J. Org. Chem. **1994**, *59*, 8047–8052

Li^+ Ion-Selective Binding and Transport Properties of 12-Membered Ring Lariat Ethers: Experimental and Computational Studies on Crown Ring–Sidearm Cooperativity

Hiroshi Tsukube,*,[†] Takayuki Inoue,[‡,§] and Kenzi Hori[∥]

Department of Chemistry, College of Liberal Arts & Science, Okayama University, Okayama 700, Japan, Computer Science Department, Asahi Chemical Industry Co. Ltd., Fuji, Shizuoka 416, Japan, Institute for Fundamental Chemistry, 34-4 Takano-Saikai Cho, Sakyo-ku, Kyoto 606, Japan, and Department of Chemistry, Faculty of Liberal Arts, Yamaguchi University, Yamaguchi 753, Japan

Received June 10, 1994[⊗]

A variety of lariat ethers were prepared in which amine, ether, ester, amide, nitrile, and pyridine moieties were attached as cation-ligating sidearms to azacrown rings. Among them, amine-armed aza-12-crown-4 compounds specifically accommodated a Li^+ cation in a three dimensional fashion and clearly distinguished it from other metal cations. FAB-MS and $^7Li/^{13}C$ NMR binding and liquid membrane transport studies confirmed that amine-armed aza-12-crown-4s formed stable and encapsulated Li^+ complexes suitable for specific recognition and transport, while other aza-12-crown-4 derivatives exhibited Na^+ ion selectivity. Using the density functional method, stabilization energies were estimated for some lariat ether–metal complexes. Since this nonempirical calculation offered results consistent with several experimental observations, combined studies of lariat ether chemistry and computer calculation may provide a new and interesting approach to the design of a specific cation receptor.

Introduction

Lariat ethers, double armed crown ethers and related armed macrocycles were designed to mimic biological ion-carriers, which are characterized by a parent macrocyclic ligand and a cation-ligating sidearm.[1] They often display encapsulated complexation, dynamic binding, high lipophilic character, and unique guest specificity *via* macroring–sidearm cooperativity. Lariat ethers having a single functionalized sidearm are the simplest representatives of this family, and have the advantage of easy synthesis and versatility of molecular structure. Many attempts have been reported to enhance the cation binding properties of lariat ethers by altering their sidearm structures, adjusting the size of the crown ring, and varying the arrangement of component donor atoms, but the molecular design of selective lariat ethers remains an essentially empirical exercise.[2]

Here, we report the highly Li^+ ion-selective binding and transport properties of amine-armed 12-membered ring lariat ethers in which the functionalized sidearm specifically coordinates the Li^+ ion trapped within the crown ring.[3] Among alkali and alkaline earth metal cations, the Li^+ cation is of particular interest for analysis and separation in medical and environmental systems.[4] Its diameter is formally that of a 12-membered ring, but 12-crown-4 derivatives generally prefer the Na^+ ion to the Li^+ ion. We systematically investigated cation binding properties of various lariat ethers and found that amine-armed aza-12-crown-4 derivatives offered specific Li^+ cation recognition. We first applied nonempirical calculations based on the density functional method[5] for characterization of lariat ether–cation complexes.[6] Since the results were, in principle, consistent with several experimental observations, the present study offers an interesting possibility in designing a new and specific receptor/carrier.

Results and Discussion

Lariat Ethers Employed. To investigate the sidearm effect on cation binding and transport properties, we prepared a series of aza-12-crown-4 and aza-15-crown-5 derivatives **2-9** and **11-13** having a variety of donor groups such as amine, ether, ester, amide, nitrile, and pyridine on their sidearms (Chart 1). These were directly prepared from unsubstituted azacrown ethers **1** and **10** and the appropriate chlorides, except for compound **2** which was obtained by a BH_3-reduction of amide **6**. Although numerous lariat ethers bearing oxygen donor-arms have been reported,[2] the number of lariat ethers having nitrogen donor-arms remains limited at present.[7] We demonstrate below that only amine-armed aza-12-crown-4 derivatives **2** and **3** showed high Li^+ ion selectivity. Their cation binding and transport abilities

---

[†] Okayama University.

[‡] Asahi Chemical Industry Co.

[§] Institute for Fundamental Chemistry.

[∥] Yamaguchi University.

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1994.

[1] Reviews: (a) Weber, E. In *Crown Ethers and Analogs*; John Wiley & Sons: Chichester, 1989; p 305. (b) Lindoy, L. F. In *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, 1989; p 103. (c) Tsukube, H. In *Liquid Membranes: Chemical Applications*; CRC Press: Boca Raton, 1990; p 51. (d) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J.; Izatt, R. M. *Chem. Rev.* **1989**, *89*, 929.

[2] (a) Gokel, G. W.; Trafton, J. E. In *Cation Binding by Macrocycles*; Mercel Dekker: New York, 1990; p 253. (b) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. In *Aza-Crown Macrocycles*; John Wiley & Sons: New York, 1993; p 173. (c) Tsukube, H. In *Crown Ethers and Analogous Compounds*; Elsevier: Amsterdam, 1992; p 100.

[3] Preliminary communication: Tsukube, H.; Hori, K.; Inoue, T. *Tetrahedron Lett.* **1993**, *34*, 6749.

[4] Kimura, K.; Shono, T. In *Cation Binding by Macrocycles*; Marcel Dekker: New York, 1990; p 429.

