Lanthanide Complexes in Molecular Recognition and Chirality Sensing of Biological Substrates

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Contents

1. Introduction

Lanthanides occupy unique positions in the periodic table, which correspond to the first period of f-block elements from lanthanum to lutetium, and their trivalent cations possess characteristic $4f^n$ open-shell configurations ($n = 0-14$).[1−4] They exhibit interesting variability of the coordination characteristics across the lanthanide series, though the variability is much less pronounced than that found among transition-metal ions. The effective ionic radii of the trivalent lanthanide cations typically decrease in the order of atomic numbers.[5] Since those reported in the octacoordination complexes range between 0.98 and 1.16 Å, we can pick the most suitable one from 15 kinds of lanthanide cations and use it in the synthesis of tailor-made lanthanide complex. Several types of lanthanide complexes have successfully been developed as functional molecular devices in the fields of chemistry, biology, medicine, and materials science. For example, (a) luminescent sensors and light converters,[6−9] (b) nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) probes,[10−13] and (c) practical catalysts in organic and biological reactions[14,15] have been presented. These examples offer a possibility that precise molecular architecture can lead to development of more intelligent lanthanide complexes in which the geometry and property of the complex as well as its environment are well programmed to generate the up-graded functionality.

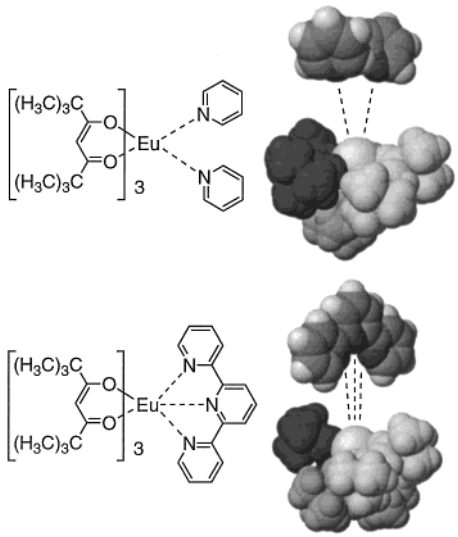

Figure 1. Europium tris(2,2,6,6-tetramethyl-3,5-heptanedionate) and highly coordinated complexation with pyridine and terpyridine.

The lanthanide coordination occurs predominantly via ionic bonding interactions, leading to a strong preference for negatively charged donor groups. When the lanthanide cation is coordinatively unsaturated by original ligands, the additional neutral or anionic substrate coordinates with the lanthanide center to form a "highly coordinated complex". Water molecule and hydroxide ion provide particularly strong coordination with the lanthanide center in the aqueous media, and other neutral molecules containing oxygen or nitrogen atoms can occupy these coordination sites. Figure 1 schematically illustrates the highly coordinated complexation in which europium tris(2,2,6,6-tetramethyl-3,5-heptanedionate) **1** binds two pyridine molecules or one terpyridine.[16,17] In each highly coordinated complex, the charge of Eu^{3+} cation is neutralized by three β-diketonate anions and further binds neutral substrate. The additional coordination has a great influence on the geometrical arrangements of three β-diketonate ligands in the lanthanide coordination sphere. This means that a proper combination of lanthanide

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Hiroshi Tsukube was born in Osaka, Japan, in 1953 and obtained his B.A. degree in Polymer Science from Osaka University in 1975. He completed his graduate study for his Master's degree at Osaka University in 1977 and for his Doctor's degree at Kyoto University in 1981, where he worked with Professors Takeo Araki, Akira Nakamura, and Kazuhiro Maruyama. He was appointed to a Lectureship in the Department of Chemistry, College of Liberal Arts and Science, Okayama University in 1981 and was promoted to Associate Professor in 1984. He spent half a year with Professor Kenneth N. Raymond at the University of California, Berkeley, in 1990. Since 1995 he has been Professor in the Department of Chemistry, Graduate School of Science, Osaka City University. His research interests focus on molecular recognition and supramolecular chemistry involving crown ethers, macrocycles, naturally occurring ionophores, lanthanide complexes, bioproteins, and their assemblies. He was an Associate Editor of the *Journal of Chemical Society, Japan* (1993–1995) and of the *Bulletin of the Chemical Society, Japan* (1999–2002). Professor Tsukube was the recipient of the Nodzu Memorial Award (1982), a Progress Award from the Chemical Society of Japan (1987), and the Shiokawa Award from the Rare Earth Society of Japan (2002).

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center and original ligand can finely control the highly coordinated complexation with a specific substrate.

This review focuses on the applications of lanthanide complexes in molecular recognition and chirality sensing of biological substrates. The "chirality" is a main subject in all studies of the molecular

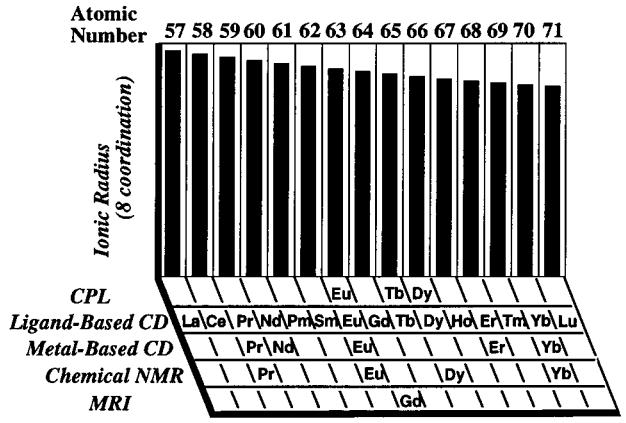


Figure 2. Applicability of lanthanide complexes in recognition and sensing.

basis of biological and artificial chemistry. This is manifested by natural products such as proteins, nucleic acids, sugars, amino acids, hormones, and antibiotics and also by drugs, foods, and other synthetic chemicals. Since they often exhibit specific activity and functionality depending on their chirality, many kinds of methods have been presented for determination of the absolute configuration of chiral substrates and separation of their enantiomers.[18] These methods include several chiral recognition processes in which the diastereomers derived from the enantiomers can be detected or separated: (1) covalent synthesis of diastereomers using chiral derivatizing reagents and their discrimination, (2) complexation with chiral receptors and detection of diastereomeric differences, and (3) use of chiral gas and liquid chromatography. The lanthanide complexes have outstanding features in not only chiral recognition but also chirality sensing of the targeted substrates. When the lanthanide cation or complex couples or binds with chiral substrate, specific interactions occur in the inner or outer sphere of lanthanide coordination. If these interactions induce the chirality-dependent changes detectable with circular dichroism (CD) and other techniques, the chirality sensing of the substrate can be done.

The applicability of the lanthanide complexes in the molecular recognition and chirality sensing of biological substrates is outlined in Figure 2, together with ionic radii and atomic numbers of the lanthanide centers. NMR spectroscopy is one of the most valuable techniques in the characterization of chiral biological substrates, but its use is frequently restricted due to insufficient signal separation of the stereoisomers. Lanthanide shift reagents are effective in alteration of the chemical shifts[10,11] which can be caused by (1) transfer of electron spin density from the lanthanide center to the associated nuclei, *"contact shift"*, or (2) magnetic effects of the unpaired electron magnetic moment, *"pseudocontact shift"*. Several types of Pr^{3+}, Eu^{3+}, Dy^{3+}, and Yb^{3+} complexes are commercially available as NMR shift reagents, while some Gd^{3+} complexes are practically used as contrast agents in the MRI method.[12,13]

CD spectroscopy is a widely used technique to detect and determine a chiral substrate.[19] This answers whether the system is chiral or not and gives

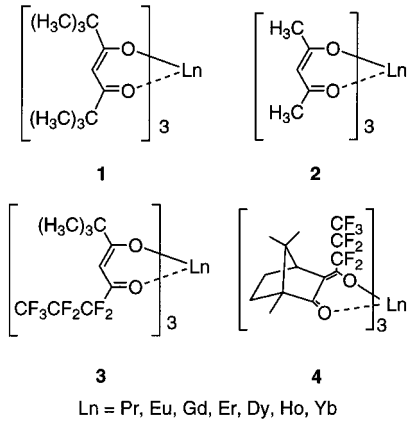


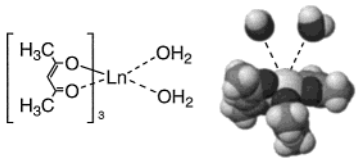
Figure 3. Lanthanide tris(β-diketonates) reported in recognition and sensing of chiral biological substrates.

information about the optical transition and the absolute configuration of the substrate. Among the lanthanide cations, Eu^{3+} and Yb^{3+} cations form complexes with various chiral substrates of biological interest and exhibit characteristic CD signals associated with f−f electronic transitions. The observed CD signals relate to the chirality of coordinating substrates but are often too weak to be sensed. When the chiral substrate is bound with a chromophoric lanthanide complex, another type of CD signal is induced at the absorption region of the corresponding chromophore. This can be amplified by combinations of intense chromophoric ligands with suitable lanthanide centers. The circularly polarized luminescence (CPL), an emission analogue of CD, is observed with emissive Eu^{3+}, Tb^{3+}, and Dy^{3+} complexes.[19] It is possible to observe CPL from excited states that are only weakly accessible via direct absorption processes from the ground electronic state and therefore only weakly observable in CD. Since the lanthanide complexes have versatile coordination characteristics, there are many possibilities for their use in recognition and sensing of chiral biological substrates.

