Development of Synthetic Self-assembling Molecular Capsule: from Flexible Spacer to Rigid Spacer

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The synthesis and characterization of a synthetic self-assembling molecular capsule are described. The originally designed flexible molecule **1** was collapsing on itself, forming hydrogen bonds within monomer rather than forming a dimer due to the flexibility of the central diimide. A more rigid system **23** was designed and synthesized. The preorganization of this molecule for dimerization led the system self-assembling molecular capsule successfully.

Introduction

Self-organizing assemblies have been the subjects of numerous studies.[1] Recently, new concepts were developed giving molecules that self-assemble to give cavities suitable for encapsulation of selected molecular targets.[2] Here we describe how we developed a self-assembling dimeric molecule that can have a large cavity, so that reversible encapsulation of sizable, complementary guest is possible.

Molecule **1** consists of 5-fused ring and ethylene bridged diimide. This molecule should adopt a C-shaped conformation as depicted in three-dimensional view in Figure 1. Not only glycoluril units provide the hydrogen bonding as a donor (from the four N-H bonds to the four carbonyl oxygens in the central ring) but also they provide the hydrogen bonding acceptor(from the four phenolic O-H bonds to the four amidic carbonyl oxygens). When two molecules of **1** come together with their concave surfaces facing towards each other, a structure of roughly spherical shape can result from 16 hydrogen bonds. The angle and length of hydrogen bond in the dimeric state from amber calculation is shown in Table 1. The way the two pieces are assembled in this dimer resembles the structure of softball. This dimer has some resemblance with carcerand and cryptophanes of Cram[3] and Collet[4] but this dimer is formed reversibly.

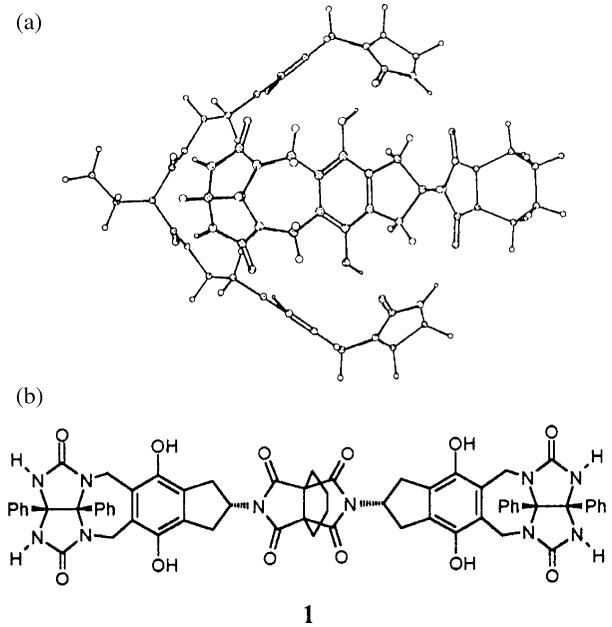

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Figure 1. The large volume sef-assembling dimeric molecule (a) Energy minimized dimeric structure (b) Two dimensional monomeric structure.

Synthesis

The synthesis of the molecule **1** began from diphenyl glycolurils **3** which are easily obtained from the condensation reactions of urea and benzil **2** in the presence of trifluoroacetic acid in benzene.[5]

The synthesis of central diimide **7** started from Diels-Alder reaction of butadiene **4** and tetracyanoethylene **5**. Hydrolysis of Diels-Alder product **6** directly gave the central diimide[6] **7**.

The synthesis of 4,7-dimethoxy-2-indanol **14** started from commercially available 2,3-dimethylhydroquinone **8**. Methylation of 2,3-dimethylhydroquinone using sodium hydroxide and methyl iodide in DMF gave compound **9** in high yield. Radical bromination of compound **9** gave compound **10** and this was followed by the substitution reaction with

Table 1. Hydrogen bond length and angles in self-assembling dimeric molecule **1**

	N-H-----O	O-H-------O
length	2.76 Å	2.68 Å
angle	161~162°	167°

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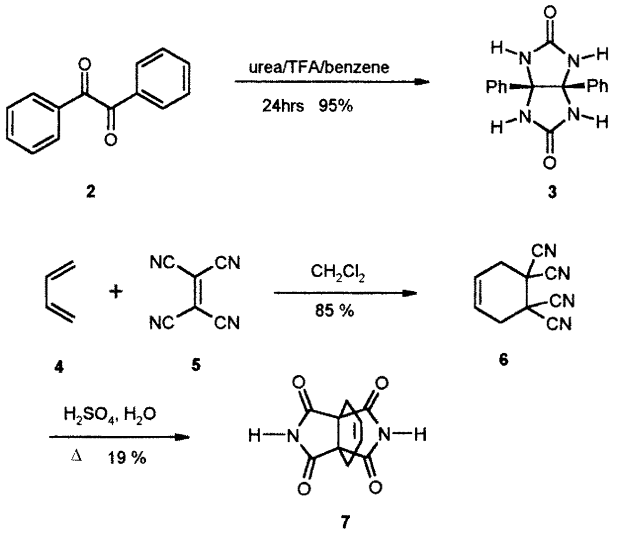


Figure 2. The synthesis of diphenyl glycoluril **3** and diimide **7**.

sodium cyanide to give compound **11**. Cyclization under basic conditions using sodium ethoxide in ethanol solution gave compound **12**. Hydrolysis of compound **12** in mixture of acetic acid and phosphoric acid gave compound **13**. Reduction with sodium borohydride in ethanol gave compound **14** and benzylation with benzylbromide gave the expected the protected 2-indanol **15**.

To couple 2-benzyloxy-4,7-dimethoxyindane **15** and glycoluril **3**, the compound **15** was functionalized by double chloromethylation using chloromethyl methyl ether[7] with 60% H_2SO_4 to give functionalized 2-benzyloxy-4,7-dimethoxyindane **16**. Then **16** was coupled with glycoluril **3** using potassium hydroxide in DMSO at 100 °C to give compound **17** in 65% yield.