[5] We employed DGauss program which is available commercially from Cray Research Inc., Eagan, MN.

[6] Several empirical and semiempirical calculations have been applied to host–guest complex systems: (a) Drew, M. G. B.; Nicholson, D. G. *J. Chem. Soc., Dalton Trans.* **1986**, 1543. (b) Hase, W. L.; Richou, M. C.; Mondro, S. L. *J. Phys. Chem.* **1989**, *93*, 539. (c) Baderscher, M.; Musso, S.; Welti, M.; Pretsch, E.; Maruizumi, T.; Ha, T. *J. Comput. Chem.* **1990**, *11*, 820. (d) Dang, L. X.; Kollman, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 5716. (e) Ranghino, G.; Romano, S.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1985**, *107*, 7873. (f) Hori, K.; Haruna, Y.; Kamimura, A.; Tsukube, H.; Inoue, T. *Tetrahedron* **1993**, *49*, 3959.

0022-3263/94/1959-8047$04.50/0

Chart 1. Structures of Lariat Ethers and Related Materials

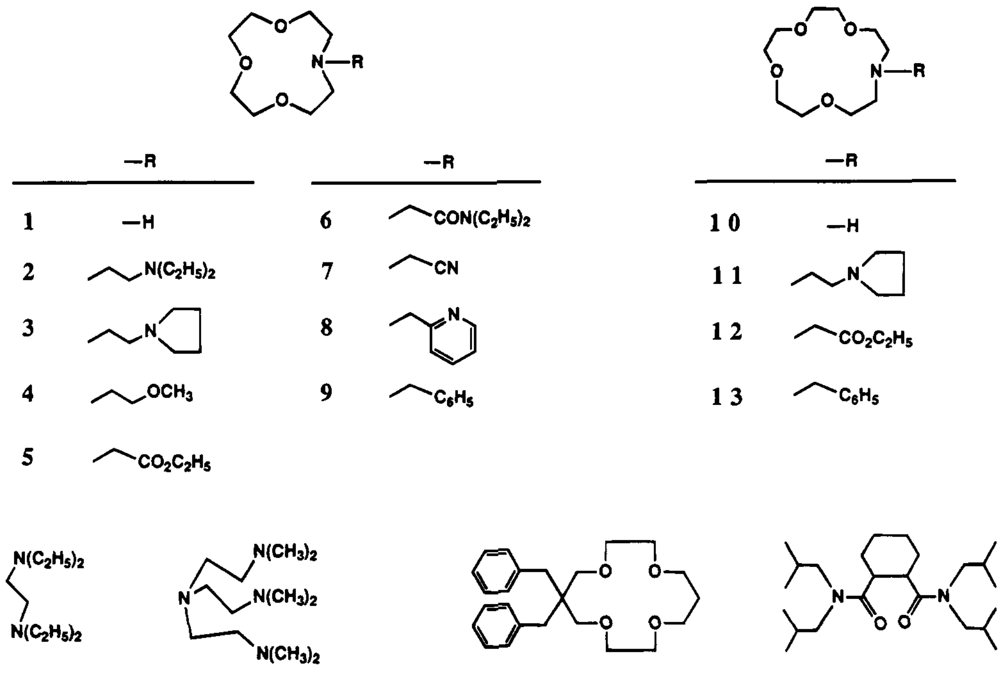


Table 1. Cation Binding Selectivities of Lariat Ethers Assessed by FAB-MS[a]

ether	relative peak intensity		
	ether + Li^+	ether + Na^+	ether + K^+
1	100	57	20
2	100	20	23
3	100	24	11
4	21	100	5
5	12	100	2
6	86	100	3
7	100	55	7
8	100	98	4
9	100	25	4
10	49	100	13
11	83	100	5
12	64	100	3
13	51	100	4
14	100	88	50

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

were superior to those of commercially available Li^+ ion-specific receptors **16** and **17**.[8]

FAB MS Binding Experiments. The cation binding behaviors of the employed lariat ethers were largely dependent on the natures of their attached sidearms. The FAB MS competition technique was used to assess the binding ability of Li^+, Na^+, and K^+ cations with lariat ethers **1-13** and diamine **14** on a semiquantitative level.[9] Table 1 summarizes relative peak intensities of [ether + metal]$^+$ ions which reflect the relative cation binding affinities. Typically, introduction of amine-functionalized sidearm enhanced binding selectivity for Li^+ cation (see lariat ethers **2** and **3**). In contrast, ether- and ester-armed aza-12-crown-4 derivatives **4** and **5** showed Na^+ ion selectivity, while amide- and pyridine-armed derivatives **6** and **8** did not discriminate between these cations. Some 12-crown-4 derivatives have been reported to form sandwich-type 2:1 complexes,[10] but no corresponding peak was recorded in FAB MS spectra under the conditions we employed. Takahashi and his colleagues analyzed several lariat ether–Na^+, –K^+, and –Ca^{2+} complexes by FAB MS method, and concluded, as we observed, that the presence of cation-ligating sidearms in lariat ethers suppressed sandwich-type 2:1 complexation.[11] Aza-15-crown-5 derivatives **10-13** were also examined. Since the peaks for the Na^+ complexes were larger than those for the Li^+ and K^+ complexes, all 15-membered crown ethers were confirmed to exhibit Na^+ ion selectivity. A combination of amine-functionalized sidearm and 12-membered crown ring is, therefore, an essential factor in attaining Li^+ ion-specificity.

