C_{4v} Hemicarcerand Having Four Five-Atom Pillars with Amide Functionality

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Carcerand is an organic host compound which complexes small compound(s) within its cavity and the complexed guest molecule cannot escapes even at elevated temperature without breaking host's covalent bond(s). So it exists as carceplex instead of carcerand.[1] Carceplex possesses many unprecedented issues regarding the phase state of the inner guest and the isomerisms. In some cases the occupancy of guest within host cavity allocates the phase of guest between liquid and gas phase[2] and the new isomerisms, carceroisomer[3] and twistomer,[4] can be observed.

Usually carceplexes are convergently synthesized *via* the final capping or shell-closing reaction of two functionalized cavitands. Resorcin[4]arene-based cavitands have been manipulated in various kinds of functionality and have been used as well organized northern or southern hemispheres of container molecules.[5] The number and the length of the bridging units (pillars, X in Figure 1) between two hemispheres determine the final container molecules to be cavitand, hemicarcerand, or carceplex.

Generally resorcin[4]arene-based carceplexes need four pillars composed of less than 5 atoms such as **1** (X = a-c) in Figure 1. The final shell-closing reactions for prototype carceplexes **1a**[6] and **1b** (n = 1)[2] were accomplished in surprisingly high yields in proper solvents such as DMF, DMSO, or DMA which acted as an efficient template and stayed as a complexed guest. Carceplex DMF@**1c** having flattened five-atom pillars formed portals through which acetonitrile can transport reversibly at room temperature resulting in the manipulable "paired carceroisomers".[7] But the container hosts having sulfur-incorporated five-atom pillars (**1d**)[4c] or six-atom pillars (**1b** (n = 4)[8] or **1e**[9]) are used to be hemicarcerands which have portals large enough for the transport of guest molecule with a substantial energy barrier.

New container host **1f** was designed and synthesized. The pillar **f** is a five-atom bridge containing an amide group, which is shorter than **b** (n = 3), but longer than **c**. Container host **1f** seems to be a carceplex **G@1f** and possibly its carceroisomers could be observed at ambient temperature due to its C_{4v} symmetry and the potential hydrogen bonding between host's amide group and a polar guest.

