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# Pyridine-Armed Diaza-Crown Ethers: Molecular Design of Effective Synthetic Ionophores

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A variety of double-armed diaza-crown ethers were examined as synthetic ionophores in which pyridine- and quinoline-functionalized arms were attached as secondary donor sites. Binding constant determinations and $^{13}C$ NMR titration experiments revealed that introduction of a pyridine-functionalized arm, if in the proper geometrical arrangement, significantly enhanced complex stabilities for divalent metal cations via three-dimensional encapsulation. In a $CH_2Cl_2$ liquid membrane transport system, some pyridine-armed diaza-crown ethers exhibited unique and excellent transport abilities for transition-metal cations as well as for alkali and alkaline earth cations. Since these transport profiles differed greatly from those observed with conventional crown ethers, the present study offers new possibilities for designing novel types of synthetic ionophores.

## Introduction

Double-armed crown ethers and related macrocyclic ligands represent a new class of synthetic cation binders,[1] which are characterized by a parent macrocyclic ligand and a cation-ligating functionalized arm. In this class of compounds, the donor group on the flexible side arm can provide further coordination to the cation trapped in the parent macroring by wrapping around the guest. Because these armed macrocycles exhibit both the dynamic properties of simple monocyclic crown ethers and the three-dimensional binding characteristics of bicyclic cryptand compounds, they may be considered very promising candidates for use in the design of new synthetic ion-carrier molecules, the so-called "ionophores".[2]

In previous studies, we prepared a variety of diaza-crown ether and cyclam derivatives bearing ether-, ester-, amide-, and furan-functionalized arms.[3] Interestingly, all of these compounds showed highly characteristic and enhanced cation transport abilities, especially for alkali and alkaline earth metal cations, at levels not attained by common crown ether type ionophores. Because it was found that cation-binding and transport properties were significantly affected by the nature of the cation-ligating side arm and parent macroring, we believe that a new combination of cation-ligating donor group and macrocyclic ligand may offer excellent cation-binding and transport functions. Herein, we report the unique and excellent cation-binding and transport properties of a family of double-armed diaza-crown ethers[4] which incorporate pyridine and quinoline heterocycles as potential cation-ligating donors on their side arms. We successfully demonstrated that the molecular combination of the nitrogen-functionalized arm group and the diaza-crown ring effectively provided three-dimensional complexation with both transition-metal cations and alkaline earth metal cations, as well as their efficient transport across membranes. Many kinds of lariat ethers and related armed macrocycles have recently been recognized as useful cation binders,[1] but attempts to use them as membrane carriers for transition-metal cations and other guest species have been rare. The present study reveals the interesting transport characteristics of pyridine-armed diaza-crown ethers.

## Results and Discussion

Table I. Sodium, Calcium, and Copper Binding Constants for Pyridine-Armed Diaza-Crown Ethers and Related Macrocycles in $H_2O$

| | stability constant (log *K*) | | |
|---|---|---|---|
| compd | $Na^+$ | $Ca^{2+}$ | $Cu^{2+}$ |
| **1** | 2.64 | 4.01 | 8.98 |
| **2** | 2.55 | 3.09 | *a* |
| **6** | 2.44 | 3.43 | (7.59)[b] |
| **7** | 2.88 | 3.92 | *c* |
| **8** | 2.88 | 3.46 | 7.33<br>(7.17)[b] |
| **9** | 2.92 | 3.37 | 8.10 |
| **10** | 2.92 | 3.48 | 7.53 |
| **11** | 4.22<br>(4.11)[b] | 4.69<br>(4.57)[b] | *d*<br>(6.81)[b] |

[a] This compound forms an insoluble, probably intermolecular complex with $Cu^{2+}$ ion. [b] These values have been reported in ref 5. [c] The spectra of this system gradually changed. [d] Not determined.

**Pyridine-Armed Diaza-Crown Ethers.** Pyridine and quinoline heterocycles were introduced into the side arms of diaza-crown ethers having 15-, 18-, and 21-membered rings, **1**–**3**, **7**, and **9** (Chart I). These compounds were directly prepared from commercially available, unsubstituted diaza-crown ethers **6**, **8**, and **10** and the corresponding (chloromethyl)pyridines. While the parent diaza-crown rings effectively bind several hard alkali and alkaline earth metal cations, the introduced pyridine and quinoline moieties act as powerful binding sites for soft heavy and transition metal cations. Thus, the combination of a pyridine-functionalized arm and a parent diaza-crown ring is expected to exhibit new host–guest binding and cation transport functions, which differ greatly from simple diaza-crown ethers and related macrocycles.

