Mono-functionalization on a Foot of Carceplex: An Intermediate for Carceplex Engineering

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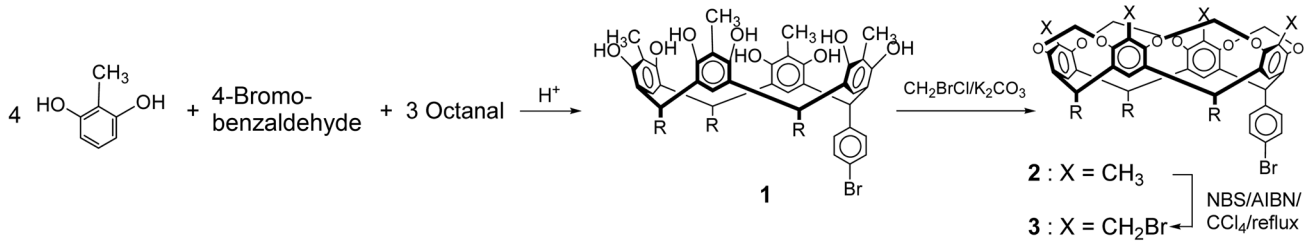
The selective functionalizations of container molecules are important tasks to expand its research fields. In case of covalent-bonded container molecules based on resorcin[4]-arene their functionalization methods are quite limited compared to those for molecular capsules or calixarenes.

The functionalizations on tropical region of resorcin[4]-arene-based container molecules with D_{4h} symmetry have been usually accomplished by applying functionalized bridging reagent at the final convergent shell-closing step, which were successful for the manipulation of intrinsic properties of cavity,[1] the solubility control,[2] or the incorporation of metal ligands for multidimensional assembly of host.[3] The step-wise shell-closing reactions were also successful for C_{4v} or less symmetric carceplexes,[4] hemicarceplexes[5] or cavitands[6], which are mostly functionalized on their tropical regions.

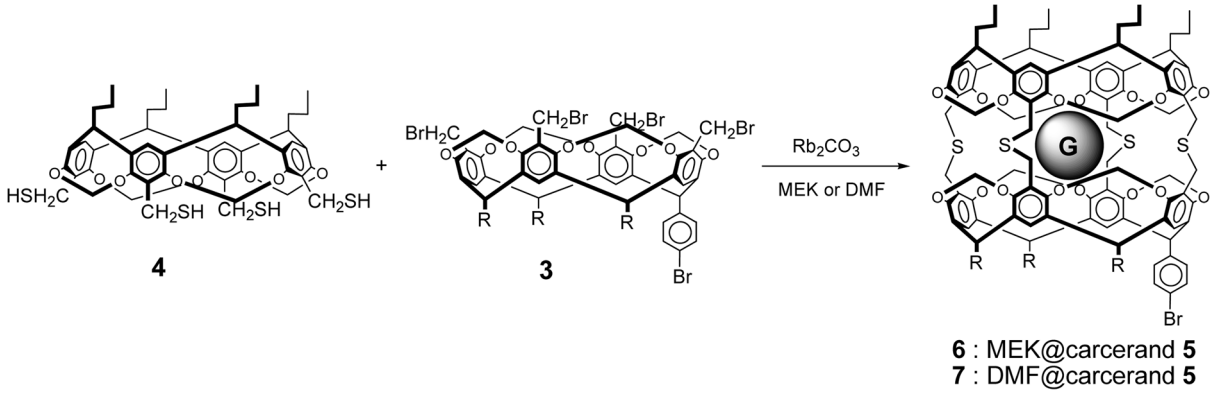
The homogeneous four-feet functionalizations of C_{4v} resorcin[4]arene gave various functional container molecules such as monolayer of carceplex,[7b] metal-coordinated oligomers,[7c] and water soluble molecular capsules.[7d] Especially the selective monofunctionalization methods on a foot[8a,b] of resorcin[4]arene gave the important intermediates for the new kinds of self-assemblies such as π-π stacked oligomers,[8b,9a] star-shaped supramolecular polymer,[9b] and self-sorting hexameric capsules.[9c] Here are reported carceplexes **6** and **7** having a *p*-bromophenyl foot which can be used as a platform for the molecular engineering of carceplexes.

The key compound **1**, *p*-bromophenyl tetramethyloctol, was obtained by the hetero condensation among 2-methylresorcinol, 4-bromobenzaldehyde, and octanal in about 40% yield.[8b] Tetramethylcavitand **2** was obtained in 33% yield by the 4-fold intramolecular cyclization of octol **1** using CH_2BrCl and K_2CO_3. Tetramethylcavitand **2** was converted to *p*-bromophenyl tetrakis(bromomethyl)cavitand **3** by NBS/AIBN in 42% yield.

