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Conformational Study of a Rigid-Structured Octathiabiscavitand from [2 + 2] Coupling of Caps and Bridging Units

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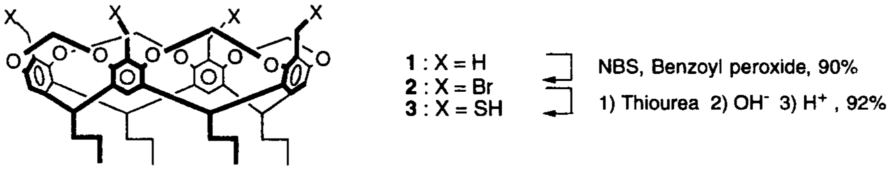
***Abstract*:** An octathiacavitand was stereoselectively obtained in good yield by [2 + 2] coupling reaction between a tetrakis(thiomethyl)cavitand and 1,2,4,5-tetrakis(bromomethyl)benzene. Its NOESY spectrum showed that its cavity was divided into two small ones by π - π stacking of two bridging benzene units. © 1997 Elsevier Science Ltd.

Host molecules having a defined cavity for selective and stable binding of a guest (cavitands) have been important targets in molecular recognition chemistry.[1] The analyses of cavitand - guest interactions have been focused on highly preorganized cavitands with one[2] or two[3] binding sites, which showed interesting binding behaviors with respect to the complementary guests. Cavitands based on resorcin[4]arene used to have a organized tridimensional cavity which are rigid and complementary to potential guests,[4] but the binding energies are relatively low unless the cavitands have a constrictive binding property enough to be a hemicarcerand[5] and/or additional noncovalent interactions such as hydrogen bonding, charge-dipole, charge-charge or π -stacking interactions.[6]

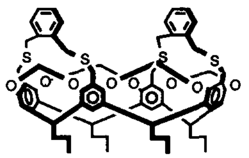
Based on these points, new tridimensional hosts which would show a constrictive binding and/or an additional π -stacking interactions were designed and the conformation of a host was determined by NOESY spectrum and VT ^{1}H-NMR experiment.



Scheme 1

Compound **1** was easily obtained (90%) from an resorcin[4]arene synthesized from 2-methylresorcinol and butanal by the known procedure.[7] It was efficiently functionalized to tetrabromide **2** by NBS bromination (90%)[8] and the subsequent treatment of tetrabromide **2** with thiourea followed by basic hydrolysis gave tetrathiol **3** in good yield (92%).[9]

Tetrathiol **3** was treated with 1,2-bis(bromomethyl)benzene in DMF/K_2CO_3 mixture to give a cavitand **4**[10] in 43%. Due to the fast intramolecular bridging reaction various attempts gave only this [1 (cap) + 2 (bridge)] cavitand **4** instead of a desired [2 + 4] host which would show a constrictive binding property around its tridimensional cavity. Cavitand **4** showed a high affinity for Ag$^+$ by picrate extraction experiment.



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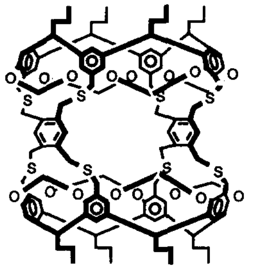

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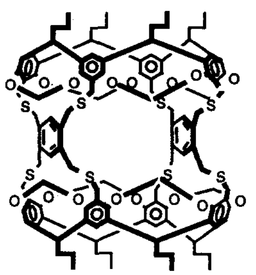

