© 1982 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 55, 3882—3886 (1982) [Vol. 55, No. 12

Pyridine-containing Acyclic Crown Ethers and Their Polymers as Specific Carrier of Biogenetic Amine Derivatives[1]

Hiroshi Tsukube

Department of Chemistry, College of Liberal Art and Science, Okayama University, Okayama 705

(Received June 26, 1982)

A variety of crown ethers and their analogs which contain powerful hydrogen bonding sites such as pyridine and quinoline moieties were examined as new synthetic carrier. Among the examined carriers, acyclic crown ethers and their polymers having pyridine groups were found to be selective and efficient carriers for some organic ammonium cations of great biological significances. Their transport properties were largely different from those of usual crown ether compounds, and essentially dependent on the combined characteristics of polyether sequence, hydrogen bonding site, co-transported anion, and others.

There has been much interest in synthetic cyclic and acyclic crown ethers[2] because of their unique coordination abilities. Various modifications have been made to the basic polyether structures and attained a variety of functions. In particular, introduction of donor atoms such as sulfur and nitrogen atoms provided stronger and interesting coordination properties for ammonium cations and transition metal ions.

Cram *et al.*[3] and Christensen *et al.*[4] have shown that pyridine-containing cyclic crown ethers such as **2** form more stable complexes with organic ammonium cations than corresponding parent crown ethers. Vögtle *et al.*[5] have also reported that quinoline-bearing acyclic crown ethers such as **4** show higher complex stabilities for ammonium cation complexes. These findings strongly suggest that pyridine nitrogen atoms of the cyclic and acyclic crown ethers can form stronger hydrogen bonding with guest ammonium hydrogen atoms than does as ether oxygen atoms.

Here we examine a variety of pyridine unit-containing polyethers ("pyridino-crown ethers") as artificial carrier in the chloroform liquid membrane system (see Fig. 1). They include cyclic crown ethers, acyclic crown ethers, and their polymers. Among them, acyclic crown ether **4**, containing quinoline-terminal groups, was found to discriminate some kinds of organic ammonium cations from K^+ ion in the transport process. Since such a unique transport selectivity was not attained by using cyclic crown ether compounds **1** and **2**, this is an important example of acyclic crown ether which shows more excellent property than corresponding cyclic crown ethers. Although some pyridino-crown ethers were known to effectively transport Ag^+[4] and Pb^{2+}[6] ions, a series of pyridino-crown ethers were firstly applied to the highly selective transport of "biogenetic amines and drugs" of great biological significances.[7]

Results and Discussion

Transport Properties of Cyclic and Acyclic Crown Ether Carriers (1—5). We measured the transport rates of several cations through a chloroform liquid membrane which contains one of the carriers **1**—**5** and which separates two aqueous phases. As shown in Fig. 1, guest cation salts are complexed with carrier and transported from aqueous phase I to an aqueous phase II using an experimental apparatus previously reported (see Experimental Section). Hence, the present transport process occurs by carrier-mediated facilitated diffusion along the concentration gradient of the guest salts.

Among the employed carriers (see Fig. 2), **2** and **4** contain nitrogen atoms as stronger hydrogen bonding sites for ammonium cations, and are expected to be an effective carrier of them. In particular, acyclic crown ether **4** provides interesting structural features:[5] (a) The quinoline moiety also functions as anchoring points with locally fixed donor sites on which guest cation can take hold; (b) The flexible nature of acyclic carrier can permit effective conformational changes in the binding and releasing processes, like as naturally occurring acyclic ionophores.[8] Recently a number of acyclic crown ethers have already been prepared as ionophore models, and most of them form pseudocyclic conformations on complexations of guest cations, which are stabilized by intramolecular interactions between two terminal groups. Since their transport selectivities may be determined by the sizes and shapes of the formed cavities, they may be similar to those observed in the cyclic crown ether systems.[2] In a marked contrast, the transport selectivity of the present carrier **4** can be controlled mainly by the nature of terminal donor group *via* terminal group-guest cation interaction. This is largely different from those of previously reported acyclic crown ethers. Hence, new and characteristic transport properties are expected by using this type of acyclic crown ether.

