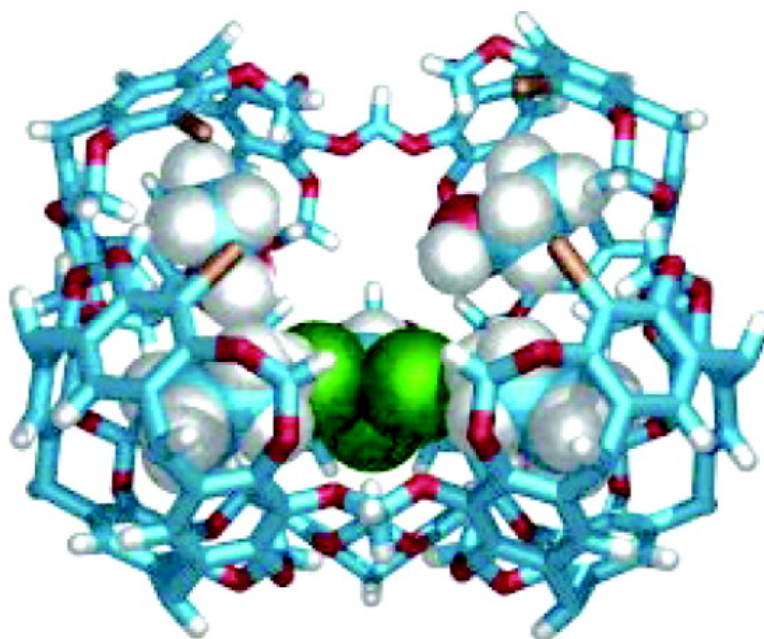


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Superbowl Container Molecules

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Synthetic container molecules have potential in areas as diverse as sensing, catalysis, drug delivery, and separation science.^{1–3} The first rigid cavity molecules—cavitands—were small, shallow bowls inside which one small guest can perch.^{4,5} Molecules with deeper cavities were subsequently reported,⁶ yet remarkably few molecular vessels with large, noncollapsible interiors have been prepared. In 1997, Atwood and MacGillivray reported the crystal structure of a self-assembling hydrogen-bonded array comprising six *C*-methyl-resorcinarene molecules and eight water molecules.⁷ The roughly spherical space enclosed by this extraordinary noncovalent assembly contains a volume of $\sim 1375 \text{ \AA}^3$. Self-assembling, noncovalent systems offer unrivalled ease of preparation, yet their covalent cousins offer considerably greater stability, structural variation, functional group tolerance, and solubility in organic solvents. Such attributes promote a deeper understanding of the nature of these important systems and their potential applications. Herein we present the chemical synthesis and properties of a covalently linked, noncollapsible tureen-shaped container molecule with an internal volume of $\sim 1050 \text{ \AA}^3$ inspired by the spherical hexameric resorcinarene assembly.

Following the original report of the resorcinarene spheroid,⁷ studies by Mattay⁸ and Atwood⁹ revealed a similar hexameric structure from pyrogallol-derived resorcinarenes. In this case the spheroidal structure forms without the assistance of water molecules. More recent investigations by Atwood,^{10,11} Rebek,^{12–15} Cohen,^{16–20} and Kaifer²¹ provide evidence for the existence of the same structures in certain solutions and for their reversible encapsulation of large guests such as tetraalkylammonium, -phosphonium, and -antimony(V) salts and ferrocenium ions.

Whereas these noncovalent arrays comprise six cone-conformation resorcinarenes held together by H-bonds through phenolic residues, the “superbowls” are made up of five cavitand bowls linked by eight covalent bonds through their four rim aromatic carbons. The target host comprises a unique cavitand located at the base of the structure and four equivalent cavitands, which represent the walls. The retrosynthetic analysis of the superbowl, depicted in cartoon format in Figure 1, exploits the C_{4v} symmetry of the structure. Wall–wall disconnections reveal a cruciform pentamer of cavitands, which is further broken down into five constituent bowls, four of which are equivalent. Chemical synthesis thus requires an unsymmetrically functionalized cavitand for the walls and a symmetrical tetrafunctionalized species for the base. After inspecting models of many potential targets, we chose $-\text{CH}_2\text{O}-$ linkers between base and walls, and $-\text{OCH}_2\text{O}-$ linkers between the walls. This combination allowed the necessary flexibility for interbowl bond formation, while preventing holes in the superbowl structure large enough for entry and exit of all but the smallest of guests.

