Molecular Engineering 6.[1] The Enhancement of Binding Ability and Selectivity of a Cavitand by Solubilizing in Basic Water

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Received April 10, 2000

Molecular recognition in aqueous media is particularly interesting due to its similarity to a variety of biological phenomena. Designed aqueous host-guest complexation is stabilized by various noncovalent interactions, especially by hydrophobic interaction. It is difficult to design a host having highly organized hydrogen bonding interactions for guest, which is the most frequent in nature, due to the difficulty to compete with the strong water interaction to guests.

If a container host[2] is to be a candidate for biological application, it should not only bind a wide variety of biologically active molecules with a high controllable selectivity and stability but it should be soluble in water not far from physiological pH values.[3]

CPK molecular model study shows that cavitand **4** has a well-shaped cavity complementary to EtOH, THF, toluene, xylene, and DMA etc., but it was only a weak THF binder at low temperature (K_a = 14 M^{-1} at -40 °C in $(CDCl_2)_2$).[4] To increase its binding ability by enforcing hydrophobic interaction, the basic-water soluble cavitand **6** was obtained and characterized.

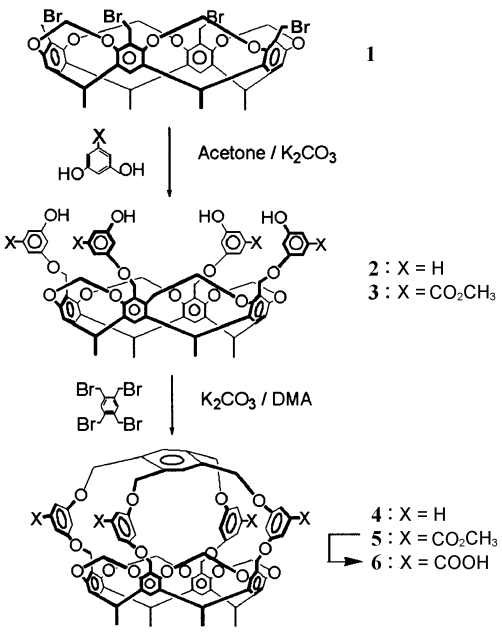
Results and Discussion

Methyl-feet bromocavitand **1** was synthesized by a known procedure[5] and transformed to the fenced cavitand **3** by treatment with an excess of methyl 3,5-dihydroxybenzoate in 54.4% yield.[6]

New C_{2v} cavitand **5** was synthesized from cavitand **3** in 18% yield, using 1,2,4,5-tetrakis(bromomethyl)benzene as a capping agent, which was subsequently hydrolyzed to tetracarboxycavitand **6** using $(CH_3)_4NOH$ in refluxing THF. These two 3D cavitands **5** and **6** were characterized by ^1H, ^{13}C NMR spectra showing their C_{2v} symmetry as well as IR and FAB+ Mass spectra.

Tetracarboxycavitand **6** was not soluble in CH_2Cl_2 or acetone, but soluble in basic aqueous solution (pH > 8.0).

The molecular recognition property was studied by ^1H NMR (300 MHz) spectrometry. Cavitand **5** didn't show any detectable complexing behavior even at -40 °C in $(CD_2Cl_2)_2$. Among many potential guests, e.g. MeOH, EtOH, propanols, butanols, THF, dioxane, CH_2Cl_2, $CHCl_3$, CH_3CN, acetone, cavitand **6** complexed only with 2-propanol (K_a = 80 M^{-1}) and dioxane (K_a = 15 M^{-1}) in 0.1 N $NaOH/D_2O$ solution at 300 K (Fig. 1). The complexation-decomplexation kinetics of these two guests were slow on NMR time scale to show the distinct complexed peaks of guest. The methyl and methine peaks of *i*-PrOH were upfield-shifted by 2.50 ppm and 1.40 ppm, respectively, and the methylene peak of dioxane was upfield-shifted by 2.42 ppm, which manifests the inclusion binding mode. The binding constants calculated directly from ^1H NMR spectra are shown on Table 1. Methyl peak of cavitand **6** and methyl peaks of free



Scheme 1. Synthesis of cavitands **4**, **5** and **6**.

