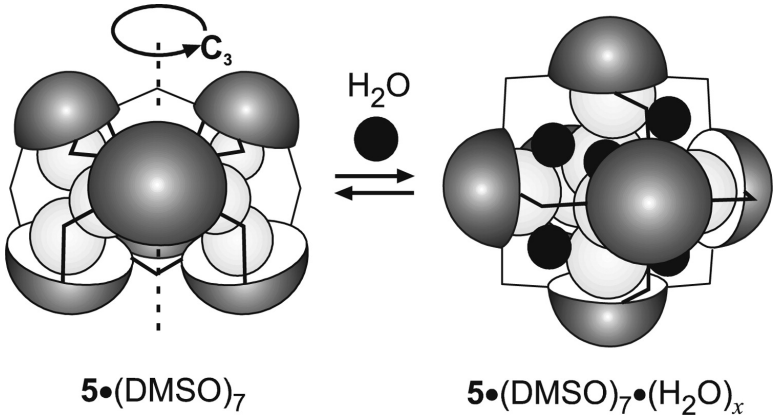
Article

A Six-Bowl Carceplex That Entraps Seven Guest Molecules

Darren A. Makeiff, and John C. Sherman

J. Am. Chem. Soc., **2005**, 127 (35), 12363-12367• DOI: 10.1021/ja0520621 • Publication Date (Web): 13 August 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 4 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 08/13/2005

A Six-Bowl Carceplex That Entraps Seven Guest Molecules

Darren A. Makeiff and John C. Sherman*

Contribution from the Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z1

Received March 31, 2005; E-mail: sherman@chem.ubc.ca

Abstract: A six-bowl carceplex that entraps seven guest molecules, **5**·$(DMSO)_7$, was synthesized and characterized. The dynamics of the host shell was studied in solution in the absence and presence of water. A multiple-molecule template was found to drive the formation of **5**·$(DMSO)_x$·$G_{(7-x)}$ (G = DMA, DMF; $x = 5-7$). Higher selectivity was found for species containing greater numbers of DMSO molecules.

Introduction

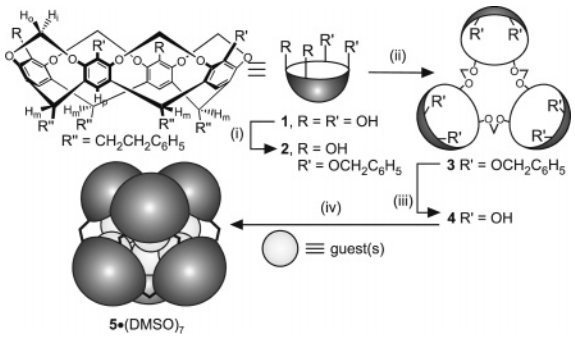
Molecular containment has fascinated chemists for decades. A variety of strategies have been successfully employed to create hosts that encapsulate smaller guest molecules. For example, the spherical or ellipsoid shells of fullerene cages can be opened and filled with metal ions, atomic nitrogen, or H_2.[1] Tubular fullerenes (carbon nanotubes) can be filled with small simple molecules (e.g., KI, H_2, N_2, O_2, and H_2O)[2] or fullerenes (i.e., "nanopea pods").[3] 3-D networks such as zeolites, molecularly imprinted polymers, and dendrimers all possess pores or channels in their structures, which can be occupied by a variety of specific guest molecules. Entire fluids can be contained noncovalently in micelles.[4]

Homogeneous, single entity molecular containers have been reported that bind one or several guest molecules. These nanoscale systems have well-defined 3-D structures, which facilitates their characterization. Molecular containers have been reported that are constructed of two or more subunits held together by metal−ligand interactions,[5−7] hydrogen-bonding,[8] and covalent bonds.[9] Mattay,[10] Atwood,[11] Rebek,[12] Kaifer,[13] and Cohen[14] have reported noncovalent assemblies of six resorcinarenes or pyrogallolarenes into octahedral arrays. Although both hexamers were initially prepared by crystallization and observed in the solid state, they are stable in solution where their hydrogen-bond stitching remains intact.[11−14] Pyrogallolarene hexamers are even stable in highly polar solvents where many solvent molecules are encapsulated as guests; Atwood and coworkers reported that the pyrogallolarene hexamer may hold up to 18 MeOHs.[11] Rebek and others have shown that resorcinarene/pyrogallolarene hexamers can encapsulate several guest or solvent molecules as well as a single large molecule.[12]

