Chiral Microenvironments in Self-Assembled Capsules

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Abstract: A nonracemic compound is synthesized and shown to assemble reversibly through hydrogen bonding to form a cyclic tetramer. The chiral arrangement of atoms in the individual pieces becomes amplified through self-assembly to yield multiple functional groups asymmetrically arranged within the cavity. The tetrameric capsule shows a special affinity for ketones and is able to discriminate between their enantiomers in solution.

Introduction

Enantioselective recognition in self-assembled structures requires sufficient space for a chiral guest[1] and a handed environment capable of being sensed by an occupant.[2] The capacity of these spaces for chiral discrimination can be intensified through multiple surface contacts between the dissymmetrically arranged functionality of the host and the guest. The molecular capsules that arise from the self-assembly of multiple copies of concave surfaces feature solvent-excluded cavities,[3] and it has been shown that chiral information can be transferred *from* a guest *to* such a capsular assembly: the asymmetric guest guides chiral capsule formation.[4] Here, we report flow of instruction in the opposite direction: an assembled, dissymmetric cavity leads to enantioselective binding of a targeted guest molecule. Instructions for the tetrameric assembly to self-organize into a chiral, nonracemic cavity are written in the three-dimensional structure of its subunits. The asymmetric arrangement of atoms in the individual pieces becomes amplified through self-assembly to yield multiple functional groups orchestrated for the concert of enantioselective recognition.

Results and Discussion

Structure of the Tetrameric Assemblies. Structures **1a** and **1b** contain self-complementary glycoluril and cyclic sulfamide functionalities. The curved geometry of **1a** (Figure 1b) coupled with the hydrogen-bonding preference between glycoluril (tail) and sulfamides (head) has been shown to produce cyclic, tetrameric capsules (Figure 1c).[5] Each end of the capsule is comprised of a circular seam of 8 hydrogen bonds between the alternating glycoluril and cyclic sulfamide functionalities (Figure 1d). The capsule formed from subunit **1a** is achiral and D_{2d} symmetric. The addition of a hydroxyl function on the central phenyl ring **(1b)** imparts chirality to each of the subunits (Figure 2a). The union of four of these *nonracemic* pieces produces a single enantiomer of a chiral capsule with a volume[6] of 170 Å^3. It has no mirror planes and is overall D_2 symmetric,

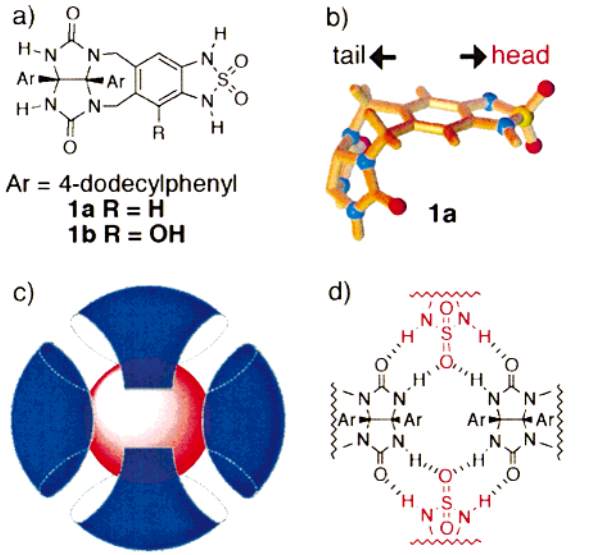

Figure 1. (a) The chemical structure of achiral **1a** and chiral **1b** tetramer subunits. (b) A three-dimensional representation showing the shape and curvature of **1a** (side chains have been omitted for clarity). (c) The four identical subunits (blue) arrange in a head-to-tail manner and encapsulate a guest molecule (red), as shown in this schematic. (d) The seam of 8 hydrogen bonds between sulfamide and glycolurils present at each end of the tetrameric capsule.

(1) Structures that self-assemble into discreet, nonracemic assemblies are known but their superstructures leave little room for guests. Hydrogen-bonded: (a) Simanek, E. E.; Qiao, S.; Choi, I. S.; Whitesides, G. M. *J. Org. Chem.* **1997**, *62*, 2619. (b) Sanchez-Quesada, J.; Seel, C.; Prados, P.; de Mendoza, J.; Dalcol, I.; Giralt, E. *J. Am. Chem. Soc.* **1996**, *118*, 277. (c) Prins, L. J.; Huskens, J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498. Metal-based: (d) Zarges, W.; Hall, J.; Lehn, J. M.; Bolm, C. *Helv. Chim. Acta* **1991**, *74*, 1843 and references therein. (e) Enemark, E. J.; Stack, D. T. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 932. (f) Case, M. A.; Ghadiri, M. R.; Mutz, M. W.; McLendon, G. L. *Chirality* **1998**, *10*, 35. Rrotaxanes/catenanes: (g) Asakawa, M.; Janssen, H. M.; Meijer, E. W.; Pasini, D.; Stoddart, J. F. *Eur. J. Org. Chem.* **1998**, *6*, 983 and references therein.