Coupling reaction of **16** with the glycoluril gave two stereoisomers. As the next Mitsunobu reaction inverts the stereochemistry of alcohol, compound **17a** is the right isomer. However, it was difficult to separate them and even after the

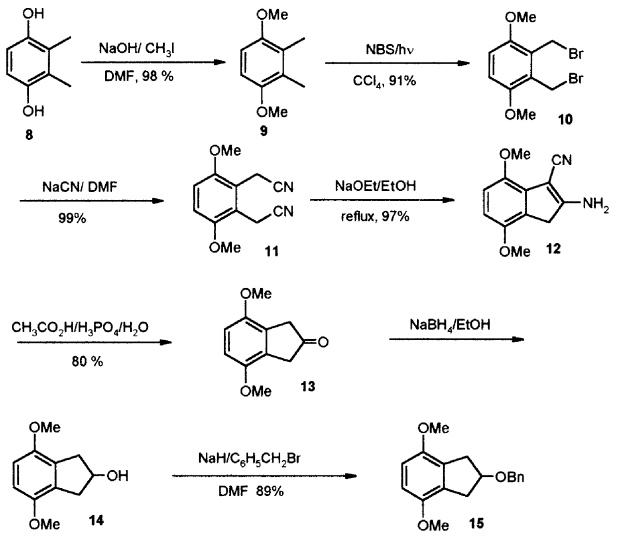


Figure 3. The synthesis of 2-benzyloxy-4,7-dimethoxy-2-indane **15**.

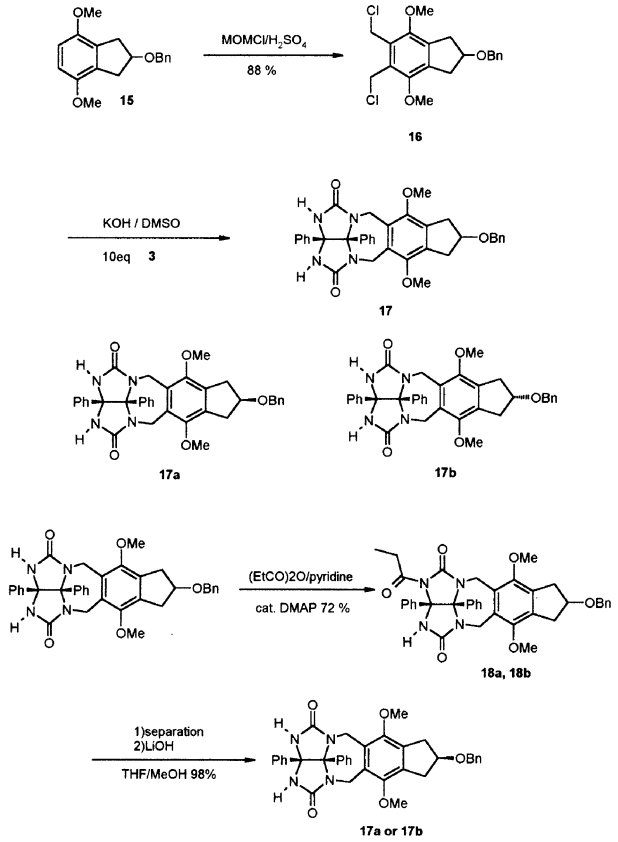


Figure 4. The coupling reactions between 2-benzyloxy-4,7-dimethoxyindane **15** and diphenyl glycoluril **3**. The separations of two isomers were achieved after propionation.

separation, it was difficult to properly assign the structure. Therefore, both compounds were taken through the final synthesis and it was expected that only the right isomer would give a self-assembling dimer. To separate two isomers easily, the glycoluril part of molecule was selectively propionated to give **18** and the two isomers were separated by flash column chromatography. The ratio of isomers was polar : nonpolar = 2 : 1 (polarity is based on TLC).

After the separation of isomers, the propionate group was removed by lithium hydroxide in THF-MeOH to give stereochemically pure compound **17a** and **17b**. As the solubility of compound **17a** and **17b** was low, and the unprotected glycoluril N-H moiety gave complication in Mitsunobu reaction, the tert-butoxycarbonyl (BOC group) was added to compound **17a and 17b** using di-tert-butyldicabonate and DMAP to give **19**. Then the benzyl group was removed using H_2/5% Pd-C to give compound **20**. Double Mitsunobu reaction[8,9] of compound **20** and central diimide **7** gave the compound **21**. The olefin of the central diimide **21** proved unstable to BBr_3 used in the deprotection of the methyl ethers; therefore it was hydrogenated before the deprotection reaction. Then, deprotection of the Boc group and methyl group using boron tribromide gave the final compound **1**.

