Resorcinarene assemblies as synthetic receptors†

Liam C. Palmer,[a] Alexander Shivanyuk,[b] Masamichi Yamanaka[a] and Julius Rebek, Jr.*[a]

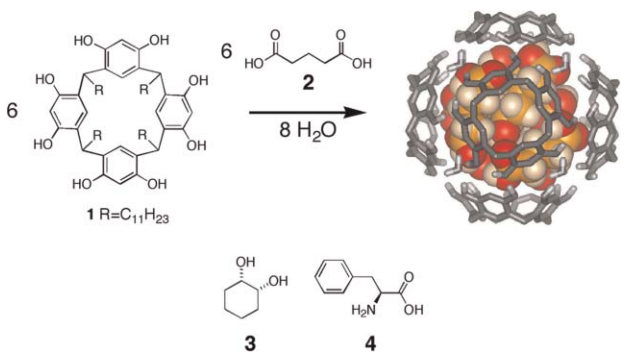
Received (in Columbia, MO, USA) 21st September 2004, Accepted 22nd November 2004
First published as an Advance Article on the web 10th January 2005
DOI: 10.1039/b414252g

The host–guest complexes of resorcinarenes are re-examined in solution through modern spectroscopic methods; the assemblies are characterized by ^{1}H NMR and the guest exchange rates are measured by EXSY NMR spectroscopy.

Some 15 years ago, Aoyama introduced resorcinarenes (*e.g.*, **1**, Scheme 1) as hosts in supramolecular chemistry.[1] The complexes were initially interpreted in terms of a 1 : 1 stoichiometry, in which a guest was held in the concavity of a resorcinarene host through intermolecular hydrogen bonding. The range of guests recognized was so broad—small diacids, alcohols, and even steroids—and the dynamics so unusual—slow guest exchange on the NMR timescale—that some principle in addition to hydrogen bonding must be involved. There is a recent body of evidence that the resorcinarene assembles as a hexamer under a variety of conditions: in the solid state,[2] in solution[3] with certain guests,[4] and even in wet organic solvents.[5] We report here newer examples of encapsulation by the hexameric assembly.

Polar, uncharged[1,4a] (*e.g.* **2** and **3**) and cationic compounds[4b,c] (ammonium salts) generally make excellent guests, while a variety of other molecules (including cyclic and acyclic alkanes) do not. For example, certain amino acids also form host–guest complexes with **1**. Prolonged sonication of L-phenylalanine (**4**) with **1** in $CDCl_3$ results in a sharp, but complex NMR spectrum. The hexamer is chiral in the crystalline state,[3] so diastereomeric complexes should exist with chiral guests. Adding CD_3OD—a solvent that disrupts hydrogen-bonded assemblies—simplified the spectrum to the unassembled components. Encapsulation is also observed for cyclohexylalanine and *p*-methylphenylalanine in ~ 1 : 6 guest/**1** ratio, but other amino acids with hydrophobic side chains (Leu, Val, Tyr, Trp) do not bind to **1**.

The assembly of resorcinarene hexamers with various large tetraalkylammonium (propyl to octyl) salts in solution has been



Scheme 1 Encapsulation of guests within the resorcinarene hexamer.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b414252g/

well characterized in previous reports.[6,7] As expected for discrete capsules, binding is not observed with salts that cannot fit: cations that are extremely large (*e.g.*, $(C_{10}H_{21})_4N^+$) or long, rigid cations ($Bn_2Me_2N^+$).

The solution-phase structure of the resorcinarene with small ammonium guests has received less attention. In wet $CDCl_3$, **1** associates with various small onium salts (Et_3NH^+, Et_4N^+, Et_4P^+), as indicated by a 1.3 to 1.6 ppm upfield shift of the guests' methyl protons. Encapsulated Et_4NCl and Et_3NHCl give distinct triplet resonances at −0.03 and −0.08 ppm, respectively (Fig. 1), which integrate to nearly three cations per hexamer, or one cation in a dimeric capsule.[8] In the presence of both salts, host **1** shows *new upfield resonances* at 0.04 and −0.13 ppm (Fig. 1c). This indicates a new complex involving two different guests, *i.e.*, a capsule larger than a dimer. Similar results are obtained when $(C_5H_{11})_4N^+$ (a large cation) and Et_4N^+ (a small cation) are mixed with **1**. Two new upfield resonances appear at low proportions of Et_4N^+, and at higher proportions, the equilibrium is driven toward a capsule containing only the smaller Et_4N^+ guest. A mixture of Et_3NHCl and $^iPr_2EtNHCl$ also gives a capsule with new upfield signals.

