ELSEVIER

Coordination Chemistry Reviews
148 (1996) 151–169

COORDINATION CHEMISTRY REVIEWS

Regulation of ion recognition by utilizing information at the molecular level

Tatsuya Nabeshima

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

Received 1 February 1995

Contents

Abstract

The regulation of molecular functions utilizing information at the molecular level is important and necessary to elucidate the mechanisms of allostery, cooperativity, feed-back, etc. in biological systems and to regulate biological molecular systems by artificial functionalized molecules responsive to such information. In particular, ion recognition among molecular functions has drawn much attention, because many enzymatic activities and the transport of stimuli in nervous systems are controlled by ion binding.

Thus, in this article, we describe very efficient strategies and examples to regulate the ion recognition of artificial systems utilizing a heavy metal ion, an electron, and a small organic molecule as an external effector. The first strategy is to produce a pseudocrown ether. A heavy metal ion is used as an effector. Complexation of a linear polyether bearing the metal binding

SSDI 0010-8545(95)01164-1

sites at the two termini gives the corresponding cyclic compound (pseudocrown ether). This methodology is very effective to control alkali metal recognition. This concept is applied to a pseudocryptand and a pseudothiacrown ether, which is a nice double recognition system for heavy metal ions. In addition, complexation with a heavy metal ion is used for regulation of molecular recognition. Secondly, redox reactions between thiol and disulfide are employed for regulation of ion recognition. Conformational change and/or change of spatial arrangement of binding site are useful for the regulation. However, these methods are not sufficient to construct perfect all-or-none type control. The ideal regulation is successfully performed by crown ethers with a redox gate in the binding site for metal ions. The gate responds to redox reactions between thiol and disulfide to afford an open and a closed state. The open state provides a remarkably selective binding site for Ag(I). The Ag(I) selectivity is considered to result from synergistic coordination of sulfur and oxygen atoms. This is a general binding mode for the high Ag(I) selectivity of crown ethers containing sulfur atom(s). The third strategy to modulate ion recognition is molecular assembly using a receptor which has hydrogen bonding sites. A new binding site of the molecular assembly for alkali metal ion is formed from several polyether chains each of which does not exhibit binding ability toward metal ions.

Keyword: Ion recognition

1. Introduction

In biological systems, molecular functions, such as molecular and ion recognition, catalytic activities, etc., are regulated finely by structural change due to catching and releasing information at the molecular level [1,2]. These amazing mechanisms are seen in allostery, cooperativity, feed-back, etc. [3–5]. Substances and properties of substances can be utilized to transfer and modulate the information [6,7]. Metal ions, molecules, electrons and photons are considered such substances. Chirality, combination of atoms and molecules, arrangement, and order are considered properties of substances.

I believe that these mechanisms are also very useful to control the molecular functions of artificial systems, and that they will be quite powerful and important ways to regulate biological molecular systems by artificial functionalized molecules responsive to such information.

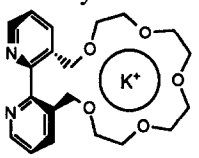
Ion recognition plays an important role in activating the functions of proteins and especially transferring and amplifying stimuli in nervous systems [8]. Therefore, control of ion recognition utilizing external information will provide a new field of enzymatic and neuro chemistry. I have therefore designed artificial ionophores to regulate ion recognition. Here I describe several strategies and examples to regulate ion recognition utilizing a heavy metal ion, an electron, and a small organic molecule as an external effector.

2. Regulation of ion recognition by metal ions

2.1. Conformational change of a crown ring

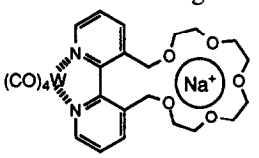
Activities of many enzymes are controlled by metal ions such as Ca^{2+}, and Mg^{2+} [3]. Actions of hormones often relate to ion binding [1]. Moreover, recognition of

neurotransmitters by the receptors is directly connected with controlling the ion flux. Much attention, thus, has been focused on allosteric regulation of alkali metal ion affinity by the use of a metal ion as an effector. One example was reported by Rebek et al.: a tungsten ion works as an effector for an artificial ionophore **1**, a crown ether containing a bipyridine moiety in the cyclic framework [9]. Complexation of the bipyridine with tungsten gives rise to conformational change of the crown ring, so that the binding selectivity toward alkali metal ions is changed.



(1)

selectivity in transport
$K^+/Na^+ = 2.3$

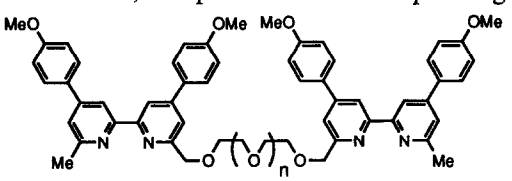


$W(CO)_4$-(1)

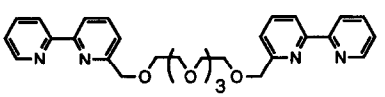
$K^+/Na^+ = 0.5$

2.2. Formation of pseudocrown ethers

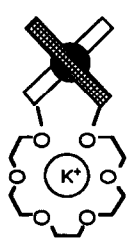
A different strategy reported by us is employing dynamic conformational change, i.e. a linear structure to a cyclic one, to modulate binding of alkali metal ions using a heavy metal ion as an effector, as shown in Fig. 1 [10,11]. The structural change is induced by complexation with heavy metal ions. In other words, we utilize the macrocyclic effect [12] on ion recognition to regulate the ion binding ability, because an enormous enhancement of the affinity of polyether compounds for metal ions is observed in crown ethers, compared to the corresponding glymes [13].



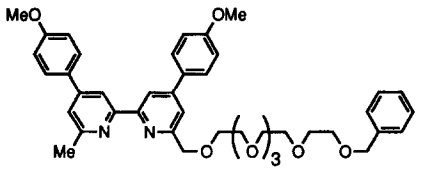
(2a) (n = 2)
(2b) (n = 3)
(2c) (n = 4)



(2d)



Cu^{2+}-(**2**)-K^+



(3)

We designed linear polyethers (**2a,b,c**) bearing hydrophobic bipyridine moieties at the ends of the chain. The hydrophobicity is necessary for the use of liquid–liquid extraction and transport experiments through a liquid membrane to estimate the binding ability of the ionophores and examination of heavy-metal-ion effect on the ability. *p*-Methoxyphenyl groups and methyl substituents at the 6 positions of the bipyridine nucleus are important for selective complexation with Cu(I), because the former groups are effective for back donation [14] to the metal ion and the latter ones are of great advantage for tetrahedral geometry over other structures [15,16]. In fact, solvent extraction indicates high selectivity of **2a,b,c** toward Cu(I) over other heavy metal ions [17]. A specific metal-to-ligand charge-transfer band (ca. 460 nm) [14,18] due to the tetrahedral geometry is observed upon complexation with Cu(I). The structure of the complexes generated by intramolecular cyclization is supported by NMR, IR, MS spectroscopies, vapor pressure osmometry, and elemental analysis.

