J. Am. Chem. Soc. 1985, 107, 3950-3955

Redox-Switched Crown Ethers. 3. Cyclic–Acyclic Interconversion Coupled with Redox between Dithiol and Disulfide and Its Application to Membrane Transport[1]

Seiji Shinkai,* Kenichi Inuzuka, Osamu Miyazaki, and Osamu Manabe*

Contribution from the Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852, Japan. *Received December 18, 1984*

Abstract: A pair of "redox-switched" monobenzo-21-crown-7 (Cr) analogues with a dithiol group at α,ω-positions (Cr_{red}) and a disulfide bond in the ring (Cr_{ox}) has been synthesized. The interconversion between these two forms was effected by treatment with redox reagents. It was found that the oxidation process ($Cr_{red} \rightarrow Cr_{ox}$) is remarkably subject to the metal template effect: the oxidation of Cr_{red} in the absence of the template gave the polymeric products (MW > 2000, 66%) in addition to Cr_{ox} (5.2%), cyclic dimer (15%), and cyclic trimer (3.6%), whereas the main products in the presence of Cs^+ were Cr_{ox} (70%) and cyclic dimer (28%) and no polymeric material was detected. The polymeric products yielded in the absence of the template depolymerized slowly to the cyclic products. Also interesting is the finding that the "kinetic" template effect is observed for the oxidation process: the pseudo-first-order rate constants for the oxidation of Cr_{red} by 3-methyllumiflavin are significantly enhanced with increase in the concentrations of Rb^+ and Cs^+. Such a rate increase could not be found for the oxidation of 1,4-butanedithiol by 3-methyllumiflavin. The results of solvent extraction and evaluation of the association constants (K) established that (i) Cr_{ox} has the highest selectivity for Cs^+, as has Cr, (ii) the Ex% (and K) of Cr_{ox} is smaller than that of Cr, and (iii) most importantly, Cr_{red} scarcely binds alkali metal cations. In ion transport across a liquid ($CHCl_3$) membrane, Cr_{ox} carried Cs^+ 6.2 times faster than Cr_{red}. Thus, it was demonstrated that the rate of Cs^+ transport can be regulated by the interconversion between Cr_{red} and Cr_{ox} in the membrane phase. This is a new method to control the membrane transport rates by a redox-switch.

Macrocyclic polyethers contain intramolecular cavities delineated by molecular segments and are capable of specific chelation with alkali and alkaline earth metal cations. It is now established that the specificity stems from a host–guest relationship:[2-5] for example, the ion selectivity is largely governed by the size of the intramolecular cavities. Thus, one may expect that if the topological ring shape can be reversibly changed, it would lead to the control of ion-binding ability and ion selectivity. It is well-known that certain natural ionophores such as monensin and nigericin utilize the medium pH as a trigger to change the topological ring shapes.[6-8] In order to mimick the functions of these natural antibiotics, several pH-responsive crown ethers have been synthesized.[8-12] More recently, several "photoresponsive" crown ethers have been reported in which crown ethers are combined intramolecularly with photofunctional groups.[13-18] As their topological ring shapes change in response to photoirradiation, they may be regarded as a new class of ionophores imitating the functions of the natural ionophores. It occurred to us that the most direct change in the cavity shape would be attained by reversible bond formation and bond scission leading to cyclic–acyclic interconversion and that the redox reaction of a thiol–disulfide couple which is ubiquitously seen in nature would be the most sutiable candidate for this. We and Raban et al.[1,19-21] have communicated a few examples of this type of "redox-switched" crown ethers which involve the breakable disulfide bond as a ring member.

We here report a pair of new "redox-switched" crown ether analogues bearing a disulfide bond in the ring and a dithiol group at its α,ω-positions. The oxidized form (Cr_{ox} = 2,3-benzo-1,4,7,10,17,20-hexaoxa-13,14-dithiacyclodocos-2-ene) is a coronand analogue and is expected to bind metal ions in the cavity. The reduced form (Cr_{red} = 10,11-benzo-3,6,9,12,15,18-hexaoxaeicos-10-ene-1,20-dithiol) is a podand analogue and is expected to show poor ion affinity. We have found that (i) Cr_{ox} has the extractability much greater than Cr_{red}, (ii) the oxidation step ($Cr_{red} \rightarrow Cr_{ox}$) is significantly subjected to the template effect, (ii) the disulfide-containing polymers slowly depolyermize to Cr_{ox}, and (iv) $Cr_{red} \rightleftarrows Cr_{ox}$ interconversion is useful to control the rate of ion transport across a liquid membrane.

Experimental Section

Materials. Cr_{ox} and Cr_{red} were synthesized according to eq 1 and 2. Purification of Cr_{red} in eq 1 was very difficult because of ready oxidation

---

(1) Preliminary communication: Shinkai, S.; Inuzuka, K.; Miyazaki, O.; Manabe, O. *J. Org. Chem.* **1984**, *49*, 3440.

(2) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8.

(3) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49.

(4) Gokel, G. W.; Korzeniowski, S. H. In "Macrocyclic Polyether Syntheses"; Springer-Verlag: Berlin, 1982.

(5) Weber, E.; Vögtle, F. In "Host Guest Complex Chemistry I"; Springer-Verlag: Berlin, 1981; p 1.

(6) Choy, E. M.; Evans, D. F.; Cussler, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 7085.

(7) Molnar, W. J.; Wang, C.-P.; Evans, D. F.; Cussler, E. L. *J. Membr. Sci.* **1978**, *4*, 129.

(8) Wierenga, W.; Evans, B. R.; Woltersom, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 1334.

(9) Nakatsuji, Y.; Kobayashi, H.; Okahara, M. *J. Chem. Soc., Chem. Commun.* **1983**, 800.

(10) (a) Frederick, L. A.; Fyles, T. M.; Malik-Diemer, V. A.; Whitfield, D. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1211. (b) Yamazaki, N.; Nakahama, S.; Hirao, A.; Negi, S. *Tetrahedron Lett.* **1978**, 2429.

(11) (a) Hiratani, K.; Aiba, S.; Nakagawa, O. *Chem. Lett.* **1980**, 477. (b) Charewicz, W. A.; Bartsch, R. A. *J. Membr. Sci.* **1983**, *12*, 323.