Other cyclic and acylic crown ethers (**1**, **3**, and **5**) were also examined for comparisons. Typical results of passive transport experiments are shown in Table 1. Blank experiments (no carrier present) were performed

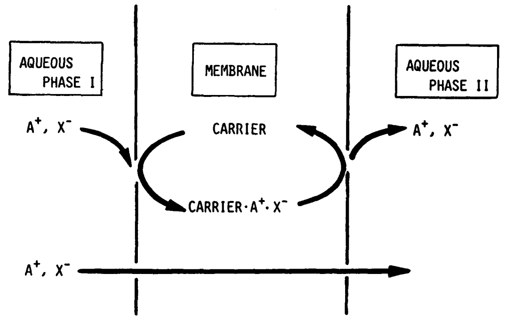


Fig. 1. Liquid membrane system for ammonium cation transport. A^+: Ammonium cation, X^-: cotransported anion.

TABLE 1. CATION-TRANSPORT MEDIATED BY CROWN ETHER CARRIERS (**1**—**5**)

Salt		Transport rate/10^{-6} mol h^{-1}				
		1	**2**	**3**	**4**	**5**
$LiClO_4$	(A)	0.5	0.2	1.5	0	0.1
$NaClO_4$	(A)	0.3	0.3	0.4	0.1	0.3
$KClO_4$	(A)	4.7	1.7	0.1	0.1	0.4
NH_4ClO_4	(A)	0.3	0.5	0.2	0.3	0.3
KCl	(B)	28.5	5.9	0.2	0.9	2.5
NH_4Cl	(B)	8.6	5.3	0.2	3.0	3.5
$C_6H_5\underset{CH_3}{CH}NH_3Cl$	(B)	11.6	10.0	1.0	10.7	3.9
$C_6H_5CH_2CH_2NH_3Cl$	(B)	12.9	12.2	1.2	12.5	8.6
$C_6H_5CH_2\overset{CH_3}{\underset{CH_3}{C}}\text{-}NH_3Cl$ (phentermine)	(B)	18.5	16.0	0.1	17.1	4.9
$C_6H_5\underset{OH}{CH}\underset{CH_3}{CH}NH_3Cl$ (norephedrine)	(B)	6.9	8.6	0.5	6.2	1.1
$(CH_3O)_2C_6H_3CH_2CH_2NH_3Cl$ (homoveratrylamine)	(B)	14.1	12.0	1.0	12.7	6.6
$HOC_6H_4CH_2CH_2NH_3Cl$ (tyramine)	(B)	1.4	1.0	1.0	0.6	0.2
$(HO)_2C_6H_3CH_2CH_2NH_3Cl$	(B)	1.0	0.1	0.3	0.2	0

Initial concentrations: aqueous phase I; salt, 0.3 mmol. Additive ($NaClO_4$), 0 mmol(A) or 1.5 mmol(B)/H_2O, 3 ml. Membrane; carrier, 0.0372 mmol/$CHCl_3$, 8 ml. Aqueous phase II; distilled water, 9 ml.

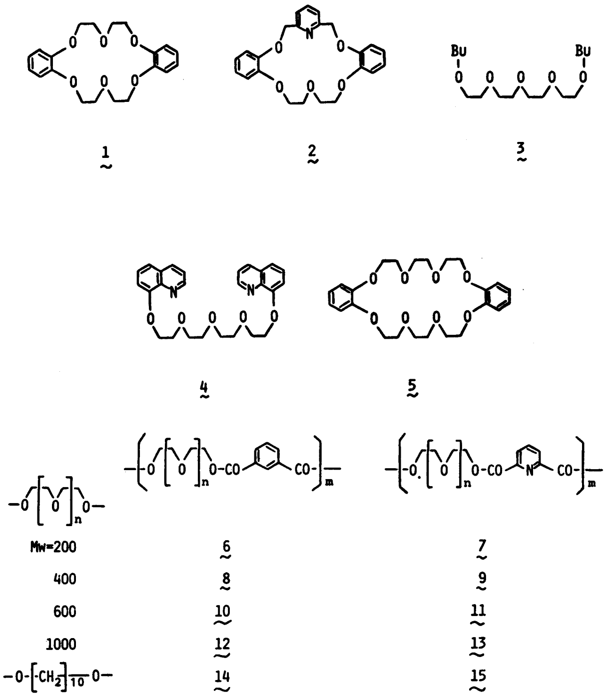


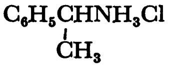
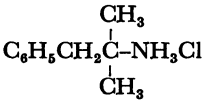
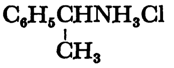
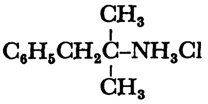
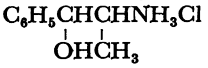
Fig. 2. Examined synthetic polyether carriers.

for each system to determine membrane leakages. The obtained amounts of cation leakages varied with used cations, but were generally much smaller than those indicated in Table 1.

