Octa-amidocavitand: Paired Anion Binding through N-H···X⁻ and C-H···X⁻ Interactions

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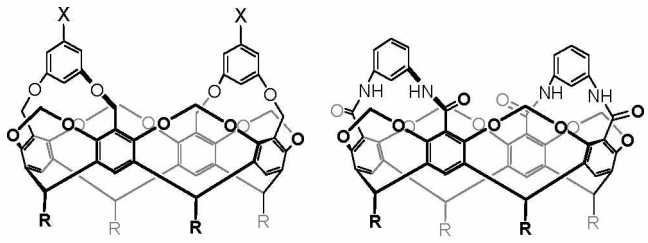
Anion recognition has grown since late 1960s just after the beginning of cation recognition. In the early stage the major problem of anion recognition was the designing difficulty of an efficient anion host because of the multi atomic structures except halides and the strong solvation of anions.

Anions are ubiquitous throughout biological systems and important for the development of medicines and catalysts, while various pollutant anions from the industries and the reprocessing of nuclear fuel have been serious environmental concerns. It has only been in the last twenty years that the fields of anion recognition have been expanded.[1] Hydrogen bonding interactions,[2] coordination chemistries,[3] and anion-π interactions[4] *etc.* were systematically adopted for many successful anion receptors.

Hydrogen bonds enable the designing of receptors that bind anions strongly and selectively. Recent reports describe anion recognitions with emphasis on the functional groups of amine,[5] amide,[6] urea,[7] thiourea,[8] pyrrole,[9] and guanidinium.[10] A substantial number of artificial anionic hosts incorporate strong hydrogen bonds, mostly N-H···X⁻ interaction. Quite a few anionic receptors make use of the enforced C-H···X⁻ interactions due to their intrinsic weakness.[11]

Resorcin[4]arene-based cavitands are versatile hosts because a variety of functional groups can be attached to their upper and lower rims. However, the application of hydrogen-bonding groups on resorcin[4]arenes for anion binding is still in its early stage.[12]

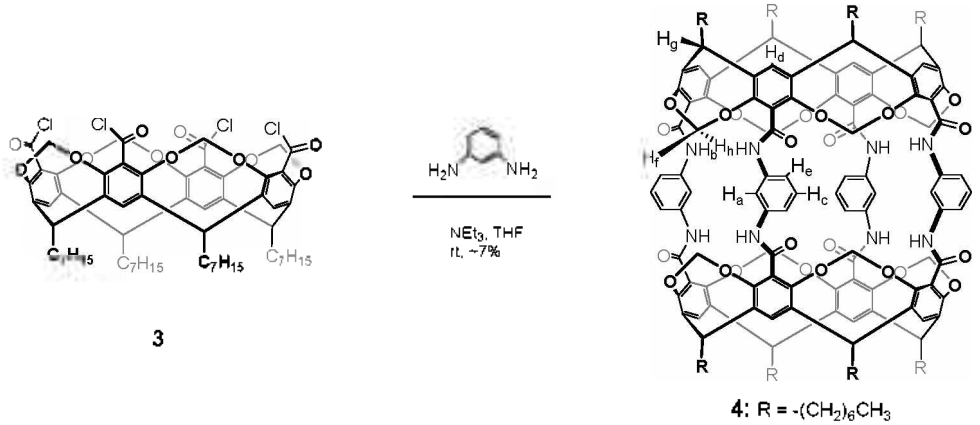
Recently the resorcin[4]arene-based cavitands **1** were reported to bind water or anions in CD_2Cl_2 or $CDCl_3$ due to the solvophobicity of anionic guest, their structural complementarity, and the Ar-H···G⁻ interaction, but their affinities were extremely low.[13] New cyclic amidocavitand **2** which was supposed to be a stronger anion binder due to its N-H···X⁻ interactions was designed.



