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Synthesis and Binding Behavior of an Artificial Receptor Based on "Upper Rim" Functionalized Calix[5]arene

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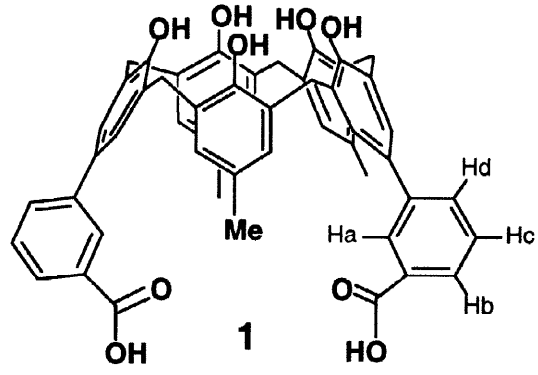
Abstract: A new calix[5]arene possessing two benzoic acid moieties was synthesized as an artificial receptor and its ability of binding to a variety of amine guests was investigated. The structures of the complexes with the amines were proposed by the molecular mechanics calculation using MacroModel V. 4.0. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Investigation of artificial receptors for neutral molecules is of interest in bioorganic chemistry. Recently, a large number of small organic hosts with a variety of functional groups have been synthesized for the evaluation of the guest-binding behavior by non-covalent forces, such as hydrogen bonding, van der Waals, π-π, cation-π, CH-π interactions.[1,2] Calixarenes[3] play an important role as host molecules in host-guest chemistry. The small-size members of the series, calix[n]arenes (n=4, 5), are known to have an ideal cone shape which is responsible for a preorganized cavity.[4] Our current attention is to apply the calix[5]arene cone cavity to the host-guest chemistry.[5] A well-designed arrangement of the various functional groups on the receptor should be a prerequisite for the effective binding of guest molecules. In this paper, we report the synthesis and binding behavior of a new receptor based on calix[5]arene.

RESULT AND DISCUSSION

Design and Synthesis of Receptor



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As an artificial receptor, "upper rim" functionalized calix[5]arene **1** is designed. In the cone conformation, five phenol rings of **1** form a cup-shaped cavity. The two carboxyl groups on the upper rim

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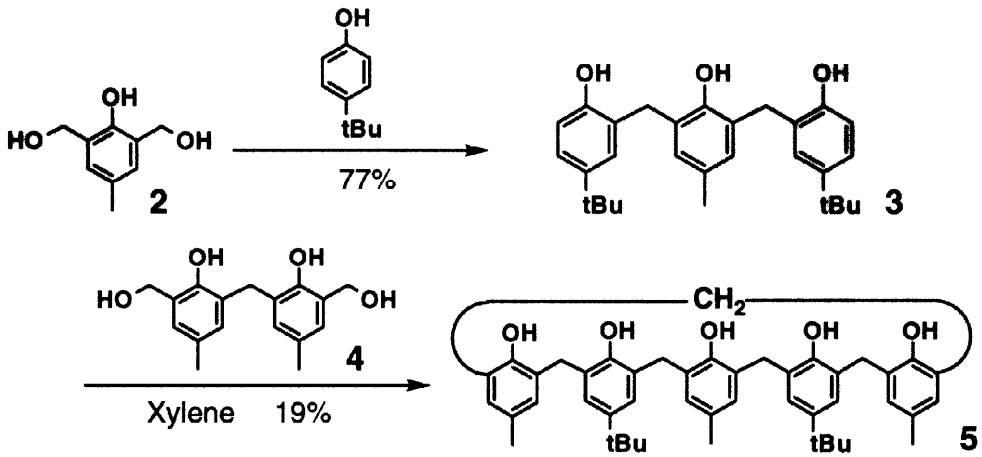
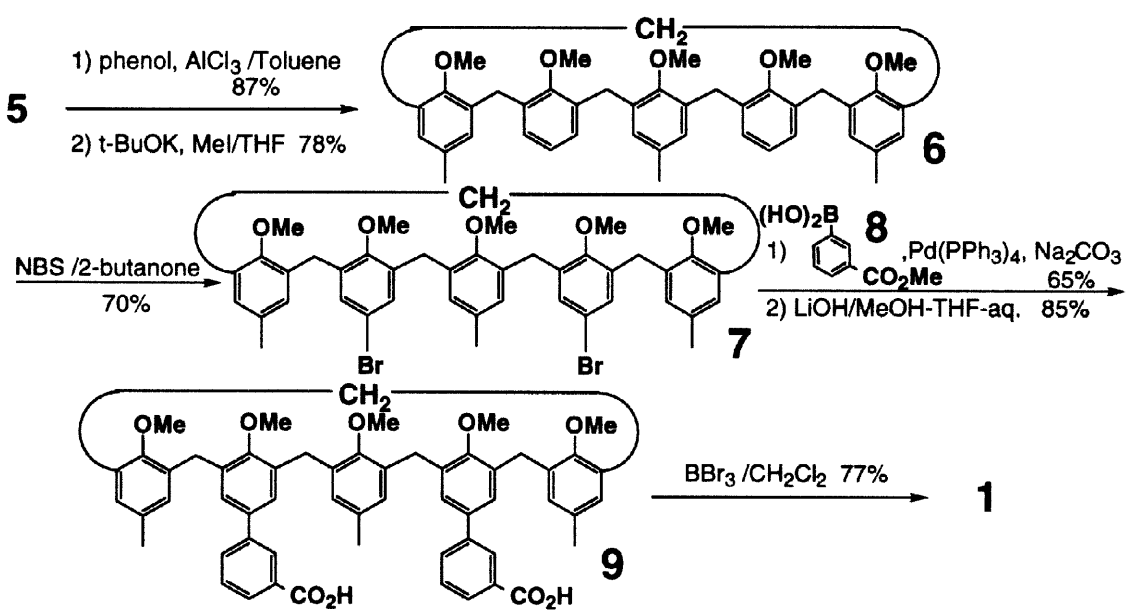
can grasp some neutral guests having polar functional groups. The synthesis of the target compound is shown in Schemes 1 and 2. The synthesis of the basic skeleton was carried out starting from bis(hydroxymethyl)cresol 2[6]. Treatment of 2 with a large excess of *tert*-butylphenol gave 3 in 77% yield. Condensation of 3 and 4 in xylene under refluxing condition gave dibutylcalix[5]arene 5 in 19% yield.

