New "Open-Chain Cryptands" with Specific Ion Transport Abilities

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Abstract: A new family of macrocyclic polyethers and polyamines
having pendant "arms" available for cation binding were prepared
and examined as synthetic ion carriers. They offered characteristic
cation transport phenomena, based on their unique ligand topology.
By appropriate choice of parent macrocyclic ligand and pendant donor
group, specific transport of K^+, Ba^{2+}, Pb^{2+}, and NH_4^+ cations was
realized.

1. Introduction

Several types of synthetic macrocyclic host molecules have been
developed, which mimic the biological cation transport phenomena.[1] In
particular, cryptand molecules are well-recognized as specific carriers
for alkali and alkaline earth cations. They offer highly stable and
selective complexation as well as effective shielding of complexed
guest cations. However, further dynamic complexing properties of the
potential carriers (effective binding and rapid releasing) are required
to realize efficient transport as observed in the naturally occurring
ion carrier systems.

Here we present a new family of "open-chain cryptands" showing
specific cation transport abilities, which are characterized by parent
macrocyclic ligands (polyethers and polyamines) and ligating pendant
donor arms. They are expected to wrap around the guest cations in such
a way that pendant groups on their side arms would provide further
coordination to the guest cations trapped into the parent macrocycles.
Although their complex structures, based on three-dimensional ligand
topology, are somewhat similar to those of cryptand systems, higher
mobilties of the pendant arms attached to the macrocycles may permit the
highly dynamic cation binding that is required for efficient cation
transport.

We prepared two typical examples of "open-chain cryptands" ——
"double armed crown ethers"[2] and "multi-armed cyclams"[3]—— and examined
them in a bulk liquid membrane system. Some kinds of armed macrocycles
have been reported,[4] but we know only a few examples of effective

cation carriers. Hence, the present study can provide new possibilities in modelling biomembrane transport systems as well as in designing specific host molecules.

2. Experimental

2. 1. Materials

"Double armed crown ethers" were prepared from corresponding di-azacrown ethers (Kryptofix 21, 22, and 23, Merck Japan).[2] Typically, Kryptofix 22 (1,7,10,16-tetraoxa-4,13-diazacyclooctadecane) was condensed with 2-furoyl chloride, and the resultant diamide was reduced by diborane in THF. Recrystallization from CH_2Cl_2-hexane gave white crystals 4. Mp, 37-38°C. Elemental analysis: Calcd.; C 62.54, H 8.11, N 6.63. Found; C 62.76, H 7.91, N 6.86. ^{1}H-NMR ($CDCl_3$, ppm from Me_4Si) 2.80 (8H) 3.67 (20H) 6.27 (4H) 7.40 (2H).
Crown ethers 2, 3, 5, and 6 were similarly obtained. The structures of the prepared "double armed crown ethers" are shown in Figure 1.
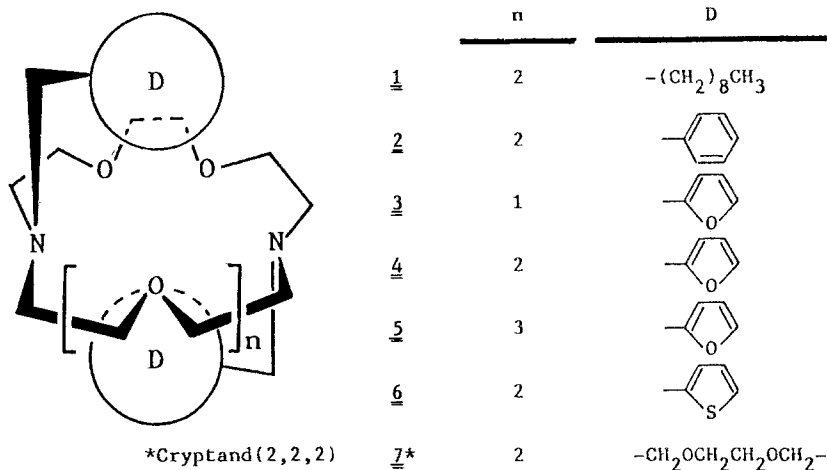

	n	D
1	2	$-(CH_2)_8CH_3$
2	2	
3	1	
4	2	
5	3	
6	2	
Cryptand(2,2,2) 7	2	$-CH_2OCH_2CH_2OCH_2-$