1 (X = H, CH_3, $COOCH_3$, Br, CN) **2**

But the attempted syntheses of cavitand **2** from tetrakis (chloroacyl)cavitand **3**[12b] and 1,3-phenylenediamine in various conditions (base *vs.* temp. *vs.* solvent) only gave octa-amidocavitand **4** in less than 7% yield, which is presumable due to the extreme strain of cyclic -N-C(=O)- bonds of amidocavitand **2**. The analogous octa-amidocavitands (R = $-(CH_2)_4CH_3$ or $-CH_2CH_2C_6H_5$) were reported by Cram *et al.*[14]

Cram et al attempted to complex octa-amidocavitand **4** (R = $-CH_2CH_2C_6H_5$) with twelve neutral guests, but only obtained a stable 1:1 complex with 1,4-diacetoxybenzene.[14] Octa-amidocavitand **4** has well organized, inward-directing eight N-H bonds for anion binding. Tetrabutylammonium salts of various



3 **4**: R = $-(CH_2)_6CH_3$

Scheme 1

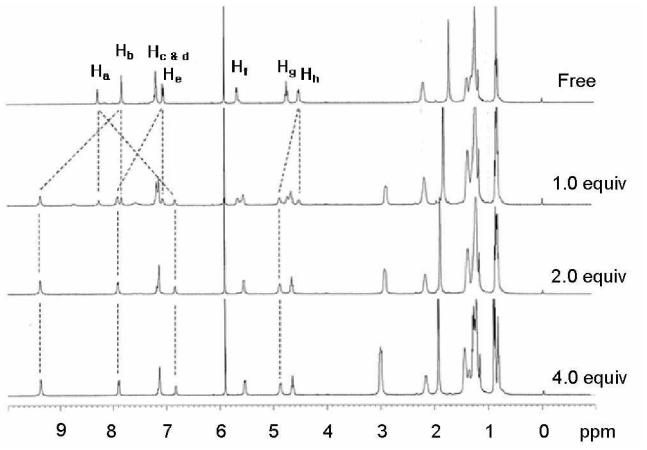


Figure 1. The ^{1}H NMR spectra showing the chemical shift changes of octa-amidocavitand **4** by the titration of tetrabutylammonium chloride in $C_2D_2Cl_4$ at 25 °C.

anions were titrated into a solution of octa-amidocavitand **4** which has two potential anion binding sites. The anion binding stoichiometry was monitored by chemical shifts changes in ^{1}H NMR spectra (Figure 1). The chemical shift changes in the ^{1}H NMR spectra are all consistent with the [H] : [G] = 1 : 2 complex with small anions in a slow exchange process.

Figure 1 shows ^{1}H NMR spectra of cavitand **4** titrated with tetrabutylammonium chloride (TBACl) in $C_2D_2Cl_4$ at 25 °C. When 1.0 equiv TBACl was added to cavitand **4** in $C_2D_2Cl_4$, the proton peaks of H_a, H_b, H_e, H_f and H_h were splitted into two 1 : 1 peaks for free cavitand **4** and caviplex 2 Cl^-@**4**. Those proton peaks of free cavitand **4** were disappeared by the addition of 2 equiv of TBACl, and the further addition of TBACl up to 4 equiv doesn't change the peaks of cavitand, which confirms that cavitand **4** and chloride ion forms a stable 1 : 2 caviplex and the rate of the second Cl^- complexation (k_2) is much greater than that of the first Cl^- complexation (k_1).[12b]

$$\text{cavitand } \mathbf{4} + 2\ Cl^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{caviplex } Cl^-@\mathbf{4} + Cl^- \rightleftharpoons \text{caviplex } 2\ Cl^-@\mathbf{4}$$

The energy-minimized structure of octa-amidocaviplex 2Cl^-@**4** using Spartan'04 V1.03 (Molecular Mechanics MMFF) shows a well defined 1 : 2 structure (Figure 2).

Table 1 shows the selected chemical shift changes in ^{1}H NMR spectra. The peaks of H_a and H_e which are both ortho to amide group shifted upfield ($\Delta\delta$ = −1.44 ppm) and downfield ($\Delta\delta$ = 0.85 ppm), respectively. The peak of amido proton H_b which exchanged with D_2O shifted far downfield from 7.82 to 9.37 ($\Delta\delta$ = 1.55 ppm). The peak of acidic inner proton H_h of the dioxymethylene (-O-CH_fH_h-O-)[12a] also moves downfield from 4.51 to 4.86 ppm ($\Delta\delta$ = 0.35 ppm), but the outer H_f shifted slightly upfield ($\Delta\delta$ = −0.11 ppm). The down field shifts of H_b and H_h are due to the strong N-H···Cl^- and the weak C-H···Cl^- interactions, respectively, both of which contribute to the stability of caviplex 2 Cl^-@**4**. The far down field shift of H_e implies their hydrogen bondings with adjacent carbonyl oxygens as

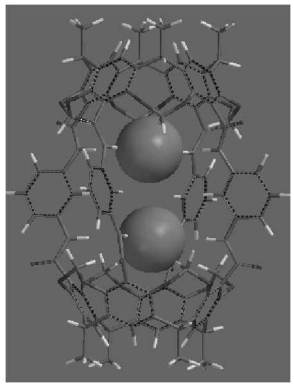


Figure 2. The energy-minimized structure of caviplex 2 Cl^-@**4** using Spartan'04 V1.03 (Molecular Mechanics MMFF).

