Molecular Design of Crown Ethers. VII.[1] Syntheses and Cation Selectivities of Unsubstituted 12- to 16-Crown-4

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Synopsis. Solvent extraction of aqueous alkali and some heavy metal picrates with the title compounds showed that, with most cations except for Li^+, Na^+, and Ag^+, the extractability decreases monotonically as the ring size increases from 12 to 16. However, 14-crown-4 showed the highest extractability and selectivity for Li^+ over the larger alkali metals, while 15-crown-4 exhibited the highest Ag^+/Tl^+ selectivity.

We have recently shown that molecular symmetry plays a crucial role in determining cation binding ability and/or selectivity of less-symmetrical $(3m+n)$-crown-m ($m>3$, $n\neq0$), especially small-sized, rigid ones,[1,2] although its effect is mostly negative with ring-contracted $(3m-1)$-crown-m ($m=5$ or 6)[3] and large-sized, ring-enlarged crown ethers ($m=6$—8, $n=1$—4),[4-6] resulting in more or less lower binding ability and selectivity than symmetrical crown ethers. In this context, it is of our special interest to examine the effect of molecular symmetry in the crown-4 series.

A wide variety of less symmetrical crown-4 derivatives and their salt complexes have been synthesized and characterized.[7-16] As expected from its cavity diameter (1.2—1.7 Å), most crown-4 derivatives exhibit Li^+ selectivity over larger alkali metal ions. The effects of extra methylenes introduced have been fragmentally surveyed to some extent with crown-4 derivatives possessing benzo or alkyl substituents.[10,13] However, no systematic survey has been conducted to reveal the relationship between molecular symmetry and cation binding ability/selectivity, using a series of unsubstituted 12- to 16-crown-4 (**1**—**5**). In this paper, we synthesized the unsubstituted 13- to 16-crown-4 and evaluated their cation binding abilities and relative cation selectivities by the solvent extraction of aqueous alkali and some heavy metal picrates. The present study enables us to discuss the effect of crown-4's cavity size and molecular symmetry upon their cation binding ability/selectivity.

Results and Discussion

Synthesis. All less-symmetrical crown-4 ethers were synthesized by using a mixed base, i.e. LiOH/NaOH. Use of LiOH or NaOH alone in the synthesis of 13-crown-4 led to no reaction or a very low yield, probably due to poor reactivity or template effect, so that the use of the mixed base is highly recommended.

It is interesting to note that, although comparable reaction conditions were employed and the template effect is likely to be operating in each synthesis, the product yields do not simply reflect the tendency of cation binding abilities of the product crown ethers **2**—**6** discussed below.

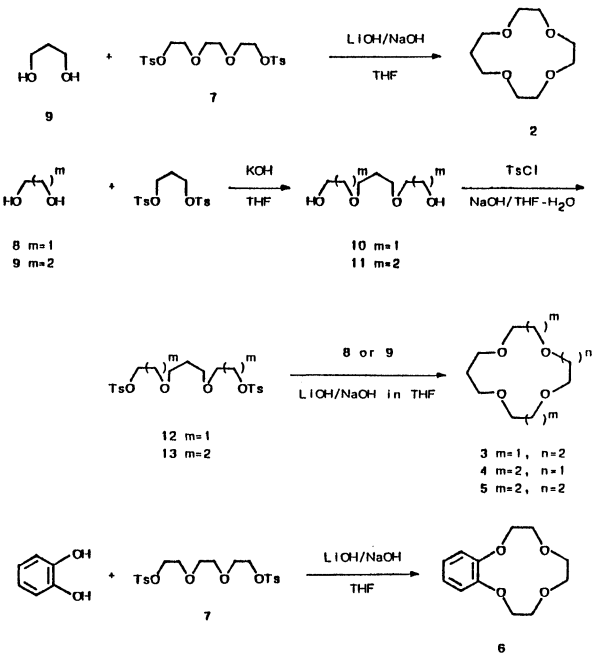
Solvent Extraction. Carrying just four donor oxygens in the ring, any of the crown-4 **1**—**6**, dissolved in dichloromethane, did not extract appreciable amount of aqueous alkali or heavy metal picrates under our standardized condition: [ligand]=[picrate]=3 mM, where common 15-crown-5 or 18-crown-6 exhibit moderate to high extractabilities for most univalent metal picrates.[2] Hence, a higher ligand concentration (30 mM) was employed. The extractabilities (% Ex) obtained for 12- to 16-crown-4 **1**—**5** are shown in Table 1, along with those of benzo-12-crown-4 **6**. Also listed are the selected relative cation selectivities of Li^+/Na^+ and Ag^+/Tl^+, calculated from the distribution ratio of metal ion between the organic and aqueous phases: $D_M=[M^+]_{org}/[M^+]_{aq}=\%Ex/(100-\%Ex)$.