(12) Shinkai, S.; Kinda, H.; Araragi, Y.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 559.

(13) Yamashita, I.; Fujii, M.; Kaneda, T.; Misumi, S.; Otsubo, T. *Tetrahedron Lett.* **1980**, *21*, 541.

(14) Shiga, M.; Takagi, M.;, Ueno, K. *Chem. Lett.* **1980**, 1021.

(15) Shinkai, S.; Nakaji, T.; Nishida, Y.; Ogawa, T.; Manabe, O. *J. Am. Chem. Soc.* **1980**, *102*, 5860.

(16) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, S.; Manabe, O. *J. Am. Chem. Soc.* **1981**, *103*, 111.

(17) Shinkai, S.; Minami, T.; Kusano, Y.; Manabe, O. *J. Am. Chem. Soc.* **1983**, *105*, 1851.

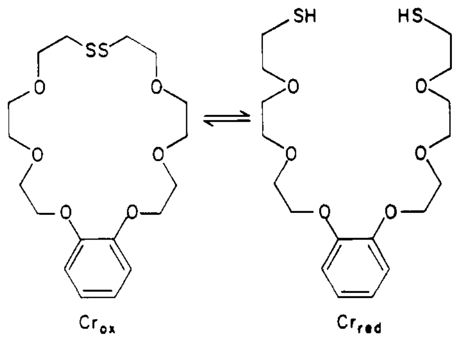
(18) For a comprehensive review on photoresponsive crown ethers see: Shinkai, S.; Manabe, O. In "Host Guest Complex Chemistry III"; Springer-Verlag: Berlin, 1984; p 67.

(19) (a) Minami, T.; Shinkai, S.; Manabe, O. *Tetrahedron Lett.* **1982**, *23*, 5167. (b) Shinkai, S.; Minami, T.; Araragi, Y.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2*, in press.

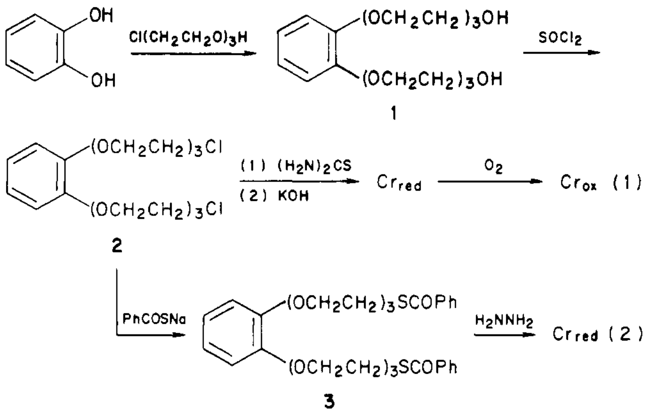
(20) (a) Shinkai, S.; Inuzuka, K.; Manabe, O. *Chem. Lett.* **1983**, 747. (b) Shinkai, S.; Inuzuka, K.; Hara, K.; Sone, T.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2150.

(21) Raban, M.; Greenblatt, J.; Kandil, F. *J. Chem. Soc., Chem. Commun.*, **1983**, 1409.

0002-7863/85/1507-3950$01.50/0



either to Cr_{ox} or to oligomeric materials. We thus developed eq 2 in which the final step (H_2NNH_2 treatment) proceeded under reductive atmosphere. In this method the product was protected from air oxidation, so that Cr_{red} could be easily isolated.



***O*,*O*-Bis(8-hydroxy-3,6-dioxaoctyl)catechol (1).** Catechol (11.0 g, 0.10 mol) and sodium methoxide (10.8 g, 0.20 mol) were dissolved in 300 mL of 1-butanol under a N_2 stream. To this solution 1-chloro-8-hydroxy-3,6-dioxaoctane (43.1 g, 0.24 mol) was added dropwise at 80 °C. The reaction was continued at 100–110 °C for 55 h. The solution was evaporated to dryness in vacuo, the residue being dissolved in water. The aqueous solution was extracted with chloroform, and the chloroform solution was evaporated to dryness. The oily residue dissolved in water was extracted with ligroin in a continuous extraction apparatus in order to remove remaining 1-chloro-8-hydroxy-3,6-dioxaoctane. The aqueous phase was treated with active charcoal and then evaporated to dryness: oil, yield 48.9%, single spot on TLC; IR(neat) ν_{OH} 3400 cm^{-1}, ν_{C-O-C} 1110 cm^{-1}; NMR($CDCl_3$) δ 3.38 (2 H, br, OH), 3.60 (16 H), 3.82 (4 H), and 4.14 (4 H), (m, t, and t, respectively, OCH_2), 6.84 (4 H, s, benzene protons). Anal. ($C_{18}H_{30}O_8 \cdot H_2O$) C, H.

***O*,*O*-Bis(8-chloro-3,6-dioxaoctyl)catechol (2).** 1 (17.2 g, 45.9 mmol) in 80 mL of benzene was treated with thionyl chloride (21.8 g, 184 mmol) and pyridine (14.5 g, 184 mmol) at 70–80 °C for 24 h. The reaction mixture was poured into water, the aqueous solution being extracted with benzene. The benzene solution was washed well with water, and finally benzene was evaporated in vacuo: oil, yield 57.2%; single spot on TLC; IR (neat) no ν_{OH}, ν_{C-O-H} 1120 cm^{-1}; NMR ($CDCl_3$) δ 3.64 (16 H), 3.80 (4 H), and 4.14 (4 H) (m, t, and t, respectively, OCH_2), 6.87 (4 H, s, benzene protons). Anal. ($C_{18}H_{28}O_6Cl_2 \cdot H_2O$) C, H.

