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Enhanced Li+ Ion-Selective Ionophoric Properties of Double Armed Diaza-12-Crown-4 Derivatives

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Abstract: A variety of double armed crown ethers were prepared in which amine, amide, ester, nitrile and pyridine moieties were attached as cation-ligating sidearms to diaza-12-crown-4 ring. FAB-MS and ^{7}Li/^{13}C/^{23}Na NMR binding and liquid membrane transport studies revealed that most of them exhibited Li^+ cation selectivity, though corresponding single armed lariat ethers showed Na^+ cation selectivity. Among them, amine-armed diaza-12-crown-4 derivative offered the highest Li^+ ion-selective ionophoric property. Its transport efficiency and selectivity were particularly superior to those of commercially available Li^+ ion-selective ionophores. © 1997 Elsevier Science Ltd. All rights reserved.

Armed crown ethers are characterized by a parent crown ring and a cation-ligating sidearm, and offer interesting cation binding properties *via* crown ring - sidearm cooperativity.[1,2] Because of the ease of synthesis and versatility of molecular structure, they have potential as cation selective ionophores in extraction, chromatography, phase transfer reaction, membrane transport and related processes. Various combinations of crown rings and sidearms have been attempted to attain specific cation recognition. Li^+ ion-selective ionophores are particularly recognized as important tools for analysis and separation in biological and environmental systems.[3] We recently developed highly Li^+ ion-selective "single armed" lariat ethers in which an amine-functionalized sidearm provided further coordination with Li^+ cation trapped in an aza-12-crown-4 ring.[4] Although most of the reported 12-crown-4 derivatives preferred Na^+ cation to Li^+ cation, a combination of amine-functionalized sidearm and aza-12-crown-4 uniquely offered Li^+ ion-selective ionophores.

Here, we attach two amine-functionalized sidearms to a diaza-12-crown-4 ring to prepare a new series of Li^+ ion-selective "double armed" crown ethers. Since double armed crown ether may have great advantage over single armed lariat ether as a specific ionophore, our approach is expected to improve both selectivity and efficiency in the Li^+ ion binding and transport processes. We systematically introduce various sidearms into the diaza-12-crown-4 system and examine their effects on cation binding and transport properties. FAB-MS, ^{7}Li / ^{13}C / ^{23}Na NMR binding and liquid membrane transport studies reveal that the present type of double armed crown ether exhibited Li^+ ion-selective ionophoric functions superior to corresponding lariat ethers and commercially available ionophores.

RESULTS AND DISCUSSION

Double Armed Diaza-12-Crown-4

We chose a diaza-12-crown-4 as a parent macroring, because Li^+ cation is formally size-fitted to the hole of a 12-membered crown ring.[5] To optimize the sidearm structure, we attached sidearms with amine-, amide-, ester-, nitrile- or pyridine-moieties to the diaza-12-crown-4 ring (Fig. 1). They were directly prepared from unsubstituted diaza-12-crown-4 **1** and appropriate halides, while crown ether **2** was obtained by BH_3-reduction of the amide **3**. Although many kinds of 15- and 18-membered double armed crown ethers have been reported,[6] the number of 12-membered derivatives remains limited.[7] Double armed diaza-12-crown-4 derivatives have several advantages for cooperative binding of guest cations. Figure 2 shows coordination modes of cation complexes with the double armed crown ether and corresponding single armed lariat ether. We have reported that amine-armed lariat ether **8** exhibited excellent Li^+ cation binding and transport abilities *via* sidearm participation (see mode **A**).[4] When two sidearms are introduced to interact cooperatively with the guest cation, there are two feasible binding modes: One is the coordination with guest cation from the same side (mode **B**) and the other places donor atoms of the sidearm at upper and lower sides of the guest cation (mode **C**). In these cases, double armed crown ether is expected to exhibit different cation selectivity from that of single armed lariat ether (mode **A**). Mode **D** is also possible. Although only one of sidearms interacts with the guest cation, the double armed crown ether still has a statistical advantage over single armed lariat ether for encapsulation. The cation binding profiles of double armed crown ether and single armed lariat ether may be parallel,[8] because modes **A** and **D** have structural similarities.

