An achiral form of the hexameric resorcin[4]arene capsule sustained by hydrogen bonding with alcohols†

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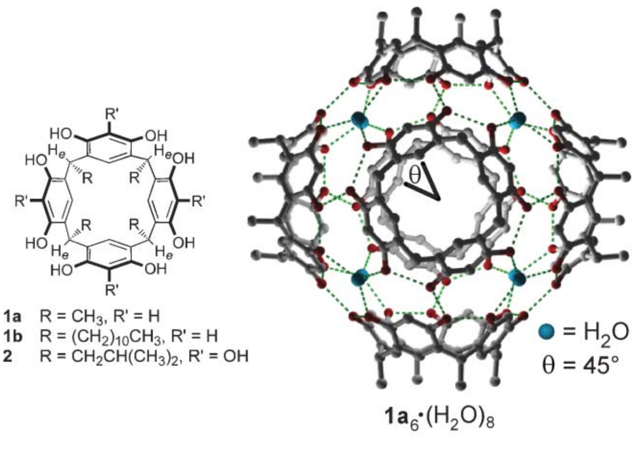
The well-known hexameric capsules sustained by self-assembly of resorcin[4]arenes 1 with water molecules (1_6·$(H_2O)_8$) are shown to assemble similarly with (±)-2-ethylhexanol (2EH) as an achiral 1_6·$(2EH)_6$·$(H_2O)_2$ species which further encapsulates 2EH.

The discovery in 1997 by Atwood and MacGillivray of large, chiral, hexameric assemblies of calix-resorcin[4]arenes, namely **1**$_6$·$(H_2O)_8$ (Scheme 1),[1] and the subsequent report of a related hexamer, **2**$_6$,[2] were of particular significance to the fields of self-assembly and molecular encapsulation.[3] Whereas the building blocks of some designer molecular capsules may require multi-step syntheses and yield cavities that encapsulate a few small molecules, the discovery of **1**$_6$·$(H_2O)_8$ and **2**$_6$ demonstrated that particularly large cavities (1.3–1.5 nm^3) can be achieved from simple, commercially available starting materials. Indeed, **1**$_6$·$(H_2O)_8$ and **2**$_6$ assemble nearly quantitatively in solution[4] and **2**$_6$ has even been synthesized in a single step by solvent-free means.[5] Perhaps more significant, however, is the notion that these species may guide design strategies toward increasingly sophisticated many-component supramolecular assemblies.[6] Extensive study of these assemblies and other related large molecular containers has therefore been of broad interest.[3,7] We report herein the discovery that hexameric assemblies related to **1**$_6$·$(H_2O)_8$ are possible wherein alcohols, namely (±)-2-ethylhexanol (**2EH**), replace water molecules on the surface of the assembly.



Scheme 1

The “hexamer” of **1**$_6$·$(H_2O)_8$ is actually a fourteen-component particle that may further encapsulate several small molecule guests.[1,4] The assembly is sustained by an impressive array of sixty complementary H-bonds and the eight water molecules of **1**$_6$·$(H_2O)_8$ play an integral role by participating in twenty-four of the thirty-six intermolecular H-bonds. That alcohols might effectively replace the water molecules of the hexameric capsule **1**$_6$·$(H_2O)_8$ is not immediately obvious. In a supramolecular sense, alcohols are by no means isomorphous with water. Clearly, water, with its two hydrogens, is capable of functioning as a double H-bond donor whereas alcohols are single H-bond donors. Moreover, it has already been demonstrated that certain alcohols (*e.g.*, isopropanol) promote the assembly of **1a** into “dimeric” (actually, ten-component), carcerand-like capsules, **1a**$_2$·$(ROH)_8$, wherein each alcohol participates in two intermolecular H-bonds and functions simultaneously as a single donor and a single acceptor.[8] In **1**$_6$·$(H_2O)_8$, however, each water molecule participates in three intermolecular H-bonds. The H-bonding pattern dictates that four of the eight water molecules must function as double donors and single acceptors and four must serve as single donors and double acceptors. Four water molecules therefore direct their “extra” O–H groups away from the surface of the capsule. So, it was conceivable to us that these four might be readily replaced by alcohols to give assemblies of the form **1**$_6$·$(ROH)_4$·$(H_2O)_4$, exhibiting an H-bonding array identical to **1**$_6$·$(H_2O)_8$, but decorated with selected, perhaps strategically functionalized, alcohols.