Cr_{ox} (According to eq 1). 2 (3.00 g, 7.29 mmol) and thiourea (1.67 g, 21.9 mmol) were refluxed in ethanol (70 mL) for 96 h. The progress of the reaction was followed by a TLC method. The solvent was evaporated to dryness, and the resultant thiuronium salt was dissolved in 30 mL of deaerated water containing KOH (1.10 g, 19.6 mmol). The mixture was heated at 70–80 °C for 2 h. The aqueous solution containing Cr_{red} was extracted with chloroform, the chloroform solution being evaporated to dryness. The residue (Cr_{red}) was dissolved in sulfolane (100 mL)–methanol (100 mL) containing 400 mg of NaOH, and an O_2 stream was introduced into this solution at room temperature. After 20 h the white precipitate was removed by filtration, the filtrate being concentrated in vacuo. The products thus obtained were purified by a preparative TLC method (silica gel–ethyl acetate): mp 45–49 °C, yield 47.0%; IR (neat) ν_{C-O-C} 1120 cm^{-1}; NMR ($CDCl_3$) δ 2.92 (4 H, t, SCH_2), 3.76 (16 H) and 4.16 (4 H) (m and t, respectively, OCH_2), 6.87 (4 H, s, benzene protons); mass spectrum, *m/e* 404 (M^+). Anal. ($C_{18}H_{28}O_6S_2 \cdot 0.5H_2O$) C, H, S.

***O*,*O*-Bis(8-benzoylthio-3,6-dioxaoctyl)catechol (3).** 2 (4.10 g, 9.97 mmol) and sodium thiobenzoate (3.32 g, 24.0 mmol) in 50 mL of deaerated ethanol were heated at the reflux temperature for 24 h in the presence of sodium hydrogencarbonate (2.00 g, 23.8 mmol). The precipitate was removed by filtration, the filtrate being treated with active charcoal. The solution was subjected to separation by a preparative TLC method (silica gel–chloroform): oil, one spot on TLC, yield 36.4%; IR (neat) ν_{COS} 1660 cm^{-1}; NMR ($CDCl_3$) δ 3.29 (4 H, t, SCH_2) 3.71 (12 H), 3.87 (4 H), and 4.19 (4 H) (m, t, and t, respectively, OCH_2), 6.91 (4 H) and 7.68 (5 H) (s and m, respectively, benzene protons). Anal. ($C_{32}H_{38}O_8S_2$) C, H, S.

Cr_{red} and Cr_{ox} (According to eq 2). 3 (1.63 g, 2.65 mmol) and hydrazine monohydrate (5 mL, 97.7 mmol) in 200 mL of methanol were refluxed for 1 h under a N_2 stream. The progress of the reaction was monitored by a TLC method. The solution was acidified by concentrated HCl and evaporated by dryness in vacuo. The residue (Cr_{red}) taken in chloroform was washed with water, treated with active charcoal, and evaporated to dryness; slightly yellow oil (viscous), yield 96.5%; single spot on TLC; IR (neat) ν_{SH} 2560 cm^{-1}, no ν_{COS}; NMR ($CDCl_3$) δ 1.58 (2 H, t, SH), 2.68 (4 H, h, SCH_2), 3.68 (4 H), 3.86 (4 H), and 4.18 (4 H), (m, t, and t, respectively, OCH_2), 6.92 (4 H, s, benzene protons). Anal. ($C_{18}H_{30}O_6S_2$) C, H, S.

Cr_{red}(1.00 mM) was oxidized to Cr_{ox} by I_2 (1.10 mM) in methanol at room temperature in the presence of potassium tosylate (50 mM) and tetraethylammonium hydroxide (50 mM). After 1 day, the solution was acidified by concentrated HCl and subjected to a preparative TLC separation: yield 56%. The analytical data were identical with those described for eq 1.

Product Analyses. In order to evaluate the metal template effect, the oxidation of Cr_{red} (1.00×10^{-3} M) by I_2 (1.10×10^{-3} M) was carried out in methanol (containing 5.00×10^{-2} M Et_4NOH) at room temperature in the absence or the presence of alkali tosylates (5.00×10^{-2} M). After 5 min, the reaction mixture was neutralized by concentrated HCl and evaporated in vacuo. The residue was dissolved in tetrahydrofuran (THF), the insoluble material being removed by filtration. The THF solution thus obtained was subjected to the analysis by gel-permeation chromatography (column, Shimadzu HSG-20). The time spent for the workup was about 30 min.

The content of the thiol groups remaining unoxidized in the product mixture was determined in the reaction with Ellman's reagent (5,5′-dithiobis(2-nitrobenzoic acid))[22] in aqueous solution buffered to pH 8.0 (0.01 M phosphate). The concentration was calculated from the increase in the absorption band at 412 nm (ϵ_{412} 13 600).[22]

Solvent Extraction and Association Constants. The ion-binding ability was estimated by anaerobic solvent extraction of alkali metal salts of 8-anilinonaphthalene-1-sulfonate (ANS) from water to chloroform at 30 °C. Picrate ion, usually employed for solvent extraction, was not used in the present redox system because of its oxidative properties. The extractability (Ex %) was determined by the partition of ANS between the aqueous and the chloroform phase. The pH of the aqueous phase was adjusted to 5.0 where ANS is fully dissociated while the thiol groups in Cr_{red} are undissociated. Under these conditions neither Cr_{red} nor Cr_{ox} leaked into the aqueous phase.

The association constants (*K*) for Cr_{ox} and monobenzo-21-crown-7 (Cr) were estimated conductometrically[23] in dehydrated propylene carbonate at 30 °C. The conductivity measurements for Cr and Cr_{ox} were carried out at $[Cr]/[M^+] = 0–4.8$ and $[Cr_{ox}]/[M^+] = 0–14$, respectively. The data were analyzed by a nonlinear least-squares procedure with a computer program.[24]

Flavin Oxidation of Dithiols. The oxidation of Cr_{red} and 1,4-butanedithiol by 3-methyllumiflavin was carried out at 30 °C in anaerobic water–ethanol (20:80 v/v) solvent adjusted to pH 9.0. The progress of the reaction was followed spectrophotometrically by monitoring the disappearance of the absorption band of oxidized 3-methyllumiflavin at 445 nm. The time dependence of the absorbance well satisfied the first-order rate equation for up to 3 half-lives. Introduction of O_2 into the final solution regenerated the absorption spectrum of 3-methyllumiflavin quantitatively.

