

Encapsulation of Ion–Molecule Complexes: Second-Sphere Supramolecular Chemistry

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Received May 26, 1999

The invention of crown ethers and their three-dimensional counterparts, the cryptates, initiated supramolecular chemistry¹ and spurred the development of more elaborate inclusion complexes. For example, covalently bound molecule-within-molecule complexes² can stabilize reactive intermediates³ and exhibit new types of stereochemistry.⁴ Newer, self-assembling complexes are held together by hydrogen bonds.⁵ These systems act as hosts that reversibly encapsulate guest molecules in solution, accelerate, or even catalyze chemical reactions,⁶ and can assemble into functional polymers.⁷ Reported here is the synthesis and characterization in solution and the gas phase of a self-assembling host large enough to encapsulate cryptates inside its cavity. The resulting systems are complexes-within-complexes and represent a second sphere of supramolecular chemistry.

We have previously introduced glycoluril derivative **1** (Figure 1) for use in modular syntheses of self-assembling systems.⁸ Its richness of hydrogen bonding sites, rigidity of structure, and gentle curvature contributed to predictable assemblies when appropriate spacer units were used as scaffolds. For the synthesis of a capsule large enough to accommodate a cryptate, the tetrahydroxy cavitand **2**⁹ was coupled with the acid module **1** using PyBOP as the dehydrating agent as shown in Figure 1.¹⁰ Molecular modeling¹¹ of **3** predicted that the self-complementary shape and recognition surfaces of the C_{4v} symmetric monomer would encourage dimerization to produce a D_{4d} symmetric capsule **3•3** with a seam of 16 hydrogen bonds (Figure 2). The resulting cavity features a volume¹² of $\sim 950 \text{ \AA}^3$ that is sufficiently large to accommodate guests **4–7**²⁺. The guest volumes are in the range of $390\text{--}420 \text{ \AA}^3$, which translate to packing coefficients of ~ 0.45 , a value shy of ideal for neutral guests in similar capsules.¹³

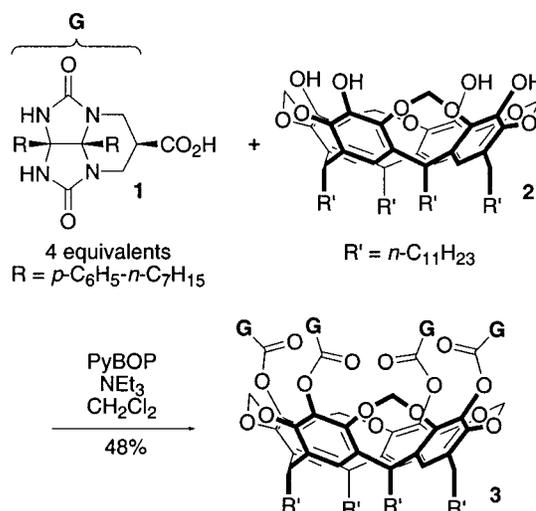


Figure 1. Modular synthesis of cavitand-based monomer **3** by 4-fold PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) coupling of glycoluril module **1** to centerpiece **2**.

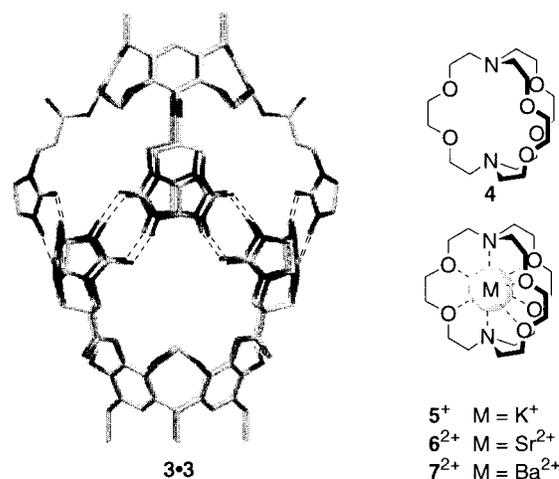


Figure 2. Optimized structure¹¹ of the dimer **3•3** and guests used for encapsulation studies.

