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Synthesis and Binding Study of New Aminopyridinyl Cavitand Receptors for the Recognition of Cationic Guests

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Readily available calix[4]arene derivatives have been utilized as starting materials for the synthesis of metal selective ionophores.[1] On the other hand, it has been only few years since cavitand derivatives have been used extensively as ionophores. Cavitands are rather rigid and have enforced cavities compared to calix[4]arenes. Recent efforts to improve the yield of tetrabromocavitand[2] or tetrakis-(bromomethyl)cavitand[3] initiated the recent reports utilizing these intermediates for the syntheses of various host compounds based on cavitand moiety. Recently, various cavitand derivatives have been synthesized as host compounds for metal ion recognition,[4] anion recognition[5] and organic guests.[6]

Noteworthy and most related was a paper reported by Abidi *et al.* in which synthesis and cation complexation studies of tetra(2-pyridylmethyl)amide calix[4]arene were described.[7] In this paper, its binding properties towards various metal ions have been determined and they also investigated the locations of cations in the receptor using ^{1}H NMR technique. The rigidity of cavitand derivatives may introduce the different binding properties towards various cations compared to calix[4]arene derivatives. Herein, we report the sytheses and binding properties of two new cavitands bearing four (2-pyridylmethyl)amide groups and (3-pyridylmethyl)amide groups as binding sites.

Results and Discussion

Our synthesis began with tetrahydroxy-cavitand **3**, which was prepared in four steps following the published procedure.[2,8] This compound has been better known as an intermediate for the synthesis of hemicarcerands and carcerands.[9] It is worth to mention that the recent report from Kaifer and co-workers[2] regarding the improved preparation of tetrabromo-cavitand helped to increase the overall yield (up to 45%) of **3**. Treatment of **3** with methyl bromoacetate and potassium carbonate in acetone (reflux, 2 days) gave tetraester-cavitand **4** in 85% yield (Scheme 1). Compound **4**

was then heated in neat 2-(aminomethyl)pyridine at 50 °C for 24 hours to give compound **1** as a white solid in 50% yield after recrystallization with hexane. Application of above procedure gave **2** in 57% yield.
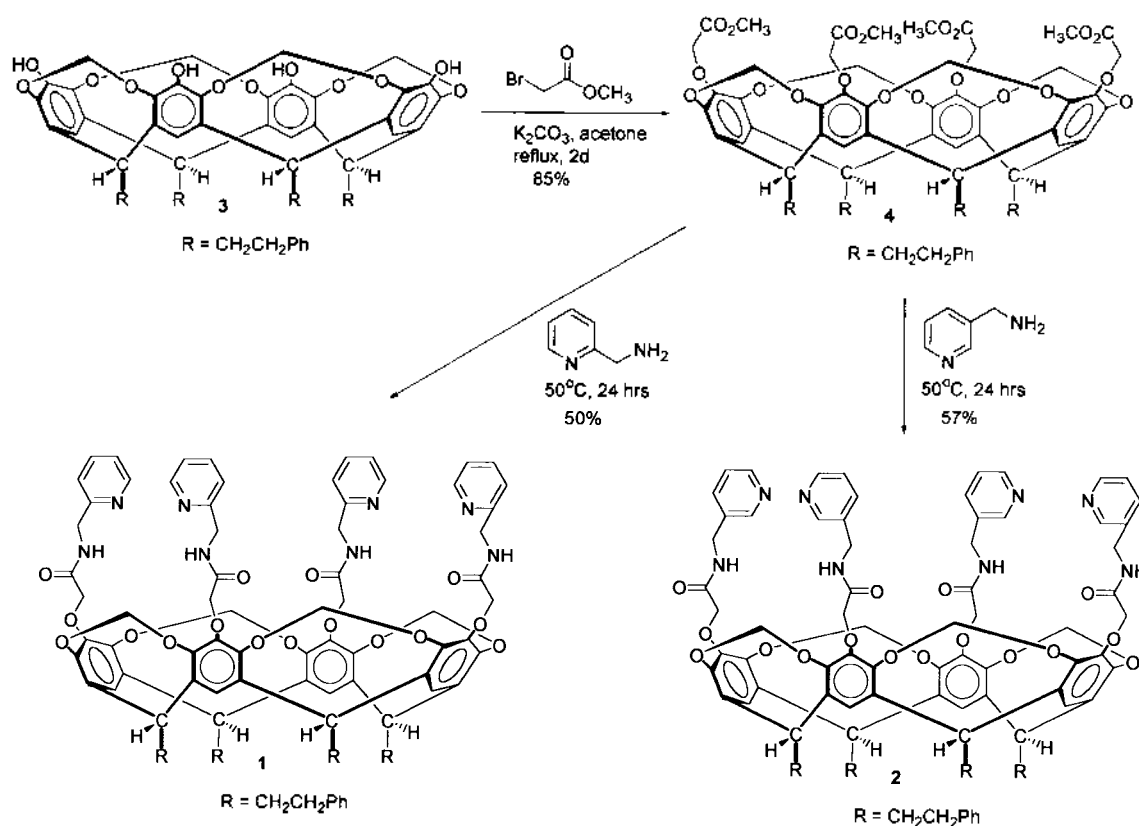
In Abidi's work,[7] tetra(2-pyridylmethyl)amide calix[4]-arene consists of two binding sites: four carbonyl units and four phenolic oxygens which may complex *hard* cations such as alkali metals, four pyridine moieties capable of complexing *soft* cations by the nitrogen atoms. Indeed, with sodium picrate, relatively small $\Delta\delta$ shifts were observed for the signals corresponding to the pyridine moiety while a large shift was observed for the N-H triplet. On the other hand, with zinc picrate, larger $\Delta\delta$ shifts were observed for the pyridine moiety leading to the conclusion that the cation is located close to the nitrogen atoms forming the soft site.