Ion Transport across a Liquid Membrane. Transprt of alkali metal cations across a chloroform liquid membrane was examined anaerobically within a U-tube (diameter = 2.5 cm) immersed in a thermostated (30 °C) water bath. The transport system consisted of IN aqueous phase (10 mL)/membrane phase (40 mL)/OUT aqueous phase (10 mL). The membrane phase was stirred at a constant speed (ca. 400 rpm). The rates of ion transport were determined either by the increase in the absorbance of the counteranions (ANS, λ_{max} 350 nm) or by directly measuring the concentration of alkali metal cations by atomic absorption spectroscopy.

---

[22] Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70.

[23] Takeda, Y.; Yano, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1720.

[24] Evans, D. F.; Wellington, S. L.; Nadis, J. A.; Cussler, E. L. *J. Solution Chem.* **1972**, *1*, 499.

Table I. Extraction of Alkali Metal Salts of ANS with Cr_{red}, Cr_{ox}, and Monobenzo-21-crown-7 (Cr)[a]

metal	Ex (%) Cr_{red}	Cr_{ox}	Cr
Na^+	0	0	1.9
K^+	0.3	3.3	33.8
Rb^+	0.5	5.6	66.4
Cs^+	1.2	6.7	72.3

[a] 30 °C, N_2. Aqueous phase: [MCl] = 0.05 M, [ANS] = 5.00×10^{-4} M, pH 5.0 with MOH (0.01 M)-phosphoric acid. Organic phase ($CHCl_3$): [crown] = 1.00×10^{-3} M.

Table II. Association Constants of Cr_{ox} and Cr in Propylene Carbonate at 30 °C[a]

crown	K (M^{-1}) Na^+	K^+	Rb^+	Cs^+
Cr_{ox}	*b*	180	290	320
Cr	410	1270	1850	2070

[a] Alkali perchlorates were used. [b] The K is too small to determine accurately ($K \approx$ ca. 30 M^{-1}).

Further details were described in ref 16 and 20.

The oxidation of Cr_{red} to Cr_{ox} in the membrane was easily effected by addition of equimolar I_2. It was confirmed on the basis of a TLC method that the oxidation was completed in 5 min at room temperature. On the other hand, the reduction of Cr_{ox} to Cr_{red} in the membrane was more difficult: finally, we found that the disulfide bond in Cr_{ox} can be cleaved by 1,4-butanedithiol in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU). The reaction was completed in about 30 min.

Results and Discussion

Estimation of Ion-Binding Ability. The ion-binding ability of Cr_{red} and Cr_{ox} was estimated by anaerobic solvent extraction of alkali metal salts of ANS from water to chloroform and was compared with that of monobenzo-21-crown-7 (Cr) in which the disulfide bond is replaced by an ethereal oxygen. The results are summarized in Table I. Examination of Table I reveals the following results: (i) Cr_{ox} has as high a selectivity for Cs^+ as Cr has, (ii) the absolute Ex % of Cr_{ox} (6.7%) is smaller than that of Cr (72.3%), and (iii) most importantly, Cr_{red} scarcely extracts alkali metal cations into the organic phase.

A similar trend was obtained from evaluation of the association constants (K) in propylene carbonate by a conductometrical method (Table II). The K values for Cr_{red} (about all metals) and Cr_{ox} (about Na^+) were too small to determine by this method. Cr gave the greatest K ($\log K = 3.32$) for Cs^+, which may be comparable with that of Cs^+ and dibenzo-24-crown-8 in propylene carbonate ($\log K = 3.46$).[23] Cr_{ox} also gave the greatest K for Cs^+, which is smaller by a factor of 6.5 than that of Cs^+ and Cr. Similarly, other K values for Cr_{ox} are 6.4–7.1 times smaller than the corresponding K for Cr.

Inspection of Corey–Pauling–Koltun (CPK) models suggests that the ring size of Cr_{ox} is close to or slightly larger than that of Cr. This is the origin of the Cs^+ selectivitiy as Cr usually shows.[2-5] Comparison of Ex % and K of Cr_{ox} with those of Cr indicates, however, that the replacement of an ethereal oxygen with a disufide bond brings forth a big difference in the Cs^+ affinity. This is due to the incorporation of the disulfide bond having no coordination ability. It is surprising that the elimination of only one chelating oxygen of seven causes such a conspicuous change. Previously, Drewes and Riphagen[25] synthesized crown ether analogoues in which $-O(CH_2CH_2O)_n-$ (n = 3, 4) is linked to –CO–(*o*-phenyl)–SS–(*o*-phenyl)–CO–. Unfortunately, they could not find any positive result for binding of alkali metal ions. More recently, Raban et al.[21] synthesized 1,2-dithia-5,8,11,14,17-pentaoxacyclononadecane, a disulfide analogue of 18-crown-6. Preliminary solvent extraction of alkali picrates indicated that the Ex % of Na^+ and K^+ for this compound are smaller than those for dibenzo-18-crown-6 and rather comparable with those for hexaethylene glycol. These results consistently suggest that the incorporation of the long noncoordinative unit into the polyether ring is very unfavorable to ion binding.

Table III. Effect of Metal Ions on the Product Distribution

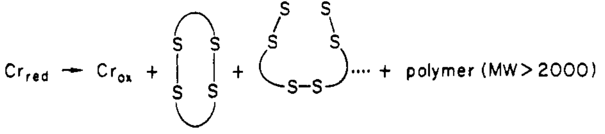
metal	product (%) Cr_{ox}	cyclic dimer	cyclic trimer	polymer
	After 30 min			
none	5.2	15	3.6	66
Na^+	62	33	0	0
K^+	67	33	trace	0
Cs^+	70	28	1.6	0
	After 20 h			
none	23	24	6.4	42

Meanwhile, there is another way to elucidate the Ex % decrease in Cr_{ox}. It is known that the azimuthal angle of the disulfide bond is usually 90° in the lowest energy state.[26] If this is the case in Cr_{ox}, the ring cannot adopt a planar conformation as do the "regular" crown ethers. Thus, the unfavorable, distorted conformation may also increase the Ex % and K of Cr_{ox} relative to Cr.