(2) Nonracemic structures whose peripherally located chirality does not translate to significant enantioselective recognition: (a) Tokunaga, Y.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 66. (b) Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 12671. (c) Mueller, C.; Whiteford, J. A.; Stang, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 9827.

(3) (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647. (b) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278.

(4) Rivera, J. M.; Martín, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1041. Rivera, J. M.; Martín, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1041.

(5) Martín, T.; Obst, U.; Rebek, J., Jr. *Science* **1998**, *281*, 1842.

(6) All molecular modeling was performed with MacroModel 6.5 and the structures were energy minimized with the Amber* force field: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. The volumes of the cavities were calculated for these structures by using the GRASP program: Nicholls, A.; Sharp, K. A.; Honig, B. *Proteins* **1991**, *11*, 281.

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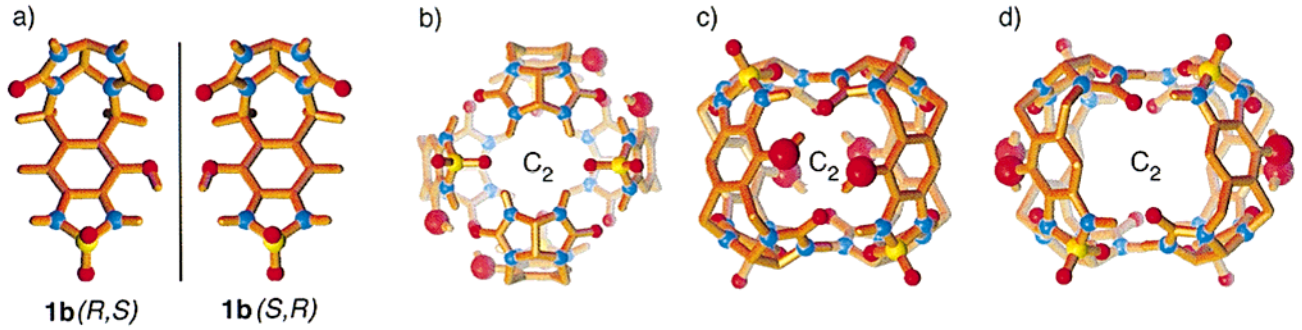


Figure 2. (a) Three-dimensional representations of both enantiomers of **1b**. (b−d) Views down each of the mutually perpendicular C_2-axes when a *single* enantiomer of **1b** is arranged in a head-to-tail, tetrameric assembly. The hydroxyl groups which break the mirror symmetry of the capsule are highlighted as larger, red spheres (side chains and some protons have been omitted for clarity).

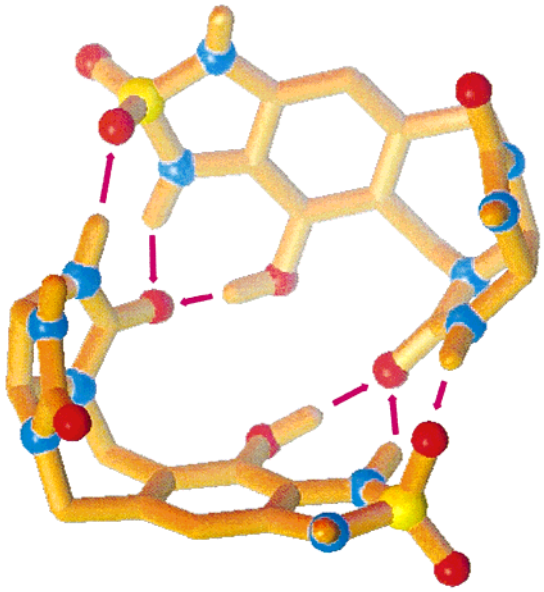


Figure 3. A representation of two adjacent monomers of **1b** oriented as in the nonracemic tetrameric assembly. The phenol reduces the symmetry of the structure and acts as an additional hydrogen-bond donor to the carbonyl of the adjacent glycoluril. The head-to-tail arrangement of the subunits gives rise to the pairing of the hydroxyl groups in space (side chains and some protons have been omitted for clarity).

