Intramolecular Complexation of 18-Crown-6 Containing a Primary Ammonium Group and Application to Proton-Driven Selective Transport of a Potassium Cation

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A new series of 18-crown-6 ether derivatives containing an amino group were prepared. The UV spectrum of the mixture of the derivative having a primary amino group and picric acid showed a characteristic peak assigned to intramolecular complexation. With these kind of ionophores, a new active transport system was devised to give the selective K^+/Na^+ transport.

A lot of efforts have been devoted to elucidate the complexation of crown compounds with a variety of cations or neutral molecules.[1] In ion transport system, macrocyclic polyethers are excellent candidates for the recognition or binding site of carriers toward specified cations because of their selective complexation properties. However, additional devices should be necessary in the active transport system.[2] Proton-gradient,[3] electron-gradient,[4] or light irradiation[5] has been used as the driving force in that system. For example, crown ether carboxylic acids are good synthetic ionophores with the proton-gradient.[2,3] In this system, intramolecular complexation plays an important role in the uptake of the specified cation. In this paper, we will report synthesis, intramolecular complexation, and application to the active transport system of a new series of 18-crown-6 ethers containing an amino group.[6]

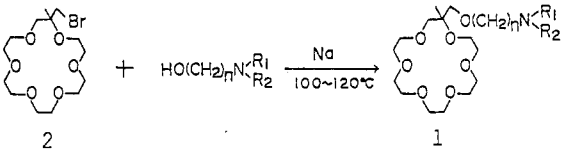
Results and Discussion

(Aminoalkoxy)methyl crown ethers **1** were prepared by the reaction of 2-(bromomethyl)-2-methyl-18-crown-6 (**2**)[7] with sodium alkoxides of appropriate amino alcohols for 4 h at 100–120 °C (Scheme I). Under these reaction conditions, O-alkylation was preferred to N-alkylation.[8]

The interaction between the 18-crown-6 ring and the amino group as the side chain of compounds **1** under acidic conditions was examined by using UV spectrometry. The UV spectra of synthetic multidentates **1b–d** in THF at room temperature in the presence of picric acid are shown in Figure 1. The mixed system of hexylamine and picric acid was used as the reference. It is noteworthy that the absorption at 380 nm was specific in the system of ligand **1b** having a primary amino group and picric acid (run 2) compared with other systems. The peak at about 380 nm had been assigned to the absorption of the picrate ion, which forms the solvent separated ion pair.[9] In this case, this peak demonstrates the effective complexation of the primary ammonium ion and the 18-crown-6 ring. On the other hand, ligand **1c**, having a secondary amino group, and ligand **1d** having a tertiary amino group, did not show the peak at about 380 nm (runs 3 and 4). Thus, the complexation of these ligands seems to be much weaker than that of **1b**. The complexation data of 18-crown-6 with ammonium ions reported in the literature[10,11] also support this consideration.

Figure 2 shows the complexation of 18-crown-6 and hexylammonium picrate. As the ratio of 18-crown-6 to the ammonium ion increases, the absorption maximum is gradually shifted from 350 to 378 nm. The predominant occurrence of the peak at about 380 nm needs over five times concentration of 18-crown-6. So the efficiency of 18-crown-6 forming a loose ion pair in this system is less than that of ligand **1b** having a primary amino group. This

Scheme I



2 1

1a: n=5 $R_1 = R_2 = H$
1b: n=2 $R_1 = R_2 = H$
1c: n=2 $R_1 = H$ $R_2 = C_2H_5$
1d: n=2 $R_1 = R_2 = C_2H_5$

Table I. Stability Constants and Transport Ability in Transport System A[a] of Compounds 1a–d for K^+ and Na^+

compd	log K^b		transported cations,[c] %	
	Na^+	K^+	Na^+	K^+
1a	3.59	5.43	6	60
1b	3.77	5.60	5	58
1c	4.10	5.82	5	60
1d	4.03	5.77	6	61

[a] Aqueous phase 1 (10 mL): KSCN (0.1 M); NaSCN (0.1 M); Me_4NOH (0.1 M)/organic membrane (CH_2Cl_2 20 mL: ionophore 5.0×10^{-5} mol/aqueous phase 2 (10 mL): Me_4NOH (0.1 M). [b] In MeOH, 25 °C. [c] After 48 h.