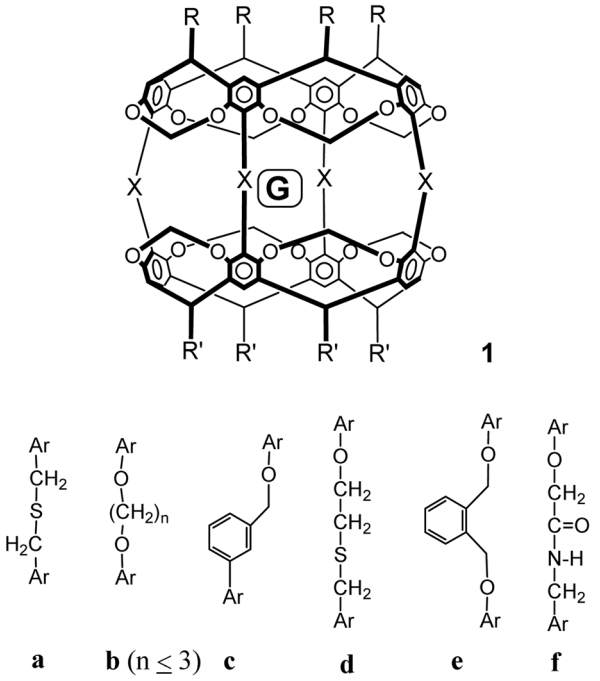
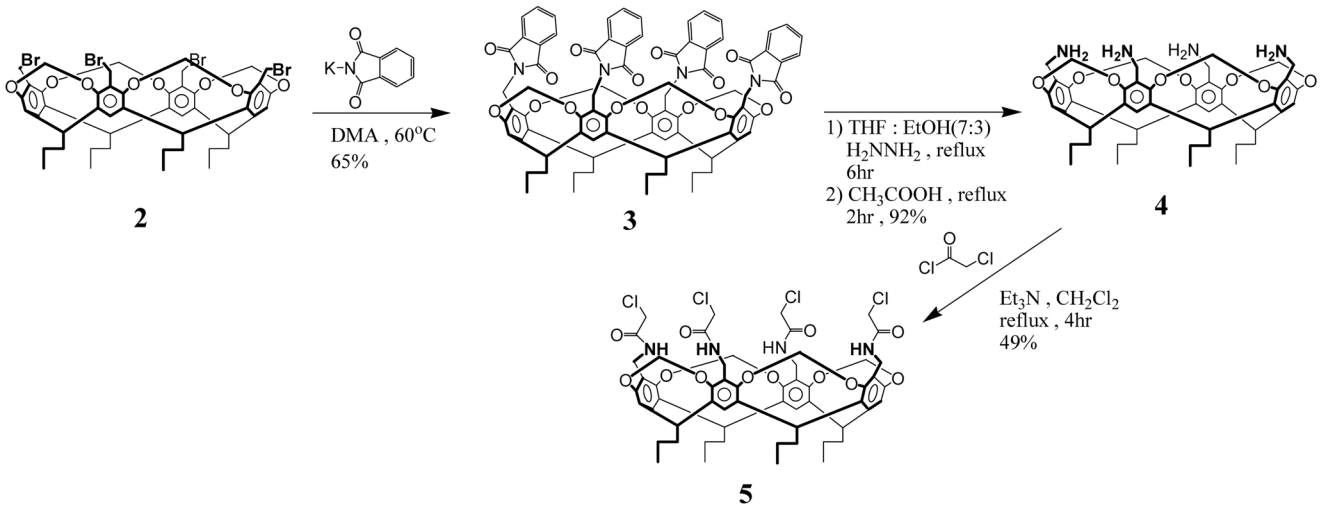


Figure 1. Container Molecules **G@1** based on Resorcin[4]arene and Its pillars (X = a-f).

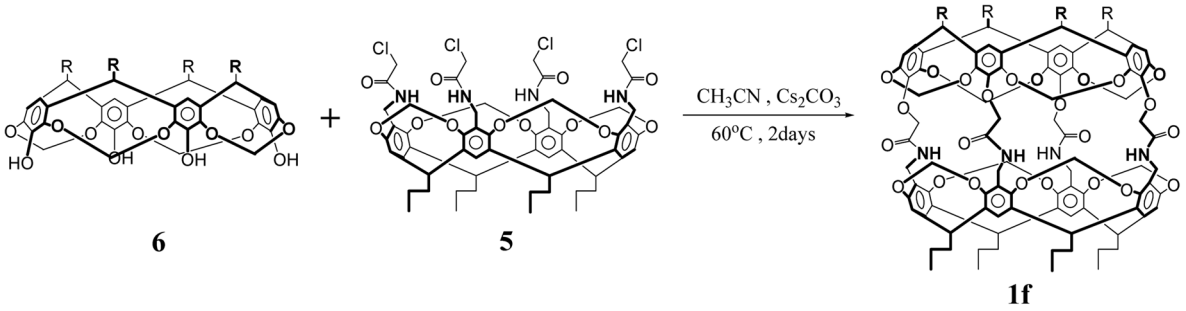
Results and Discussion

Tetrakis(chloroacetamido)cavitand **5** was synthesized by three-step reaction from tetrakis(bromomethyl)cavitand **2** (Scheme 1).[10] Tetrakis(bromomethyl)cavitand **2**[11] was reacted with potassium phthalimide in DMA at 60 °C for 12 hrs to give tetrakis(phthalimido)cavitand **3** in 65% yield. Tetrakis(phthalimido)cavitand **3** was treated with hydrazine hydrate in refluxing ethanol/THF to give tetrakis(aminomethyl)cavitand **4** in 92% yield. Acylation of tetrakis(aminomethyl)cavitand **4** with chloroacethyl chloride and Et_3N in refluxing CH_2Cl_2 afforded tetrakis(chloroacetamido)cavitand **5** in 49% yield.

