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Redox-Switched Crown Ethers. 1. Redox-Coupled Control of Metal-Ionophore Interactions and Their Application to Membrane Transport[1)]

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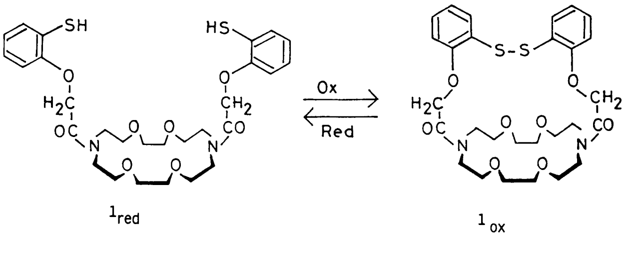
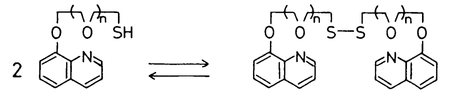
Polyether ionophores with redox-functional thiol groups were synthesized: they are a diaza-18-crown-6 with a disulfide cap that exhibits redox-responsive interconversion between crown($\mathbf{1}_{\mathrm{red}}$) and cryptand($\mathbf{1}_{\mathrm{ox}}$) and tri- and tetra(oxyethylene)s having a mercapto and an 8-quinolyl group as their terminal groups that feature redox-responsive interconversion between monopodands ($\mathbf{2}_{\mathrm{red}}$) and dipodands ($\mathbf{2}_{\mathrm{ox}}$). For Na^+ $\mathbf{1}_{\mathrm{red}}$ and $\mathbf{1}_{\mathrm{ox}}$ showed a similar ion affinity, but $\mathbf{1}_{\mathrm{ox}}$ bound K^+, Rb^+, and Cs^+ more efficiently than $\mathbf{1}_{\mathrm{red}}$ because of the coordination of the cap oxygens to the complexed metal cations. The difference was rationalized by such that "K^+ (Rb^+ and Cs^+ also) perches on the crown-ring whereas Na^+ nests in it," $\mathbf{2}_{\mathrm{ox}}$ showed, in most cases, the ion affinity significantly higher than corresponding $\mathbf{2}_{\mathrm{red}}$, indicating the cooperative action of the two poly(oxyethylene) chains on the ion-binding. The rate of K^+ transport with $\mathbf{2}_{\mathrm{red}}$ across a liquid membrane was very slow but $\mathbf{2}_{\mathrm{ox}}$ carried K^+ more efficiently. It was found that the rate of K^+ transport started with $\mathbf{2}_{\mathrm{red}}$ is efficiently accelerated by the addition of I_2. This is due to the redox-switch of the carrier from $\mathbf{2}_{\mathrm{red}}$ to $\mathbf{2}_{\mathrm{ox}}$. These results suggest that the redox-functionalized ionophores provide novel applications of ion-extraction and ion-transport.

Macrocyclic polyethers contain intramolecular cavities delineated by molecular segments and are capable of specific chelation with alkali and alkaline earth metal ions. The specificity in the chelation stems from a host-guest relationship[2—4)]: that is, the ion-selectivity is primarily subjected to the size and shape of the intramolecular cavities. One may thus expect that if the ring conformation or the topological ring shape can be reversibly changed in response to some input energy, it would lead to the "control" of ion-binding ability and ion-selectivity by an on-off switch. Furthermore, this is important in relation to the membrane transport phenomenon mediated by some antibiotic carriers where the reversible interconversion between the cyclic and the acyclic form of the antibiotics plays the crucial role.[5)] There are several synthetic ionophores that exhibit pH-dependent interconversion between the acyclic and the pseudo-cyclic form,[6—11)] but to the best of our knowledge there is no example for the redox-dependent acyclic-cyclic interconversion.[1)] We considered that the interconversion would be realized more directly by utilizing the reversible bond-formation and bond-scission. The most suitable candidate to this purpose would be the redox reaction of a thiol-disulfide couple, because the reversibility is excellent and the reaction occurs under mild conditions. Here, we wish to report such examples of "redox-switched" ionophores, the ion affinity of which changes in response to redox of a thiol-disulfide bond: that is, (i) a crown ether with a disulfide cap which features a crown ($\mathbf{1}_{\mathrm{red}}$)-cryptand($\mathbf{1}_{\mathrm{ox}}$) interconversion, and (ii) a monopodand($\mathbf{2}_{\mathrm{red}}$)-dipodand($\mathbf{2}_{\mathrm{ox}}$) interconversion in which two 8-quinolyl groups are linked by a disulfide bond *via* poly(oxyethylene) chains.