Figure 1. "Double Armed Crown Ethers"

"Multi-armed cyclams" were also obtained from cyclam (Strem).[3] Cyclam (1,4,8,11-tetraazacyclotetradecane) was condensed with 2-furoyl chloride, and the resultant tetraamide was reduced by diborane in THF. Recrystallization from ether-hexane gave colorless crystals 9. Mp, 83-84°C. Elemetal analysis: Calcd.; C 69.20, H 7.74, N 10.76. Found; C 69.25, H 7.70, N 10.88. ^{1}H-NMR ($CDCl_3$, ppm from Me_4Si) 1.67 (4H) 2.60 (16H) 3.67 (8H) 6.17 (4H) 6.40 (4H) 7.43 (4H).

Simple macrocyclic polyamine 8 and polyamide 10 were also employed for comparisons (see Figure 2).
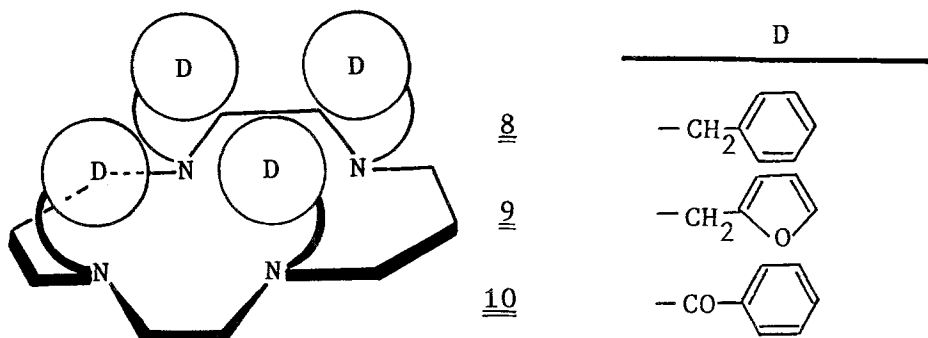
Figure 2. "Multi-Armed Cyclams"

2. 2. Transport Experimental Procedure

Cation transport experiments were performed in a U-tube glass cell (2.0 cm, i.d.) as reported before.[5] The carrier in CH_2Cl_2 or $CHCl_3$ (12 ml) was placed in the base of the U-tube, and two aqueous phases (5 ml, each) were placed in the arms of the U-tube, floating on the membrane phase. The membrane phase was stirred constantly with a magnetic stirrer. The transport rates were calculated from the initial rates of appearance of guest cations and cotransported anion (ClO_4^-) into the receiving aqueous phase, which were determined by means of ion selective electrodes (Orion Model 92-32 for Ba^{2+}; 94-82 for Pb^{2+}; 95-12 for NH_4^+; 93-19 for K^+; 93-81 for ClO_4^-).
Under the employed conditions, H^+-leakage was usually negligible. Reproducibility was confirmed as ±15 per cent or better.

3. Results and Discussions

3. 1. Membrane System

The liquid membrane system operated here is shown schematically in Figure 3. The employed carriers are much less soluble in the aqueous solution than in the CH_2Cl_2 or $CHCl_3$ "membrane". After complexation of the carrier with metal cation on the left side of the membrane, the complex slowly diffuses down its concentration gradient, together with cotransported anion. On the right side of the membrane, matal cation is released into the receiving aqueous phase. Then free carrier diffuses back across the membrane. The net result is that metal cation is transported across a bulk liquid membrane, with cotransported anion. Although the nature of cotransported anion largely influenced the cation transport process,[6] ClO_4^- anion was generally effective as a cotransported anion for providing fast cation transport.
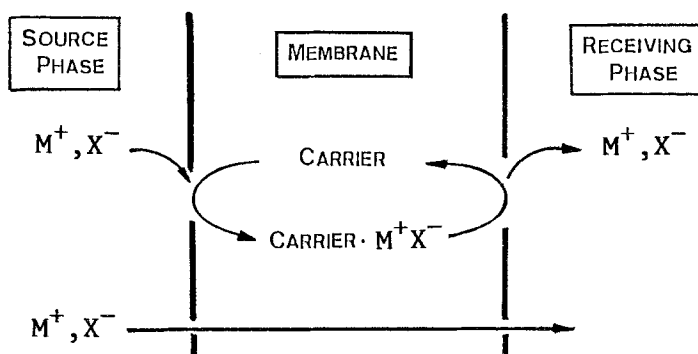
Figure 3. Liquid Membrane for Cation Transport
(M^+:Guest Cation; X^-:Cotransported Anion)

