Artificial Allosteric Ionophores: Regulation of Ion Recognition of Polyethers Bearing Bipyridine Moieties by Copper(I)

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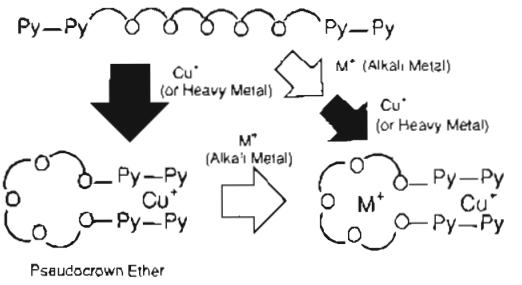
Artificial allosteric ionophores, oligoethylene glycols bearing 2,2′-bipyridine derivatives at the termini, were synthesized. Solvent extraction experiment indicated that the polyethers bind Cu^+ firmly and selectively among heavy metal ions because of a chelate and a steric effect of the two bipyridines on the ligation. The complexation with Cu^+ takes place rapidly and quantitatively in organic media to result in intramolecular cyclization of the linear polyether moiety, giving a novel type of crown ethers, *pseudocrown ethers*. The UV–vis and ^1H NMR spectroscopies indicated that the bipyridine complexes have a tetrahedral geometry. Allosteric regulation of ion recognition (*heterotropic cooperativity*) has been performed successfully in transport experiment through a liquid membrane (methylene chloride) by using the ionophore and Cu^+ as an effector. The transport selectivity to alkali metal ions was dramatically enhanced by the addition of Cu^+ due to the formation of the cyclic framework. The transport experiment and measurement of uptake and release rates of ionophores for alkali metals suggested that the remarkably high transport selectivity results from a suitable cavity size of the pseudocrown ring and electrostatic repulsion between alkali metal and Cu^+ ions bound in the same ionophore. Moreover the pseudocrowns exhibit molecular chirality at −28 °C in the presence of excess Pirkle's reagent, but racemization occurs at room temperature. In contrast, a pseudocrown formed from Cu^+ and a polyether with four bipyridines maintains its molecular chirality even at room temperature, promising application of the pseudocrowns to asymmetric recognition. The facts obtained here indicate clearly that our strategy, conversion of a linear polyether with heavy metal binding sites to the corresponding pseudocrown by the addition of heavy metals, is quite convenient and powerful for modulation of molecular recognition and molecular information.

Regulation of molecular functions by obtaining some suitable information (effector) from conditions is often seen in phenomena such as allostery, cooperativity, feedback, etc., in biological systems.[1] The sophisticated regulation plays essential roles to control transport and balance of materials and energies for living things. Application of the methodology to artificial ionophores has been investigated by utilizing pH gradient,[2] photoreactions,[3] and redox reactions.[4] Recently we and other groups have also focused on modulation of ion recognition in artificial systems by the use of a metal ion as an effector.[5-16] Our original and basic strategy to construct such a system is illustrated in Scheme I. Conformational change of a linear polyether with ligands for heavy metals is induced by the addition of a heavy metal ion to

Scheme I. Allosteric Regulation of Ion Recognition by Cu^+



Py—Py : 2,2′-bipyridine

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(1) Cantor, C. R.; Schimmel, P. R. *Biophysical Chemistry*; W. H. Freeman and Co.: New York, 1980; Vol. III.
(2) (a) Fredirick, L. A.; Fyles, T. M.; Gurprasad, N. P.; Whitfield, D. M. *Can. J. Chem.* **1981**, *59*, 1724–1733. (b) Charewicz, W. A.; Bartsch, R. A. *Anal. Chem.* **1982**, *54*, 2300–2303. (c) Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Izatt, S. R.; Chistensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1782–1785. (d) Izatt, R. M.; LindH, G. C.; Clark, G. A.; Bradshaw, J. S.; Nakatsuji, Y.; Lamb, J. D.; Christensen, J. J. *J. Chem. Soc. Chem. Commun.* **1985**, 1676–1677.
(3) (a) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O. *J. Am. Chem. Soc.* **1981**, *103*, 111–115. (b) Shinkai, S.; Shigematsu, K.; Kusano, Y.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3279–3283. (c) Shinkai, S.; Manabe, O.; In *Host Guest Complex Chemistry III*; Vögtle, F., Weber, E., Eds.; Springer-Verlag: Berlin, 1984; pp 67–104. (d) Irie, M.; Kato, M. *J. Am. Chem. Soc.* **1985**, *107*, 1024–1028. (e) Soumillion, J. P.; Weiler, J.; Man, X. d.; Touillaux, R.; Declercq, J. P.; Tinant, B. *Tetrahedron Lett.* **1989**, *30*, 4509–4512.
(4) (a) Shinkai, S.; Inuzuka, K.; Miyazaki, O.; Manabe, O. *J. Am. Chem. Soc.* **1985**, *107*, 3950–3955. (b) Saji, T.; Kinoshita, I. *J. Chem. Soc., Chem. Soc.* **1986**, 716–717. (c) Echeverria, L.; Delgado, M.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1986**, *108*, 6825–6826. (d) Nabeshima, T.; Sakiyama, A.; Yagyu, A.; Furukawa, N. *Tetrahedron Lett.* **1989**, *30*, 5287–5288.
(5) (a) Rebek, J., Jr.; Wattley, R. V. *J. Am. Chem. Soc.* **1980**, *102*, 4853–4854. (b) Rebek, J., Jr. *Acc. Chem. Res.* **1984**, *17*, 258–264.
(6) Nabeshima, T.; Inaba, T.; Furukawa, N. *Tetrahedron Lett.* **1987**, *28*, 6211–6214.
(7) Nabeshima, T.; Inaba, T.; Furukawa, N. *Heterocycles* **1989**, *29*, 431–434.
(8) Nabeshima, T.; Inaba, T.; Sagae, T.; Furukawa, N. *Tetrahedron Lett.* **1990**, *31*, 3919–3922.
(9) Nabeshima, T.; Inaba, T.; Furukawa, N.; Ohshima, S.; Hosoya, T.; Yano, Y. *Tetrahedron Lett.* **1990**, *31*, 6543–6546.
(10) Beer, P. D.; Rothin, A. S. *J. Chem. Soc. Chem. Commun.* **1988**, 52–54.
(11) Schepartz, A.; McDevitt, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 5976–5977.
(12) (a) Nijenhuis, W. F.; van Doorn, A. R.; Reichwein, A. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 3607–3608. (b) van Staveren, C. J.; Fenton, D. E.; Reinhoudt, D. N.; van Eerden, J.; Harkema, S. *J. Am. Chem. Soc.* **1987**, *109*, 3456–3458.
(13) Schneider, H.-J.; Ruf, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1159–1160.
(14) Scrimin, P.; Tecilla, P.; Tonellato, U.; Vignaga, N. *J. Chem. Soc., Chem. Commun.* **1991**, 449–451.
(15) Schall, O. F.; Robinson, K.; Atwood, J. L.; Gokel, G. W. *J. Am. Chem. Soc.* **1991**, *113*, 7434–7435.
(16) Very recently, an example very similar to our original system (see ref 6) has been reported. See: Kobuke, Y.; Satoh, Y. *J. Am. Chem. Soc.* **1992**, 789–790.

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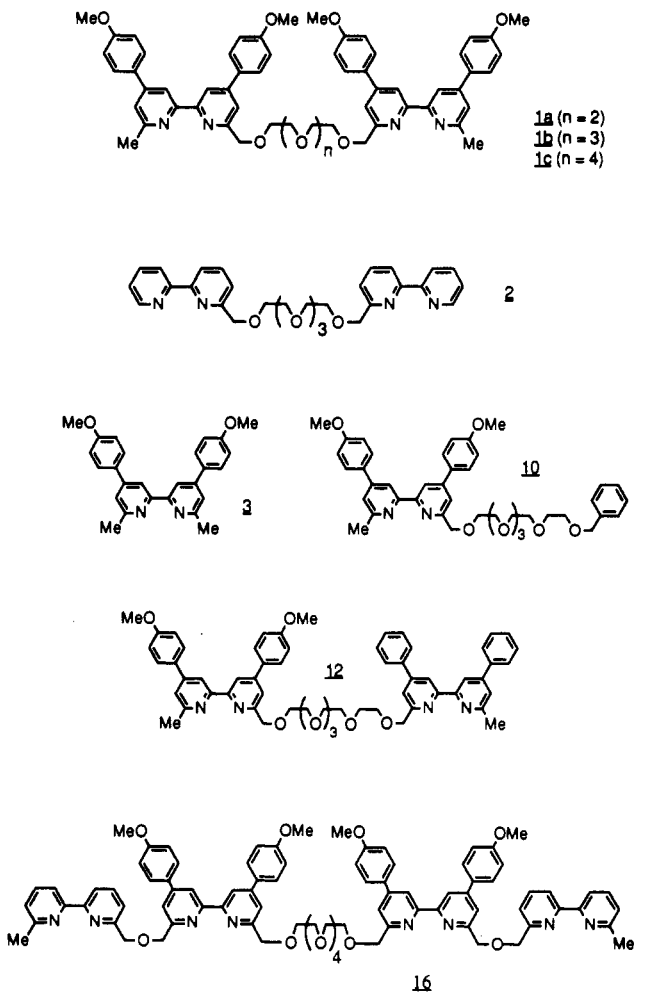
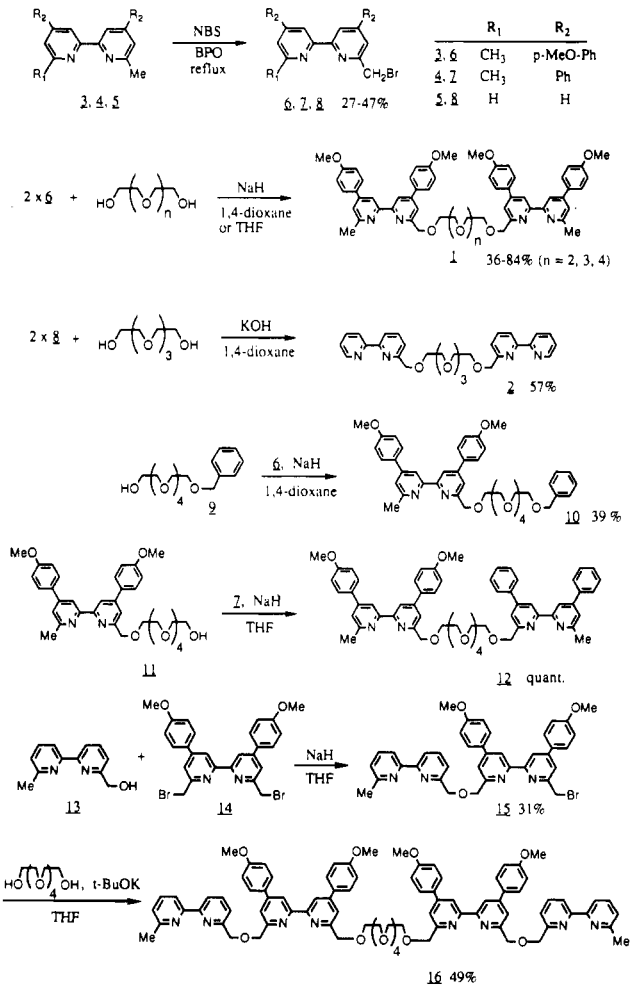
Chart I. Structural Formulas