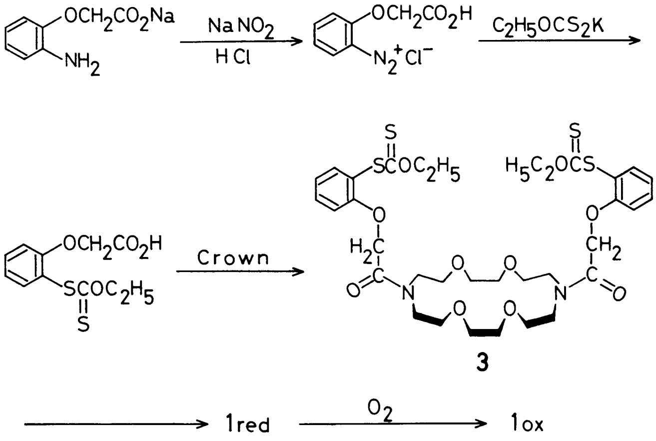
1_{red} 1_{ox}



$2_{\mathrm{red}}(n=2,3)$ $2_{\mathrm{ox}}(n=2,3)$

Experimental

Materials. $\mathbf{1}_{\mathrm{red}}$ and $\mathbf{1}_{\mathrm{ox}}$ were synthesized according to a following reaction Scheme 1.



Scheme 1.

Sodium *o*-aminophenoxyacetate (18.9 g; 0.10 mol) and $NaNO_2$ (6.90 g; 0.10 mol) were dissolved in 100 ml of water. This solution was added dropwise to 60 ml of 6 $M^{\dagger}$ HCl solution at 0—5 °C. After 5 min excess $NaNO_2$ was decomposed by sulfamic acid. The solution was mixed slowly with 200 ml of aqueous solution containing potassium ethyl xanthate (19.2 g; 0.12 mol) and sodium hydrogencarbonate (25.5 g; 0.30 mol) in an ice-water bath. The progress of the reaction was followed by a color test with H-acid. The solution was treated with active charcoal at room temperature. After filtration the solution was acidified to pH 1 with concd. HCl, the precipitate being recovered by filtration. The raw product (*o*-(ethoxythiocarbonylthio)phenoxyacetic acid) thus obtained was again dissolved in $NaHCO_3$ solution, treated with active charcoal, and recovered by acidification

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† $1\,M=1\ \mathrm{mol\,dm^{-3}}$.

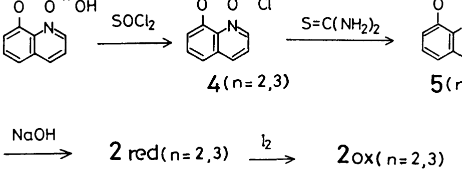
with concd. HCl; mp 119—120 °C, single spot on TLC, yield from sodium *o*-aminophenoxyacetate 30.9%. IR (KBr): $\nu_{C=O}$ 1750 cm^{-1}, ν_{C-O-C} 1090 and 1230 cm^{-1}; M$^+$ (*m/z*) 272; NMR (Me$_2$SO-d_6, δ): CH$_3$, 1.22, 3H; O-CH$_2$, 4.54, 2H; O-CH$_2$-CO, 4.73, 2H; benzene protons, 7.20, 4H. Found: C, 48.70; H, 4.46%. Calcd for $C_{11}H_{12}O_4S_2$: C, 48.51; H, 4.44%.

In 150 ml of anhydrous tetrahydrofuran (THF) *o*-(ethoxythiocarbonylthio)phenoxyacetic acid (7.20 g; 0.0264 mol) and pivaloyl chloride (3.72 g; 0.0309 mol) were reacted for 30 min at 0 °C. To the stirred solution was added dropwise a THF solution (100 ml) containing 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (3.0 g; 0.0114 mol) and triethylamine (4.8 ml; 0.034 mol). The reaction was continued for 2 h at room temperature and then refluxed for 1 h. The white precipitate formed on cooling was collected by filtration, and triethylamine hydrochloride was removed by washing with water. The remaining product (**3** in Scheme 1) was recrystallized from 1-butanol; mp 161—164 °C, yield 84.0%. IR (KBr): $\nu_{C=O}$ 1650 cm^{-1}, ν_{C-O-C} 1130 and 1230 cm^{-1}; NMR (Me$_2$SO-d_6, δ) CH$_3$, 1.19, 6H; crown protons, 3.36, 24H; O-CH$_2$, 4.53, 4H; O-CH$_2$-CO, 4.89, 4H; benzene protons, 7.20, 8H. Found: C, 53.14; H, 6.34; N, 3.50%. Calcd for $C_{34}H_{46}N_2O_{16}S_4$: C, 52.97; H, 6.01; N, 3.63%.

3 was hydrolyzed to $\mathbf{1}_{red}$. **3** (7.77 g; 0.0101 mol) was suspended in 600 ml of ethanol and mixed with 200 ml of 75 vol% ethanol solution containing NaOH (1.75 g; 0.0407 mol). The reaction mixture was refluxed under a nitrogen stream and the progress of the reaction was followed by a TLC method. After 1 h, 2-mercaptoethanol (2.0 g; 0.0256 mol) and then 3 ml of acetic acid were added. The white precipitate was obtained from the cooled solution; mp 166—168 °C, yield 85.1%. IR (KBr): $\nu_{C=O}$ 1650 cm^{-1}, ν_{C-O-C} 1130 and 1225 cm^{-1}, ν_{SH} 2580 cm^{-1}; NMR (Me$_2$SO-d_6, δ) SH, 3.24, 2H; crown protons, 3.54, 24H; CH$_2$, 4.93, 4H; benzene protons, 7.05, 8H. Found: C, 56.29; H, 6.69; N, 4.57%. Calcd for $C_{28}H_{38}N_2O_8S_2$: C, 56.55; H, 6.44; N, 4.71%.