2. Molecular Recognition of Biological Substrates

2.1. Lanthanide Coordination Chemistry for Molecular Recognition

The lanthanide complexes have high coordination numbers and characteristic geometry which are principally determined by the nature of the coordinating ligand, lanthanide center, competitive solvent, and other environments. Most trivalent lanthanide cations form octa- or nonacoordination complexes in which the mechanical distortions required to accommodate steric interactions usually occur. Since the lanthanide coordination has little or no directionality, such steric constraints significantly influence the structure and stability of the lanthanide complex. Lanthanide tris(β-diketonates) are representative of rare-earth metal complexes (Figure 3). Since Hinckley employed complex **1** (Ln = Eu) as an NMR shift reagent,[20] this type of lanthanide complex has been recognized as a useful device in luminescence, CVD, and other processes. As described above, one or more



Ln	La	Pr	Sm	Ho	Er
Ln – O (H_2O) / Å	2.56	2.52	2.47	2.36	2.34
	2.57	2.52	2.49	2.42	2.42
O(H_2O)···O(H_2O) / Å	3.17	3.04	2.98	2.79	2.78
∠O(H_2O)–Ln–O(H_2O) / deg.	76.0	74.3	73.9	71.5	71.4

Figure 4. Highly coordinated complexation between lanthanide tris(acetylacetonates) **2** and two H_2O molecules.

additional ligands usually are bound to form the highly coordinated complexes. Several nitrogen-containing ligands such as aliphatic amines,[21,22] pyridine,[16,23] imidazole,[24] 2,2′-bipyridine,[25] 1,10-phenanthroline,[26] and 2,2′:6′,2″-terpyridine[17] as well as oxygen-containing ones such as water,[27−33] alcohol,[34] acetone,[35] acetamide,[36] dimethylformamide,[37] polyether,[38] and phosphate[39,40] were incorporated into the highly coordinated complexes.

The X-ray structures of a series of highly coordinated complexes between lanthanide tris(acetylacetonates) **2** and two H_2O molecules were reported by Phillips et al. (La^{3+} complex),[27] Cheng et al. (Pr^{3+} and Sm^{3+} complexes),[28] Aslanov (Nd^{3+} complex),[29] Il'inskii (Eu^{3+} complex),[30] Cheng et al. (Gd^{3+}, Tb^{3+}, Er^{3+}, and Tm^{3+} complexes),[31] Kooijman et al. (Ho^{3+} complexes),[32] and Martynenko et al. (Yb^{3+} complexes).[33] Figure 4 summarizes crystal structural data of the selected examples. Each complex has a polyhedron coordination structure which is formed by eight oxygen atoms around the lanthanide center in a distorted square antiprism fashion. With a decrease in the ionic radius of the lanthanide center, the distances of Ln−O(H_2O) and O(H_2O)···O(H_2O) decrease and the angle of O(H_2O)−Ln−O(H_2O) narrows. All of the lanthanide cations formed similar octacoordination complexes, but the interactions of H_2O/acetylacetonate and acetylacetonate/acetylacetonate significantly vary depending on the size of the lanthanide center.

Tsukube et al. determined log *K* values of highly coordinated complexes between lanthanide tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadionates) **3** (Ln = Pr, Eu, Gd, Dy, Ho, Yb) and 2-amino-3-methyl-1-butanol in CH_3OH/CH_2Cl_2 (1/99) (Figure 5).[41,42] Although the competition between substrate and solvent molecules for coordination with the lanthanide center must be considered, the stability constant of the highly coordinated complex increases in the order $Pr^{3+} < Eu^{3+} < Gd^{3+} < Dy^{3+} > Ho^{3+} > Yb^{3+}$. Since the ionic radii of the lanthanide centers decrease in the order $Pr^{3+} > Eu^{3+} > Gd^{3+} > Dy^{3+} > Ho^{3+} > Yb^{3+}$, the smaller lanthanide center provides shorter and stronger coordination but larger steric repulsion between amino alcohol and β-diketonate ligands. The log *K* values were estimated as 4 or 5 for various amino alcohols and 2 or less for the corresponding monoalcohol, monoamine, and diol substrates. These confirmed that amino alcohols acted as bidentate ligands in the highly coordinated

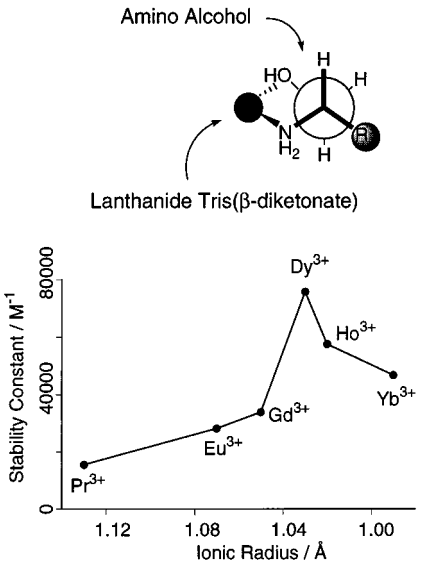


Figure 5. Stability constants vs ionic radii of lanthanide centers in highly coordinated complexation between lanthanide tris(*β*-diketonates) **3** and 2-amino-3-methyl-1-butanol. (Reprinted with permission from ref 42. Copyright 2001 Rare Earth Society of Japan.)

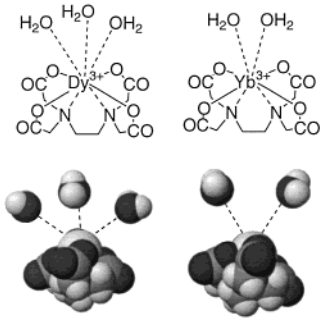


Figure 6. Lanthanide complexes of EDTA-type ligand **5** and highly coordinated complexation with H_2O molecules.

complexation process. Yang and Brittain reported similar log *K* values between amino alcohols and europium tris(*β*-diketonates) such as **3** (Ln = Eu) in $CHCl_3$.[43]

The lanthanide complexes of ethylenediaminetetraacetic acid (EDTA) **5** and related ligands are also well characterized. Figure 6 schematically illustrates the structures of two lanthanide complexes of EDTA[44] in which the lanthanide centers are coordinated by four carboxylate anions and two nitrogen atoms of the ligand and further interact with two or three water molecules: the larger Dy^{3+} complex has three H_2O molecules and smaller Yb^{3+} complex incorporates two H_2O molecules. Kido et al. reported the stability constants of the highly coordinated complexes between chiral Eu^{3+} complex and chiral amino acids in the aqueous solution.[45] When (*S*,*S*)-ethylenediamine-*N*,*N*′-disuccinic acid **6** was employed as a chiral EDTA type ligand, its Eu^{3+} complex formed ternary complexes with D- and L-amino acids in an enantiomer-selective fashion. The stability constants of the ternary complexes were estimated at pH = 9 as 6.1 for D-phenylglycine and 3.7 for L-phenylglycine. The observed difference in the stability constants between substrate enantiomers offers a possibility that the lanthanide complexes of EDTA-type ligands

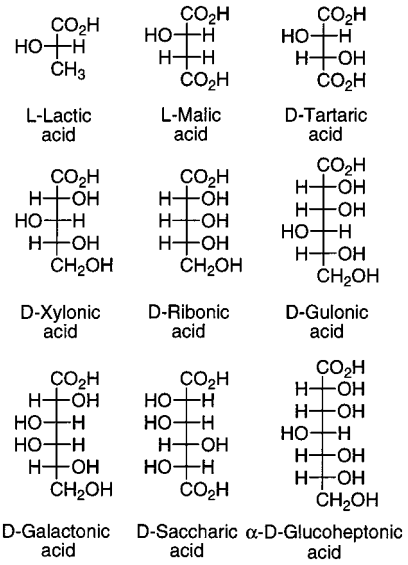


Figure 7. Biological hydroxycarboxylic acids coordinating with lanthanide cations and their complexes.

as well as those of *β*-diketonates can permit recognition and sensing of chiral biological substrates.