afford an intramolecularly cyclized polyether, whose cavity is expected to act as a new binding site for alkali metal ions. We call the novel cyclic polyether thus prepared a *pseudocrown ether*, because the cyclic structure resembles that of crown ethers although the framework is maintained firmly by coordination to a heavy metal ion instead of covalent bonding. Compared to the original linear compound, a pseudocrown should reveal a different binding strength and selectivity for alkali metal ions due to the preorganization of the binding site for ions (macrocyclic effect).[17] As a result, regulation of ion recognition can be achieved. The first example for the regulation of ion recognition based on this concept has been reported in a previous communication.[6] We have designed oligoethylene glycols bearing bipyridine moieties at the ends of the chains (**1**, **2**; see Chart I) as precursors of the pseudocrowns. This is due to the fact that bipyridines are known to have very low affinity for alkali metal ions[18] but are remarkably good ligands for various heavy metal ions and polyethers usually behave as a binding site for alkali metals only. Moreover the chemistry of bipyridine complexes has been investigated intensely and a variety of ideas have been demonstrated, promising diverse applications of the pseudocrown with bipyridines to multifunctional molecules. For instance, the heavy metal ion incorporated in the framework of the pseudocrown ether can be used as a

Scheme II. Synthesis of Oligoethylene Glycol with Bipyridines as a Precursor of Pseudocrown Ether



catalytic site of a certain chemical reaction and event and as a connector of the termini of the polyether chain. The example has been described in our preliminary report on double catalysis[19] (catalyses of epoxidation of olefins and phase transfer). If other ligands are chosen instead of bipyridine, various kinds of multifunctional systems will be constructed in a similar way. Thus, the strategy using pseudocrowns is expected to be quite useful in designing systems for transfer and modulation of chemical or physical information in molecular level.[20]

Here we report the synthesis of the oligoethylene glycols with bipyridines as precursors of pseudocrowns and their characteristic properties: (i) selective recognition of heavy metal ions, (ii) allosteric regulation of alkali metal ion transport by Cu^+ (*heterotropic cooperativity*), and (iii) molecular chirality of the pseudocrown prepared by the reaction with Cu^+.

Results and Discussion

Synthesis of Polyethers with Bipyridine Moieties. As shown in Scheme II, 6,6′-dimethyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine (**3**) was brominated to 6-(bromomethyl)-6′-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine (**6**) in 39% yield by treatment of *N*-bromosuccinimide and a catalytic amount of benzoylperoxide or 2,2′-azobis(isobutylonitrile). The monobromide **6** was allowed to react with oligoethylene glycol and sodium hydride in THF or dioxane at reflux temperature or 80 °C to give the corresponding ionophores **1** in 36–84% yield. Ionophore **2**,

(17) Cram, D. J.; Kaneda, T.; Gelgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645–3657.

(18) However several examples have been reported wherein recognition for alkali metal ions is achieved by remarkably well organized systems consisting of several bipyridines or phenanthroline derivatives. For example, see: (a) Caron, A.; Guihelm, J.; Riche, C.; Pascard, C.; Alpha, B.; Lehn, J.-M. *Helv. Chim. Acta* **1985**, *68*, 1577–1582. (b) Bell, T. W.; Firestone, A.; Ludwig, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1902–1904.

(19) Nabeshima, T.; Inaba, T.; Furukawa, N. *Heterocycles* **1990**, *31*, 2095–2098.

(20) (a) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304–1319. (b) Stoddart, F. *Chem. Br.* **1991**, 714–718.

Table I. Extraction of Transition Metals by Bipyridine Derivatives at 25 °C

	$E(\%)^a$						
	Fe^{3+}	Co^{2+}	Ni^{2+}	Zn^{2+}	Mn^{2+}	Cr^{3+}	$Cu^{+\,d}$
1a[b]	0.01	0.15	0.1	15.3	0	0	~100
1c[b]	0.09	0.39	0.4	15.4	0.07	0	~100
3[c]	0.01	0	0	6.8	0	0	54
pentaglyme[b]	0.03	0	0	0.05	0	0	0

[a] Extractability was determined according to the following equation, unless otherwise mentioned: Ex (%) = ([metal ion]$_{org}$/(7 × 10^{-4} M)) × 100; [metal ion]$_{org}$: concentration of the metal ion (M) in organic phase after extraction. Determined by atomic absorption spectroscopy, with the aqueous phase (10 mL) containing 1 mM metal nitrate, adjusting the pH at 5.5 by using bis-tris buffer. [b] Organic phase (CH_2Cl_2, 10 mL) containing the ligand, 7 × 10^{-4} M. [c] [ligand] = 1.4 × 10^{-3} M. [d] Determined by UV–vis and atomic absorption spectroscopies for the solvent system H_2O–CH_2Cl_2 (0.02% CH_3CN). [Cu^+] = 8.75 × 10^{-5} M; [**1**]$_{org}$ = 1.75 × 10^{-4} M; [**3**]$_{org}$ = 3.5 × 10^{-4} M. Ex (%) = ([Cu^+]$_{org}$/(8.75 × 10^{-5} M)) × 100.

which does not have *p*-methoxyphenyl and methyl groups in the bipyridine nuclei, was also prepared from tetraethylene glycol, the monobromide **8**, and KOH in 57% yield. Unsymmetrical ionophores **10** and **12** were synthesized similarly by the reaction of bromides **6** and **7** with pentaethylene glycol benzyl ether (**9**) and pentaethylene glycol mono(6-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl ether (**11**), respectively. Introduction of two bis(bipyridine) moieties into pentaethylene glycol has been also performed successfully by the treatment of pentaethylene glycol and bromide **15**, which was prepared from 6-(hydroxymethyl)-6′-methyl-2,2′-bipyridine (**13**) and dibromide **14**. Thus **16** was obtained in 49% yield.

Selective Recognition for Heavy Metal Ions. A solvent extraction experiment was carried out to evaluate the affinity of the ionophores to heavy metal ions (Table I). A methylene chloride solution of an ionophore (7 × 10^{-4} M except for Cu^+) was mixed vigorously with an aqueous phase containing 1.0 mM metal nitrate in bistris solution (pH 5.5) at 25 °C, followed by analysis of the organic phase using atomic absorption spectroscopy to determine the amount of the metal ion extracted. In the case of Cu^+, the extractability was determined from the amount of **1**-Cu^+ complex that remained in the organic phase by both UV–vis and atomic absorption spectroscopies after stirring of a 1:2 mixture of CuI and **1** in 0.02% acetonitrile–methylene chloride with deionized water. Ionophores **1** show remarkably high affinity toward Cu^+ (Ex = ca. 100%) among the heavy metals in spite that the total amount of metal ion used in the case of Cu^+ was much smaller than the other metals. Zn^{2+} is extracted with a fairly good extractability (Ex = 15%), probably because of the geometrical factor. Since pentaglyme exhibits no binding ability to the heavy metal ions as expected, only bipyridine moieties were found to bind Cu^+ and Zn^{2+}. However, the polyether chains in the ionophores **1** play a significant role in increasing the binding affinity of the bipyridines, because the chains connect the two bipyridines in a moderate proximity to enhance the local concentration of the ligands. In other words, the short distance of the two ligands gives rise to a chelate effect to enlarge the extractability toward the metal ions twice as much as that of 6,6′-dimethyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine (**3**) (Ex = 54% in Cu^+, 6.8% in Zn^{2+}). Methyl groups at the ortho positions of the nitrogen atoms in 2,2′-bipyridine are known to be quite favorable for tetrahedral complexation with Cu^+.[21] It is also reported that formation of complexes with other configurations is inhibited by a steric effect of the substituents.[22] Consequently the markedly high and selective extractability of **1** to Cu^+ is considered to be achieved by the chelation as well as the steric effect of methyl and methylene substituents at the 6 and 6′ positions of the bipyridine rings.

Structural Determination and Characterization of 1-Cu^+ and 1-Zn^{2+} Complexes. The tetrahedral complexation of **1** with Cu^+ was evidenced by the characteristic absorption of the UV–vis spectra. On the addition of Cu^+ into organic solutions (methylene chloride–acetonitrile = 98:2, v/v) of ionophores **1**, the colorless solutions immediately turn to be deep red ones, whose electronic absorption spectra show bathochromic shifts at a region of shorter wavelength and appearance of a new absorption at 476 nm (Figure 1a). The latter absorption assigned to a metal-to-ligand charge-transfer (MLCT) band is the most characteristic for a tetrahedral complex with two bipyridine derivatives and Cu^+.[23] Results of mole ratio method in absorption spectrometry suggest that strong 1:1 complexation takes place between the ionophores **1** and Cu^+. Absorbance at 476 nm is increased proportionally to the amount of the Cu^+ added up to the ratio of 1.0 and then saturation is observed even in the presence of an excess amount of Cu^+ (Figure 2).

