Functions of Acyclic Poly(ethylene Oxide) Homologs: Acceleration of Nucleophilic Reactions and Selective Ion Transport through Membranes

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ABSTRACT

The acceleration effect of poly(ethylene oxide) on nucleophilic reactions was investigated. The enhancement of the reaction rate was interpreted by the cooperative solvation of alkali metal ions with ethereal oxygens of PEO resulting in active nucleophilic anions. In relation to the complex formation of alkali metal ions with PEO, the oligo(ethylene oxide) derivatives were prepared as the synthetic ionophores, which were able to transport alkali metal ions selectively through a liquid membrane against the alkali metal ion concentration.

INTRODUCTION

Ionophilic oligomers and polymers have attracted much attention due to their remarkable ability to form hydrophobic or lipophilic complexes with a variety of organic and inorganic cations. Since Brown discovered outstanding characters of glymes with the general formula, $CH_3O[CH_2CH_2O]_xCH_3$, with x = 1-6, as solvent in the borohydride reduction, it is well known that glymes are very effective alkali metal solvating reagents. Glymes have often been used to enhance the reactivities of organo alkali metal compounds and metal salts and have also been found to exert an acceleration effect on nucleophilic reactions [1, 2]. In particular, recently developed

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macrocyclic polyethers, cyclic derivatives of glymes, have revealed a remarkable enhancement of the reactivities of metal salts [3].

On the other hand, little attention has been paid to the effect of poly(ethylene oxide) (PEO) on the reactions. This seems to be curious, since PEO can be considered as a polymeric form of glymes or a polyglyme and the ability of glymes to coordinate cations depends on the number of available oxygen atoms and generally increases with the chain length of the corresponding glymes [4].

Recently, Panayotov and co-workers have reported that the ion dissociation of metal salts is greatly promoted by the presence of PEO [5, 6]. In connection with the progress of the chemistry of macrocyclic polyethers, the interaction of open-chain PEO derivatives with metal cations has attracted special interest, because of the strong coordinating powers [7] of these compounds.

We have found that the addition of a small amount of PEO causes a remarkable acceleration in several nucleophilic reactions such as oxidation with $KMnO_4$ and alkylations of metal salts with alkyl halides [8-10]. The acceleration effect of PEO is much greater than those of glymes in all the above reactions. It is of interest that their effects are comparable to those of dibenzo-18-crown-6, one of the most well known macrocyclic polyethers, under the certain conditions.

During the course of separate studies on cyclization of glymes, we have found that the cyclization took place with ease in the presence of alkali metal salts, such as lithium chloride and iodide. Complexes of the glymes with these salts, isolated as crystals from organic solutions, were very hygroscopic.

The structure of the complexes of acyclic oligoethylene glycol derivatives with alkali metal ions resembles closely those of alkali metal salts of the naturally occurring antibiotics nigericin and monensin, which can recognize alkali metal ions and play important roles in selective ion transportation through a lipid membrane.

Both nigericin and monensin, which are called carboxylic ionophores, are linear polyethers ranging in molecular weight from 600 to 700, with two hydroxy groups and a carboxy group at each end and are capable of forming macrocyclic rings by means of cooperative solvation of alkali metal ions with ethereal oxygens and end-to-end hydrogen bonds.

The important features of the antibiotics as alkali metal ion carriers are the following: the cooperative solvation of an alkali metal ion with ethereal oxygens facilitates cyclization of the polyether chain around a cation to form a lipid-soluble complex which carries an alkali metal ion through a lipid membrane and the selective complexation occurring on fitting of the diameter of an alkali metal ion to the inner diameter of the macroring formed. The other interesting property of these carboxylic ionophores is the active ion transport against the alkali metal ion concentration gradient.

TABLE 1. Oxidation of Trans-Stilbene with Potassium Permanganate (KMnO$_4$) in the Presence of PEO in Benzene at 25°C[a]

Additive	Amt (mmole)	Time (hr)	C$_6$H$_5$COOH (%)
	-	45	3
PEO	5.0	5	26
PEO	18.2	5	63
PEO	18.2	10	67
DB-18-C-6	18.2	10	48
Dicyclohexyl-18-crown-6			100[b]

[a]Conditions: trans-stilbene, 6.8 mmole; KMnO$_4$, 18.2 mmole; solvent, benzene (50 ml).
[b]Data of Sam and Simmons [17].

Recently syntheses of acyclic model compounds of the natural ionophores have been attempted [11, 12], and selective complex formation between the synthetic ionophores and alkali metal ions has been reported [13, 14]. Ion transportation by synthetic ionophores, however, has been known only with cyclic compounds, for instance, with cryptates [15] and cyclic polytetrahydrofuran [16].

In this paper we wish to review our recent studies which concern acceleration of some nucleophilic reactions with poly(ethylene oxide), and selective and active transport of metal ions with acyclic homologs of ethylene oxide.

ACCELERATION EFFECT OF POLY(ETHYLENE OXIDE) IN NUCLEOPHILIC REACTIONS

Oxidation of Trans-Stilbene with KMnO$_4$

The oxidation of trans-stilbene in benzene was markedly enhanced on addition of PEO (Table 1). When PEO was added to a mixture of KMnO$_4$ and benzene, a purple solution was immediately obtained like "purple benzene" which could be formed in the presence of crown ethers. This seems to indicate that KMnO$_4$ partly dissolves in benzene in the presence of PEO, probably yielding a soluble complex between KMnO$_4$ and PEO. This is also supported by the identity of adsorption

TABLE 2. Rates of Alkylation of Potassium Acetate (CH_3COOK) with Benzyl Bromide in Various Solvents[a]

Solvent	Rates in the presence of additives, (10^2 mole/liter-hr)			
	None (r_0)	DME	PEO (r_p)	r_0/r_p
Benzene	0	0	0.2	> 200
1,4-Dioxane	0	0	0.4	> 200
Tetrahydrofuran (THF)	0	0	1.5	> 200
THF/ethanol (85/15)	0.1	0.1	15	150
THF/ethanol (50/50)	2.2	3.0	20	9.1
Ethanol	5.0	5.0	25	5.0
1-Butanol	1.5	1.7	25	17
1,2-Dimethoxyethane	0.2	-	-	-

[a]Conditions: CH_3COOK, 5.0 mmole; $C_6H_5CH_2Br$, 2.5 mmole; additive 15 mmole; total volume, 10 ml; temperature 45°C.

bands in the visible spectrum of the purple solution at 507, 526, 547, and 569 nm with that of aqueous solutions of permanganate ion. Accordingly, the observed acceleration may be explained by the increased solubility of $KMnO_4$ in benzene. It has also been considered that the formation of free permanganate ion, resulting from the coordination of PEO to K^+, plays an important role in the acceleration as indicated in the studies of the crown ethers.

