Pergamon

Tetrahedron Letters 39 (1998) 3161–3164

TETRAHEDRON
LETTERS

New Salt Binders Whose Ligands Were Composed of Four Aromatic sp^2 Nitrogens and Purely Based on a Cavitand

Jaehyung Yoon and Kyungsoo Paek*

Department of Chemistry, Soong Sil University, Seoul, 156-743, Korea
Center for Biofunctional Molecules, P.O. Box 125, Pohang 790-600, Korea

Received 7 January 1998; revised 17 February 1998; accepted 20 February 1998

Abstract: New salt binders whose ligands were composed of four aromatic sp^2 nitrogens and purely based on a cavitand were efficiently synthesized and characterized. Imidazolylcavitand **3** showed high affinity for picrate salts ($-\Delta G^\circ = 7.0 \sim 11.0$ kcal mol^{-1}) and pyrazolylcavitand **4** showed unusual high selectivity for silver picrate. © 1998 Elsevier Science Ltd. All rights reserved.

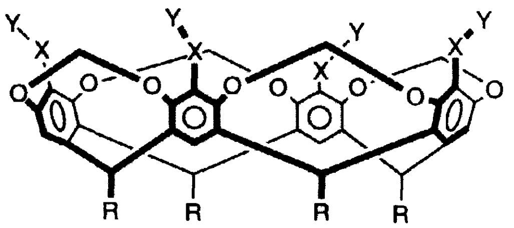
Effective neutral hosts for alkali metal and alkaline earth metal cations have been largely classified as podands, crown ethers, cryptands, and cyclophanes.[1] And their major ligating hetero atoms are sp^{3}oxygen and nitrogen.

Nitrogen atoms have significant intrinsic affinities for IA and IIA group cations, but compared to oxygen, they have been much less frequently adopted in host systems for IA or IIA group cations.[2] Nitrogens of sp^3 hybrid are far less effective in complexing alkali metals than sp^3 oxygen and also cannot be easily organized to give a substantially preorganized binding site in which the sp^3 lone pair orbitals are convergently directing to its center due to the steric congestion and the feasible orbital inversion. Nitrogen with sp lone pair applicable as a genuine part of an organic host exists only in cyano group and its ligating properties were well studied using cyanospherands.[3] Except designing problem, sp nitrogen showed much higher intrinsic binding abilities for IA cations than sp^3 oxygen. Well-organized ester, amide or urea sp^2 oxygens[4] showed high affinity for IA or IIA group cations and sp^2 nitrogen also has good chances to be organized in the strong and selective host systems in terms of its straight direction of lone pair and its diversity in aromatic rings.

Nitrogens of sp^2 hybrid in imine,[2] pyridine,[5] phenanthroline,[6] etc. have been incorporated to give good hosts for transition metals or organic guests. But they are known to be less effective than sp^3- oxygen in complexing akali metals. In this paper we report the synthesis and the high affinity to alkali and ammonium ions of new salt binders that are constructed on a cavitand and possess four aromatic sp^2- nitrogens which can face inward to form a cation binding site.

Tetrakis(bromomethyl)cavitands **2**[7] were easily obtained from tetramethylcavitands **1** with NBS bromination (~80%) and reacted with an excess of imidazole, pyrazole, benzimidazole or indazole in $CHCl_3$ to give hosts **3a**[8] (55%), **3b** (77%), **4** (65%), **5** (78%), or **6** (30%) in good yields. Host **7** was obained from a tetrol (Y = H and X = O)[9] and 2-(chloromethyl)pyridine (85%). New hosts were purified by exclusive washing with deionized water several times followed by repeated recrystallizations from a mixed solution.

PII: S0040-4039(98)00448-1



1 : X = CH_2, Y = H, R = propyl or pentyl
2 : X = CH_2, Y = Br, R = propyl or pentyl
3a : X = CH_2, Y = imidazolyl, R = propyl
3b : X = CH_2, Y = imidazolyl, R = pentyl
4 : X = CH_2, Y = pyrazolyl, R = propyl
5 : X = CH_2, Y = benzimidazolyl, R = propyl
6 : X = CH_2, Y = indazolyl, R = propyl
7 : X = O, Y = 2-pyridinylmethyl, R = pentyl

The 1:1 complexation between $NaClO_4$ and host **3b** was confirmed by solid-liquid extraction which showed the upfield proton chemical shift saturations of endo-OCH_2O ($\Delta\delta$ = 0.23 ppm) and imidazolyl 2'-CH ($\Delta\delta$ = 0.28 ppm) at 1:1 of solid $NaClO_4$ and host **3b** in $CDCl_3$: CD_3CN = 3 : 1. The free energies of complexation ($-\Delta G^\circ$ in kcal mol^{-1}) of hosts were determined by the picrate extraction method[10] of 1 or 4 mM host solution in $CHCl_3$ and aqueous guest solution of the same concentration. Interestingly only hosts **3** showed substantial affinities for alkali or ammonium picrate and the results are summarized in Table 1. The binding study of host **5** was difficult due to its low solubility.

