Communications to the Editor

Chiral Space in a Unimolecular Capsule

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Self-assembled molecular hosts capable of completely surrounding their guests are one of the most recent vehicles for enantioselective recognition.[1,2] Earlier, we reported the synthesis and characterization of systems in which symmetrical molecules assembled through hydrogen bonds to produce racemic capsules with dissymmetric cavities—the chiral "softballs".[2a] A chiral guest dictates which enantiomeric capsule is preferentially formed: an asymmetric cavity is imprinted on the capsule by the chiral guest. Removal of the guest leaves a chiral, nonracemic host capsule that "remembers" the guest template (rather than its mirror image) for up to 20 h in organic solvents.[3] Useful enantioselective complexation and chiral catalysis requires even higher kinetic stability and we report here our progress, using a combination of noncovalent and covalent interactions.[4,5]

The chiral softballs racemize by dissociation to their achiral monomers followed by reassembly to either enantiomer. If the monomers were covalently linked in such a way that permitted only their return to the original enantiomer, this racemization process could be abolished. This notion led us to the system depicted in Figure 1, a *c*ovalently *l*inked *a*ssembled *m*olecule (hereafter CLAM), featuring intramolecular self-assembly. The glycoluril units at the ends of the monomers were the most likely sites for covalent linkages to be introduced and this consideration led us to the pentacyclic structure **7**, in which a linking group protrudes from only one edge of the glycoluril.

The synthesis of the modified glycoluril started with commercially available 1,2-cyclohexanedione **1** which was sequentially bis silylated to give 1,2-bis(trimethylsilyloxy)-1,3-cyclohexadiene **2**.[6] This electron-rich diene pairs readily in Diels−Alder reactions with complementary dienophiles,[7] and reaction with maleimide **3**[8] gave the adduct **4**. Oxidation of the crude product with bromine afforded the hydrated ketone **5** (Scheme 1).[7] The formation of the expected *endo* product was confirmed by NOE signals in the NMR spectrum. Condensation of **5** with excess urea afforded glycoluril **6** in moderate yield and subsequent silylation of the hydroxy group gave the desired glycoluril **7**.

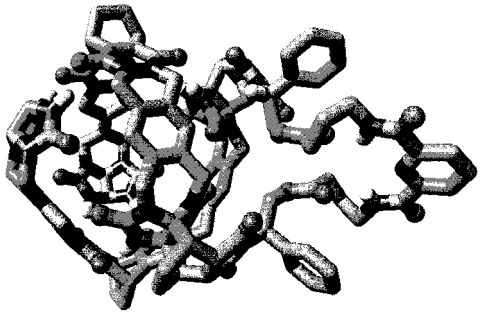
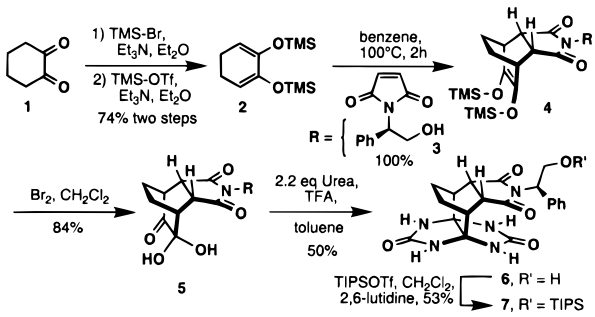


Figure 1. Structural depiction of the CLAM (**14**). Some hydrogens and other solubilizing groups have been omitted for clarity.

Scheme 1



Condensation of **7** with dibromide **8** gave roughly equal amounts of diastereomers **9** and **9′**, in 67% combined yield, which could be separated by normal phase chromatography. Both **9** and **9′** were desilylated using standard conditions and the resulting diastereomers, **10** and **10′**, were separately converted to the appropriate monomers, **11** and **11′**, using procedures developed previously.[9] Either diastereomer (**11** or **11′**) self-assembled in noncompetitive solvents such as benzene-d_6, to give capsules. The covalent linkage of two molecules of **11** or **11′** with *N*-BOC-4-aminobutyric acid followed by deprotection with trifluoroacetic acid and coupling with **13** gave the desired CLAMs **14** and **14′** in good yields (Scheme 2).

