Enantioselective binding and extraction of zwitterionic amino acids by chiral lanthanide complexes

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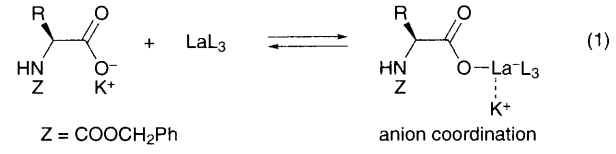
Lanthanide complexes with chiral camphor-derived β-diketonate ligands extract zwitterionic amino acids from neutral aqueous solutions into CH_2Cl_2 media with high efficiency and in good enantioselectivity.

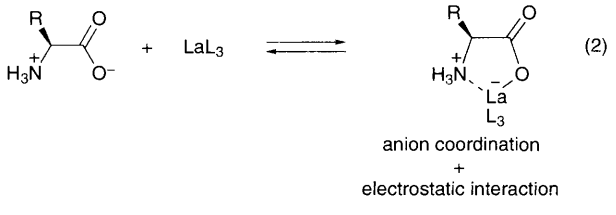
Amino acids exist as zwitterions in neutral water and their desolvation is a costly energetic process. Although a variety of synthetic receptors have been reported to bind ammonium or carboxylate moieties of the amino acid derivatives,[1] the zwitterionic amino acids are only extracted to a small extent by crown ethers, charged surfactants or related receptors.[2] Enantioselective extraction is more difficult and only a few examples exhibited satisfactory enantioselectivities for the extraction of zwitterionic amino acids.[3]

Here we demonstrate that chiral lanthanide tris(β-diketonates) enantioselectively extract amino acids from neutral aqueous solutions into CH_2Cl_2 phases. These were reported to induce enantiomeric shifts of NMR signals but form non-enantioselective complexes with racemic guests thermodynamically.[4] We present the first successful application of a lanthanide complex in enantioselective binding and extraction of zwitterionic amino acids. Some lanthanide complexes with chiral camphor-derived ligands specifically bind these amino acids, although they are electrically neutralized by three β-diketonate ligands. They interestingly offer enantioselective extraction of unsubstituted amino acids *via* 1 : 1 complexation.

We examined three kinds of receptors in the extraction of zwitterionic amino acids (Fig. 1): lanthanide tris(β-diketonates) **1a–d** and **2**, copper bis(β-diketonate) **3** and a binary receptor composed of crown ether **4** and surfactant **5**. We recently reported that some lanthanide tris(β-diketonates) non-enantioselectively bound organic carboxylate anions with K^+ [(eqn. 1)].[5] Since the resulting anionic complex may interact with



cationic species,[6] the lanthanide complex is expected to serve as an enantioselective receptor of zwitterionic amino acids *via* two-point binding [eqn. (2)].



Using the chiral lanthanide complexes **1a–d**, we successfully extracted unsubstituted amino acids from neutral aqueous solutions into CH_2Cl_2 solutions (Table 1). The extractions were carried out by adding a CH_2Cl_2 solution of the complex (3 ml, 0.030 mmol) to an aqueous solution of amino acid (3 ml, 0.015 mmol). After the mixture had been stirred for 2 h, the aqueous phase was separated and characterized. Since no β-diketonate ligand was observed in the aqueous phase and the pH value changed slightly during the extraction, these lanthanide complexes formed highly coordinated complexes with amino acids without ligand exchange. The extraction percentage of the amino acid was estimated spectroscopically and its ee was determined based on chiral HPLC analysis [Crownpak CR(+), Daicel Chem. Ind.]. When racemic amino acids were employed

