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Highly Preorganized Bis(benzocrown ether)s for the Binding of Metal Ions

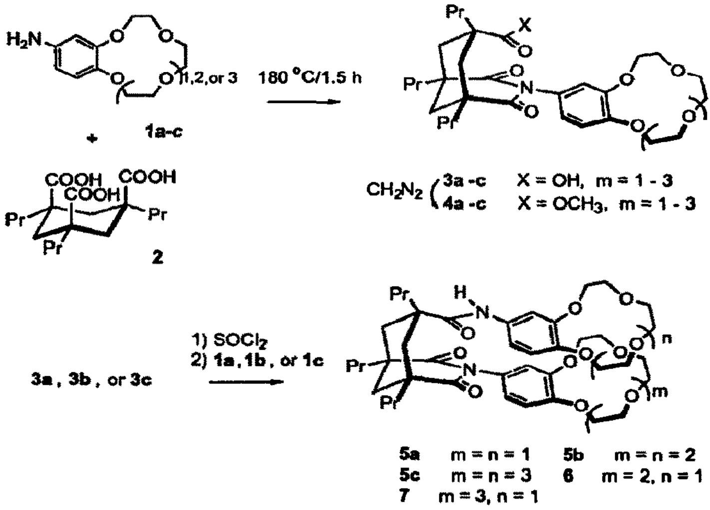
Kyu-Sung Jeong* and Seung Yup Pyun

Department of Chemistry, Yonsei University
Seoul 120-749, Korea

Abstract: Several bis(crown ether)s consisting of benzo-12-crown-4, benzo-15-crown-5, and benzo-18-crown-6, were prepared and their complexation properties with Na^+ and K^+ were determined by the liquid-liquid extraction method. The remarkable "biscrown effect" was observed in the extractions of both Na^+ and K^+ using bis(benzo-12-crown-4) and bis(benzo-15-crown-5). Unsymmetrical bis(crown ether)s also exhibit much higher extractabilities of both Na^+ and K^+ than the corresponding mono(benzocrown ether)s.

Metal ions have been the most popular targets for the recognition studies using synthetic hosts since Pedersen's discovery of crown ether in 1967.[1] Several bis(crown ether)s in which two crown ethers are connected to each other by appropriate linkers have been prepared for high stability and selectivity.[2] Most of the linkers reported are relatively flexible and metal ions induce the conformations of bis(crown ether)s to form sandwich-type complexes. This results in decreases of stabilities and selectivities of complexes.

We report here symmetrical bis(crown ether) hosts, **5a-c**, having same size of two benzocrown ethers, and unsymmetrical bis(crown ether) hosts, **6** and **7**, having different size of two benzocrown ethers.



Scheme 1

As shown in Scheme 1, heating of a well-ground mixture of triacid[3] **2** and amines, **1a-c**, having various sizes of crown ethers,[4] provides imide acids, **3a-c**, which have been converted to the corresponding imide acid chlorides with thionyl chloride, and then coupled again with appropriate amines, **1a-c**, to afford the desired hosts, **5a-c**, **6**, and **7** (3 steps; 50-60% total yields).[5]

Our new hosts are highly rigid and preorganized to be capable of forming sandwich-type complexes with metal ions. Two benzocrown rings in hosts are lying cofacial to and separated 3 - 3.5 Å from one another. Furthermore, two crown rings in our hosts are independent of each other, conformationally and electronically. It is, therefore, possible to know the exact effects caused by change of a binding site in hosts.

The hosts and their complexes with metal ions are highly soluble in most of organic solvents and not soluble at all in water. The binding affinities are determined by the liquid-liquid extraction method described by Cram.[6] The extraction experiments have been performed employing 15 - 90 mM of hosts in $CHCl_3$ and 15 mM of metal picrates[7] in H_2O. Under these conditions most of hosts show 15 - 85 % of extractabilities, in which range the reliable data can be obtained. The amount of extraction has been determined by measuring changes in absorbances of metal picrates in aqueous layer at 374 nm. The results are summarized in Table 1.