The most significant difference between Abidi's calix[4]-arene and our cavitands may be that the four phenolic oxygens in our compounds cannot participate in the binding processes because of the relative rigidity of the cavitands. Also, we synthesized both tetra(2-pyridylmethyl)amide cavitand (**1**) and tetra(3-pyridylmethyl)amide cavitand (**2**) to compare the cooperative binding of carbonyl units and nitrogens in pyridine moieties.

When silver picrate or zinc picrate in D_2O were extracted by (2-pyridylmethyl)amide cavitand **1** or (3-pyridylmethyl)-amide cavitand **2** in CD_2Cl_2, we observed large deshielding effects on pyridine moiety. The deshielding effects were maximized for cavitand **1** with zinc picrate and as large as 0.78 ppm was observed for H_c of cavitand **1**. (Table 1) As shown in Table 1, there are distinct differences between chemical shift changes of **1** and **2** with silver picrate or zinc picrate. For 2-pyridyl cavitand **1**, large shielding effects were observed for cavitand moiety, which can lead to the conclusion that the picrate ion is located close to the cavitand pocket. On the other hand, small shielding effects were observed in the case of cavitand **2**.

Different binding properties of these two cavitands were also productively compared using extraction experiments. (Table 2) The extraction experiments[10] display that cavitand **1** binds more tightly with rubidium picrate and potassium picrate over the other cationic guests. Also, cavitand **1** tends to bind spherical cation (NH_4^+) better than n-$BuNH_4^+$ or t-$BuNH_4^+$. The association constants were calculated using

Scheme 1. Syntheses of tetra(2-pyridylmethyl)amide cavitand **1** and tetra(3-pyridylmethyl)amide cavitand **2**.

the literature procedure.[10] Compared to cavitand **1**, cavitand **2** displays relatively weak bindings with cationic guests examined in our experiments. For example, the selectivity ratio of cavitand **1**/cavitand **2** for rubidium picrate approaches almost 150. Comparisons of CPK models suggest that four pyridine nitrogens in cavitand **1** can readily make a binding pocket with four carbonyl oxygens while this cooperative binding was severely prohibited in cavitand **2**.

In conclusion, two new cavitand derivatives containing either four 2-aminopyridyl groups (**1**) or four 3-amino-pyridyl groups (**2**) have been synthesized and their binding properties for cationic guests were productively compared using ^{1}H NMR and extraction method.

