Molecular engineering. Part 7.[1] Cavitands having four aromatic sp^2 nitrogens as salt binding ligands

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Nine new salt binders built on resorcin[4]arene or calix[4]arene and having four aromatic sp^2 nitrogens as salt binding ligands were designed and characterized. Structurally rigid cavitands based on resorcin[4]arene showed much higher affinities toward metal cations compared to those based on flexible calix[4]arene. In particular, imidazolylcavitand **7** showed high affinity for alkali metal cations ($-\Delta G^\circ$ = 7.0–10.9 kcal mol^{-1}) and pyrazolylcavitand **8** showed unusually high selectivity for silver cations, which are presumably due to their different binding modes, nesting *vs.* inclusion fashion, respectively.

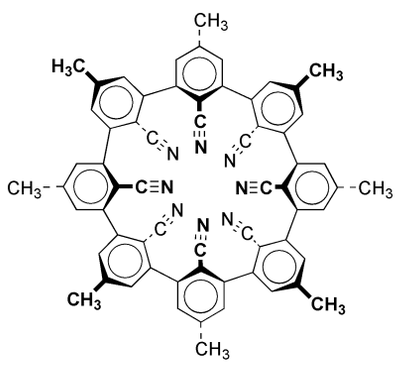
Introduction

Selective recognition of metal cations has been one of the central research themes for the last three decades in host–guest chemistry, and many targets are met using either naturally-occurring ionophores or synthetic receptors such as crown ethers, cryptands and spherands, whose major ligating hetero-atoms are sp^3 oxygens.[2]

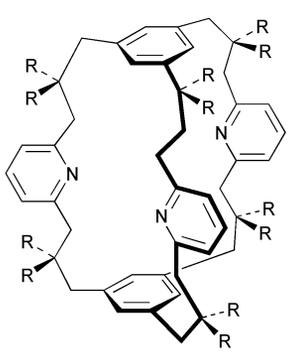
Nitrogen atoms have significant intrinsic affinities for IA and IIA group cations as well as transition metal cations, but compared to oxygen, they have been much less frequently adopted in host systems for IA or IIA group cations.[3] sp^3 Hybridised nitrogen atoms are less effective in complexing alkali metals than sp^3 oxygen and also cannot be easily incorporated to give a substantially preorganized binding site in which the sp^3 lone pair orbitals point directly to its center due to steric congestion and feasible orbital inversion. Nitrogen atoms with an sp lone pair present as an integral part of an organic host exist only in cyano groups and its ligating properties were well studied using octacyanand **1**.[4] Once this problem of design was overcome, sp nitrogen showed much higher intrinsic binding abilities for IA group cations than sp^3 oxygen.

sp^2 Hybridised nitrogen atoms can also be incorporated into strong and selective host systems as the planar lone pair has directionality as well as diversity in aromatic rings, even though they are usually less feasible than sp^3 oxygen in forming a preorganized binding site. sp^2 Hybridised nitrogen atoms in imines,[3] pyridine,[5] phenanthroline,[6] *etc*. have been incorporated to give good hosts for transition metals or organic guests. Recently, Voegtle *et al*. reported a macrobicyclic tripyridine cage host **2**,[7] whose pyridine sp^2 N cooperatively binds included guest ions in the cavity. This host turned out to be remarkably selective for the Ag^+ cation. Also Kim *et al.* reported that tripodand **3** shows high selectivity for NH_4^+ by charge–dipole and cation–π interactions.[8]

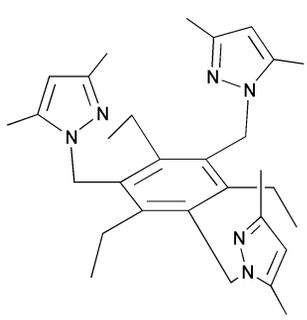
In this paper we report the synthesis and the high affinity to alkali cations, transition metal cations and ammonium ions of new salt-binding cavitands that possess four aromatic sp^2 nitrogens which can face inward to form a cation binding site.[9]



Cyanospherand **1**



Cavitand **2**



Tripodand **3**

Results and discussion

Synthesis of cavitands 7, 8, 9, 10, 11, 12, 13 and 14

Tetrakis(bromomethyl)cavitands **4a** and **4b**[10] easily obtained from the corresponding tetramethylcavitands **4** (X = CH_3) by NBS bromination (80%) were reacted with an excess of imidazole, pyrazole, indazole or benzimidazole in $CHCl_3$ to give hosts **7a** (55%), **7b** (77%), **8** (65%), **9** (78%), or **10** (30%) in good yields (Fig. 1). Host **11** was obtained from a tetraol **5**[11] and 2-(chloromethyl)pyridine (85%). Cavitands **12** (50%), **13** (50%), and **14** (46%) were obtained from tetrakis(*p*-chloromethyl)-calix[4]arene **6**[12] in $CHCl_3$ or CH_3CN with an excess of imidazole, pyrazole and indazole, respectively. The new hosts were purified by washing exclusively with deionized water several times followed by repeated recrystallizations from a mixed solution.

^{1}H NMR spectra of cavitands **12**–**14** show that they exist as cone conformers, as structurally rigid cavitands **7**–**11** do, but the binding studies of cavitands **10** and **12** cannot be pursued due to their low solubility in $CHCl_3$.