Pyridino-crown ether **2** showed somewhat different transport behaviors from parent crown ether **1**. Although it has been reported that substitution of pyridine nitrogen for an oxygen in 18-crown-6 gives slight influences on the complex stabilities of K^+ and other cations, the transport rates of K^+ ion appreciably weakened in the carrier **2** system, while organic ammonium cation-transport rates were slightly influenced. These facts clearly indicate that pyridine nitrogen atom plays a more significant role in the transport of organic ammonium cations than in the transport of K^+ ion. Probably hydrogen bonding between pyridine nitrogen and guest ammonium cations would be effectively operated.

A pronounced effect of introducing donor sites into the carrier on the transport properties was observed in the quinoline-bearing acyclic crown ether **4** system. The carrier **4** was found to be an effective and selective carrier of some organic ammonium cations, compared to the cyclic crown ethers (**1** and **2**). Acyclic crown ether **4** preferentially transported several biogenetic amines and drugs of great significance such as phentermine, norephedrine, and homoveratrylamine. In marked contrast, cyclic crown ethers were confirmed to effectively transport a variety of ammonium cations as well as K^+ ion as reported before. Although Vögtle *et al.* have demonstrated that this type of acyclic crown ethers complex with a number of cations such as Li^+, Na^+, K^+, and others,[5)] it was firstly found to show highly discriminative transport abilities for ammonium cations. Therefore, this is an important example of acyclic crown ether which shows more excellent functions than corresponding cyclic crown ether. As well-known, nigericin, monensin, and other acyclic bioionophores change their conformations on guest complexations, and form "pseudocyclic conformations."[8)] This affects not only the rates of complexation and of decomplexation, but also transport selectivities. These coordination behaviors of naturally occurring antibiotics could be mimicked in the present artificial system. Quinoline-nitrogen atoms of the carrier **4** can act as stronger hydrogen bonding sites, and their coordination to the

TABLE 2. CATION-TRANSPORT MEDIATED BY ACYCLIC CROWN ETHER POLYMERS

Salt	Transport rate/10^{-6} mol h^{-1}				
	Acyclic crown ether polymer system				
	6	**8**	**10**	**12**	**14**
KCl	0	0.1	0.1	0.2	0
NH_4Cl	0	0	0.1	0.1	0
 $C_6H_5\underset{CH_3}{\underset{\mid}{C}}HNH_3Cl$	0.2	1.1	2.5	5.8	0.4
 $C_6H_5CH_2\overset{CH_3}{\overset{\mid}{\underset{CH_3}{\underset{\mid}{C}}}}-NH_3Cl$	0.7	1.6	2.4	6.1	0.6
 $C^6H_5\underset{OH}{\underset{\mid}{C}}H\underset{CH_3}{\underset{\mid}{C}}HNH_3Cl$	0.6	0.6	1.1	2.2	0.6
$(CH_3O)_2C_6H_3CH_2CH_2NH_3Cl$	0.4	2.6	4.5	11.7	0
$HOC_6H_4CH_2CH_2NH_3Cl$	0	0	0	0.1	0
	Pyridino-crown ether polymer system				
	7	**9**	**11**	**13**	**15**
KCl	0	0.2	0.1	0.2	0
NH_4Cl	0	0.2	0	0.2	0
 $C_6H_5\underset{CH_3}{\underset{\mid}{C}}HNH_3Cl$	1.2	1.6	2.8	6.4	0.6
 $C_6H_5CH_2\overset{CH_3}{\overset{\mid}{\underset{CH_3}{\underset{\mid}{C}}}}-NH_3Cl$	0.2	6.8	9.0	7.0	4.3
 $C_6H_5\underset{OH}{\underset{\mid}{C}}H\underset{CH_3}{\underset{\mid}{C}}HNH_3Cl$	0.3	0.8	1.0	2.3	0.4
$(CH_3O)_2C_6H_3CH_2CH_2NH_3Cl$	2.3	2.8	5.5	12.2	0.8
$HOC_6H_4CH_2CH_2NH_3Cl$	0	0	0	0	0

