Molecular Recognition with Lanthanide(III) Tris(β-diketonate) Complexes: Extraction, Transport, and Chiral Recognition of Unprotected Amino Acids

Hiroshi Tsukube,*,† Satoshi Shinoda,† Jun'ichi Uenishi,‡ Tatsuya Kanatani,‡ Hiroyuki Itoh,‡ Mihoko Shiode,‡ Tadashi Iwachido,§ and Osamu Yonemitsu‡

Department of Chemistry, Faculty of Science, Osaka City University, Sugimoto, Sumiyoshi-ku, Osaka 558, Japan, Department of Chemistry, Faculty of Science, Okayama University of Science, Ridai-cho, Okayama 700, Japan, and Department of Chemistry, Faculty of Science, Okayama University, Okayama 700, Japan

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Lipophilic lanthanide complexes of fluorinated β-diketonate ligands were demonstrated to bind unprotected phenylalanine, leucine, and other amino acids under neutral conditions. Extraction experiments supported that these lanthanide tris(β-diketonates) formed highly coordinated 1:1 complexes with amino acids, although they were electrically neutralized. NMR and CD spectroscopic studies further suggested that the lanthanide tris(β-diketonates) bound amino acids at two points. Their extraction, transport, and chiral recognition behaviors were significantly controlled by a combination of central lanthanide cation and coordinating ligand: Chiral ytterbium complex offered good enantioselectivity in the extraction of unprotected amino acids, and the related praseodymium complex provided their efficient membrane transport. Thus, these lipophilic lanthanide tris(β-diketonates) were confirmed to be a new class of receptors for amino acids.

Introduction

Amino acids are one of the most important guests in both biological and artificial recognition systems, because of their relevance in nature and their chemical richness. Synthetic receptors for amino acids can be of great utility in modeling biological molecular recognition and also in the detection and separation of complex mixtures. A variety of receptors, therefore, have been designed to recognize amino acids, but most of them bind the ammonium or carboxylate parts of protected amino acid derivatives.[1,2] Since the amino acids themselves exist as zwitterions in neutral water and their desolvation is a costly energetic process, effective receptors should have multiple binding sites complementary to zwitterionic sites of the amino acids. A limited number of examples have been reported,[3] in which two or more different kinds of binding sites were geometrically and functionally arranged. Reetz et al. typically employed a crown ether−boronic acid hybrid as a receptor in which the boronic acid bound the carboxylate anion and the crown ether ring trapped the ammonium cation.[4] Schmidtchen and his colleagues connected a chiral bicyclic guanidinium cation for carboxylate binding and a triaza-crown ether for an ammonium binding.[5] Aoyama et al. chose a rhodium complex with a functionalized porphyrin which bound neutral amino acids at two points *via* coordination and hydrogen-bonding interactions.[6] Since these examples were systems of high sophistication but too complicated, synthetic efforts were excessive. Thus, there is a need for straightforward synthesis of specific receptors for unprotected amino acids.

Here we report that lanthanide(III) tris(β-diketonates) are a new class of receptors for unprotected amino acids. The employed lanthanide complexes are known to coordinate with polar substrates in solutions and are frequently examined as shift reagents in NMR spectroscopy[7] and as catalysts in organic synthesis.[8] Although several kinds of lanthanide complexes have received much attention as sensitive fluorescence/MRI probes and potential hydrolytic catalysts for proteins and RNAs,[9]

† Osaka City University.
‡ Okayama University of Science.
§ Okayama University.

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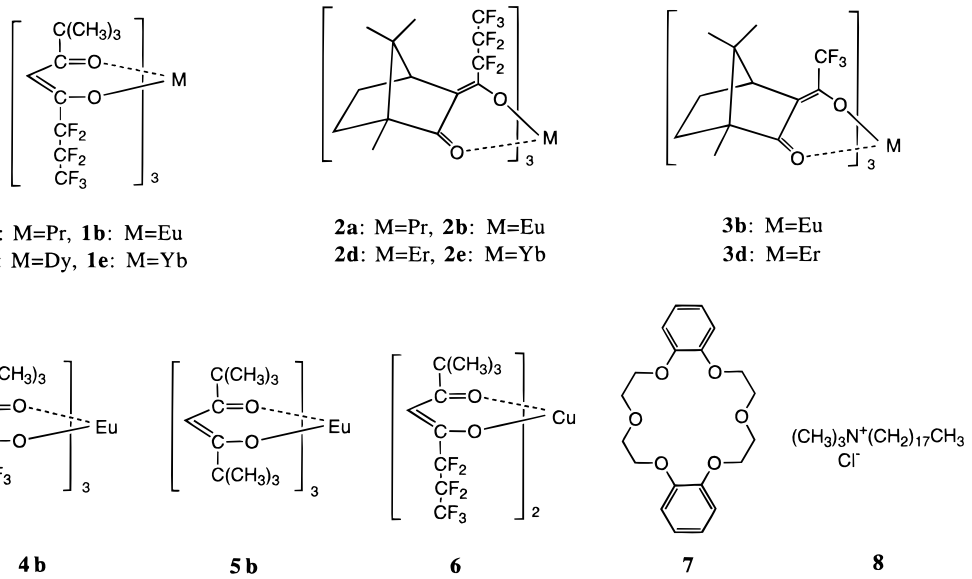
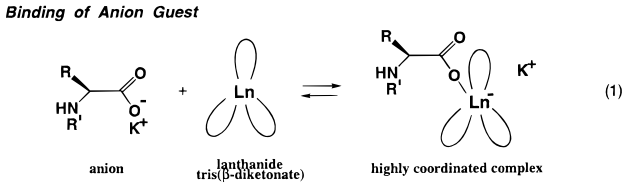
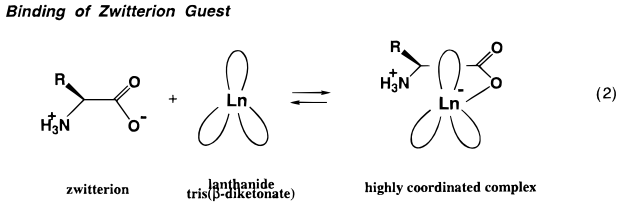