Characterization and Discussion

Each diastereomer of the intermediate alcohol (**17a** and

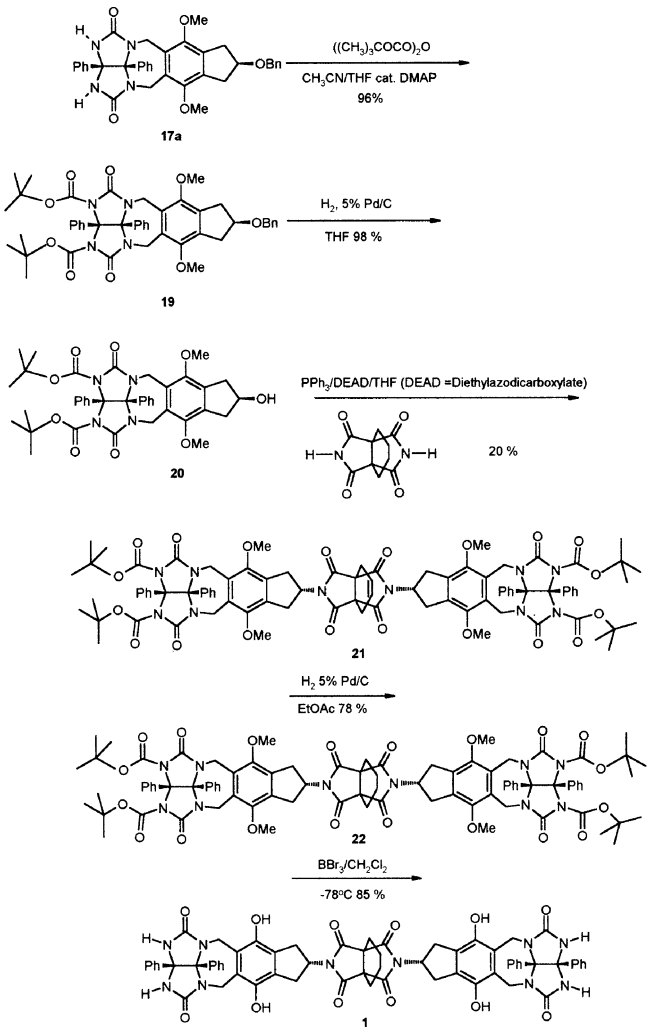


Figure 5. The coupling reactions of **21** and **7** finally gave the expected compound **1**.

17b) was carried though the synthesis separately, producing two molecules, designated the nonpolar (SBn) and polar (SBp) isomer. The absolute stereochemistry of the two soft-ball diastereomers has not been determined unequivocally. However, their properties should differ as a result of their different gross structural shapes as illustrated in Figure 6. The polar isomer was soluble in DMSO-d_6, DMF-d_6, and $CDCl_3$/MeOD and it was not soluble in less polar solvents such as chloroform, acetone, benzene or toluene. The ^{1}H NMR spectra of polar isomer in DMSO-d_6 and DMF-d_7 show complete symmetry between the two sides of the molecule. The ^{1}H NMR spectra in DMF-d_7 and DMSO-d_6 are shown in Figure 7. The nonpolar isomer was soluble in DMSO-d_6, DMF-d_7. The ^{1}H NMR of nonpolar isomer in this solvent is shown in Figure 8. In addition, the nonpolar isomer was soluble $CDCl_3$, CD_2Cl_2, C_6D_6, toluene-d_8, THF-d_8, and acetone-d_6. The ^{1}H NMR spectra in $CDCl_3$, CH_2Cl_2, C_6D_6, toluene-d_8, THF-d_8, acetone-d_6, <50% DMF-d_6/CD_2Cl_2, and <50% DMSO-d_6/$CDCl_3$ shows a loss of C_2 symmetry between the two sides of the molecule (two sets of peak for each hydrogen). Two of the urea N-H bonds appear to be

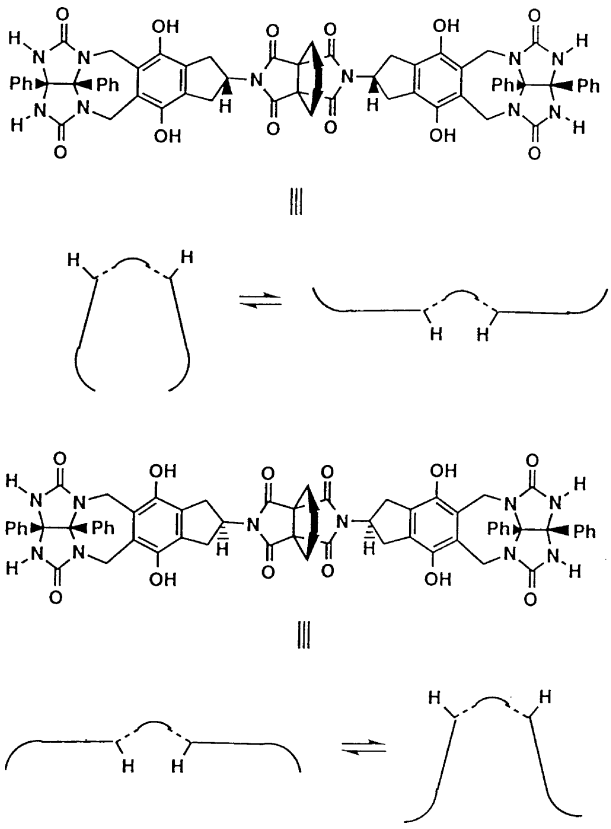


Figure 6. Conformational analysis of two diastereomers. Only one isomer with the right conformation can have dimer or intramolecular hydrogen bond.

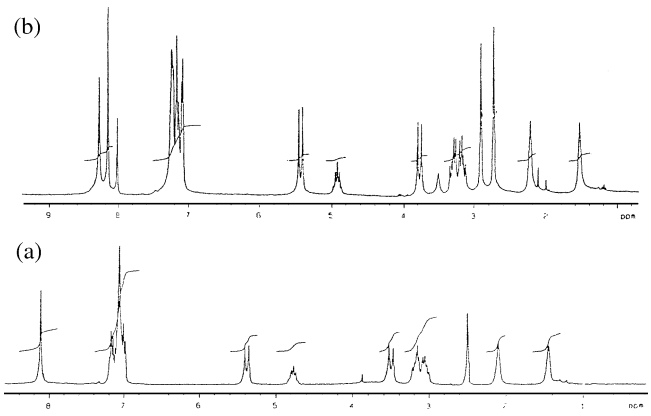


Figure 7. The ^{1}H NMR spectrum of polar isomer in (a) DMSO-d_6 and (b) DMF-d_7.

hydrogen bonded, and two do not. The ^{1}H NMR of the nonpolar isomer in these solvents is shown in Figure 9. These characteristics are temperature independent between -40 °C and 40 °C, and concentration independent. At >50% DMF-d_6/CD_2Cl_2, and >50% DMSO-d_6/$CDCl_3$ there is a retention of C_2 symmetry between the two sides of the molecule. The presence of adamantane, tetra methyl adamantane, and Kemp's methyl ester-imide had no effect on the NMR spectra for both isomers. Plasma desorption mass spectrometry also shows only the monomer is present under the instrumental conditions for both isomers. The most important

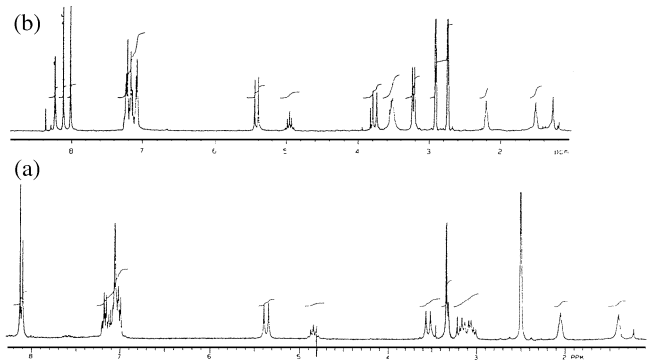


Figure 8. The ^{1}H NMR spectrum of nonpolar isomer in (a) DMSO-d_6. (b) DMF-d_7.