2.2. Molecular Recognition of Biological Substrates

The trivalent lanthanide cations themselves had been reported to coordinate with a series of hydroxycarboxylic acids and amino acids in the aqueous solutions, some of which are listed in Figure 7. Earlier studies of Katzin revealed that these biological substrates effectively worked as bidentate ligands of the lanthanide cations.[46−48] The multidentate chelated lanthanide complexes exhibit further interesting molecular recognition properties upon highly coordinated complexation. A series of lanthanide tris(*β*-diketonates) **3** and **4** typically have outstanding features as extracting reagents of amino acids:[49,50] (a) Highly coordinated complexation with hydrophilic substrates; (b) Stability against hydrolysis and ligand exchange at neutral pH; and (c) Substitution feasibility by chiral, fluorinated, and chromophoric *β*-diketonate ligands. For example, lanthanide tris(*β*-diketonates) **3** extracted phenylalanine (Phe), tryptophan (Trp), leucine (Leu), and phenylglycine (PhGly) from neutral aqueous solutions into organic media, though more hydrophilic alanine (Ala) and glycine (Gly) were rarely extracted. In contrast, copper bis(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadionate), dibenzo-18-crown-6, and other common synthetic receptors did not extract these unprotected amino acids at neutral pH. The lanthanide tris(*β*-diketonate) was confirmed to form a negatively charged ternary complex with anionic guest which was detectable by the negative fast atom bombardment mass spectroscopy (FAB MS) method.[51] When the $-CO_2^-$ part of the amino acid coordinates with the neutral lanthanide complex, the resulting anionic species can interact with the $-NH_3^+$ part of the amino acid intramolecularly via electrostatic interaction or direct hydrogen bonding between $-NH_3^+$ hydrogen and *β*-diketonate oxygen (Figure 8). A similar binding model of zwitterionic amino acid with

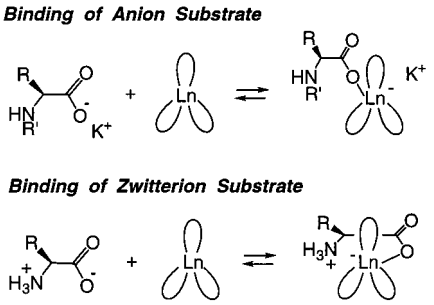


Figure 8. Coordination modes from anion and zwitterion substrates toward lanthanide complexes.

lanthanide complex was recently reported by Aime et al.[52] They characterized the formation of ternary complexes between amino acids and Gd^{3+} complex with 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid. The proton relaxation enhancement titrations supported that the $-NH_3^+$ part of the amino acid was bound with the lanthanide center through the water molecules.

Amino acids and oligopeptides are the most fundamental substrates in biological and artificial processes.[53−55] When they are targeted, the recognition and sensing should be performed in neutral aqueous solutions (pH = 6−8). A variety of synthetic receptors have been developed for these substrates, but most of them have proven effective for cationic or anionic forms. Figure 9 illustrates recent examples of synthetic receptors effective for amino acid and oligopeptide substrates,[56−64] which have two different binding sites for $-NH_3^+$ (or $-NH_2$) and $-CO_2^-$ (or $-CO_2H$) in the single receptor molecule. Their sophisticated structures permitted multipoint binding of multifunctional amino acids, but their synthesis required a series of laborious experimental tasks.

The lanthanide complexes have great advantages of facile preparation and unique receptor functions. Figure 10 illustrates a liquid membrane transport system in which the lanthanide tris(β-diketonate) carrier is distributed in a CH_2Cl_2 liquid membrane and an amino acid substrate exists as a zwitterion in a source aqueous phase.[65] The lanthanide complex first forms the highly coordinated complex with amino acid at the left side of the membrane. The resulting ternary complex moves across the membrane and releases the guest amino acid into a receiving aqueous phase. The lanthanide tris(β-diketonate) **3** exhibited satisfactorily high transport efficiencies for the unprotected PhGly, Phe, and Leu under neutral pH conditions, comparable to that of dibenzo-18-crown-6-mediated K^+ cation transport. It also facilitated membrane transport of cationic or anionic amino acid derivatives via highly coordinated complexation. Tsukube et al. reported efficient transport of a series of N-protected amino acids as carboxylates with lanthanide complexes **3**.[66] The crown ether-mediated transport of amino acid ester cations was also accelerated by the addition of lanthanide complexes **3**.[67]

2.3. Chiral Recognition of Biological Substrates

The chiral recognition of amino acids and other biological substrates plays an important role in many biological processes. This generally requires that the ternary complexes with a pair of substrate enantiomers have different stability constants upon diastereomeric complexation. Since their differences are usually small and not always detected, the chiral recognition is a more difficult task with artificial receptors than substrate discrimination. The chiral lanthanide tris(β-diketonates) **4** offered enantiose-

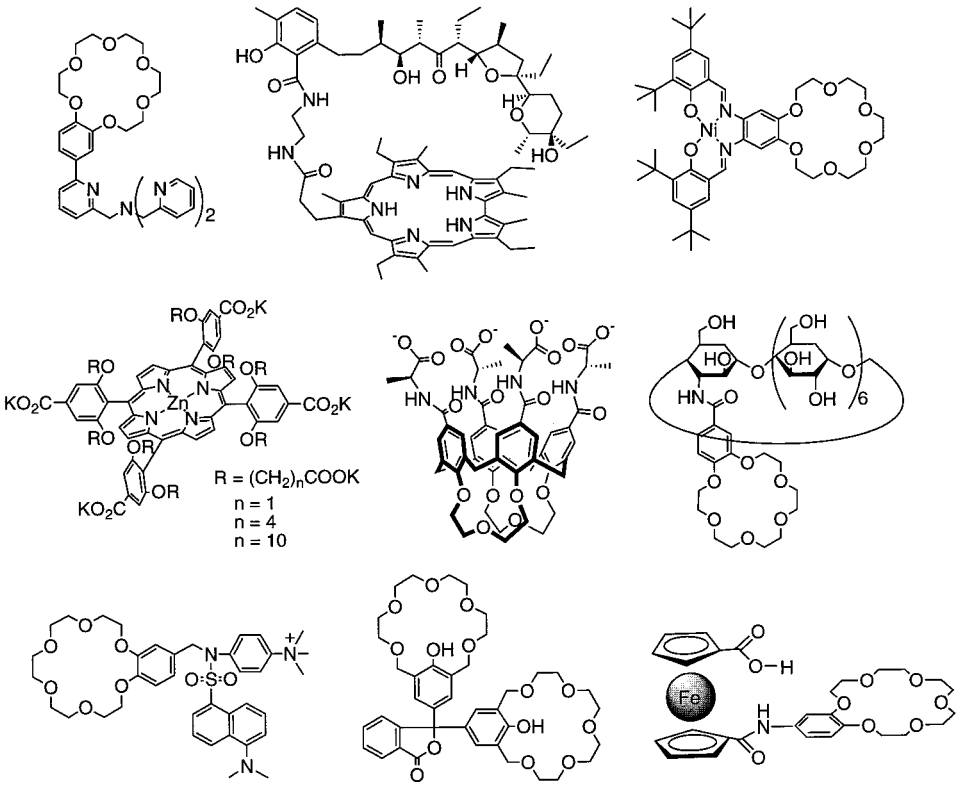


Figure 9. Synthetic receptors reported for amino acids and oligopeptides.

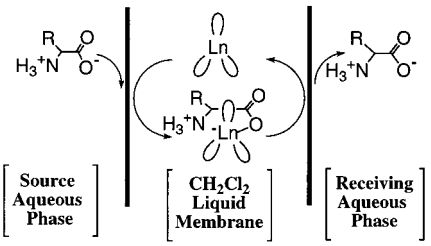


Figure 10. Liquid membrane transport of zwitterionic amino acid.

