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Cation Binding Properties of Benzo-type Crown Ethers.2.[1)]

Effect of Large Ring Size upon Complexation Phenomena of Crown-7 and Crown-8 Derivatives[2)]

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Abstract
 The cation-binding by two large ring-sized benzo-21-crown-7 and benzo-24-crown-8 has been performed by the solvent extraction of monovalent metal picrates (Na^+, K^+, Rb^+, Cs^+, Ag^+, and Tl^+) between water and dichlolomethane. The effect of ring size and benzo group upon the cation binding ability is discussed. The results are compared with benzo-18-crown-6 and simple unsubstituted crown ethers (18-crown-6, 21-crown-7 and 24-crown-8). It was found that large ring benzo-crown ethers have lower cation binding ability as the ring size increases compared with simple unsubstituted crown ethers while cation selectivity for large cations (Cs^+ and Tl^+) has been observed.

Key Words: crown ethers, solvent extraction, supramolecular chemistry

1. Introduction
 A wide variety of functionalized crown ether compounds have been synthesized to control the complexation phenomena with cations. The original papar by Pedersen's pioneering work in 1967 [3] still gives the idea of the approach for the design of supramolecular systems. We have recently reported the cation-binding abilities of less-symmetrical benzo-type crown ethers and found that dibenzo-crown-6 derivatives were superior to monobenzo-crown-ethers in view of cation binding and cation selectivity. It was also further suggested the role of benzene ring toward heavy metal binding especially for silver and thallium (I)[1].

 It has been believed that the cation-binding ability, and the cation selectivity of a crown ether mainly depend upon the following factors; 1) relationship between the cavity size of the crown ether and the cation diameter, 2) number of donor atoms, 3) conformational flexibility or rigidity of a crown ether, and 4) lipophilicity of the crown ether [4]. The synthetic approach for the molecular design of crown ethers has started from mono- or dibenzo-type crown ethers because of the feasibility of introducing the substituents. This study has been done in many papers, however, the structures of benzo-type crown ethers are mainly dibenzo type crown ethers or mono-benzo type crown ethers with small ring size (e.g. benzo-crown-4, 5, and 6 derivatives). In this context, it is our special interest to investigate the cation binding abilities of mono-benzo large crown ethers, benzo-21-crown-7 (**1**) and benzo-24-crown-8 (**2**). Their syntheses are described, and their cation binding abilities have been evaluated by solvent extraction of aqueous metal picrates. The results were compared with those of 21-crown-7 (**3**), 24-crown-8 (**4**), benzo-18-crown-6 (**13**), and commercially available 18-crown-6 (**14**).

2. Experimental Details
 Infrared spectra were obtained on a JASCO A-100 grating spectrophotometer. Mass spectra were measured using Shimazu GCMS-QP5000. ^1H NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer in chloroform-*d* solution containing 1% tetramethylsilane as internal standard. UV-VIS spectra were recorded on a Hitachi U-3500 spectrophotometer. Melting points were measured with a MEL-TEMP apparatus and are uncorrected. Solvent tetrahydrofuran (THF) was distilled from sodium hydride. Commercially available

reagents were used in the following syntheses without further purification unless noted otherwise.