Table 1 The Liquid-Liquid Extractions[a] of Metal Picrates into $CHCl_3$ with Hosts at 296 ± 1 K.

host[b]	concentration of host (mM)	% extraction of metal picrates[c]	
		Na^+	K^+
4a [4]	15	< 1	< 1
	90	< 2	< 2
5a [4,4][d]	45	12	16
4b [5]	15	21	21
	30	31	42
5b [5,5][e]	15	50	85
6 [5,4]	15	32	52
4c [6]	15	22	61
	30	32	85
5c [6,6]	15	46	85
7 [6,4]	15	36	79

a) All of experiments were duplicated and errors are within 3%.

b) The numbers in parentheses indicates the numbers of oxygens in crown ether rings.

c) The concentrations of sodium and potassium picrate are 15 mM in distilled water in all cases.

d) We used, in this case,45 mM of **5a** to obtain more reliable data of extractions because 15 mM of **5a** extracted less than 10% of metal ions (5% of Na^+ and 7% of K^+).

e) When 30 mM of **5b** was employed, there were extracted 69% of Na^+ and 96% of K^+, respectively.

The extractions of both metal picrates by 15 to 90 mM of host **4a**, having a benzo-12-crown-4, are negligible (1 -2%), while 45 mM of the bis(benzo-12-crown-4), **5a**, extracts 12% of Na^+ and 16% of K^+, respectively. Therefore, the extractions by host **5a** occur mostly through the intramolecular sandwich-type complexes with metal ions, Na^+ and K^+.

The monobenzo-15-crown-5 host **4b** shows similar affinities toward both cations, Na^+ and K^+. It is, however, worthwhile noting that the ratio of K^+/Na^+ slightly increases as the concentration of host **4b** increases from 15 to 30 mM. This may be because extraction occurs not only through **4b**/ K^+ 1:1 complex,but also through **4b**/ K^+ 2:1 sandwich-type complex[8] shown in figure 1, (a).

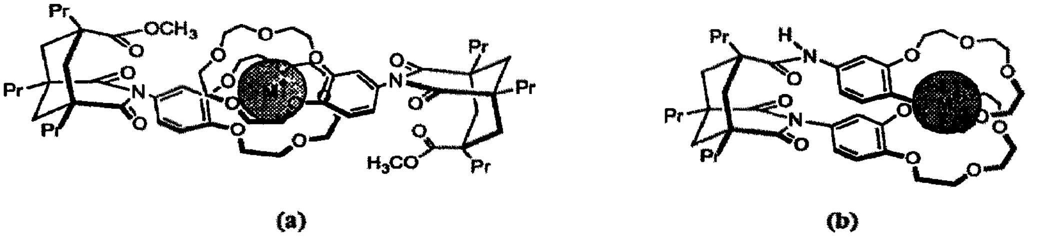


Figure 1 Two possible sandwich-type complexes; (a) host **4b**/K^+ 2:1 complex. (b) host **5b**/Na^+ or K^+ 1:1 complex

The monobenzo-12-crown-4 itself could not extract cations into chloroform layer, but its addition to benzo-15-crown-5 remarkably increases the extractabilities of cations as demonstrated in the unsymmetrical host **6**. The differences in percentages of extractions by **6** compare with equimolar **4b** are 11% for Na^+ and 31% for K^+, which are corresponding to 3 and 10 times increases in stability constants,[9] respectively, for Na^+ and K^+. The bis(benzo-15-crown-5) host **5b** extracts cations, especially K^+, much more effectively than twice molar equivalents of monobenzo-15-crown-5 host **4b** does. This can be rationalized by extracting both cations through intramolecular sandwich-type complexes shown in figure 1, (b). The stability constants[9] of bis(benzo-15-crown-5) **5b** are roughly 10 times for Na^+ and 10^3 times for K^+ higher than those of the **4b**, and the biscrown effect are much larger in K^+ than in Na^+. It is interesting that Na^+ also forms intramolecular sandwich-type complex with bis(benzo-15-crown-5) since the biscrown effect has been usually observed in the systems where sizes of cations are greater that those of crown rings.