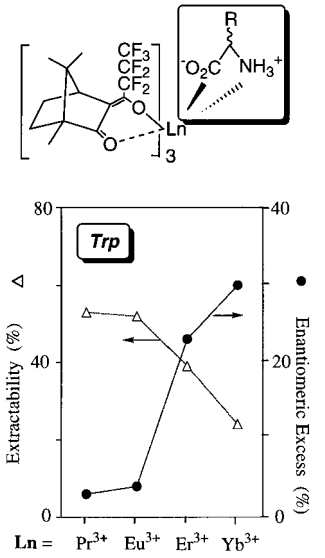


Figure 11. Enantiomer-selective extraction of tryptophan by chiral lanthanide tris(*β*-diketonates) **4**. (Reprinted with permission from ref 69. Copyright 2000 Gordon and Breach Publishing.)

lective extraction of unprotected amino acids from neutral aqueous solution.[49,50] As illustrated in Figure 11, the extractability of Trp was apparently dependent on the ion size of the lanthanide center and decreased from Pr^{3+} or Eu^{3+} to Er^{3+} and then to Yb^{3+}. Enantioselectivity, in contrast, had a "reversed order": $Pr^{3+} \leq Eu^{3+} < Er^{3+} < Yb^{3+}$. These lanthanide complexes offered higher enantioselectivity for aromatic PhGly, Phe, and Trp than aliphatic Leu, and the most sterically crowded PhGly was extracted with the highest ee value of 49%. Although there should be some stereoisomers of the employed lanthanide complexes in the solution states, a smaller lanthanide center provides closer asymmetric interaction between *β*-diketonate ligand and amino acid substrate to give the enhanced enantioselectivity. Willner et al. reported that the highly coordinated complexes between **4** and inorganic anions bound cationic amino acid derivatives as countercations and mediated their enantiomer-selective transport, though the details have not yet been reported.[68]

3. Chirality Sensing of Biological Substrates

3.1. Lanthanide Complex Strategy for Chirality Sensing

The NMR and CD spectroscopic methods with lanthanide complexes provide practical approaches to define the configuration of biological substrates

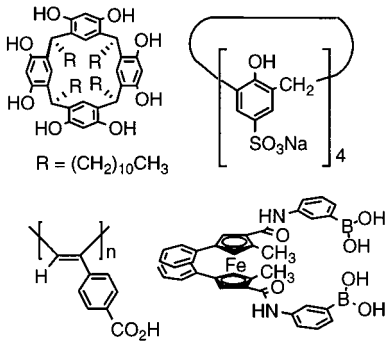


Figure 13. Synthetic receptors reported for complexation method.

and to determine their conformations in solution states. Before these measurements, an intense signal molecule should be attached to the chiral substrate to make it detectable (Figure 12).[69] Mosher's reagent

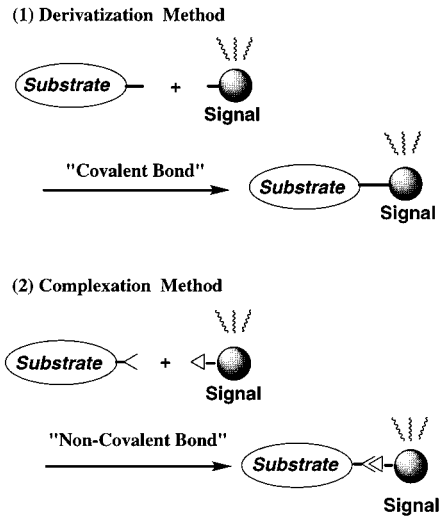


Figure 12. Two approaches to chirality sensing: derivatization method vs complexation method.

and other derivatizing agents were frequently applied in the derivatization method to couple the signal molecules with chiral substrates.[70] The lanthanide complexes can be attached to the substrates through covalent bonds using Meares' reagents and related commercially available ligands.[71] Since this method involves the covalent bond formation between target substrate and signal molecule, it requires a series of laborious procedures which include coupling reaction and product purification and sometimes is accompanied by racemization and/or optical resolution. The complexation method is a promising alternative in which the signal molecule is bound with chiral substrate via noncovalent interaction. This has great advantages of simplicity in experiments, only several micrograms of substrate, no coupling reaction, no purification, and facile recovery of substrate. On the basis of ion pairing, solvation, host−guest complexation, metal coordination, and other weak interactions, calixarenes, polymer helices, boronic acids, and other receptors were employed in this complexation method (Figure 13).[72−75] The lanthanide complexes have interesting possibilities in chiral recognition and chirality sensing: (1) the highly coordinated complexes between lanthanide receptor and substrate

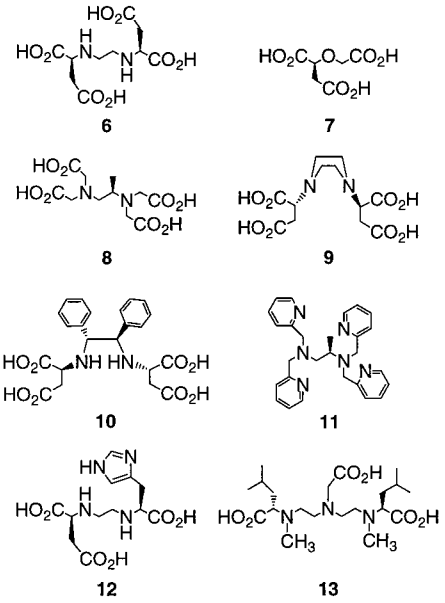


Figure 14. Chiral ligands for lanthanide shift reagents effective in aqueous media.

enantiomers have different stability constants upon diastereomeric complexation and (2) they have the same stability but different geometry, which can be detected spectroscopically.

3.2. Chirality Sensing in NMR Spectroscopy

The lanthanide complexes are known as powerful probes in chemical and biomedical NMR applications.[10,11] In the chemical NMR method, chiral lanthanide complexes, in principle, differentially interact with substrate enantiomers and often give the resolved NMR signals, though a limited number of lanthanide complexes operate in aqueous solutions. Since Reuben observed the separated ^{1}H NMR signals for enantiomeric lactate in the presence of Eu^{3+} complex of chiral mandelate,[76,77] the direct enantiomeric excess percent determination of biological substrates in the aqueous solutions has become a practical goal. Typical examples of chiral ligands are listed in Figure 14, and their lanthanide complexes were characterized as chiral shift reagents in aqueous media. Peters et al. used Eu^{3+} and Yb^{3+} complexes of (*S*)-[(carboxymethyl)-oxy]succinic acid **7** to resolve the enantiomeric NMR signals of chiral α-amino acids and α-hydroxycarboxylic acids.[78] Kabuto and Sasaki demonstrated that the Eu^{3+} complex of (*R*)-propylene-1,2-diaminetetraacetic acid **8** acted as an effective chiral shift reagent for amino acids and aldonic acids (Figure 15).[79−83] This Eu^{3+} complex typically gave ca. 0.13 ppm separation of $-CH_3$ proton signals of alanine with a 90 MHz NMR spectrometer. Kido and co-workers used an Eu^{3+} complex of (*S*,*S*)-ethylendiamine-*N*,*N*′-disuccinic acid **6**,[45] and Feringa et al. developed Eu^{3+} complexes with EDTA-type ligands **9** and **10**.[84] In these complexes, four carboxylate anions and two amine nitrogen atoms of the ligands provide potential coordination with the lanthanide center. Their coordination modes and the numbers of charges are significantly dependent on pH values of the solutions. Although they are restricted to give the well-separated NMR signals

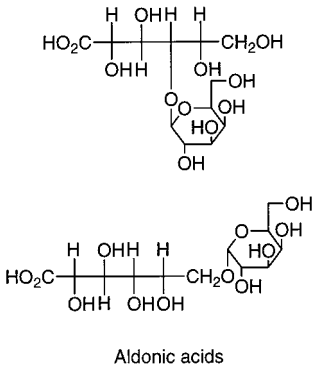


Figure 15. Biological aldonic acids reported for NMR sensing.

under acidic or basic conditions, a good relationship between the chirality of the substrate and the chemical shifts of the separated proton signals was established.

When the chirality sensing of biological substrates is practically planned, most of the lanthanide shift reagents still have several inherent drawbacks: (1) they work poorly at neutral pH and (2) they often cause line broadening for strong coordinating substrates. To overcome the former problem, a new type of chiral ligand was reported which formed positively charged lanthanide complexes. Kabuto et al. examined *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-(*R*)-propylenediamine **11**.[85] Its Eu^{3+} complex exhibited definitely separated signals for α-H protons of various amino acids in the neutral aqueous solutions. The X-ray crystal structure of this complex revealed that the Eu^{3+} cation was octacoordinated by four pyridine and two propylenediamine nitrogen atoms as well as two H_2O molecules. Kojima et al. observed that neutral and positively charged lanthanide complexes of tricarboxylic acid derivatives **12** and **13** operated well in the neutral aqueous solutions.[86,87]

The line-broadening phenomenon has serious practical problems when lanthanide shift reagents are used on high-resolution NMR apparatus. When the observed NMR spectra are compared with 100 and 500 MHz instruments, the latter provides 25 times more severe line broadening. Kabuto et al. recently applied Sm^{3+} and La^{3+} complexes as shift reagents, though such lanthanide complexes have rarely been used as NMR shift reagents on a low-resolution NMR apparatus.[88,89] Their complexes of (*R*)- and (*S*)-propylenediaminetetraacetic acids **8** resolved the enantiomer signals of α-amino acids on a high-field NMR apparatus without signal broadening, while the corresponding Eu^{3+} complexes caused serious broadening. The uncommon lanthanide complexes have the potential to exhibit unexpected functions.