New C_{4v} hemicarcerand **1f** was synthesized from tetrahydroxy cavitand **6**[2] and tetrakis(chloroacetamido)cavitand **5** in CH_3CN for 2 days at 60 °C in less than 5% yield. The same reactions in DMF, DMA, NMP, or DMSO in various conditions gave no product. It is presumable that the so-called "Guest-inhibited shell closure" happened.[12] The strong hydrogen bonding of tetrol **6** with itself, which results in the solvent-templated dimer of tetrol **6**,[13] inhibits the shell closure and directs the reaction to oligomerization. Container host **1f** was isolated as empty. Even if acetonitrile were captured, it might escape through the portal during the isolation procedure. Hemicarcerand **1f** was characterized by ^{1}H NMR and



Scheme 1. Synthesis of tetrakis(chloroacetamido)cavitand **5**.



Scheme 2. Synthesis of new C_{4v} hemicarcerand **1f** (R = Heptyl).

FAB+ mass spectra.

Unfortunately the attempted complexations of hemicarcerand **1f** with an 20 eq excess of various potential guests such as DMA, toluene, xylenes, toluic acids, and toluamides, in $C_2D_2Cl_4$ were unsuccessful. For container hosts which have borderline characteristics between carcerand and hemicarcerand the energy barrier of complexation happened to be too high in the manageable conditions.[4c]

Molecular mechanics calculations using Spartan® '04 V1.0.3 (Semi-empirical AM1 level) show that host **1f** prefers linear guest among the complementary nonpolar isomeric guests (*p*-xylene >> *o*-xylene ~ *m*-xylene), but among the complementary isomeric guests having hydrogen bonding donor group (phthalic acid, toluic acid, or toluamide etc.) its preferences to *p*-isomer and *o*-isomer are similar. It is presumable the hydrogen bonding donor group of guest can interact with carbonyl groups of host which are located in the tropical region of complex G@**1f** in which the hydrogen bonding group of *o*-isomer seems to be oriented better than that of *m*-isomer. Such postulate can be answered when the analogues of host **1f** were developed and characterized.

Experimental Section

General. All chemicals were reagent grades and directly used unless otherwise specified. All anhydrous reactions were conducted under an argon atmosphere. FAB+ Mass spectra were run on a HR MS (vg70-VSER) at Korea Basic Science Institute. The ^{1}H NMR spectra were recorded on a Brucker Avance (400 MHz) in $CDCl_3$. Gravity column chromatography was performed on silica gel 60 (E. Merck, 70-230 mesh ASTM). Thin layer chromatography was done on silica plastic sheets (E. Merck, silica gel 60 F254, 0.2 mm).

Tetrakis(phthalimidomethyl)cavitand 3. A solution of tetrakis(bromomethyl)cavitand **2** (3.0 g, 2.79 mmol), potassium phthalimide (4.14 g, 22.3 mmol) in DMA was stirred for 12 hrs at 60 °C. The mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated under vacuum. The residue was partitioned between CH_2Cl_2 and water. The organic phase was separated and washed with brine, and then dried over $MgSO_4$. The solvent was evaporated under vacuum. The residue was purified by silica gel chromatography using a mixture of EtOAc/Hexane (1:1) as a mobile phase to give 2.3 g (65%) of product; ^{1}H NMR (400 MHz, $CDCl_3$) 0.98 (t, 12H, *CH*$_3$), 1.29 (m, 8H, *CH*$_2$), 2.17 (m, 8H, *CH*$_2$), 4.42 (d, *J* = 8 Hz, 4H, inner O*CH*$_2$O), 4.64-4.71 (m, 12H, *CH* methine and Ar*CH*$_2$), 5.77 (d, *J* = 8 Hz, 4H, outer O*CH*$_2$O), 7.09 (s, 4H, Ar*H*), 7.72 (d, 8H, Ar*H*), 7.82 (d, 8H, Ar*H*).

