Optical Resolution of Amino Acids and Mandelic Acid by Complex Formation with Copper(II) Ion

Hiroshi YAMASHITA, Shin KAYADA, and Takashi MAEKAWA*
Department of Applied Chemistry, Faculty of Engineering, Ehime University, Bunkyo-cho, Matsuyama 790
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Synopsis. The optical resolutions of amino acids and mandelic acid (MA) are done by complexation with copper(II). The optical purity of MA is the best when phenylalanine is used, i.e. 81%, and phenylglycine (PG) is well resolved by using L-MA with the optical purity of 74%. These results are interpreted in terms of the optical absorption energies of the copper(II) complexes in aqueous solution.

The optical resolution of chiral molecules such as amino acids and oxoacids have been done by a ligand-exchange chromatographic technique.[1—5] Among them the optical resolution of mandelic acid (MA=Hma) enantiomers was done by crystallization on the basis of an apparent difference in the solubility of the MA complexes with L-phenylalanine (PA=Hpa) in aqueous solution.[6,7] Leach and Angelici[8] measured equilibrium constants for the complexation of optically active amino acids (such as leucine, phenylalanine, alanine, and serine) and their esters to (L-valine-*N*-monoacetato)-copper(II).

We have found that optical resolution of PA and MA enantiomers could be done by using complexing with copper(II) on the basis of a ligand exchange reaction.[9] MA enantiomers were completely resolved by complexing with L-PA, while the maximum optical purity of PA enantiomer was about 65% by using D-MA. Both floated scums were [Cu^{II}(D-ma)(L-pa)] complex. These results were interpreted in terms of the optical absorption energies in the aqueous solution. In this paper this technique was used for the optical resolution of a few amino acid (AA=Haa) racemates. The relation between optical purity and thermodynamic stability of the copper(II) complexes is discussed.

Experimental

Apparatus. The flotation cell comprises a glass cylinder (2.5 cm diameter and 20 cm height) with a glass filter (No. 2) attached to its bottom. The optical purity was measured with a Toso TSK gel Enantio L1 column (25×0.46 cm i.d.) and a high-performance liquid chromatography (Toso, CCPD·UV-8000·CO-8000). Other apparatus was the same as described in our previous paper.[9]

Procedure. The flotation method was similar to that described previously.[9] The floated scums were washed with water, methanol, and diethyl ether, and dried in open air. After dissolving it in 2 cm^3 of 6 mol dm^{-3} nitric acid, the optical purity of the floated scum was measured by high-performance liquid chromatography at 40 °C. The flow rate of the mobile phase of a 1×10^{-3} mol dm^{-3} copper(II) sulfate aqueous solution was 1 cm^3 min^{-1}. The detection wavelength and pH were 254 nm and 5.0, respectively.

Results and Discussion

Figure 1 illustrates the relation between the d–d band maxima of the Cu^{2+} complexes in aqueous solution and the mole fraction of [Cu^{II}(D-aa)$_2$] and [Cu^{II}(L-aa)$_2$] (X); here, the counter complex is [Cu^{II}(L-ma)$_2$]. The absorption energy of the L-MA and L-AA system changes linearly with X, but it gave a convex curve for the L-MA and D-AA system. Some compositions of a more stable complex should be present in the latter system than in the former system. Figure 2 illustrates the differences of $\tilde{\nu}_{max}$ values from the dashed line in Fig. 1 (excess stability, $\Delta\tilde{\nu}$) in the L-MA and D-tryptophan (TR=Htr) system. The plot gives a parabolic curve and has the characteristic peaks at a mole fraction of 0.5. The plot in the L-MA and D-phenylglycine (PG=Hpg) system is also similar in shape to that of the L-MA and D-TR system. Therefore, a complex the Cu^{2+} : L-MA : D-TR (or D-PG) of which is 1 : 1 : 1 preferable in the mixture. It is thus considered that the [Cu^{II}(L-tr)(L-ma)] complex was dissolved in water by an electrostatic interaction and the π–π bond between L-TR in the complex and excess L-MA.

