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The Facile Synthesis of a Carceplex with Four Disulfide Bridges

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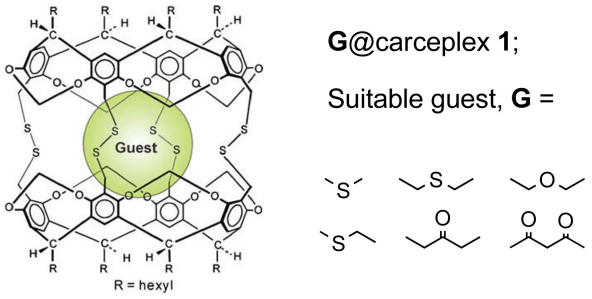
Container molecules have their potentials as receptors, sensors, reaction chambers, and storage or delivery systems.[1] The disulfide-functionalized container molecules have attracted many interests because of their feasibilities to be assembled and to be controlled by redox conditions. Disulfide bonds also play an important role in the folding and stability of some proteins. The bond dissociation energy of disulfide bond is about 60 kcal/mole, which is about 40% weaker than C–C and C–H bonds. Due to the polarizability of divalent sulfur, the S–S bond is susceptible to scission by polar reagents, both electrophiles and nucleophiles.

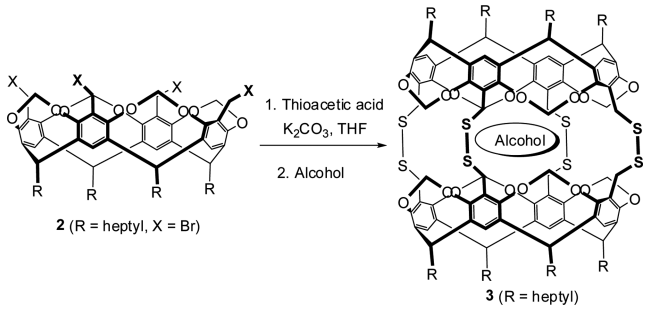
There are many examples of the utilization of disulfide connection in supramolecular systems such as chemosensors,[2] dendrimers,[3] cyclophanes,[4] cyclodextrines,[5] and hemicarcerands.[6]

Sherman and co-workers reported the synthesis of interesting carceplex **1** with disulfide linkages.[7] Usually the templation effect is very important for the formation of container molecules, but only 6 guests out of 42 were suitable templates with extremely low yield of **G**@carceplex **1** (< 16%). Carceplex **G**@**1** was synthesized from tetrakis (bromomethyl)cavitand **2** (R = hexyl, X = Br) *via* tetrakis(thiomethyl)-cavitand **2** (R = hexyl, X = SH). In this route the conversion of alkyl bromide to thiol was done by treatment with thiourea followed by strong basic hydrolysis and the isolated thiol **2** (R = hexyl, X = SH) was subjected to shell-closing reaction by just stirring with a mixture of DMF, template guest molecule, and Cs_2CO_3.



The potentials as metal ionophores or chiral receptors by selective oxidation of the disulfide groups of **G**@carceplex **1** lead us to explore a facile synthetic route to improve its yield and to find smaller template which can be exchanged with other guest.

The milder reagent for the conversion of alkyl halide to thiol is the potassium thioacetate followed by the methanolysis.[8] This method seems to be good to the activated benzyl bromide **2** (R = heptyl, X = Br) and also it could directly give carceplex in the presence of complementary guest. In fact, this one-pot reaction (cavitand **2** (x = Br) → its thioacetate → its thiolate → carceplex) was successful to give 2MeOH@carceplex **3** (R = heptyl) in 32% yield when methanol was used (Scheme 1).



Scheme 1. One-pot synthesis of disulfide-linked carceplex **G**@**3**.

To optimize the one-pot reaction various alcohols were tested (Table 1). When cavitand **2** (x = Br) was treated with thioacetic acid and K_2CO_3 in THF at rt, thioester of cavitand **2** was formed. And upon addition of MeOH thiol **2** (X = SH) was formed, and then slowly carceplex **G**@**3** was formed by air oxidation. A mixture of MeOH and EtOH gave thiol **2** but none of **G**@carceplex **3**. Also the larger alcohols didn't transform the thioester to thiol even at high temperature. Sherman's group failed to put smaller guest such as methanol.

The energy minimized structure of disulfide-linked carceplex 2MeOH@carceplex **3** by Spartan® (Semi-Empirical, PM3) was shown in Figure 1. Two MeOHs are in the northern and southern hemisphere as guest because four disulfide bridges are constrictively twisted to divide the cavity

Table 1. Results of one-pot reaction of cavitand **2** in a mixture of K_2CO_3 and THF with various alcohols

Alcohol	Thiol **2** (X=SH)	Carceplex **G**@ **3**
Methanol	○	~32%
Ethanol	×	×
MeOH/EtOH	○	×
n-Propanol	×	×
Isopropanol	×	×