**Binding Constant Determinations.** The homogeneous stability constants for $Na^+$ and $Ca^{2+}$ ions were

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[†] Okayama University.

[‡] Okayama University of Science.

(1) Recent reviews: (a) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929. (b) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875. Recent examples: (a) Echegoyen, L. E.; Yoo, H. K.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1989**, *111*, 2440. (b) Nakatsuji, Y.; Wakita, R.; Harada, Y.; Okahara, M. *J. Org. Chem.* **1989**, *54*, 2988. (c) Alcock, N. W.; McLaren, F.; Moore, P.; Pike, G. A.; Roe, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 629. (d) Krakowiak, K. E.; Bradshaw, J. S.; Dalley, N. K.; Jiang, W.; Izatt, R. M. *Tetrahedron Lett.* **1989**, *30*, 2897. (e) Hosseini, M. W.; Blacker, A. J.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 596. (f) Moi, M. K.; Meares, C. F.; DeNardo, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 6266. (g) Akkaya, E. U.; Czarnik, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 8553.

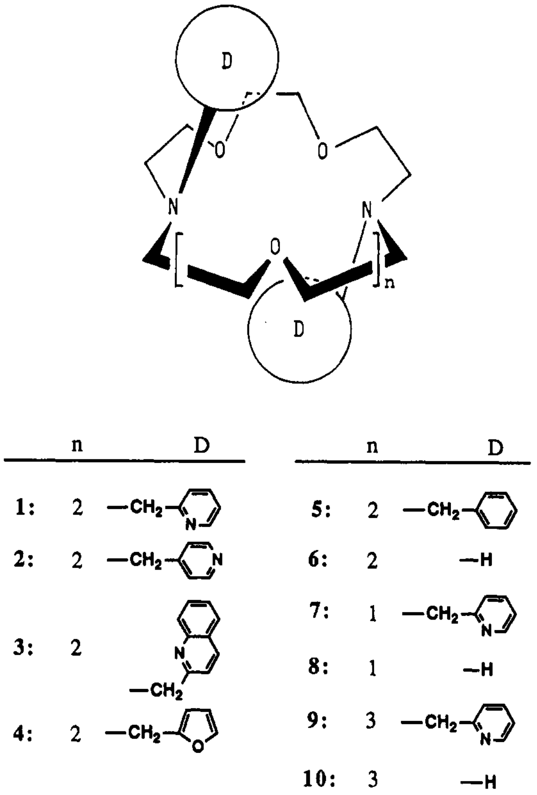
(2) Recent review: Tsukube, H. *J. Coord. Chem.* **1987**, *B-16*, 101.

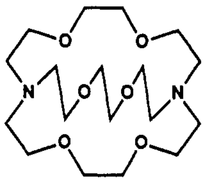
(3) (a) Tsukube, H. *J. Chem. Soc., Chem. Commun.* **1984**, 315. (b) Tsukube, H. *Chem. Lett.* **1984**, 1961. (c) Tsukube, H.; Takagi, K.; Higashiyama, T.; Iwachido, T.; Hayama, N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1033. (d) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 89. (e) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc., Perkin Commun.* **1989**, 1537.

(4) Preliminary communication: Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *Tetrahedron Lett.* **1988**, *29*, 569.

0022-3263/91/1956-0268$02.50/0

**Chart I. Molecular Structures of Pyridine-Armed Diaza-Crown Ethers and Related Macrocycles**





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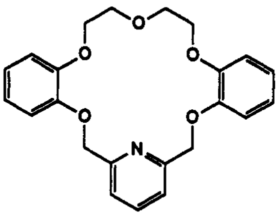

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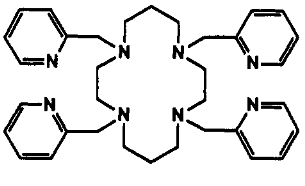

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measured in $H_2O$ for pyridine-armed crown ethers 1, 2, 7, and 9, using $Na^+$ and $Ca^{2+}$ ion-selective electrodes, while the UV spectroscopic competition method was applied to determine the stability constants for the $Cu^{2+}$ ion (see Experimental Section). Table I summarizes the values obtained as decadic logarithms with the data of unsubstituted diaza-crown ethers 6, 8, and 10 and bicyclic cryptand 11. Some of these values agreed closely with those reported earlier.[5]