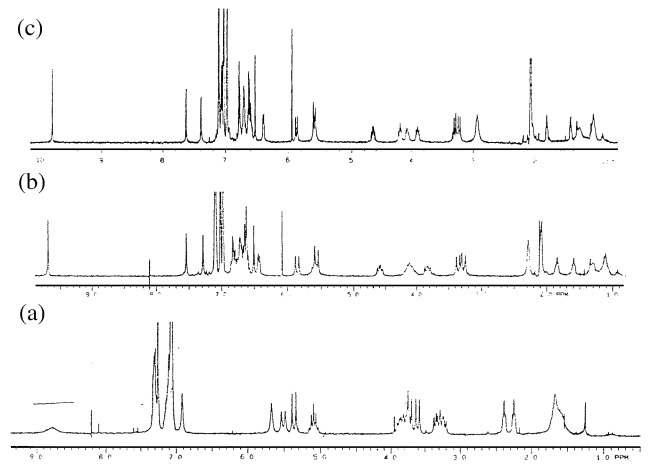


Figure 9. The ^{1}H NMR spectrum of nonpolar isomer in (a) $CDCl_3$ and (b) toluene-d_8 at 298 K (c) toluene-d_8 at 273 K.

observation from the spectral data is that ^{1}H NMR of the nonpolar isomer showed two kinds of peaks for the each hydrogen and the ratio of two peaks was about 50 : 50. The ^{1}H NMR also showed that only 50% of the N-H bonds are hydrogen bonded. It can be interpreted as 50% of molecule stays as dimer and 50% of the molecule stays as monomer. However, the ratio was always same with different solvents and the ratio was temperature independent. If the two kinds of peaks from the ^{1}H NMR came from the monomer and dimer and it reflected the ratio of monomer to the dimer, the ratio of the peaks should depend on the solvent and the temperature. Therefore, it seemed more plausible that the downfield signals came from intramolecular hydrogen bonding rather than intermolecular hydrogen bonding. In addition, no guest inclusion was observed and no dimeric mass peak was observed in the plasma desorption mass spectrum. Therefore it was concluded that the compound from the nonpolar isomer was the C-shaped isomer as only C-shaped isomer can have intramolecular hydrogen bond (Figure 6). It was also concluded that C-shaped isomer was collapsing on itself, forming hydrogen bonds within monomer rather than forming a dimer, as shown in Figure 10.

Analysis of the molecular of the collapsed C-shaped molecule indicates that the central diimide is the structural feature that contains the majority of the molecule's flexibility. This

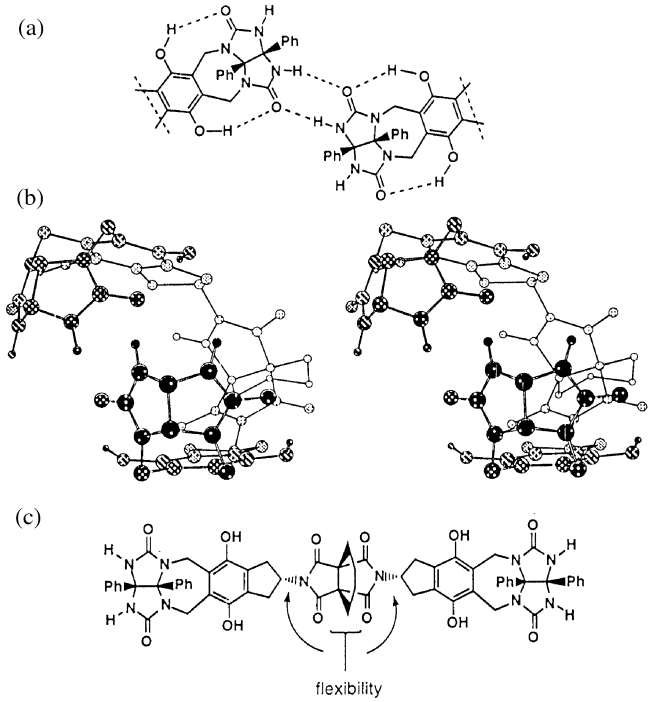
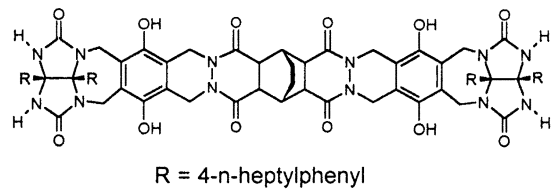


Figure 10. Intramolecular collapse of the C-shaped isomer; the stereoview is given in (b).

flexibility is apparently too great, allowing the molecule to fold on itself, at least under the experimental conditions employed. The central diimide is able to twist significantly at the fusion of the three rings, it is apparently too curved to