3. 2. Transport Properties of "Double Armed Crown Ethers"

The "double armed crown ether" $\underline{4}$, bearing furan rings as secondary oxygen donor groups, transported K^+ ion much more effectively than corresponding diazacrown ethers $\underline{1}$ and $\underline{2}$ (Table 1). Its oxygen donor groups on both arms clearly enhanced complexing and transporting abilities for K^+ ion. Cryptand $\underline{7}$, which forms a highly stable and static complex with K^+ ion, showed lower transport efficiency than the carrier $\underline{4}$. The present result strongly suggests that cation binding property of the carrier $\underline{4}$ would be dynamic as observed with single armed crown ethers (so-called "lariat ethers"), though the carrier $\underline{4}$ has a three-dimensional ligand topology.

Table 1. Membrane Transport of Alkali Metal Cations

Carrier	Transport Rate x 10^6 (mol/h)				
	Li^+	Na^+	Ag^+	K^+	Cs^+
$\underline{1}$	0.22	0.24	0.68	2.16	0.29
$\underline{2}$	0.20	0.23	1.62	0.97	0.33
$\underline{4}$	0.16	0.78	1.68	7.52	0.92
$\underline{6}$	0.23	0.23	*	2.59	0.56
$\underline{7}$	0.84	6.45	2.02	1.21	1.42

Transport Conditions: Source phase; Metal perchlorate(0.50 mmol)/ H_2O(5 ml). Membrane; Carrier (0.0372 mmol)/$CHCl_3$(12 ml). Receiving phase; H_2O(5 ml).

pH Values of the aqueous phases were ca.6 except for Pb^{2+} systems (pH ca. 3).

*Considerable amounts of Ag(0) were deposited on the cell wall.

Table 2. Membrane Transport of Alkaline Earth Cations

Carrier	Transport Rate $\times 10^6$ (mol/h)			
	Ca^{2+}	Sr^{2+}	Pb^{2+}	Ba^{2+}
1	0.23	0.23	2.32	3.76
2	0.27	0.25	9.09	0.53
4	0.16	1.37	8.17	12.50
6	0.26	0.32	16.00	1.86
7	0.75	2.85	1.63	7.33

Transport Conditions: see Footnote to Table 1.

Table 2 also shows that thiophene-bearing crown ether 6 is an excellent carrier for Pb^{2+} ion. The replacement of oxygen atoms in the carrier 4 by sulfur atoms in the carrier 6 decreased transport rates for hard K^+ and Ba^{2+} ions, but offered fast transport of soft Pb^{2+} ion. Since the coordination character of the pendant donor group clearly reflected on the cation transport properties, further modifications of "arm" donor groups may offer new and unique transport selectivities.
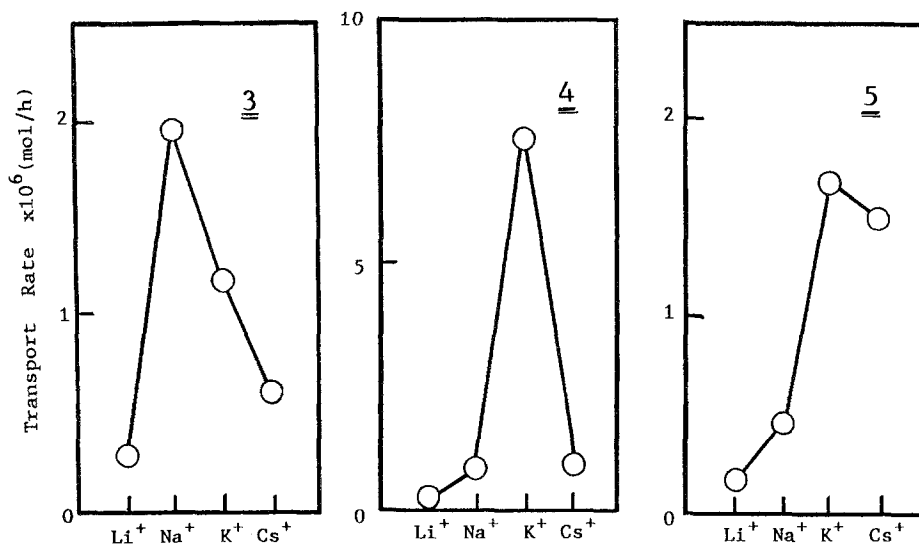

