Ester-Armed Cyclens: From Metal Complexation to Supramolecular Functionalization

（エステルアームド・サイクレン：金属錯体化から超分子機能化への展開）

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Tomoko N. PLAYER（Tomoko NISHIMURA）

（プレイヤー 智子（西村 智子））

Abstract

Armed cyclens form stable metal complexes with high selectivity, which have quadruple helicated structures in crystal and solution states. These metal complexes may make it possible to develop interesting applications due to the thermodynamic stability and ordered structures. This thesis highlights structures and functions of ester-armed cyclen - metal complexes. In addition to their coordination chemistry, their interesting functions are reported: visual sensing of Ca^{2+} with photoreactive armed cyclen and chiral recognition with self-aggregates of armed cyclen - metal complexes.

In Chapter 1, a series of ester-armed cyclens were successfully prepared and their Na^+ selectivity among alkali metal cations, binding constants and structures of the Na^+ complexes were fully characterized by FAB-MS, liquid-liquid extraction, ^1H NMR titration, variable temperature ^{13}C NMR and X-ray crystal structure analysis. They formed stable octacoordinated metal complexes in solutions, even when bulky fluorenyl- and cholesteryl-ester residues were incorporated. In Chapter 2, the photoreaction of fluorenyl ester-armed cyclen is detailed. It gave "green fluorescent" fluorenone and related decomposed species upon photoirradiation. Since the reaction was effectively suppressed by the formation of octacoordinated Ca^{2+} complex, this photoreactive armed cyclen offered the naked-eye detection of the Ca^{2+} ion in aqueous samples. In Chapter 3, cholesteryl-armed cyclen - metal complexes were used as chiral building blocks for self-aggregates. The chiral recognition and induction were successfully arisen with these self-aggregates, which were not observed at a monomolecular level.

It was extensively characterized from the basic to the practical standpoint that ester-armed cyclens had the capability to be used in many applications as prospective artificial receptors. Their metal complexes were demonstrated to have interesting properties at a monomolecular level, and also unique functions at a supramolecular level.

♦ Contents ♦

Preface

Molecular recognition provides an effective basis of the highly specific reaction, transport, and regulation in nature, which specifically govern many biological processes such as substrate binding of protein, enzymatic reaction, assembly of multi-protein complexes and signal indúction. Mimicry of the biological recognition systems offers unlimited possibilities to highly organized systems, which exhibit more structured and functionalized properties than biological systems if proper manipulation of the intermolecular forces define molecular architecture.[1] Many kinds of artificial receptors have been reported since Lehn, Pedersen and Cram received the Nobel Prize in 1987. Macrocyclic ligands such as crown ethers, cryptands, spherands, and calixarenes have been developed as cation receptors and employed as specific ion carriers, catalysts, molecular devices and supramolecular assemblies.

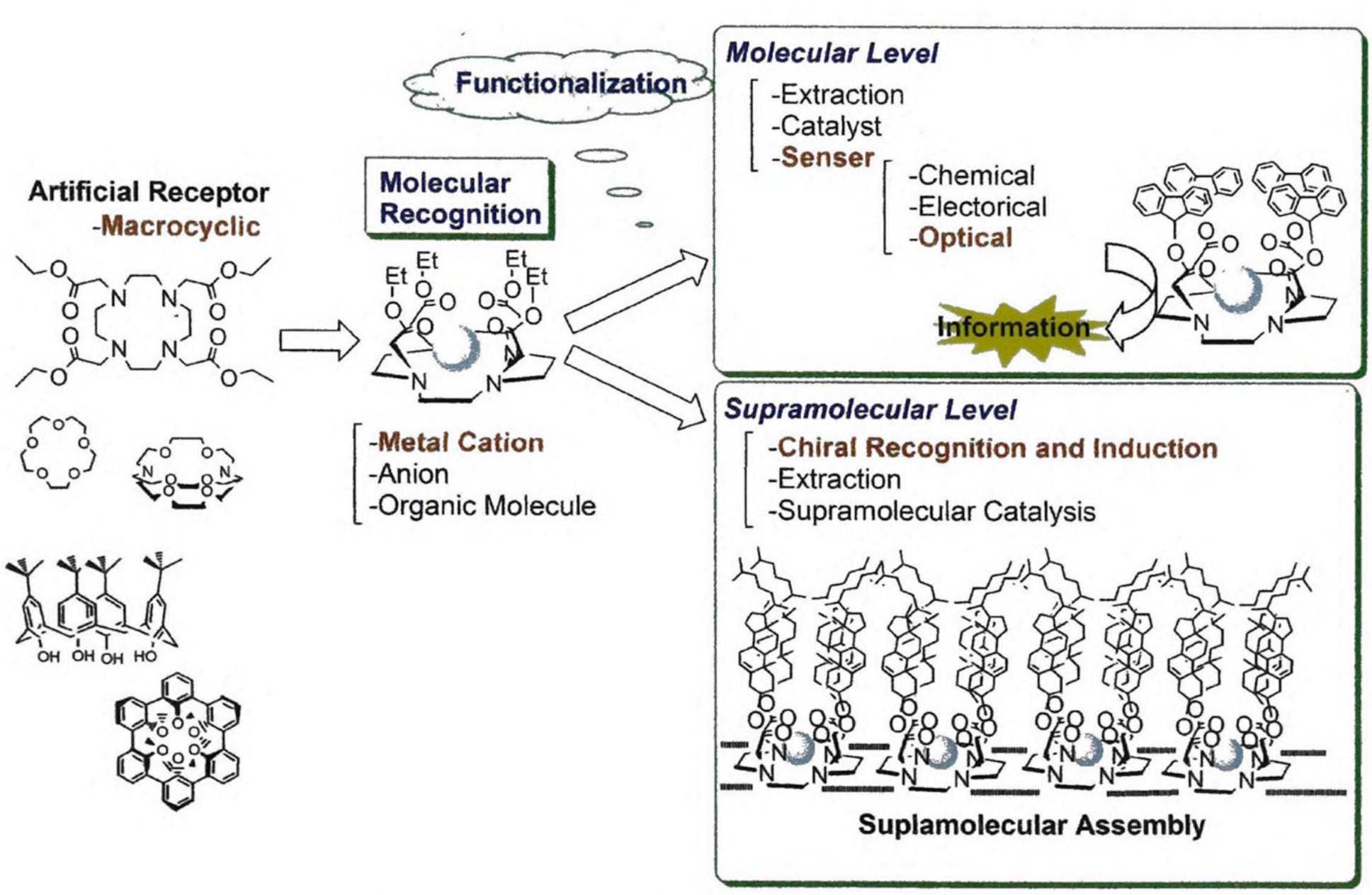

Figure 0-A. Applications of Artificial Receptors.

Optical molecular sensing is one of the most successful applications in the molecular recognition technologies, because the information on the molecular recognition is possible to read out easily and rapidly as optical signals. Optical sensors can be designed to have a recognition part and a signalling part at will and are widely used in chemical, biological, environmental and medical analysis. Macrocyclic receptors work well as specific molecular recognition sites. Several chemo- and lumino-ionophores of macrocyclic types are now commercially available as analytical tools for environmental analysis and biological sensing. For example, macrocycles having intense azophenol chromophores[2] and emissive anthracene moieties[3] are known to display marked changes in their absorption and fluorescence signals, coupled with complexation of alkali metal cations.

Recent attention has been paid to the supramolecular assemblies of functionalized metal complexes as supreme bio-mimetic systems. Several kinds of biological self-aggregates often exhibit excellent functions in biological systems that cannot be observed at monomolecular level. The multi-protein complexes are the typical example: four haemoglobin molecules assemble to exhibit high oxygen binding ability. If it is possible to design artificial self-assemblies, they could bring many new possibilities in developing new fields of chemistry.

Armed cyclens have the potential to be effective macrocyclic receptors, which are characterized by 1,4,7,10-tetraazacyclododecane, "cyclen", and four metal-ligating sidearms. They form a wide variety of transition and lanthanide metal complexes that are used in characteristic chemical,[4] biological[5] and catalytic[6] processes, and it enables their use in many applications that their 1 : 1 complexes are often kinetically and thermodynamically stable in solutions.

In this thesis, I show that a series of ester-armed cyclens has wide applications based on characteristic cation recognition phenomena: (1) They form selective and stable complexes with several metal cations and work as specific receptors (Chapter 1); (2) Fluorenyl ester-armed

cyclen - metal complexes exhibit an interesting photochemical reaction, and are valuable in visual sensing of Ca^{2+} (Chapter 2); and (3) Cholesteryl ester-armed cyclen - metal complexes work as building blocks for supramolecular assemblies and offer chirality recognition functions (Chapter 3).

Chapter 1 focuses on the excellent Na^+ selectivity of a series of ester-armed cyclens and the stability of their Na^+ complexes. They bound Na^+ in the presence of K^+ and Li^+ more selectively than cryptand [2.2.1], a specific ligand of Na^+. Their octacoordination complexes had unique helical structures denoted as Δ- and Λ- configurations. Such stereochemical features were successfully utilized to build a chirality-integrated system (see Chapter 3). Since the metal complex properties of these ester-armed cyclens were not changed by the natures of their sidearm ester residues, unlimited possibilities were provided by adoption of various functional sidearms. Their specific metal complexation behaviours offered the further sophisticated functions as described in Chapters 2 and 3.

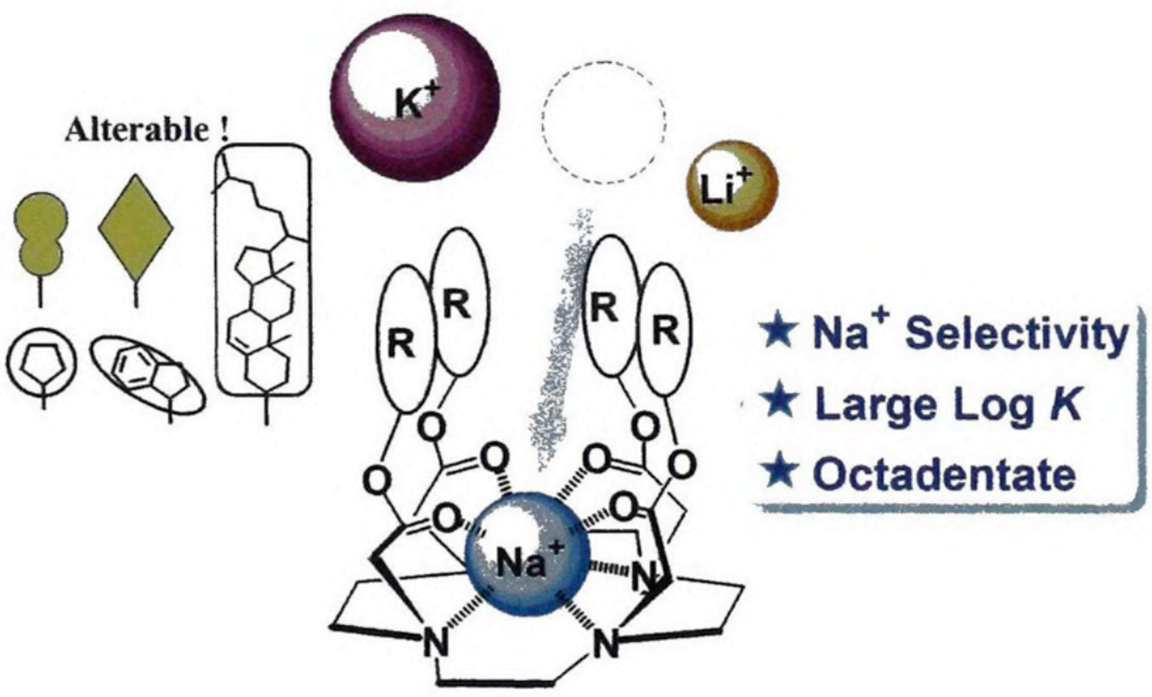

Figure 0-B. Ester-Armed Cyclens as Na^+ Selective Receptors. (Chapter 1)

In Chapter 2, I demonstrate that fluorenyl ester-armed cyclen exhibits new molecular sensing functions. Although the photoreaction of armed cyclens were rarely reported, a visual sensing system of Ca^{2+} was successfully built using a photoreactive armed cyclen. In this system,

Ca^{2+} complexation with the armed cyclen effectively suppressed the photoreactivity of the fluorenyl ester sidearms as the unique octacoordination largely changed the photoreaction paths. The Ca^{2+} detection ability was not high enough for practical use, but the ester-armed cyclens provided a new approach toward biological sensing.

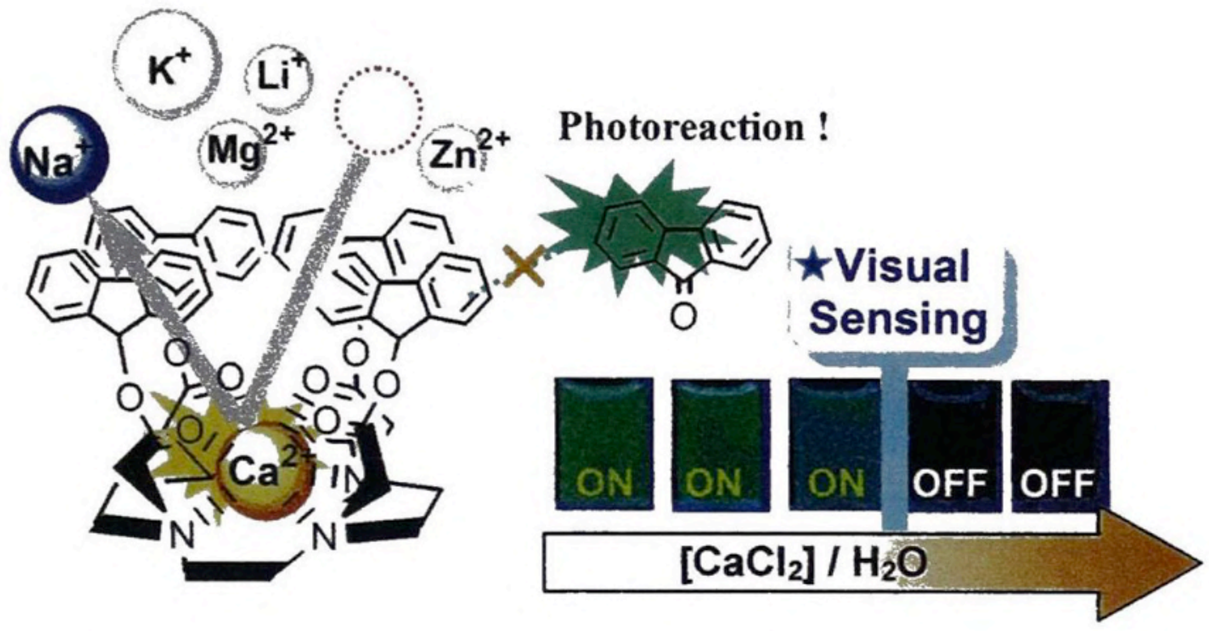

Figure 0-C. Visual Sensing Based on the Photoreaction of Fluorenyl-Armed Cyclen - Metal Complexes. (Chapter 2)

Chapter 3 describes supramolecular chemistry in which the stable ester-armed cyclen - metal complexes worked as building blocks for supramolecular architecture. Because the cholesteryl ester-armed cyclen had detergent-like structure upon metal complexation, it formed a self-aggregate in an aqueous solution. It should be noted that chirality of cholesteryl moieties and helicity of octacoordinated metal complexes were integrated by the formation of the self-aggregate. As a haemoglobin self-aggregate system includes (1) chirality of amino acids; (2) α-helix of protein; (3) high order protein structure; and (4) integrated chirality at supramolecular level, our self-aggregate of cholesteryl ester-armed cyclen - metal complex offers similar integration of chirality. The chirality induction and chiral recognition abilities were uniquely observed, though monomolecular complexes did not show such phenomena.

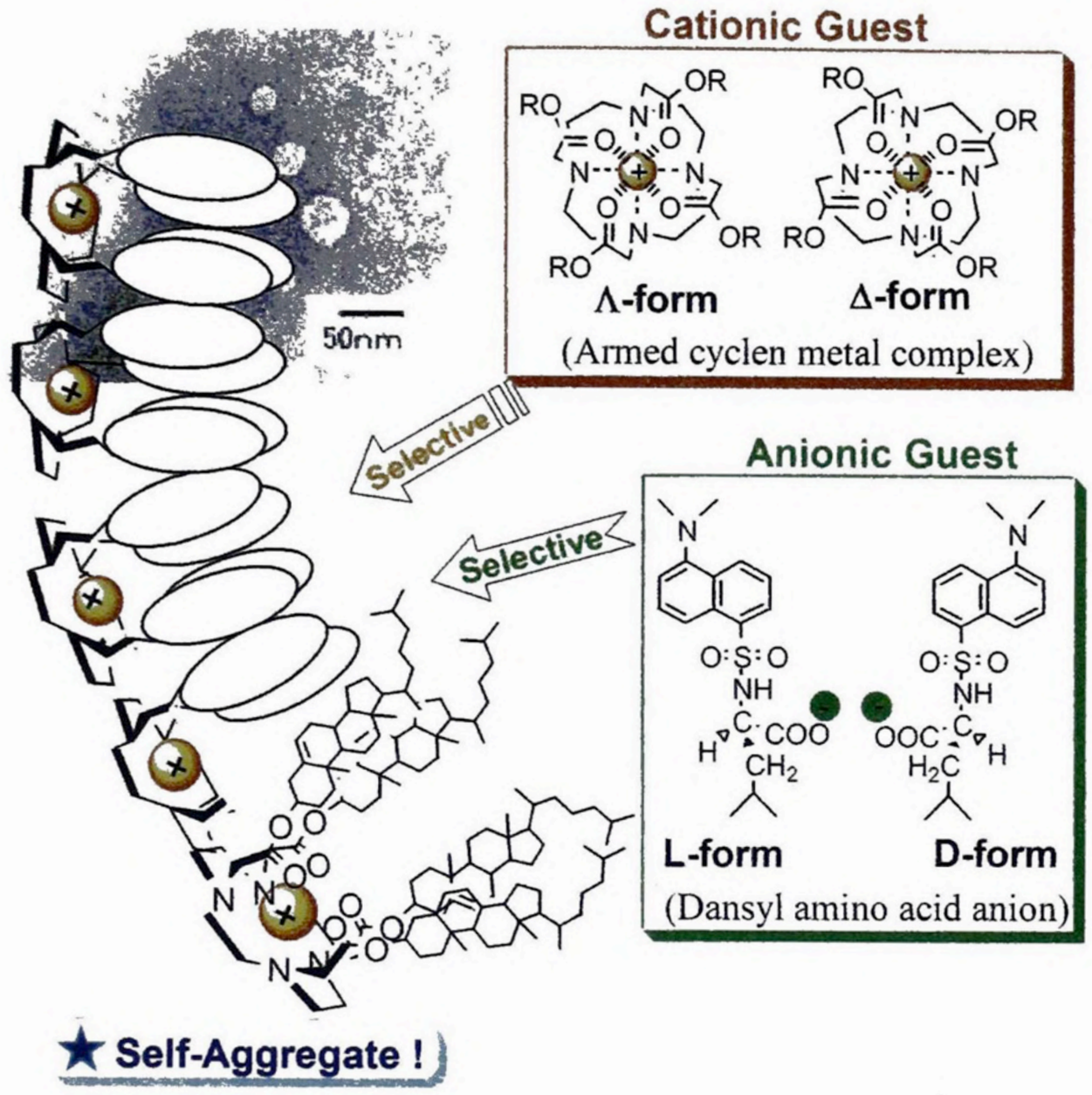

Figure 0-D. Supramolecular Chirality Recognition with Self-Aggregate of Cholesteryl Ester-Armed Cyclen - Metal Complexes. (Chapter 3)

The usage of artificial metal complexes allows many possibilities to adjust the final functionality with the modification of metal complexes, such as the introduction of chirality on the ligands and exchanging of metal cations. Especially, ester-armed cyclens I demonstrate here have many advantages; easy modification of sidearms; simple preparation of metal complexes; stability of metal complexes in solutions; and the availability of metal exchanging. In this thesis, I successfully demonstrate the potential usefulness of ester-armed cyclens from metal complexation to supramolecular functionalization.

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These points were detailed in our following papers:

Chapter 1.

[1] Ester-Armed Cyclens Having Quadruplicated Helical Geometry: Remarkably Stable and Selective Encapsulation of Na^+ Ion.

Satoshi Shinoda, Tomoko Nishimura, Makoto Tadokoro and Hiroshi Tsukube

J. Org. Chem. **2001**, *66* (18), 6104 – 6108. (Article)

Chapter 2.

[2] Visual Sensing of Aqueous Ca^{2+} Ion via Photoreaction of Fluorenyl Ester-Armed Cyclen.

Tomoko N. Player, Satoshi Shinoda and Hiroshi Tsukube

Org. Biomol. Chem. submitted. (Communication)

Chapter 3.

[3] Cholesterol-Armed Cyclen - Na^+ Complex as a Chiral, Helicated Amphiphile for Supramolecular: Architecture: Self-Aggregation and Chirality Induction in Aqueous Solution.

Satoshi Shinoda, Tsuyoshi Okazaki, Tomoko Nishimura and Hiroshi Tsukube

Chem. Commun. **2001**, *11*, 976 – 977. (Communication)

[4] Chirality Induction in Supramolecular Aggregate: Chiral Recognition between Armed Cyclen - Na^+ Complexes Having Quadruplicated Helical Geometry.

Tomoko Nishimura, Satoshi Shinoda and Hiroshi Tsukube

Chirality, **2002**, *14* (7), 555 – 557. (Communication)

[5] Cholestrol-Armed Cyclens for Helical Metal Complexes for Chiral Self-Aggregatation and Sensing of Amino Acid Anions in Aqueous Solutions.