Scheme 1



Treatment of 5 with aluminum trichloride and phenol, followed by protection of the hydroxyl groups gave pentamethyl ether 6. Subsequent bromination of 6 with NBS afforded dibromide 7. Suzuki's coupling reaction[7] between 7 and boric acid 8[8] gave the diester in good yield. Subsequent hydrolysis of the ester groups afforded dicarboxylic acid 9. Deprotection of the methyl ether furnished the desired compound 1.

Scheme 2



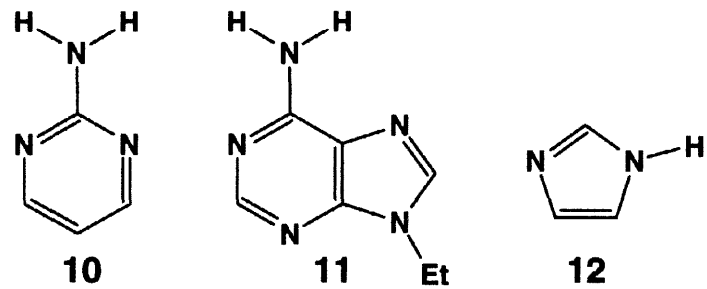
Self-association Study

Before examining the binding behavior of the host molecule to some amine guests, the self-association of **1** was investigated over a wide range of concentration (10^{-4} to 10^{-2}M in $CDCl_3$). The ^{1}H-NMR chemical shifts of the benzoic acid moiety remained constant within <0.04 ppm (Table 1). Thus, **1** does not form an intermolecular hydrogen bonding dimer nor an oligomer, and the aggregation of **1** is negligible under the conditions employed for the binding studies. IR measurement supports this conclusion. The IR absorption bands due to the carboxyl groups in **1** did not show any concentration-dependent change in a wide range of concentration of **1** in CCl_4, suggesting an intramolecular hydrogen bonding between the two carboxyl groups of **1**.

Table 1 Chemical shifts (ppm) of benzoic acid moiety of **1**.

Conc. (M)	Ha	Hb	Hc	Hd
5×10^{-4}	8.29	7.80	7.53	8.03
4×10^{-3}	8.29	7.80	7.53	8.05
4×10^{-2}	8.30	7.76	7.51	8.05

Binding Studies



Standard titration experiments were carried out by ^{1}H-NMR spectroscopy. The binding constants of the amine guests were examined in $CDCl_3$. The signal of the NH proton of 2-aminopyrimidine **10** shifted downfield when **1** was added to the guest solution, indicating that **10** was captured by **1** with the hydrogen bonding interaction to form the host-guest complex. The stoichiometry of the complex (1:1) was determined by Job's plot. The non-linear curve fitting analysis[9)] of the complexation induced down-field shift data of the NH protons gave the association constant (870±100 M^{-1}) using Gauss-Newton algorithm (Fig. 1). The stoichiometry of the complex of 9-ethyladenine **11** with **1** was also determined to be 1:1 in a similar manner. By contrast, a 2:1 complex was deduced in the case of **1** and imidazole **12**. The association constants of these complexes were determined by a similar curve-fitting analysis based on the complexation-induced chemical shift change of Ha in the benzoic acid moiety of **1** with Simplex algorithm (Table 1). The binding behavior of the pentamethyl ether host **9** to these guests was also examined.

These non-linear curve fitting analyses gave not only the binding constants but also the complexation-induced shift of the protons in the completely bound guest. The amine protons of the guests

were shifted significantly to the lower-field but the aromatic protons of the guest did not show any appreciable induced shift when bound in the host cavity of **1**.