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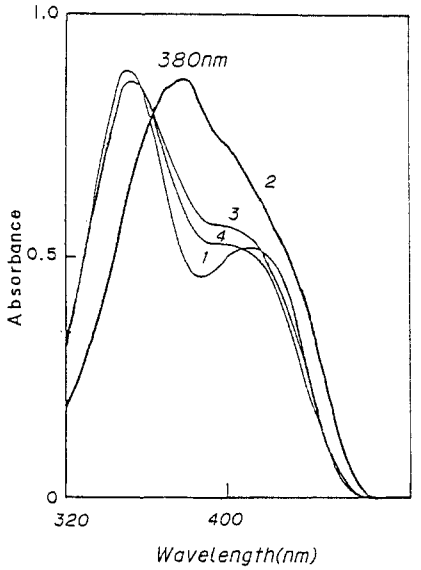

Figure 1. Absorbance of picric acid and amine in THF (1) picric acid and hexylamine; (2) picric acid and compound **1b**; (3) picric acid and compound **1c**; (4) picric acid and compound **1d**. [picric acid] = [amine] = 6.0×10^{-5} M.

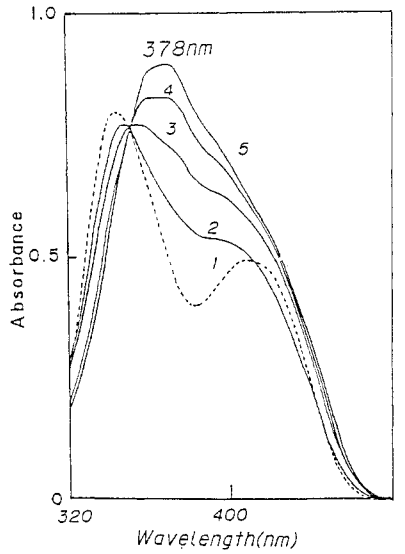

Figure 2. Absorbance of picric acid, hexylamine, and 18-crown-6 in THF. (1) [Picric acid]/[hexylamine]/[18-crown-6] = 1:1:0; [picric acid]/[hexylamine]/[18-crown-6] = 1:1:1; (3) [picric acid]/[hexylamine]-[18-crown-6] = 1:1:3; (4) [picric acid]/[hexylamine]/[18-crown-6 = 1:1:5; (5) [picric acid]/[hexylamine]/[18-crown-6] = 1:1:10; [picric acid] = 5.6×10^{-5} M.

result seems to originate in the difference of the type of complexation, that is, intermolecular or intramolecular complexation.

Transport experiments were performed at 25 °C in a U-type cell using dichloromethane as the liquid membrane. In order to clarify the active transport ability of synthetic ionophores in detail, two kinds of transport systems, differing in the release conditions, were examined. In transport system A, the aqueous phase 2 involves only tetramethylammonium hydroxide. On the other hand, in transport system B, the initial concentrations of Na^+ and K^+ were arranged to be equal in both phases. In addition, phase 1 is basic and phase 2 is acidic, and so transport system B is an active transport system.

The stability constants (log K_s) of compounds 1 toward K^+ in methanol at 25 °C are summarized in Table I along with the transport data in transport system A. All these compounds showed the stability constants for K^+ in the

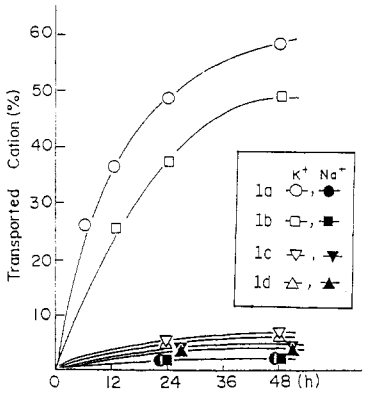

Figure 3. Competitive transport of K^+ and Na^+ in transport system B. Aqueous phase 1 (10 mL): KSCN 0.1 M; NaSCN 0.1 M; Me_4NOH 0.1 M. Organic membrane (CH_2Cl_2 20 mL): ionophore, 5.0×10^{-5} mol. Aqueous phase 2 (10 mL): KSCN 0.1 M; NaSCN 0.1 M; HCl 0.1 M.