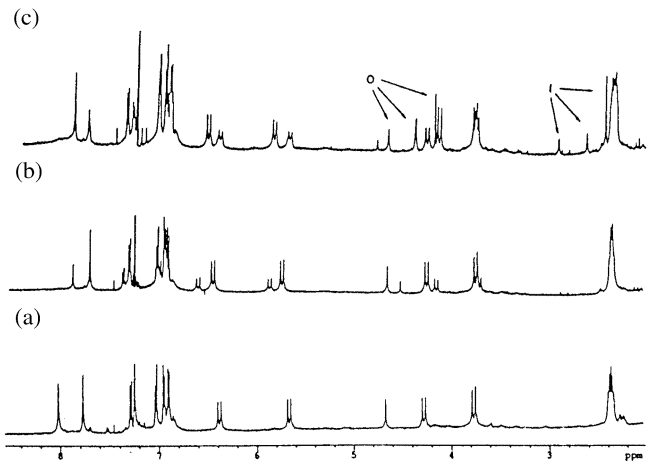


Figure 11. The more rigid system 23 and its ^{1}H NMR (a) in $CDCl_3$. (b) 0.5 equivalents of 1-adamantane carboxylic acid added. (c) 0.6 equivalents of 1-ferrocenecarboxylic acid added. The signals of the guest inside and outside are labeled with "i" and "o" respectively.

prevent collapse, and the C-N imide single bond allows excessive rotation of the two glycoluril surfaces toward each other. Therefore, a more rigid system **23** was designed. Molecular modeling indicates that these molecules are highly preorganized for dimerization. The only significant source of flexibilities is the methylenes to which hydrazide nitrogens are attached. These rings are capable of only small distortions, allowing the glycoluril ends to breathe to a small degree. The hydrogen bond distances and angles in the dimers are nearly same as molecule **1**. The phenyl group in the glycoluril was changed to 4-heptylphenyl group to improve the solubility of the molecule. Figure 11 showed ^{1}H NMR spectrum of the molecule **23** and encapsulation of suitable guests. The synthesis and behavior of molecule **23** were already reported in detail elsewhere.[10]

In conclusion, the first designed self-assembling dimeric molecule with large cavity collapsed due to intramolecular hydrogen bond and its large flexibility. However, self-assembling dimeric system was achieved by introducing a more rigid system **23** which lowered conformation energy and inhibit intramolecular hydrogen bond.

Experimental Section

Diphenyl glycoluril (3). To a solution of urea (36.03 g, 0.6 mol) and benzil (63.06 g, 0.3 mol) in benzene (1200 mL) was added trifluoroacetic acid (60 mL) and refluxed with Dean-Stark trap until no water was formed. White solid product was filtered and washed with cold ethanol. Drying with high vacuum gave 83.5 g (95%) of product. ^{1}H NMR (300 MHz; DMSO) 7.70 (s, 4H, NH) 7.01 (m, 10H, arom) HRMS (FAB) calculated for $C_{16}H_{14}N_4O_2H^+$, 295.1184

4,4,5,5-Tetracyanocyclohexene (6). Butadiene (0.84 g, 15.5 mmol) from gas tank was condensed with cold finger at -78 ^{o}C. Then tetracyanoethylene (2 g, 12.6 mmol) in tetrahydrofuran (15 mL) was added at -78 ^{o}C.

Temperature was raised to room temperature and stirred 30 min. Evaporation of THF and washing the residue with ether gave 1.83 g (85%) of product. ^{1}H NMR (300 MHz; $CDCl_3$) 5.93 (t, 2H, J = 1.6, -CH=CH-) 3.16 (d, 4H, J = 1.6, CH_2) HRMS (EI) calculated for $C_{10}H_6N_4$ 182.0592; found for 182.0538.

4-Cyclohexene-1,1,2,2-tetracarboxylric diimide (7). 4,4,5,5-Tetracyanocyclohexene **6** (4.03 g, 22.1 mmol) was refluxed in conc. H_2SO_4 (25 mL) for 5h. The reaction mixture was cooled in freezer in 1 hr. White crystal precipitate. The crystals were filtered. Washing the solid product with cold water (10 mL) gave 0.93 g (19%) of product. ^{1}H NMR (300 MHz; DMSO) 11.08 (s, 2H, NH) 5.92 (t, 2H, J = 2.8, -CH=CH-) 2.59 (d, 4H, J = 2.8, CH_2) HRMS (FAB) calculated for $C_{10}H_8N_2O_4Na^+$ 243.0382 found for 243.0379.

1,4-Dimethoxy-2,3-dimethylbenzene (9), 1.4-Dimethoxy-2,3-dibromomethylbenzene (10). The synthesis and characterization of the compound **9** and **10** are reported in reference 10C.

1,4-Dimethoxy-2,2-dicyanomethylbenzene (11). To a solution of 8.13 g (25.1 mmol) of compound **10** in 160 mL DMF was added 2.70 g (55.1 mmol) sodium cyanide ad stirred for an hour. DMF was evaporated at reduced pressure and residue was washed with 500 mL of $CHCl_3$. Evaporation of $CHCl_3$ gave 5.41 g (99%) of product. ^{1}H NMR (300 MHz; $CDCl_3$) 6.83 (s, 2H, arom) 3.79 (s, 6H, OMe) 3.77 (s, 4H, CH_2CN) HRMS (EI) calculated for $C_{12}H_{12}N_2O_2$, 216.0899; found for 216.0874.

2-Amino-1-cycano-1,2-ene-4,7-dimethoxyindan (12). To a solution of 8.7 g (40.2 mmol) of compound **11** in 80 mL of ethanol was added 0.3 mL of NaOEt/EtOH (50 mg of Na 1 mL of EtOH) and refluxed for 6 hrs. Acetic acid (1 mL) was added to the reaction mixture and stirred for 10 min. Evaporation of ethanol gave the 8.05 g (97%) of product . ^{1}H NMR (300 MHz; $CDCL_3$) 6.68 (d, 1H, J = 8.8, arom) 6.46 (d, 1H, J = 8.8, arom) 5.03 (br, 2H, NH_2) 3.79 (s, 3H, Ome) 3.74 (s, 3H, Ome) 3.44 (s, 2H, CH_2) HRMS (EI) calculated for $C_{12}H_{12}N_2O_2$, 216. 0899 ; does not give right mass spectrum.