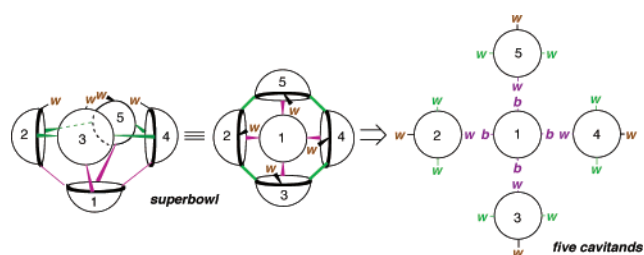


Figure 1. Disconnection of “superbowl” pentacavitands. The “base” cavitand is labeled 1 and “wall” cavitands are labeled 2–5. Different substituents on the wall bowls (*w*) are represented in different colors.

The synthesis begins with *n*-pentyl-footed tetrabromocavitand **1** (Scheme 1).²² Chemo- and regioselective double lithium–bromine exchange with *n*-BuLi allowed the high-yielding conversion into the A,C-dibromodiols **2**,²³ which was protected as the bis-MOM ether **3**. Selective single lithium–bromine exchange²⁴ of A,C-dibromide **3** followed by boronate ester formation and oxidative hydrolysis gave the required unsymmetrically functionalized bowl **4**, which was reductively debrominated to phenol **5** by way of the organolithium intermediate. Four molar equivalents of phenols **4** and **5** were united with the base bowl building block, tetrabromomethyl cavitand **6**,²⁵ to form protected cruciform pentamers **7** and **8**. Following hydrolysis of the eight MOM ethers to give octols **9** and **10**, the scene was set for closure to superbowl **11** and **12**. This reaction proceeds smoothly under conditions which mimic the conversion of resorcinarenes into cavitands,²⁶ a result that is hardly surprising, considering the parallels between the two transformations.

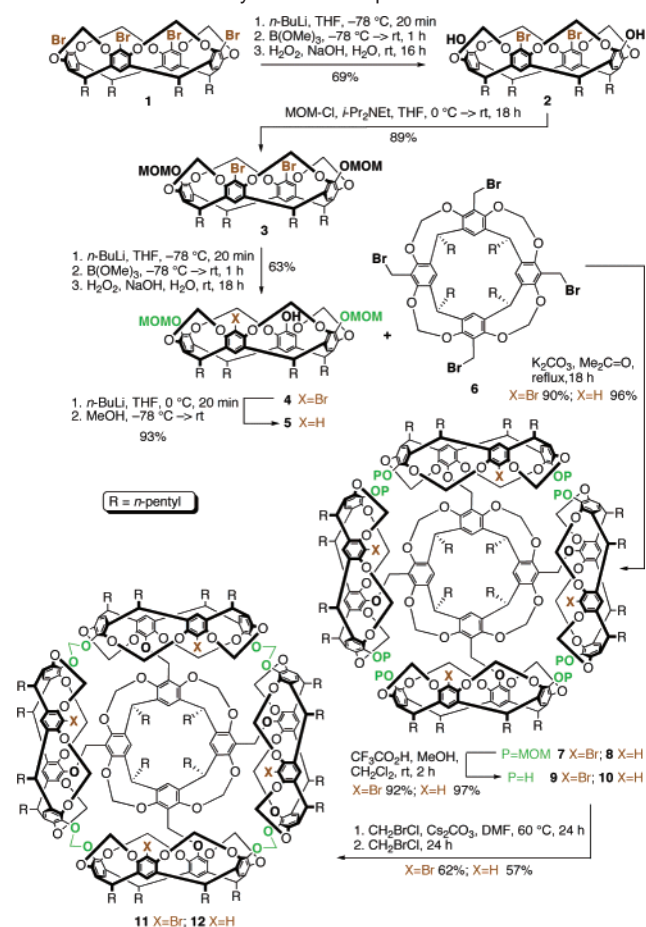
An X-ray crystal structure of tetrabromo superbowl **11** was obtained from diffraction data collected on a crystal grown from a mixture of deuteriochloroform, ethanol, and methyl ethyl ketone. The molecular structure, minus the 20 *n*-pentyl side chains (Figure 2) shows the three-dimensional shape of the new covalently linked container molecule and its very sizable, noncollapsible cavity. The shape of the molecule without the alkyl feet, with its bulging sides and narrower opening, is reminiscent of a lidless tureen. The four bromine substituents reside over the chasm, with the C–Br bonds $\sim 30^\circ$ out of the plane of the rim. The crystal structure exhibits an unsymmetrical orientation of wall cavitands—most clearly manifested in the positions of the rim bromines—evidently arising from the conformational flexibility in the $-\text{OCH}_2\text{O}-$ interbowl linkers.