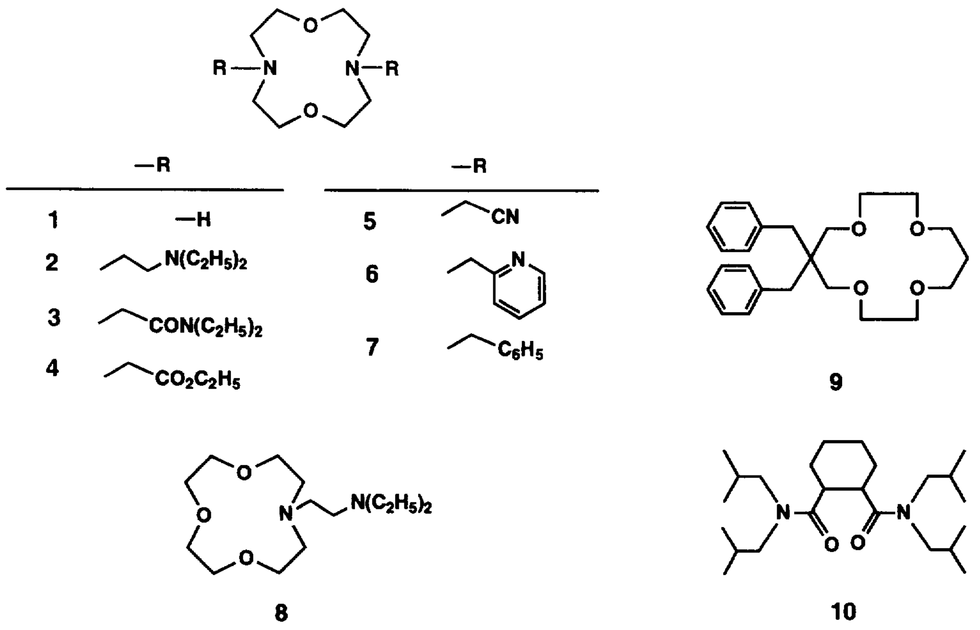
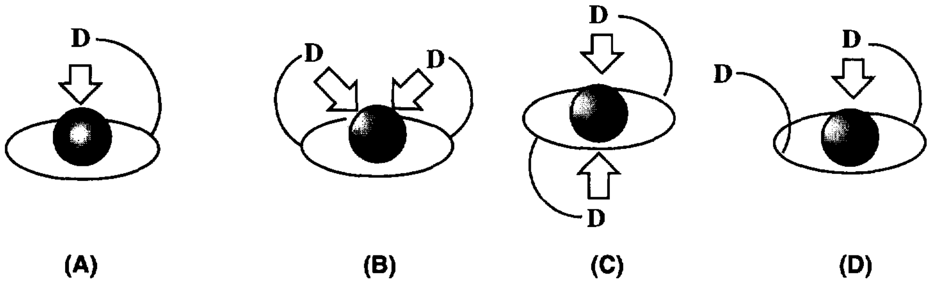


Fig. 1. Structures of double armed crown ethers and references



Lariat Ether Complex Derived from Aza-12-Crown-4

Double Armed Crown Ether Complex Derived from Diaza-12-Crown-4

Fig. 2. Coordination modes of armed crown ethers

We demonstrate below that several double armed crown ethers offer Li$^+$ cation selectivity in the binding process, though corresponding lariat ethers favored Na$^+$ cation.[4] Exceptionally, double armed crown ether **2** having amine-functionalized sidearms attains cation selectivity similar to lariat ether **8**, but its efficiency and selectivity in the Li$^+$ ion recognition process are superior to not only lariat ether **8** but also commercially available ionophores **9**[9] and **10**.[10] Therefore, our strategy using "double armed crown ether" provides a promising possibility in design of a specific ionophore.