The effect of the pyridine-functionalized arm on the stability constant was clearly demonstrated by comparing double-armed crown ethers with their parent diaza-crown ethers. Table I indicates that the attachment of pyridine-functionalized arms to the diaza-crown ring significantly increased binding constants for the $Ca^{2+}$ and $Cu^{2+}$ ions. Typically, the stability constant of pyridine-armed diaza-18-crown-6 1 for $Cu^{2+}$ ion was an order of magnitude greater than that of the unsubstituted 6, whereas only slight enhancement was observed for $Na^+$ ion. Pyridine-armed diaza-15-crown-5 7 and diaza-21-crown-7 9 exhibited large enhancements for $Ca^{2+}$ and $Cu^{2+}$ ions, respectively, and it was confirmed that the pyridine nitrogen atoms on the side arms provide more effective coordination with divalent $Ca^{2+}$ and $Cu^{2+}$ ions than with the monovalent $Na^+$ ion. Pyridine-armed crown ether 2, which has all the structural elements present in the rest of series, yet behaves differently, was also compared. Because its pyridine nitrogen atoms are too remote to interact with the crown-bound guest cations, the methylpyridine substituent seems to act as an electron-withdrawing group and thus to reduce stability constants.[6] Clearly, one precondition for cation-binding enhancement is that the donor groups must be appropriately situated on the side arms to provide further coordination with the guest cation trapped in the parent crown ring.

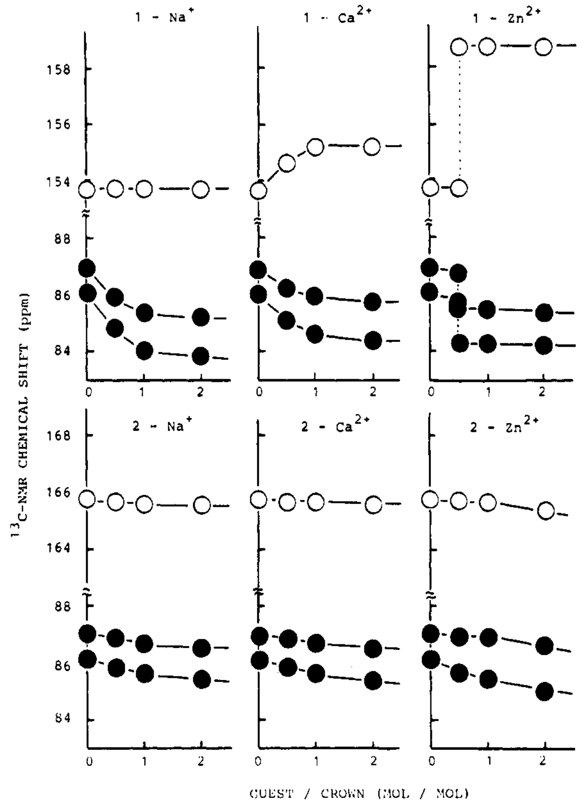

Figure 1. $Na^+$-, $Ca^{2+}$-, and $Zn^{2+}$-induced changes in $^{13}C$ NMR chemical shifts of pyridine-armed diaza-crown ethers 1 and 2: (-●-) crown ring carbon as indicated by *a* in Table II; (-○-) pyridine ring carbon as indicated by *b* in Table II.

**$^{13}C$ NMR Binding Studies.** Further detailed information on the cation-binding behavior of pyridine-armed

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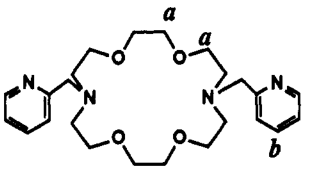
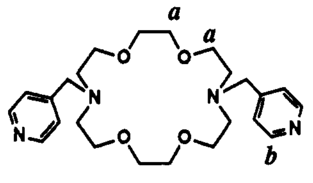
(5) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271.

(6) Gustowski, D. A.; Gatto, V. J.; Mallen, J.; Echegoyen, L.; Gokel, G. W. *J. Org. Chem.* **1987**, *52*, 5172.

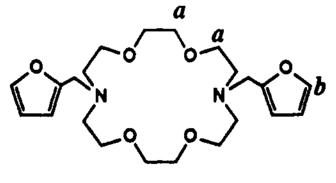
**Table II. Guest-Induced Changes in $^{13}C$ NMR Chemical Shifts of Pyridine-Armed Crown Ethers**[a]