The interior of the host contains five separate binding pockets of fixed size and shape, which are located in well-defined locations. Each of the four wall cavitands binds an ethanol molecule, oriented with the methyl group in. A chloroform molecule resides in the base cavitand with one of its chlorine atoms pointing down. This chloroform molecule is located some 7 \AA from the rim of the tureen. Why do ethanol molecules reside in the equatorial cavitands, and why does a chloroform reside in the base? The ethanol oxygens point downward toward the central chloroform, consistent with the

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Scheme 1. Chemical Synthesis of Superbowls



formation of O–H \cdots Cl interactions. The remaining space inside the vast interior of the superbowl (estimated remaining volume $\sim 450\text{ \AA}^3$) contains highly disordered solvent molecules.

The complete molecular structure, including those atoms of the alkyl feet included in the model, is depicted in Figure 3. Only 15 out of the 100 carbon atoms in the feet could not be located for inclusion into the model. In addition to the five guest molecules

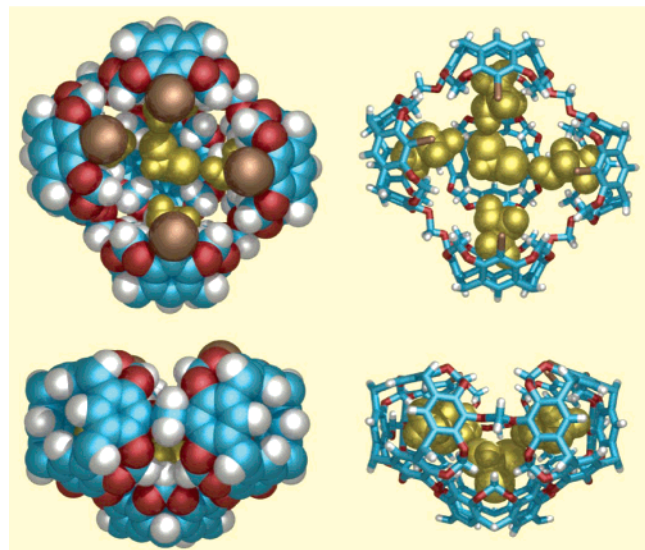


Figure 2. Molecular structure of 4EtOH+CDCl₃·tetrabromosuperbowl (11) from single-crystal X-ray analysis (*n*-pentyl chains omitted). (Top) View into cavity. (Bottom) Side view. Guests are colored gold for clarity.

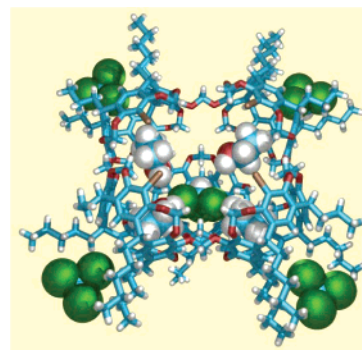


Figure 3. Molecular structure of 4EtOH+5CDCl₃·tetrabromosuperbowl (11) from single-crystal X-ray analysis (*n*-pentyl included).