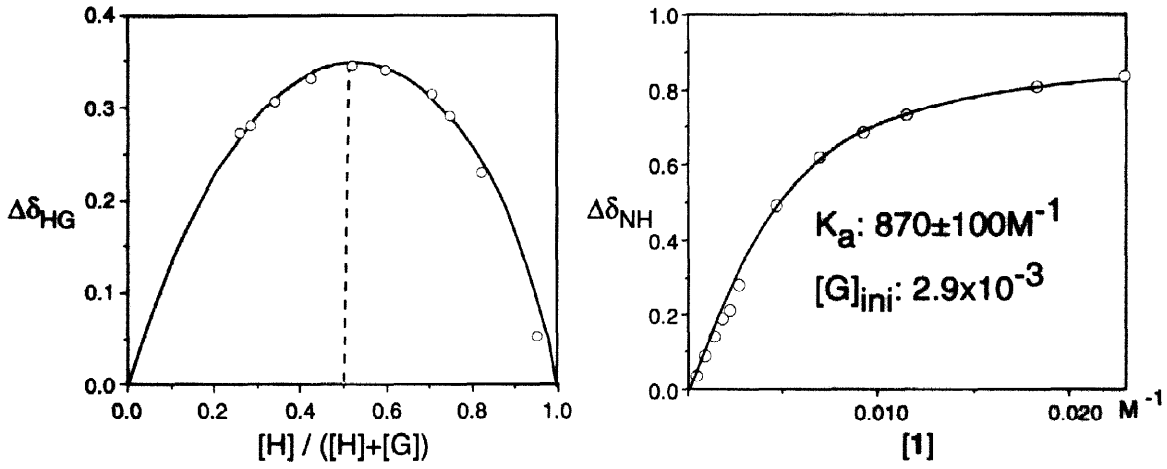


Figure 1 Job's plot and complexation-induced shift of NH proton of **10**.

These induced shifts of the guest proton gave us important information about the structure of the host-guest complexes. The large down-field shift of the NH_2 protons indicated the strong hydrogen bonding between the NH_2 protons of the guest and the carboxyl groups of **1**. Thus, a four-fold hydrogen bonded structure was suggested. From a molecular model consideration it was suggested that, to attain the strong hydrogen bonding interaction, the NH_2 group of the guest should come closer to the carboxyl groups and the aromatic protons of the guest should stay outside of the host cavity. The inverse arrangement of the guest can be possible, in which the aromatic protons reside deeply inside of the host cone cavity. However, this does not give undistorted hydrogen bonds, and could not be supported by the ^{1}H-NMR titration experiment because in this structure the aromatic protons of the guest should show a large complexation-induced up-field shift. The absence of a prominent shift change of the guest aromatic proton thus supported the former arrangement of the guest.

The association constants of the complexes of **9** with the guests, **10** and **11** are smaller than those of **1** with respective guests. The difference in these association constants should be due to the difference in the magnitude of the attractive hydrogen bonding energies. Extra stabilization of the complex other than the hydrogen bonds between the host and guest is another possible explanation. A simple model construction suggested that the extra stabilization should be a strengthening of the lower rim intramolecular hydrogen bonds of the phenolic OH groups in the host. In the free host of **1**, the intramolecular hydrogen bond between the upper rim two carboxyl groups resulted in a partial break of the cyclic hydrogen bond of the lower rim five OH groups (Figure 3). The two carboxyl groups of the host move away from each other when the amine guest is bound between them. This movement of the carboxyl groups causes partial recovery of the cyclic hydrogen bond of the phenolic OH groups. Such type of extra stabilization cannot be expected in the complex formation between the host **9** and the amine guests.

Table 2 Association constants (M^{-1}); with stoichiometry in parenthesis.

Guests	1	9
2-aminopyrimidine **10**	870 ± 100 (1:1)	310 ± 30 (1:1)
9-ethyladenine **11**	43000 ± 8000 (1:1)	2300 ± 300 (1:1)
imidazole **12**	K_1 = 100 (1:1)	
	K_2 = 40000 (1:2)	

The host-guest complex of **1** and **12** is in a ratio of 1:2 (H:G). From the consideration of pKa values of benzoic acid and the imidazolium ion, the binding phenomena should arise from hydrogen bonding between two carboxylates and the imidazolium ion. The large K_2/K_1 value of these bindings is quite different when compared to a similar case. In Rebek's cleft-type receptor, two imidazolium ions bound in a parallel arrangement by two carboxylates and showed small K_2/K_1 (~0.05)[10] because of the unfavorable electrostatic repulsion between the guests. Hence, two imidazolium ions should not have a parallel arrangement in our case.

Molecular Modeling Study

While the precise structure for the complexes remains to be determined, the result of the molecular mechanics calculations is informative. To obtain the structure of the most stable complex with two imidazolium ions, we carried out a 10000-step MacroModel/MCMM conformational search[11] using AMBER*[12] force field. The most stable structure is shown in Figure 2. In this structure, one guest ion is bound between the two carboxylates by hydrogen bonding interaction. The other ion is folded within the π-basic cavity of the host by using hydrogen bonding and cation-π interactions while one acidic proton of the guest ion within the cavity projects into the π-cloud of the facing benzene ring. Complexation-induced shifts of the guest ion gave experimental support of the guest inclusion into the host cavity; when one equivalent of the guest was added to the host solution, H_2 and $H_{4,5}$ of the guest ion exhibited up-field shifts of 0.78 and 0.5 ppm, respectively, as compared to the shifts of the imidazolium ion.[13]

In the cases of **10** and **11**, the stochastic dynamics simulation for 60-ps was employed to obtain the initial structures. These structures were optimized using AMBER* force field in GB/SA solvation model.[14] The most stable conformations of the complexes are also shown (Figure 2). As is clearly seen in this Figure, the amine guests were squeezed by the two carboxyl groups of **1**. The orientation of the guest and the four-fold hydrogen bonding pattern was confirmed by this calculation. In the complex of **11**, both the Watson-Crick and Hoogsteen type hydrogen bonding chelations worked simultaneously. Because of these chelations, the distance between the two carboxyl carbons of **1** is larger than the corresponding distance in the complex of **1** and **10**.