NMR Binding Studies. ^7Li NMR spectroscopy provided direct information on sidearm participation in the Li^+ complex.[12] Table 2 summarizes the ^7Li NMR chemical shift changes in the presence of several lariat ethers. Because Li^+ cation is spherical and since the chemical shift is largely dependent on its electron density, the change in ^7Li NMR chemical shift relates well with the coordination ability of the employed lariat ether. Among

---

[7] (a) Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuya, H.; Okahara, M. *J. Am. Chem. Soc.* **1988**, *110*, 531. (b) Bradshaw, J. S.; Krakowiak, K. E.; An, H.; Izatt, R. M. *Tetrahedron* **1990**, *46*, 1163. (c) Tsukube, H.; Uenishi, J.; Higaki, H.; Kikkawa, K.; Tanaka, T.; Wakabayashi, S.; Oae, S. *J. Org. Chem.* **1993**, *58*, 4389. (d) Matsumoto, K.; Hashimoto, M.; Toda, M.; Tsukube, H.; Uchida, T. *Chem. Express* **1993**, *8*, 105.

[8] (a) Kimura, K.; Oishi, H.; Miura, T.; Shono, T. *Anal. Chem.* **1987**, *59*, 2331. (b) Erne, D.; Ammann, D.; Zhukov, A. F.; Behm, F.; Pretsch, E.; Simon, W. *Helv. Chim. Acta* **1982**, *65*, 538.

[9] (a) Bonas, G.; Bosso, C.; Vignon, M. R. *Rapid Commun. Mass Spectrom.* **1988**, *2*, 88. (b) Johnstone, R. A. W.; Rose, M. E. *J. Chem. Soc., Chem. Commun.* **1983**, 1268. (c) Stibor, I.; Holy, P.; Závada, J.; Koudelka, J.; Novák, J.; Zajicek, J.; Belohradsky, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1581. (d) Tsukube, H. In *Comprehensive Supramolecular Chemistry*; Pergamon Press, Oxford; Vol. 8, in press.

[10] (a) Calverley, M. J.; Dale, J. *Acta Chem. Scand.* **1982**, *B36*, 241. (b) White, B. D.; Arnold, K. A.; Garrell, R. L.; Fronczek, F. R.; Gandour, R. D.; Gokel, G. W. *J. Org. Chem.* **1987**, *52*, 1128.

[11] Takahashi, T.; Uchiyama, A.; Yamada, K.; Lynn, B. C.; Gokel, G. *Supramol. Chem.* **1993**, *2*, 177.

[12] Kimura, K.; Yamashita, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 613.

Table 2. Crown Ether-Induced Changes in ^7Li NMR Chemical Shifts[a]

ether	induced chemical shift (ppm): ^7Li
1	1.6
2	2.4
3	2.1
4	1.5
5	1.6
6	2.3
7	1.2
8	2.3

[a] Conditions: lariat ether, 0.025 mmol; $LiClO_4$, 0.025 mmol in CD_3CN-CH_3CN (2/3) 0.5 mL. Positive is downfield shift.

the examined aza-12-crown-4 derivatives, **2**, **3**, **6**, and **8** which included amine, amide, and pyridine moieties on their sidearms offered larger shift values for Li signal ($\Delta\delta = 2.1-2.4$ ppm) than unsubstituted aza-12-crown-4 **1** ($\Delta\delta = 1.6$ ppm). This clearly indicates that amine, amide, and pyridine donor groups on the sidearms provide effective coordination with the Li^+ cation trapped in aza-12-crown-4 ring. On the other hand, lariat ethers **4**, **5**, and **7** having ether, ester, and nitrile groups induced similar shift values ($\Delta\delta = 1.2-1.6$ ppm) as crown **1**, suggesting that their sidearms could not act as effective Li^+ binding sites. Thus, the nature of sidearm greatly influenced Li^+ binding behavior.

^{13}C NMR spectroscopy provided further structural information on the lariat ether–alkali metal complexes. Figure 1 shows the Li^+- and Na^+-induced changes in the chemical shifts for the selected carbons of the lariat ethers **2** and **4**. When $LiClO_4$ salt was added to an acetonitrile solution of amine-armed aza-12-crown-4 **2**, significant and continuous shifts were observed for both crown ring and sidearm carbons (Figure 1(A)). The titration curves obtained have sharp bends in the presence of 1 equiv of Li^+ cation, indicating that 1:1 complexation predominantly occurs in the acetonitrile. Since the shifts in the crown ring and sidearm carbons were large ($\Delta\delta = -4.1$ ppm and -2.1 ppm), amine-functionalized sidearm was demonstrated to effectively coordinate with the Li^+ cation bound with the aza-12-crown-4 ring. $NaClO_4$ salt induced somewhat different spectral changes in the lariat ether **2** system. Although the shifted value of the crown ring carbon ($\Delta\delta = -4.2$ ppm) is almost the same as that observed with Li^+ cation, the signal for sidearm carbon shifted by only -0.8 ppm. The amine-functionalized sidearm seemed to interact loosely with the Na^+ cation. In the ether-armed aza-12-crown-4 **4** system (Figure 1(B)), on the other hand, Li^+-induced chemical shift of the sidearm carbon was modest ($\Delta\delta = +0.5$ ppm) and similar to that Na^+-induced shift ($\Delta\delta = +0.6$ ppm). Since the signal of the crown ring carbon shifted greatly in the presence of Li^+ or Na^+ cation ($\Delta\delta = -3.9$ ppm or -4.6 ppm), ether-functionalized sidearm was confirmed to provide weak coordination with both Li^+ and Na^+ cations.