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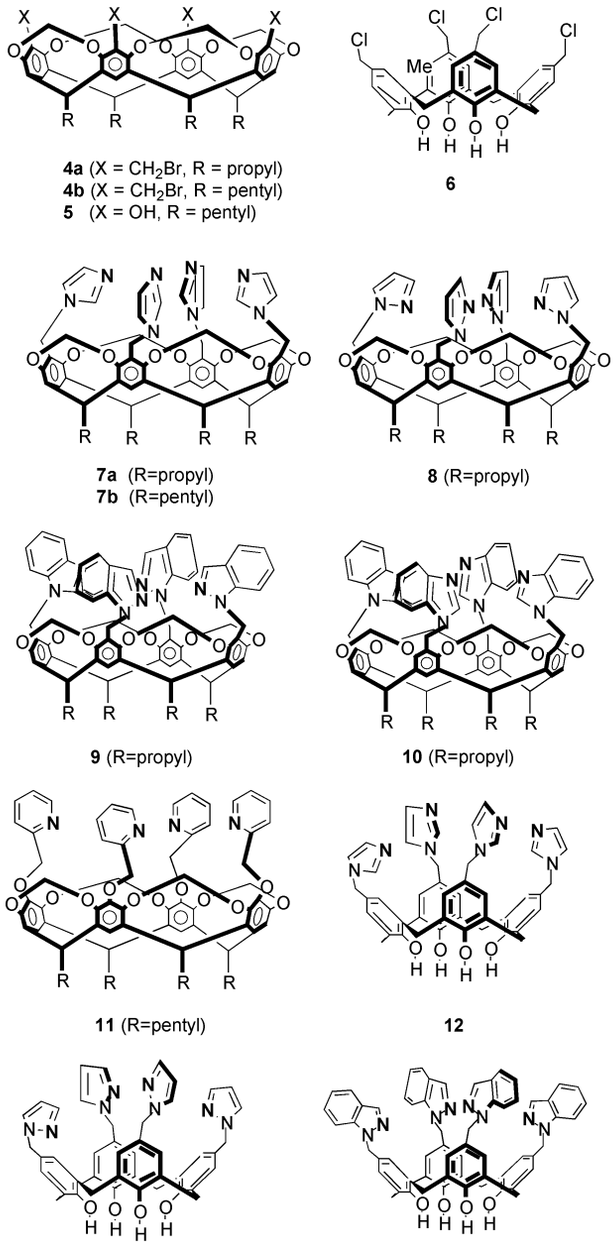

Fig. 1 Cavitands **4**–**14**.

Binding stoichiometry and picrate extraction experiments

Quite a few salt binders based on resorcin[4]arene have been developed,[13] because typical container hosts constructed on resorcin[4]arene do not bind salts.[14] However, quite a lot of those based on calix[4]arene have been reported due to the conformational and chemical diversity of calix[4]arene.[15]

The 1 : 1 complexation between $NaClO_4$ and host **7b** was confirmed by solid–liquid extraction (Fig. 2) which showed the chemical shift saturations at a 1 : 1 ratio of solid $NaClO_4$ to host **7b** in $CDCl_3$–CD_3CN = 3 : 1 (v/v) at room temperature. The ^{1}H NMR data for imidazolylcaviplex **7b**·$Na^+ClO_4^-$ (400 MHz) suggest all four imidazolyl groups are coordinated to sodium. Compared to the free **7b**, the resonances of the imidazole unit and methylenedioxy protons in the complex showed large upfield chemical shifts (NCHN, 0.28 ppm, from 7.53 to 7.25 ppm; one of NCHCHN, 0.02 ppm, from 6.93 to 6.91 ppm; *exo*-OCH_2O, 0.19 ppm, from 6.02 to 5.83 ppm; *endo*-OCH_2O, 0.23 ppm, from 4.20 to 3.97 ppm). A computer-generated (HyperChem with MM+ force field) stereo view of imidazolylcaviplex **7a**·Na^+ in the gas phase (Fig. 3) shows its nesting binding mode.

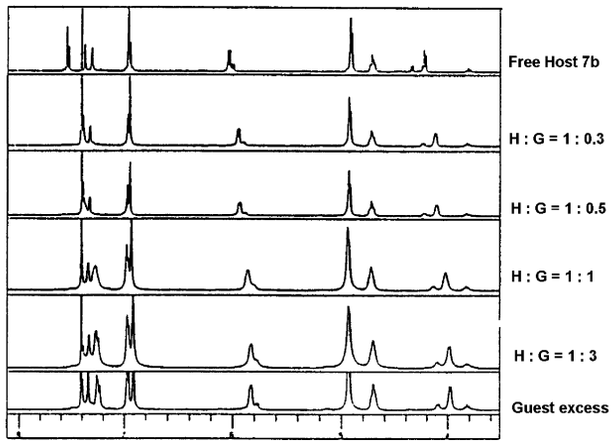

Fig. 2 ^{1}H NMR spectroscopic titration with $Na^+ClO_4^-$ of imidazolylcavitand **7b** in $CDCl_3$–CD_3CN = 3 : 1 (v/v).

The free energies of complexation ($-\Delta G°$ in kcal mol^{-1}) were determined at 22 °C in H_2O-saturated $CHCl_3$ by Cram's liquid extraction method[16] on a 1 or 4 mM scale host solution binding Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates. Among the cavitands, except cavitands **10** and **12** which are very insoluble in $CHCl_3$, only hosts **7** showed substantial affinities for alkali or ammonium picrate and the results are summarized in Table 1 (average of two determinations whose difference was <0.5 kcal mol^{-1}). Imidazolylcavitand **7a** tends to precipitate in the organic phase ($CHCl_3$) on the 4 mM scale, but imidazolylcavitand **7b** is soluble on the 4 mM scale. At the 1 mM scale imidazolylcavitands **7a** and **7b** showed similar tendencies for alkali and ammonium metal picrate extraction, experimental differences being within 0.5 kcal mol^{-1}.

Fig. 4 illustrates the host–guest structure–binding relationships for complexation of eight cations and imidazolylcavitand **7b**. For a comparison the binding free energies of octacyanand **1** having two rigidly preorganized binding sites solely composed of four sp nitrogens for each are also shown. It is reported that octacyanand **1** showed 1 : 1 binding at 10^{-3} M solution ($CHCl_3$) in a perching fashion.

