Four-directionally Functionalized Hemicarcerands: Intermediates for 2D Square Grid Network of Container Molecules

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Molecular vessels having defined dimensions and stability, resorcin[4]arenes or calix[4]arenes, have been used for the construction of various supramolecular systems such as container molecules[1] and self-assembling molecular capsules,[2] which are prototypes having a defined inner cavity with substantial activation energy barriers for complexation-decomplexation process of their complementary guests.

When complexed, these prototypes showed many unprecedented isomers called carceroisomers, twistomers, social isomers, constellation isomers, and orientational isomers.[3] These isomers could work as molecular switches when they could be aligned on a matrix and their equilibrium could be controlled by an energy efficient method. Aligning container molecules on gold surface was successful by self-assembling of a carceplex having thia groups on feet of a hemispheric part.[4]

Especially the net-work of container molecules would also be an efficient method for these purposes. Self-assembled net works of container molecules will become unique materials due to uniform dimensions, high stablilities, and dense properties.

For the purpose of 2D square grid network of container molecules as illustrated in Figure 1, 4-directionally functionalized hemicarcerands **4** and **5** were designed and synthesized by the shell closing reactions between tetrol **1**[5] and bridging reagents **2** or **3** as shown in Scheme 1. The bridging reagent 3,5-bis(bromomethyl)benzonitrile **2** was prepared from 5-iodo-*m*-xylene through two step reactions, cyanation[6] and then NBS bromination.[7] The bridging reagent 3,5-bis(bromomethyl)-1-bromobenzene **3** was prepared from 5-bromo-*m*-xylene by NBS bromination.[7] The shell closing reactions, 8-bonds formation in one step, in a mixture of tetrol **1**, bridging reagents **2** or **3**, and Cs_2CO_3 in NMP at 25-60 °C gave hemicarcerands **4** and **5** in moderate yields, 11 and 7%, respectively.

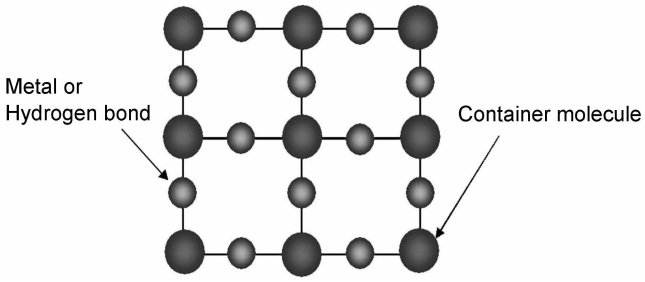
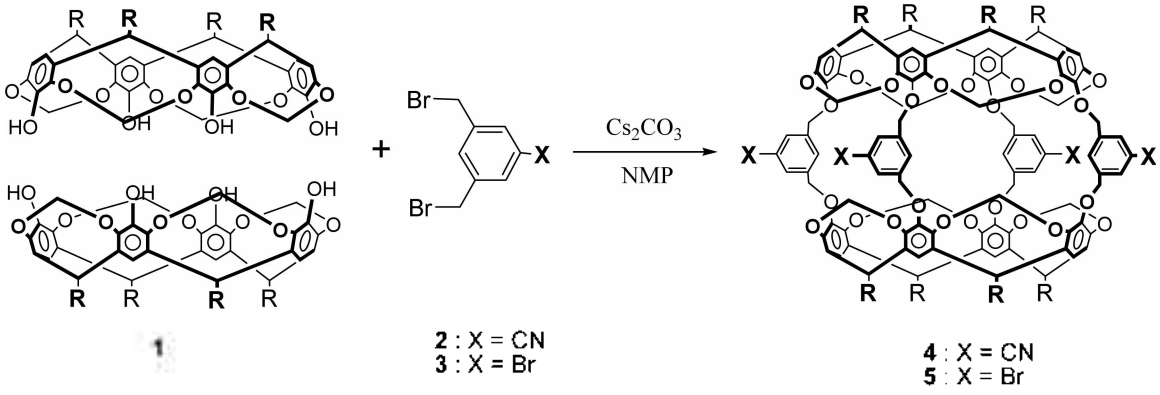


Figure 1. Illustration of a part of 2D square grid network of a 4-directionally functionalized container molecule.