4,7-Dimethoxy-2-indanone (13). To a solution of 8.05 g (37.2 mmol) of compound **12** in 260 mL of acetic acid was added 16 mL of H_2O and 105 mL of H_3PO_4. The reaction mixture was refluxed for 24 hrs. Acetic acid was evaporated at reduced pressure and reaction mixture was poured into 300 mL of water. The resulting mixture was extracted with 100 mL of $CHCl_3$ layer was washed with 50 mL of sat. $NaHCO_3$ aqueous solution 3 times and 100 mL of cold water 2 times. Drying organic layer over $MgSO_4$ and evaporation gave 5.75 g (80%) of product. ^{1}H NMR (300 MHz; $CDCL_3$) 6.70 (s, 2H, arom) 3.78 (s, 6H, OMe) 3.45 (s, 4H, CH_2) HRMS (EI) calculated for $C_{11}H_{12}O_3$, 192.0786; found for 192.0723

4,7-Dimethoxy-2-indanol (14). To a solution of 2.29 g (11.9 mmol) of compound **13** in a mixture of 80 mL of ethanol and 50 mL of CH_2Cl_2 was added 0.56 g (14.8 mmol) of $NaBH_4$ in 100 mL of ethanol dropwise and stirred for an hour. Reaction mixture was poured into 400 mL of 1 N H_3PO_4 aqueous solution and extracted with 100 mL chloroform 3 times. Drying with $MgSO_4$ and evaporation gave the 1.84 g (85%) of product. ^{1}H NMR (300 MHz; $CDCl_3$) 6.62 (s, 2H, arom) 4.67 (br, 1H, CHOH) 3.75 (s, 6H, OMe) 3.15 (dd, 2H, J = 6.2, 6.7 CH_2 in five membered ring) 2.90 (dd, 2H, J = 6.2, 6.7 CH_2 in five membered ring).

2-Benzyloxy-4,7-dimethoxyindane (15). To a solution of 15.14 g (78.0 mmol) of compound **14** was added 4.5 g (11.2 mmol, 1.4eq, 60% dispersion in mineral oil, washed with hexane) of NaH and stirred for 30 min. Then, 16 g (93.5 mmol, 1.2 eq) of benzyl bromide was added dropwise at 0 ^{o}C. Temperature of reaction mixture was raised to room temperature and stirred for 24 hrs. Reaction mixture was poured into 500 mL of water and extracted with 200 mL of $CHCl_3$ 3 times. Evaporation of chloroform and column chromatography on the silica gel gave 19.7 (89%) of product. ^{1}H NMR (300 MHz; $CDCL_3$) 7.27 (m, 5H, arom) 6.59 (s, 2H, atom) 4.41 (m, 1H, CHO-) 4.53 (d, 2H, J = 4.8, CH_2Ph) 3.74 (s, 6H, OMe) 3.15 (dd, 2H, J = 15,9, 6.3, CH_2 in five membered ring) 3.10 (dd, 2H, J = 15.9, 6.3, CH_2 in five membered ring) HRMS (EI) calculated for $C_{18}H_{20}O_3$, 284.1412; found for 284.1490

2-Benzyloxy-5,6-dichloromethyl-4,7-dimethoxyindane (16). To a solution of 1.09 g (3.83 mmol) of compound **15** in 8ml of chloromethyl methyl ether was added 8ml of 60% H_2SO_4 at 40 °C and stirred for 24 hrs. Reaction mixture was poured into 200 mL of water and extracted with 100 mL of $CHCl_3$ 3 times. Drying with $MgSO_4$ and evaporation gave 1.27 g (88%) of product. ^{1}H NMR (300 MHz; $CDCl_3$) 7.33 (m, 5H, arom) 4.82 (s, 4H, CH_2Cl) 4.58 (s, 2H, CH_2Ph) 4.45 (m, 1H, CHO) 3.86 (s, 6H, OMe) 3.25 (dd. 2H, *J* = 16.4, 6.5, CH_2 in five membered ring) 3.09 (dd, 2H, *J* = 16.4, 6.5, CH_2 in five membered ring) HRMS (EI) calculated for $C_{20}H_{22}Cl_2O_3$, 380.0946 found for 380.0966.

1,6-(2-Benzyloxy-5,6-dichloromethyl-4,7-dimethoxyindane)-tetrahydro-3a,6a-diphenylimidazo[4,5]imidazole-2,5-(1H,3H)-dione (17). To a solution of 9.83 g (33.4 mmol) of diphenyl glycoluril in 300 mL of DMSO was added 5.62 g (100.2 mmol) of KOH at 100 °C and stirred for 20 min. 1.27 g (3.34 mmol) of compound **16** in 50 mL of DMSO was added dropwise and stirred for an hour. Reaction mixture was poured into 500 mL of water and precipitated white solid was filtered. Solid was boiled with 200 mL of CH_2Cl_2 and filtered. This boiling and filtering was repeated 3 times. Evaporation of CH_2Cl_2 and chromatography on silica gel gave 0.66 g (65%) of mixture of two isomer. HRMS (EI) calculated for $C_{36}H_{34}N_4O_5$, 602.2529; found for 602.2518.