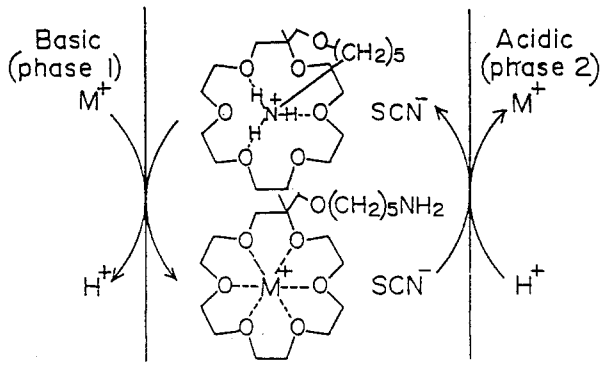

Figure 4. Postulated mechanism of active transport using ionophore **1a**.

range of about 5.4–5.8 and for Na^+ in the range of about 3.6–4.1. They have similar complexation properties for both K^+ and Na^+. The trend observed for the transport of these cations in transport system A is also well coincident with the trend for the complexation. 18-Crown-6 ether derivatives are well-known to selectively complex with K^+.[1] So it is reasonable that these compounds have the higher complexing ability and show the selective transport ability toward K^+. In other words, the difference of transport ability in transport system A was not remarkably observed among ionophores by differing the types of the amino groups, that is, primary, secondary, or tertiary amino group.

The active and competitive transport ability for K^+ and Na^+ using ionophores from **1a** to **1d** are shown in Figure 3. Although the transport ability of these ionophores in transport system A were hardly different, ionophores **1a** and **1b**, which both have a primary amino group, displayed an effective transport of K^+. Na^+ were transported much less than K^+, so the high selectivity for K^+ was attained. On the other hand, ionophore **1c**, having a secondary amino group, and ionophore **1d**, having a tertiary amino group, scarcely carried both cations.

Judging from the UV data and the transport data, the marked difference in the active transport ability among ionophores examined in this study seems to be reasonably explained by considering intramolecular complexation between the 18-crown-6 ring and the primary ammonium ion.

On the basis of findings obtained in this study, the mechanism of transport is illustrated in Figure 4. Ionophore **1a** or **1b** selectively complexes with K^+ in preference to Na^+ in the basic region (phase 1) and transfers it with

the counteranion (thiocyanate) to the acidic region (phase 2) across the liquid membrane. In phase 2, the amino group is protonated, and the primary ammonium ion formed in situ competes with K^+ for complexation. The intramolecular complex with the primary ammonium thiocyanate is lipophilic enough to be soluble in the liquid membrane and is transferred to phase 1. The deprotonation of the ammonium ion in basic phase completes the active transport cycle. Consequently, K^+ is concentrated against its concentration gradient by a coupled counter flow of proton.

This transport system needs the presence of lipophilic anions. On the other hand, in the case of carboxylic ionophores,[2,3] lipophilic anions remarkably lower the transport efficiency because the leak reaction becomes larger.[12]

Experimental Section

^{1}H NMR spectra were recorded at 100 MHz on a JEOL JNM-PS 100 spectrometer. Infrared spectra and UV spectra were obtained with a Hitachi 260-10 spectrometer and a Shimadzu UV-200 spectrometer respectively. Mass spectra were measured with a Hitachi RMU-6E mass spectrometer at an ionization potential of 70 eV. 2-(Bromomethyl)-2-methyl-18-crown-6 (**2**) was prepared according to the literature.[7] Stability constants were measured with a Beckmann 4500 digital pH meter and calculated by the reported method.[13]