We named these novel crown ethers pseudocrown ethers, because their cyclic structure is maintained by coordination to a metal ion instead of covalent bonding. Compounds Cu(I)–**2a,b,c** are the first examples of pseudocrown ethers for allosteric switching of ion recognition. Advantageous characteristics of pseudocrowns for switching and modulation of molecular functions are (i) facile interconversion between the linear and the cyclic forms and (ii) extendibility of the functions, because easy chemical modification of the binding site for heavy metal ions is possible to afford various kinds of metal complexes which have different geometries and can be used as a catalytic site for many reactions [19,20].

Transport experiments across a liquid membrane clearly reveal a tremendous effect

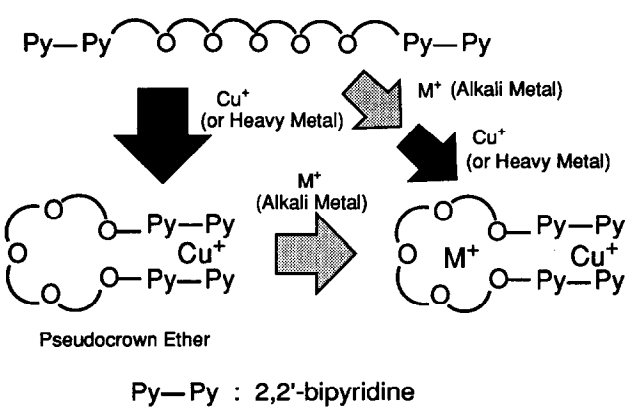


Fig. 1. Allosteric regulation of ion recognition by Cu(I). Reproduced with permission from Ref. [11].

Table 1
Amounts (%) of alkali metal ions transported through liquid membrane (CH_2Cl_2) by ionophores at 25 °C[a]

	2c	2c+Cu^+	18-crown-6[b]	pentaglyme[b]	3	3+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.
[b] After 30 h, [ionophore] = 7.0×10^{-6} M.
Reproduced with permission from Ref. [11].

of Cu(I) as an effector on ion recognition of **2a,b,c**. In the absence of Cu(I), **2a,b,c** transport K^+ preferentially over Na^+, Li^+, although the selectivity is not high (see Table 1). Addition of Cu(I) into the source and the receiving phases results in a dramatic change of transport rates. In ionophores **2a** and **2b** containing four and five polyether oxygen atoms, respectively, the rates for Li^+, Na^+ and K^+ are reduced significantly and the enhancement of selectivity is not attained. However, in ionophore **2c**, K^+ selectivity is increased dramatically, though the absolute rate decreases compared to **2c** itself. This ring size dependency on the selectivity might not seem to be novel, but the enhancement of selectivity is not caused just by formation of the cyclic Cu(I) complex similar to 18-crown-6. Indeed, the transport preference of pentaglyme and 18-crown-6 is almost the same under the conditions employed above, while the crown ether carries alkali metal ions faster. An intermolecular complex formed between two **3** and Cu(I) does not exhibit high K^+ selectivity, but a decrease of the rates occurs. These results indicate clearly that the formation of a pseudocrown is inevitable but not sufficient to explain the large enhancement on complexation. The results of transport experiments described above and up-take and release rates of ionophores and their Cu(I) complexes toward alkali metal ions suggest that electrostatic repulsion certainly exists between the Cu(I) bound with the bipyridines and alkali metal ions captured in the cavity. This interaction is an important factor to perturb the selectivity significantly.

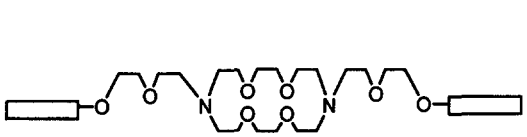
2.3. Formation of pseudocryptand

Formation of a new binding site for alkali metal ions by the addition of Cu(I) is also applied to a pseudocryptand system (Cu(I)–**4**) [21]. This double recognition system for metal ions shows good binding affinity toward alkali metal ions in the presence of Cu(I) despite electrostatic repulsion in a similar fashion to Cu(I)–**2**.

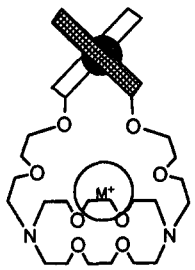
2.4. Formation of pseudothiacrown ethers

Pseudothiacrown is a nice double recognition system for Ag(I) and Cu(I). Cu(I) is bound to the bipyridine moieties of thiopolyether derivatives (**5**) (see scheme 1) to give the corresponding pseudothiacrowns (Scheme 1) [22]. Ag(I) is taken into the thi-

acrown ring selectively. Positive allostery is performed in the transport experiment for Ag(I) using Cu(I) as an effector, when the polyether has side chains containing a sulfide group (**5d**).

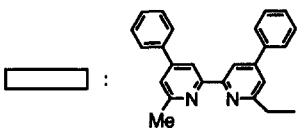


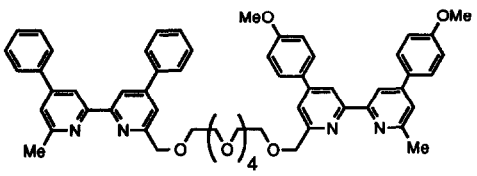
(4)



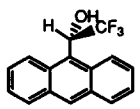
Cu^+-(4)

M^+ = alkali metal ion

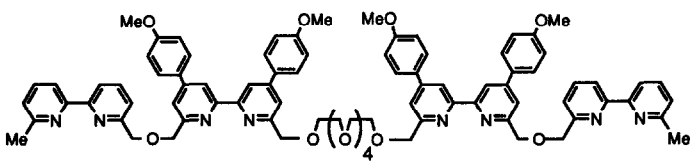




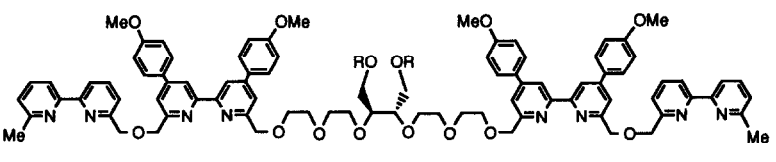
(6)



