The Size and Shape Selectivity for Diamines by a Tetrahydroxycavitand

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The design and synthesis of model receptors to recognize substrates of biochemical significance to mimic biological events is an important area in molecular recognition research.[1] Synthetic receptors for neutral molecules are mostly stabilized by hydrogen bonding,[2a] π-π,[2b] hydrophobic interactions[2c-d] and constrictive binding forces.[2e]

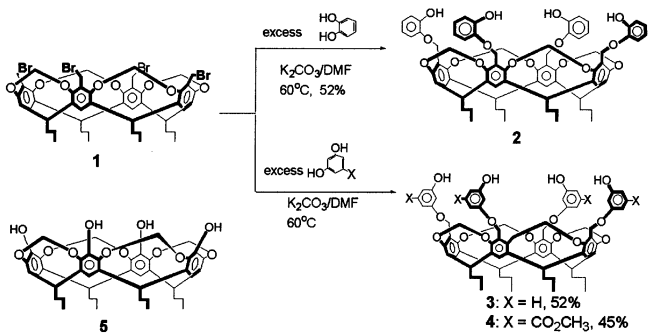
Especially hydrogen bonding has been used in many cases as a primary binding force for neutral molecule recognition, in which two principles, the multipoint interaction[3] and the complementarity[4] of shape and size between those of guest and host's binding site, have been applied to obtain a substantial selectivity with a high binding energy.

Amines and ammoniums are biologically important functional molecules and their synthetic hosts are mostly based on hydrogen bonding interactions such as Guest-N-H···O=C-Host, Guest-N-H···O(H)-Host,[5] Guest-N-H···N-Host or Guest-N-H···N=C-Host.[6] Diamines are also important targets and here the cooperative diamine binding properties of a tetrahydroxycavitand was reported.

The tetrahydroxy cavitands **2**,[7] **3**[7] and **4** were obtained from tetrabromocavitand **1**[7] with an excess of catechol, resorcinol or methyl 3,5-dihydroxybenzoate in 52, 52 and 45% yield, respectively (Scheme 1).

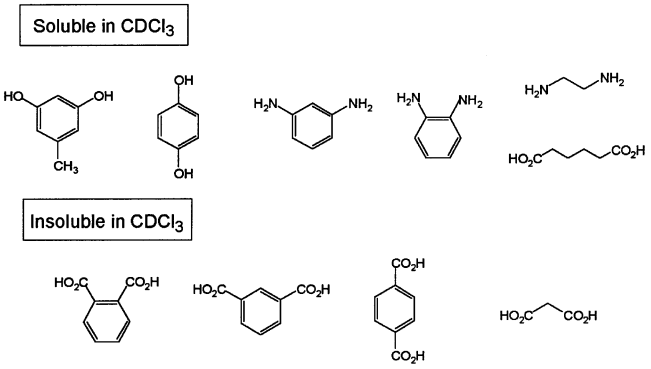
The molecular recognition properties were observed by 300 MHz ^{1}H NMR spectrometer in a $CDCl_3$ solution of host at 300K. The qualitative complexation behavior of tetrahydroxycavitands **2**, **3**, **4**, and **5**[8] were observed with an excess of various potential guests listed in Table 1. For $CDCl_3$ insoluble guests the liquid-solid extraction by host solution was tried.

Catechol-fenced cavitand **2** showed its significant chemical shift changes for only ethylenediamine. It implies that tetrahydroxy groups of host **3** or **4** are too much divergent and host **5** has a too shallow cavity and the hydrogen bonding interaction between hydroxy groups or hydroxy and carboxy or hydroxy and anilino groups of host and guest,



Scheme 1

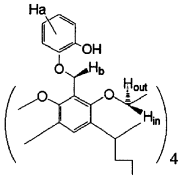
Table 1. The potential bifunctional guests



respectively, seems not to be strong enough to sustain a $CDCl_3$ soluble complex. But the chemical shift of guests cannot be observed, which, presumably, is due to their fast exchange or lesser sensitivity. Also the peak of hydroxy of hosts was overlapped with other peaks.

The qualitative complexation tests for a series of diamines were performed and the resulted chemical shift changes of host **2** are summarized in Table 2. The inward-turned proton (H_{in}) peak of host's dioxymethylene units was downfield

Table 2. ^{1}H NMR spectral chemical shift changes ($\Delta\delta H_{in}$, ppm) upon addition of potential guest (50 eq) to a $CDCl_3$ solution of 0.02 M host **2**



	NH_2—$(CH_2)_n$—NH_2								
	n=2	3	4	5	6				
H_{in}	0.185	0.147	0.155	0.132	0.118	0.115	0.156	0.079	0.028
H_{out}	0.003	0.010	0.058	0.123	0.107	0.157	0.060	0.067	0.000
H_b	-0.012	-0.030	-0.039	-0.058	-0.049	-0.016	-0.010	-0.084	-0.026
H_a	(-0.10~-0.20)								

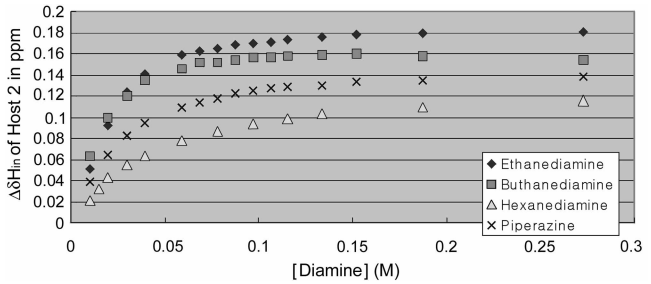


Figure 1. Plot of H_{in} of host **2** *vs.* diamines concentration ([**2**]= 0.02 M).

shifted and most sensitive, whose $\Delta\delta H_{in}$ are ranging 0.028-0.185 ppm.