Multiple molecule containment in covalently bound, cavitand-based containers was first demonstrated by the Cram group with the entrapment of two acetonitriles in a two-cavitand carceplex.[15] Our group has reported entrapment of two DMFs (dimethylformamides) in a carceplex composed of two "widened" [5]-cavitand subunits linked by five disulfide bonds.[16] We have also entrapped up to three guest molecules in a carceplex formed by capping a cyclic trimer of cavitands and have assessed the

(1) (a) Mauser, H.; Hirsch, A.; van Eikerna Hommes, N. J. R.; Clark, T.; Pietzak, B.; Weidinger, A.; Dunsch, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2835−2838. (b) Komatsu, K.; Murata, M.; Murata, Y. *Science* **2005**, *307*, 238−240.
(2) Meyer, R. R.; Sloan, J.; Dunin-Borkowski, R. E.; Kirkland, A. I.; Novotny, M. C.; Bailey, S. R.; Hutchison, J. L.; Green, M. L. H. *Science* **2000**, *289*, 1324−1326.
(3) Hornbaker, D. J.; Kahng, S.-J.; Misra, S.; Smith, B. W.; Johnson, A. T.; Mele, E. J.; Luzzi, D. E.; Yazdani, A. *Science* **2002**, *295*, 828−831.
(4) Hamley, I. W. *Introduction to Soft Matter: Polymers, Colloids, Amphiphiles and Liquid Crystals*; John Wiley & Sons, Ltd.: England, 2000.
(5) (a) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **1999**, *121*, 1397−1398. (b) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 6311−6312. (c) Yu, S.-Y.; Kusukawa, T.; Birada, K.; Fujita, M. *J. Am. Chem. Soc.* **2000**, *122*, 2665−2666.
(6) (a) Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613−615. (b) Fochi, F.; Jacopozzi, P.; Wegelius, E.; Rissanen, K.; Cozzini, P.; Marastoni, E.; Fisicaro, E.; Manini, P.; Fokkens, R.; Dalcanale, E. *J. Am. Chem. Soc.* **2001**, *123*, 7539−7552. (c) Cuminetti, N.; Ebbing, M. H. K.; Prados, P.; de Mendoza, J.; Dalcanale, E. *Tetrahedron Lett.* **2001**, *42*, 527−530.
(7) (a) Fox, O. D.; Dalley, K.; Harrison, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 7111−7112. (b) Fox, O. D.; Leung, J. F.-Y.; Hunter, J. M.; Dalley, K.; Harrison, R. G. *Inorg. Chem.* **2000**, *39*, 783−790. (c) Fox, D. O.; Dalley, N. K.; Harrison, R. G. *Inorg. Chem.* **1999**, *38*, 5860−5863.
(8) (a) Hof, F.; Craig, S.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488−1508. (b) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286. (c) de Mendoza, J. *Chem.-Eur. J.* **1998**, *4*, 1373−1377. (d) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (e) Rebek, J., Jr. *Chem. Soc. Rev.* **1996**, 255−264.
(9) Cram, D. J.; Cram, J. M. *Container Compounds and Their Guests*; The Royal Society of Chemistry: Cambridge, 1994.
(10) Gerkensmeier, T.; Iwanek, W.; Agena, C.; Fröhlich, R.; Kotila, S.; Näther, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 2257−2262.
(11) (a) Atwood, J. L.; Barbour, L. J.; Jerga, A. *J. Chem. Soc., Chem. Commun.* **2001**, 2376−2377. (b) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469. (c) Cave, G. W. V.; Antesberger, J.; Barbour, L. J.; McKinlay, R. M.; Atwood, J. L. *Angew. Chem.* **2004**, *43*, 5263−5266.
(12) (a) Shivanyuk, A.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7662−7665. (b) Shivanyuk, A.; Rebek, J., Jr. *J. Chem. Soc., Chem. Commun.* **2001**, 2424−2425. (c) Shivanyuk, A.; Rebek, J., Jr. *J. Chem. Soc., Chem. Commun.* **2001**, 2374−2375. (d) Yamanaka, M.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 2939−2943. (e) For another host that binds a large exchanging guest, see: Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 275−277.
(13) Philip, I. E.; Kaifer, A. E. *J. Am. Chem. Soc.* **2002**, *124*, 12678−12679.
(14) (a) Avram, J.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148−15149. (b) Avram, J.; Cohen, Y. *Org. Lett.* **2002**, *4*, 4365−4368. (c) Avram, L.; Cohen, Y. *Org. Lett.* **2002**, *5*, 3329−3332. (d) Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 1099−1102. (e) Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 1099−1102. (f) Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 3329−3332. (g) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11556−11563. (h) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2003**, *125*, 16180−16181.
(15) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1403−1405. Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167−2172.
(16) Naumann, C.; Place, S.; Sherman, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 16−17.

