Chiral Capsules. 1. Softballs with Asymmetric Surfaces Bind Camphor Derivatives

Yuji Tokunaga and Julius Rebek, Jr.*

Contribution from The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037

Received August 15, 1997

Abstract: Self-assembling "softballs" are hollow pseudospherical dimers held together by hydrogen bonds in organic solvents. They encapsulate smaller molecules of suitable size and shape. Stereochemical aspects of these systems are explored through the encapsulation of camphor derivatives. Both symmetrical softballs and those rendered chiral by functional groups on the softball's surface are examined by ^{1}H NMR methods.

Introduction

Molecule-within-molecule complexes are proving ever more useful in physical organic chemistry. They provide means of stabilizing reactive intermediates,[1] observing new forms of stereoisomerism,[2] and accelerating certain reactions.[3] Although a number of chiral cavitands and complexes have been made,[4−8] and guests inside these have been expected to experience intensified sensations of asymmetry as a result of cramped quarters, the stereochemical features in these microenvironments remain largely unexplored. The possibilities range from asymmetric outer surfaces through asymmetric cavity linings to asymmetric cavities. We now have them all in hand and introduce here the initial molecules with asymmetric surfaces. In the sequel, we will trace the gradual shift of research focus from the outside to the inside of the self-assembling "softball" **1·1**.

Asymmetric Guests

The softball assembles through hydrogen bonds and exists as a pseudospherical dimer (Figure 1) in organic solvents. Solvent molecules and solute guests that fill, optimally, 55−60% of the dimer's interior volume are reversibly encapsulated under ambient conditions.[9,10] Guests the size of adamantane or ferrocene fit well inside, and we have encapsulated, for the first time, optically active guests such as the camphor derivatives **2**−**5**. Figure 2 compares the ^{1}H NMR spectra of the softball **1b·1b** in $CDCl_3$ alone and with excess camphanic acid (**3**). The sharp signals, upfield shifts, and widely separated resonances

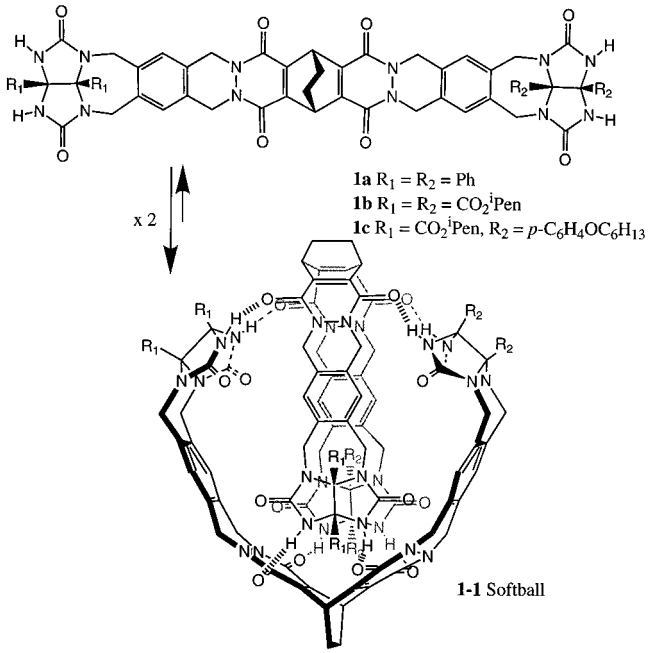

Figure 1. Structure of monomer unit (top) and assembled dimeric softball (bottom).