3.3. Chirality Sensing in CD Spectroscopy

Three types of CD methods are employed in chirality sensing:[19] (1) the lanthanide centers themselves exhibit CD spectra based on f−f transition under chiral coordination environments; (2) achiral, chromophoric ligands coordinating with lanthanide centers give intense CD signals upon highly coordinated complexation with chiral substrates; and (3) the lanthanide-based circular polarized luminescence

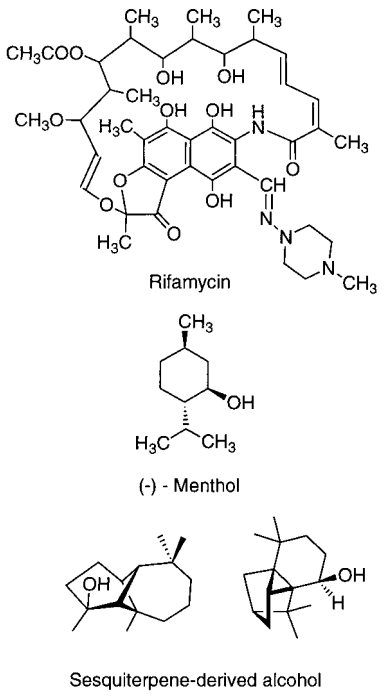


Figure 16. Biological substrates reported for lanthanide-based CD sensing.

(CPL) behaviors are observed with some emissive lanthanide complexes. When the lanthanide center and original ligand are carefully chosen to control the competitive coordination of substrate and water, the chirality of biological substrate dissolved in water can be sensed with these CD methods.

3.3.1. Chirality Sensing with Lanthanide-Based CD

The CD spectra based on f−f electronic transitions were observed with several lanthanide cation-containing systems. Since most organic molecules show very weak CD bands at >300 nm, the lanthanide-based CD provides precise information on the chirality around the lanthanide center. Katzin et al. earlier observed CD signals of Eu^{3+} and Pr^{3+} complexes of chiral hydroxycarboxylic acids, sugar acids, and amino acids in aqueous media (Figure 7).[46−48] Since these trivalent lanthanide cations have similar coordination geometry and ionic radii to those of divalent alkaline-earth metal ions, they worked as substitutional (or replacement) CD probes for spectroscopically "transparent" Ca^{2+} and Mg^{2+} ions and provided chirality information on biological substrates.

Salvadori et al. applied Yb^{3+} ion to probe the interaction between rifamycin and Ca^{2+} ion (Figure 16).[90] The Yb^{3+} ion exhibited a magnetic-dipole-allowed transition around 1000 nm and easily replaced the Ca^{2+} ion. A mixture of rifamycin and Yb^{3+} ion offered strong near-IR−CD bands between 700 and 1100 nm. Since this substrate has several −OH groups in a chiral cyclic skeleton, some of them directly linked with chiral centers were suggested to coordinate with the Ca^{2+} ion in a multidentate fashion. Messori et al. used the Yb^{3+} ion in studies of the transferrin-metal binding systems.[91] This was confirmed to bind transferrins up to a metal-to-protein ratio of 2:1 by monitoring characteristic near-IR−CD spectra around 950 nm, indicating that the two binding sites of the transferrins were indistinguishable or had comparable affinity.

Several lanthanide complexes were also reported to exhibit the observable lanthanide-based CD via highly coordinated complexation with chiral substrates. Andersen et al. employed europium tris(β-diketonate) **3** which formed highly coordinated complexes with a series of chiral alcohols such as 2-alkanols, menthol, 2-arylcyclohexanols, and sesquiterpene-derived alcohols as well as α-phenethylamine and amphetamine (Figure 16).[92,93] The resulting 2:1 (substrate: Eu^{3+}) type of ternary complexes gave the induced CD spectral changes around 525 nm, the signs of which correlated with substrate chirality.

More recently, Parker et al. reported that Yb^{3+} complex with a chiral, octadentate cyclen **15** gave rise to observable CD signals around 980 nm (Figure 17).[94,95] In this C_4-symmetric Yb^{3+} complex, the central Yb^{3+} ion was cooperatively coordinated with four nitrogen atoms of the cyclen ring and four neutral amide oxygen atoms on the chiral sidearms. As described below, this type of lanthanide complex was used as a CPL probe to sense the supramolecular chirality.[96,97] Chiral transition-metal complexes are known to give intense CD signals based on d−d transition, which provide useful information on chiral environments around the metal centers. Because of very low molecular extinction coefficients associated with Laporte-forbidden f−f transition, the lanthanide cations generally offer weak CD signals and are limited to use in chirality sensing. Furthermore, the relationships between the observed CD profiles and the stereochemical structures of ligating substrates are not yet available, but the lanthanide-based CD

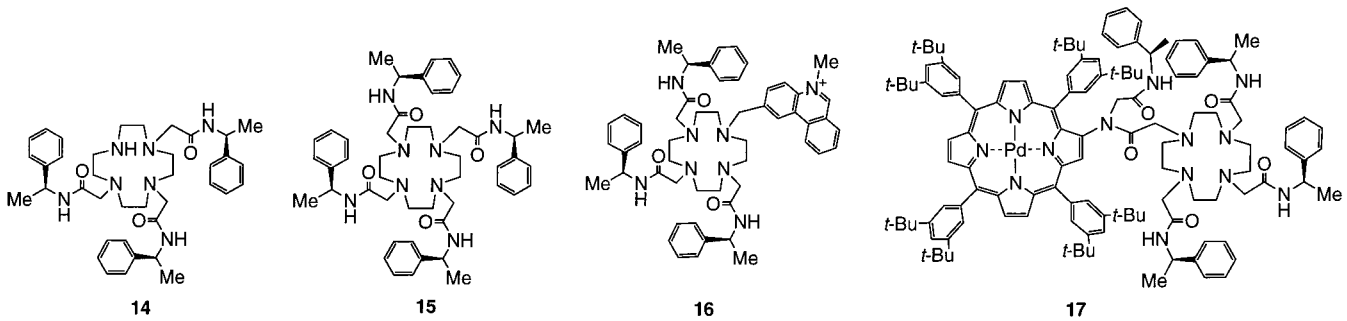


Figure 17. Chiral cyclen ligands for emissive Yb^{3+} complexes.

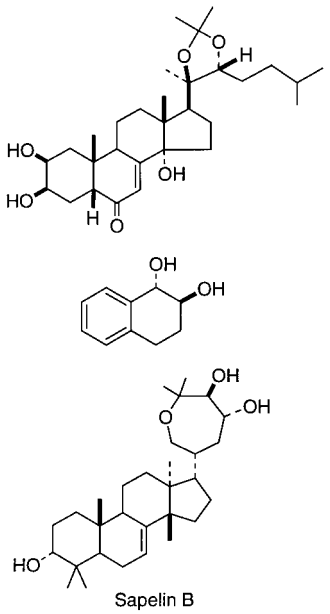


Figure 18. Chiral substrates for CD sensing with lanthanide tris(β-diketonates).

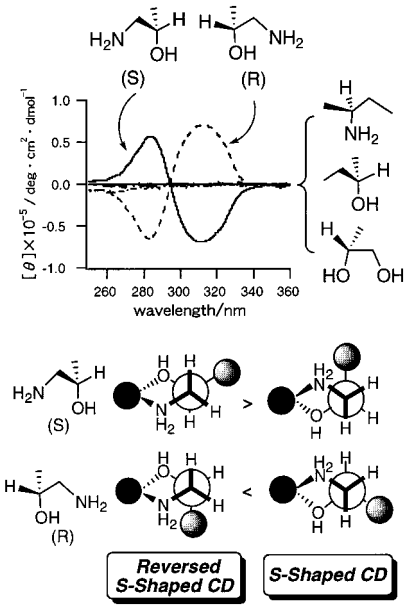


Figure 19. CD spectra of lanthanide tris(β-diketonate) **3** (Ln = Yb) in the presence of chiral, bidentate amino alcohols.

method can yield "fingerprints" of chiral biological substrates.

