BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 130—135 (1968)

The Partial Resolution of Racemic α-Alanine through the Cobalt(III) Complexes of Optically Active Aspartic or Glutamic Acid[*1]

Muraji SHIBATA, Hiroaki NISHIKAWA and Kinya HOSAKA

Department of Chemistry, Faculty of Science, Kanazawa University, Kanazawa

(Received July 20, 1967)

When a hundred per cent excess of racemic α-alanine was reacted, in the presence of activated charcoal, with a reaction mixture of tricarbonatocobaltate(III) and L-asparate, water-insoluble β-tris(alaninato)cobalt(III) was precipitated. The recovery of alanine from this triscomplex showed a partial resolution; the D form of alanine was preferentially complexed, and the optical purity of the alanine recovered was about 38%. Spectroscopic measurements (absorption, ORD and CD) showed that the predominantly-existing species in the above reaction mixture was the $(-)$-$[\mathrm{Co\,CO_3(L\text{-}asp)_2}]^{3-}$ anion, and that the reaction of this complex anion with racemic alanine led to the predominant formation of $\beta(-)$-$[\mathrm{Co(D\text{-}ala)_2(L\text{-}ala)}]$ (the $(-)$ sign refers to the sign of the Cotton effect in the first absorption band region). Similar experiments were carried out with D-aspartate and L-glutamate in place of L-aspartate. Through all the experiments, we have found that the complexes which are effective for the resolution of racemic alanine and the product or tris(alaninato)cobalt(III) have the same sign of the Cotton effect in their first-band regions.

Gott and Bailar1) first reported that when the carbonatobis(levo-propylenediamine)cobalt(III) cation was treated with a racemic organic acid, the dextro form of the acid entered the coordination sphere of the complex more readily than the levo form. By means of this preferential coordina-

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[*1] Presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

1) A. D. Gott and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, **74**, 4820 (1952).

tion of one of the active forms, Sarma and Bailar²⁾ resolved propylenedimaine, tartaric acid, and α-alanine; the resolutions of racemic alanine attained through the L-tartratocopper(II) complex and copper(II) L-glutamate were 3.8 and 3.3% respectively.

Later, we reported in a short paper³⁾ that the same amino acid was more effectively resolved by the use of a cobalt(III) complex with L-aspartate (about 30%). Incidentally, the resolution of DL-aspartic acid by the utilization of copper(II) chelates of D- or L-alanine, *etc.*, has been reported by Harada.⁴⁾ The present paper is an augmentation of the previous one;³⁾ it will report further investigations of the partial resolution of α-alanine. In addition to the cobalt(III) complexes of L- or D-aspartic acid, those of L-glutamic acid were also used as a material that effects the resolution. We found a correlation between the active form of alanine preferentially coordinated and the configuration of the cobalt(III) complexes.

Experimental

Resolution through the Complexes of L(or D)-Aspartic Acid. *Procedure 1.* Throughout the procedures described below, "the green solution" of tricarbonatocobaltate(III) was first prepared as a stock for the preparation of aspartato or glutamato complexes. A cold mixture of an aqueous solution (about 20 *ml*) containing cobalt chloride hexahydrate (6.0 g, 0.025 mol) and 30% hydrogen peroxide (10 *ml*, excess) was added, drop by drop, to an ice-cooled slurry of potassium bicarbonate (17.5 g, 0.175 mol) in water (18 *ml*); the resulting green solution was then stirred for a few minutes further in the cold.

Monopotassium L(or D)-aspartate (8.6 g, 0.050 mol) was added to the green solution, and the mixture was stirred at 60°C for 5 hr, whereupon the color of the solution became red-violet. A hundred per sent excess of racemic α-alanine (13.5 g, 0.150 mol) was added to the above solution, and the mixture was adjusted to pH 9.5—10 with an aqueous solution of potassium hydroxide. After the addition of activated charcoal (2 g), the solution was stirred at about 50°C for 2 hr, whereby the β(cis-cis)-complex of tris(alaninato)-cobalt(III) was precipitated. The complex was collected with the charcoal and washed thoroughly with hot water and ethanol, and then ether. After dyring, this material was suspended in hot dilute aqueous ammonia and treated with hydrogen sulfide to decompose the complex. After the removal of the cobalt sulfide by filtration, the filtrate was concentrated to a small volume under reduced pressure. When the concentrate became turbid, it was clarified by filtering it with a small amount of activated charcoal. Acetone was added in the cold to the final clear concentrate to recover alanine. A 5% solution of this alanine in 1 N hydrochloric acid was used for the measurement of the optical rotation at the sodium-D line. The percentage of the resolution or the "optical purity" was represented by the quotient of the observed specific rotation divided by the value for pure L-alanine ($[\alpha]_D=14.47$).