Table 1. Association Constants (K_a, M^{-1}) and Binding Free Energies ($-\Delta G^\circ$, kcal mol^{-1}) for Complexation of Imidazolylcavitand **3b** with Alkali Metal, Ammonium and Alkylammonium Picrates in $CHCl_3$ Saturated with H_2O at 25 °C.

K_a (M^{-1})							
Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	$CH_3NH_3^+$	$t\text{-}BuNH_3^+$
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

$-\Delta G^\circ$ (kcal mol^{-1})							
Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	$CH_3NH_3^+$	$t\text{-}BuNH_3^+$
10.1	11.0	9.5	9.4	9.2	9.2	8.5	7.0

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

Imidazolylcavitand **3b** shows rather high binding energies of $-\Delta G^\circ_{av}$ = 9.2 kcal mol^{-1} ranging from 7.0 kcal mol^{-1} for $t\text{-}BuNH_3^+$ to 11.0 kcal mol^{-1} for Na^+ with a maximum spread of 4.0 kcal mol^{-1}. The less soluble host **3a** showed similar values at 1 mM scale experiment. The low degrees of structural recognition of host **3b** in complexation are attributable to its binding modes. For host **3b** the binding mode is the guest-induced size-fit binding (a nesting fashion on a less preorganized binding site). Its free energy cost for the reorganization must be paid for by the almost rectangular-planar binding to form nesting complexes. Imidazolylcavitands **3** tend to bind spherical cations better: NH_4^+ a little better than $CH_3NH_3^+$ and $CH_3NH_3^+$

somewhat better than t-BuNH$_3^+$.

The association constant of host **3a** for Na$^+$ was also determined by ^{1}H NMR spectroscopic titration with Na$^+$BPh$_4$in a mixture of CDCl$_3$ and CD$_3$OD (7:1 v/v) at 25 °C. The chemical shifts on host **3a** (OCH_2O, benzylic hydrogen and imidazole ring) cannot be observed by the titration with (CH$_3$)$_4$N$^+$BPh$_4^-$, which supports Na$^+$ binding to host **3a**. The average association constant calculated using Benesi-Hildebrand plot[11] was 541 M^{-1}.

The affinities of those new hosts for alkaline earth and transition metal picrates were also tested by liquid-liquid extraction and the results are shown in Table 2. Imidazolylcavitand **3a** showed the largest affinities and the low selectivity in general. Pyrazolylcavitand **4** showed unusual high selectivity for silver ion (93%), but indazolylcavitand **6** showed weak affinities even to Ag$^+$ (22%), which might be due to the steric congestion of **6** to form a binding site.

Table 2. Percent Extraction of Metal Picrate

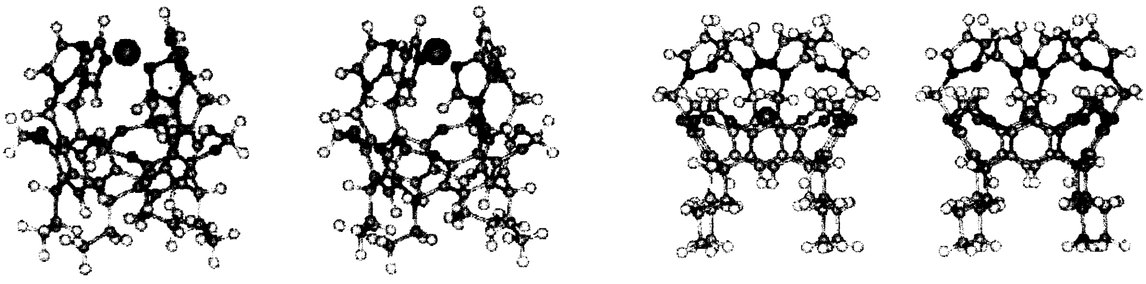
	Extraction %							
Host	Ag$^+$	Mg^{++}	Ca^{++}	Co^{++}	Ni^{++}	Cu^{++}	Zn^{++}	Cd^{++}
Imidazolylcavitand **3a**	100	43	57	47	47	55	49	31
Pyrazolylcavitand **4**	93	0	0	0	3	9	0	0
Indazolylcavitand **6**	22	0	0	0	11	4	0	0
Pyridinylcavitand **7**	74	8	10	5	27	30	9	0

* Organic phase (2 mL of CHCl$_3$) contains Host (1.0 mM) and aqueous phase (2 mL) contains picric acid (1.0 mM) and M(NO$_3$)$_n$ (10 mM).

* Two-phase mixture was vortexed for 1 min, and then centrifuged for 1 min and Extraction% values were determined spectrophotometrically.