As shown in Fig. 3, an increase of the optical purity of PA with increasing pH may be due to complexation

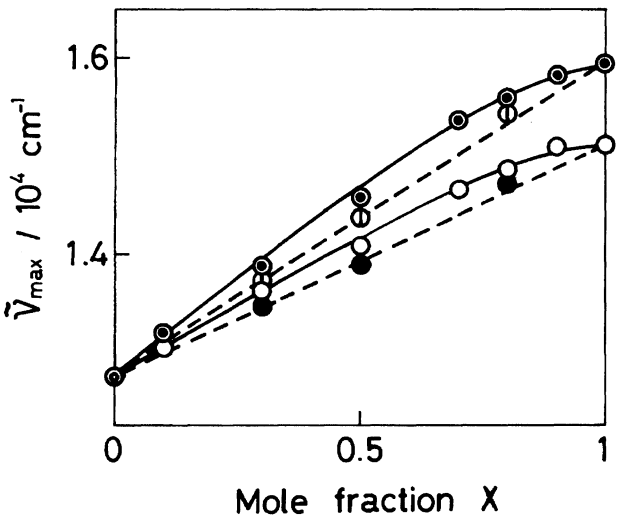

Fig. 1. Relation between the d–d band maxima of copper(II) complexes and mole fraction (X) in (1−X)(L-mandelic acid=MA)–0.5 Cu^{2+}–X (amino acid=AA) systems. ◉ : D-tryptophan (TR), ⓓ : L-TR, ○ : D-phenylglycine (PG), ● : L-PG. [Cu^{2+}] = 8.0×10^{-4} mol dm^{-3}, pH 5.8.

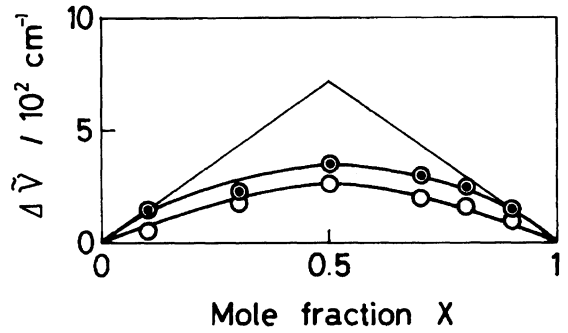

Fig. 2. Relation between $\Delta\tilde{\nu}$ of copper(II) complexes and the mole fraction (X) in $(1-X)$(L-MA)–0.5 Cu^{2+}–X(D-TR) system. All symbols and experimental conditions are the same as in Fig. 1.

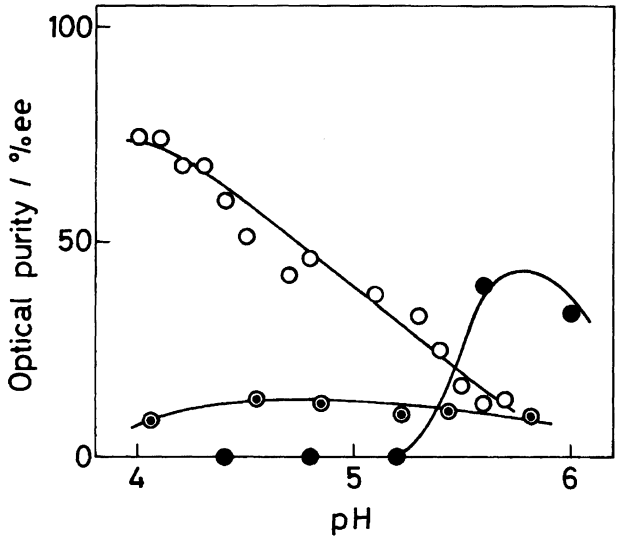

Fig. 3. Optical resolution of D- and L-AA by using L-MA. $[Cu^{2+}]:[MA]:[AA]=1:2:1$. ●: phenylalanine (PA); $[Cu^{2+}]=5.0\times10^{-3}$ mol dm^{-3}, ○: PG; $[Cu^{2+}]=2.5\times10^{-3}$ mol dm^{-3}, ◉: TR; $[Cu^{2+}]=2.5\times10^{-3}$ mol dm^{-3}.