Figure 4. Relationship between Ring-Size of Parent Crown and Transport Efficiency

The ring size of the double armed crown ether was an essential factor determining transport properties. We examined furan-bearing crown ethers having 15- to 21-membered rings, $\underline{3} \sim \underline{5}$. As shown in Figure 4, they showed characteristic transport selectivities, depending on their ring sizes.[7] The carrier $\underline{3}$ with 15-membered ring effectively mediated Na$^+$ transport, while 21-membered crown ether $\underline{5}$ transported K$^+$ and Cs$^+$ ions with relatively high efficiencies. Therefore, the present transport process was significantly controlled by two factors at least: the cavity size of the parent crown ether ring and the nature of the arm coordination group.

Recently, "lariat ethers" and other single armed crown ethers have extensively been investigated.[8] They exhibited interesting cation binding and extracting profiles, based on their three-dimensional coordination geometry. Similar principles should be involved in the present "double armed crown ether" systems.

3. 3. Transport Properties of "Multi-Armed Cyclams"

As a new series of "open-chain cryptands", "multi-armed cyclams" were designed and employed in the cation transport experiments. Parent polyamine macrocycle (cyclam) is well known to show somewhat different cation binding properties from those of macrocyclic polyethers.[9] It effectively bind ammonium cations _via_ strong hydrogen bonding as well as transition metal cations _via_ coordination interaction. Hence, new "multi-armed cyclams" are expected to exhibit unique cation transport abilities. Their cation transport results are summarized in Table 3.

Table 3. Membrane Transport Mediated by "Multi-Armed Cyclams"

Carrier	Transport Rate x10^6(mol/h)				
	Na$^+$	K$^+$	NH$_4^+$	Ag$^+$	Cs$^+$
$\underline{8}$	0.05	0.07	1.19	0.35	0.15
$\underline{9}$	0.07	0.08	3.68	0.23	0.14
$\underline{10}$	0.10	0.09	1.12	0.30	0.57
DB18C6*	0.34	10.94	1.19	2.39	2.79

Transport Conditions: Source phase; Metal perchlorate(0.50 mmol)/ H$_2$O(5 ml). Membrane; Carrier(0.0372 mmol)/CH$_2$Cl$_2$(12 ml). Receiving phase; H$_2$O(5 ml).

*Dibenzo-18-crown-6 was employed in these cases.

"Multi-armed cyclam" $\underline{9}$ bearing furan oxygen atoms on its four arms mediated specific transport of NH_4^+ cation across a liquid membrane, while H^+, K^+, and other metal cations were hardly transported under the employed conditions. Since simple cyclam derivatives $\underline{8}$ and $\underline{10}$ exhibited low transport rates of NH_4^+ cation, the furan oxygen atoms attached to the cyclam ring may play an important role in complexation and transportation of NH_4^+ cation.

As well known, 18-crown-6 type carriers transported NH_4^+ cation but could not discriminate NH_4^+ cation from K^+ cation in the transport process. Furan-bearing double armed crown ether $\underline{4}$ also showed high transport efficiencies for both cations and seemed to be non-selective carrier in some sense.