Pirkle's Reagent



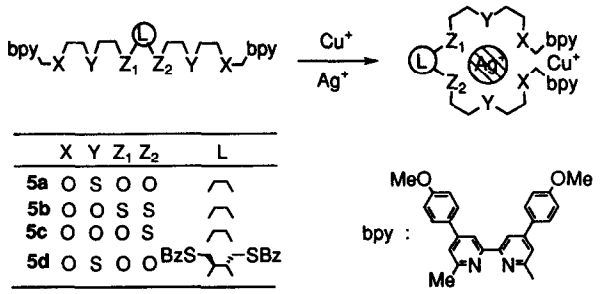
(7)



(8) R = 1-naphthyl

2.5. *Molecular chirality of pseudocrown ethers*

Pseudocrown ethers (Cu(I)–**2**) have molecular chirality due to their helical structure, if the Cu(I) complexes are inert (Fig. 2). However, ^{1}H NMR spectra of the pseudocrown indicate that intramolecular ligand exchange proceeds fast on the NMR time scale at room temperature to racemize the complexes [17]. Intermolecular ligand exchange is ruled out, because two kinds of resonances ascribed



Scheme 1.

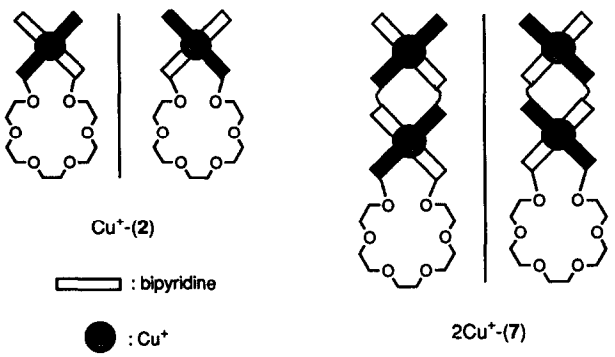


Fig. 2. Molecular chirality of pseudocrown ethers. Adapted from Ref. [11].

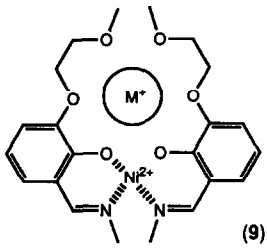
to the free and the complexed ionophores are seen in the spectra of a mixture of **2c** (or **6**) and Cu(I) ([**2c**] > [Cu(I)]) [23]. At −28 °C the ligand exchange is prohibited, because splitting of the methyl protons at the 6 positions of the bipyridine nucleus of **6** takes place in the presence of chiral Pirkle's reagent [24].

Introduction of two more bipyridine nuclei into the heavy metal binding site of **2** is useful to increase the binding strength toward Cu(I), so that inert pseudocrown ether ($Cu(I)_2$–**7**) is obtained even at room temperature [11]. ^1H NMR spectroscopy reveals that a similar bis-metal complex ($Cu(I)_2$–**8**) bearing side chains in the polyether moiety interacts differently with chiral potassium mandelates [25]. This differentiation is considered to result from interaction between the chiral host and guests. Thus this new chiral framework will be utilized to construct artificial allosteric chiral hosts.

2.6. Other systems for regulation of ion recognition utilizing metal ions

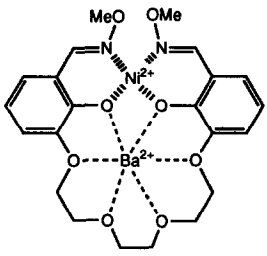
Ni(II) is employed to control ion recognition by assembling polyether chains [26–28]. Alkali metal ions are transported into an organic phase from an aqueous one by the metal complexes (**9**), whereas the free ligand is unable to extract the ions. Thereby affinity for metal ions is increased by the addition of Ni(II). Pseudocrown ethers (M(II)–**10**) which are formed by complexation with Ni(II), Cu(II) or Zn(II) were also reported by Reinhoudt and coworkers [29,30]. These metallohosts bind

Ba^{2+} in the cavity. Accurate X-ray structural analysis of complexes of the Cu(II) and Zn(II) pseudocrowns with Ba^{2+} clearly shows that Ba^{2+} is nicely coordinated by the oxygen atoms of the pseudocrown ethers. An electrochemical study of the complexes was also reported. Complexation between β-diketone derivatives and metal ions is also chosen in the third example of pseudocrowns (**11**) [31].

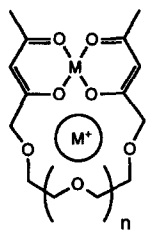


(9)

M^+ = alkali metal ion



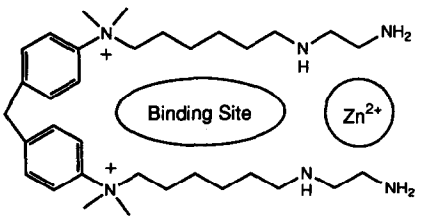
Ni^{2+}-(**10**)-Ba^{2+}

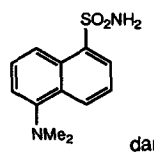


(**11**)

M = Zn^{2+}, Cu^{2+}

n = 1, 2





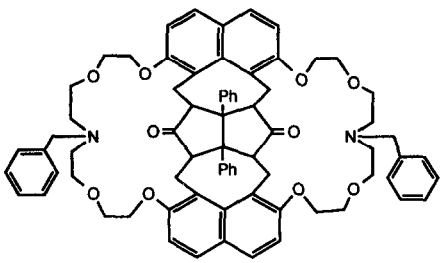
dansylamide

Cu^{2+}-(**12**)

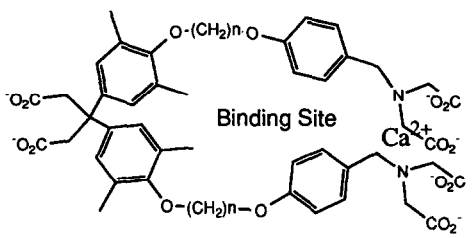
2.7. *Systems for regulation of molecular recognition utilizing metal ions*

Complexation with a metal ion is applied to control molecular recognition. Schneider et al. prepared (**12**), which binds Cu(II) and Zn(II) [32]. The Zn(II)

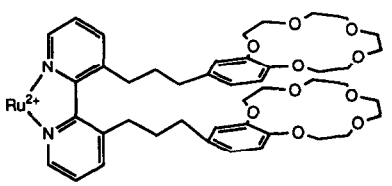
complex captures dansylamide in the recognition site formed from the two benzene rings and two alkyl chains upon the complexation. A conformational change of host (**13**) takes place upon the addition of K^+ to make the planes of the naphthalene rings parallel in the same direction [33]. This is caused by complexation between K^+ and the azacrown moieties. Consequently, the binding constant of the host toward 1,3-dinitrobenzene is increased. The binding strength of host (**14**) bearing two aminodicarboxylate groups toward 6-(toluidino)-2-naphthalenesulfonic acid in water is significantly enhanced by the addition of Ca^{2+}, because a hydrophobic cavity is formed on complexation [34]. A decrease of binding affinity to diquat dianion as a guest due to complexation with Ru(II) ion was reported in the case of biscrown derivative (**15**) [35].