As shown in Table 1, benzo-12-crown-4 **6** possesses not only substantially low extractabilities but also distinctly different cation selectivities compared with

Table 1. Solvent Extraction of Aqueous Metal Picrates with 12- to 16-Crown-4 and Benzo-12-crown-4[a]

Ligand	% Extractability[b]							Selectivity[c]	
	Li^+	Na^+	K^+	Rb^+	Cs^+	Ag^+	Tl^+	Li^+/Na^+	Ag^+/Tl^+
Benzo-12-crown-4(**6**)	0.14	1.62	0.76	0.70	0.56	1.87	4.61	0.08	0.39
12-Crown-4 (**1**)	2.67	14.4	3.52	3.55	3.10	13.3	15.3	0.16	0.85
13-Crown-4 (**2**)	0.80	3.80	1.25	0.83	0.65	8.74	6.13	0.20	1.47
14-Crown-4 (**3**)	13.9	0.98	0.58	0.19	0.19	4.58	2.49	16.3	1.88
15-Crown-4 (**4**)	1.66	1.21	0.15	0.17	0.10	6.44	0.92	1.38	7.41
16-Crown-4 (**5**)	0.29	0.20	0.05	d)	d)	1.21	0.28	1.45	4.36

a) Temperature 25.0±0.1 °C; aqueous phase (10 mL): [picrate]=3 mM; organic phase (CH_2Cl_2, 10 mL): [crown ether]=30 mM. b) Defined as percent picrate extracted into the organic phase. Average of two or three independent runs; error <3% of the reported value. c) Relative cation selectivity determined by the distribution ratio of metal ion between the organic and aqueous phases. d) Not determined.



Scheme 1. Syntheses of 13- to 16-crown-4 and benzo-12-crown-4.

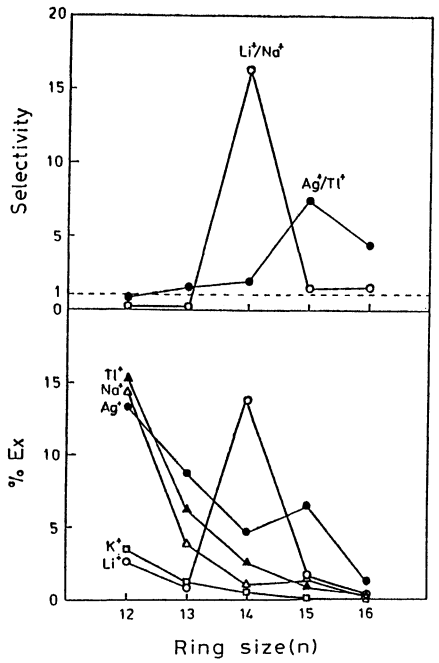


Fig. 1. Percent extractability (% Ex; lower traces) and relative cation selectivity (upper traces) for selected cations as functions of ring size (n) upon solvent extraction of aqueous metal picrates with 12- to 16-crovn-4 **1**- **5**.

the parent 12-crown-4, owing to the altered spatial arrangement and reduced electron density of donor atoms through incorporation of the benzo substituent. This demonstrates that the ring size effect can be assessed only by comparing unsubstituted crown ethers.

