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Extraction of Unprotected Amino Acids by Mixed-Ligand Nickel(II) and Copper(II) Chelates

Yoshinori Ihara[*], **Shinji Kurose,** and **Takashi Koyama**

Department of Chemistry, Faculty of Education, Kanazawa University, Kanazawa 920-1192, Japan

Summary. Six mixed-ligand Nickel(II) and Copper(II) chelates with square-planar geometry of the formula [Ni/Cu(O-O)(*S-tmpn*)]$B(C_6H_5)_4$ were prepared, where O-O represents acetylacetonate, tropolonate, or hinokitiolate and *S-tmpn* is (*S*)-tetramethyl-1,2-propanediamine. The compounds were investigated with respect to their function as receptor for unprotected amino acids, taking advantage of their high solubilities in non-polar organic solvents. In liquid-liquid extraction experiments between a 1,2-dichloroethane phase containing the metal chelates and an aqueous phase containing amino acids (*rac*-phenylglycine, *rac*-phenylalanine, or *rac*-tryptophan), the nickel(II) chelates effectively extracted amino acids from the aqueous phases under neutral conditions, forming octahedral ternary chelates.

Keywords. Mixed-ligand chelate; Extraction of amino acids; Solvatochromism.

Introduction

Mixed-ligand nickel(II) and copper(II) chelates consisting of β-diketonates (β-*dike*) and N- or N,N′-alkylated ethylenediamines ($R_n en$), [Ni/Cu(β-*dike*)($R_n en$)]X (X: univalent anion such as ClO_4^-), are soluble in polar and non-polar solvents, exhibiting pronounced solvatochromic behavior [1–4]. The metal chelates which show high solubilities in non-polar solvents may serve as receptors to extract guest-ligand molecules from their aqueous solutions, and also to recognize chirality of the guest molecules in liquid(polar)-liquid(non-polar) extraction systems. In fact, *Tsukube et al.* have recently reported that some lanthanide complexes act as useful receptors of amino acids in liquid-liquid extraction experiments between non-polar organic phases containing chiral lanthanide(III) *tris*-(β-diketonate) complexes and aqueous phases containing unprotected amino acids; especially the ytterbium complex offered excellent enantioselectivity in the extraction process [5]. It appears that an attempt to utilize metal complexes as extraction reagents for chiral recognition of amino acids and other substrates is unique and interesting, because the stereochemistry of metal complexes can be designed to control steric effects, and chiral recognition owing to electronic effects on the basis of symmetry of metal orbitals is also anticipated [6–9].

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[*] Corresponding author. E-mail: ihara@ed.kanazawa-u.ac.jp

The investigations on the possibilities of extraction of amino acids and of chiral recognition were performed using transition metal complexes with high solubilities in non-polar solvents. We prepared square-planar nickel(II) and copper(II) mixed-ligand chelates containing (*S*)-tetramethyl-1,2-propanediamine (*S-tmpn*), acetylacetonate (*acac*), tropolonate (*trop*), or hinokitiolate (*hino*) as ligands, which are simple chiral model compounds, and tested whether or not they can extract unprotected amino acids as a preliminary examination directed toward chiral recognition.

Results and Discussion

Extraction of amino acids by the metal chelates

Table 1 summarizes solid state properties and analytical data of the chelates prepared for the extraction of amino acids. The presence of two molecules of crystal water in the Cu-*trop* and Cu-*hino* chelates was confirmed by thermogravimetric analyses. All the chelates have square-planar geometry in the solid state and are in most cases, slightly soluble in water but fairly soluble in most organic solvents as expected, exhibiting pronounced solvatochromic behavior. 1,2-Dichloroethane was selected as non-polar solvent in this study.

Extraction experiments were carried out for all metal chelates except for Cu-*acac* because the aqueous solutions of amino acids separated from dichloroethane phases initially containing the Cu-*acac* were colored after extraction, indicating the entering of Cu(II) ions into the aqueous phases. Table 2 shows the results of extraction for aqueous solutions of three aliphatic amino acids, *i.e.* *rac*-phenylglycine (*Phe-Gly*), *rac*-phenylalanine (*Phe-Ala*), and *rac*-tryptophan (*Trp*), using the above five metal chelates dissolved in dichloroethane.

The nickel(II) chelates displayed satisfactory efficiency as receptors of the amino acids; particularly in the Ni-*acac* systems high extractabilities were observed, and *Phe-Ala* was quantitatively extracted. Equilibrium was attained within 2 hours (Table 2); the *pH* values of the aqueous solutions of amino acids before and after the reactions were nearly constant around neutrality (6.6–7.4), suggesting that the amino acids were extracted in the zwitterionic form.