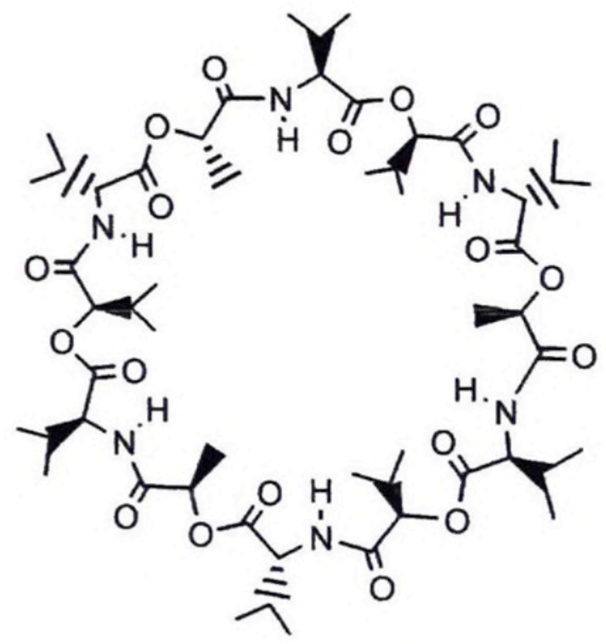
Satoshi Shinoda, Tsuyoshi Okazaki, Tomoko N. Player, Hitomi Misaki, Kenzi Hori and Hiroshi Tsukube

J. Org. Chem. in press. (Article)

Chapter 1. Ester-Armed Cyclens as Na^+ Selective Receptors

1-1. Introduction

The recognition of spherical metal cations such as alkali and alkaline earth metal cations is a simple but important phenomenon in biological processes. Typically, valinomycin and other biological macrocyclic ionophores incorporate many chiral centres and offer selective recognition of spherical K^+ and Na^+ in biological membrane transport processes.



Valinomycin

Crown ethers and related synthetic macrocycles[1] have been developed as specific ligands for metal cations, and are widely used in chemistry, biology, medicine and related fields of science. In particular, they offer selective extraction of metal ions, selective decorporation of radioactive or toxic metals,[2] and cation-selective analytical methods at a practical level.[3]

Among a large number of reported synthetic ligands, three-dimensional ligands such as cryptands, spherands and further cage-type macrocycles have shown the most outstanding recognition abilities for spherical cations. In these systems, the coordination structure was significantly emphasized as well as the size complementarity between guest cation and ligand cavity. In contrast, armed macrocycles have been recognized as flexible three-dimensional ligands, which are characterized by a macrocyclic ligand and metal-ligating sidearms.[4] This type of ligands provided effective coordination with guest metal cations from the parent macrocyclic ligand and additional metal ligating sidearms. They have often been reported to work as more

specific ligands of alkali, alkaline earth and lanthanide metal cations than common macrocyclic ligands.[5]

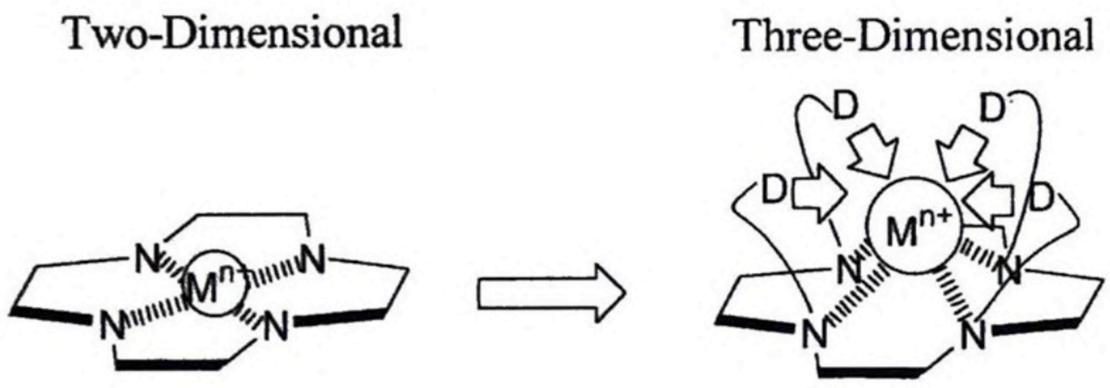


Figure 1-A. Coordination Geometry of Cyclen and Armed Cyclen.

1,4,7,10-Tetraazacyclododecane, "cyclen", is a representative of macrocyclic polyamines. Its derivatives accommodated transition metal cations nicely with 0.7 ~ 0.8 Å ionic radii in their 12-membered rings.[6] We developed "armed cyclens" as flexible three-dimensional ligands, which are characterized by a cyclen ring and four metal-ligating sidearms. Since they can vary the number of sidearms they use for metal cation coordination, they form different types of complexes with different series of metal cations. Indeed, some armed cyclens were reported to offer hexacoordination for Li^+ and octacoordination for Na^+ and K^+.[7] In other words, their molecular structures can be optimized to target alkali metal cations of biological significance, and some armed cyclens have been applied as effective ionophores for several metal cations.[8]

Recently, a new series of cyclen derivatives having ester-, amide- and pyridine-functionalized sidearms have been presented as receptors of alkali metal cations.[9] Among them, ester-armed cyclen (**1a** in Figure 1-B) was demonstrated to exhibit excellent Na^+ selectivity. Since the Na^+ has a larger ionic radius than the cyclen ring size, and because the nitrogen atoms of the cyclen ring are not effective donors for hard Na^+, the parent cyclen ring rarely forms an Na^+ complex. Thus, the cooperative action of the cyclen ring and ester-functionalized sidearms give stable octacoordinated Na^+ complexes.

In this chapter, several ester–armed cyclens **1a-1f** were prepared to investigate the effects of

sidearm substituents on the alkali metal cation complexation behaviours. Their cation recognition properties were characterized by FAB-MS, liquid-liquid extraction, ^{1}H NMR titration, and X-ray diffraction experiments. All the examined ester-armed cyclens showed far greater selectivity and stability for Na^+ complexation than amide- and alcohol-armed cyclens **2a** and **3**.[10]

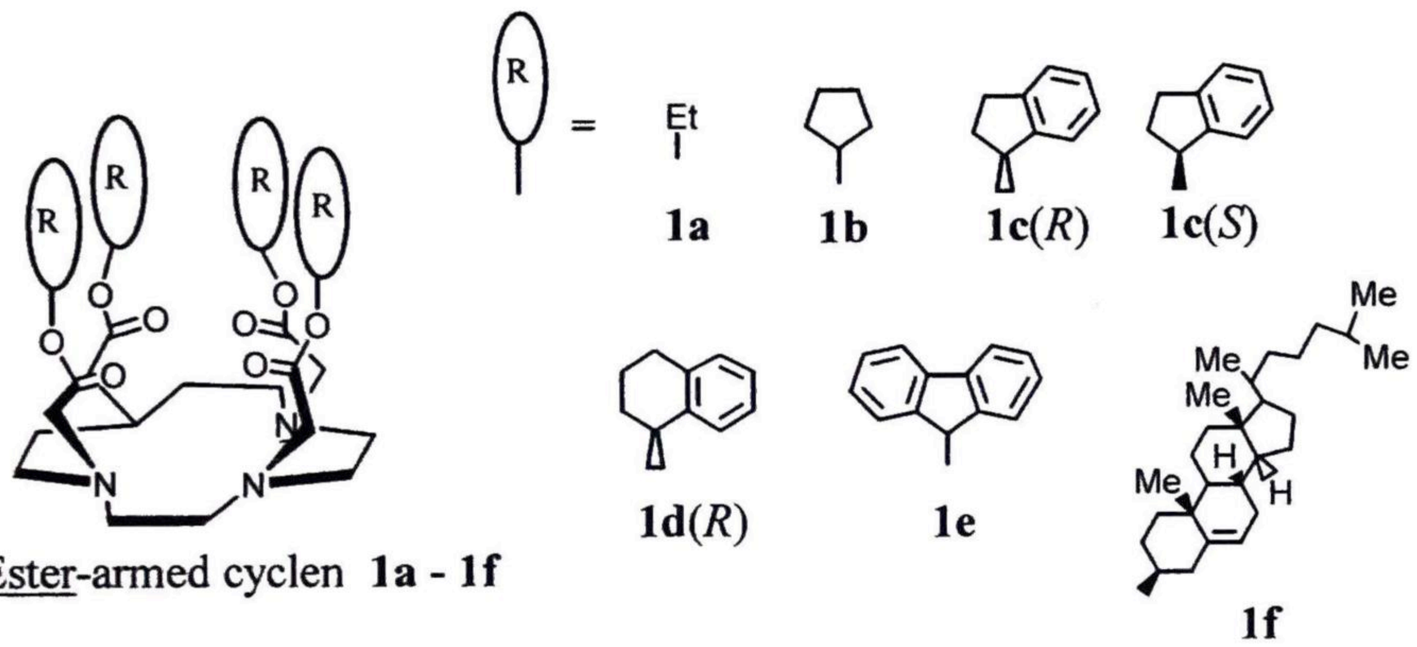


Figure 1-B. Armed Cyclens Having Ester-, Amide- and Alcohol-Functionalized Sidearms.

1-2. Synthesis of Armed Cyclens

A series of ester-armed cyclens **1a-1f**, an amide-armed cyclen **2a** and an alcohol-armed cyclen **3** were prepared to compare their metal complexation abilities. The NaCl complexes with ester- and amide-armed cyclens were synthesized directly by the reaction of corresponding chlorides and cyclen·4HCl in the presence of Na_2CO_3 (see 1-8. Experimental Section). The alcohol-armed cyclen was synthesized by reaction with propylene oxide and free cyclen, and isolated as a free ligand as reported by Hancock *et al.*[6(a),11]

The prepared ester-armed cyclens had various substituents as the ester residues. The bulkiness of the ester residues is in order of **1a** (ethyl) < **1b** (cyclopentyl) < **1c** (indanyl) < **1d** (tetrahydronaphthyl) < **1e** (fluorenyl). Cholesteryl ester-armed cyclen **1f** was also prepared, because the introduction of hydrophobic units possessing many chiral centres to the armed cyclen system was expected to provide specific features. In fact, it uniquely formed self-aggregates with integrated chirality as described in Chapter 3. Armed cyclens **1a**, **2a** and **3** seemed to have sidearm groups with similar bulkiness but showed different coordination characters. Therefore, these series of armed cyclens could allow systematic studies on the relationship between sidearm structures and their cation recognition properties.

1-3. Na^+ Selective Binding of Ester-Armed Cyclens

1-3-1. FAB-MS Experiments

Fast Atom Bombardment Mass Spectrometry, FAB-MS, is an effective method for the detection of metal complexes, because its "soft ionization" does not need to heat the sample. Metal ion selectivity of receptors can also be assessed on a semiquantitative level,[12] though the cation binding strength of metal complexes cannot be determined in a quantitative manner.

When armed cyclen was mixed with Li^+, Na^+ and K^+ in *m*-nitrobenzyl alcohol matrix, the resulting complexes gave corresponding [armed cyclen + metal]$^+$ peaks in the FAB-MS spectrum. Since the intensity of the observed MS signals related well with the concentrations of the metal complexes, the relative peak intensity was a good indication of cation selectivity.[9,12] The relative peak intensities of [armed cyclen + metal]$^+$ were summarized for a series of armed cyclens in Table 1-A, indicating that ester-armed cyclens **1a**-**1f** had a strong preference for Na^+ binding. In particular, ester-armed cyclen **1c**(*R*) showed the intensity more than 50 times higher for Na^+ complex than for K^+ and Li^+ ones. Other ester-armed cyclens **1a**, **1b**, **1d**, **1e** and **1f** also exhibited excellent Na^+ selectivity under FAB-MS binding conditions. On the other hand,

amide- and alcohol-armed cyclens **2a** and **3** did not have Na^+ selectivity, and gave slightly stronger peaks for [armed cyclen + $Li]^+$ than for [armed cyclen + $Na]^+$ and [armed cyclen + $K]^+$. Thus, it was clear that the natures of sidearm donor groups largely influenced cation selectivity.

Table 1-A. Cation Selectivity of Armed Cyclens Assessed by FAB-MS Method.

Armed cyclen[a]	Relative peak intensity			
	$[M + H]^+$	$[M + Li]^+$	$[M + Na]^+$	$[M + K]^+$
1a	< 2	7	100	4
1b	< 2	< 2	100	4
1c(*R*)	< 2	< 2	100	< 2
1d	< 2	< 2	100	3
1e	< 2	< 2	100	4
1f	< 2	< 2	100	15
2a	< 2	100	14	< 2
3[b]	14	100	93	< 2

[a]Conditions: Armed cyclen-NaCl complex, 0.00330 mol L^{-1}; LiCl and KI, 0.00830 mol L^{-1}; NaI, 0.00500 mol L^{-1} in *m*-nitrobenzyl alcohol. [b]Conditions: Armed cyclen, 0.00330 mol L^{-1}; LiCl, NaI and KI, 0.00830mol L^{-1} in *m*-nitrobenzyl alcohol.

1-3-2. Liquid-Liquid Extraction Experiments

The alkali metal cation selectivity of each armed cyclen was also investigated by liquid-liquid extraction experiments. After vigorously shaking a $CHCl_3$ solution of armed cyclen–NaCl complex with an aqueous solution of $LiClO_4$ and $KClO_4$, the concentration of each alkali metal cation that remained in the aqueous phase was determined and the distribution percentage was estimated as $\{([M^+]_{total} - [M^+]_{aq}) / [M^+]_{total}\} \times 100$.

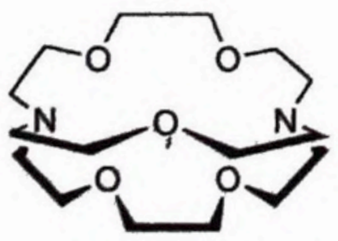
Table 1-B summarizes the distribution percentages for Li^+, Na^+ and K^+ with armed cyclens **1a-1f** and **3**. Since armed cyclen **3** was used as a free ligand, an equimolar amount of $NaClO_4$ was further added to the aqueous solution. Unfortunately amide-armed cyclen **2a** was not employed here because of its low solubility into the organic phase.

Ester-armed cyclens **1a-1f** selectively extracted Na^+ in the presence of equimolar Li^+ and K^+. All ester-armed cyclens **1a-1f** showed similar Na^+ preferences and their extraction percentages

were estimated as 38~94% for Na^+, < 3% for Li^+ and K^+. The observed extraction efficiencies seemed to be reflected by both the lipophilicity of the armed cyclen derivatives and the stability of the metal complexes: poor lipophilicity might cause the effusion of the armed cyclen ligand and its Na^+ complex from the organic phase to the aqueous phase; low stability of Na^+ complex does not hold the Na^+ well in the organic phase.

The sidearm effects on the lipophilicity of armed cyclen ligands were examined using the distribution constant (*D*), which is defined as a distribution ratio of the materials between *n*-octanol and water. The log *D* values of armed cyclens **1a – 1f** were assessed by considering the sidearms as whole molecules. Typically, $-CH_2CO_2C_2H_5$ was considered to be $CH_3CO_2C_2H_5$ in the case of armed cyclen **1a**. These values for CH_3CO_2-R (R was indicated in Figure 1-B) were calculated using the PALLAS program[13] and are listed in Table 1-C, in which CH_3CO_2-R (R=**1a**: Ethyl-) is defined as **1a'**. These values suggest that the lipophilicity of armed cyclen ligand increases in the order **1a** << **1b** < **1c** < **1d** < **1e** << **1f**. On the other hand, the stability constants (*K*) of their Na^+ complexes in CD_3CN or CD_3CD_2OD are tabulated in the next section (1-4), which are in the order **1b** < **1a** < **1d** < **1e** < **1c** < **1f** (see Table 1-D).

Alcohol-armed cyclen **3** was reported to have similar log *K* values for Li^+, Na^+ and K^+: log *K* 3.24(Li^+), 3.76(Na^+), and 3.63(K^+) in dimethylformamide,[11(a)] and this showed a modest extraction ability and selectivity in our experiment. Moreover, the liquid-liquid extraction experiment with cryptand [2.2.1] **4**, a cage-type specific ligand for Na^+, reported that **4** did not have Na^+ selectivity with similar conditions: extraction percentages were < 3 % for Li^+, 97 % for Na^+, 89 % for K^+.[9] Therefore, ester-armed cyclen **1a – 1f** exhibited outstanding Na^+ selectivity.



Cryptand [2.2.1] **4**

$\log K_{Na}$ [17] = 10.2_0 (in EtOH)

> 11.3_1 (in CH_3CN)

Table 1-B. Liquid-Liquid Extraction of Alkali Metal Cations with Armed Cyclens.

Armed cyclen[a]	Extraction %		
	Li^+	Na^+	K^+
1a	< 3	73	< 3
1b	< 3	38	< 3
1c(*R*)	< 3	66	< 3
1d	< 3	71	< 3
1e	< 3	91	< 3
1f	< 3	94	< 3
3[b]	10	17	< 3

[a]Conditions: $LiClO_4$, 0.0100 mmol; $KClO_4$, 0.0100 mmol in H_2O, 1.50 mL; Armed cyclen-NaCl complex, 0.0100 mmol in $CHCl_3$, 1.50 mL. [b]Conditions: $LiClO_4$, $NaClO_4$ and $KClO_4$, 0.0100 mmol each in H_2O, 1.50 mL; Armed cyclen, 0.0100 mmol in $CHCl_3$, 1.50 mL.

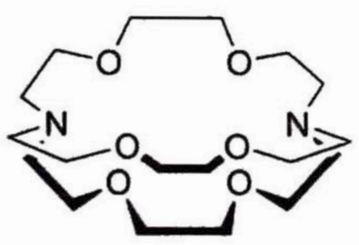
Table 1-C. Log *D* values of Derivatives for Ester-Armed Cyclens.

Sidearm analog	log *D*
1a'	0.54
1b'	2.33
1c'	2.97
1d'	3.48
1e'	4.14
1f'	8.98

e.g.
1a' = CH_3CO_2-R (R = **1a**: Ethyl-)

1-4. Stability Constants of Ester-Armed Cyclen - Na^+ Complexes

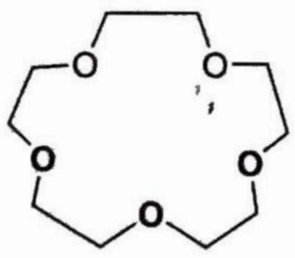
Stability constants of ester-armed cyclen – Na^+ complexes were determined in CD_3CN and CD_3CD_2OD by ^1H NMR measurements. Since the stability constants of Na^+ complexes with armed cyclens **1a-1f**, **2a** and **3** were too large to be determined, the competitive binding method was employed, in which cryptand [2.2.2] **5** or 15-crown-5 **6** competed with each cyclen in the Na^+ complexation process. The experimental details were described in the Experimental Section (1-8).



$\log K_{Na}{}^{17} = 8.5_7$ (in EtOH)

$= 9.63$ (in CH_3CN)

Cryptand [2.2.2] **5**



$\log K_{Na}{}^{19} = 4.92$ (in CD_3CN)

15-Crown-5 **6**

Table 1-D. Stability Constants of Armed Cyclen - Na^+ Complexes at 298 K.

Armed cyclen	Solvent	log *K*
1a	CD_3CN	9.85 ± 0.01
	CD_3CD_2OD	9.45 ± 0.04
1b	CD_3CN	9.34 ± 0.09
1c(*R*)	CD_3CN	10.29 ± 0.03
1d(*R*)	CD_3CN	10.08 ± 0.01
	CD_3CD_2OD	10.23 ± 0.03
1e	CD_3CN	10.09 ± 0.04
1f	CD_3CD_2OD	11.23 ± 0.08
2a	CD_3CD_2OD	7.63 ± 0.17
3	CD_3CN	6.40 ± 0.21

Conditions: see 1-8. Experimental Section.

The estimated log *K* values of armed cyclen - Na^+ complexes are summarized in Table 1-D. Ester-armed cyclen **1a-1f** showed much larger log *K* values than amide- and alcohol-armed cyclens **2a** and **3**. The polarity of the three reference compounds is in the order: $CH_3CO_2C_2H_5$ < $CH_3CH(OH)CH_3$ < $CH_3CONHC_2H_5$,[14] suggesting that determined stability constants do not simply depend on the donor ability of sidearms. In amide- and alcohol-armed cyclens **2a** and **3** systems, intramolecular hydrogen bonds between their sidearms should be considered when they exist as free ligands. Wainwright *et at.* demonstrated similar hydrogen bonds in the armed cyclen **3** system based on molecular orbital calculation and ^{13}C NMR measurements.[15] Since ester-armed cyclens **1a-1f** have no sites for hydrogen bonding, no extra energy to break the intramolecular hydrogen bonds should be required. Actually, tertiary amide-armed cyclen **2b** and **2c** (Figure 1-C) exhibited remarkably large log *K* values (log $K > 12.6$ in CD_3CN),[16] due to the absence of hydrogen bonding and large polarities. Several kinds of ester-, amide- and alcohol-armed cyclens were reported to form octacoordinated Na^+ complexes, in which four metal ligating sidearms were arranged in a helical fashion.[9,10] Such three-dimensional octadentate armed cyclen ligands were thought to offer stable octacoordinated complexes.

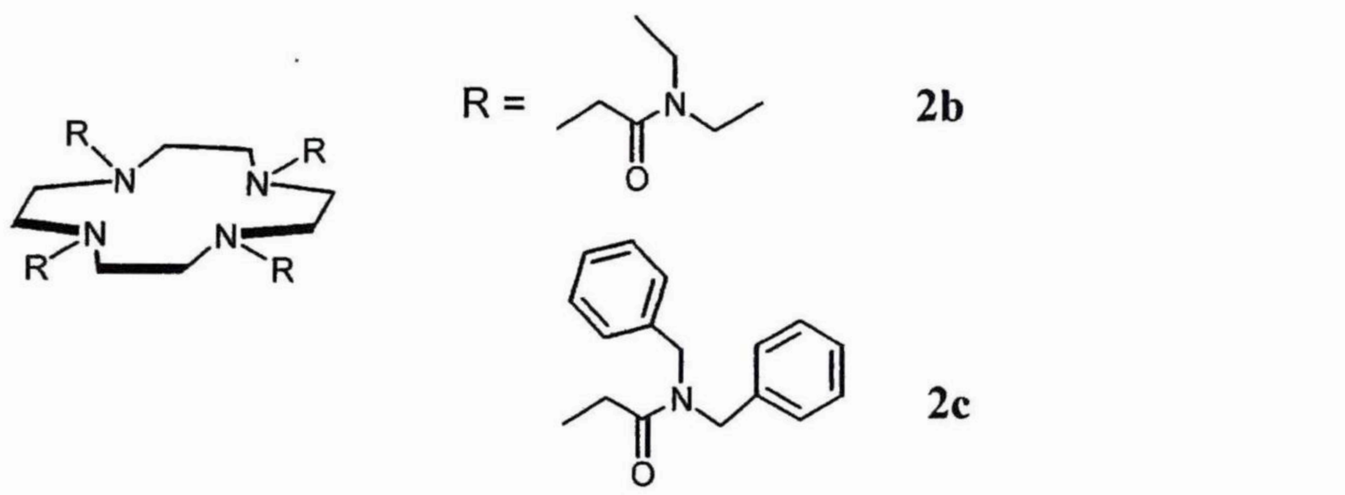


Figure 1-C. Related Amide-Armed Cyclens.