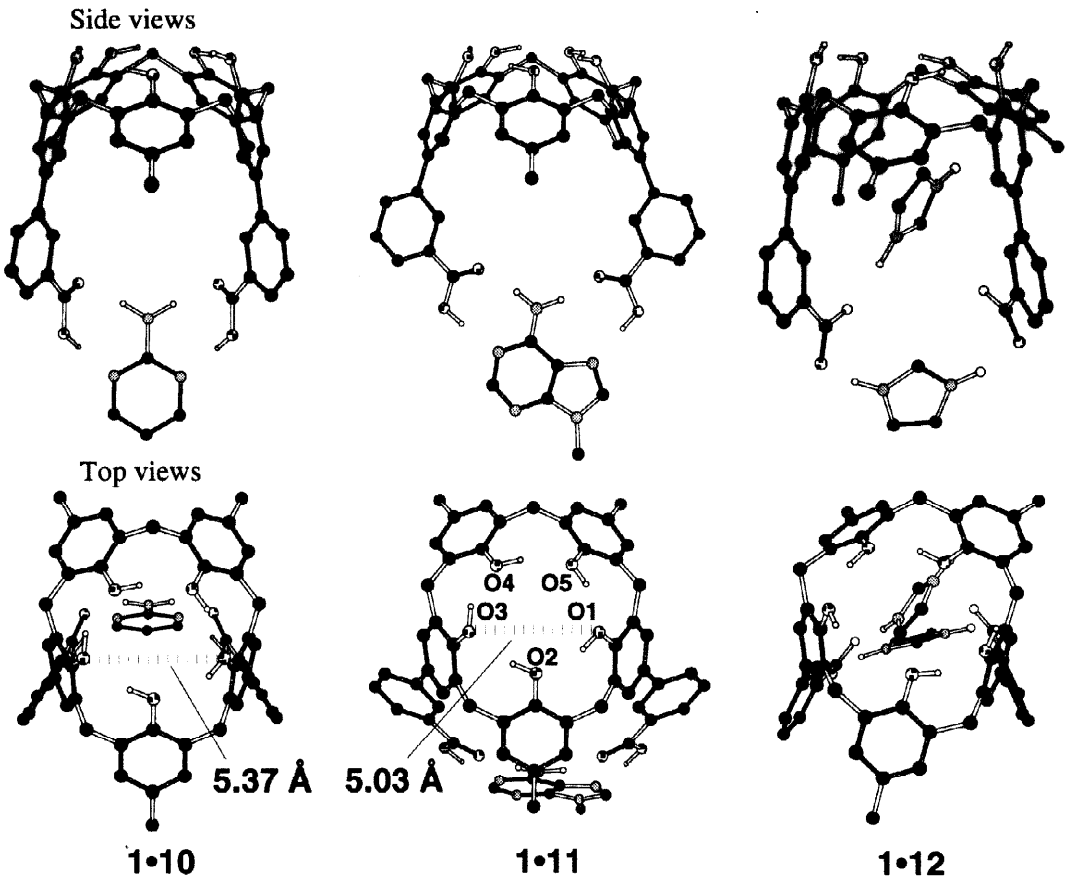


Figure 2 The most stable strucutures of the complexes.

This induced fit type of movement of the two carboxyl group in the guest binding process changed the lower rim O1---O3 distance (5.37 Å in **1-10** and 5.03 Å in **1-11**). The same movement also changed the magnitude of the intramolecular hydrogen bonding strength in the cyclic array of the lower rim five hydroxyl groups, as is predicted by the simple molecular model consideration (*vide supra*). The O--O distances of the cyclic array in the complex of **1** and **10** are 3.14, 3.10, 2.91, 2.95, and 2.94 Å in the order of O1-O2, O2-O3, O3-O4, O4-O5, and O5-O1 and 2.92, 3.05, 2.89, 2.93, and 2.90 Å, respectively, in the complex of **1** and **11**. The two distances O1-O2 and O2-O3 in the former are larger than the corresponding values of the latter, reflecting the longer distance of O1---O3. The difference between the two association constants of the neutral amine complexes can thus be well explained mainly by the difference in the magnitude of the intramolecular hydrogen bonding strength on the cyclic array of the lower rim hydroxyl groups. The same discussion of the lower rim hydrogen bonding array can be valid in the explanation of the small association constant in the first stage of the complex formation process of **1** and **12**. The size of the hydrogen bonding portion of the imidazolium ion guest is smaller than that of the guest **10**. Thus, the small association constant of the first stage suggested a squeezing process of the guest ion by the two carboxylates. The intramolecular hydrogen bonds within the cyclic array of the lower rim hydroxyl groups should thus be weaker than those of the complex of **1** and **10**. However, the binding of the first guest gave at the same time a formation of the vacant cavity suitable for the second guest. Thus, the second guest ion

can be easily bound into this preorganized cavity. The large association constant for the second guest can be explained both by the attractive Coulombic interactions and the small entropic change for the inclusion of the second guest into the preorganized host.