In exploration of this theme, **1a**[9] was crystallized from several alcoholic solvents. As expected, single crystal X-ray analysis reveals that some alcohols yield dimeric capsules of the form **1a**$_2$·$(ROH)_8$ (*e.g.* ROH = 2-ethylbutanol, (±)-2-butanol) and others yield non-capsular structures. X-ray analysis of crystals of **1a** grown by evaporation from **2EH**, however, reveals a large, self-assembled capsule consisting of six molecules of **1a**, six molecules of **2EH**, and two adventitious water molecules. The capsule is thus formulated as **1a**$_6$·(**2EH**)$_6$·$(H_2O)_2$, hereafter **3a** (Fig. 1).‡ Though the atomic positions of the guests encapsulated by **3a** are highly disordered in the structure, SQUEEZE[10] analysis estimates the cavity volume and number of electrons corresponding to encapsulated species to be 1290 Å^3 and 220 electrons, respectively. These data correspond well to three molecules of **2EH** (calc. 222 electrons). Moreover, ^{1}H NMR, thermal gravimetric, and elemental analysis support the contention that **3a** encapsulates three molecules of **2EH** in the solid state.† The crystals are thus formulated as **3a**⊂3(**2EH**).

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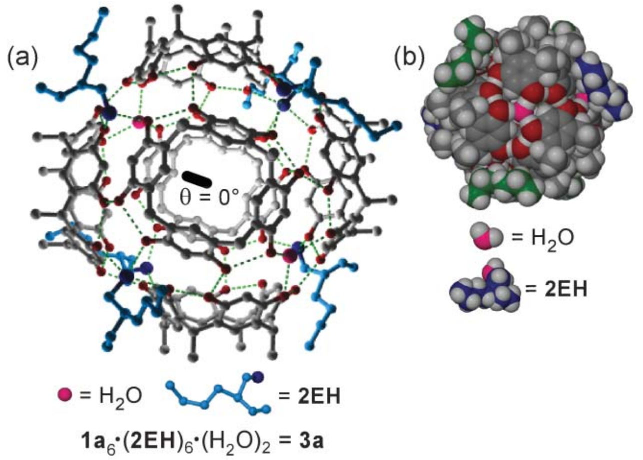


Fig. 1 The $\mathbf{1a}_6\cdot(\mathbf{2EH})_6\cdot(H_2O)_2$ assembly (**3a**) as observed in the X-ray single crystal structure of $\mathbf{3a}\subset3(\mathbf{2EH})$. Encapsulated **2EH** guests have been omitted for clarity. a) Ball and stick model illustrating the topology of the resorcinarenes. b) Spacefill model (smaller) as viewed down the S_6 improper rotation axis.

On cursory examination, **3a** bears a strong resemblance to Atwood's hexamer, except that six of the eight water molecules have been replaced by **2EH** molecules, the six sites being disordered between the two enantiomers of **2EH**. A more careful inspection, however, reveals several important differences between **3a** and $\mathbf{1a}_6\cdot(H_2O)_8$. The most significant difference is perhaps the fact that, neglecting hydrogen atoms, **3a** adopts perfect 3-bar (S_6) point group symmetry and is *achiral* (Fig. 1b), whereas $\mathbf{1a}_6\cdot(H_2O)_8$ exhibits 432 (O) symmetry and is chiral. The differing point group symmetries arise not because of packing effects or structural specifics of the alcohol, but rather because of significant differences in the three-dimensional arrangements of the resorcinarenes about the surface of the capsules. This difference is most noticeable upon viewing the two capsules from a direction normal to the resorcinarene-capped faces (Scheme 1, Fig. 1a). From this perspective, the foremost and furthest resorcinarenes in $\mathbf{1a}_6\cdot(H_2O)_8$ are rotated from one another by an angle of $\theta = 45°$, whereas in **3a** the two resorcinarenes are perfectly eclipsed ($\theta = 0°$).