The finding (iii) suggests, on the other hand, that the ion-binding ability of crown ether analogues would be regulated by redox-switched cyclic–acyclic interconversion. We have found that Cr_{ox} is reduced to Cr_{red} by sodium dithionite, 2-mercaptoethanol, 1,4-butanedithiol, tri-*n*-butylphosphine, or $NaBH_4$, while Cr_{red} is readily oxidized to Cr_{ox} by O_2, I_2, etc. The more interesting process is the latter oxidation of Cr_{red} to Cr_{ox}, because one may expect the metal template effect on the ring-formation step. We have studied the metal template effect as a preclude to ion transport controlled by a redox switch.

Template Effects on the Ring-Formation Process. Recently, the template effect of metal cations on the ring-formation step of crown ethers has widely been investigated by Mandolini et al.,[27] but the method (carried out in strongly basic solutions) is not necessarily convenient, particularly for the kinetic studies. We have found that the facile oxidation of Cr_{red} to Cr_{ox} is very useful as a convenient method to evaluate the metal template effect.

Basically, the oxidation of Cr_{red} is a competitive reaction either to Cr_{ox} or to polymeric products, and the relative rates of these two processes can be evaluated by the product analysis. Cr_{red} (1.00 mM) was treated with I_2 (1.10 mM) in methanol (10 mL) at room temperature in the presence of 50 mM tetraethylammonium hydroxide. The solution was acidified by concentrated HCl and evaporated to dryness in vacuo, and the residue was dissolved in THF (10 mL). The THF solutions thus prepared were subjected to analysis by gel-permeation chromatography. The operation from I_2 oxidation to GPC analysis took 30 min. As shown in Table III, the oxidation of Cr_{red} in the absence of the template mainly gave the polymeric products (MW > 2000, 66%). The cyclic products detected were Cr_{ox} (5.2%), cyclic dimer (SS–SS, 15%), and cyclic trimer (SS–SS–SS, 3.6%). There is a precedent for the formation of similar cyclic dimer and trimer: Sisido et al.[28] have found that air oxidation of polysarcosine (degree of polymerization, $\bar{n}$ = 20) bearing thiol groups at its chain ends gives cyclic monomer, dimer, and trimer in the molar ratio of 1:2:1. Thus, the present oxidation proceeds according to eq 3. In the presence



(3)

---

(25) Drewes, S. E.; Riphagen, B. G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2574.

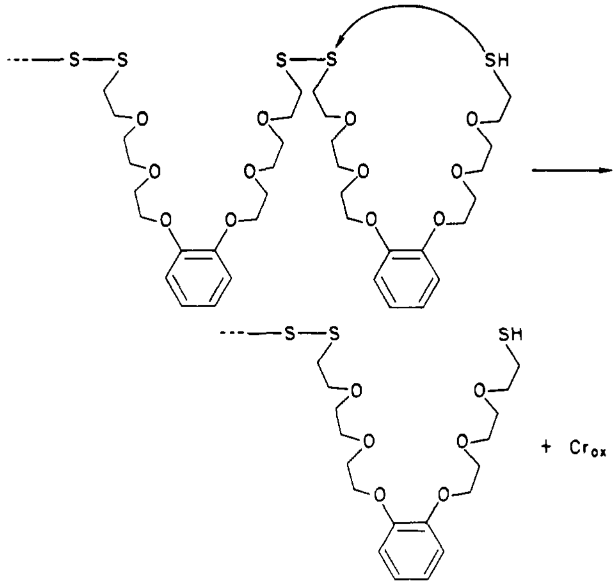
(26) Pryor, W. P. In "Mechanisms of Sulfur Reactions"; McGraw-Hill: New York, 1962; p 18.

(27) Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1984**, *106*, 168 and references cited therein.

(28) Sisido, M.; Tamura, F.; Imanishi, Y.; Higashimura, T. *Biopolymers* **1977**, *16*, 2723.

of alkali tosylates (50 mM) as template, on the other hand, the main products were Cr_{ox} (62–70%) and cyclic dimer (28–33%) and no polymeric material was detected, and the most effective template was Cs^+ ion which associates with Cr_{ox} most strongly. These findings show that the metal template strikingly affects the product distribution in the oxidation of Cr_{red}.

Interestingly, we have found that when the THF solution containing the polymeric products was left at room temperature, the product distribution is remarkably time dependent: Figure 1 shows the time dependence of each species obtained in the absence of the template metal. It is seen from Figure 1 that (i) the fraction of the polymeric products decreases linearly with time, and correspondingly the sum of the cyclic products increases, and (ii) Cr_{ox} rapidly increases in the initial stage (10 h), and (iii) cyclic dimer and trimer increase gradually after 10 h. We estimated the concentration of the terminal thiol groups by Ellman's reagent. The sample taken 30 min after I_2 oxidation contained 1.0 mol % of the thiol groups. Provided that these thiol groups remained unreacted at the two sides of the chain, it follows that the average degree of polymerization of this product mixture is 200. On the other hand, the remaining thiol was scarcely detected for the sample prepared 2 days after I_2 oxidation. The results clearly establish that the polymeric products depolymerize slowly to the low molecular weight cyclic products. Conceivably, the degradation proceeds via a thiol–disulfide exchange in the terminal monomeric unit according to the so-called zippering mechanism (eq 4). The fact that the depolymerization to Cr_{ox} initially occurs followed by the increase in cyclic dimer and trimer suggests that the formation of Cr_{ox} is kinetically controlled while that of the larger macrocycles is thermodynamically controlled.



