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Singly bridged double resorcin[4]arene bearing sixteen hydroxyl groups. Formation of capsular-type inclusion complexes in methanol

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Dedicated to Emeritus Professor Soichi Misumi on the occasion of his 77th birthday

Abstract—The $Sc(OTf)_3$-catalyzed mixed cyclocondensation of bis-1,2-(2,6-dihydroxyphenyl)ethane and 2-hexylresorcinol gave a singly bridged double-resorcinarene bearing sixteen hydroxyl groups at the peripheral positions. In methanol, the double-resorcinarene binds quaternary ammonium ions to form capsular-type 1:1 complexes.

Calixarenes and resorcinarenes are bowl-shaped $[1_4]$metacyclophane compounds and versatile building blocks for the construction of molecular capsules.[1–4] In particular, a number of double metacyclophanes have been assembled from two metacyclophane units. Their structural mobility and efficiency in molecular recognition processes are largely dependent upon the nature, length, geometry, and number of bridging groups. In a system linked by a single covalent bond, it is presumed that the two subunits are free to rotate about the bridge. However, they mostly form a 1:1 complex with quaternary ammonium ions and pyridinium ions in a capsular conformation,[5–8] indicating the cooperative action of the two macrocycles and the efficiency of the cation-π[9] and CH-π interaction.[10,11] These observations prompted us to synthesize the double resorcinarene **4**, bearing sixteen phenolic hydroxyl groups at the peripheral position. Since strong electron-donating hydroxyl groups increase the π-basicity, **4** should show an enhanced inclusion ability for organic ammonium cations. We now report the synthesis and inclusion properties of the singly bridged double resorcinarene **4**.

We employed bis-1,2-(2,6-dihydroxyphenyl)ethane **3** as a key compound in this synthetic pathway (Scheme 1). Debrominated coupling of 2,6-bis(methoxymethoxy)-benzyl bromide **1**[12] with magnesium in THF gave the MOM ether derivative **2**[†] in 42% yield. Removal of the MOM function of **2** was easily accomplished by treatment with HCl in methanol to give **3**[‡] in 89% yield. The mixed cyclocondensation of **3** and 2-hexylresorcinol (molar ratio 1:18) with an excess of

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Keywords: resorcinarene; inclusion complex; capsular molecule; quaternary ammonium ion.

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[†] (**2**): A solution of 1,3-bis(methoxymethoxy)-2-bromomethylbenzene **1** (1.35 g, 4.64 mmol) in dry THF (8 ml) was added into a suspension of magnesium powder (0.15 g, 6.0 mmol) in dry THF (20 ml) under an argon atmosphere. The mixture was stirred for 0.5 h and then iodine (10 mg) was added. After 3 h stirring at 40°C, the solvent was removed in vacuo. The residue was triturated with diethyl ether, and the ether soluble fraction was separated and concentrated. The residue was recrystallized from ethanol to give the MOM ether **2** as white prism; yield 42%. Mp 98–99°C. ^{1}H NMR (270 MHz, $CDCl_3$, 30°C): δ 2.97 (s, 4H, $ArCH_2$), 3.45 (s, 12H, OCH_3), 5.02 (s, 8H, OCH_2O), 6.73 (d, 4H, ArH, $J=8.2$ Hz), 7.01 (t, 2H, ArH, $J=8.2$ Hz). IR (KBr, cm^{-1}) 2999, 1598, 1474, 1143, 1094. Anal. calcd for $C_{22}H_{30}O_8$: C, 62.55: H, 7.16. Found: C, 62.39: H, 7.07.

