Dodecylphosphoric Acid-Armed Crown Ethers: Specific Complexing Abilities toward Alkali Metal Cations

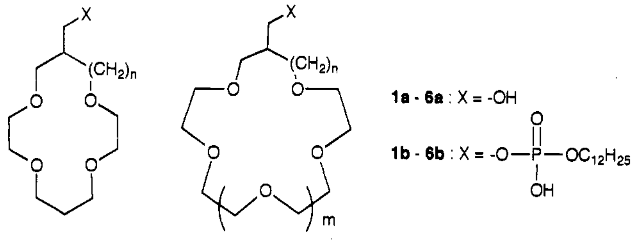
Yoichi Habata,* Harumi Ugajin, and Sadatoshi Akabori*

Department of Chemistry, Faculty of Science, Toho University, Funabashi, Chiba 274, Japan

Received September 27, 1993

Crown ethers possessing ionizable groups (*e.g.* phenolic OH, carboxylic, or arylphosphonyl groups) as an additional binding site have recently attracted much attention from chemists.[1] Advantages of the ionizable crown ether, when compared with simple crown ethers, are (i) rapid incorporation of cations from the basic aqueous phase to the organic phase and rapid release to the acidic aqueous phase, and (ii) enhancement of cation selectivity by formation of a three-dimensional cavity using the crown ring and the anion site of the pendant arm.[2] We previously reported that benzo- and dibenzo-14-crown-4 derivatives having an alkylphosphoric acid functional group are useful as a selective and efficient Li^+ ion carrier for liquid–liquid extraction and liquid membrane transport.[3] In this paper, we report the complexing abilities of a series of dodecylphosphoric acid armed crown-4, crown-5, and crown-6 ethers.

Hydroxymethyl crown ethers (**1a**–**6a**) and dodecyl phosphate were prepared according to the procedures described in the literature.[4,5] The new crown ethers having a dodecylphosphoric acid moiety were prepared by a one-pot reaction of the appropriate hydroxymethyl crown ether (4.3 mmol) with dodecyl phosphate (8.6 mmol) in the presence of dicyclohexylcarbodimide (21.2 mmol) in dry pyridine (40 mL) at room temperature. After the reaction mixture was treated in the usual manner, and isolation and purification were performed by silica gel TLC ($CHCl_3$:EtOAc:MeOH = 2:2:1 as eluent) followed by gel-permeation column chromatography (Sephadex LH-20, EtOH as eluent), pure **1b**–**6b** are obtained as pale yellow hygroscopic oils. The structures of **1b**–**6b** were confirmed by ^1H NMR, mass spectroscopy, and elemental analyses. From the elemental analyses, it was also confirmed that the **1b**–**6b** contained 0.5–2.5 mol equiv of water. (Compounds **2b**, **3b**, and **4b** were dried with Abderhalden's dryer (0.1 Torr, 100 °C) for 2–3 h, while **1b**, **5b**, and **6b** were dried for 0.5 h under the same condition.)



1a, **1b** : n = 0
2a, **2b** : n = 1

3a, **3b** : n = 0, m = 1
4a, **4b** : n = 1, m = 1
5a, **5b** : n = 0, m = 2
6a, **6b** : n = 1, m = 2