The nature of solvent employed dramatically influenced the lariat ether–cation complexation. As shown in Figure 1(C), no large change in the chemical shifts of the lariat ether **2** was observed for either sidearm carbon ($\Delta\delta < 0.1$ ppm) or crown ring carbon ($\Delta\delta < -1.2$ ppm) in CH_3OH/CD_3OD. This probably indicates that the lariat ether **2** does not completely encapsulate the Li^+ and Na^+ cations in such a polar medium.

Table 3 summarizes results of ^{13}C NMR binding experiments for 12- and 15-membered lariat ethers **2-8** and **11**, together with those for parent crown ethers **1** and **10**. All the crown ethers exhibited metal cation-induced spectral changes in CH_3CN/CD_3CN. When the lariat ether **3** having an amine-functionalized sidearm was employed, the Li^+ cation offered larger shift of the sidearm carbon by 0.8 ppm than did the Na^+ cation. Both metal cations effected almost the same changes in the crown ring carbon signal ($\Delta\delta = -2.2$ ppm for Li^+; $\Delta\delta = -2.4$ ppm for Na^+), and amine function on the sidearm of lariat ether **3** provided effective coordination with the Li^+ cation as observed with lariat ether **2**. Large cation-induced shifts of the sidearm carbon signals were observed with lariat ethers **5**, **6**, and **8**, indicating that ester, amide, and pyridine functions acted as cooperative binding sites for alkali metal cations with the aza-12-crown-4 ring. Lariat ether **11** having an amine-functionalized sidearm and a large aza-15-crown-5 ring was examined for comparison. Since induced spectral changes of lariat ether **11** were much smaller than those of lariat ether **3**, cooperativity of the amine-functionalized sidearm and the aza-12-crown-4 ring is effective in offering Li^+ ion-specific encapsulation.

The present ^7Li and ^{13}C NMR experimental results suggest cation binding equilibria of lariat ether as schematically shown in Figure 2. There are three typical states: [I] metal cation M^+ is not bound with the lariat ether and is surrounded solely by solvent molecules; [II] crown ring accommodates the M^+ which does not interact with donor group D on the sidearm; and [III] M^+ is cooperatively coordinated with donor atoms of both the crown ring and the sidearm. The sidearm coordination competes with solvation, but our spectroscopic observations revealed that the amine-functionalized sidearm of the aza-12-crown-4 provided very effective coordination with Li^+ cation and discriminated it from Na^+ cation.

Li^+ Ion-Specific Liquid Membrane Transport. The amine-armed lariat ethers **2** and **3** also have Li^+ ion-specific transport abilities in a CH_2Cl_2 liquid membrane system.[13] Tables 4 and 5 summarize initial transport rates for Li^+, Na^+, K^+, Mg^{2+}, and Ca^{2+} ions obtained under the single and the competitive transport conditions.

Among the examined crown ethers **2-9** and **11-13**, only amine-armed aza-12-crown-4 derivatives **2** and **3** mediated highly selective transport of Li^+ ion, while they rarely carried Na^+, K^+, Mg^{2+}, or Ca^{2+} cation. Table 4 shows the results of single cation transport experiments. The Li^+/Na^+ transport selectivities of the crown ethers **2** and **3** were calculated as 4.5 and 7.1, respectively. In contrast, ether- and ester-armed aza-12-crown-4 derivatives **4** and **5** transported Na^+ ion more effectively by 3.6 and 8.2 times than did the Li^+ cation, though attachment of the functionalized sidearm clearly enhanced carrier activities. Amide- and pyridine-armed crown ethers **6** and **8** showed enhanced transport rates for Li^+ and Na^+ cations, and their Li^+/Na^+ selectivities were estimated as 1.7 and 0.84. Amine-armed aza-15-crown-5 **11** exhibited larger transport rates for alkali metal cations than did 12-membered **3**, but Li^+ ion selectivity was lost. Oligoamines **14** and **15**, which have similar ethylenediamine moieties to lariat ethers **2** and **3**, were unable to act as carriers for the examined metal cations. Both the nature of sidearm and the ring-size of the parent crown ether significantly determined transport rate and selectivity.

---

[13] Tsukube, H. *Talanta* **1993**, *40*, 1313.