(4)

Here, two questions arise on the template mechanism. The first question is as to where metal cations act as template. In eq 5 metal cations may directly facilitate process 1, leading to the increase in Cr_{ox}. As an alternative elucidation the increase in Cr_{ox} may be caused by the metal catalysis of process 2: that is, metal cations may rapidly catalyze the conversion of polymer to cyclic compounds. We added potassium tosylate (50 mM) to the sample solution oxidized in the absence of template and examined whether the depolymerization (process 2) is subjected to the template effect. We found that the time dependence in Figure 1 is scarcely affected by the addition of potassium tosylate. The finding establishes that process 2 is a less important route. Hence, the template effect should be operative directly on process 1. The second question is associated with a discrepancy between the K and the template effect. As shown in Table I, Cr_{ox} scarcely extracts Na^+. Nevertheless, Na^+ serves as a template metal as effective as Cs^+ (Table III). This discrepancy suggests that in process 1, the template effect is operative on the initial state (i.e., as an interaction between M^+ and Cr_{red}) or on the ring-forming transition state but not on the final state.

$$\begin{tikzcd}
 & & Cr_{ox} \\
Cr_{red} \arrow[urr, "\text{process 1}"] \arrow[drr] & & \\
 & & \text{polymer} \arrow[uu, "\text{process 2}"']
\end{tikzcd} \qquad (5)$$

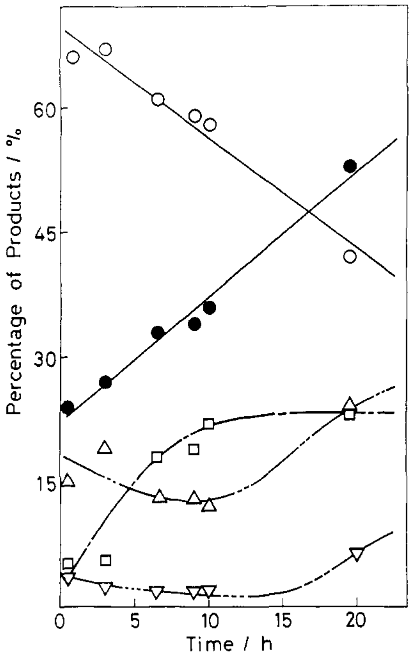


Figure 1. Time dependence of product distribution in aerobic THF at room temperature: ○, polymeric products; ●, sum of cyclic oligomers; □, Cr_{ox}; △, cyclic dimer; ▽, cyclic trimer.

Table IV. Pseudo-First-Order Rate Constants (k_1) for the Oxidation of Cr_{red} and 1,4-Butanedithiol by 3-Methyllumiflavin[a]

alkali tosylate (mM)	10^2k_1 (min^{-1})	
	Cr_{red}	1,4-butanedithiol
none	0.44	3.45
$p\text{-}CH_3C_6H_4SO_3^-Na^+$ (12.9)[b]	0.65	3.26
$p\text{-}CH_3C_6H_4SO_3^-Rb^+$ (50.0)	1.37	3.11
$p\text{-}CH_3C_6H_4SO_3^-Cs^+$ (60.1)	2.01	2.87

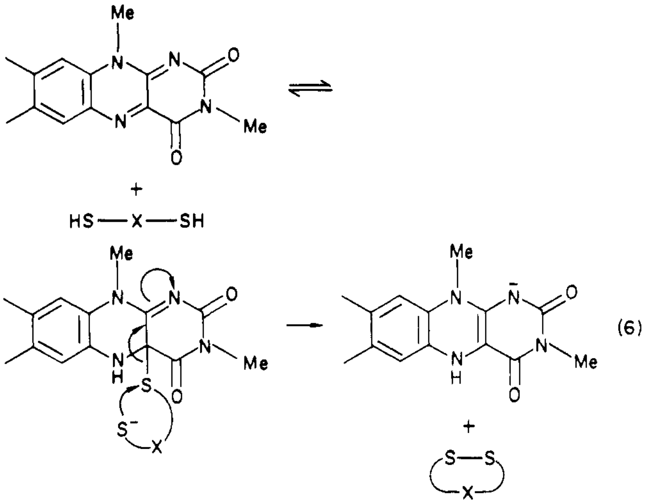
[a] 30 °C, water (pH 8.9. with 0.10 M borate–LiOH):ethanol = 20:80 v/v, [3-methyllumiflavin] = 1.99×10^{-5} M, [dithiol] = 1.01×10^{-3} M. [b] The concentration of sodium tosylate could not be enhanced because of the poor solubility.

Another interesting aspect of the template effect is the kinetics for the ring-formation step. It is known that flavin coenzymes oxidize dithiols to cyclic disulfides at ambient temperature.[29-31] This is one of the important flavin-dependent reactions and occurs according to eq 6. Therefore, the oxidation rate which is exected to reflect the template effect can be easily followed by monitoring the disappearance of the absorption band of flavin. We carried out the oxidation of Cr_{red} and 1,4-butanedithiol, a reference dithiol, by 3-methyllumiflavin (λ_{max} 445 nm) in water–ethanol (20:80 v/v) at 30 °C under anaerobic conditions. The time dependence of OD_{445} in the presence of excess dithiol satisfied a first-order rate equation for up to 3 half-lives. The pseudo-first-order rate constants (k_1) thus obtained are plotted as a function of the template (alkali tosylate) concentrations in Figure 2, and the typical rate constants are summarized in Table IV.

In the absence of the template, 1,4-butanedithiol gave the k_1 7.8 times greater than Cr_{red}. The difference is accounted for either

---

(29) Yokoe, I.; Bruice, T. C. *J. Am. Chem. Soc.* **1975**, *97*, 450.
(30) Loechler, E. L.; Hollocher, T. C. *J. Am. Chem. Soc.* **1975**, *97*, 3236.
(31) Shinkai, S.; Kunitake, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2400.



by the pK_a difference (pK_a = 11.50 for 1,4-butanedithiol; pK_a of Cr_{red} is probably close to that of 2-mercaptoethanol (9.3))[32,33] or by the efficiency in the cyclization step. Interestingly, the k_1 values for the oxidation of Cr_{red} increased with increasing template concentrations, whereas those for the oxidation of 1,4-butanedithiol decreased gradually. The rate decrease observed for 1,4-butanedithiol is attributed either to the effect of ionic strength or to the formation of ion pairs. On the other hand, the rate increase observed for Cr_{red} implies that the intramolecular nucleophilic attack of the thiolate anion (eq 6) is significantly facilitated by alkali metal cations. The effect is in the order $Cs^+ > Rb^+ > Na^+$ (slight increase), which is in accord with the order of the association constants. It is concluded, therefore, that the "kinetic" template effect is also operative on the ring-formation step in the flavin oxidation of Cr_{red}.