The complexing abilities of the hydroxymethyl- and dodecylphosphoric acid-armed crown ethers (**1a**–**6b**) toward alkali metal cations (Li^+, Na^+, and K^+) were evaluated by the competitive liquid membrane transport.[3] Each experiment was repeated three times, and the reproducibility of the transport rate is ±10% or better. As shown in Table 1, the hydroxymethyl crown ethers (**1a**–**6a**) rarely exhibited a transport rate toward the tested cations ($<0.01 \times 10^{-6}$ mol/h) under these conditions, because they have a hydrophilic character. In contrast, drastic enhancement in the transport rate was observed by introduction of a dodecylphosphoric acid moiety into the crown ethers. Interestingly, there are significant differences in cation selectivity between **1b** and **2b**, and **3b** and **4b**, which had the pendant arm introduced to the dimethylene and trimethylene units. Among the crown-4 derivatives, **2b**, which had the pendant arm added to the 14-crown-4, showed Li^+-selective transport, although **1b** (13-crown-4 derivative) did not show selectivity toward Li^+. It is also shown that **4b** (16-crown-5 derivative) transported Na^+ selectively, although **3b** (15-crown-5 derivative) had a slight selectivity toward K^+. In the crown-6 derivatives, there was no significant change in the transport rates of Na^+ and K^+ between **5b** and **6b**, although a slight enhancement of the Li^+ transport rate was observed in **6b**. From an examination of a CPK molecular model, differences in cavity size between **1** and **2**, **3** and **4**, and **5** and **6** were estimated to be 0.1 Å.[6] In addition, Bartsch et al. reported that lipophilic carboxylic acid-armed 13-crown-4 and 15-crown-5 derivatives efficiently extracted size-matched alkali metal cations.[1a] Therefore, the selectivity changes in these new crown ethers having the same oxygen atoms may be attributed to the introduction of the dodecylphosphoric acid moiety to the crown ring. Concerning these differences in cation selectivities, the CPK molecular model and the computer modeling as shown in Figure 1 (Chem 3D Plus was used as a computer modeling software. Minimization of the crown ring was carried using the Chem 3D parameter) showed that **2b** and **4b** formed three-dimensional cavities which fit Li^+ and Na^+, respectively, using the phosphate anion of the side arm and oxygens of the crown ring. However, **1b** and **3b** could not favorably form the cavities to bind them.

It is well known that information on cation-binding behavior of the armed crown ethers was obtained via ^{13}C-NMR spectroscopy.[7] In order to obtain more detailed structural information on the alkali metal complexes of **1b**–**6b**, we carried out ^{13}C-NMR titration experiments in CD_3CN/D_2O (1/1) solution. (Titration experiments were carried out by addition of 0.5, 1.0, and 2.0 equiv of alkali

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Table 1. Competitive Transport of Alkali Metal Cations with 1a–6a and 1b–6b[a]

	transport rate[b]				transport rate[b]			selectivity of 1b–6b	
carrier	Li^+	Na^+	K^+	carrier	Li^+	Na^+	K^+		
								Li^+/Na^+	Li^+/K^+
1a	<0.01	<0.01	<0.01	**1b**	0.79	1.18	0.78	0.7	1.0
2a	<0.01	<0.01	<0.01	**2b**	0.81	0.14	0.02	5.8	40.5
								Na^+/Li^+	Na^+/K^+
3a	<0.01	<0.01	<0.01	**3b**	0.33	0.47	0.52	1.4	0.9
4a	<0.01	<0.01	<0.01	**4b**	0.35	1.44	0.51	4.1	2.8
								K^+/Li^+	K^+/Na^+
5a	<0.01	<0.01	<0.01	**5b**	0.04	0.17	1.15	18.8	6.8
6a	<0.01	<0.01	<0.01	**6b**	0.31	0.19	1.21	3.9	6.4

[a] Transport conditions: [source phase], mixture solution of 0.1 M of LiOH, NaOH, and KOH (3 mL); [membrane], 5 mM of the crown ethers in $CHCl_3$ (6 mL); [receiving phase], 1 M of HCl (3 mL). Reproducibility is ±10% or better. [b] $\times 10^6$ mol/h.

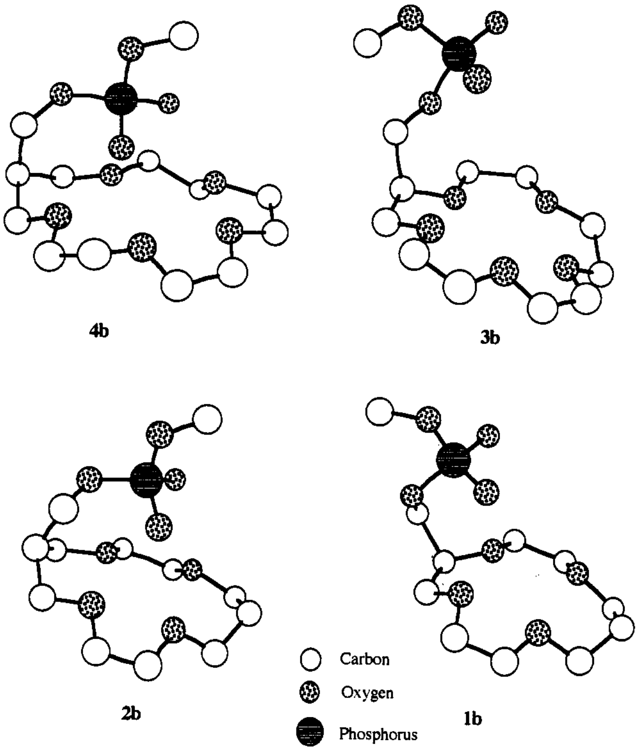
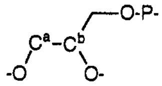
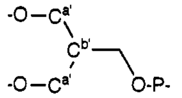