2-[((5-Aminopentyl)oxy)methyl]-2-methyl-18-crown-6 (1a). Sodium metal (0.12 g, 5.2×10^{-3} mol) was dissolved in 5-amino-1-pentanol (1.4 g, 1.2×10^{-2} mol). To this solution was gradually added **2** (1.0 g, 2.7×10^{-3} mol) and the resulting mixture was stirred for 4 h at 120 °C. After cooling to room temperature water (15 mL) was added to the residue and extracted with three 20-mL portions of dichloromethane. The combined organic layers were concentrated. The crude product was purified by distillation in vacuo (Kugelrohr) [180 °C (0.05 torr)] to give a yellow oil (0.80 g, 75%): ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 1.26–1.76 (m, 8 H), 2.66 (t, 2 H), 3.34–3.80 (m, 26 H); mass spectrum, m/e (relative intensity) 393 (M^+), 277 (11), 102 (24), 101 (100), 86 (37), 57 (30), 45 (41), 44 (24); IR (neat) 3350 (s), 2870 (s), 1640 (m), 1460 (m), 1100 (s), 950 (m) cm^{-1}. Anal. Calcd. for $C_{19}H_{39}NO_7$: C, 57.99; H, 9.99; N, 3.56. Found: C, 58.05; H, 10.13; N, 3.63.

2-[((2-Aminoethyl)oxy)methyl]-2-methyl-18-crown-6 (1b): bp 140 °C (0.01 torr; Kugelrohr distillation); yellow liquid; 58% yield; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 1.71 (br s, 2 H), 2.82 (t, 2 H), 3.40–3.80 (m, 26 H); mass spectrum, m/e (relative intensity) 351 (M^+), 277 (12), 101 (100), 100 (32), 57 (32), 45 (78), 44 (48); IR (neat) 3350 (s), 2870 (s), 1640 (m), 1100 (s), 950 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{33}NO_7$: C, 54.68; H, 9.46; N, 3.99. Found: C, 54.50; H, 9.68; N, 4.01.

2-[((*N*-Ethyl-2-aminoethyl)oxy)methyl]-2-methyl-18-crown-6 (1c): bp 160 °C (0.01 torr; Kugelrohr distillation); yellow liquid; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3 H), 1.18 (s, 3 H), 1.80 (br s, 1 H), 2.52–2.88 (m, 4 H), 3.36–3.84 (m, 26 H); mass spectrum, m/e (relative intensity) 379 (M^+), 241 (25), 101 (34), 74 (27), 73 (31), 72 (40), 58 (100), 45 (39); IR (neat) 3350 (s), 2860 (s), 1350 (m), 1290 (m), 1250 (m), 1120 (s), 950 (m) cm^{-1}. Anal. Calcd for $C_{18}H_{37}NO_7$: C, 56.97; H, 9.83; N, 3.69. Found: C, 56.63; H, 9.90; N, 3.72.

2-[((*N*,*N*-Diethyl-2-aminoethyl)oxy)methyl]-2-methyl-18-crown-6 (1d): bp 165 °C (0.01 torr; Kugelrohr distillation); 65% yield; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 6H), 1.18 (s, 3 H), 2.42–2.84 (m, 6 H), 3.28–3.88 (m, 26 H); mass spectrum, m/e (relative intensity) 407 (M^+), 172 (9), 101 (42), 100 (42), 87 (38), 86 (100),73 (25), 45 (33); IR (neat) 2860 (s), 1460 (m), 1350 (m), 1290 (m), 1250 (m), 1120 (s), 950 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{41}NO_7$: C, 58.94; H, 10.14; N, 3.44. Found: C, 58.73; H, 10.35; N, 3.26.

Registry No. **1a**, 88194-18-7; **1b**, 88194-19-8; **1c**, 103959-10-0; **1d**, 88194-21-2; **2**, 78827-96-0; K, 7440-09-7; Na, 7440-23-5; HO-$(CH_2)_5NH_2$, 2508-29-4; $HO(CH_2)_2NH_2$, 141-43-5; $HO(CH_2)_2MHEt$, 110-73-6; $HO(CH_2)_2NEt_2$, 100-37-8.

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