The log *K* values for Na^+ complexes with armed cyclens are represented in Figure 1-D, in which the log *K* values reported with cryptand [2.2.1] **4** and [2.2.2] **5** are included.[17] Although armed cyclens had more flexible structures than these cryptands, they showed log *K* values comparable to that of cryptand [2.2.2] **5**. Even ester-armed cyclens containing bulky residues **1e** and **1f** exhibited high stability constants for Na^+ complexation, suggesting that the bulky sidearms did not interrupt the octacoordination around the Na^+. In other words, various types of substituents can be introduced into the ester-armed cyclen system without lowering the cation binding ability.

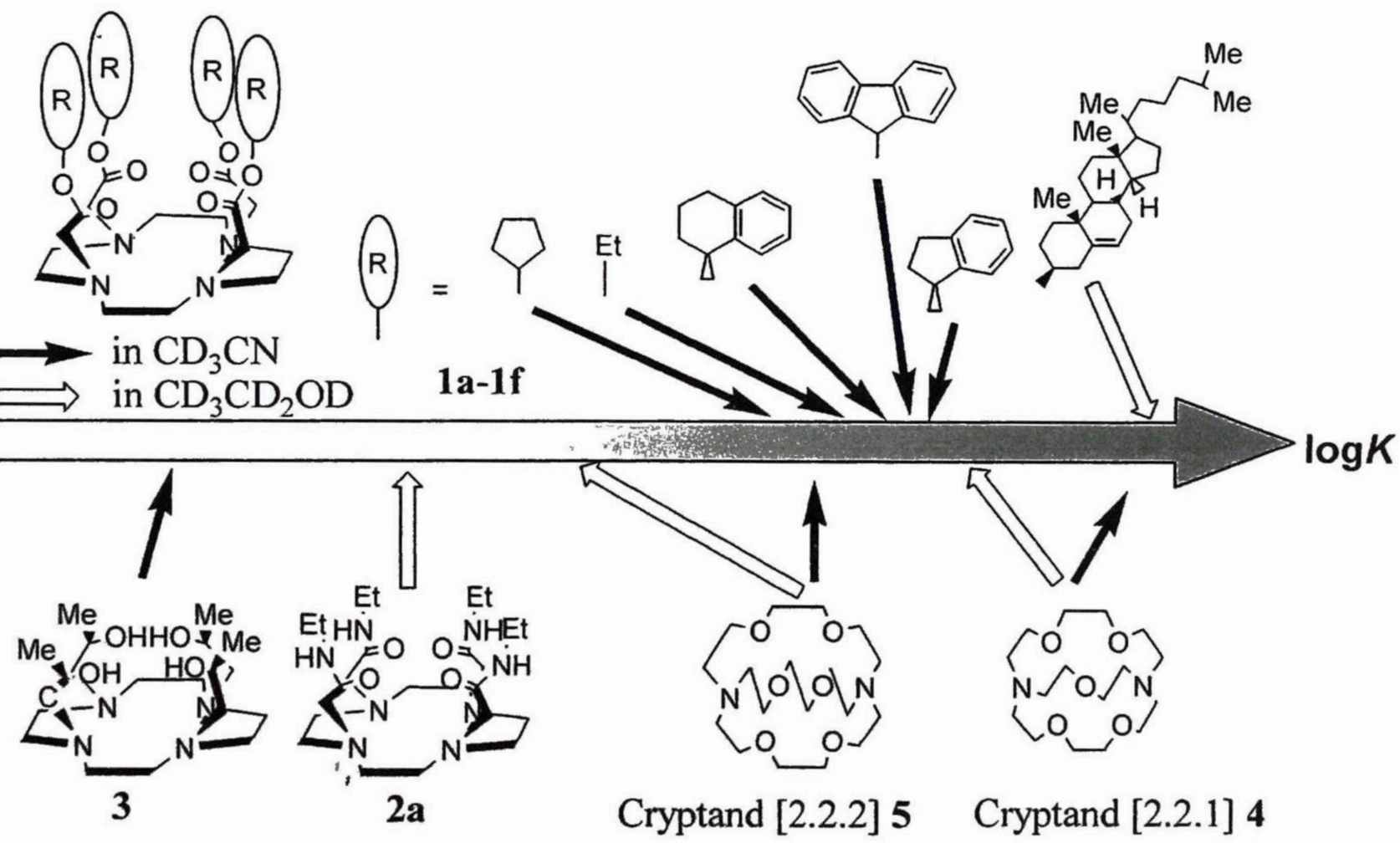
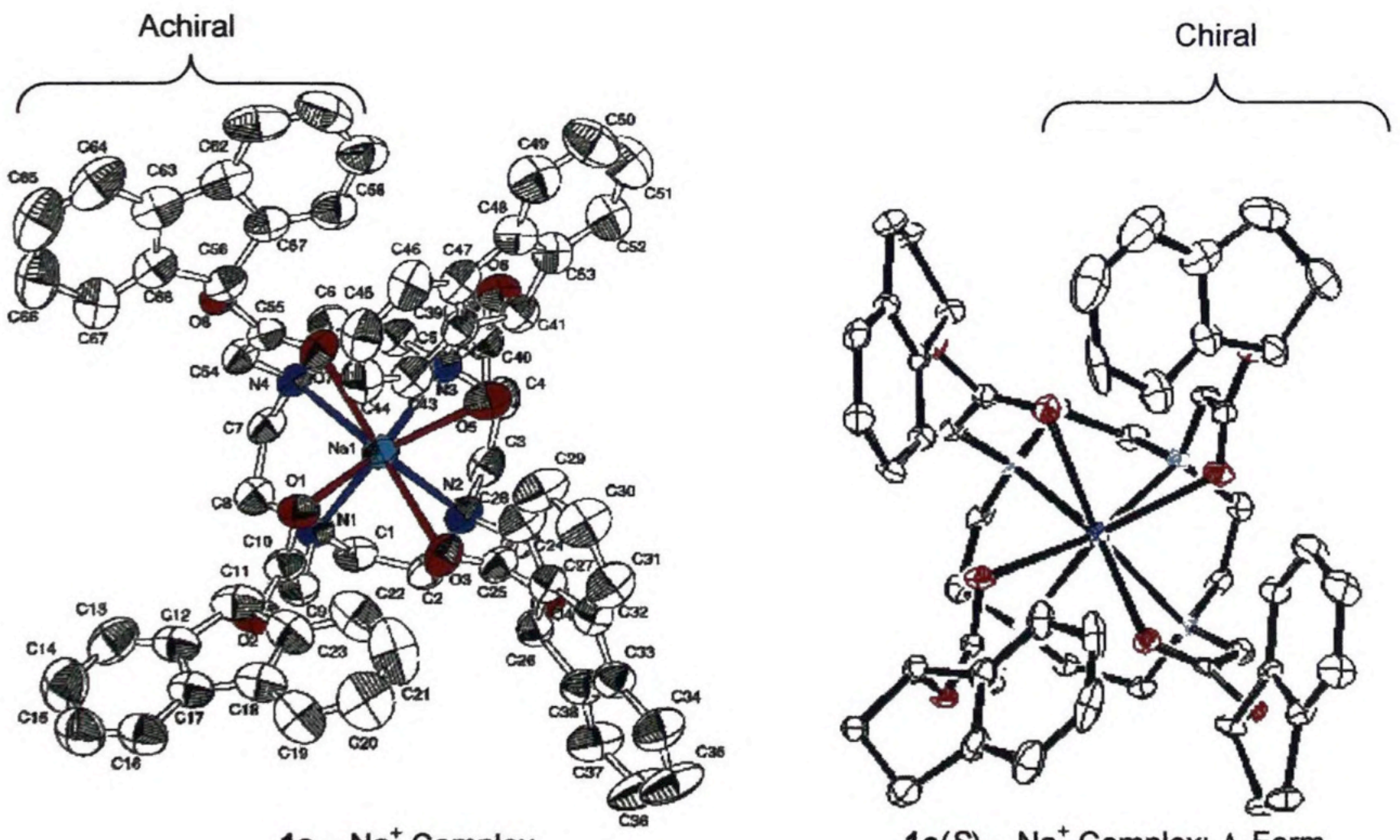


Figure 1-D. Stability Constants of Na^+ Complexes with Armed Cyclens and Related Ligands.

1-5 Crystal Structures of Armed Cyclen – Na^+ Complexes

Na^+ complexes of ester-armed cyclens **1c**(*S*) and **1e** were successfully isolated as crystals and their crystal structures were determined by X-ray crystallographic analysis (Figure 1-E). In armed cyclen **1e** – Na^+ complex, four sidearms were located upon the cyclen plane and twisted about 20 ~ 25 ° in the same direction around the centre axis. The Na^+ located on the axis and was octacoordinated by four nitrogen atoms of the cyclen ring and four carbonyl oxygen atoms of the ester sidearms. The fact that the counter Cl^- anion was located remote from the Na^+ (5.55Å) suggested that the Na^+ was stabilized well by the octacoordination from the armed cyclen ligand. Although it had a quadruple helical structure, both right- and left-handed twisted complexes (see Figure 1-F) were included in equal quantity.

When the chiral substituents, (*S*)-indanyl, were introduced on the sidearms, left-handed Λ-form of the quadruple helical Na^+ complexes was predominantly isolated. Thus, the stereochemistry of chiral substituents can control the helicity of octacoordinated armed cyclen metal complex.



1e – Na^+ Complex
(Both Δ- and Λ-Forms)

1c(*S*) – Na^+ Complex: Λ-Form
(Only Λ-Form)

Figure 1-E. Crystal Structures of Armed Cyclen - Na^+ Complexes.

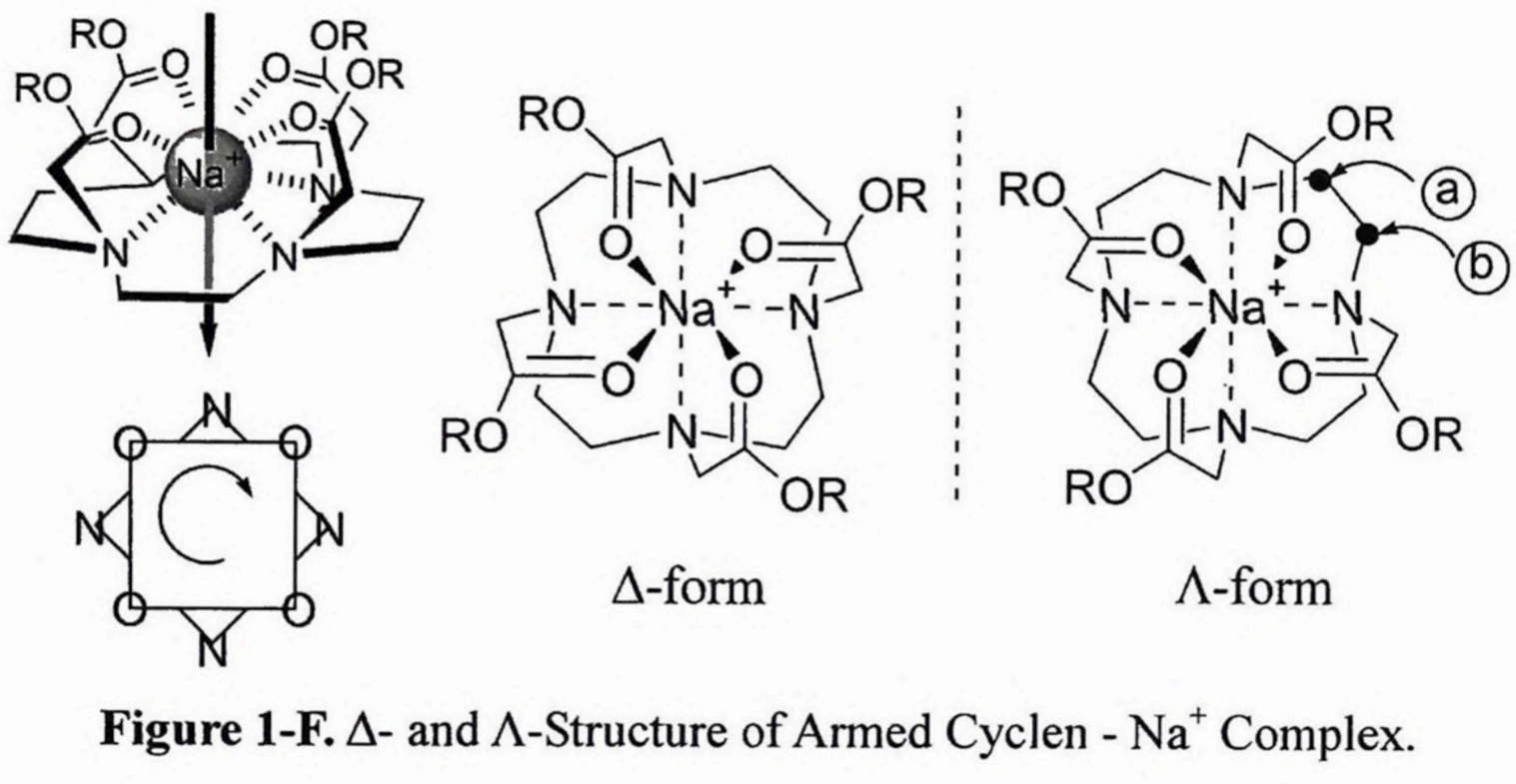


Figure 1-F. Δ- and Λ-Structure of Armed Cyclen - Na^+ Complex.

1-6. Variable Temperature ^{13}C NMR Experiments

^{13}C NMR spectra of armed cyclen **1e** - Na^+ complex were measured in $CDCl_3$, CD_3CN and CD_3CD_2OD. They all showed two kinds of carbon signals for cyclen ring N-CH_2-CH_2-N at room temperature. Similar phenomena were reported in the octacoordinated complexes with other kinds of armed cyclens,[18] indicating that armed cyclen **1e** - Na^+ had a helical structure even in solution. Since the two signals were assigned as carbons ⓐ and ⓑ in Figure 1-F, the exchange process between right-handed (Δ-form) and left-handed (Λ-form) structures occurred very slowly in solution, as compared with the NMR time scale.

With increasing temperatures, the two peaks broadened and then coalesced as shown in Figure 1-G, suggesting that a rapid exchange occurs at > 55 °C. The Gibbs free energy ($\Delta G^{\neq}$) for the exchange process of armed cyclen **1e** - Na^+ complex was estimated from the coalescence temperature as $\Delta G^{\neq}$ = 59.4 ~ 61.4 kJ mol^{-1} at 298 K in CD_3CD_2OD. (see 1-8. Experimental Section) A similar exchange process was reported by Lincoln *et al.* with ether-type armed cyclen – Na^+ complex, in which $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were obtained as 31.4 kJ mol^{-1} and –78.8 JK^{-1} mol^{-1} in methanol.[18(a)] Thus, $\Delta G^{\neq}$ 54.9 kJ mol^{-1} at 298 K which was close to our result, though different ligands and solvents were used.

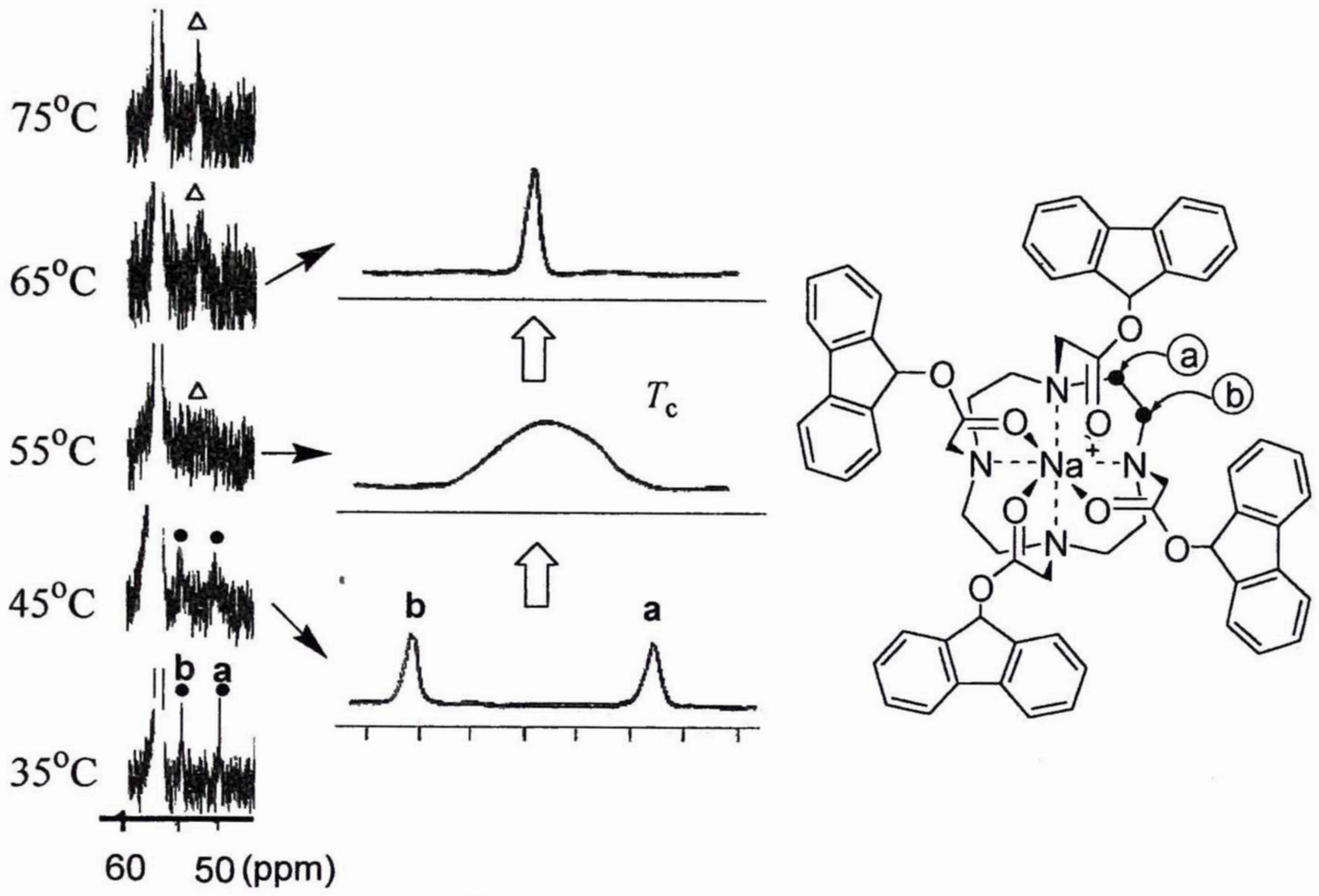


Figure 1-G. Variable Temperature ^{13}C NMR Spectra (150MHz) of Armed Cyclen **1e** - Na^+ Complex in CD_3CD_2OD.

1-7. Conclusion

I successfully developed a new series of ester-armed cyclens that exhibited excellent selectivity and high stability for Na^+ complexes. Their cation selectivity was superior to those of amide- and alcohol-armed cyclens. This type of armed cyclens has unique quadruplicated helical structure upon Na^+ complexation both in solid and solution states. Since very stable Na^+ complexes were obtained even if bulky fluorenyl and cholesteryl residues were introduced on their sidearms, the functional armed cyclens that would be detailed in Chapters 2 and 3, respectively, were applicable as supramolecular devices.