characterized by three mutually perpendicular C_2-axes (Figure 2b−d). Upon head-to-tail assembly, the four hydroxyl groups are positioned in two pairs adjacent to each other (Figure 2c). Likewise, small openings in the structure are created where the aromatic hydrogens are positioned side-by-side (Figure 2d). The added phenolic function not only desymmetrizes the cavity, but can also strengthen the assembly by acting as an additional hydrogen-bond donor to the adjacent glycoluril carbonyls (Figure 3).[7]

It has been shown previously that guest molecules containing a carbonyl can participate in the hydrogen bonding of the capsule by insertion of the carbonyl oxygen into the hydrogen-bonding seam located at each end of the capsule.[5] The energy-minimized, molecular models[6] shown in Figure 4 show the orientation of 2-adamantanone in the tetrameric assembly **1b** and demonstrate that additional hydrogen bonds can be formed between the four glycoluril N−H's located at one end of the cavity and the ketone without disrupting the sulfamide−glycoluril hydrogen bonds. This bifurcation of hydrogen bonds by the guest results in an observed preference for the encapsulation of ketone containing guest molecules.[5]

(7) Phenols have been shown to increase the encapsulating power of other hydrogen-bonded capsules in a similar fashion: Kang, J.; Hilmersson, G.; Santamaría, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650.

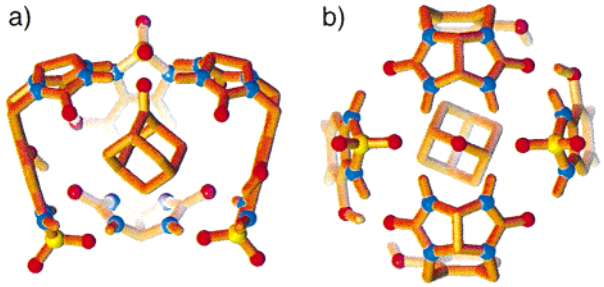
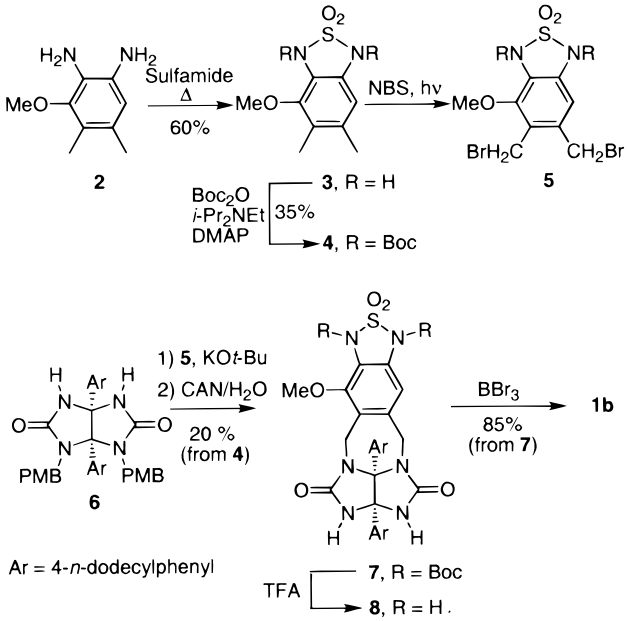


Figure 4. Energy-minimized[6] structure of a tetrameric assembly of **1b** with 2-adamantone encapsulated. The ketone oxygen becomes localized in the hydrogen-bonding network at each end of the capsule: (a) front view (closest subunit deleted after minimization) and (b) top view. Side chains and some protons have been omitted for clarity.

Scheme 1. Synthesis of (−)-**1b**



Synthesis and Resolution of Enantiomers. The synthesis of **1b** is modeled after that of the original tetrameric molecule **1a**[5] and proceeds in 6 steps from **2** (Scheme 1). The known diamine **2**[8] is converted to the cyclic sulfamide **3** followed by protection of the nitrogens as their *tert*-butylcarbamate to give **4**. Bromination of **4** and alkylation with the PMB-protected glycoluril **6**[5] yields racemic **7** after cerium ammonium nitrate

(8) Tracy, M.; Acton, E. M. *J. Org. Chem.* **1984**, *49*, 5116.

