing of disulfide [5]carceplex $7 \cdot (DMF)_2$.
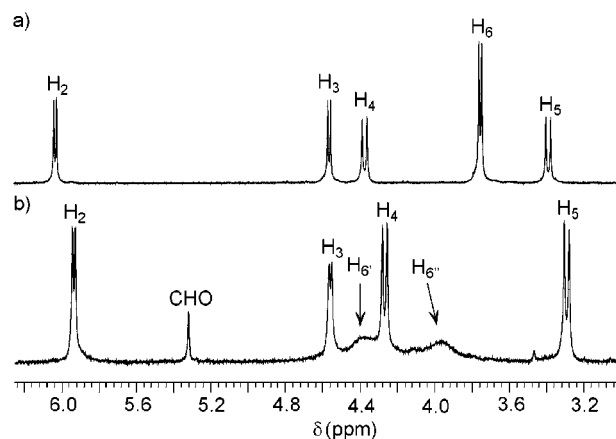

Figure 2. Parts of the ^1H NMR spectra of benzyl thiol **5** (a) and disulfide [5]carceplex $7 \cdot (DMF)_2$ (b) in CDCl$_3$ at 27 °C (at 400 MHz). H$_{6'}$ and H$_{6''}$ are labeled arbitrarily.

[4]Cavitand

[5]Cavitand

1, X = H	**4**, X = OH
2, X = Br	**5**, X = SH
3, X = OAc	**6**, X = SAc

The ^1H NMR spectrum of $7 \cdot (DMF)_2$ in CDCl$_3$ at 27 °C shows two singlets (0.28 and 0.20 ppm) for the NMe groups, and a singlet at 5.32 ppm for the formyl protons for the entrapped DMF molecules (see Figure 2); the two DMF molecules are indistinguishable. The ArCH$_2$S protons (H$_6$) appear as two diastereotopic doublets below −10 °C at 400 MHz, and as a sharp singlet above 97 °C at 500 MHz. The rate constant for interconversion of H$_6'$ and H$_6''$ resonances was measured by 1D NOESY (EXSY)[11] at −25 °C in CDCl$_3$ at 400 MHz, and found to be 1.0 ± 0.2 s^{-1}; $\Delta G^{\ddagger}_{248}$ was calculated to be 14.4 ± 0.1 kcal mol^{-1}. Strain-free dibenzyl

disulfides have been found to have $\Delta G^{\ddagger}$ values that are too small to be measured by dynamic NMR experiments.[12] It appears that for **7** the activation barrier for the interconversion of the diastereotopic H$_6$ protons is raised by the additive effect of five disulfide bonds and the restrictions imposed by the rigid bowls: each individual disulfide bond in $7 \cdot (DMF)_2$ is likely under only a small steric constraint[13] but since all five disulfide bonds presumably can only interconvert in unison, the transition state is raised accordingly.

We recorded 1D NOESY spectra for $7 \cdot (DMF)_2$ (CDCl$_3$, 400 MHz, 27 °C) to link the DMF resonances unambiguously to the host resonances and to gather information about the orientation of the guest molecules inside the cavity.[14] The H$_3$ protons point inside the cavity, the ArCH$_2$Ar protons are outside, and the H$_1$ protons are at the bottom of the cavity.[15] The NOEs between H$_3$ and the DMF resonances are about twice as strong as the NOEs between H$_1$ and the DMF resonances. In each case (from H$_3$ or H$_1$), the two *N*-methyls have equally intense NOEs. In addition, all three DMF resonances are equally shifted upfield ($\Delta\delta$ are 2.66−2.67 ppm at 27 °C) compared to free solvent, so they must each experience a similar shielding effect.[16] We conclude that the DMFs reside in parallel equatorial positions inside the cavity as depicted
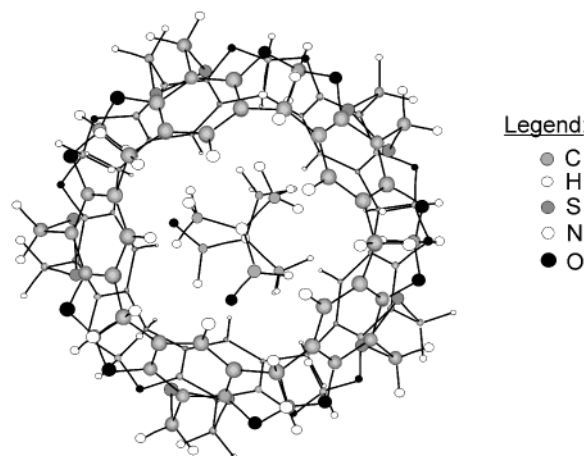
Figure 3. Top view of [5]carceplex **7**·(DMF)$_2$ as predicted by MM2 calculations. The entrapped DMFs are predicted to be perpendicular to the C_5 symmetry axis of **7**.