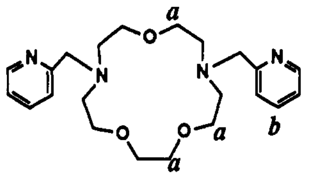
**1**



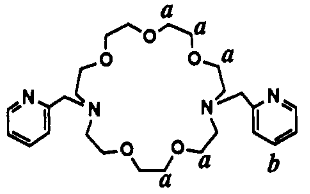
**2**



**4**



**7**



**9**

| crown | carbon | induced chemical shift (ppm) |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|
|  |  | $Na^+$ | $K^+$ | $Ag^+$ | $Ca^{2+}$ | $Ba^{2+}$ | $Pb^{2+}$ | $Zn^{2+}$ |
| 1 | a | -1.7 | -0.5 | -1.3 | -1.0 | $-0.5^{b}$ | $-1.1^{b}$ | $-1.5^{b}$ |
|  |  | -2.1 | -1.5 | -1.9 | -1.5 | $-1.3^{b}$ | $-1.3^{b}$ | $-1.8^{b}$ |
|  | b | <+0.1 | +0.2 | +1.0 | +0.6 | +1.2 | +2.6 | +5.0 |
| 2 | a | -0.4 | -0.4 | -2.5 | -0.1 | -0.2 | $-1.0^{c}$ | -0.2 |
|  |  | -0.5 | -1.0 | -4.8 | -0.2 | -1.5 | $-1.8^{c}$ | -0.8 |
|  | b | -0.2 | -0.1 | +0.9 | -0.1 | <-0.1 | 0 | -0.1 |
| 4 | a | -1.2 | -0.4 | $-1.7^{c}$ | -0.7 | -0.2 | $-1.0^{b}$ | -0.4 |
|  |  | -1.8 | -1.8 | $-3.3^{c}$ | -1.4 | -1.6 | $-1.6^{b}$ | -3.1 |
|  | b | +0.4 | +0.3 | +1.2 | +0.4 | +0.9 | +1.0 | $+1.5^{c}$ |
| 7 | a | -1.5 | -1.3 | $-1.5^{c}$ | $-1.4^{c}$ | $-1.2^{c}$ | $-1.6^{b}$ | $-2.6^{b}$ |
|  |  | -2.6 | -2.3 | $-1.7^{c}$ | $-2.4^{c}$ | $-0.9^{c}$ | $-0.9^{b}$ | $-4.2^{b}$ |
|  |  | -1.8 | -0.8 | $-3.1^{c}$ | $-3.6^{c}$ | $-2.6^{c}$ | $-2.1^{b}$ | $-5.7^{b}$ |
|  | b | +0.5 | +0.2 | +1.1 | +2.1 | +1.3 | +2.3 | +3.9 |
| 9 | a | -0.5 | -1.0 | -0.2 | -0.4 | -1.0 | $-1.4^{c}$ | $+0.8^{c}$ |
|  |  | $-0.5^{d}$ | $-1.0^{d}$ | $-0.5^{d}$ | $-0.3^{d}$ | $-1.3^{d}$ | $-1.7^{c,d}$ | $<-0.1^{c,d}$ |
|  |  | $-0.7^{d}$ | $-1.5^{d}$ | $-0.8^{d}$ | $-0.4^{d}$ | $-2.0^{d}$ | $-2.8^{c,d}$ | $-2.3^{c,d}$ |
|  | b | <+0.1 | 0 | +1.4 | +0.2 | +1.2 | +2.9 | +4.7 |

[a] Conditions: crown, 0.025 mmol; guest perchlorate, 0.025 mmol in DMF-$D_2O$ (4:1) 0.5 mL. Positive is downfield shift. [b] These signals were split in the presence of excess crown, and individual assignment is impossible. [c] They were broadening in the presence of excess crown ethers. [d] The averaged values of two carbon signals were indicated that were not assignable.

crown ethers was obtained via $^{13}C$ NMR spectroscopy in DMF/$D_2O$ (4/1) solution. Figure 1 illustrates the $Na^+$-, $Ca^{2+}$-, and $Zn^{2+}$-induced changes in the $^{13}C$ NMR chemical shifts of selected carbon signals of pyridine-armed diaza-crown ethers 1 and 2. Typically, the addition of $Ca(ClO_4)_2$ salt to a solution of pyridine-armed crown ether 1 caused significant and continuous shifts of the signals for both pyridine and crown ring carbons via 1:1 complexation. This result clearly indicates that the pyridine nitrogen atom on the flexible side arm effectively coordinates with the $Ca^{2+}$ ion trapped in the diaza-crown ring. $Zn(ClO_4)_2$ salt induced even more remarkable spectral changes. When 0.5 equiv of $Zn^{2+}$ ion was present, each carbon signal was split into two signals corresponding to the free and complexed forms. The pyridine-armed crown ether 1 probably forms a three-dimensional $Zn^{2+}$ complex with very high stability. On the other hand, this pyridine-armed crown ether was thought to effect circular coordination for $Na^+$ cation in the same way as do simple crown ethers, because only the signals for the crown ring carbons were shifted as a result of $Na^+$ complexation.[7] The pyridine-armed diaza-crown ether 1 provided different coordination geometries for $Na^+$, $Ca^{2+}$, and $Zn^{2+}$ cations.