Table 1. Chemical shift changes of the selected protons in ^{1}H NMR spectra.

	Chemical shift changes ($\Delta\delta$) of selected protons (ppm, $C_2D_2Cl_4$)				
	H_a	H_b	H_e	H_f	H_h
Free **4**	8.27	7.82	7.05	5.66	4.51
Cl^-@**4**	6.83	9.37	7.90	5.55	4.86
$\Delta\delta$	−1.44	1.55	0.85	−0.11	0.35

well as the deshielding effect of carbonyl group, which may result from the intramolecular planar 6-membered ring formation by the conformational freezing of bridging phenyl units upon anion binding. Notice the far upfield shift of H_a. It is also presumable that upon anion binding H_a directs inward where the magnetic shielding effects of south and north poles are operating.

The anion binding tendencies are fairly similar for fluoride, chloride, cyanide, or methanesulfonate ions. When octa-amido cavitand **4** in $C_2D_2Cl_4$ was titrated with TBA methanesulfonate, the peak of methanesulfonate was appeared at −1.57 ppm on ^{1}H NMR spectrum and the maximum complexation ratio of [H] : [G] was also 1 : 2. But unfortunately the selectivity and thermodynamic parameters of octa-amidocavitand **4** could not be observed due to its strong anion binding even in a mixture of 1 : 1 CD_3OD : $CDCl_3$ and the insolubility of **4** in more polar solvents.

In conclusion, octa-amidocavitand **4** binds strongly anions such as F^-, Cl^-, CN^-, and $CH_3SO_3^-$ through N-H···X^- and C-H···X^- interactions. The amide groups play an crucial role in anion binding receptor, and the binding stoichiometries with various small anions were 1 : 2. ^{1}H NMR titration experiment showed the slow guest exchange on ^{1}H NMR time scale and the rate of the second Cl^- complexation (k_2) is much greater than that of the first Cl^- complexation (k_1) in $C_2D_2Cl_4$ or $CDCl_3$ at 25 °C .

Experimental Section

General details. All commercially available solvents and reagents were used without further purification except tetrahydrofuran (THF). THF was distilled from sodium benzophenone

ketyl. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F254 glass plate and column chromatography was performed on Merck silica gel 60 (70-230 mesh). ^{1}H NMR spectra were obtained using a Bruker Avance Digital 400 (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to tetramethylsilane peak or solvent peak. Matrix assisted laser desorption/ionization mass-time of flight (MALDI-TOF) spectra was obtained using an Applied Voyager-DETM STR Biospectrometry (*NCIRF*). Elemental analyses were performed using a CE Instrument EA 1110 elemental analyzer (*NCIRF*). Melting point was measured using a Stuart® Melting point Apparatus SMP10.

Octa-amidocavitand 4. To a stirred solution of triethylamine (1.25 mL) in THF simultaneously were added dropwise a solution of tetra acid chloride cavitand **3** (500 mg) and a solution of 1,3-phenylenediamine (100 mg) in THF at room temperature under an argon atmosphere for 2 h, and then the mixture was stirred for 1 day. The solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2, wash with water, and dried over $MgSO_4$. After the evaporation of solvent, the product was purified by silica gel chromatography with a mixture of CH_2Cl_2/EA (98 : 2) as mobile phase (39 mg, 7%): MALDI-TOF MS *m/z* : 2499 ($M + H^+$, 100%); ^{1}H NMR (400 MHz, $C_2D_2Cl_4$) δ 8.30 (s, 4H, Ar-*H*), 7.80 (s, 8H, -CON*H*, exchange with D_2O), 7.18 (m, 12H, Ar-*H*), 7.03 (d, J = 8.0 Hz, 8H, Ar-*H*), 5.66 (d, J = 7.6 Hz, 8H, outer -OCH_2O-), 4.50 (d, J = 7.6 Hz, 8H, inner -OCH_2O-), 4.85 (t, J = 8.0, 8H, *CH* methine), 2.18 (m, 16H, -CH_2-), 1.44-1.25 (m, 80H, -(CH_2)$_5$-), 0.86 (t, J = 6.8 Hz, 24H, -CH_3); ^{13}C NMR (100.6 MHz, $C_2D_2Cl_4$, 25 °C) δ 162.3, 151.5, 151.0, 138.6, 138.0, 129.5, 126.4, 125.5, 121.7, 115.9, 100.0, 36.4, 31.7, 29.7, 29.3, 27.8, 22.6, 14.1; Anal. Calcd for $C_{96}H_{88}N_4O_{12}$ + 3 Ethyl acetate: C, 69.82; H, 7.46; N, 3.70; Found: C, 70.05; H, 7.52; N, 3.98; m.p > 280 °C (decomposed).