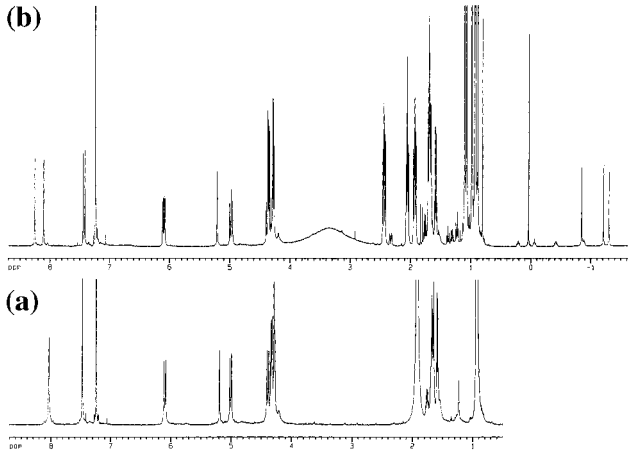

Figure 2. NMR spectrum (600 Mhz) of softball **1a·1a** in $CDCl_3$ at 3.4 mM: (a) alone; (b) after addition of 12.4 mM camphanic acid. Signals upfield of TMS represent encapsulated camphor, and the doubling of signals of the softball (e.g., at ∼5, 6, and 8 ppm) indicate loss of symmetry planes within the complex.

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S0002-7863(97)02885-0 CCC: $15.00
Published on Web 01/14/1998

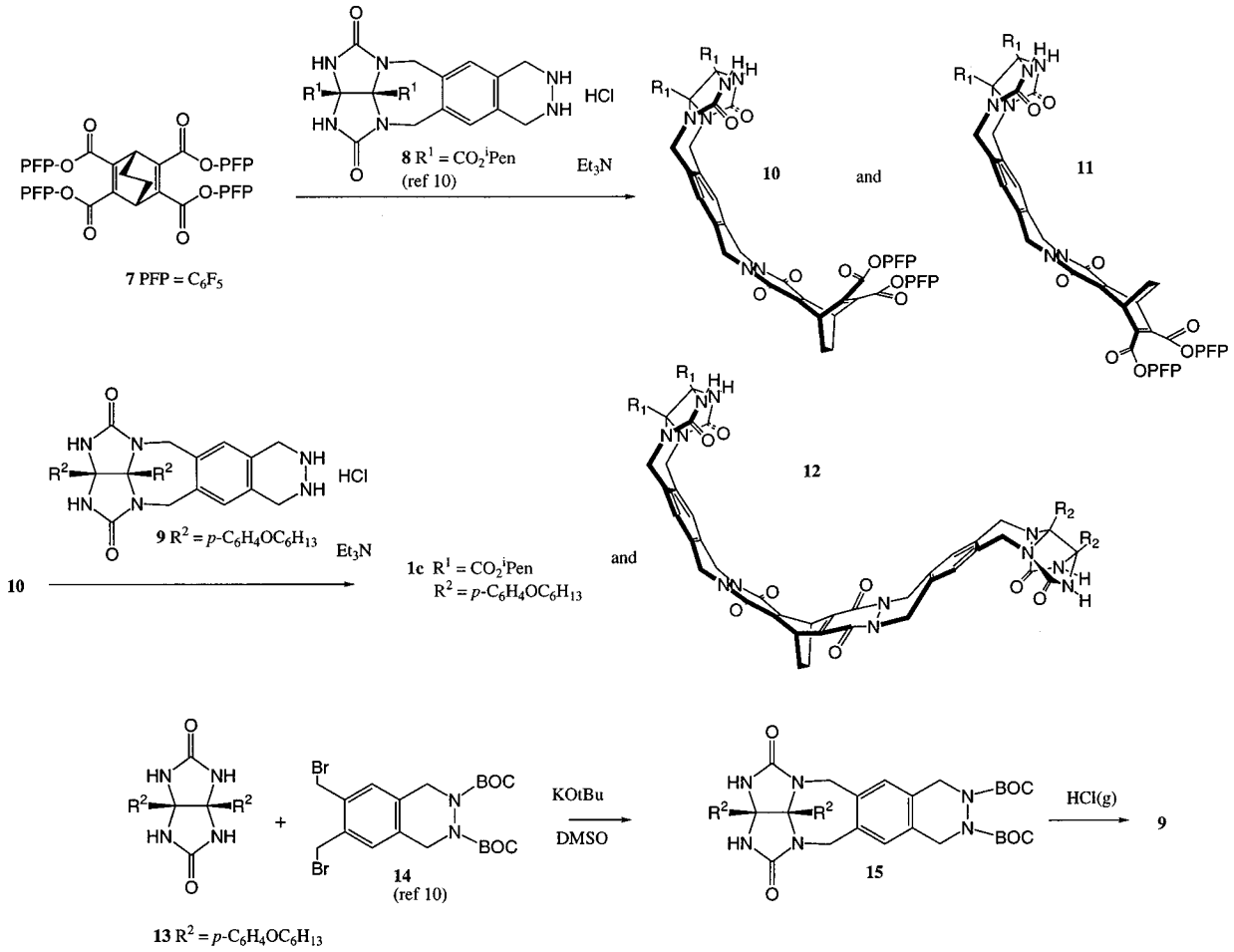
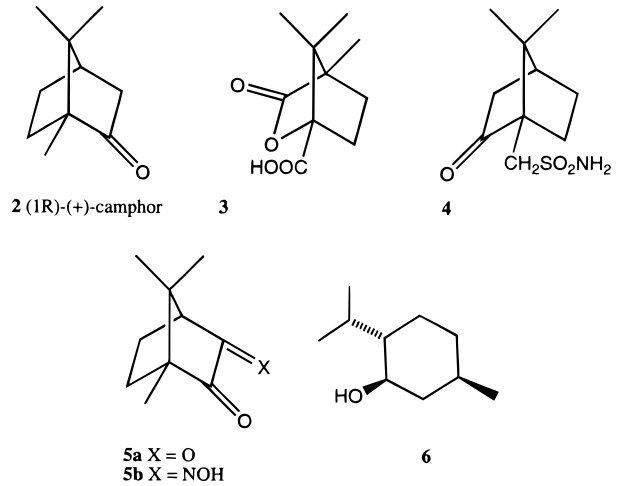