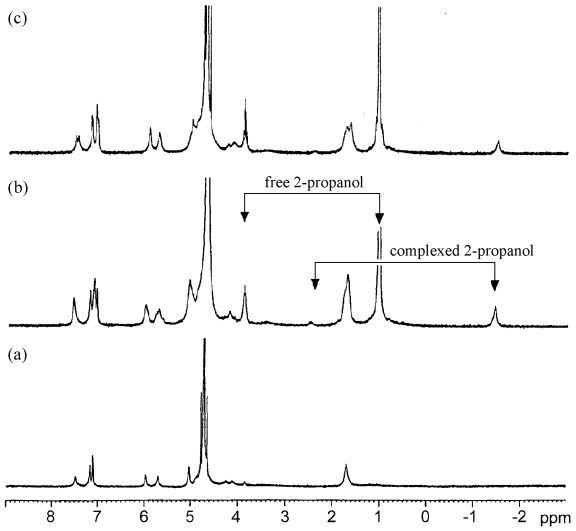


Figure 1. Changes in ^1H NMR spectra by cavitand **6** and 2-propanol complexation at 27 °C. (a) **[6]** = 3.0×10^{-3} M in 0.1 N $NaOH/D_2O$ solution. (b) **[6]** 3.0×10^{-3} M − [2-propanol] 1.2×10^{-2} M in 0.05 N $NaOH/D_2O$ solution. (c) **[6]** = 3.0×10^{-3} M + [2-propanol] = 1.2×10^{-2} M in 0.10 N $NaOH/D_2O$ solution.

Table 1. The binding constants of cavitand 6@Guest in basic D_2O at 27 °C[a]

Guest	K_a (M^{-1})	$-\Delta G$ (kcal mol^{-1})
MeOH	nd[b]	–
EtOH	nd	–
1-Propanol	nd	–
2-Propanol	119[c]	2.85
	80[d]	2.61
	68[e]	2.52
1-Butanol	nd	–
2-Butanol	nd	–
t-Butanol	nd	–
Acetonitrile	nd	–
THF	nd	–
Dioxane	15[d]	1.61
Acetone	nd	–

[a]average values of three trials and estimated error < 10%. [b]not detectable. [c]0.05 N NaOH/D_2O solution. [d]0.10 N NaOH/D_2O solution. [e]0.20 N NaOH/D_2O solution

and complexed *i*-PrOH or methylene of free and complexed dioxane were compared to determine the concentrations of equilibrium species.

MeOH, EtOH, acetonitrile, acetone, and THF seem to be too soluble in water so it may be hard for these guest to reorganize the shrank hydrophobic binding site of host **6**. Also due to their small size they could not be captured by host **6** with a sustainable activation barrier. The latter explanation might be significant at least for dioxane vs. THF complexation. Dioxane is much more soluble in water than THF, but complexed more strongly due to its size complementarity, which means van der Waals interaction reinforced by constricting ability of host **6** is important in addition to hydrophobic interaction. The attempted titration experiment with small guests didn't give any noticeable chemical shift changes of both partners.

The size selectivity toward alcohols is quite impressive. Butanols are too large to be captured. 1-Propanol cannot be captured but 2-propanol was captured most strongly.

The binding ability of cavitand **6** for 2-propanol was dependent on pH. pK_a Values of carboxyl group, water, and 2-propanol are about 4.5, 15.7, and 16.5, respectively. As the concentration of OH^- is increased, the binding constant of host **6** for 2-propanol was decreased due to the 2-propoxide formation which has higher water solubility than 2-propanol in water.

Molecular mechanics calculation (MM+ force-field) using HyperChem® showed that 2-propanol complexes with host **6** (stabilization energy, ΔE = 15.0 kcal mol^{-1}) better than 1-propanol (ΔE = 13.4 kcal mol^{-1}). Dioxane also gives slightly larger ΔE (13.7 kcal mol^{-1}) than THF does (ΔE = 13.6 kcal mol^{-1}).

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, 400, or 500 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).