Figure 3a shows the ¹H NMR spectrum of **3** in a 1:3 mixture of DMSO-*d*₆ and CDCl₃. Under these conditions, the hydrogen bond donors are bound to DMSO and the monomers do not assemble. The glycoluril N-*H* protons give a signal at $\delta = 8.1$ ppm. In less competitive solvents such as mesitylene-*d*₁₂ (Figure 3b), a significant downfield shift of $\Delta\delta \approx 1.7$ ppm for the N-*H* resonance indicates the formation of an assembly. A highly symmetric structure for the assembly (as shown in Figure 2) is supported by the simple set of signals in the rest of the spectrum.⁵

The solution-phase encapsulation behavior of dimer **3•3** was also evaluated by ¹H NMR using mesitylene-*d*₁₂ as the solvent. Titration of free cryptand **4** into a solution of **3** (Figure 3c) led to the appearance of a new set of peaks for **3•3** and the disappearance of the original dimer. Three signals for encapsulated **4** (filled circles in Figure 3c) were identified at positions downfield of the signals for free **4** (open circles) by $\Delta\delta \approx 0.6$ ppm.¹⁴ Integration of host and guest resonances indicated a highly symmetric 1:1 complex of host **3•3** and guest **4**.

(13) A packing coefficient of $0.55 \pm 0.09\%$ appears to be ideal for guests with shapes congruent to that of the cavity. See: Mecozzi, S.; Rebek, Jr. *J. Am. Chem. Soc.* **1998**, *120*, 1016–1022.

(14) This unusual downfield shift has been observed earlier with smaller, but structurally similar, capsules and seems to be characteristic for guests inside this type of host. See ref 8.

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(12) Volumes were calculated with the GRASP program: Nicholls, A.; Sharp, K. A.; Honig, B. *Proteins: Struct., Funct., Genet.* **1991**, *11*, 281–296.

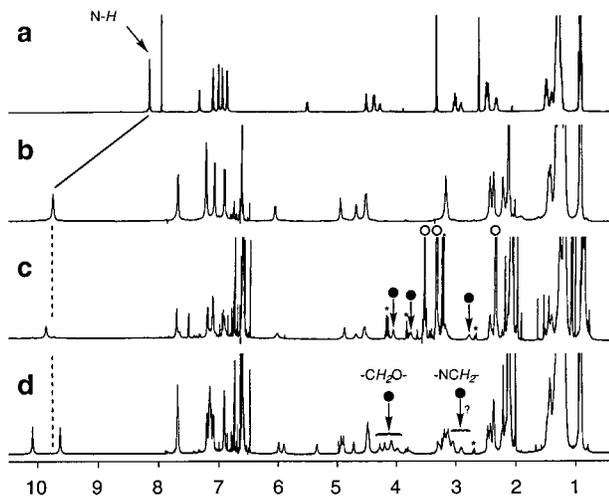


Figure 3. ^1H NMR spectra (600 MHz) of (a) **3** in $\text{DMSO-}d_6/\text{CDCl}_3$ (1:3); **3** in mesitylene- d_{12} (b) alone, (c) with excess **4**, and (d) with 5^+SCN^- . Solvent impurities are denoted by asterisks and were shown not to participate in encapsulation processes. See text for other label descriptions.

The capsule also encapsulated the K^+ -filled cryptate 5^+ . While its thiocyanate salt 5^+SCN^- is not soluble in mesitylene- d_{12} , addition of **3** to a suspension of 5^+SCN^- rendered the salt soluble and gave the ^1H NMR spectrum shown in Figure 3d. Signals for the CH_2O protons of the encapsulated cryptate are visible at $\delta = 3.95\text{--}4.20$ ppm, downfield of the signals given by the encapsulated free cryptand by $\Delta\delta \approx 0.3$ ppm due to deshielding of the cryptate by the K^+ ion inside.¹⁵ Again, signal integration gave the expected 1:1 stoichiometry of host **3** and guest 5^+ . However, the signals for host and guest were now split into two sets and no signals for the solvent-filled capsule were present. We interpret that the splitting results from desymmetrization of the complex due to restricted guest motion within the capsule; that is, the two halves of the capsule are in different magnetic environments.