1-8. Experimental Section

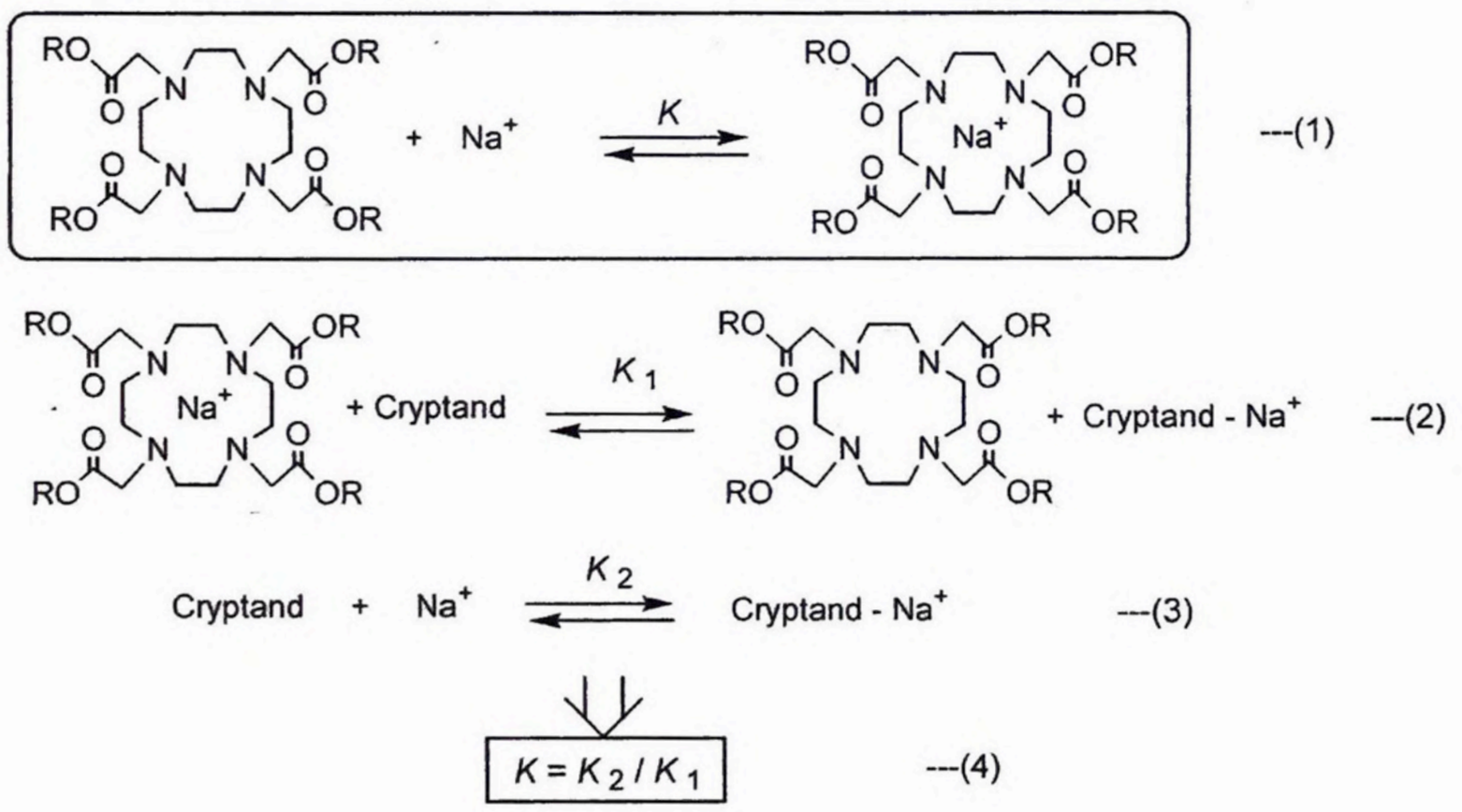
General Procedures

FAB-MS Experiments. *m*-Nitrobenzyl alcohol solutions containing armed cyclen derivatives (0.00330 mmol L^{-1}) and Li^+, Na^+ and K^+ (0.00830 mmol L^{-1}) were prepared, and their FAB-MS spectra were measured under competitive conditions. Since NaCl complexes with ester- and amide-armed cyclens **1a** - **1f** and **2a** (0.00330 mmol L^{-1}) were employed, the total Na^+ concentration was adjusted by the addition of NaCl to 0.00830 mmol L^{-1}, and LiCl and KI were used for sample preparations. LiCl, NaI and KI (0.00830 mmol L^{-1}, each) were used for alcohol-armed cyclen **3** (0.00330 mmol L^{-1}), because it was employed as a free ligand. The mixture solution was stirred for 12 h in order to complete the exchange of Na^+ with Li^+ or K^+. FAB-MS spectra were recorded with a JEOL AX 500 instrument (a beam energy of Xe, 6 keV). The averaged peak intensities of 20 scans are shown in Table 1-A.

Liquid-Liquid Extractions. The extraction experiment with armed cyclen was carried out by adding a $CHCl_3$ solution of armed cyclen - NaCl complex (0.0100 mmol in 1.5 mL) to an aqueous mixture of Li^+ and K^+ perchlorates (0.0100 mmol, each in 1.5 mL). For armed cyclen **3**, a $CHCl_3$ solution of free ligand (0.0100 mmol) and an aqueous mixture of Li^+, Na^+ and K^+ perchlorates (0.0100 mmol each) were used. After the mixture had been stirred for 2 h, the concentrations of three kinds of metal cations in the aqueous phase were determined by atomic absorption or the flame spectroscopic method (Exlan Technical Center, Okayama, Japan). It was confirmed that negligible amounts of metal perchlorates were extracted into the $CHCl_3$ phase in the absence of cyclen ligand.

Stability Constant Determination of Na^+ Complexes. The stability constants *K* of various armed cyclen - Na^+ complexes were determined using the ^1H NMR competitive binding method. The existence of free Na^+ could assume to be negligible because the log *K* values of both armed cyclens and cryptand [2.2.2] against Na^+ were large. When cryptand [2.2.2] **5** or 15-crown-5 **6** was added to a solution of ester-armed cyclen - NaCl complex, both NaCl

complex and free ligand offered separated signals. For example, signals for the -$CO_2C\underline{H}<$ proton of cyclen **1e** were observed at 6.75 ppm for the free form and 6.92 ppm for the complex form. The integration of these two signals conducted the K_1 defined in eq. (2). Because K_2 of cryptand - Na^+ complex was previously published in the literature,[17] K was calculated from K_1 and K_2 (eq. (4)). The experiment was carried out with three different amounts of added cryptand or crown ether for each armed cyclen-Na^+ complex, and the three K values obtained were averaged. Amide- or alcohol-armed cyclen exhibited only one signal at the averaged position of the free form and the Na^+ complex form because of the fast exchange. In these cases, the existence ratio could be estimated from the chemical shifts, and used in the calculation of K values. 15-crown-5 **6**[19] was used in alcohol-armed cyclen **3** system instead of cryptand [2.2.2] **5** due to its small log K value. 1H NMR spectra were recorded on JEOL LA-400 and Bruker AMX 600.



Crystal Structure Determination of Armed Cyclen 1e - NaCl Complexes. The data collection was carried out at 23 °C on a Rigaku RAXIS-RAPID Imaging Plate diffractometer equipped with graphite monochromated Mo-Kα radiation (μ = 1.27 cm^{-1}). The structure was solved by the automated direct method (SIR92).[20] Atomic coordinates and anisotropic thermal parameters of the non-hydrogen atoms were refined on F by a full-matrix least-squares

calculation. The remaining hydrogen atom coordinates were calculated at the optimum positions. All computer programs used were from teXsan software (Molecular Structure Corporation). Crystal and structure refinement data for this complex are as follows: empirical formula, $C_{72}H_{72}O_{10}N_4ClNa$; formula weight, 1211.82; crystal size (mm), 0.30x0.30x0.20; crystal system, monoclinic; space group, *P*2/n; *a* (Å), 18.4124(7); *b* (Å), 15.4028(5); *c* (Å), 23.3264(9); *B* (deg), 99.167(1); *V* (Å^3), 6531.0(4); *Z*, 4; *γ* calculated (g cm^{-3}), 1.232; *F*(000) 2560.00; scan mode, *ω*; 2*θ* max (deg), 55.0; total measured reflections, 56752; unique measured reflections, 14335; observed reflections, 4634 ($I > 3.00\sigma(I)$) ($R_{int} = 0.053$); refined parameters, 769; residue electron density (eÅ^{-3}), 0.58/-0.28; *R*, 0.057; *Rw* , 0.077; GOF, 0.53.

Crystal Structure Determination of Armed Cyclen 1c(*S*) – $NaB(C_6H_5)_4$ Complex. Armed cyclen **1c**(*S*) – NaCl complex and $NaB(C_6H_5)_4$ were stirred in CH_3OH for 30 minutes and the precipitate was collected. The CH_2Cl_2-soluble fraction was recrystallized from CH_3OH, to yield a colourless needle-like crystal. A Single crystal of armed cyclen **1c**(*S*) – $NaB(C_6H_5)_4$ complex was recrystallized from CH_3OH. This crystal was mounted on top of a glass fibre. X-ray data of the complexes were collected with graphitec-monochromated Mo-K*α* radiation on a Rigaku/MSC Mercury CCD diffractometer at –160 °C. The structure was solved by direct methods (SIR-2002)[21] and expanded using DIRDIF 99.[22] The structure was refined anisotropically by full-matrix least squares on F^2. The non-hydrogen atoms were attached at idealized positions on carbon atoms and were not refined. The structure converted in the final stages of refinement showed no movement in atom positions. All calculations were performed using Single Crystal Structure Analysis Software, Ver. 3.6.0.[23] Crystal data: colourless plate with 0.18 × 0.17 × 0.08 mm, $C_{152}H_{154}N_8B_2Na_2O_{16}$, M_w = 2416.53, a = 11.9036(10), b = 13.6727(10), c = 20.090(2) Å, α = 92.329(4)°, β = 99.964(5)°, γ = 91.082(4)°, V = 3216.6(5) Å^3, Mo-Kα: l = 0.7169 Å, GOF = 0.9709, T = -160°C, space group $P\bar{1}$ (no. 1), Z = 1, μ = 0.86 cm^{-1}, number of parameter 1776, 17526 (all reflections) were used in calculation, R = 8.3%, Rw = 16.9%, $R1$ ($I > 2\sigma I$) = 6.4%.

Determination of Gibbs Energy of Enantiomeric Process. The Gibbs free energy $\Delta G^{\neq}$ for the enantiomer inversion process (Figure 1-F) of armed cyclen **1e** – Na^+ complex was calculated using equation (5).[24]

$$\Delta G^{\neq} = 19.14\ Tc\ (9.97 + \log Tc\ /\delta v) \cdots\cdots\cdots (5)$$

where T_c, coalescence temperature [K],

δv, the chemical shift difference [Hz] between **a** and **b** in Figure 1-G.

^{13}C NMR spectra (150 MHz) of armed cyclen **1e** – Na^+ complex were measured at 25, 35, 45, 55, 65 and 75°C in CD_3CD_2OD. The coalescence of the exchange process of armed cyclen **1e** – Na^+ complex occurred at 50~60°C, and the chemical shift difference (δv) was estimated as 730 Hz at 25 °C (298 K).

Synthesis

Preparation of Ester-Armed Cyclen – NaCl Complexes. All the employed ester-armed cyclen–NaCl complexes were directly prepared from cyclen tetrahydrochloride and corresponding chlorides.[9,10] These Na^+ complexes were isolated as white or pale yellow powders and fully characterized by ^1H-, ^{13}C-, and ^{23}Na NMR (JEOL LA-300 and 400), IR (Jasco FT/IR-420), microanalysis and mass spectroscopy (JEOL AX500). $[\alpha]_D$ values were also measured for chiral substances (Jasco DIP-370). Selected data of the newly obtained complexes and their precursors are summarized below.

Cyclopentyl chloroacetate. Triethylamine (3.10 g, 30.6 mmol) was added to a solution of cyclopentanol (1.72 g, 20.0 mmol) in dry dichloromethane (20 mL). The mixture was cooled to –10 °C and chloroacetyl chloride (3.80 g, 33.7 mmol) was added dropwise, with the temperature being maintained below 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 6 h. The reaction was stopped with the addition of ice, and extracted with three potions of dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, and then evaporated. Chromatography on silica gel using dichloromethane :

hexane (2 : 3) as the eluent led to the isolation of cyclopentyl chloroacetate (2.29 g, 70 %) as colourless oil.

(*R*)- and (*S*)-1-Indanyl chloroacetate, (*R*)-tetrahydro-1-naphtyl chloroacetate, and fluorenyl chloroacetate were also prepared using similar procedures.

1,4,7,10-Tetrakis[(ethyloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane 1a – NaCl complex was prepared as reported previously.[9]

1,4,7,10-Tetrakis-[(cyclopentyloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane 1b – NaCl Complex. A solution of cyclen tetrahydrochloride (0.20 g, 0.62 mmol), cyclopentyl chloroacetate (0.50 g, 3.1 mmol) and Na_2CO_3 (0.98 g, 9.2 mmol) in dry CH_3CN (25 mL) was refluxed for 4 h and then filtered. The solvent was evaporated and the residue was washed with hexane. Recrystallization from CH_2Cl_2 / hexane gave white crystals of NaCl complex. Yield, 20 %: mp. 79-81 °C (decomposition); IR (neat) υ 1727 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m/z* 699 (M^+); ^1H NMR ($CDCl_3$) δ 1.25 – 1.79 (br m, 32H), 2.37 (br s, 12H), 3.15 (br s, 12H), 5.14 (br m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.55, 32.29, 48.58, 52.50, 55.14, 78.38, 173.51. Anal. Calcd for $C_{36}H_{60}N_4O_8$ - NaCl · $4.5H_2O$: C, 52.96; H, 8.52; N, 6.86. Found: C, 52.99; H, 8.14; N, 6.93.

1,4,7,10-Tetrakis{[(*R*)-1-indanyloxycarbonyl]methyl}-1,4,7,10-tetraazacyclododecane 1c(*R*) – NaCl complex: yield, 24 %: mp. 105 – 106 °C (decomposition); $[\alpha]_D = 215$ ($c = 0.985$, $CHCl_3$); IR (KBr) υ 1725 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m/z* 891 (M^+); ^1H NMR ($CDCl_3$) δ 2.17 – 2.53 (br m, 20H), 2.80 – 2.89 (m, 4H), 3.06 – 3.17 (m, 8H), 3.54 (br m, 8H), 6.26 – 6.30 (m, 4H), 6.67 (br s, 4H), 7.11 (br s, 4H), 7.26 (s, 4H), 7.68 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 30.05, 31.70, 48.58, 52.77, 55.48, 79.07, 124.89, 125.49, 126.61, 129.16, 140.64, 144.35, 174.06. Anal. Calcd for $C_{52}H_{60}N_4O_8$ - NaCl · $3.5H_2O$: C, 63.05; H, 6,82; N, 5.66. Found: C, 62.95; H, 6.76; N, 5.42.

1,4,7,10-Tetrakis{[(*S*)-1-indanyloxycarbonyl]methyl}-1,4,7,10-tetraazacyclododecane 1c(*S*) – NaCl complex: yield, 38 %: mp. 104 – 106 °C (decomposition); $[\alpha]_D = -224$ ($c =$

0.989, $CHCl_3$); IR (KBr) υ 1725 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m/z* 891 (M^+); ^1H NMR ($CDCl_3$) δ 2.17 – 2.53 (br m, 20H), 2.80 – 2.89 (m, 4H), 3.06 – 3.17 (m, 8H), 3.54 (br m, 8H), 6.26 – 6.30 (m, 4H), 6.67 (br s, 4H), 7.10 (br s, 4H), 7.25 (s, 4H), 7.68 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 30.10, 31.71, 48.57, 52.75, 55.47, 79.07, 124.90, 125.50, 126.60, 129.16, 140.63, 144.35, 174.06. Anal. Calcd for $C_{52}H_{60}N_4O_8$ - NaCl · $(C_5H_{10}O)_{0.8}$ · $3.5H_2O$: C, 64.58; H, 6,97; N, 5.46. Found: C, 64.52; H, 6.94; N, 5.45.

1,4,7,10-Tetrakis{[(*R*)-1,2,3,4-tetrahydro-1-naphtyloxycarbonyl]methyl}-1,4,7,10-tetraazacyclododecane 1d – NaCl complex: yield, 23%; mp 114 - 115 °C (decomposition); $[\alpha]_D$ = 129 (*c* = 0.850, $CHCl_3$); IR (neat) υ 1724cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m/z* 947 (M^+); ^1H NMR ($CDCl_3$) δ 1.78 – 3.80 (br m, 48H), 6.14 (br s, 4H), 6.86 – 7.66 (br m, 16H); ^{13}C NMR ($CDCl_3$) δ 18.62, 28.79, 29.09, 48.58, 52.49, 55.60, 70.93, 126.03, 128.48, 129.29, 129.37, 133.74, 138.04, 173.73. Anal. Calcd for $C_{56}H_{68}N_4O_8$ – NaCl · $3H_2O$: C, 64.82; H, 7.19; N,5.40. Found: C, 65.18; H,7.07; N, 5.49.

1,4,7,10-Tetrakis[(fluorenyloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane 1e – NaCl complex: yield, 70%: mp. 164 - 166 °C (decomposition); IR (neat) υ 1727cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m/z* 1083 (M^+); ^1H NMR ($CDCl_3$) δ 2.38 (br s, 4H), 2.73 (br s, 8H), 3.31 (br s, 4H), 3.88 (br s, 8H), 6.54 (br s, 4H), 6.85 (s, 4H), 7.03 – 7.89 (br m, 28H); ^{13}C NMR ($CDCl_3$) δ 48.75, 53.18, 55.63, 76.21, 120.04, 125.64, 127.71, 129.75, 140.83, 141.07, 175.55. Anal. Calcd for $C_{68}H_{60}N_4O_8$ – NaCl · $2H_2O$ · $0.25CH_2Cl_2$ · $0.75C_4H_{10}O$: C, 69.43; H, 5.89; N, 4.55. Found: C, 69.70; H,5.76; N, 4.55.

1,4,7,10-Tetrakis[(cholesteryloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane 1f – NaCl complex:[25] Yield, 71%: mp. 151 - 152 °C (decomposition); $[\alpha]_D$ = - 83.4 (*c* = 0.500, $CHCl_3$); IR (neat) υ 1725 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m/z* 1902 (M^+); ^1H NMR ($CDCl_3$) δ 0.70 (s, 4H), 0.80 - 2.40 (m, 112H), 0.86 (d, 12H), 0.88 (d, 12H), 0.92 (d, 12H), 0.99 (s, 12H), 2.15 - 2.35 (br m, 4H), 2.40 - 2.70 (br m, 8H), 2.98 (br d, 4H), 3.25 - 3.45 (br m, 4H), 3.45 (br d, 4H), 4.53 (br m, 4H), 5.26 (br, 4H); ^{13}C NMR ($CDCl_3$) δ 11.93, 18.69, 19.08, 21.03,

22.54, 22.77, 23.57, 24.26, 27.64, 27.97, 28.13, 31.63, 32.49, 35.69, 36.20, 36.36, 36.90, 38.15, 39.57, 39.90, 42.32, 48.46, 50.34, 53.01, 54.80, 56.07, 57.23, 75.48, 122.49, 139.71, 173.49. Anal. Calcd for $C_{124}H_{204}N_4O_8 - NaCl \cdot 5H_2O$: C, 73.46; H, 10.64; N, 2.76. Found: C, 73.76; H, 10.49; N, 2.76.

1,4,7,10-Tetrakis[(ethylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododecane 2a – NaCl complex: This was similarly prepared from cyclen terahydrochloride and *N*-ethylchloro-acetamide in the presence of Na_2CO_3. Yield, 53 %: mp. 200 - 201 °C; IR (KBr) υ 1658, 1556 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (t, 12H), 2.37 (br s, 8H), 2.65 (br s, 8H), 3.04 (br s, 8H), 3.22 (q, 8H); ^{13}C NMR ($CDCl_3$) δ 15.0, 35.2, 49.0 (overlapped with CD_3OD), 51.8, 58.2, 173.0. Anal. Calcd for $C_{44}H_{56}N_8O_4 - NaCl - 2H_20$: C, 47.48; H, 8.63; N, 18.45 Found: C, 47.54; H, 8.55; N, 18.36.

1,4,7,10-Tetrakis((*S*)-2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane 3: This was prepared as reported previously.[6(a),11]

1-9. References and Notes

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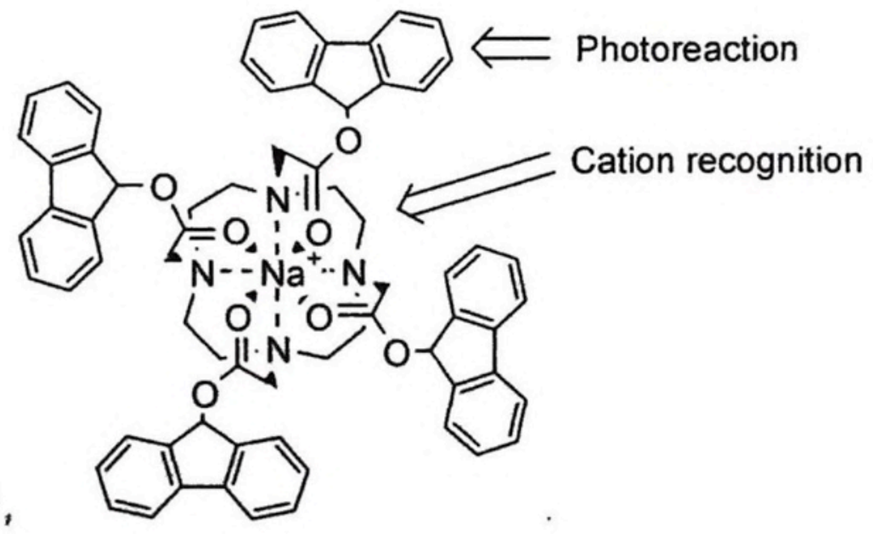
Chapter 2. Visual Sensing *via* Photoreaction of Fluorenyl Ester-Armed Cyclen - Metal Complexes

2-1. Introduction

Attention has been paid to visual sensing systems because they do not require expensive instruments and have wide applications in practical processes. Various kinds of metal cations,[1] inorganic anions,[2] and organic substrates[3] are targeted, and the detection of Ca^{2+} or Zn^{2+} is biologically important.[4] A number of cation-selective fluorescent and colorimetric chemosensors have been reported and some of them exhibited high sensitivity and selectivity for biological analysis.[5] The chemosensors are usually designed to have cation recognition moieties and signalling fluorescence groups. Macrocyclic ligands are one of the potential candidates as cation recognition moieties due to their high cation selectivity.[6] In particular, cyclen derivatives have already been used in fluorescent and luminescent sensing processes.[7] Kimura *et al.*[7(a)] developed fluorescent probes of armed cyclen type for Zn^{2+}. Parker *et al.*[7(b)] and Sherry *et al.*[7(c)(d)] presented a series of armed cyclen – lanthanide complexes as luminescent materials specific for anions.

In this chapter, I present a new approach toward developing visual sensing of Ca^{2+} using photo-reactive fluorenyl-armed cyclen **1e**. As demonstrated in Chapter 1, armed cyclen **1e** formed stable octacoordination complexes with Na^+ and expected to also coordinate to related spherical metal cations.[8]



Fluorenyl ester-armed cyclen **1e** – Na^+ complex

The fluorenyl ester moiety of the armed cyclen is photoreactive to produce green emissive fluorenone[9] upon irradiation, and its reactivity can be varied by metal complexation. Since Ca^{2+} complexation with armed cyclen **1e** effectively suppressed the formation of this green emissive fluorenone, the photoreaction was successfully utilized to offer the naked-eye detection of Ca^{2+} at the biological concentration.