[‡] (**3**): The MOM ether (0.124 mg, 0.29 mmol) was dissolved in methanol (10 ml). To this solution was added two drops of concd HCl with stirring. The solution was heated to reflux for 1 h, diluted with water, and then extracted with ethyl acetate (3×20 ml). The combined organic phase was concentrated to leave white solid, which was recrystallized from water to produce **3** in 89%. Mp 231–237°C (dec.). ^{1}H NMR (270 MHz, DMSO-d_6, 50°C) δ 2.65 (s, 4H, $ArCH_2$), 6.27 (d, 4H, ArH, $J=7.9$ Hz), 6.75 (t, 2H, ArH, $J=8.1$ Hz), 8.77 (s, 4H, OH). IR (KBr, cm^{-1}) 3272, 1654, 1618, 1592. Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28: H, 5.73. Found: C, 67.98: H, 5.90. FAB-MS calcd for $C_{14}H_{14}O_4$, 246.1. Found: 246.2.

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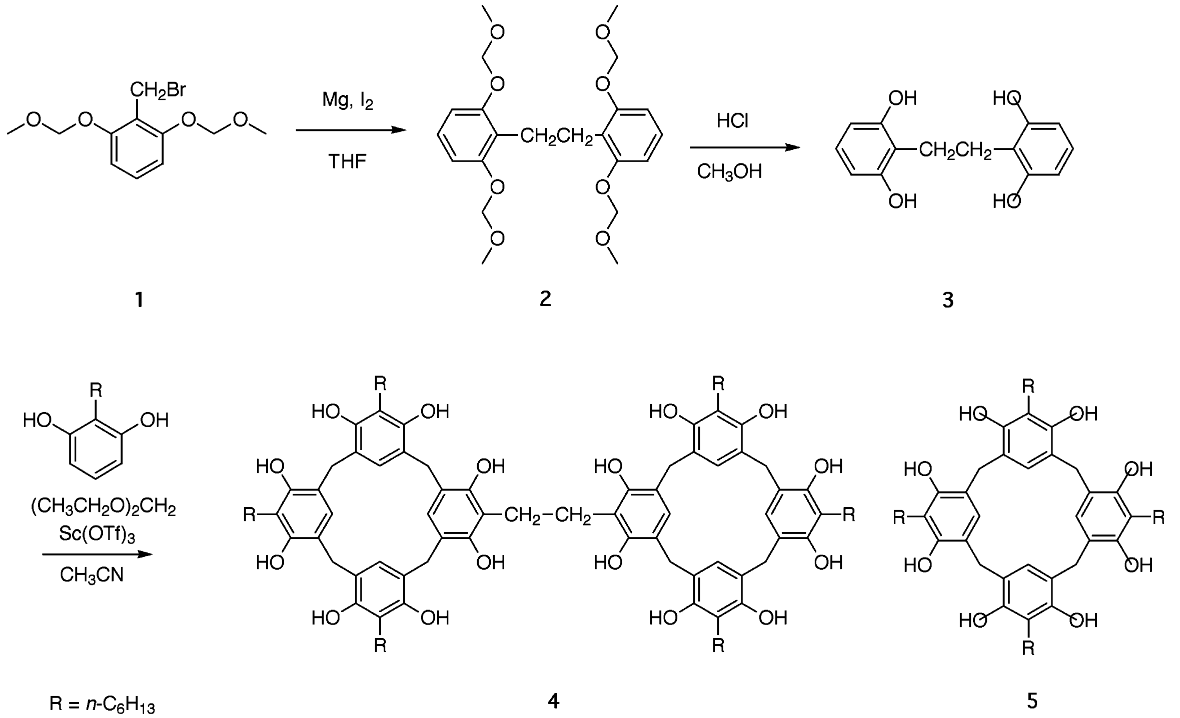

Scheme 1. Synthesis of the double-resorcinarene **4**.

diethoxymethane in acetonitrile using $Sc(OTf)_3$ as a catalyst,[13] produced the double resorcinarene **4**[§] and resorcinarene **5**[14] in 29 and 42% yields, respectively. The structure of **4** was unambiguously proved by ^{1}H NMR spectroscopy and FAB mass spectrometry. Its ^{1}H NMR spectrum (CD_3OD) exhibits two singlets (1:1 ratio) for the bridging methylene protons of the resorcinarene skeleton ($ArCH_2Ar$), and three singlets (1:2:1 ratio) for the aromatic protons in accordance with the expected pattern for a monosubstituted resorcinarene. In addition, the four protons of the ethano bridge are seen as a singlet. Finally the dimeric nature of **4** was confirmed by a molecular ion peak at $m/z = 1506.9$ (calcd 1506.8).