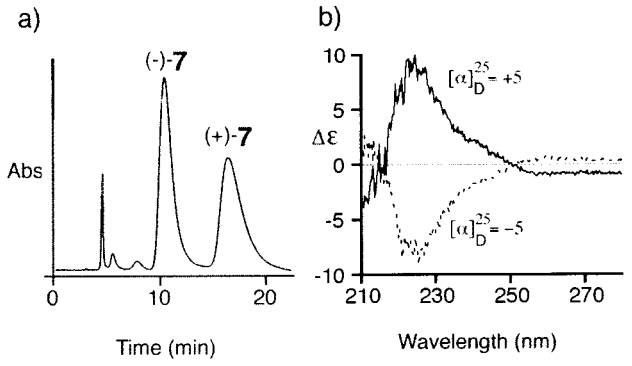


Figure 5. (a) HPLC chromatogram showing the resolution of **7** into its enantiomers. (b) Circular dichroism spectra and specific rotations from HPLC-resolved **7**. For the CD measurements the path length is 1 mm and the concentration is 7.9×10^{-5} M for (−)-**7** (dotted line) and 6.6×10^{-5} M for (+)-**7** (solid line) in THF.

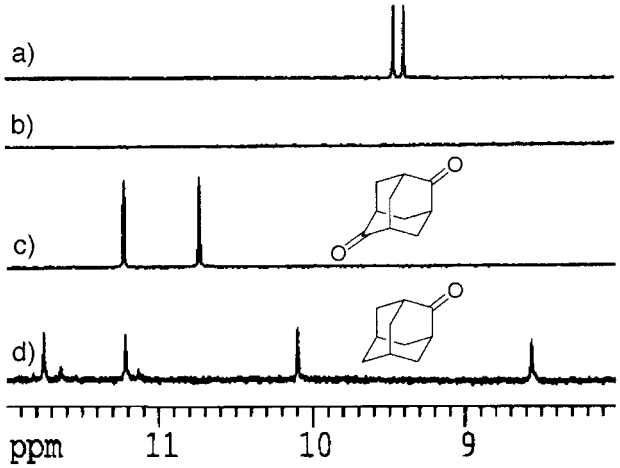


Figure 6. The downfield region of the ^{1}H NMR spectra (600 MHz) showing the sulfamide protons of (−)-**1b**: (a) unassembled in THF-d_8; (b) a nonspecific aggregate in *m*-xylene-d_{10}; (c) encapsulating 2,6-adamantanedione in *m*-xylene-d_{10}; and (d) encapsulating 2-adamantanone and desymmetrizing the capsule.

mediated deblocking of the glycoluril. Intermediate **7** can be cleanly resolved into its enantiomers on a chiral, HPLC stationary phase (Figure 5a). The isolated enantiomers display equal and opposite circular dichroism spectra and specific rotations (Figure 5b). Upon reinjection of one collected enantiomer into the HPLC, the other enantiomer could not be detected. The enantiomerically pure building block was deprotected to expose the sulfamide and phenol of target molecule **1b**. Further evidence for optical purity of the capsule is given by the lack of mixtures of diastereomeric complexes (as observed by ^{1}H NMR) when forming assemblies with optically pure guests (for an example, see Figure 7c).

Encapsulation Behavior. The NMR spectrum of (−)-**1b** showed the expected features, including two chemically distinct sulfamide protons. These can be seen in a solvent (THF-d_8) that prevents assembly by effectively competing for hydrogen bonds (Figure 6a). The formation of the capsule in noncompetitive solvents can be conveniently monitored through observation of the downfield region (8−12 ppm) of the ^{1}H NMR spectrum. The self-assembly of compounds such as **1a** and **1b** is dependent upon the presence of a guest molecule of appropriate size and shape for the resulting cavity.

Solvents such as CD_2Cl_2, toluene-d_8, and benzene-d_6 can serve as guest molecules for the tetrameric assembly of **1b**. Neither *p*-xylene-d_{10} nor *m*-xylene-d_{10} are the correct size or shape to promote assembly, and accordingly a broad, uninterpretable spectrum results. No signals for specifically hydrogen-bonded sulfamides can be detected in the downfield region (Figure 6b). However, many small organic molecules can template the formation of the assembly in these solvents.

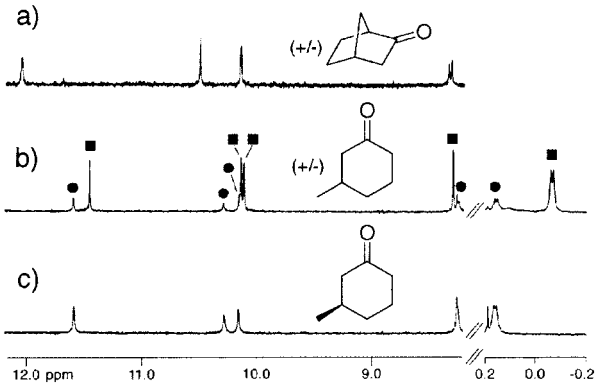


Figure 7. Sulfamide ^{1}H NMR resonances (600 MHz) for the tetrameric assembly of (−)-**1b** (2.0×10^{-3} M) in *m*-xylene-d_{10}: (a) nonselective encapsulation from a racemic mixture of norcamphor (4.0×10^{-2} M); (b) highly selective encapsulation from a racemic mixture of 3-methylcyclohexanone (4.0×10^{-2} M), high-field resonances are for the methyl groups of the guest inside the capsule; and (c) encapsulation of (*R*)-(+)-3-methylcyclohexanone. (●) Resonances attributable to encapsulation of the (*R*)-ketone and (■) the (*S*)-ketone.