Studies by Sam et al. [17] have shown that the oxidation of trans-stilbene with dicyclohexyl-18-crown-6 under the same conditions affords benzoic acid in a quantitative yield, whereas 67% was obtained in the presence of PEO and 48% with dibenzo-18-crown-6 (DB-18-C-6) in our results. This is presumably due to the precipitation of the residual PEO-$KMnO_4$ complex coated with MnO_2 as a sticky gel during the course of the reaction. Hence, efficient and abrasive stirring should be required to obtain high yields as suggested by Sam et al. [17].

TABLE 3. Comparison of the Effect of PEO and DB-18-C-6 in Alkylation of CH_3COOK with n-C_4H_9Br[a]

Solvent	Temp (°C)	Rates in the presence of additives (10^2 mole/ liter-hr)	
		PEO	DB-18-C-6
THF	60	0.19	0.63
Ethanol	45	0.34	0.16
Ethanol	60	1.80	1.20

[a]Conditions: CH_3COOK, 5.0 mmole; C_4H_9Br, 2.5 mmole; additive, 15 mmole; total volume 10 ml.

Alkylation of Potassium Acetate and Diethyl Benzylsodiomalonate with Alkyl Bromides

The rates of alkylation of potassium acetate (CH_3COOK) with benzyl bromide in various solvents in the presence of PEO are summarized in Table 2. Marked acceleration effects by PEO expressed as r_p/r_0 were observed in benzene, 1,4-dioxane (DOX), tetrahydrofuran (THF), and THF-ethanol (85/15, v/v) mixed solvents. When alcoholic solution was used, the effect was comparatively low, its factor being only 5.0 in ethanol.

1,2-Dimethoxyethane (DME), a monomeric analog of PEO, shows only a slight effect in all runs. Even in DME solution, the rate was slower than in DOX and in THF-PEO systems. The rates of this reaction in the presence of DB-18-C-6 are approximately comparable with those with PEO (Table 3).

In the alkylation of diethyl benzylsodiomalonate with butyl bromide, the additive effect of PEO was much larger than that of DME, demonstrating again the superiority of the polymer over its monomeric analog (Tables 4 and 5). The effect of DB-18-C-6 appears more than ten times as large as that of PEO in this reaction.

Williamson Reaction of Sodium Phenolate with Alkyl Bromides

The rates of the Williamson reaction between sodium phenolate (PhONa) and butyl bromide in various solvents in the presence of

TABLE 4. Rates of the Alkylation of Diethyl Benzylsodiomalonate with Butyl Bromide in Various Solvents[a]

Solvent	Rates in the presence of additives (10^2 mole/liter-min)		
	None (r_0)	PEO (r_p)	r_p/r_0
THF	6.3	8.3	1.3
Benzene	0.24	3.8	14
Benzene/hexane (50/50, v/v)	0.10	5.5	55

[a]Conditions: diethyl benzylsodiomalonate 0.5 mmole; C_4H_9Br 5.4 mmole; PEO, 2.7 mmole; total volume, 20 ml; temperature, 30°C.

TABLE 5. Comparison of the Effects of Additives in the Alkylation of Diethyl Benzylsodiomalonate with n-C_4H_9Br[a]

Additive	Rate (10^5 mole/liter-min)
none	0.24
DME	0.38
PEO	3.6
DB-18-C-6	40

[a]Conditions: diethyl benzylsodiomalonate, 0.5 mmole; C_4H_9Br, 5.4 mmole; additive, 2.7 mmole; solvent, benzene (20 ml); temperature, 30°C.

PEO as additive are summarized in Table 6. Addition of PEO caused an enhancement of the reaction rate in all runs, particularly in DOX by a factor of around 100. Such a marked effect in DOX, however, reveals the drastic decrease by addition of polar solvents like ethanol. It seems that these accelerations appear to be more pronounced in nonpolar and weakly polar media like benzene, THF, and DOX than in polar media like ethanol and 1-butanol. The superiority of the polymers to DME as acceleration agent is again demonstrated in the reaction system.

TABLE 6. Rates of the Williamson Reaction between Sodium Phenolate (PhONa) and Butyl Bromide in Various Solvents[a]

Solvent	Rates in the presence of additives (10^6 mole/liter-min)			
	None (r_0)	DME	PEO (r_p)	r_p/r_0
Benzene	0.6	0.6	11	18
Tetrahydrofuran (THF)	5.3	5.5	56	11
1,4-Dioxane (DOX)	0.35	0.38	39	111
DOX/ethanol (85/15)	7.9	8.6	27	3.4
DOX/ethanol (50/50)	20	21	39	2.0
Ethanol	43	43	51	1.2
1-Butanol	20	20	46	2.3

[a]Conditions: PhONa, 0.5 mmole, C_4H_9Br, 5.4 mmole; additive, 2.7 mmole; total volume, 20 ml; temperature, 45°C.

As PhONa is dissolved under the experimental conditions, most of the reactions proceed homogeneously. In THF or DOX, however a marked acceleration effect was found, where a PEO-PhONa complex is precipitated when the solution of PhONa is mixed with the solution of PEO. The facts that a PEO-PhONa complex was isolated and that a postulated structure of the complex could be presumed from analogous complexes of PEO with mercuric and cadmium salts shown by x-ray analysis [18] might be strong evidence for the coordination of PEO to Na⁺ of PhONa. The formation of a coordination complex is expected to lead to dissociation of the ion pair to provide reactive free phenoxy anion or a loose ion pair, causing a marked acceleration effect. The rate acceleration by PEO was found to be approximately as high as that caused by DB-18-C-6 (Table 7).