$\mathbf{1}_{red}$ (1.0 g; 1.68×10^{-3} mol) was dissolved in 400 ml of 0.1 M KOH solution and an oxygen stream was introduced at room temperature. After 5 h, the white precipitate ($\mathbf{1}_{ox}$) was recovered by filtration and recrystallized from ethylene glycol monomethyl ether; mp 172—175 °C, yield 54.2%. IR (KBr): $\nu_{C=O}$ 1650 cm^{-1}, ν_{C-O-C} 1075 and 1220 cm^{-1}; M$^+$ (*m/z*) 592; NMR (Me$_2$SO-d_6, δ) crown protons, 3.51, 24H; CH$_2$, 4.89, 4H; benzene protons, 7.00, 8H. Found: C, 56.45; H, 6.65; N, 4.62%. Calcd for $C_{28}H_{36}N_2O_8S_2$: C, 56.74; H, 6.12; N, 4.73%.

$\mathbf{2}_{red}$ and $\mathbf{2}_{ox}$ were synthesized according to Scheme 2. Since the synthesis of **4** has been described by Hiratani *et al.*,[7,8] we here record only the analytical data.



Scheme 2.

4 (n=2); oil, single spot on TLC, yield 90.9%. IR (neat) quinoline 1500 and 1600 cm^{-1}, ν_{C-O-C} 1120 cm^{-1}; NMR (CDCl$_3$, δ) methylene protons, 3.70 (8H), 4.04 (2H), and 4.40 (2H); quinoline protons, 7.05 (1H), 7.35 (3H), 8.05 (1H), and 8.85 (1H).

4 (n=3); oil, single spot on TLC, yield 59.6%. IR (neat) quinoline 1500 and 1600 cm^{-1}, ν_{C-O-C} 1120 cm^{-1}; NMR (CDCl$_3$, δ) methylene protons, 3.65 (12H), 4.10 (2H), and 4.45 (2H); quinoline protons, 7.15 (1H), 7.40 (3H), 8.10 (1H), and 8.90 (1H).

4 (n=2) (5.13 g; 0.0173 mol) was treated with thiourea (1.45 g; 0.0190 mol) in 30 ml of ethanol at boiling temperature. The progress of the reaction was followed by a TLC method. After 40 h, the solution was epavorated to dryness and the remaining solid (**5** (n=2)) was dissolved in 100 ml of water and washed with chloroform. The aqueous solution was mixed with 20 ml of NaOH (0.69 g) solution and heated at 80 °C. After cooling the solution was adjusted to pH 6—7 with 0.1 M HCl and extracted with chloroform. The chloroform solution of $\mathbf{2}_{red}$(n=2) thus obtained was treated with I$_2$ to give $\mathbf{2}_{ox}$(n =2). $\mathbf{2}_{ox}$(n=2) was isolated by a preparative TLC method (silica gel and chloroform); oil, single spot on TLC, yield 43.5%. IR (neat) quinoline 1500 and 1600 cm^{-1}, ν_{C-O-C} 1120 cm^{-1}; M$^+$ (*m/z*) 584; NMR (CDCl$_3$, δ) methylene protons, 2.80 (2H), 3.65 (6H), 4.02 (2H), and 4.38 (2H); quinoline protons, 7.10 (1H), 7.36 (3H), 8.10 (1H), and 8.85 (1H). Found: C, 57.49; H, 6.33; N, 4.44; S, 10.16%. Calcd for $C_{30}H_{36}N_2O_6S_2\cdot3.35\,H_2O$: C, 57.46; H, 6.12; N, 4.47; S, 10.23%.

$\mathbf{2}_{ox}$(n=3) was similarly synthesized from **4**(n=3) *via* **5**(n= 3) and $\mathbf{2}_{red}$(n=3); oil, single spot on TLC, yield 59.6%. IR (neat) quinoline 1500 and 1600 cm^{-1}, ν_{C-O-C} 1100 cm^{-1}; NMR (CDCl$_3$, δ) methylene protons, 2.90 (2H), 3.65 (10H), 4.10 (2H), and 4.45 (2H); quinoline protons, 7.18 (1H), 7.39 (3H), 8.10 (1H), and 8.92 (1H). Found: C, 59.82; H, 6.54; N, 4.01%. Calcd for $C_{34}H_{44}N_2O_8S_2$: C, 60.69; H, 6.59; N, 4.16%.

