

Chiral Guests and Their Ghosts in Reversibly Assembled Hosts**

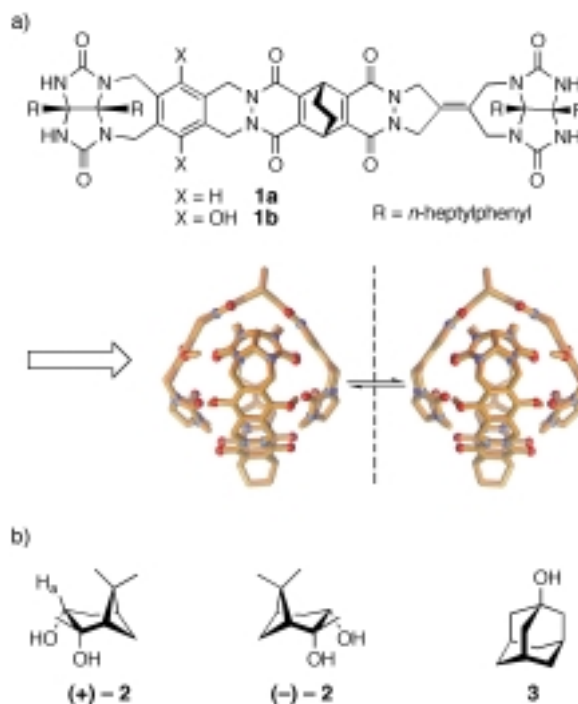
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Encapsulation complexes are assemblies in which small molecular guests are completely by large molecular hosts.^[1–4] The hosts are made up of subunits held together by intermolecular forces: hydrogen bonds, van der Waal's forces, and/or metal–ligand interactions. The assemblies are formed reversibly and are dynamic; they come together and dissipate on time scales ranging from milliseconds to days, long enough for their study by NMR methods. When multiple hosts can assemble from a given set of subunits, template effects can be expected and these have recently been reported.^[5–9]

Here we report an encapsulation complex with the additional characteristic that hydrogen bonds maintain an imprint—the ghost—of a long-departed guest. Specifically, an asymmetric microenvironment is imprinted in a reversibly formed capsular host by a chiral guest template. Removal of the template leaves a chiral, nonracemic (g)host capsule that can be characterized by NMR spectroscopy. Recognition of the guest rather than its mirror image persists for hours in organic solvents.

We recently reported a capsule known as the chiral “softball” **1a·1a** (Scheme 1a).^[5] It is formed when two self-complementary subunits **1a** dimerize in organic solvents through a seam of eight hydrogen bonds. The subunits feature a plane of symmetry and are achiral, but the dimer has only C_2 axes and exists as a pair of enantiomers. The cavity of the capsule is a distorted sphere and asymmetric guests generally prefer one enantiomer of the capsule to its mirror image. The enantiomeric capsules can interconvert (racemize) only by complete dissociation and recombination of their subunits (monomer exchange). Evidence reported elsewhere^[10–12] indicates that guests get in and out of these capsules through flaps that are opened by the breaking of hydrogen bonds as conformational changes occur.

A related structure **1b** was prepared for the imprinting studies.^[13] It dimerizes into capsules that are more robust and assemble in a number of solvents. The phenolic groups introduce four additional hydrogen bonds in the corresponding capsule **1b·1b** and slow its rate of racemization. Figure 1 shows how the NMR spectrum of **1b·1b** with added chiral



Scheme 1. a) Structure of the monomer **1b** and model of its dimeric assemblies.^[22] Some protons and *n*-heptylphenyl groups in the dimers are omitted for clarity. Atoms are colored as follows: carbon and hydrogen: orange, oxygen: red, nitrogen: blue. b) Guests used in the study.