Reduction of Carbonyl Compounds with Sodium Borohydride

Unlike the cases of acceleration mentioned before, the reduction of carbonyl compounds with sodium borohydride ($NaBH_4$) was retarded by the presence of PEO [19]. Typical results are summarized

TABLE 7. Comparison of the Effects of Additives in the Williamson Reaction between PhONa and n-C_4H_9Br in DOX at 45°C[a]

Additive	Rate (10^6 mole/liter-min)
none	0.35
DME	0.38
PEO	39
DB-18-C-6	35

[a]Conditions: PhONa, 0.5 mmole, C_4H_9Br, 5.4 mmole; additive, 2.7 mmole; total volume, 20 ml.

in Table 8. Addition of a small amount of PEO induces decreases in the reduction yields of aldehydes and benzophenone. In the cases of acetone, tert-butyl methyl ketone, and acetophenone, the reductions are completely suppressed under the experimental conditions employed here. When DB-18-C-6 was used, similar suppression in the reduction can be observed. These retardation effects by PEO and especially by DB-18-C-6 in our results are clearly in contrast to the effectiveness of crown ethers in the borohydride reductions already reported [20, 21]. In this system, PEO was also found to form a complex with $NaBH_4$ at 4:1 molar ratio. Accordingly, this may possibly cause an ion pair dissociation of $NaBH_4$.

It is generally accepted that the reducing power of a borohydride depends on the character of the metal cation associated with the borohydride group, increasing as the electronegativity of the metal increases [22]. This behavior is elucidated to be attributed to a tendency towards $BH_3 + H^-$ character as opposed to BH_4^- character. We suppose in the PEO-$NaBH_4$ complex that the coordination of oxygen atoms to Na^+ causes weakening of the electron-withdrawing power of Na^+, that is, a decrease of the electronegativity. Therefore, the ion dissociated species seems to be less reactive than the tight ion pair of $NaBH_4$, resulting in the retardation of the reduction.

Reductions with other various alkali metal borohydrides and aluminum hydrides such as $LiBH_4$, $NaBH_2S_3$, $NaBH(OCH_3)_3$, $LiAlH_4$, $LiAlH(tert-C_4H_9O)_3$, and $LiAl(C_5H_6N)_4$ were also found to be suppressed in the presence of PEO or DB-18-C-6, although their effects were not so significant as the case of $NaBH_4$ reduction.

Grignard reagents, RMgX, have been known to form stable complexes with ether derivatives. We have found that PEO easily forms complexes with C_4H_9MgCl, C_6H_5MgCl, and $C_6H_5CH_2MgCl$ insoluble in THF or in benzene [23]. The addition of PEO to the Grignard reactions

TABLE 8. Effects of PEO or DB-18-C-6 in the Reduction of Carbonyl Compounds with Sodium Borohydride (NaBH$_4$) in THF at 30°C[a]

RCOR'	Yield in the presence of additives (%)		
	None	PEO	DB-18-C-6
C$_2$H$_5$CHO	85	58	52
i-C$_4$H$_9$CHO	98	65	-
C$_6$H$_5$CHO	82	47	-
CH$_3$COCH$_3$	39	0	-
t-C$_4$H$_9$COCH$_3$	29	0	0
C$_6$H$_5$COCH$_3$	79	0	0
C$_6$H$_5$COC$_6$H$_5$	89	24	-

[a]Conditions: RCOR; 2 mmole; NaBH$_4$, 2 mmole; PEO or DB-18-C-6, 10 mmole; total volume, 10 ml; time, 10 min for aldehydes and 66 hr for ketones reduction.

of the above Mg compounds with ketones and nitriles led to a great decrease in the reaction yields. For example, the reaction yield between C$_6$H$_5$MgCl and benzonitrile in benzene decreased from 70% to only 18% when PEO was present at [PEO]/[C$_6$H$_5$MgCl] = 4.

Selectivity for Reagents in Acceleration of the Reaction

It is of interest that the rates of alkylation of diethyl benzylsodiomalonate and the Williamson reactions with unbranched alkyl bromides were affected by the alkyl chain length in the presence of PEO, whereas they are almost constant in the presence of DME and DB-18-C-6 as well as without additive (Tables 9 and 10).

It has been generally accepted that the rate of the Williamson reaction and other S$_N$2 reactions are not affected by the length of the alkyl chain more than butyl in the case of alkyl halide as reagent. In the presence of PEO, however, the relative rates were found to be 1.0, 0.6, and 0.3, respectively in the Williamson reaction. Not only the chain length but the bulkiness of the alkyl group in the alkyl halides and in substituted phenolate cause similar effects. Since the reaction appeared to proceed in the precipitates as mentioned before,

TABLE 9. Relative Rates of Alkylation of Diethyl Benzylsodiomalo-
nate with Butyl, Octyl, and Hexadecyl Bromide in Benzene at $30°C$[a]

Additive	Rates (10^5 mole/liter-min)			Relative rate for		
	C_4	C_8	C_{16}	C_4	C_8	C_{16}
none	0.24	0.25	0.23	1	1.0	1.0
DME	0.38	0.40	0.38	1	1.1	1.0
PEO	3.6	3.0	2.5	1	0.8	0.7
DB-18-C-6	40	43	38	1	1.1	1.0

[a]Conditions: diethyl benzylsodiomalonate, 0.5 mmole; RBr, 5.4
mmole; additive, 2.7 mmole; total volume, 20 ml.

TABLE 10. Relative Rates of the Williamson Reaction between
PhONa and n-C_4H_9Br, n-$C_8H_{17}Br$, and n-$C_{16}H_{33}Br$ in DOX at $45°C$[a]

Additive	Rates (10^6 mole/liter-min)			Relative rate for		
	C_4	C_8	C_{16}	C_4	C_8	C_{16}
None	0.35	0.34	0.33	1	1.0	1.0
DME	0.38	0.38	0.38	1	1.0	1.0
PEO	39	24	12	1	0.6	0.3
DB-18-C-6	35	34	27	1	1.0	0.8

[a]Conditions: PhONa, 0.5 mmole; RBr, 5.4 mmole; additive, 2.7
mmole; total volume, 20 ml.

the difference of rate dependency on the alkyl chain length may be
attributable to the steric hindrance of complexed polymer chains in
the vicinity of PhONa.

Formation of the PEO-PhONa Complex and Its Relation to the Reaction Rate

As mentioned before, marked acceleration in a Williamson reaction
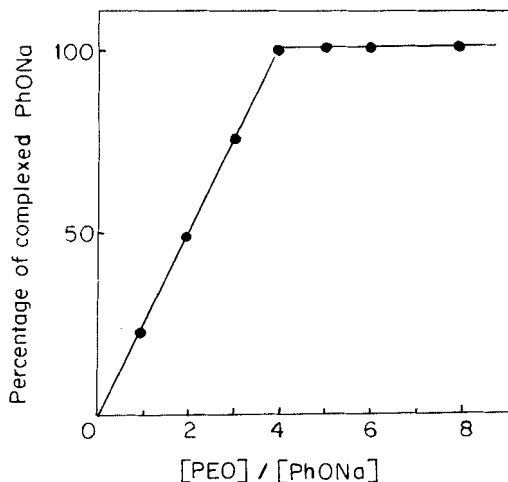was found in weakly polar solvents like THF and DOX, where a fine

FIG. 1. Dependence of complexed PhONa fraction on the ratio [PEO]/[PhONa] in DOX at 45°C. Conditions: PhONa, 0.5 mmole; PEO, 0-4.0 mmole; volume, 20 ml.
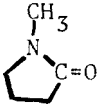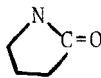
precipitate immediately appeared when the PhONa solutions were added to the PEO solutions. The precipitate obtained was found from its IR spectrum to be composed of PEO and PhONa.