Scheme 1. Synthesis of Carceplex **5**·(DMSO)$_7$[a]



[a] (i) DBU, BnBr, acetone. (ii) CH_2ClBr, K_2CO_3, DMSO. (iii) H_2, Pd/C, benzene:methanol (1:1). (iv) $BrCH_2Cl$, Cs_2CO_3, DMSO, 60 °C.

guests' roles as templates.[17] Multiple guests have also been permanently contained in separate chambers (one per chamber) in multi-carceplexes formed from cyclic oligomers of cavitands.[18,19] Permanent entrapment requires rigid subunits and small portals with respect to guest size. For potential applications such as delivery devices, long-term containment (as well as controlled release) is essential, likewise for stabilization of reactive intermediates. One can step closer to virus-like large containment[20] by covalently stitching together more units. An impressive convergent approach, leading to a five-cavitand "superbowl", has been reported by Sherburn;[21] this large host still requires a sixth cavitand to seal off the opening of the molecular cookie jar. We report here an alternative approach to a full six-cavitand single chamber covalent carceplex, **5**·(guest)$_7$ (Scheme 1). Carceplex **5**·(guest)$_7$ is the largest carceplex reported and is the covalent analogue of Atwood, Mattay, Rebek, Kaifer, and Cohen's pyrogallolarene hexamer capsules. The conformational dynamics and the mobility of the entrapped guests in **5**·guests is described, as is a multiple-molecule template study in the formation of **5**·(guest)$_7$.

Results and Discussion

Synthesis. Carceplex **5**·(guests)$_7$ was synthesized in four steps from tetrol **1** (Scheme 1).[22] A,B (adjacent hydroxyls)-benzylation to give diol **2** (26%) was carried out using the same conditions reported for the corresponding A,C (opposing hydroxyls)-isomer: tetrol **1**, DBU, and benzyl bromide in acetone.[17b] Cyclization of A,B-diol **2** with K_2CO_3 and bromochloromethane in DMSO afforded benzylated A,B-trimer **3** (16%). A,B-trimer **3** was debenzylated with H_2, Pd/C to afford hexahydroxyl A,B-trimer **4** (58%), which was then bridged with CH_2BrCl in the presence of Cs_2CO_3 or K_2CO_3 at 60 °C in DMSO solvent to give carceplex **5**·(DMSO)$_7$ (35%). This yield reflects organization of 15 discrete components and formation of 12 bonds.[23]

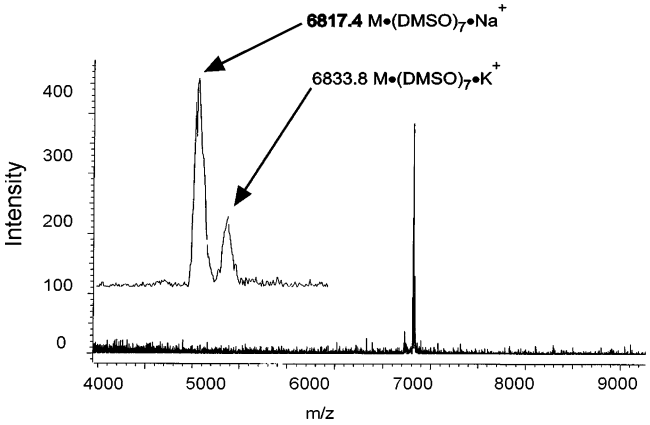


Figure 1. MALDI MS spectrum of carceplex **5**·(DMSO)$_7$.

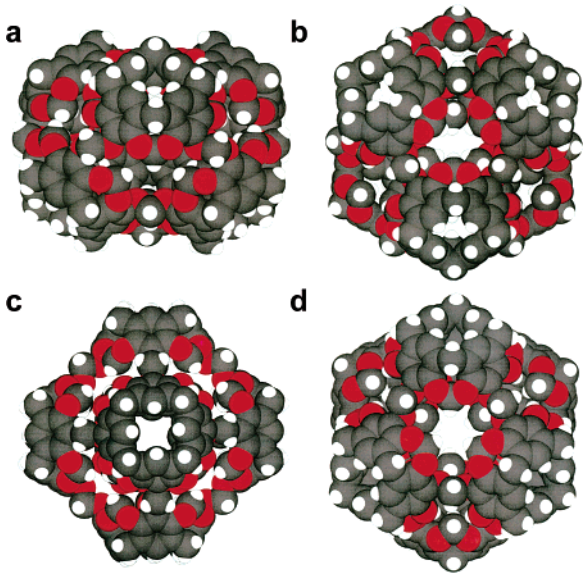


Figure 2. MM2 minimized space filling representations of (a) the C_{3v} conformation of **5**·(DMSO)$_7$ viewed down the C_3-axis, (b) the C_{3v} conformation of **5**·(DMSO)$_7$ viewed from the side perpendicular to the C_3-axis, (c) the O_h-symmetric conformation of **5**·(DMSO)$_7$ viewed down the C_3-axis, and (d) the O_h-symmetric conformation of **5**·(DMSO)$_7$ viewed from the side perpendicular to the C_3-axis. To simplify calculations, the phenylethyl groups on each [4]cavitand were replaced with hydrogens. For clarity, the entrapped guests are omitted.