Experimental Section

NMR spectra were recorded at 500 MHz (for ^{1}H-NMR) and at 125 MHz (for ^{13}C-NMR) using a Varian Gemini 500 Spectrometer. Mass spectra and elemental analysis were obtained using the JEOL-JMS-HX 110A/110A High Resolution Tendem Mass Spectrometry and Vario EL of Elemental Analyzer in the Korea Basic Science Institute in Taejon, Korea. Melting points were determined in open capillaries, and are uncorrected. UV absorption spectra were obtained on UVIKON 933 Double Beam UV/VIS Spectrometer. ICP-IRIS from Thermo Jarrell Ash was used to obtain the concentrations of metal ions. Flash chromatography was carried out using Merck silica gel 60 (230 to 400 mesh). Thin layer chromatography was carried out using Merck 60

F$_{254}$ plates with a 0.25-mm thickness.

2,8,14,20-Tetrakis(2-aminomethyl)pyridinyl(carbonyl-methyloxy)cavitand (1). Compound **4** (200 mg, 0.184 mmol) in a single-necked round bottom flask was dissolved with 5 mL of 2-(aminomethyl)pyridine (48.5 mmol). The reaction mixture was then stirred at 50 °C for 24 h. After cooling down to room temperature, 30 mL of ethyl acetate was added to this reaction mixture. The organic layer was concentrated under reduced pressure after washing with distilled water (3 × 15 mL). Purification by recrystallization with hexane yielded **1** (120 mg, 0.920 mmol, 50%) as a white solid: m.p. 135 °C dec; IR (KBr) 1317, 1593, 1670, 3368 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 2.42-2.68 (m, 16H), 4.53 (d, J = 7.2 Hz, 4H, inner OCH$_2$O), 4.62 (s, 8H, C(O)CH$_2$O), 4.65 (d, J = 4.9 Hz, 8H, PyCH$_2$NH), 4.80 (t, J = 7.6 Hz, 4H, CH), 6.02 (d, J = 6.9 Hz, 4H, outer OCH$_2$O), 6.90 (s, 4H), 7.12-7.24 (m, 20H), 7.12-7.24 (hidden, 4H, PyH), 7.12-7.24 (hidden, 4H, PyH), 7.63 (td, J = 7.6 Hz & J = 1.7 Hz, 4H, PyH), 8.45 (t, J = 4.9 Hz, 4H, NH), 8.49 (d, J = 4.0 Hz, 4H, PyH); ^{1}H-NMR (CD$_2$Cl$_2$, 500 MHz) δ 2.46-2.67 (m, 16H), 4.42 (d, J = 7.3 Hz, 4H, inner OCH$_2$O), 4.57 (s, 8H, C(O)CH$_2$O), 4.60 (d, J = 4.8 Hz, 8H, PyCH$_2$NH), 4.79 (t, J = 7.8 Hz, 4H, CH), 6.04 (d, J = 6.9 Hz, 4H, outer OCH$_2$O), 6.97 (s, 4H), 7.12-7.24 (hidden, 4H, PyH), 7.12-7.24 (hidden, 4H, PyH), 7.12-7.24 (m, 20H), 7.64 (td, J = 7.8 Hz & J = 2.0 Hz, 4H, PyH), 8.37 (t, J = 4.9 Hz, 4H, NH), 8.47 (d, J = 4.9 Hz, 4H, PyH); ^{13}C-NMR (CDCl$_3$, 125 MHz) δ 32.3, 34.4, 37.0, 44.1, 72.3, 76.4, 77.2, 77.7, 99.6, 114.7, 122.0, 126.1, 128.3, 128.5, 136.7, 138.9, 141.3, 144.0,

Table 1. Chemical shifts changes of **1** and **2** in their ^{1}H NMR spectra (500 MHz) upon the complexation with silver picrate or zinc picrate

	$\Delta\delta$			
	1 + Ag(I)	**1 + Zn(II)**	**2 + Ag(I)**	**2 + Zn(II)**
H$_a$	0.06	0.37	0.11	0.10
H$_b$	-	-	-0.05	0.06
H$_c$	0.14	0.78	0.16	0.18
H$_d$	-	-	0.21	0.23
H$_e$	0.13	0.42	0.05	0.05
H$_f$	-	-	0.28	0.41
H$_g$	-0.08	-0.17	-0.11	-0.01
H$_h$	-0.12	-0.30	0.06	0.03
H$_i$	-0.22	-0.30	0.12	0.06
H$_j$	-0.08	-0.15	0.06	0.02
H$_k$	-0.04	-0.14	0	-0.01

