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 Cram3 and Collet4 but this dimer is formed reversibly.

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-

![Figure 1. The large volume self-assembling dimeric molecule (a) Energy minimized dimeric structure (b) Two dimensional monomeric structure.](image)

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

<table>
<thead>
<tr>
<th></th>
<th>N-H-----O</th>
<th>O-H------O</th>
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<tbody>
<tr>
<td>length</td>
<td>2.76 Å</td>
<td>2.68 Å</td>
</tr>
<tr>
<td>angle</td>
<td>161~162°</td>
<td>167°</td>
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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 benzyl bromide 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 with 60% H₂SO₄ 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 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 stereoisomerically 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-butyldicarbonate and DMAP to give 19. Then the benzyl group was removed using H₂/5% Pd-C to give compound 20. Double Mitsunobu reaction of compound 20 and central diimide 7 gave the compound 21. The olefin of the central diimide 21 proved unstable to BBr₃ 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
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 these solvents is shown in Figure 8. In addition, the nonpolar isomer was soluble CDCl$_3$, CH$_2$Cl$_2$, C$_6$D$_6$, toluene-d$_8$, THF-d$_8$, and acetone-d$_6$. The $^1$H NMR spectra in CDCl$_3$, CH$_2$Cl$_2$, C$_6$D$_6$, toluene-d$_8$, THF-d$_8$, acetone-d$_6$, <50% DMF-d$_6$/CD$_2$Cl$_2$, 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 hydrogen bonded, and two do not. The $^1$H NMR of the non-polar 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$_2$Cl$_2$, 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
observation from the spectral data is that $^1$H NMR of the nonpolar isomer showed two kinds of peaks for 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 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 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.

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

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 4-4-phenylenegroup to improve the solubility of the molecule. Figure 11 showed 1H 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. 1H NMR (300 MHz; CDCl3) 6.83 (s, 2H, arom) 3.79 (s, 6H, OMe) 3.77 (s, 4H, CH2CN) HRMS (EI) calculated for C12H12N2O2, 284.1490; found for 284.1482.

4,4,5,5-Tetracyanocyclohexene (6). Butadiene (0.84 g, 15.5 mmol) from gas tank was condensed with cold finger at -78 °C. Then tetracyanoethylene (2 g, 12.6 mmol) in tetrahydrofuran (15 mL) was added at -78 °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. 1H NMR (300 MHz; DMSO) 7.70 (s, 4H, NH) 7.01 (m, 10H, arom) HRMS (FAB) calculated for C18H14N6O2H+ 295.1184; found for 295.0914.

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2-Benzoyl-5,6-dichloromethyl-4,7-dimethoxyindane (16). To a solution of 1.09 g (3.83 mmol) of compound 15 in 8 ml of chloromethyl methyl ether was added 8 ml of 60% H$_2$SO$_4$ 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$_2$Cl) 4.58 (s, 2H, CH$_2$Ph) 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) polar isomer HRMS (EI) calculated for C$_36$H$_{34}$N$_4$O$_5$, 659.2870; found for 659.2884.

1.6-(2-Benzoyl-5,6-dichloromethyl-4,7-dimethoxyindane)-3,4-(di-tert-butoxycarbonyl)-tetrahydro-3a,6a-diphenylimidazo[4,5d]imidazo[2,5-1H,3H]-dione (17). To a solution of 0.8 g (3.34 mmol) of mixture of two isomer 17a and 17b in 15 mL of pyridine was added 0.065 mL (0.43 mmol) of propionyl anhydride and refluxed for 30 min. 1.27 g (88%) of product. 1H NMR (300 MHz; CDCl$_3$) 7.33 (m, 15H, arom) 6.13 (s, 1H, NH) 5.54 (d, 2H, J $=$ 15.9, CH$_2$N) polar isomer HRMS (FAB) calculated for C$_{39}$H$_{38}$N$_4$O$_6$H$^+$, 602.2581.

1.6-(2-Benzoyl-5,6-dichloromethyl-4,7-dimethoxyindane)-3-propionyl-tetrahydro-3a,6a-diphenylimidazo[4,5d]imidazo[2,5-1H,3H]-dione (18). To a solution of 3.65 mg (0.026 mmol) PPh$_3$ in 1 mL THF was added 0.0108 g (0.0491 mmol) diimide, and THF was added 0.031 g (0.126 mmol) diimide was added 0.0198 mL (0.126 mmol) diethylazodicarboxylate. After stirring for 12 h, the solution 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 1H NMR (300 MHz; CDCl$_3$): 7.14 (m, 15H, arom) 6.13 (s, 1H, NH) 5.54 (d, 2H, J $=$ 15.9, CH$_2$N) $\delta$ (s, 6H, OMe) 8.73 (d, 2H, J $=$ 16.4, 5.5, CH$_2$ in five membered ring) 3.19 (dd, 2H, J $=$ 16.4, 5.5, CH$_2$ in five membered ring) polar isomer 1H NMR (CDCl$_3$): 7.12 (m, 15H, arom) 5.58 (d, 2H, J $=$ 15.9, CH$_2$N) 4.68 (br, 1H, CHOH) 3.89 (s, 6H, OMe) 8.73 (d, 2H, J $=$ 15.7, CH$_2$N) 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 (FAB) calculated for C$_{38}$H$_{42}$N$_4$O$_8$H$^+$, 625.2928.

1.6-(4,7-dimethoxy-2-indanoyl)-3,4-(di-tert-butoxycarbonyl)-tetrahydro-3a,6a-diphenylimidazo[4,5d]imidazo[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 $=$ 15.9, CH$_2$N) 4.67 (m, 1H, CHO), 3.94 (s, 6H, OMe), 3.73 (dd, 2H, J $=$ 15.8, CH$_2$N) 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, CHO), 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$_2$N) 4.68 (br, 1H, CHO), 3.89 (s, 6H, OMe) 3.69 (d, 2H, J $=$ 15.8, CH$_2$N) 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$_{42}$N$_4$O$_8$C$_3$-, 845.2163; found for 845.2188.
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$_2$N) 5.01 (m, 2H, CHN) 3.88 (s, 12H, OMe) 3.78 (d, 4H, $J = 15.8$, CH$_2$N) 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$_2$N) 4.89 (m, 2H, CHN) 3.94 (s, 12H, OMe) 3.73 (d, 4H, $J = 15.8$, CH$_2$N) 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$_2$N) 5.03 (m, 2H, CHN) 3.88 (s, 12H, OMe) 3.78 (d, 4H, $J = 15.8$, CH$_2$N) 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$_2$N) 4.89 (m, 2H, CHN) 3.94 (s, 12H, OMe) 3.73 (d, 4H, $J = 15.8$, CH$_2$N) 3.53 (dd, 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) plasma desorption mass spectroscopy 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$_2$Cl$_2$ at -78 °C was added 0.1 mL BB$_3$. 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$_2$N) 4.95 (m, 2H, CHN) 3.87 (d, 4H, $J = 15.6$, CH$_2$N) 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$_6$): 8.24 (s, 4H, OH) 8.12 (s, 4H, NH) 7.16 (m, 20H, arom) 5.42 (d, 4H, $J = 15.6$, CH$_2$N) 4.95 (m, 2H, CHN) 3.87 (d, 4H, $J = 15.6$, CH$_2$N) 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) plasma desorption mass spectroscopy calculated for C$_{64}$H$_{54}$N$_{10}$O$_{12}$Cs$^+$, 1287.2979; found for 1287.2963.

References