Solvent Extraction. The method of solvent extraction has been described in detail previously.[12–14] In this study, 5 ml of organic solution containing the ionophore was agitated with 5 ml of buffered aqueous solution containing alkali metal salts of 8-anilinonaphthalene-1-sulfonate (ANS). The extractability (Ex%) was estimated from the partition of ANS between the organic and the aqueous phase. Since the isolation of $\mathbf{2}_{red}$(n=2, 3) was extremely difficult, $\mathbf{2}_{red}$(n=2, 3) reduced from $\mathbf{2}_{ox}$(n=2, 3) with Na$_2$S$_2$O$_4$ was directly used for extraction. The extraction with $\mathbf{1}_{red}$ and $\mathbf{2}_{red}$(n=2, 3) was carried out under anaerobic (N$_2$) conditions. After determining Ex% the contents of $\mathbf{1}_{ox}$ or $\mathbf{2}_{ox}$(n=2, 3) formed during the extraction were evaluated by a TLC method using a high-speed TLC scanner (Shimadzu CS-920): usually the amounts of concomitant $\mathbf{1}_{ox}$ or $\mathbf{2}_{ox}$(n=2, 3) were negligible (less than 2%).

Membrane Transport. Transport of Na$^+$ and K$^+$ across a liquid (chloroform) membrane was carried out in a U-tube which consisted of two (IN and OUT) aqueous phases (10 ml each) and a membrane phase (40 ml). The membrane phase was stirred at a constant speed (180 rpm) and thermostated to 30 °C. The rates of K$^+$-transport were estimated from the absorption band of ANS (350 nm) in the OUT aqueous phase.

Results and Discussion

Comments on the Oxidation Methods. We have found that iodine is the most suitable to the oxidation of $\mathbf{2}_{rex}$ to $\mathbf{2}_{ox}$ because the reaction is very fast and occurs under mild conditions. Furthermore, the progress of the reaction can be monitored by the color change. However, it turned out to be rather unsuitable to the oxidation of $\mathbf{1}_{red}$ to $\mathbf{1}_{ox}$ because the intermolecular disulfide formation significantly competed with the intramolecular one. The TLC analysis showed that the oxidation of $\mathbf{1}_{red}$(3.36×10^{-4} mol) by iodine in 50 ml of chloroform gave mainly the polymeric products and $\mathbf{1}_{ox}$ was a minor product. We attempted the isolation of $\mathbf{1}_{ox}$ by preparative TLC but the isolated product was always contaminated with some unknown materials

Table 1. Extraction of alkali metal salts of ANS with $\mathbf{1}_{\text{red}}$ and $\mathbf{1}_{\text{ox}}$ and their association constants (K_c)[a)]

Ionophore	Metal	Ex%	$K_e \cdot 10^{-3}/\text{M}^{-2}$ [b)]	K_c/M^{-1} [c)]
$\mathbf{1}_{\text{red}}$	Na^+	39.9	3.59	756
	K^+	39.0	3.95	697
	Rb^+	31.6	2.89	416
	Cs^+	26.5	2.92	284
$\mathbf{1}_{\text{ox}}$	Na^+	40.2	3.66	771
	K^+	53.3	12.8	2250
	Rb^+	46.7	9.55	1370
	Cs^+	35.6	6.53	635

a) 30 °C. Organic phase: $[\mathbf{1}_{\text{red}}$ or $\mathbf{1}_{\text{ox}}]=4.00\times10^{-3}\,\text{M}$ in *o*-dichlorobenzene: 1-butanol=80:20 by volume. Aqueous phase: pH 4.0 with MOH(0.010 M)–H_3PO_4, [MCl]=0.10 M, [ANS]=5.00×10^{-5} M. b) $K_e=[\text{M}^+\text{A}^-\cdot\mathbf{1}^*]/[\text{M}^+][\text{A}^-][\mathbf{1}^*]$ where the asterisk and A^- refer to the species in the organic phase and the counteranion, respectively. c) $K_c=[\text{M}^+\text{A}^-\cdot\mathbf{1}^*]/[\text{MA}^*][\mathbf{1}^*]=K_e/K_d$ where $K_d=[\text{MA}^*]/[\text{M}^+][\text{A}^-]$.

(probably oligomeric oxidation products).

On the other hand, O_2-oxidation of $\mathbf{1}_{\text{red}}$ in the presence of KOH gave $\mathbf{1}_{\text{ox}}$ as a main product, although the reaction was not so fast. Pure $\mathbf{1}_{\text{ox}}$ could be isolated without using the preparative TLC method. As a control experiment, we oxidized $\mathbf{1}_{\text{red}}$ by O_2 in the presence of triethylamine. Although the main product was still $\mathbf{1}_{\text{ox}}$, a considerable amount of the polymeric products was formed. These results suggest that the "template effect" of K^+ which facilitates the intramolecular disulfide formation may be operative on the oxidation process.