FAB-MS Binding Experiments

The FAB-MS competition technique was used to assess the binding ability for Li$^+$, Na$^+$ and K$^+$ cations with diaza-crown ethers **1** - **7** and aza-crown ether **8** on a semi-quantitative level.[11] Table 1 summarizes relative peak intensities of [crown ether + 1]$^+$ and [crown ether + metal]$^+$ ions. The intensity reflects the relative cation binding affinities. When unsubstituted and dibenzylated crown ethers **1** and **7** were employed, the peaks of [crown ether + 1]$^+$ ions were predominantly observed. Since these peaks were probably derived from protonated forms, parent diaza-12-crown-4 ring was suggested to bind a proton more effectively than alkali metal cations under the FAB-MS conditions. In contrast, double armed crown ethers **2** - **6** mainly provided the peaks of [crown ether + metal]$^+$, the intensities of which were at least 9 times higher than [crown ether + 1]$^+$. Since single armed crown ether **8** gave both peaks with comparable intensity, introduction of two cation-ligating sidearms remarkably increased cation binding ability of the diaza-12-crown-4 ring. Among the employed double armed crown ethers, amine-armed crown ether **2** exhibited the highest Li$^+$ cation selectivity. The ratios of relative peak intensity were estimated as 33 for [crown ether + Li]$^+$ / [crown ether + Na]$^+$ and >100 for [crown ether + Li]$^+$ / [crown ether + K]$^+$. Although the lariat ether **8** having amine-functionalized sidearm has been confirmed as a Li$^+$ cation-specific ionophore,[4] its Li$^+$ ion selectivity was much lower than that of **2**: [crown ether + Li]$^+$ / [crown ether + Na]$^+$ = 5.4; [crown ether + Li]$^+$ / [crown ether + K]$^+$ is 4.3. Thus, the two arms in crown ether **2** clearly enhanced selectivity and efficiency for the Li$^+$ cation, compared with one arm in lariat ether **8**. Table 1 also indicates that double armed crown ethers **3** - **6** having amide, ester, nitrile and pyridine moieties on their sidearms showed the Li$^+$ cation selectivity. Since corresponding single armed

Table 1. Cation Binding Selectivities of Double Armed Crown Ethers Assessed by FAB-MS[a].

Crown Ether	Relative Peak Intensity			
	Crown+1	Crown+Li^+	Crown+Na^+	Crown+K^+
1	100	13	6	7
2	11	100	3	<1
3	1	100	7	0
4	1	100	55	0
5	5	100	14	23
6	0	100	13	0
7	100	0	0	0
8	100	81	15	19

[a]Conditions: LiCl, 0.0083 mol/L; NaI, 0.0083 mol/L; KI, 0.0083 mol/L; Crown ether, 0.0033 mol/L; in *m*-nitrobenzyl alcohol.

lariat ethers were reported to exhibit Na^+ cation selectivity,[4] the ionophoric properties of 12-membered crown ether are dependent on the number of attached sidearms. Double armed crown ethers **3** - **6** probably have different coordination modes from their lariat ether-type analogs (see Fig. 2). Some 12-crown-4 derivatives have been reported to form sandwich-type 2 : 1 complexes with Na^+ and K^+ cations,[6] but no corresponding peak was recorded in the FAB-MS spectra of the employed crown ethers. Takahashi and his colleagues analyzed the FAB-MS spectra of several lariat ether complexes and concluded, as we observed, that the presence of cation-ligating sidearms suppressed the sandwich-type complexation.[12] This also offered high Li^+ ion selectivity.