Counterions affect the kinetics and thermodynamics of assembly with large ammonium salts.[8] Different counterions also cause spectral changes with smaller ammonium cations: a mixture of solutions of **1** saturated with Et_4NBr and Et_4NBF_4 shows a new upfield peak, as would be expected if anions were co-encapsulated within the hexameric assembly.

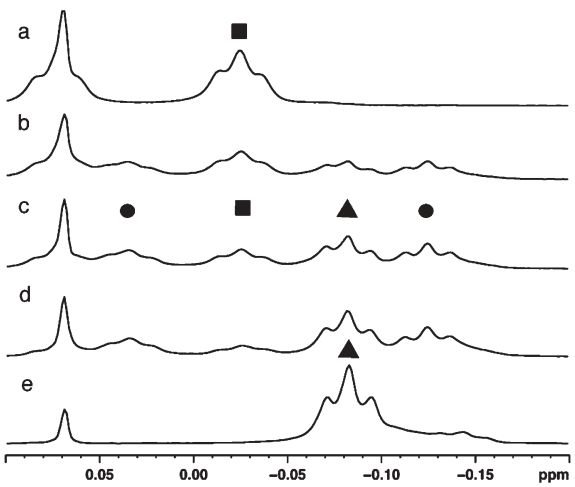


Fig. 1 ^{1}H NMR (600 MHz, 300 K) of host **1** (12 mM) + mixture of small ammonium chlorides. (a) Et_4NCl alone, $[Et_4NCl]/[Et_3NHCl]$ = (b) 2 : 1, (c) 1 : 1, (d) 1 : 2, and (e) Et_3NHCl alone. For each spectrum, the total salt concentration is 9 mM. The encapsulated methyls are marked for Et_4NCl (■), Et_3NHCl (▲), and new, co-encapsulated ammoniums (●). The peak at 0.1 ppm is due to silicon grease.

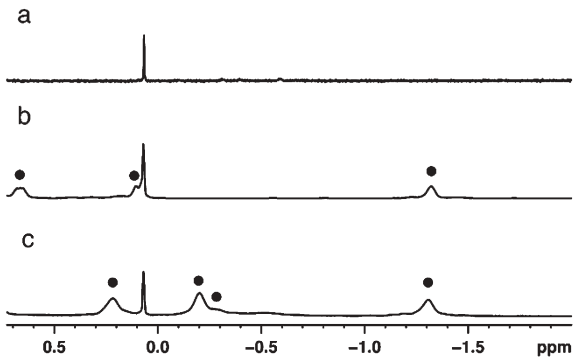


Fig. 2 ^{1}H NMR (600 MHz, 300 K) of (a) **1** (12 mM) in water-saturated $CDCl_3$, with (b) **2** (24 mM) and (c) **3** (24 mM). Encapsulated guests are indicated by closed circles (●). The peak at 0.1 ppm is due to silicon grease.

We reexamined some earlier complexes and found that glutaric acid (**2**) is solubilized by **1** in $CDCl_3$ and NMR integration shows a 1 : 1 stoichiometric ratio of 5 to 1, exactly as described by Aoyama (Fig. 2b).[9] The complexes show slow exchange between free and bound **2** on the NMR timescale and large upfield shifts of 2 to 3 ppm, as adduced for the guest methylenes in the aromatic concavity of the host (Scheme 1). While slow exchange is unusual for a complex held together by so few hydrogen bonds,[10] it has been observed in the complexation of **1** with many different guests.[3,4,9,11] The observed stoichiometry could as well be a hexameric capsule containing six guest molecules, and VPO studies showing molecular weights consistent with a hexamer were reported by Aoyama.[1] Molecular modeling shows that six guests in such a capsule would occupy about 43% of the available 1375 Å^3. The same packing coefficient was earlier observed in the encapsulation of eight benzenes within the hexamer.[12]

The methine triplet of hexameric resorcinarene in $CDCl_3$ (4.3 ppm) was irradiated in a series of 1D NOESY experiments (mixing time = 0.1–0.8 s).[12] Strong, negative intermolecular NOEs were observed to the resorcinarene aryl proton at 7.2 ppm. The same NOE intensities were observed for the host in the presence of **2**, indicating a similar molecular size for the assembly with and without guest.[13,14] This NOE disappears upon addition of CD_3OD (*ca.* 10% v/v) as the assembly reverts to monomeric species.