(13)



Ca^{2+} - (14)



Ru^{2+} - (15)

As described above, control of recognition of guests utilizing metal ions is very effective. Regulation of catalytic activity for epoxidation of olefins can be combined with control of ion recognition using the Ru(II) complex of **2d** [36]. Obviously, catalytic ability for various chemical reactions will be easily incorporated in the pseudocrown systems, because many kinds of catalytic reactions mediated by metal complexes have been reported. Consequently, the concept of a pseudocrown will afford many regulation systems with diverse molecular functions.

3. Regulation of ion recognition by an electron as an effector

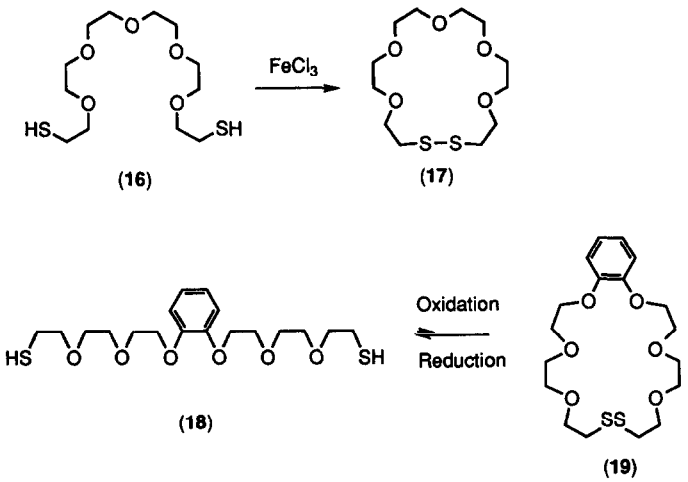
Disulfide linkages of cystine residues usually maintain tertiary structures of enzymes and the enzymatic activities [37]. Redox reactions between thiols and disulfides are known to regulate the activities well [38]. For instance, a native ribonuclease is converted quantitatively to the corresponding thiol derivative which does not show activity at all [39]. In addition, the reduced form is reverted quantitatively to the native form. It is noteworthy that there are 105 ways to reform the disulfide linkages of the four cystine residues, but only one oxidation product is obtained.

3.1. Formation of cyclic structure

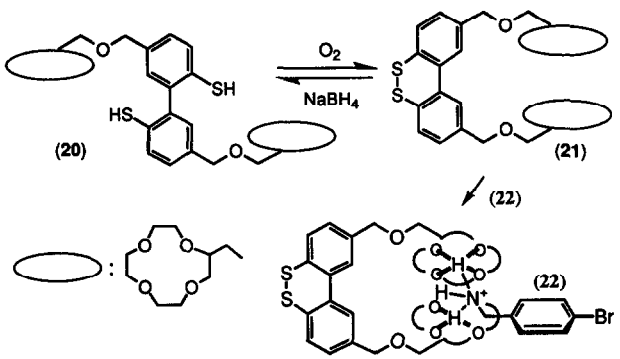
This important regulation mechanism should also be useful to control ion recognition of artificial systems. Conformational change of a recognition site coupled with a redox reaction is utilized (Scheme 2). Linear polyethers (**16**, **18**) containing thiol groups at the termini are oxidized to the corresponding cyclic polyethers (**17**, **19**) [40,41]. The disulfide linkage is easily cleaved by reduction to give the linear one. Binding affinities of the cyclic and the linear polyethers to alkali metal ions are different. The cyclic compound (**17**) extracts K^+ with higher extractability than Na^+. However, **17** exhibits very low affinity toward both metal ions. The cyclic ionophore (19) extracts Cs(I) more preferentially than Na^+ and K^+ [40]. However, the linear ionophore (**19**) has very low binding ability toward alkali metal ions [41]. In both cases, intramolecular interconversion is possible, but quantitative conversion of the reduced form to the oxidized one cannot be performed. Upon oxidation a large amount of oligomeric polyethers are generated owing to intermolecular oxidation (i.e., from **18** to **19**, 5% yield). Hence, these compounds are not suitable for ideal redox switching systems.

3.2. Change of spatial arrangement of binding sites

Quantitative intramolecular interconversion between redox forms is achieved by the use of ionophores (**20**, **21**) bearing two 12-crown-4 rings (Scheme 3) [42]. The reduced form (**20**) has two thiol groups at the 2 positions of the biphenyl skeleton. Ionophore (**20**) is converted quantitatively to **21**, because the two thiol groups are in close proximity and the dibenzothiophene ring thus obtained is considered not to have severe ring strain. The binding behavior of these two ionophores to ammonium salt (**22**) is much different. The oxidized form (**21**) shows much higher extractability (15%, using CH_2Cl_2 as an organic phase) toward **22** as a cationic host than **20** (3%). Probably **21** captures the guest in a face-to-face fashion, because the arrangement of the binding site is kept rigidly due to the disulfide linkage. This binding mode is very favorable for the recognition of **22**, because proton is a nice guest for a 12-crown-4 ring [43]. In contrast, the flexibility of the binding sites due to free rotation of the biphenyl moiety significantly reduces the fraction of the face-to-face structure. This system is suitable for regulation of ion recognition utilizing



Scheme 2.



Scheme 3.

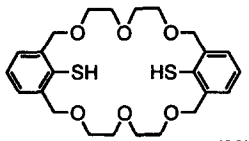
the redox reactions. However, **20** is hard to treat because of high sensitivity to autoxidation. A quantitative amount of **21** is produced quickly by bubbling molecular oxygen into a solution of **20**. The instability may be a disadvantage for the use of this framework for application to other recognition systems.