Initial concentrations: carrier, 0.0372 mmol/Ph or Py unit base. Other conditions, See Table 1 (B).

ammonium cations may induce the conformational changes of the carrier, promoting the successive interactions of polyether sequence with ammonium cations. Butyl-bearing acyclic crown ether **3**, which has similar polyether linkages to the carrier **4**, was confirmed to hardly transport ammonium cations and other metal ions. Therefore, attachment of quinoline moiety as terminal groups to the open polyether chain can offer both high efficiencies and excellent selectivities in the transport phenomena. In particular, it was noted that such a higher transport selectivity could not be attained in the cyclic crown ether systems.

The larger ring crown ether **5** with higher flexibility was also attempted as membrane carrier. It exhibited relatively higher transport selectivity for ammonium cations than the 18-membered crown ether **1**, even though its transport rates were modestly lower. This fact may suggest that molecular flexibility of the carrier is an another important factor to design a selective carrier for ammonium cation salts.

The employed crown ether carriers (**1**, **2**, **4**, and **5**) showed similar cation selectivities for a series of organic ammonium cations. As substrates, we chose a variety of phenethylammonium salts to which the biogenetic amines and drugs of great biological importance belong. Their transport efficiencies were clearly dependent on the hydrophobicities of the guest cations: phentermine> phenethylamine> norephedrine> tyramine> dopamine. Inorganic cation, NH_4^+, was found to be hardly transported because of its higher hydrophilicity.[10] Lehn *et al.* have studied crown ether-mediated transport of a similar series of phenethylamine salts,[7] and found that substitution beyond the nitrogen atom of the phenethylamine diminishes the transport rates: phentermine< phenethylamine. Although the natures of employed crown ethers were somewhat different, the results obtained here demonstrate that the hydrophobicity of the guest cation is more essential factor to determine the transport rate than the steric hindrance around the coordination site. Other experiments show that this type of carrier appeared of little use for hydroxy group containing ammonium cations such tyramine and dopamine derivatives. Probably, hydroxy group would enhance the hydrophilicity of the cation and occupy the coordination site of the carrier for ammonium cation hydrogen atom.

Transport Properties of "Acyclic Crown Ether Polymers." The polymer carriers, in which pyridine unit and acyclic crown ether moiety were incorporated, were applied to the membrane transport of ammonium cation salts. Many investigators have already prepared a variety of polymers which contain the crown ether units in the main chain and/or side chain. The former shows a parallel cation coordination property to that of monomeric analog,[11] while the latter favors the formation of the sandwich-type 2 : 1 crown ether/guest cation complexes.[12] Since they are mostly limitted to the cyclic crown ether polymers, the present study will present interesting examples of "acyclic crown ether polymers" as cation-carrier.[13] Transport experiments were performed in a similar cell as described above, and the typical results are summarized in Table 2.

Table 2 shows that an increase in the number of ether oxygen atoms raises the transport efficiencies. Polymer carriers (**14** and **15**) having no ether oxygen atom were confirmed to exhibit lower transport rates than other polymer carriers (**6**—**13**). Hence, coordination properties of acyclic crown ether moieties can be significantly involved in the present transport system. Chaput *et al.*[14] have measured the complex stability constants of monomeric "acyclic crown ethers" of various polyether chain lengths for alkali metal cations, and observed a similar relationship between number of ether oxygen atoms and complex stabilities. Therefore, this may be characteristic behaviors of acyclic crown ether families.

Introduction of pyridine moiety into the polymer carrier also allows effective transport of organic ammonium cation salts. Since pyridine-containing polymer carriers (**7**, **9**, **11**, and **13**) offered higher transport abilities for some organic cations, same factors would be involved to determine the transport behaviors both in crown ether system and in crown ether polymer system.