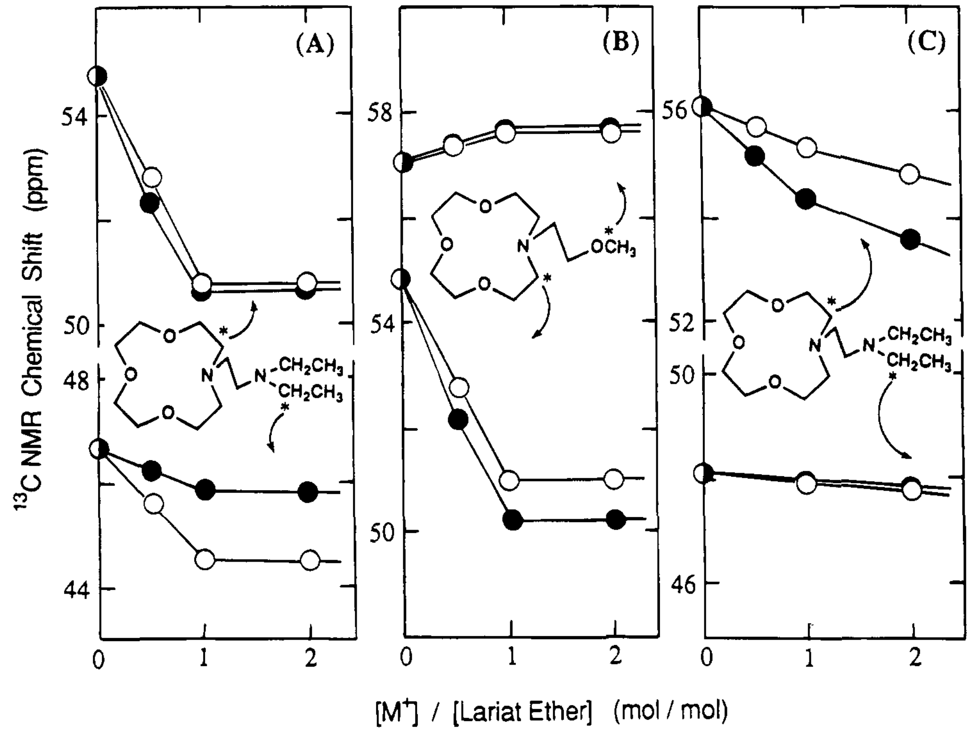
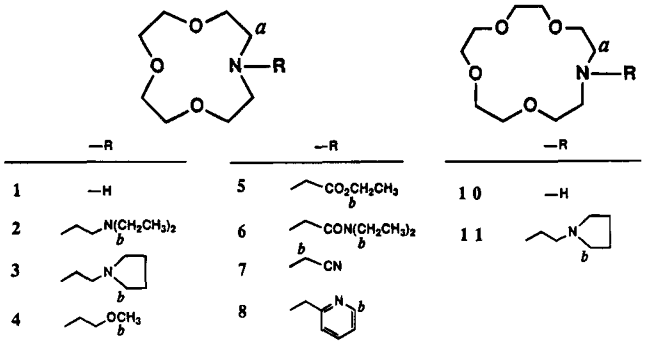


Figure 1. Li$^+$- and Na$^+$-induced changes in ^{13}C-NMR spectra of lariat ethers **2** and **4**: (A) Lariat ether **2** in CH$_3$CN/CD$_3$CN; (B) lariat ether **4** in CH$_3$CN/CD$_3$CN; (C) lariat ether **2** in CH$_3$OH/CD$_3$OD. ○: M$^+$ = Li$^+$, ●: M$^+$ = Na$^+$.

Table 3. Guest-Induced Changes in ^{13}C NMR Chemical Shifts of Lariat Ethers[a]



ether	carbon	induced chemical shift (ppm) +Li$^+$	+Na$^+$
1	***a***	−2.7	−2.4
2	***a***	−4.1	−4.2
	b	−2.1	−0.8
3	***a***	−2.2	−2.4
	b	−2.0	−1.2
4	***a***	−3.9	−4.6
	b	+0.5	+0.6
5	***a***	(−1.5)[b]	−2.6
	b	(+2.3)[b]	+1.7
6	***a***	−1.3	−3.0
	b	*c*	+1.0
7	***a***	−2.6	−3.0
	b	−0.8	−0.5
8	***a***	−2.1	−3.4
	b	+0.4	+1.3
10	***a***	−1.9	−1.4
11	***a***	−1.2	−0.2
	b	−0.9	−1.2

[a] Conditions: lariat ether, 0.025 mmol; LiClO$_4$ or NaClO$_4$, 0.025 mmol in CD$_3$CN−CH$_3$CN 2/3, 0.5 mL. Positive is downfield shift. [b] Precipitate was observed. [c] Broadening.

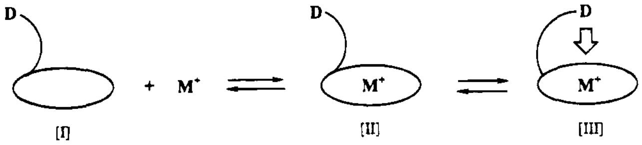


Figure 2. Schematic illustration of cation binding modes of the lariat ether.

Table 4. Single Cation Transport Properties of Lariat Ethers and Related Carriers[a]

carrier	transport rate × 10^7 mol/h Li$^+$	Na$^+$	K$^+$	Mg^{2+}	Ca^{2+}
2	6.3	1.4	0.2	<0.1[c]	<0.1
3	8.5	1.2	0.5	<0.1	0.2
4	1.9	6.8	4.3	<0.1	0.3[c]
5	0.6	4.9	2.8	<0.1	<0.1
6	28.8	17.4	6.5	<0.1	1.7
7	<0.2	0.4	<0.1	<0.1	<0.1
8	7.4	8.8	3.8	0.1	0.5
9	0.3	0.6	0.4	<0.1	<0.1
11	50.0	54.4	26.9	<0.1	0.1
12	29.8	59.6	63.8	<0.1	0.1
13	0.6	8.7	4.1	<0.1	<0.1
14	<0.2	0.4	<0.1	<0.1	<0.1
15	<0.2	0.2	<0.1	<0.1	<0.1
16	1.9	0.3	<0.1	<0.1	<0.1
17	1.1	0.4	<0.1	*b*	*b*

[a] Conditions: MClO$_4$ or M(ClO$_4$)$_2$, 0.50 mmol in H$_2$O (5 mL)//carrier, 0.0372 mmol in CH$_2$Cl$_2$ (12 mL)//H$_2$O (5 mL). [b] Not determined. [c] Turbid.