Ion Transport Controlled by a Redox-Switch. Various kinds of chemical and physical phenomena have been utilized to increase or control the rate of ion transport across membranes: pH differences,[9-12] pH-dependent lactone cyclization,[34] countercurrent of metal ions,[35] light energies,[13-17] etc.[18,36] Some of these systems have been applied to active transport. On the other hand, the utilization of redox energies which are frequently employed to promote the ion transport across biological membranes[37] has been very limited.[38,39] In particular, there exist only a few precedents for the ion transport controlled by the redox interconversion of ionophores.[19-21] We here demonstrate that the rate of Cs^+ transport can be regulated well by the redox-mediated interconversion between Cr_{ox} and Cr_{red}.

As a prelude to "redox-switched" ion-transport experiments, we determined the rates of ion transport across a liquid (chloroform) membrane about Cr_{ox} and Cr_{red}. As illustrated in Figure 3, the ion concentrations in the OUT aqueous phase increased linearly after an induction period (about 10 h). The transport rates were calculated from the slopes of the linear portions. The results (Table V) indicate that Cr_{ox} can carry metal ions (3.1 times for K^+ and 6.2 times for Cs^+) faster than Cr_{red}. The rate for the Cs^+ transport with Cr was further enhanced (7.8 times relative to Cr_{ox}). These trends are roughly in line with the Ex % data in Table I, indicating that the ion extraction into the membrane phase is rate limiting. Since the larger rate difference between Cr_{red} and Cr_{ox} was observed for Cs^+, we conducted the "redox-switched" ion-transport experiments with Cs^+.

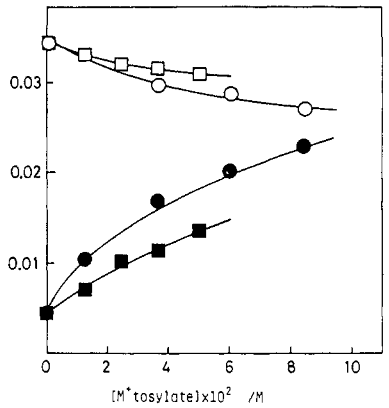


Figure 2. Oxidation of Cr_{red} (●, Cs^+; ■, Rb^+) and 1,4-butanedithiol (○, Cs^+; ●, Rb^+) by 3-methyllumiflavin (1.20×10^{-5} M) at 30 °C. Water (pH 9.0 with 0.10 M LiOH-boric acid)-ethanol (20:80 v/v), N_2, [dithiol] = 1.01×10^{-3} M.

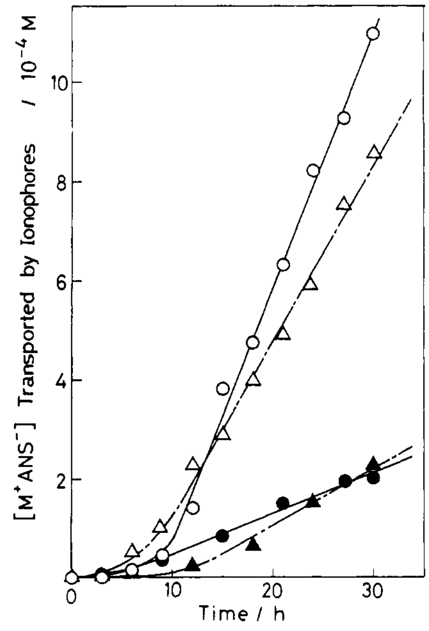


Figure 3. Ion transport across an anaerobic liquid ($CHCl_3$) membrane with Cr_{ox} (△, K^+; ○, Cs^+) and Cr_{red} (▲, K^+; ●, Cs^+) at 30 °C. The transport conditions are recorded in a footnote to Table V.

Table V. Rates of Ion Transport across a Liquid Membrane[a]

run	metal	carrier	transport rate (10^{-7} mol h^{-1})
1	K^+	Cr_{red}	1.17
2	K^+	Cr_{ox}	3.57
3	Cs^+	Cr_{red}	0.83
4	Cs^+	Cr_{ox}	5.10
5	Cs^+	Cr	39.7

[a] IN aqueous phase (10 mL): [MCl] = 0.090 M, [ANS] = 5.00×10^{-3} M, pH 6.0 with MOH(0.010 M)-phosphoric acid. OUT aqueous phase (10 mL): water. Membrane phase (40 mL $CHCl_3$): [carrier] = 2.00×10^{-3} M.

In Figure 4, Cs^+ transport was started with Cr_{red}. Although the buffer concentrations in the IN and the OUT aqueous phase are somewhat enhanced in order to obviate the pH change after I_2 addition, the linear slope at 15–21 h is quite comparable with that of Cr_{red} (broken line). After 21 h an equimolar amount of I_2 was added to the membrane phase. The oxidation of Cr_{red} was completed in 5 min, and the Cs^+ concentration in the OUT aqueous phase increased rapidly. A plot after 33 h is linear, the slope of which is almost equal to that of Cr_{ox} (dotted line). The result supports, therefore, that the conversion of Cr_{red} to Cr_{ox} in

---

(32) Whitaker, J. R. *J. Am. Chem. Soc.* **1962**, *84*, 1900.

(33) Jencks, W. P.; Regenstein, J. In "Handbook of Biochemistry and Molecular Biology"; CRC Press: Cleveland, 1976; p 346.

(34) Shimidzu, T.; Yoshikawa, M.; Hasegawa, M.; Chiba, H. *Kobunshi Ronbunshu* **1977**, *34*, 753.

(35) Sugiura, M.; Shinbo, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 684.

(36) Rebek, J., Jr.; Wattley, R. V. *J. Am. Chem. Soc.* **1980**, *102*, 4853.

(37) Raymond, K. N.; Carrado, C. J. *Acc. Chem. Res.* **1979**, *12*, 183.

(38) Matsuo, S.; Ohki, A.; Takagi, M.; Ueno, K. *Chem. Lett.* **1981**, 1543.

(39) (a) Grimaldi, J. J.; Lehn, J.-M. *J. Am. Chem. Soc.* **1979**, *101*, 1333. (b) Lehn, J.-M. *Nature (London)* **1977**, *265*, 229.