Figure 3. Synthesis of the new monomer subunit **1c**.



for free and bound guest confirm that camphanic acid is encapsulated within the softball under conditions of slow exchange on the NMR time scale. The resonances of the softball undergo doubling: with camphanic acid inside no planes of symmetry exist and the two edges of the tape-like, monomeric subunits are now in different magnetic environments. These edges can exchange environments only through dissociation, rotation, and subsequent recombination of the subunits, the costly energetics of which are described elsewhere.[11] Similar spectra (not shown) were observed for the other camphor derivatives; the stoichiometries of the complexes were such that one camphor derivative was seen within each softball. Menthol (**6**) was not encapsulated. Its more extended structure is too long to fit comfortably, although a more compact conformation, featuring an axial isopropyl group, differs little in size and shape from the camphor derivatives. This level of selectivity of the softball, or any other capsule held together by only weak intermolecular forces, remains to be explored.

Asymmetric Hosts

The softballs with an asymmetric surface were next examined. In their simplest embodiment they are available through the dimerization of two subunits that feature different substituents on each end of the tape-like monomer.[11] When two such achiral subunits associate, the result is a chiral capsule that maintains a C_2 axis but no longer has the planes of symmetry featured in **1a·1a** or **1b·1b**. Accordingly, the dimeric assembly is racemic (Figure 4). The enantiomers can interconvert by dissociation and recombination of the subunits, and the attendant dynamic properties of these capsules are not without interest, even if the cavity itself lacks asymmetry.