2-2. Photoreaction of Fluorenyl-Armed Cyclen – Na^+ Complex

Fluorenyl ester and fluorenol derivatives are known to give several photoproducts in polar solvents *via* several pathways.[10] (Figure 2-A)

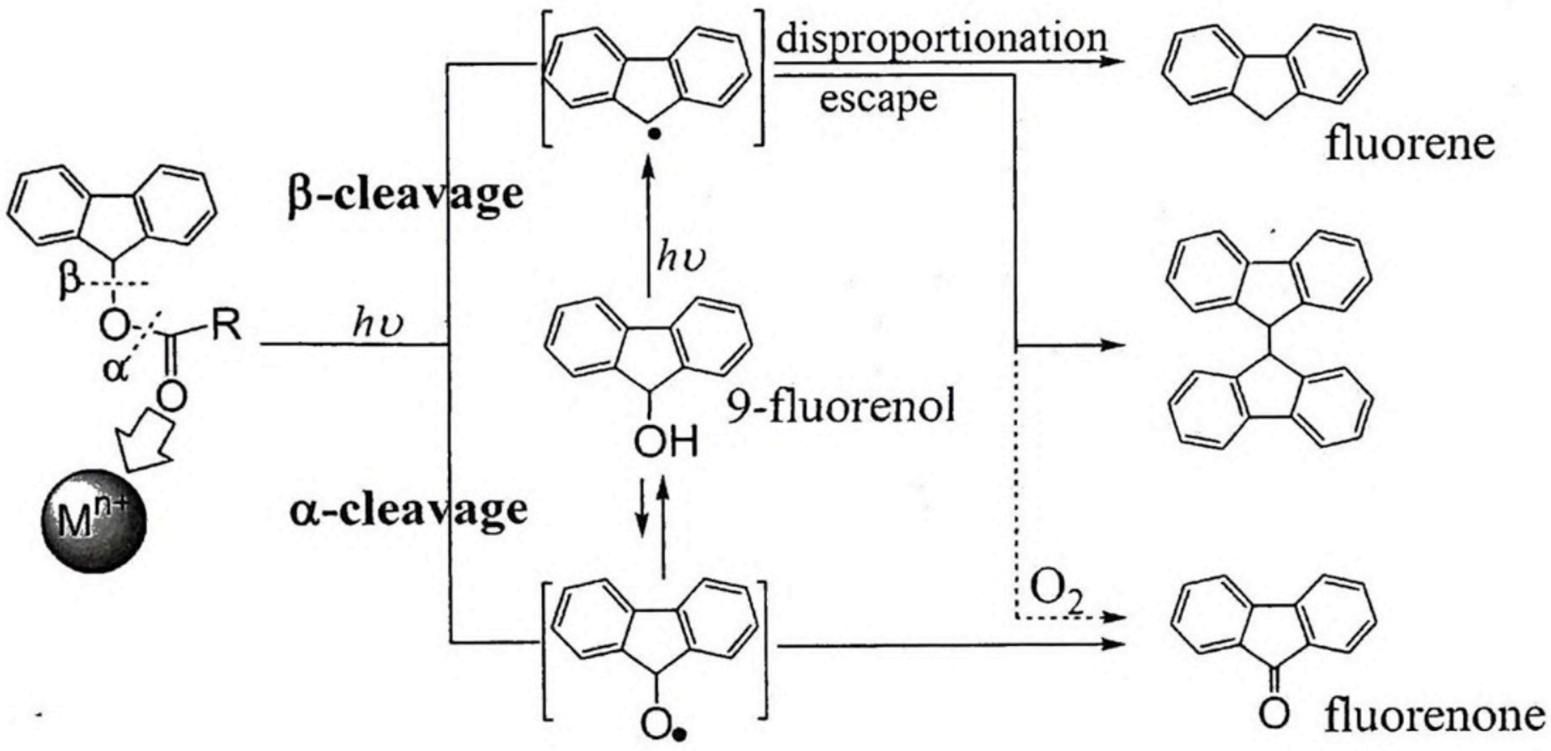


Figure 2-A. Photoreaction Pathways of Fluorenyl Ester

Typically, an CH_3CN solution of armed cyclen **1e** – Na^+ complex (6.25×10^{-3} mol L^{-1}) was irradiated for 60 minutes by UV lamp for TLC detection (λ = 254 nm), though this irradiation period was insufficient to complete the photoreaction. The hexane-soluble fraction of the reaction mixture was separated by column chromatography on silica gel, eluting with hexane / ethyl acetate, and fluorenone (35 % yield), fluorene derivatives (10 %) and 9-fluorenol (6 %) were isolated. These product distributions suggested that both α- and β-cleavage reactions occurred. The hexane-insoluble fraction was also characterized by ESI-MS method, which included partially decomposed cyclen derivatives. The cyclen derivative having two

methylfluorene sidearms by decarboxylation of fluorenyl ester and one unreacted fluorenyl ester was typically detected (Figure 2-B).

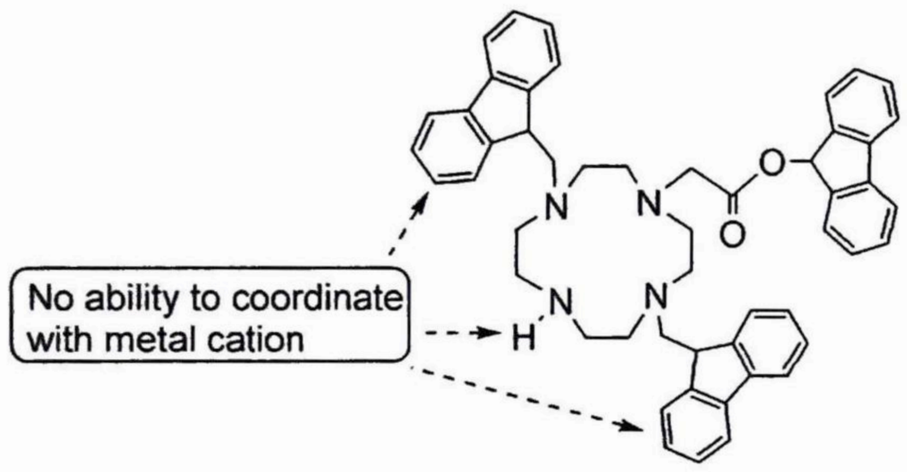


Figure 2-B. One of Partially Decomposed Cyclen Derivatives Detected by ESI – MS.

2-3. Photoreaction of Na^+ Complex Followed by UV Method

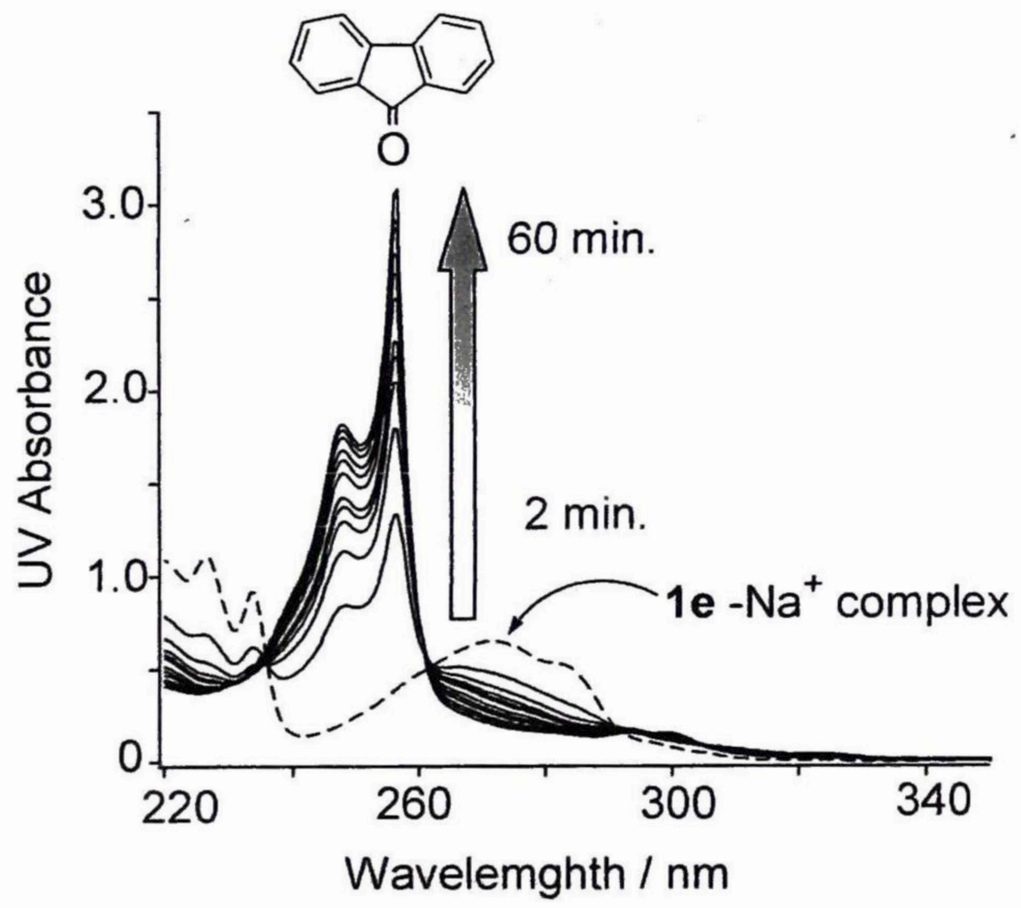


Figure 2-C. UV Spectral Change of Armed Cyclen **1e** – Na^+ Complex upon Irradiation.

When the CH_3CN solution of armed cyclen **1e** – Na^+ complex, (1×10^{-5} mol L^{-1}) was irradiated by TLC lamp, the reaction time course was followed by UV method. The new peak at 256 nm, which was characteristics of fluorenone, appeared even after short irradiation period. This absorption peak rose gradually with increasing irradiation time and finally reached 3.0 as UV absorbance. As illustrated in Figure 2-D, fluorene and 9-fluorenol had small ε values at 256 nm and their product yields were not so high. Thus the absorbance at 256 nm could be a good

indication of the fluorenone generation. Typically, Figure 2-C indicated that the yield of fluorenone was about 70 % after 60 minutes of irradiation.

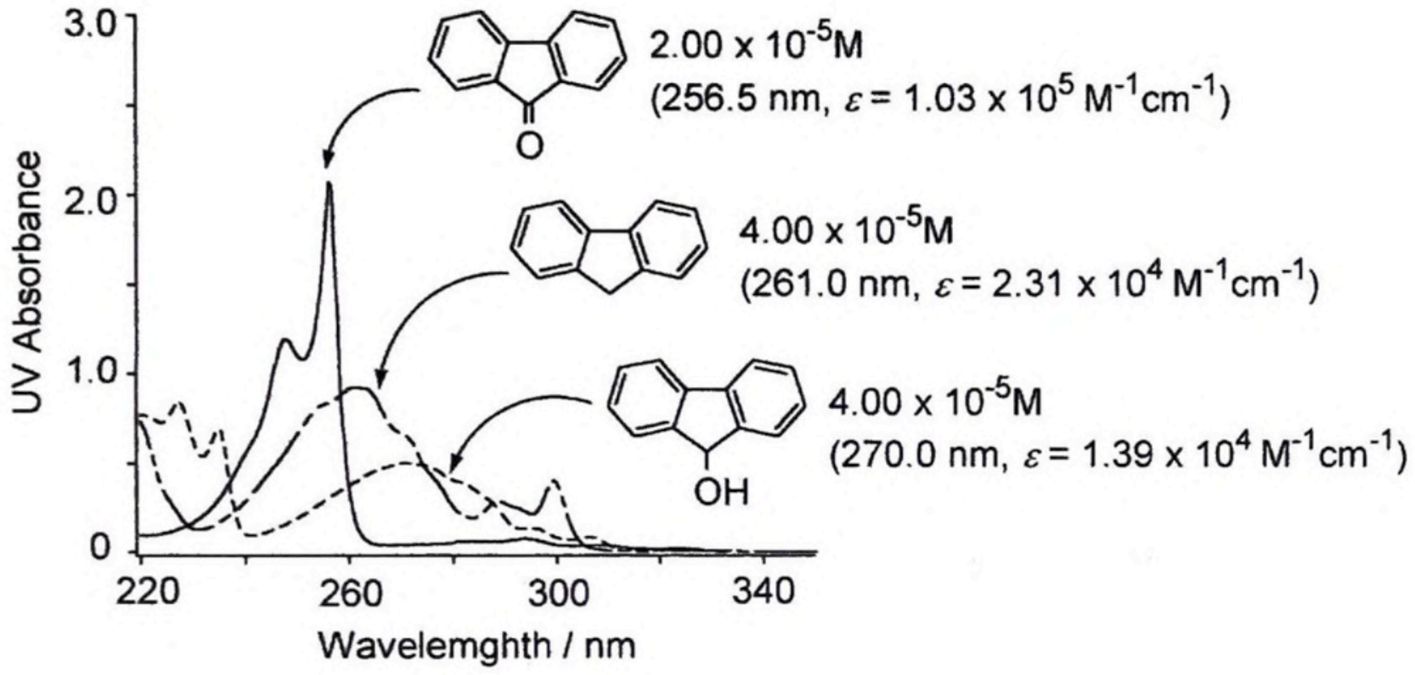


Figure 2-D. Comparison of UV Spectra of Fluorenyl Derivatives.

2-4. Metal Exchange of Fluorenyl-Armed Cyclen Complex

Because the photo-reactive fluorenyl esters cooperatively coordinated the metal cation with cyclen nitrogen atoms in armed cyclen **1e** – Na^+ complex, its photoreaction profile was expected to depend on the nature of the bound metal cation. The addition of cryptand [2.2.1] **4** (structure: see page 13) removed Na^+ from armed cyclen **1e** to give the cation-free armed cyclen ligand, and the resulting ^1H NMR showed sharp signals for all protons. In contrast, the addition of metal triflates (trifluoromethanesulfonates) to armed cyclen **1e** – Na^+ complex solution readily promoted metal exchange process. The obtained Ca^{2+} complex offered a similar NMR spectrum to that of Na^+ complex, while the La^{3+} complex exhibited a rather broader ^1H NMR spectrum in which peaks of Na^+ complex disappeared but most of the peaks were not identified. The selected spectral data of free ligand **1e**, its Na^+ complex and Ca^{2+} complex are summarized in Table 2-B. Armed cyclen **1e** – $Ca(CF_3SO_3)_2$ complex was also isolated as a white powder by mixing armed cyclen **1e** – NaCl complex with $Ca(CF_3SO_3)_2$ (see 2-8. Experimental Section), and exhibited the same spectral profile to the mixture of armed cyclen **1e** – NaCl complex and two equivalents of $Ca(CF_3SO_3)_2$. When armed cyclen **1e** - NaCl complex was mixed with one

equivalent of Na^+ and two equivalents of Ca^{2+} in CH_3CN (**1e** : Na^+ : Ca^{2+} = 1 : 2 : 2), its ESI-MS spectrum exhibited much higher peaks due to the Ca^{2+} complex than that of Na^+ complex: [armed cyclen **1e** + Ca^{2+}]$^{2+}$/ [armed cyclen **1e** + Ca^{2+} + $CF_3SO_3^-$]$^+$/ [armed cyclen **1e** + Na^+]$^+$ = 18 / 61 / 1. This confirmed that the Ca^{2+} complex had a much larger binding constant in CD_3CN solution than Na^+ complex (log K_{Na} =10.1, see 1-4).[8] ^{1}H NMR competitive experiments with cryptand [2.2.2] **5** (page 14) also supported that the Ca^{2+} complex was more stable than the Na^+ complex. Addition of six equivalents of cryptand [2.2.2] **5** (log K_{Ca} = 10.5 in CH_3CN)[11] to the CD_3CN solution of Ca^{2+} complex rarely changed the signals of the Ca^{2+} complex. The signals of free armed cyclen protons appeared when cryptand was added to the Na^+ complex solution; 58 % of Na^+ complex and only 0.6 % of Ca^{2+} complex were decomplexed.

2-5. Metal Cation-Controlled Photolysis of Fluorenyl-Armed Cyclen

To compare the degree of the metal cation effects in the photoreactivity of armed cyclen **1e**, I measured time-dependent UV spectra in the presence of Na^+, Ca^{2+} and La^{3+} (Figure 2-E). These cations have similar ion sizes (Na^+, 1.18 Å; Ca^{2+}, 1.12 Å; La^{3+}, 1.16 Å for octacoordination),[12] but different charge states. The addition of Ca^{2+} and La^{3+} effectively suppressed the fluorenone production in the early stage, though Na^+ rarely affected the photoreaction of free armed cyclen **1e**. Because armed cyclen **1e** lost its coordination ability after photo-decarboxylation (see Figure 2-B), the effects of cation complexation could only be observed for a few minutes.

Since the addition of six equivalents of $Na(CF_3SO_3)$ did not affect the photo-reactivity, the ion strength rarely influenced the photoreaction of present types. Both $CaCl_2$ and $Ca(ClO_4)_2$ showed the same suppression effects as $Ca(CF_3SO_3)_2$, and eight equivalents of *N*-ethyldiisopropylamine (tertiary amine base) had no effect. These results indicated that the photoreaction of fluorenyl ester sidearms was significantly controlled by metal complexation with armed cyclen **1e**.

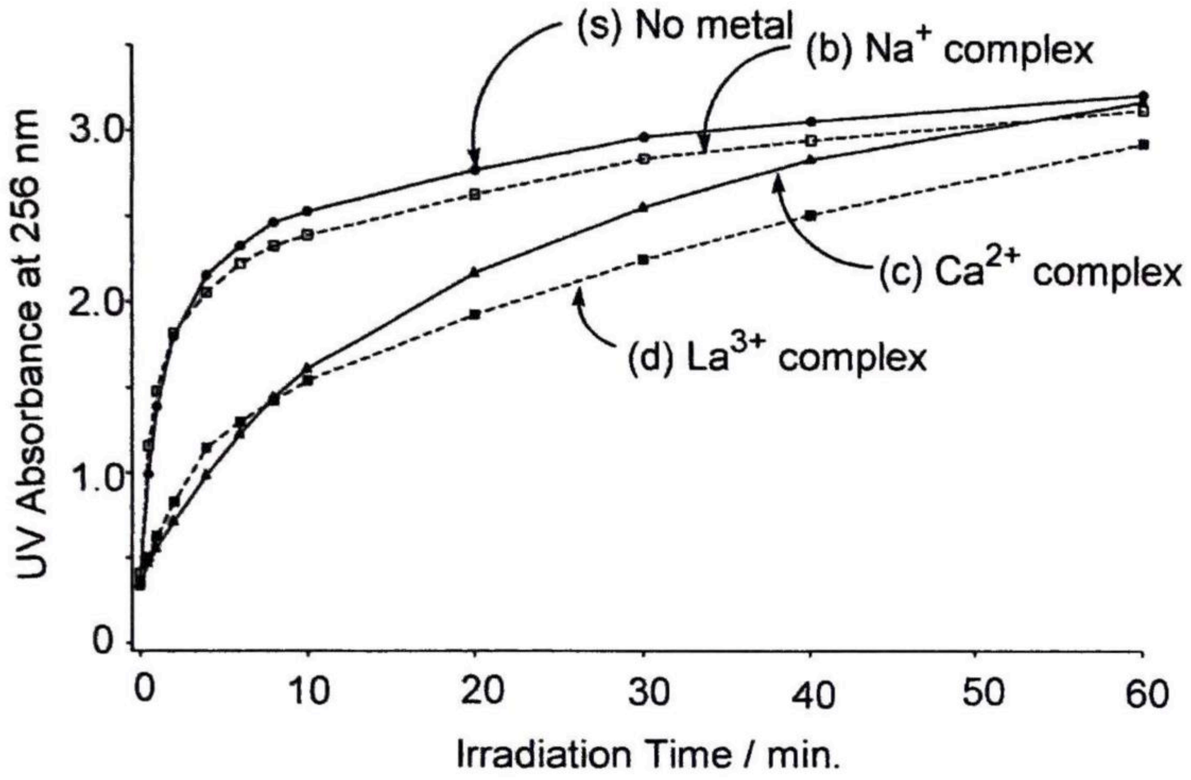


Figure 2-E. Metal Cation Effects on Time-Dependence Profiles of Photoreaction.

Conditions: Armed cyclen **1e** – Na^+ complex, 1.0×10^{-5}mol L^{-1}; (a) + cryptand [2.2.1], 4.0×10^{-5} mol L^{-1}; (b) itself; (c) + $Ca(CF_3SO_3)_2$, 2.0×10^{-5} mol L^{-1} and (d) + $La(CF_3SO_3)_3$, 2.0×10^{-5} mol L^{-1} in CH_3CN.

I also compared the yields of photoproducts after a short irradiation period (5 minutes), which were determined by HPLC analysis. Table 2-A summarizes the product distribution of the hexane-soluble fraction. Commercially available fluorene, 9-fluorenol, and fluorenone were used as authentic samples in HPLC analysis and product yields were estimated from their absorption coefficients.

Table 2-A. Photoreaction Products Distributions of Armed Cyclen **1e** and Its Metal Complexes.

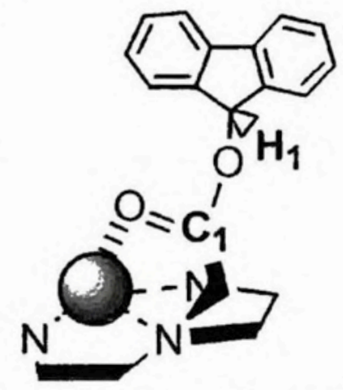
	Yield (%)[a]		
	fluorene derivatives	fluorenone	fluorenol
No metal	7 (± 1)	35 (± 3)	< 1
1e - Na^+	5 (± 1)	39 (± 4)	2 (± 1)
1e - Ca^{2+}	7 (± 1)	9 (± 1)	1 (± 1)
1e - La^{3+}	4 (± 1)	18 (± 2)	2 (± 1)

[a] Estimated from HPLC peak area and each absorption coefficient.

