Nano-scaled Deep-Cavity Cavitands

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The potential applicabilities of container molecules are being expanded from molecular recognition systems or molecular storages to controlled molecular releasing systems or molecular reactors.[1,2] Methylene-bridged resorcin[4]arene cavitands have been used for a variety of purposes because of their rigid structures, bowl-shaped cavities, and efficient synthetic accessibility. The dimensions of these cavitands have been manipulated by extending the bridging units between hydroxy groups of adjacent resorcinolic units or by fencing on the 2-position of resorcinolic units. Cram *et al.*[3] used the former stategy and Rebek *et al.*[4] have been very successful to obtain many smart cavitands or molecular capsules using the latter strategy.

Here, the syntheses and identification of nano-scaled deep-cavity cavitands by the combination of two strategies were described. By fencing with dimethyl 5-hydroxyisophthalate on tetrakis(bromomethyl)cavitand **1**, octaester **2** was easily constructed. Subsequently nano-scaled deep-cavity cavitands **5a**, **5b**, and **6** whose upper-rim dimensions were controlled by variation of diamines (ethylenediamine, 1,3-diaminopropane, *m*-xylylenediamine) were obtained. The energy-minimized structure (MM+ Force-Field) of octaamidocavitand **5b** showed that its dimensions are larger than those of γ-cyclodextrin.[5]

Results and Discussion

Heptyl-feet bromocavitand **1** was synthesized by a known procedure[6] and transformed to the fenced octaester **2** in 62% yield by treatment with an excess of dimethyl 5-hydroxyisophthalate (Scheme 1). Octaester **2** was hydrolyzed to octacarboxylic acid **3** by 10% aqueous tetramethylammonium hydroxide in refluxing THF. *Via* acid chloride **4**, various octaamidocavitands **5a**, **5b**, and **6** were obtained by bridging with various diamines (ethylenediamine, 1,3-diaminopropane, and *m*-xylylenediamine) under high dilution conditions. All Octaamidocavitands **5a**, **5b**, and **6** were characterized by ^{1}H-NMR, FAB+ mass, and FT-IR spectra.

CPK molecular model studies suggest that octaamidocavitands **5a**, **5b**, and **6** have a cavity large enough to include C_{60} (diameter, 1.00 nm)[7] or even larger guest. The energy-minimized structure (MM+ Force-Field using HyperChem®) shows that the dimensions of octaamidocavitands **5b** are larger, especially in depth, than those of γ-cyclodextrin (*e.g.*

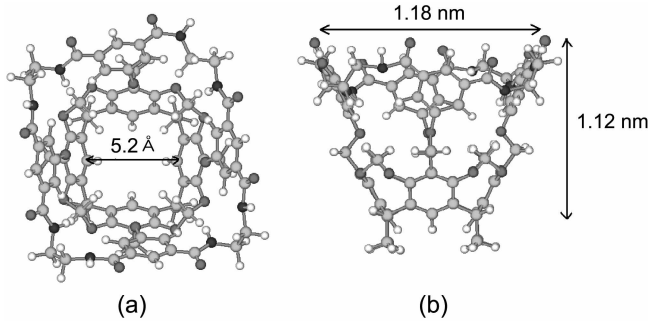


Figure 1. Energy-minimized structures (MM+ Force-Field) of **5a** ((a) top view, (b) side view).

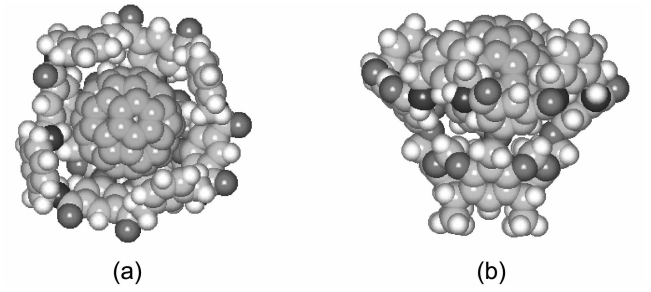
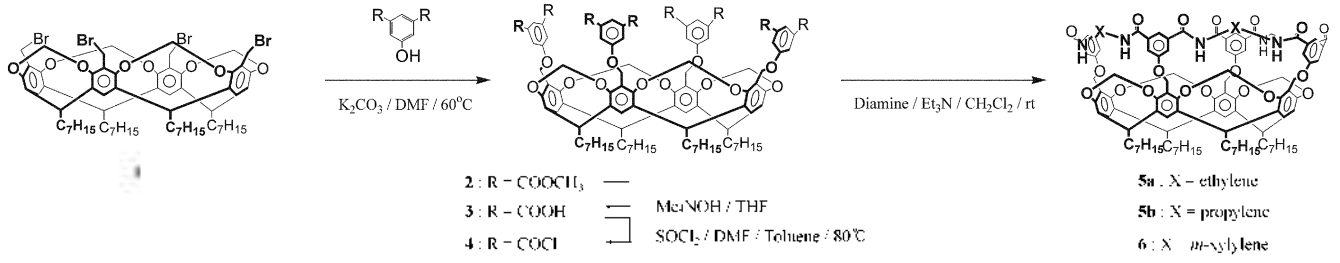


Figure 2. Energy-minimized structures of **6**@C_{60} ((a) top view, (b) side view).