The synthesis was accomplished through the intermediates shown (Figure 3) and followed precedents firmly established in this research program. The centerpiece[10,12] of the structure—the tetraester **7**—was used first to acylate a hydrazine bearing a glycoluril with isopentyl esters (**8**) and then with one bearing *p*-(hexyloxy)phenyl esters (**9**). The intermediate **10** and undesired isomer of the initial coupling **11** were formed in roughly

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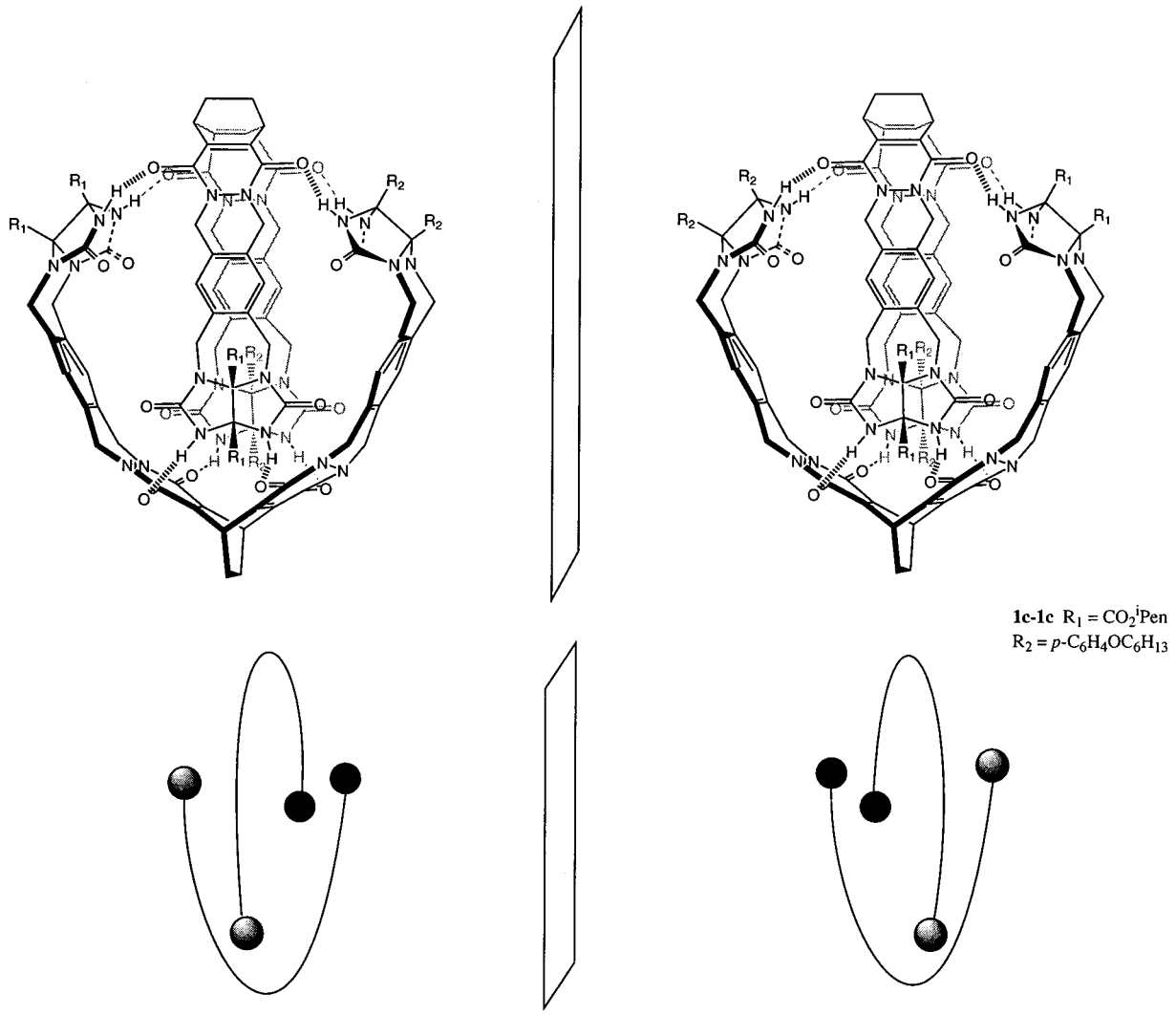

Figure 4. Structure (top) and schematic (bottom) renderings of the racemic softball dimer **1c·1c**.

equal amounts but were readily separated. The yield of the undesired S-shaped isomer **12** of the final coupling, featuring the glycoluril substituents on opposite faces of the molecule, varied depending on the solvent. This role of molecular recognition in the synthesis of the softball is described elsewhere[12] and is consistent with the observations of Cram[13] and Sherman[14] during the synthesis of covalently bound systems surrounding guest templates.