In a separate experiment, at various ratios of [PEO] to [PhONa], PhONa was found to be complexed with PEO up to molar ratio [CH$_2$CH$_2$O]/[PhONa] = 4 (Fig. 1). At ratios < 4, no PhONa was detected in the supernatant solution, indicating that PhONa forms a complex with PEO having four oxyethylene repeating units per mole of PhONa. The structure of the complex will be discussed in the following.

In order to ascertain the dissociation of the ion pair with aid of PEO, the well characterized optical spectra of sodium picrate instead of PhONa were measured. The λ_{max} of sodium picrate shows a bathochromic shift following the ion dissociation. As shown in Table 11, the presence of both PEO and DME in the sodium picrate-DOX solution indeed allowed a bathochromic shift of λ_{max}. Addition of PEO appeared to be more effective for the shift than that of DME, indicating superiority of the former in inducing dissociation at the same concentration.

A similar superiority of PEO was also suggested by the spectra when PhONa was used instead of sodium picrate, although the

TABLE 11. Additive Effect of Various Polymers in the Williamson
Reaction between PhONa and n-C_4H_9Br in DOX at $45°C$[a]

Additive polymer	Structure	Rate (10^6 mole/liter-min)
None	–	0.35
DME	$CH_3OCH_2CH_2OCH_3$	0.38
PEO	$\left(CH_2CH_2O\right)_n$	39
Poly(oxetane)	$\left(CH_2CH_2CH_2O\right)_n$	0.40
Poly(tetrahydrofuran)	$\left(CH_2CH_2CH_2CH_2O\right)_n$	0.80
Poly(ethylvinylether)	$\left(CH_2CH\right)_n$ $\quad\quad OCH_2CH_3$	0.40
NMP	CH_3 (N-methyl-2-pyrrolidone ring, C=O)	4.20
PVP	$\left(CH_2CH\right)_n$ (N-vinylpyrrolidone ring, C=O)	$\overline{M\eta}$ = 7200 134 = 24800 313 = 47000 420

[a]Conditions: PhONa, 0.5 mmole; C_4H_9Br, 5.4 mmole; additive, 2.7
mmole; total volume, 20 ml.

absorption peaks of PhONa are somewhat complex and have not been
sufficiently assigned at the present time. Panayotov et al. recently
reported that the addition of PEO causes marked ion pair dissociation
of fluorenyl Na and K in THF solution. These findings lead us to
consider that PEO promotes ion pair dissociation in PhONa, result-
ing in production of reactive free anion or a loose ion pair which may
cause the enhancement of the reaction rate.

     It is very peculiar that there was a clear discrepancy between the
complexation of PEO with PhONa and the reaction rate as seen in
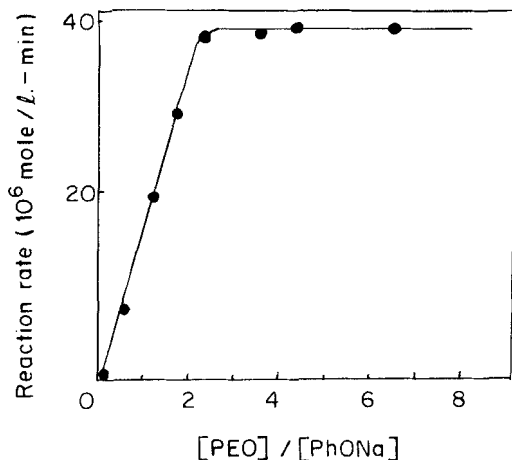Fig. 2. The rate increases linearly with the ratio of [PEO]/[PhONa],

FIG. 2. Relationship between the rate and the ratio [PEO]/[PhONa] in DOX at 45°C. Conditions: PhONa, 0.5 mmole; C₄H₉Br, 5.4 mmole; PEO, 0-4.0 mmole; total volume, 20 ml.

but it attains its maximum value already at a ratio of around 2, at which only 50% of PhONa is complexed, according to the result shown in Fig. 1. The reason for such deviation in acceleration effect from the viewpoints of the complex formation alone not known.

Molecular Weight Dependence of Additive PEO on the Rate of the Williamson Reaction

During the course of this study, we have found the dependence of the reaction rate on the molecular weight of additive PEO in the Williamson reaction. As can be seen in Fig. 3, the reaction rate increased markedly with the molecular weight of PEO and leveled off at $\overline{M}_\eta$ as high as about 1.0×10^4 (degree of polymerization = 230).

The relationship between the ion pair dissociation of sodium salt and the molecular weight of PEO was examined by means of optical spectroscopy of sodium picrate characterized as mentioned above. The addition of PEO to the system causes a bathochromic shift of λ_{max}, and it shifts to longer wavelengths with increasing molecular weight of PEO, indicating that PEO of higher molecular weight favors for the dissociation of the ion pair of the sodium salt.

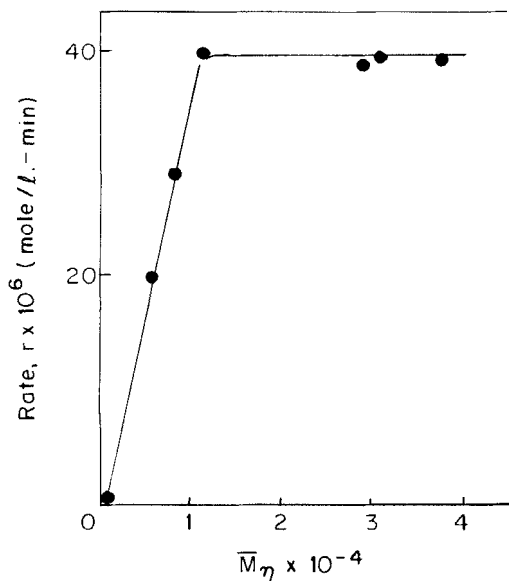In the studies on complexation ability of the glyme derivatives with

FIG. 3. Dependency of the molecular weight on the reaction rate in the Williamson reaction. Conditions: PhONa, 0.5 mmole; C_4H_9Br, 5.4 mmole; PEO, 2.7 mmole; total volume, 20 ml; 45°C.

alkali metal cations, Ugelstad and Rokstad [24] pointed out that the increased complexation ability of the higher glymes with more than five oxygen atoms is to be expected for statistical reasons. However, a perfect agreement with experimental results is not shown because conformational effects may also become important when the chain length of the glymes increases. In the cases of PEO in this study, conformational effects should be, in particular, considered.

