

CONTROL OF HIGHLY SELECTIVE Ag^+ TRANSPORT BY REDOX
REACTIONS BETWEEN THIOL AND DISULFIDE LOCATED INSIDE
A CAVITY OF CROWN ETHER

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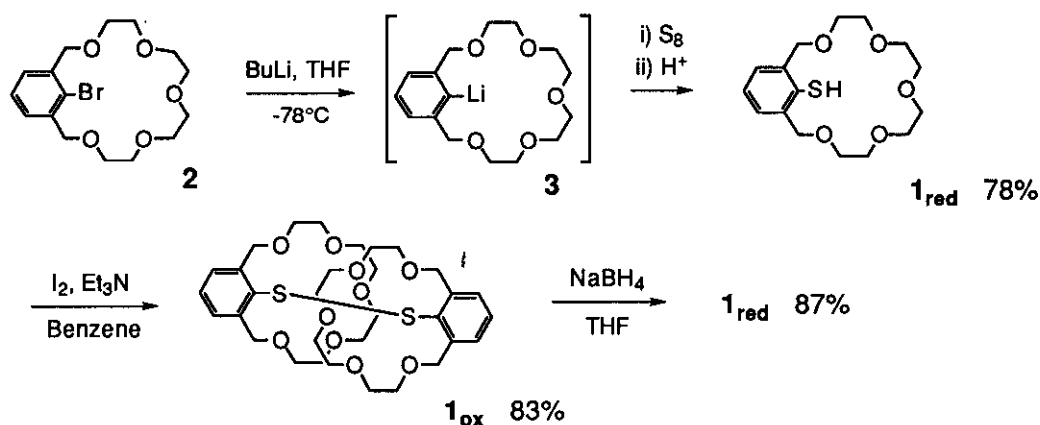
Abstract - A novel crown ether containing a thiol group inside the ring has been prepared in good yield and exhibits Ag^+ selectivity on transport of metal ions through a liquid membrane. However, the corresponding disulfide loses the affinity significantly.

Redox reactions between thiol and disulfide can switch the tertiary structure of ribonuclease quantitatively so that the enzymatic activity is regulated perfectly by the reaction.¹ In artificial systems conformational change induced by these redox reactions has been utilized for control of ion recognition.² However, interconversion between an active form and a completely nonactive one for ion recognition has been quite difficult. Unstability of the reduced forms under aerobic conditions was also a serious problem.² Here, we report i) facile synthesis of stable crown ethers bearing a thiol group inside the ring ($\mathbf{1}_{\text{red}}$, reduced form) and the corresponding disulfide linkage ($\mathbf{1}_{\text{ox}}$, oxidized form), ii) interconversion of these forms, and iii) drastic difference of Ag^+ transport ability between the two forms.

2-Bromo-1,3-xylyl crown ether ($\mathbf{2}$) prepared from 2-bromo-1,3-bis(bromomethyl)benzene and tetraethylene glycol in high yield was treated with *n*-BuLi in THF at $-78\text{ }^\circ\text{C}$ for 2 h under N_2 to afford the corresponding lithiated compound ($\mathbf{3}$) (Scheme 1), as reported by Reinhoudt.³ To the solution of $\mathbf{3}$ was added S_8 (1.5 eq) at $-78\text{ }^\circ\text{C}$. The reaction mixture was stirred for 1 h, and then gradually warmed. When the temperature reached to $0\text{ }^\circ\text{C}$, the mixture was acidified by the addition of 3 N hydrochloric acid to give the desired 2-mercapto-1,3-

xylyl crown ether (**1_{red}**) in 78% yield after purification with a flash column (SiO₂, AcOEt-n-hexane-ethanol = 10:15:1, v/v). **1_{red}** is stable under aerobic conditions. However, oxidation of **1_{red}** to **1_{ox}** with I₂ and Et₃N in benzene proceeded rapidly. Tlc analysis of the reaction suggested formation of a single product. Indeed, pure **1_{ox}** was obtained in high isolated yield (83 %) by column chromatography (SiO₂, AcOEt-ethanol = 10:1, v/v). **1_{ox}** was easily reverted to **1_{red}** by NaBH₄ reduction in 87 % yield after purification (SiO₂, AcOEt-n-hexane-ethanol = 5:4:1). Thus, intermolecular and facile interconversion was performed.⁴ The structure of **1** was confirmed by nmr (¹H and ¹³C), high resolution ms and/or ir spectroscopy.⁵