1 : k = 1
2 : k = 2

3 : l = 1
4 : l = 2

5

6 : m = 3
7 : m = 4
8 : m = 5

9 : n = 2
10 : n = 3
11 : n = 4
12 : n = 5

13

14
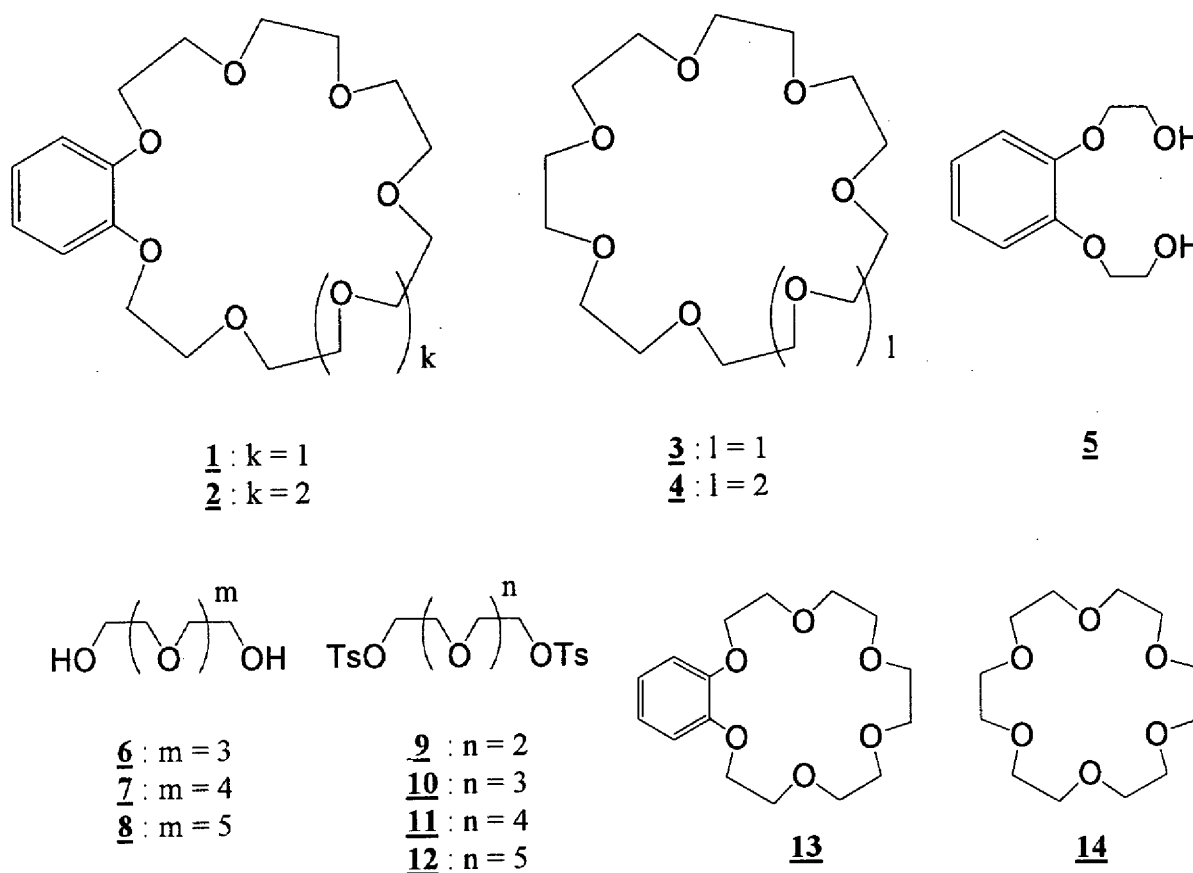
Synthesis. 1,2-Bis[(2-hydroxyethyl)oxy]benzene (5) was synthesized from catechol and 2-chloroethanol in ethanol in the presence of NaOH in 37% yield according to the similar reported method [5].mp 76-78°C (lit.78-80°C[5]), ^{1}H NMR δ 3.24-3.29 (t.2H), 3.91-3.92 (m.4H), 4.10-4.14 (t.4H), 6.98 (s.4H), IR (KBr) 2935, 2810, 1510, 1450, 1260, 1120, 1040, 740 cm^{-1}.

Pentaethylene glycol (7) was synthesized from triethylene glycol dichloride and excess amount of ethylene glycol in the presense of KOH in 45% yield according to the previous reported method [6].bp 172°C/0.6Torr (lit.175°C/0.6 Torr [6]), ^{1}H NMR δ 3.42 (s.2H), 3.56-3.78 (m.20H). IR(neat) 3350, 2850, 1460, 1350, 1240, 1100 cm^{-1}.

Hexaethylene glycol (8) was synthesized from diethylene glycol dichloride and excess amount of diethylene glycol in the presence of sodium metal in 40% yield according to the reported method [7]. bp 190°C/0.3Torr, ^{1}H NMR δ 2.95(br.s.2H), 3.62(s.24H). IR (neat) 3360, 2860, 1650, 1460, 1360, 1300, 1260, 1110 cm^{-1}.

Oligoethylene glycol ditosylates (9,10,11,12) were synthesized from the corresponding oligoethylene glycol and p-toluenesulfonyl chloride in THF in the presence of NaOH in 83-89% yield according to the reported method from the authors' group [8]. The ^{1}H NMR and IR spectra were in agreement with the published data [8].