^{1}H NMR spectra of caviplex X$^-$@4. To a NMR tube were added 2.5 mg (0.001 mmol) of octa-amidocavitand **4**, 4 eqiv Bu_4NX, and 0.4 mL of $C_2D_2Cl_4$, and then ^{1}H NMR (400 MHz) spectrum was measured.

Caviplex F$^-$@4: δ 9.39 (s, 8H, -CON*H*), 7.17 (m, 12H, Ar-*H*), 7.90 (d, J = 8.0 Hz, 8H, Ar-*H*), 6.82 (s, 4H, Ar-*H*), 5.54 (d, J = 7.6 Hz, 8H, outer -OCH_2O-), 5.01 (d, J = 7.2 Hz, 8H, inner -OCH_2O-), 4.65 (t, J = 8.0, 8H, *CH* methine), 2.15 (m, 16H, -CH_2-), 1.44-1.25 (m, 80H, -(CH_2)$_5$-), 0.86 (t, J = 6.8 Hz, 24H, -CH_3).

Caviplex Cl$^-$@4: δ 9.37 (s, 8H, -CON*H*, exchange with D_2O), 7.13 (m, 12H, Ar-*H*), 7.91 (d, J = 8.0 Hz, 8H, Ar-*H*), 6.83 (s, 4H, Ar-*H*), 5.55 (d, J = 7.6 Hz, 8H, outer -OCH_2O-), 4.86 (d, J = 7.2 Hz, 8H, inner -OCH_2O-), 4.65 (t, J = 8.0, 8H, *CH* methine), 2.15 (m, 16H, -CH_2-), 1.44-1.25 (m, 80H, -(CH_2)$_5$-), 0.86 (t, J = 6.8 Hz, 24H, -CH_3).

Caviplex CN$^-$@4: δ 9.39 (s, 8H, -CON*H*), 7.13 (m, 12H, Ar-*H*), 7.90 (d, J = 8.0 Hz, 8H, Ar-*H*), 6.84 (s, 4H, Ar-*H*), 5.55 (d, J = 7.6 Hz, 8H, outer -OCH_2O-), 4.88 (d, J = 7.2 Hz, 8H, inner -OCH_2O-), 4.65 (t, J = 8.0, 8H, *CH* methine), 2.16 (m, 16H, -CH_2-), 1.44-1.25 (m, 80H, -(CH_2)$_5$-), 0.86 (t, J = 6.8 Hz, 24H, -CH_3).

Caviplex $CH_3SO_3^-$@4: δ 8.97 (s, 8H, -CON*H*), 7.06 (m, 12H, Ar-*H*), 7.72 (d, J = 8.0 Hz, 8H, Ar-*H*), 6.56 (s, 4H, Ar-*H*), 5.49 (d, J = 7.6 Hz, 8H, outer -OCH_2O-), 4.94 (d, J = 7.2 Hz, 8H, inner -OCH_2O-), 4.71 (t, J = 8.0, 8H, *CH* methine), 2.16 (m, 16H, -CH_2-), 1.44-1.25 (m, 80H, -(CH_2)$_5$-), 0.86 (t, J = 6.8 Hz, 24H, -CH_3), -1.57 (s, 3H, $CH_3SO_3^-$).