In CD_3OD solution at 30°C, both the double resorcinarene **4** and the resorcinarene **5** showed sharp singlets for the $ArCH_2Ar$ protons in the ^{1}H NMR spectrum. In addition, the broadening of these signals could not be observed at −60°C. Furthermore, the chemical shifts of all the protons in **4** are very similar to those of the corresponding protons of **5**; the differences are within 0.03 ppm. Therefore, it is concluded that **4** is a very flexible molecule and there is no interaction between the two resorcinarene units in this solvent.

The binding property of the double resorcinarene **4** to tetraethylammonium (TEA) chloride and 4-*tert*-butyl-*N*-methylpyridinium (BMP) iodide in CD_3OD was measured by ^{1}H NMR titration. For comparison, the complexation property of resorcinarene **5** was also studied. The stoichiometry of the complexes was evalu-

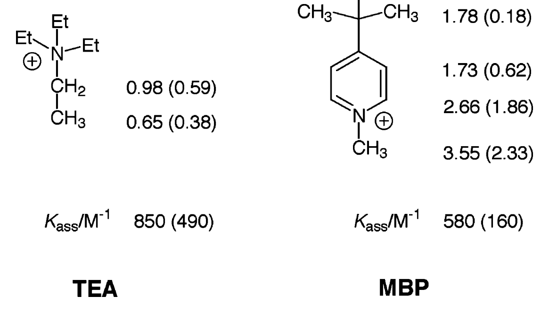

Figure 1. Association constants K_{ass} and complex induced shifts (CIS, ppm) for 1:1 complex for host **4** in CD_3OD. The values in parentheses are for the complexes with **5**.

[§] Double resorcin[4]arene (**4**): The diphenylethane **3** (46 mg, 0.19 mmol), 2-hexylresorcinol (0.65 g, 3.30 mmol) and diethoxymethane (1.50 g, 14.0 mmol) were dissolved in acetonitrile (25 ml). The solution was stirred and $Sc(OTf)_3$ (30 mg, 0.06 mmol) was added. After stirring for 3 h at 80°C, the solution was concentrated. The residue was dissolved in ethyl acetate and washed with water. The solvent was removed and the residue was purified by recycle-type HPLC. The double-resorcin[4]arene **4** (87 mg, 29%) and resorcin[4]arene **5** (42%) were isolated as pure materials. **4**: mp 220°C (dec.). IR ($CDCl_3$, cm^{-1}) 3598, 3394. ^{1}H NMR (270 MHz, CD_3OD, 30°C) δ 0.78 (m, 18H, CH_3), 1.19–1.47 (m, 48H, $CH_2(CH_2)_2CH_2$), 2.56 (m, 4H, Ar CH_2), 2.60 (m, 12H, Ar CH_2), 3.70 (s, 8H, bridge CH_2), 3.74 (s, 8H, bridge CH_2), 7.02 (s, 2H, ArH), 7.03 (s, 4H, ArH), 7.07 (s, 2H, ArH). Anal. calcd for $C_{94}H_{122}O_{16}$: C, 8.15: H, 74.87. Found: C, 8.27: H, 74.73. FAB-MS calcd for $C_{94}H_{122}O_{16}$, 1506.9. Found 1506.8.