Although the details of NH_4^+ cation binding and transport mechanism are not clear, NH_4^+ cation may be distinguished from K^+ cation not by "ion size" (NH_4^+ : 2.89 Å; K^+: 2.66 Å) but by "charge distribution" (NH_4^+ : tetrahedral; K^+: spherical).[10] Corey-Pauling-Koltun molecular model of carrier $\underline{9} \cdot NH_4^+$ cation complex suggests that NH_4^+ cation can be encapsulated, "tetrahedrally", donating two hydrogen bonds to two diametric ring nitrogen atoms as well as two furan oxygen atoms. Similar complex structure has been reported in the complex of 1,4,7,10-tetrahydroxyethyl-1,4,7,10-tetraazacyclododecane $\cdot H_2O$.[11]

4. Concluding Remarks

The "open-chain cryptands" represent an interesting class of host molecules, which combine both properties of parent macrocyclic system with those of arm donor groups. Our transport results clearly indicate that cooperative participation of side arm groups in the cation binding can offer complex of intermediate stability and microdynamic property, which are required for effective ion transport systems. Our present strategy in the design of specific host molecules may be applied to the open-chain cryptands based on thiamacrocycles, cyclophanes, and cyclic oligopeptides. A variety of new armed macrocycles are now being studied in our laboratory.

5. References and Notes

1) J.M.Lehn, 'Chemistry of Transport Processes : Design of Synthetic Carrier Molecules', Physical Chemistry of Transmembrane Ion Motion, Ed. by G.Spach, Elsevier Sci. Pub., 1983, p181.
2) H.Tsukube, 'Double Armed Crown Ethers With Specific Cation Transport Ability', J.Chem.Soc.,Chem.Commun., 315 (1984).
3) H.Tsukube, 'Multi-Armed Cyclam For Specific Transport of NH_4^+ Cation' Chem.Lett., in press.

4) Th.A.Kaden, 'Synthesis and Metal Complexes of Aza-Macrocycles with Pendant Arms Having Additional Ligating Groups', Topics in Current Chemistry, Vol.121, Ed. by F.L.Boschke, Springer-Verlag, 1984, p158.

5) H.Tsukube, 'Artificial Transport of Amino Acid, Oligopeptide, and Related Anions by Macrocyclic Polyamine·Transition Metal Complex Carriers', J.Chem.Soc.Perkin I, 29 (1983).

6) J.D.Lamb, J.J.Christensen, S.R.Izatt, K.Bedke, M.S.Astin, R.M.Izatt, 'Effects of Salt Concentration and Anion on the Rate of Carrier Facilitated Transport of Metal Cations Through Bulk Liquid Membrane Containing Crown Ethers', J.Am.Chem.Soc., 102, 3399 (1980): H.Tsukube, 'Effects of Cation on Transport Efficiency and Selectivity of Amino Acid Derivative Anions', Bull.Chem.Soc.Jpn., 56, 1883 (1983).

7) Cavity size of crown ether (diameter, $\mathring{A}$): 15-membered (ca. 2.0); 18-membered (ca. 2.9); 21-membered (ca. 3.9).
Ion diameter ($\mathring{A}$): Na^+(1.90); Ag^+(2.52); K^+(2.66); NH_4^+(2.84); Cs^+ (3.34).

8) D.M.Dishong, C.J.Diamond, M.I.Cinoman, G.W.Gokel, 'Syntheses and Cation Binding Properties of Carbon Pivot Lariat Ethers', J.Am.Chem. Soc., 105, 586 (1983).

9) H.Tsukube, 'Specific Cation Transport Ability of New Macrocyclic Polyamine Compounds', J.Chem.Soc.Chem.Commun., 970 (1983).

10) Another possibility is remaining at the present stage: NH_4^+ cation can be moved as free NH_3 and proton, which is bound to the basic polyamine macrocycle. But under the employed conditions (pH > 5), we confirmed that proton was not easily transported, together with ClO_4^- anion.

11) S.Buøen, J.Dale, P.Groth, J.Kran, '1,4,7,10-Tetrakis(2-hydroxy-ethyl)-1,4,7,10-tetraazacyclododecane: A Strong Cation Complexer', J.Chem.Soc.Chem.Commun., 1172 (1982).