Quite different ring-size dependence is observed for the individual cation. In Fig. 1, the profiles of extractability and selectivity for the cations of interest are plotted against the ring size. In sharp contrast to the monotonic decrease in % Ex of the larger cations with increasing ring size (n) from 12 to 16, the % Ex values for Li^+, Na^+, and Ag^+ behave specifically. The % Ex for Li^+ shows a sharp global maximum at n=14, while those for Na^+ and Ag^+, being highest at n=12, exhibit local maxima at n=15. The distinctive changes in % Ex of the small cations are demonstrated more clearly in the selectivity plot in Fig. 1 (upper traces); the peak selectivities for Li^+ and Ag^+ are found at n=14 and 15, respectively. Since the lipophilicity of ligand increases with increasing number of extra methylene groups, the monotonic decreases for larger cations cannot be attributed to an unrealistic increase in distribution of ligand to aqueous phase, but is rather ascribed to the mismatched cavity size, disordered spatial arrangement of donor oxygens, and increased flexibility of ring-enlarged crown ethers **2**—**5**. Since the extraction of aqueous metal picrate with ligand is known to require fairly extensive dehydration,[17,18] the burst of Li^+ extraction at n=14 and the local maxima of Na^+ and Ag^+ extraction at n=15 are somewhat unexpected in view of their much higher free energies of hydration than those of the larger cations; ΔG_h°: Li^+, 115; Na^+, 90; K^+, 73; Rb^+, 67; Cs^+, 62; Ag^+, 105; Tl^+, 74 kcal mol^{-1}.[19] Examination with CPK molecular models revealed that the successive introduction of extra methylenes into 12-crown-4 not only increases the cavity size but also makes the crown ring more flexible. Thus the enlarged cavity size (1.4 Å) and the favorable orientation of donor atoms in 14-crown-4 **3** are jointly responsible for the highly selective extraction of the size-matched Li^+(diameter 1.52 Å).[20] The local maxima at n= 15 for Na^+ and Ag^+ may also be accounted for in terms of the size-fit concept.

It is concluded that, in the crown-4 series, the fine adjustment of cavity size to the diameter of specific cation is achieved by introducing extra methylenes in the ring, and indeed this strategy works well as an effective tool for enhancing cation binding ability and/or selectivity of the resulting less-symmetrical crown ethers, as is the case with the crown-5 series.[1,2]

Experimental

General. Melting points, measured with a YANACO MP-21 apparatus, are uncorrected. Mass spectra were obtained by electron impact (EI), chemical ionization (CI), or fast-atom bombardment (FAB) on a JEOL AX-500 instrument. ^{1}H NMR spectra were recorded on a JEOL GX-400 spectrometer at 400 MHz in $CDCl_3$ solution. Infrared and electronic spectra were recorded on JASCO A-100 and UVIDEC-660 instruments, respectively.

Materials. Tetrahydrofuran (THF) was dried over $CaCl_2$ and distilled from NaH. Dichloromethane was distilled prior to use. 12-Crown-4 (Merck) and other commercially available reagents were used as received. Metal picrates were prepared as reported.[2,21]

3,7-Dioxanonane-1,9-diol (10). To a stirred suspension of finely ground KOH (67.3 g, 1.2 mol) in THF (800 mL) was added **8** (161 g, 2.4 mol), and the mixture was refluxed for 2 h under N_2. Then, 1,3-propanediol bis(p-toluenesulfonate)[22] (134.4 g, 0.35 mol) in THF (400 mL) was added

to the stirred mixture over 2 h, and stirring was continued for 96 h under reflux. Evaporation of the solvent and the subsequent distillation in vacuo gave **10** (12 g, 32%): bp 95—125 °C (0.3 Torr, 1 Torr≈133.322 Pa); MS (CI) *m/z*, 165 (M^++1); ^{1}H NMR δ=3.65—3.69 (m, 4H), 3.57 (t, 4H), 3.50—3.53 (m, 4H), 3.05 (br, 2H), 1.84 (quintet, 2H); IR (neat) 3400, 2950, 2875, 1125, 1075, 900 cm^{-1}.

4,8-Dioxaundecane-1,11-diol (11) was synthesized from **9** (1.2 mol) and its bis(*p*-toluenesulfonate)[22] (0.20 mol) in 27.3%: bp 110—130 °C (0.4 Torr); MS (FAB) *m/z*, 193 (M^++1); ^{1}H NMR δ=3.73 (br, 4H), 3.59 (t, 4H), 3.50 (t, 4H), 3.00 (br, 2H), 1.82 (quintet, 2H), 1.79 (quintet, 4H); IR (neat) 3370, 1108 cm^{-1}.

3,7-Dioxanonane-1,9-diol Bis(*p*-toluenesulfonate) (12) was prepared from **10** in 76% yield:[22] MS (EI) *m/z*, 472 (M^+); ^{1}H NMR δ=7.78 (d, 4H), 7.31 (d, 4H), 4.13 (t, 4H), 3.58 (d, 4H), 3.43 (t, 4H), 2.43 (s, 6H), 1.70 (quintet, 2H); IR (neat) 3050, 2960, 2930, 2875, 1600, 1360, 1180, 920, 820, 780 cm^{-1}.