The shell-closing reaction between *p*-bromophenyl tetrakis-(bromomethyl)cavitand **3** and tetrakis(thiomethyl)cavitand **4** in a mixture of methyl ethyl ketone (MEK) or *N,N*-dimethylformamide (DMF) and Rb_2CO_3 gave MEK@carcerand **5** (carceplex **6**) or DMF@carcerand **5** (carceplex **7**) in 56% and 25% yield, respectively. The structures of MEK@-carcerand **5** and DMF@carcerand **5** were characterized with



Scheme 1. Synthesis of *p*-Bromophenylcavitand **3** (R=Heptyl).



Scheme 2. Synthesis of carceplexes **6** and **7** (R=Heptyl) having a functionalized foot.

Table 1. ^{1}H NMR Chemical shift changes of complexed guests

Guest structure		chemical shift (δ, ppm)		
		free	carceplex **6** or **7**	$\Delta\delta$
$CH_{3,a}COCH_{2,b}CH_{3,c}$	H_a	2.10	−1.89	3.99
	H_b	2.45	0.78	1.67
	H_c	1.05	−3.02	4.07
H_d-C(O)N-$CH_{3,e}$	H_d	8.02	5.86	2.16
|	H_e	2.98	0.01	2.97
$CH_{3,f}$	H_f	2.89	−0.23	3.12

$\Delta\delta = \delta_{free} - \delta_{complexed}$

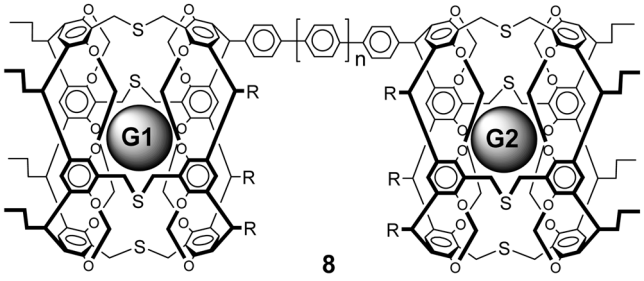


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Figure 1. Biscarceplex **8** connected through a oligophenylene foot.

MALDI TOF Mass and ^{1}H NMR spectrometry.

Carceplexes **6** and **7** have a US football-shaped cavity whose dimensions are roughly 11 Å × 6 Å. The complexed linear guest tends to orient through the long axis of cavity in which guest's terminal hydrogen nests deep into the two poles of host where the magnetic shielding effects from the four benzene units are overlapped. Table 1 shows the chemical shift changes of hydrogens of incarcerated guests. MEK is more linear compared to DMF, so the terminal methyls of MEK nest proximal to the poles to give the two largest $\Delta\delta$ of 3.99 and 4.07. The larger $\Delta\delta$ of H_c, 4.07, than that of H_a, 3.99, is also due to their steric effect difference.

Such intrinsic properties of monomeric carceplexes have been extensively studied,[1] but the studies on the cooperative multi-properties of dimer, oligomer, network, micelle, or membrane of container molecules are yet left to be explored. Figure 1 shows a prototypical biscarceplex **8**, two different carceplexes connected through a oligophenylene foot, which can be obtained from carceplexes **6**, **7**, or their analogues. The interactions between two incarcerated guests through oligophenylene bridge would change the electric or magnetic properties and the redox potentials, which could influence the relative orientational preferences or the stabilities of incarcerated guests. Such an interesting study will open a new era of supramolecular chemistry.

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. Melting points were determined using an Electrothermal IA9100 apparatus without calibration. MALDI-TOF Mass spectra were run on a Voyager-DE^{TM} STR Biospectrometry at National Center for Inter University Research Facilities (Seoul National University). The ^{1}H NMR spectra were recorded on a Brucker Avance (400 MHz) spectrometer in $CDCl_3$ unless stated otherwise. Gravity column chromatography was performed on silica gel 60 (E. Merck, 70-230 mash ASTM).