Figure 5 shows the ^{1}H NMR spectrum of the racemic assembly **1b·1b** in benzene. Again, two sets of signals are observed for protons along the edges of the tape-like structure. Addition of camphor to this species in *p*-xylene-d_{10}, itself a poor guest for the softball, further complicates the spectrum. Diasteromeric complexes are formed as evidenced by the upfield signals for encapsulated camphor which are doubled (Figure 5b,c). The equal intensity of these signals provides confirmation that the asymmetry of this system is limited to the outer surface of the assembly, rather than extending into the cavity: the asymmetry is not felt by the guest in a steric sense, but only in a magnetic sense.

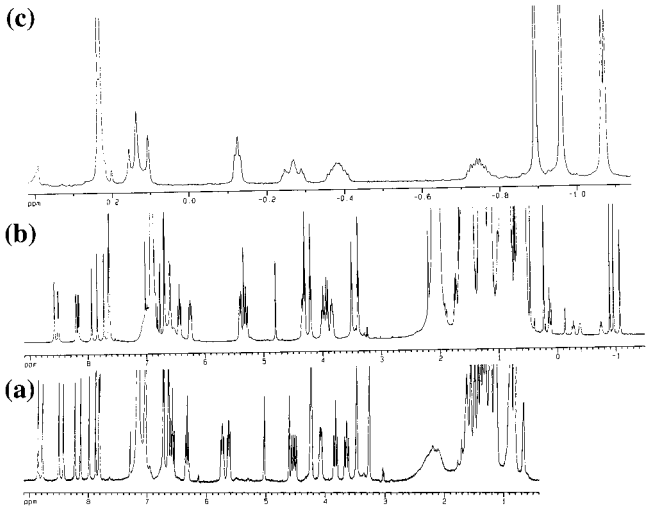

Figure 5. NMR spectrum (600 MHz) of racemic softball **1c·1c** and its complex with camphor: (a) **1c·1c** at 3.8 mM in benzene-d_6; (b) **1c·1c** at 3.8 mM in *p*-xylene-d_{10} after addition of 460 mM camphor; (c) expanded upfield region of b showing the two diastereomeric complexes.

Summary and Outlook

As the asymmetric elements are moved inward, a chiral cavity will result and it is reasonable to expect that molecule-within-

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molecule complexes of this sort will prove useful for enantioselective recognition; a better environment for such recognition is hard to imagine. The experience with cyclodextrins does, however, give cause for concern. The dozens of asymmetric centers lining their cavities do not often translate into efficient enantioselection.[15] This may be a result of their open-ended structures or their relatively smooth, rather than bumpy or cratered interiors. Using calixarene-based capsules, it has recently been possible to introduce handedness to the *lining* of the cavity.[16] The clockwise or anticlockwise arrangement of the series of hydrogen-bonded ureas in these systems emerges in heterodimers and affects guests accordingly. We will report on these in due course.[17]

Experimental Section

Tetrakis(pentafluorophenyl)ester 7. To a solution of the corresponding tetraacid chloride[10] (110 mg, 0.30 mmol), pentafluorophenol (220 mg, 1.20 mmol), and a catalytic amount of 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) in CH_2Cl_2 (3 mL) was added Et_3N (273 mg, 270 mmol). The mixture was heated under reflux overnight, cooled, washed with 10% aqueous HCl and water, and then dried over Na_2SO_4. Purification of the residue by silica gel column chromatography with CH_2Cl_2 as the eluent gave active ester **7** (170 mg, 60%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 2H), 2.01 (s, 4H); IR (neat) 1762, 1652, 1520, 1274, 1208, 1036, 996 cm^{-1}; LRMS (FAB, M + H$^+$) calcd for $C_{36}H_7F_{20}O_8$ 947, found 946. The product was further characterized as its tetra-*p*-methoxybenzylamide after reaction with 4 equiv of *p*-methoxybenzylamine and Et_3N in CH_2Cl_2: HRMS (FAB, M + Cs$^+$) calcd for $C_{44}H_{46}N_4O_8Cs$ 891.2370, found 891.2334.