MALDI mass spectrometry yields $m/z = 6817$ and 6834, which are attributed to the corresponding Na^+ and K^+ adducts, respectively (Figure 1). This is in agreement with integration from the ^{1}H NMR spectrum, which suggests a 1:7 host:guest ratio. There is no sign of entrapment of other numbers of guests.

Host Conformation. The host shell of carceplex **5**·(DMSO)$_7$ was expected to be highly symmetric (i.e., O_h in Figure 3c and d) based on examination of Corey−Pauling−Koltun (CPK) molecular models and on the solid-state structures observed for the related resorcinarene and pyrogallolarene hexamers. However, NMR data and MM2 calculations indicate a less symmetric, flattened conformation (Figure 2a and b).

In sieve-dried $CDCl_3$ (Figure 3f), the host shell for **5**·(DMSO)$_7$ shows three signals each for H_o, H_{ac}, H_m, and H_i in 1:1:2 ratios, which is consistent with a structure characterized by upper and lower A,B-cavitand trimers connected in a staggered arrangement by six equatorial methylene bridges. The key feature is the set of three signals for H_{ac}: a major signal (12H, H_{ac2}) corresponding to the equatorial enantiotopic meth-

(17) (a) Chopra, N.; Sherman, J. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1955−1957. (b) Makeiff, D. A.; Sherman, J. C. *Chem.-Eur. J.* **2003**, *9*, 3253−3262.
(18) (a) Chopra, N.; Naumann, C.; Sherman, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 194−196. (b) Mungaroo, R.; Sherman, J. C. *J. Chem. Soc., Chem. Commun.* **2002**, 1672−1673.
(19) Yoon, J.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1997**, 2065−2066.
(20) Atwood, J. L.; Barbour, L. J.; Dalgarno, S. J.; Hardie, M. J.; Raston, C. L.; Webb, H. R. *J. Am. Chem. Soc.* **2004**, *126*, 13170−13171.
(21) Barrett, E. S.; Irwin, J. L.; Edwards, A. J.; Sherburn, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 16747−16749.
(22) Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194−2204.
(23) For semiquantitative estimation of the efficiency in the formation of self-assembling structures, see: Gibb, C. L. D.; Gibb, B. C. *J. Supramol. Chem.* **2001**, 39−52.

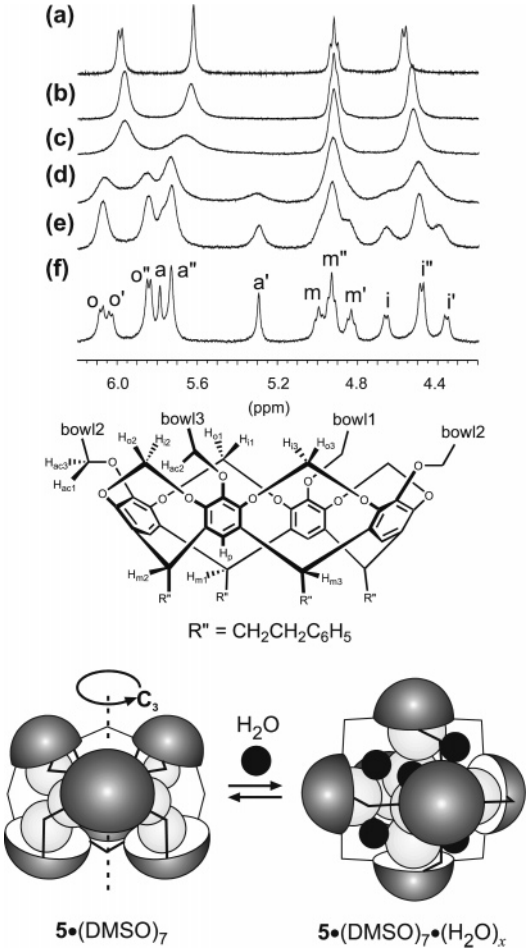


Figure 3. Sections of ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of **5**·$(DMSO)_7$ at various ratios of H_2O:**5**·$(DMSO)_7$. (a) **5**·$(DMSO)_7$ in H_2O-saturated $CDCl_3$. (b) H_2O:**5**·$(DMSO)_7$ ~113:1. (c) H_2O:**5**·$(DMSO)_7$ ~68:1. (d) H_2O:**5**·$(DMSO)_7$ ~33:1. (e) H_2O:**5**·$(DMSO)_7$ ~20:1. (f) **5**·$(DMSO)_7$ in dry $CDCl_3$. a = H_{ac1}, a′ = H_{ac2}, a″ = H_{ac3}, etc.