3.3.2. Chirality Sensing with Chromophoric Ligand-Based CD

The lanthanide complexes exhibit intense CD signals responsive to chirality of coordinating substrates when they include chromophoric ligands. The lanthanide tris(β-diketonates) are typical examples of this type of CD probe.[98,99] In their highly coordinated complexes, additional coordination from chiral substrates enforces asymmetric arrangements of three chromophoric β-diketonates around the lanthanide centers. Nakanishi and Dillon earlier reported that lanthanide tris(β-diketonates) **1** (Ln = Pr, Eu) interacted with steroidal diols and gave CD signals around 300 nm specific to their chirality (Figure 18).[100,101] Lyons and Taylor applied this method to assign the chirality of Sapelin B having a diol moiety.[102] Although the chirality of several natural products was successfully sensed with this type of lanthanide complex, the observed CD signals sometimes had solvent-, time-, and concentration-dependent natures due to the lower stability of the highly coordinated complexes.[103]

Toome and Wegrzynski employed lanthanide complexes having fluorinated β-diketonates to stabilize the highly coordinated complexes.[104,105] When the chirality of bidentate hydroxyesters and amino acid esters was sensed by Eu^{3+} complex **3**, steady CD spectra with favorable signal-to-noise ratios were recorded around 300 nm. Although stoichiometric and thermodynamic profiles were not characterized in detail, the introduction of the fluorinated ligands greatly enhanced the sensing ability of the lanthanide tris(β-diketonate). We compared a series of lanthanide tris(β-diketonates) **1**, **2**, and **3** and optimized the complex structure to design a specific CD probe of amino alcohols.[41,106] Among them, lanthanide complexes **3** (M = Pr, Eu, Gd, Dy, Ho, Yb) formed very stable 1:1 complexes with amino alcohols and offered steady CD signals, the sign of which depended on the substrate chirality. The Eu^{3+} complex **3** typically exhibited a split Cotton effect in the CD spectrum around 280 nm upon addition of (*S*)- or (*R*)-2-amino-1-propanol, though both europium complex and chiral amino alcohol were themselves CD silent under the employed conditions (Figure 19). Since chiral diol, monoalcohol, and monoamine did not induce any spectral change, bidentate amino alcohols specifically formed the highly coordinated complexes which were stable enough to give intense CD signals. A variety of (S)-amino alcohols gave reversed S-shaped CD signals upon the highly coordinated complexation, while their (*R*)-isomers exhibited S-shaped CD signals. The signs of the induced CD signals can be predicted by assuming the bidentate coordination models of chiral amino alcohols as shown in Figure 19. When (*S*)-2-amino-1-propanol coordinates with the lanthanide center in the bidentate fashion, a "left" conformation should be more energetically favored than a "right" conformation for steric reasons, which offers a reversed S-shaped CD signal. In the case of (*R*)-2-amino-1-propanol, the "right" conformation must be more stable than the "left" one to give an S-shaped CD signal. Since the CD amplitude observed and enantiomer excess percentage of the amino alcohol have a linear relationship, the optical purity of the amino alcohol was determined quantitatively on a microgram scale.

When the chirality sensing of biological substrate is practically planned, the employed lanthanide complex should include intense chromophoric ligands to offer high sensitivity in the CD detection. The porphyrinate ligands are no doubt promising candidates of powerful chromophoric ligands for this purpose.[107−109] Choon and Rodley presented pioneering work in which optically inactive magnesium porphyrinates responded to the chirality of amino acids.[110] They observed the induced Cotton effects

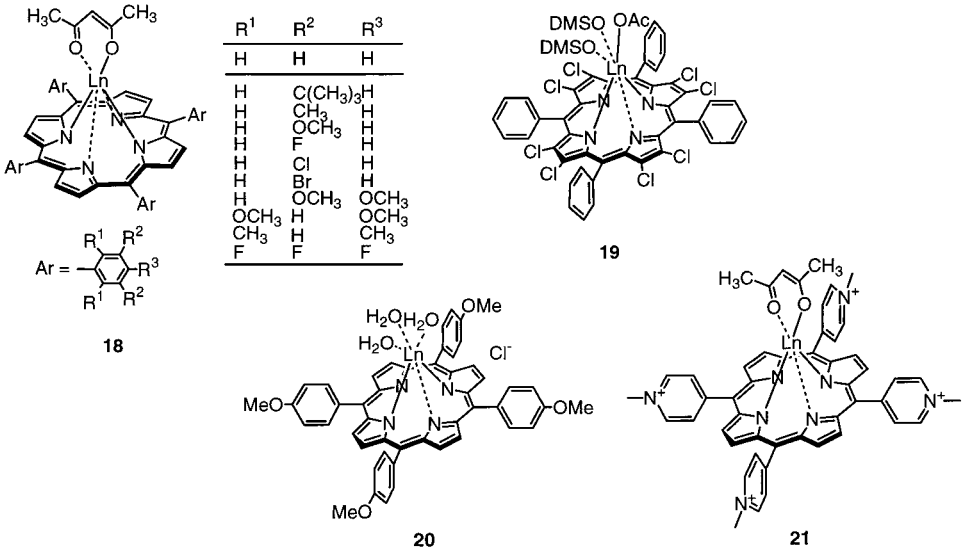


Figure 20. Typical examples of lanthanide porphyrinates.

depending upon substrate/metalloporphyrin interaction. Benson et al. recently demonstrated the effective perturbations of the aromatic amino acid residues on the induced CD signals observed in biological heme protein systems.[111] Ogoshi et al. synthesized zinc porphyrinates including additional binding sites to bind chiral neutral substrates at two points.[112,113] Since their Soret absorptions around 420 nm were strong enough to induce intense CD signals, they offered CD chirality detection of amino acid esters in organic solvents. Transition-metal porphyrinates were further recognized as signal molecules in the derivatization method for CD chirality sensing of neutral substrates (Figure 12). Berova et al. attached zinc porphyrinates to the chiral natural products through covalent bonds. The exciton-coupled CD signals were observed at porphyrin's Soret regions, which were specific to the substrate chirality.[114−116]

Lanthanide porphyrinates have potential as nondestructive probes in biological and medical analysis because they have photochemical, magnetic, and other interesting properties. Since their synthesis and potential use were reported,[117,118] the lanthanide porphyrinates **18**, **19**, **20**, and **21** have typically been characterized, which included dianionic porphyrinates and anionic ligands (Figure 20). Radzki and Giannotti reported that lanthanide porphyrinates **18** (Ln = Gd) gave significant UV spectral changes upon complexation with achiral amines, phenols, and nucleic bases.[119] Coutsolelos et al. determined the crystal structure of complex **19** (Ln = Tb)[120] in which four nitrogen atoms of porphyrinate, two oxygen atoms of bidentate acetate, and two oxygen atoms of two Me_2SO solvent molecules coordinated with Tb^{3+} cation. This complex exhibited an intense Soret band signal, though the Tb^{3+} cation lay 1.28 and 1.47 Å out of the mean N_4 and mean O_4 planes. Wong et al. reported similar crystal structures of lanthanide tetrakis(*p*-methoxyphenyl)porphyrinates **20** (Ln = Yb, Er, Y).[121]

The lanthanide porphyrinates offer useful scaffolds for molecular architecture and give intense CD responses via substrate coordination. The latter permits highly sensitive sensing at low substrate concentrations, while the former ensures the precise targeting of specific biological substrates. A series of gadolinium *meso*-tetraphenylporphyrinates **18** functioned as sensitive CD probes especially for zwitterionic amino acids.[122,123] They effectively extracted zwitterionic amino acids from neutral aqueous solutions into organic solutions, though the corresponding zinc porphyrinates rarely extracted them. The formed 1:1 highly coordinated complexes gave induced CD signals at Soret band regions, the signs of which were specific to the chirality of the bound amino acids. The 16 kinds of L-amino acids gave reversed S-shaped CD signals upon complexation, and their D-isomers yielded S-shaped CD signals. The induced CD spectra of L- and D-Phe with Gd^{3+} porphyrinate are shown in Figure 21. Compared with the CD spectrum of Phe alone in aqueous solution, both ca. 100 fold amplification of the intensity and a large red shift of the CD signal were attained with this CD method. The nature of the lanthanide center greatly influenced CD sensing ability toward amino acids:[124] $Gd^{3+} > Er^{3+} > Yb^{3+}$ as observed in the extraction with lanthanide tris(*β*-diketonates) as described in section 2.3. The substitution of the porphyrinate skeleton affected both the extraction efficiency and CD sensitivity, suggesting that the steric crowding around the lanthanide center induced the asymmetric arrangement of *β*-diketonate and porphyrinate chromophores. Since water-soluble derivatives **21** (Ln = Sm, Eu, Gd, Tb) have been prepared,[125] the CD probing functions of biological substrates can be fine-tuned through structural modification of the lanthanide porphyrinates.[126]

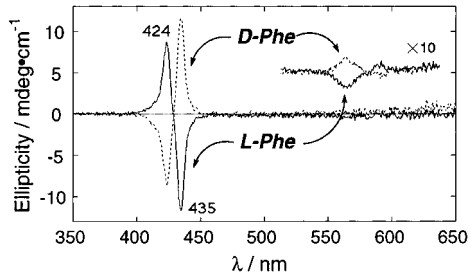


Figure 21. Induced CD spectra of D- and L-phenylalanines with gadolinium porphyrinate **18**.