^{1}H NMR spectrometry provided detailed information on the structure of the Cu^+ and Zn^{2+} complexes. Distinct and characteristic changes of signals are detected on the addition of Cu^+ or Zn^{2+} into solutions of the ionophores **1** (Figures 3 and 4). Most of resonances of protons at the 2,2′-bipyridine rings are shifted downfield, indicating metal ion binding to the bipyridine moieties. In the Cu^+ complex, the most characteristic changes of signals suggesting tetrahedral geometry are observed in the methyl and the methylene protons at the 6 and 6′ positions of the bipyridine rings. Resonances of the methyl and methylene protons of free ionophore **1c** appear at 2.686 and 4.815 ppm, respectively, while those of the Cu^+ complex appear at 2.327 and 4.422 ppm (Table II). The upfield shifts are considered to result from magnetic anisotropy of the other bipyridine nucleus,[24] because in the tetrahedral configuration containing cisoid bipyridine geometry the methyl and methylene groups of the one bipyridine are located almost above the center of the other bipyridine plane, judging from inspection of the CPK model. In contrast to **1**-Cu^+, **1c**-Zn^{2+} displays an upfield shift of methyl protons (appearing at 2.08 ppm) and a downfield shift of methylene protons, accompanied by splitting to two doublets (5.08 and 5.46 ppm, J = 16 Hz). The changes of the chemical shifts are probably ascribed to formation of a tetracoordinate Zn^{2+} complex, which leads to a fairly high extractability of **1** toward Zn^{2+}.

^{1}H NMR titration also supports the formation of 1:1 complexes of the ionophores with Cu^+ and Zn^{2+}. As the ratio of Cu^+ or Zn^{2+} to **1** increases up to 1.0, intensities of new signals assigned to the complex increase. It is worthwhile to point out that on the addition of Cu^+ or Zn^{2+} signals with chemical shifts averaged those of **1** and the complex do not appear at least for the aromatic, picolyl methyl, and picolyl methylene protons. This fact reveals the inertness of the complexes, i.e. *intermolecular* ligand exchange (vide infra) is restricted on the NMR time scale. Bipyridine **3** also binds Cu^+ to give the corresponding tetrahedral complex, which is identified by ^{1}H NMR as well as absorption spectroscopy. Additionally line widths of the NMR signals in **3**-Cu^+ complex are larger than those of **1**-Cu^+, suggesting that the former complex is more labile than the latter. The NOESY spectrum of **1c**-Cu^+ complex in dimethyl-d_6 sulfoxide also shows a cross peak between H-3 of the one bipyridine nucleus and methyl protons of the other, supporting the proximate location of the two bipyridine plane in a tetrahedral fashion. The ^{13}C NMR spectrum is also in accordance with the structure of the complex (see Experimental Section). These NMR experiments reveal clearly that **1** binds

(21) Hoste, J. *Anal. Chim. Acta* **1950**, *4*, 23–37.
(22) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*; John Wiley & Sons: New York, 1980; pp 71.
(23) Kitagawa, S.; Munakata, M. *Inorg. Chem.* **1981**, *20*, 2261–2267.
(24) (a) Lehn, J.-M.; Rigault, A.; Siegel, J.; Harrowfield, J.; Chevrier, B.; Moras, D. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2565–2569. (b) Lehn, J.-M.; Rigault, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1095–1097.

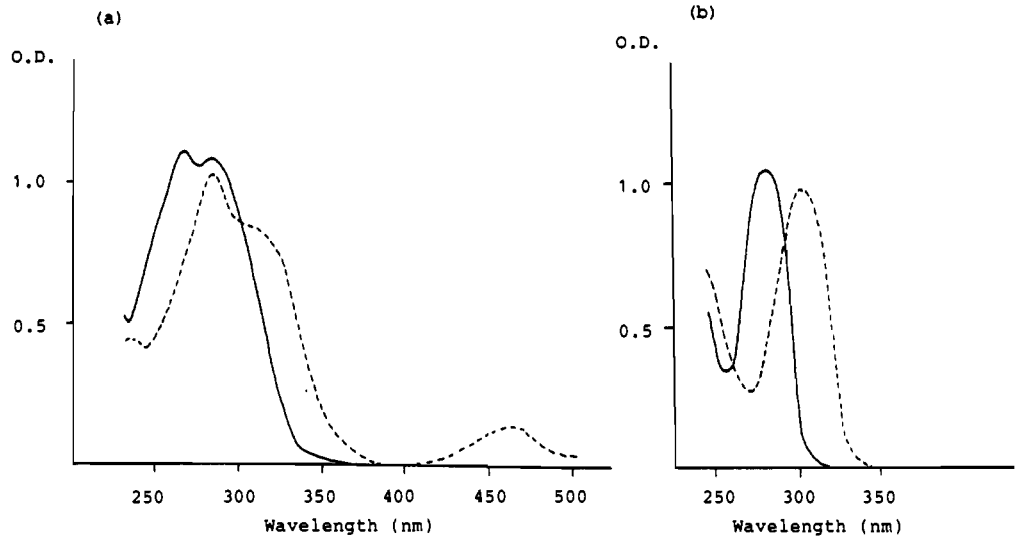


Figure 1. Absorption spectra of **1c** and **2** and their metal complexes: (a) [**1c**] = 1.4×10^{-5} M and an excess amount of CuCl in CH_2Cl_2; (b) [**2**] = 3.7×10^{-5} M and $[Ni^{2+}] = 6.6 \times 10^{-5}$ M in 0.16% MeOH–CH_2Cl_2.

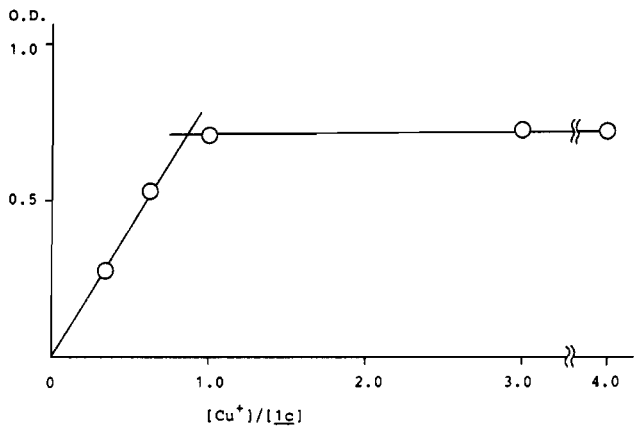


Figure 2. Mole ratio method for complexation between **1c** and Cu^+ in 2% CH_3CN–CH_2Cl_2. Spectral changes were monitored at 476 nm.

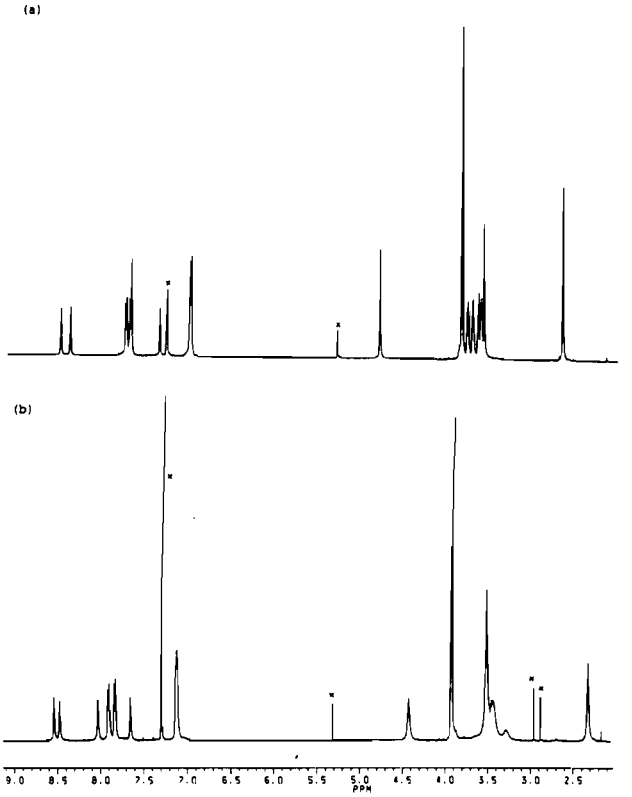


Figure 3. 500-MHz ^1H NMR spectra of **1c** and **1c**-Cu^+: (a) **1c** in $CDCl_3$–CD_3CN (95:5, v/v); (b) **1c** and 1 equiv of CuCl in $CDCl_3$–CD_3CN (95:5, v/v).

Cu^+ smoothly to afford stable 1:1 complexes with a tetrahedral configuration.

Results of vapor pressure osmometry for **1c**-CuCl complex (MW = 1126) in chloroform imply a molecular weight of 1064–1049, also indicative of exclusive formation of the 1:1 complex. The FABMS spectrum also supports the stoichiometry. As described above, all spectral data are consistent with quantitative formation of the desired pseudocrown ether by the addition of Cu^+. TLC analysis also proved formation of the single species. Interestingly, these Cu^+ complexes readily revert to the linear polyether **1** by the addition of a large excess amount of acetonitrile. This feature will be critical for switching ion recognition using the present system, since formation and dissociation of the pseudocrown in situ will be executed just by the addition of Cu^+ and acetonitrile, respectively.

The Cu^+ complexes of **1** persist against oxidation by molecular oxygen, while Cu^+ complexes, such as CuX (X = Cl, I, etc.), are easily oxidized to Cu^{2+} in general. Electronic absorption and ^1H NMR spectra of organic solutions ($CHCl_3$, CH_2Cl_2, $CDCl_3$) of the complexes do not change, even when the solutions are allowed to stand for a week under aerobic conditions or the oxygen is bubbled into the solutions. The resistance toward oxidation may be elucidated by electrochemical properties of similar Cu^+ compounds (6,6′-dimethyl-2,2′-bipyridine,[25] 2,9-dimethyl-1,10-phenanthroline,[26] and 2,9-di-*p*-anisyl-1,10-phenanthroline complexes[27]) reported previously, which have higher Cu^{2+}/Cu^+ redox potentials (ca. 0.6 V vs SCE) than unsubstituted 2,2′-bipyridine complex (0.19 V vs SCE[27]).

Ionophore **2** is converted to the corresponding metal complex with Ni^{2+}, Fe^{3+}, etc., in chloroform or methylene chloride. The spectroscopic mole ratio method suggests that 1:1 complexation takes place with Ni^{2+} (Figure 1b). However these complexes unfortunately can not be used for the solvent extraction and a transport experiment through a liquid membrane described below, because the complexes are soluble in water.

