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Studies on Synthetic Ionophores. VIII.1) Transport of Alkaline Earth Metal Ions by Polyether Carboxylic Acids through Liquid Membrane

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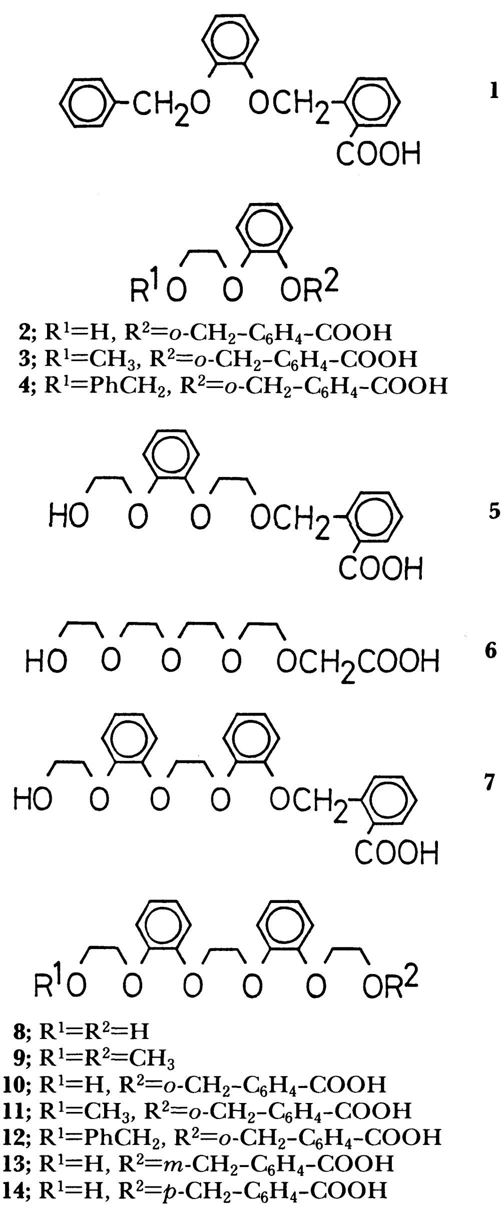
Seven ω-hydroxy carboxylic acids bearing 2—5 ether oxygens with or without aromatic rings and five ω-alkoxy carboxylic acids bearing 2—6 ether oxygens with aromatic rings were employed as carriers for the active transport of alkaline earth metal ions as well as alkali metal ions through 1,2-dichloroethane or 1-hexanol as an organic liquid membrane. The relatively hydrophobic ω-hydroxy and ω-alkoxy carboxylic acids ($\log P > 7$) exhibited a high M^{2+} transport ability and selectivity over M^+ through 1,2-dichloroethane, regardless of the number of ether oxygen. However, a marked selectivity among alkaline earth metal ions (Mg^{2+}, Ca^{2+}, Ba^{2+}) was not observed. The less hydrophobic carboxylic acids ($\log P < 6$) did not transport Ba^{2+} through 1,2-dichloroethane. Ba^{2+} transport ability of the hydrophobic acids through 1-hexanol was lower than that through 1,2-dichloroethane. Linoleic acid in the presence of oligo- and polyethylene glycols showed efficient Ba^{2+} transport through 1,2-dichloroethane, although a long-chain fatty acid was not able to transport Ba^{2+} by itself.

Naturally occurring carboxylic acid ionophores have ether linkages in the framework and hydroxyl group at the other end. The ionophore forms a pseudo-cavity by head-to-tail hydrogen bonding between carboxyl and hydroxyl groups. When the ionophore forms a salt with a cation, the cation is trapped in the cavity and is coordinated with ether oxygen atoms of ionophores. The cation was thereby lipophilized and transported through biological and organic liquid membranes.2) Each ionophore exhibits a particular ion selectivity. A few of the ionophores, such as lasalocid and A 23187, which are able to complex and transport divalent cations as well as monovalent ones, are called divalent polyether antibiotics.2,3) Their backbones are considerably shorter than those of monovalent polyether antibiotics. Despite the short chain length, the coordination of two ionophore anions to M^{2+} makes the complex lipophilic.