Organic phase (1 mL of CD$_2$Cl$_2$) containing (1.0 mM) and aqueous phase (1 mL of D$_2$O) contains metal picrate (1.0 mM). Two-phase mixture was centrifuged by Vortex-Genie for 1 min.

147.3, 148.9, 155.8, 168.9; FAB MS m/e = 1609.5 (M$^+$). Anal. Calcd for C$_{96}$H$_{88}$N$_8$O$_{16}$: C, 71.63; H, 5.57; N, 6.96. Found: C, 71.51; H, 5.51; N, 7.02.

1·Ag$^+$Pic$^-$: ^{1}H-NMR (CD$_2$Cl$_2$, 500 MHz) δ 2.45-2.64 (m, 16H), 4.30 (d, J = 7.8 Hz, 4H, inner OCH_2O), 4.49 (s, 8H, C(O)CH_2O), 4.71 (t, J = 8.3 Hz, 4H, CH), 4.73 (s, 8H, PyCH_2NH), 5.82 (d, J = 7.3 Hz, 4H, outer OCH_2O), 6.93 (s, 4H), 7.12-7.24 (m, 20H), 7.28 (t, J = 6.3 Hz, 4H, PyH), 7.48 (d, J = 7.8 Hz, 4H, PyH), 7.78 (td, J = 7.8 Hz & J = 1.5 Hz, 4H, PyH), 8.52 (s, 2H, Pic$^-$), 8.53 (d, J = 4.8 Hz, 4H, PyH).

1·Zn^{2+}2Pic$^-$: ^{1}H-NMR (CD$_2$Cl$_2$, 500 MHz) δ 2.45-2.64 (m, 16H), 4.12 (d, J = 6.8 Hz, 4H, inner OCH_2O), 4.40 (s, 8H, C(O)CH_2O), 4.64 (t, J = 7.8 Hz, 4H, CH), 5.02 (s, 8H, PyCH_2NH), 5.74 (d, J = 6.8 Hz, 4H, outer OCH_2O), 6.86 (s,

4H), 7.12-7.24 (m, 20H), 7.86 (t, J = 6.3 Hz, 4H, PyH), 8.09 (d, J = 7.8 Hz, 4H, PyH), 8.42 (t, J = 7.9 Hz, 4H, PyH), 8.84 (d, J = 4.4 Hz, 4H, PyH), 8.85 (s, 4H, Pic$^-$).