NMR Binding Studies

^7Li / ^{23}Na NMR spectroscopy provided useful information on structures of double armed crown ether complexes.[13] We compared ^7Li / ^{23}Na NMR chemical shift changes in the presence of diaza-crown ethers **1** - **7** with those in the presence of amine-armed lariat ether **8**. Because Li^+ and Na^+ cations are spherical and since their chemical shifts are largely dependent on their electron density, the change in chemical shift should be a good index for the ability of the employed crown ether. Figure 3 indicates ^7Li / ^{23}Na NMR chemical shift changes in the presence of double armed crown ethers. Double armed crown ethers **2**, **3**, **4**, and **6** including amine, amide, ester and pyridine moieties on their sidearms caused larger shifts for Li signals ($\Delta\delta$ = 2.5 - 3.4 ppm) than parent diaza-12-crown-4 **1** ($\Delta\delta$=2.2 ppm). Similar spectral changes were observed for Na signals, though their shifted values were much larger than those for Li signals: $\Delta\delta$ = 8.4 - 15.2 ppm for **2**, **3**, **4**, and **6**; $\Delta\delta$=7.4 ppm for **1**. Therefore, introduction of proper functionalized sidearms effectively enhanced the binding ability of the crown ether with Li^+ and Na^+ cations. Nitrile- and benzyl-armed crown ethers **5** and **7**, in contrast, offered smaller shifted values than parent crown ether **1**, and their sidearms were believed to act not as effective binding sites but as bulky substituents.

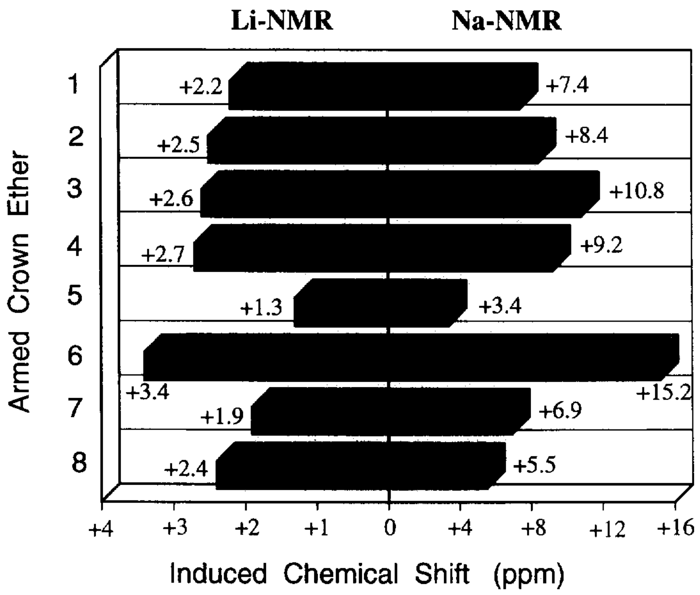


Fig. 3. Induced changes in ^{7}Li- and ^{23}Na-NMR chemical shifts by armed crown ethers