Examination of CPK molecular model implies that the binding modes of imidazolylcavitand **3** and pyrazolylcavitand **4** might be different. For imidazolylcavitand **3**, 3'-N atom from each imidazole units can face convergently to form a binding site for spherical cations in a nesting fashion. But for pyrazolylcavitand **4**, 2'-N atom from each pyrazole unit can face convergently to form a binding site in an inclusion fashion. Computer-generated (HyperChem® with MM+ Force Field) stereo-views of imidazolylcaviplex **3**·Na$^+$ and pyrazolylcaviplex **4**·Ag$^+$ in gas phase (Figure 1) also support their binding modes. The high affinity of sp^2 nitrogen to Ag$^+$ was known[5d] and the additional Ag$^+$ - π interaction of pyrazolylcaviplex **4**·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.

In conclusion, six new hosts based on a cavitand and having four aromatic sp^2 nitrogens as potential ligands were efficiently obtained and large affinities of imidazolylcavitands **3** for metal cations were observed. These results strongly supports the substantial intrinsic affinities of aromatic sp^2 nitrogen for alkali metal and ammonium cations when organized in a good binding mode. Especially pyrazolylcavitand **4** showed a strong selectivity for Ag$^+$ which was embraced in the host **4** owing to the synergic attractions between Ag$^+$ - 2'-N and Ag$^+$ - π cloud. Various alkyl feet on cavitand are being adopted to control the solubility as well as the stability in polymer matrix applicable as ion-selective electrodes.



Imidazolylcaviplex 3·Na$^+$ Pyrazolylcaviplex 4·Ag$^+$

Figure 1. Stereo Views of Energy Minimized Structures of Imidazolylcaviplex 3·Na$^+$ and Pyrazolylcaviplex 4·Ag$^+$ in Gas Phase Using HyperChem® with MM+ Force Field.

Acknowledgement: The financial support from the Korean Science and Engineering Foundation (No.971-0302-011-2) is gratefully acknowledged.

References

1. (a) *Cation Binding by Macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990. (b) *Crown Compounds: Toward Future Applications*; Cooper, S. R., Ed.; VCH Publishers: New York, 1992.
2. Bell, T. W.; Guzzo, F.; Drew, G. B. *J. Am. Chem. Soc.* **1991**, *113*, 3115 and references cited therein.
3. Paek, K.; Knobler, C. B.; Maverick, E. F.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 8662.
4. (a) Ungaro, R.; Arduini, A.; Pochini, A.; Reverberi, S. *Tetrahedron Letters*, **1986**, *42*, 2089. (b) Cram, D. J.; Cram, J. M. In*Container Molecules and Their Guests*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, U.K., 1994; pp70-84.
5. (a) Bell, T. W.; Firestone, A. *J. Am. Chem. Soc.* **1986**, *108*, 8109. (b) Bell, T. W.; Firestone, A.; Ludwig, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1902. (c) Wang, B.; Wasielewski, M. R. *J. Am. Chem. Soc.* **1997**, *119*, 12. (d) Voegtle, F.; Ibach, S.; Nieger, M.; Chartroux, C.; Krueger, T.; Stephan, H.; Gloe, K. *J. Chem. Soc., Chem. Commun.* **1997**, 1809.
6. Amabilino, D. B.; Dietrich-Buchecker, C. O.; Livoreil, A.; Perez-Garcia, L.; Sauvage, J.-P.; Stoddart, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 3905.
7. (a) Kim, K.; Paek, K. *Bull. Korean Chem. Soc.* **1993**, *14*, 658. (b) Boerrigter, H.; Verboom, W.; van Hummel, G. J.; Karkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1996**, *37*, 5167.
8. All compounds are characterized fully. Selected data for **3a**: mp > 242.0 °C (dec.); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 (s, 4H, Imidazolyl-$H_{2'}$), 720 (s, 4H, Imidazolyl-$H_{4'}$), 6.89 (s, 4H, Imidazolyl-$H_{5'}$), 7.02 (s, 4H, ArH), 5.91 (d, J = 7.2 Hz, 4H, exo-OCH_2O), 4.87 (s, 8H, $ArCH_2N$), 4.76 (t, J = 8.0 Hz, 4H, ArCHAr), 4.11 (d, J = 7.2 Hz, 4H, endo-OCH_2O), 2.21 (m, 8H, $CH_2CH_2CH_3$), 1.34 (m, 8H, $CH_2CH_2CH_3$), 1.00 (t, J = 7.3 Hz, 12H, $CH_2CH_2CH_3$); Anal. Cald for $C_{60}H_{64}O_8N_8$+CH_3CN+CH_2Cl_2C, 65.73; H, 6.04; N, 10.95. Found: C, 65.56; H, 6.29; N, 10.96; MS (FAB) m/z 1026 (M+ H$^+$, 100%).
9. Cram, D. J.; Jaeger, R.; Deshayes, K. *J. Am. Chem. Soc.* **1993**, *115*, 10111.
10. Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928.
11. Tucker, J. A.; Knobler, C. B.; Trueblood, K. N.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 3688.