Benzo-21-Crown-7 (1). KOH (19.8g, 0.35mol) and THF (400mL) were introduced into a 2-L three necked flask equipped with a magnetic stirrer, reflux condenser, dropping funnel, and nitrogen inlet tube. To the stirred suspension at 66 °C was added bis[(2-hydroxyethyl)oxy]benzene (5) (19.8g, 0.1mol) in THF (400mL), and stirring was continued for 1 h with consecutive bubbling of nitrogen. Tetraethylene glycol ditosylate (10) (50.2g, 0.1mol) in THF(200mL) was then added dropwise to the stirred mixture over 2 h, and the stirring was continued for 2 days at 66 °C under a nitrogen atmosphere. The solvent was evaporated and the residue was extracted with chloroform. The chloroform extract was dried over magnesium sulfate and the solvent was

evaporated. After work-up, it was purified by column chromatography (alumina, chloroform-hexane 2:1) to give 15.9g (45%) of the product 1(as the oily product): ^{1}H NMR δ 3.68 (s.8H), 3.80-3.82 (t.4H), 3.91-3.94 (t.4H), 4.15-4.18 (t.4H), 6.90 (s.4H); MS m/e 379 (M$^+$+ Na$^+$).

The alternative method was from cathecol (29.5g, 0.05mol) and hexaethylene glycol ditosylate (12) (6.1g, 0.055mol) in THF in the presence of KOH (10.8g, 0.19mol) for 24 hours in 13% (2.3g) yield. The ^{1}H NMR spectrum was identical with the above data.

Benzo-24-Crown-8 (2) was synthesized from 5 (2.5g, 0.013mol) and pentaethylene glycol ditosylate (11) (5.5g, 0.010mol) in THF in the presence of KOH (5.1g, 0.09mol) in 36% (1.5g) yield as the oily product according to the procedure described above. ^{1}H NMR δ 3.64-3.81 (t.20H), 3.89-3.92 (t.4H), 4.14-4.20 (t.4H), 6.90 (s.4H); MS m/e 424 (M$^+$+ Na$^+$).

21-Crown-7 (3) was synthesized from tetraethylene glycol (6) (21.7g, 0.11mol) and triethylene glycol ditosylate (9) (45.8g, 0.10mol) in THF in the presence of KOH (19.6g, 0.35mol) in 29% (9.0g) yield. according to the similar procedure described above. It was purified by distillation under reduced pressure. bp 153℃/0.85 Torr; ^{1}H NMR δ 3.69 (s.28H); IR (neat) 2860, 1460, 1350, 1300, 1250, 1110 cm^{-1}; MS 308 (M$^+$).

24-Crown-8 (4) was synthesized from 6 (19.4g, 0.10mol) and 10 (47.7g, 0.095mol) in THF in the presence of KOH (16.5g, 0.25mol) in 7% (2.4g) yield according to the procedure described above (21-Crown-7). bp 175℃/0.8 Torr; ^{1}H NMR δ 3.63 (s.32H); IR (neat) 2850, 1450, 1350, 1300, 1250, 1120cm^{-1}; MS 352 (M$^+$).

Benzo-18-Crown-6 (13) was synthesized from 5 (0.50g, 0.0025mol) and 9 (1.15g, 0.0025mol) in THF in the presence of KOH (1.54g, 0.027mol) in 36% yield according to the procedure mentioned above. mp 40℃ (lit.43℃[3]); ^{1}H NMR δ 3.70-3.80 (t.12H), 3.90-3.95 (t.4H), 4.14-4.20 (t.4H), 6.90 (s.4H).

Solvent Extraction. The general extraction procedures employed are similar to those previously presented [9]. Distilled dichloromethane and demineralized water were used. The solvents were saturated with each other before use in order to prevent volume changes of the phase during extraction. Equal volumes (10 mL) of dichloromethane solution of the respective crown ether (3.0mM) and of an aqueous solution of the corresponding metal picrate (3.0 mM) were shaken for 10 minutes at 25 ℃ in a Taiyo M100L incubator. The mixture was then allowed to stand for at least 90 minutes at that temperature in order to complete phase separation. The organic phase was separated by filtration (Toyo filter paper No.2s). Since the picrates do not dissolve in dichloromethane, the molar extinction coefficients in 1:1 mixture of dichloromethane and acetonitrile were determined. The concentration of alkali and heavy metal picrate in the organic phase was determined from absorbance at 375 nm in a mixture of dichloromethane and acetonitrile.

3. Results and Discussion

Synthesis. The general idea of the synthesis of mono-benzo-crown ethers has been presented in Pedersen's work [3]. The product is obtained by the reaction of catechol and oligoethylene glycol dichlorides (or ditosylates) in the presence of NaOH (or KOH). However, oligoethylene glycols possessing more than 6 oxygen atoms (e.g. penta-, hexa-, and hepta ethylene glycols) are not commercially available. They should be synthesized and purified by distillation under high reduced pressure. It needs sometimes careful attention and techniques of their preparation for students. Then they are converted to their dichlorides and ditosylates for the synthesis of mono-benzo-crown ethers with 6-8 oxygen atoms in the crown ether ring (e.g. benzo-18, 21,and 24 crown ether derivatives) using catechol as starting material.