Regulation of Ion Recognition toward Alkali Metal Ions by Cu^+. Ion Transport across a Liquid Membrane. Methylene

(25) James, B. R.; Williams, R. J. P. *J. Chem. Soc.* **1961**, 2007–2019.
(26) Hawkins, C. J.; Perrin, D. D. *J. Chem. Soc.* **1963**, 2996–3002.
(27) Dietrich-Buchecker, C.; Sauvage, J.-P.; Kern, J.-M. *J. Am. Chem. Soc.* **1989**, *111*, 7791–7800.

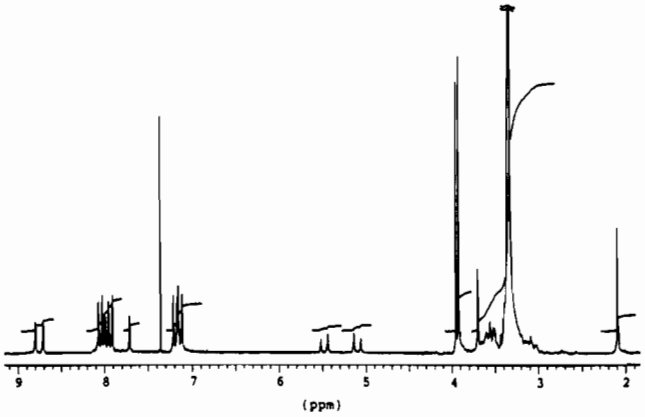


Figure 4. 200-MHz ^{1}H NMR spectrum of **1c**-Zn^{2+}. **1c** and 1 equiv of $Zn(NO_3)_2$ in $CDCl_3$–CD_3OD (90:10, v/v).

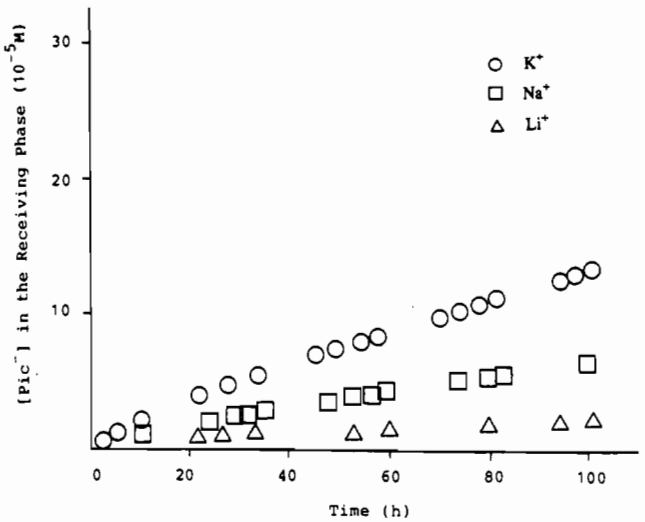


Figure 5. Course of ion transport by **1a** at 25 °C. [**1a**] = 5.7×10^{-5} M in CH_2Cl_2. Initial concentration of metal picrate was 0.01 M in the source phase.

Table II. 500-MHz ^{1}H NMR Chemical Shifts of **1c** and **1c**-Cu^+ Complex[a]

	H3	H3′	H5	H5′	bpy-CH_2–O	–OMe	–Me
1c	8.524	8.416	~7.69	7.366	4.815	3.866 3.868	2.686
1c-Cu^+	8.544	8.479	8.030	7.653	4.422	3.919 3.924	2.327

[a] In CD_3Cl–CH_3CN (95:5, v/v).

chloride was used as a liquid membrane containing ionophore with a concentration of 5.7×10^{-5} M. The source aqueous phase contains metal picrate with a concentration of 0.01 M, and receiving phase consists of deionized water. The amount of alkali metal ion transported was estimated from the absorbance of picrate anion at 354 nm in the receiving phase. First, we estimated the transport ability of linear polyether **1** without Cu^+. As seen in Figures 5–7, **1** transports the alkali metal ion. Though quite high ion selectivity is not observed, both **1b** and **1c** carry K^+ 3 times faster than Na^+. Li^+ is transported most slowly by **1** among the alkali metals. On the other hand, when the aqueous phases contain Cu^+ (1.2×10^{-4} M), the transport rates and/or selectivity are changed dramatically. In **1a** and **1b**, transport is suppressed considerably for Li^+, Na^+, and K^+, whereas the selectivity sequence is not perturbed significantly (Figures 8 and 9). In **1c**, however, K^+ is transported ca. 13 times as much as Na^+ after 100 h (Figure 10). Under the present transport conditions, the absorption spectra of the organic layers containing **1** display the fact that ionophores **1** are converted quantitatively into the

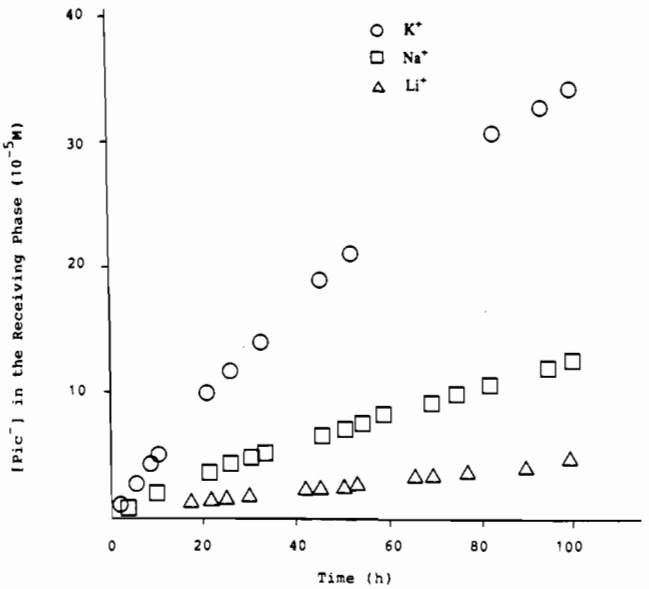


Figure 6. Course of ion transport by **1b** at 25 °C. [**1b**] = 5.7×10^{-5} M in CH_2Cl_2. Initial concentration of metal picrate was 0.01 M in the source phase.

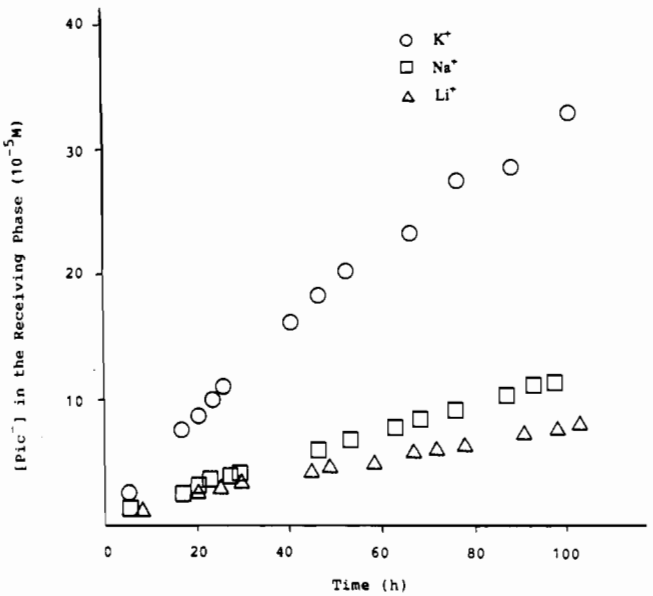


Figure 7. Course of ion transport by **1c** at 25 °C. [**1c**] = 5.7×10^{-5} M in CH_2Cl_2. Initial concentration of metal picrate was 0.01 M in the source phase.

corresponding Cu^+ complexes. These facts seem to indicate that the cavity size of the pseudocrown is the most important factor for the transport selectivity. Interestingly, 18-crown-6 exhibits a moderate K^+ selectivity (K^+:Na^+ = 1.7) in the transport, and a similar selectivity is also obtained in pentaglyme under the conditions employed here, although the rate in pentaglyme is slower than that in the crown (Table III). In addition, it is noteworthy that in the unsymmetrical ionophore **10** decrease of transport rates takes place but that enhancement of the selectivity is not observed in the presence of Cu^+ (Table III). Since **10** is an unsymmetrical polyether bearing a phenyl substituent instead of the hydrophobic bipyridine moiety of **1**, **10** cannot generate a pseudocrown but instead an intermolecular 2:1 complex with Cu^+. Hence, formation of the cyclic structure is proved to be quite important and necessary but not sufficient for the large enhancement of the transport observed in the pseudocrown **1c**-Cu^+. Another factor must be required for the high selectivity. Most likely, a repulsive electrostatic interaction is one of the most significant factors. The CPK models of the **1**-Cu^+ complexes predict that the interaction may well exist, because a cavity of

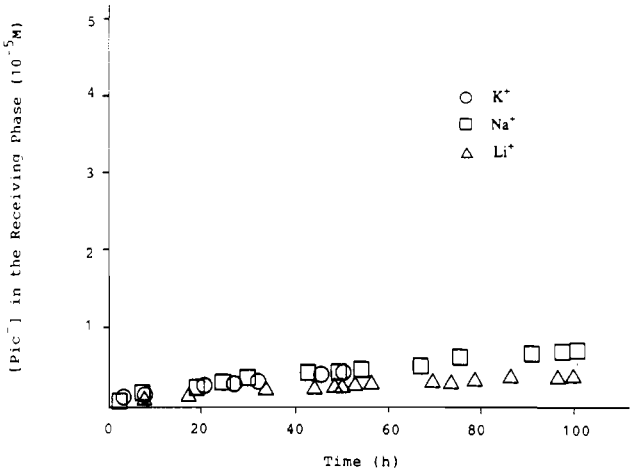


Figure 8. Course of ion transport by **1a** in the presence of Cu^+ at 25 °C. [**1a**] = 5.7×10^{-5} M in CH_2Cl_2. Initial concentration of metal picrate was 0.01 M in the source phase. [CuCl] = 1.2×10^{-4} M in the source and receiving phases.