Imidazolylcavitand **7b** showed unexpected high binding energies of $-\Delta G°_{av} = 9.2$ kcal mol^{-1} ranging from 7.0 for $(CH_3)_3CNH_3^+$ to 10.9 for Na^+ with a maximum spread of 3.9 kcal mol^{-1}. Imidazolylcavitand **7b** tends to bind spherical cations better: NH_4^+ a little better than $CH_3NH_3^+$ and $CH_3NH_3^+$ somewhat better than *t*-$BuNH_3^+$ showing a peak binding for Na^+. Imidazolylcavitand **7b** has lower binding energies [$\Delta(-\Delta G°) = -0.5$ for Li^+ to -4.6 kcal mol^{-1} for K^+] than octacyanand **1**. Compared to octacyanand **1**, imidazolylcavitand **7b** has a much less preorganized binding site due to the free rotation of the imidazolylmethyl arms, which also caused its relatively low selectivity.

^{1}H NMR titration experiments

Binding studies were also carried out using the chemical shift change caused by incremental addition of $Na^+BPh_4^-$ to imidazolylcavitand **7a** in $CDCl_3$–MeOH-d_4 (7 : 1, v/v) at 298 K. Fig. 5 shows the observed chemical shift changes of three different hydrogens ($H_{m,exo}$, $H_{4'}$ and H_b) of **7a** *vs.* guest–host ratio.

The protons whose signals were chosen for K_a determinations exhibited a relatively large chemical shift change upon complexation (>0.05 ppm). The sensitivity of $H_{4'}$ and $H_{m,exo}$ were similar to those from solid–liquid extraction, but the large sensitivity of H_b and the weak sensitivity of $H_{m,endo}$ are unexpected. The K_a value calculated using a Benesi–Hildebrand plot[17] for cavitand **7a** binding Na^+ at 298 K was 541 M^{-1}.

The probable anion effect was also tested. A small quantity of host **7a** was dissolved in $CDCl_3$–MeOH-d_4 (7 : 1, v/v) to be

Table 1 Apparent association constant (K_a/M^{-1}) and binding free energy ($-\Delta G°$/kcal mol^{-1}) for complexation of imidazolylcavitand **7b** with alkali metal, ammonium and alkylammonium picrates in $CHCl_3$ saturated with H_2O at 25 °C[a]

	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	$CH_3NH_3^+$	t-$BuNH_3^+$
K_a/M^{-1}	3.1×10^7	1.3×10^8	1.3×10^7	1.6×10^7	5.9×10^6	6.5×10^6	2.1×10^6	1.7×10^5
$-\Delta G°$/kcal mol^{-1}	10.1	11.0	9.5	9.4	9.2	9.2	8.5	7.0

[a] The values are average values from organic and aqueous phases of two trials at the 4 mM scale whose difference was <0.5 kcal mol^{-1}.

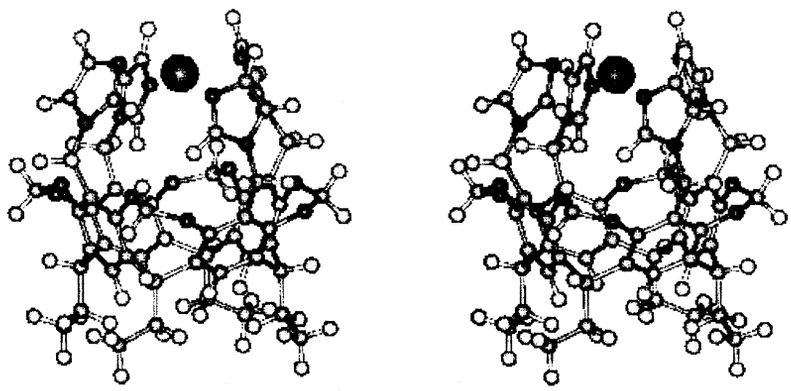

Fig. 3 Stereo view of the energy minimized structure of imidazolylcaviplex **7a**·Na^+(Hyperchem with MM+ force field).

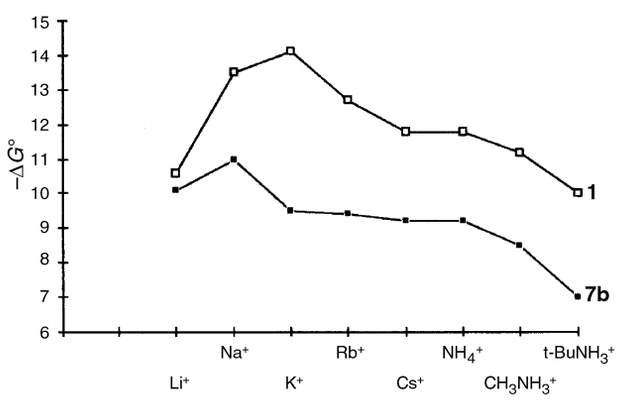

Fig. 4 Comparison of binding free energy ($\Delta G°$) between octacyanand **1** and imidazolylcavitand **7b**.

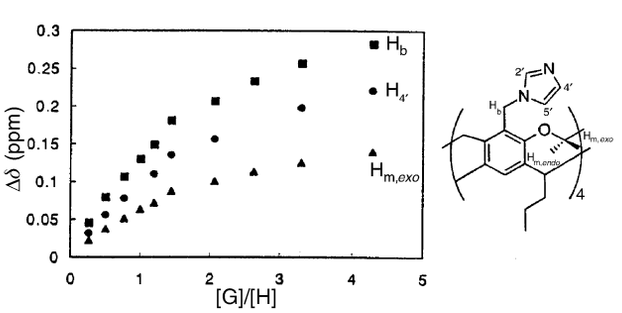

Fig. 5 Observed chemical shift changes ($\Delta\delta$) of the three different hydrogens of **7a** *vs.* [G]/[H] ratio.

about 1 mM, and its 300 MHz ^1H NMR spectrum was recorded. To this solution about 20 equivalents of $Bu_4N^+BPh_4^-$ was added and then the ^1H NMR spectrum was recorded. Chemical shift changes did not occur for H-4′ or $H_{m,exo}$ but were found for H_b. However, its change (<0.05 ppm) is very much smaller than that with $Na^+BPh_4^-$ (>0.26 ppm at 5 eq.), which supports the theory that the chemical shifts were induced by cation binding to host.