Acyclic crown ether polymers (**6**, **8**, **10**, and **12**) showed somewhat effective transport of organic ammonium cations, though their transport abilities were generally lower than those of pyridine-containing polymers (**7**, **9**, **11**, and **13**). These facts may suggest that effective interaction between aromatic moieties of guest cation and of polymer carrier can attribute the higher stability of ammonium cation-carrier complex. Similar observations have been reported in the cyclic crown ether systems.[15]

Anion Effects on Transport Rates. Recently some investigators have demonstrated that the rates of cation-transport by using crown ethers are largely influenced by the natures of anion species which accompanies the guest cation-crown ether complex. Lamb *et al.* revealed an empirical correlation between transport rate of alkali metal cation and anion hydration energy.[16]

By using four kinds of crown ether compounds (**1**, **4**, **10**, and **11**) the transport rates of phentermine ammonium cation were determined in the presence of several inorganic anions. The obtained results, listed in Table 3, indicate that the anion has a large effect on the rate of cationt-ran sport mediated by acyclic crown ethers as well as by cyclic crown ethers. It was clearly demonstrated that perchlorate and thiocyanate anions allow faster transport of ammonium cation than carbonate, sulfate, and chloride anions, suggesting that similar factors determined transport behaviors both in the crown ether system and in the crown ether polymer system.

Table 3. Anion effect on transport rate of phentermine ammonium cation

Anion	Transport rate/10^{-6} mol h^{-1}			
	1	**4**	**10**	**11**
ClO_4^-	18.5	17.1	2.4	9.0
SCN^-	14.1	19.4	7.2	12.0
CO_3^{2-}	1.7	0.4	0.5	0.5
SO_4^{2-}	0.9	0.2	0.3	0.5
Cl^-	0.9	0.9	0.4	0.4

Initial concentrations: additive (Sodium salt of anion), 1.5 mmol/aqueous phase I. Other conditions: See Table 1.

Experimental

Polymer Carrier Synthesis. The polymer carriers (**6**, **8**, **10**, and **12**) were prepared from isophthaloyl dichloride and corresponding polyethylene glycols. Typically, the carrier **12** was obtained by the reaction of isophthaloyl dichloride (0.01 mol), polyethylene glycol, Mw=1000, (0.01 mol), and pyridine (0.02 mol) in chloroform (100 ml) at 60 °C. After 15 h's refluxing, reaction solution was washed with water repeatedly. White wax polymer was obtained (65% yield) by removal of chloroform and dried *in vacuo*. The other polymers (**7**, **9**, **11**, **13**, **14**, and **15**) were similarly prepared. Some characteristic properties of them are summarized in Table 4.

Transport Experiments. The transport experiments were performed at room temperature in a similar apparatus as described before.[17] A cylindrical glass cell (4.0 cm, i.d.) holds a glass tube (2.0 cm, i.d.) which separates two aqueous phases. Typically, the inner aqueous phase (aqueous phase I) contains ammonium cation salt and additive such as $NaClO_4$ in 3 ml of water. The aqueous phase II, outer aqueous phase› contains 9 ml of distilled water. The membrane phase (8 ml of chloroform), in which carrier is dissolved, lies below two aqueous phases, and bridges them. This membrane phase is stirred constantly by magnetic stirrer. A similar experiment was carried out in the absence of carrier. The ammonium cation concentration in the aqueous phase II, monitored spectroscopically, was confirmed to increase linearly with running time (<12 h), and the initial transport rates were calculated. The values indicated in Tables 1, 2, and 3, were estimated from the differences in the transport rates of carrier-containing systems and blank systems (no carrier present).

The co-transported anion was also observed to move from aqueous phase I to II. When the perchlorate anion was employed as symport anion, we found that the amount of

Table 4. Characterizations of acyclic crown ether polymers

Carrier	Yield/%[a]	$\nu_{C=O}$/cm^{-1} [b]	Mw[c]	Remark
6	68	1720	1800	Oil
7	60	1730	1700	Powder
8	66	1720	2000	Oil
9	62	1737	2000	Wax
10	61	1717	3000	Oil
11	60	1727	3000	Wax
12	65	1720	4000	Wax
13	60	1739	4000	Wax
14	66	1722	1500	Powder
15	60	1732	1500	Powder

a) Yield of chloroform-soluble fraction was shown. b) Nujol mull (cm^{-1}). c) Determined by GPC (column; Shodex GPC A-803). Calibration was made with standard polystyrene samples.

perchlorate anion transported, determined by Methylene Blue method,[18] was almost equal to that of ammonium cation transferred under the employed conditions. The detailed conditions were shown in Tables.