Figure 1. Postulated conformation of **1b–4b**. In **2b** and **4b**, the phosphate oxygens can bear the crown ring to give three-dimensional cavities, although the phosphate oxygens of **1b** and **3b** can not favorably bear the crown ring.

Table 2. Alkali Metal Cation-Induced Changes in ^{13}C-NMR Chemical Shifts of 1b–6b[a,b]

compd	 C^a	C^b	 $C^{a'}$	$C^{b'}$	other ring carbons
1b + LiOH	−0.2	+0.3			−0.2
1b + NaOH	−0.2	+0.1			−0.2
2b + LiOH			+2.3	−0.2	+2.0[c] −0.3
2b + NaOH			<±0.1	−0.1	−0.1
3b + NaOH	−0.2	−0.3			−0.2 to −0.3
3b + KOH	−0.2	−0.3			−0.2 to −0.3
4b + NaOH			+1.7	−0.1	−0.1 to −0.3
4b + KOH			+0.3	<±0.1	−0.1 to −0.3
5b + NaOH	<±0.1	<±0.1			<±0.1
5b + KOH	−0.1	<±0.1			+0.3 to −0.5
6b + NaOH			<±0.1	<±0.1	<±0.1
6b + KOH			+0.5	<±0.1	+0.5 to −0.1

[a] Conditions: [crown] = 0.05 mmol, [alkali metal hydroxide] = 0.05 mmol in $CD_3CN–D_2O$ (1:1) 0.65 mL. [b] Positive is downfield shift. [c] The methylene carbons which attached to oxygen in the other trimethylene unit.

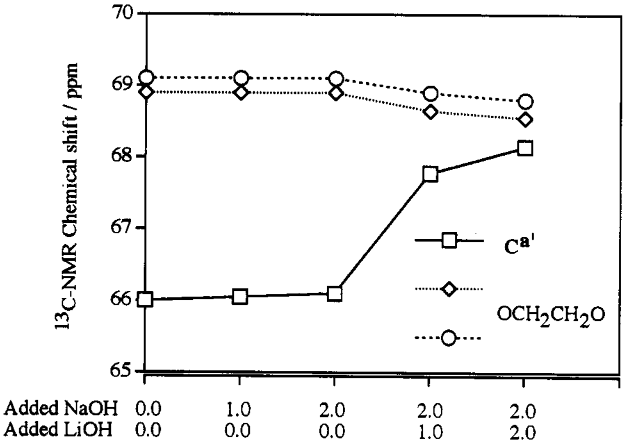


Figure 2. Titration profile of **2b** on addition of NaOH and LiOH.