Table 1. Solid-state properties and analytical data of the chelates

Chelate	Color	μ_{eff}/B.M.	$\tilde{\nu}_{\max}/10^3\ \mathrm{cm}^{-1}$ [a]	Analytical data[b]		
				C (%)	H (%)	N (%)
[Ni(*acac*)(*S-tmpn*)]$B(C_6H_5)_4$	red-orange	diamag	20.4	70.94 (71.21)	7.50 (7.47)	4.67 (4.61)
[Ni(*trop*)(*S-tmpn*)]$B(C_6H_5)_4$	orange	diamag	20.5	71.99 (72.53)	6.75 (6.89)	4.35 (4.45)
[Ni(*hino*)(*S-tmpn*)]$B(C_6H_5)_4$	orange	diamag	20.7	73.62 (73.35)	7.46 (7.36)	4.25 (4.17)
[Cu(*acac*)(*S-tmpn*)]$B(C_6H_5)_4$	blue-violet	1.88	19.2	70.06 (70.64)	7.46 (7.41)	4.53 (4.58)
[Cu(*trop*)(*S-tmpn*)]$B(C_6H_5)_4 \cdot 2H_2O$	violet	1.96	20.1	68.51 (68.11)	6.68 (7.07)	4.13 (4.18)
[Cu(*hino*)(*S-tmpn*)]$B(C_6H_5)_4 \cdot 2H_2O$	brown-violet	1.84	20.5	69.23 (69.14)	7.11 (7.50)	3.86 (3.93)

[a] Wave number of the d-d band in the reflectance spectrum; [b]calculated values in parentheses

Table 2. Extraction of amino acids by the metal chelates (2 h → 4 h[a])

Chelate	Extraction (%)		
	Phe-Gly	*Phe-Ala*	*Trp*
[Ni(*acac*)(*S-tmpn*)]B$(C_6H_5)_4$	40→38	86→90	50→52
[Ni(*trop*)(*S-tmpn*)]B$(C_6H_5)_4$	10→9	28→30	24→28
[Ni(*hino*)(*S-tmpn*)]B$(C_6H_5)_4$	3	20→19	16→20
[Cu(*trop*)(*S-tmpn*)]B$(C_6H_5)_4$	4	0	0
[Cu(*hino*)(*S-tmpn*)]B$(C_6H_5)_4$	6→7	0	0

[a] Reaction times

Extraction profiles of amino acids

The Ni-*trop* chelate is considered to form a 1:1 adduct with the amino acids on the basis of the following experiments. When the total concentration of the chelate in the dichloroethane phase and *Phe-Ala* in the aqueous phase was fixed at 10 m*M*, the extracted amounts of *Phe-Ala* showed a bell-shaped dependence on the mole fraction of *Phe-Ala*, and the maximum was observed at 1:1 stoichiometry (Fig. 1). In addition, when the concentration of the chelate in the dichloroethane phase was fixed at 2.5 m*M*, the extracted amount of *Phe-Ala* increased with its concentration in the aqueous phase (0–15 m*M*); the saturated amount of *Phe-Ala* extracted is anticipated to approximate unity which also indicates the formation of a 1:1 adduct in the dichloroethane phase (Fig. 2).

On the other hand, a similar plot for Ni-*acac* and *Phe-Ala* (Fig. 3) suggests the formation of 1:2 and/or 1:3 adducts, in which the chelate accepts 2 and/or 3 *Phe-Ala*

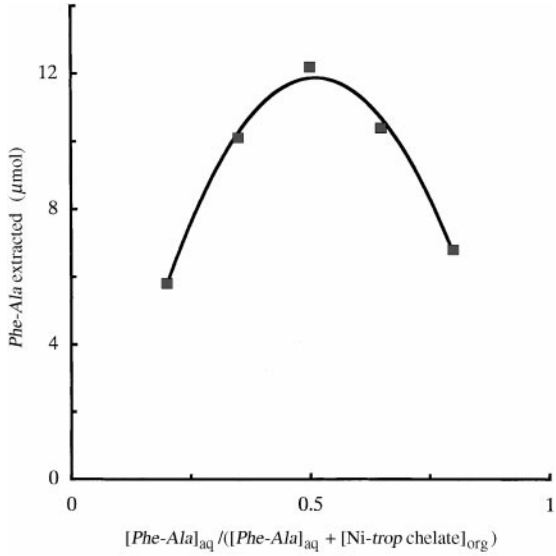

Fig. 1. Extraction profile in the system of *Phe-Ala* and [Ni(*trop*)(*S-tmpn*)]B$(C_6H_5)_4$ at constant total concentration