Scheme 1. Synthesis of Octacarboxylic acid **3** and Octaamidocavitands **5a**, **5b**, and **6**.

1.38 *vs.* 1.32 nm for wide gate, 1.12 *vs.* 0.78 nm for depth). The wide-gate diameters of cavitands **5a** and **6** are calculated to be 1.18 and 1.49 nm, respectively.

Molecular mechanics calculation (MM+ Force-Field) using HyperChem® showed that the stabilization energies of the complexes of hosts **5a**, **5b**, and **6** with C_{60} in nesting fashion are about 305, 275, and 625 kcal/mol, respectively. The large stability of host **6**@C_{60} may be due to their most probable π-π interaction as shown on Figure 2. But unfortunately spectrometric evidences cannot be confirmed.

In summary, deep cavity cavitands **5a**, **5b**, **6** of nanometric dimensions were obtained through 4-step synthetic routes from bromocavitand **1**. These cavitands having larger cavity dimensions than cyclodextrins could be used as an open-ended molecular containers in various purposes.

Experimental Section

General. All chemicals were reagent grade (Aldrich) and used directly unless otherwise specified. All anhydrous reactions were conducted under argon or nitrogen atmosphere. Melting points were measured on a electrothermal 9100 apparatus and uncorrected. The ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) in $CDCl_3$ unless stated otherwise. FT-IR spectra were taken with a Mattson 3000 FT-IR spectrometer. FAB+ mass spectra were run on a HR MS (VG70-VSEQ) at Korea Basic Science Institute using *m*-nitrobenzyl alcohol as a matrix. Gravity column chromatography was performed on silica gel 60 (E. Merck, 70-230 mesh ASTM). Flash chromatography was performed on silica gel 60 (E. Merck, 230-400 mesh ASTM). Thin layer chromatography was done on silica plastic sheets (E. Merck, silica gel 60 F_{254}, 0.2 mm).

Octaester 2. Tetrabromomethyl cavitand **1** (10 g, 7.69 mmol), dimethyl 5-hydroxyisophthalate (9.69 g, 6 eq.), catalytic amount of *n*-Bu_4NI and K_2CO_3 (8.50 g, 8 eq.) were dissolved in 50 mL of dry DMF. The mixture was stirred overnight at 65°C under argon atmosphere. After cooling to room temperature, the mixture was filtered through glass filter. The solution was partitioned with CH_2Cl_2 and 3 N HCl. The organic phase was separated and washed with water, brine, and then dried over $MgSO_4$. It was concentrated and purified by silica gel column chromatography with Hexane : EtOAc (3 : 1) as a mobile phase and the product was recrystallized from hexane to give a white solid product **2** (8.66 g, yield 62%): mp > 178 °C dec; FT-IR (KBr) 1727 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) 0.89 (t, 12H, CH_3), 1.24-1.45 (m, 40H, $CH_2(CH_2)_5CH_3$), 2.29 (m, 8H, $CH_2(CH_2)_5CH_3$), 3.84 (s, 24H, upper ArCOOCH_3), 4.59 (d, 4H, inner OCH_2O), 4.87 (m, 4H, methine), 4.98 (s, 8H, ArCH_2Ar), 5.80 (d, 4H, outer OCH_2O), 7.29 (s, 4H, Ar*H*), 7.78 (s, 8H, upper Ar*H*), 8.27 (s, 4H upper Ar*H*).

Octacarboxylic acid 3. Octaester **2** (5 g, 2.75 mmol) and 10% tetramethylammonium hydroxide (30 mL) were mixed in 50 mL of THF. The mixture was refluxed overnight and then cooled to room temperature and concentrated under vacuum. The mixture was partitioned between 30 mL of 3 N NaOH and 30 mL of Et_2O. After 6 N HCl was slowly added to the aqueous phase, the mixture was extracted with Et_2O. The organic phase was separated and washed with water. Hexane was added to give a white solid product (4.46 g, yield 95%): mp > 245 °C dec; FT-IR (KBr) 3300 cm^{-1} (ν_{O-H}), 1703 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR (400 MHz, Acetone-d_6) 0.91 (t, 12H, CH_3), 1.27-1.46 (m, 40H, $CH_2(CH_2)_5CH_3$), 2.48 (m, 8H, $CH_2(CH_2)_5CH_3$), 4.62 (d, 4H, inner OCH_2O), 4.92 (m, 4H, methine), 5.15 (s, 8H, ArCH_2Ar), 5.98 (d, 4H, outer OCH_2O), 7.77 (s, 8H, upper Ar*H*), 7.84 (s, 4H, Ar*H*), 8.25 (s, 4H upper Ar*H*).

