Assembly of Resorcinarene Capsules in Wet Solvents

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When crystallized from nitrobenzene, resorcinarenes such as shown (Figure 1) assemble as spectacular hexamers **1**.[1,2] The overall shape is that of an inflated cube resembling a volleyball, where the six resorcinarenes are the "sides" and a water molecule is at each of its "corners". Little is known about its solvent capacity. Disorder of small molecules in the crystal structure leaves the number of solvents inside uncertain, although exceptions exist.[3] In solution, the deuterated solvents that are convenient media for NMR studies make it difficult to determine how many − and even which − solvents are detained inside the resting state of any capsule. This research was undertaken to determine the nature of the assembly and its solvent occupancy in solution. We report here two solutions − literal and figurative − and, inevitably, additional problems concerning the inner solvation of capsules.

The hexameric structure assembles in CHCl₃ solution when appropriate guests, for example, tetraalkylammonium ions are present.[4] The resorcinarene is insoluble in dry CHCl₃, but different species can be seen by NMR when water is present. In wet CHCl₃, the NMR spectrum shows encapsulated solvent molecules as two large resonances at 5.1 and 4.9 ppm (Figure 2a) and a smaller third species at 4.87 ppm. The assignments were confirmed by 1D GOESY experiments that show exchange of these signals with free solvent. In CHCl₃ saturated with water, the signals broaden, and a third type of encapsulated CHCl₃ appears (Figure 2b). The relative intensities of the guest peaks vary with the amount of water present, but integration shows that approximately one CHCl₃ is encapsulated for each resorcinarene subunit. The slow exchange between bulk solvent and the new solvent signals indicates high energetic barriers that are the earmarks of capsular structures, but many possibilities exists − two guests in a dimeric capsule, four in a tetrameric capsule, and so on.

To determine the nature of the capsule(s) that surround the solvent, we made use of NOE methods.[5] Irradiation of the triplet for the methine protons resulted in negative NOEs of the resonances for the adjacent methylene protons and the aromatic protons at the 5-positions of the resorcinol rings. The kinetics of the NOE[6] are characterized by the cross relaxation constant (σ_{IS}).[7] In water-saturated CDCl₃, strong and negative NOEs ($\sigma_{IS} = -0.2$ s^{-1}) developed for the system. *The same relaxation constant was observed for a hexameric complex of the resorcinarene with Bu₄SbBr.*[8] Dilution of the CHCl₃ resorcinarene by 4-, 10-, and 20-fold failed to alter the spectrum. In short, a slowly tumbling species, comparable to a hexameric capsule, is present in wet chloroform. Addition of methanol (10%) denatures the capsule and results in the positive NOEs typical for a rapidly tumbling, monomeric resorcinarene.

The presence of more than one type of encapsulated solvent in **1** is unexpected, because limited mobility of the guests in the cubelike cavity is hard to imagine. Instead, we propose that the three types of guest represent three slightly different capsules. Specifically, hexameric capsules could have the same number of
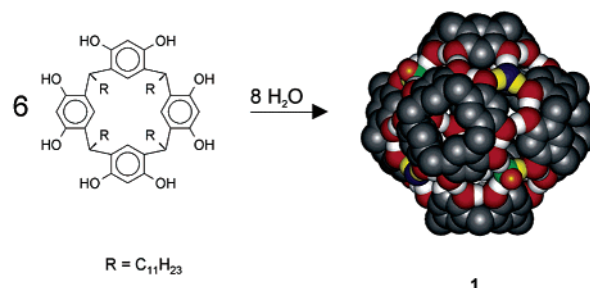

Figure 1. Line drawing of the resorcinarene monomer and space-filling model of the hexamer **1** from the X-ray structure. Water molecules may have hydrogens in the network (blue O, yellow H), directed outward (green O, orange H) or inward (not shown). The C−H bonds and the peripheral alkyl groups are removed for viewing clarity.
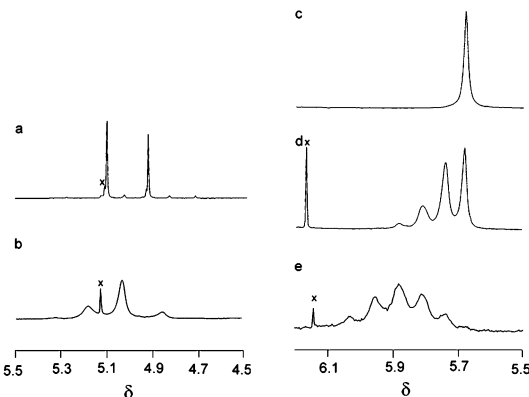
Figure 2. ¹H NMR spectra of the solvents encapsulated in **1** at 20 mM (600 MHz, 323 K). Impurities in the solvents are indicated with ×. (a) Signals of encapsulated CHCl₃ in the presence of water at [water]/[resorcinarene] = 4. (b) Same as (a) at [water]/[resorcinarene] = 6 (CHCl₃ saturated with water). (c) Signal of encapsulated benzene in water saturated benzene. (d) As in (c) with added CHCl₃ at [benzene]/[CDCl₃] = 5:1. (e) As in (c) with [benzene]/[CHCl₃] = 1:1.

