Optical Resolution of Aspartic Acid by Using Copper Complexes of Optically Active Amino Acids

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Synopsis. DL-Aspartic acid was resolved with high optical purity in the presence of an optically active amino acid copper complex. The mechanism of the optical resolution was explained by the competitive inhibition of crystallization.

We have reported a new method for the optical resolution of DL-aspartic acid by crystallization from a solution of DL-aspartic acid with a copper complex of optically active alanine, glutamic acid, and proline.[1,2] When the mixture was kept at a room temperature, the optically active aspartic acid copper complex crystallized spontaneously. The resolved aspartic acid had high optical purity and a configuration opposite to the optically active amino acid used in this resolution. This phenomenon had been explained as a stereoselective ligand exchange reaction.[1] However, the last communication confirmed that the proposed stereoselective ligand exchange did not represent the mechanism of these reactions, and that the phenomenon might be explained by the competitive inhibition of crystallization.[3]

L-Amino acid–Cu + DL-Asp → D-Asp–Cu ↓ crystallized
+ L-Asp + L-Amino acid ↓ in solution

This paper reports an optical resolution of DL-aspartic acid using a copper complex of the optically active amino acids other than those stated above. We also confirmed that the mechanism of the optical resolution of DL-aspartic acid was explained by competitive inhibition of crystallization.

Experimental

The optically active amino acids used in this experiment were D- or L-enantiomers of alanine, serine, threonine, valine, histidine, leucine, isoleucine, phenylalanine, methionine, glutamine, aspargine, lysine, and arginine. A solution (10 ml) of an optically active amino acid (2.5 mmol) was mixed with cupric carbonate ($CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$, about 1.25 mmol) and was heated, and the solution was filtrated to remove the excess of cupric carbonate. DL-Aspartic acid (2.5 mmol) was dissolved in 10 ml of hot water and this was added to the solution of the amino acid copper complex and filtered. The solution was kept still at room temperature for 1 d. The crystallized optically active aspartic acid copper complex was collected by filtration. *N*-(trifluoroacetyl)aspartic acid isopropyl ester was prepared in the usual way. The enantiomeric ratios of the resolved aspartic acid were determined by gas chromatography (Hitachi 163 Gas Chromatograph) by using Chirasil-Val capillary glass column (Applied Science, U. S. A.).

Results and Discussion

The results of the resolution of racemic aspartic acid in the presence of copper ion and optically active amino acids (Ala, Ser, Thr, Val, and His) are summarized in Table 1. Racemic aspartic acid was successfully resolved in high optical purity. When L-amino acid was used, D-aspartic acid copper complex crystallized spontaneously. Whereas, L-aspartic acid copper complex precipitated by using D-amino acids as shown in Table 1. By using the other optically active amino acids (Leu, Ile, Phe, Met, $GluNH_2$, $AspNH_2$, Lys, and Arg), the resolution of DL-aspartic acid was not successful under the conditions described in the experimental section.

Table 2 shows the effect of D- or L-aspartic acid addition to the DL-aspartic acid resolution in the presence of a L-serine copper complex. The amount of D- or L-aspartic acid added to the solution was 1/10—1/2 in molar ratio of DL-aspartic acid. When D-aspartic acid was added to the aqueous mixtures of a L-serine copper complex and DL-aspartic acid, the time required for the crystallization was shorter than the case without addition of any other amino acid (control). And the amount of the crystallized copper complex and the

TABLE 1. OPTICAL RESOLUTION OF DL-Asp BY USING COPPER COMPLEXES OF OPTICALLY ACTIVE AMINO ACIDS

Optically active amino acid	Optically active aspartic acid copper complex			
	Crop (mg)	Recovery[a] %	Confign.	Optical purity/%
L-Ala	150	43.5	D	95
D-Ala	151	43.8	L	80
L-Ser	120	34.8	D	96
D-Ser	107	31.0	L	87
L-Thr	61	17.7	D	92
D-Thr	43	12.5	L	87
L-Val	68	19.7	D	100
D-Val	40	11.6	L	82
L-His	225	65.2	D	77

a) Recovery = $\frac{\text{isolated L-(or D-Asp)}}{\text{total L-(or D-Asp)}} \times 100$.