Diesters 10 and 11. To a mixture of the isoamyl hydrazine salt **8**[10] (327 mg, 0.476 mmol) and Et_3N (241 mg, 2.38 mmol) in THF (2.5 mL) was quickly added a solution of tetraester **7** (713 mg, 0.713 mmol) in THF (2 mL). After 10 h of stirring, the solvent was removed. Chromatography of the residue on silica gel with THF/$CHCl_3$ (3:1) gave **10** (187 mg, 31 %) and with THF/$CHCl_3$ (1:1) gave the isomer **11** (155 mg, 26 %). Spectroscopic data for **10**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.08 (s, 2H), 8.07 (s, 2H), 7.79 (s, 2H), 7.48 (s, 2H), 6.95 (d, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.8 Hz), 6.74 (d, 2H, J = 8.8 Hz), 6.61 (d, 2H, J = 8.8 Hz), 5.36 (d, 2H, J = 15.5 Hz), 5.16 (d, 2H, J = 15.5 Hz), 4.99 (s, 2H), 4.65 (d, 2H, J = 15.5 Hz), 4.06 (d, 2H, J = 15.6 Hz), 3.82 (t, 2H, J = 6.5 Hz), 3.79 (t, 2H, J = 6.5 Hz), 1.80−1.74 (m, 2H), 1.65−1.55 (m, 6H), 1.47−1.23 (m, 12H), 0.85 (t, 6H, J = 6.7 Hz); IR (neat) 3645, 3248, 2957, 2915, 1695, 1629, 1511, 1460, 1230, 1027, 860 cm^{-1}; LRMS (FAB, M + Cs$^+$) calcd 1389; found 1389.

Hydrazine 9 via 15. To a solution of glycolurea **13**[10] (770 mg, 1.56 mmol) in DMSO (80 ml) at 70 °C was added KOtBu (0.331 mg, 2.95 mg). After 1.5 h of stirring, dibromide **14**[10] (76.4 mg, 0.148 mmol) in DMSO (20 ml) was added dropwise, and the mixture was heated for 1.5 h. The reaction mixture was poured into 1% aqueous HCl. The mixture was filtered, and the solid was washed with water and then triturated with MeOH. Subsequent filtration recovered excess glycolurea as a white solid. The filtrate was evaporated, and the residue was chromatographed on silica gel with CH_2Cl_2/AcOEt (3:1) to give compound **15** (64.1 mg, 51%) as a foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, 2H, J = 8.4 Hz), 6.95 (d, 2H, J = 8.4 Hz), 6.65 (d, 2H, J = 8.4 Hz), 6.55 (d, 2H, J = 8.4 Hz), 6.17−5.81 (m, 2H), 5.05−4.62 (m, 4H), 4.45−3.99 (m, 4H), 3.81 (t, 2H, J = 6.7 Hz), 3.76 (t, 2H, J = 6.7 Hz), 1.73−1.60 (m, 4H), 1.48−1.24 (m, 30H), 0.90−0.82 (m, 6H); IR (neat) 3256, 2931, 1708, 1610 1513, 1463, 1248, 1175 cm^{-1}; HRMS (FAB, M + Cs$^+$) calcd for $C_{48}H_{64}N_6O_8Cs$ 985.3840, found 985.3880.