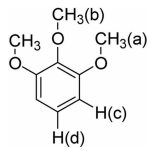
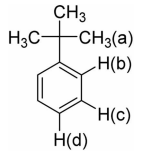
The network of container molecules will be useful only if the orientation of complexed guest can be confirmed and manipulable. For hemicarceplexes to be isolable enough at ambient temperature, the sizes and shapes of potential guests must be complementary enough to the host's portals and inner cavities so that the constrictive and intrinsic binding interactions work together properly.[8]

Hemicarceplexes, guest@**4**, were synthesized by heating a mixture of free host **4** and an excess amount of guest (> 1000 fold), cooling reaction mixture, and then flooding with MeOH. The precipitated hemicarceplex was filtered and dried *in vacuo*. The ^{1}H NMR spectral changes of guest



Scheme 1. Synthesis of 4-directionally functionalized hemicarcerands **4** and **5** (R = Heptyl).

Table 1. Chemical shift differences of guests ($\Delta\delta$) in 400 MHz ^{1}H NMR spectra in $CDCl_3$ at 25 °C

Guest	chemical shift of complexed guest, δ(ppm)				$\Delta\delta$(ppm) ($\delta_{free} - \delta_{compl}$)			
	Ha	Hb	Hc	Hd	Ha	Hb	Hc	Hd
	−0.15	2.94	5.19	6.49	4.04	0.94	1.52	0.51
	−0.03	6.28	4.95	3.58	1.35	1.05	1.25	3.59

in $CDCl_3$ solution at 25 °C before and after complexation ($\Delta\delta = \delta_{free} - \delta_{complexed}$) are summarized with their guest structures in Table 1.

The chemical shift differences ($\Delta\delta$) illustrated the orientation of guest in host's cavity. The higher up-field shift of a hydrogen means its closer nesting to the north or south poles composed of 4 benzene units of host, through which C_4 axis of host penetrates. For 1,2,3-trimethoxybenzene, $\Delta\delta$ of two 1- and 3-methoxy groups (H_a) was the largest, 4.04, which tells the axis connecting these two methoxy groups is most probably oriented parallel to C_4 axis of host. The small $\Delta\delta$s of H_b and H_d, 0.94 and 0.51, respectively, also supports their concurrent positions around tropical region of host where the magnetic shielding effect is weakest within the cavity. Probably the steric bulkiness of 1,2,3-trimethoxy groups inhibits their nesting in the same hemisphere. For *t*-butylbenzene, $\Delta\delta$ of H_d was the largest, 3.59, which tells the axis connecting *t*-butyl and H_d is most probably oriented parallel to C_4 axis of host. In this case the large *t*-butyl group seems to push H_d deeply to a pole.

4-Directionally functionalized hemicarcerands **4** and **5** as well as two hemicarceplexes **G@4** were synthesized and the orientations of guests in hemicarceplex **G@4** were confirmed. Tetracyano- and tetrabromo groups of hemicarcerands **4** and **5** can be further transformed to various functional groups eligible for 2D square grid network. For instance hydrolysis of cyano to carboxy group or further derivatization to multiple hydrogen bonding group will result in 4-way hydrogen bonding 2D network. Also the versatile bromo group can be converted to 4-pyridyl group through Suzuki coupling reaction with 4-pyridylboronic acid to give 4-directionally coordinating hemicarcerand.