schematically in Figure 1. MM2 calculations (Figure 3) support this conclusion. Such an orientation is highly unusual in carceplexes.[16,17]

DMF amide rotation barriers were determined by 1D NOESY (EXSY) experiments in C$_6$D$_5$NO$_2$ at 77 °C at 400 MHz for the following carceplexes[18] (see Supporting Information for structures): disulfide [5]carceplex **7**·(DMF)$_2$, thioether [4]carceplex·DMF,[2] acetal [4]carceplex·DMF,[3] and trimer [4]carceplex·(DMF)$_3$.[4] The $\Delta G^{\ddagger}$ values were found to be 20.8, 20.5, 19.1, and 20.5 kcal mol^{-1}, respectively.[18] Under the same conditions, the amide rotation barrier for 9% DMF in C$_6$D$_5$CD$_3$ and in C$_6$D$_5$NO$_2$ was found to be 20.7 and 21.1 kcal mol^{-1}, respectively. The barriers for all DMF carceplexes are similar or slightly lower than for free DMF in nitrobenzene, except for the acetal [4]carceplex·DMF case. The acetal [4]carceplex appears to have the most nonpolar and/or gas-phase environment, while the other cavities are polarized by the additional DMF guest(s) and/or the bridging sulfur atoms.

In conclusion, we have characterized the first disulfide [5]-carceplexes·(guests)$_2$, using the new [5]cavitands as building blocks. The disulfides have unusually high energy barriers to interconversion due to their cooperativity. The guests reside in an unusual orientation in parallel planes that are perpendicular to the principal axis of the host. These new carceplexes hold promise for novel studies. For example, it may be possible to study the thermodynamic template effect in forming the most stable disulfide-linked carceplex by subjecting **7**·(guests)$_2$ (and/or **5**) to equilibrium conditions using redox buffers. Thus we should be able to directly compare thermodynamic and kinetic template effects for the first time.[19,20]

Supporting Information Available: Experimental details of compounds **2**−**7**, mass spectroscopic data of **7**·(guests)$_2$ (Figure S1), ^{1}H NMR and 1D NOESY spectra of **7**·(DMF)$_2$ (Figures S2 and S3), upfield parts of the ^{1}H NMR spectrum of **7**·(DMA)$_2$ (Figure S4), side-view of **7**·(DMF)$_2$ (Figure S5), schematic drawing of different DMF [4]-carceplexes (Figure S6), chemical shift differences between free and bound guest for different DMF (DMA) carceplexes (Tables S1 and S2), initial rate graphs for amide rotation barriers of DMF carceplexes (Figure S7) and resulting $\Delta G^{\ddagger}$ values (Table S3) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For instance, acetal linkages between three [4]cavitands in 1,3 positions created the large, rigid trimer, which was converted into a trimer [4]carceplex·(DMF)$_3$ by capping the top and bottom hole. (a) Chopra, N.; Sherman, J. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1727. (b) Chopra, N.; Sherman, J. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1995.

(5) The number of resorcinol units is indicated by *n*. We have prepared [*n*]-cavitands where *n* = 4, 5, 6, and 7. Naumann, C.; Román, E.; Peinador, C.; Ren, T.; Patrick, B. O.; Kaifer A. E.; Sherman, J. C. *Chem. Eur. J.* **2001**, *7*, 1637.