It was found that molecules containing a ketone were especially effective, presumably due to the participation of the carbonyl in the seam of hydrogen bonds.[5] 2,6-Adamantanedione[9] is an ideal guest in this regard as the ketone-to-ketone distance is optimal for participation in the seam of hydrogen bonds at both ends of the capsule.[10] Upon encapsulation of this guest, no symmetry is broken and two sharp, well-defined ^{1}H signals for the sulfamides of the tetrameric assembly appear (Figure 6c). In contrast, binding of 2-adamantanone localizes the lone ketone in one end of the capsule. The capsule's end-to-end symmetry is broken[11] and four distinct sulfamide NH's are now observed (Figure 6d), indicating that on the NMR time scale there is slow end-to-end tumbling of the guest within the cavity.

The peaks attributed to hydrogen-bonding protons are concentration independent, indicating that a discreet molecular assembly has formed. Evidence for the proposed capsular structure of these assemblies is given by the observation of signals representing encapsulated guest upfield of those of the free guest, due to the shielding environment created by the aromatic walls of the capsule. The relative integration of peaks for a single encapsulated guest molecule (Figure 7b,c) and the signals attributed to the assembled capsule show a 4:1 stoichiometry and allow for confirmation of the proposed tetrameric nature of the capsule.

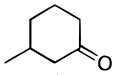
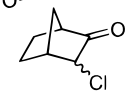
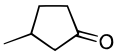
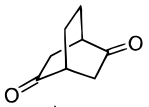
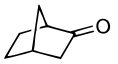
A variety of chiral guests were encapsulated in the cavity formed by the assembly of (−)-**1b**, and numerous ^{1}H NMR resonances for the diastereomeric complexes can be resolved and integrated to give the ratio of each bound enantiomer. Shown in Figures 7a and 7b are two representative examples of diastereomeric complexes formed by using (−)-**1b** to

(9) Synthesized by the procedure given by: Morat, C.; Rassat, A. *Tetrahedron Lett.* **1979**, *45*, 4409.

(10) This guest was shown to have the highest binding constant in the original tetrameric assembly (see ref 5).

(11) Breaking of the end-to-end symmetry is accompanied by rotation of the guest that must be slow on the NMR time scale. This type of hindered rotation of guests has been observed for other encapsulated molecules: (a) See ref 2b. (b) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081.

Table 1

	K_{eq}	de (%)	Volume (Å^3)
	4.0	60	113
	1.6	23	111
	1.6	23	120
	1.3	13	98
	1.2	9	126
	ca. 1.0	ca. 0	104

encapsulate racemic mixtures of chiral ketones. When norcamphor is encapsulated (Figure 7a) there exists only a slight excess in the binding of one enantiomer of norcamphor relative to the other, and the signals for diastereomeric complexes are relatively similar. Remarkably, a constitutional isomer of norcamphor, 3-methylcyclohexanone, is encapsulated with a 4:1 diastereoselectivity (Figure 7b). Modeling[6] indicates that 3-methylcyclohexanone binds with the ketone oxygen in one circle of hydrogen bonds while the pendant methyl group is directed at the hydroxyls that define the chirality of the cavity. Table 1 shows results obtained for a variety of other guests.[12] There appears to be no correlation between guest size and chiral discrimination. Rather, it seems that it is the positioning of functional groups within the cavity that controls enantioselection.

Summary and Outlook. Similar to the pockets and cavities found in nature, these capsules achieve enantioselective recognition through multiple interfaces between the lining of the cavity and the chiral guest molecule. Despite the relative weakness and elasticity of the hydrogen bonds that are responsible for its structure, this self-assembled capsule is capable of discriminating enantiomers, even enantiomers of molecules that are sparsely functionalized. This augurs well for the use of such synthetic systems for carrying out asymmetric reactions within their cavities or for chiral resolutions. We will report on these developments in due course.

Experimental Section

General. ^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra were recorded on a Bruker DRX-600 spectrometer. Matrix-assisted laser desorption/ionization (MALDI) FTMS experiments were performed on an IonSpec FTMS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp. Circular dichroism (CD) spectra were recored on an AVIV 62DS CD spectrometer. Dichloromethane and THF were passed through columns of activated aluminum oxide as described by Grubbs and co-workers prior to use.[13] The chiral HPLC column used to separate the enantiomers of **7** was purchased from Regis Technologies Inc., Morton Grove, IL.