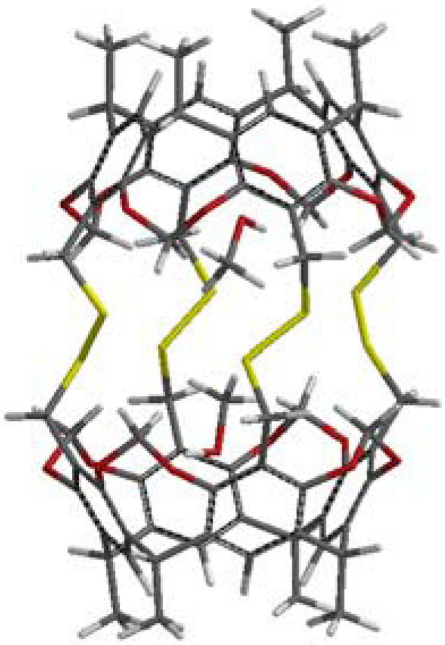


Figure 1. Energy minimized structure of 2MeOH@carceplex **3** using Spartan® (Semi-Empirical, PM3, The feet were substituted by methyl for clarity).

into two compartments. Methanol has complemenstary size to nest suitably into the compartment of two hemispheres. The structure of 2MeOH@carceplex **3** was confirmed by ^{1}H NMR spectroscopy and MALDI-TOF MS spectrometry.

In conclusion, the facile one-pot synthesis of disulfide 2MeOH@carceplex **3** from cavitand **2** (X=Br, R = heptyl) in a mixture of thioacetic acid /K_2CO_3/MeOH at rt was successful. Unfortunately the attempts to exclude MeOH or to exchange MeOH with other guests such as EtOH or CH_3CN were failed. Heating 2MeOH@carceplex **3** in bigger solvents to exclude MeOH gave only unidentifiable mixture, which seems due to the lability and the large torsional energy of disulfide bonds.

Experimental

All commercial solvents and reagents were used without further purification except as noted below. THF was distilled from sodium benzophenone ketyl. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60F254 glass plate and column chromatography was performed on Merck silica gel 60 (70-230 mesh). ^{1}H-NMR spectra was obtained using a Bruker Advanced Digital 400 spectrometer. Chemical shifts are reported relative to tetramethylsilane peak. MALDI-TOF spectrum was obtained using an Applied Biosystems Voyager-DE STR biospectrometer at NCIRF (Seoul National University).

2MeOH@carceplex 3. To a stirred solution of cavitand **2** (R = heptyl, X = Br, 100 mg) and K_2CO_3 (106 mg) in THF (1.0 mL) was added thioacetic acid (28.1 mg), and then the mixture was stirred for 2 h at rt. To the reaction mixture was added methanol (1.0 mL) and stirred for 4 h at rt. After stirring for another 24 h, the reaction mixture was neutralized by 2 mL of 1 N HCl. The mixture was partitioned with 10 mL of CH_2Cl_2 and 10 mL of water. The organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by silica gel chromatography with a mixture of CH_2Cl_2/Hexane (1:1) as mobile phase (27 mg, 32%): MALDI-TOF MS *m/z* : 2304 ((carcerand **3** + 2 MeOH + Na^+), 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 8H, Ar-*H*), 5.86 (d, *J* = 7.6 Hz, 8H, outer -OC*H*$_2$O-), 4.70 (t, *J* = 8.0 Hz, 8H, C*H* methine), 4.44 (d, *J* = 7.6 Hz, 8H, inner -OC*H*$_2$O-), 4.36 (d, *J* = 12.4 Hz, 8H, outer -C*H*$_2$SSC*H*$_2$-), 3.79 (d, *J* = 13.2 Hz, 8H, inner -C*H*$_2$SSC*H*$_2$-), 2.15 (m, 16H, -C*H*$_2$-), 1.40-1.27 (m, 80H, -(C*H*$_2$)$_5$-), 0.88 (t, *J* = 6.8 Hz, 24H, -C*H*$_3$), -0.30 (m, 6H, encapsulated C*H*$_3$OH).

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References

1. (a) Warmuth, R.; Yoon, J. *Acc. Chem. Res*. **2001**, *34*, 95. (b) Ihm, C.; Jo, E.; Kim, J.; Paek, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2056.
2. Lee, M. H.; Yang, Z.; Lim, C. W.; Lee, Y. H.; Dongbang, S.; Kang, C.; Kim, J. S. *Chem. Rev.* **2013**, *113*, 5071.
3. (a) Liu, H.; Wang, H.; Yang, W.; Cheng, Y. *J. Am. Chem. Soc*. **2012**, *134*, 17680. (b) Satoh, N.; Yamammoto, K. *Org. Lett.* **2009**, *11*(8), 1729.
4. Hayashida, O.; Ichimura, K.; Sato, D.; Yasunaga, T. *J. Org. Chem*. **2013**, *78*, 5463.
5. (a) Kumprecht, L.; Budesınsky, M.; Vondrasek, J.; Vymetal, J.; Cerny, J.; Cısarova, I.; Brynda, J.; Herzig, V.; Koutnık, P.; Zavada, J.; Kraus, T. *J. Org. Chem*. **2009**, *74*, 1082. (b) Ooya, T.; Choi, S.; Yamashita, A.; Yui, N.; Sugaya, Y.; Kanto, A.; Maruyama, A.; Akita, H.; Ito, R.; Kogure, K.; Harashima, H. *J. Am. Chem. Soc*. **2006**, *128*, 3852.
6. Helgeson, R. C.; Hayden, A. E.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 570.
7. Sun, J.; Patrick, B. O.; Sherman, J. C. *Tetrahedron* **2009**, *65*, 7296.
8. Han, C. C.; Balakumar, R. *Tetrahedron Lett*. **2006**, *47*, 8255.