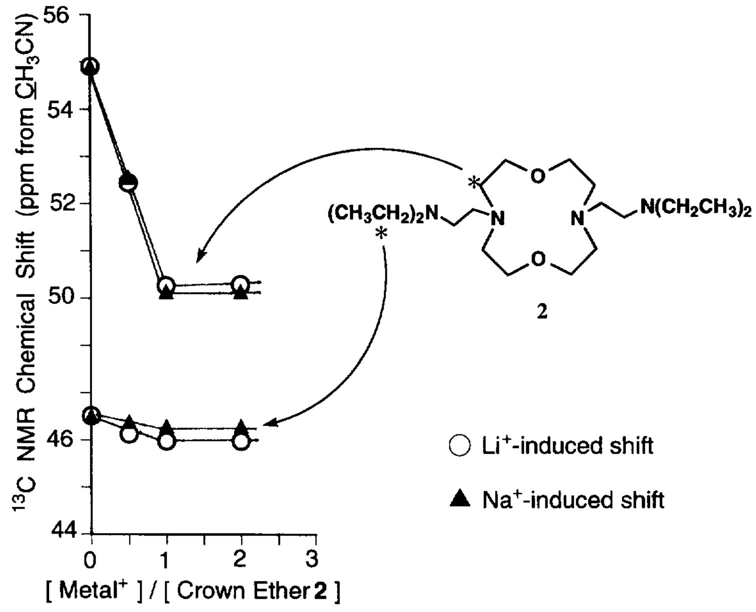


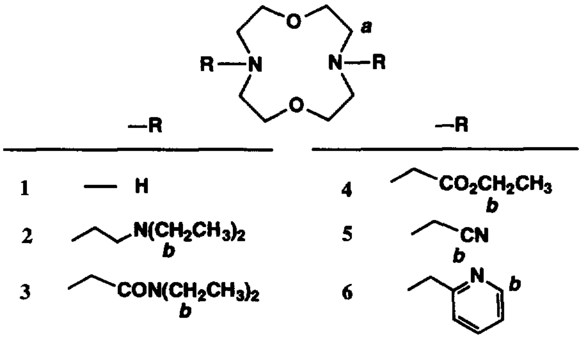
Fig. 4. ^{13}C NMR titration curves of double armed crown ether 2 with Li$^+$ and Na$^+$ cations

Figure 4 shows the Li+- and Na+-induced changes in the ^{13}C NMR chemical shifts for the selected carbons of crown ether **2**. When $LiClO_4$ salt was added to a CH_3CN / CD_3CN solution of the diaza-12-crown-4 **2**, significant and continuous changes in the chemical shifts were observed for both crown ring and sidearm carbon signals. The titration curves obtained have sharp bends in the presence of 1 equiv. of Li^+ cation. This result indicates that an 1:1 complex predominantly forms. $NaClO_4$ salt also induced spectral changes, suggesting 1:1 complexation. The shifted value of the crown ring carbon ($\Delta\delta$ = -4.1 ppm) is almost the same as that observed with Li^+ cation, but the signal for sidearm carbon shifted by only -0.2 ppm. Since larger shifted value ($\Delta\delta$ = -0.5 ppm) was observed in the presence of Li^+ cation, the amine-functionalized sidearm was suggested to interact more effectively with Li^+ cation than with Na^+ cation. Thus, amine-functionalized sidearm was demonstrated to cooperatively coordinate with Li^+ cation trapped within the diaza-12-crown-4 ring.

Table 2. Guest-Induced Changes in ^{13}C NMR Chemical Shifts of Armed Crown Ethers[a].

Crown Ether	Carbon	Induced Chemical Shift (ppm)	
		$+Li^+$	$+Na^+$
1	*a*	-1.4	-1.7
2	*a*	-4.6	-4.8
	b	-0.5	-0.2
3	*a*	-1.9	-2.9
	b	+0.6	+0.7
4	*a*	-1.6	-3.9
	b	+0.6	+1.0
5	*a*	0.0	-0.1
	b	-0.8	-0.8
6	*a*	-2.6	-3.4
	b	+0.4	+1.2
8[b]	*a*	-4.1	-4.2
	b	-2.1	-0.8

[a] Conditions: Crown ether, 0.025 mmol; $LiClO_4$ or $NaClO_4$, 0.025 mmol in CD_3CN/CH_3CN (2/3, v/v) 0.5 ml. [b] Cited from Ref. 4.