There were compelling reasons for using a chiral, nonracemic maleimide. First, model compounds analogous to **9** and **9′** without a chiral auxiliary had been prepared, and all attempts to separate the enantiomers by HPLC with a chiral stationary phase failed. Second, molecular modeling studies[10] suggested that only one of the two diastereomeric CLAMs was likely to fold into a capsule

(1) For recent reviews on self-assembled capsules see: (a) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286. (b) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668.

(2) (a) Rivera, J. M.; Martín, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1021−1023. For examples of other chiral nonracemic capsules, see: (b) Nuckolls, C.; Hof, F.; Martín, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 10281−10285. (c) Castellano, R. K.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 11156−11163.

(3) Rivera, J. M.; Craig, S. L.; Martín, T.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 2130−3132.

(4) For examples of covalent-based chiral capsules see: (a) Park, B. S.; Knobler, C. B.; Eid, C. N., Jr.; Warmuth, R.; Cram, D. J. *Chem. Commun.* **1998**, 55−56. (b) Costante-Crassous, J.; Marrone, T. J.; Briggs, J. M.; McCammon, J. A.; Collet, A. *J. Am. Chem. Soc.* **1997**, *119*, 3818−3823. (c) Yoon, J.; Cram, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11796−11806. (d) Judice, J. K.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2790−2791. (e) Collet, A. *Tetrahedron* **1987**, *43*, 5725−5759.

(5) For other examples of self-assembly with covalent modifications see: Clark, T. D.; Kobayashi, K.; Ghadiri, M. R. *Chem. Eur. J.* **1999**, *5*, 782−792 and references therein.

(6) Emde, H.; Götz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643−1657.

(7) Reetz, M. T.; Neumeier, G. *Chem. Ber.* **1979**, *112*, 2209−2219.

(8) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652−2654.

(9) Tokunaga, Y.; Rudkevich, D. M.; Santamaría, J.; Hilmersson, G.; Rebek, J., Jr. *Chem. Eur. J.* **1998**, *4*, 1449−1457.

(10) Molecular modeling of capsules was carried out using MacroModel 6.5 and the Amber* force field: Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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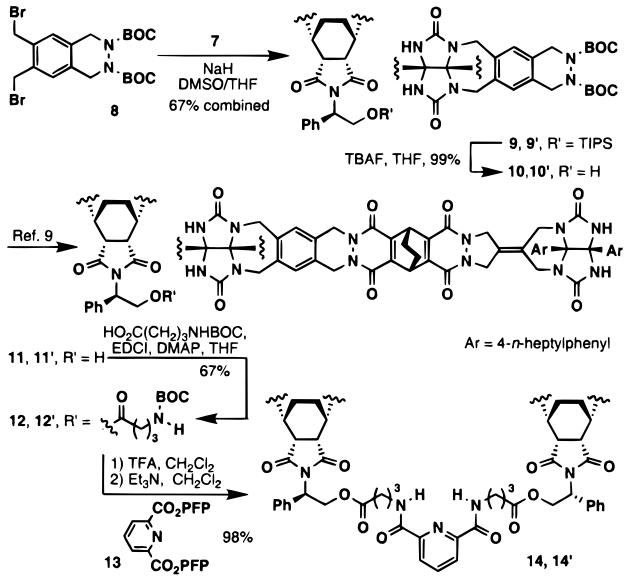
Scheme 2



(Figure 2); the other experiences severe steric clashes. Third, in the absence of other structural information, we could not determine the absolute stereochemistry of the chiral cavities. The identity of the chiral capsule responsible for selecting an enantiomer in a racemic mixture is the only way to understand the details of the molecular recognition phenomena responsible for the selectivity.