Figure 1. Lanthanide tris(β-diketonates) and references employed.

their basic receptor/carrier functions for amino acids have rarely been characterized. We recently reported that some lanthanide tris(β-diketonates) acted as effective receptors for anionic substrates.[10] As schematically shown in eq 1, they can form





negatively charged and highly coordinated complexes with anionic guests, and the resulting complexes were detectable by the negative FAB-MS method.[10a] Such anionic species are known to interact with cationic species[11] and can bind the ammonium parts of the amino acids intramolecularly via electrostatic interaction. Since hydrogen bonding between hydrogen of the ammonium cations and oxygen of the β-diketonate ligand may be also involved, the lanthanide tris(β-diketonates) are expected to serve as effective receptors of zwitterionic amino acids via two-point binding as illustrated in eq 2. We examine a series of lanthanide tris(β-diketonates) and demonstrate that some of them specifically bind amino acids under neutral conditions.[12] Extraction, transport, CD, and NMR experiments indicate that a proper combination of central lanthanide cation and coordinating ligand offers enantioselective extraction and efficient membrane transport of unprotected amino acids. This is the first systematic study of amino acid recognition with lanthanide complexes[13] and provides interesting possibilities for the design of metal complex type receptors for amino acids, peptides, and other biologically important guests.

Results and Discussion

1. Lanthanide Tris(β-diketonate) as a Receptor. We examined three kinds of lanthanide tris(β-diketonates) as receptors of unprotected amino acid guests: those having fluorinated ligands **1a**−**e** and **4b**, having nonfluorinated ligand **5b**, and having chiral fluorinated ligands **2a**−**e** and **3b**−**d**. These included various lanthanide cations as metal centers: praseodymium, europium, dysprosium, erbium, and ytterbium cations (Figure 1). The ionic radii of the employed lanthanide cations ranged from 0.86 to 1.01 Å and were much larger than those of copper(II) and common transition metal cations. Although trivalent lanthanide cations were electrically neutralized by three anionic β-diketonate ligands, their coordination numbers were estimated as 8 or 10.[14] Thus, another 2 or 4 sites are available to form highly coordinated complexes with guest species. Indeed, several highly coordinated complexes were isolated and their crystal structures were determined.[15] The lanthanide tris(β-diketonates) employed are insoluble in water but well soluble in organic solvents. We first characterized their binding abilities for amino acids using liquid−liquid (H_2O/CH_2Cl_2) extraction. The lanthanide complexes **1a**−**e**, **2a**−**e**, and **3b**,**d** were predominantly distributed in the CH_2Cl_2 phase and rarely decomposed when their CH_2Cl_2 solutions contacted aqueous amino acid solutions (pH = 4−9).[16] Thus, their extraction efficiencies were confirmed rarely to change at this pH range. Copper bis(β-diketonate) **6** was employed to elucidate the effect of central metal cation on receptor functions. Other types of copper

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(16) Decomposition was observed at pH > 9.

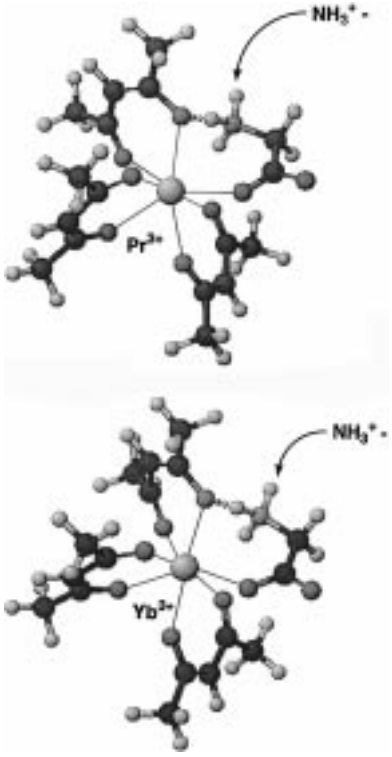

Figure 2. Optimized structure of ternary complex $Pr(acac)_3$−Gly (top); $Yb(acac)_3$−Gly (bottom).