The production of fluorenone was significantly suppressed when Ca^{2+} and La^{3+} complexes were employed. Since 9-fluorenol and fluorene derivatives were similarly produced, α-cleavage on fluorenyl ester (see Figure 2-A) occurred less easily when Ca^{2+} or La^{3+} was coordinated *via* carbonyl oxygen atoms. Table 2-B shows the spectral data of Na^{+} complex, Ca^{2+} complex and free ligand. When Ca^{2+} was coordinated with carbonyl oxygen, the stretch vibration of C=O bond red-shifted: No metal, 1731 cm^{-1}; Na^{+} complex, 1727 cm^{-1}; Ca^{2+} complex, 1683 cm^{-1}. Since ^{13}C NMR signal for carbonyl carbon ($\mathbf{C_1}$) of Ca^{2+} complex was deshielded more effectively than that of Na^{+} complex, the coordinated Ca^{2+} was confirmed to pull electrons of the C=O bond more strongly than Na^{+}. Therefore, the C=O bond of fluorenyl ester moiety was weakened more by the Ca^{2+} complexation than by the Na^{+} complexation.

Table 2-B. Selected Spectral Data of Armed Cyclen **1e** and its Na^{+} and Ca^{2+} Complex.

	IR υ (C = O)	^{13}C NMR (C_1 / $CDCl_3$)	^{1}H NMR (H_1 / CD_3CN)
No metal	1731 cm^{-1}	172.3 ppm	6.75 ppm
Na^{+} complex	1727 cm^{-1}	175.6 ppm	6.94 ppm
Ca^{2+} complex	1683 cm^{-1}	177.2 ppm	7.06 ppm



Free ligand and Ca^{2+} complex were prepared *in situ*: Armed cyclen **1e** – NaCl complex + 4 Cryptand [2.2.1] and armed cyclen **1e** – NaCl complex + 2 $Ca(CF_3SO_3)_2$. The isolated armed cyclen **1e** – $Ca(CF_3SO_3)_2$ complex showed similar spectra as the mixture of armed cyclen **1e** – NaCl complex and $Ca(CF_3SO_3)_2$ in CH_3CN.

Since the photoreactivity of armed cyclen **1e** must be governed by the electronic nature of the ester moiety, metal complexation with armed cyclen **1e** can tune its photochemical reactivity. The employed Ca^{2+} has a similar ionic size as an Na^{+}, but its divalent charge state provided effective coordination with ester moiety and suppressed the photoreaction. α-Cleavage of the fluorenyl ester occurs mostly by n-π* excitation of carbonyl bond as shown in Figure 2-F.[13] Because the electron density of carbonyl oxygen in Ca^{2+} complex was lower than that in Na^{+} complex, its n-π* excitation would occur less easily. The resonance on O=C-O may further increase the strength of the O-C bond when Ca^{2+} is coordinated by carbonyl oxygen atoms.

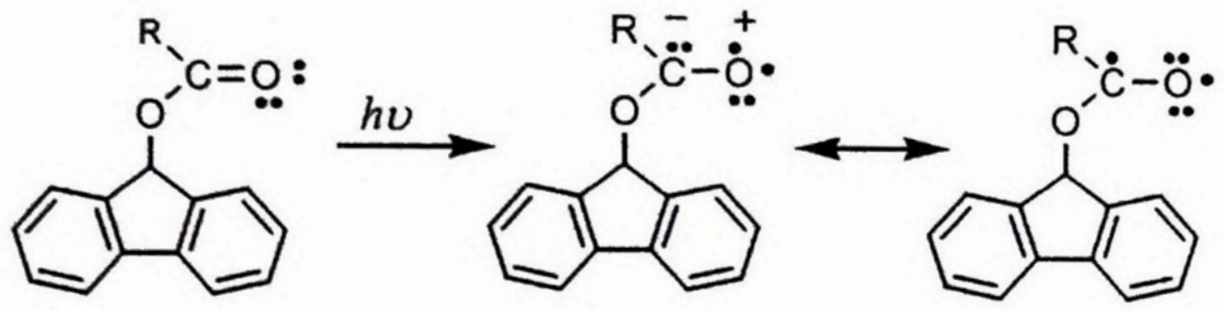


Figure 2-F. Carbonyl n-π^* Excitation of Fluorenyl Ester.

2-6. Visual Sensing of Ca^{2+} Concentration in Aqueous Samples

The concentration flux of Ca^{2+} inside and outside a living cell (10^{-3} M and 10^{-6} M) is finely tuned in order to control many important living processes. Many optical sensors for Ca^{2+} have been reported[14] due to the desire to understand the critical roles this cation plays in cells. The metal cation-controlled photoreaction of ester armed cyclen **1e** is applicable in the naked-eye detection of Ca^{2+} in aqueous samples, because fluorenone, the major photoproduct, possesses a green emission property.[9] As described above, the fluorenone production was greatly suppressed in the presence of Ca^{2+}. When an aqueous solution of Ca^{2+} was added to the CH_3CN solution of armed cyclen **1e** – Na^+ complex, the Ca^{2+} complex resulting from cation exchanging rarely produced fluorescent fluorenone upon 30 seconds of irradiation. Figure 2-G illustrates a series of pictures taken under the following conditions: after an aqueous $CaCl_2$ sample solution (0, 0.5, 1.0, 2.0, 3.0 or 4.0 mM, 0.05 mL) was added to an CH_3CN solution containing armed cyclen **1e** – NaCl complex (1.0, 2.5, 5.0 or 7.5 μ M, 10.0 mL), the mixtures were UV irradiated for 30 seconds. When the green fluorescence was strong, the presented colour appeared somewhat white in the picture.

If the aqueous sample (0.05 mL) containing 1mM of Ca^{2+} was added to a series of armed cyclen **1e** – NaCl complex solutions (1.0, 2.5, 5.0 and 7.5 μ M, 10.0 mL), the observed "green" fluorescence after 30 seconds of irradiation provided an good indication such as "off" "off" "on" and "on". Therefore, the Ca^{2+} concentration was determined as 1 mM by naked-eye tests.

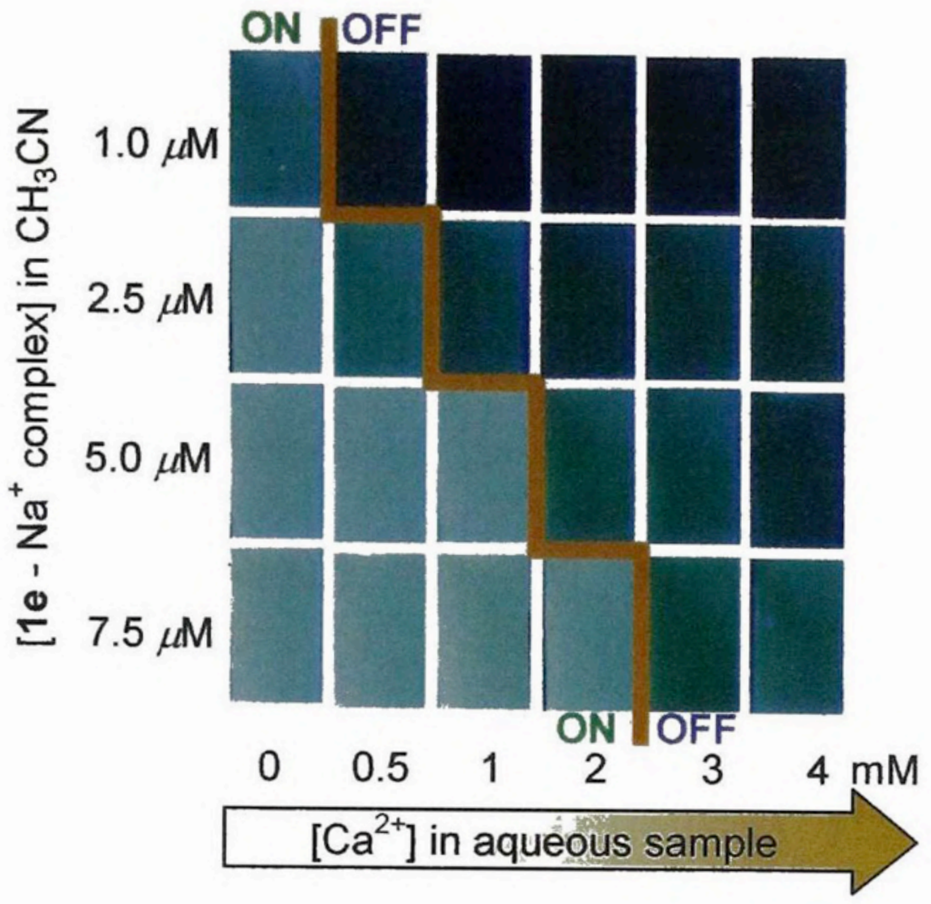


Figure 2-G. Colour Chart for Ca^{2+} Detection.

The photoreaction of armed cyclen **1e** was suppressed only by Ca^{2+} complexation even in the presence of other biological metal cations; Li^+, Na^+, K^+, Mg^{2+} and Zn^{2+}. Figure 2-H displays the UV absorbance changes at 256 nm before irradiation and after 1 minute of irradiation. Other metal cations (Li^+, Na^+, K^+, Mg^{2+} and Zn^{2+}) did not affect this photoreaction even if they were bound with cyclen ligand.

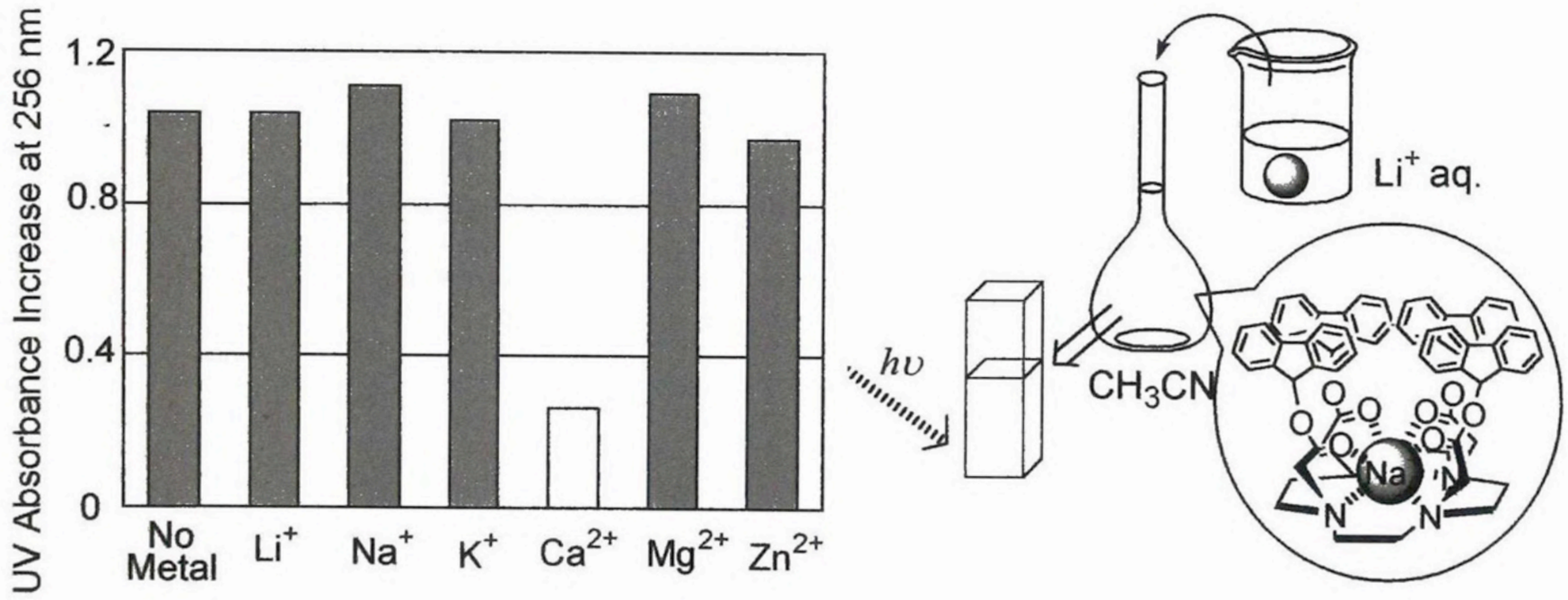


Figure 2-H. Differential UV Absorbance Increase in Single Metal Cation System.

A mixture solution of armed cyclen **1e** – NaCl complex (1.0×10^{-5} M) and each metal cation (5.0×10^{-5} M) in H_2O / CH_3CN, 1 / 100 was irradiated for 1 minute. These values were obtained by subtraction the absorbance at 256 nm before irradiation from the one after irradiation.

When equimolar Li^+, K^+, Mg^{2+} and Zn^{2+} were also added to the solution of Ca^{2+} complex ((c) in Figure 2-I), the photoreaction efficiency remained suppressed, indicating that these metal

cations did not compete with Ca^{2+} in the complexation process. Although armed cyclen **1e** formed a more stable complex with Ca^{2+} than Na^+, the addition of five equivalents of Na^+ slightly promoted the photoreaction ((e) in Figure 2-I), and ten equivalents of Na^+ interrupted this suppression more.[15] From these observations, some improvements are needed to use this armed cyclen type receptor in the sensing of biological targets.

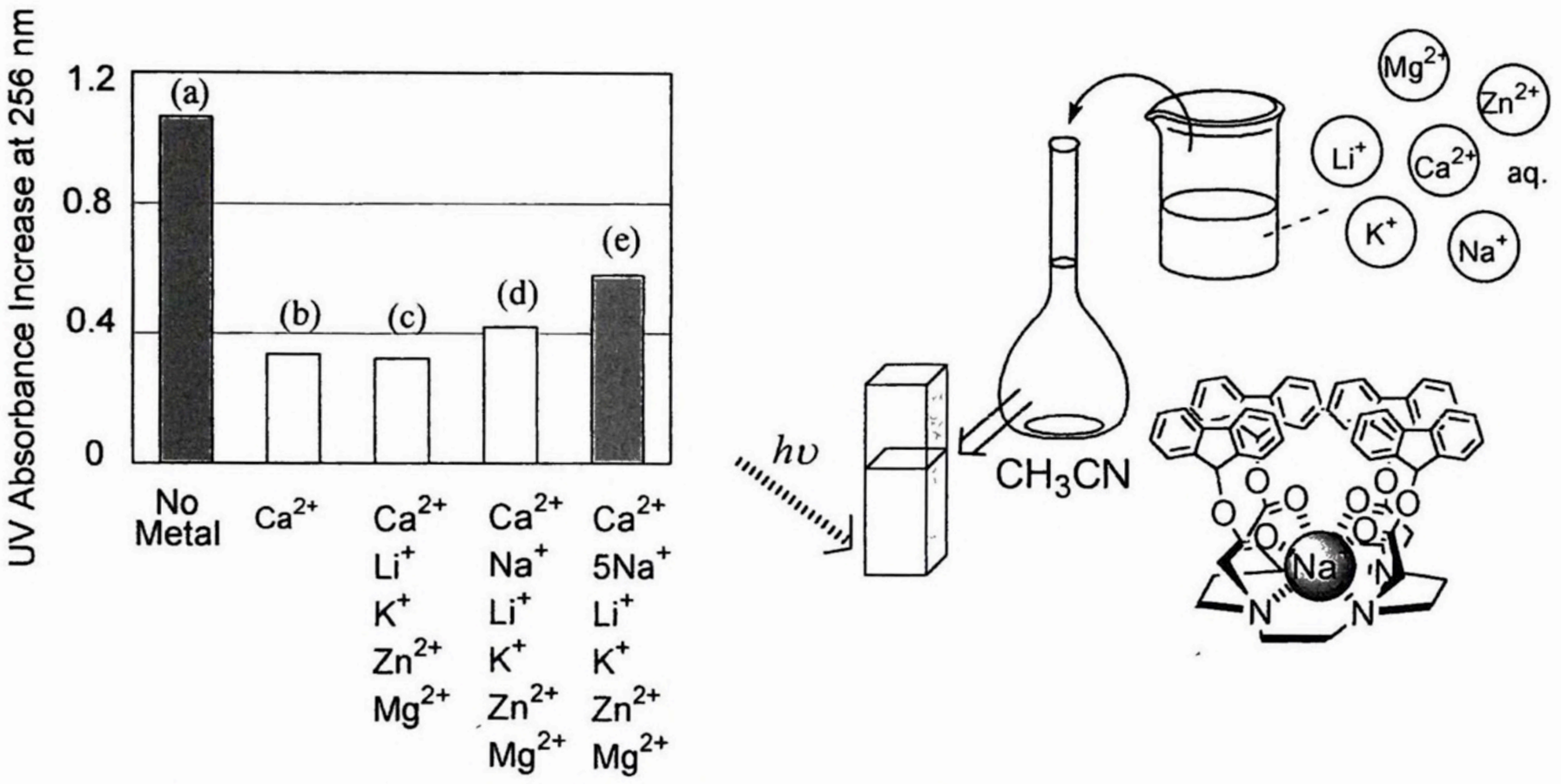


Figure 2-I. UV Absorbance Increases in Mixed Metal Cations System.

The solution (H_2O / CH_3CN, 1 / 100) of armed cyclen **1e** – NaCl complex (1.0×10^{-5} M) containing 2.5 equivalents of other metal cations (2.5×10^{-5} M, each) was irradiated for 1 minute. These values were obtained by subtraction the absorbance at 256 nm before irradiation from the one after irradiation.

Table 2-C. Metal Cation Concentrations in Intra- and Extra- Cell*

ion	$[M^{n+}]_{in}$ (mM)	$[M^{n+}]_{out}$ (mM)
Na^+	10	145
K^+	140	5
Mg^{2+}	30	1
Ca^{2+}	1	4
H^+	5×10^{-4}	5×10^{-4}
Cl^-	4	110

*Cowan J. A. In *Inorganic Biochemistry*: An Introduction, 2nd Ed.

2-7. Conclusion

Fluorenyl ester-armed cyclen **1e** reacted under UV irradiation to give fluorenone as a major photoproduct. This photoreaction was suppressed effectively by Ca^{2+} complexation with armed cyclen **1e**, while Na^+ and other metal cations did not affect it. Therefore, the Ca^{2+} concentration of the aqueous sample was detected by monitoring the green emission of the produced fluorenone. Equimolar Li^+, Na^+, K^+, Mg^{2+} and Zn^{2+} did not interfere with the Ca^{2+} effect on the photoreaction efficiency, though a high Na^+ concentration disturbed the Ca^{2+} detection. The photoreaction of armed cyclen offered the new capability of the naked-eye detection of Ca^{2+}, and it can be envisaged that further structural modifications of armed cyclen ligands could allow their use in biological samples.

2-8. Experimental Section

General Procedures

Isolation of Photoreaction Products of Armed Cyclen 1e – NaCl Complex. The CH_3CN solution of armed cyclen **1e** – NaCl complex (6.25×10^{-3} mol L^{-1}, 10 mL) was irradiated for 6 h by a TLC lamp. After removal of solvent, the residue was stirred with hexane. The hexane-soluble component including fluorene was separated by chromatography on silica gel, eluting with 10 % CH_2Cl_2 / hexane then 100 % CH_2Cl_2. 9-Florenol (6 %), fluorenone (35 %) and the mixture of fluorene and 9,9'-bifluorene (10 %) were isolated and characterized by ^1H NMR method. ESI-MS spectrum indicated that the hexane-insoluble component included partially decomposed armed cyclen derivatives.

HPLC Analysis of Photoreaction Products. The hexane soluble-fraction was analyzed by HPLC (Mightysil Si 60 150-4.6, Kanto Chemical Co., Inc.) using ethyl acetate/hexane (1/4), and fluorene, fluorenone and 9-fluorenol were eluted in this order, The yield of each product shown in Table 2-A was calculated from the HPLC peak area and absorption coefficient of each

compound.

UV Monitoring of Photoreaction of Armed Cyclen 1e – NaCl complex. An CH_3CN solution (1.0×10^{-5} mol L^{-1}, 2mL) of armed cyclen **1e** – NaCl complex or a mixture of armed cyclen **1e** – NaCl complex with two equivalents of $Ca(CF_3SO_3)_2$, two equivalents of $La(CF_3SO_3)_3$ or four equivalents of cryptand [2.2.1] **4** was irradiated in the quartz cell (1 cm × 1 cm) by UV lamp (λ = 254 nm, distance of 1cm). UV spectra (HITACHI U-3500L) were recorded after several minutes of irradiation, and absorbance changes at 256 nm were plotted against irradiation time.

Preparation of Colour Chart for Naked-Eye Detection. A series of armed cyclen **1e** – NaCl complex solutions were prepared (1.0, 2.5, 5.0 and 7.5 μ M in CH_3CN). The aqueous solutions of $CaCl_2$ were also prepared (0.5, 1.0, 2.0, 3.0 and 4.0 mM in H_2O). For the measurement of each combination, 0.05 mL of $CaCl_2$ aqueous solution was poured into the CH_3CN solution of armed cyclen **1e** – NaCl complex (10 mL). The resulting 24 combination of the samples (including the blanks, $CaCl_2$ 0mM) were stirred for 5 h. Each picture illustrated in Figure 2-G was taken after 30 seconds of irradiation.

Synthesis

1,4,7,10-Tetrakis[(fluorenyloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane 1e – NaCl complex was prepared in Chapter 1.

1,4,7,10-Tetrakis[(fluorenyloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane 1e - $Ca(CF_3SO_3)_2$ complex: Armed cyclen **1e** – NaCl complex (220 mg, 0.20 mmol) and $Ca(CF_3SO_3)_2$ (110 mg, 0.33 mmol) were dissolved in CH_3CN and stirred overnight. The solvent was evaporated and the CH_2Cl_2 insoluble-component was filtered off. After removal of the solvent, the residue was recrystallized from hexane/CH_2Cl_2. yield, 31%: mp. 209 - 211 °C (decomposition): IR (neat) υ 1683 cm^{-1}; ESI-MS (CH_3CN) *m/z* 550 (M^{2+}), 1250 ($M+CF_3SO_3^+$); ^1H NMR (CD_3CN) δ 2.61 (br d, 4H), 2.81 (br d, 4H), 3.07 (br s, 4H), 3.42 (br s, 4H), 3.68 (br d,

4H), 4.27 (br d, 4H), 6.27 (br s, 4H), 7.06 (s, 4H), 7.11 (br s, 4H), 7.34 (br s, 4H), 7.49 (br s, 4H), 7.64 (br s, 4H), 7.73 (br s, 8H), 8.05 (br s, 4H); ^{13}C NMR (CD_3CN) δ 48.86, 54.29, 57.39, 79.37, 121.61, 126.75, 129.20, 131.33, 140.06, 141.30, 181.14. Anal. Calcd for $C_{68}H_{60}N_4O_8-Ca(CF_3SO_3)_2 \cdot 2.5H_2O$: C, 58.20; H, 4.54; N, 3.88. Found: C, 58.15; H, 4.25; N, 3.98.