3.3. Regulation of ion recognition by a redox gate

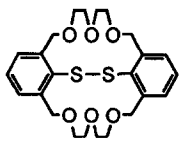
Various examples of regulation systems for ion recognition using an external stimulus have been reported so far [44,45]. Perfect regulation (quantitative and all-or-none type switching), however, was not carried out successfully. There have been two main strategies to regulate ion recognition. One is to use a conformational change of a recognition site, when a certain stimulus is introduced into the system. Conversion of a linear to a cyclic form is a representative example. The other is to

change spatial arrangement of the sites upon catching a stimulus, as seen in the biscrown system described above. Neither method is sufficient to construct ideal switching systems. In the former case a linear polyether chain exhibits a lower affinity to alkali metal ions. However, the ability cannot be diminished completely, since free conformation change takes place to wrap an ion effectively. In the latter strategy binding selectivity can be modulated, but all-or-none type regulation cannot be executed. Both forms which are interconvertible by redox reactions possess crown rings as binding sites. Thus the affinity of either ionophore to metal ions cannot be lost completely. It would therefore seem very difficult to make an all-or-none-type system for ion recognition by utilizing an external stimulus.

There are at least three requirements in the design of such systems controlled by redox reactions between thiol and disulfide. Firstly, interconversion between two forms of ionophores must be performed quantitatively. Secondly, the two forms exhibit completely different binding affinity toward metal ions (strength and/or selectivity); one is an active ionophore, while the other is a definitely non-active host. The final requisite, which is less important, is that the reduced compound is stable enough especially under aerobic conditions.



(23)



(24)

We have also provided a new and important concept for gating a recognition site, interconversion between an open and a closed state (Fig. 3) [46]. Gating of an ion channel actually regulates very efficiently the control of ion flow through a biological bilayer membrane [8]. As a result, the gate moiety controls transportation of a stimulus signal in nervous systems.

On the basis of the concept of gating, hosts (**23** and **24**) were designed. Compound (**23**) in a reduced form is apparently the open state bearing thiol groups inside the

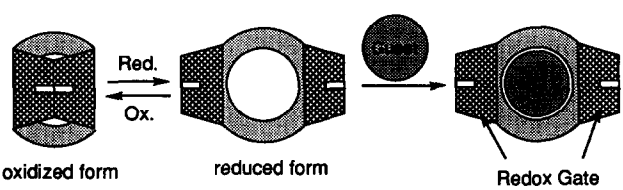


Fig. 3. Interconversion between open and closed states of a recognition site. Reproduced with permission from Ref. [46].

binding cavity. In contrast, compound (**24**) is considered the closed state, because the oxidized form possesses a disulfide linkage inside the cavity. It is reasonably expected that the reduced compound is an active form and that the oxidized form is a non-active one because of occupation of the recognition site by the disulfide bond prohibiting metal coordination. The thiol groups of **23** are arranged inwardly and in close proximity. In addition, the substituents are surrounded by the polyether chains. Consequently, this arrangement should prevent oligomerization upon oxidation of **23** and autoxidation. **24** is the expected product which is generated intramolecularly from **23** by oxidation. In fact quantitative interconversion between **23** and **24** is achieved by H_2O_2 and $NaBH_4$ as oxidant and reductant, respectively. **23**, however, is very stable under aerobic conditions. Compound **24** is not produced by bubbling of molecular oxygen into a chloroform solution of **23** for several hours.

Solvent extraction (H_2O–1,2-dichloroethane) indicates that both **23** and **24** exhibit very low affinity toward alkali metals. Ionophore **23**(**24**) extracts 1.6(1.6), 1.6(3.8) and 1.9(2.2)% of the initial amount of picrate of Li^+, Na^+ and K^+, respectively (extractability = $[\text{picrate}]_{\text{organic phase}}/[\text{picrate}]_{\text{initial aqueous phase}} \times 100$). CPK model inspection suggests that the sulfur atoms permit coordination of only two oxygen atoms in the ring, which are apparently insufficient for alkali metal recognition. In contrast, **23** extracts several soft heavy metal ions. Values of picrate extracted into the organic phase are estimated to be 44, 36, and 13% for Pb(II), Cu(II), and Cd(II), respectively. Ag(I) is extracted most preferentially (ca. 100%). However, very low, if any, values are observed for Cr(III), Mn(II), Fe(III), Co(II), Ni(II), and Zn(II) (0, 1, 0, 3, 0, 3%). Without picric acid, remarkably high Ag(I) selectivity is achieved on monitoring by atomic absorption spectroscopy. The values of extractability are 216, 8, and 8% for Ag(I), Cu(II), and Pb(II), respectively. Here, the definition of extractability ($=[\text{metal ion}]_{\text{organic phase}}/[\text{host}]_{\text{organic phase}}$) is different from that used above. In this case extractability of 100% means that an average stoichiometry of the complexation is 1:1. As a result, the average number of Ag(I) bound to **23** is ca. 2. As suggested in the extraction experiment, 1:2 complexation between **23** and Ag(I) is implied by a Job plot using change of absorption at 295 nm. Ag(I) is specifically extracted (extractability; 175, 0 and 0% for Ag(I), Cu(II), and Pb(II), respectively) from a mixture of Ag(I), Cu(II), and Pb(II).

Dithiol (**23**) also reveals significantly high Ag(I) selectivity in transport experiment through a 1,2-dichloroethane layer as a liquid membrane using a dual cylindrical apparatus [11]. Ag(I) is exclusively transported by **23**. In contrast, Cu(II), Pb(II), Zn(II), Cd(II), Na^+, and K^+ are not detected within experimental errors, although **23** exhibits a low extractability to Cu(II) and Pb(II) in the absence of picrate. As in the case of the solvent extraction, **24** does not transport Ag(I), Pb(II) or Cu(II) to the receiving phase. These facts indicate that Ag(I) is bound only when the gate is open. Moreover the high Ag(I) selectivity of **23** is not changed, in competitive transport ($[\text{Ag(I)}]=[\text{Pb(II)}]=[\text{Cu(II)}]=0.01$ M in the source phase). In a single ion transport, acidification of the source phase results in an increase of the transport rate. However, the rate is decreased when 0.1 M nitric acid is used as a receiving phase. These results and analysis of NO_3^- concentrations in the receiving phase (initially deionized water) for a single ion transport by ion chromatography suggest

that the undissociated thiol groups of **23** mainly contribute to the Ag(I) recognition. An open chain analog (**25**) shows a much lower transport rate for Ag(I) and even worse selectivity. Thus the cyclic structure of **23** is necessary for high Ag(I) selectivity.