Affinities for alkaline earth and transition metal picrates

Solvent extractions of aqueous alkaline earth or transition metal cations into H_2O-saturated organic host solutions were performed at 25 °C. An aqueous solution containing $M(NO_3)_n$ (10 mM) and picric acid (1.0 mM) was extracted with the host solution ($CHCl_3$, 1.0 mM).

The percentage extraction (Ex%) was calculated by measuring the picrate concentration in the aqueous phase. The results are summarized in Table 2 and Fig. 6. Imidazolylcavitand **7a** showed the highest extractabilities for IIA and transition metal

Table 2 Percentage extraction of metal picrates by cavitands **7a**, **8**, **9**, **11**, **13** and **14** at 298 K

	Ex%[a]							
Host	Ag^+	Mg^{2+}	Ca^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}
7a	100	43	57	47	47	55(56)[b]	49	31
8	93	0	0	0	3	9	0	0
9	22	0	0	0	11	4	0	0
11	74	8	10	5	27	30	9	0
13	20	0	0	0	0	0	0	0
14	25	0	0	0	0	0	0	0

[a] Organic phase (2 mL of $CHCl_3$) contains cavitand (1.0 mM) and aqueous phase (2 mL) contains picric acid (1.0 mM) and $M(NO_3)_n$ (10 mM). The two-phase mixture was stirred for 1 min and centrifuged for 1 min and then Ex% values were determined spectrophotometrically. [b] Ref. 18.

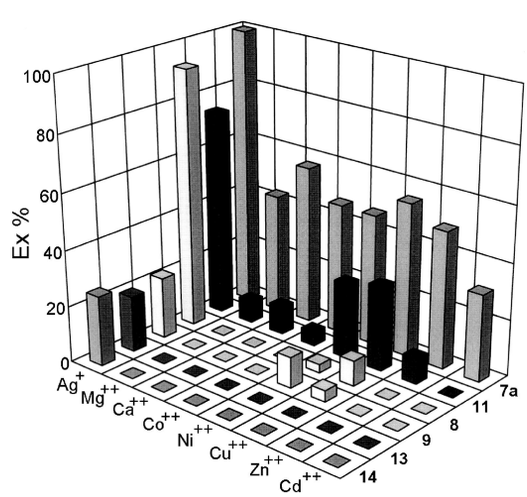

Fig. 6 Illustration of percentage extraction of metal picrates by cavitands **7a**, **8**, **9**, **11**, **13** and **14** at 298 K.

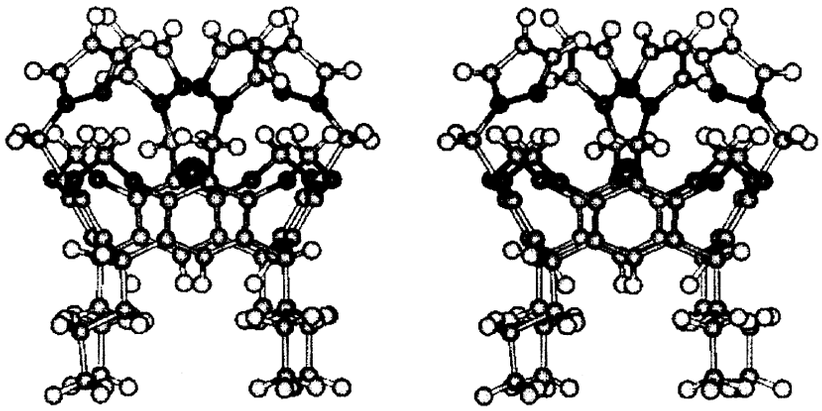

Fig. 7 Stereo view of energy minimized structure of pyrazolylcaviplex **8**·Ag^+(Hyperchem with MM+ force field).

cations with the highest for Ag^+ (100%). The ionic radius of Ca^{2+} (0.99 Å) is very similar to that of Na^+ (0.96 Å), which may explain the higher Ex% (57 *vs.* 43%) for Ca^{2+} than for Mg^{2+} (the ionic radius of Mg^{2+} is 0.65 Å).

Pyridinylcavitand **11** also showed a high affinity for Ag^+ (74%), but overall it showed lower affinities for other metal cations, compared to those of cavitand **7**, due to its higher flexibility. The Ex% (<25%) for Ag^+ by calix[4]arene-based cavitands **13** or **14** is insignificant, but that (93%) by pyrazolylcavitand **8** was exceptional.

The remarkably high selectivity by pyrazolylcavitand **8** for Ag^+ over Mg^{2+}, Ca^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Cd^{2+} and the CPK molecular model study suggest that the four lone pair electrons of the N-2 atoms of host **8** can converge to form a binding site for a spherical cation in an inclusion fashion. π-Base receptors which feature cation–π interactions display a high metal affinity,[19] which is true for **8**·Na^+. Computer-generated (HyperChem with MM+ force field) stereo views of imidazolylcaviplex **8**·Na^+ (Fig. 7) also support its inclusion binding mode. Pyrazolylcavitand **8** showed much more efficient silver extraction ability (93%) than pyridine-containing cage **2** (19.5%) which complexes with a silver ion by a linear coordination between the two adjacent pyridine donor atoms.[7] Indazolylcavitand **9** could bind in a similar binding mode, but compared to **8**, the rotation of indazolyl arms to permit an inclusion mode seemed to be much more sterically hindered, which resulted in low affinities for the tested metal cations, even for Ag^+.

Conclusions

Nine new hosts based on cavitands and having four aromatic sp^2 nitrogens as potential ligands were efficiently obtained and the largest affinities of imidazolylcavitands **7** for various metal cations were observed. These results strongly support the substantial intrinsic affinities of aromatic sp^2 nitrogen for alkali metal and ammonium cations when organized in a good binding arrangement.