Figure 1 also indicates that diaza-crown ether 2 with pyridine nitrogen atoms at the remote position operated as a simple and weak crown-type ligand: $Na^+$, $Ca^{2+}$, and $Zn^{2+}$ cations induced slight shifts in the signals of the pyridine and crown ring carbons. These $^{13}C$ NMR titration experiments clearly demonstrate the cooperative binding of the pyridine-functionalized arm and parent crown ring in the crown ether 1, while no such cooperative binding was evident for crown ether 2. Thus, complexation is strong when three-dimensional encapsulation of the guest cation is possible.

Table II summarizes the results of $^{13}C$ NMR binding studies for 15-, 18-, and 21-membered pyridine-armed crown ethers 1, 2, 7, and 9 and furan-armed crown ether 4 toward various guest cations and indicates that pyridine-armed crown ethers 1, 7, and 9 form encapsulated complexes with several metal cations. Typically, pyridine-armed diaza-18-crown-6 1 efficiently accommodated $Ag^+$, $Ca^{2+}$, $Ba^{2+}$, $Pb^{2+}$, and $Zn^{2+}$ cations in its three-dimensional molecular cavity. The shifted value for the pyridine carbon signal was highly dependent on the nature of the guest cation. Interestingly, heavy and transition metal cations induced larger shifts than did alkaline earth metal cations. Furthermore, broadening and splitting were

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(7) 1-$Na^+$ complex has been isolated, but not fully characterized: Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 8240. Damu, K. V.; Shaikjee, M. S.; Michael, J. P.; Howard, A. S.; Hancock, R. D. *Inorg. Chem.* **1986**, *25*, 3879.

**Table III. Cation Transport Properties of Pyridine-Armed Diaza-Crown Ethers and Related Macrocycles[a]**

| guest cation | transport rate × $10^6$ (mol/h) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 12 | 13 |
| $Li^+$ | 5.0 | * | 1.4 | * | * | 7.3 | 6.8 | * | 0.4 |
| $Na^+$ | 10.5 | 0.3 | 12.2 | 9.0 | 2.4 | 6.4 | 8.5 | 0.4 | 2.2 |
| $K^+$ | 7.9 | 1.9 | 6.5 | 11.5 | 6.8 | 10.3 | 10.6 | 5.9 | * |
| $Cs^+$ | 7.3 | * | 3.0 | 8.2 | 1.2 | 1.6 | 10.2 | 3.7 | * |
| $Ag^+$ | * | *[c] | * | * | * | * | * | 8.2 | 0.4 |
| $Mg^{2+}$ | * | * | * | * | * | * | * | * | * |
| $Ca^{2+}$ | 11.5 | * | * | * | * | 6.4 | 0.4[c] | * | * |
| $Ba^{2+}$ | 3.4 | * | 10.3 | 17.6 | 2.4 | 4.0[c] | 7.8 | * | * |
| $Pb^{2+}$ | 1.6 | * | 1.0 | 3.7 | 2.9 | 1.6 | 1.0 | * | * |
| $Cu^{2+}$ | 2.2 | * | 2.9 | *[d] | *[c] | 2.3 | 2.6 | * | 0.4[c] |
| $Ni^{2+}$ | * | * | * | *[d] | * | 0.7 | 0.6 | * | 0.3 |
| $Co^{2+}$ | 0.8 | 0.3 | * | * | * | 2.0 | 0.7 | * | 0.5[c] |
| $Zn^{2+}$ | 4.1 | * | 0.5 | *[d] | *[c] | 2.6 | 4.0 | * | *[c] |

[a] Conditions: aqueous 1, guest perchlorate, 0.50 mmol/$H_2O$, 5 mL; membrane, macrocycle, 0.0372 mmol/$CH_2Cl_2$, 12 mL; aqueous 2, $H_2O$, 5 mL. [b] Asterisk denotes below limit of detection (<0.3). [c] A precipitate was observed. [d] A slight turbidity appeared.

observed in several carbon signals when 0.5 equiv of divalent metal cation was added. Although individual assignments of these signals are virtually impossible, they are a good indication of very stable complexation.

Furan-armed diaza-18-crown-6 **4**, which has similar ligand geometry, has been reported to exhibit enhanced binding constants for $Na^+$ and $Ca^{2+}$ ions in MeOH.[7] Table II clearly indicates that **4** formed three-dimensional complexes with various metal cations, but its shifted values for the side arm carbon signals were sometimes smaller than those of pyridine-armed crown ether **1**. Thus we can select the nature of the ligating side arm to suit a particular target guest cation in the design of double-armed crown ethers.