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References

1. (a) Beer P. D.; Gale P. A. *Angew. Chem., Int. Ed.* **2001**, *40*(3), 486. (b) Gale, P. A.; Garcia-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151. (c) Kim, J. S.; Quang, D. T. *Chem. Rev.* **2007**, *107*(9), 3780. (d) Kim, D.-S.; Chung, Y.; Jun, M.; Ahn, K. H. *J. Org. Chem.* **2009**, *74*(13), 4849. (e) Kim, S. K.; Lee, D. H.; Hong, J.-I.; Yoon, J. *Acc. Chem. Res.* **2009**, *42*(1), 23.
2. (a) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*(47), 7882. (b) Vilar, R. *Eur. J. Inorg. Chem.* **2008**, 347. (c) Wu, J. S.; Zhou, J. H.; Wang, P. F.; Zhang, X. H.; Wu, S. K. *Org. Lett.* **2005**, *7*, 2133. (d) Chen, B.; Wang, L.; Zapata, F.; Qian, G.; Lobkovsky, E. B. *J. Am. Chem. Soc.* **2008**, *130*(21), 6718.
3. (a) Romero, T.; Caballero, A.; Tmraga, A.; Molina, P. *Org. Lett.* **2009**, *11*(15), 3466. (b) Singh, A. S.; Chen, B.-Y.; Wen, Y.-S.; Tsai, C.; Sun, S.-S. *Org. Lett.* **2009**, *11*(9), 1867. (c) Hudnall, T. W.; Chiu, C.-W.; Gabba, F. P. *Acc. Chem. Res.* **2009**, *42*(2), 388.
4. (a) Yuste, C.; Caadillas-Delgado, L.; Labrador, A.; Delgado, F. S.; Ruiz-Prez, C.; Lloret, F.; Julve, M. *Inorg. Chem.* **2009**, *48*(14), 6630. (b) Estarellas, C.; Rotger, M. C.; Cap, M.; Quionero, D.; Frontera, A.; Costa, A.; Dey, P. M. *Org. Lett.* **2009**, *11*(9), 1987.
5. Kang, S. O.; Day, V. W.; Bowman-James, K. *Org. Lett.* **2008**, *10* (13), 2677.
6. Bernier, N.; Carvalho, S.; Li, F.; Delgado, R.; Flix, V. *J. Org. Chem.* **2009**, *74*(13), 4819.
7. (a) Jeon, N. J.; Ryu, B. J.; Lee, B. H.; Nam, K. C. *Bull. Korean Chem. Soc.* **2009**, *30*(7), 1675. (b) Amendola, V.; Boiocchi, M.; Colasson, B.; Fabbrizzi, L. *Inorg. Chem.* **2006**, *45*(16), 6138.
8. Amendola, V.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E.; Sancenón, F. *Inorg. Chem.* **2005**, *44*(24), 8690.
9. (a) Sessler, J. L.; Kamas, E.; Kim, S. K.; Ou, Z.; Zhang, M.; Kadish, K. M.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2008**, *130*(46), 15256. (b) Sessler, J. L.; Kim, S. K.; Gross, D. E.; Lee, C. H.; Kim, J. S.; Lynch, V. M. *J. Am. Chem. Soc.* **2008**, *130*(39), 13162.
10. Jadhav, V. D.; Schmidtchen, F. P. *J. Org. Chem.* **2008**, *73*(3), 1077.
11. (a) Li, Y.; Flood, A. H. *J. Am. Chem. Soc.* **2008**, *130*(36), 12111. (b) Chellappan, K.; Singh, N. J.; Hwang, I.; Lee, J. W.; Kim, K. S. *Angew. Chem. Int. Ed.* **2005**, *44*(19), 2899.
12. (a) Zhu, S. S.; Staats, H.; Brandhorst, K.; Grunenberg, J.; Gruppi, F.; Dalcanale, E.; Lützen, A.; Rissanen, K.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2008**, *47*(4), 788. (b) Park, Y. S.; Paek, K. *Org. Lett.* **2008**, *10*(21), 4867. (c) Park, H. S.; Paek, K. *Bull. Korean Chem. Soc.* **2009**, *30*(2), 505.
13. (a) Ihm, C.; In, Y.; Park, Y.; Paek, K. *Org. Lett.* **2004**, *6*, 369. (b) Ihm, C.; Cho, S.; Paek, K. *Bull. Korean Chem. Soc.* **2007**, *28*(10), 186. (c) Yan, S.; Cho, S. J.; Lee, S. J.; Kang, S.; Paek, K.; Lee, J. Y. *Phys. Chem. Chem. Phys.* **2008**, *10*, 7079.
14. Choi, H.-J.; Buhring, D.; Quan, M. L. C.; Knobler, C. B.; Cram, D. J. *Chem. Commun.* **1992**, 1733.