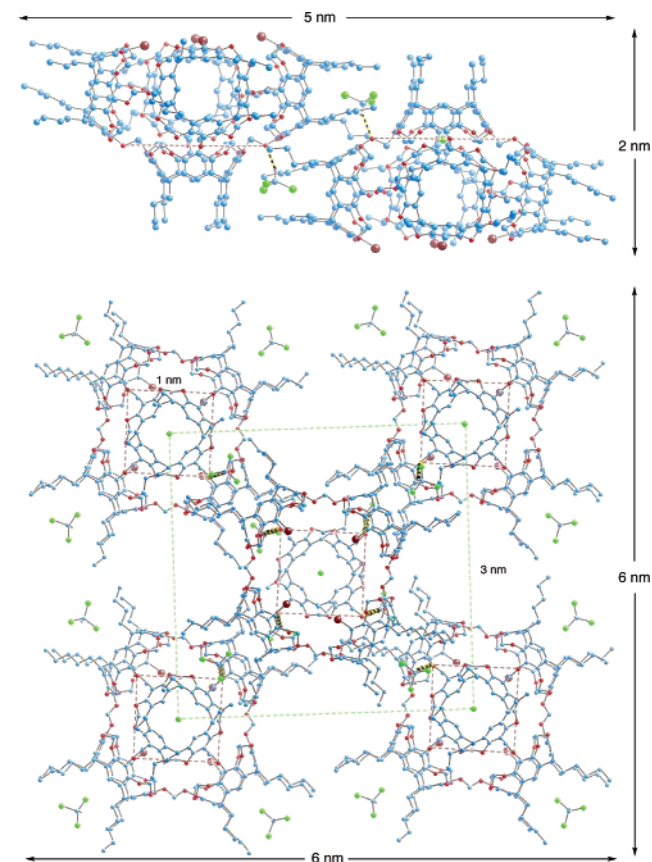


Figure 4. Arrangement of molecules of compound 11 in the crystal lattice. (Top) Two adjacent superbowl molecules enjoy mutual chloroform nesting/D \cdots O interaction. (Bottom) Five superbowl molecules of one layer: the opening of the central twelve points toward the viewer, the remaining four hosts point away. The four benzylic ether oxygens of each host molecule are connected with dashed red lines. D \cdots O interactions are depicted with yellow/black striped lines. Guests inside superbowl and H atoms are omitted.

located inside the container, a chloroform molecule resides between the alkyl feet of each of the wall cavitations. Intriguingly, these four external chloroforms adopt essentially the same orientation i.e., the C–D bonds point down, along an axis roughly perpendicular to the plane described by the superbowl's rim. The reason for this striking ordering becomes apparent when the location of adjacent superbowl molecules in the crystal structure is considered (Figure 4). Each of the deuteriochloroform molecules nestled between the feet of one superbowl participates in a C–D \cdots O interaction with a benzylic ether oxygen of an adjacent superbowl molecule. An equivalent interaction from the nesting chloroform of the neighboring superbowl to the proximate ether oxygen of the original

superbowl completes a complementary pair. This matching pair of noncovalent interactions occurs with all four wall cavitands, resulting in a grid-like arrangement in which each superbowl has four neighbors oriented in the opposite direction. Thus, these superbowls are assembled in sheets with a thickness of ~ 2 nm. It would appear that the *n*-pentyl chains are integral to the assembly of this structure.

A large noncollapsible cavity of well-defined shape offers new possibilities in guest binding. Preliminary experiments show that tetraprotiosuperbowl **12** binds tetra-*n*-hexylammonium bromide or tetra-*n*-octylammonium bromide with association constants of ~ 460 and $\sim 120 \text{ M}^{-1}$ (25 °C, CDCl_3), respectively. The stoichiometry of host:guest association is 1:1. In marked contrast to the spherical resorcinarene hexamer,¹⁵ guest exchange for **12** is fast on the NMR time scale at ambient temperature in CDCl_3 . Fast guest exchange for superbowl **12** is presumably the result of its permanently lidless structure; nevertheless, this observation lends credence to Rebek's proposed mechanism for the exchange of tetraalkylammonium ions from hexameric H-bonded resorcinarene capsules.¹⁵ Tetrabromo-superbowl **11** shows no detectable guest binding of tetraalkylammonium ions under the same conditions. Bromine substituents located at the rim of superbowl thus serve either to decrease the aperture and inhibit guest exchange or to render these particular guests unpalatable to superbowls by perturbing the binding ability of their inner phase.