Ultimately, the different symmetries of **3a** and $\mathbf{1a}_6\cdot(H_2O)_8$ arise in consequence to subtly different intermolecular H-bonding patterns. **3a** does not exhibit the 6 : 4 : 4 **1a** : ROH : H_2O stoichiometry that is rationalized above and therefore cannot be isostructural to $\mathbf{1a}_6\cdot(H_2O)_8$. Indeed, the observed 6 : 6 : 2 stoichiometry dictates that the surface of **3a** is deficient of two H-bond donors relative to $\mathbf{1a}_6\cdot(H_2O)_8$. Thus, **3a** is held together by a total of *fifty-eight* H-bonds (*vs.* sixty in $\mathbf{1a}_6\cdot(H_2O)_8$). Interestingly, the loss of two intermolecular H-bonds at the surface of **3a** is compensated for by formation of H-bonds between the two surface water molecules and two of the three encapsulated **2EH** guests, bringing the total number of H-bonds in the particle, including guests, to sixty. Though the encapsulated **2EH** guest molecules are significantly disordered in the crystal structure, their oxygen atoms are clearly located 2.62(2) Å from the surface water oxygens, indicating a significant H-bonding interaction.

Preliminary ^1H NMR spectroscopic evidence suggests that **3b**, the dodecyl footed equivalent of **3a**, and/or similar species assemble spontaneously in chloroform solution and that **2EH** is encapsulated within (Fig. 2). Fig. 2a shows the room temperature ^1H NMR spectrum (300 MHz) of a 27 mM solution of **1b**[9] dissolved in partially dried $CDCl_3$. The sample contains approximately a 6 : 10 ratio of **1b** to residual H_2O. The conditions and spectral features are nearly identical to the experiments of Cohen and co-workers wherein the predominant **1b**-containing species, according to diffusion coefficients, was demonstrated to be the $\mathbf{1b}_6\cdot(H_2O)_8$ assembly.[4] Of particular importance here is the residual water resonance, appearing at 4.6 ppm in the spectrum of Fig. 2a. At near stoichiometric ratios of **1b** : H_2O, almost all of the water molecules are engaged in H-bonding with **1b** as the $\mathbf{1b}_6\cdot(H_2O)_8$ species. Thus, the water signal resonates well downfield from 'free' water in chloroform, its chemical shift reflecting the molar ratio of bound to free waters in this fast-exchange system. Upon addition of 2.5 μL of rigorously dried **2EH** (0.7 equivalents relative to water),[11] the water signal shifts dramatically upfield, but its integrated area remains unchanged (Fig. 2b). Additionally, the hydroxyl resonance of **2EH** that appears is downfield shifted from the 'free' hydroxyl peak as it appears in simple chloroform solutions of this concentration.

Though diffusion NMR studies may yet provide a more conclusive picture of the behavior in this system, a plausible explanation for these data is as follows (see Scheme 2). Replacement of some number, x, of the eight water molecules on the surface of $\mathbf{1b}_6\cdot(H_2O)_8$ by **2EH** results in $\mathbf{1b}_6\cdot(\mathbf{2EH})_x\cdot(H_2O)_{8-x}$ species and x liberated water molecules. An increase in the molar ratio of free relative to bound waters results in a significant upfield shift of the water resonance. Moreover, as some percentage of the **2EH** molecules are engaged

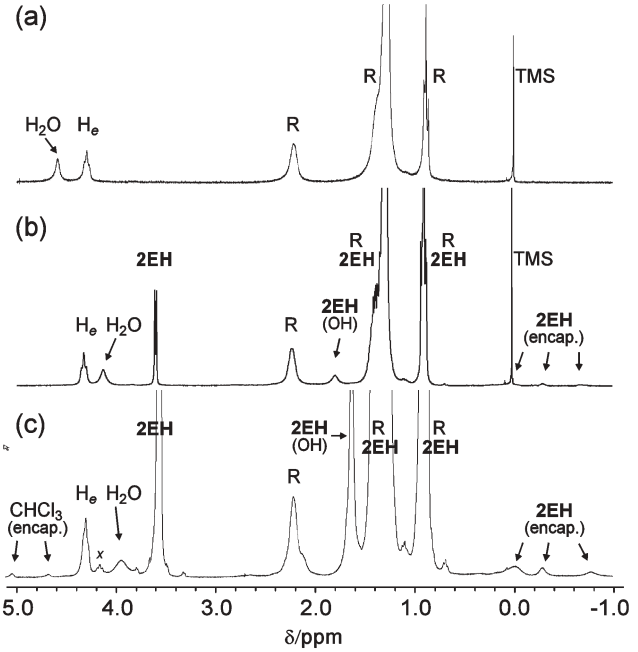
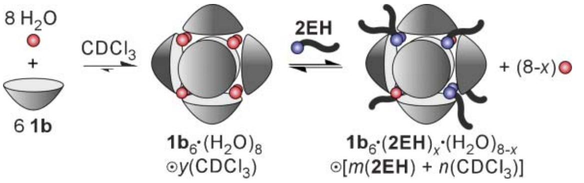