Scheme 1



Transport experiment was carried out using a dual cylindrical apparatus.⁶ A 1,2-dichloroethane solution of a host (2×10^{-4} M) was employed as a liquid membrane. The source and the receiving phases were solutions of metal nitrate and deionized water, respectively. Amounts of metal ions transported after 24 h into the receiving phase were determined by atomic absorption spectroscopy. The results are summarized in Tables 1 and 2. In noncompetitive transport, Ag⁺ and Pb²⁺ were transported by **1_{red}** to the receiving phase much more preferentially than Mn²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, and Cd²⁺ (e.g. Mn²⁺, Co²⁺, Ni²⁺, Cu²⁺, and Zn²⁺ were not detected within experimental errors 24 h after the experiment started). Ag⁺ moved fastest through the liquid membrane, but transport rate of Pb²⁺ is rather high. In contrast, Ag⁺, Mn²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Cd²⁺, and Pb²⁺ hardly moved when **1_{ox}** was used as a carrier. This drastic decrease of transport ability was probably caused by the fact that occupation of the binding site by the disulfide linkage and decrease of flexibility of the crown ring prohibit effective coordination of oxygen and sulfur atoms of **1_{ox}** to metal ions.

In competitive transport ([AgNO₃] = [Cu(NO₃)₂] = [Pb(NO₃)₂] = [Cd(NO₃)₂] = 0.01 M in the source phase, [1] = 2×10^{-4} M in the organic phase) through a 1,2-dichloroethane layer, remarkably high Ag⁺ selectivity was

observed in $\mathbf{1}_{\text{red}}$, and a larger amount of Ag^+ was observed in the receiving phase, compared to noncompetitive transport (Table 2). Increase of ion concentration in the source phase and exclusive occupation of the binding site by Ag^+ may be reasons for the enhancement of the transport rate and the selectivity. As in the case of noncompetitive transport, $\mathbf{1}_{\text{ox}}$ transported a very small amount of Ag^+ only. Therefore, in competitive transport experiment, nice interconversion of active and nonactive species (*all-or-none-type switching*) utilizing redox reactions between thiol and disulfide was successfully performed by the novel molecular system ($\mathbf{1}$).

Table 1 Transport of Heavy Metal Ions by $\mathbf{1}$

Host	[Metal Ion] (10^{-5} M)							
	Ag^+	Cu^{2+}	Cd^{2+}	Pb^{2+}	Mn^{2+}	Co^{2+}	Ni^{2+}	Zn^{2+}
$\mathbf{1}_{\text{red}}$	25.2	0	0.7	18.5	0	0	0	0
$\mathbf{1}_{\text{ox}}$	1.2	0	0	0	0	0	0	0
none	0	0	0	0	0	0	0	0

The values were determined after 24 h; org. phase ($\text{CH}_2\text{ClCH}_2\text{Cl}$), $[\mathbf{1}] = 2 \times 10^{-4}$ M; source phase (dist. H_2O), [metal nitrate] = 0.01 M; receiving phase (dist. H_2O)

Table 2 Competitive Transport of Heavy Metal Ions by $\mathbf{1}$

Host	[Metal Ion] (10^{-5} M)			
	Ag^+	Cu^{2+}	Cd^{2+}	Pb^{2+}
$\mathbf{1}_{\text{red}}$	32.0	0	0	0
$\mathbf{1}_{\text{ox}}$	1.6	0	0	0

The values were determined after 24 h; org. phase ($\text{CH}_2\text{ClCH}_2\text{Cl}$), $[\mathbf{1}] = 2 \times 10^{-4}$ M; source phase (dist. H_2O), [AgNO_3] = [$\text{Cu}(\text{NO}_3)_2$] = [$\text{Cd}(\text{NO}_3)_2$] = [$\text{Pb}(\text{NO}_3)_2$] = 0.01 M; receiving phase (dist. H_2O)

Coordination of the sulfur atom in $\mathbf{1}_{\text{red}}$ and the crown ring is important for the Ag^+ selectivity⁷ observed here. Crown ether ($\mathbf{4}$)⁸ containing a sulfide substituent instead of a thiol group also shows high Ag^+ selectivity which was performed by such a synergistic coordination. Additionally, important contribution of a sulfur atom located near a crown ring to high Ag^+ selectivity was found in thiolariet ethers.^{10,11} Addition of Ag^+ to $\mathbf{1}_{\text{red}}$

caused uv-vis spectral changes, and increase of an absorption (λ_{max} , 273 nm in CH_3CN) was observed. Job plot of $\mathbf{1}_{\text{red}}$ and Ag^+ in CH_3CN by monitoring the absorption band suggested a 1 : 1 stoichiometry of the complexation.

Very importantly and interestingly, in competitive transport using $\mathbf{1}_{\text{red}}$, addition of *m*-chloroperbenzoic acid (*m*-CPBA) into the organic layer during the transport (after 8h) resulted in considerable increase of transport rate

for Ag^+ and subsequent termination of transport (Figure 1). The other metal ions were not detected in the receiving phase during the experiment. Thus, the oxidant specifically affected transport rate of Ag^+ . This dramatic and very selective regulation of transport rate is well rationalized by conversion of the active reduced form $\mathbf{1}_{\text{red}}$ to the corresponding nonactive oxidized form $\mathbf{1}_{\text{ox}}$. The abrupt increase of the concentrations of Ag^+ was caused by release of Ag^+ bound in the cavity of $\mathbf{1}_{\text{red}}$ upon quantitative oxidation to $\mathbf{1}_{\text{ox}}$ with *m*-CPBA. No transport ability of $\mathbf{1}_{\text{ox}}$ obviously resulted in the termination of the transport.