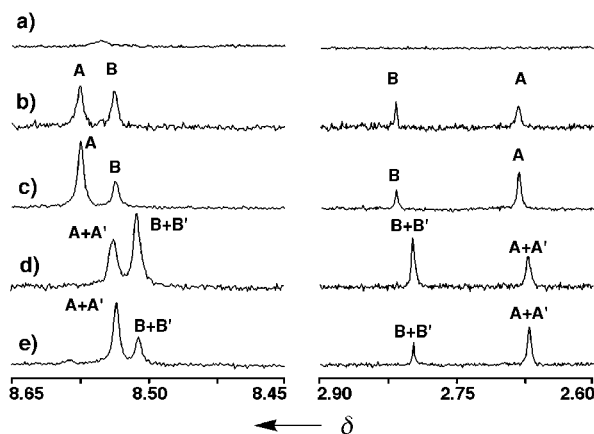


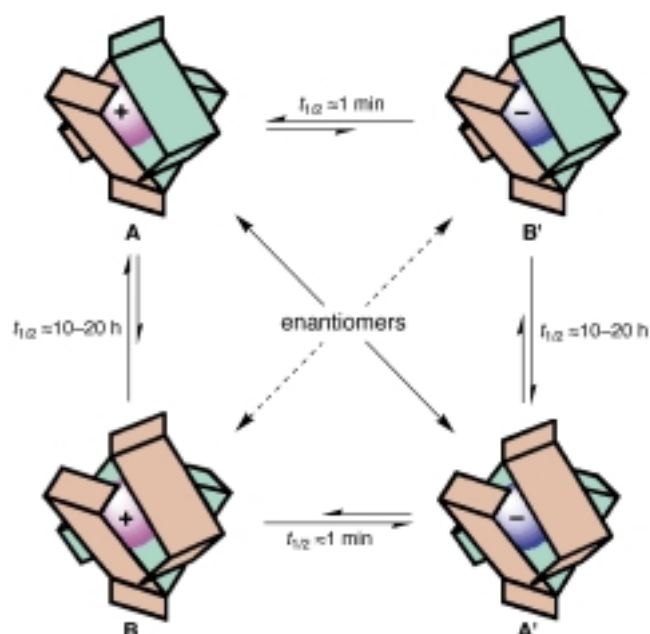
Figure 1. Portions of the ^1H NMR spectra showing the selected NH peaks of the dimer (8.65–8.45 ppm) and H_a peaks for the guest inside the capsules (2.90–2.60 ppm). The labels A and A' denote the thermodynamically more-stable complexes of (+)-**2** and (–)-**2**, respectively, while B and B' denote the respective less-stable complexes. a) **1b·1b** in $[\text{D}_{10}]p$ -xylene ($8.25 \times 10^{-4} \text{ M}$); b) 4 min and c) 120 h after addition of 3 equiv of (+)-**2**; d) 17 min and e) 191 h after addition of 30 equiv of (–)-**2**.

guest, (+)-pinanediol ((+)-**2**; Scheme 1b), varies with time. The broad NMR spectrum of a solution of 0.825 mM **1b·1b** in $[\text{D}_{10}]p$ -xylene is characteristic of unspecific aggregates, but the addition of three equivalents of (+)-**2** yields, within seconds, a sharp spectrum in which the two diastereomeric complexes are initially observed in nearly equal amounts (Figure 1b). Over the course of a few days the system reaches its stereochemical equilibrium—a 50% diastereomeric excess of the favored isomer (Figure 1c). The 19 h half-life for equilibration is also the lifetime of the assembly.

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Thirty equivalents of the enantiomer (–)-**2** were then added to the equilibrated mixture. Within minutes the ratio of the two diastereomers partially inverts, giving a temporary excess of the less stable diastereomer (Figure 1 d). This effect can only result from a guest exchange process that is much faster than dissociation of the assembly, so that the guest (–)-**2** is now present in excess in the capsule that formed preferentially around (+)-**2** (Scheme 2). The rate of guest exchange ($t_{1/2} \approx 1$ min) is in line with that observed in similar systems.^[12]



Scheme 2. Schematic representation of the exchange equilibria. Horizontal equilibria represent guest exchanges and vertical equilibria represent monomer exchanges. The pictures are illustrative only and do not imply the exact stereochemistry of the assemblies.

The diastereomers then re-equilibrate, with a half-life of 9.5 h, until the original 50 % *d.e.* is achieved (Figure 1 e). The rate is twice as fast as that measured for the initial equilibration, and may reflect the greater concentration of the polar, hydrogen-bonding compound **2** in the latter experiment.^[14]

The preference of the ghost for its template was established through competition experiments. When the (+)-**2**-templated capsule is exposed to a mixture of (+)-**2** and (–)-**2**, the ratio of the diastereomers ($[A + A']:[B + B']$, Scheme 2) after guest exchange reflects the relative affinity of (+)-**2** and (–)-**2** for the capsule. We observe that $[A + A']:[B + B'] = 1:1.3$ for a guest ratio (–)-**2**:(+)-**2** = 10:1. This is the expected value based on the 50 % *d.e.* observed in the original templation, and confirms that the ghost prefers the template to its enantiomer.^[15]

The memory persists through multiple guest exchanges and physical manipulations. A solution of **1b**·**1b** was templated with (+)-**2**, and the solvent was removed by evaporation. The excess guest was extracted with hexane, leaving only **1b**·(+)-**2**·**1b**. The complex was dissolved in benzene and an excess of 1-adamantanol (**3**, Scheme 1) was added to displace the remaining (+)-**2**. The NMR spectrum shows that the adamantanol rinses out the chiral guest. The solvent

was removed and extraction gives a solution free of (+)-**2**. To this solution was added an excess of (–)-**2**, which displaced adamantanol from the capsule interior. The corresponding NMR spectrum shows a 2:1 excess of the less-stable diastereomeric complex, which establishes that the chiral memory is maintained even in the absence of the chiral guests. The reaction mixture slowly re-equilibrates, and overnight shows a 2:1 excess of the more stable complex.