(12) [2.2.1]-Bicycloheptane-2,5-dione is prepared by the procedure given by: Hawkins, R. T.; Hsu, R. S.; Wood, S. G. *J. Org. Chem.* **1978**, *43*, 4648. [2.2.2]-Bicyclooctane-2,5-dione is prepared by the procedure given by: Werstiuk, N. H.; Yeroushalmi, S.; Hong, G. L. *Can. J. Chem.* **1992**, *70*, 974.

(13) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

Encapsulation Studies. All spectra of capsule formation were recorded in *m*- or *p*-xylene-d_{10}. For convenience, the (−) enantiomer of **1b** was used for all measurements. The concentration of capsule monomer was 2 mM, resulting in a capsule concentration of 0.5 mM. Guests were present in a 20-fold excess at a concentration of 10 mM. In general, encapsulation of achiral ketones gave rise to four singlets in the sulfamide region. Encapsulation of racemic mixtures of chiral ketones gave rise to two diasteromeric complexes, represented by two sets of four singlets in this region. Diastereomeric excess was calculated by relative integration of ^{1}H NMR signals for the diastereomers. The systems equilibrated quickly and the ratios did not change with time (7 days). As expected, encapsulation of an optically pure single enantiomer of a chiral ketone gave rise to only one set of singlets representing a single diastereomeric complex.

Molecular Modeling. All molecular models were created using MacroModel V.6.5 and were energy minimized using the Amber* force field.[6] The tetramer subunits displayed hydrogen bonds between each of the subunits when minimized. The total number of hydrogen bonds was 16 for **1a** and 20 for **1b**. Guest could be included in the energy-minimized structures that were again minimized. Ketones that were of the proper shape to fit into the cavity localized their ketone oxygens in hydrogen-bonding network and displayed up to four hydrogen bonds with the glycoluril NHs. The cavity and guest volumes were calculated by importing the minimized structures from macromodel into the GRASP program.[6]

Synthesis of Cyclic Sulfamide 3. Diglyme (6 mL) was added to an oven-dried flask under a nitrogen atmosphere and brought to a vigorous reflux. A solution of **2**[8] (0.52 g, 3.1 mmol) and sulfamide (0.36 g, 3.7 mmol) in diglyme (3 mL) was added dropwise via syringe through the septa to the boiling diglyme over 10 min. After the addition reflux was continued for 15 min, then the flask was cooled to room temperature and the solvent removed with a rotary evaporator. The residue was dissolved in ether (50 mL), washed with 2 N HCl (20 mL), brine (20 mL), and water (20 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was redissolved with sonication in a small amount of ether. The ethereal solution was passed through a plug of silica gel (5 cm × 3 cm) that was washed with more ether to yield **3 (**0.42 g, 60%) as a buff-colored solid. ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 3H), 2.14 (s, 3H), 3.66 (s, 3H), 6.42 (s, 1H), 10.65 (s, 1H), 10.70 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 12.29, 20.46, 60.50, 108.23, 120.86, 122.57, 129.37, 131.04, 143.56. HRMS (MALDI-FTMS; M+) calcd for $C_9H_{12}N_2O_3S$ 228.0569, found 228.0568.

Synthesis of Boc-Protected Sulfamide 4. 3 (0.30 g, 1.3 mmol) was dissolved in dry THF (20 mL) and di-*tert*-butyl dicarbonate (0.58 g, 2.6 mmol) was added. The mixture was cooled in an ice-bath and diisopropylethylamine (450 μL, 2.6 mmol) was added dropwise via syringe followed by DMAP (32 mg, 0.26 mmol). The light-orange solution was then allowed to warm to room temperature and stirred under nitrogen for 3 days. The solvent was removed, the oily residue was dissolved in CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL), and the solvent was removed under reduced pressure. Chromatography (9:1 benzene/hexanes) gave **4** (0.20 g, 35%) as a clear oil that solidified upon standing. ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 1.64 (s, 9H), 2.19 (s, 3H), 2.30 (s, 3H), 3.73 (s, 3H), 7.42 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.57, 21.01, 28.04, 28.37, 86.50, 86.78, 111.50, 111.53, 114.59, 126.11, 126.98, 137.06, 147.03, 147.38, 147.88. HRMS (MALDI-FTMS; M + Na^+) calcd for $C_{19}H_{28}N_2O_7SNa$ 451.1515, found 451.1497.