Alanine recovered in the case of the L-aspartato complex, 3.0 g, 3.0 g; $[\alpha]_D=-5.62$, -5.52; optical purity, 38.8%, 38.1%.

Alanine recovered in the case of the D-aspartato complex, 2.8 g; $[\alpha]_D=5.60$; optical purity, 38.7%.

In order to isolate the complex existing in the reaction mixture of tricarbonatocobaltate(III) and L-aspartate, we prepared the same solution, neutralized it with dilute acetic acid, and then added a large amount of methanol. A red-violet material precipitated, but it was very hygroscopic (it probably was potassium salt). Therefore, it was treated with an aqueous solution of silver nitrate to produce a less soluble silver salt.

Found: C, 13.65; H, 1.94; N, 3.65%. Calcd for $Ag_3[CoCO_3(C_4H_5NO_4)_2]\cdot 4H_2O$; C, 13.91; H, 2.33; N, 3.60%.

Thus, it was assumed that the predominant complex in the reaction mixture was the carbonatobis(L-aspartato)cobaltate(III) anion.

Procedure 2. The reaction mixture mentioned above was prepared with L-aspartate, and the mixture was once acidified with dilute acetic acid in order to decompose all of its carbonate ions. The resulting solution was then adjusted to pH 10 with dilute potassium hydroxide. This was treated with racemic alanine under the same conditions as have been described in Procedure 1.

Alanine recovered, 2.6 g; $[\alpha]_D=-5.91$; optical purity, 40.8%.

Procedure 3. A little higher resolution was attained by a slight alteration of Procedure 1, *i. e.*, the amount of L-aspartate was increased (12.1 g, 0.075 mol). Tricarbonatocobaltate(III) was reacted with aspartate in the presence of activated charcoal (0.5 g) at room temperature for 2 hr. Thereafter, the process was the same as has been described in Procedure 1.

Alanine recovered, 1.9 g, 1.8 g; $[\alpha]_D=-6.45$, -6.34; optical purity, 44.5%, 43.8%.

Procedure 4. Recently, we reported the isolation of the four isomers of trihydrogen tris(L-aspartato)-cobaltate(III).⁵⁾ By the use of solubility differences depending on the pH values, the $\alpha(+)$-, $\alpha(-)$-, $\beta(+)$- and $\beta(-)$-isomers were obtained from a reaction mixture of tricarbonatocobaltate(III) and L-aspartate. The fourth procedure concerns these isomers.

A certain amount (0.025 mol) of each isomer was dissolved in a very diluted aqueous solution of potassium hydroxide. Racemic alanine was then added to this solution, and the mixture was adjusted to pH 9.5—10. In the presence of activated charcoal (2 g), the mixture was stirred at 50°C for 2 hr. It was found that only one isomer of the four, $\alpha(-)$, produced a precipitate of water-insoluble β-tris(alaninato)cobalt(III).

Alanine recovered, 4.3 g; $[\alpha]_D=-4.47$; optical purity, 30.0%.

Resolution through the Cobalt(III) Complexes of L-Glutamic Acid. Except for the use of L-glutamate in place of L (or D)-aspartate, the same procedure was followed. Monopotassium L-glutamate (9.3 g,

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2) D. Sarma and J. C. Bailar, Jr., *ibid.*, **78**, 895 (1956).

3) M. Shibata, Y. Fujita, N. Naito and K. Hori, This Bulletin, **36**, 485 (1963).

4) K. Harada, *Nature*, **205**, 590 (1965).

5) M. Shibata, H. Nishikawa and K. Hosaka, This Bulletin, **40**, 236 (1967).

0.05 mol) was added to a tricarbonatocobaltate(III) solution, and the mixture was stirred at 60°C for 5 hr. The resulting red-violet solution was treated with racemic alanine.

Alanine recovered, 4.3 g, 4.3 g; $[\alpha]_D = -2.60$, -2.75; optical purity, 18.0%, 19.0%.