The response of the transport ability of **23** to oxidant was examined by the addition of *m*-chloroperbenzoic acid (m-CPBA) into the transport system 8 h after the start of the transport. The oxidant causes an abrupt increase in the Ag(I) transported and successive termination of the transport (Fig. 4). Closing of the binding site due to formation of the disulfide linkage explains the drastic change in Ag(I) transport. Ag(I) bound in the cavity is released quickly by the closing of the cavity. These results explicitly show that the sulfur atoms of **23** and **24** work very efficiently as a redox gate to regulate selectivity as well as binding strength to metal ions.

All-or-none type regulation was extremely difficult. However, introduction of a gate responsive to redox reactions into a binding site is found to be one of the most convenient and capable ways of acheiving such regulation. Therefore, the new concept shown here will be useful and important for constructing perfect switchable recognition systems toward various guests. Very recently, the opening and closing of a molecular-recognition site using a photo reaction has been reported using a modified cyclodextrin [47].

Intermolecular interconversion between the redox forms of hosts also controls Ag(I) transport well [48]. A crown ether (**26**) containing a mercapto group in the ring transports Ag(I) most preferentially in a single ion transport, but Pb(II) is also transported efficiently. The corresponding disulfide **27** has quite low, if any, transport

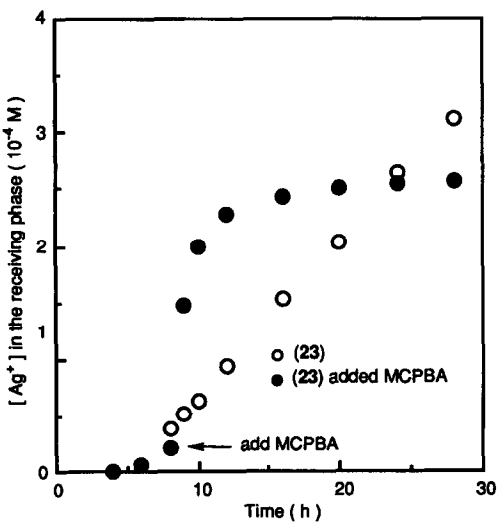
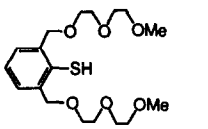
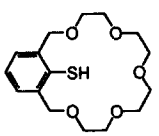


Fig. 4. Transport of Ag(I) by (**23**), and the effect of m-CPBA. The concentration of **23** in the organic phase (1,2-dichloroethane) is 2×10^{-4} M. The initial concentration of $AgNO_3$ in the aqueous source phase is 0.01 M, and the receiving phase consists of deionized water. Reproduced with permission from Ref. [46].

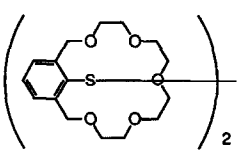
ability toward Ag(I), Pb(II), Cu(II), Cd(II), Mn(II), Co(II), Ni(II), and Zn(II). Interestingly, in competitive transport using a mixture of Ag(I), Cu(II), Cd(II), and Pb(II) for the source phase **26** shows considerably high Ag(I) selectivity. Only Ag(I) ion is detected in the receiving phase. The enhancement of selectivity is probably caused by exclusive occupation of the cavity with a Ag(I) ion. A 1:1 stoichiometry of the complexation is supported spectrophotometrically by a Job plot.



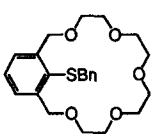
(25)



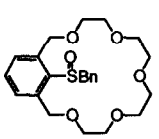
(26)



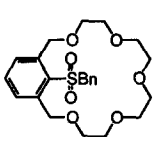
(27)



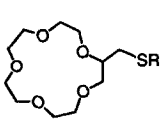
(28)



(29)



(30)



(31) R = Bn
C_4H_9
$C_{12}H_{25}$

The response of the transport rate in the competitive transport using **26** to oxidation with m-CPBA is slightly less than with the intramolecular interconvertible system (**23**, **24**). The intermolecular formation of **27** by the oxidant obviously proceeds more slowly than **24** from **23**. The most advantageous feature of **26** over **23** is that **26** is prepared much more easily in higher yield than **23**. Hence, the framework of **23** and

24 will be developed to synthesize an all-or-none-type switching moiety of various ion-recognition systems controlled by the redox reactions.

Ag(I) selectivity is also acheived by the use of crown ethers (**28**) with a benzylsulfenyl group inside the ring [49]. In solvent extraction, only Ag(I) is extracted with high extractability. However, this host shows low affinity to Pb(II), Cu(II), Zn(II), Cd(II), and Ni(II), while the thiol analog (**26**) extracts Pb(II) well. Probably the coordination of oxygen atoms of the cavity to Pb(II) is sterically hindered by the benzyl substituent. Pb(II) is effectively surrounded and coordinated by several oxygen atoms, because good affinity to Pb(II) is achieved by coordination of oxygen atoms of 18-crown-6 [50]. Extractability of Ag(I) in the sulfoxide and sulfone analogs (**29**, **30**) is severely decreased due to the decrease in the number of lone pairs on the sulfur atom. The affinity of the open chain analog (**25**) is very low, as mentioned above. Hence, the Ag(I) selectivity observed in the sulfur-containing crown ethers is attributed to synergistic coordination of lone pairs on a sulfur and several oxygen atoms of a crown ring. Although the structure of the **23**–Ag(I) is unclear, a similar synergistic coordination probably results in the Ag(I) selectivity.

Thiolariat ethers (**31**) with a 15-crown-5 ring exhibit remarkably high Ag(I) selectivity among heavy metal ions, though the sulfur oxygen exists outside the crown ring [51,52]. In this system the synergistic coordination of sulfur and oxygen atoms is also the most important factor for the selectivity.

The examples discussed above describe a new and interesting binding mode for Ag(I) with crown ethers. Thiacrown ethers which contain sulfur atom(s) as a component of the macroring are well known to bind Ag(I) well [53–58], but crown ethers **23**, **26**, **28** and **31** do not have such a sulfur atom but one in the side chain. These new crown ethers will be used for diverse applications, because chemical modification of the crown ethers can be carried out easily to introduce other functions into the hosts.

4. Regulation of ion recognition by molecular assembly utilizing an artificial receptor

In biological systems many specific functions of proteins are induced on assembling several proteins. Proteins called molecular chaperones are known to participate in such protein assembling [59]. However, interestingly, this kind of protein does not contribute the functions directly. This remote controlling methodology must be very important and efficient to regulate diverse functions of artificial molecules. The strategic procedures to design such systems are as follows. A recognition site is divided into several pieces each of which does not recognize a guest. The recognition site is reconstituted by assembling the species again with an artificial receptor. Consequently, all-or-none-type switching for ion or molecular recognition is expected using this method of assembly.