TABLE 2. EFFECT OF D- OR L-Asp ADDITION TO DL-ASPARTIC ACID RESOLUTION

L-Ser–Cu +DL-Asp	Crop (mg)	Recovery[a] %	D-Asp (%)	Time h
Control	120	34.8	98	25
+D-Asp (1/2)	180	52.2	100	18
+D-Asp (1/4)	170	49.3	100	18
+D-Asp (1/10)	160	46.4	100	18
+L-Asp (1/2)	83	24.1	75	25
+L-Asp (1/4)	84	24.3	96	25
+L-Asp (1/10)	75	21.8	97	25

a) Recovery = $\frac{\text{isolated L-(or D-Asp)}}{\text{total L-(or D-Asp)}} \times 100$.

Table 3. Seeding effect to DL-aspartic acid resolution using D-Ser or L-Ser–Cu complexes

	D-Ser–Cu+DL-Asp Seed			L-Ser–Cu+DL-Asp Seed		
	No	L	D[a)]	No	L[b)]	D
Crop (mg)	99	151	58	134	58	171
Recovery/%	28.7	43.8	16.8	38.9	16.8	49.6
Confign.	L	L	D	D	L	D
O.P./%	97	97	99	96	100	100
Time/h	10	2.5	2.5	20	2.5	2.5

Seed; L: L-Asp–Cu, D: D-Asp–Cu. a) 2nd crop; 77.4 mg (recovery: 22.4%), 92% L. b) 2nd crop; 114.8 mg (recovery: 33.3%), 97% D.

c) Recovery $= \frac{\text{isolated L-(or D-Asp)}}{\text{total L-(or D-Asp)}} \times 100.$

optical purity of aspartic acid both increased. The amount of the crystals increased 1.5 times compared with the control when the amount of L-aspartic acid was 1/2 molar ratio of DL-aspartic acid. However, by the addition of L-aspartic acid, the optical purity of the resolved aspartic acid decreased gradually. When the amount of L-aspartic acid reached 1/2 molar ratio of DL-aspartic acid, the optical purity of aspartic acid decreased to 75% and the amount of crystallized D-aspartic acid copper complex reduced to 40% of the control. Therefore, the results indicate that the newly added L-aspartic acid inhibits the crystallization of a D-aspartic acid copper complex.

We have reported that the racemic aspartic acid copper complex was resolved by seeding with a L- or D-aspartic acid copper complex.[4)] The effect of the seeding to this selective crystallization was studied and the results are summarized in Table 3. L- or D-Aspartic acid copper complex was added to the aqueous mixtures of a D-serine copper complex and DL-aspartic acid. Without seeding, L-aspartic acid copper complex crystallization took place in 10 h. When L-aspartic acid copper complex was added to the mixture as seed, the time required for the crystallization was shortened remarkably (2.5 h), and the amount of the crystallized complex increased. On the contrary, when D-aspartic acid copper complex was added to the mixtures, a small amount of optically active D-aspartic acid copper complex crystallized. After removal of D-aspartic acid copper complex, L-aspartic acid copper complex with high optical purity crystallized spontaneously in 24 h. The resolution of DL-aspartic acid by using L-serine copper complex was similar to that described above. Thus it was found that the seeding procedure crystallized optically active aspartic acid copper complex effectively when the configuration of the seeds have the same configuration as the first crop (Table 3 2nd and 6th columns), which was obtained without seeds. However, when the configuration of the seeds has the opposite configuration to the first crop, the seeds initiate the crystallization of small amount of optically active aspartic acid copper complex which has the same configuration as the seed. After removal of the crystallized complex from the solution, the optically active aspartic acid copper complex, which is favored to precipitate, was crystallized spontaneously.

These experiments indicate that the configuration of optically active amino acids determines the configuration of the crystallized optically active aspartic acid copper complex, and the configuration of the aspartic acid is opposite to the optically active amino acid used in the resolution. The mechanism of the optical resolution could be explained by the stereoselective inhibition of crystallization. When the DL-aspartic acid was resolved in the presence of D-serine copper complex, the solution was composed of L- and D-aspartic acid, D-serine and copper ions. The crystallization of L-aspartic acid copper complex is faster than that of D-aspartic acid copper complex in the presence of D-serine. The crystallization of D-aspartic acid copper complex was inhibited by the presence of D-serine copper complex in the solution. Because these two D-amino acid copper complexes have the same configuration and have stronger interaction between these two. Therefore the rate of the crystal growth is affected by the presence of the other optically active amino acid. The addition of L- or D-aspartic acid, and the seeding of L- or D-aspartic acid copper complex in the reaction mixture could also affect the rate of crystallization of optically active aspartic acid copper complex. All these results could support the competitive inhibition mechanism of crystallization proposed in this kind of the optical resolution of aspartic acid. This type of optical resolution could be applicable to other racemic compounds.

References

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