complexes were reported to act as effective receptors of amino acids via a ligand exchange process,[17] but a different mechanism might be involved in the present lanthanide complex system (see eq 2). A hybrid carrier composed of crown ether **7** and cationic surfactant **8** was used for comparison: The former acted as an ammonium binding site, and the latter as a carboxylate binding site.[18] Similar types of binary carriers successfully mediated transport of phenylalanine.[4]

Figure 2 illustrates optimized structures of ternary complexes between lanthanide tris(acetylacetonates) and zwitterionic glycine. Although the detailed structure of the ternary complex is unclear, several experimental results described below suggest that the amino acid guest is fixed on the lanthanide metal center at two points. Thus, the structures of ternary complexes were optimized using CAChe extended MM2 calculations[19] (see Experimental Section). When two-point binding of the glycine with lanthanide tris(acetylacetonate) was assumed, both praseodymium and ytterbium tris(acetylacetonates) had space enough for additional binding of zwitterionic glycine: The carboxylate anion of the glycine directly coordinates with the lanthanide center, and the resulting anionic complex may interact with the ammonium moiety of the guest via electrostatic interaction. The hydrogen bonding between hydrogen of the ammonium group and oxygen of acetylacetonate ligand can be postulated instead of an electrostatic interaction. Since we performed calculations for structural optimization on both assumptions and obtained similar results, we illustrate optimized structures of the obtained

Table 1. Extraction of Amino Acids by Lipophilic Lanthanide Tris(β-diketonates)

amino acid[a] (pH value)	extraction %[b]					
	1a	**1b**	**1c**	**1e**	**6**	**7 + 8**
PhGly (pH = 6.2)	31	28	25[c]	19	*d*	0
Phe (pH = 6.2)	52	48	39[c]	37	0	0
Trp (pH = 6.1)	46	42	36	30	*d*	0
ThGly (pH = 6.2)	30	26	21	19	*d*	0
ThAla (pH = 6.2)	53	46	43	37	*d*	0
Leu (pH = 6.2)	41	38	34	25	0	0
Ala (pH = 6.7)	0	0	0	0	0	0
Gly (pH = 5.9)	0	0	0	0	0	0

[a] D,L-Amino acid, 0.015 mmol, in H_2O, 1.5 mL//lanthanide tris(β-diketonate), 0.030 mmol, in CH_2Cl_2, 1.5 mL. [b] Extraction (%) = {([amino acid extracted in the presence of complex] − [amino acid extracted in the absence of complex])/[amino acid added initially in the aqueous solution]} × 100. [c] Trace amount of precipitate appeared. [d] Considerable amount of precipitate appeared.

ternary complexes between lanthanide tris(β-diketonate) and zwitterionic glycine, assuming that the guest glycine is fixed via coordination and hydrogen bonding. It was suggested that the smaller ytterbium cation offered shorter distances (stronger binding) between the lanthanide cation and the carboxylate group of the glycine than did the larger praseodymium.[20] Since space for accommodation of the glycine was also smaller in the ytterbium complex than in the praseodymium complex, the nature of central lanthanide cation was thought to influence binding behavior of the amino acid with the lanthanide tris(β-diketonate).

2. Extraction of Unprotected Amino Acids under Neutral Conditions. Liquid−liquid extraction experiments were carried out using phenylglycine (PhGly), phenylalanine (Phe), tryptophane (Trp), (2-thienyl)glycine (ThGly), (2-thienyl)alanine (ThAla), leucine (Leu), alanine (Ala), or glycine (Gly) as an amino acid guest. The pH values of the employed aqueous amino acid solutions were recorded as about 6, and the guest species were mainly zwitterions in the aqueous phase. Since the pH values did not change after extraction experiments, amino acids were suggested to be extracted as zwitterionic forms.[21]

Table 1 summarizes extraction behaviors of a series of lanthanide tris(β-diketonates) **1a**−**e** for D,L-amino acid guests. We examined not only aromatic PhGly, Phe, Trp, ThGly, and ThAla but also aliphatic Leu, Ala, and Gly. Complexes **1a**−**e** effectively extracted aromatic PhGly, Phe, Trp, ThGly, and ThAla and aliphatic Leu from neutral aqueous solutions into CH_2Cl_2 solutions,[22] while Ala and Gly were rarely extracted.[23] No β-diketonate ligand was leaked into the aqueous phase, and the pH value changed only slightly during the extraction. These observations suggest that the lanthanide tris(β-diketonates) form highly coordinated complexes with several amino acids without loss of three diketonate ligands (see eq 2). The extraction percentage of each amino acid guest decreased as the central ion changed from Pr^{3+} or Eu^{3+} to Dy^{3+} and then to Yb^{3+}: larger sized Pr^{3+} and Eu^{3+} ions offered higher extractabilities than smaller sized Dy^{3+} and Yb^{3+}.[20] As expected from the optimized structures of ternary complexes (Figure 2), the larger metal