ylene protons, and two minor signals (6H each, H_{ac1} and H_{ac3}) for the geminal diastereotopic pairs of the trimer subunits. The high symmetry of the water complex (see Figures 2 and 3) renders all of the inter-bowl acetals equivalent, while the lower symmetry dry carceplex manifests two nonequivalent inter-bowl acetals. The upper rim of the diastereotopic acetals (H_{ac1} and H_{ac3}) is visible in the lower right drawing in Figure 3, as are four of the eight equatorial acetals. The absence of splitting between H_{ac1}/H_{ac3} is because of weak coupling (small coupling constant), which may arise as a result of torsional strain from small O−CH_2−O bond angles (large H_{ac1}−C−H_{ac3} angle).[24] Weak coupling between H_{ac1}/H_{ac3} was detected by long-range COSY, while the HMQC spectrum confirmed that H_{ac1} and H_{ac3} are attached to the same carbon atom. An arrangement of two A,B-trimer subunits with eclipsing bowls can be ruled out because four doublets of equal intensity for H_{ac} would be expected. A host shell symmetry induced by a unique arrangement of the DMSO guests can also be ruled out because only one averaged DMSO environment is observed. Conjugation of the phenolic oxygens into the bowl rings appears to be better in the low symmetry dry form, but the energy gain from binding water molecules appears to offset the concomitant loss of this conjugation.

MM2 calculations were performed on each conformation in the presence and absence of the DMSO guests. The results agreed with experimental observations: With the seven DMSO guests, the C_3 host conformation ($G° = 360$ kcal/mol) is predicted to be ~15 kcal/mol more stable than the more symmetric O_h counterpart ($G° = 375$ kcal/mol). Without the DMSO guests, the two conformations are predicted to be equal in energy ($G° = 470$ kcal/mol). We conclude that the main driving force behind the host adopting the flat conformation is the maximization of favorable host−guest (van der Waals) interactions.

Host Dynamics. The flattened conformation for **5**·$(DMSO)_7$ in sieve-dried $CDCl_3$ is dynamic at 300 K and interconverts with other degenerate flattened conformers. Exchange is detected between the three signals for each set of H_o, H_{ac}, H_m, and H_i in 2D ROESY spectra. We determined an average chemical rate constant (k_{chem}) of 6.4 s^{-1} for the exchanging H_i using 1D EXSY experiments (see Supporting Information);[25] this rate yields an energy barrier of 16.5 kcal/mol for interconversion of degenerate flat conformers (300 K, $CDCl_3$). This energy barrier is interpreted largely as the steric and torsional strain encountered upon rotation of the 24 Ar−O and O−CH_2 bonds of the 12 flexible interbowl methylene linkages in a concerted fashion. Naturally, reorientation of guests and the concomitant breaking of host−guest and guest−guest interactions may also contribute to this energy barrier.

The conformational behavior described for **5**·$(DMSO)_7$ is unusual and was not reported for the structurally related noncovalently linked resorcinarene and pyrogallolarene hexamers. Perhaps the hydrogen-bond stitching of the noncovalent hexamers cannot withstand a flattened conformation. Related dynamic host conformational processes have been observed for smaller carceplexes (i.e., "twistomerism").[16,26]

Water Binding. In a recent paper, we reported the reversible complexation of H_2O to the interior of three-cavitand carceplexes.[17] Here, we likewise report that **5**·guest reversibly complexes H_2O, which affects the conformational mobility of the host. Increasing the water concentration in $CDCl_3$ at 300 K causes broadening and coalescence of the triplicate sets of host resonances into single sharp signals for each of H_o, H_{ac}, H_m, and H_i in the ^{1}H NMR spectra of **5**·$(DMSO)_7$ (Figure 3a−f). Water saturation either drives the host into an O_h structure, enhances interconversion between C_{3v} structures, or drives a pseudo-O_h structure that interconverts rapidly.