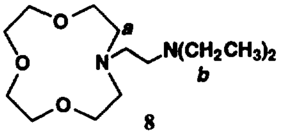


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Table 2 summarizes results of ^{13}C NMR binding experiments for double armed crown ethers **2** - **6**, with unsubstituted crown ether **1** and lariat ether **8**. Double armed crown ether **2** having two amine-functionalized sidearms showed similar spectral changes to those of single armed lariat ether **8**. Although its induced shift values of the sidearm carbon were smaller than those in double armed crown ether **2**, both crown ethers were thought to have similar coordination modes. Double armed crown ethers **3**, **4** and **6** having amide-, ester- and pyridine-functionalized sidearms, on the other hand, showed spectral changes greatly different from those with amine-armed crown ether **2**: smaller shifted values for crown carbons and opposite shift direction for sidearm carbons. Since the polar amine-functionalized sidearm favors Li^+ cation with high charge density[14] and has three substituents around cation-coordinating nitrogen atom, amine-armed crown ether **2** was suggested to have a different binding mode from other double armed crown ethers **3**, **4** and **6**.

Li^+ Ion Selective Liquid Membrane Transport

The amine-armed crown ether **2** mediated a Li^+ ion-selective and efficient transport across a CH_2Cl_2 liquid membrane. Table 3 summarizes initial transport rates obtained under competitive transport conditions, in which an aqueous source phase included equimolar Li^+, Na^+ and K^+ cations.

Among the examined double armed crown ethers, only amine-armed diaza-12-crown-4 **2** mediated highly selective and efficient transport of Li^+ cation. This crown ether exhibited 12 and 240 times higher transport rates of Li^+ cation than Na^+ and K^+ cations, respectively. Furthermore, its transport rate was 8.5 times as large as that of lariat ether **8**. Benzyl-armed diaza-12-crown-4 **7** also exhibited Li^+ cation selectivity, but its efficiency was much lower than those with amine-armed crown ethers **2** and **8**. Since FAB-MS experiments demonstrated that crown ether **7** could not act as an effective binder of Li^+ cation, cooperative actions of

Table 3. Competitive Cation Transport Properties of Double Armed Crown Ethers and Related Carriers[a].

Crown Ether	Transport Rate × 10^6 (mol/h)		
	Li^+	Na^+	K^+
2	9.58	0.77	0.04
3	0.92	1.02	0.03
4	4.00	6.80	0.92
5	0.07	0.02	<0.01
6	2.90	2.00	0.03
7	0.13	<0.01	<0.01
8	1.12	0.24	0.04
9	0.21	0.06	<0.01
10	0.14	0.02	<0.01

[a] Conditions: $LiClO_4$, 0.50 mmol; $NaClO_4$, 0.50 mmol; $KClO_4$, 0.50 mmol in H_2O (5 ml) / Carrier, 0.0372 mmol in CH_2Cl_2 (12 ml) / H_2O, 5 ml.

functionalized sidearms and parent diaza-12-crown-4 ring effectively promoted selective transport of Li^+ cation. Crown- and podand-types of ionophores **9** and **10** were examined for comparison, which had been developed as Li^+ cation-selective ionophores in the ion-selective electrode systems and were employed for practical use.[9,10] They mediated Li^+ ion selective transport, but their transport rates were much lower than amine-armed crown ether **2**. It was noted that ion-selective electrode system required binding selectivity rather than efficiency. In contrast, amide-, ester- and pyridine-armed crown ethers **3**, **4**, and **6** transported both Li^+ and Na^+ cations at comparable rates, though they exhibited the Li^+ ion selectivity in FAB-MS binding experiments. Although many factors are probably involved in determining the overall transport rate,[15]their binding abilities were thought to be not sufficient to extract highly hydrophilic Li^+ cation into the membrane phase.[16]

In conclusion, crown ether **2** having two amine-functionalized sidearms exhibited Li^+ ion-selective and efficient ionophoric properties, though other double armed crown ethers showed less effective ionophoric properties. The combination of two amine-functionalized sidearms and diaza-12-crown-4 ring particularly offered Li^+ ion-selective binding and transport functions. Further extensions of double armed crown ether strategy offer a new type of specific ionophores.