Fig. 2 a) Partial ^1H NMR spectrum of **1b** dissolved in $CDCl_3$ (27 mM, **1b** : H_2O ≈ 6 : 10, 300 MHz, 298 K). $\mathbf{1b}_6\cdot(H_2O)_8$ is known to be the predominant **1b**-containing species under these conditions; b) after addition of 2.5 μL (**1b** : H_2O : **2EH** ≈ 6 : 10 : 7) of dry **2EH**; c) a similar experiment conducted in $CHCl_3$ (22 mM, **1b** : H_2O ≈ 6 : 11), after addition of 22.5 μL (**1b** : H_2O : **2EH** ≈ 6 : 11 : 65) of dry **2EH**. The peak labeled x corresponds to the appearance of non-hexameric **1b** species.



Scheme 2

in **1b**$_6$·(**2EH**)$_x$·$(H_2O)_{8-x}$ complexes, the resonance of the **2EH** hydroxyl group appears downfield shifted relative to a free **2EH** signal. Addition of more **2EH** releases more water molecules from the assembly and the water signal shifts further upfield. So, too, does the **2EH** hydroxyl resonance shift upfield as the molar ratio of free to bound **2EH** molecules increases. With increasing **2EH**, however, the observed shift in the water resonance decreases to a point where it almost ceases to be affected by the addition of more **2EH**, maintaining a position near 3.9 ppm, depending upon the **1b** : H_2O ratio (Fig 2c). That is, the water resonance does not approach the chemical shift observed for free water in dilute **2EH** solutions of $CDCl_3$ (1.56 ppm). This observation suggests that **2EH** is unable to completely expel water from the surface of the **1b**$_6$·(**2EH**)$_x$·$(H_2O)_{8-x}$ assemblies and, regardless of the excess **2EH**, there remain sites on the surface of the particles that are preferentially or exclusively occupied by water molecules. The equilibrium between the water at these sites and the available free water is apparently unaffected by the further addition of **2EH**, and thus the chemical shift of the water resonance settles near 3.9 ppm.

With addition of **2EH**, new signals also appear in the upfield region of the spectrum, corresponding to encapsulated **2EH** molecules (Fig. 2c). Consistent with the work of others,[4] ^1H NMR experiments identical to those described above, but using the proteo-form of the solvent (C*H*Cl_3), reveal signals for the encapsulated $CHCl_3$ solvent molecules at chemical shifts between 4.8 and 5.1 ppm. As **2EH** is added to these samples, the integrated areas of the resonances corresponding to encapsulated $CHCl_3$ diminish as signals for encapsulated **2EH** appear (Fig. 2c). It is therefore apparent that the capsular **1b**$_6$·(**2EH**)$_x$·$(H_2O)_{8-x}$ species show a strong preference for **2EH** binding *vs.* $CHCl_3$. This preference is likely related to the entropic benefits associated with releasing to solution up to seven molecules of $CHCl_3$ in exchange for up to three molecules of **2EH**. Moreover, in accordance with the X-ray structure of **3a**⊂3(**2EH**), H-bonding interactions between the encapsulated **2EH**s and water molecules at the surface of **1b**$_6$·(**2EH**)$_x$·$(H_2O)_{8-x}$ hexamers may constitute a significant enthalpic driving force for **2EH** encapsulation.

It is interesting to observe that crystallization of **1a** from other alcoholic solvents tends to give rise to **1a**$_2$·$(ROH)_8$ dimers, or other structures, as opposed to the hexameric capsular assemblies. This may in part be due to the size and shape of **2EH** relative to the other alcohols. From 2-ethylbutanol (**2EB**), for example, **1a** crystallizes as the carcerand-like **1a**$_2$·(**2EB**)$_8$⊂**2EB** dimer, with one molecule of **2EB** encapsulated within. The shape of **2EH**, however, is seemingly non-complementary to the dimeric capsule and thus dimer formation is likely frustrated in pure **2EH** solution. Consequently, formation of the hexameric capsule may be favored. This hypothesis, however, will have to bear the scrutiny of further experiment.