In the manner of Procedure 1, a carbonato complex was isolated as a silver salt.

Found: C, 15.97; H, 2.48; N, 3.83%. Calcd for $\mathrm{Ag_3[CoCO_3(C_5H_7NO_4)_2]\cdot 4H_2O}$: C, 16.42; H, 2.73; N, 3.48%.

A higher percentage of resolution was obtained by a procedure similar to Procedure 2.

Alanine recovered, 3.6 g, 3.0 g; $[\alpha]_D = -4.33$, -4.38; optical purity, 29.9%, 30.3%.

Instrumental Measurements. Optical rotations at the Na-D line were measured with a Yanagimoto Model OR-20 photo-magnetic direct-reading polarimeter at room temperature. The absorption, optical rotatory dispersion (ORD), and circular dichroism (CD) spectra were all measured on a Jasco Model UV-5 optical rotatory dispersion recorder with a CD attachment. X-Ray powder patterns were taken with a Rigaku-denki Geigerflex, using a Co-target.

Results and Discussion

On the Reaction. A distinctive feature of the reactions which we adopted for the partial resolution of alanine is that the water-insoluble β-tris(alaninato)cobalt(III) precipitates from the reaction mixture of the asparatato (or glutamato) complex and racemic alanine. For this precipitation reaction, the presence of activated charcoal is an indispensable condition. The amount of charcoal influenced the yield and the optical purity of the recovered alanine. A series of experiments were carried out according to the previously-described procedure;[3] when the amounts of the charcoal were 0.4, 2.0, 4.0 and 6.0 g, the yields of alanine were 2.3, 3.4, 2.9 and 2.4 g, and the optical purities were 13.8, 33.5, 38.0 and 34.1%, respectively. Consequently, it may be assumed that activated charcoal is necessary for both the reactions of ligand exchange and preferential coordination. In the present experiments, 2.0 g of charcoal were used for easier handling and for a higher recovery of alanine. In our previous paper,[3] we reported that the co-existence of cellulose powder with activated charcoal increases the percentage of resolution. We now believe that not only the cellulose, but also the charcoal plays an effective role in the preferential coordination of one active form of racemic alanine.

On the Mechanism. Although the mechanism of the present reaction has not yet been clarified, there seems to be a certain correlation between the active form of alanine preferentially complexed and the configuration of the cobalt(III) complex that effects this resolution. Recently, several workers reported the isolation of the possible geometrical-optical isomers of tris(L- or D-alaninato)cobalt(III).[6-8] They stated that one of the four isomers of [Co(L or D-ala)$_3$], the β(+)- or the β(−)-isomer, was completely insoluble in water (the (+) and (−) signs refer to the sign of the Cotton effect in the first absorption band region). If this solubility property holds in our reaction product, it must be a non-equimolar mixture of the β(−) and β(+) isomers. In this respect, the CD spectrum of the product obtained by Procedure 1 is compared with that of β(+)-[Co(L-ala)$_3$] under the same conditions (in 50% H_2SO_4) (Fig. 1). The two spectra differ considerably in the intensity of the first CD peaks, $\Delta\varepsilon = -1.27$ (or $+1.27$) for the product and $\Delta\varepsilon = -1.00$ for the [Co(L-ala)$_3$]. This fact suggests that the product concerned is not a mixture of the β(−) and β(+) isomers, and that the formation