metal hydroxides to crown ethers. Remarkable shift changes appeared when 1.0 equiv of size-matched salts were added in all cases.) These results are summarized in Table 2. Significant chemical shift changes to downfield of the methylene carbons ($C^{a'}$) in the trimethylene unit of **2b** and **4b** were observed in the cases for the addition of size-matched alkali metal hydroxides (**2b** + LiOH: +2.3 ppm, **4b** + NaOH: +1.7 ppm), although small shift changes were observed when larger metal cations were added. The downfield shifts of the $C^{a'}$ carbons suggested that the oxygen atoms in the crown ring provide the major coordination for cations. On the other hand, signals of the bridgehead methine (C^b) and the adjacent methylene (C^a) carbons in the dimethylene unit of **1b** and **3b** shifted only +0.3 to −0.3 ppm in all cases. There was a slight spectral change in the **6b**–KOH system. Next, we examined the ^{13}C-NMR titration of **2b** in a guest–mixture system. Figure 2 illustrates the ^{13}C-NMR titration profile of **2b** on addition of NaOH and LiOH (**2b**–Na^+–Li^+ system). Although no spectral change was observed with the addition of 1 and 2 equiv of NaOH, significant chemical shift changes to downfield of $C^{a'}$ carbons and upfield of the dimethylene carbons (OCH_2CH_2O) were observed by addition of 1 equiv of the LiOH in the presence of 2 equiv of NaOH. These titration experiments suggested that the three-dimensional cavities may be formed to facilitate addition of size-matched cations in **2b** and **4b** which has the trimethylene unit, and the results support the CPK and computer-modeling examination.

In conclusion, the present study demonstrated that the structure neighborhood around the bridgehead carbon bearing the pendant arm influences the alkali metal cation selectivity in the alkylphosphoric acid armed crown-4 and crown-5 ethers.

Experimental Section

General Procedure for the Reaction of Hydroxymethyl Crown Ethers with Dodecylphosphoric Acid. A mixture of hydroxymethyl crown ether (4.3 mmol) and dodecyl phosphate (8.6 mmol) in the presence of dicyclohexylcarbodiimide (21.1 mmol) in dry pyridine (40 cm^3) was stirred for 24 h at room temperature. After the pyridine was removed under reduced pressure, water (40 cm^3) was added to the residue and then extracted with $CHCl_3$ (30 cm^3 × 3). The combined organic extracts were washed with water, dried (Na_2SO_4), and then evaporated under reduced pressure. Separation and isolation of the residual oil (ca. 2 g) were performed by silica gel TLC ($CHCl_3$:EtOAc:MeOH = 2:2:1 as eluent) followed by gel-permeation column chromatography (Sephadex LH-20, EtOH as eluent). Pure **1b**–**6b** were obtained as pale yellow hygroscopic oils.

2-[[[(Dodecyloxy)hydroxyphosphoryl]oxy]methyl]-13-crown-4 (1b): oil; yield 20%; ^{1}H NMR ($CDCl_3$) δ 4.35–3.05 (m, 19H), 2.10–1.04 (m, 22H), 0.89 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (CD_3CN/D_2O = 1/1) δ 13.1, 22.0, 24.9, 28.7, 28.8, 29.0, 29.7, 31.2, 65.3, 66.6, 68.3, 68.5, 68.9, 69.3, 69.6, 77.0; IR (KBr) 2250, 1240, 1050, and 860 cm^{-1}; mass (20 eV) *m/z* (rel inten) 468 (M$^+$, 25%). Anal. Calcd for $C_{22}H_{45}O_8P{\cdot}2.5H_2O$: C, 51.45; H, 9.81. Found: C, 51.67; H, 9.99.

3-[[[(Dodecyloxy)hydroxyphosphoryl]oxy]methyl]-14-crown-4 (2b): oil; yield 25%; ^{1}H NMR ($CDCl_3$) δ 4.40–3.27 (m, 20H), 2.61–1.04 (m, 23H), 0.87 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (CD_3CN/D_2O = 1/1) δ 13.0, 21.9, 25.0, 28.6, 28.7, 28.9, 29.7, 29.9, 31.1, 39.9, 63.4, 65.2, 66.0, 67.4, 68.9, 69.1; IR (KBr) 2250, 1240, 1055, and 850 cm^{-1}; mass (20 eV) *m/z* (rel inten) 482 (M$^+$, 24%). Anal. Calcd for $C_{23}H_{47}O_8P{\cdot}1.0H_2O$: C, 55.18; H, 9.87. Found: C, 55.19; H, 9.90.