In particular, pyrazolylcavitand **8** showed a strong selectivity for Ag^+ which was embraced in the host **8**. The high affinity of sp^2 nitrogen for Ag^+ was known[7] and the additional Ag^+–π interaction of pyrazolylcaviplex **8**·Ag^+ seems to be crucial to sustain the inclusion of Ag^+, which was not possible in case of alkali, alkaline or other transition metal cations tested.

These results support the high intrinsic affinities of imidazolyl sp^2 nitrogen for alkali metal and ammonium cations, especially when they are preorganized to form a good binding site. Also the selectivity by a cavitand can be manipulated by controlling the direction of the lone pair of sp^2 nitrogen atoms and the secondary interactions, such as cation–π interactions.

Experimental

General

Chemicals were reagent grade (Aldrich), and used as received, unless otherwise noted. All anhydrous reactions were conducted under an atmosphere of argon. Melting points (mp) were measured on an electrothermal 9100 apparatus and are uncorrected. The ^1H NMR spectra were run on a Gemini-300 (300 MHz) or Jeollamad-400 (400 MHz) spectrometer. Spectra taken in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm, *J* values are given in Hz. FAB^+ MS spectra were determined on a VG-VSEQ spectrometer with 3-nitrobenzyl alcohol as a matrix. Infrared spectra were recorded on a Mattson 300 FT-IR spectrometer. UV–VIS absorbance readings were taken on a Perkin-Elmer 551 spectrometer. Gravity chromatography was performed on E. Merck silica gel 60 (70–230 mesh ASTM). Thin-layer chromatography was carried out on plastic sheet silica gel 60 F_{254} (E. Merck, 0.2 mm). The elementary analyses were conducted at Institute of Basic Sciences of Korea.

5,11,17,23-Tetrakis(chloromethyl)-25,26,27,28-tetrahydroxycalix[4]arene (6)[12]

To a cold solution (−10 °C) of 1.0 g (2.4 mmol) of calix[4]arene and 14.4 g (81 mmol) of chloromethyl *n*-octyl ether in 100 mL of $CHCl_3$, 4.7 mL (40.3 mmol) of $SnCl_4$ were added dropwise over a period of about 15 min. The cooling bath was removed and the reaction mixture was stirred at room temperature for an additional 50 min, after which time all the calix[4]arene had reacted (TLC, hexane–ethyl acetate = 4 : 3). Water (100 mL) was then added slowly and the organic phase was separated. The organic layer was washed twice with distilled water, dried over $MgSO_4$ and concentrated to give a residue which was treated with *n*-hexane. The precipitate was filtered to give **6** (1.23 g, 80%), mp >153.5–154.6 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3092 (OH), 1479 (C–O); δ_H (400 MHz, $CDCl_3$) 3.54 (4H, br s, *exo*-ArCH_2Ar), 4.17 (4H, br s, *endo*-ArCH_2Ar), 4.40 (8H, s, ArCH_2Cl), 7.09 (8H, s, Ar*H*), 10.12 (4H, s, O*H*).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(imidazolylmethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino-[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (7a)

Imidazole (6.32 g, 0.093 mol, 100 eq.) was dissolved in 50 mL of CH_3CN, and stirred at rt for 30 min. Tetrakis(bromomethyl)-cavitand **4a** (1.00 g, 0.93 mmol) was added, and the mixture was stirred for 1.5 h. The reaction mixture was concentrated, dissolved in CH_2Cl_2, and washed with basic water (3 M NaOH). The organic phase was washed with deionized water several times followed by repeated recrystallizations from a mixture of methyl ethyl ketone (MEK)–CH_3CN–CH_2Cl_2 to give **7a** (52 mg, 55%), mp >243.0 °C (decomp.) (Found: C, 65.56; H, 6.29; N,

10.96. $C_{60}H_{64}O_8N_8$ CH_2Cl_2 CH_3CN requires C, 65.73; H, 6.04; N, 10.95%); ν_{max} (KBr)/cm^{-1} 1618 (C=N); δ_H (400 MHz, $CDCl_3$) 1.00 (12H, m, $CH_2CH_2CH_3$), 1.34 (8H, m, $CH_2CH_2CH_3$), 2.21 (8H, m, $CH_2CH_2CH_3$), 4.11 (4H, d, *J* 7.2, inner -OCH_2O-), 4.76 (4H, m, ArC*H*Ar), 4.87 (8H, s, ArCH_2N), 5.91 (4H, d, *J* 7.2, outer -OCH_2O-), 6.89 (4H, d, *J* 7.0, imidazolyl-$H_{5'}$), 7.02 (4H, s, Ar*H*), 7.20 (4H, d, *J* 7.2, imidazolyl-$H_{4'}$), 7.40 (4H, s, imidazolyl-$H_{2'}$); FAB MS *m*/*z* 1025.27 (M + H$^+$, 100%).

1,21,23,25-Tetrapentyl-7,11,25,28-tetrakis(imidazolylmethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino-[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (7b)