The size of the parent diaza-crown ring is an important factor in controlling the guest-binding behavior of pyridine-armed crown ethers, especially toward alkali and alkaline earth cations. Guest-induced spectral changes shown in Table II strongly suggest that 15-membered crown **7** formed a three-dimensional complex with $Ca^{2+}$ ion nicely and that 21-membered **9** efficiently encapsulated $Ba^{2+}$ ion. On the other hand, such an "ion-cavity selectivity" is not apparent in $Ag^+$-, $Pb^{2+}$–, and $Zn^{2+}$-binding processes. Regardless of their ring sizes, these metal cations induced large shifts in the values of both the crown ring and pyridine ring signals. Thus, pyridine-armed crown ethers **1**, **7**, and **9** effectively formed three-dimensional complexes with heavy and transition metal cations of various sizes. The flexible armed crown ether may be directed by the guest cation to envelop in the geometry most appropriate for the cation and not for the crown ring. This three-dimensional binding property of double-armed crown ethers can offer the strong and selective binding, lipophilic properties, and dynamic binding kinetics that are essential in making an excellent ionophore.

**Cation Transport across a Liquid Membrane.** With double-armed crown ethers as synthetic ionophores, transport experiments were performed in a $CH_2Cl_2$ liquid membrane system. Table III summarizes the transport properties of several pyridine-armed crown ethers **1-3**, **7** and **9**, comparing them with those of the simple crown ether **5**, furan-armed crown ether **4**,[3c] and pyridine-functionalized macrocycles **12** and **13**.[8] Our pyridine-armed diaza-crown ethers **1**, **3**, **7**, and **9** showed better transport abilities, especially for divalent metal cations, than macrocyclic ionophores **2**, **4**, **5**, **12**, and **13**, and arm functionalization successfully generated unique and specific ionophoric activity in the diaza-crown ether system as discussed below.

Pyridine-armed diaza-18-crown-6 **1** effectively transported $Cu^{2+}$ and $Zn^{2+}$ cations as well as $Na^+$ and $Ca^{2+}$, while the furan-armed and simple crown ethers **4** and **5** did little to mediate the transport of any transition-metal cations. Since efficient transport of transition-metal cations was similarly observed with quinoline- and pyridine-armed diaza-crown ethers **3**, **7**, and **9**, introduction of the nitrogen heterocycle into the side arm of the diaza-crown ring clearly provides a characteristic cation transport ability for transition-metal cations.[9] Pyridino-crown ether **12** and pyridine-armed cyclam **13** were also examined. They have previously been recognized as potential ligands for transition-metal cations,[10] but their transport abilities were considerably poorer. The specific combination of a pyridine-functionalized side arm and a parent diaza-crown ring was believed to be essential for the fast transport of transition-metal cations. Although most crown compounds, including the simple diaza-crown ethers **6**, **8** and **10**, are known to bind more strongly with transition-metal cations than with alkali and alkaline earth metal cations,[5] they have rarely been used as efficient carriers for transition-metal cations in extraction and transport processes. As demonstrated above, the present type of pyridine-armed diaza-crown ethers possesses the complex stability, ligand topology, and binding kinetics required for an effective ionophore involved in the transport of transition-metal cations.[11]

For alkali and alkaline earth metal cations, pyridine-armed diaza-crown ethers showed enhanced and different transport abilities from those observed with other diaza-crown derivatives. Typically, pyridine-armed diaza-18-crown-6 **1** exhibited high rates of transport for $Ca^{2+}$ and $Na^+$ cations, while furan-armed diaza-18-crown-6 derivative **4** effectively transported $K^+$ and $Ba^{2+}$ cations. The cation-transport abilities of these double-armed crown ethers could be adjusted by the appropriate arm functionalization, and further arrangement of binding arrays could be carried out in accord with the requirements of the target guest cation.

We have successfully demonstrated the unique and effective cation-binding and transport abilities of double-armed crown ethers bearing characteristic nitrogen-containing heterocycles on the side arms. Some of these compounds formed specifically encapsulated complexes with uncommon transition-metal cations and alkaline earth metal cations via "side arm–crown ring cooperativity". Three-dimensional coordination provided both strong cation binding and efficient membrane transport properties. To the best of our knowledge, this is the first example

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(8) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *Tetrahedron Lett.* **1989**, *30*, 3983.

