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Optical Resolution of DL-Alanine by Formation of Ternary Copper(II) Complexes with L-Isoleucine

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Synopsis. A ternary complex, (D-alaninato)(L-isoleucinato)copper(II) (abbreviated as [Cu(D-ala)(L-ile)]), was crystallized selectively at 0 °C from an aqueous solution containing DL-alanine (DL-Ala), L-isoleucine (L-Ile), and copper(II) acetate monohydrate ($Cu(OAc)_2 \cdot H_2O$) in the molar ratio of 1:1:1.

Many studies have been reported on optical resolution of DL-amino acids through formation of ternary copper(II) complexes.[1—4] Most of such optical resolutions have taken advantage of electrostatic ligand–ligand interaction or stereoselective ligand exchange, and little work has been reported on resolution of DL-amino acids having an aliphatic side chain through formation of ternary complexes composed of two kinds of such amino acids. This note describes the possibility of optical resolution of DL-Ala by formation of ternary copper(II) complexes with L-Ile. [Cu(D-ala)(L-ile)] was crystallized selectively at 0 °C from an aqueous solution containing DL-Ala, L-Ile, and $Cu(OAc)_2 \cdot H_2O$ in the molar ratio of 1:1:1. This was confirmed by preparation of [Cu(D-ala)(L-ile)] and [Cu(L-ala)(L-ile)]. The cis-trans isomers for the two nitrogen or two oxygen donor atoms exist in these complexes. Such geometrical isomerism was also investigated from infrared spectra.

Experimental

Amino Acids. DL-Ala and L-Ile ($[\alpha]^{20}_{436}$+78.8 ° (*c* 1.00, 1 mol dm^{-3} HCl)) were purchased from Wako Pure Chemical Ind., Ltd., L-Ala ($[\alpha]^{20}_{436}$+34.6 ° (*c* 1.00, 1 mol dm^{-3} HCl)) from Kanto Chemical Co., Ltd., and D-Ala ($[\alpha]^{20}_{436}$−34.6 ° (*c* 1.00, 1 mol dm^{-3} HCl)) from Sigma Chemical Co. These amino acids were recrystallized from water–ethanol.[5]

Optical Resolution. DL-Ala (0.01 mol) and L-Ile (0.01 mol) were dissolved in 70 cm^3 of water and the solution was kept at 0 °C. To the solution was added a solution containing 0.01 mol of $Cu(OAc)_2 \cdot H_2O$ in 30 cm^3 of water at 0 °C. A ternary complex [Cu(D-ala)(L-ile)] was crystallized on standing at 0 °C overnight or by adding ethanol (100, 200, 300, or 400 cm^3) to the reaction mixture. The ternary complex was filtered and dissolved in 300 cm^3 of water by being heated at a temperature below 50 °C. An acetone solution of 8-quinolinol was added to precipitate the copper(II) in the aqueous solution as bis(8-quinolinolato)-copper (II). After filtration, a mixture of Ala and L-Ile was obtained by evaporating the filtrate to dryness under reduced pressure, and thoroughly washed with acetone. On the other hand, the filtrate from the reaction mixture was treated with 8-quinolinol in a similar manner. The amounts[6] and optical purities[7] of Ala in these mixtures were determined on the basis of specific rotation and ^{1}H NMR data.

Preparation of Ternary Complexes. Ternary complexes were prepared in a similar manner to the procedure for optical resolution. An aqueous solution containing D- or L-Ala, L-Ile, and $Cu(OAc)_2 \cdot H_2O$ in the molar ratio of 1:1:1 gave crystalline ternary copper(II) complexes at 0 °C. The complexes were recrystallized from water. Elemental analysis and specific rotation of [Cu(D-ala)(L-ile)]: C, 38.28; H, 6.43; N, 10.08%; ($[\alpha]^{20}_{436}$+24.3 ° (*c* 0.50, 1 mol dm^{-3} HCl). [Cu(L-ala)(L-ile)]: C, 38.52; H, 6.57; N, 10.09%; ($[\alpha]^{20}_{436}$+48.3 ° (*c* 0.50, 1 mol dm^{-3} HCl). Calcd for $C_9H_{18}N_2O_4Cu$: C, 38.36; H, 6.44; N, 9.94%.

Measurements. Specific rotations were measured with a Union Giken high sensitivity PM-101 digital polarimeter in 1 mol dm^{-3} hydrochloric acid using a 0.5 dm path length quartz cell. ^{1}H NMR spectra were recorded on a JEOL JNM-PMX 60 NMR spectrometer in deuterium oxide. Infrared spectra were obtained in the range 4000—400 cm^{-1} with a JASCO A-102 infrared spectrophotometer by the KBr disk method.