Capped C_{2v} tetrakis(methyl benzoate) cavitand 5. Fenced cavitand **3** (75 mg, 57.1 mmol) and 1,2,4,5-tetrakis (bromomethyl)benzene (27 mg, 60.0 mmol) were dissolved in 300 mL of DMA at room temperature and 100 mg (723.5 mmol) of K_2CO_3 was added. The mixture was stirred for 12 h at 50 and stirred for 12 h at 80 °C. The mixture was cooled to room temperature and partitioned with 3 N HCl (200 mL), and CH_2Cl_2 (100 mL). The organic phase was washed with 3 N HCl (100 mL) twice and then with H_2O and brine. The organic phase was dried over $MgSO_4$, and concentrated. The concentrated residue was purified by silica gel column chromatography with (EtOAc : Hexane = 2 : 3) to give 13 mg (18%) of product: mp > 260 °C (dec.); FT-IR (KBr) 1725 cm^{-1} ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (d, 12H, CH_3), 3.89 (s, 12H, $COOCH_3$), 4.47 (t, 4H, J = 7.6 Hz, inner OCH_2O), 4.85 (q, 4H, methine), 5.00, 5.23 (two d, 8H, J = 9.3 Hz, capping $ArCH_2$), 5.16 (s, 8H, $ArCH_2$), 5.68 (t, 4H, J = 7.6 Hz, outer OCH_2O), 6.21 (s, 4H, benzoate Ar*H*), 7.07 (s, 2H, capping Ar*H*), 7.24 (s, 8H, benzoate Ar*H*), 7.33 (s, 4H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.5 (CH_3), 21.3 (OCH_3), 31.4 (CH), 60.8 (cap $ArCH_2$), 70.9 ($ArCH_2$), 100.8, 100.2 (OCH_2O), 105.8, 108.0, 113.4 (resorcinol), 120.9 (capping aryl), 122.6, 123.3, 139.1, 154.4 (resorcin[4]arene's aryl C), 132.7 (capping aryl), 133.9, 160.1, 160.7 (resorcinol C), 121.4, 123.1, 138.2, 154.8, 154.1 (resorcin[4]arene's ArC), 171.0 (C=O).

C_{2v} Tetracarboxycavitand 6. Capped cavitand **5** (12 mg, 8.34 mmol) and tetramethylammonium hydroxide (10 wt. % in H_2O, 0.5 mL) were dissolved in 10 mL of THF at rt. This mixture was refluxed for 12 h. After 1 N HCl (10 mL) was added, the mixture was concentrated. The residue was filtered and washed with water, acetone and CH_2Cl_2. The dried cavitand **6** in vacuum was obtained in 90% yield (10.4 mg): mp > 275 °C (dec.); FT-IR (KBr) 3447 cm^{-1} (ν_{O-H}), 1711 cm^{-1} ($\nu_{C=O}$); FAB+ MS m/z 1383 ($M-H^-$ 14%); ^1H NMR (500 MHz, CD_3SOCD_3) δ 1.84 (d, 12H, CH_3), 4.23, 4.48 (two d, 4H, J = 7.7 Hz, inner OCH_2O), 4.85 (q, 4H, methine), 4.72, 5.00 (two d, 8H, J = 10.1 Hz, capping $ArCH_2$), 5.19 (s, 8H, $ArCH_2$), 5.51, 5.70 (two d, 4H, J = 7.7 Hz, outer OCH_2O), 6.47 (s, 4H, carboxy Ar*H*), 7.16 (s, 4H, Ar*H*), 7.18 (s, 2H, Ar*H*), 7.23 (s, 4H, carboxy Ar*H*), 7.85 (s, 4H, carboxy Ar*H*); ^{13}C NMR (100.6 MHz, CD_3SOCD_3) δ 16, (CH_3), 31.1 (CH), 61.0 (cap's $ArCH_2$), 69.0 ($ArCH_2$), 99.5, 99.8 (OCH_2O), 106.5, 111.9 (benzoate's ArH) 108.1 (benzoate's aryl C_{in}), 122.0 (cap aryl CH), 132.9 (cap aryl

C), 153.0, 152.8, 138.9, 122.2, 121.8 (resorcin[4]arene's aryl C), 133.3, 159.6, 159.9 (benzoate aryl C), 166.6 (C=O).

Acknowledgment. The financial support from the Ministry of Education, Korea, by BK21 Program (1999) is gratefully acknowledged.

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