The rate of exchange between the free and bound state for water, **5**·$(DMSO)_7$·$(H_2O)_x$, where $x = 1, 2, 3$ ..., appears to be fast on to the ^{1}H NMR time scale. We observe no bound water signal in the ^{1}H NMR spectra, and the chemical shift of the "free" H_2O signal is dependent on the concentration of H_2O: in $CDCl_3$ containing **5**·$(DMSO)_7$ and trace amounts of H_2O,

(24) Paudler, W. W. *Nuclear Magnetic Resonance: General Concepts and Applications*; Wiley-Interscience: New York, 1987; pp 149−151.

(25) (a) Perrin, C. L.; Engler, R. E. *J. Magn. Reson.* **1991**, *49*, 188−195. (b) Naumann, C.; Román, E.; Peinador, C.; Ren, T.; Patrick, B. O.; Kaifer, A. E.; Sherman, J. C. *Chem.-Eur. J.* **2001**, *7*, 1637−1645. (c) Naumann, C.; Patrick, B. O.; Sherman, J. C. *Tetrahedron* **2002**, 787−798. (d) Naumann, C.; Patrick, B. O.; Sherman, J. C. *Chem.-Eur. J.* **2002**, *8*, 3717−3723. (e) Naumann, C. Ph.D. thesis, University of British Columbia, 2001. (f) Brotin, T.; Devic, T.; Lesage, A.; Emsley, L.; Collet, A. *Chem.-Eur. J.* **2001**, *7*, 1561−1573.

(26) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1999**, *121*, 1962−1963.

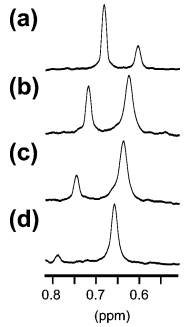


Figure 4. DMSO methyl proton signals for **5**·$(DMSO)_7$ in ^1H NMR spectra (400 MHz, CD_2Cl_2, 300 K) at different H_2O concentrations. (a) H_2O:**5**·$(DMSO)_7$ = 16:1. (b) H_2O:**5**·$(DMSO)_7$ = 140:1. (c) H_2O:**5**·$(DMSO)_7$ = 550:1. (d) H_2O:**5**·$(DMSO)_7$ > 1000:1 (saturated). Downfield signals = DMSO methyls of **5**·$(DMSO)_7$; upfield signals = DMSO methyls of **5**·$(DMSO)_7$·$(H_2O)_x$.

H_2O appears at 1.67 ppm, which is 0.13 ppm downfield from H_2O in $CDCl_3$ (1.54 ppm) without **5**·$(DMSO)_7$. When several equivalents of H_2O is added to **5**·$(DMSO)_7$ in $CDCl_3$, the H_2O proton signal shifts toward 1.54 ppm. This concentration dependence was not observed when water was added to a sieve-dried $CDCl_3$ blank or a solution containing A,B-trimer **3**. The upfield shift for bound H_2O is typical of incarcerated guests, including bound water in a three-cavitand carceplex.[17b] The number of waters, *x*, in **5**·$(DMSO)_7$·$(H_2O)_x$ is not known, nor do we know how many water species are in exchange (vide infra).

The rapid exchange between free/bound water is not surprising, because the host shell of **5**·$(DMSO)_7$ is more porous than smaller two- and three-cavitand carceplexes. Exchange between free and bound H_2O for a three-cavitand carceplex is slow on the NMR time scale;[17b] H_2O probably enters through the 16-membered ring holes at the bottom of one of the three cavitand subunits. Cram suggested that H_2O (or D_2O) may pass through similar such holes in the protonation of amine guests within a small two-cavitand hemicarceplex.[27] For **5**·$(DMSO)_7$, the passage of water through the host likely occurs through the eight large 30-membered ring holes between each set of three interconnecting cavitand subunits.

The chemical shift of bound DMSO methyl protons is also dependent on the H_2O concentration. In sieve-dried $CDCl_3$, bound DMSO in **5**·$(DMSO)_7$ appears at 0.59 ppm. A downfield shift to 0.65 ppm was observed upon addition of H_2O. At all H_2O concentrations, only a single bound DMSO signal is observed, which suggests that bound DMSOs in **5**·$(DMSO)_7$ and **5**·$(DMSO)_7$·$(H_2O)_x$ are in fast exchange or have coincidental chemical shifts. This is consistent with fast exchange of H_2O (vide supra).