We investigated 1,2-*cis*-cyclohexanediol (**3**), which forms a ~1 : 1 complex with the resorcinarene (Fig. 2c), also as reported.[15] The in–out guest exchange rate constant for **3** was determined by an exchange (EXSY)[16] NMR experiment to be 0.36 s^{-1} at 30 °C ($\Delta G^{\ddagger}$ = 20 kcal mol^{-1}). This activation barrier is far too high to be caused by a maximum of four hydrogen bonds that can exist between **1** and **3**, but it is comparable to barriers for guest exchange found for tetraalkylammonium halides in the hexameric capsule host ($\Delta G^{\ddagger}$ = 17–21 kcal mol^{-1}).[6]

For a 1 : 1 system, adding excess guest should drive the equilibrium toward the host–guest complex. However, an excess of guest **2** actually causes *diminished guest complexation* (based on integration of upfield peaks) and the appearance of peaks for *monomeric host* in exchange with the assembled host. A variable-temperature ^{1}H NMR experiment of this exchange revealed an activation barrier of 16 kcal mol^{-1}. This value is consistent with previous EXSY studies of the hexamer–monomer exchange of **1** with tetraalkylammonium guests ($\Delta G^{\ddagger}$ = 15–17 kcal mol^{-1}).[6] Such melting by excess guest is less likely for a simple 1 : 1 complex.

In summary, the resorcinarene provides a versatile module for host–guest assembly. It is on the verge of assembly, and an appropriate guest or combination of guests in wet solvents is all that is required for the hexameric capsule to emerge. Indeed the resorcinarene may have been the first example of a hydrogen-bonded capsule.[1] The generalized feature of molecular recognition here involves the proper filling of space: optimal guests fill about half the available space in the cavity by themselves or together with additional solvent molecules.[6] Even three different guests have been observed in this capsule.[4] Recently popularized NMR methods point to a hexameric capsule and reconcile the results from several laboratories, but other capsular assemblies cannot be excluded.[17] It may be possible to resolve the nature of the host–guest complexes of resorcinarenes by Diffusion-Ordered NMR Spectrometry (DOSY),[5] and we are working toward this goal.

We are grateful to the Skaggs Institute for Research and the NIH (GM50174) for support, and to Prof. Y. Aoyama for his helpful comments. L.C.P. and A.S. are Skaggs Fellows; M.Y. is sponsored by the JSPS Fellowship for Young Scientists.

Liam C. Palmer,[a] Alexander Shivanyuk,[b] Masamichi Yamanaka[a] and Julius Rebek, Jr.*[a]
[a]*The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California, 92037, USA*
[b]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 02094 Kyiv 94, Murmanska str. 5, Ukraine*

Notes and references

1 Y. Aoyama, Y. Tanaka, Y. H. Toi and H. Ogoshi, *J. Am. Chem. Soc.*, 1988, **110**, 634–635; Y. Aoyama, Y. Nonaka, Y. Tanaka, H. Toi and H. Ogoshi, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1025–1029.
2 L. R. MacGillivray and J. L. Atwood, *Nature*, 1997, **389**, 469–472.
3 C. F. Wilson, M. P. Eastman and C. J. Hartzell, *J. Phys. Chem. B*, 1997, **101**, 9309–9313.
4 A. Shivanyuk and J. Rebek, Jr., *Chem. Commun.*, 2001, 2424–2425; A. Shivanyuk and J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA*, 2001, **98**, 7662–7665; I. E. Philip and A. E. Kaifer, *J. Am. Chem. Soc.*, 2002, **124**, 12678–12679.
5 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, *J. Am. Chem. Soc.*, 2003, **125**, 16180–16181.
6 M. Yamanaka, A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 2939–2943.
7 L. Avram and Y. Cohen, *Org. Lett.*, 2003, **5**, 1099–1102.
8 K. Murayama and K. Aoki, *Chem. Commun.*, 1998, 607–608; A. Shivanyuk, K. Rissanen and E. Kolehmainen, *Chem. Commun.*, 2000, 1107–1108.
9 Y. Tanaka, Y. Kato and Y. Aoyama, *J. Am. Chem. Soc.*, 1990, **112**, 2807–2808.
10 A. Wu, P. Mukhopadhyay, A. Chakraborty, J. C. Fettinger and L. Isaccs, *J. Am. Chem. Soc.*, 2004, **126**, 10035–10043.
11 Y. Aoyama, Y. Tanaka and S. Sugahara, *J. Am. Chem. Soc.*, 1989, **111**, 5397–5404.
12 A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2003, **125**, 3432–3433.
13 D. Neuhaus and W. Williamson, *The Nuclear Overhauser Effect In Structural and Conformational Analysis*; VCH Publishers Inc.: New York, 1989.
14 For the use of dynamic NOE experiments to determine assembly sizes, see: R. H. Vreekamp, J. P. M. van Duynhoven, M. Hubert, W. Verboom and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1215–1218.
15 Y. Kikuchi, Y. Kato, Y. Tanaka, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, 1991, **113**, 1349–1354.
16 C. L. Perrin and T. J. Dwyer, *Chem. Rev.*, 1990, **90**, 935–967.
17 Y. Kikuchi, Y. Tanaka, S. Sutarto, K. Kobayashi, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, 1992, **114**, 10302–10306.