The 2,6-pyridyldicarboxamide linker lends some rigidity to the system, and, combined with the chiral auxiliary, allows only one of the two diastereomeric capsules to form. The two diastereomers, **14** and **14′**, exhibit very similar ^{1}H NMR spectra in DMF-d_7, a solvent that disrupts the hydrogen bonds and favors the open conformation. In contrast, with benzene-d_6 the spectrum of **14** shows the characteristics of a closed capsular conformation (Figure 3a), whereas **14′** exhibits a complex spectrum indicating the presence of a mixture of higher order oligomers (Figure 3b).[11]

In the earlier softballs a guest was the template and the chiral information flowed from the guest to the host. In the CLAM the chiral information flows from the host to the guest. Encapsulation studies with pinanediol and camphorsultam were performed in order to assess the effect. Two solutions of **14** were independently titrated with (+)- and (−)-pinanediol and their ^{1}H NMR spectra were recorded in 12% CD_2Cl_2/CCl_4. After establishing the identity of each individual diastereomeric complex each sample was titrated with equal amounts of the enantiomer of the guest used initially. After a few minutes ($t_{1/2}$ = 57 s for the guest exchange process) both samples reached equilibrium at about 1.4:1 or 18% DE. Analogous experiments with camphorsultam gave a 20% DE. These experiments established that the a*S*−*R* capsule prefers the (+)-pinanediol.[12]

(11) A compound similar to **14′**, but with a flexible linker, showed the predominant formation of the closed conformation, although small amounts of other unidentified species were also present: Rivera, J. M. Ph.D. Thesis, Massachusetts Institute of Technology, 2000.

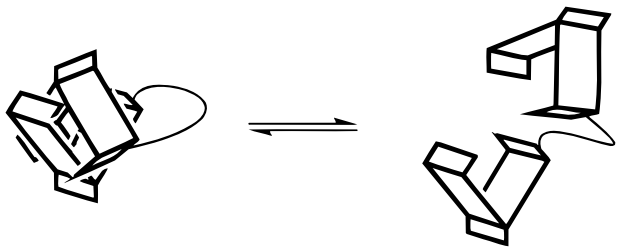


Figure 2. Cartoon representation of the CLAM in its closed and open conformations.

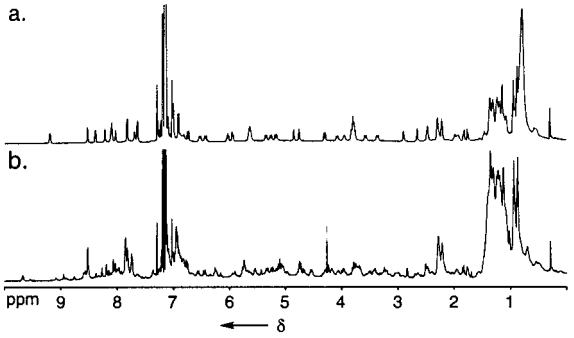


Figure 3. ^{1}H NMR spectra (600 MHz) of (a) **14** and (b) **14′** in benzene-d_6.

We have previously shown that self-assembled capsules can function as catalysts for encapsulated reagents.[13] Covalent interactions can complement noncovalent interactions and give unimolecular capsules of increased kinetic stability.[14] The results presented here augur well for the use of the CLAM as a chiral catalytic reaction chamber.

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Supporting Information Available: Procedures and spectral data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The R in aS−R describes the configuration of the chiral auxiliary used in the glycoluril. In the chiral softballs as well as in **14** the chirality of the cavity is determined primarily by the spacers used in the monomers (i.e., the phenyl ring and the ethylene spacers of **14**). When the linker of the CLAM in Figure 1 is disregarded, there is a vertical chiral axis running through the middle of the capsule. A view down this chiral axis shows two "arms" pointing up and two pointing down. We classify the chiral cavities in these systems by using the length of the spacers to determine priorities. Near arms precede far arms and the longer arm gets the highest priority (1 and 3 respectively). If sense from 1 to 3 is clockwise, the configuration is a*S* (a for axial) or *P*.; if counterclockwise, the configuration is a*R* or *M*. For more on nomenclature of chiral compounds see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 1119−1122.

(13) (a) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50−52. (b) Kang, J.; Santamaría, J.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650−3656.

(14) Brody, M. S.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1640−1644.