We synthesized polyether carboxylic acids, the structures of which were analogous to the natural carboxylic ionophores (as mentioned above). These synthetic ionophores were employed for the transport of alkali metal ions through an organic liquid membrane in order to investigate the relationship between the primary structures of ionophores and the transport ability and selectivity.1a,4) We report here the transport of alkaline earth metal ions by synthetic carboxylic ionophores with a variety of chain lengths, the carboxylic acid moiety at the terminal, and the structure at the other terminal. Although a few synthetic ionophores have already been reported for the transport of alkaline earth metal ions,5) the purpose of this study is to use a series of our synthetic carboxylic ionophores for the transport of divalent ions as well as monovalent ones for a comparison. The cooperative transport of alkaline earth metal ions with carboxylic acid and polyether in separate molecules is also described.



1

2; R^1=H, R^2=*o*-CH_2-C_6H_4-COOH
3; R^1=CH_3, R^2=*o*-CH_2-C_6H_4-COOH
4; R^1=$PhCH_2$, R^2=*o*-CH_2-C_6H_4-COOH

5

6

7

8; R^1=R^2=H
9; R^1=R^2=CH_3
10; R^1=H, R^2=*o*-CH_2-C_6H_4-COOH
11; R^1=CH_3, R^2=*o*-CH_2-C_6H_4-COOH
12; R^1=$PhCH_2$, R^2=*o*-CH_2-C_6H_4-COOH
13; R^1=H, R^2=*m*-CH_2-C_6H_4-COOH
14; R^1=H, R^2=*p*-CH_2-C_6H_4-COOH

Scheme 1. Polyether carboxylic acids.

Results and Discussion

Synthetic ionophores employed in this study are shown in the order of numbers of hydroxyl and ethereal oxygens in Scheme 1. Some of the compounds (**2**, **5**, **7**, **9**—**14**) have already been reported for the transport of alkali metal ions,[1a] and the rest of them (**1**, **3**, **4**, **6**, **8**) are newly synthesized for this study (as described in the experimental sections).

Transport of Alkaline Earth Metal Ions by Synthetic Carboxylic Ionophores. The stoichiometry of **10** and metal ions in chloroform was investigated (Fig. 1). It was revealed that at pH ca. 7, neither K^+ nor Ba^{2+} was incorporated into organic layer, but that at higher pH, 1 : 1 and 2 : 1 complexes of **10** were formed with K^+ and Ba^{2+}, respectively. Compound **10** containing one carboxyl group forms a neutral 1 : 1 complex of a potassium carboxylate, whereas divalent Ba^{2+} was complexed with two ionophore anions. This is consistent with the stoichiometry of complex for natural carboxylic ionophores.[3b,6] A 2 : 1 complex of ionophore and alkaline earth metal ion, where the cation is surrounded by two ionophore carboxylate molecules, is anticipated to be more hydrophobic than the corresponding 1 : 1 complex with alkali metal ion. This would result in an easy incorporation of M^{2+} into the organic layer, compared with M^+.

The competitive transport of alkali and alkaline earth metal ions by **10** and **7** through 1,2-dichloroethane was carried out as shown in Table 1. Both ionophores exhibited K^+ selectivity among Li^+, Na^+, and K^+, as previously reported.[1a] Divalent cations (Ba^{2+}, Ca^{2+}, and Mg^{2+}) were transported in preference to monovalent cations. Among the divalent cations, little selectivity was observed.

Through a 1-hexanol membrane mono- and divalent ions were transported by **10** (Table 2). Compared with 1,2-dichloroethane the 1-hexanol membrane lowered the transport ability and the selectivity of the ionophore. From these results, it can be presumed that the ionophore functions only as an anionic ligand of the carboxylate in 1-hexanol, and that a cation in the salt is solvated by 1-hexanol molecules instead of ether oxygens of the ionophore.