Deprotection. Through a solution of protected hydrazine **15** (713 mg, 0.724 mmol) in $CHCl_3$ (35 ml) was bubbled HCl(g) through a pipette for 3 min. After 8 h of stirring, the solution was purged with N_2. The solvent was removed *in vacuo*, and the material was used in the next step without further purification: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (s, 2H), 7.16 (s, 2H), 6.94 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 9.0 Hz), 6.74 (d, 2H, J = 8.9 Hz), 6.62 (d, 2H, J = 8.9 Hz), 4.60 (d, 2H, J = 15.6 Hz), 4.24−4.00 (m, 4H), 4.03 (d, 2H, J = 15.6 Hz), 3.86−3.74 (m, 4H), 1.63−1.54 (m, 4H), 1.38−1.19 (m, 12H), 0.86−0.75 (m, 6H); IR (neat) 3399, 3231, 2931, 1691, 1611, 1511, 1468, 1250, 1178, 835 cm^{-1}; HRMS (FAB, M + Cs$^+$) calcd for $C_{38}H_{48}N_6O_4$-Cs 653.3815, found 653.3845.

Softball 1c·1c. To a suspension of the isoamyl diester **10** (19 mg, 0.017 mmol) and Et_3N (8.8 mg, 0.087 mmol) in benzene (2 mL) was added a solution of hydrazine hydrochloride **9** (12 mg, 0.017 mmol) in benzene (1.5 mL). After 10 h of stirring, the solvent was removed. The C-shaped compound (3.2 mg) was obtained by preparative TLC (eluent $CHCl_3$/AcOEt/MeOH = 65:25:10). For 1c·1c: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.45 (s, 2H), 8.04 (s, 2H), 7.44 (s, 2H), 7.42 (s, 2H), 6.93 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.73 (d, 2H, J = 8.8 Hz), 6.60 (d, 2H, J = 8.8), 5.29 (d, 2H, J = 15.7 Hz), 5.24 (d, 2H, J = 15.7 Hz), 5.09 (d, 2H, J = 15.7 Hz), 5.08 (d, 2H, J = 15.7 Hz), 4.97 (s, 2H), 4.63 (d, 2H, J = 15.7 Hz), 4.60 (d, 2H, J = 15.7 Hz), 4.45 (d, 2H, J = 15.7 Hz), 4.18 (t, 2H, J = 6.8 Hz), 4.05 (t, 2H, J = 6.8 Hz), 3.82 (d, 2H, J = 6.4 Hz), 3.79 (t, 2H, J = 6.4 Hz); ^{1}H NMR (600 MHz, C_6D_6) δ 8.56 (s, 1H), 8.78 (s, 1H), 8.50 (s, 1H), 8.43 (s, 1H), 8.23 (s, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.88 (s, 1H), 7.84−7.80 (m, 2H), 7.08−7.02 (m, 2H), 6.78−6.71 (m, 2H), 6.68−6.62 (m, 2H), 6.59 (d, 1H, J = 16 Hz), 6.56 (d, 1H, J = 16 Hz), 6.34 (d, 1H, J = 16 Hz), 6.32 (d, 1H, J = 16 Hz), 5.75 (d, 1H, J = 16 Hz), 5.73 (d, 1H, J = 16 Hz), 5.64 (d, 1H, J = 16 Hz), 5.62 (d, 1H, J = 16 Hz), 5.62 (s, 1H), 4.61 (s, 1H), 4.52 (d, 1H, J = 16 Hz), 4.51 (d, 1H, J = 16 Hz), 4.08 (d, 1H, J = 16 Hz), 4.07 (d, 1H, J = 16 Hz), 3.85 (d, 1H, J = 16 Hz), 3.82 (d, 1H, J = 16 Hz), 3.67 (d, 1H, J = 16 Hz), 3.63 (d, 1H, J = 16 Hz), 3.52−0.81 (4m, 48H); HRMS (FAB, M + Cs$^+$) calcd for $C_{76}H_{86}N_{12}O_{14}Cs$ 1523.5441, found 1523.5525.

Acknowledgment. We are grateful to the National Institutes of Health and The Skaggs Research Foundation for support of this work and to Christopher Bayne for preliminary experiments.

JA972885T

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