(9) Pyridine-functionalized host molecules have been designed but rarely applied to the membrane transport process: (a) Nakatsuji, Y.; Bradshaw, J. S.; Tse, P. K.; Arena, G.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Chem. Soc., Chem. Commun.* **1985**, 749. (b) Albrecht-Gary, A. M.; Saad, Z.; Dietrich-Buchecker, C. O.: Sauvage, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3205. (c) Weber, E.; Franken, S.; Puff, H.; Ahrendt, J. *J. Chem. Soc., Chem. Commun.* **1986**, 467. (d) Kimura, E.; Koike, T.; Nada, H.; Iitaka, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1322. (e) Alpha, B.; Lehn, J. M.; Mathis, G. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 266. (f) Chang, S. K.; Hamilton, A. *J. Am. Chem. Soc.* **1988**, *110*, 1318.

(10) Alcock, N. W.; Balakishnan, K. P.; Moore, P. *J. Chem. Soc., Dalton Trans.* **1986**, 1743.

(11) Carrier-mediated transport of transition-metal cations has rarely been reported: (a) Maruyama, K.; Tsukube, H.; Araki, T. *J. Am. Chem. Soc.* **1980**, *102*, 3246. (b) Matsuo, S.; Ohki, A.; Takagi, M.; Ueno, K. *Chem. Lett.* **1981**, 1543. (c) Kimura, E.; Dalimute, C. A.; Yamashita, A.; Machida, R. *J. Chem. Soc., Chem. Commun.* **1985**, 1041.

of synthetic ionophores for transition-metal cations that have an armed crown ether structure.

## Experimental Section

$^1$H NMR spectra were recorded on a JEOL 90A (89.95 MHz) spectrometer in $CDCl_3$ with $Me_4Si$ as internal reference. $^{13}$C NMR spectra were also recorded on the same spectrometer at 25.12 MHz in DMF/$D_2O$ (4/1). Chemical shifts were determined by using the peak of the DMF carbonyl carbon ($\delta_C$ 180.00 ppm) as reference. IR and UV/vis spectra were run on a Hitachi 260-10 and a Shimadzu UV-365 spectrophotometer, respectively.

Chemical reagents employed were purchased from Nacalai Tesque Inc., Kishida Chemical Co., Tokyo Kasei Co., Kanto Chemical Co., Wako Pure Chemical Industries, Alfa Products, and Aldrich Chemical Co. Solvents and commercially available materials including unsubstituted diaza-crowns **6**, **8**, and **10**, cryptand [2.2.2] **11**, and pyridino-crown **12** were used without additional purification. Furan-armed diaza-18-crown-6 **4** and pyridine-armed cyclam **13** were synthesized by methods described in the literature.[3c,10] All new compounds were confirmed as pure materials by TLC analysis and had correct elemental compositions determined by microanalysis (MES Testing & Research Centre Co., Tamano, Okayama) and high-resolution mass spectroscopy (Analytical Center, Department of Chemistry, Kyoto University). Melting points were measured on a Yanaco MP-3 micro-melting point apparatus and are uncorrected.

**Preparation of *N*,*N'*-Bis(2-pyridylmethyl)diaza-18-crown-6 (1).** A solution of diaza-18-crown-6 (**6**) (1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, 1 g, 3.81 mmol), triethylamine (5 g, 49.1 mmol), and 2-(chloromethyl)pyridine hydrochloride (1.6 g, 9.75 mmol) in ethanol (20 mL) was refluxed for 12 h and then extracted with chloroform. The organic phase was washed with water and dried over $Na_2SO_4$. The solvent was evaporated and the residue was chromatographed (alumina activated 200, Nacalai Tesque Inc., chloroform). Recrystallization from ether gave slightly yellowish crystals of the title product (60%): mp 62–63 °C; IR (Nujol) $\nu$ 1593, 1570, 1460, 1430, 1105, 1050, and 770 cm$^{-1}$; $^1$H NMR $\delta$ 2.88 (t, 8 H, 4 × $NCH_2CH_2$), 3.60 and 3.65 (s + t, 16 H, 8 × $OCH_2$), 3.86 (s, 4 H, 2 × $CH_2$-pyridine), 7.09, 7.53, and 8.47 (m, 8 H, 2 × pyridine-H). Anal. Calcd for $C_{24}H_{36}N_4O_4$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.52; H, 8.09; N, 12.23.

***N*,*N'*-Bis(4-pyridylmethyl)diaza-18-crown-6 (2)** was similarly prepared from diaza-18-crown-6 (**6**) and 4-(chloromethyl)pyridine hydrochloride (72%): mp 60–61 °C; IR (Nujol) $\nu$ 1595, 1455, 1105, and 795 cm$^{-1}$; $^1$H NMR $\delta$ 2.82 (t, 8 H, 4 × $NCH_2CH_2$), 3.60 and 3.62 (s + t, 16 H, 8 × $OCH_2$), 3.71 (s, 4 H, 2 × $CH_2$-pyridine), 7.27, 7.34, 8.48, and 8.55 (m, 8 H, 2 × pyridine-H). Anal. Calcd for $C_{24}H_{36}N_4O_4$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.71; H, 8.01; N, 12.47.