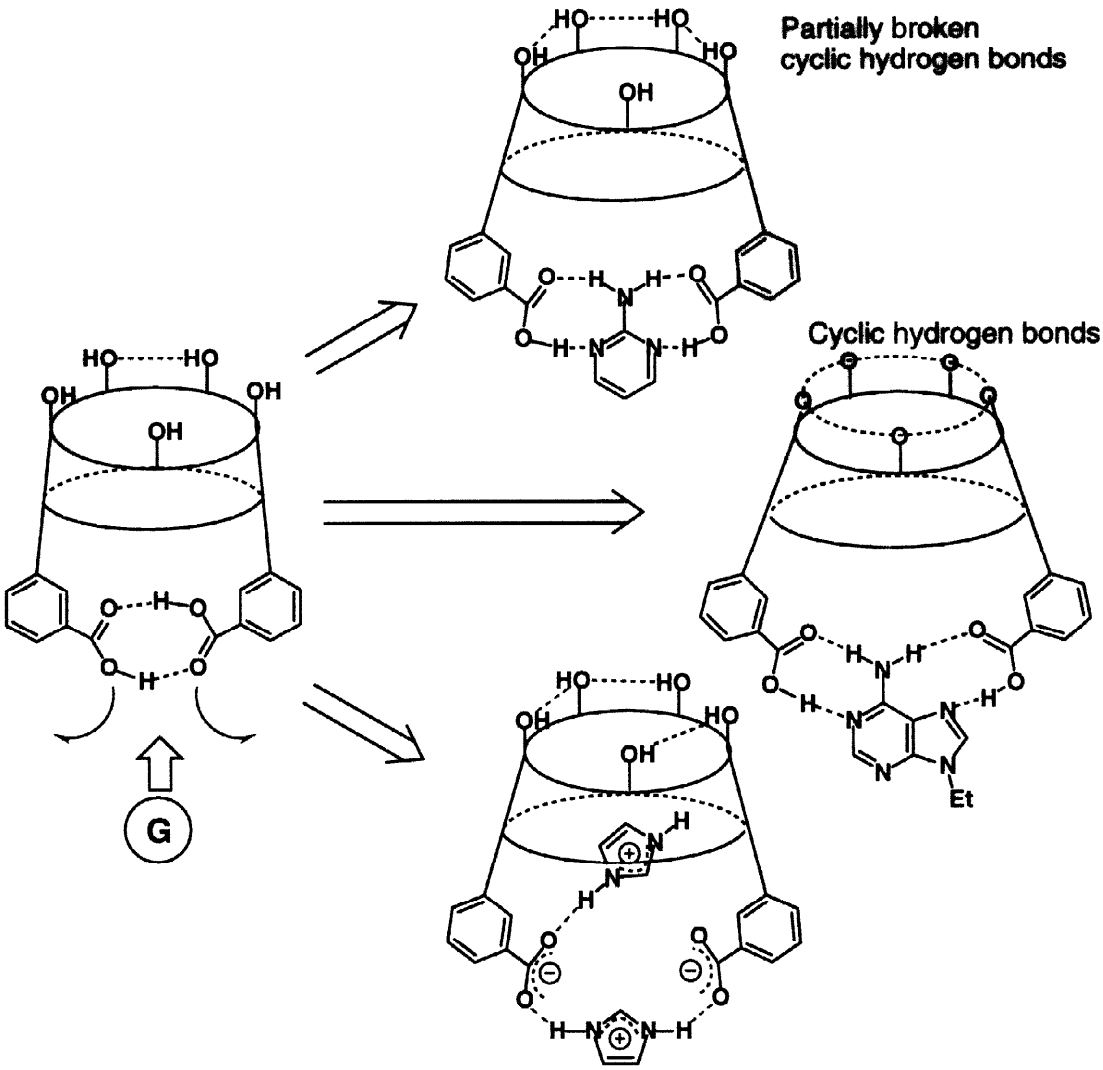


Figure 3 Schematic representation of the guest binding process.

CONCLUSION

The binding studies of the host molecules toward the amine guests demonstrated that the host **1** shows a prominent shape-selectivity. The selectivity is closely related to the structural change in the host-guest complexes. The molecular mechanics calculations gave us an agreeable reasoning for the shape-selectivity to the guests. The cyclic hydrogen bonds of the host play an important role in the guest binding. The molecular modeling study of the host-guest complex give us important information for the guest binding process, and play a crucial role in designing a host molecule.

EXPERIMENTAL SECTION

^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL Type EX-90, EX-400, and GSX-270 spectrometers. Chemical shifts are reported in parts per million (δ, ppm) relative to the solvent residual or tetramethylsilane. FAB and EI mass spectra were measured on JEOL Type SX-102. Elemental analyses were recorded using Perkin-Elmer 2400 CHN instrument. Infrared spectra were measured on HITACHI 260-10S instrument. GPC chromatography was carried out by using JAI model LC-908s.