Solvent Extraction of Alkali Metal Cations. The binding ability of $\mathbf{1}_{\text{red}}$ and $\mathbf{1}_{\text{ox}}$ was estimated by solvent extraction of alkali metal salts of 8-anilinonaphthalene-1-sulfonate (ANS) from water to the organic phase (*o*-dichlorobenzene: 1-butanol=80:20 by volume). Alkali picrates which are frequently used for solvent extraction were not employed in the present study, because the oxidative nature of picrate ion is unfavorable to the redox treatment of the ionophores. The extractability(Ex%) was estimated by the partition of ANS between the aqueous and the organic phases. The pH of the aqueous phase was buffered to 4.0 where ANS is fully dissociated while the thiol groups of $\mathbf{1}_{\text{red}}$ are undissociated. We confirmed that both $\mathbf{1}_{\text{red}}$ and $\mathbf{1}_{\text{ox}}$ do not leak into the aqueous phase under the extraction conditions. The results are summarized in Table 1.

Examination of Table 1 reveals that (i) $\mathbf{1}_{\text{red}}$ and $\mathbf{1}_{\text{ox}}$ have the similar Ex% values for Na^+, (ii) $\mathbf{1}_{\text{ox}}$ is capable of extracting K^+, Rb^+, and Cs^+ more efficiently than $\mathbf{1}_{\text{red}}$ and (iii) the maximum Ex% is observed for the extraction of K^+ with $\mathbf{1}_{\text{ox}}$. The inspection of CPK model of $\mathbf{1}_{\text{ox}}$ suggests that two phenolic oxygens can be directed towards the crown ring, indicating the coordination ability to metal ions complexed in the crown ring. However, the oxygens are apparently far from the crown ring plane as compared with those of cryptand 222 which exhibits a high affinity with Na^+ and K^+.[2)] The expansion of the intramolecular cavity of $\mathbf{1}_{\text{ox}}$ is due to six atoms (two sulfurs and four carbons) present between the two oxygens in the disulfide cap. Conceivably, small Na^+ is deeply bound to the diaza-18-crown-6 ring, so that the two oxygens are too far to coordinate to the complexed Na^+ ion. In contrast, other alkali metal ions with relatively large ion-radii would be able to interact with the oxygens owing to the shallow-binding to the crown ring. The situation would be well expressed by "K^+ (Rb^+ and Cs^+ also) perches on the crown ring whereas Na^+ nests in it."[15)]

According to the established procedure,[16—18)] we estimated K_e (extraction equilibrium constants) and K_c(complexation contants). The results in Table 1 indicate again that the K_c values of $\mathbf{1}_{\text{ox}}$ for K^+, Rb^+, and Cs^+ are greater by 2—3 fold than those of $\mathbf{1}_{\text{red}}$, whereas there is no difference in the K_c for Na^+. Conceivably, $\mathbf{1}_{\text{ox}}$ is expected to act as a cryptand analogue, whereas $\mathbf{1}_{\text{red}}$ is a simple crown ether (or at most, a lariat-type crown ether).[19,20)]

The absolute K_c values in Table 1 are smaller by about two orders of magnitude than those of conventional 18-crown-6 analogues.[2—4)] This is due to the two amide nitrogens present in the diaza-18-crown-6 ring. We thus attempted to reduce the carbonyls in $\mathbf{1}_{\text{red}}$ to the methylene groups with B_2H_6 or LiAlH_4. Although we confirmed the disappearance of the carbonyls with IR, the isolation was very difficult and unsuccessful.

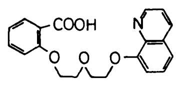
The redox scheme for the interconversion between $\mathbf{2}_{\text{red}}$ and $\mathbf{2}_{\text{ox}}$ can be more simplified, because one need not take the competition between intra- and intermolecular oxidations into account. The results of solvent extraction between water and chloroform are summarized in Table 2. Neither $\mathbf{2}_{\text{red}}$ nor $\mathbf{2}_{\text{ox}}$ leaked into the aqueous phase under the extraction conditions. Unfortunately, the partition of ANS to the chloroform phase was so small that we could not determine the K_d values (see footnote c to Table 1) accurately. Therefore, we determined Ex% and K_e and summarized in Table 2.

It is seen from Table 2 that (i) $\mathbf{2}_{\text{red}}(n=2)$ and $\mathbf{2}_{\text{ox}}(n=2)$ have the highest selectivity towards Na^+ while $\mathbf{2}_{\text{red}}(n=3)$ and $\mathbf{2}_{\text{ox}}(n=3)$ show the highest selectivity towards K^+ (ii) when comparing the $n=2$ series with the $n=3$ series, there is little difference in Ex% for Na^+, but Ex%'s of the $n=3$ series for K^+, Rb^+, and Cs^+ are significantly higher than those of the $n=2$ series, and (iii) most importantly, Ex%'s of $\mathbf{2}_{\text{ox}}$ are higher than $\mathbf{2}_{\text{red}}$, indicating the cooperative ion-binding by two chains of $\mathbf{2}_{\text{ox}}$. It is well known that acyclic polyethers have a relatively good ion-selectivity like cyclic polyethers.[6—11)] The selectivity is particularly associated with the length of the poly(oxyethylene) chain. For example, Hiratani *et al.*[7,8)] demonstrated that **6** and **7** exhibit the selectivity for Li^+ and Na^+, respectively. $\mathbf{2}_{\text{red}}(n=2)$ and $\mathbf{2}_{\text{red}}(n=3)$ which have the chain length similar to **6** and