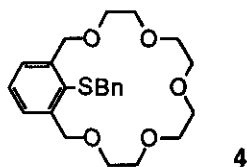
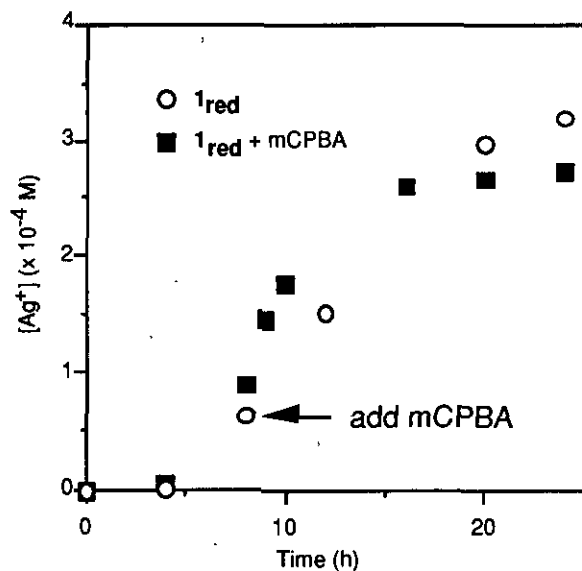


Figure 1 Competitive Transport of Heavy Metal Ions by **1**



org. phase; $\text{CH}_2\text{ClCH}_2\text{Cl}$, $[\mathbf{1}] = 2 \times 10^{-4} \text{ M}$
 source aqueous phase; dist. H_2O ,
 $[\text{AgNO}_3] = [\text{Cu}(\text{NO}_3)_2] = [\text{Cd}(\text{NO}_3)_2]$
 $= [\text{Pb}(\text{NO}_3)_2] = 0.01 \text{ M}$
 receiving phase; dist. H_2O

The new redox system (**1**) might achieve repeated switching of high Ag^+ selective binding by redox reactions using suitable reagents or an electrode. Crown ethers containing a thiol group are sometimes very difficult to treat because of their sensitivity to autoxidation.² $\mathbf{1}_{\text{red}}$, however, is stable under aerobic conditions. Moreover, $\mathbf{1}_{\text{red}}$ was prepared much easier in much higher yield than a reduced form in an intramolecular redox system previously reported.⁴ Hence, the preliminary results obtained here indicate that a similar framework to **1** will be developed into an all-or-none-type switching moiety of various ion recognition systems controlled by the redox reactions.

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- 4 For an intramolecular interconversion system, see T. Nabeshima, H. Furusawa, and Y. Yano, *Angew. Chem. Int., Ed. Engl.*, 1994, 33, 1750.
- 5 **1_{red}**: ¹H nmr (CDCl₃, 200 MHz): δ 3.5-3.8 (m, 16H), 4.68 (s, 4H), 4.93 (s, 1H, ArSH), 7.0-7.3 (m, 3H); ¹³C nmr (CDCl₃, 125 MHz): δ 68.88, 70.30, 70.49, 70.57, 72.49, 124.92, 130.21, 134.41, 137.52; ir (NaCl): 2532 (SH) cm⁻¹; HRms (FAB) Found: 329.140. Calcd for C₁₆H₂₄O₅S ([M+H]⁺): 329.1423.
1_{ox}: ¹H nmr (CDCl₃, 200 MHz): δ 3.3-3.8 (m, 32H), 4.08 (d, *J* = 12.1 Hz, 4H), 4.66 (d, *J* = 12.1 Hz, 4H), 7.31 (s, 6H); ¹³C nmr (CDCl₃, 125 MHz): δ 68.76, 70.46, 70.52, 70.59, 71.05, 129.09, 129.50, 136.41, 142.87; HRms (FAB) Found: 655.2589. Calcd for C₃₂H₄₆O₁₀S₂ ([M+H]⁺): 655.2611.
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- 7 In solvent extraction experiments (ClCH₂CH₂Cl - water), **1_{red}** shows Ag⁺ selectivity as seen in the transport experiments. Hence, **1_{red}** is considered to bind Ag⁺ most preferentially among the heavy metal ions examined here. Detailed study of solvent extraction and further discussion will appear in a full article.
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- 9 Crown ether (**5**) does not transport Ag⁺ at all under the same conditions employed for **1**. Thiophenol shows no transport ability toward Ag⁺, either. These results clearly indicate importance of coordination of the sulfur and oxygen atoms of **1_{red}** for the high Ag⁺ selectivity.
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