14-Membered crown ether **16** and acyclic amide **17** were recognized as excellent ionophores for Li$^+$ ion-selective electrodes and are now commercially available.[8] Interestingly, our lariat ethers **2** and **3** showed carrier activities for Li$^+$ ion which were superior to these. Competitive cation transport experiments were also carried out using a mixture of LiClO$_4$, NaClO$_4$, and KClO$_4$ (Table 5). Although the results were almost parallel to those of single cation transport, the transport rate increased about 2-fold in the presence of an excess of

Table 5. Competitive Cation Transport Properties of Lariat Ethers and Related Carriers[a]

carrier	transport rate × 10^7 mol/h Li^+	 Na^+	 K^+
2	11.2	2.4	0.4
3	19.2	3.5	0.8
4	2.4	8.8	4.0
5	0.7	3.3	2.9
6	41.7	18.8	5.4
7	<0.2	0.4	<0.1
8	10.4	15.7	2.5
9	0.8	0.8	0.1
11	17.0	60.0	5.7
12	15.2	60.9	34.8
13	0.9	16.1	5.7
14	<0.2	0.4	<0.1
15	<0.3	0.4	<0.1
16	2.1	0.6	<0.1
17	1.4	0.2	<0.1

[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).

ClO_4^- anion. The cooperative action of aza-12-crown-4 ring and amine-functionalized sidearm was also confirmed to offer Li^+ ion-selective encapsulation suitable for fast and specific transport.

Computational Studies. Density functional calculation was applied to obtain detailed information on the complexes of lariat ethers **2** and **4**. This has recently been recognized as a promising alternative to the Hartree–Fock approach,[14] but had not been employed in such crown ether metal complex systems. Figure 3 illustrates the optimized structure of lariat ether **4**–Na^+ complex, which corresponds to state [III] as shown in Figure 2. Na^+–O (crown ring) distances were estimated to range from 2.316 and 2.351 Å, which are longer by ca. 0.1 Å than that for the sidearm O atom (2.242 Å). The Na^+–N distance was calculated to be 2.391 Å. There is a space where the Na^+ cation can access anion or solvents. We also performed calculations for lariat ether **4**–Li^+ complex. Its calculated distances of Li^+–O and Li^+–N were comparable with those reported for common crown ether complexes, though this Li^+ complex has not been isolated.[16]

Arnold et al. determined the crystal structure of the lariat ether **4**–NaI complex and demonstrated that five donor atoms in lariat ether **4** and I^- cooperatively coordinate with the Na^+ cation.[15] The Na^+–O distances were observed in the range between 2.411 and 2.459 Å, and the Na^+–N length was estimated to be 2.561 Å. These observed lengths are longer by ca. 0.1 Å than those calculated above, though the conformation of the observed azacrown ring resembled that calculated. In the crystal state, an I^- ion coordinates with the Na^+ cation, and thus this sixth ligand may be the cause of such differences.[17]

We optimized the structures of free lariat ethers **2** and **4** and their Li^+ and Na^+ complexes and estimated two kinds of stabilization energies due to the complexation:

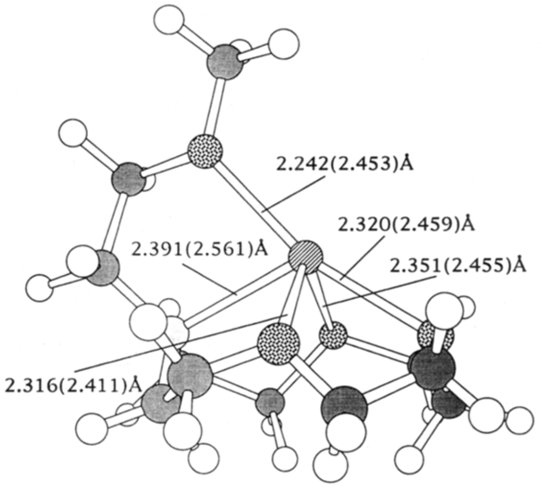
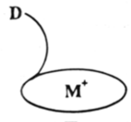
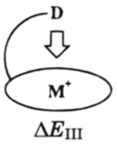


Figure 3. Optimized structure of lariat ether **4**–Na^+ complex. The calculated Na^+–O and Na^+–N distances are indicated, while the distances determined in the lariat ether **4**–NaI crystal are shown in parentheses.

Table 6. Stabilization Energies of Complexes with Lariat Ethers 2 and 4

complex	stabilization energy (kcal/mol)  ΔE_{II}	  ΔE_{III}	 ΔE_{III-II}
2-Li^+	−90.9	−104.6	−13.7
2-Na^+	−69.5	−79.6	−10.1
4-Li^+	−88.3	−102.3	−14.0
4-Na^+	−65.6	−78.8	−13.2

ΔE_{II} is obtained by the formation of the type [II] complex and ΔE_{III} by that of type [III] (see Figure 2). Table 6 shows these energies together with stabilization energy ΔE_{III-II} coming from the sidearm coordination. All ΔE_{II} and ΔE_{III} values for the Li^+ complexes are larger by ca. 22 kcal/mol than those for the Na^+ complexes. Therefore, these lariat ethers bind the Li^+ cation more strongly than the Na^+ cation in the "gas phase".