H_2O also binds to **5**·$(DMSO)_7$ in nitrobenzene-d_5, pyridine-d_5, and tetrachloroethylene-d_4, with the most interesting behavior occurring in CD_2Cl_2. In contrast to the single signal observed for bound DMSO in most solvents, two signals are observed in sieve-dried CD_2Cl_2, one at 0.67 and one at 0.59 ppm (Figure 4a). As the H_2O concentration is increased, the major signal (0.67 ppm) decreases in intensity while the minor signal increases. Both signals also shift downfield. In H_2O-saturated CD_2Cl_2, only one DMSO guest signal appears, which corresponds to the hydrated species **5**·$(DMSO)_7$·$(H_2O)_x$ (Figure 4d).

No exchange is detected between the two bound DMSO signals observed in CD_2Cl_2 spectra. However, as in $CDCl_3$, exchange between free and bound H_2O is rapid on the ^1H NMR time scale in CD_2Cl_2, because only a single average H_2O signal is observed. Intuitively, one would expect the exchange rates between free and bound H_2O to be the same as the exchange rates between bound DMSO in **5**·$(DMSO)_7$ and **5**·$(DMSO)_7$·$(H_2O)_x$, but this is clearly not the case. Indeed, one would expect the $\Delta\delta$ for bound/free water be larger than the $\Delta\delta$ for bound DMSO in **5**·$(DMSO)_7$ versus **5**·$(DMSO)_7$·$(H_2O)_x$, and thus one would expect the DMSOs to coalesce before the waters. The opposite is observed. A plausible explanation is that the two species observed differ by the presence of several waters. The loss or gain of single H_2O molecules appears to be fast, while the loss or gain of several H_2Os is slow on the NMR time scale.[28] It is unclear why this effect is unique to CD_2Cl_2.

Guest Orientation and Mobility. The ^1H NMR chemical shifts of the bound guest signals can give information regarding the orientation of the guest within the host shell. For most carceplexes and hemicarceplexes, the inner phase is highly shielding and the difference between the chemical shifts of free and bound guests ($\Delta\delta$) is large.[22,29,30] Bound DMSO in **5**·$(DMSO)_7$ comes at 0.59 ppm ($CDCl_3$) and possesses the smallest $\Delta\delta$ (1.87 ppm) of any DMSO-containing carceplex. $\Delta\delta$ values for DMSO in other carceplexes and hemicarceplexes range from 2.52 to 3.70 ppm.[17,22] The methyl protons of bound DMSO probably spend less time oriented into the highly shielding bowls in the more spacious cavity of **5**·$(DMSO)_7$ than in smaller two- or three-bowl carceplexes. Although low-temperature NMR spectroscopy was used to probe the mobility and preferred orientations of the DMSO guests in the host cavity for **5**·$(DMSO)_7$ in sieve-dried and H_2O-saturated CD_2Cl_2 and in $CDCl_3$, complex spectra precluded any definitive conclusions.

Heterogeneous Guest Mixtures. We conducted carceplex reactions in other neat solvents as well as in mixed solvents and analyzed the products formed by ^1H NMR spectroscopy and MALDI mass spectrometry. Mixtures of carceplex **5**·guests were obtained from the mixed solvents DMSO:DMF and DMSO:DMA (dimethylacetamide); individual carceplexes differing by the composition of entrapped guests could not be separated by conventional chromatography, but product ratios could be detected by ^1H NMR (vide infra). With those three solvents/guests/templates, the host cavity of carceplex **5**·guests was observed to have a high affinity for only seven-molecule templates. Carceplexes **5**·$(DMSO)_7$, **5**·$(DMSO)_6$·DMF, and **5**·$(DMSO)_5$·$(DMF)_2$ were obtained from DMSO:DMF (1:1), while **5**·$(DMSO)_7$, **5**·$(DMSO)_6$·DMA, and **5**·$(DMSO)_5$·$(DMA)_2$ were obtained from DMSO:DMA (1:1) solvent. No carceplexes were obtained from reactions in neat DMF or DMA. For the two mixtures above, MALDI MS identified the three products, and the two new compounds were differentiated by NMR integration (6:1 versus 5:2 ratios of guests). See the Supporting Information.

Templation Study. Template effects in the formation of carceplexes by suitable guests can be easily evaluated from the

(27) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717−7727.

(28) CD_2Cl_2 solvent entering the host cavity was ruled out based on the absence of a signal for bound CD_2Cl_2 or CH_2Cl_2 and analysis of CPK molecular models, which suggest that CD_2Cl_2 is too large to squeeze through the small openings in the host shell.

(29) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717−7727.

(30) Yoon, J.; Sheu, C.; Houk, K. N.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1996**, *61*, 9323−9339.