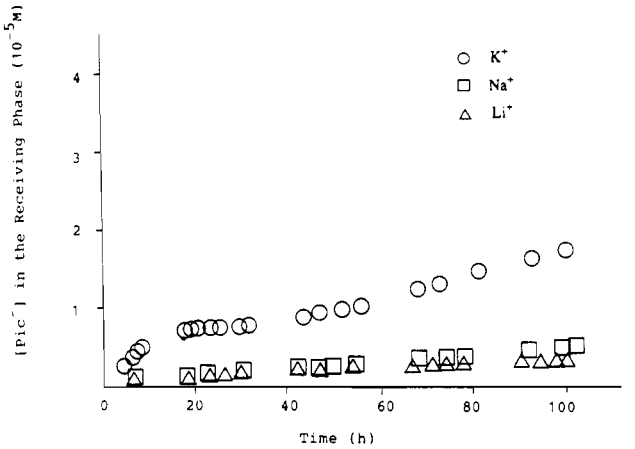


Figure 9. Course of ion transport by **1b** in the presence of Cu^+ at 25 °C. [**1b**] = 5.7×10^{-5} M in CH_2Cl_2. Initial concentration of metal picrate was 0.01 M in the source phase. [CuCl] = 1.2×10^{-4} M in the source and receiving phases.

the pseudocrown apparently locates in close proximity to the Cu^+ bound in the bipyridines. The decrease of the transport rates by the complexation with Cu^+ is well rationalized in terms of the Coulombic repulsion between Cu^+ and the alkali metal ion bound in the same ionophore. The presence of the electrostatic repulsion is also supported strongly by an effect of Cu^+ on uptake and release rates of alkali metal ions in a biphasic (water–methylene chloride) system. Measurements of the uptake and release rates in **1c** and the Cu^+ complex were carried out by monitoring absorbance of picrate anion at 354 nm in the aqueous phase. From the initial slopes of the curves in Figure 11, the uptake and release rates toward K^+ in the absence of Cu^+ are estimated to be ca. 1.7×10^{-5} and 2.1×10^{-5} mol/h, respectively. As shown in Figure 12, the release rate is enhanced in the presence of Cu^+ (ca. 5.5×10^{-5} mol/h). The uptake rate could not be measured accurately because of the low extractability of **1c**-Cu^+ toward K^+. But the uptake rate of **1c**-Cu^+ should be even slower than that of free **1c**, because in **1c**-Cu^+ the decrease of the transport rate through a liquid membrane is performed (Table III) despite the increase of the release rate in the biphasic system. The effect of Cu^+ on the uptake and release rates can be well interpreted by the Coulombic repulsion described above. Therefore it is strongly suggested that the remarkable enhancement of K^+ selectivity achieved in **1c**-Cu^+ is caused by not only formation of an appropriate pseudocrown, i.e. the cyclic framework with a suitable ring size for a metal ion, but also the electrostatic repulsion.

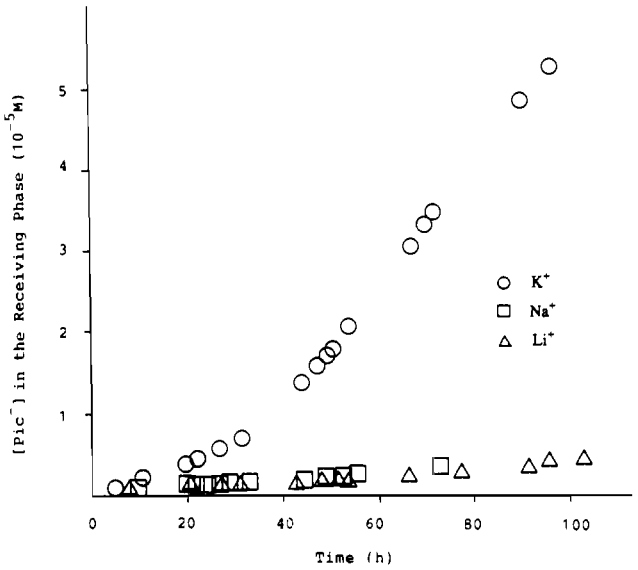


Figure 10. Course of ion transport by **1c** in the presence of Cu^+ at 25 °C. [**1c**] = 5.7×10^{-5} M in CH_2Cl_2. Initial concentration of metal picrate was 0.01 M in the source phase. [CuCl] = 1.2×10^{-4} M in the source and receiving phases.

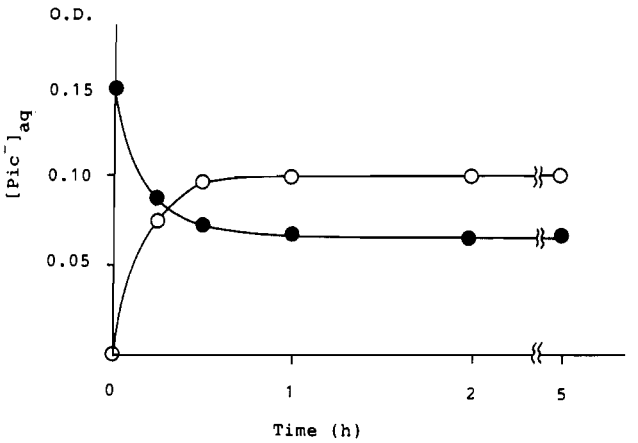


Figure 11. Uptake (●) and release (○) of potassium picrate by **1c**. For measurement of the uptake rate, the aqueous phase contained KCl (0.01 M) and potassium picrate (the initial concentration was 1×10^{-5} M); the organic phase (CH_2Cl_2) contained **1c** (5.7×10^{-5} M). For the release rate the aqueous phase was deionized water; the organic phase contained **1c** (5.7×10^{-5} M) and potassium picrate (the initial concentration was 1×10^{-5} M).

Table III. Amounts (%) of Alkali Metal Ions Transported through Liquid Membrane (CH_2Cl_2) by Ionophores at 25 °C[a]

	1c	**1c** + Cu^+	18-crown-6[b]	pentaglyme[b]	**10**	**10** + Cu^+
Li^+	7.6	0.43	2.0	0.94		
Na^+	11	0.43	5.7	1.9	10	5.1
K^+	32	5.4	10	3.5	30	13

[a] After 100 h, [ionophore] = 5.7×10^{-5} M, unless otherwise mentioned. [b] After 30 h, [ionophore] = 7.0×10^{-6} M.

Molecular Chirality of Pseudocrown Ethers. If a stable and inert complexation of **1** and Cu^+ with tetrahedral geometry takes place, the complexes should have molecular chirality because of their characteristic helical structure (Figure 13). In order to clarify the asymmetric properties, we performed an NMR study on the Cu^+ pseudocrown ethers. Measurement of the 500-MHz ^1H NMR of the **1c**-Cu^+ complex was carried out in the presence of an excess amount of Pirkle's reagent, which is often used for confirmation of a chiral structure in catenane compounds bearing 1,10-phenanthroline moieties.[28] No meaningful change of signals is observed at various temperatures (+27 to −28 °C), although broadening of signals occurs at lower temperatures (not shown).

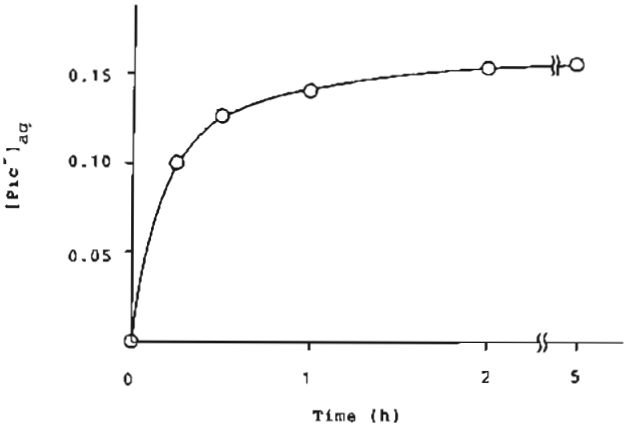


Figure 12. Release of potassium picrate by **1c**-Cu^+ complex. The organic phase contained **1c**-Cu^+Pic^- (5.7×10^{-5} M) and potassium picrate (the initial concentration was 1×10^{-5} M).

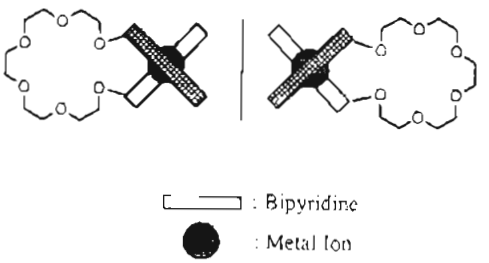


Figure 13. Molecular chirality of pseudocrown ether.

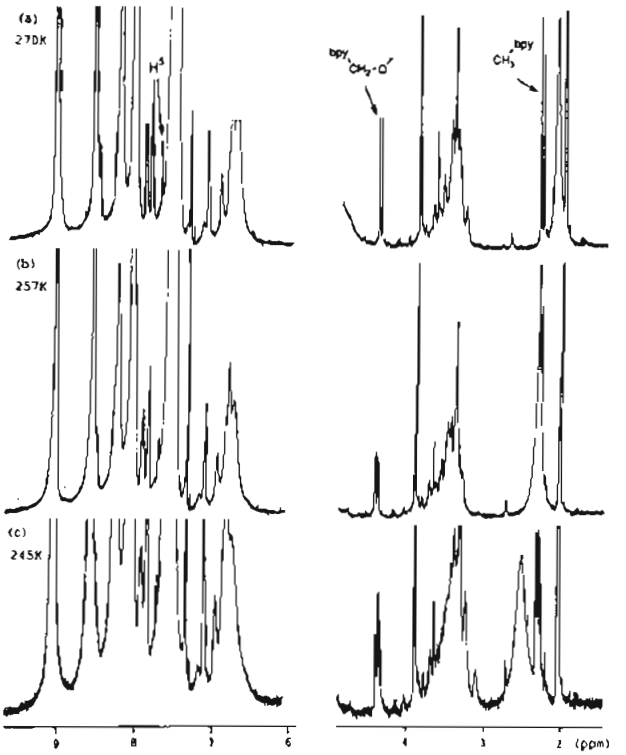


Figure 14. Variable-temperature ^1H NMR spectra of **12**-Cu^+ in the presence of Pirkle's reagent.