The memory effect reflects the relative rates of guest and monomer exchange. While monomer exchange involves the complete dissociation of the capsule (Figure 2 a), guest

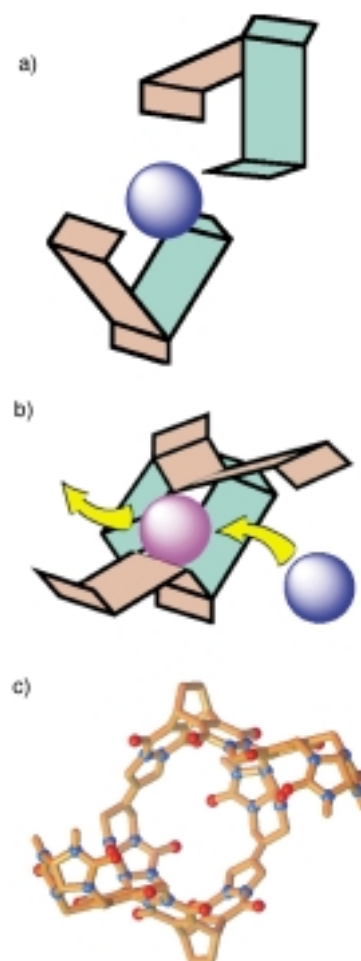


Figure 2. Putative intermediates a) for monomer exchange and b) guest exchange. c) Structural depiction of intermediate (b) showing the “doorways” for guest exchange.

exchange must proceed through doorways that form without disrupting the entire hydrogen-bonded seam of the capsule (Figure 2 b). The pyridazinyl ring of **1b** has a very low barrier to inversion, a process that creates openings in the dimer that are large enough to accommodate incoming and outgoing guests (Figure 2 c).^[11] On average, hundreds to many thousands of molecules enter and depart the capsule during its lifetime, and each guest in turn will experience the imprinted asymmetric microenvironment of the capsule.

Encapsulation influences the conformation, dynamics, and reactivity of the guest,^[1] but examples of nonracemic chiral

encapsulation complexes are rare.^[16–18] Imprinting^[19, 20] in hydrogen-bonded assemblies provides another route to such systems, and recent work promises that behaviors similar to those observed here will also be found in metal–ligand assemblies.^[8] The result augurs well for the application of these capsules in dynamic combinatorial libraries and other enantioselective processes, such as the catalysis of reactions with rates comparable to that of guest exchange.^[21]