Experimental Section

Materials and General Procedures. All chemicals were reagent grades and directly used unless otherwise specified. All anhydrous reactions were conducted under an argon atmosphere. MALDI-TOF Mass spectra was run on a HR MS (vg70-VSER) at Korea Basic Science Institute. IR spectra were taken with a Mattson 3000 FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Brucker Avance (400 MHz) in $CDCl_3$ unless stated otherwise. Gravity column chromatography was performed on silica gel 60 (E. Merck, 70-230 mash ASTM). Flash chromatography was performed on silica gel 60 (E. Merck, 230-400 mesh ASTM).

3,5-Bis(bromomethyl)benzonitrile 2. A mixture of 3,5-dimethylbenzenonitrile **5** (1.0 g, 7.6 mmol), NBS (1.35 g, 8.0 mmol, 1 eq) and catalytic amount of AIBN in 50 mL of dry CH_2Cl_2 was irradiated with visible light (110 V, 100 W) under Ar gas for 1 hr at 25 °C. To the mixture were added NBS (1.35 g, 8.0 mmol, 1 eq) and catalytic amount of AIBN. After 24 hr, the solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2, washed with water and CH_2Cl_2 layer was dried with $MgSO_4$, concentrated, and flash chromatographed on silica gel. Elution of the column with a mixture of CH_2Cl_2/Hexane (6:1) gave 703 mg (32%) of 3,5-bis(bromomethyl)benzonitrile **2**. FT-IR (KBr): 2230 cm^{-1} ($\nu_{C\equiv N}$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (s, 4H, *CH*$_2$), 7.61 (s, 2H, *ArH*), 7.64 (s, 1H, *ArH*).

D_{4h} Tetracyanohemicarcerand 4. A mixture of tetrol **1** (500 mg, 0.5 mmol), 3,5-bis(bromomethyl)benzonitrile **2** (680 mg, 2.5 mmol) and Cs_2CO_3 (1.1 g, 5 mmol) in NMP (350 mL) was stirred at room temperature for 3 days under Ar. An additional portion of 3,5-bis(bromomethyl)benzonitrile **2** (680 mg, 2.5 mmol) was added. The mixture was heated to 60 °C and stirred for 3 days. The solvent was evaporated under vacuum and the residue was partitioned between CH_2Cl_2 and 10% aqueous HCl, and the organic layer was dried with $MgSO_4$, concentrated, and flash chromatographed on silica gel. The column was eluted with a mixture of CH_2Cl_2/Hexane (2:1) to give 68 mg (11%) of hemicarcerand **4**. MALDI-TOF MS (m/z): 2518([M+Na]$^+$, 65%); FT-IR (KBr): 2231 cm^{-1} ($\nu_{C\equiv N}$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 24H, *CH*$_3$), 1.26-1.45 (m, 80H, *(CH*$_2$*)*$_5$), 2.17-2.23 (q, 16H, CH*CH*$_2$), 4.17 (d, J = 6.8 Hz, 8H, inner O*CH*$_2$O), 4.83 (t, J = 8.0 Hz, 8H, *CH* methine), 4.92 (s, 16H, O*CH*$_2$Ar), 5.44 (d, J = 6.8 Hz, 8H, outer O*CH*$_2$O), 6.88 (s, 8H, Ar*H*), 7.38 (s, 8H, Ar*H*), 7.85 (s, 4H, Ar*H*).