Imidazole (5.72 g, 0.083 mol, 100 eq.) was dissolved in 50 mL of CH_3CN and stirred at rt for 30 min. Tetrakis(bromomethyl)cavitand **4b** (1.00 g, 0.84 mM) was added and the mixture was stirred for 3 h. The reaction mixture was concentrated, dissolved in CH_2Cl_2 and washed with basic water (3 M NaOH). The organic phase was washed with deionized water several times and the concentrated crude product was dissolved in acetone, and the precipitate was filtered. The filtrate was concentrated and the residue was recrystallized from a mixture of CH_2Cl_2–CH_3CN to give cavitand **7b** (0.73 g, 77%), mp 207.0 °C (Found: C, 67.78; H, 7.01; N, 10.11. $C_{68}H_{80}O_8N_8$ CH_2Cl_2 CH_3CN requires C, 67.50; H,6.78; N, 9.98%); ν_{max} (KBr)/cm^{-1} 1610.66 (C=N); δ_H (400 MHz, $CDCl_3$) 0.89 (12H, m, $(CH_2)_4CH_3$), 1.31 (24H, m, $CH_2(CH_2)_3CH_3$), 2.17 (8H, m, $CH_2(CH_2)_3CH_3$), 4.07 (4H, d, *J* 7.03, inner-OCH_2O-), 4.70 (4H, m, ArC*H*Ar), 4.85 (8H, s, ArCH_2N), 5.88 (4H, d, *J* 7.03, outer -OCH_2O-), 6.87 (4H, d, *J* 7.0, imidazolyl-$H_{5'}$), 6.99 (4H, d, *J* 7.4, imidazolyl-$H_{4'}$), 7.16 (4H, s, Ar*H*), 7.38 (4H, s, imidazolyl-$H_{2'}$); FAB MS *m*/*z* 1137.4 (M$^+$, 100%).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(pyrazolylmethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino-[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (8)

Tetrakis(bromomethyl)cavitand **4a** (0.50 g, 0.46 mmol) and pyrazole (0.60 g) were dissolved in 50 mL of CH_3CN with K_2CO_3 (2.5 g) at 50 °C and the mixture was stirred for 3 h. The mixture was concentrated, dissolved in CH_2Cl_2, washed with water several times, and dried over $MgSO_4$. The concentrated crude product was purified by silica gel column chromatography using EtOAc–hexane (2 : 1 to 5 : 1). The best fractions were collected and concentrated. The residue was dissolved in CH_2Cl_2 and washed with deionized water several times. The organic phase was concentrated to give cavitand **8** (310 mg, 65%), mp 239 °C (Found: C, 69.05; H, 6.46; N, 10.47. $C_{60}H_{64}O_8N_8$ H_2O requires C, 69.08; H, 6.38; N, 10.74%); ν_{max} (KBr)/cm^{-1} 1707.11 (N=N), 1637.67 (C=N); δ_H (400 MHz, $CDCl_3$) 0.94 (12H, m, $CH_2CH_2CH_3$), 1.30 (8H, m, $CH_2CH_2CH_3$), 2.10 (8H, m, $CH_2CH_2CH_3$), 4.16 (4H, d, *J* 7.4, inner -OCH_2O-), 4.74 (4H, m, ArC*H*Ar), 4.98 (8H, s, ArCH_2N), 5.70 (4H, d, *J* 7.4, outer -OCH_2O-), 6.11 (4H, t, *J* 2.0, pyrazolyl-$H_{4'}$), 7.09 (4H, s, Ar*H*), 7.31 (4H, d, *J* 2.1, pyrazolyl-$H_{5'}$), 7.34 (4H, d, *J* 0.8, pyrazolyl-$H_{3'}$); FAB MS *m*/*z* 1025.48 (M$^+$, 100%).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(indazolylmethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino-[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (9)

Tetrakis(bromomethyl)cavitand **4a** (1.00 g, 0.93 mmol) and indazole (2.2 g) were dissolved in 50 mL of CH_3CN with K_2CO_3 (2.57 g). The mixture was refluxed for 24 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2. It was washed with water several times and dried over $MgSO_4$. The concentrated crude product was purified by silica gel column chromatography using EtOAc–hexane (2 : 1) as eluent. The best fractions were collected and concentrated. The residue was dissolved in CH_2Cl_2 and washed with deionized water several times. The solvent was evaporated to give cavitand **9** (340 mg, 30%), mp 269.0 °C; ν_{max} (KBr)/cm^{-1} 1691.66 (N=N), 1626.09 (C=N); δ_H (400 MHz, $CDCl_3$) 1.01 (12H, m, $CH_2CH_2CH_3$), 1.34 (8H, m, $CH_2CH_2CH_3$), 2.22 (8H, m, $CH_2CH_2CH_3$), 4.23 (4H, d, *J* 7.4, inner -OCH_2O-), 4.80 (4H, m, ArC*H*Ar), 5.52 (8H, s, ArCH_2N), 5.54 (4H, d, *J* 7.4, outer -OCH_2O-), 7.07 (4H, s, Ar*H*), 7.39–7.18 (8H, m, indazolyl-*H*), 7.47 (4H, d, *J* 8.5, indazolyl-*H*), 7.72 (4H, d, *J* 7.2, indazolyl-*H*), 7.93 (4H, s, indazolyl-*H*); FAB MS *m*/*z* 1225.4 (M$^+$, 100%).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(benzimidazolylmethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (10)

Benzimidazole (11.2 g) was dissolved in 80 mL of CH_3CN, and stirred at 50 °C for 30 min. Tetrakis(bromomethyl)cavitand **4a** (1.0 g, 0.93 mmol) was added, and the mixture was stirred for 3 h. The solvent was evaporated, and benzimidazole was washed out with MeOH. The precipitate was filtered, washed with methanol several times to give cavitand **10** (89 mg, 78%) as a white solid, mp >268.0 °C (decomp.); ν_{max} (KBr)/cm^{-1} 1608.73 (C=N); δ_H (400 MHz, $CDCl_3$) 0.89 (12H, m, $CH_2CH_2CH_3$), 1.22 (8H, m, $CH_2CH_2CH_3$), 2.09 (8H, m, $CH_2CH_2CH_3$), 4.10 (4H, d, *J* 5.1, inner -OCH_2O-), 4.68 (4H, m, ArC*H*Ar), 4.98 (8H, s, ArCH_2N), 5.62 (4H, s, outer -OCH_2O-), 7.15 (4H, s, Ar*H*), 7.24 (8H, m, benzimidazolyl-*H*), 7.48 (4H, d, *J* 7.8, benzimidazolyl-*H*), 7.66 (4H, m, benzimidazolyl-*H*), 7.73 (4H, s, benzimidazolyl-*H*); FAB MS *m*/*z* 1225.4 (M$^+$, 100%).