Ionophores which have fewer ether oxygens or fewer aromatic rings than **10** were employed for Ba^{2+} transport through 1,2-dichloroethane. Table 3 shows the results together with the hydrophobicity parameter ($\log P$) of the ionophores.[1a] Compounds with $\log P$ of less than 6 (**6**, **2**, **5**, and **3**) did not transport Ba^{2+}. Ionophores with $\log P$ greater than 7 (**1**, **4**, **7**, **10**) transported Ba^{2+}, except for linoleic acid. Even **1**, bearing only two ether oxygens, has a high transport ability. In the case of ionophores with a low $\log P$ value, the salt complex formed at the interface is too hydrophilic to diffuse into the organic layer. Compounds, **6**, **2**, **5**,

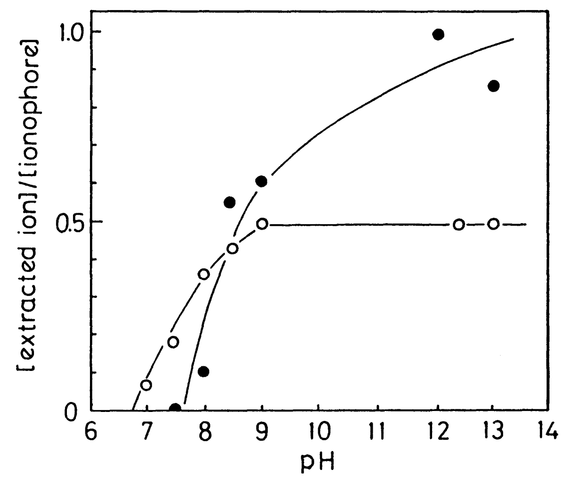


Fig. 1. Extracted amount of ions from aqueous solutions at various pH's to chloroform layer by **10**.
●: K^+, ○: Ba^{2+}

Table 1. Active Ion Transport by **10** and **7** through 1,2-Dichloroethane

Compound	Transported ion (%)[a]						
	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Ba^{2+}	total
10	—	—	11	—	—	82	93
	—	3	—	—	—	94	97
	0	—	—	—	—	100	100
	—	—	17	—	74	—	91
	—	2	—	—	86	—	88
	0	—	—	—	99	—	99
	1	—	—	75	—	—	76
	—	—	—	—	45	48	93
	—	—	—	35	—	44	79
	0	—	—	41	45	—	86
7	—	—	8	—	—	91	99
	—	—	—	—	52	41	93

a) No ion is transported without ionophore.

Table 2. Active Ion Transport by **10** through 1-Hexanol

Transported ion (%)[a]				
Li^+	Na^+	K^+	Ba^{2+}	total
22(7)	—	—	38(0)	60(7)
—	17(9)	—	50(4)	67(13)
—	—	26(13)	38(0)	64(13)

a) Values in parentheses are transported ion without **10**.

Table 3. Ba^{2+} Transport through 1,2-Dichloroethane Using Various Ionophores

Ionophore	$\log P$	Transported Ba^{2+} (%)
6	−1.2	0
2	4.4	4
5	4.4	0
3	5.1	0
1	7.2	100
4	7.3	100
7	7.5	100
10	7.6	100
Linoleic acid	7.3	0

Table 4. Active Ion Transport Using Various Compounds

Compound	Liquid membrane	Transported ion (%)		
		K^+	Ca^{2+}	Ba^{2+}
10	1,2-Dichloroethane	—	—	100
		—	67	—
		49	—	—
11		—	75	—
12		—	—	98
		—	75	—
13		—	—	91
		0	—	—
14		—	—	89
		0	—	—
Linoleic acid		—	—	0
		0	—	—
10	1-Hexanol	—	—	68
13		—	—	66
14		—	—	60
Linoleic acid		—	—	67

Table 5. Ba^{2+} Transport through 1,2-Dichloroethane Using Various Carboxylic Acids and **8**

Carboxylic acid	log*P*	Transported Ba^{2+} (%)
CH_3COOH	−0.2	0
$HOOC(CH_2)_4COOH$	0.7	0
PhCOOH	1.6	0
$CH_3(CH_2)_4COOH$	1.9	0
$CH_3(CH_2)_8COOH$	3.9	0
$CH_3(CH_2)_{10}COOH$	4.9	19
$CH_3(CH_2)_{12}COOH$	5.9	72
$CH_3(CH_2)_{14}COOH$	6.9	52
Linoleic acid	7.3	85

and **3** ($\log P<6$) are not sufficiently hydrophobic to be an ion carrier. For more lipophilic compounds ($\log P>7$) two ether oxygens are sufficient for Ba^{2+} transport.