TABLE 2. EXTRACTION OF ALKALI METAL SALTS OF ANS WITH $\mathbf{2}_{\mathrm{red}}(n=2,\ 3)$ AND $\mathbf{2}_{\mathrm{ox}}(n=2,\ 3)$ AND THEIR EXTRACTION EQUILBRIUM CONNSTANTS $(K_e)^{a)}$

Ionophore	Metal	Ex%	K_e·$^{b)}$/M^{-2}
$\mathbf{2}_{\mathrm{red}}(n=2)$	Li^+	4.7	16.5
	Na^+	8.1	29.5
	K^+	4.8	17.0
	Rb^+	5.3	19.5
	Cs^+	2.5	8.5
$\mathbf{2}_{\mathrm{ox}}(n=2)$	Li^+	10.6	79.9(39.7)
	Na^+	11.9	92.0(45.7)
	K^+	11.0	84.2(41.9)
	Rb^+	9.8	73.1(36.3)
	Cs^+	6.8	49.8(24.5)
$\mathbf{2}_{\mathrm{red}}(n=3)$	Na^+	9.5	35.2
	K^+	10.3	38.1
	Rb^+	9.9	36.8
	Cs^+	5.9	21.0
$\mathbf{2}_{\mathrm{ox}}(n=3)$	Na^+	13.3	105(52.5)
	K^+	15.6	125(61.7)
	Rb^+	12.8	100(50.1)
	Cs^+	10.8	81.6(40.7)

a) 30 °C. Organic phase: $[\mathbf{2}_{\mathrm{red}}(n=2,\ 3)]=2[\mathbf{2}_{\mathrm{ox}}(n=2,\ 3)]=1.00\times10^{-2}$ M in chloroform. Aqueous phase: pH 6.0 with MOH(0.010 M)–H_3PO_4, [MCl]=0.29 M, [ANS]=5.00×10^{-4} M. b) $K_e=[M^+A^-\cdot\mathbf{2}^*]/[M^+][A^-][\mathbf{2}^*]$. The values in the parenthesis are obtained by the same equation on the basis that one quinoline chain corresponds to one ligand (*i.e.*, [ligand]=2[**2**]).



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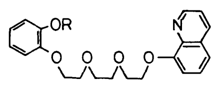

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7, repectively, showed the ion-selectivity towards Na^+ and K^+, respectively. This implies that the maximum selectivity of $\mathbf{2}_{\mathrm{red}}(n=2)$ and $\mathbf{2}_{\mathrm{red}}(n=3)$ shifts a little to the larger metal cations. According to Hiratani *et al.*,[7,8] the pseudo-cyclic structures from **6** and **7** are formed so that the terminal benzene and quinoline can overlap each other. Such a stacking association of the aromatic terminal groups cannot be expected for $\mathbf{2}_{\mathrm{red}}$. Conceivably, the sizes of the psuedo-cyclic structures of $\mathbf{2}_{\mathrm{red}}$ are somewhat greater than those of corresponding **6** and **7**.

The extraction data showed that Ex%'s of $\mathbf{2}_{\mathrm{ox}}$ are significantly greater than those of $\mathbf{2}_{\mathrm{red}}$, indicating that the two chains in $\mathbf{2}_{\mathrm{ox}}$ act cooperatively on metal-binding. On the other hand, the ion-selectivities of $\mathbf{2}_{\mathrm{ox}}$ are similar to those of $\mathbf{2}_{\mathrm{red}}$, indicating that the two chains in $\mathbf{2}_{\mathrm{ox}}$ would act rather independently. The apparently incompatible results may be rationalized in terms of the peculiar conformation of the central disulfide linkage. The azimuthal angle in the lowest energy conformation of diethyl disulfide is considered to be 90°, although the bulky substituents may enlarge the angle.[21] It is unconceivable, therefore, that the two chains in $\mathbf{2}_{\mathrm{ox}}$ enjoy the coplanarity around a metal ion. Probably, $\mathbf{2}_{\mathrm{ox}}$ wraps a metal cation by forming a helical structure. In fact, several podands having the coordinative terminal groups adopt helical structures to bind metal ions, [6–8,10] and the azimuthal angle of the central disulfide linkage would be rather advantageous to the helical structure. If one accepts the hypothesis, one can elucidate the enhanced Ex%'s of $\mathbf{2}_{\mathrm{ox}}$ relative to $\mathbf{2}_{\mathrm{red}}$ as well as the unchanged ion-selectivities. To obtain evidence for this, we took the NMR spectra of $\mathbf{2}_{\mathrm{ox}}$ in the presence of K^+ and Rb^+, but could not detect the appreciable change in chemical shifts probably because of the low association abilities.