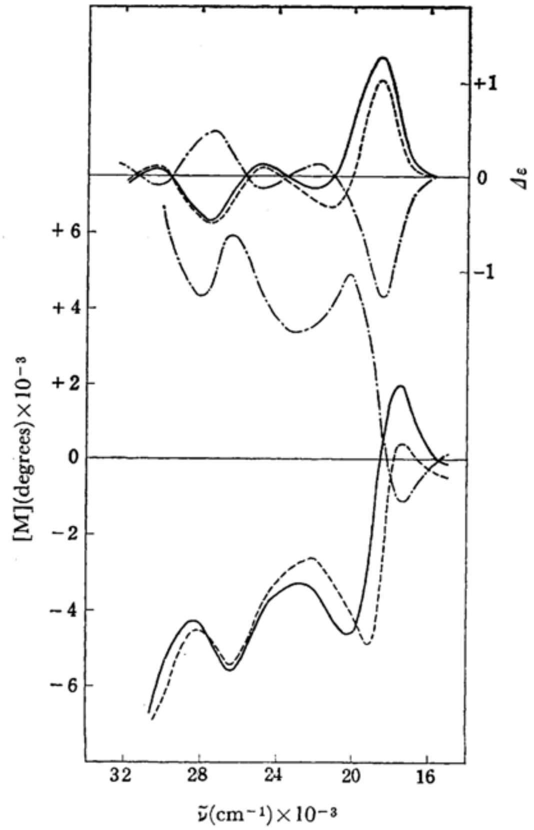

Fig. 1. ORD and CD curves for:
(·—·) Reaction product of L-aspartato complex with racemic alanine in 50% H_2SO_4,
(——) Reaction product of D-aspartato complex with racemic alanine in 50% H_2SO_4,
(······) β(+)-[Co(L-ala)$_3$] in 50% H_2SO_4.

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[6] B. E. Douglas and S. Yamada, *Inorg. Chem.*, **4**, 1561 (1965).

[7] J. H. Dunlop and R. D. Gillard, *J. Chem. Soc.*, **1963**, 6531.

[8] R. G. Denning and T. S. Piper, *Inorg. Chem.*, **5**, 1056 (1966).

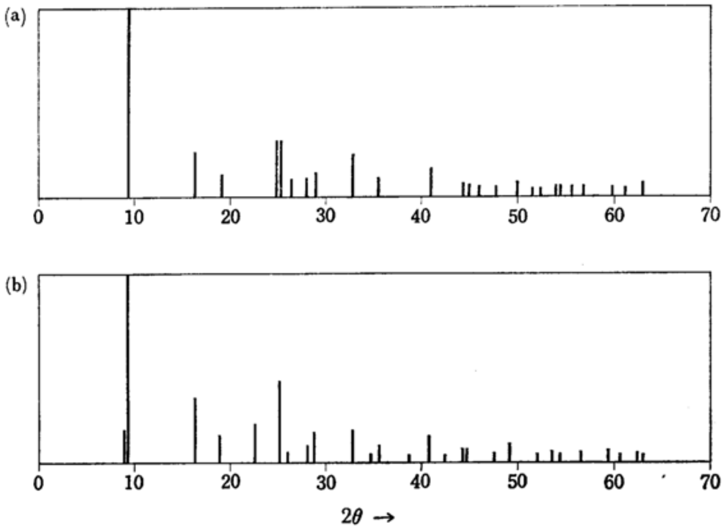

Fig. 2. X-Ray powder diffraction patterns of:
(a) Reaction product of L-aspartato complex with racemic alanine,
(b) $\beta(+)$-$[Co(L\text{-}ala)_3]$.

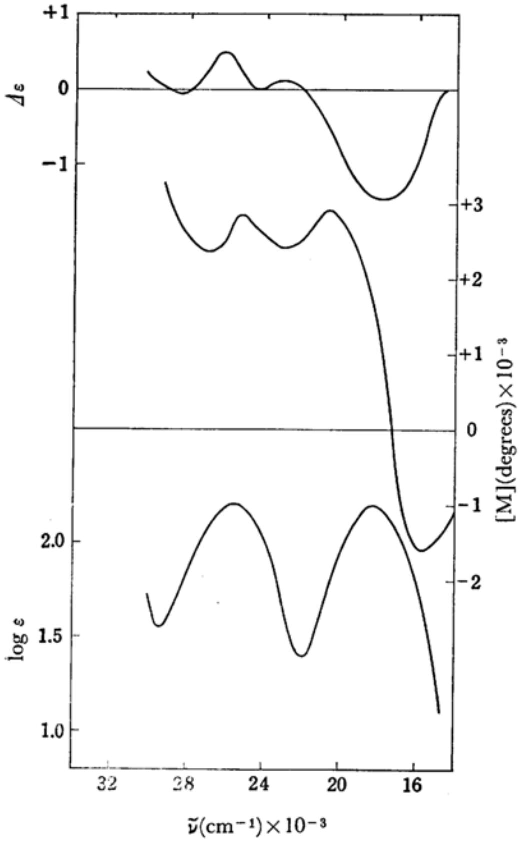

Fig. 3. Absorption, ORD and CD curves for $[CoCO_3(L\text{-}asp)_2]^{3-}$ in N NaCl.