***N*,*N'*-Bis(2-quinolylmethyl)diaza-18-crown-6 (3)** was prepared from diaza-18-crown-6 (**6**) and 2-(chloromethyl)quinoline hydrochloride (45%); mp 86–87 °C; IR (Nujol) 1600, 1460, 1105, 1050, and 765 cm$^{-1}$; $^1$H NMR $\delta$ 2.93 (t, 8 H, 4 × $NCH_2CH_2$), 3.60 and 3.67 (s + t, 16 H, 8 × $OCH_2$), 4.02 (s, 4 H, $CH_2$-quinoline), 7.26–8.05 (m, 12 H, 2 × quinoline-H). Anal. Calcd for $C_{32}H_{40}N_4O_4$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.42; H, 7.31; N, 10.03.

***N*,*N'*-Bis(2-pyridylmethyl)diaza-15-crown-5 (7)** was obtained from diaza-15-crown-5 (**8**) and 2-(chloromethyl)pyridine hydrochloride (yellow oil, 55%): IR (neat) 1593, 1437, 1108, 1045, 783, and 755 cm$^{-1}$; $^1$H NMR $\delta$ 2.85 and 2.88 (t + t, 8 H, 4 × $NCH_2CH_2$), 3.62 (s + t, 12 H, 6 × $OCH_2$), 3.84 (s, 4 H, 2 × $CH_2$-pyridine), 7.09, 7.59, 8.48 (m, 8 H, 2 × pyridine-H). HRMS (*m/e*) calcd for $C_{22}H_{32}N_4O_3$ 400.2474, found 400.2475.

***N*,*N'*-Bis(2-pyridylmethyl)diaza-21-crown-7 (9)** was prepared from diaza-21-crown-7 (**10**) and 2-(chloromethyl)pyridine hydrochloride (yellow oil, 45%): IR (neat) 1593, 1415, 1103, 780, and 755 cm$^{-1}$; $^1$H NMR $\delta$ 2.87 (t, 8 H, 4 × $NCH_2CH_2$), 3.59–3.70 (m, 20 H, 10 × $OCH_2$), 3.88 (s, 4 H, 2 × $CH_2$-pyridine), 7.05–8.53 (m, 8 H, 2 × pyridine-H); HRMS (*m/e*) calcd for $C_{26}H_{40}N_4O_5$ 488.2998, found 488.2998.

**Measurement of Binding Constant.** The stability constants for $Na^+$ and $Ca^{2+}$ ions were determined on Orion 97-11 and 93-32 ion-selective electrodes, respectively, in $H_2O$ at ambient temperature. The emf was measured with a DKK IOC-10 ion meter. The procedures used were those described by Frensdorff.[12] The stability constants for $Cu^{2+}$ ion were evaluated by a displacement method in $H_2O$, because their values were too high to be determined by a $Cu^{2+}$ ion-selective electrode. Typically, an aqueous solution of diaza-18-crown-6 **6** was added to a solution of $Cu(ClO_4)_2$ and pyridine-armed diaza-crown ether **1**, and the progress of the displacement was followed spectrophotometrically (at 750 nm). The calculation method was the same as that described by Shinkai et al.[13] Reproducibility was confirmed as ±0.2 (log scale).

**Transport Experiments.** Transport experiments were performed at room temperature (ca. 16 °C) in a U-tube glass cell (2.0 cm i.d.).[2] The ionophore, dissolved in methylene chloride, was placed in the base of the U-tube, and two aqueous phases were placed in the tube arms, floating on the methylene chloride membrane phase. The membrane phase was constantly stirred with a magnetic stirrer. The transport rates indicated in Table III were calculated from the initial rates of appearance of co-transported $ClO_4^-$ anion into aqueous 2 phase, which was determined by a $ClO_4^-$ ion-selective electrode (Orion 93-81). The transported amount of each guest cation was also determined by atomic absorption and flame spectroscopic methods (carried out at Exlan Technical Center Co., Okayama) and was almost equal to that of the co-transported anion. We confirmed that all guest salts were rarely transported in the absence of ionophore (transport rate $< 0.3 \times 10^{-6}$ mol/h).

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**Supplementary Material Available:** $^{13}$C and $^1$H NMR spectra for compounds **7** and **9** (4 pages). Ordering information is given on any current masthead page.

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(12) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600.

(13) Shinkai, S.; Koreishi, H.; Ueda, K.; Arimura, T.; Manabe, O. *J. Am. Chem. Soc.* **1987**, *109*, 6371.