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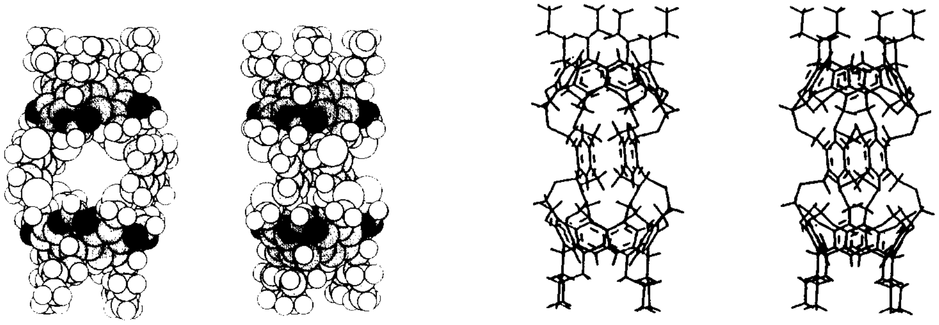
Tetrathiol **3** was also treated with 1,2,4,5-tetrakis(bromomethyl)benzene in DMA/Cs_2CO_3 mixture using high dilution condition to give a [2 + 2] host. CPK molecular model examination shows both of [2 + 2] hosts **5** and **6** are possible together with a [1 + 1] cavitand. [1 + 1] cavitand seems unlikely due to a serious steric congestion, but both of hosts **5** and **6** seem not to have any notable steric hindrance. Host **5** and **6** have four 15- and 16-membered cycles, respectively, between caps and bridges, which implies host **6** should be less sterically hindered than host **5**. Also each of these could exist as conformers **A** (open conformer) and/or **B** (closed conformer). Conformer **A** has a large cavity enough to accomodate a large guest such as p-xylene, but in conformer **B** (a potential biscavitand) this cavity is divided into two small ones separated by the stacked two bridging units (Figure 1 for **6**). Two conformers could isomerize one into another by controlled temperature or solvent.



6A **6B** **Stereoviwe of 6B**

Figure 1. Space-Filling Models of Conformers **6A** and **6B** and the Stereoview of **6B** (Energy Minimized Structures Using MM+ Force-field by HyperChem®).

Only one isomer[11] was isolated in about ~15 % yield. ^{1}H NMR study showed it does not change its conformation in various conditions (300 MHz ^{1}H NMR, -40 °C ~ 150 °C in CD_2Cl_2, $CDCl_3$, DMSO-d_6 or C_6D_5-NO_2). Figure 2 shows the partial NOESY spectrum of this product from 3.0 to 8.0 ppm and the hydrogen labeling. As depicted in Figure 2 aryl hydrogens of bridging benzene unit is labeled as H_a and dioxymethylene within 16-membered ring labeled as H_i and the other oxymethylenes as H_o. Benzyl hydrogens from bridging benzene units are labeled as H_b and those from cap as H_c. For each methylene, hydrogens facing inward were labeled with the second subscript "i" and those facing outward were labeled with the second subscript "o".

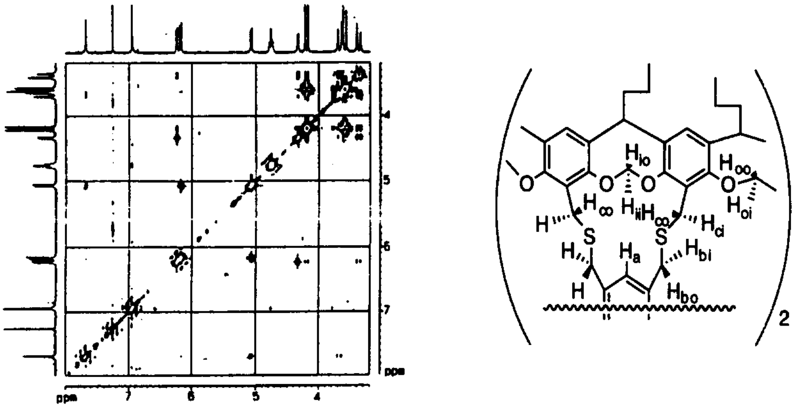


Figure 2. The 300-MHz NOESY Spectrum (3.0 ~ 8.0 ppm) of Host **6** Measured in $CDCl_3$ Using 200 ms Mixing Time and 2.0 s of Pulse Delay and the hydrogen labeling.

The NOEs within this host were summarized in Table 1 together with the average distances between the corresponding hydrogens of conformer **6A** and **6B**, which were measured from their energy-minimized structures (MM+ force field using HyperChem®). At first the significant NOE between H_a and dioxymethylene hydrogen H_{ii} (6.6 %) rules out the possibility of conformers **5A** and **5B** (The calculated minimized energy of conformer **5** in the gas phase is about 150 kcal mol^{-1} higher than that of **6**). The large NOE between H_a and H_{ii} compared to that between H_a and H_{io} (6.6 vs. 0.0 %) implies that H_a is much closer to H_{ii}. Even the calculated distances between H_a and H_{ii} of **6A** and **6B** (1.90 vs. 2.22 Å) or H_a and H_{io} (2.34 vs. 3.93 Å) appeared to be closer in **6A**, the large differences of NOEs (6.6 vs. 0.0 %) matches better to conformer **6B**. Also the distances between H_{bi} and H_{ci} for **6A** and **6B** and its NOE (3.33 vs. 2.81 Å, 3.2 %) or those between H_{bi} and H_{oo} (6.20 vs. 3.75 Å, 1.4 %) match much better to conformer **6B** than to conformer **6A**. Especially NOE between H_{bi} and H_{oi} (8.1 %) exclusively support conformer **6B** (2.75 Å), because for conformer **6A** these two hydrogens are far apart (4.12 Å). Conclusively the [2 + 2] product exists as conformer **6B**. Conformer **6B** is the first preorganized biscavitand whose cavity is divided into two by the intra π - π stacking.