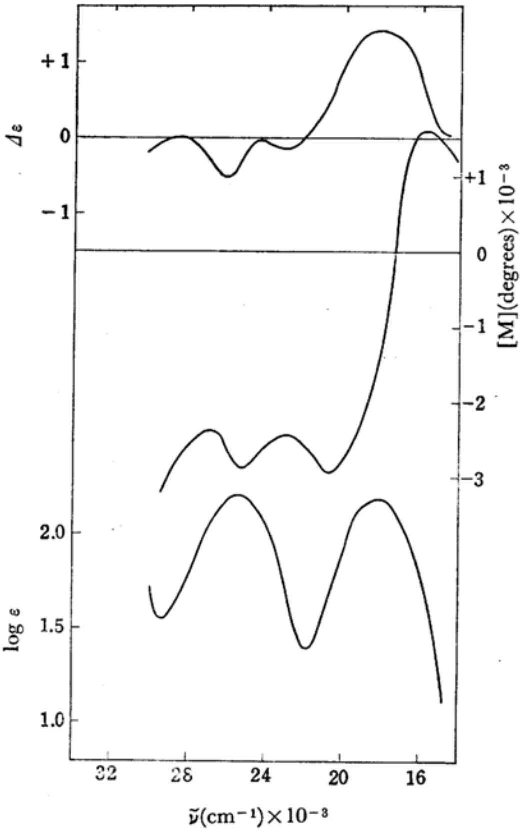

Fig. 4. Absorption, ORD and CD curves for $[CoCO_3(D\text{-}asp)_2]^{3-}$ in N NaCl.

of such a mixed-ligand isomer as $\beta(-$ or $+)$-$[Co(D$- or $L\text{-}ala)_2(L$- or $D\text{-}ala)]$ must be considered. In order to ascertain whether or not the product is such a mixture, the X-ray powder patterns of the reaction product and of $\beta(+)$-$[Co(L\text{-}ala)_3]$ were compared (Fig. 2). The two patterns are

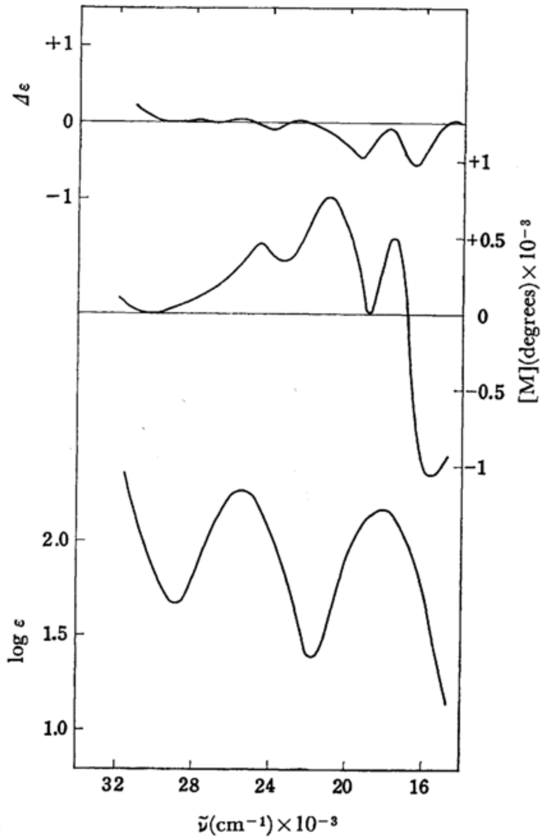

Fig. 5. Absorption, ORD and CD curves for $[CoCO_3(\text{L-glu})_2]^{3-}$ in N NaCl.

similar, but are not identical with each other. By the way, the pattern for the reaction product obtained by the use of D-asparatate was identical with that for the product obtained by the use of L-aspartate (Fig. 2(a)). Very recently, we⁹⁾ have prepared $\beta(+)$-$[Co(\text{L-ala})_2(\text{D-ala})]$ by the reaction of $[Co(\text{L-ala})_2CO_3]^-$ with D-alanine; the $\Delta\varepsilon$ value was found to be 1.33.