of PA with copper(II) by means of acid dissociation of PA. When D- and L-PA and D- and L-PG are resolved by using L-MA, optimum pH are 5.8 and 4.0, respectively. A decrease of the optical purity beyond this pH may be due to hydrolysis of the complex. The optical purity of PG is higher at lower pH than that of PA owing to the low pK_{a2} of PG; thus, the pK_{a2}s of PA and PG are 9.11 and 4.38, respectively.[10] The optical purity of TR is about 10% ee in the pH 4 to 6 region, because the stabilities of the copper(II) complexes comprising D-TR and/or L-TR are large and have no difference. As shown in Table 1, the complexing ability of ligand with copper(II) increases in the following order: MA<PG<PA<TR. This coincides with the thermodynamic stability constants of those copper(II) complexes: $\log K_1$ values of $[Cu^{II}(ma)]^+$, $[Cu^{II}(pg)]^+$, $[Cu^{II}(pa)]^+$, and $[Cu^{II}(tr)]^+$ are 2.90,[11] 4.6,[10] 7.86,[10] and 8.29,[10] respectively. Thus, the optical purity of AA is more

Table 1. d–d Band Maxima of Cu^{2+}–MA–AA Complexes in Aqueous Solution[a]

	$\tilde{\nu}_{max}/10^4$ cm^{-1}			
	MA[c]	PA[c]	PG	TR
L-AA–L-AA		1.56	1.51	1.59
L-AA–D-AA		1.56	1.49[b]	1.58
D-AA–D-AA		1.55	1.51	1.59
D-MA–L-AA		1.45	1.42	1.45
L-MA–L-AA		1.42	1.39	1.44
L-MA–D-AA		1.41	1.41	1.45
D-MA–D-AA		1.39	1.41	1.44
L-MA–L-MA	1.28			
L-MA–D-MA	1.27			
D-MA–D-MA	1.27			

a) $[Cu^{2+}]:([MA]+[AA])=1:2$, $[Cu^{2+}]=8.0\times10^{-4}$ mol dm^{-3}, pH 5.8. b) $[Cu^{2+}]=1.6\times10^{-4}$ mol dm^{-3}. c) Previous results.[9]

effective with decreasing of the complexing ability of AA.

It was now considered to resolve MA by using L-AA. As shown in Fig. 4, optimum pHs are 5.0, 5.0, or 4.6 when D- and L-MA are resolved by using PA, TR, or PG, respectively. The optical purity of resolved MA is more effective when using L-PA compared to L-PG, due to the high stability of the PA complex. However, the optical purity of the MA made by using L-TR is too low in spite of the high stability of the copper(II)–TR complex. This may be due to the stereospecific structure of the TR (for example, the presence of a five-ring structure), so that an electrostatic interaction and the π–π bond between L-TR in the complex and excess L-MA are reduced. To separate D- and L-MA successfully, it is also necessary to consider the stereospecific structure of chiral ligands.

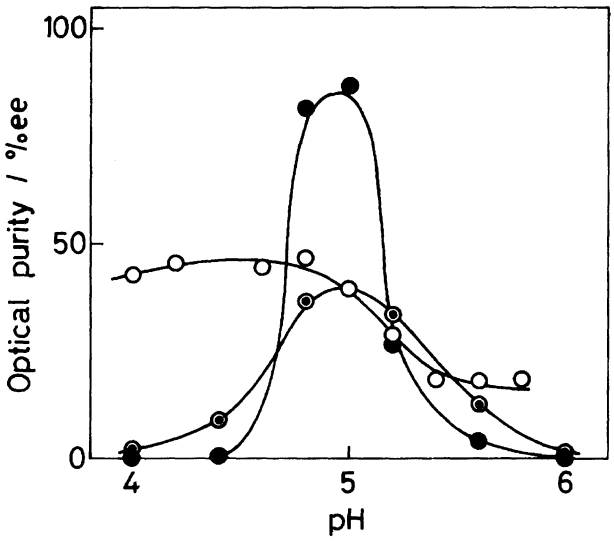

Fig. 4. Optical resolution of D- and L-MA by using L-AA. All symbols and experimental conditions are the same as in Fig. 3.

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