No clear reason is offered at the present time why the polymer effect is influenced to such a large extent by $\overline{M}_\eta$ of PEO. It is difficult, at least, to explain the results simply on the basis of the neighboring effect of the oxyethylene units, but the repeating etheral unit along the long polymer chain does play an important role in the acceleration.

Additive Effect of Other Polymers in the Williamson Reaction

The additive effect of various polymers containing ether groups was investigated to understanding the contribution of the polymer

structure to the rate acceleration (Table 11). No acceleration was observed with polyoxetane, polytetrahydrofuran, and poly(vinyl ethyl ether). The results demonstrate the greatest effect when the oxygen atoms are separated by two carbon atoms in the polymeric chain, PEO being an outstanding example. These polymers, except PEO, neither coordinate to PhONa nor accelerate the reaction. When the diglyme was introduced into crosslinked (2%) polystyrene, a slight rate increase was observed.

A surprisingly marked polymer effect was found in the case of polyvinylpyrrolidone (PVP) [25, 26], which is considered a polymer of N-methylpyrrolidone (NMP), one of the well known dipolar aprotic solvents. It is generally known that the S_N2 type reactions are accelerated in dipolar aprotic solvents. The Williamson reaction was accelerated by the aid of PVP, being over 100 times as rapid as in a solution containing the same concentration of NMP (concentration of PVP calculated based on pyrrolidone pendant units). Acceleration by PVP interestingly appeared to be again dependent upon its molecular weight.

METAL ION TRANSPORTATION WITH OLIGO(ETHYLENE OXIDE)

Selective Ion Transport with Synthetic Ionophores

The natural ionophores possess a characteristic molecular structure especially designed for carrying an ion across biological lipid membranes. The backbone chains of most ionophores are constituted of oxyethylene units which facilitate incorporation of small ions into inside of the macrorings.

Appreciable interactions between oxyethylene units and alkali metal ions are substantiated by the complex formation of acyclic oligoethylene glycols and their derivatives with alkali metal salts as shown in Table 12. These complexes, however, easily release alkali metal ions in aqueous solution.

As a model compound for carboxylic ionophores, introduction of carboxy group at the terminal position of oligoethylene glycol is preferred for capturing a cation. A hydroxy group at the other end would play an important role in ring closure by hydrogen bonding with the carboxy group as shown in Fig. 4.

In order to make up lipid-soluble synthetic ionophores having strong binding power of alkali metal ions, introduction of hydrophobic groups into the backbone as well as carboxy and hydroxy groups is anticipated to be essential.

Conclusively, in this study, α-carboxy, ω-hydroxy polyethers

TABLE 12. Complex Formation of Oligoethylene Glycol Derivatives with Alkali Metal Salts

Oligoethylene glycol derivatives (A)[a]	Alkali metal salts (B)	A:B	I^- or SCN^- (%)	
			Found	Calcd
TEG	LiI	1:1	38.1	38.7
TEG	NaI	2:1	27.5	27.9
PEG	NaI	1:1	32.6	32.7
PEG	KSCN	1:1	14.4	17.3
XII	NaSCN	2:1	7.8	8.9
XIII	LiI	1:1	25.4	27.1
XIII	NaSCN	1:1	11.1	14.0
XIII	KSCN	2:1	7.4	7.5
XIV	LiI	1:1	19.0	24.8
XIV	NaSCN	1:1	18.0	12.6

[a]TEG, tetraethylene glycol; PEG, pentaethylene glycol.

XII   XIII   XIV
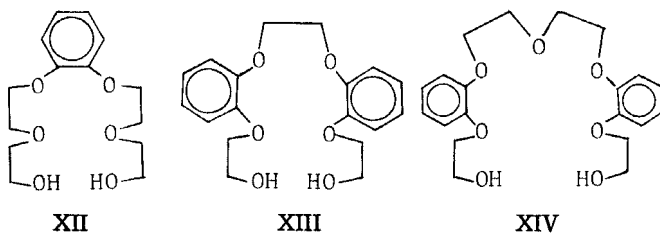
containing ethylene, 1,2-phenylene, and tetrahydrofuranyl units (I ~ XI) were synthesized as model compounds for the carboxylic ionophores and their abilities of selective and active ion transportation examined.

As listed in Table 13, the solubilities of the model compounds in organic solvents of low dielectric constant increased with increasing number of hydrophobic groups along the backbone. As an ion carrier, a lipid-soluble but water-insoluble model compound is preferable. The sodium salt of monensin is, in fact, soluble in common organic solvents. The alkali metal salts of model compounds VIII and IX are
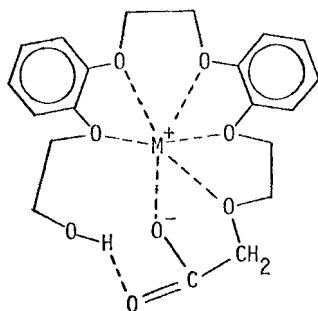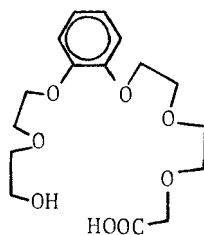
FIG. 4. Postulated structure of the complex between the synthetic ionophore IV and an alkali metal ion.
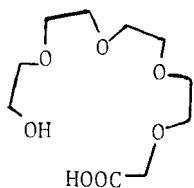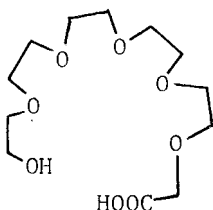
I   I I   III
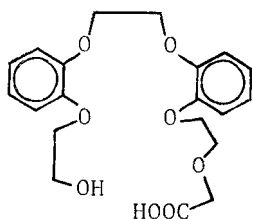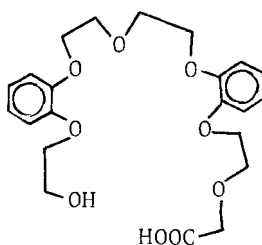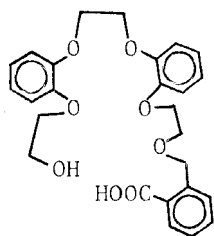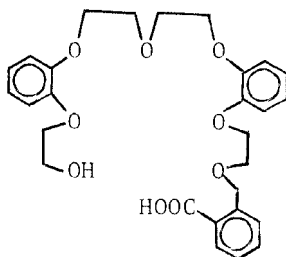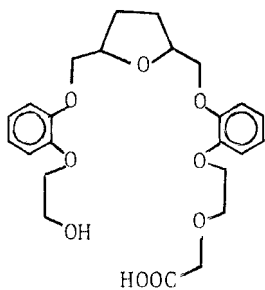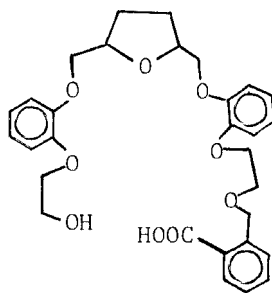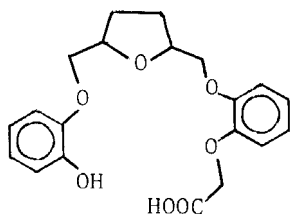
IV   V
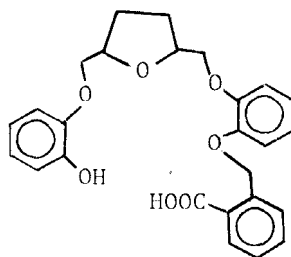
VI