TABLE 3. RATES (k) OF ION TRANSPORT THROUGH A LIQUID MEMBRANE (30 °C)$^{a)}$

Run	Metal	Carrier	Transport rate
			10^{-6} mol h^{-1}
1	Na^+	$\mathbf{2}_{\mathrm{red}}(n=2)$	0.07
2	Na^+	$\mathbf{2}_{\mathrm{ox}}(n=2)$	0.09
3	Na^+	$\mathbf{2}_{\mathrm{red}}(n=3)$	0.06
4	Na^+	$\mathbf{2}_{\mathrm{ox}}(n=3)$	0.20
5	K^+	$\mathbf{2}_{\mathrm{red}}(n=2)$	0.10
6	K^+	$\mathbf{2}_{\mathrm{ox}}(n=2)$	0.18
7	K^+	$\mathbf{2}_{\mathrm{red}}(n=3)$	0.12
8	K^+	$\mathbf{2}_{\mathrm{ox}}(n=3)$	0.50
9$^{b)}$	K^+	$\mathbf{2}_{\mathrm{red}}(n=3)\rightarrow\mathbf{2}_{\mathrm{ox}}(n=3)$	0.10→0.75

a) In aqueous phase (10 ml): [MCl]=0.290 M, pH 6.0 with MOH(0.010 M)–H_3PO_4(0.011 M), [ANS]=5.00×10^{-3} M. OUT aqueous phase (10 ml): water. Membrane phase (40 ml $CHCl_3$): $[\mathbf{2}_{\mathrm{red}}]=2[\mathbf{2}_{\mathrm{ox}}]=2.00\times10^{-3}$ M. b) In order to suppress the pH change in the IN aqueous phase by added I_2 the buffer concentration is enhanced while $[K^+]$ is constant: [MCl]=0.100 M, pH 6.0 with MOH(0.200 M)–H_3PO_4 (0.114 M), [ANS]=5.00×10^{-3} M.

Ion-Transport across a Liquid Membrane. Various kinds of chemical and physical phenomena have been utilized to increase the rate of ion transport through membranes: redox energies,[22,23] light energies,[13,14,24–27] countercurrent of metal cations,[28] pH-dependent lactone cyclization,[29] *etc.*[30] Some of these systems have been applied to active transport. To the best of our knowledge, however, there exists no precedent for the ion-transport mediated by the redox interconversion of ionophores such as **1** or **2**.[31] We here demonstrate that the ion-transport rate can be changed by the redox interconversion between $\mathbf{2}_{\mathrm{red}}$ and $\mathbf{2}_{\mathrm{ox}}$.

Table 3 shows the rates of Na^+ or K^+ transport across a liquid (chloroform) membrane. The leak of the metal ions was not detected in the absence of **2**. For $\mathbf{2}_{\mathrm{red}}(n=2)$ and $\mathbf{2}_{\mathrm{ox}}(n=2)$, the rates of Na^+ transport are similar but the rate of K^+ transport with $\mathbf{2}_{\mathrm{red}}(n=2)$ is significantly higher than that with $\mathbf{2}_{\mathrm{red}}$ $(n=2)$. The results are well compatible with the extraction data in Table 2: for example, Ex% of Na^+ with $\mathbf{2}_{\mathrm{ox}}(n=2)$(11.9%) is close to that with $\mathbf{2}_{\mathrm{red}}(n=2)$(8.1%), whereas Ex% of K^+ with $\mathbf{2}_{\mathrm{ox}}(n=2)$(11.0%) is more than two times greater than that with $\mathbf{2}_{\mathrm{red}}(n=2)$(4.8%). A similar trend was observed for the transport with $\mathbf{2}_{\mathrm{red}}(n=3)$ and $\mathbf{2}_{\mathrm{ox}}(n=3)$: that is $\mathbf{2}_{\mathrm{ox}}(n=3)$ exhibits the transport ability higher than $\mathbf{2}_{\mathrm{red}}(n=3)$. Figure 1 shows the plot of Ex% against the rate of ion-transport. It is clearly seen from Fig. 1 that the higher is the Ex%, the faster is the ion-transport rate. One can conclude on the basis of this fact that the ion-extraction step from the IN aqueous phase to the membrane phase, but not the ion-release step from the membrane phase to the OUT aqueous phase, is totally rate-determining.

The largest rate increase was observed for K^+ transport with $\mathbf{2}_{\mathrm{ox}}(n=3)/\mathbf{2}_{\mathrm{red}}(n=3)$(4.2-fold). We thus con-

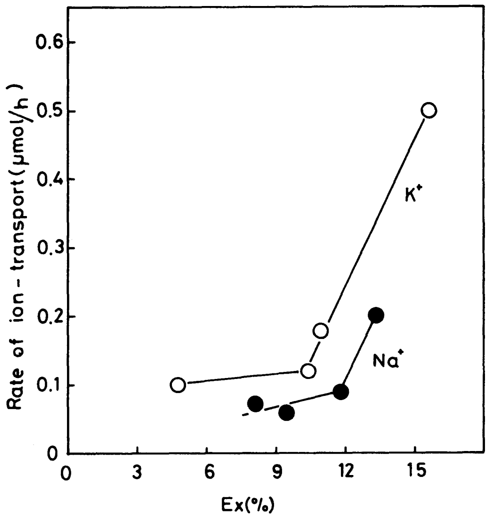

Fig. 1. Plots of rate of ion-transport *vs.* Ex%.