We prepared receptor (**32**), containing two 2,6-diacylaminopyridine moieties at the peri positions of the naphthalene nucleus, and flavin (**33**) bearing a short polyether chain at the 8 position of the isoalloxiazine ring [60]. Molecular assembling between **32** and **33** is expected, because 2,6-diacylaminopyridine derivatives are known to be

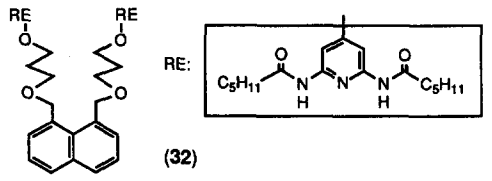
5. Conclusions

The regulation of molecular functions plays an essential role in maintaining life by balancing materials and supplying the energy necessary for life. This regulation is usually triggered by external stimuli and molecular recognition. In artificial regulation systems for ion recognition, such methodology utilizing metal ions, electrons, and molecules as stimuli is convenient and very efficient. Formation of a pseudocrown, gating of a recognition site, and molecular assembling by an artificial receptor are excellent strategies for the design of the regulation systems. It is obvious that the strategies can be applied to molecular recognition systems responding to external information. The concepts described here and new ones to be obtained during further studies are important and necessary to construct systems containing molecular recognition abilities and catalysis whose activities appear only when the functions are required. Moreover, they promise construction of artificial cascade systems and general systems for amplification and modulation of molecular information.

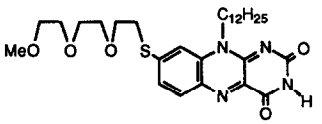
References

[1] B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts and J.D. Watson, Molecular Biology of the Cell, Garland Publishing, New York, 1983, Chapter 13.
[2] L. Stryer, Biochemistry, Freeman, New York, 3rd edn., 1988, Parts II and III.
[3] M.F. Perutz, Mechanisms of Cooperativity and Allosteric Regulation in Proteins, Cambridge University Press, Cambridge, England, 1989.
[4] J. Rebek, Jr., Acc. Chem. Res., 17 (1984) 258.
[5] I. Tabushi, Pure. Appl. Chem., 60 (1988) 581.
[6] J.-M. Lehn, Angew. Chem. Int. Ed. Engl., 29 (1990) 1304.
[7] F. Stoddart, Chem. Britain, (1991) 714.
[8] B. Hille, Ionic Channels of Excitable Membranes, Sinauer Associates, Sunderland, MA, 1984.
[9] J.J. Rebek and R.V. Wattley, J. Am. Chem. Soc., 102 (1980) 4853.
[10] T. Nabeshima, T. Inaba and N. Furukawa, Tetrahedron Lett., 28 (1987) 6211.
[11] T. Nabeshima, T. Inaba, N. Furukawa, T. Hosoya and Y. Yano, Inorg. Chem., 32 (1993) 1407.
[12] D.J. Cram, T. Kaneda, R.C. Gelgeson, S.B. Brown, C.B. Knobler, E. Maverick and K.N. Trueblood, J. Am. Chem. Soc., 107 (1985) 3645.
[13] F. Vögtle and E. Weber in S. Patai (ed.), The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues, John Wiley & Sons, New York, 1980, Part 1, p. 59.
[14] S. Kitagawa and M. Munakata, Inorg. Chem., 20 (1981) 2261.
[15] F.A. Cotton and G. Wilkinson, Advanced Inorganic Chemistry, John Wiley & Sons, New York, 1980, p. 71.
[16] J. Hoste, Anal. Chim. Acta, 4 (1950) 23.
[17] T. Nabeshima, T. Inaba, N. Furukawa, S. Ohshima, T. Hosoya and Y. Yano, Tetrahedron Lett., 31 (1990) 6543.
[18] F. Kröhnke, Synthesis, (1976) 1.
[19] A. Yamamoto, Organotransition Metal Chemistry: Fundamental Concepts and Applications, Wiley Interscience, New York, 1986.
[20] J.P. Collman, L.S. Hegedus, J.R. Norton and R.G. Finke, Principles and Applications of Organotransition Metal Chemistry, University Science Books, Mill Valley, CA, 1987.
[21] T. Nabeshima, T. Inaba, T. Sagae and N. Furukawa, Tetrahedron Lett., 31 (1990) 3919.
[22] T. Nabeshima, I. Yosejima and Y. Yano, Heterocycles, 38 (1994) 1471.
[23] T. Nabeshima, T. Inaba and N. Furukawa, Heterocycles, 29 (1989) 431.

excellent binding sites of receptors for imido compounds such as uracyl derivatives [61–64] and flavins [65–68] due to triple hydrogen bonding. In a supramolecule formed from **32** and two **33**, a new binding site for alkali metal ions will be produced, since the two polyether chains are collected in close proximity. Six oxygen atoms of ethylene glycol oligomers capture the ions efficiently, whereas three oxygen atoms are insufficient for alkali metal recognition [26,45].



(32)



(33)

Interaction due to triple hydrogen bonding between **32** and **33** is supported by downfield shifts of the ^1H NMR ($CDCl_3$) resonances assigned to the amide protons of **32** and **33**, as seen in other flavin receptors [67]. Titration using the resonance of **32** suggests that one diacylaminopyridine moiety binds one flavin molecule.

Receptor (**32**) and guest (**33**) alone have very low affinity for K^+ in solvent extraction (H_2O–1,2-dichloroethane, extractability $\leq 2\%$). On the other hand, a mixture of **32** and excess **33** extracts much more K^+ (15%). This increase of extractability is ascribed to formation of a recognition site by assembling the two guest molecules as described above. A probable structure of the supramolecule is depicted in Fig. 5, though a more detailed study is necessary.

This new assembled system illustrates a new concept, evolution of host molecules, i.e., conversion of a host as a first generation to the second generation having different or more sophisticated functions at the molecular level. In the system of **32** and **33**, receptor (**32**) is the first generation of host, and the supramolecule is considered the second generation of host.