Another unsymmetrical host **7** also exhibits higher extractabilities of cations than **4c** does. The enhancements of binding affinities in host **7** by additional benzo-12-crown-4 are almost same extent as in host **6**. Unlike other biscrown hosts, **5a** and **5b**, bis(benzo-18-crown-6) host **5c** does not form intramolecular sandwich-type complex with K^+ and two binding sites behave independently on extraction of potassium ion. The host **5c**, therefore, extracts exactly same amount of potassium ion with twice molar equivalents of monobenzo-18-crown-6, **4c**. However, the host **5c** extracts approximately 15% more Na^+ than twice molar equivalents of monobenzo-18-crown-6, **4c** does, suggesting intramolecular sandwich-type complex of **5c** with Na^+. These phenomena might be attributed to intrinsically high stability of complex between potassium ion and monobenzo-18-crown-6 itself, and low stability of complex between sodium ion and monobenzo-18-crown-6.[9]

In conclusion, our new hosts nicely demonstrated the biscrown effect on Na$^+$ and K$^+$ complexation. The biscrown effect is dependent not just on difference between sizes of crown ether and cation, but on intrinsic stability of complex between monocrown ether and cation. The symmetrical biscrown hosts, 5a and 5b and unsymmetrical biscrown hosts, 6 and 7, exhibit much higher binding affinities toward both Na$^+$ and K$^+$ through intramolecular sandwich-type complexes than the corresponding mono(benzocrown ether)s.

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References and Notes

1. (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495. (b) Pedersen, C. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021.
2. (a) Shinkai, S.; Ogawa, T.; Kusano, Y.; Manabe, O.; Kikukuwa, K.; Goto, T.; Matsuda, T. *J. Am. Chem. Soc.* **1982**, *104*, 1960. (b) Beer, P. D. *J. Chem. Soc., Chem. Comm.* **1985**, 1115. (c) Sakamoto, H.; Kimura, K.; Koseki, Y.; Matsuo, M.; Shono, T. *J. Org. Chem.* **1986**, *51*, 4974. (d) Kikukawa, K.; He, G.-X; Abe, A.; Goto, T.; Arata, R.; Ikeda, T.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin. Trans. 2*, **1987**, 135. (e) Beer, P. D.; Tite, E. L. *J. Chem. Soc., Dalton. Trans.* **1990**, 2691. (f) Inoue, Y.; Nakagawa, K.; Hakushi, T. *J. Chem. Soc., Dalton. Trans.* **1993**, 2279.
3. The tripropyl triacid **2** has been used in this study instead of commercially available Kemp triacid to enhance solubilities of hosts in organic solvents. For a preparation of **2**, see: (a) Jeong, K.-S.; Muehldorf, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *119*, 201. (b) Jeong, K.-S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201.
4. The amines, **1a-c**, were prepared by nitration (HNO$_3$/CH$_3$CO$_2$H) and hydrogenation (H$_2$/Pd-C) of the corresponding benzocrown ethers in 90-95% yield. The benzo-12-crown-4 was prepared by following literature procedure; Czech, B. P.; Czech, A.; Bartsch, R. A. *J. Heterocyclic Chem.* **1985**, *22*, 1297.
5. All new hosts were fully characterized by NMR, IR, and MS spectra. Mp : (**4a**) 49 -52 °C; (**4b**) oil (19 -20 °C); (**4c**) 45 -47 °C; (**5a**) 80 - 83 °C; (**5b**) 84 - 86 °C; (**5c**) 57 - 59 °C; (**6**) 100 - 103 °C; (**7**) 55 - 58 °C.
6. (a) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553. (b) Gokel, G. W. In *Crown Ethers and Cryptands*; Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; RSC: Cambridge, 1991; Chapter 3.
7. (a) Coplan, M. A.; Fuoss, R. M. *J. Phys. Chem.* **1964**, *68*, 1177. (b) Silberrad, O.; Phillips, A. *J. Chem. Soc.* **1908**, *93*, 474.
8. (a) Mallinson, P. R.; Truter, M. R. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1818. (b) Kimura, K.; Tamura, H.; Tsuchida, T.; Shono, T. *Chem. Lett.* **1979**, 611.
9. The stablity constants have been determined applying the equation described in literature 6a,.assuming host/cation 1:1 complex. Stability constants (M^{-1}): **4b** (15 mM) Na$^+$(1.1 x 10^6), K$^+$(0.8 x 10^6); **4c** Na$^+$(1.2 x 10^6) K$^+$(1.7 x 10^7); **5a** Na$^+$(1.4 x 10^5), K$^+$(1.4 x 10^5); **5b** Na$^+$(1.1 x 10^7), K$^+$(7.5 x 10^8); **6** Na$^+$(2.9 x 10^6), K$^+$(8.0 x 10^6); **7** Na$^+$(3.6 x 10^7), K$^+$(1.5 x 10^8).

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