In summary, short chemical syntheses of superbowls **11** and **12** from tetrabromocavitand **1** have been accomplished (overall yields **1** \rightarrow **11**, 20%; **1** \rightarrow **12**, 19%). These compounds represent the first members of a new family of container molecules with large noncollapsible interiors. In sharp contrast to the H-bonded resorcinarene hexamers, whose guest species could not be identified in the solid state,⁷ superbowl **11** binds nine solvent molecules in well-defined locations, five inside and four outside the container. Furthermore, preliminary studies show that entry into the $\sim 1050 \text{ \AA}^3$ volume interior by larger guests can be modulated by "gate-keeper" substituents around the rim. The covalent attachment of a cavitand lid to the superbowl will furnish a fully encapsulating covalent cage molecule with an inner phase considerably larger than those of existing structures.^{5,27} These and related studies are in progress.

Crystal data for **11**: the crystal chosen for this experiment was representative, on optical examination, of the bulk solid material. Triclinic, space group $P\bar{1}$ (No. 2), $a = 22.4832(6) \text{ \AA}$, $b = 25.2863(7) \text{ \AA}$, $c = 31.2864(8) \text{ \AA}$, $\alpha = 81.514(2)^\circ$, $\beta = 80.2321(14)^\circ$, $\gamma = 78.3354(9)^\circ$, $U = 17048.3(8)$, $Z = 2$. Mo $K\alpha$ radiation ($\lambda = 0.71073$), Kappa CCD diffractometer, $T = 120 \text{ K}$. Least-squares refinement based on 5279 reflections ($I > 3\sigma I$), 26105 unique reflections to $\Theta_{\text{max}} = 18.85^\circ$ (few reflections were observed beyond $\Theta = 16^\circ$, 1.25 \AA resolution). The structure was solved by direct methods, SIR97 using default settings,²⁸ and refined using the

CRYSTALS program suite²⁹ making extensive use of restraints and special shapes³⁰ to achieve a chemically and physically reasonable model with good fit to the data. A detailed description of the refinement will be published elsewhere. At convergence of a least-squares refinement based on F , $R = 0.106$, $R_w = 0.077$, and $S = 1.03$.

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Supporting Information Available: Crystallographic information file (CIF) for compound **11** (CCDC 246604). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488–1508.
- Rudkevich, D. M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 393–413.
- MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018–1033.
- Cram, D. J. *Science* **1983**, *219*, 1177–1183.
- Cram, D. J.; Cram, J. M. *Container Molecules and their Guests*; Monographs in Supramolecular Chemistry, Vol. 4; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1994.
- Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991–2005.
- MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469–472.
- Gerkensmeier, T.; Iwanek, W.; Agena, C.; Frohlich, R.; Kotila, S.; Nather, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 2257–2262.
- Atwood, J. L.; Barbour, L. J.; Jerga, A. *J. Supramol. Chem.* **2001**, *1*, 131–134.
- Atwood, J. L.; Barbour, L. J.; Jerga, A. *Chem. Commun.* **2001**, 2376–2377.
- MacGillivray, L. R.; Holman, K. T.; Atwood, J. L. *J. Supramol. Chem.* **2001**, *1*, 125–130.
- Shivanyuk, A.; Rebek, J., Jr. *Chem. Commun.* **2001**, 2424–2425.
- Shivanyuk, A.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7662–7665.
- Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 3432–3433.
- Yamanaka, M.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 2939–2943.
- Avram, L.; Cohen, Y. *Org. Lett.* **2002**, *4*, 4365–4368.
- Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148–15149.
- Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 1099–1102.
- Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 3329–3332.
- Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2003**, *125*, 16180–16181.
- Philip, I. E.; Kaifer, A. E. *J. Am. Chem. Soc.* **2002**, *124*, 12678–12679.
- Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167–2172.
- Barrett, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 8227–8229.
- Irwin, J. L.; Sherburn, M. S. *Org. Lett.* **2001**, *3*, 225–227.
- Sorrell, T. N.; Pigge, F. C. *J. Org. Chem.* **1993**, *58*, 784–785.
- Cram, D. J.; Karbach, S.; Kim, H. E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 0, 2229–2237.
- Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 9, 931–967.
- Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *SIR97. J. Appl. Crystallogr.* **1999**, *32*, 115–119.
- Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. *CRYSTALS*, Issue 11; Chemical Crystallography Laboratory: Oxford, UK, 2001.
- Schröder, L.; Watkin, D. J.; Cousson, A.; Cooper, R. I.; Paulus, W. J. *Appl. Crystallogr.* **2004**, *37*, 545–550.

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