The cryptate cation alone is not expected to cause such desymmetrization, but the combination of the cryptate and anion can do so:¹⁶ one occupies the upper half and the other the lower, with slow exchange of their positions on the NMR time scale. As with the cryptand, the cryptate cation alone would give a rather small packing coefficient, but this value increases to almost 0.50 upon co-inclusion of the anion.¹³ Complexation of the full ion pair 5^+SCN^- was supported by using isotopically labeled salt $5^+\text{S}^{13}\text{CN}$. A ^{13}C NMR spectrum could not be recorded for this salt due to its insolubility. In the presence of the capsule **3**, however, an intense signal for the S^{13}CN anion arose at 132.5 ppm, suggesting that the whole salt is solubilized by encapsulation. In contrast, the ion pair of the much larger salt $5^+\text{B}(p\text{-ClPh})_4^-$ gave no sign of encapsulation despite its greater solubility in mesitylene.¹⁷

(15) The NCH_2 protons are likely to be buried under the capsule signals at $\delta \approx 3$ ppm as shown in Figure 3. In this case, they experience a $\Delta\delta$ similar to that of the CH_2O signals.

(16) The simultaneous binding of anions and cations has been described a number of times and ion pairs less frequently. For a recent review, see: Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443–448.

In gas-phase studies, we used electrospray ionization mass spectrometry (ESI-MS) for the detection and characterization of the capsules.¹⁸ Here, cryptates not only are the guests but also provide the ion labels necessary for ESI-MS characterization of the capsule (6890 amu) dissolved in aprotic solvents. The limited mass range of the instrument ($m/z < 4000$ amu) necessitated the use of cryptate salts with doubly charged cations [$6^{2+}(\text{ClO}_4^-)_2$ and $7^{2+}(\text{Cl}^-)_2$].¹⁹ The base peak of the ESI mass spectrum of an acetone solution of **3** and $6^{2+}(\text{ClO}_4^-)_2$ corresponds to the cryptate dication encapsulated in the capsule dimer ($[6^{2+}@3\bullet 3]$, m/z 3677).²⁰ The only other signal is significantly less intense and corresponds to the monomer–guest complex $[6^{2+}\bullet 3]$ (m/z 1955). A very similar spectrum with signals for $[7^{2+}\bullet 3]$ (m/z 1980) and $[7^{2+}@3\bullet 3]$ (m/z 3702) was obtained with $7^{2+}(\text{Cl}^-)_2$ as the guest salt. Interestingly, the absolute intensity of the $[6^{2+}@3\bullet 3]$ signal increased substantially upon performing collisional activation of the ions at acceleration voltages of -10 to -20 V. We believe that this finding results from ion pair encapsulation. In the electrospray process, singly charged complexes $[(6^{2+}\text{ClO}_4^-)@3\bullet 3]$ could be formed and would possess a m/z far beyond the mass range of the spectrometer. Upon collisional activation, the rather small anion could leave the capsule through one of the holes in its walls. This escape produces $[6^{2+}@3\bullet 3]$ and magnifies the intensity of the small signal already present in the absence of collisions. Another explanation, incomplete desolvation, is less likely but cannot be ruled out.²¹

Double-inclusion of host–guest complexes has been a rare phenomenon limited to the solid-state complexation of coronates and cryptates by cyclodextrins.^{22,23} The complexes-within-complexes reported here in solution and gas phases represent novel “second-sphere” supramolecular systems reminiscent of simple Russian *Matroschka* dolls. The increasing availability of larger capsules will permit the construction and study of ever-more elaborate architectures that approach the size and complexity of biological systems.

Acknowledgment. We thank Prof. Gary Siuzdak and Prof. Dmitry Rudkevich for advice and instrumental support. We are grateful for financial support from the Skaggs Research Foundation and the National Institutes of Health. A.L. and C.A.S. thank the Deutsche Akademische Austauschdienst (DAAD) and the BMFT/Deutsche Akademie der Naturforscher Leopoldina for postdoctoral fellowships.

Supporting Information Available: ESI mass spectrum of an acetone solution of **3** with $6^{2+}(\text{ClO}_4^-)_2$ as the guest salt. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA991747W

(17) Computational modeling found a packing coefficient of 0.85 for the proposed complex. This value exceeds that found in many super-dense solids.

(18) For a description of our experimental methods and leading references on ESI-MS, see: Schalley, C. A.; Martin, T.; Obst, U.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 2133–2138.

(19) The doubly charged guest $6^{2+}(\text{ClO}_4^-)_2$ was also encapsulated by **3** in solution (mesitylene- d_{12}) as evidenced by NMR spectroscopy.

(20) For a discussion of the @ symbol in chemistry, see: Braun, T. *ACH – Models Chem.* **1996**, *133*, 427–428.

(21) Incomplete desolvation seems unlikely because no signals have been observed that would indicate complexes of the capsule containing one or more solvent molecules in addition to the guest.

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