VII

VIII

IX

X

XI

TABLE 13. Solubilities of Alkali Metal Salts of the Synthetic Ionophores[a]

Alkali metal salts of the ionophores	Solvent						
	H_2O	CH_3OH	1-Hexanol	CH_2Cl_2	$CHCl_3$	THF	Benzene
I	S	S	S	I	I	I	I
II	S	S	S	S	S	I	I
III	S	S	S	S	S	I	I
IV	S	S	S	S	S	I	I
V	S	S	S	S	S	I	I
VI	S	S	S	S	S	S	I
VII	S	S	S	S	S	S	I
VIII	SS	S	S	S	S	S	I
IX	SS	S	S	S	S	S	I
X	S	S	S	S	S	S	I
XI	S	S	S	S	S	S	I

[a] I, insoluble; SS, slightly soluble; S, soluble.
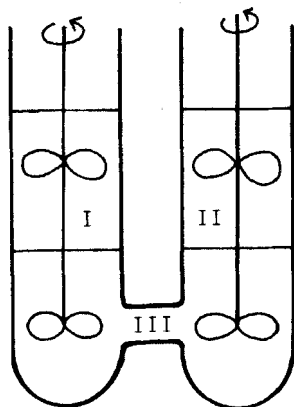
FIG. 5. U-type cell for ion transport: (I) 10 ml of 1.0 $\underline{N}$ aqueous
HCl solution; (II) 10 ml of 1.0 $\underline{N}$ aqueous MCl solution (where M
denotes alkali metal); (III) chloroform membrane, 20 ml, including
2×10^{-6} mole of synthetic ionophores.

sparingly soluble in water and exhibit remarkable ion transport
activities, whereas the salts of the others, I-VII, X, and XI are quite
soluble or partially soluble in water.

The cyclic structure of the model IV wrapping an alkali metal ion
was proposed as illustrated in Fig. 4 by analogy with those of mono-
valent metal salts of monensin [27]. The cyclic conformation of
the synthetic ionophores, IV, VI, and VII, with sodium, potassium,
and rubidium ions were supported by the characteristic absorption
maxima split at 275 and 280 nm in the UV spectra of the carboxylates
as was observed in the case of crown ether complex with alkali metal
salts [28].

Transportation of alkali metal ion was carried out in U-type
and H-type cells with stirring, where chloroform and 1-hexanol
including synthetic ionophores were employed as liquid membranes,
respectively (Figs. 5 and 6).

The amount of alkali metal ion transported through the chloroform
membrane was followed by measuring the concentration of proton
transported in the reverse of alkali metal ion by pH meter. Typical
results are shown in Figs. 7 and 8, where it was obvious that sodium
and potassium ions were selectively transported with the model
compound IV, and potassium and rubidium ions with the model com-
pound VIII. Other synthetic ionophores I, II, III, V, VI, and VII and
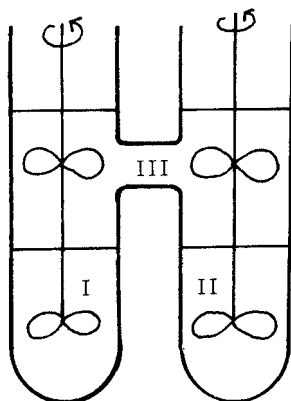the oligoethylene glycol derivatives XII, XIII, and XIV, however,

FIG. 6. H-type cell for ion transport: (I) 10 ml of 0.05 $\underline{N}$ aqueous HCl solution; (II) 10 ml of 0.05 $\underline{N}$ aqueous MOH solution (where M denotes alkali metal); (III) 1-hexanol membrane, 20 ml, including 2×10^{-5} mole of synthetic ionophores.
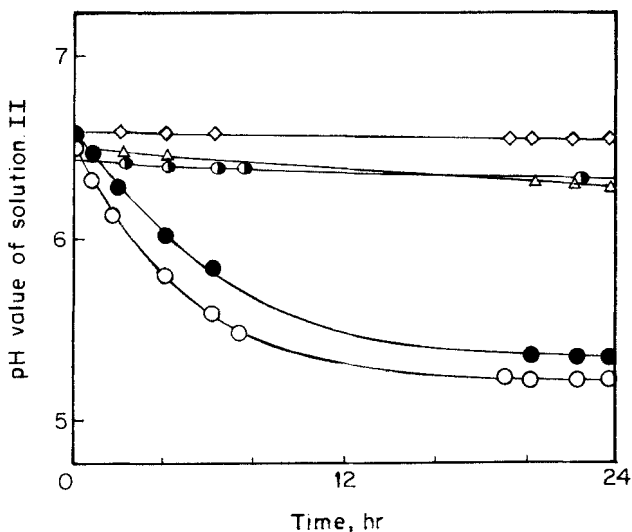