Similar measurement was performed on the unsymmetrical ionophore **12**, which has two kinds of ligands, i.e. bipyridines with two *p*-methoxyphenyl substituents at the 4,4′-position of the one bipyridine nucleus and with two unsubstituted phenyl groups in the other. As in the case of **1c**, an excess amount of Pirkle's reagent does not affect the spectrum significantly at room temperature. In contrast to **1c**, however, explicit splittings are observed at −28 °C in the signals of H-5 protons in the bipyridine ring bearing phenyl groups, the two methylene and methyl groups at the 6 and 6′ positions of the bipyridines (Figure 14). The splitting of the methyl is the most noticeable evidence for molecular chirality, since the presence of rotamers resulting from the free rotation around the axis between C-6 of the bipyridine and the methyl substituent can be ruled out. The energy barrier of a rotation of a usual methyl group is known to be ca. 3 kcal/mol, which is too small to freeze the rotation at −28 °C. Therefore the results of the NMR measurement confirm that the **12**-Cu^+ complex exists as a racemic mixture and that the racemization caused by intramolecular ligand exchange is restricted at −28 °C. Thus the **12**-Cu^+ complex is *intermolecularly* inert (vide supra) but *intramolecularly* labile on the NMR time scale at room temperature. The **1c**-Cu^+ complex must have molecular chirality at lower temperature, but a similar splitting is not detected presumably due to the higher symmetry of **1c**-Cu^+ than **12**-Cu^+. However, in Zn^{2+} complex of **1c**, the picolyl methyl protons exhibit two singlets at 1.97 and 1.98 ppm in the presence of an excess amount of Pirkle's reagent. The two singlets clearly show inhibition of racemization at room temperature on the NMR time scale. Very interestingly, ionophore **16** bearing two bis(bipyridine) moieties also forms a racemic mixture of 1:2 adducts of **16** and Cu^+ with tetrahedral configuration, which was ascertained by UV–vis and ^1H NMR analyses. Each of the enantiomeric pseudocrowns should have a characteristic double helical structure (Figure 15).[29] Similar ^1H NMR experiments (200 MHz) using Pirkle's reagent indicates that the racemization of the Cu^+ complex is also prevented at room temperature due to the stronger ligation of the bis(bipyridine) to two Cu^+, because splitting of the picolyl methyl protons occurs. Furthermore addition of L-potassium mandelate to **16**-Cu^+_2 in chloroform-*d*–acetonitrile-d_3–methanol-d_4 (86:4:10) gives rise to a splitting of the resonance at 8.78 ppm, assigned to one set of H-3 protons in 4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine moieties (the other set appears at 8.88 ppm), into two singlets (8.72, 8.74 ppm). In contrast, L-methyl mandelate and potassium laurate do not result in the splitting. This fact unambiguously shows that the splitting observed in a mixture of **16**-Cu^+_2 and L-potassium mandelate results from interaction between the chiral host and the chiral guest. If predominant formation of one enantiomer of helical pseudocrowns is successfully performed by the addition of a chiral ionic guest prior to producing the pseudocrown, switching of the chirality will be achieved facilely, because the chiral pseudocrown thus obtained should be reverted to the original linear form by an excess amount of acetonitrile. Consequently, if a stable and chiral pseudocrown is isolated from the racemic mixture, pseudocrowns will become a novel class of chiral hosts and may open a way to construct a new system which can transfer and store chiral information of molecules. An intensive and detailed study on chiral recognition using pseudocrowns is currently taking place in our laboratory.

Conclusion

Allosteric regulation of recognition toward alkali metal ions induced by Cu^+ as an effector (*heterotropic cooperativity*) has been achieved by conformational change of linear polyethers bearing bipyridines to the cyclic ones (*pseudocrown ethers*) including a tetrahedral Cu^+ complex. The dramatic enhancement of K^+ selectivity in the transport experiment takes place on exclusive formation of a pseudocrown ether with an appropriate ring size. Most likely, an electrostatic repulsion between two

(28) (a) Dietrich-Buchecker, C. O.; Edel, A.; Kintzinger, J. P.; Sauvage, J. P. *Tetrahedron* **1987**, *43*, 333–344. (b) Mitchell, D. K.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 930–931. (c) Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 189–192.

(29) For other examples, see: (a) Reference 24. (b) Koert, U.; Harding, M. M.; Lehn, J.-M. *Nature* **1990**, *346*, 339–342.

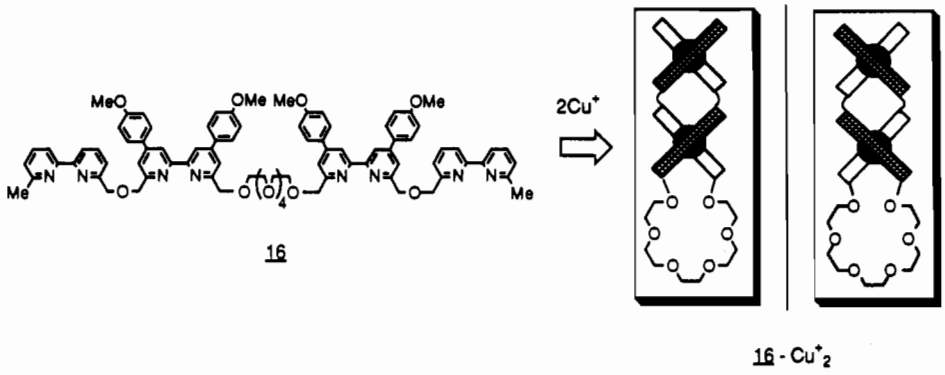


Figure 15. Formation of pseudocrown ether with double helical structure.

different metal ions bound in the same pseudocrown plays one of the most essential roles in the selectivity. Pseudocrown has another interesting feature, molecular chirality, which will be applied to allosteric regulation of chiral recognition. Hence, our strategy, i.e. conversion of a linear polyether with heavy metal binding sites to the corresponding pseudocrown by the addition of heavy metals, will be a quite convenient and powerful method to construct intelligent molecular systems that store, transfer, amplify, and regulate molecular functions and information.

Experimental Section

General Data. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Hitachi R 600 (60 MHz), JEOL FX-100 (100 MHz), Varian Gemini-200 (200 MHz), or Bruker AM-500 (500 MHz) instrument. The chemical shifts are given in δ values relative to tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini-200 (50 MHz) or Bruker AM-500 instrument (125 MHz) and are reported in ppm from TMS. Spectra were obtained in $CDCl_3$ and where specified in $CDCl_3$–CD_3CN, $CDCl_3$–CD_3OD, or $CDCl_3$–CD_3OD–CD_3CN. Infrared spectra (IR) were recorded on a Hitachi 260-50 or 270-50 spectrophotometer and reported in wavenumbers (cm^{-1}). Electronic absorption spectra were measured on a JASCO Ubest-50 spectrophotometer. Fast atom bombardment (FAB) mass spectrometry was performed on a Shimadzu/Kratos Concept 1S or a JEOL JMS SX 102A spectrometer with use of *m*-nitrobenzyl alcohol as the matrix and a parallel run of cesium iodide for the reference. Vapor pressure osmometry in chloroform was carried out on a Corona Model 117 molecular weight apparatus. Melting points were obtained using a Yanagimoto micro melting point apparatus and are uncorrected. Flash column chromatography was performed with the indicated solvents using Wakogel C-200 (silica gel, 70–150 μm, Wako). High-performance liquid chromatography (HPLC) was performed preparatively on a JAI Model LC-09 instrument with two JAIGEL-1H columns (two 20 mm × 60 cm columns connected successively) using chloroform as eluent. Elemental analyses were performed at Chemical Analysis Center, University of Tsukuba, or the Microanalytical Laboratory, Gunma University.

All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran (THF) and dioxane were purified by distillation from sodium benzophenone ketyl just prior to use. Sodium hydride purchased from Wako Pure Chemical Industries, Ltd., was employed as a 50 wt % dispersion in mineral oil, and weights are recorded for the dispersion. *N*-Bromosuccinimide (Waco) was purified by recrystallization from deionized water before use. Benzyl peroxide (BPO) and 2,2′-azobis(isobutyronitrile) (AIBN) were used as received. 6-(Bromomethyl)-2,2′-bipyridine (**8**, 47% yield),[30] 6,6′-dimethyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine (**3**),[31] and 6,6′-dimethyl-4,4′-diphenyl-2,2′-bipyridine (**4**)[31] were synthesized according to the literature methods. 6-(Hydroxymethyl)-6′-methyl-2,2′-bipyridine (**13**) was obtained from hydrolysis (86% yield, Na_2CO_3, H_2O:1,4-dioxane = 1:1 (v/v)) of 6-(bromomethyl)-6′-methyl-2,2′-bipyridine.[32] 6,6′-Bis(bromomethyl)-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine (**14**)[33] was prepared from **3**, *N*-bromosuccinimide, and AIBN in benzene (34% yield).

6-(Bromomethyl)-6′-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine (6). 6,6′-Dimethyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridine (**3**, 500 mg, 1.25 mmol), *N*-bromosuccinimide (202 mg, 1.13 mmol), and BPO (20 mg, 0.083 mmol) were refluxed in benzene (20 mL) for 4 h. The mixture was cooled to room temperature, and then the succinimide precipitated was filtered off. After the filtrate was concentrated in vacuo, the residual mixture was purified by flash column chromatography (50:3:0.2, methylene chloride–ether–acetone) to yield 232 mg (39%) of the product as colorless crystals, mp 205.5–206 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.699 (3H, s), 3.889 (6H, s), 4.708 (2H, s), 6.99–7.10 (4H, m), 7.388 (1H, d, J = 1.5 Hz), 7.663 (1H, d, J = 1.5 Hz), 7.69–7.80 (4H, m), 8.475 (1H, d, J = 1.5 Hz), 8.576 (1H, d, J = 1.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.61, 160.41, 158.31, 156.82, 156.67, 155.79, 149.86, 149.04, 130.99, 130.47, 128.42, 128.35, 120.79, 120.65, 118.07, 116.27, 114.46, 114.41, 55.39, 34.50, 24.75. IR (KBr): 1590, 1540, 1510, 1440, 1395, 1255, 1190, 1030, 830, 575 cm^{-1}. Anal. Calcd for $C_{26}H_{23}N_2O_2Br$: C, 65.69; H, 4.88; N, 5.89. Found: C, 65.47; H, 5.01; N, 5.68.