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15. This photoreaction suppression phenomenon was tested with the sample including Na^+ and Ca^{2+} adjusted to the concentration of intra-cell. The mixture of the CH_3CN solution of armed cyclen **1e** – NaCl complex (2.5 μM, 10 mL) and the aqueous solution of Na^+ and Ca^{2+} (10 mM and 1 mM, 0.05 mL) was stirred overnight and then the solution was irradiated for 1 minute. The absorbance increase at 256 nm was 0.33 for blank (added 0.05 mL of water) and 0.22 for this test sample.

Chapter 3. Chirality Recognition with the Self-Aggregate of Helical Ester-Armed Cyclen - Metal Complex

3-1. Introduction

Various types of metal complexes have recently been developed as effective building blocks for supramolecular architectures, which have highly organized structures and sophisticated functions.[1] The helical metal complexes, so-called "helicates", with one or more coordinating ligands, are the typical examples. They have well-defined coordination topology and high stability even in solution. In addition to various oligopyridine ligand metal complexes,[2] a series of hexacoordinated transition metal complexes,[3] and octa- / nona-coordinated lanthanide complexes[4] have received considerable attention as functional helicates.

As I have demonstrated in the previous chapters, armed cyclens formed helicated complexes with alkali and alkaline earth metal cations. Their helical structures were constructed by stereochemical arrangement of four sidearms and kept in solutions (see Chapters 1 and 2).[5] When chiral centres were introduced into the armed cyclen system, the four sidearms stood up in the same direction above the cyclen plane and were arranged in an asymmetrically quadruple helical fashion.[6,7] Wainwright *et al.* characterized Cd^{2+} complex with chiral alcohol-armed cyclens and observed stereoselective ternary complexation with D- and L-histidinate anions in DMSO solution.[6(a),(b)] Parker *et al.* recently employed Yb^{3+} complexes with chiral, heptadentate amide-armed cyclen in the enantiomer recognition of lactate and alaninate anions in aqueous solutions.[7(c),(d)]

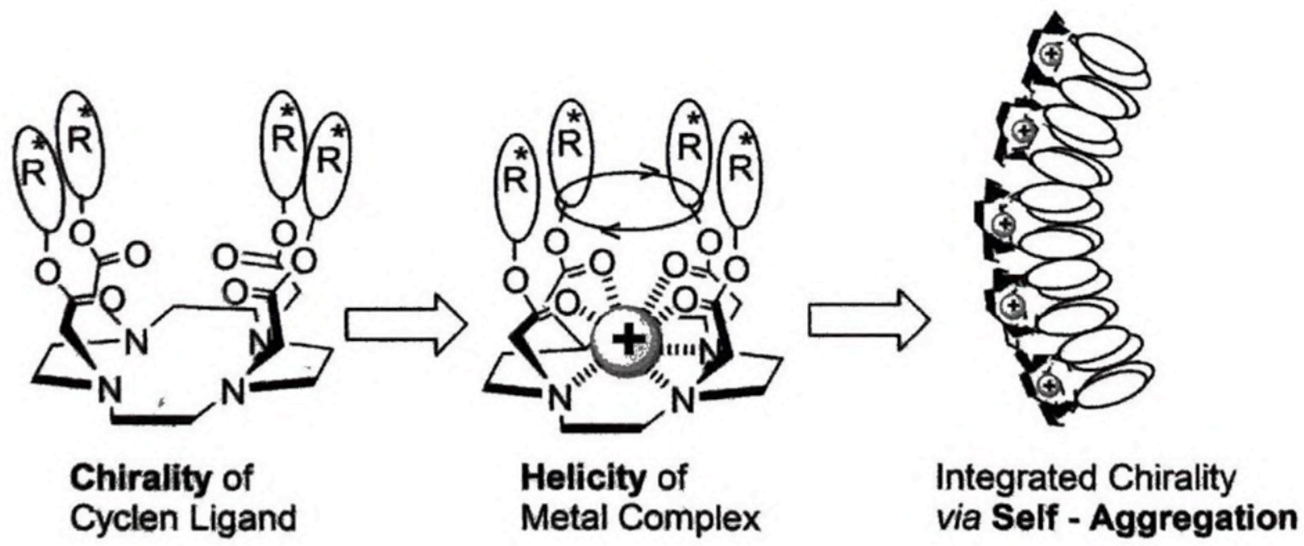
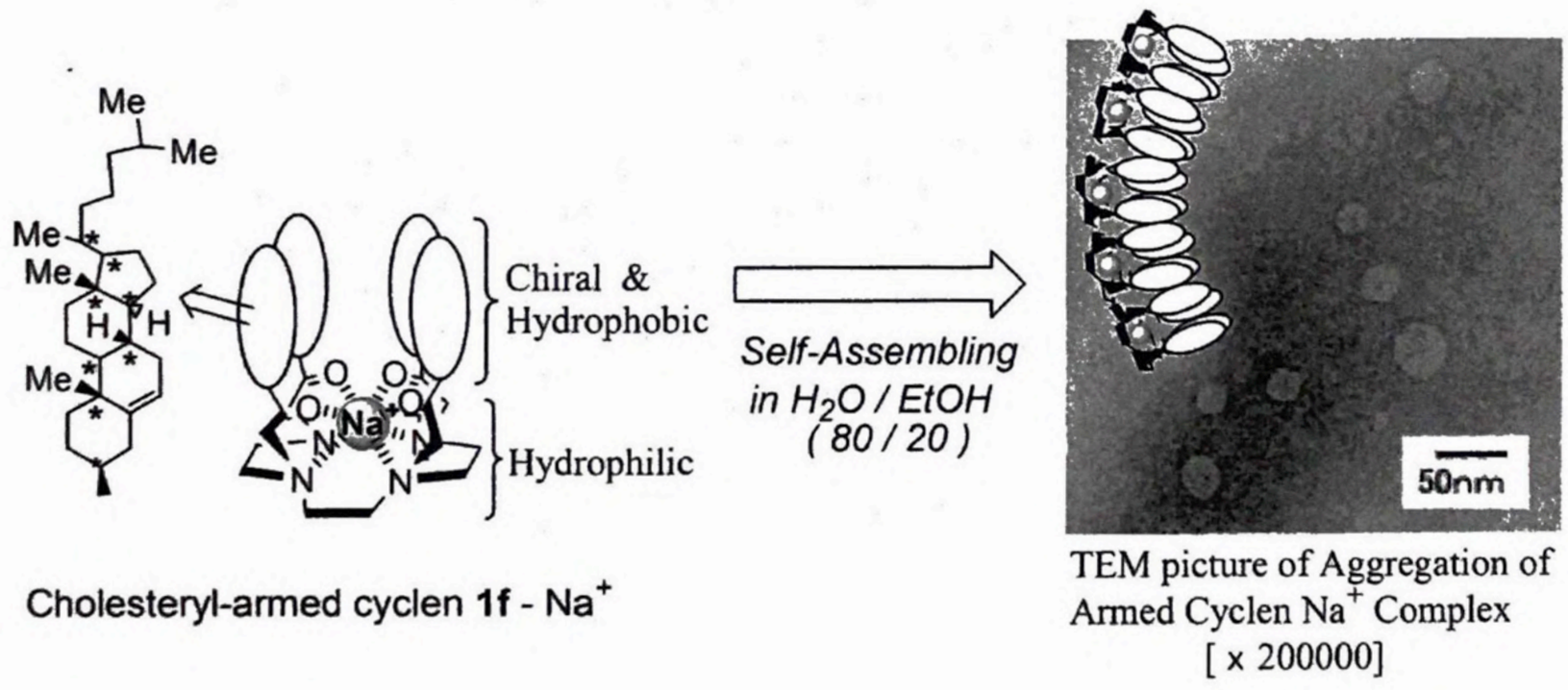


Figure 3-A. Integration of Chirality with Armed Cyclen - Metal Complexes.

Recently, we reported that cholesteryl ester-armed cyclen **1f** - Na^+ complex exhibited chiral and amphiphilic natures, and spontaneously formed a stable self-aggregate in an aqueous solution.[8] In this aggregate, the Na^+ complexes were arrayed on a supramolecular scale and the chirality was effectively integrated. Figure 3-A schematically shows the chirality integration of armed cyclen **1f** - metal complexes: (1) chirality of cholesteryl moieties; (2) helicity of asymmetrically twisted octacoordinated metal complex; and (3) integrated chirality of highly structured metal complexes on a supramolecular aggregation.[9] Because this aggregate was made of positively charged Na^+ complexes, replacement of Na^+ with Ca^{2+} or Y^{3+} might finely control the chiral environments of the self-aggregates. In this chapter, I compared the self-aggregate properties of several metal complexes with cholesteryl-armed cyclen **1f**, which provided unique chiral recognition properties upon self-assembly. The aggregate was confirmed to offer D / L chirality recognition of dansyl amino acid anions when Na^+, Ca^{2+} or Y^{3+} was incorporated.[8(c)] Δ / Λ Chirality induction of racemic octacoordinated Na^+ complex was also observed with the aggregate.[8(b)] The self-aggregation of armed cyclen **1f** - Na^+ complex offered unique integration of chirality at a supramolecular level for guests with different driving forces.



Cholesteryl-armed cyclen **1f** - Na^+

TEM picture of Aggregation of Armed Cyclen Na^+ Complex [x 200000]

Figure 3-B. Self-Aggregate of Cholesteryl Armed Cyclen **1f** – Na^+ Complex.

3-2. Metal Complexes of Cholesteryl-Armed Cyclen and Their Aggregates

Cholesteryl-armed cyclen **1f** - NaCl complex spontaneously formed a stable self-aggregate having a supramolecular array of chiral Na^+ complex in an aqueous ethanol solution (H_2O / EtOH = 80 / 20, *v* / *v*)(Figure 3-B). The critical aggregation concentration (c.a.c.) was estimated as 4.0×10^{-6} mol L^{-1} by the fluorescence probe method.[10]

Cholesteryl-armed cyclen **1f** - $Na(CF_3SO_3)$, $Ca(CF_3SO_3)_2$ and $Y(CF_3SO_3)_3$ complexes were prepared by mixing each metal trifluoromethanesulfonate salt and armed cyclen **1f**.[8(c)] NMR spectra of the resulting $Na(CF_3SO_3)$ and $Ca(CF_3SO_3)_2$ complexes clearly indicated octacoordinated complex formation. On the other hand, the NMR spectrum of the Y^{3+} complex was somewhat complicated, though the peaks for free ligand protons disappeared. Since the lanthanide complexation of armed cyclen is extremely slow,[6(a)] it may still be in process even after 6 h reflux. The formation of Na^+ and Ca^{2+} complexes were also confirmed by ESI-MS spectra. They similarly formed aggregates in aqueous ethanol solutions, when they were dispersed at 3.3×10^{-5}mol L^{-1}. Dynamic light scattering experiments showed that the resulting self-aggregates had mean hydrodynamic radii of 58 nm for Na^+ complex,[11] 112 nm for Ca^{2+} complex and 29 nm for Y^{3+} complex. Since these three cations have similar ionic radii (Na^+, 1.18 Å; Ca^{2+}, 1.12 Å; Y^{3+}, 1.02 Å for octacoordination),[12] the charge state of the metal centre was recognized as an important factor in the self-aggregation process.

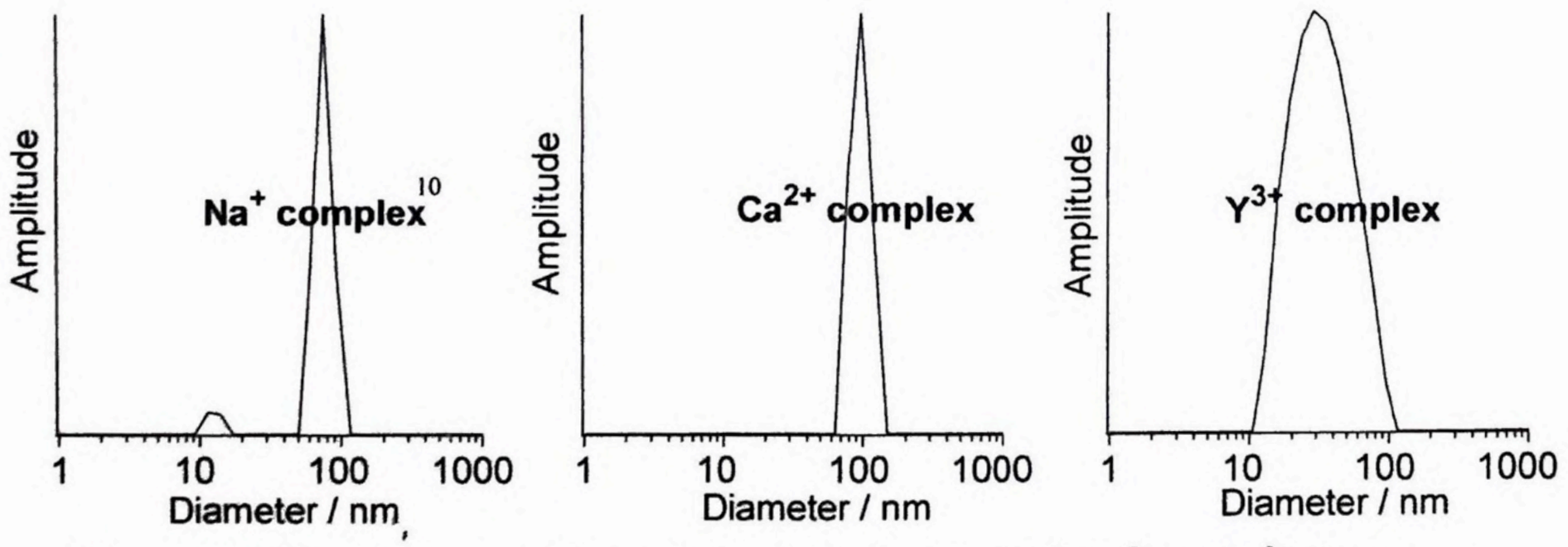
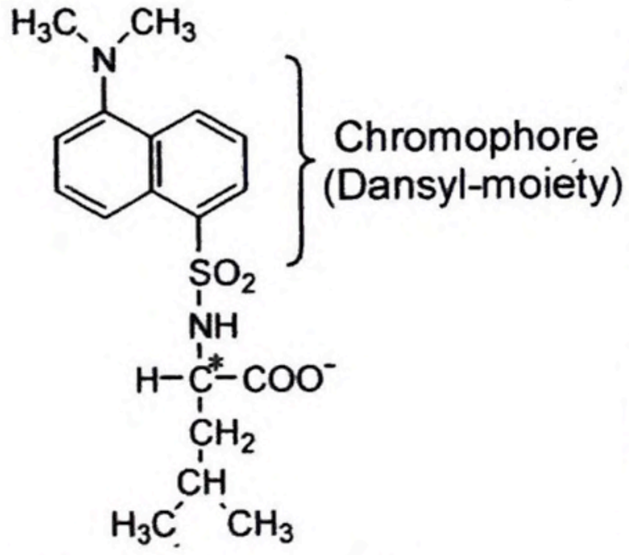


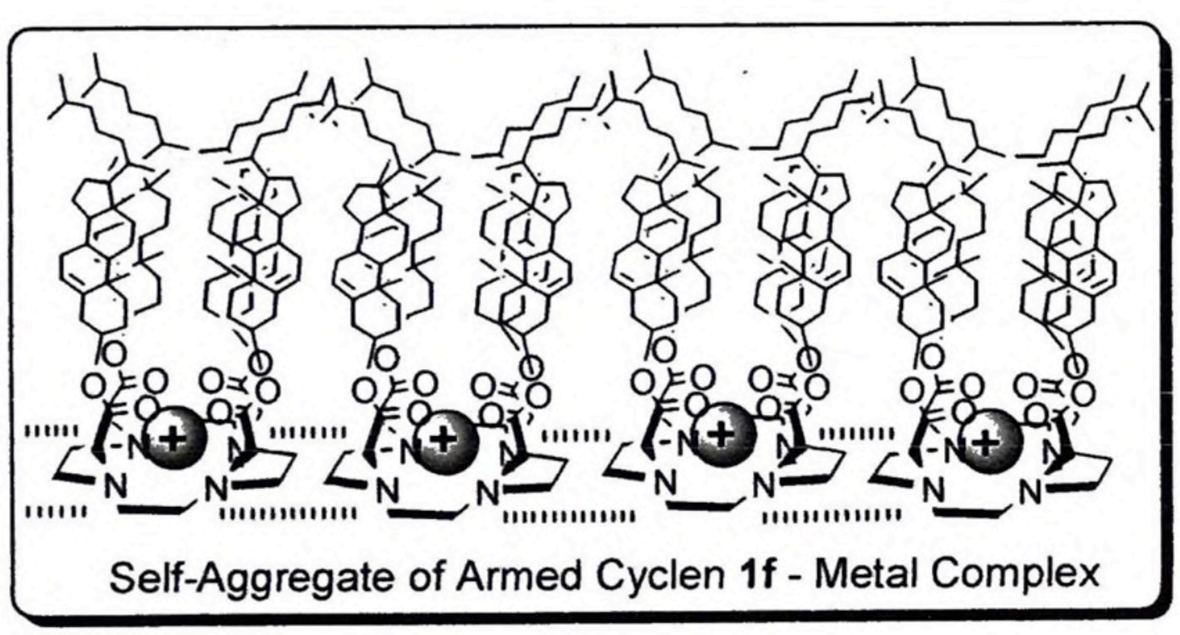
Figure 3-C. Self-Aggregate Sizes of Armed Cyclen **1f** – Na^+, Ca^{2+} and Y^{3+} Complexes.

Determined by dynamic light scattering method at 15 °C. Conditions: Each metal complex were dispersed at 3.3×10^{-5} mol L^{-1} in H_2O / EtOH (80 / 20, *v* / *v*, pH = 7.2).

Cholesteryl-armed cyclen **1f** - NaCl complex aggregates nicely accommodated dansyl-amino acid anions and exhibited characteristic chiral recognition.[8(a)(c), 10] As widely used in biological and analytical processes, the fluorescence intensity and maximum wavelength of the dansyl amino acids provides good indications of the microenvironments. When an aqueous ethanol solution of dansyl-L-leucine anion was added to the solution of the aggregate, the fluorescence maximum of dansyl-chromophore shifted from 538 nm to 507 nm and the fluorescence intensity showed a 6.5-fold enhancement. These results clearly indicate that the dansyl-moiety locates in the hydrophobic domain of the self-aggregate. Because one of the main driving forces for this process should be the electrostatic force between cationic self-aggregate and anionic dansyl-amino acids, the nature of the cyclen metal centre may largely influence the recognition behaviours as well as structural characteristics of amino acid guests.



Dansyl-Leucine Anion


Self-Aggregate of Armed Cyclen **1f** - Metal Complex

3-3. D / L Chirality Recognition of Amino Acid Anions in Aqueous Media: Fluorescence Experiments

In earlier reports,[8(a),10] we demonstrated that the aggregate of cholesteryl-armed cyclen **1f** – NaCl complex offered chiral recognition of D / L dansyl amino acid anions. Figure 3-D compares the enhanced fluorescence spectral profiles of dansyl-D- and L-leucine anions with self-aggregates of armed cyclen **1f** - Na^+, Ca^{2+} and Y^{3+} complexes. Although only weak fluorescence signals of dansyl-D- and L-leucine were observed in the absence of aggregates ((c)

in Figure 3-D), the fluorescence based on dansyl-D- and L-leucine were clearly enhanced in the presence of aggregates ((a) and (b) in Figure 3-D). Among the three self-aggregate I prepared in foregoing section, armed cyclen **1f** - Na^+ complex exhibited the largest fluorescence enhancement for the dansyl-L-leucine anion: 6.1 times for the Na^+ complex; 2.5 times for the Ca^{2+} complex; and 3.6 times for the Y^{3+} complex. The enantiomer-selective fluorescence behaviours were also observed in these helicate aggregates, and Na^+ complex gave a greater difference between D- and L-enantiomers of the guest than Ca^{2+} and Y^{3+} complexes.

Thus, the self-aggregate of armed cyclen **1f** – Na^+ complex provided the most suitable chiral environment for recognition of dansyl-amino acid anions in the aqueous media.