***p*-Bromophenyl Tetramethylcavitand 2.** A mixture of octol **1** (10 g, 10 mmol), CH_2BrCl (3.4 mL, 50 mmol), K_2CO_3 (8.5 g), and DMF (50 mL) was stirred at 50 °C overnight. The mixture was partitioned between 3 N HCl (100 mL) and CH_2Cl_2 (50 mL), and the organic phase was separated, washed with 3 N HCl, brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel chromatography using a mixture of EtOAc/Hexane (1:11). The best fractions were collected, concentrated, and the residue was recrystallized in a mixture of CH_3CN/CH_2Cl_2 to give a product (3.5 g, 33%); mp 145-148 °C; MALDI TOF MS m/z 1041.58 (100%, M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (9H, m, $CH_2(CH_2)_5CH_3$), 1.25-1.52 (30H, m, $CH_2(CH_2)_5CH_3$), 1.97 (6H, s, $ArCH_3$), 2.02 (6H, s, $ArCH_3$), 2.11 (6H, bs, $CH_2(CH_2)_5CH_3$), 4.22 (1H, d, J = 7.2 Hz, inner OCH_2O), 4.28 (2H, d, J = 7.2 Hz, inner OCH_2O), 4.33 (1H, d, J = 6.8 Hz, inner OCH_2O), 4.75 (3H, m, *CH* methine), 5.91 (4H, m, outer OCH_2O), 6.34 (1H, s, *CH* methine), 6.86 and 6.95 (two 2H, two s, Ar*H*), 7.29 (2H, d, J = 8.2 Hz, *p*-bromophenyl), 7.49 (2H, d, J = 8.2 Hz, *p*-bromophenyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 9.5, 13.2, 13.3, 21.8, 21.9, 27.0, 27.3, 28.5, 28.7, 28.8, 29.0, 29.3, 30.9, 31.1, 36.1, 36.2, 41.3, 97.7, 116.8, 119.3, 119.7, 122.8, 123.3, 130.2, 135.8, 137.0, 137.2, 139.0, 152.3, 153.1.

***p*-Bromophenyl Tetrakis(bromomethyl)cavitand 3.** A mixture of cavitand 2 (2 g, 2 mmol), NBS (2 g, 11 mmol), AIBN (2 mg), and CCl_4 (50 mL) was refluxed for 5 hrs. The mixture was cooled to rt and the solvent was evaporated. The residue was partitioned between water (100 mL) and CH_2Cl_2 (50 mL), and the organic phase was separated, washed with brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel chromatography using a 2:1 mixture of Hexane/CH_2Cl_2. The best fractions were collected, concentrated, and the residue was recrystallized in a mixture of CH_2Cl_2/EtOH to give a product (1.08 g, 42%); mp 192-195 °C; MALDI TOF MS m/z 1277.31 (100%, $[M-Br]^+$), 1357.23 (50%, M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (9H, m, $CH_2(CH_2)_5CH_3$), 1.24-1.32 (30H, m, $CH_2(CH_2)_5CH_3$), 2.09 (6H, bs, $CH_2(CH_2)_5CH_3$), 4.42 (4H, s, $ArCH_2Br$), 4.47 (6H, s, $ArCH_2Br$), 4.60 (4H, m, inner OCH_2O), 4.75 (3H, m, *CH* methine), 6.04 (4H, m, outer OCH_2O), 6.34 (1H, s, *CH* methine), 7.00 and 7.10 (two 2H, two s, Ar*H*), 7.21 (2H, d, J = 8.4 Hz, *p*-bromophenyl), 7.51 (2H, d, J = 8.4 Hz, *p*-bromophenyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 22.7, 22.9, 27.8, 28.1, 29.3, 29.5, 29.8, 30.2, 31.8, 31.9, 36.9, 41.9, 99.2, 121.0, 123.9, 124.5, 125.0, 130.9, 131.4, 136.8, 137.9, 138.3, 138.8, 153.4, 154.3.

Tetrakis(thiomethyl)cavitand 4. A mixture of tetrakis-(bromomethyl)cavitand[10] (1.0 g, 0.93 mmol), thiourea (566 mg, 7.4 mmol), and DMF (5 mL) was stirred for 3 hrs at 60

°C and then for 2 hrs at 80 °C under argon. To the reaction mixture 4 mL of 3 N NaOHwas added and stirred for 30 min and then 5 mL of 3 N HCl was added. The product was extracted with 20 mL of CH_2Cl_2 and the organic phase was washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was recrystallized in a mixture of hexane and CH_2Cl_2 to give a product (light pink powder, 542 mg, 66%); mp > 138 °C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (12H, t, J = 8.0 Hz, $CH_2CH_2CH_3$), 1.39 (8H, m, $CH_2CH_2CH_3$), 1.87 (4H, t, J = 8.0 Hz, SH), 2.21 (8H, m, $CH_2CH_2CH_3$), 3.58 (8H, d, J = 8.0 Hz, CH_2SH), 4.46 (1H, d, J = 8.0 Hz, inner OCH_2O), 4.78 (4H, t, J = 8.0 Hz, *CH* methine), 5.96 (4H, d, J = 8.0 Hz, outer OCH_2O), 7.07 (4H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.5, 21.3, 32.5, 37.0, 100.3, 119.7, 127.6, 138.4, 153.5.