The magnitude of ΔE_{III-II} can be considered a measure of effectiveness of sidearm coordination. ΔE_{III-II} values for lariat ether **2** were calculated to be −13.7 kcal/mol and −10.1 kcal/mol for Li^+ and Na^+ complexes, respectively, the difference being as large as 3.6 kcal/mol. In contrast, lariat ether **4** binds these cations with similar stabilization since the ΔE_{III-II} values are −14.0 kcal/mol and −13.2 kcal/mol for Li^+ and Na^+ complexes. Although solvent effects must be included to estimate the proper stabilization energies,[18] the trend of the ΔE_{III-II} is closely related to the cation selectivity of the lariat ethers **2** and **4**. These calculation results paralleled our described observations and confirmed that the amine-functionalized sidearm of the lariat ether **2** offered specific recognition of Li^+ cation.

We successfully demonstrated above that arm-functionalization based on lariat ether strategy provided good

---

[14] (a) Andzelm, J.; Wimmer, E. *J. Chem. Phys.* **1992**, *96*, 1280. (b) Andzelm, J.; Sosa, C.; Eades, R. A. *J. Phys. Chem.* **1993**, *97*, 4664.

[15] Arnold, K. A.; Mallen, J.; Trafton, J. E.; White, B. D.; Fronczek, F. R.; Gehrig, L. M.; Gandour, R. D.; Gokel, G. W. *J. Org. Chem.* **1988**, *53*, 5652.

[16] Calculated length (Å): Li^+–O = 1.968–2.104; Li^+–N = 2.140. See (a) Fronczek, F. R.; Gandour, R. D. In *Cation Binding by Macrocycles*; Marcel Dekker: New York, 1990; p 311. (b) Goldberg, I. In *Crown Ethers and Analogs*; John Wiley & Sons: Chichester, 1989; p 399.

[17] The calculation of lariat ether **4**–Na^+ complex including one H_2O molecule as a sixth ligand gave lengthened Na^+–O and Na^+–N bonds: Na^+–O(crown) = 2.319–2.398 Å; Na^+–O(sidearm) = 2.275 Å; Na^+–N = 2.454 Å.

[18] (a) Yamabe, T.; Hori, K.; Akagi, K.; Fukui, K. *Tetrahedron* **1979**, *35*, 1065. (b) Wipff, G.; Weiner, P.; Kollman, P. *J. Am. Chem. Soc.* **1982**, *104*, 3249.

potential for development of Li^+ ion-specific receptors/carriers. We also employed nonempirical calculation for the first time in the crown ether complex system. Since this proved useful in characterization of the lariat ether complex process, the present study provides new possibilities for the design of a specific cation receptor.

Experimental Section

General. Crown ethers **1**, **10**, and **16** and related materials **14**, **15**, and **17** were commercially available and used without additional purification. Aza-12-crown-4s **4**, **5**, and **9** and aza-15-crown-5s **12** and **13** were synthesized by methods described in the literature.[10b,19] New compounds **2**, **3**, **6**, **7**, and **11** were prepared from parent crown ethers **1** and **10** in a similar fashion to that reported for diazacrown ethers.[20] They were chromatographed (alumina, about 200 mesh; CH_2Cl_2/hexane) and had correct elemental compositions determined by microanalysis or high-resolution mass spectroscopy (EI mode). The purity of all new compounds was established by ^1H and ^{13}C NMR spectroscopies (see supplementary material). Selected data of the newly obtained materials are summarized below.

10-[(*N,N*-Diethylamino)ethyl]-1,4,7-trioxa-10-azacyclododecane (2) was obtained by BH_3-reduction of crown **6** (oil, 70%): ^1H NMR ($CDCl_3$) δ 1.03 (t, 6H), 2.55 (q, 4H), 2.60 (t+t, 4H), 2.73 (t, 4H), 3.65 (t, 4H), 3.68 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 11.79, 47.55, 51.21, 55.18, 55.55, 70.42, 70.49, 71.30; HRMS *(m/e)* calcd for $C_{14}H_{30}N_2O_3$ 274.2255, found 274.2253.

10-(Pyrrolidinoethyl)-1,4,7-trioxa-10-azacyclododecane (3) was prepared from crown **1** and *N*-(chloroethyl)-pyrrolidine hydrochloride (oil, 65%): ^1H NMR ($CDCl_3$) δ 1.77 (m, 4H), 2.56 (m, 4H), 2.67 (t+t, 4H), 2.74 (t, 4H), 3.65 (t, 4H), 3.68 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 23.76, 54.60, 54.72, 55.82, 55.89, 70.47, 70.57, 71.52; HRMS *(m/e)* calcd for $C_{14}H_{28}N_2O_3$ 272.2100, found 272.2122.

10-[(*N,N*-Diethylcarbamoyl)methyl]-1,4,7-trioxa-10-azacyclododecane (6) was prepared from crown **1** and *N,N*-diethylchloroacetamide (oil, 70%): IR (neat) ν 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H), 1.17 (t, 3H), 2.91 (t, 4H), 3.35 (q+q, 4H), 3.47 (s, 2H), 3.62 (t, 4H), 3.67 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 12.87, 14.11, 39.83, 41.14, 55.04, 57.84, 69.88, 70.23, 71.03; HRMS *(m/e)* calcd for $C_{14}H_{28}N_2O_4$ 288.2049, found 288.2073.