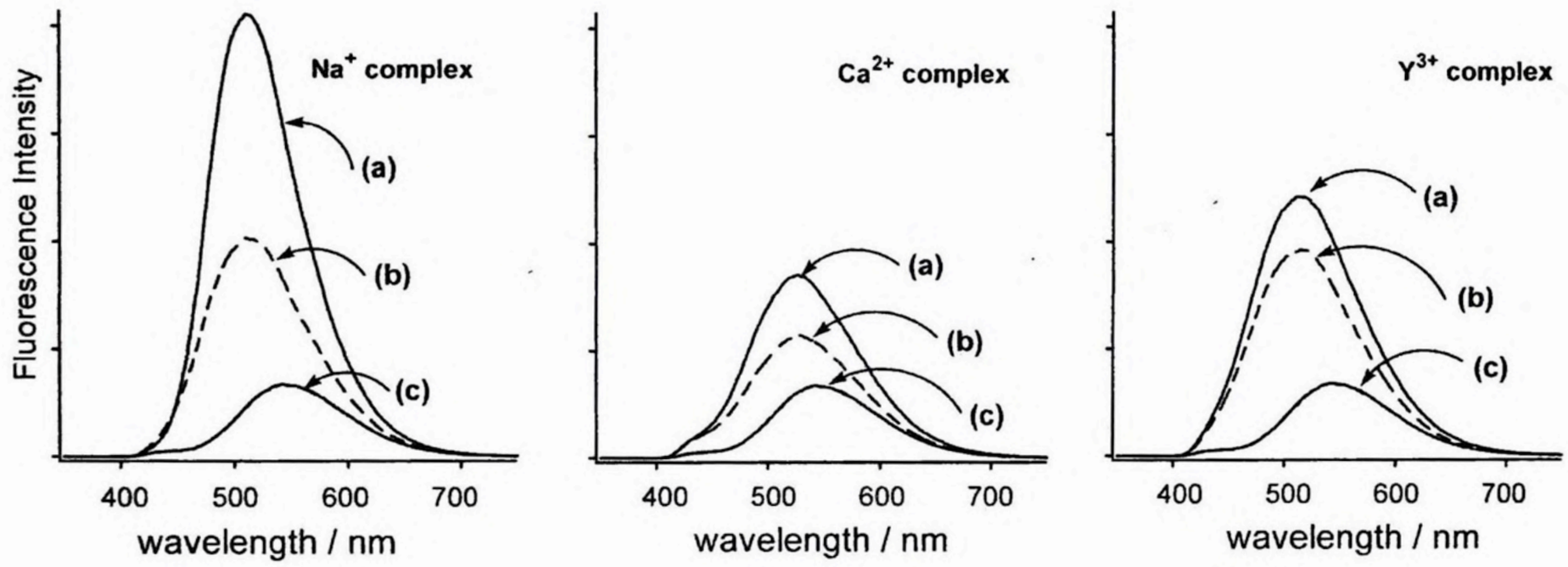


Figure 3-D. Fluorescence Enhancements of Dansyl-L- and D-Leucine Anions with Armed Cyclen **1f** - Metal Complex Aggregates.

(a) Dansyl-L-leucine (bound), (b) Dansyl-D-leucine (bound), (c) Dansyl-L- and D-leucine (free). Conditions: Armed cyclen **1f** - metal complex, 3.3×10^{-5} mol L^{-1}; Dansyl–leucine, 1.0×10^{-6} mol L^{-1}; in H_2O / EtOH (80 / 20, *v* / *v*); pH=7.2.

3-4. Chirality Induction with Self-Aggregate of Cholesteryl-Armed Cyclen - Na^+ Complex: CD Experiments

Circular dichroism (CD) spectroscopy usually gives stereochemical information about substrates that have both chromophore and chirality,[13] and the matter in which a chromophore and a chirality are related non-covalently is still detectable.[14] The self-aggregate of armed cyclen **1f** - NaCl complex provided a specific microenvironment for chirality induction of

achiral dansyl-glycine anion.[8(a)] Dansyl-glycine anion was incorporated in the self-aggregate and then exhibited a negative CD signal around 260 nm (Figure 3-E). The direction of the CD signal indicated that an anti-clockwise conformation of dansyl-glycine was more stable than a clock-wise one, when this achiral anion was incorporated in the self-aggregate.[15]

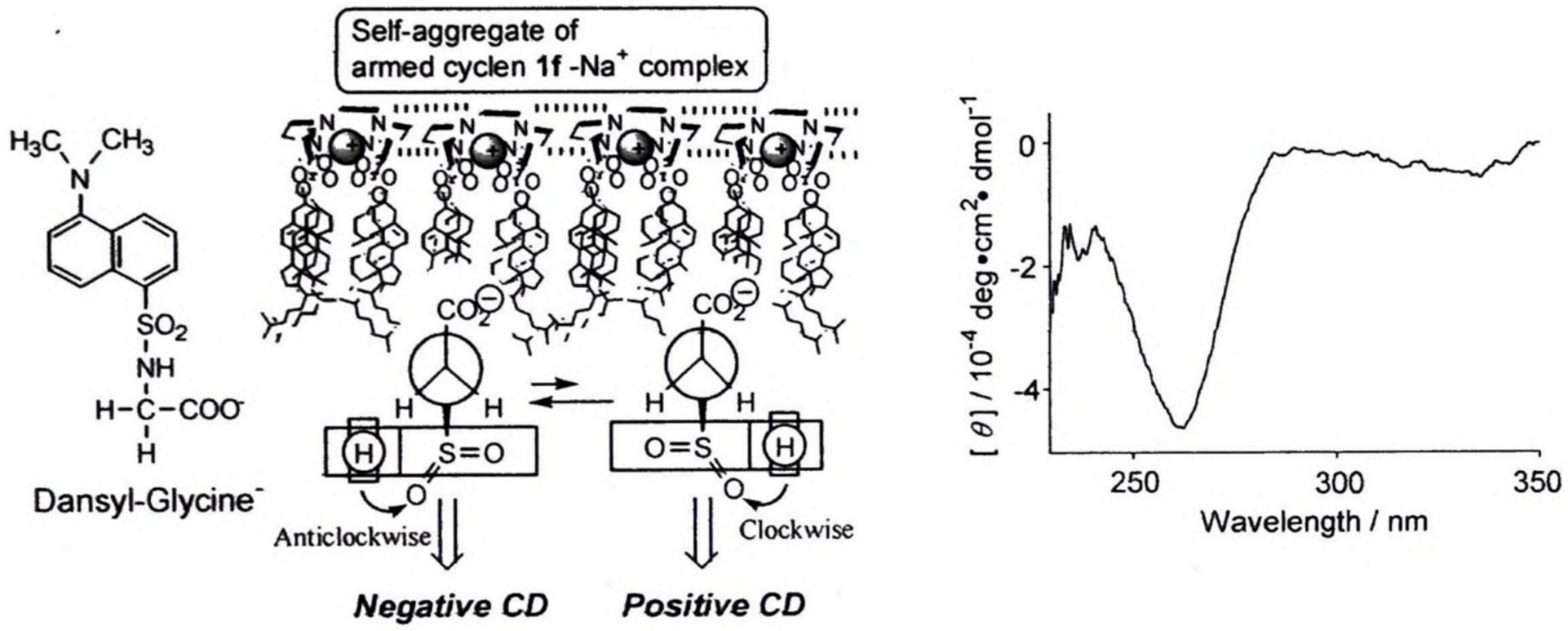


Figure 3-E. Induced CD Spectrum of Dansyl-Glycine Anion.

Conditions: Armed cyclen **1f** – Na^+ complex, 3.0×10^{-5} mol L^{-1}; Dansyl–glycine, 5.0×10^{-5} mol L^{-1}; in H_2O / EtOH (80 / 20, *v* / *v*); pH=7.2.

Racemic ester-armed cyclen **1e** – Na^+ complex was incorporated in the self-aggregate of the cationic armed cyclen **1f** – NaCl complex, though the protonated dansyl-ethylendiamine substance was rarely accommodated. The guest armed cyclen **1e** - Na^+ complex itself gave no CD signal ((a) in Figure 3-F), and the aggregate of chiral armed cyclen **1f** – Na^+ complex also did not show a CD signal because it had no chromophore ((b) in Figure 3-F). When this aggregate was mixed with cationic armed cyclen **1e** - Na^+ complex in aqueous media, an induced CD signal was observed around 280 nm, corresponding to the absorption of the fluorenyl group on the cyclen sidearms ((c) in Figure 3-F). Thus, armed cyclen **1e** – Na^+ complex was accommodated in chiral aggregate of armed cyclen **1f** – Na^+ complex, and fixed in an asymmetric fashion.

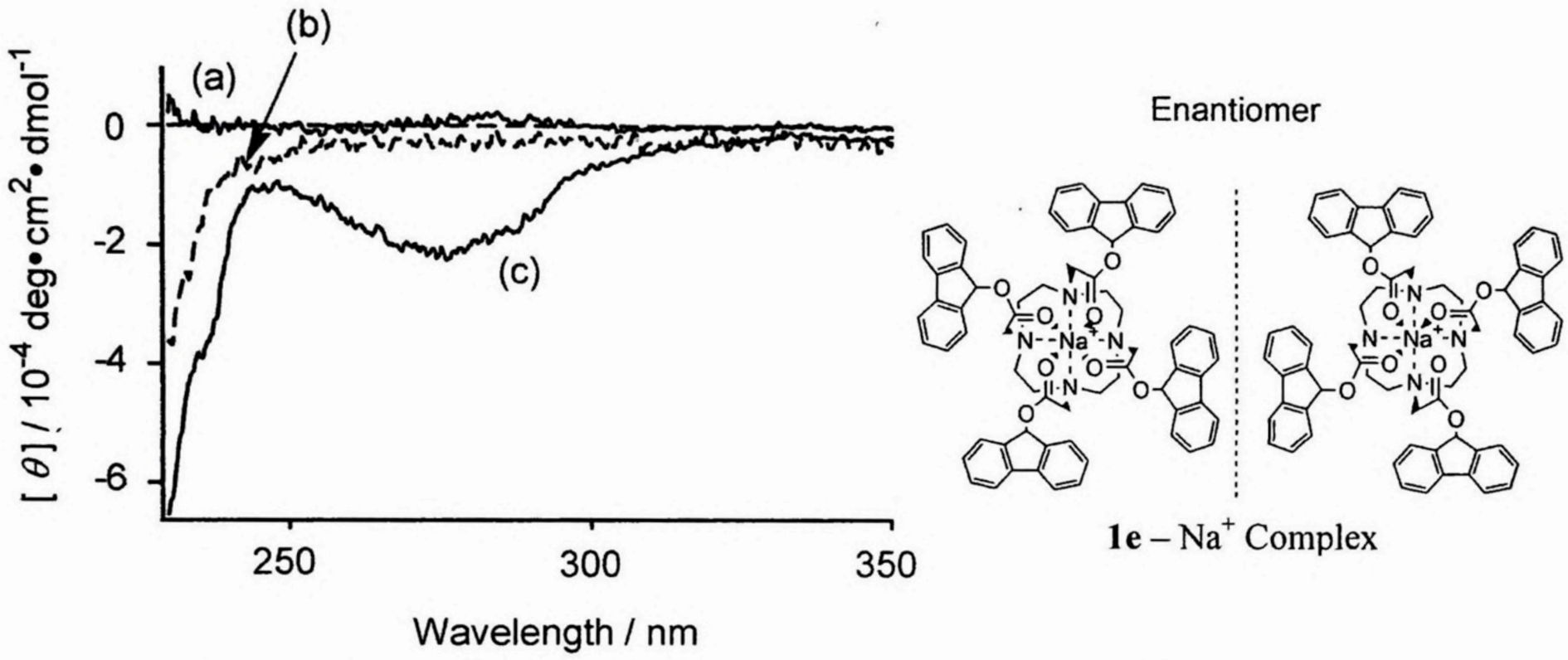


Figure 3-F. Induced CD Spectrum of Armed Cyclen **1e** – NaCl Complex.

(a) Armed cyclen **1e** – NaCl complex : 2.0×10^{-5} mol L^{-1}, (b) Self-aggregate of armed cyclen **1f** – NaCl complex: 1.0×10^{-4} mol L^{-1}, (c) Armed cyclen **1e** – NaCl complex: 2.0×10^{-5} mol L^{-1} in the solution of self-aggregate: 1.0×10^{-4} mol L^{-1}, in H_2O / EtOH (80 / 20, *v* / *v*).

With an increase of the ethanol content in the aqueous solution, the intensity of the observed CD signal rapidly decreased and no induced CD signal at all was observed in the 30% ethanol aqueous solution. Since the armed cyclen **1e** - Na^+ complex also had hydrophobic sidearms, it formed a self-aggregate in a 20 % aqueous ethanol solution.[16] In a 30% ethanol aqueous solution, cholesteryl-armed cyclen **1f** - Na^+ complex still formed an aggregate[8(c)] but armed cyclen **1e** - Na^+ complex exhibited as a monomolecular form. Thus, the hydrophobic interaction between fluorenyl-moiety and self-aggregate of armed cyclen **1f** – Na^+ complex was significantly involved in this recognition process.

CD spectra of chiral armed cyclen **1c**(*R*) – Na^+ and **1c**(*S*) – Na^+ complex were recorded for comparison of the CD direction, which showed symmetric CD signals with positive and negative signs. Because the Δ and Λ conformations of these armed cyclens complex have a diastereomeric relationship,[17] the one conformer should be more stable than another. In fact, armed cyclen **1c**(*S*) – Na^+ complex has Λ-form preferably in the crystal (see Chapter 1, Figure 1-E).

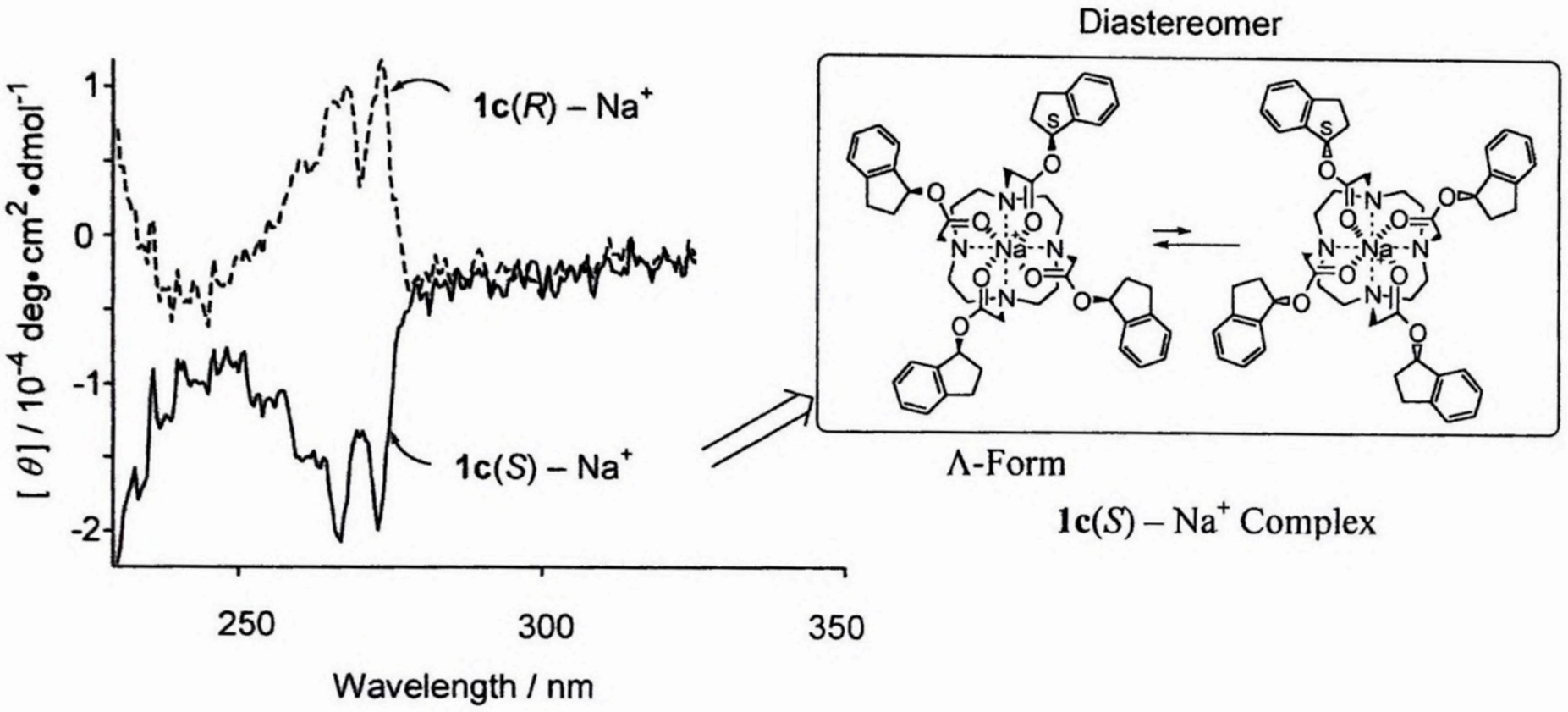
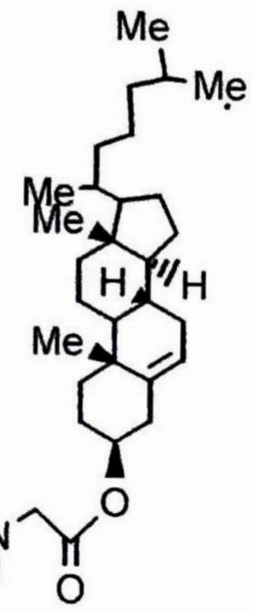


Figure 3-G. CD Spectra of Chiral Armed Cyclen **1c**(*R*) and **1c**(*S*) – Na^+ Complexes.

Condition: Armed cyclen **1c**(*R*) – NaCl complex, 2.0×10^{-5} mol L^{-1}; armed cyclen **1c**(*S*) – NaCl complex, 2.0×10^{-5} mol L^{-1} in H_2O / EtOH (80 / 20, *v* / *v*).

Armed cyclen **1e** – Na^+ complex exhibited a negative CD signal around 280 nm in the presence of the self-aggregate of armed cyclen **1f** – Na^+ complex. Since armed cyclen **1c**(*S*) – Na^+ complex was confirmed to have an Λ-form preference from crystal structure determination, the negative CD signal observed in the solution seemed to signify the Λ-form of armed cyclen - metal complex. This probably indicates that armed cyclen **1e** – Na^+ complex was fixed as Λ-form conformer in the self-aggregate of armed cyclen **1f** – Na^+ complex, though the helicity of armed cyclen **1f** – Na^+ complex was still not clear.

Cholesteryl morpholine derivative **7** was examined for comparison to study the importance of the chiral supramolecular array of armed cyclen **1f** – Na^+ complex. This formed a water-soluble self-aggregate, but rarely offered a CD signal upon the guest armed cyclen **1e** – Na^+ complex accommodation. Since albumin[18] and γ-cyclodextrin[19] did not induce a CD signal with armed cyclen **1e** - Na^+ complex, the chirality induction of this type only occurs in the supramolecular aggregate of armed cyclen - metal complex.



Morpholine derivative **7**

3-5. Conclusion

Cholesteryl ester-armed cyclen **1f** formed quadruple helical complexes in which Na^+, Ca^{2+} and Y^{3+} were octacoordinated in solution states. Their chiral amphiphilic natures gave stable self-aggregates in aqueous solutions, and offered characteristic chirality induction phenomena. They nicely accommodated dansyl-leucine anions in their chiral domains and expressed chirality preference for L-isomer.[8(c),10] The largest enantiomer-dependent fluorescence enhancement was observed with the aggregate of armed cyclen **1f** – Na^+ complex. This stable self-aggregate could fix the stereochemistry (Δ- or Λ-) of racemic armed cyclen **1e** – Na^+ complex. These observations clearly demonstrated that the self-aggregate of cholesteryl ester-armed cyclen **1f** - metal complexes provided chiral environments for both anionic organic guests and cationic armed cyclen - metal complex. Since armed cyclen - metal complexes worked well as supramolecular building blocks, their characteristic coordination chemistry can provide wide variations in the development of supramolecular functional systems.

3-6. Experimental Section

General Procedures

Preparation of Self-Aggregates. An ethanol solution of cholesteryl-armed cyclen **1f** -

NaCl complex (5.0×10^{-4} mol L^{-1}) was diluted with Bis-Tris-HCl buffer solution (6.3×10^{-3} mol L^{-1}, pH = 7.2). The resulting aqueous solution (1.0×10^{-4} mol L^{-1}, H_2O / EtOH = 80 / 20, *v* / *v*) was spectroscopically clear and gave no precipitate for several days. $Na(CF_3SO_3)$, $Ca(CF_3SO_3)_2$ and $Y(CF_3SO_3)_3$ complexes with armed cyclen **1f** were prepared *in situ*. When 1.5 equivalents of $Ca(CF_3SO_3)_2$ were typically mixed with free armed cyclen **1f** in CH_3CN / $CHCl_3$, ESI-MS and NMR measurements confirmed a cation complexation process. After evaporation, the EtOH solution of the complex was diluted with an aqueous buffer solution. These metal trifluoromethanesulfonate complexes also formed stable aggregates in Bis-Tris-HCl buffer solutions (3.3×10^{-5} mol L^{-1}, pH = 7.2, H_2O / EtOH = 80 / 20, *v* / *v*).

Light Scattering Experiments. The particle sizes of self-aggregates were determined by dynamic light scattering (Malvern HPPS). The resulting clear solutions prepared above were measured at 15 °C, and obtained the distributions of their average particle sizes.

Fluorescence Experiments. Fluorescence measurements (Perkin Elmer LS-50B) were usually carried out in a 20 % ethanol aqueous solution (Bis-Tris-HCl buffer solution: 6.3×10^{-3} mol L^{-1}; pH = 7.2). The initial concentrations of self-aggregates and guest dansyl-leucine anions are shown in each Figure. The fluorescence spectra were recorded upon excitation at 327 nm.

CD Experiments. Fluorenyl ester–armed cyclen **1e** – Na^+ complex (2.0×10^{-5} mol L^{-1}) was used for CD measurement (Jasco J-720) in the ethanol 20 % aqueous solution of cholesteryl ester–armed cyclen **1f** – Na^+ complex (1.0×10^{-4} mol L^{-1}). When other host molecules were used instead of cholesteryl ester–armed cyclen **1f** – Na^+ complex, the concentration was adjusted to 3.3×10^{-5} mol L^{-1} for albumin, 1.0×10^{-4} mol L^{-1} for *γ*-cyclodextrin and 4.0×10^{-4} mol L^{-1} for cholesteryl derivative 7.

Synthesis

1,4,7,10-Tetrakis[(cholesteryloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane 1f

was prepared in our report.[8(c)]

1,4,7,10-Tetrakis[(cholesteryloxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane

1f – NaCl complex: This was prepared in Chapter 1.

1,4,7,10-Tetrakis{[(*R*)-1-indanyloxycarbonyl]methyl}-1,4,7,10-tetraazacyclododecane

1c(*R*) – NaCl complex: This was prepared in Chapter 1.

1,4,7,10-Tetrakis{[(*S*)-1-indanyloxycarbonyl]methyl}-1,4,7,10-tetraazacyclododecane

1c(*S*)– NaCl complex: This was prepared in Chapter 1.

3-7. References and Notes

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