It is presumable that the solvent templation effect for the formation of conformer **6A** is very weak and the intermediate leading to the empty **6A** in N,N-dimethylacetamide would be a high energy state. So the self-templation by the weak π - π interaction, which collapses the cavity to give a lower energy state, would play a crucial role for the formation of **6B**. The conformational stability of **6B** arises from the high rotational barrier through CH_2-S-CH_2bond due to the large steric hindrance of sulfur atom and the π - π attraction of two benzene units which are sustaining the rigid four pillared system. The calculated average distance between two bridging benzene units of **6B** is about 3.88 Å which is close to van der Waals distance (3.45 Å) of graphite.

The binding study of biscavitand **6B** for potential small guests such as O_2, N_2, Ar, NH_4^+, CH_4[12] or transition metals and the resolution of its crystal structure are under investigation.

Table 1. The Average Distances between Two Hydrogens in **6A** and **6B** and the Corresponding NOEs.

		H_a-H_{ii}	H_a-H_{io}	H_{bi}-H_{ci}	H_{bi}-H_{oo}	H_{bi}- H_{oi}
Average	**6A**	1.90	2.34	3.33	6.20	4.12
Distance (Å)[a]	**6B**	2.22	3.93	2.81	3.75	2.75
NOE[b] (%)		6.6	0.0	3.2	1.4	8.1

[a] Average Distances were measured from the Energy-Minimized Conformation (MM+ force field) of **6A** and **6B**.

[b] NOEs are from the volume integration of cross peaks in the NOESY spectrum.

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10. Selected data for **4**: mp >296 ℃ (dec.); ^1H NMR (300MHz, $CDCl_3$) δ 1.00 (m, 12H, CH_3), 1.35 (m, 8H, $CH_2C\mathit{H}_2CH_3$), 2.20 (m, 8H, $C\mathit{H}_2CH_2CH_3$), 2.85 (q, 8H, SCH_2 from xylyl), 3.75 (q, 8H, SCH_2), 4.25 (d, J = 7.4 Hz, 2H, OCH_2O), 4.65, (m, 4H, OCH_2O), 4.80 (t, 2H, CH), 4.90 (t, 2H, CH), 6.18 (d, J = 7.1 Hz, 2H, OCH_2O), 7.10 (s, 4H, Ar-H), 7.18 (m, 4H, xylyl-H), 7.50 (m, 4H, xylyl-H); MS (FAB+) m/e 1094 (M^+, 13%)
11. Selected data for **6B**: mp >232 ℃ (dec.); ^1H NMR (300MHz, $CDCl_3$) δ 0.98 (m, 24H, CH_3), 1.30 (m, 16H, $CH_2C\mathit{H}_2CH_3$), 2.15 (m, 16H, $C\mathit{H}_2CH_2CH_3$), 3.30 (d, J = 18.0 Hz, 8H, H_{bi}), 3.60 (d, J = 14.7 Hz, 8H, H_{ci}), 3.80 (d, J = 18.0 Hz, 8H, H_{bo}), 4.20 (d, J = 14.7 Hz, 8H, H_{co}), 4.30 (d, J = 5.4 Hz, 4H, H_{oi}), 4.80 (t, 8H, CH), 5.10 (d, J = 8.1 Hz, 4H, H_{ii}), 6.20 (d, J = 8.1 Hz, 4H, H_{io}), 6.30 (d, J = 5.4 Hz, H_{oo}), 6.90 (s, 8H, ArH), 7.70 (s, 4H, ArH_a); MS (FAB+) m/z 2026 (M^+, 9%).
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