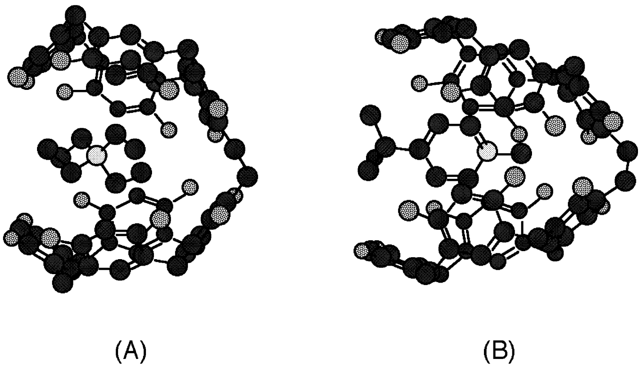

Figure 2. Schematic representation for the complexes of the double-resorcinarene **4** with (A) TEA and with (B) MBP. The hexyl groups and hydrogen atoms are omitted for clarity.

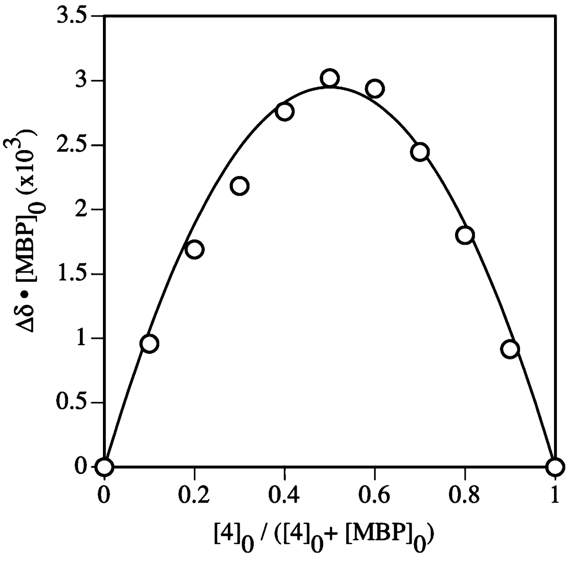

Figure 3. A Job's plot for the double-resorcinarene **4** and MBP. Total concentration: 5.0×10^{-3} mol/l.

ated by the Job's plot analysis (Fig. 1). Next, the association constants (K_{ass}) of these complexes and the complex induced shifts (CIS) of the guest molecules were determined by a computer-assisted nonlinear least square-analysis.[15]

The spherical TEA molecule is effectively bound by both host resorcinarenes. Thus, the **4**: TEA 1:1 complex has a $K_{ass}=850$ M^{-1}, while for the **5**: TEA 1:1 complex, a value of $K_{ass}=490$ M^{-1} was determined. Moreover, the CIS values of TEA observed for **4** are 1.6 times greater than those for **5**. These data strongly suggest that TEA is encapsulated into a capsular that is cooperatively formed by two resorcinarne units as shown in Figure 2 (A).

Next, we examined the complexation of MBP, a bulkier *N*-methylpyridinium ion, with **4** and **5**. It is well known that the *N*-methyl groups of pyridinium ions are selectively included into the cavity of metacyclophane core.[16] By analysis of the CIS value of MBP observed for the complexation with **5**, it is also concluded that MBP is deeply bound in the host cavity through an *N*-methyl-π interaction. Therefore, it was reasonably expected that each of the resorcinarene units of host **4** should include MBP molecule to form a 1:2 complex. However, as seen in Figure 3, the Job's plot evidently confirmed the 1:1 complex formation between **4** and MBP. More remarkable is the large CIS values of all the protons of **4**. On the basis of these results, it can be presumed that the guest molecule is included in an equatorial orientation between two cavities as shown in Figure 2 (B). The K_{ass} for the complex of **4** with MBP was 580 M^{-1}, which is greater by 3.6-fold than that of **5**. This enhancement in K_{ass} is attributed to the addition of four CH-π interactions between the acidic pyridinium CH bonds with two π-basic resorcinarene cores.[17]

In conclusion, we have demonstrated the usefulness of the mixed cyclocondensation of resorcinols for the synthesis of a double-resorcinarene bearing sixteen hydroxyl groups, which behaves as a molecular capsule in the presence of quaternary ammonium ions. The double-resorcinarene can be considered as a versatile molecular platform for the design of carcelands. Further work in this direction is currently underway in our laboratory.

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