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(19) Modified MM van der Waals parameters: $E = (\epsilon_i\epsilon_j)^{1/2}[2.9 \times 10^{-5} \exp\{-12.5r_{ij}/(r_{oi} + r_{oj})\} - 2.25[(r_{oi} + r_{oj})/r_{ij}]^6]$. ϵ (hardness factor) = 0.325 for Pr^{3+} and 0.325 for Yb^{3+} (kcal/mol). r_o (van der Waals radius) = 2.20 for Pr^{3+} and 2.00 for Yb^{3+} (Å). Metal−O(acetylacetonate) stretching parameters: $E = 143.88 \times K_s[(\gamma - \gamma_o)^2 - 2(\gamma - \gamma_o)^3]/2$. K_s (stiffness) = 4.400 for Pr^{3+} and Yb^{3+} (mdyne). γ_o (standard length) = 2.388 for Pr^{3+} and 2.297 for Yb^{3+} (Å).
(20) Ionic radii of the employed metal cations were reported as 1.01 Å for Pr^{3+}, 0.95 Å for Eu^{3+}, 0.91 Å for Dy^{3+}, and 0.86 Å for Yb^{3+}.
(21) The possibility that the amino acid was bound as a neutral form, NH_2-$CHRCO_2H$, could not be disregarded.
(22) K_{ex} values of Phe were typically estimated as 73 for **1a** and 120 for **2a**: $K_{ex} = [\mathbf{1a} - \text{Phe or } \mathbf{2a} - \text{Phe}]_{org}/\{[\mathbf{1a} \text{ or } \mathbf{2a}]_{org} \times [\text{Phe}]_{aq}\}$.
(23) Histidine was moderately extracted under the same conditions: 12% with **1a** and 13% with **1b**. Since these values were much smaller than those for ThAla (see Table 1), the nature of the side chain greatly influenced extraction phenomena.

center provides a larger space to accommodate a guest amino acid. Complexes **1a**−**e** showed interesting guest selectivity of ThAla = Phe > Trp > Leu > PhGly = ThGly. This appears to be more than simple hydrophobicity of the amino acid. We calculated log *D* values for each amino acid guest at pH = 6.2 using the PALLAS program,[24] which can be considered a measure of hydrophobicity of the amino acid guest: log *D* = −1.50 for ThAla, −1.54 for Phe, −0.70 for Trp, −1.92 for Leu, −2.22 for PhGly, and −2.64 for ThGly. Among them, Trp had the largest log *D* value (highest hydrophobicity), but its extraction percentages were lower than those of ThAla and Phe. Although more hydrophilic amino acids such as Ala and Gly were rarely extracted, the steric factor of the guest must be considered as well as the hydrophobicity. Copper bis(*β*-diketonate) **6** was examined under the same extraction conditions, which was soluble in CH_2Cl_2 but rarely extracted amino acid guests from the neutral aqueous phase. The aqueous phase turned a blue color during the extraction experiment, indicating that copper complex **6** decayed and could not act as an effective receptor. It was noted that crown ether **7** extracted organic ammonium cations and cationic surfactant **8** extracted organic carboxylate anions,[18] but **7** and **8** did not operate synergistically in the binding of zwitterionic amino acids and rarely extracted amino acid guests. These extraction results revealed that the lanthanide tris(*β*-diketonates) exhibited unique binding abilities for amino acids under neutral conditions.

The lanthanide tris(*β*-diketonates) were suggested to form 1:1 ternary complexes with amino acid guests in the following extraction experiments: When the total concentration of complex **2b** in the CH_2Cl_2 phase and guest L-PhGly in the aqueous phase was fixed at 0.05 mol/L, the extracted amount of the PhGly displayed a bell-shaped dependence toward mole fraction of the PhGly and the maximum was observed at 1:1 stoichiometry (Figure 3a). When the concentration of **1b** in the CH_2Cl_2 phase was fixed at 0.04 mol/L, the extracted amount of the L-Phe increased with its concentration in the aqueous phase (0−0.16 mol/L) and the saturated amount of the extracted Phe also indicated 1:1 complexation (Figure 3b). Since other combinations of lanthanide receptors and amino acid guests offered similar relationships, the amino acid was believed to form a 1:1 complex with lanthanide complex receptor. We carried out several spectroscopic experiments to characterize the ternary complex of **1b** with amino acid. A ^{13}C NMR spectrum was recorded after extraction experiments of Phe with **1b** (conditions: same as those in Table 1). The Phe extracted exhibited signals only for three phenyl carbons at 129.8, 129.5, and 127.7 ppm from CD_2Cl_2 (53.1 ppm), while other carbon signals broadened and disappeared. When 5 mol % of europium complex **1b** was added to a $CDCl_3$ solution of *N*,*N*-dipropylalanine, carbon signals for $-CH_2NCHCO_2-$ broadened and disappeared, and other carbon signals shifted but were still observed. Thus, two functional groups of the amino acid guest were confirmed to be located near the europium center. CD spectroscopic studies also supported two-point binding of amino acid guest with lanthanide tris(*β*-diketonate). After the extraction experiment was performed using **1b** and L-Leu, a CD spectrum was taken for the CH_2Cl_2 phase in which all the extracted Leu was bound with complex **1b**. It showed characteristic CD peaks around 300 nm corresponding to the UV absorption of the europium complex **1b**. The M-shaped