Ba^{2+} and Ca^{2+} were transported separately through 1,2-dichloroethane by **10** and its analogues (Table 4). For a comparison, K^+ transport was also carried out. Compounds **11** and **12**, hydroxyalkylated derivatives of **10**, revealed a comparable transport ability to **10**. Compounds **13** and **14**, *m*- and *p*-substituted isomers of **10**, were employed for Ba^{2+} transport. While neither **13** nor **14** transported K^+, both ionophores exhibited as high a transport ability for Ba^{2+} as **10**. A 2 : 1 complex of ionophore and M^{2+} seems to have a less rigid structure than the 1 : 1 complex does.[1b)] In the 2 : 1 complex, ether oxygens of even *m*- and *p*-isomers are able to coordinate M^{2+} to be solubilized in the organic layer. These results show that if a ionophore has a carboxyl group and ether oxygens, the substituted position of the carboxyl group does not affect M^{2+} transport through 1,2-dichloroethane, in contrast to M^+ transport.

When 1-hexanol was used as a liquid membrane, linoleic acid had a similar transport ability to those of **10** and its isomers (Table 4). As mentioned above, the carboxylate anion of the ionophore interacts with the cation electrostatically and neither oxygens are very important for the transport of M^{2+}, compared to that of M^+. Water molecules are replaced out of the hydration sphere by 1-hexanol to solvate the divalent cation.

Transport of Alkaline Earth Metal Ions by Carboxylic Acids and Polyethers. As mentioned above, and reported previously,[1a)] **10** exhibited the ability to transport monovalent ions through 1,2-dichloroethane, while its *m*- and *p*-substituted isomers, **13** and **14**, transported no alkali metal ion. On the other hand, divalent ions were transported by both **10** and its isomers. For alkaline earth metal ion transport, the relative position of the carboxyl group of ionophore to polyether linkages should not be important. It was expected that a simple carboxylic acid could transport M^{2+} in the presence of another polyether molecule. When a mixture of linoleic acid and diol **8**, each of which could not transport M^{2+}, was employed, 85% of Ba^{2+} was transported through 1,2-dichloroethane at 35 °C for 5 days. Under the same conditions, no K^+ was transported. A mixed system of carboxylic acid and ether was found to transport M^{2+} selectively. A mixture of diol **8** with various carboxylic acids as well as linoleic acid was applied to the transport of Ba^{2+}. The results are shown in Table 5. The hydrophobicity of the acids corresponds to the transport ability. Hydrophilic acids such as acetic, adipic, benzoic, hexanoic, and decanoic acids did not transport Ba^{2+}. A long-chain fatty acid such as lauric, myristic, palmitic, and linoleic acids transported Ba^{2+} in the presence of **8**. The transported amount of Ba^{2+} increased with an increase in the lipophilicity at acids. Unless the carboxylic acid was fully hydrophobic, the mixed system of carboxylic acid and **8** had no transport ability. Barium salts of hydrophilic carboxylic acids should be dissolved in an aqueous layer. Even if the salt is coordinated with polyether at the interface, the complex is not sufficiently hydrophobic to be incorporated into the organic layer. On the other hand, barium salts of lipophilic acids stayed mainly at interface, then, the replacement of water molecules out of the hydration sphere by the oxygens of **8** dissolved Ba^{2+} into the organic layer.