2,8,14,20-Tetrakis(3-aminomethyl)pyridinyl(carbonyl-methyloxy)cavitand (2). Application of above procedure to 500 mg (0.383 mmol) of **4**, 5 mL of 3-(aminomethyl)pyridine (49.1 mmol) gave 350 mg (0.218 mmol, 57%) of **2** as a white solid after recrystallization with hexane. m.p. 130 °C dec; IR (KBr) 1318, 1594, 1669, 3360 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 2.42-2.68 (m, 16H), 4.28 (d, J = 7.9 Hz, 4H, inner OCH_2O), 4.54 (d, J = 5.8 Hz, 8H, PyCH_2NH), 4.60 (s, 8H, C(O)CH_2O), 4.67 (t, J = 8.3 Hz, 4H, CH), 5.55 (d, J = 7.3 Hz, 4H, outer OCH_2O), 6.86 (s, 4H), 7.12-7.24 (m, 20H), 7.27 (dd, J = 7.8 Hz, 4H, PyH), 7.36 (dt, J = 7.8 Hz & J = 1.4 Hz, 4H, PyH), 7.92 (t, J = 5.4 Hz, 4H, NH), 8.54 (d, J = 4.9 Hz, 4H, PyH), 8.59 (s, 4H, PyH); ^{1}H-NMR (CD$_2$Cl$_2$, 500 MHz) δ 2.42-2.68 (m, 16H), 4.20 (d, J = 7.3 Hz, 4H, inner OCH_2O), 4.51 (d, J = 5.9 Hz, 8H, PyCH_2NH), 4.57 (s, 8H, C(O)CH_2O), 4.68 (t, J = 8.3 Hz, 4H, CH), 5.62 (d, J = 7.3 Hz, 4H, outer OCH_2O), 6.93 (s, 4H), 7.12-7.24 (m, 20H), 7.26 (dd, J = 7.8 Hz & J = 4.9 Hz, , 4H, PyH), 7.65 (dt, J = 7.8 Hz & J = 2.0 Hz, 4H, PyH), 7.89 (t, J = 5.9 Hz, 4H, NH), 8.49 (dd, J = 4.9 Hz & J = 1.5 Hz, , 4H, PyH), 8.56 (d, J = 2.5 Hz, 4H, PyH); ^{13}C-NMR (CDCl$_3$, 125 MHz) δ 32.2, 34.3, 40.0, 40.7, 73.0, 76.4, 77.0, 77.6, 99.4, 114.8, 123.5, 126.2, 128.3, 128.6, 133.5, 135.7, 139.0, 141.0, 143.7, 146.8, 149.0, 149.2, 168.8; FAB MS m/e = 1609.5 (M$^-$). Anal. Calcd for C$_{96}$H$_{88}$N$_8$O$_{16}$: C, 71.76; H, 5.46; N, 6.95. Found: C, 71.51; H, 5.47; N, 6.91.

2·Ag$^+$Pic$^-$: ^{1}H-NMR (CD$_2$Cl$_2$, 500 MHz) δ 2.42-2.68 (m, 16H), 4.26 (d, J = 7.3 Hz, 4H, inner OCH_2O), 4.46 (s, 8H, C(O)CH_2O), 4.56 (d, J = 4.9 Hz, 8H, PyCH_2NH), 4.74 (t, J = 8.3 Hz, 4H, CH), 5.74 (d, J = 7.3 Hz, 4H, outer OCH_2O), 6.93 (s, 4H), 7.12-7.24 (m, 20H), 7.42 (dd, J = 7.8 Hz & J = 5.3 Hz, 4H, PyH), 7.86 (d, J = 8.2 Hz, 4H, PyH), 8.17 (t, J = 6.2 Hz, 4H, NH), 8.39 (s, 2H, Pic$^-$), 8.44 (dd, J = 4.9 Hz & J = 1.5 Hz, 4H, PyH), 8.67 (d, J = 1.9 Hz, 4H, PyH).

2·Zn^{2+}2Pic$^-$: ^{1}H-NMR (CD$_2$Cl$_2$, 500 MHz) δ 2.42-2.68 (m, 16H), 4.23 (d, J = 7.3 Hz, 4H, inner OCH_2O), 4.56 (d, 16H, PyCH_2NH & C(O)CH_2O), 4.70 (t, J = 7.8 Hz, 4H, CH), 5.68 (d, J = 7.3 Hz, 4H, outer OCH_2O), 6.92 (s, 4H), 7.12-7.24 (m, 20H), 7.44 (t, J = 7.4 Hz, 4H, PyH), 7.88 (d, J = 8.3 Hz, 4H, PyH), 8.30 (t, 4H, NH), 8.55 (br s, 4H, PyH), 8.66 (s, 4H, PyH), 8.73 (s, 4H, Pic$^-$).

Table 2. Association constants for complexation of cavitand **1** and **2** with alkali metal, ammonium and alkyl ammonium picrates in CHCl$_3$ saturated with H$_2$O

	Na$^+$	K$^+$	Rb$^+$	Cs$^+$	NH$_4^+$	nBuNH$_3^+$	tBuNH$_3^+$
Cavitand **1**	7.7×10^3	1.0×10^5	2.4×10^3	1.9×10^4	3.9×10^4	3.0×10^3	2.4×10^3
Cavitand **2**	6.2×10^3	2.1×10^3	1.6×10^3	1.2×10^3	2.9×10^3	1.9×10^3	1.1×10^3

All experiments were carried out at 298 K; errors estimated to be less than 15%.

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