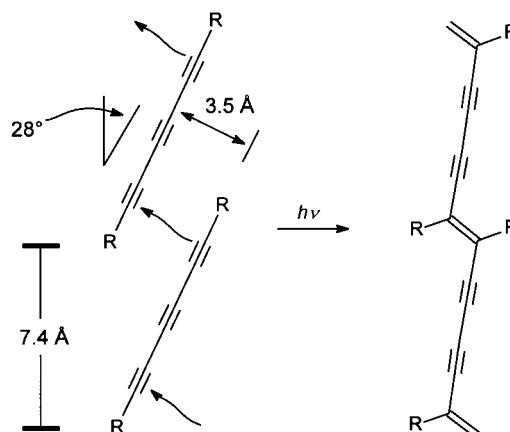
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- [1] M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, 97, 1647–1668.
- [2] T. Kusukawa, M. Fujita, *J. Am. Chem. Soc.* **1999**, 121, 1397–1398.
- [3] T. N. Parac, D. L. Caulder, K. N. Raymond, *J. Am. Chem. Soc.* **1998**, 120, 8003–8004.
- [4] R. G. Chapman, J. C. Sherman, *J. Am. Chem. Soc.* **1998**, 120, 9818–9826.
- [5] J. M. Rivera, T. Martín, J. Rebek, Jr., *Science* **1998**, 279, 1021–1023.
- [6] M. Scherer, D. L. Caulder, D. W. Johnson, K. N. Raymond, *Angew. Chem.* **1999**, 111, 1690–1694; *Angew. Chem. Int. Ed.* **1999**, 38, 1588–1592.
- [7] F. Ibukuro, T. Kusukawa, M. Fujita, *J. Am. Chem. Soc.* **1998**, 120, 8561–8562.
- [8] S. Hiraoka, M. Fujita, *J. Am. Chem. Soc.* **1999**, 121, 10239–10240.
- [9] F. Hof, C. Nuckolls, J. Rebek, Jr., unpublished results.
- [10] T. Szabo, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, 120, 6193–6194.
- [11] X. Wang, K. N. Houk, *Org. Lett.* **1999**, 1, 591–594.
- [12] J. Santamaría, T. Martín, G. Hilmersson, S. L. Craig, J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA* **1999**, 96, 8344–8347.
- [13] J. M. Rivera, T. Martín, J. Rebek, Jr., unpublished results.
- [14] Even low concentrations of hydrogen-bonding molecules can have dramatic effects on the rates of assembly processes. R. K. Castellano, S. L. Craig, C. Nuckolls, J. Rebek, Jr., *J. Am. Chem. Soc.*, submitted.
- [15] After templation, A:B = 3:1. By assuming that the capsule of A prefers (+)-2 and the capsule of B prefers (–)-2, each by the same 3:1 ratio, then, if (–)-2:(+)-2 = 10:1, $Aa(3) \times (3) \times (1) = 9$, $A'a(1) \times (3) \times (10) = 30$, $Ba(1) \times (1) \times (1) = 1$, and $B'a(3) \times (1) \times (10) = 30$. We expect, then, that $(A + A'):(B + B') = (31):(39) = 1:1.26$. If, on the other hand, there were no preference for the template, the ratio would be 1:2.4.
- [16] R. K. Castellano, B. H. Kim, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, 119, 12671–12672.
- [17] R. K. Castellano, C. Nuckolls, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, 121, 11156–11163.
- [18] C. Nuckolls, F. Hof, T. Martín, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, 121, 10281–10285.
- [19] For examples of imprinting in covalent materials, see a) K. J. Shea, *Trends Polym. Sci.* **1994**, 2, 166–173; b) G. Wulff, *Angew. Chem.* **1995**, 107, 1958–1979; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1812–1832; c) K. Mosbach, O. Ramstroem, *Biotechnology* **1996**, 14, 163–170; d) H. Shi, W.-B. Tsai, M. D. Garrison, S. Ferrari, B. D. Ratner, *Nature* **1999**, 398, 593–597; e) K. Polborn, K. Severin, *Chem. Commun.* **1999**, 24, 2481–2482; f) K. Dabulis, A. M. Klibanov, *Biotechnol. Bioeng.* **1992**, 39, 176–185.
- [20] For examples of memory effects in noncovalent materials, see a) Y. Furusho, T. Kimura, Y. Mizuno, T. Aida, *J. Am. Chem. Soc.* **1997**, 119, 5267–5268; b) E. Yashima, K. Maeda, Y. Okamoto, *Nature* **1999**, 399, 449–451.
- [21] J. Kang, J. Santamaría, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, 120, 7389–7390.
- [22] F. Mohamadi, N. G. Richard, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, 11, 440.

A Supramolecular Solution to a Long-Standing Problem: The 1,6-Polymerization of a Triacetylene**

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The 1,6-polymerization of a triacetylene is an unknown transformation.^[1, 2] Unsuccessful attempts to accomplish this polymerization were reported as early as 1972, soon after the remarkable discovery of the topochemically controlled 1,4-polymerization of diacetylenes.^[3] It was recognized that a successful 1,6-polymerization would require preorganization of the reactants. In 1994 Enkelmann gave a more up-to-date report of other unsuccessful attempts of the 1,6-polymerization of triacetylenes and provided a more complete analysis of the criteria necessary for a successful polymerization.^[4] The structural parameters needed for a topochemical triacetylene polymerization can be derived if one assumes that the monomeric units must be preorganized with a defined simple translational distance of 7.4 Å, matching the geometric parameters of the expected polymer (Scheme 1). If the



Scheme 1. A triacetylene should polymerize if it is preorganized with a defined geometry that matches the geometrical parameters of the expected polymer product.

monomers are spaced at this distance and tilted at an angle just under 30° then the neighboring triacetylene functionalities will be in 3.5 Å van der Waals contact, a condition that should maximize the chances of polymerization. These exacting structural requirements are unlikely to be met by any randomly chosen triacetylene.

The 1,6-polymerization of a triacetylene is thus a curious chemical problem. It is a long-standing synthetic problem of

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