2,6-(bishydroxymethyl)cresol 2 and 2-(3-hydroxymethyl-5-methylsalicyl)-6-hydroxylmethyl cresol 4

To a solution of cresol (81.6 mL, 0.78 mol) and 46% aqueous formaldehyde solution (245 mL, 3.24 mol) in water (1 L) was added K_2CO_3 (165 g, 1.20 mol). After being stirred at 60 °C for 6 hr, aqueous 6M HCl was added to the resulting mixture until pH of the solution becomes less than 1. The precipitate was filtered and collected. The recrystallization of the precipitate from ethyl acetate gave **4** (44g, 39%). The filtrate was extracted with ethyl acetate. The organic layer was concentrated *in vacuo* to obtain the crude solid **2**. The solid was recrystallized from ethyl acetate to give **2**[6] (30g, 23%). **4**: IR (KBr) 3350, 1610, 1480, 1230; ^{1}H-NMR (90 MHz, $CDCl_3$) 6.70-7.30 (m, 4H), 4.80 (s, 4H), 3.90 (s, 2H), 2.3 (s, 6H). HRMS calcd. for $C_{17}H_{20}O_4$ 288.1362; found 288.1369.

2,6-(bis(5-*tert*-butylsalycyl))-4-methylphenol 3

To the solution of **2** (29.8 g, 178 mmol) and *t*-butylphenol (266 g, 1.78 mol) in methanol was added aqueous 6N hydrochloric acid (30 mL). After refluxing for 7.5 hr, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was recrystallized from hexane to give **3** (59.5g, 77%). IR (KBr); 3240, 2990, 1630, 1525. ^{1}H-NMR (90MHz, $CDCl_3$); 8.30 (s, 3H), 7.33 (d, 2H, *J*=2 Hz), 7.10 (dd, 2H, *J*=8, 2 Hz), 7.02 (s, 2H), 6.78 (d, 2H, *J*=8 Hz). Anal. Calcd. for $C_{29}H_{36}O_3$: C, 80.52; H, 8.39. Found: C, 80.51; H, 8.39.

11,23-di-*tert*-butyl-5,17,29-trimethyl-31,32,33,34,35-pentahydroxycalix[5]arene 5

A solution of **3** (20.0 g, 46.3 mmol) and **4** (18.7 g, 64.9 mmol) in xylene was refluxing for 24 hr. After removal of the solvent, the crude product was purified by column chromatography on SiO_2 with 5% ethyl acetate in hexane to give the calix[5]arene **5** (6.01 g, 19%). IR (KBr); 3270, 2950, 1745, 1618, 1480, 1450. ^{1}H-NMR (400 MHz, $CDCl_3$); 8.83 (bs, 5H), 7.17 (s, 4H), 6.99 (s, 2H), 6.98 (s, 4H), 3.6-4.0 (m, 10H), 2.23 (s, 9H), 1.28 (s, 18H). ^{13}C-NMR (100MHz, $CDCl_3$); 147.87, 147.83, 144.0, 130.6, 130.55, 129.6, 126.7, 126.6, 126.5, 126.0, 125.9, 34.0, 31.7, 31.5, 31.44, 31.37, 20.5. EIMS (m/z) 684. Anal. Calcd. for $C_{46}H_{52}O_5$: C, 80.67; H, 7.65. Found: C, 80.60; H, 7.50.

5,17,29-trimethyl-31,32,33,34,35-pentahydroxycalix[5]arene

To a solution of the calix[5]arene **5** (1.74 g, 2.54 mmol) and phenol (1.48 g, 158 mmol) in toluene (120 mL) was added anhydrous aluminum chloride (2.54 g, 18.4 mmol) at room temperature. The solution was stirred until the color of the solution turned to dark red, then aqueous 1N hydrochloric acid was added, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by recrystallization from methanol to give the desired calix[5]arene derivative (1.26 g, 87%). IR (KBr); 3250, 1600, 1480, 1470, 1450, 1220. ^{1}H-NMR

(270 MHz, $CDCl_3$); 8.97 (s, 2H), 8.78 (s, 3H), 7.20 (d, 4H, J=7.8 Hz), 6.99 (s, 6H), 6.83 (m, 2H), 3.50-4.00 (m, 10H), 2.22 (s, 9H). ^{13}C-NMR (67.5 MHz, $CDCl_3$); 150.1, 147.8, 130.6, 129.8, 129.6, 129.1, 126.8, 126.5, 126.4, 121.4, 31.3, 20.4. EIMS (m/z) 572. Anal. Calcd. for $C_{38}H_{36}O_5$: C, 79.70; H, 6.34. Found: C, 79.83; H, 6.29.

5,17,29-trimethyl-31,32,33,34,35-pentamethoxycalix[5]arene 6

To a solution of the above calix[5]arene (0.95 g, 1.89 mmol) in THF (80 mL) was added *t*-BuOK (2.24 g, 22.7 mmol) at room temperature. After a few minutes, iodomethane (5.2 mL) was added to this solution, and stirred for 2.5 hr. The reaction mixture was poured into aqueous 1M hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 to give pentamethylether **6** (942 mg, 78%). IR (KBr); 2940, 1600, 1580, 1460, 1420, 1230, 1015. ^{1}H-NMR (400 MHz, $CDCl_3$); 6.96 (t, 2H, J=8.0 Hz), 6.74-6.82 (m, 10H), 3.8-3.90 (bs, 10H), 3.21 (s, 6H), 3.19 (s, 9H), 2.2 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$); 156.6, 154.5, 154.4, 134.6, 134.3, 134.2, 134.1, 132.2, 129.5, 129.4,128.9, 123.1, 60.5, 31.4, 31.1, 30.6, 20.1. EIMS (m/z); 642. HRMS calcd. for $C_{43}H_{46}O_5$ 642.3345; found 642.3319.