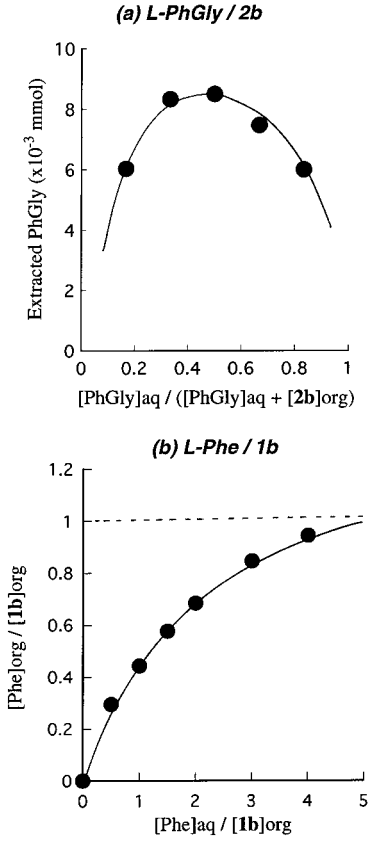

Figure 3. Extraction profile of amino acid with lanthanide tris(*β*-diketonate).

CD curve was observed: strong positive peak at 278 nm, strong negative peak at 291 nm, and weak positive peak at 320 nm. In other words, the chiral L-Leu was strongly fixed on the achiral complex **1b** at two points. When *N*-acetyl-L-Leu was employed as a substrate, the observed CD peaks were very weak. As observed in the achiral zinc(II)−porphyrin receptor system,[25] the two-point fixation of an amino acid guest may induce strong CD signals. Unfortunately, we did not obtain crystals of the ternary complex suitable for X-ray crystal structure determination, but these extraction and spectroscopic results support two-point fixation of the amino acid on the lanthanide metal center (see Figure 2).[26]

Table 2 summarizes extraction abilities of various europium tris(*β*-diketonates) which have fluorinated ligands **1b**, **2b**, **3b**, and **4b** and nonfluorinated ligand **5b**. Complex **2b** exhibited excellent extraction ability for amino acids. As frequently reported,[7,8] electronegative fluorinated moieties of the ligand increased Lewis acidity of the lanthanide tris(*β*-diketonate) and led to strong coordination of carboxylate anion of the amino acid guest. In addition, fluorinated ligands enhanced solubilities of lanthanide tris(*β*-diketonates) themselves and of their ternary complexes with amino acids in the organic media. Actually, complexes **4b** and **5b** produced insoluble materials and could not be used as extracting reagents. Thus, the ligand structure influenced the extraction behavior of the lanthanide complex receptors.

(24) PALLAS for Windows 1.2, CompuDrug Chemistry Ltd., was employed. Definition of log *D*, data for common amino acids, and relationship with free energy of transfer of amino acid side chain from vapor phase to water were reported: Tayar, N. E.; Tsai, R. S.; Carrupt, P. A.; Testa, B. *J. Chem. Soc., Perkin 2*, **1992**, 79.

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(26) Some complexes of amino acids with lanthanide complexes were characterized in the aqueous solutions: (a) Spaulding, L; Brittain, H.G. *Inorg.Chem.* **1985**, *24*, 3692. (b) Sherry, A.D.; Pascual, E. *J. Am. Chem. Soc.* **1977**, *99*, 5871. Also see ref 7.

Table 2. Extraction of Amino Acids by Various Europium Tris(β-diketonates)

amino acid[a] (pH value)	extraction %[b]				
	1b	**2b**	**3b**	**4b**	**5b**
PhGly (pH = 6.2)	28	43	32[c]	*d*	*d*
Phe (pH = 6.2)	48	62	54[c]	*d*	*d*
Trp (pH = 6.1)	42	52	49[c]	*d*	*d*

[a] D,L-Amino acid, 0.015 mmol, in H_2O, 1.5 mL/lanthanide tris(β-diketonate), 0.030 mmol, in CH_2Cl_2, 1.5 mL. [b] Extraction (%) = {([amino acid extracted in the presence of complex] − [amino acid extracted in the absence of complex])/[amino acid added initially in the aqueous solution]} × 100. [c] Trace amount of precipitate appeared. [d] Considerable amount of precipitate appeared.

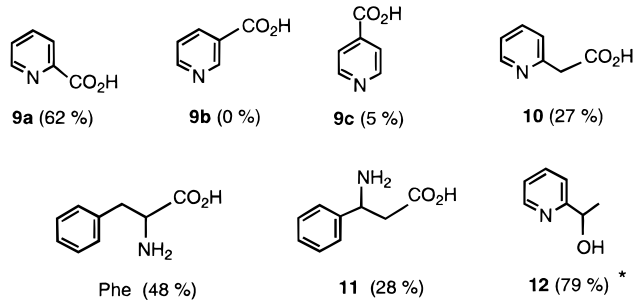

Figure 4. Extraction of various water-soluble guests by europium complex **1b**. Conditions: See Table 1. Asterisk indicates CCl_4 was used as the organic phase.