FIG. 7. Selective transport of alkali metal ions through IV-chloroform membrane at room temperature, where pH value of solution (II) corresponds to logarithm of the concentration of an alkali metal ion transported from (II) to (I): (◐) Li$^+$; (●) Na$^+$; (○) K$^+$; (◇) Rb$^+$; (△) Cs$^+$.
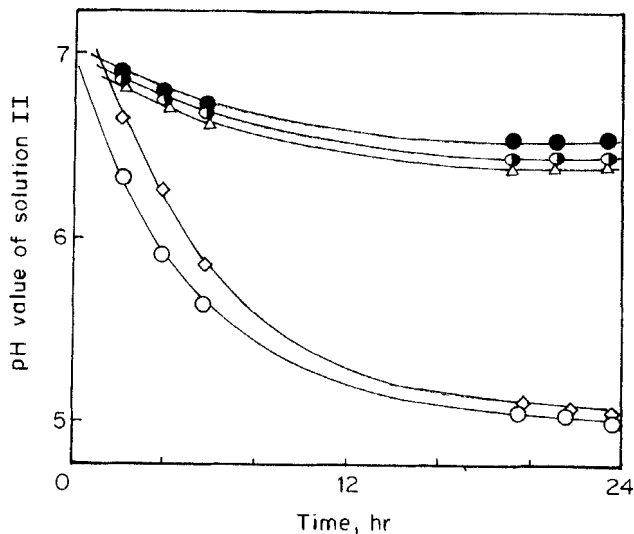
FIG. 8. Selective transport of alkali metal ions through VIII-chloroform membrane at room temperature: (◑) Li$^+$; (●) Na$^+$; (○) K$^+$; (◇) Rb$^+$; (△) Cs$^+$.
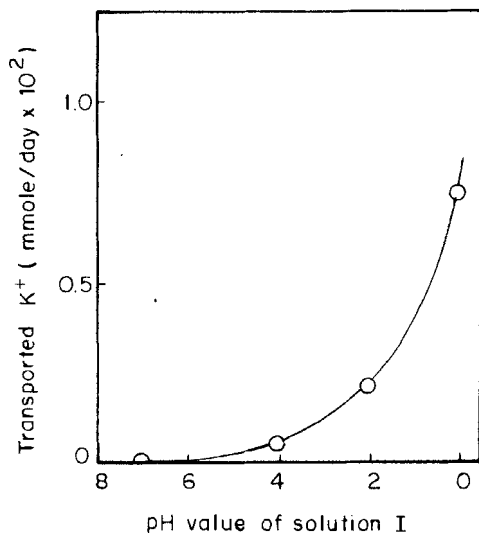

FIG. 9. pH dependence of the transportation of potassium ion through IV-chloroform membrane at room temperature; IV, 2×10^{-6} mole in 20 ml of CHCl$_3$.
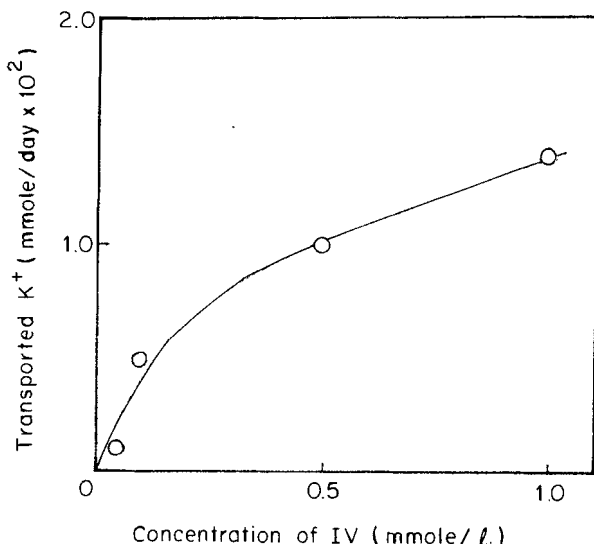
FIG. 10. Relationship between transported K^+ and concentration of synthetic ionophore IV; solution (I), 1 $\underline{N}$ HCl; solution (II), 1 $\underline{N}$ KCl; liquid membrane, IV-chloroform; at room temperature, 24 hr.

exhibited little activity of ion transportation. Figure 9 shows the dependence of the amount of potassium ion transported by the model IV on pH value of the K^+ receiving solution. This indicates that the driving force of ion transportation is the pH gradient between the separated aqueous solutions. Naturally, the amount of potassium ion transported increased as increasing the concentration of the model IV in chloroform membrane (Fig. 10). These results support also the ion transportation scheme on monensin proposed by Cussler [29] as shown in Fig. 11. In the interface between aqueous potassium chloride solution and chloroform membrane, the synthetic ionophore incorporated potassium ion and then reached opposite interface by agitation, where potassium ion was exchanged by proton. Consequently, potassium ion was transported from KCl solution to HCl solution through chloroform membrane and alternatively proton in the reverse.

The transportation of alkali metal ions through 1-hexanol membrane was difficult to measure by using pH meter, since the amount of transported proton in the control experiment was comparable to that in the presence of synthetic ionophores. Therefore, the ion transportation in this case was followed by flame analysis [30]. A preferential transportation of rubidium ion by the synthetic ionophore VI having three phenylene groups and five ethereal oxygens is
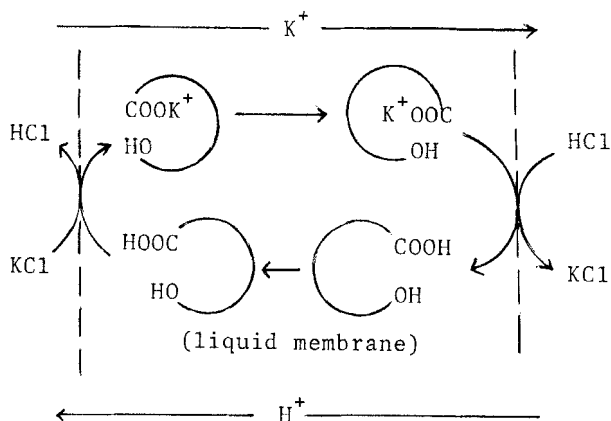
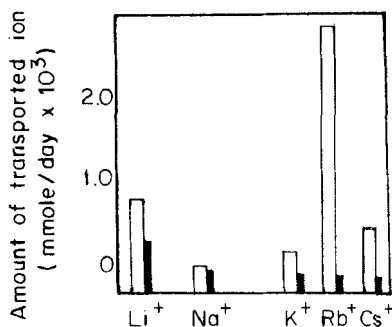FIG. 11. Ion transportation scheme for monensin.