6-(Bromomethyl)-6′-methyl-4,4′-diphenyl-2,2′-bipyridine (7). Following the above procedure, 6,6′-dimethyl-4,4′-diphenyl-2,2′-bipyridine (**4**, 5.66 g, 16.8 mmol), *N*-bromosuccinimide (2.67 g, 15.0 mmol), and BPO (210 mg, 0.86 mmol) in benzene (20 mL) gave **7** in 27% yield (1.86 g) as colorless crystals, after flash column chromatography (100:1:1, methylene chloride–ether–methanol); mp 189–190 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.715 (3H, s), 4.720 (2H, s), 7.40–7.60 (7H, m), 7.703 (1H, d, J = 1.7 Hz), 7.73–7.83 (4H, m), 8.526 (1H, d, J = 1.3 Hz), 8.633 (1H, d, J = 1.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.44, 156.78, 155.74, 150.45, 149.61, 138.76, 138.24, 129.13, 129.04, 128.98, 128.86, 127.22, 121.46, 121.32, 118.69, 116.82, 34.34, 24.75. IR (KBr): 3040, 1592, 1552, 1494, 1450, 1386, 1200, 1076, 876, 766, 740, 698, 624, 594, 578, 520 cm^{-1}. Anal. Calcd for $C_{24}H_{19}N_2Br$: C, 69.41; H, 4.61; N, 6.74. Found: C, 69.18; H, 4.61; N, 6.70.

Tetraethylene Glycol Bis((2,2′-bipyridin-6-yl)methyl) Ether (2). 6-(Bromomethyl)-2,2′-bipyridine (**8**, 300 mg, 1.20 mmol), tetraethylene glycol (117 mg, 0.602 mmol), and KOH (1.0 g, 15 mmol) in dioxane were heated at 80 °C for 12 h. The mixture was cooled to room temperature and then filtered. The filtrate was concentrated in vacuo. The crude product was purified preparatively by HPLC to afford 181 mg (57%) of **2** as a pale yellow oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 3.68 (12H, s), 3.74 (8H, s), 4.77 (4H, s), 7.10–7.35 (1H, m), 7.50 (1H, d, J = 7.4 Hz), 7.60–7.45 (2H, m), 7.55–7.70 (1H, m). IR (neat): 2870, 1580, 1560, 1460, 1430, 1110, 770 cm^{-1}. HRMS calcd for $C_{30}H_{34}N_4O_5$ (M^+): 530.2529. Found: 530.2532.

Pentaethylene Glycol Bis((6-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl) Ether (1c). Pentaethylene glycol (170 mg, 0.713 mmol) was added to a suspension of sodium hydride (90 mg, 1.88 mmol) (washed with hexane) in 10 mL of dioxane. Bromide **6** (700 mg, 1.47 mmol) in 20 mL of dioxane was syringed into the mixture, which was then heated at reflux for 4 h. After cooling, the precipitates were filtered off, followed by evaporation of the dioxane in vacuo. The crude product was purified by recrystallization from chloroform–methanol to provide 618 mg (84%) of the product as colorless crystals, mp 130–130.5 °C. ^{1}H NMR (500 MHz, 5% CD_3CN in $CDCl_3$): δ 2.686 (6H, s), 3.459 (4H,

(30) Newkome, G. R.; Gupta, V. K.; Fronczek, F. R. *Inorg. Chem.* **1983**, *22*, 171–174.
(31) Kröhnke, F. *Synthesis* **1976**, 1–24.
(32) Rodriguez-Ubis, J.-C.; Alpha, B.; Plancherel, D.; Lehn, J.-M. *Helv. Chim. Acta* **1984**, *67*, 2264–2269.
(33) Alpha, B.; Anklam, E.; Deschenaux, R.; Lehn, J.-M.; Pietraskiewicz, M. *Helv. Chim. Acta* **1988**, *71*, 1042–1052.

s), 3.62–3.68 (8H, m), 3.72–3.75 (4H, m), 3.78–3.81 (4H, m), 3.866 (6H, s), 3.868 (6H, s), 4.815 (4H, s), 6.98–7.05 (8H, m), 7.366 (2H, d, J = 1.5 Hz), 7.67–7.73 (6H, m), 7.73–7.78 (4H, m), 8.414 (2H, d, J = 1.5 Hz), 8.524 (2H, d, J = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.42, 160.37, 158.62, 158.28, 156.34, 156.24, 149.30, 148.99, 131.00, 128.45, 128.34, 120.60, 118.36, 117.47, 116.16, 114.37, 114.36, 74.34, 70.67, 70.62, 70.58, 70.27, 55.38, 53.43, 24.74. IR (KBr): 1610, 1590, 1510, 1290, 1250, 1180, 1110, 830 cm^{-1}. Anal. Calcd for $C_{62}H_{66}N_4O_{10}$: C, 72.49; H, 6.47; N, 5.45. Found: C, 72.36; H, 6.48; N, 5.52.

Tetraethylene Glycol Bis((6-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl) Ether (1b). Following the above procedure, tetraethylene glycol (123 mg, 0.633 mmol), bromide **6** (633 mg, 1.33 mmol), and sodium hydride (80 mg, 1.7 mmol) in 40 mL of dioxane were heated at 80 °C for 4 h. After workup, the crude product was purified by flash column chromatography (50:5:2, methylene chloride–ether–methanol) to give 221 mg (36%) of **1b** as a pale yellow solid, mp 148–148.5 °C. ^{1}H NMR (500 MHz, 5% CD_3CN in $CDCl_3$): δ 2.686 (6H, s), 3.60–3.70 (8H, m), 3.70–3.77 (4H, m), 3.77–3.82 (4H, m), 3.859 (6H, s), 3.866 (6H, s), 4.808 (4H, s), 7.015 (8H, d, J = 8.7 Hz), 7.365 (2H, d, J = 1.4 Hz), 7.65–7.72 (6H, m), 7.753 (4H, d, J = 8.7 Hz), 8.414 (2H, s), 8.523 (2H, s). ^{13}C NMR ($CDCl_3$): δ ^{13}C NMR (125 MHz, 5% CD_3CN in $CDCl_3$): δ 160.48, 160.41, 158.69, 158.34, 156.42, 156.29, 149.26, 148.91, 131.01, 130.98, 128.44, 128.34, 120.58, 118.33, 117.35, 116.50, 116.05, 114.42, 114.41, 74.35, 70.70, 70.64, 70.32, 55.42, 24.77. IR (KBr): 1610, 1590, 1510, 1290, 1250, 1180, 1110, 830 cm^{-1}. Anal. Calcd for $C_{60}H_{62}N_4O_9$: C, 73.29; H, 6.35; N, 5.69. Found: C, 72.78; H, 6.33; N, 5.62.

Triethylene Glycol Bis((6-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl) Ether (1a). Following the above procedure, triethylene glycol (21 mg, 0.14 mmol), bromide **6** (134 mg, 0.282 mmol), and sodium hydride (14 mg, 0.29 mmol) in THF gave 105 mg (80%) of **1a** as a pale yellow solid after purification by recrystallization from chloroform–methanol; mp 138.5–139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.729 (6H, s), 3.70–3.82 (12H, m), 3.840 (6H, s), 3.863 (6H, s), 4.819 (4H, s), 6.94–7.06 (8H, m), 7.378 (2H, d, J = 1.5 Hz), 7.66–7.84 (10H, m), 8.435 (2H, d, J = 1.5 Hz), 8.570 (2H, s). IR (KBr): 2932, 2908, 2872, 2836, 1610, 1596, 1550, 1516, 1464, 1440, 1292, 1254, 1182, 1116, 1074, 1032, 830, 578 cm^{-1}. MS(FAB): m/e 961.9 (M + Na^+).

Pentaethylene Glycol Phenylmethyl (6-Methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl Ether (10). Following the above procedure, pentaethylene glycol monobenzyl ether (**9**, 276 mg, 0.840 mmol), bromide **6** (415 mg, 0.873 mmol), and sodium hydride (42 mg, 0.88 mmol) in 20 mL of dioxane gave after purification by flash column chromatography (50:2, methylene chloride–methanol) 236 mg (39%) of **10** as a pale yellow solid. ^{1}H NMR (5% CD_3CN in $CDCl_3$): δ 2.718 (3H, s), 3.55–3.85 (10H, m), 3.880 (6H, s), 4.539 (2H, s), 4.833 (2H, s), 7.01–7.10 (4H, m), 7.22–7.47 (6H, m), 7.67–7.87 (5H, m), 8.439 (1H, s), 8.563 (1H, s). ^{13}C NMR (125 MHz, 5% CD_3CN in $CDCl_3$): δ 160.53, 158.74, 158.26, 156.11, 149.36, 138.37, 130.93, 128.49, 128.39, 128.37, 127.75, 127.59, 120.69, 118.44, 117.53, 116.49, 116.23, 114.47, 114.45, 74.33, 73.22, 70.71, 70.62, 70.60, 70.35, 69.50, 55.44, 24.63. IR (KBr): 3064, 3040, 2916, 2868, 1720, 1630, 1598, 1582 (sh), 1550, 1516, 1462, 1440, 1408, 1384, 1358, 1292, 1276, 1254, 1216, 1178, 1114, 1074, 1030, 832, 716, 578 cm^{-1}. HRMS (FAB) calcd for $C_{43}H_{51}N_2O_8$ (M + H^+): 723.3645. Found: 723.3623.

Pentaethylene Glycol Mono(6-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl Ether (11). Following the above procedure, pentaethylene glycol (610 mg, 2.56 mmol), bromide **6** (238 mg, 0.501 mmol), and sodium hydride (30 mg, 0.63 mmol) in dioxane gave 173 mg (55%) of **11** as a pale yellow solid after purification by flash column chromatography (50:5:2, methylene chloride–ether–methanol), followed by preparative HPLC. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.709 (3H, s), 3.56–3.87 (21H, m), 3.889 (6H, s), 4.851 (2H, s), 6.98–7.09 (8H, m), 7.382 (1H, d, J = 1.5 Hz), 7.68–7.84 (5H, m), 8.423 (1H, d, J = 1.5 Hz), 8.537 (1H, d, J = 1.5 Hz). IR (KBr): 3450 (br), 2900, 1610, 1596, 1580, 1550, 1516, 1462, 1442, 1292, 1252, 1178, 1128, 1114, 1074, 1030, 832, 578 cm^{-1}. Anal. Calcd for $C_{36}H_{44}N_2O_8$: C, 68.34; H, 7.01; N, 4.43. Found: C, 68.05; H, 6.94; N, 4.42.