Synthesis of Dibromide 5. 4 (0.25 g, 0.58 mmol) and NBS (0.22 g, 1.2 mmol) were placed in a dry round-bottomed flask fitted with a reflux condenser, dissolved in CCl_4 (25 mL), and stirred under nitrogen. The flask was irradiated with a 250 W sunlamp (20 in. from the flask) for 1.5 h. The reaction mixture was filtered to remove the succinimide, and the solvent was removed under reduced pressure. The yield of crude **5** was quantitative, and this material was used without further purification.

Synthesis of Racemic 7. PMB protected glycoluril **6** (0.52 g, 0.62 mmol) was stirred in dry DMF (10 mL) under a nitrogen atmosphere and KO*t*-Bu (0.14 g, 1.24 mmol) was added. The mixture was stirred for 30 min and then the dibromide **5** (0.58 mmol, from above) in DMF

(6 mL) was added via cannula. After the mixture was stirred at room temperature for 4 h the solvent was removed under reduced pressure. The crude residue was flash chromatographed twice (90:10 hexane/EtOAc and 75:25 hexane/EtOAc) to give 0.18 g of the PMB-protected material. ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6 H), 1.27 (m, 36 H), 1.44 (m, 4 H), 1.62 (s, 9 H), 1.64 (s, 9 H), 2.44 (m, 4 H), 3.73, (s, 3 H), 3.77 (s, 3 H), 3.86 (m 4 H), 4.00 (s, 3 H), 4.23 (d, 1 H, J = 15.7 Hz), 4.78 (d, 1 H, J = 16.0 Hz), 4.85 (d, 1 H, J = 15.7 Hz), 5.78 (d, 1 H, J = 16.0 Hz), 6.50 (m, 2 H), 6.68 (d, 2 H, 8.6 Hz), 6.80 (m, 8H), 7.04 (m, 4 H), 7.77 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 14.52, 23.10, 28.03, 28.42, 29.66, 29.77, 29.92, 30.04, 30.08, 30.10, 30.13, 30.16, 31.70, 32.32, 35.68, 35.83, 37.15, 45.47, 45.99, 46.59, 55.56, 55.58, 61.03, 86.87, 86.93, 87.21, 88.44, 112.89, 114.09, 114.35, 116.39, 127.69, 127.73, 127.80, 128.32, 128.45, 128.55, 129.07, 129.26, 129.80, 129.84, 130.48, 137.45, 144.38, 144.48, 146.54, 146.87, 147.56, 158.78, 158.98, 159.10, 160.02.

This PMB-protected material (0.075 g, 0.059 mmol) was deprotected immediately by stirring in a 1:1 acetonitrile/THF mixture (6 mL) and adding a water (1.5 mL) solution of cerium ammonium nitrate (0.32 g, 0.59 mmol). The mixture was stirred for 2 h and then extracted with EtOAc (10 mL). The separated organic layer was washed with water (5 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude compound was chromatographed (gradient 3:1 to 1:1 hexanes/EtOAc) to give **7** (0.049 g, 20% from **4**) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6 H), 1.27 (m, 36 H), 1.44 (m, 4 H), 1.61 (s, 9 H), 1.64 (s, 9H), 2.42 (m, 4 H), 3.75 (d, 1 H, J = 16.1 Hz), 3.80 (s, 3 H), 4.13 (d, 1 H, J = 15.7 Hz), 4.83 (d, 1 H, 15.8 Hz), 5.54 (d, 1 H, J = 16.2 Hz), 6.06 (s, 1H), 6.42 (s, 1H), 6.86 (d, 2 H, J = 8.1 Hz), 6.97 (m, 4 H), 7.08 (d, 2 H, J = 8.1 Hz), 7.69 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 14.08, 22.65, 27.55, 27.92, 29.12, 29.33, 29.44, 29.60, 29.64, 29.67, 26.69, 31.88, 35.30, 45.10, 60.51, 78.50, 86.46, 86.74, 88.47, 111.50, 115.59, 127.05, 127.35, 127.64, 127.67, 127.91, 128.67, 130.26, 133.74, 136.72, 143.63, 143.95, 146.50, 147.14, 158.95. MS (electrospray, M + Na^+) expected for $C_{59}H_{86}N_6O_9SNa$ 1077, found 1077.