The effect of the polyether structure on ion transport was examined. Ba^{2+} transport by using linoleic acid together with various polyether compounds is shown in Table 6. Glycols and their derivatives were used as polyether. Ba^{2+} was not transported by ethylene glycol and the transported amount of Ba^{2+} increased with an increase in the oxyethylene units. Since a short-chain glycol is, itself, slightly soluble in an organic solvent, the coordinated glycol with Ba^{2+} of the salt is not sufficiently lipophilic to be incorporated into the organic layer. However, a stable complex of the salt with a long-chain glycol, such as tetraethylene glycol and polyethylene glycols, results in an increase in Ba^{2+} transport. Methyl ether derivatives (diglyme, tetraglyme, and **9**) exhibited a much lower transport ability

Table 6. Ba^{2+} Transport through 1,2-Dichloroethane by Linoleic Acid and Polyethers

Polyether	Transported Ba^{2+} (%)
Ethylene glycol	0
Diethylene glycol	38
Diglyme	22
Triethylene glycol	33
Tetraethylene glycol	75
Tetraglyme	9
Poly(ethylene glycol) (M_n=1000)	96
Poly(ethylene glycol) (M_n=7500)	95
8	85
9	2

than the corresponding glycols. The terminal hydroxy groups of the glycols seem to play an important role in the transport of Ba^{2+}.

Experimental

Methods. IR spectra were run with a Jasco IR-G spectrophotometer. ^{1}H NMR spectra were recorded with a JEOL JNM-PMX 60 instrument. UV spectra were recorded on a Hitachi 124 spectrophotometer. Mass spectra were obtained on a Hitachi M-80 mass spectrometer operating at 30 eV. Elemental analyses were performed on a Yanaco Model MT-3. Atomic absorption and flame spectrochemical analyses were performed with Hitachi 170—30 Atomic Absorption Spectrophotometer.

Materials. Unless stated otherwise reagent grade reactants and solvents were obtained from commercial suppliers and used without further purification.

Compound **1** was synthesized from 2-benzyloxyphenol[7] and with methyl 2-bromomethylbenzoate similar to synthesis of **7** previously reported.[1a]

2-[2-(2-Benzyloxyphenoxy)methyl]benzoic Acid (1). Yield (0.70 g, 48%). IR(KBr) 1685 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=5.2 (s, 2H, benzyl), 5.6 (s, 2H, benzyl), 6.9 (s, 4H, phenylene), 7.2—8.3 (m, 9H, phenyl and aromatic of toluic acid). Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43%. Found: C, 75.60 ; H, 5.45%.

Compound **3** was prepared from **2** and methyl iodide and **4** was prepared from **2** and benzyl chloride by the same procedure as that for **11**.[1a]

2-[[2-(2-Methoxyethoxy)phenoxy]methyl]benzoic Acid (3). Yield (0.35 g, 75%). IR(KBr) 1715 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=3.45 (s, 3H, CH_3O), 3.83 (m, 2H, CH_2OMe), 4.20 (m, 2H, CH_2OAr), 5.51 (s, 2H, benzyl), 6.90 (s, 4H, phenylene), 7.3—8.1 (m, 4H, aromatic of toluic acid). High-resolution mass spectrum for $C_{17}H_{18}O_5$, Calcd 302.1154, Found 302.1116.

2-[[2-(2-Benzyloxyethoxy)phenoxy]methyl]benzoic Acid (4). Yield (0.13 g, 33%). IR(KBr) 1675 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=3.9 (m, 2H, CH_2), 4.3 (m, 2H, CH_2), 4.7 (s, 2H, benzyl), 5.6 (s, 2H, benzyl), 6.9 (s, 4H, phenylene), 7.3—8.3 (m, 8H, aromatic of toluic acid). Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86%. Found: C, 72.54; H, 5.81%.