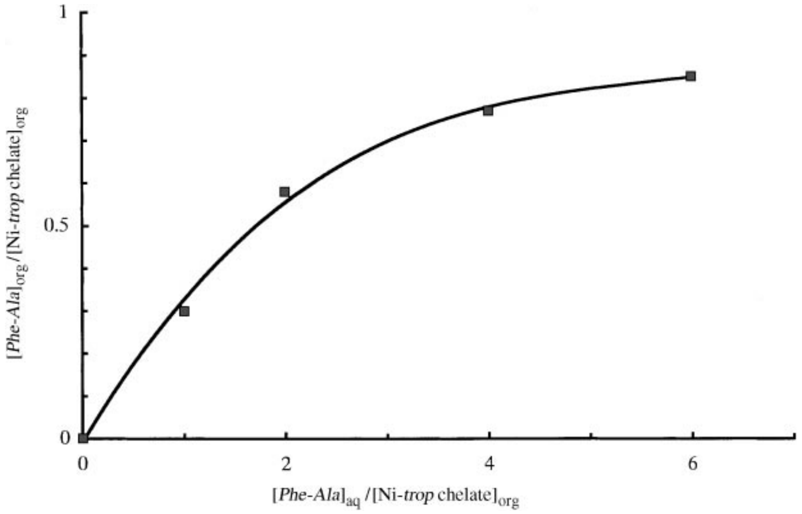

Fig. 2. Extraction profile in the system of *Phe-Ala* and [Ni(*trop*)(*S-tmpn*)]$B(C_6H_5)_4$ with increasing concentration of *Phe-Ala*

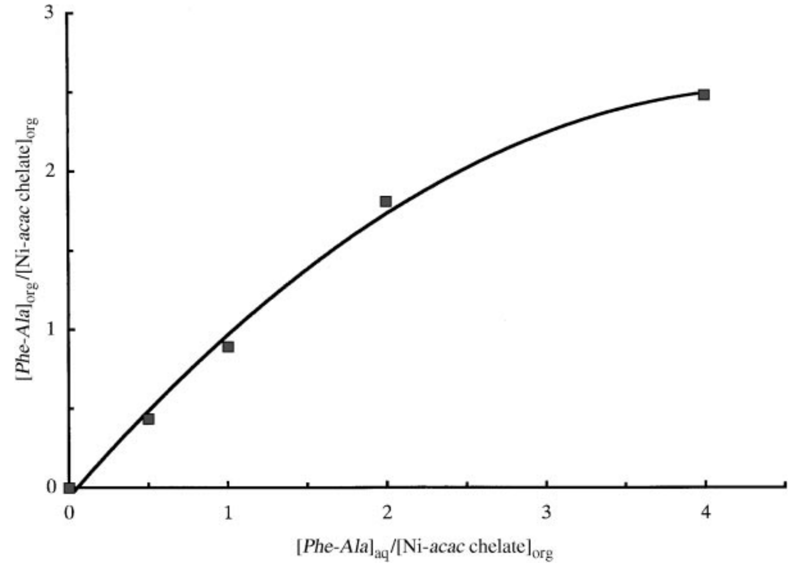

Fig. 3. Extraction profile in the system of *Phe-Ala* and [Ni(*acac*)(*S-tmpn*)]$B(C_6H_5)_4$ with increasing concentration of *Phe-Ala*

molecules per chelate molecule. This result implies that the reactions of Ni-*acac* proceed by a mechanism different from Ni-*trop*.

Spectroscopic changes of the dichloroethane phases

When reacting nickel(II) chelates with amino acids, the dichloroethane phases containing chelates with an effective extraction ability turned into weak green

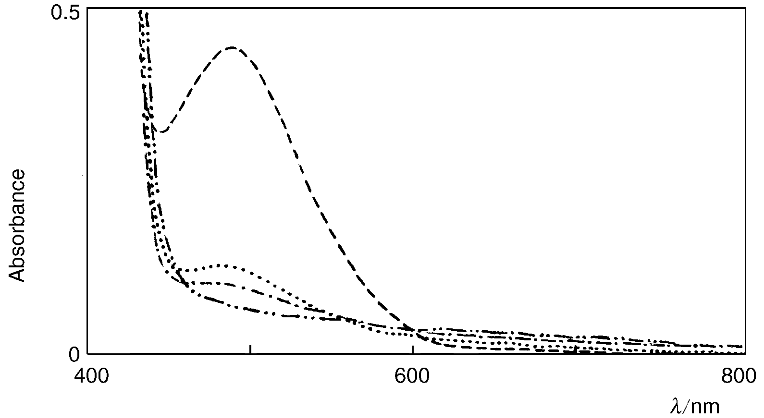

Fig. 4. Spectroscopic changes of the dichloroethane phases in the system of *Phe-Ala* and [Ni(*trop*)(*S-tmpn*)]$B(C_6H_5)_4$ with increasing concentration of *Phe-Ala*: $[\text{chelate}]_{\text{org}} = 2.5\,\text{m}M$ (- - -); $[\textit{Phe-Ala}]_{\text{aq}}/[\text{chelate}]_{\text{org}} = 2.5\,\text{m}M/2.5\,\text{m}M$ (· · ·); $[\textit{Phe-Ala}]_{\text{aq}}/[\text{chelate}]_{\text{org}} = 5.0\,\text{m}M/2.5\,\text{m}M$ (– · –); $[\textit{Phe-Ala}]_{\text{aq}}/[\text{chelate}]_{\text{org}} = 10\,\text{m}M/2.5\,\text{m}M$ (– · · · –)