Resolution of 7. The resolution of **7** was accomplished with an HPLC chiral stationary phase. **7** (50.0 mg) was dissolved in 600 μL of 55:45 hexane/2-propanol and sonicated for 20 min. Four separate injections of 150 μL were made onto an (*R*,*R*)-Whelk-O 2 semipreparative column (25 cm × 10 mm i.d., 100 Å particle size), eluting with 55:45 hexane/2-propanol at 4.5 mL/min. A typical chromatogram is shown in Figure 5a. The yield of collected (−) enantiomer (t = 8.5 min to 14 min) was 20.5 mg and that of collected (+) enantiomer (t = 15 min to 25 min) 23.2 mg. The resulting enantiomers were characterized by CD spectroscopy and optical rotations, see Figure 5b.

Synthesis of (−)-8. (−)-**3** (0.02 g, 0.019 mmol) was dissolved in dry dichloromethane (3 mL), and 1 mL of trifluoroacetic acid was added. The solution was stirred at room temperature for 2 h, and the solvent was removed with a rotary evaporator. The crude white solid was chromatographed on silica gel (gradient elution from 95:5 to 93:7 CH_2Cl_2/MeOH) to give pure (−)-**8** (0.016 g, ca. 100%). ^{1}H NMR (THF-d_8) δ 0.89 (m, 6H), 1.20−1.50 (m, 40H), 2.41 (t, 2H, J = 7.6 Hz), 2.44 (t, 2H, J = 7.6 Hz), 3.73 (d, 1H, J = 15.8 Hz), 3.98 (s, 3H), 4.03 (d, 1H, J = 15.4 Hz), 4.65 (d, 1H, J = 15.4 Hz), 5.40 (d, 1H, J = 15.8 Hz), 6.63 (s, 1H), 6.83 (d, 2H, J = 8.1 Hz), 6.90 (d, 1H, J = 8.1 Hz), 6.95 (d, 1H, J = 8.1 Hz), 6.97 (d, 1H, J = 8.1 Hz), 7.01 (d, 1H, J = 8.1 Hz), 7.08 (d, 2H, J = 8.1 Hz), 7.16 (s, 1H), 7.20 (s, 1H), 9.63 (s, 1H), 9.66 (s, 1H). ^{13}C NMR (THF-d_8) δ 14.63, 23.76, 30.21, 30.32, 30.53, 30.67, 30.83, 30.87, 30.90, 32.55, 32.62, 33.07, 36.28, 36.38, 37.03, 45.81, 60.87, 79.29, 89.06, 109.39, 123.29, 125.67, 128.39, 128.50, 129.05, 129.17, 129.36, 131.26, 133.49, 133.61, 137.00, 143.62, 143.83, 144.09, 159.48, 160.00. HRMS (MALDI-FTMS; M + Na^+) calcd for $C_{49}H_{70}N_6O_5SNa$ 877.5026, found 877.5027.

Synthesis of (−)-1b. (−)-**8** (0.015 g, 0.019 mmol) was dissolved in dry dichloromethane and the solution was cooled in an ice/water bath. BBr_3 (200 μL) was added via syringe, and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was re-cooled in an ice/water bath and methanol was added dropwise. The solvent was then removed with a rotary evaporator followed by the repeated addition of methanol and rotary evaporation. The crude buff solid was triturated sequentially with hexanes and methanol yielding pure (−)-**1b** (0.013 g, 85%). ^{1}H NMR (THF-d_8) δ 0.89 (t, 6H, J = 6.5 Hz), 1.2−1.5 (m, 40H), 2.41 (t, 2H, J = 7.6 Hz), 2.44 (t, 2H, J = 7.6 Hz), 3.82 (d, 1H, J = 15.8 Hz), 4.09 (d, 1H, J = 15.4 Hz), 4.67 (d, 1H, J = 15.4 Hz), 4.98 (d, 1H, J = 15.8 Hz), 6.46 (s, 1H), 6.84 (d, 2H, J = 8.1 Hz), 6.89 (d, 1H, J = 8.1 Hz), 7.00 (d, 2H, J = 8.1 Hz), 7.03 (d, 1H, J = 8.1 Hz), 7.07 (d, 2H, J = 8.1 Hz), 7.15 (s, 1H), 7.52 (s, 1H), 8.09 (s, 1H), 9.48 (s, 1H), 9.50 (s, 1H). ^{13}C NMR (THF-d_8) δ 11.80, 20.93, 27.35, 27.49, 27.69, 27.83, 28.00, 28.04, 29.69, 29.79, 30.24, 33.43, 33.55, 35.19, 42.43, 77.16, 86.39, 102.88, 117.84, 117.99, 125.61, 126.02, 126.47, 126.52, 128.39, 130.88, 131.31, 133.73, 138.78, 140.93, 141.40, 156.16, 159.32. HRMS (MALDI-FTMS; M + H^+) calcd for $C_{48}H_{69}N_6O_5SNa$ 841.5050, found 841.5036.

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