References

1) Preliminary communication: H. Tsukube, *Tetrahedron Lett.*, **23**, 2109 (1982).

2) For review: E. Weber and F. Vögtle, "Topics in Current Chemistry," 98, Springer-Verlag, Berlin, Heidelberg, New York (1981), p. 1. Recent reports on "cyclic crown ether"-type carriers: J. D. Lamb, J. J. Christensen, S. R. Izatt, K, Bedke, M. S. Astin, and R. M. Izatt, *J. Am. Chem. Soc.*, **102**, 3399 (1980). S. Shinkai, T. Minami, Y. Kusano, and O. Manabe, *ibid.*, **104**, 1967 (1982). H. Tsukube, *Tetrahedron Lett.*, **22**, 3981 (1981). Recent reports on "acyclic crown ether"-type carriers: W. Wierenga, B. R. Evans, and J. A. Woltarson, *J. Am. Chem. Soc.*, **101**, 1334 (1979); K. Maruyama, H. Tsukube, and T. Araki, *ibid.*, **102**, 3246 (1980); N. Yamazaki, S. Nakahama, A. Hirao, and S. Negi, *Tetrahedron Lett.*, **1979**, 2429; K. Hiratani, *Chem. Lett.*, **1981**, 21.

3) M. Newcomb, J. M. Timko, D. M. Walba, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 6392 (1977).

4) J. S. Bradshow, G. E. Maas, J. D. Lamb, R. M. Izatt, and J.J. Christensen, *J. Am. Chem. Soc.*, **102**, 467 (1980).

5) B. Tümmler, G. Maass, E. Weber, W. Wehner, and F. Vögtle, *J. Am. Chem. Soc.*, **99**, 4683 (1977).

6) J. D. Lamb, R. M. Izatt, P. A. Robertson, and J. J. Christensen, *J. Am. Chem. Soc.*, **102**, 2452 (1980).

7) Some artificial carriers for selective transport of organic ammonium cations have been reported: E. Bacon, L. Jung, and J. M. Lehn, *J. Chem. Res.*, (S) **1980**, 136; K. Maruyama, H. Tsukube, and T. Araki, *J. Chem. Soc., Chem. Commun.*, **1980**, 1222.

8) F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, **18**, 753 (1976).

9) R. M. Izatt, J. D. Lamb, R. E. Asay, G. E. Maas, J. S. Bradshow, J. J. Christensen, and S, S. Moore, *J. Am. Chem. Soc.*, **99**, 6134 (1977).

10) J. W. Larsen and L. J. Magid, *J. Am. Chem. Soc.*, **96**, 5774 (1974).

11) S. Bormann, J. Brossas, E. Franta, P. Gramam, M. Kirch, and J. M. Lehn, *Tetrahedron*, **31**, 2791 (1975); E. Blasius and P. G. Maurer, *Makromol. Chem.*, **178**, 649 (1977).

12) J. Smid, A. Varma, and S. C. Shah, *J. Am. Chem. Soc.*, **101**, 5764 (1979).

13) Recently some "acyclic crown ether polymers" were employed as a specific anion carrier. See H. Tsukube, *J. Polym. Sci., Polym. Chem. Ed.*, **20**, 2982 (1982).

14) G. Chaput, G. Jeminet, and J. Juillard, *Can. J. Chem.*, **53**, 2240 (1975).

15) D. A. Laidler and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, **1977**, 481.

16) J. D. Lamb, J. J. Christensen, S. R. Izatt, K. Bedke, M. S. Astin, and R. M. Izatt, *J. Am. Chem. Soc.*, **102**, 3399 (1980).

17) K. Maruyama, H. Tsukube, and T. Araki, *J. Chem. Soc., Dalton Trans.*, **1981**, 1486; *J. Am. Chem. Soc.*, **104**, 5197 (1982).

18) D. F. Boltz, "Colorimetric Determination of Non-Metals," Interscience, New York (1958), p. 176.