Table 1. Template Ratios for **5**·[$(DMSO)_x$·$(DMF)_{(7-x)}$] and **5**·[$(DMSO)_x$·$(DMA)_{(7-x)}$][a]

	TR_{77}	
carceplex	G = DMF	G = DMA
5·$(DMSO)_7$	230	14
5·$(DMSO)_6$·G	52	4
5·$(DMSO)_5$·G_2	8	1
5·$(DMSO)_4$·G_3	1	

[a] [DMF] = 6.04 M, [DMA] = 5.37 M, [DMSO] = 7.04 M. TR_{77} = template ratio for a seven-molecule template versus another seven-molecule template. Values are a lower limit estimate based on the integration of the two DMSO signals. This does not take into account other guest signals (i.e., COCH_3 signals) hidden under the DMSO methyl proton resonances.

product ratios determined via competition reactions in the presence of two or more competing templates (guests). The determination of template effects for carceplexes is greatly facilitated by the fact that they are permanently "tagged" with their templates, which eliminates the need to isolate reaction intermediates and determine individual rate constants. Template effects by single-molecule guests in the formation of carceplexes and hemicarceplexes have been studied in some detail.[31] We recently reported the first study involving multiple-molecule templates in the formation of a container molecule species (i.e., carceplex) involving 1−3 molecule templates.[17b]

Template ratios for competing seven-molecule templates (TR_{77}) in the formation of **5**·$(DMSO)_x$·$G_{(7-x)}$ for reactions in DMSO:G (G = DMF or DMA, Table 1) were evaluated. TR_{77} values are calculated similarly to other previously reported multiple-molecule *TR*,[17b] except that an additional statistical factor is included to account for the probabilities for each possible seven-molecule combination for a 2-guest system. For **5**·$(DMSO)_x$·$G_{(7-x)}$, the templating ability for seven-molecule templates increases with increasing numbers of encapsulated DMSO molecules, as carceplexes with four or more DMFs or DMAs are not even observed. For such a roomy container, and for guests of such similar size, shape, and polarity, this selectivity is remarkable. DMSO is likely a better guest than DMA or DMF because its interactions with the bowl subunits are more favorable during the formation of the host shell. This is also consistent with the reports that DMSO is a superior template to DMF and DMA in two- and three-bowl carceplexes (one and three guest templates, respectively).[17b,32] Guest−guest interactions and desolvation are also likely to play a role in the thermodynamics of the template effects.

Conclusions

The challenge of producing a sufficiently rigid, small-pored, large container molecule such as a six-bowl carceplex **5**·$(DMSO)_7$ vessel has been met. Carceplex **5**·guests demonstrates permanent entrapment of the largest number of guests for such a container molecule. Notable large nonpermanent encapsulations are the 18 methanol molecules that may reside in Atwood's hexamer,[11] and Fujita's nano-bowl dimer cage which binds six *cis*-stilbene molecules.[5c] The synthesis of **5**·$(DMSO)_7$ holds promise for designing large covalently bonded molecular containers having tailored sizes and well-defined structures. The host's baleen-like ability to entrap larger guests (e.g., DMSO) permanently and smaller guests (e.g., water) temporarily may have ramifications for future work involving innermolecular reactions.[33] As supramolecular chemistry keeps ever an eye on biomimicry, it is noteworthy that such control of substrate entry and egress is the hallmark of cell membranes. In addition, delivery devices for larger molecules (e.g., drug-sized), which rely on long-term storage, are brought one modest step closer to fruition.

The formation of carceplex **5**·$(guests)_7$ was shown to be driven by a seven-guest multiple-molecule template effect. The observed selectivity is unexpectedly and immeasurably high, in favor of a template of specific molecularity. The remarkable selectivity for the statistically unfavored seven-molecule templates over templates with other molecularities may arise from each of the six bowls binding one guest with enough room in the center of the forming host cavity for a seventh. The selectivity of DMSO over DMF or DMA is also marked, as the template ratio for $(DMSO)_7$ versus $(DMF)_7$ or $(DMA)_7$ cannot even be measured. The seven-molecule templates already begin to blur the distinction between template effects and solvent effects.

Acknowledgment. We thank the NSERC, PRF, and NIH for financial support of this work. We would also like to thank Naveen Chopra for providing the characterization of A,B-diol **2**.

Supporting Information Available: Details of all of the experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0520621

(31) Sherman, J. C. *Chem. Commun.* **2003**, 1617−1623.
(32) Chapman, R. G.; Sherman, J. C. *J. Org. Chem.* **1998**, *63*, 4103−4110.
(33) (a) Warmuth, R. *J. Inclusion Phenom.* **2000**, *37*, 1−38. (b) Makeiff, D. A.; Vishnumurthy, K.; Sherman, J. C. *J. Am. Chem. Soc*. **2003**, *125*, 9558−9559.