(6) Benzyl bromide **2** was indirectly characterized by reacting the crude product with NaOAc in DMF to yield benzyl acetate **3** (40% from **1**), which is soluble and was fully characterized. A pure sample of **2** was obtained by hydrolyzing benzyl acetate **3** to the alcohol **4** (82%), and reacting **4** with PBr$_3$ to give **2** (75%).

(7) It should be noted that the lack of "feet" (R′ groups) in **1** yields Ar$_2$CH$_2$ groups, which reduce the efficiency of clean radical bromination at the upper rim. It is somewhat surprising to get any yield of penta-substitution at the upper rim with no substitution at the lower rim, though a referee pointed out that the conformation and rigidity of the [5]cavitand would largely preclude resonance stabilization of benzyl radical intermediates at the lower rim (see Figure S5).

(8) Crude benzyl bromide **2** was also directly converted to benzylthiol **5** by standard methods (ref 2). The yield for benzylthiol [5]cavitand **5** was significantly lower (10%) than yields obtained for the equivalent [4]-cavitand benzyl thiols (ref 2).

(9) Disulfide [5]carceplex **7**·(DMA)$_2$ was obtained in 16% yield with DMA as solvent.

(10) A thioether [5]carceplex·(guests)$_2$ (DMF or DMA) having five ArCH$_2$-SCH$_2$Ar linkages was obtained by reacting compounds **2** and **5** under exclusion of O$_2$, but could only be characterized by mass spectroscopy due to its limited solubility. The correspondingly linked [4]carceplex with methyl "feet" is completely insoluble (ref 2).

(11) Pulse sequence used: selnogp.2 (Bruker, avance-version (00/02/07): 1D NOESY using selective excitation with a shaped pulse; dipolar coupling may be due to NOE or chemical exchange. Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. See also ref 5 and: Naumann, C.; Patrick, B. O.; Sherman, J. C. *Tetrahedron* **2001**/**2002**, in press. Errors are ±20% for rate constants, or ±0.1 kcal mol^{-1} for $\Delta G^{\ddagger}$ values.

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(13) Computer modeling (CS Chem 3D Pro) of **7**·(guests)$_2$ predicts the C−S−S−C dihedral angle to be between 108° and 112°, close to the ideal of 90° (ref 12).

(14) [5]Carceplex **7**·(DMF)$_2$ retains its guest molecules and is unchanged when dissolved in nitrobenzene-d_5 and heated at 100 °C for two weeks.

(15) The proton regions are based on the crystal structure of [5]cavitand **1** (ref 5).

(16) The DMF resonances inside [4]carceplexes experience significant shielding differences (e.g. $\Delta\delta$ 2.98−3.88 ppm for the acetal [4]carceplex) because DMFs occupy a plane containing the C_4 symmetry axis. Thus, one Me resides in the strongly shielding polar region of the host, and one near the weakly shielding equator (refs 2−4).

(17) **7**·(DMA)$_2$ also shows little variation in shielding differences for its three different guest resonances ($\Delta\delta$ 2.45−2.62 ppm), which again contrasts with [4]cavitand-based DMA [4]carceplexes (e.g. $\Delta\delta$ 1.98−4.49 ppm, ref 3 and Supporting Information).

(18) For comparitive reasons, all amide barriers were determined under identical conditions. Amide barriers determined via the coalescence point method have been reported previously. They are in agreement with the data here for the acetal [4]carceplex (18.9 kcal mol^{-1}, ref 3). The values reported for trimer [4]carceplex·(DMF)$_3$ (19.3−19.5 kcal mol^{-1}, ref 4) were based on an estimated T_c; this value was likely underestimated.

(19) For thermodynamic template effects see: (a) Chapman, R. G.; Sherman, J. C. *J. Org. Chem.* **1998**, *63*, 4103. (b) Makeiff, D. A.; Sherman, J. C. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; WILEY-VCH: Weilheim, Germany, 2000; p 105.

(20) A dimeric trisdisulfide formed under kinetic and thermodynamic conditions was described by: Tam-Chang, S.-W.; Stehouwer, J. S.; Hao, J. *J. Org. Chem.* **1999**, *64*, 334.

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