The lanthanide tris(β-diketonates) also showed interesting extraction behaviors for other types of guests. Figure 4 includes extraction results of picolinic acids **9a**−**c**, pyridine acetic acid **10** and other amino acids Phe and **11** as well as pyridyl alcohol **12**. Among three geometrical isomers of picolinic acids **9a**−**c**, 2-picolinic acid (**9a**) was much more effectively extracted by complex **1b** than 3- and 4-derivatives **9b**,**c**: it was also more effectively extracted than pyridine acetic acid **10**. Since their log *D* values were calculated to decrease in the order of **10** (−0.27) ≫ **9a** (−1.52) > **9b** (−1.93) = **9c** (−1.95), extraction ability seemed to relate not only to the hydrophobicity of the guest but also to the geometry of two ionic moieties in the guest. Europium tris(β-diketonate) **1b** exhibited higher extraction percentage for Phe than for amino acid **11**. Since Phe and **11** had similar log *D* values of −1.54 and −1.64, complex **1b** recognized the separation between carboxylate and ammonium moieties of the guest. These results indicate that the two-point binding more easily occurs in the five-membered ring system than in the large ring systems. Since neutral amino alcohol **12** was also extracted, the present type of lanthanide tris(β-diketonates) may have broad application in separation and detection of organic substrates of biological interest.

3. Transport of Unprotected Amino Acids under Neutral Conditions. We demonstrated above that several lanthanide complexes of fluorinated β-diketonate ligands had outstanding features in the binding of amino acids under neutral conditions. Since they are quite soluble in organic solvents and solubilize amino acids effectively in them, these are promising candidates for specific carriers of amino acids. Their transport properties were investigated using a CH_2Cl_2 liquid membrane cell as described.[18] Scheme 1 illustrates a transport system in which lanthanide tris(β-diketonate) is distributed in a bulk CH_2Cl_2 membrane and an amino acid guest exists as a zwitterion in a source aqueous phase I. The lipophilic lanthanide tris(β-diketonate) first forms a highly coordinated complex with the amino acid at the left side of the membrane. The resulting ternary complex is thus electrically neutral and well soluble in the liquid membrane phase. This ternary complex moves across the membrane and releases the guest amino acid into the receiving aqueous phase II. We demonstrate below that the lanthanide tris(β-diketonate) effectively transports unprotected amino acid from the neutral source phase to the neutral receiving phase. The abilities of ammonium and carboxylate ions to interact with the carrier are diminished, and most of the synthetic carriers reported could not transport the unprotected amino acids under neutral conditions.[1−3] We present a new type of carrier which transports the amino acids on the basis of the unique lanthanide coordination chemistry. Since membrane transport of amino acids is one of the most fundamental biological processes, the present study provides an excellent model of biomembrane transport and a promising prototype for new sensing and separation of biologically important amino acids.

Scheme 1. Liquid Membrane Transport of an Amino Acid by a Lanthanide Tris(β-diketonate) Carrier

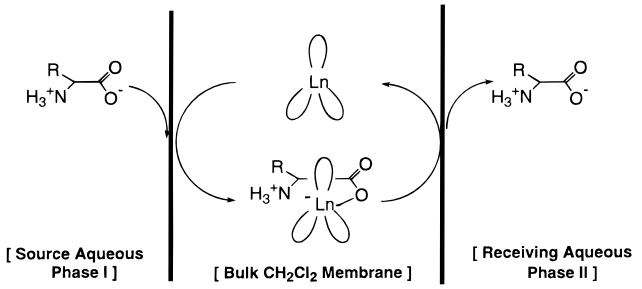

Table 3. Transport of Amino Acids by Lanthanide Tris(β-diketonates)

lanthanide complex	transport rate[a] × 10^7 (mol/h)			
	PhGly	Phe	Leu	Gly
1a	5.1	4.2	2.6	0.6
1b	5.7	4.0	2.8	2.0
1c	5.5	4.0[b]	5.2	1.2
1e	5.2[b]	4.7	2.9	0.6
2a	10.8	6.5	6.5	3.8
2e	4.4	6.4	3.2	0.4
6	0	0	0	0
7+**8**	0	0	0	0

[a] Amino acid, 0.05 mmol in H_2O, 5 mL//lanthanide tris(β-diketonate), 0.05 mmol, in CH_2Cl_2, 12 mL//H_2O 5 mL. [b] Precipitate appeared.

Table 3 shows that complexes **1a**−**e**, and **2a**,**e** which have fluorinated ligands effectively transported PhGly, Phe, and Leu under neutral conditions, while Gly was modestly transported. When these lanthanide tris(β-diketonates) were employed as carriers, pH change and β-diketonate leakage were rarely observed in either aqueous phase, supporting the transport mechanism illustrated in Scheme 1. In contrast, copper complex **6** and binary carrier composed of **7** and **8** were demonstrated to seldom carry amino acids. Lanthanide complexes **1a**−**e**, and **2a**,**e** provided satisfactorily high transport rates for amino acids comparable to that of crown ether **7**-mediated K^+ cation transport.[27] The guest selectivity of the transport process was somewhat different from that of the extraction process. Higher transport rates were obtained for PhGly, though Phe was more effectively extracted (see Table 2). Phe is probably too strongly bound to be transported efficiently. Similar relationships

(27) Although transport rates of aliphatic amino acids were also dependent on a combination of central lanthanide cation and ligand, they were compared with that of K^+ cation under similar conditions: Tsukube, H.; Shinoda, S.; Uenishi, J.; Shiode, M.; Yonemitsu, O. *Chem. Lett.* **1996**, 969.