7,11,15,28-Tetrakis(2-pyridylmethyl)-1,21,23,25-tetrapentyl-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino-[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine stereoisomer (11)

2-Picolyl chloride hydrochloride† (0.74 g) and tetraol **5** (0.20 g, 0.23 mmol) were dissolved in 30 mL of DMF, at 70 °C. The mixture was stirred for 3 h and then 3 M HCl (30 mL) was added. The mixture was extracted with CH_2Cl_2 and washed with H_2O, and then dried over $MgSO_4$. The product was crudely purified by silica gel gravity column chromatography using 5% MeOH in CH_2Cl_2. The best fractions were collected and washed with deionized water several times. The solution was concentrated to give cavitand **12** (240 mg, 85%), mp >215 °C (decomp.) (Found C, 71.89; H6.70; N, 4.85. $C_{76}H_{84}O_{12}N_4$ H_2O requires C, 72.24; H, 6.86; N, 4.43%); ν_{max} (KBr)/cm^{-1} 1618.36 (C=N); δ_H (400 MHz, $CDCl_3$) 0.90 (12H, m, $(CH_2)_4CH_3$), 1.35 (24H, m, $CH_2(CH_2)_3CH_3$), 2.19 (8H, m, $CH_2(CH_2)_3CH_3$), 4.47 (4H, d, *J* 7.0, inner -OCH_2O-), 4.72 (4H, m, ArC*H*Ar), 5.08 (8H, s, ArOCH_2), 5.73 (4H, d, *J* 7.0, outer -OCH_2O-), 6.84 (4H, s, Ar*H*), 7.18 (4H, t, J_1 6.3, J_2 6.11, pyridinyl-*H*), 7.57 (4H, d, *J* 7.8, pyridinyl-*H*), 7.69 (4H, t, *J* 7.8, pyridinyl-*H*), 8.52 (4H, d, *J* 4.2, pyridinyl-*H*); FAB MS *m*/*z* 1245.6 (M$^+$, 100%).

Tetrakis(*p*-imidazolylmethyl)-25,26,27,28-tetrahydroxycalix[4]-arene 12

Tetrakis(chloromethyl)calix[4]arene **6** (100 mg, 0.16 mmol) was dissolved in 2 mL of $CHCl_3$, and stirred at −10 °C for 20 min. Imidazole (720 mg, 10.5 mmol) was added, and the mixture was stirred for 2 h. The reaction mixture was washed with basic water (3 M NaOH) and then with deionized water. Undissolved powder was filtered and washed with deionized water several times to give cavitand **12** (60 mg, 50%), mp >170 °C (decomp.); δ_{13C} (100.4 MHz, DMF-d_7) 33.30 ($ArCH_2Ar$), 50.63 ($ArCH_2N$), 120.01 (ArC), 127.07 (ArC), 127.92 (imidazolyl 5′-C), 128.89 (imidazolyl 4′-C), 131.61 (NCHN), 137.76 (ArC), 155.85 (ArCOH); δ_H (300 MHz, DMF-d_7) 3.13 (4H, d, *J* 12.4, *exo*-

† The IUPAC name for 2-picolyl chloride hydrochloride is 2-(chloromethyl)pyridine hydrochloride.

$ArCH_2Ar$), 4.56 (4H, d, *J* 12.4, *endo*-$ArCH_2Ar$), 5.11 (8H, s, $ArCH_2N$), 7.07 (8H, s, ArH), 7.11 (4H, d, *J* 4.2, imidazolyl-H), 7.3 (4H, d, *J* 4.2, imidazolyl-H), 8.20 (4H, s, imidazolyl-H).

Tetrakis(*p*-pyrazolylmethyl)-25,26,27,28-tetrahydroxycalix[4]-arene 13

Pyrazole (600 mg, 8.3 mmol) was dissolved in 5 mL of CH_3CN, and stirred at rt for 10 min. Tetrakis(chloromethyl)calix[4]arene **6** (100 mg, 0.16 mmol) was added, and the mixture was stirred for 1 d. The reaction mixture was evaporated, dissolved in CH_2Cl_2, washed with basic water (3 M NaOH) and deionized water three times, and then dried over $MgSO_4$. The solvent was evaporated under vacuum. The residue was purified by silica gel chromatography with 2% MeOH–CH_2Cl_2 as a mobile phase to give cavitand **13** (60 mg, 50%), mp >126 °C; δ_{13C} (100.4 MHz, $CDCl_3$) 148.60 (ArCOH), 139.49 (pyrazolyl 3′-C), 130.39 (ArC), 129.11 (pyrazolyl 5′-C), 128.60 (ArC), 128.35 ($ArCCH_2N$), 105.92 (pyrazolyl 4′-C), 55.24 ($ArCH_2N$), 31.59 ($ArCH_2Ar$); δ_H (300 MHz, $CDCl_3$) 3.53 (4H, d, *J* 12.4, *exo*-$ArCH_2Ar$), 4.16 (4H, d, *J* 12.4, *endo*-$ArCH_2Ar$), 5.11 (8H, s, $ArCH_2N$), 6.28 (4H, t, *J* 2.1, pyrazolyl-4′-H), 6.90 (8H, s, ArH), 7.28 (4H, d, *J* 1.2, pyrazolyl-5′-H), 7.33 (4H, d, *J* 1.7, pyrazolyl-3′-H), 10.12 (4H, s, OH).