FIG. 12. Amount of alkali metal ions transported through VI-1-hexanol membrane; solid bar shows the results of control experiment.

illustrated in Fig. 12. Furthermore, the ionophores IV and VII, which have five and six ethereal oxygens, selectively transported potassium and rubidium ions, respectively. Similarly to the case of chloroform membrane, the amount of transported rubidium ion increased with the concentration of the ionophore VI in 1-hexanol (Fig. 13), whereas little ion transportation was observed with other synthetic ionophores (I, II, III, and V) and oligoethylene glycol derivatives (XII, XIII, XIV).
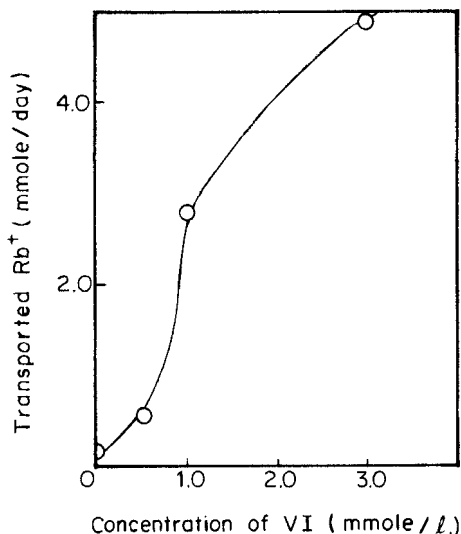
FIG. 13. Relationship between transported Rb^+ and concentration of synthetic ionophore VI; liquid membrane, 1-hexanol; other conditions as shown in Fig. 6.

It is reasonable to assume that ion transportation may be favorable when the hole sizes of the synthetic ionophores, which were estimated by assuming the ring closure by the end-to-end hydrogen bonding, correspond to radii of the alkali metal ions. Lithium ion was also carried to some extent by VI and VII, although the ionic diameter is much smaller than the inner diameters of VI and VII. This seems to be difficult to interpret by the fit of size between the cavity of the macroring and lithium ion. Presumably, the large solubility of the lithium salts in 1-hexanol affects the transportation.

The several features of the synthetic ionophores were clarified from the experimental results on a series of the model compounds as follows. The organic medium in the liquid membrane affected the ion transportation, for instance, the model compounds VI and VII transported rubidium ion selectively through 1-hexanol membrane, but they did not transport any alkali metal ions through chloroform membrane. The hole size fit of the synthetic ionophores to the radii of the favorable alkali metal ions was a very important factor for the transportation. Also, introduction of appropriate hydrophobic groups, such as phenylene and tetrahydrofuranyl groups, into the backbone of the synthetic ionophores decreased their
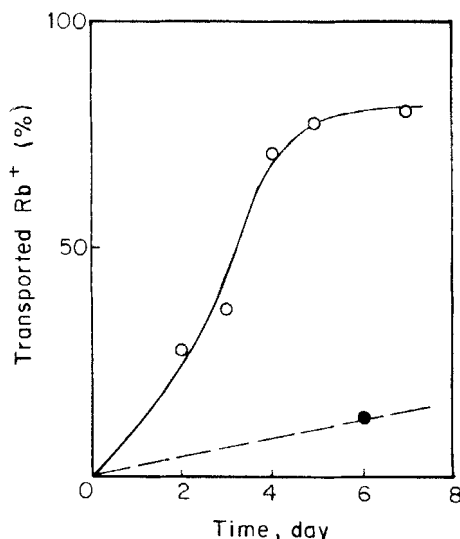
FIG. 14. Active ion transport of Rb$^+$ with synthetic ionophore VI:
solution (1), 0.1 N RbCl and 0.1 N HCl, liquid membrane, 10^{-4} mole
of VI in 20 ml of 1-hexanol; solution (2), 0.1 N RbOH: at 35 °C; (--)
result of the control experiment.

solubilities in the aqueous solution and stabilized their cyclic confor-
mation with the aid of the rigid structure of the substituents.

Active Ion Transport with Synthetic Ionophores

Another interesting property of carboxylic ionophores is the active
ion transport against the alkali metal ion concentration gradient. The
active transport of rubidium ion by the ionophore VI was clearly sub-
stantiated from the experimental results described below. The pH
gradient and concentration of the ionophore were increased to accel-
erate the ion transportation, because the amount of the ion transported
was so small and the active ion transport was not explicitly observed
under the conditions mentioned in the previous section. Rubidium
ions of the same concentration were initially placed in tube as (1) an
acidic solution and (2) an alkaline solution. The driving force for
transport of rubidium ion is only the pH gradient between two aqueous
solutions (1) and (2) which is a typical condition for the active ion
transport. As shown in Fig. 14, more than 80% of the rubidium ion

TABLE 14. Active and Selective Ion Transport of Sodium and Potassium Ions with Synthetic Ionophores[a]

Synthetic ionophore	Transported ion (%)		
	Na$^+$	K$^+$	Total
Control	13	10	23
VI	31	54	85
VIII	31	41	82
IX	34	52	86

[a]Temperature, 35 ± 2°C; time, 5 days.

0.1 N NaCl	Synthetic ionophore,	0.1 N NaOH
0.1 N KCl	10^{-4} mole/20 ml 1-hexanol	0.1 N KCl
0.1 N HCl		

TABLE 15. Active and Selective Transport of Sodium, Potassium and Cesium Ions with Synthetic Ionophores[a]

Synthetic ionophore	Transported ion (%)			
	Na$^+$	K$^+$	Cs$^+$	Total
Control	12	11	9	32
VI	26	42	21	89
VIII	29	42	17	88
IX	25	42	22	89

[a]Temperature, 35 ± 2°C; time, 5 days.

0.1 N NaCl	Synthetic ionophore	0.1 N NaCl
0.1 N KCl	10^{-4} mole/20 ml 1-hexanol	0.1 N KCl
0.1 N CsCl		0.1 N CsOH
0.1 N HCl		

was transported from the alkaline solution to the acidic solution with the ionophore VI after 7 days.

Selective and active ion transport was also examined by employing the mixture of alkali metal ions with the synthetic ionophores VI, VIII, and IX under analogous conditions. From the results shown in

Tables 14 and 15, potassium ion was transported in preference to sodium and cesium ions with these ionophores. As compared with the small-scale cases described above, the selectivity among sodium, potassium, and cesium ions became ambiguous to some extent.

In order to raise the selectivity of alkali metal ions in the active ion transport, it is necessary to seek more hydrophobic synthetic ionophores with rigid structure.

ACKNOWLEDGMENTS

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