10-(Cyanomethyl)-1,4,7-trioxa-10-azacyclododecane (7) was synthesized from crown **1** and chloroacetonitrile (oil, 80%): IR (neat) ν 2230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (t, 4H), 3.64 (t, 4H), 3.65 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 44.70, 54.18, 68.85, 70.35, 70.67, 115.67; HRMS *(m/e)* calcd for $C_{10}H_{18}N_2O_3$ 214.1317, found 214.1308.

10-(2′-Pyridylmethyl)-1,4,7-trioxa-10-azacyclododecane (8) was prepared from crown **1** and 2-(chloromethyl)-pyridine hydrochloride (oil, 60%): IR (neat) ν 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.82 (t, 4H), 3.65 (t, 4H), 3.71 (s, 8H), 3.84 (s, 2H), 7.11 (m, 1H), 7.63 (m, 2H), 8.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 55.28, 62.67, 70.27, 70.74, 71.49, 121.86, 123.25, 136.39, 148.92, 160.33. Anal. Calcd for $C_{14}H_{22}O_3N_2$: C, 63.14; H, 8.33; N, 10.52. Found: C, 63.21; H, 8.06; N, 10.46.

13-(Pyrrolidinoethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (11) was prepared in a similar fashion to that for crown **3** (oil, 40%): ^1H NMR ($CDCl_3$) δ 1.77 (m, 4H), 2.56 (m, 4H), 2.67 (t+t, 4H), 2.78 (t, 4H), 3.66 (t+s, 16H); ^{13}C NMR ($CDCl_3$) δ 23.54, 54.57, 55.23, 55.74, 70.22, 70.32, 70.61, 71.12; HRMS *(m/e)* calcd for $C_{16}H_{32}N_2O_4$ + H 317.2440, found 317.2444.

FAB MS Experiments. Complexation of ether (0.0033 mol/L) with LiCl, NaI, and KI (0.0083 mol/L, each) in *m*-nitrobenzyl alcohol was studied by measuring the relative peak heights of [ether + M^+] ions. FAB MS spectra were recorded with a JEOL DX 300 instrument (a beam energy of Xe, 6 keV) and the peak heights were averaged over at least 12 scans.

Transport Experiments. Transport experiments were performed at room temperature (ca. 18 °C) in a U-tube glass cell (2.0 cm i.d.).[1c] The carrier, 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 Tables 4 and 5 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). We confirmed that all guest salts were rarely transported in the absence of carrier.

NMR Binding Experiments. ^{13}C NMR studies were carried out with a JEOL 90A spectrometer, while ^7Li NMR spectra were recorded with a Varian VXR-300S (Nagoya University). The lariat ether was dissolved in CD_3CN/CH_3CN (2/3, v/v) or CD_3OD/CH_3OH(2/3, v/v) at a concentration of 0.05 mol/L.

Computational Method. The calculations were carried out using the DGauss program[5] of the UniChem system on a Cray Y-MP2E. DZVP basis set was used for all calculations and exchange-correlation energy was obtained by Vosko–Wilk–Nusair method. The DZVP level was characterized by a double-ζ orbital basis set with polarization function except for hydrogen atoms, and on this level, auxiliary function A1 was used to calculate the exchange-correlation energy. The nonlocal corrections based on the Becke–Perdew method were performed perturbatively after geometry optimization.[21]

Azacrown ethers are very flexible so that it is very difficult to search all the stationary points of their geometries and to obtain global minima of their structures. We made initial geometries of free and complexed azacrown ethers on the basis of the crystal structures and the optimized geometries we obtained before for crown ethers without a sidearm.[6f] The Li^+ complexes were first optimized using the MNDO method in the MOPAC ver.6.[22] The obtained geometries were adopted as the initial ones for density functional calculations. The central metal cation of the Li^+ complex was replaced with Na^+ ion to make a starting structure of the Na^+ complex. Therefore, the optimized structures of alkali metal complexes were essentially similar to each other. Although we could not estimate quantitative stabilization energies due to the complex formation, our calculations gave a qualitative insight into the effect of the sidearm participation on cation binding behavior of the lariat ether.

Acknowledgment. The authors are grateful to Professor Osamu Yamauchi and Dr. Akira Odani of Nagoya University for measurement of ^7Li NMR spectra and valuable discussion. This research was supported in part by a Grant from the Salt Science Research Foundation (No. 9312).

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **2**, **3**, **6**, **7**, and **11** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(19) (a) Schultz, R. A.; White, B. D.; Dishong, D. M.; Arnold, K. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6659. (b) Gandour, R. D.; Fronczek, F. R.; Gatto, V. J.; Minganti, C.; Schultz, R. A.; White, B. D.; Arnold, K. A.; Mazzocchi, D.; Miller, S. R.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 4078.

(20) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc. Perkin Trans. 1* **1989**, 89.

(21) Details of our employed calculation method will be fully reported elsewhere.

(22) We used MOPAC ver. 6.01 program: Stewart, J. J. P. MOPAC ver. 6.01, QCPE No. 455. See (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (b) Dewar, M. J. S.; Reynolds, C. H. *J. Comput. Chem.*, **1986**, 140.