Hemicarceplex 1,2,3-Trimethoxybenzene@4. To a pyrex test tube equipped with an inert gas inlet were added hemicarcerand **4** (15 mg, 0.006 mmol) and 1,2,3-trimethoxybenzene (1.3 g, 7.93 mmol). The mixture was heated at 160 °C for 36 hrs, cooled to 80 °C and then flooded with 60 mL of MeOH. The solid was filtered, dried *in vacuo* to give 13 mg (81%) of Hemicarceplex **1,2,3-trimethoxybenzene@4**. ^{1}H NMR (400 MHz, $CDCl_3$): δ−0.15 (s, 6H, O*CH*$_3$), 0.93 (t, 24H, *CH*$_3$), 1.32-1.51 (m, 80H, *(CH*$_2$*)*$_5$), 2.27 (q, 16H, CH*CH*$_2$), 2.94 (s, 3H, O*CH*$_3$), 4.26 (d, J = 8 Hz, inner O*CH*$_2$O), 4.83 (m, 24H, O*CH*$_2$Ar and *CH* methine), 5.19 (d, J = 8 Hz, 2H, Ar*H*), 5.58 (d, J = 8 Hz, 8H, outer O*CH*$_2$O), 6.49 (t, J = 8 Hz, 1H, Ar*H*), 6.62 (s, 8H, Ar*H*), 7.48 (s, 4H, Ar*H*), 7.55 (s, 8H, Ar*H*).

Hemicarceplex *t*-Butylbenzene@4. To a pyrex test tube equipped with an inert gas inlet was added hemicarcerand **4** (20 mg, 0.008 mmol) and *t*-butylbenzene (1.5 mL, 10

mmol). The mixture was heated at 120 °C for 48 hrs. cooled to 80 °C and then flooded with 60 mL of MeOH. The solid was filtered. dried *in vacuo* to give 11 mg (54%) of Hemicarceplex ***t*-butylbenzene@4**. ^{1}H NMR (400 MHz, $CDCl_3$): δ –0.03 (s. 9H, C*(CH$_3$)$_3$*), 0.93 (t, 24H, CH$_2$*CH$_3$*), 1.35-1.60 (m, 80H, *(CH$_2$)$_5$*), 2.29 (q. 16H, CH*CH$_2$*), 3.58 (t, 1H, Ar*H*). 4.15 (d, J = 8 Hz. inner O*CH$_2$*O. 8H) 4.78 (t, J = 8.0. 8H, *CH* methine). 4.84 (s, 16H, O*CH$_2$*Ar). 4.95 (t. 5.19 t, 2H. Ar*H*). 5.45 (d. J = 8 Hz, 8H, outer O*CH$_2$*O). 6.26 (d, J = 8 Hz. 2H. Ar*H*). 7.00 (s, 8H, Ar*H*). 7.55 (s, 8H. Ar*H*), 7.58 (s. 4H. Ar*H*).

***D*$_{4h}$ Tetrabromohemicarcerand 5.** A mixture of tetrol **1** (500 mg. 0.5 mmol). 1-bromo-3,5-bis(bromomethyl)benzene **3** (860 mg. 1.5 mmol) and an excess of Cs_2CO_3 (2 g) in 350 mL of NMP was stirred at room temperature for 3 days under Ar. An additional 860 mg of 1-bromo-3,5-bis(bromomethyl)benzene **3** (1.5 mmol) was added. The mixture was heated to 60 °C and stirred for 3 days. The solvent was evaporated under vacuum and the residue was partitioned between CH_2Cl_2 and 10% aqueous HCl. The organic layer was dried over $MgSO_4$, concentrated, and flash chromatographed on silica gel. The column was eluted with a mixture of CH_2Cl_2/Hexane (1:3) to give 50 mg (7.2%) of tetrabromohemicarcerand **5**. MALDI-TOF MS (m/z): 2734 ([M+Na]$^+$. 60%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 24H. *CH$_3$*). 1.25-1.44 (m. 80H. *(CH$_2$)$_5$*), 2.19 (q. 16H. CH*CH$_2$*), 4.17 (d. J = 7.2 Hz. 8H, inner O*CH$_2$*O). 4.71 (t. J = 7.6 Hz, 8H, *CH* methine), 4.86 (s, 16H. O*CH$_2$*Ar). 5.48 (d, J = 7.6 Hz. 8H, outer O*CH$_2$*O). 6.84 (s. 8H, Ar*H*). 7.30 (s. 8H, Ar*H*), 7.45 (s, 4H. Ar*H*).

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