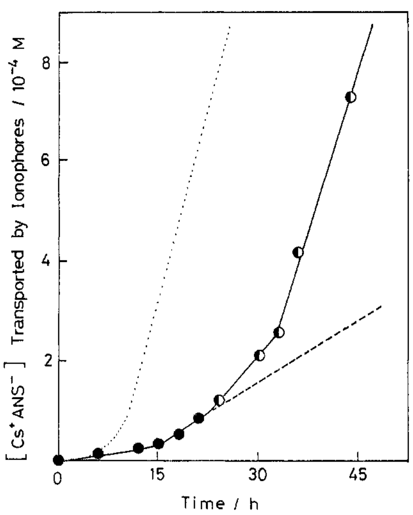


Figure 4. Effect of a redox-switch ($Cr_{red} \rightarrow Cr_{ox}$) on the transport rate. IN and OUT aqueous phases were adjusted to pH 6.0 with CsOH (0.040 M)–phosphoric acid and LiOH (0.050 M)–phosphoric acid, respectively. Other transport conditions are identical with those described in Table V. I_2 was added to the membrane phase after 21 h. (---) and (···) denote the ion transport with Cr_{red} and Cr_{ox}, respectively, under the present conditions.

the membrane phase is directly reflected as the change in the Cs^+-transport rate.

Subsequently, we attempted the reverse control, $Cr_{ox} \rightarrow Cr_{red}$. The reduction of Cr_{ox} in the chloroform membrane at 30 °C was fairly difficult, but we finally found that among reducing agents tested, 1,4-butanedithiol plus DBU can cleave the disulfide bond quantitatively, the reduction being completed in 30 min. Although the reduction rate is not fast enough, this method is available as a redox-switch because the induction period expected for the present transport system is much longer. Instead, the aqueous phase must be made alkaline to avoid the possible protonation of DBU in the membrane phase. In Figure 5, Cs^+ transport was started with Cr_{ox}. The plot from 10 to 24 h gave a good straight line which is consistent with the slope of Cr_{ox} under the present conditions (dotted line). After 24 h, 1,4-butanedithiol (8.50×10^{-4} mol: 10.6 fold of Cr_{ox}) and DBU (8.50×10^{-4} mol) were added to the membrane phase. Surprisingly, the permeation of Cs^+ stopped almost completely after 3 h. The disappearance of the Cs^+ permeation is ascribed probably to leakage of reduced Cr_{red} as its anionic species ($HS–S^-$) into the aqueous phases adjusted to pH 10. In fact, Cr_{red} was detected in the aqueous phases by Ellman's reagent, and the rate of Cs^+ transport started with Cr_{red} was close to zero under the present transport conditions.

Thus, Figures 4 and 5 demonstrate that the rate of Cs^+ transport can be controlled by the interconversion between Cr_{red} and Cr_{ox}. A few examples for the switched-on crown ethers involving a $2RSH \rightarrow RSSR$ process have been reported,[19–21] but the present study is the first example for the "reversible" switched-on and switched-off system which is the most important to control the transport rate.

Conclusion

The present study demonstrated that ion extraction and ion transport, typical functions of a crown ether family, can be controlled by using redox-switched dithiacrown ether anaogues. These findings suggest possible applications of the redox-switched crown ethers to ion pumps driven by redox energies although the framework of the transport system should be further improved. Basically, the molecular design of redox-switched crown ethers is achieved by a combination of a redox-switch which accepts redox energy from the outside with a crown ether which acts as a functional group. In a similar sense, crown ethers bearing redox-active groups such as ferrocene, flavin, heme, etc.,[40–44] have latent capabilities to act as redox-switched crown ethers. We expect that this concept might lead to a more generalized method to control the chemical and physical functions of a crown ether family.

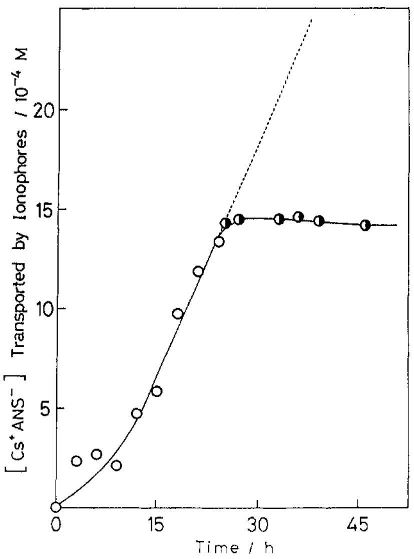


Figure 5. Effect of a redox-switch ($Cr_{ox} \rightarrow Cr_{red}$) on the transport rate. IN aqueous phase (10 mL): [CsCl] = 0.050 M, [ANS] = 5.00×10^{-3} M, pH 10.0 with CsOH (0.050 M)–boric acid. OUT aqueous phase (10 mL): pH 10.0 with Me_4NOH (0.025 M)–boric acid. Membrane phase (40 mL): [carrier] = 2.00×10^{-3} M. 1,4-Butanedithiol and DBU were added to the membrane phase after 24 h. (···) denotes the ion transport with Cr_{ox} under the present conditions.

Acknowledgment. We thank Dr. M. Sisido (Kyoto University) for helpful discussions. This research was supported by a grant from the Ministry of Education of Japan.

Registry No. 1, 88037-68-7; **2**, 88037-69-8; **3**, 96363-60-9; ANS, 82-76-8; $Cl(CH_2CH_2O)_3H$, 5197-62-6; catechol, 120-80-9; 3-methyllumiflavin, 18636-32-3; monobenzyl-21-crown-7, 67950-78-1.

---

(40) Hammond, P. J.; Beer, P. D.; Hall, C. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1161.

(41) Akabori, S.; Ohtomi, M.; Sato, M.; Ebine, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1455.

(42) Shinkai, S.; Ishikawa, Y.; Shinkai, H.; Tsuno, T.; Makishima, H.; Ueda, K.; Manabe, O. *J. Am. Chem. Soc.* **1984**, *106*, 1801.

(43) Thanabal, V.; Krishnan, *J. Am. Chem. Soc.* **1982**, *104*, 3643.

(44) van Bergen, T. J.; Kellog, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 3882.