Octaamido cavitand 5a, 5b, 6. Octacarboxylic acid **3** (1 g, 0.59 mmol), 15 mL of thionyl chloride and catalytic amount of DMF were dissolved in 30 mL of toluene. The reaction mixture was warmed to 80°C under argon atmosphere and stirred until all solids were dissolved. The mixture was cooled to room temperature and the solvent and excess thionyl chloride were removed under vacuum. Dry toluene was added and then the solution was concentrated under vacuum again to give octaacid chloride cavitand **4** (1.09 g, 0.59 mmol). It was dissolved in dry CH_2Cl_2 (100 mL) and added for 6 hrs together with a separate solution of diamine (4 eq.) in dry CH_2Cl_2 (100 mL) to a solution of triethylamine (8.02 mL, 100 eq.) at room temperature. The mixture was stirred for 3 days and then washed with 2 N HCl, water, and brine. The organic phase was separated and acetone was added slowly to precipitate polymeric byproducts. The precipitate was filtered through glass filter. The filtrate was concentrated and the residue was purified by silica gel column chromatography (4% MeOH in CH_2Cl_2).

5a. 34 mg (3.0% yield); mp > 189°C dec; FT-IR (KBr) 3380 cm^{-1} (ν_{N-H}), 1640 cm^{-1} ($\nu_{C=O}$); FAB+ mass m/z 1800.8; ^{1}H NMR (400 MHz, $CDCl_3$) 0.90 (t, 12H, CH_3), 1.04 (s, 24H, NHCH$_2CH_3$), 1.26-1.44 (m, 40H, $CH_2(CH_2)_5CH_3$), 2.32 (m, 8H, $CH_2(CH_2)_5CH_3$), 3.71 (m, 16H, NHCH_2CH_2NH), 4.23 (d, 4H, inner OCH_2O), 4.84 (m, 4H, methine), 4.98 (s, 8H, ArCH_2Ar), 5.81 (d, 4H, outer OCH_2O), 7.20-7.35 (m, 4H, Ar*H*), 7.55 (m, 8H, upper Ar*H*), 7.88 (m, 4H upper Ar*H*).

5b. 46 mg (3.9% yield); mp > 189°C dec; FT-IR (KBr) 3388 cm^{-1} (ν_{N-H}), 1647 cm^{-1} ($\nu_{C=O}$); FAB+ mass m/z 1858.4; ^{1}H NMR (400 MHz, Acetone-d_6) 0.90 (t, 12H, CH_3), 1.29-1.43 (m, 40H, $CH_2(CH_2)_5CH_3$), 1.97 (m, 8H, NHCH$_2CH_2$-CH$_2$NH), 2.32 (m, 8H, $CH_2(CH_2)_5CH_3$), 3.41-3.53 (m, 16H, NHCH_2CH$_2CH_2$NH), 4.80-4.82 (d, J = 8, 4H, inner OCH_2O), 4.87 (m, 4H, methine), 5.48 (s, 8H, ArCH_2Ar), 6.10 (d, 4H, outer OCH_2O), 7.05 (s, 8H, NHCH$_2$CH$_2$CH$_2NH$), 7.70-7.74 (m, 4H, Ar*H*), 7.81-8.22 (m, 8H, upper Ar*H*), 8.40 (m, 4H upper Ar*H*).

6. 78 mg (5.9% yield); mp > 189°C dec; FT-IR (KBr) 3392 cm^{-1} (ν_{N-H}), 1653 cm^{-1} ($\nu_{C=O}$); FAB+ mass m/z 2106.0; ^{1}H NMR (400 MHz, Acetone-d_6) 0.90 (t, 12H, CH_3), 1.29-1.44 (m, 40H, $CH_2(CH_2)_5CH_3$), 2.45 (m, 8H, $CH_2(CH_2)_5CH_3$), 4.39-4.43 (m, 16H, NHCH_2ArCH_2NH), 4.80-4.82 (d, 4H, inner OCH_2O), 4.89 (m, 4H, methine), 5.05 (s, 8H, ArCH_2Ar), 6.05 (d, 4H, outer OCH_2O), 7.12-7.41 (m, 8H,

NH$CH_2CH_2CH_2$*NH*), 7.25-7.51 (m, 4H, Ar*H*), 7.77-7.88 (m, 8H, upper Ar*H*), 8.38 (m, 4H upper Ar*H*).

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