4,8-Dioxaundecane-1,11-diol Bis(*p*-toluenesulfonate) (13) was prepared from **11** in 67% yield:[22] MS (FAB) *m/z*, 501 (M^++1); ^{1}H NMR δ=7.79 (d, 4H), 7.34 (d, 4H), 4.11 (t, 4H), 3.40 (t, 4H), 3.34 (t, 4H), 2.44 (s, 6H), 1.87 (quintet, 4H), 1.67 (quintet, 2H); IR (neat) 3050, 2920, 2850, 1600, 1350, 1170, 1090, 940, 810 cm^{-1}.

1,4,7,10-Tetraoxacyclotridecane (13-crown-4, 2). Propanediol **9** (19.2 g, 0.25 mol) was added to a stirred suspension of finely ground LiOH·H_2O (12.6 g, 0.3 mol) and NaOH (4.0 g, 0.1 mol) in THF (400 mL) at 66 °C, and the mixture was refluxed for 1 h under N_2. To the mixture was added **7**[22] (45.8 g, 0.1 mol) in THF (200 mL) over 2 h, and stirring was continued for 96 h at 66 °C. The solvent was evaporated, water (100 mL) was added to the residue, and the resultant mixture was extracted with chloroform (100 mL×3). Pale yellow oil obtained upon evaporation of the solvent was distilled in vacuo to give **2** (6.90 g, 36.3%) as colorless oil: bp 80—105 °C (0.8 Torr); MS (EI) *m/z*, 191 (M^++1); ^{1}H NMR δ=3.62—3.68 (m, 16H), 1.77 (quintet, 2H); IR (neat) 2920, 2860, 1120 cm^{-1}; Anal. Calcd for $C_9H_{18}O_4$: C, 56.84; H, 9.47%; Found: C, 56.32; H, 9.73%.

1,4,8,11-Tetraoxacyclotetradecane (14-crown-4, 3) was synthesized from **9** (0.12 mol) and **12** (0.049 mol) in 21% yield: colorless crystal; bp 60—80 °C (0.15 Torr): mp 33—34 °C (lit, 23—24 °C,[23] 34 °C[8]); MS (EI) *m/z*, 205 (M^++1); ^{1}H NMR δ=3.67 (t, 8H), 3.65 (s, 8H), 1.78 (quintet, 4H); IR (neat) 2930, 2870, 1130 cm^{-1}.

1,4,8,12-Tetraoxacyclopentadecane (15-crown-4, 4) was synthesized from **8** (0.25 mol) and **13** (0.047 mol) in 33% yield: colorless oil; MS (EI) *m/z*, 219 (M^++1); ^{1}H NMR δ=3.65 (t, 4H), 3.64 (s, 4H), 3.57 (t, 8H), 1.78 (quintet, 6H); IR (neat) 2930, 2860, 1140 cm^{-1}; Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16%; Found: C, 60.73; H, 10.18%.

1,5,9,13-Tetraoxacyclohexadecane (16-crown-4, 5) was synthesized from **9** (0.15 mol) and **13** (0.042 mol) in 11% yield; colorless needles: bp 80—110 °C (0.9 Torr); mp 67—69 °C (lit, 67.5 °C,[23] 70 °C[7]); MS (EI) *m/z*, 233 (M^++1); ^{1}H NMR δ=3.55 (t, 16H), 1.80 (quintet, 8H); IR (KBr) 2930, 2850, 1130 cm^{-1}.

2,3-Benzo-1,4,7,10-tetraoxacyclododecane (Benzo-12-crown-4, 6) was synthesized from pyrocatechol (0.12 mol) and **7** (0.10 mol) in 21.6% yield: colorless crystal; bp 95—115 °C (0.5 Torr); mp 44—45 °C (lit, 44—45.5);[24] MS (EI) *m/z*, 224 (M^+); ^{1}H NMR δ=6.95—6.99 (m, 4H), 4.18 (t, 4H), 3.86 (t, 4H), 3.80 (s, 4H); IR (KBr) 3060, 2930, 2860, 1595, 1500, 1260, 1120, 930 cm^{-1}.

Solvent Extraction was performed as described previously.[1,2]

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