Pentaethylene Glycol (6-Methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl (6-Methyl-4,4′-diphenyl-2,2′-bipyridin-6′-yl)methyl Ether (12). Following the above procedure, pentaethylene glycol mono-(6-methyl-4,4′-bis(4-methoxyphenyl)-2,2′-bipyridin-6′-yl)methyl ether (**11**, 40 mg, 0.063 mmol), bromide **7** (26 mg, 0.063 mmol), and sodium hydride (3 mg, 0.063 mmol) in THF gave a quantitative amount of **12** as a pale yellow solid after purification by flash column chromatography (100:1:1, methylene chloride–ethyl acetate–methanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.698 (3H, s), 2.707 (3H, s), 3.55–3.83 (20H, m), 3.867 (6H, s), 4.827 (2H, s), 4.839 (2H, s), 6.96–7.06 (4H, m), 7.35–7.56 (8H, m), 7.67–7.83 (10H, m), 8.416 (1H, d, J = 1.2 Hz), 8.465 (1H, d, J = 1.1 Hz), 8.534 (1H, s), 8.579 (1H, d, J = 1.6 Hz). IR (KBr): 3052, 3036, 2924, 2864, 1726, 1608, 1594, 1550, 1516, 1462, 1442, 1384, 1364, 1342, 1292, 1252, 1180, 1114, 1076, 1030, 990, 880, 832, 798, 766, 696, 622, 578 cm^{-1}. MS(FAB): m/e 989.9 (M + Na^+).

6-(Bromomethyl)-4,4′-bis(4-methoxyphenyl)-6′-((((6-methyl-2,2′-bipyridin-6′-yl)methoxy)methyl)-2,2′-bipyridine (15). A mixture of 6-hydroxymethyl-6′-methyl-2,2′-bipyridine (**13**, 112 mg, 0.559 mmol), dibromide **14** (309 mg, 0.557 mmol), and NaH (32 mg, 0.67 mmol) in 120 mL of THF was refluxed for 12 h. After the mixture was cooled to room temperature, the solvent was distilled off in vacuo. To the residue was added 10 mL of water; the resulting solution was extracted with methylene chloride and then dried over anhydrous $MgSO_4$. The solution was filtered and the solvent was removed, yielding the crude product, which was purified by flash column chromatography (100:1:1, chloroform–ethyl acetate–acetone) to give a pale yellow solid **15** (115 mg, 31%), mp 151.5–153 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.64 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 4.71 (2H, s), 4.95 (2H, s), 4.97 (2H, s), 6.97–7.08 (4H, m), 7.15 (1H, d, J = 7.9 Hz), 7.56–7.89 (9H, m), 8.19 (1H, d, J = 7.9 Hz), 8.33 (1H, d, J = 7.9 Hz), 8.58–8.62 (2H, m). IR (KBr): 2952, 2928, 2836, 1610, 1594, 1582, 1548, 1516, 1462, 1442, 1424, 1416, 1292, 1254, 1182, 1114, 1072, 1032, 830, 800, 786, 578 cm^{-1}. MS(FAB): m/e 672 (M + H^+).

Pentaethylene Glycol Containing Two Bis(bipyridine) Moieties (16). To a mixture of t-BuOK (19 mg, 0.17 mmol) and pentaethylene glycol (19 mg, 0.08 mmol) in 5 mL of THF was added bromide **15** (105 mg, 0.156 mmol) in 5 mL of THF, and the reaction was then refluxed for 12 h. After the solvent was removed in vacuo, the residue was mixed with water and extracted with methylene chloride (10 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The residue thus obtained was recrystallized from chloroform–methanol to give **16** (54 mg, 49%), mp 122–123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 2.63 (6H, s), 3.6–3.9 (32H, m), 4.83 (4H, s), 4.95 (4H, s), 4.96 (4H, s), 6.95–7.08 (8H, m), 7.15 (2H, d, J = 7.9 Hz), 7.56–7.89 (18H, m), 8.19 (2H, d, J = 7.9 Hz), 8.32 (2H, d, J = 7.9 Hz), 8.52–8.58 (4H, m). IR (KBr): 2956, 2920, 2860, 1730, 1610, 1596, 1580, 1550, 1516, 1464, 1442, 1416, 1290, 1254, 1180, 1134, 1114, 1100, 1032, 830, 800, 786, 578 cm^{-1}. MS(FAB): m/e 1461 (M + K^+).

1c-Cu^+ Complex. To a methylene chloride solution of **1c** was added 1.1 equiv of an acetonitrile solution of CuCl at room temperature, giving a red solution of the complex. The solvent was evaporated in vacuo, and then methylene chloride was added to the residue. After filtration of the mixture by a membrane filter (PTFE membrane, pore size 50 μm, Corning), the filtrate was concentrated in vacuo to afford a quantitative amount of the Cu complex as red powder, mp 78–79 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.327 (6H, s), 3.2–3.6 (20H, m), 3.919 (6H, s), 3.924 (6H, m), 4.422 (4H, s), 7.1–7.2 (8H, m), 7.653 (2H, s), 7.835 (4H, d, J = 3.8 Hz), 7.908 (4H, d, J = 3.8 Hz), 8.030 (2H, s), 8.479 (2H, s), 8.544 (2H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.52, 160.47, 158.73, 158.34, 149.30, 130.99, 128.46, 128.37, 120.62, 118.38, 117.39, 116.50, 116.10, 114.46, 114.44, 74.37, 70.72, 70.66, 70.35, 55.44, 24.76. IR (KBr): 2932, 2904, 2868, 2836, 1606, 1580, 1548, 1518, 1462, 1442, 1402, 1366, 1294, 1256, 1184, 1112, 1102, 1032, 832, 800, 580 cm^{-1}. MS(FAB): m/e 1090 (M + H^+ – Cl).

Extraction Experiments. Except for Cu^+ extraction an aqueous phase containing a heavy metal ion (1 mM) was prepared by dissolving metal nitrate into an aqueous 0.05 M (bis(2-hydroxyethyl)imino)tris(hydroxymethyl)methane (bis-tris) solution whose pH was adjusted to 5.5 by the addition of 0.1 M hydrochloric acid. Extraction of metal ion from the aqueous solution into methylene chloride was performed in capped vials. After the biphasic mixture (the volumes of the aqueous and organic phases are 10 mL each) was stirred vigorously for 11 h at 25 ± 1 °C, the organic phase was centrifuged and then concentrated in vacuo. The residue was dissolved in acetone–0.01 M hydrochloric acid (1:1). The solution thus obtained was analyzed by atomic absorption spectroscopy to determine the extractability. In Cu^+ an organic phase (0.02% acetonitrile in methylene chloride) containing ionophore and CuI was used, since the solubility of the copper salt is very low in water. After the organic solution was stirred with an equal volume of deionized water as an aqueous phase, the copper concentrations in the organic phase were determined from the absorbance of λ_{max} around 476 nm and by atomic

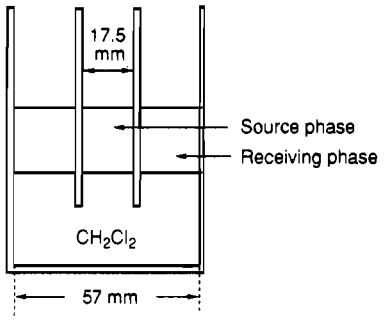


Figure 16. Apparatus for the transport experiment.

absorption spectroscopy, giving extractabilities. All experiments were carried out in duplicate or triplicate, and the respective results were averaged.

Transport Experiments. An apparatus (a dual cylindric cell, Figure 16) for the transport experiment across liquid membrane was designed on the basis of that of Lamb et al.[34] The inner aqueous source phase contained alkali metal picrate (4 mL, 0.01 M) and the outer receiving phase consisted of deionized water (40 mL). Methylene chloride (50 mL) containing ionophore (5.7×10^{-5} M) was used as a liquid membrane, unless otherwise mentioned. On examination of the effect of Cu^+ on the transport selectivity, [CuCl] in both of the source and receiving phases was adjusted to 1.2×10^{-4} M for the initial concentration. The three phases in the transport cell were agitated carefully by a stirring bar (200 rpm) on the bottom of the cell at 25 ± 1 °C. The concentrations of the metal ion in the aqueous receiving phase were determined at intervals during the transport run by monitoring the absorbances of picrate anion at 354 nm.

(34) Lamb, J. D.; Christensen, J. J.; Oscarson, J. L.; Nielsen, B. L.; Asay, B. W.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6820–6824.

Measurement of Ion Uptake and Ion Release. For an organic phase in measurement of uptake rate without Cu^+, a methylene chloride solution of **1c** (5.7×10^{-5} M) was employed. Deionized water containing potassium picrate (1×10^{-5} M) and potassium chloride (0.01 M) was used as an aqueous phase for the measurement of ion uptake. The organic solution (10 mL) was placed at the bottom of a cell (27 mm, i.d.), and then an equal amount of the aqueous phase was placed gently on the organic phase. The two phases were gently stirred at 200 rpm without mixing at 25 ± 1 °C. The concentrations of metal picrate in an aqueous phase at prescribed intervals were determined by UV–vis spectroscopy. From the concentrations, the rate of ion uptake was evaluated. Release rate of metal ion from an organic phase was estimated in a similar way by the use of a methylene chloride solution containing potassium picrate (1.0×10^{-5} M) and **1c** (5.7×10^{-5} M) for the organic phase and deionized water for the aqueous phase. In order to measure the release rate of pseudocrown (**1c**-Cu^+), deionized water was employed as an aqueous phase and methylene chloride (10 mL) containing **1c**-Cu^+Pic^- and metal picrate (1.0×10^{-5} M) was used as an organic phase. **1c**-Cu^+Pic^- was prepared by mixing an aqueous lithium picrate solution (0.01 M) and a methylene chloride solution of **1c**-Cu^+Cl^-, because from the solvent extraction experiment lithium ion was found not to be extracted into the organic solution of the complex at all. Completion of the counteranion exchange was ascertained spectrophotometrically by monitoring decrease of picrate anion in the aqueous phase. When the organic **1c**-Cu^+Pic^- solution thus obtained was agitated at 200 rpm with deionized water, the amount of picrate anion released from the organic phase to the aqueous phase was so small that the measurement of the release rate of potassium picrate was not disturbed.

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