Next, let us discuss the configuration of the complexes containing optically active aspartate or glutamate anions. The absorption, ORD, and CD spectra for carbonatobis(L- or D-aspartato)-cobaltate(III) are given in Figs. 3 and 4, while Fig. 5 gives the data for the corresponding glutamato complex. For these complexes, three geometrical isomers are possible, *i. e.*, (a) *cis*(*N*)-*cis*(*O*), (b) *cis*(*N*)-*trans*(*O*) and (c) *trans*(*N*)-*cis*(*O*). Among these, the possibility of (c) may be excluded because of the non-splitting of the first absorption band. Matsuoka *et al.*¹⁰⁾ have recently reported that the *trans*(*N*) isomer of the oxalatobis(glycinato)cobaltate(III) complex shows a splitting of the first band.

The carbonato complex with L-aspartate anions shows a distinctive negative Cotton effect in the region of the first band. The complex with D-aspartate anions shows a distinctive positive Cotton effect. These facts indicate the predominance of the (−)- or (+)-isomer in the reaction mixture of tricarbonatocobaltate(III) and L- or D-aspartate. On the other hand, the corresponding carbonato complex with L-glutamate ions has a somewhat complicated ORD and CD spectra, although the sign of the CD is unchanged (negative).

Figure 6 shows the absorption, ORD, and CD spectra of $\alpha(-)$-$[Co(\text{L-asp})_3]^{3-}$ in water. The ORD and CD spectra show a distinctive negative Cotton effect in the region of the first band. Thus, we may generalize that the complexes which are effective for the resolution of racemic alanine and the reaction product have the same sign of the Cotton effect in the first band region. An X-ray study¹¹⁾ has shown that the absolute configuration of $\alpha(+)$-$[Co(\text{L-ala})_3]$ is

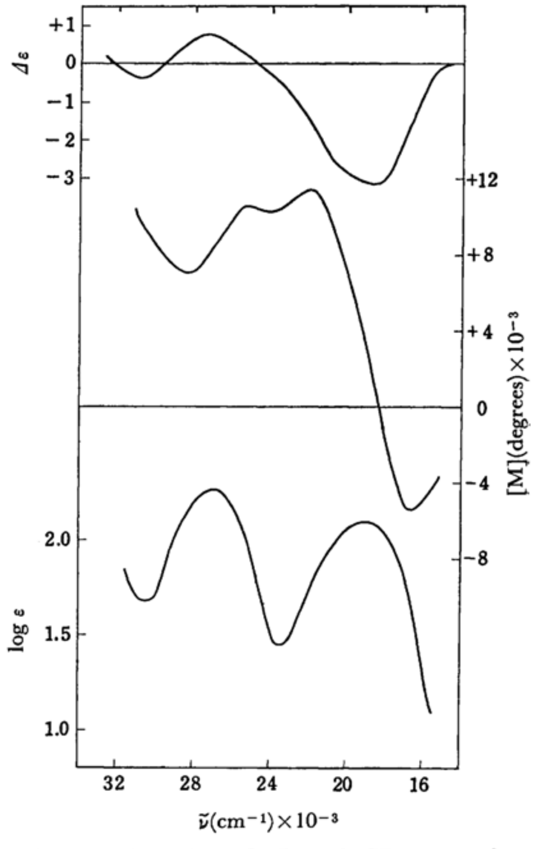

Fig. 6. Absorption, ORD and CD curves for $\alpha(-)$-$[Co(\text{L-asp})_3]^{3-}$ in water.

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9) M. Shibata, H. Nishikawa and Y. Nishida, *Inorg. Chem.*, in contribution.

10) N. Matsuoka, J. Hidaka and Y. Shimura, presented at the 16th Symposium on Coordination Chemistry, Tokyo, Dec., 1966.

11) M. G. B. Drew, J. H. Dunlop, R. D. Gillard and D. Rogers, *Chem. Commun.*, 42 (1966).

$\Delta(C_2)$; hence, that of the corresponding $\alpha(-)$-isomer is $\Lambda(C_2)$. From this the present $\alpha(-)$-$[Co(L\text{-}asp)_3]^{3-}$ may be identified as $\Lambda(C_2)$. The configuration of the carbonato complex of L or D-aspartic acid would also be Λ or $\Delta(C_2)$. Thus, it may be concluded that the Λ(or Δ) (C_2)-complex reacts with racemic alanine to produce the predominant formation of the β-Λ (or Δ)-isomer of DDL(or LLD)-tris(alaninato)cobalt(III). The fact that the $\alpha(+)$-isomer of tris(L-aspartato)cobaltate(III) does not participate in the formation of the insoluble product may be due to the inertness of the isomer for a ligand-exchange reaction.