2-[[[(Dodecyloxy)hydroxyphosphoryl]oxy]methyl]-15-crown-5 (3b): oil; yield 28%; ^{1}H NMR ($CDCl_3$) δ 4.44–3.30 (m, 23H), 2.00–1.08 (m, 20H), 0.87 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (CD_3CN/D_2O = 1/1) δ 13.0, 21.9, 25.0, 28.6, 28.7, 28.9, 29.8, 31.1, 63.4, 65.3, 68.2, 68.4, 68.5, 68.8, 69.3, 77.0; IR (KBr) 2250, 1255, 1050, and 840 cm^{-1}; mass (20 eV) *m/z* (rel inten) 498 (M$^+$, 54%). Anal. Calcd for $C_{23}H_{47}O_9P{\cdot}0.5H_2O$; C, 54.42; H, 9.53. Found: C, 54.15; H, 9.55.

3-[[[(Dodecyloxy)hydroxyphosphoryl]oxy]methyl]-16-crown-5 (4b): oil; yield 25%; ^{1}H NMR ($CDCl_3$) δ 4.30–3.40 (m, 24H), 2.55–1.06 (m, 21H), 0.89 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (CD_3CN/D_2O = 1/1) δ 13.1, 21.9, 24.9, 28.6, 29.0, 29.7, 31.4, 39.8, 64.5, 66.5, 68.8, 69.1, 69.2, 69.5; IR (KBr) 2250, 1255, 1045, and 840 cm^{-1}; mass (20 eV) *m/z* (rel inten) 512 (M$^+$, 50%). Anal. Calcd for $C_{24}H_{49}O_9P{\cdot}0.5H_2O$: C, 55.26; H, 9.66. Found: C, 55.15; H, 9.87.

2-[[[(Dodecyloxy)hydroxyphosphoryl]oxy]methyl]-18-crown-6 (5b): oil; yield 13%; ^{1}H NMR ($CDCl_3$) δ 4.40–3.33 (m, 27H), 2.15–1.10 (m, 20H), 0.89 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (CD_3CN/D_2O = 1/1) δ 13.0, 21.9, 25.0, 28.5, 28.7, 28.8, 28.9, 29.7, 29.8, 29.9, 31.1, 62.9, 65.3, 67.7, 68.9, 68.9, 69.1, 69.3, 69.4, 69.8, 76.0; IR (KBr) 2250, 1245, 1045, and 840 cm^{-1}; mass (20 eV) *m/z* (rel inten) 542 (M$^+$, 40%). Anal. Calcd for $C_{25}H_{51}O_{10}P{\cdot}2.5H_2O$: C, 51.09; H, 9.60. Found: C, 51.13; H, 9.80.

3-[[[(Dodecyloxy)hydroxyphosphoryl]oxy]methyl]-19-crown-6 (6b): oil; yield 11%; ^{1}H NMR ($CDCl_3$) δ 4.40–3.40 (m, 28H), 2.60–1.10 (m, 21H), 0.89 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (CD_3CN/D_2O = 1/1) δ 13.0, 21.9, 25.0, 28.5, 28.7, 28.9, 29.7, 29.9, 31.1, 39.9, 63.1, 65.2, 68.7, 69.3, 69.4, 69.5, 69.6; IR (KBr) 2250, 1245, 1040, and 845 cm^{-1}; mass (20 eV) *m/z* (rel inten) 556 (M$^+$, 22%). Anal. Calcd for $C_{26}H_{53}O_{10}P{\cdot}2.5H_2O$: C, 51.90; H, 9.72. Found: C, 51.89; H, 9.62.

Transport Experiments. The transport experiments were carried out using a U-tube (surface area = 3.5 cm^2) at 25 ± 2 °C. Initial conditions of the competitive transport were as follows; [source phase] = aqueous solution (3 cm^3) containing 0.1 mol dm^{-3} of LiOH, NaOH, and KOH: [membrane phase] = 5 mmol dm^{-3} of crown ether in $CDCl_3$ (6 cm^3); [receiving phase] = 1 mol dm^{-3} of HCl (3 cm^3). The concentration of the receiving phase was determined by atomic absorption spectrometry. The transport rates were calculated from the amounts of alkali-metal cations in the receiving phase. The aqueous and organic phases were stirred at 135 and 540 rpm, respectively, by synchronous motors in order to avoid a stirring error.

Acknowledgment. The authors wish to thank Mr. Kiyoshi Uchida for preparation of the starting materials.