Table 4. Enantioselective Extraction of Amino Acids by Chiral Lanthanide Tris(β-diketonates)

amino acid (pH value)	extraction %[c] (enantiomeric excess %)[d]				
	2a	**2b**	**2d**	**2e**	**3d**
PhGly[a] (pH = 6.2)	31 (11)	43 (13)	33 (19)	14 (49)	34 (10)
Phe[a] (pH = 6.2)	62 (2)	62 (7)	55 (15)	36 (24)	58 (5)
Trp[a] (pH = 6.1)	53 (3)	52 (4)	39 (23)	24 (30)	50 (3)
ThGly[a] (pH = 6.2)	45 (8)	45 (9)	29 (18)	15 (23)	38 (3)
ThAla[a] (pH = 6.2)	60 (3)	59 (6)	47 (15)	31 (15)	59 (2)
Leu[a] (pH = 6.2)	45 (5)	61 (7)	45 (17)	26 (17)	
potassium *N*-acetyltryptophanate (pH = 6.2)[b]	5 (*e*)	13 (4)	3 (*e*)	3 (*e*)	

[a] D,L-amino acid, 0.015 mmol, in H_2O, 1.5 mL//lanthanide tris(β-diketonate), 0.030 mmol, in CH_2Cl_2, 1.5 mL. [b] *N*-Acetyl-D,L-tryptophan, 0.015 mmol; KCl, 3 mmol; KOH, 0.015 mmol, in H_2O 1.5 mL// lanthanide tris(β-diketonate), 0.030 mmol, in CH_2Cl_2, 1.5 mL. [c] Extraction (%) = {([amino acid extracted in the presence of complex] − [amino acid extracted in the absence of complex])/[amino acid added initially in the aqueous solution]} × 100. [d] Enantiomeric excess % was calculated from the L/D ratio of amino acid complexed in CH_2Cl_2. [e] Enantiomeric excess % was not determined because the extractability was too small.

between extraction efficiency and transport rate have frequently been reported in other transport systems.[28]

4. Enantioselective Extraction of Unprotected Amino Acids. Chiral recognition of amino acids is an important process in many biological and artificial processes but has rarely been realized by artificial receptors. We successfully applied chiral lanthanide tris(β-diketonates) **2a**−**e** to the enantioselective extraction of unprotected amino acids. Extraction experiments were done using racemic amino acids as guests, and the extraction efficiency and enantioselectivity determined are summarized in Table 4. For chiral lanthanide complexes **2a**−**e**, the extractability was apparently dependent on the ion size of the central metal cation and generally decreased as the central cation changed from Pr^{3+} or Eu^{3+} to Er^{3+} and then to Yb^{3+}. Enantioselectivity, in contrast, had a "reversed order": $Pr^{3+} \leq Eu^{3+} < Er^{3+} < Yb^{3+}$. Although there should be some stereoisomers of the lanthanide complexes under the employed extraction conditions, the small central cation is expected to provide close contact between coordinating ligand and guest amino acid and to enhance the enantioselectivity. Indeed, ytterbium complex **2e** with a (+)-camphor-derived ligand bound L-PhGly with an ee value as high as 49%,[29] while the corresponding praseodymium complex **2a** gave 11% ee. Both chiral complexes offered higher enantioselectivities for aromatic PhGly, Phe, and Trp than aliphatic Leu. The sterically crowded PhGly was a preferred substrate in the present chiral recognition system. Erbium complex **3d** was examined for comparison since it has a different chiral ligand. **3d** offered comparable extractability to complex **2d**, but its enantioselectivity was largely suppressed. Thus, the nature of the fluorinated moiety only slightly changed extraction efficiency but greatly influenced chiral recognition profile. We also extracted potassium N-substituted-D,L-amino acidates using chiral complexes **2a**−**e**. These chiral complexes gave much lower extractabilities for *N*-acetyl-D,L-tryptophanate anion than those for the unprotected Trp, and their enantioselectivities could not be determined precisely. Since complex **2b** was confirmed to extract potassium *N*-(benzyloxy)-D,L-amino acidates nonenantioselectively,[10a] one-point binding of carboxylate to the lanthanide center was not enough for effective binding and chiral recognition. The two-point complexation between lanthanide tris(β-diketonate) and amino acid postulated above must play an important role in the binding and chiral recognition of the unprotected amino acids.[30]

Conclusion

We have demonstrated that the lanthanide(III) tris(β-diketonates) were unique and excellent receptors of unprotected amino acids. Their characteristic coordination chemistry made possible three of the hardest tasks in molecular recognition chemistry: (i) efficient extraction; (ii) fast membrane transport; (iii) excellent chiral recognition of the unprotected amino acids under neutral conditions. Although most common receptors did not operate well under neutral conditions, the efficiencies and selectivities of these lanthanide tris(β-diketonates) were sufficient. Thus, our lanthanide coordination strategy offers many potential extensions in various fields of chemistry and related technology.