14-Hydroxy-3,6,9,12-tetraoxatetradecanoic Acid (6). Small pieces of Na (9.2 g, 0.4 mol) were by portions added to tetraethylene glycol (120 ml) (distilled under reduced pressure) under a nitrogen atmosphere. The mixture was heated at 100 °C for 6 h. Chloroacetic acid (18.9 g, 0.2 mol) in tetraethylene glycol (40 ml) was added dropwise to the alkoxide solution and the mixture was heated at 100 °C for 3 h. Excess of tetraethylene glycol was distilled under reduced pressure. To the residue was added concd HCl (100 ml) to form a white precipitate. The solid was removed by suction and the filtrate was evaporated under reduced pressure to remove water and HCl. The residue was distilled under vacuum to afford **6** (30 g, 60%). Bp 148—151 °C/1 mmHg (1 mmHg=133.322 Pa). IR(neat) 1740 cm^{-1} (C=O); ^{1}H NMR (CD_3OD) δ=3.65 (m, 16H, $OC\underline{H}_2COOH$ and CCH_2OC), 4.19 (t, 2H, $C\underline{H}_2OH$, J=6 Hz). Calcd for $C_{10}H_{20}O_7$: C, 47.61; H, 7.99%. Found: C, 47.42; H, 8.27.

1,2-Bis[2-(2-methoxyethoxy)phenoxy]ethane (9). 1,2-Bis-[2-(2-hydroxyethoxy)phenoxy]ethane (3.4 g, 10 mmol) and 60% NaH (0.8 g, 20 mmol) in dry DMF (30 ml) were stirred at room temperature for 30 min. To this was added dropwise methyl iodide (2.9 g, 20 mmol) in dry DMF (20 ml); the mixture was stirred at room temperature for 2 h. DMF was removed in vacuo and the residue, dissolved in chloroform, was washed with water. The organic layer dried over sodium sulfate was evaporated and applied to a silica-gel column (chloroform/methanol=100/1) to afford 1,2-bis[2-(2-methoxyethoxy)phenoxy]ethane (2.9 g, 80%). ^{1}H NMR ($CDCl_3$) δ=3.40 (s, 6H, CH_3O), 3.73 (m, 4H, $OCH_2C\underline{H}_2OCH_3$), 4.16 (m, 4H, $OC\underline{H}_2CH_2OCH_3$), 4.38 (s, 4H, $ArOCH_2CH_2$), 6.90 (s, 8H, aromatic).

Stoichiometry of Complex of 10 and Metal ion in Chloroform. Chloroform saturated with water and water saturated with chloroform were used. A 10-ml chloroform solution of 5×10^{-5} mol of **10** and a 5-ml aqueous tris buffer solution (pH 7—9) containing $BaCl_2$ (0.05 M) or KCl (0.1 M) (1 M=1 mol dm^{-3}) in a 30-ml vial were vigorously shaken 60 times by hand. The vial was allowed to stand for 1 day in order to separate the organic layer from the aqueous layer. At higher pH, a metal hydroxide solution at an appropriate concentration was used instead of a tris buffer solution. A part of the organic layer (5 ml) was transferred to another 30-ml vial. To this was added a 5-ml HCl solution (0.2 M). The mixture was vigorously shaken 60 times by hand. The vial was allowed to stand for 1 day in order to separate the layers. The organic solution was diluted 100 times to determine the concentration of **10** by UV spectroscopy (273 nm). The aqueous solution was diluted 10 times to determine the concentration of K^+, or Ba^{2+} by flame spectrochemical analysis or atomic absorption analysis.

Ion Transport Experiment. Ion transport was carried out in U-type or H-type cells[4b] at 35±1 °C for 5 days with stirring at 200 rpm. Donor phase-I contains a 10-ml aqueous solution of an alkaline earth metal hydroxide (0.05 M). Acceptor phase -II contains a 10-ml aqueous solution of HCl (0.1 M) and an alkaline earth metal chloride (0.05 M). In the case of competitive ion transport, both the donor and acceptor phases also contain alkali or alkaline earth metal chlorides at the same concentration. Organic phase-III contains a 20-ml organic solution of a 10^{-4} mol carboxylic acid (and a 10^{-4} mol polyether). An aqueous solution at acceptor phase was diluted to an appropriate volume. The concentration of ions (10—100 ppm for M^+, 20—140 ppm for Ba^{2+} and Ca^{2+}, 1—20 ppm for Mg^{2+}) was determined to be c_0 and c_1 before and after the transport experiment by a flame spectrochemical analysis for alkali metal ions and by an atomic absorption analysis for alkaline earth metal ions. The transported ions (%) were calculated by $[(c_1-c_0)/c_0]\times100$.

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