EXPERIMENTALS

Crown ethers **1** and **9** were purchased from Sorl Laboratory (Mie, Japan) and Dojindo Laboratories (Kumamoto, Japan), respectively. Compound **10** was also commercially available from Fluka Fine Chemical Ltd., while lariat ether **8** was synthesized by methods described earlier.[4]

Double armed crown ethers **2** - **7** were synthesized from unsubstituted diaza-crown ether **1** in a similar fashion to that reported for corresponding lariat ethers.[4] They were chromatographed (alumina, about 200 mesh; CH_2Cl_2 / hexane) and had correct elemental compositions determined by microanalysis and high resolution mass spectroscopy. Their selected spectroscopic data are summarized below.

1,7-Bis-[(N,N-diethylamino)ethyl]-1,7-diaza-12-crown-4 **2** was obtained by BH_3-reduction of crown ether **3** (oil, 40%): δ_H ($CDCl_3$) 1.03 (12H, t, 4 × CH_3), 2.50+2.60+2.69 (24H, m, 12 × NCH_2) and 3.60 (8H, t, 4 × OCH_2); δ_C ($CDCl_3$) 11.89, 47.55, 51.01, 55.54 and 55.69; ν (neat) 1126 (Found M^+, 372.3438. $C_{20}H_{44}N_4O_2$ requires 372.3464).

1,7-Bis-[(N,N-diethylcarbamoyl)methyl]-1,7-diaza-12-crown-4 **3** was prepared from crown ether **1** and *N,N*-diethylchloroacetamide (oil, 70%): δ_H ($CDCl_3$) 1.11+1.15 (12H, t, 4 × CH_3), 2.91 (8H, t, 4 × $N\underline{C}H_2CH_2$), 3.36 (8H, q, 4 × $\underline{C}H_2CH_3$), 3.44 (4H, s, 2 × CH_2CO) and 3.57 (8H, t, 4 × OCH_2); δ_C ($CDCl_3$) 13.08, 14.30, 39.97, 41.26, 55.15, 57.72, 69.49 and 169.86; ν (neat) 1640 and 1110 (Found M^+, 400.3065. $C_{20}H_{40}N_4O_4$ requires 400.3049).

1,7-Bis-[(ethoxycarbonyl)methyl]-1,7-diaza-12-crown-4 **4** was prepared from crown ether **1** and ethyl chloroacetate and recrystallized from CH_2Cl_2 - hexane (80%): mp. 56-57°C; δ_H ($CDCl_3$) 1.26 (6H, t, 2 × CH_3), 2.92 (8H, t, 4 × $N\underline{C}H_2CH_2$), 3.48 (4H, s, 2 × CH_2CO), 3.58 (8H, t, 4 × $OC\underline{H}_2CH_2$) and 4.12 (4H, q, 2 × $\underline{C}H_2CH_3$); δ_C ($CDCl_3$) 14.37, 54.76, 56.74, 60.20, 69.61 and 171.81; ν ($CDCl_3$) 1740 and 1130 (Found: C, 55.10; H, 8.77; N, 7.89. $C_{16}H_{30}N_2O_6$ requires C, 55.47; H, 8.73; N, 8.09).

1,7-Bis-(cyanomethyl)-1,7-diaza-12-crown-4 **5** was prepared from crown ether **1** and chloroacetonitrile and recrystallized from CH_2Cl_2 - hexane (80%): mp. 139-140°C; δ_H ($CDCl_3$) 2.81 (8H, t, 4 × $N\underline{C}H_2CH_2$), 3.59 (8H, t, 4 × O<u>C</u>H_2CH_2) and 3.62 (4H, s, 2 × CH_2CN); δ_C ($CDCl_3$) 44.89, 54.33, 68.86 and 115.76; ν ($CDCl_3$) 2230 and 1105 (Found: C, 56.94; H, 8.13; N, 22.29. $C_{12}H_{20}N_4O_2$ requires C, 57.12; H, 7.99; N, 22.21).