Experimental Section

Materials. The lanthanide and copper complexes **1**−**6** illustrated in Figure 1 were obtained from Dojindo, Merck, and Gelest. These complexes were special grade reagents for NMR measurements which were soluble in CH_2Cl_2 and $CDCl_3$ but insoluble in water. We employed chiral complexes **2a**−**e**, and **3b**−**d** having (+)-camphor-derived ligands unless specified. Crown ether **7** and cationic surfactant **8** were purchased from Merck and used without additional purification. The amino acid substrates employed in Tables 1−4 were received as enantiomerically pure D- and L-forms: Chiral ThGly, ThAla, and *N*-acetyltryptophane were purchased from Sigma-Aldrich Japan, and others were obtained from Nacalai Tesque, Inc., or Wako Pure Chemical Industries, Ltd. Experiments were carried out using equimolar mixtures of D- and L-amino acids. The substrates examined in Figure 4 were also commercially available, excepting D,L-**12**:[31] **9a**−**c** and **10** from Nacalai Tesque Inc. and D,L-**11** from Aldrich Japan.

Modeling Method. The modeling of ternary complexes between lanthanide tris(acetylacetonates) and zwitterionic glycine was carried out on the basis of empirical calculations using the CAChe extended MM2 program (CAChe Scientific, Inc., version 3.8). Lanthanide complexes generally have large and variant coordination numbers so that it is very difficult to search all the stationary points of their geometries and to obtain global minima of their structures. We first optimized the structures of lanthanide tris(acetylacetonate) assuming that the lanthanide cations had unconfigurated coordination chemistry. Then, the carboxylate anion of the glycine was placed to coordinate with the lanthanide centers and to form a negatively charged ternary complex. In such complexes, the ammonium cation of the glycine could be located nearby lanthanide tris(acetylacetonate) via an electrostatic interaction. Since hydrogen bonding between hydrogen of the ammonium cation of the bound glycine and oxygen of the acetylacetonate ligand could be assumed instead of an electrostatic interaction, we performed modeling calculations for both cases and obtained similar optimized structures of the highly coordinated complexes. We could not determine the details of coordination number and stability of the ternary complex between lanthanide tris(acetylacetonate) and the zwitterionic amino acid but calculations supported that the lanthanide complex receptor had space enough for binding of zwitterionic amino acid guest.

(28) (a) Lamb, J. D.; Christensen, J. J.; Oscarson, J. L.; Nielson, B. L.; Asay, B. W.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6820. (b) Behr, J. P.; Kirch, M.; Lehn, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 241. (c) Tsukube, H.; Uenishi, J.; Higaki, H.; Kikkawa, K.; Tanaka, T.; Wakabayashi, S.; Oae, S. *J. Org. Chem.* **1993**, *58*, 4389.

(29) The enantiomer of ytterbium complex **2e** having (−)-camphor-derived ligands preferred D-PhGly.

(30) Chiral recognition was not observed in the membrane transport of D,L-amino acids. Several factors different from those in the extraction process were probably involved.

(31) Preparation of enantiomerically pure forms: Uenishi, J.; Nishiwaki, K.; Hata, S.; Nakamura, K. *Tetrahedron Lett.* **1994,** *35*, 7973.

Extraction Experiment. Extraction experiments were carried out by adding a CH_2Cl_2 solution of lanthanide tris(β-diketonate) (1.5 mL, 0.030 mmol) to an aqueous solution of amino acid (1.5 mL, 0.015 mmol). After the mixture had been stirred for 2 h, the aqueous phase was separated and characterized. The extraction percentage of the amino acid and its ee % value were estimated, based on UV spectroscopy, amino acid analysis (Hitachi, L-8500 amino acid analyzer), and chiral HPLC analysis (Daicel Chem. Ind., Crownpak CR(+)). Extraction (%) values indicated in Tables 1, 2, and 4 were calculated as follows: extraction (%) = {([amino acid extracted in the presence of complex] − [amino acid extracted in the absence of complex])/[amino acid initially added in the aqueous solution]} × 100. Reproducibility was confirmed as ±5% or better. Ee % values shown in Table 4 were obtained from the L/D ratio of the amino acid complexed in CH_2Cl_2 phase (reproducibility $<\pm$10%).

Transport Experiment. Transport experiments were performed at room temperature (ca. 16 °C) in a U-tube glass cell (internal diameter 2.0 cm).[18] Lanthanide tris(β-diketonate), dissolved in CH_2Cl_2 (0.05 mmol/12 mL), was placed in the base of the U-tube, and two aqueous phases, I and II, were placed in the tube arms which were floating on the CH_2Cl_2 membrane; I was an aqueous solution of amino acid (0.05 mmol/5 mL), while II was pure water (5 mL). We confirmed that no transport occurred in the absence of carrier. The transport rates shown in Table 3 were calculated from the initial rates of appearance of the guest salt in aqueous phase II, which were determined on the basis of UV spectroscopy, amino acid determination, and chiral HPLC analysis. Reproducibility was confirmed as ±10% or better.

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