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Hydrogen Bonds Seal Single-Molecule Capsules

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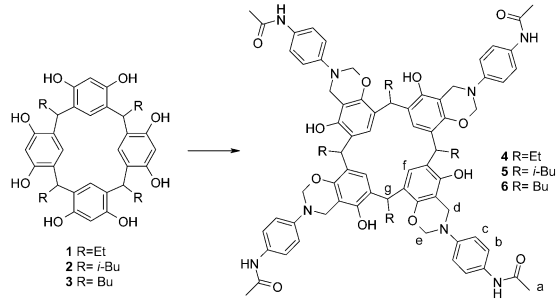
Nature utilizes principles of encapsulation for purposes such as the protection of fragile structures and the compartmentalization of functions.[1] In the laboratory, the formation of molecular capsules has followed two main themes: covalent synthesis and self-assembly. On one hand, Cram,[2] Collet,[3] and Sherman[4] have employed elegant covalent synthesis to prepare capsules capable of encapsulating up to three small molecular guests.[5] On the other hand, Rebek and others have used self-assembly to produce a variety of structures held together by hydrogen bonds.[6] Dimers,[7] tetramers,[8] hexamers,[9] and larger assemblies[10] have been constructed for the purpose of entrapping guests. Recently, the focus has been on the development of large assemblies with large cavities.[8−11] However, it is understood that small cavities can and do perform important functions.[12] Indeed, "unimolecular capsules" have been reported,[13] and three examples of Venus' Flytrap molecules have appeared.[14] We report herein the first example of a single-molecule molecular capsule which completely encloses space by means of hydrogen bonds.

Compounds **4**−**6** were synthesized via the Mannich reaction from the corresponding resorcin[4]arenes **1**−**3** (Scheme 1). The presence of four hydrogen bonds between phenolic hydroxy groups in the resorcin[4]arenes, as well as in the Mannich products, ensures the regioselectivity of the reaction and helps to maintain the cone conformation.[15] Tetrakis(benzoxazines) **4**−**6** precipitate from the reaction mixture, as they are sparingly soluble in methanol. However, upon addition of tetramethylammonium chloride (TMACl), the suspensions in MeOH dissolve and then reprecipitate as 1:1 complexes **4**·TMACl, **5**·TMACl, and **6**·TMACl. The 1:1 complexes are soluble in $CDCl_3$, and the NMR signal of the complexed Me_4N^+ appears at very high field (−0.57 ppm), indicating strong shielding by the aromatic walls (Figure 1). The complexes are kinetically stable on the NMR time scale, since upon saturation of the solution with TMACl an additional signal emerged, corresponding to uncomplexed cation, at the expected value +3.5 ppm. Comparison of the NMR spectra (in $CDCl_3$) of free **6** and **6**·TMACl reveals another important feature of complex formation. The chemical shift of the amide proton (NH) for the free **6** is rather low and concentration-dependent, which indicates formation of intermolecular hydrogen bonds. In contrast, for complex **6**·TMACl the signal is shifted downfield (by +1.6 ppm). This is consistent with simultaneous binding of the Cl^- in the upper, amide-substituted rim. This possibility was tested by titration of **6** with tetrabutylammonium chloride (TBACl), assuming that the Bu_4N^+ cation is too large to bind to the cavity. During the titration, the amide NH signal is shifted downfield, and at the saturation point, the NH signal slightly exceeds the value observed for **6**·TMACl (9.6 ppm for **6**·TMACl vs 9.8 ppm at the saturation point), demonstrating that the anion binds to the NHs regardless of the cationic guest. The calculated binding constant is log $K = 3.8 \pm 0.2$ for **6**·TMACl (see Supporting Information). Considering the relatively high association constant and the agreement between chemical shifts, it is clear that in chloroform both ions are complexed: Me_4N^+ in the interior of the cavity and Cl^- at the upper rim. Further substantiation for this behavior is found in the anion dependence of the spectra of the different complexes. For example, the NMR spectrum of **6**·$TMAPF_6$ is complicated (probably indicating a conformational equilibrium) with the NH signal at 8.0 ppm. After addition of TBACl, the spectrum sharpens and changes to one which is superimposable with that of **6**·TMACl. Finally, this solution result was confirmed by the X-ray crystal structure for **4**·TMACl, Figure 2.[16]

Most of the previously reported complexes of deep cavity calix[4]arene-type compounds with guests are stable only in chloroform solution, and they are destroyed rapidly upon addition of methanol. This is often attributed to solvation effects. For example, Rebek and co-workers in work on extended-cavity resorcin[4]arenes have noted that the complexes are kinetically stable in dry or water-saturated $CDCl_3$, however, the addition of MeOH results in complete destruction of the complex.[17] Since our complexes are

Scheme 1. Synthesis[a] and Atom Labeling



[a] 4′-aminoacetanilide, HCHO (aq), AcOH, MeOH, 60−80% yield.

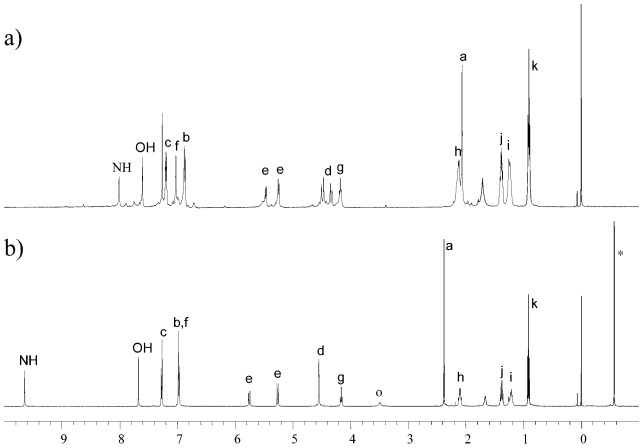


Figure 1. ^1H NMR (500 MHz, $CDCl_3$) spectra of (a) **6**, (b) **6**·TMACl (with excess TMACl guest): (*) complexed Me_4N^+, (○) uncomplexed Me_4N^+.