1,7-Bis-(2'-pyridylmethyl)-1,7-diaza-12-crown-4 **6** was prepared from crown ether **1** and 2-chloromethylpyridine (wax, 60%): δ_H ($CDCl_3$) 2.83 (8H, t, 4 × N<u>C</u>H_2CH_2), 3.62 (8H, t, 4 × O<u>C</u>H_2CH_2), 3.85 (4H, s, 2 × CH_2Py), 7.16 (2H, m, Py-H), 7.69 (4H, m, Py-H) and 8.51 (2H, m, Py-H); δ_C ($CDCl_3$) 55.18, 62.35, 69.29, 122.10, 123.49, 136.55, 148.96 and 159.59; ν ($CDCl_3$) 1597, 1585, 1435 and 1105 (Found M^+, 356.2242. $C_{20}H_{28}N_4O_2$ requires 356.2212).

1,7-Dibenzyl-1,7-diaza-12-crown-4 **7** was prepared from crown ether **1** and benzylbromide and recrystallized from CH_2Cl_2 - hexane (60%): mp. 89°C; δ_H ($CDCl_3$) 2.75 (8H, t, 4 × N<u>C</u>H_2CH_2), 3.60 (8H, t, 4 × O<u>C</u>H_2CH_2), 3.66 (4H, s, 2 × CH_2Ph) and 7.32+7.36 (10H, m, Ph-H); δ_C ($CDCl_3$) 55.13, 61.20, 69.70, 126.92, 128.22, 129.02 and 139.80; ν ($CDCl_3$) 1600 and 1125 (Found: C, 74.33; H, 8.60; N, 7.79. $C_{22}H_{30}N_2O_2$ requires C, 74.54; H, 8.53; N, 7.90).

FAB-MS Experiments

Complexation of crown ether (0.0033 mol/L) with LiCl, NaI and KI (0.0083 mol/L) in *m*-nitrobenzyl alcohol was studied by measuring the relative peak heights of [crown ether + metal]$^+$ ions. FAB-MS spectra were recorded with a JEOL DX300 or AX500 instrument (a beam energy of Xe, 6keV) and the peak heights were averaged over at least 20 scans.

Transport Experiments

Transport experiments were performed at room temperature (ca. 18°C) in a U-tube glass cell (2.0 cm, i.d.).[15] The crown ether, dissolved in CH_2Cl_2, was placed in the base of the U-tube and two aqueous phases were placed in the tube arms, floating on the CH_2Cl_2 membrane phase. The membrane phase was constantly stirred with a magnetic stirrer. The transport rates indicated in Table 3 were calculated from the initial rates of appearance of guest metal cations in the receiving aqueous phase, which were determined by atomic absorption or flame spectroscopic method (carried out at Exlan Technical Center, Okayama, Japan). We confirmed that all guest salts were rarely transported in the absence of crown ether.

NMR Binding Experiments

^{13}C NMR studies were carried out with a JEOL 90A spectrometer, while ^7Li and ^{23}Na NMR spectra were recorded with a JEOL LA-300. Induced shift values indicated in Fig. 3 mean differences in the chemical shifts of ^7Li and ^{23}Na nuclei observed with and without crown ether. Each double armed crown ether was dissolved in CD_3CN / CH_3CN (2/3, v/v) at a concentration of 0.05 mol/L. Reproducibility : <0.1 ppm for ^7Li- and ^{13}C-NMR and <0.2 ppm for ^{23}Na-NMR.

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14. According to the donor number of the corresponding compound, the polarity of sidearm function was suggested to decrease as amine > pyridine > amide > ester > nitrile.
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16. Although an effective ionophore should form "highly lipophilic" complex with guest metal cation, extraction experiments revealed that these crown ethers extracted small amounts of alkali metal cations. Conditions: $LiClO_4$, $NaClO_4$, $KClO_4$ (0.015mmol, each) in H_2O 1.5 ml // crown ether (0.015 mmol) in CH_2Cl_2 1.5 ml. Thus, extraction process must determine overall profile of the present transport system.

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