CHCl₃ guests but involve different arrangements of the water molecules holding them together. The disposition of the four water molecules that present hydrogens into or out of the cavity provides possibilities for isomerism. In water-saturated CHCl₃, there is a single broadened resonance for water at 2.2 ppm that integrates for 12 hydrogens per resorcinarene unit. Eight water molecules are held in the hydrogen bonding network, but additional water molecules could be coencapsulated with the primary CHCl₃ guests. Such coencapsulation of solvents with neutral guests[8] or with anions[9] and cations[4] is increasingly common.

The possibilities for assembly are more restricted in benzene solution, where evidence for a hexamer exists through vapor pressure osmometry[10] and NMR experiments.[11] The spectrum of the resorcinarene in wet, deuterated benzene at ambient temperature is broad and featureless as described by Atwood.[1] At 323 K the signals sharpen: two singlets are present for the C−H resonances
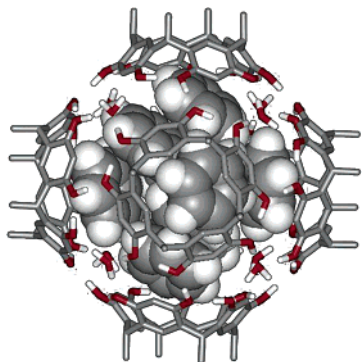
Figure 3. Energy minimized structure of the benzene encapsulation complex, viewed along the axis containing the C$_4$-symmetric resorcinarene. The eight benzene guests are represented in space filling models. The C—H bonds and the peripheral alkyl groups of the host are removed for viewing clarity.

of the resorcinarene aromatics, and only one triplet is seen for the methine protons. A single capsular species with guests emerges in the spectrum (Figure 2c); that is, all capsular species exchange rapidly, but exchange of benzene in and out of the capsule is, again, slow on the NMR time scale. The encapsulated solvent appears at 5.7 ppm, and integration shows 1.3 benzenes per resorcinarene; that is, 8 benzenes are detained in the hexamer. Molecular modeling indicates that this number of guests can be accommodated readily inside (Figure 3).

The use of solvent mixtures has been successful elsewhere,[12] and we applied the technique to the case at hand. When CDCl$_3$ is titrated into the wet benzene solution, new signals for encapsulated benzene appear. A distribution of capsules is generated (Figure 2d) as the benzene guests are successively replaced by CHCl$_3$. The spread of signals at equimolar solvents shows at least 6 species (Figure 2e). Seven are expected for assemblies with 1 to 8 benzenes inside, the remaining space being taken up by the (NMR-invisible) CDCl$_3$ molecules.

Eight benzene molecules occupy ~600 Å^3 or ~43% of the capsule's space. This value is considerably lower than the optimal 55% found for neutral encapsulation complexes in solution.[13] The coencapsulated water molecules — of which there is an unknown number — could make up some of this deficit.

Resorcinarene such as **1** provided the scaffold for the first covalently bound molecules within molecules, the cavitands and carcerands.[14,15] They also provided the framework for many dimeric, hydrogen bonded capsules.[16,17] The resorcinarene itself is reported to possess recognition capabilities: stoichiometric, 1:1 complexes with small and even large[18] guests in organic solvents have been described. In the solid state, dimeric capsules of resorcinarene with alkylammonium guests[19,20] were obtained. The complex behavior of resorcinarene in solution shows that an assembly may not be readily predicted by examination of its individual components, but rather is an emergent property of the system, strongly dependent on the initial states of temperature, concentration, humidity, and

suitable guests. The uncanny ability of these capsules to sequester trace impurities in solvents (including water) further exacerbates the problem. Whether held together by metal/ligand interactions[21] or hydrogen bonds,[22] the capsules provide an unprecedented view of isolated molecular behavior in the liquid phase and at ambient temperatures.[23]

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