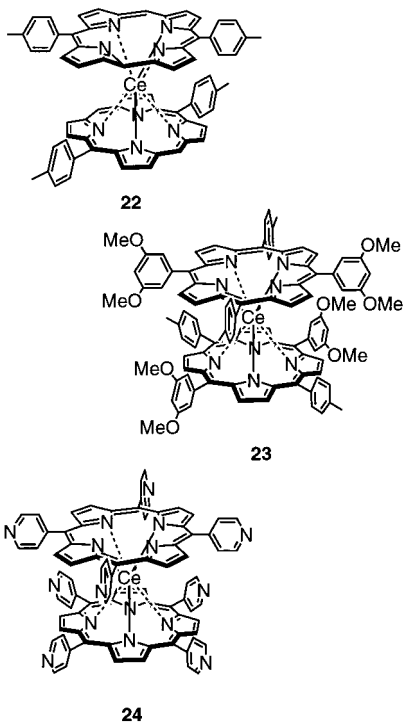


Figure 22. Ce^{4+} complexes of double-decker porphyrinates.

Following the reports by Buchler et al.,[127,128] Ce^{4+} complexes of double-decker porphyrins have received much attention as a uncommon family of porphyrin derivatives (Figure 22).[129,130] They have the square antiprismatic coordination geometry of sandwich-like bisporphyrinates in the solid state. On the other hand, they exist as a mixture of vicinal and transversal isomers in the solution state, each with square antiprismatic coordination geometry. Aida et al. resolved enantiomers of Ce^{4+} sandwich complex **23** using chiral HPLC, while the enantiomers of complex **22** having less crowded substituents were not separated.[131] Shinkai et al. applied Ce^{4+} double-decker complex **24** of tetrakis(4-pyridyl)porphyrin as a CD probe for dicarboxylic acid substrates.[132] Two porphyrinate rings were convex and severely distorted from planarity, and the two mean planes of the individual porphyrin rings lay about 3.4 Å away. When (1*R*,2*R*)-cyclohexanedicarboxylic acid or *tert*-butoxycarbonyl-L-aspartic acid (Boc-Asp) was bound via hydrogen bonds, the two porphyrin rings were restricted from rotating and fixed asymmetrically. These bidentate substrates induced the intense exciton-coupling CD bands, but the other substrates L-tartaric acid, dimethyl L-tartarate, BOC-L-glutamic acid, BOC-L-serine, BOC-L-histidine, and di-BOC-L-cystine gave no induced CD signal. Thus, the double-decker porphyrinates acted as not only intense chromophores for effective sensing but also potential scaffolds for selective binding of bifunctional substrates.

3.3.3. Chirality Sensing with CPL

CPL spectra were frequently observed with Eu^{3+}, Tb^{3+}, and Dy^{3+} complexes, in which the luminescence was derived from f−f electronic transition processes. This probes the geometry of the excited state, while

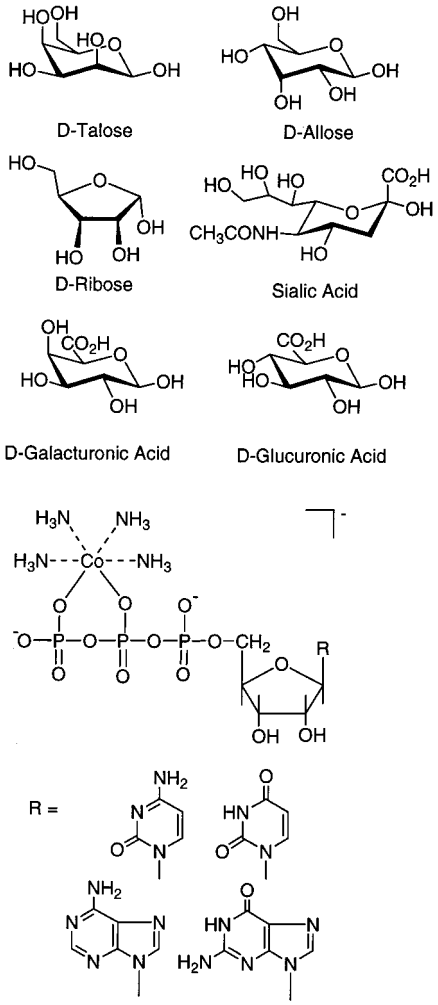


Figure 23. Chiral substrates reported for CPL sensing with lanthanide complexes.

the CD method searches that of molecules in the ground state.[133−135] The lanthanide-based CPL can be induced by (1) the presence of at least one inherently optically active ligand in an inner lanthanide coordination sphere and (2) chiral perturbation on an inherently optically inactive complex by an optically active molecule bound in an outer coordination sphere. As described in section 2.2, the trivalent lanthanide cations and their complexes bind amino acids and sugars, and this CPL method is applicable in the chirality sensing of these biological substrates.

The earlier works reported by Richardson and Brittain demonstrated that the lanthanide-based CPL took place by chiral perturbations on the lanthanide cations from the following biological substrates:[1,136,137] the sugars D-talose, D-allose, and D-ribose; the sugar acids sialic acid, D-galacturonic acid, and D-glucuronic acid; the carboxylic acids malonic acid; and amino acids (see Figures 23 and 7). Riehl et al. further used Eu^{3+} and Tb^{3+} cations as a means to study the Ca^{2+}-binding sites in calmodulin protein.[138] The largest degree of circular polarization was obtained in the presence of 2 equiv of Tb^{3+} cation, and the addition of two further equivalents of Tb^{3+} cation increased total emission. These observations indicated that two kinds of Ca^{2+}- binding sites work

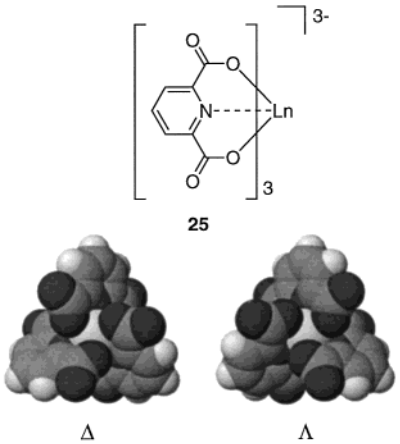


Figure 24. Δ- and Λ-Enantiomers of lanthanide tris(pyridine-2,6-dicarboxylates).

independently. The use of Tb^{3+} and Eu^{3+} cations as substitutional replacements were successfully applied in the Fe^{3+}-binding transferrin systems and revealed differences in the local structures around the binding sites among transferrin, lactoferrin, and ovotransferrin.[139]

The choice of CD vs CPL depends on which technique can afford the greater measurement sensitivity, and the latter has several advantages in the use of emissive lanthanide complexes. Riehl et al. investigated the chirality induced in lanthanide tris(pyridine-2,6-dicarboxylate) **25** upon outer-sphere complexation with a variety of chiral substrates (the so-called "Pfeiffer effect").[140,141] These have negative charges available for electrostatic interactions and are more labile than the transition-metal complexes (Figure 24). Since the presence of L-histidine, glucose, sucrose, fructose, or maltose shifted the racemic equilibrium of the labile enantiomers of these lanthanide complexes, strong CPL was detected in the racemic Dy^{3+}, Eu^{3+}, and Tb^{3+} complexes in aqueous solutions.

Richardson et al. investigated excited-state chiral recognition and enantioselective quenching kinetics involving the use of Tb^{3+} or Eu^{3+} complex **25** as a donor and the resolved enantiomer of $Ru(phen)_3^{2+}$ or $Co(en)_3^{3+}$ as an acceptor: phen = phenanthroline; en = ethylenediamine.[142,143] The energy transfer occurred via electron-exchange mechanism, and the quenching enantioselectivity was due to the structural difference between homochiral and heterochiral pairs of donor and acceptor. The enantioselective quenching was also reported when Co^{3+} complexes of diphosphate nucleotide or triphosphate nucleotide ligands were employed as acceptors (Figure 23).[144] Dekker et al. further observed the enantioselectivity in the energy transfer process leading to quenching of the luminescence of lanthanide complexes **25** by cytochrome *c* derivatives and their mutants.[145] This quenching process probably proceeded by encounter-complexation between the anionic lanthanide complex and the cationic protein surface and then electronic energy transfer near the exposed heme edge.