MEK@*p*-Bromophenyl Carcerand 5 (Carceplex 6). A solution of *p*-bromophenyl tetrakis(bromomethyl)cavitand **3** (300 mg, 0.22 mmol), tetrakis(thiomethyl)cavitand **4** (196 mg, 0.22 mmol), and MEK (100 mL) was added for 12 hrs to a refluxing mixture of Rb_2CO_3 (1.02 g) and MEK (100 mL) in a 500 mL Round-bottom flask. After additional 12 hrs refluxing, the solvent was evaporated and the residue was partitioned between water and CH_2Cl_2. The organic phase was separated and washed with brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel chromatography using a 1:3 mixture of hexane/CH_2Cl_2. The best fractions were collected, concentrated, and the residue was recrystallized in a mixture of CH_3Cl/CH_3CN to give a product (White powder, 245 mg, 56%); mp > 190 °C (decomposed); MALDI TOF MS m/z 1992.82 (15%, M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ –3.02 (3H, m, CH_3CH_2 of MEK), –1.89 (3H, m, CH_3CO of MEK), 0.78 (2H, m, CH_3CH_2 of MEK), 0.88 (9H, m, 3 x $CH_2(CH_2)_5CH_3$), 1.02 (12H, t, J = 8 Hz, 4 x $CH_2CH_2CH_3$), 1.25-1.59 (38H, m, 3 x $CH_2(CH_2)_5CH_3$ + 4 x $CH_2CH_2CH_3$), 2.00-2.20 (14H, m, 3 x $CH_2(CH_2)_5CH_3$ + 4 x $CH_2CH_2CH_3$), 3.88-3.92 (16H, m, 4 x CH_2SCH_2), 4.73 (3H, m, *CH* methine), 4.66-4.75 (12H, m, 8 x inner OCH_2O + 4 x *CH* methine), 5.90 (8H, m, outer OCH_2O), 6.29 (1H, s, *CH* methine), 6.91 and 7.00 (two 2H, two s, Ar*H*), 7.06 (4H, s, Ar*H*), 7.20 (2H, d, J = 8.0 Hz, *p*-bromophenyl), 7.48 (2H, d, J = 8.0 Hz, *p*-bromophenyl).

DMF@*p*-Bromophenyl Carcerand 5 (Carceplex 7). A solution of *p*-bromophenyl tetrakis(bromomethyl)cavitand **3** (300 mg, 0.22 mmol), tetrakis(thiomethyl)cavitand **4** (196 mg, 0.22 mmol), and DMF (100 mL) was added for 12 hrs to a mixture of Rb_2CO_3 (1.02 g) and DMF (100 mL) at 80 °C in a 500 mL Round-bottom flask. After additional 12 hrs stirring at 80 °C, the reaction mixture was cooled to room temperature and then partitioned between 3 N HCl (150 mL) and CH_2CH_2 (150 mL). The aqueous phase was extracted with 50 mL of CH_2CH_2 and the combined organic phase was washed with 100 mL of 3 N HCl. The organic phase was separated and washed with brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel chromatography using a 1:3 mixture of hexane/CH_2Cl_2. The best fractions were collected, concentrated, and the residue was recrystallized in a mixture of CH_3Cl/CH_3CN to give a product (White powder, 112 mg, 25%); mp > 190 °C (decomposed); MALDI TOF MS m/z 1923.89 ([M-DMF]$^+$, 90%), 1940.88 ([M-DMF + H_2O]$^+$, 100%), 1996.91 ([M]$^+$, 25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.23 (3H, s, N-CH_3), 0.01 (3H, s, N-CH_3), 0.90-1.07 (9H, m, 3 x $CH_2(CH_2)_5CH_3$), 0.95 (12H, t, J = 8 Hz, 4 x $CH_2CH_2CH_3$), 1.32-1.45 (38H, m, 3 x $CH_2(CH_2)_5CH_3$ + 4 x $CH_2CH_2CH_3$), 2.06-2.24 (14H, m, 3 x $CH_2(CH_2)_5CH_3$ + 4 x $CH_2CH_2CH_3$), 3.93-3.98 (16H, m, 4 x CH_2SCH_2), 4.41-4.83 (15H, m, 3x *CH* methine + 8 x inner OCH_2O + 4 x *CH* methine), 5.86-5.95 (8H, m, outer OCH_2O), 6.34 (1H, s, *CH* methine), 7.01 and 7.08 (two 2H, two s, Ar*H*), 7.09 (4H, s, Ar*H*), 7.27 (2H, d, J = 8.0 Hz, *p*-bromophenyl), 7.54 (2H, d, J = 8.0 Hz, *p*-bromophenyl).

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