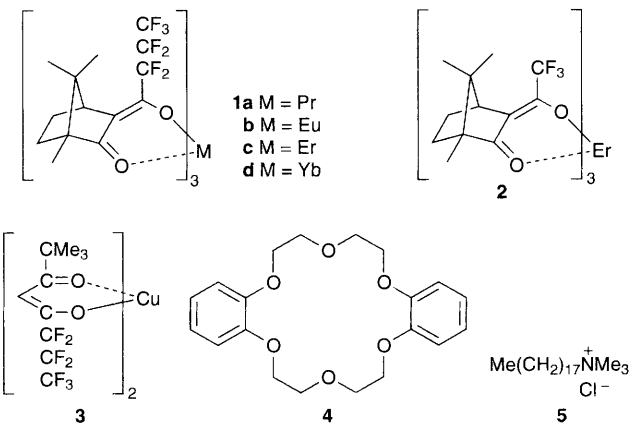


Fig. 1 Lanthanide complexes

Table 1 Extraction of zwitterionic amino acids by chiral lanthanide complexes

Amino acid (pH)	Extraction (%)[c] (ee %)[d]					
	1a	**1b**	**1c**	**1d**	**3**	**4 + 5**
D,L-phenylglycine[a] (6.2)	31 (11)	43 (13)	33 (19)	14 (49)	0	0
D,L-phenylalanine[a] (6.2)	62 (2)	62 (7)	55 (15)	36 (24)	0	0
D,L-tryptophan[a] (6.1)	53 (3)	52 (4)	39 (23)	24 (30)	0	0
potassium *N*-acetyl-D,L-tryptophanate[b] (6.2)	5 (e)	13 (4)	3 (e)	3 (e)	0	0

[a] Amino acid (0.015 mmol in 3 ml H_2O), lanthanide complex (0.030 mmol in 3 ml CH_2Cl_2). [b] *N*-Acetyl-D,L-tryptophan (0.015 mmol), KCl (3 mmol), KOH (0.015 mmol in 3 ml H_2O), lanthanide complex (0.030 mmol in 3 ml CH_2Cl_2). [c] Extraction (%) = {([amino acid extracted in the presence of complex] − [amino acid extracted in the absence of complex])/[Amino acid initially added to the aqueous solution]} × 100. Reproducibility < ±5%. [d] Ee was calculated from the ratio of amino acid complexed in CH_2Cl_2. Reproducibility < ±10%. [e] Ee was not determined because the extractability was too small.

as guests, both enantioselectivity and extractability were significantly dependent on the nature of lanthanide ion: their extractabilities generally decreased as the central ion changed from Pr^{3+} or Eu^{3+} to Er^{3+} and then to Yb^{3+}, though the enantioselectivities had a 'reversed' order ($Pr^{3+} \leqslant Eu^{3+} < Er^{3+} < Yb^{3+}$). In particular, ytterbium complex **1d** with (+)-camphor-derived β-diketonates bound L-phenylglycine with an ee value as high as 49%, and the complex with (−)-camphor-derived ligands preferred D- phenylglycine. Larger sized Pr^{3+} and Eu^{3+} ions offered higher extractabilities, while smaller Yb^{3+} and Er^{3+} ions provided higher enantioselectivities. These lanthanide tris(β-diketonates) were suggested to form 1 : 1 complexes with zwitterionic amino acids by two different extractions.[7] When the total concentration of the lanthanide complex in the CH_2Cl_2 phase and the guest L-phenylalanine in the aqueous phase was fixed at 0.05 mol dm^{-3}, the extracted amounts of the phenylalanine displayed a bell-shaped dependence and the maximum was observed at 1 : 1 stoichiometry. When the concentration of the lanthanide complex in the CH_2Cl_2 phase was fixed at 0.04 mol dm^{-3}, the extracted amount of the phenylalanine increased with concentration in the aqueous phase (0–0.16 mol dm^{-3}) and the saturated amount indicated 1 : 1 complexation. The chiral erbium complex **1c** with perfluoropropylated ligands gave higher ee values than the erbium complex **2** with trifluoromethylated ligands, though their extractabilities were comparable; the extraction (%) (ee %) of complex **2** was estimated as 34 (5) for D,L-phenylglycine, 58 (5) for D,L-phenylalanine and 50 (3) for D,L-tryptophan. Thus the natures of both the lanthanide centre and coordinating ligands greatly influenced their chiral recognition ability. In contrast, copper bis(β-diketonate) **3** and the binary receptor composed of **4** and **5** did not extract amino acids under the neutral conditions.[2d,8] Thus, the lanthanide tris(β-diketonates) showed unique receptor activities for zwitterionic amino acids.

We also extracted potassium *N*-substituted-D,L-amino acidates. Typically, the lanthanide complexes **1a–d** gave much lower extractabilities for the *N*-acetyl-D,L-tryptophanate anion than those for the unsubstituted zwitterion. Since the complex **1b** was reported to extract potassium *N*-benzyloxy-D,L-amino acidates non-enantioselectively,[5] two-point binding must be essential for chiral recognition as proposed in other receptor systems[9] [eqn. (2)]. When 5 mol% of ytterbium complex **1d** was added to a $CDCl_3$ solution of *N,N*-dipropylalanine, carbon signals for CH_2NCHCO_2 broadened and disappeared, while other carbon signals shifted and were still observed. Since both the nitrogen atom and the carbonyl group of the guest may be situated near the ytterbium centre, anion coordination and electrostatic interaction between the zwitterionic guest and the neutral lanthanide complex was assumed in the enantioselective extraction.

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