The lanthanide complexes of chiral N-substituted 1,4,7,10-tetraazacyclododecane ligands gave well-defined CPL spectra (Figure 17).[146−148] Parker et al. employed a series of positively charged Eu^{3+} and Tb^{3+} complexes of chiral heptadentate cyclen ligands such as **14**. They formed chelated ternary complexes with the biological anions citrate, malonate, lactate, and hydrogen carbonate in which two lanthanide-bound water molecules were displaced.[149] Since the lanthanide-based emission and CPL spectra were sensitively changed by the addition of these anionic substrates, CPL spectroscopy offered an anion-sensing method effective in the aqueous solution. This type of lanthanide complex was recently combined with the DNA-binding groups *N*-alkylphenanthridinium and Pd−porphyrin molecules (see **16** and **17**).[96,97] They may have interesting extensions in probing the supramolecular chirality of biopolymers and related assemblies.

4. Structural Elaboration of Lanthanide Complexes

The structural elaboration of lanthanide complexes has been attempted to enhance their selectivity, sensitivity, and availability in the recognition and sensing processes. This involves the conjugation of lanthanide complexes with other kinds of receptor molecules. Wenzel et al. coupled Dy^{3+} complexes with cyclodextrins to improve the enantiomeric resolution of NMR signals in the chirality sensing (Figure 25).[150,151] The cyclodextrins are optically active receptors and accommodate several aromatic substrates within their hydrophobic cavities. Although they often offer the chiral recognition in aqueous media,[152] the cyclodextrins themselves slightly gave resolved enantiomeric signals of amino acid substrates. Dy^{3+} complex of conjugate **26**, in contrast, exhibited pronounced separation of the NMR shifts for enantiomer pairs of aspartame, tryptophan, and propranolol.

The lanthanide porphyrinates were coupled with crown ethers as CD probes for chirality sensing. Since 18-crown-6 catches $-NH_3^+$ moiety[153,154] and lanthanide porphyrinate binds $-CO_2^-$ moiety, they act as multiple binding sites highly complementary to the $-NH_3^+$ and $-CO_2^-$ groups of zwitterionic amino acids. The conjugate **27** (Ln = Er) extracted several amino acids from neutral aqueous solution into CH_2Cl_2 solution more efficiently than the parent lan-

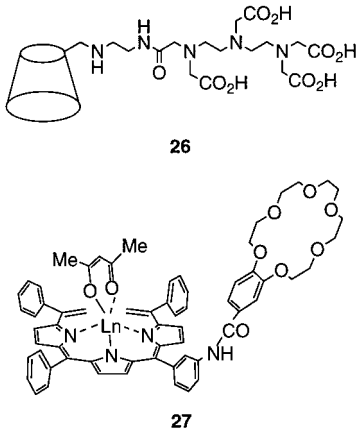


Figure 25. Conjugates of lanthanide complexes with other functional molecules.

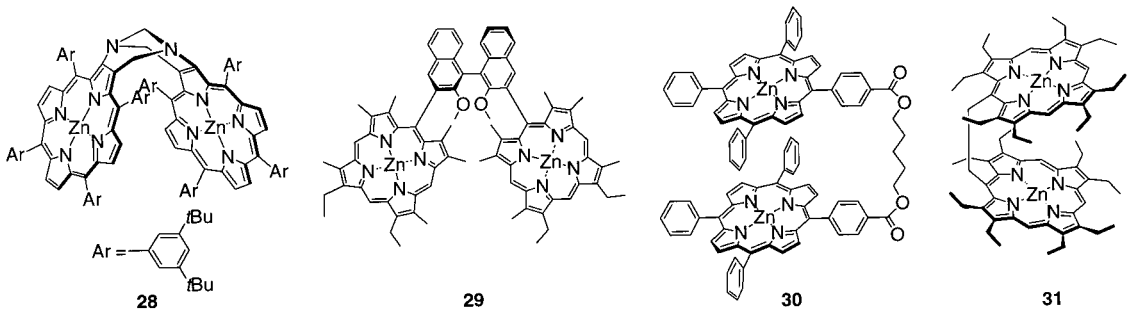


Figure 26. Metalloporphyrin dimers as conjugate receptors.

thanide porphyrinate **18** ($R^1 = R^2 = R^3 = H$, Ln = Er).[155] Thus, this conjugation successfully lowered the detection limitation of amino acids in the CD chirality sensing. After extraction experiments with L-amino acids, the conjugate **27** gave reversed S-shaped CD bands at the Soret-band region while it offered S-shaped CD bands for D-isomers. This conjugate also enhanced the binding ability of biogenetic tyramine, serotonin, noradrenaline, and other biogenetic amine salts.[124] Since Gd^{3+}- and Yb^{3+}-containing conjugates **27** resulted in no enhancement in extraction efficiency or CD sensitivity, the nature of the lanthanide center is an essential factor in the design of this type of conjugate.

Various types of zinc−porphyrin dimers are recognized as potential receptors of bifunctional substrates (Figure 26). Crossley et al.[156] and Hayashi et al.[157] linked two zinc−porphyrin complexes with rigid spacers. Both dimers **28** and **29** strongly bound histidine esters, lysine ester, and 1,8-diaminooctane through zinc−amine coordination. Nakanishi et al.[158,159] and Inoue et al.[160] recently applied more flexible zinc−porphyrin dimers **30** and **31** as CD probes of chiral diamine substrates. The presence of two chirality oriented porphyrins in a single molecule gave rise to characteristic bisignature CD curves. Since the lanthanide porphyrinates are effective receptors of zwitterionic amino acids as described in section 3.3.2, the introduction of the lanthanide center into the porphyrin dimer system may have specific receptor functions in chirality sensing, enantiomer-selective transport, and separation of more complicated biological substrates.

The conjugation of emissive lanthanide complexes with synthetic polymers, dendrimers, biopolymers, and their assemblies has potential extensions in immunoassay, MRI imaging, and other detection processes.[12,13,161−163] They involved the coupling of functionalized lanthanide complexes with macromolecules (Figure 27). Dextrans are well-known to be useful scaffolds for the attachment of various lanthanide complexes. They are available in a variety of molecular weights and easily modified to include lanthanide chelating agents. These polymeric complexes have not yet been used in chirality sensing but hold promise to detect the supramolecular chirality involved in biopolymers and their assemblies.

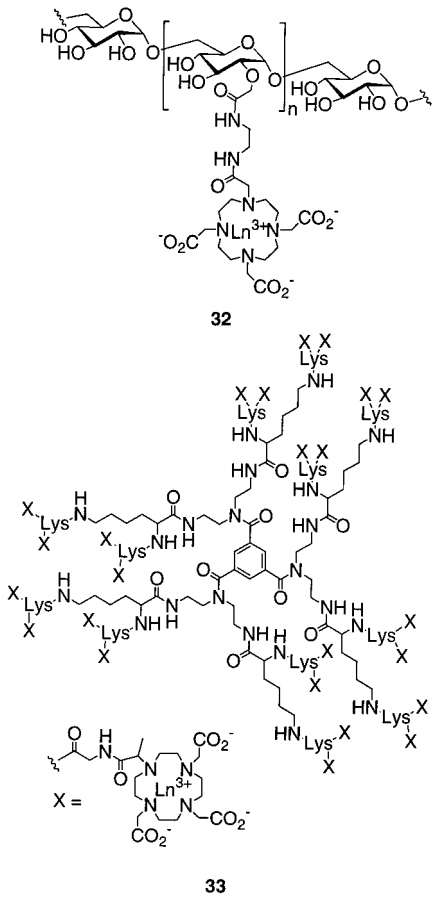


Figure 27. Polymeric lanthanide complexes reported for MRI sensing.

5. Conclusion

This review has focused on interesting applications of lanthanide complexes in molecular recognition and chirality sensing of biological substrates. On the basis of "exotic" coordination chemistry, the lanthanide cations and their complexes offer unique recognition and sensing of chiral biological substrates. Since their versatile coordination characteristics permit precise control of their structural, electronic, and other properties at the molecular level, a variety of intelligent complexes can be developed for recognition and sensing of amino acids and other biological substrates. Lanthanide tris(β-diketonates), porphyrinates, and polyaminocarboxylates are typical examples of receptors and sensing reagents of chiral biological substrates. Their structural optimizations and further conjugations with functional molecules improved the selectivity, sensitivity, and availability at a practical level. Since other kinds of lanthanide complexes are known to be hydrolytic catalysts and luminescent probes in gene and protein science, further evolution of lanthanide complexes promises

more significant positions of lanthanide-containing systems in chemistry, biology, medicine, and related technology. The lanthanide complexes are viewed as intelligent materials of the next generation.

6. Acknowledments

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