Tetrakis(*p*-indazolylmethyl)-25,26,27,28-tetrahydroxycalix[4]-arene 14

Indazole (600 mg, 5.1 mmol) was dissolved in 5 mL of CH_3CN, and stirred at rt for 10 min. Tetrakis(chloromethyl)calix[4]arene **6** (100 mg, 0.16 mmol) was added and the mixture was stirred for 1 d. The reaction mixture was evaporated and then dissolved in CH_2Cl_2. The mixture was washed with basic water (3 M NaOH) and with deionized water three times, and then dried over $MgSO_4$. The solvent was evaporated under vacuum. The residue was purified by silica gel chromatography with a 1% MeOH–CH_2Cl_2 as a mobile phase to give cavitand **14** (70 mg, 46%), mp >157 °C (decomp.); δ_{13C} (100.4 MHz, $CDCl_3$) 10.02 (s, 4H, OH), 31.44 ($ArCH_2Ar$), 56.75 ($ArCH_2N$), 117.51(indazolyl-8′-C), 120.19 (indazolyl-6′-C), 121.81 (indazolyl-6′-C), 122.07 (indazolyl-4′-C), 122.83 (indazolyl-7′-C), 126.04 (indazolyl-3′-C), 128.41 ($ArCCH_2N$), 128.81 (ArC), 129.14 (ArC), 148.85 (indazolyl-8′-C), 148.98 (ArCOH); δ_H (300 MHz, $CDCl_3$) 3.51 (4H, d, *J* 12.4, *exo*-$ArCH_2Ar$), 4.15 (4H, d, *J* 12.4, *endo*-$ArCH_2Ar$), 5.33 (8H, s, $ArCH_2N$), 6.95 (8H, s, ArH), 7.13 (4H, d, *J* 8.3, indazolyl-H), 7.30 (4H, d, *J* 8.7, indazolyl-H), 7.63 (4H, d, *J* 8.4, indazolyl-H), 7.76 (4H, m, indazolyl-H), 7.79 (4H, s, indazolyl-H).

^{1}H NMR spectrometric titration of imidazolylcavitand 7b with $Na^+ClO_4^-$

Five NMR tubes with solution **7b** (0.7 mL) (8.1×10^{-6} mol in $CDCl_3$–CD_3CN = 3 : 1 v/v) were treated with solid $Na^+ClO_4^-$ (0.3 mg, 0.3 eq.; 0.5 mg, 0.5 eq.; 1.0 mg, 1 eq.; 3.2 mg, 3 eq. and 10.7 mg, 10 eq.), respectively. The mixtures were sonicated for 10 min at room temperature and the resulting changes in the NMR spectra were monitored.

Picrate extraction experiment of 7b

A two-phase liquid–liquid extraction experiment was carried out between an aqueous solution (2.0 mL, [GPic] = 4 mM) and a chloroform solution (2.0 mL, [Host] = 4 mM). The two-phase mixture in a tightly-stoppered centrifuge tube was shaken with a Voltex-Genie for 1 min at 22 °C and then centrifuged at 1600 rpm for 1 min. After phase separation the concentration of the complexed picrate salt in the $CHCl_3$ layer was determined spectrophotometrically. For an internal check the decrease in concentration of the picrate salt in water solution was measured and found to be in agreement with that of the chloroform layer. Each K_a and $-\Delta G^\circ$ value reported in Table 1 and Fig. 4 are the average values of two independent measurements.

^{1}H NMR spectrometric titration of imidazolylcavitand 7a with $Na^+BPh_4^-$

These studies were conducted by monitoring chemical shift changes in the 400 MHz ^{1}H NMR spectra of 1.4×10^{-3} M **7a** in $CDCl_3$–MeOH-d_4 (7 : 1 v/v, containing 0.3% by volume of TMS) by incremental guest additions. A small quantity (5–10 μL) of a guest solution (1.9×10^{-2} M) in $CDCl_3$–MeOH-d_4 (7 : 1 v/v) was added *via* a micro pipette directly into the NMR tube and the ^{1}H NMR spectrum of the solution was redetermined. This process was repeated until the chemical shift changes of host appeared to be reasonably well spaced.

Picrate extraction experiment of alkaline earth and transition metal picrates

A two-phase liqid–liquid extraction experiment was carried out between an aqueous solution (2.0 mL, [picric acid] = 1.0 mM, $[M(NO_3)_n]$ = 10 mM) and a chloroform solution (2.0 mL, [Host] = 1.0 mM). The two-phase mixture in a tightly-stoppered centrifuge tube was shaken with a Voltex-Genie for 1 min at 25 °C and then centrifuged at 1600 rpm for 1 min. The extractability was determined spectrophotometrically from the decrease of the picrate ion in the aqueous phase. The extraction percentage was given by eqn. (1)

$$\text{Extractability (\%)} = \frac{[\text{Host}]_{\text{comp}}}{[\text{Host}]_{\text{o}}} \times 100 \qquad (1)$$

where $[Host]_o$ is the initial host concentration in chloroform and $[Host]_{comp}$ is the complexed host concentration after mixing, which is obtained from $[G_b]_{aq} - [G_i]_{aq}$. $[G_b]_{aq}$ is the concentration of picrate ion in the aqueous phase remaining after extraction with chloroform solution (blank test) and $[G_i]_{aq}$ is the guest concentration in the aqueous phase after extraction with host solution.

Complexometric titration[18] of Cu^{2+}

A two-phase liquid–liquid extraction experiment was carried out between an aqueous solution (3 mL, $[Cu(NO_3)_2]$ = 0.1 M) and a chloroform solution (3 mL, [Host] = 0.05 M). The two-phase mixture in a tightly-stoppered centrifuge tube was shaken with a Voltex-Genie for 1 min at 25 °C and then centrifuged at 1600 rpm for 1 min. After phase separation the aqueous solution of Cu^{2+} (1 mL) was diluted to 50 mL with water and aqueous NH_4Cl (10 mL, 1 M) and murexide‡ was added. The concentration of Cu^{2+} in the aqueous phase was determined by EDTA (0.02 M) titration experiment. At the equivalent point the colour of murexide changed from orange to dark green. The extraction percentage was obtained from eqn. (1).

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‡ The IUPAC name for murexide is ammonium bis(2,4,6-trioxo-hexahydropyrimidin-5-yl)amide.

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