1.6-(2-Benzyloxy-5,6-Dichloromethyl-4,7-dimethoxyindane)-3-(propionyl)-tetrahydro-3q,6a-diphenylimidazo-[4,5d]imidazole-2,5-(1H,3H)-dione (18). To a solution of 0.8 g (1.33 mmol) of mixture of two isomer **17a** and **17b** in 15 mL of pyridine was added 0.85 mL (6.64 mmol) of propionic anhydride and refluxed 7 hrs. Evaporation of pyridine and column chromatography on the silica gel gave 165 mg of nonpolar isomer, 183 mg of polar isomer, and 278 mg of mixture of two isomer (72% of total yield) nonpolar isomer. ^{1}H NMR (300 MHz; $CDCl_3$) 7.14 (m, 15H, arom) 6.13 (s, 1H, NH) 5.62 (d, 1H, *J* = 15.6, CH_2N) 5.53 (d, 1H, *J* = 15.9, CH_2N) 4.61 (s, 2H, CH_2Ph) 4.41 (m, 1H, CHO-) 3.95 (s, 3H, OMe) 3.93 (s, 3H, OMe) 3.85 (d, 1H, *J* = 15.6, CH_2N) 3.72 (d, 1H, *J* = 15.9, CH_2N) 3.25 (m, 2H, CH_2 in five membered ring) 3.04 (m, 4H, CH_2 in five membered ring + CH_2C=O) 1.04 (t, 3H, *J* = 7.2) polar isomer ^{1}H NMR (300 MHz; $CDCl_3$) 7.10 (m, 15H, arom) 1.07 (s, 1H, NH) 5.57 (d, 1H, *J* = 16.5, CH_2N) 5.47 (d, 1H, *J* = 15.9) 4.50 (s, 2H, CH_2Ph) 4.40 (d, 1H, *J* = 16.5, CH_2N) 3.68 (d, 1H, *J* = 15.9, CH_2N) 3.10 (m, 6H, CH_2 in five membered ring + CH_2C=O) 0.98 (t, 3H, *J* = 7.2) HRMS (FAB) calculated for $C_{39}H_{38}N_4O_6H^+$, 659.2870 found for 659.2884.

1,6-(2-Benzyloxy-5,6-dichloromethyl-4,7-dimethoxyindane)-tetrahydro-3q,6a-diphenylimidazo[4,5d]imidazol-2,5-(1H,3H)-dione (17). To a solution of 160 mg (0.24 mmol) of compound **18** in 20 mL of THF was added 20 drops of saturated aqueous LiOH and stirred for 20 hrs. 10 drops of saturated aqueous NH_4Cl was added. Drying over $MgSO_4$, filtration and evaporation gave 133 mg (98%) of product. Nonpolar isomer ^{1}H NMR (300 MHz, $CDCl_3$) 7.33 (m, 15H, arom) 5.72 (s, 2H, NH) 5.50 (d, 2H, *J* = 15.9, CH_2N) 4.60 (s, 2H, CH_2Ph) 4.38 (m, 1H, CHO) 3.38 (s,6H, OMe) 3.67 (d, 2H, *J* = 15.9, CH_2N) 3.24 (dd, *J* = 15.5, 7.2, 2H, CH_2N in five membered ring) 2.99 (dd, *J* = 15.5, 7.2, 2H, CH_2 in five membered ring) polar isomer ^{1}H NMR (300 MHz; $CDCl_3$) 7.16 (m, 15H, arom) 5.63 (s, 2H, NH) 5.57 (d, 2H, *J* = 15.9, CH_2N) 4.54 (s, 2H, CH_2Ph) 4.45 (m, 1H, CHO) 3.87 (s, 6H,OMe) 3.71 (d, 2H, *J* = 15.9, CH_2N) 3.19 (dd, 2H, *J* = 16.5, 5.8, CH_2 in five membered ring) 3.07 (dd, 2H, *J* = 16.5, 5.8, CH_2 in five membered ring).

1,6-(2-Benzyloxy-5,6-dichloromethyl-4,7-dimethyloxyindane)-3,4-(di-tertbutoxycarbonyl)-tetrahydro-3a,6a-diphenylimidazo[4,5d]iminazole-2,5-(1H,3H)-dione (19). To a solution of 78 mg (0.3 mmol) of compound **17** in a mixture of 3 mL of CH_3CN and 2 mL of THF was added catalytic amount of DMAP and 56.5 mg (0.26 mmol) of di-tert-butyl dicarbonate and stirred for 24 hrs. Evaporation of solvent and column chromatography on the silica gel gave 81.5 mg (96%) of product. Nonpolar isomer ^{1}H NMR (300 MHz, $CDCl_3$) 7.08 (m, 15H, arom) 5.54 (d, 2H, *J* = 1.63, CH_2N) 4.56 (s, 2H, CH_2Ph) 4.34 (m, 1H, CHO) 3.91 (s, 6H, OMe) 3.65 (d, 2H, *J* = 16.3, CH_2N) 3.20 (dd, 2H, *J* = 15.5, 7.0, CH_2 in five membered ring) 1.96 (dd, 2H, *J* = 7.0, CH_2 in five membered ring) 1.33 (s, 18H, $C(CH_3)_3$) polar isomer ^{1}H NMR (300 MHz; $CDCl_3$) 7.12 (m, 15H, arom) 5.58 (d, 2H, *J* = 15.7, CH_2N) 4.56 (s, 2H, CH_2Ph) 4.45 (m, 1H, CHO) 3.92 (s, 6H, OMe) 8.73 (d, 2H, *J* = 15.7, CH_2N) 3.18 (dd, 2H, *J* = 16.4, 5.5, CH_2 in five membered ring) 3.08 (dd, 2H, *J* = 16.4, 5.5, CH_2 in five membered ring) 1.38 (s, 18H, $C(CH_3)_3$) HRMS (EI) calculated for $C_{36}H_{34}N_4O_5$, 602.2529; found for 602.2581.