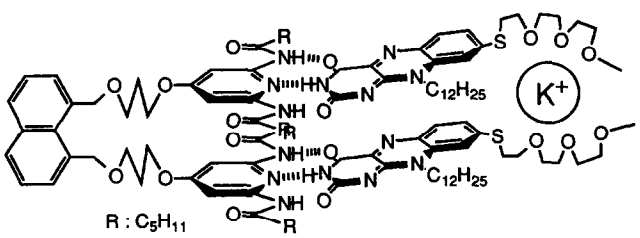


Fig. 5. Probable structure of a supramolecule from **32** and **33**.

[24] W. Pirkle and M.S. Hoekstra, J. Am. Chem. Soc., 98 (1976) 1832.
[25] T. Nabeshima, T. Hosoya and Y. Yano, unpublished results.
[26] A. Schepartz and J.P. McDevitt, J. Am. Chem. Soc., 111 (1989) 5976.
[27] O.F. Schall, K. Robinson, J.L. Atwood and G.W. Gokel, J. Am. Chem. Soc., 113 (1991) 7434.
[28] M.W. Jones, N. Gupta, A. Schepartz and H.H. Thorp, Inorg. Chem., 31 (1992) 1308.
[29] R.C. J.M. van Veggel, S. Harkema, M. Bos, W. Verboom, G.K. Woolthuis and D.N. Reinhoudt, J. Org. Chem., 54 (1989) 2351.
[30] F.C. J.M. van Veggel, W. Verboom and D.N. Reinhoudt, Chem. Rev., 94 (1994) 279.
[31] Y. Kobuke and Y. Satoh, J. Am. Chem. Soc., 114(1992) 789.
[32] H.-J. Schneider and D. Ruf, Angew. Chem. Int. Ed. Engl., 29 (1990) 1159.
[33] R.P. Sijbesma and R.J. Nolte, J. Am. Chem. Soc., 113 (1991) 6695.
[34] K.L. Cole, M.A. Farran and K. Deshayes, Tetrahedron Lett., 33 (1992) 599.
[35] P.D. Beer and A.S. Rothin, J. Chem. Soc., Chem. Commun. (1988) 52.
[36] T. Nabeshima, T. Inaba and N. Furukawa, Heterocycles, 31 (1990) 2095.
[37] L. Stryer, Biochemistry, Freeman, New York, 3rd edn., 1988, Part I.
[38] C.R. Cantor and P.R. Schimmel, Biophysical Chemistry, Vol. I, Freeman, New York, 1980.
[39] C.B. Anfinsen, E. Haber, M. Sela and J.F.H. White, Proc. Natl. Acad. Sci. USA, 47 (1961) 1309.
[40] M. Raban, J. Greenblatt and F. Kandil, J. Chem. Soc., Chem. Commun., (1983) 1409.
[41] S. Shinkai, K. Inuzuka, O. Miyazaki and O. Manabe, J. Am. Chem. Soc., 107 (1985) 3950.
[42] T. Nabeshima, A. Sakiyama, A. Yagyu and N. Furukawa, Tetrahedron Lett., 30 (1989) 5287.
[43] R.M. Izatt, J.S. Bradshaw, S.A. Nielsen, J.D. Lamb and J.J. Christensen, Chem. Rev., 85 (1985) 271.
[44] For regulation systems with photo reactions using crown ethers, see S. Shinkai and O. Manabe, in F. Vögtle and E. Weber (Eds.), Host Guest Complex Chemistry III, Springer-Verlag, New York, 1984, p. 67.
[45] For a photoregulation system utilizing open chain polyethers, see M. Irie and M. Kato, J. Am. Chem. Soc., 107 (1985) 1024.
[46] T. Nabeshima, H. Furusawa and Y. Yano, Angew. Chem., Int. Ed. Engl., 33 (1994) 1750.
[47] R. Arad-Yellin and B.S. Green, Nature, 371 (1994) 320.
[48] T. Nabeshima, H. Furusawa, N. Tsukada, T. Shinnai, T. Haruyama and Y. Yano, Heterocycles, 41 (1995) 655.
[49] T. Nabeshima, H. Furusawa and Y. Yano, Heterocycles, 38 (1994) 2045.
[50] J.D. Lamb, R.M. Izatt, P.A. Robertson and J.J. Christensen, J. Am. Chem. Soc., 102 (1980) 2452.
[51] T. Nabeshima, K. Nishijima, N. Tsukada, H. Furusawa, T. Hosoya and Y. Yano, J. Chem. Soc., Chem. Commun., (1992) 1092.
[52] T. Nabeshima, N. Tsukada, T. Haruyama and Y. Yano, Bull. Chem. Soc. Jpn., 68 (1995) 227.
[53] H.K. Frensdorff, J. Am. Chem. Soc., 93 (1971) 600.
[54] J.J. Christensen, D.J. Eatough and R.M. Izatt, Chem. Rev., 74 (1974) 351.
[55] M. Oue, K. Kimura and T. Shono, Anal. Chim. Acta, 194 (1987) 293.
[56] M. Oue, K. Kimura and T. Shono, Analyst, 113 (1988) 551.
[57] M. Oue, K. Kimura, K. Akama, M. Tanaka and T. Shono, Chem. Lett., (1988) 409.
[58] M. Oue, K. Akama, K. Kimura, M. Tanaka and T. Shono, J. Chem. Soc. Perkin Trans. 1, (1989) 1675.
[59] M.-J. Gething and J. Sambrook, Nature, 355 (1992) 33.
[60] T. Nabeshima, N. Tamura, T. Kawazu, K. Sugawara and Y. Yano, Heterocycles, in press.
[61] B. Feibush, A. Figueroa, R. Charles, K.D. Onan, P. Feibush and B.L. Karger, J. Am. Chem. Soc., 108 (1986) 3310.
[62] A.D. Hamilton and D.V. Engen, J. Am. Chem. Soc., 109 (1987) 5035.
[63] S.C. Hirst and A.D. Hamilton, Tetrahedron Lett., 31 (1990) 2401.
[64] S. Ohshima, N. Tamura, T. Nabeshima and Y. Yano, J. Chem. Soc., Chem. Commun., (1993) 712.
[65] Y. Yano, N. Tamura, K. Mitsui and T. Nabeshima, Chem. Lett., (1989) 1655.
[66] S. Shinkai, G.-X. He, T. Matsuda, A.D. Hamilton and H.S. Rosenzweig, Tetrahedron Lett., 30 (1989) 5895.
[67] N. Tamura, K. Mitsui, T. Nabeshima and Y. Yano, J. Chem. Soc., Perkin Trans. 2, (1994) 2229.
[68] N. Tamura, T. Kajiki, T. Nabeshima and Y. Yano, J. Chem. Soc., Chem. Commun., (1994) 2583.