11,23-dibromo-5,17,29-trimethyl-31,32,33,34,35-pentamethoxycalix[5]arene 7

To a solution of **6** (215 mg, 0.34 mmol) in 2-butanone (15 mL) was added NBS (236 mg, 1.33 mmol) at room temperature. After stirring for 10 hr, the reaction mixture was poured into aqueous 10% sodium bisulfate, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by GPC chromatography to give dibromide **7** (189 mg, 70%). IR (KBr); 2940, 1730, 1570, 1460, 1420, 1220, 1015. ^{1}H-NMR (270MHz, $CDCl_3$); 7.00-7.20 (m, 5H), 6.70-6.90 (m, 5H), 3.79 (bs, 10H), 3.22 (s, 6H), 3.20 (s, 6H), 3.08 (s, 3H), 2.19 (s, 9H). ^{13}C-NMR (67.5 MHz, $CDCl_3$) 155.8, 154.4, 137.0, 136.7, 134.5, 134.3, 133.5, 133.3, 132.7, 132.6, 131.4, 130.0, 131.4, 129.8, 129.7, 129.5, 116.0, 60.7, 60.4, 30.9, 30.8, 20.9. EIMS (m/z); 798, 800, 802. HRMS calcd. for $C_{43}H_{44}O_5{}^{79}Br^{81}Br$ 800.1535; found 800.1509.

(3-methoxycarbonylphenyl)boronic acid 8

m-Bromotoluene (10.6 mL, 88 mmol) was added dropwise, *via* syringe, to a suspension of magnesium (2.57g, 105.6 mmol) in THF (5mL). After being stirred over 30 min., the reaction mixture was diluted with THF (50 mL). The solution was then transferred *via* cannula into a solution of $B(OMe)_3$ (15 mL, 132 mmol) in THF (200 mL) at -78 °C, and warmed up to 0°C. This solution was acidified with 10% aqueous sulfuric acid. The mixture was worked up by extracting with ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 using eluent (20% AcOEt-Hexane) to give *m*-methylphenylboronic acid (444 mg) in 55% isolated yield.

IR (KBr); 3400, 1605, 1580, 1480, 1420, 1200. ^{1}H-NMR (90MHz, $CDCl_3$) 8.10 (bs, 2H), 7.30-7.60 (m, 2H), 2.50 (s, 3H).

To the above boronic acid (1.89 mg, 13.9 mmol) with sodium hydroxide (1.3 g) in water (115 mL), a solution of potassium permanganate (7.1 g, 44.7 mmol) in water (165 mL) was added dropwise. After being stirred over night, the suitable volume of ethanol was added to quench the excess of potassium permanganate. Then the reaction mixture was filtered through celite column, and acidified by aqueous

hydrogen chloride. The acidic solution was extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the crude carboxylic acid (2.02 g) in 88% yield. The carboxylic acid was used for the next step without further purification.
IR (KBr); 3370, 1820, 1770, 1680, 1600, 1400, 1360, 1300.

The carboxylic acid (2.02 g, 12.2 mmol) was dissolved in methanol (100 mL) with concentrated sulfuric acid (10 mL). After refluxing for 4 hr, the reaction mixture was poured into iced 10% aqueous sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 to give the methyl ester (2.10 g) in 96% isolated yield.
IR (KBr); 3350, 1700, 1605, 1420, 1355, 1280. ^{1}H-NMR (270MHz, CD_3OD); 8.37 (bs, 1H), 8.05 (ddd, 1H, *J*=8.1, 2.7, 2.7 Hz), 7.92 (d, 1H, *J*=8.1 Hz), 7.41 (t, 1H, *J*=8.1 Hz), 3.88 (s, 3H). ^{13}C-NMR (67.5 MHz, CD_3OD); 168.8, 139.4, 135.8, 131.9, 130.4, 128.7, 52.5. HRMS calcd. for $C_8H_9O_4$ 180.0594; found 180.0567.

11,23-*m*-methoxycarbonylphenyl-5,17,29-trimethyl-31,32,33,34,35-pentamethoxycalix[5]arene