1,6-(4,7-dimethoxy-2-indanol)-3,4-(di-tert-butoxycarbonyl)-tetrahydro-3a,6a-diphenylimidazo[4,5d]imidazole-2,5-(1H,3H)-dione (20). To a solution of 0.370 g (0.461 mmol) of the compound **19** in the mixture of 4 mL THF, and 0.5 mL MeOH was added ~50 mg 10% Pd/C, and the mixture stirred under a hydrogen balloon for 14 h. Filtration and evaporation of the solvent gave 0.32 g (98%) of the product as a colorless solid. Nonpolar isomer ^{1}H NMR ($CDCl_3$): 7.08 (m, 10H, arom) 5.58 (d, 2H, *J* = 15.8, CH_2N), 4.67 (m, 1H, CHOH), 3.94 (s, 6H, OMe), 3.73 (d, 2H, *J* = 15.8, CH_2N), 3.20 (dd, 2H, *J* = 6.4, 16.1, CH_2 in five membered ring), 2.85 (dd, 2H, *J* = 6.4, 16.1, CH_2 in five membered ring) 1.96 (br, s, 1H, CHOH), 1.37 (s, 18H, $C(CH_3)_3$). Polar isomer ^{1}H NMR ($CDCl_3$): 7.15 (m, 10H, arom) 5.53 (d, 2H, *J* = 15.8, CH_2N) 4.68 (br, 1H, CHOH) 3.89 (s, 6H, OMe) 3.69 (d, 2H, *J* = 15.8, CH_2N) 3.18 (dd, 2H, *J* = 16.8, 5.4, CH_2 in five membered ring) 2.90 (dd, 2H, *J* = 16.8, 5.4, CH_2 in five membered ring) 2.05 (s, 1H, OH) 1.38 (s, 18H, $C(CH_3)_3$) HRMS (FAB) calculated for $C_{39}H_{44}N_4O_9Cs^+$, 845.2163; found for 845.2188.

Compound 21. To a solution of 0.06 g (0.0842 mmol) of the compound **20**, 0.009 g (0.0421 mmol) diimide, and 0.031 g (0.126 mmol) PPh_3 in 1 mL THF was added 0.0198 mL (0.126 mmol) diethylazodicarboxylate. After stirring for 12 h, the solvent was evaporated and the residue chromatographed on silica gel (50-70% ethyl acetate/hexanes) to give 0.034 g (20%) of the product as a colorless form. Nonpolar

isomer ^{1}H NMR ($CDCl_3$): 7.04 (m, 20H, arom) 5.97 (m, t, 2H, J = 2.2, -CH=CH-) 5.55 (d, 4H, J = 15.8, CH_2N) 5.01 (m, 2H, CHN) 3.88 (s, 12H, OMe) 3.78 (d, 4H, J = 15.8, CH_2N) 3.27 (d, 8H, J = 8.2, CH_2 in five membered ring) 2,72 (d, 4H, J = 2.4) 13.6 (s, 36H, $C(CH_3)_3$). Polar isomer ^{1}H NMR ($CDCl_3$): 6.98 (m, 20H, arom) 6.08 (t, 2H, J = 2.7, CH=CH) 5.58 (d, 4H, J = 15.8, CH_2N) 4.89 (m, 2H, CHN) 3.94 (s, 12H, OMe) 3.73 (d, 4H, J = 15.8, CH_2N) 3.53 (dd, 4H, J = 14.5, 10.3, CH_2 in five membered ring) 3.10 (dd, 4H, J = 14.5, 10.3, CH_2 in five membered ring) 2.85 (d, 4H, J = 2.7, =CH-CH_2) 1.39 (s, 36H, $C(CH_3)_3$) HRMS (FAB) calculated for $C_{88}H_{92}N_{10}O_{20}Cs^+$, 1741.5544 found for 1741.5635.

Compound 22. To a solution of 40 g (0.0248 mmol) of the compound **21** in 2 mL ethyl acetate was added ~20 mg 5% Pd/C, and the mixture stirred under a hydrogen balloon for 14 h. Filtration and evaporation of the solvent gave 0.040 g (78%) of the product as a colorless form. Nonpolar isomer ^{1}H NMR ($CDCl_3$): 7.05 (m, 20H, arom) 5.55 (d, 4H, J = 15.8, CH_2N) 5.03 (m, 2H, CHN) 3.88 (s, 12H, OMe) 3.78 (d, 4H, J = 15.8, CH_2N) 3.27 (d, 8H, CH_2 in five membered ring) 2.13 (m, 4H, six membered ring in the center) 150 (m, 4H, six membered ring in the center) 1.39 (s., 36H, $C(CH_3)_3$) polar isomer ^{1}H NMR ($CDCl_3$): 6.98 (m, 20H, arom) 5.58 (d, 4H, J = 15.8, CH_2N) 4.89 (m, 2H, CHN) 3.94 (s, 12H, OMe) 3.73 (d, 4H, J = 14.5, 10.3, CH_2 in five membered ring) 2.09 (s, 4H, six membered ring in the center) 1.43 (s, 4H, six membered ring in the center) 1.39 (s, 36H, $C(CH_3)_3$) HRMS (FAB) calculated for $C_{88}H_{94}N_{10}O_{20}Cs^+$, 1743.5538; found for 1743.5592.

Compound 1. To a solution of 0.042 g (0.026 mmol) of the compound **22** in 3 mL CH_2Cl_2 at -78 °C was added 0.1 mL BBr_3. After warming to RT and stirring for 14 h, 2 mL of MeOH were added and the solvents evaporated. Following three additional MeOH additions and evaporations, the residue was subjected to high vacuum with mild heating (~50 °C) to give 0.030 g (85%) of the product as a colorless solid. Nonpolar isomer ^{1}H NMR (DMF-d_6): 8.24 (s, 4H, OH) 8.12 (s, 4H, NH) 7.16 (m, 20H, arom) 5.42 (d., 4H, J = 15.6, CH_2N) 4.95 (m, 2H, CHN) 3.87 (d, 4H, J = 15.6, CH_2N) 3.22 (d, 8H, J = 8.5, CH_2 in five membered ring) 2.21 (s, 4H, six membered ring in the center) 1.53 (s, 4H, six membered ring in the center). Polar isomer ^{1}H NMR (DMSO-d_6) 8.11 (s, 8H, CH + OH) 7.05 (m, 20H, arom) 5.37 (d, 4H, J = 15.5, CH_2N) 4.78 (m, 2H, CHN) 3.48 (d, 4H, J = 15.5, CH_2N) 3.09 (m, 8H, CH_2 in five membered ring) 2.09 (s, 4H, six membered ring in the center) 1.43 (s, 4H, six membered ring in the center) plasma desorption mass spectroscopy calculated for 1154; found for 1154 HRMS (FAB) calculated for $C_{64}H_{54}N_{10}O_{12}Cs^+$, 1287.2979; found for 1287.2963.

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