In the present study, catechol was converted to 5 by reaction of catechol and 2-chloroethanol in ethanol in the presence of NaOH in 37% yield. The compound 5 has two side chains possessing oxyethylene chains that would be the component of the crown ether ring. 5 is also obtained by crystallization and it is easy to handle it.

Thus 5 is the starting material of the synthesis of large ring mono-benzo-crown ethers. 1 was synthesized from 5 and 10 in THF in the presence of KOH in 45% yield. Benzo-24-Crown-8 (2) was synthesized from 5 and 11 in THF in the presence of KOH in 36% yield. No attempt was made to maximize the yields of the products, however, the yields of 1 and 2

Benzo-18-Crown-6 (13) was also synthesized according to the same method while it can be synthesized from catechol and 11 below 30 % yield. 13 was synthesized from 5 and 9 in THF in the presence of KOH in 36% yield.

Unsubstituted large ring-sized crown (3) was synthesized from 6 and 9 in THF in the presence of KOH in 29% yield.   Likewise, 4 was synthesized from 6 and 10 in THF in the presence of KOH in 7% yield. The oily products 3 and 4 were purified by distillation under reduced pressure.

Though the general idea of the above synthetic methods has been already reported by other and our groups[5,6], the characteristic informations of the compounds have not been described in detail.   The present results would give the detailed strategic idea and direction in case of synthesizing large ring-sized macrocyclic compounds.

Solvent Extraction. A wide variety of measurement techniques for evaluating the characters of macrocyclic compounds have been reported. For crown ethers, solvent extraction techniques are quite popular and convenient method to evaluate cation binding ability. In the present study, aqueous some alkali and heavy metal picrates (Na^+, K^+, Rb^+, Cs^+, Ag^+, and Tl^+) were extracted at 25°C with dichloromethane solution of the crown ethers (1,2,3,4,13, and 14). The extractabilities obtained are shown in Table 1. In the present study, data obtained by this solvent extraction of metal picrates are presented for general discussion.

Table 1. Solvent Extraction of Metal Picrates[a]

Ligand	%Extractability[b]					
	Na^+	K^+	Rb^+	Cs^+	Ag^+	Tl^+
1	1.7	19.7	33.1	36.4	9.0	52.8
2	11.2	13.7	18.5	18.4	22.2	41.9
3	3.2	24.9	43.1	52.2	22.4	63.6
4	5.1	16.2	22.4	32.4	19.9	48.4
13	2.9	43.0	28.6	17.0	18.2	55.0
14	6.3	69.0	57.6	36.7	31.3	73.2

a) Temperature 25°C; aqueous phase (10ml):[picrate]=3mM. Organic Phase (CH_2Cl_2, 10ml):[Ligand]=3mM.

b) Defined as percent picrate extracted into the organic phase. Average of two independent runs.

As seen from Table 1, large ring-sized crown-7 and crown-8 (1,2,3,4) possess high extractability for Cs^+ and Tl^+ while 13 and 14 possess high extractability for K^+ and Tl^+. Generally it was found that large ring-sized benzo-crown ethers have lower cation binding ability as the ring size increases, and cation selectivity for large cations (Cs^+, and Tl^+) has been observed.   This would be clearly explained by the generally accepted size-fit concept [3] and unusual high Tl^+ binding ability for most crown ethers irrespective of the ring size [10]. Compared with benzo-crown ethers and unsubstituted crown ethers with the same ring size, the cation binding ability of benzo-crown ethers are generally lower than the corresponding unsubstituted crown ethers; e.g. the data of 1 vs. 3 and those of 2 vs. 4.   The exceptions are Na^+ and Ag^+ for 2.

The results are explained by the basicity of oxygen atom of the crown ether ring. Basicity of oxygen atom next to the benzene ring of 1 and 2 is lower than that of 3 and 4 which causes the low binding ability of the crown ethers for most cations. This has been already shown for crown-6 derivatives (13, and 14).   This explanation would be based on the 1:1 crown ether-cation complex and no sandwich type complex between crown ether and cation. The unusual high Na^+ and Ag^+ extractability for Benzo-24-Crown-8 (2) might be from the change of complex formation as the possibility of 1:2 crown ether-cation complex for small size cations toward large ring-sized crown ethers. To get the clear-cut evidence, the further extraction experiments to determine the extraction equilibrium constants (K_{ex}) should be needed. This investigation is in progress.   1 and 2 would be converted to the multi-roop type benzo-crown ethers [11] which would show the new character of crown ethers.

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