To a mixture of the dibromide **7** (190 mg, 0.23 mmol) and *m*-methoxycarbonylphenylboronic acid (171 mg, 0.95 mmol) in THF (10 mL) was added a catalytic amount of tetrakistriphenylphosphine-palladium(0), ethanol (1.2 mL), and a small potion of aqueous 2M-sodium carbonate. The mixture was heated at 50 °C for 8 hr, filtered through florisil column, and concentrated *in vacuo*. The residue was purified by column chromatography on GPC to give the diester (140 mg, 65%). IR (KBr); 2950, 1710, 1600, 1580, 1460, 1440, 1430, 1280, 1260, 1230, 1210. ^{1}H-NMR (270 MHz, $CDCl_3$); 8.21 (t, 2H, *J*=1.4 Hz), 7.95 (dt, 2H, *J*=7.8, 1.4 Hz), 7.68 (dt, 2H, *J*=7.8, 1.4 Hz), 7.44 (t, 2H, H=7.8 Hz), 7.38 (d, 2H, *J*=2.4 Hz), 7.33 (d, 2H, *J*=2.4 Hz), 6.70-6.80 (m, 6H), 3.94 (s, 6H), 3.92 (s, 4H), 3.88 (s, 4H), 3.80 (s, 2H), 3.33 (s, 3H), 3.25 (s, 6H), 3.11 (s, 6H), 2.1 (s, 3H), 2.06 (s, 6H). ^{13}C-NMR (67.5 MHz, $CDCl_3$) 167.3, 157.1, 154.5, 141.5, 135.4, 135.3, 134.9, 134.3, 134.0, 133.9, 132.5, 132.45, 131.4, 130.6, 129.6, 129.3, 128.8, 128.2, 128.0, 127.9, 60.7, 60.5, 60.4, 52.1, 31.5, 31.4, 30.6, 20.7, 20.6. EIMS (m/z) 910. HRMS calcd. for $C_{59}H_{58}O_9$ 910.4081; found 910.4095.

11,23-*m*-hydroxycarbonylphenyl-5,17,29-trimethyl-31,32,33,34,35-pentamethoxycalix[5]arene 9

To a solution of the above diester (26.9 mg, 0.0296 mmol) in THF-MeOH-aq (5:4:1, 2 mL) was added $LiOH{\bullet}H_2O$ (13.0 mg, 0.310 mmol). The mixture was heated at 50 °C for 1.5 hr, and poured into aqueous 1M HCl. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the diacid **9** (22.2 mg, 85%). IR (KBr); 3000, 2940, 1695, 1600, 1580, 1475, 1450, 1425, 1280, 1260, 1220. ^{1}H-NMR (270 MHz, $CDCl_3$); 8.31 (s, 2H), 8.05 (d, 2H, *J*=7.3 Hz), 7.74 (d, 2H, *J*=7.3 Hz), 7.49 (t, 2H, *J*=7.3 Hz), 7.41 (s, 2H), 7.37 (s, 2H), 6.80 (s, 6H), 3.95 (bs, 4H), 3.92 (bs, 4H), 3.83 (bs, 2H), 3.38 (s, 3H), 3.27 (s, 6H), 3.17 (s, 6H), 2.15 (s, 3H), 2.11 (s, 6H). ^{13}C-NMR (67.5 MHz, $CDCl_3$); 172.2, 157.0, 154.3, 154.28, 141.5, 135.3, 135.2, 134.6, 134.2, 133.8, 133.78, 132.5, 132.4, 132.2, 129.6, 129.2, 128.6, 128.5, 128.0, 127.8, 60.7, 60.5, 31.5, 30.8, 20.8, 20.77. FABMS; 881 (M-H). HRMS calcd. for $C_{57}H_{53}O_9$ (M-H) 881.3689; found 881.3680.

11,23-*m*-hydroxycarbonylphenyl-5,17,29-trimethyl-31,32,33,34,35-pentahydroxycalix[5]arene 1

The diacid **9** (141 mg, 0.160 mmol) was dissolved with dry dichloromethane (7 mL). The solution (2.88 mL, 3.04 mmol) of borontribromide in dichloromethane was added to the solution at 0 °C. The mixture was stirred for 13 hr, poured into aqueous 1M HCl. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by HPLC using GPC column to give the calix[5]arene diacid (100 mg, 77%). IR (KBr); 3270, 2920, 1695, 1610, 1490, 1460, 1300, 1240. ^{1}H-NMR (400 MHz, $CDCl_3$); 9.18 (bs, 2H), 8.81 (bs, 2H), 8.79 (bs, 1H), 8.30 (s, 2H), 8.06 (d, 2H, *J*=7.3 Hz), 7.76 (d, 2H, *J*=7.3 Hz), 7.51 (t, 2H, *J*=7.3 Hz), 7.45 (s, 4H), 7.09 (s, 2H), 7.05 (s, 2H), 7.00 (s, 2H), 3.50-4.40 (m, 10H), 2.25 (s, 3H), 2.23 (s, 6H). ^{13}C-NMR (67.5 MHz, C_3D_6O); 167.7, 151.6, 148.8, 141.8, 135.0, 131.9, 131.8, 131.1, 130.6, 129.7, 128.7, 128.6, 128.3, 127.6, 127.4, 127.3, 31.6, 31.5, 30.3, 20.4. FABMS 811 (M-H). HRMS calcd. for $C_{52}H_{43}O_9$ (M-H) 811.2907; found 811.2909.

Determination of Association Constants

Binding experiments were carried out by a standard ^{1}H-NMR titration technique. 2-Aminopyrimidine was titrated with appropriate amounts of a standard stock solution of the host **1** molecule in the same solvent. The host solution was added to the solution (2.9×10^{-3} M) of 2-aminopyrimidine in chloroform-d_1. Then down field shifts of the N-H signal in addition of the host solution was detected as a fraction of the host concentration. Addition was continued through 0.1-20 equiv. The resultant titration curve was analyzed by using a non-linear regression method.

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