ducted the "redox-switched" experiment with this combination. K^+ transport was started with $\mathbf{2}_{\mathrm{red}}$ (n=3) as a carrier in the membrane phase, and iodine($[I_2]$= 0.5 [$\mathbf{2}_{\mathrm{red}}$($n$=3)]) was added to the membrane phase after 2 h. As illustrated in Fig. 2, the rate of K^+ transport was enhanced to 7.5×10^{-7} mol h^{-1} from 1.0×10^{-7} mol h^{-1} after an induction period (about 1 h). In a separate study, we corroborated that $\mathbf{2}_{\mathrm{red}}$($n$=3) has been oxidized to $\mathbf{2}_{\mathrm{ox}}$ (n=3) within 1 h in the membrane and that K^+ is not transported through the chloroform membrane containing only iodine. Therefore, the marked rate increase can be ascribed to the production of the capable ion-carrier (*i.e.*, $\mathbf{2}_{\mathrm{ox}}$(n=3)) in the membrane phase by treatment with the oxidizing agent. The induction period after I_2 addition is ascribed either to the oxidation time of $\mathbf{2}_{\mathrm{red}}$ to $\mathbf{2}_{\mathrm{ox}}$ or to the diffusion of K^+ across the liquid membrane. The slightly greater transport rate after the oxidation relative to that with $\mathbf{2}_{\mathrm{ox}}$ is probably due to the change in the buffer concentration. We also attempted the reverse control of K^+ transport by reducing $\mathbf{2}_{\mathrm{ox}}$(n=3) to $\mathbf{2}_{\mathrm{red}}$($n$=3) by tributylphosphine (0.01 M=10[$\mathbf{2}_{\mathrm{ox}}$(n=3)]). Although $\mathbf{2}_{\mathrm{ox}}$(n=3) was reduced to $\mathbf{2}_{\mathrm{red}}$($n$=3) in 1.5 h, the K^+ increase in the OUT aqueous phase was scarcely affected for 4 h after the addition of tributylphosphine. The membrane phase contained a significant amount of K^+ extracted with $\mathbf{2}_{\mathrm{ox}}$(n=3) before tributylphosphine addition. Conceivably, the K^+ ion was released gradually to the OUT aqueous phase even after $\mathbf{2}_{\mathrm{ox}}$(n=3) being reduced to $\mathbf{2}_{\mathrm{red}}$($n$=3). At present, we consider that the "volume" of the membrane phase must be considerably reduced in order to achieve the rapid response of the reverse control.

Ion transport using the interconversion between $\mathbf{1}_{\mathrm{red}}$ and $\mathbf{1}_{\mathrm{ox}}$ may be also interesting. In this case, however, one has to pay additional attention to intra- *versus* intermolecular oxidation of $\mathbf{1}_{\mathrm{red}}$ in the membrane phase. In addition, the difference in K_c values is not large enough to attain the efficient control of ion-transport by redox-switch. We thus did not perform the ion-transport with $\mathbf{1}_{\mathrm{red}}$ and $\mathbf{1}_{\mathrm{ox}}$.

Conclusions. The present system demonstrated that the ion-binding ability of redox-functionalized ionophores can be changed by the treatment with redox reagents. This is directly applicable to the control of ion transport across membranes. The novel phenomenon becomes possible because these synthetic ionophores have within the molecule both a redox-functional group and an ionophilic site. Although the framework of the present "redox-switched" functions must be further improved, we expect that this concept might be applied more generally to the control of the chemical and physical functions of synthetic ionophores by the redox energy source.

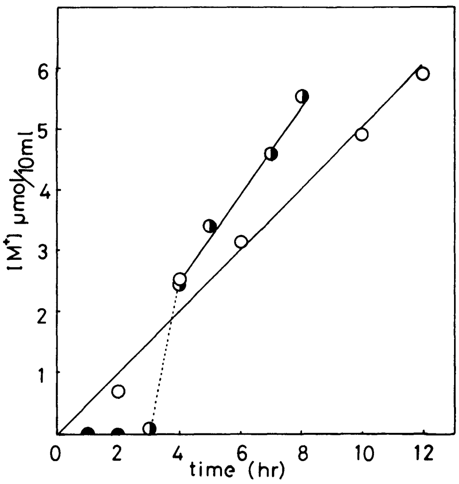

Fig. 2. Transport of K^+ across a liquid (chloroform) membrane. ○ with $\mathbf{2}_{\mathrm{ox}}$ (n=3) (run 8 in Table 3); ●→◑ transport was started with $\mathbf{2}_{\mathrm{red}}$ (n=3) and I_2 was added after 2 h (run 9 in Table 3).

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