Results and Discussion

Results of Optical Resolution. The bluish violet complex, crystallized at 20 °C from an aqueous solution containing DL-Ala, L-Ile, and $Cu(OAc)_2 \cdot H_2O$ in the molar raio of 1:1:1, was bis(L-isoleucinato)copper(II) monohydrate with a specific rotation of +62 °.[8] The precipitation of this binary complex could be avoided by keeping the reacting solution at 0 °C and the ternary complex [Cu(D-ala)(L-ile)] was crysallized. The ternary complex had an optical purity of 93.4%. The specific rotation of the complex increased with an increase in the amount of added ethanol, since more soluble [Cu(L-ala)(L-ile)] was also precipitated by adding ethanol. [Cu(D-ala)(L-ile)] was almost completely precipitated by adding 400 cm^3 of ethanol, and [Cu(L-ala)(L-ile)] with an optical purity of 96.1% was obtained from the filtrate. The copper(II) within these complexes was removed with 8-quinolinol. ^{1}H NMR spectra of the mixtures obtained showed that the mixtures were composed of equimolar amounts of Ala and L-Ile. Ala in the mixture obtained from the precipitate had an abundance of D-isomer, whereas Ala from the filtrate an abundance of L-isomer. The results of optical resolution are summarized in Table 1.

These results indicate that DL-Ala was resolved into optical isomers with high optical purity by formation of the ternary copper(II) complexes with L-Ile, though the mixtures were not separated into D- or L-Ala and L-Ile.

Infrared Spectra. The geometrical isomerism existing in [Cu(D-ala)(L-ile)] and [Cu(L-ala)(L-ile)] was investigated on the basis of infrared spectra. Subtle spectral differences in 4000—1000 cm^{-1} are observed between these ternary complexes. In the range 1000—400 cm^{-1}, however, the spectral patterns are considerably different from each other as shown in Fig. 1. The differences may come from the presence of cis-trans isomers for the two nitrogen or two oxygen atoms.[9,10] The geometrical isomerism will give rise to differences in the absorption wave number of infrared active copper-ligand bands; the cis isomer should exhibit two ν_{Cu-N} and two ν_{Cu-O}, whereas the trans

TABLE 1. RESULTS OF OPTICAL RESOLUTIONS

Amount of added ethanol	[Cu(D-ala)(L-ile)]		Ala in mixture			
	Yield	Optical purity[a]	Configuration[b]	Yield	Optical purity	Degree of resolution[c]
cm^3	g	%		g	%	%
0	0.336	93.4	D	0.10	98.5	22
			L	0.76	15.2	26
100	1.311	72.3	D	0.40	69.2	62
			L	0.44	62.2	61
200	1.547	58.4	D	0.46	62.3	64
			L	0.40	77.5	70
300	1.590	49.6	D	0.52	49.0	57
			L	0.33	81.7	61
400	1.922	39.5	D	0.58	41.8	54
			L	0.28	93.4	59

a) The optical purities were determined on the basis of the specific rotation of an equivalent mixture of [Cu(D-ala)(L-ile)] and [Cu(L-ala)(L-ile)] ($[\alpha]^{20}_{436}$ +38.0° (1 mol dm^{-3} HCl)). b) D-Isomer was obtained from the precipitate and L-isomer from the filtrate. c) Degree of resolution (%)=[Yield of Ala (g)×Optical purity (%)]/0.445 (g).

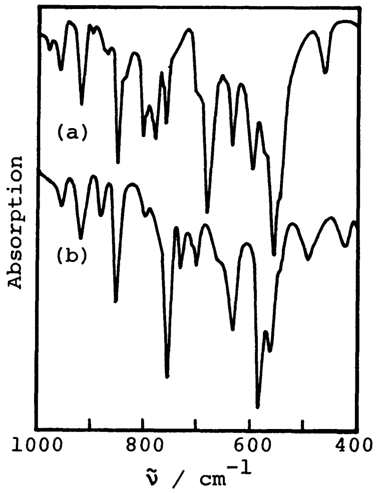

Fig. 1. Infrared spectra of the ternary copper(II) complexes.
(a): Cu[(L-ala)(L-ile)], (b): Cu[(D-ala)(L-ile)].

isomer only one for each of these modes.[10,11] In the range 500—400 cm^{-1}, [Cu(D-ala)(L-ile)] exhibits two bands at 494 and 422 cm^{-1} and [Cu(L-ala)(L-ile)] only one band at 466 cm^{-1}. These bands can be assigned to the $\nu_{\text{Cu-N}}$, since in copper(II) complexes of amino acids, $\nu_{\text{Cu-N}}$ appears in 500—400 cm^{-1} and $\nu_{\text{Cu-O}}$ in the range below 350 cm^{-1}.[10,11] These results suggeste that [Cu(D-ala)(L-ile)] has a cis structure and that [Cu(L-ala)(L-ile)] has a trans one.

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6) The molar ratio and amounts of Ala and L-Ile in their mixture can be obtained from integrated data of the methyl (Ala), *s*-butyl (L-Ile), and their α-CH proton signals in ^{1}H NMR spectra.

7) Since the optical rotation of L-Ile in the mixture could be obtained from the amount and specific rotation of L-Ile, the optical rotation of Ala in the mixture was calculated on the basis of the corresponding difference between the mixture and L-Ile.

8) The complex bis(L-isoleucinato)copper(II) monohydrate was prepared from an aqueous solution containing Cu(OAc)$_2$·H$_2$O and L-Ile in the molar ratio of 1:2. Found: C, 42.45; H, 7.72; N, 8.28%. Calcd for C$_{12}$H$_{26}$N$_2$O$_5$Cu: C, 42.16; H, 7.67; N, 8.19%. $[\alpha]^{20}_{436}$+62.2° (*c* 0.50, 1 mol dm^{-3} HCl).

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