characteristic for octahedral species. Figure 4 shows the UV/Vis spectroscopic changes of the dichloroethane phases in the system Ni-*trop*/*Phe-Ala* as a function of increasing concentration of *Phe-Ala* in the aqueous phase at constant concentration of the chelate in the dichloroethane phase. It can be seen that a strong absorption band at about 530 nm, which is observed in the absence of *Phe-Ala* and is evidently due to the square-planar chelate, decays gradually, and a very weak absorption appears in the red region. The total amount of *Phe-Ala* extracted increases with increasing relative concentration of *Phe-Ala* (Fig. 2); the spectroscopic changes represented by a drop of intensity at about 530 nm must therefore result from an increase of the amount of octahedral species newly formed in the dichloroethane phase. Accordingly, it seems reasonable to assume that the spectroscopic changes correspond mainly to structural conversion of the chelate from square-planar to octahedral. In addition, the fact that the formation of the adduct took place at a molar ratio of 1:1 for Ni-*trop* and *Phe-Ala* (Figs. 1 and 2) indicates that [Ni(*trop*)(S-*tmpn*)]$^+$ incorporates an amino acid in its coordination sites to produce the ternary octahedral complex [Ni(*Phe-Ala*)(*trop*)(*S-tmpn*)] in the extraction process.

The system of Ni-*acac* and *Phe-Ala* exhibits the same features with respect to the spectroscopic changes of the dichloroethane phases upon an increase of the relative concentration of *Phe-Ala* in the aqueous phase. From a higher extractability and the extraction profile (Fig. 3) it is supposed that the octahedral species consist of not only the ternary complex similar to that of the Ni-*trop* chelate, but other adducts such as complexes in which amino acid is combined with the *acac* ion by ligand reaction are also formed.

Further investigations will be directed towards a discussion of the extraction mechanism, the effects of different amino acids, and the possibility of enantioselective recognition.

Experimental

Materials

(*S*)-Tetramethyl-1,2-propanediamine (*S-tmpn*) was obtained by N-methylation of (*S*)-1,2-propanediamine [10]. Tropolone (*trop*) and hinokitiol (*hino*) were supplied by Tokyo Chem. Ind. Co. The mixed metal chelates were prepared as follows: Copper(II) chloride dihydrate (2 mmol) was dissolved in MeOH (5 cm^3), and a methanolic solution (5 cm^3) containing (*S*)-*tmpn* (4 mmol) and *acac*, *trop*, or *hino* (2 mmol) was added with stirring. After Na_2CO_3 (1 mmol) was added to the solution, it was gently heated for 1 h and then filtered. The crude crystals obtained upon addition of sodium tetraphenylborate (3 mmol) to the filtrate were recrystallized from dichloroethane.

Nickel(II) chloride hexahydrate (2 mmol) was dissolved in MeOH (5 cm^3), and a methanolic solution (5 cm^3) containing *S-tmpn* (4 mmol) and *acac*, *trop*, or *hino* (2 mmol) was added with stirring. After Na_2CO_3 (1 mmol) was added to the solution, it was gently heated to dryness. The resulting oily solid was treated with dichloroethane, and sodium tetraphenylborate (3 mmol) was added. The insoluble residue was filtered off, and the crude crystals precipitated from the filtrate were recrystallized from dichloroethane.

Extraction experiments

A dichloroethane solution of metal chelate (5 m*M*, 5 cm^3) was mixed with an aqueous solution of racemic amino acid (2.5 m*M*, 5 cm^3). After the mixture had been stirred for 2 h at room temperature, the aqueous phase was separated and characterized. The extraction percentage of amino acid was determined on the basis of the estimation of the residual amino acid in the aqueous phase by HPLC analysis (Kanto Chem. Co. Inc., Mightysil RP-18). Extraction values in Table 2 (%) were calculated as follows: extraction (%) = (((amino acid extracted in the presence of metal chelate) – (amino acid extracted in the absence of metal chelate))/(amino acid intially contained in the aqueous solution)) × 100.

Measurements

The electronic spectra were recorded with a Jasco V-570 spectrophotometer. The effective magnetic moments were evaluated from the susceptibilities measured by a Sherwood magnetic balance MSB-MKI. Thermogravimetry was carried out with a Seiko SSC/580 TG/DTA-30 apparatus.

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