Notes and references

‡ Single crystal structure of **3a**⊂3(**2EH**): $C_{264}H_{358}O_{59}$, 0.42 × 0.40 × 0.36 mm, trigonal, *R*-3, $a = 34.976(3)$ Å, $c = 18.246(3)$ Å, $V = 19330(4)$ Å^3, $Z = 3$, $\rho_{\text{calc.}} = 1.153$ g cm^{-3}, $\lambda = 0.71073$ Å, 188(2) K, 40584 reflns. total, 5989 unique reflns., 4130 reflns. with $I > 2\theta(I)$ ($R_{\text{int}} = 0.048$); $R_1 = 0.054$ ($I > 2\sigma(I)$) and $wR2 = 0.1557$ (all data), GooF = 1.07. This refinement has been SQUEEZED[10] and does not contain atomic positions for encapsulated, highly disordered **2EH** guests. CCDC 601015. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604148e Found: C, 69.4; H, 8.2; N, 0.5. Calc. for **3a**⊂3(**2EH**): C, 70.8; H, 8.1; N, 0%. TGA: Observed mass loss, 26.8%; Calc. for **3a**⊂3(**2EH**), 27.0%.

1 L. R. MacGillivray and J. L. Atwood, *Nature*, 1997, **389**, 469–472.
2 T. Gerkensmeier, W. Iwanek, C. Agena, R. Fröhlich, S. Kotila, C. Näther and J. Mattay, *Eur. J. Org. Chem.*, 1999, 2257–2262.
3 D. J. Cram, J. M. Cram, *Container Molecules and Their Guests*, ed. J. F. Stoddart, Royal Society of Chemistry, 1994; M. M. Conn and J. Rebek, Jr., *Chem. Rev.*, 1997, **97**, 1647; L. R. MacGillivray and J. L. Atwood, *Angew. Chem., Int. Ed.*, 1999, **38**, 1018–1033; J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2005, **44**, 2068–2078.
4 C. F. Wilson, M. P. Eastman and C. J. Hartzell, *J. Phys. Chem. B*, 1997, **101**, 9309–9313; J. L. Atwood, L. J. Barbour and A. Jerga, *Chem. Commun.*, 2001, 2376–2377; A. Shivanyuk and J. Rebek, *Chem. Commun.*, 2001, 2424–2425; L. Avram and Y. Cohen, *J. Am. Chem. Soc.*, 2002, **124**, 15148–15149; L. Avram and Y. Cohen, *Org. Lett.*, 2002, **4**, 4365–4368; L. Avram and Y. Cohen, *Org. Lett.*, 2003, **5**, 4365–4368; M. Yamanaka, A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 2939–2943; L. Avram and Y. Cohen, *J. Am. Chem. Soc.*, 2004, **126**, 11556–11563; L. C. Palmer and J. Rebek, Jr., *Org. Lett.*, 2005, **7**, 787–789; L. Avram and Y. Cohen, *Org. Lett.*, 2006, **8**, 219–222.
5 J. Antesberger, G. W. V. Cave, M. C. Ferrarelli, M. W. Heaven, C. L. Raston and J. L. Atwood, *Chem. Commun.*, 2005, 892–894.
6 R. M. Mckinlay, G. W. V. Cave and J. L. Atwood, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 5944–5948.
7 D. Fiedler, D. H. Leung, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.*, 2005, **38**, 349–358; M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res.*, 2005, **38**, 369–378; X. Liu, Y. Liu, G. Li and R. Warmuth, *Angew. Chem., Int. Ed.*, 2006, **45**, 901–904; D. A. Makeiff and J. C. Sherman, *J. Am. Chem. Soc.*, 2005, **127**, 12363–12367.
8 K. N. Rose, L. J. Barbour, G. W. Orr and J. L. Atwood, *Chem. Commun.*, 1998, 407–408.
9 L. M. Tunstad, J. A. Tucker, E. Dalcanale, J. Weiser, J. A. Bryant, J. C. Sherman, R. C. Helgeson, C. B. Knobler and D. J. Cram, *J. Org. Chem.*, 1989, **54**, 1305.
10 P. van der Sluis and A. L. Spek, *Acta Crystallogr., Sect. A*, 1990, **46**, 194–201.
11 The **2EH** was demonstrated by ^1H NMR to be completely dry. Comparison of the integrated intensity of the residual water signal in a carefully prepared (drybox) sample of $CDCl_3$ before and after addition of **2EH** showed absolutely no change in the amount of water in the samples.