Tetrakis(aminomethyl)cavitand 4. A solution of tetra-

kis(phthalimidomethyl)cavitand **3** (0.5 g, 0.39 mmol) and hydrazine hydrate (0.57 mL, 11.6 mmol) in a mixture of EtOH (70 mL) and THF (30 mL) was refluxed for 6 hrs. After addition of CH_3COOH (10 mL) the reaction mixture was refluxed for 2 hrs. The solvents were removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and 2 N NaOH. The organic phase was separated and washed with water, and then with brine. Organic phase was dried over $MgSO_4$. The solvent was evaporated under vacuum. The residue was recrystallized from Hexane/CH_2Cl_2 to give product (294 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.04 (t, 12H, *CH*$_3$), 1.39 (m, 8H, *CH*$_2$), 2.21 (m, 8H, *CH*$_2$), 3.59 (s, 8H, Ar*CH*$_2$), 4.35 (d, *J* = 8 Hz, 4H, inner O*CH*$_2$O), 4.78 (t, 4H, *CH* methine), 5.90 (d, *J* = 8 Hz, 4H, outer O*CH*$_2$O), 7.05 (s, 4H, Ar*H*).

Tetrakis(chloroacetamido)cavitand 5. To a solution of tetrakis(aminomethyl)cavitand **4** (300 mg, 0.36 mmol) and Et_3N (0.5 mL, 3.6 mmol) in CH_2Cl_2 was added chloroacetyl chloride (0.35 mL, 4.32 mmol). The reaction mixture was refluxed for 4 hrs. Subsequently, the solution was washed with 3 N HCl, H_2O, brine, and then dried over $MgSO_4$. The solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography using a mixture of MeOH/CH_2Cl_2 (4:96) as s mobile phase to give 201 mg (49%) of product; ^{1}H NMR (400 MHz, $CDCl_3$) 1.04 (t, 12H, *CH*$_3$), 1.39 (m, 8H, *CH*$_2$), 2.21 (m, 8H, *CH*$_2$), 4.02 (s, 8H, CO*CH*$_2$Cl), 4.32 (d, 8H, Ar*CH*$_2$), 4.38 (d, *J* = 8 Hz, 4H, inner O*CH*$_2$O), 4.80 (t, 4H, *CH* methine), 5.99 (d, *J* = 8 Hz, 4H, outer O*CH*$_2$O), 6.94 (t, 4H, *NH*), 7.12 (s, 4H, Ar*H*).

New C_{4v} hemicarcerand 1f. Tetrol cavitand **6** (120 mg, 0.13 mmol) and tertrakis(chloroacetamido)cavitand **5** (150 mg, 0.13 mmol) were dissolved in dry CH_3CN (150 mL) and 1 g of Cs_2CO_3 was added. The reaction mixture was refluxed for 2 days. The solvent was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water. The organic phase was separated, washed with brine, and then dried over $MgSO_4$. The solvent was evaporated under vacuum. The residue was purified by silica gel chromatography using a mixture of EtOAc/Hexane (1:2) to give product (12 mg, < 5% yield); FAB+ MS m/z 1974 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) 0.76-2.28 (m, 88H, residue), 3.92 (d, *J* = 8 Hz, 4H, inner O*CH*$_2$O), 3.98 (d, *J* = 8 Hz, 4H, inner O*CH*$_2$O), 4.44 (s, 8H, CO*CH*$_2$O), 4.52 (d, 8H, Ar*CH*$_2$NH), 4.62 (t, 4H, *CH* methine), 4.70 (t, 4H, *CH* methine), 5.62 (d, *J* = 8 Hz, 4H, outer O*CH*$_2$O), 5.69 (d, *J* = 8 Hz, 4H, outer O*CH*$_2$O), 6.74 (s, 4H, Ar*H*), 7.14 (s, 4H, Ar*H*).

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