Quantitative binding properties were observed from the chemical shift change of H_{in} in ^1H NMR spectra of host **2** induced by incremental guest additions as shown on Figure 1. The 1 : 1 stoichiometry of host **2**: diamine was determined by the molar ratio plot[9] and the association constant K_a was determined by Benesi-Hildebrand plot.[10]

Table 3 shows the binding constants of host **2** with various diamines. Catechol-fenced cavitand **2** showed significant binding constants (K_a=36-194 M^{-1} in $CDCl_3$ at 300K) for diamines. Among the homologous aliphatic diamines, 1,4-butanediamine was the best-fitting guest (K_a=194 M^{-1}), and the smaller or larger alkanediamines showed smaller K_a values. Secondary amines (piperazine) showed smaller K_a than primary amines (ethanediamine) and the tertiary amine (1,4-dimethylpiperazine) was the worst, which implies the steric repulsion between two partners seriously offset the larger H-bonding acceptability of 2°- or 3°-amines. The potential snugging of aromatic group into host's cavity was not helpful (1,5-pentanediamine *vs. m*-xylylenediamine). The better solubility of large diamines in $CDCl_3$ could also cause the low binding constants.

In conclusion, a simple tetrahydroxycavitand **2** showed interesting size and shape selectivities toward various diamines, favoring least sterically repulsive 1,4-butanediamine most. Their affinities will be enhanced by preorganizing the hydroxy groups of host **2**.

Experimental Section

General Methods. Chemicals were reagent grade (Aldrich), and used as received, unless otherwise noted. All anhydrous reactions were conducted under an atmosphere of argon. Melting point was measured on a Electrothermal 9100 apparatus and uncorrected. The ^1H and ^{13}C NMR spectra were run on a Bruker FT-NMR AVANCE 300 spectrometer. Spectra taken in $CDCl_3$ were referenced to residual proton at 7.24 ppm. IR spectrum was taken with Mattson 3000 FT-IR spectrometer. FAB+ mass spectrum was taken using HR MS (VG70-VSEQ) in *m*-nitrobenzyl alcohol as a matrix at Korea Basic Science Institute. Gravity chromatography was performed on E. Merck silica gel 60 (70-230-mesh) and thin-layer chromatography was done on plastic sheets silica gel 60 F254 (E. MERCK, 0.2 mm).

Table 3. Binding constants for host **2** with various diamines

Diamines	K_a (M^{-1})[a]	logK_a	$-\Delta G$ (Kcal/mole)
Ethanediamine	98	1.99	2.73
1.3-Propanediamine	146	2.16	2.97
1.4-Butanediamine	194	2.29	3.14
1.5-Pentanediamine	103	2.01	2.76
1.6-Hexanediamine	44	1.64	2.26
Piperazine	66	1.82	2.50
1.4-Dimethylpiperazine	36	1.56	2.14
m-Xylylenediamine	77	1.89	2.59

[a]Calculated by Benesi-Hildebrand equation (estimated error <15%).

Tetrakis(3-methoxycarbonyl-5-hydroxyphenoxymethyl) cavitand (4). Tetra(bromomethyl)cavitand **1** (500 mg, 0.46 mmol), methyl 3,5-dihydroxybenzoate (1.56 g, 9.3 mmol), and K_2CO_3 (1.6 g, 11.6 mmol) were dissolved in 15 mL of dry, degassed DMF. This was stirred at 60 °C under Ar for 12 hrs. It was cooled and acidic water (3 N HCl) was poured into reaction mixture and extracted with CH_2Cl_2. The organic phase was washed with water, brine and dried on $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc : Hexane = 1 : 2) to give 300 mg of product (45%): mp > 216 °C (decomposed); FT-IR (KBr) 3397 cm^{-1} (ν_{O-H}), 1721 cm^{-1} ($\nu_{C=O}$); FAB+ MS m/z 1425 (M^+); ^1H NMR (300 MHz, CD_3COCD_3) δ 1.08 (t, 12H, CH_3), 1.45 (m, 8H, CH_2CH_3), 2.29 (m, 8H, $CH_2CH_2CH_3$), 3.82 (s, 12H, $COOCH_3$), 4.64 (d, J = 7.1 Hz, 4H, inner OCH_2O), 4.90 (m, 12H, methine +$ArCH_2O$), 5.70 (d, J = 7.1 Hz, 4H, outer OCH_2O), 6.56 (s, 4H, benzoate-H), 7.12-7.19 (two s, 8H, benzoate-H), 7.25 (s, 4H, Ar*H*): ^{13}C NMR (100.6 MHz, CD_3- $COCD_3$) 14.5 (CH_3), 21.3 ($CH_3CH_2CH_2$), 32.5 ($CH_3CH_2CH_2$), 36.9 (CH), 52.8 ($COOCH_3$), 61.0 ($ArCH_2$), 100.6 (OCH_2O), 106.7, 108.2, 110.6, 132.2, 157.3, 160.0 (benzoate's ArC), 121.7, 123.0, 138.3, 154.8 (resorcin[4]arene's ArC).

^1H NMR spectrometric titration of tetrahydroxycavitand 2 with diamines. These studies were conducted by monitoring chemical shift changes of H_{in} in the 300 MHz ^1H NMR spectra of 0.02 M **2** in $CDCl_3$ by incremental guest additions. A small quantity (2 μL-8 μL) of a 3 M guest solution in $CDCl_3$ was added via a micro pipette in NMR tube directly and the ^1H NMR spectrum of the solution was redetermined. This process was repeated until the chemical shift changes occurring in the host appeared to be reasonably well spaced.

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