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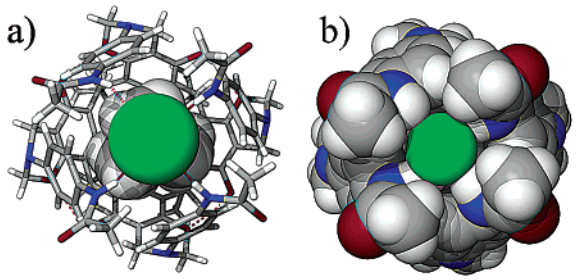

Figure 2. X-ray crystal structure of **4**·TMACl (I), crystal grown from $CHCl_3$/nitrobenzene: (a, b) top views (Cl^- green).

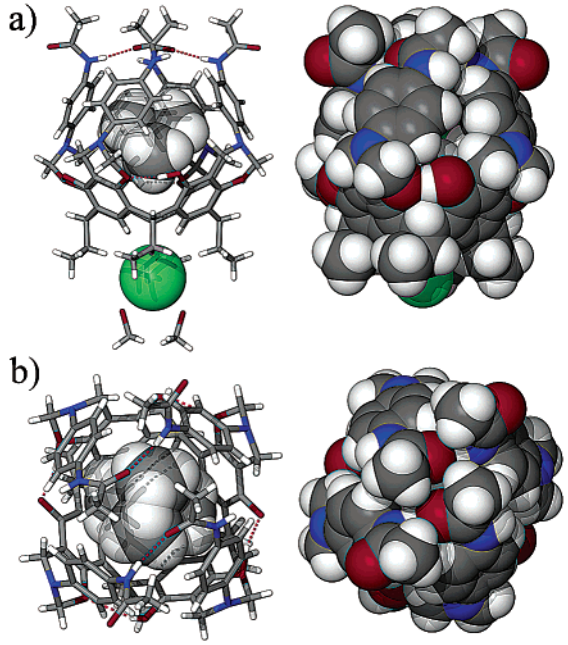

Figure 3. X-ray crystal structure of **4**·TMACl (II), crystal grown from $CHCl_3$/MeOH: (a) side view, (b) top view (Cl^- green).

formed in methanol, the stability of **6**·TMACl in $CDCl_3$/MeOH-d_4 (5%) was determined. The NMR spectrum in the presence of methanol is very similar to the one in $CDCl_3$ (Supporting Information). Yet, in the presence of excess of TMACl, signals from complexed and uncomplexed Me_4N^+ are present, which indicates that the complex is thermodynamically and kinetically (on the NMR time scale) stable, even in the presence of methanol. The amide NH signal (at 8.6 ppm) is not influenced by addition of TBACl. This probably means that methanol prevents binding of chloride anions, but not of the cations. Confirmation of this is found in the crystal structure of **4**·TMACl, Figure 3.[18] The Me_4N^+ cation is completely encapsulated within the cavity, which is closed by means of two hydrogen bonds at the upper rim. The internal dimensions of the single molecule molecular capsule are ca. 9 Å × 11 Å, and the enclosed space is 165 Å^3. Guest Me_4N^+ volume is about 110 Å^3,[19] and the occupancy factor is 67%, in keeping with observations of Rebek concerning his capsules.[20] The chloride anion resides in the hydrophobic lower rim and is solvated by two methanol molecules. In solution, the anion may well be completely solvated by methanol molecules.

Preliminary results of complexation experiments with smaller (Me_3HN^+ and $Me_2H_2N^+$) or larger (Et_4N^+) cations show that these cations form considerably weaker, kinetically unstable complexes in $CDCl_3$/MeOH (5%).

From the data gathered thus far, we propose that the Me_4N^+ cation promotes formation of the closed-shell capsule. The role of methanol in the capsule formation may be removal of the anion from the upper rim, allowing the capsule to be sealed by the two intramolecular hydrogen bonds. Given the fact that the entropic cost of intramolecular hydrogen bonds is low, sealing of the molecular surface is thermodynamically reasonable.

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Supporting Information Available: Synthetic procedures and analytical data for compounds **4**−**6**; ^{1}H NMR titration data, ^{1}H NMR data for **6**·TMACl in $CDCl_3$/MeOH (5%), and crystal structure details (PDF/CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Crystal structure **4**·TMACl (I) at 173 K: $C_{91}H_{101}Cl_{16}N_{10}O_{14}$, monoclinic, $P2_1/n$, pale yellow, a = 18.299(3) Å, b = 24.192(4) Å, c = 23.679(4) Å, β = 110.002(3)°, Z = 4, R1 = 0.069 (($I > 2\sigma(I)$)), GOF = 1.03.

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(18) Crystal structure **4**·TMACl (II) at 173 K: $C_{82}H_{100}C_{l2.39}N_9O_{14}$, monoclinic, $P2/n$, colorless, a = 13.171(2) Å, b = 20.108(3) Å, c = 15.371(2) Å, β = 100.137(3)°, Z = 2, R1 = 0.093 (($I > 2\sigma(I)$)), GOF = 1.04.

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