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Asymmetric Transformation of α-Amino Acids Promoted by Optically Active Cobalt(III) Complexes. II.[1] *N*-Methylalaninatocobalt(III) Complexes with Tetramines

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The preparation and structural assignments of *N*-methyl-(*S*)- and -(*R*)-alaninatocobalt(III) complexes with a few chiral derivatives of 2,3,2-tet (=3,7-diazanonane-1,9-diamine) and triethylenetetramine are described. The hydroxide ion-catalyzed epimerizations of these complexes are examined at pH 10. In the *N*-methylalaninato complexes the isomer ratio for *Δ*-*S*/*Δ*-*R* ranged from 76/24 to 90/10. In the most favorable case where tetramine is 2(*S*)10(*S*)-4,8-diazaundecane-2,10-diamine (abbreviated as 2(*S*)10(*S*)-Me_2-2,3,2-tet) the energy differences among the four possible diastereomers are discussed in relation to the prediction from strain energy minimization calculations.

In recent papers, bis(ethylenediamine)cobalt(III) complexes or triethylenetetraminecobalt(III) complexes of *N*-substituted amino acidate (sarcosinate,[2-5] *N*-methyl-(*S*)- and -(*R*)-alaninate,[3,6-9] and *N*-benzylglycinate[10]) have been investigated from stereochemical points of view. Buckingham and coworkers reported[2] the stereoselective coordination of the secondary nitrogen atom in the sarcosinatobis(ethylenediamine)cobalt(III) complex due to steric repulsions between the *N*-methyl group and the adjacent ethylenediamine chelate ring. The coordinated secondary N center of sarcosinate in the *Δ*-[Co(sar)$(en)_2$]$^{2+}$ ion was assumed to have the *S* configuration stereoselectively, which was confirmed later by an X-ray crystal structure analysis.[11] Though the presence of less stable isomer, *Δ*-[Co(*R*-sar)$(en)_2$]$^{2+}$ was predicted on the basis of strain energy minimization calculations, some earlier attempts to obtain the isomer failed.[3] Recently, the *Δ*-*R* isomer was isolated by Yamatera and coworkers,[4] so that the presence of all four isomers (*Δ*-*R*, *Δ*-*S*, *Λ*-*R*, and *Λ*-*S*) were proved.

In the case of the *N*-methyl-(*S*)- or -(*R*)-alaninato complex there are two chiral centers in the *N*-methylalaninate moiety: *N*-methyl and *C*-methyl groups. Consequently, nonbonded repulsive interactions possibly occur not only between the *N*-methyl group and the adjacent chelate ring but also between the *N*-methyl group and the *C*-methyl group in the *N*-methylalaninate. In the *Λ* configuration it was shown that the *N*-methyl-(*S*)-alaninato complex with the *N*-methyl group trans to the *C*-methyl group was obtained stereospecifically owing to these nonbonded interactions, while in the *N*-methyl-(*R*)-alaninato complexes (*Λ*-*R*) with trien[7] or trien derivatives[8,9] two diastereomers were found to coexist: the trans configuration involving considerable steric repulsion between the *N*-methyl group and the adjacent chelate ring, and the cis configuration having alternatively significant nonbonded repulsion between the two methyl groups.

Sargeson and coworkers showed[12] that the α-proton of chelated α-amino acidate moieties in chiral complex ions undergoes hydroxide ion-catalyzed exchange in basic aqueous solution, and gives rise to a diastereomeric mixture after the establishment of equilibrium. It was found that an equilibrated solution of the *Δ*-β_2-[Co(*N*-Me-ala)(trien)]$^{2+}$ (at pH 12) contains *Δ*-β_2-(*RRS*)-[Co(*N*-Me-(*R*)-ala)(trien)]$^{2+}$ (≈60%), *Δ*-β_2-(*RRS*)-[Co(*N*-Me-(*S*)-ala)(trien)]$^{2+}$ (≈20%), and *Δ*-β_2-(*RRR*)-[Co(*N*-Me-(*S*)-ala)(trien)]$^{2+}$ (≈20%).[7] From the viewpoint of asymmetric transformation at the C center, the isomer ratio for *Δ*-*R*/*Δ*-*S* was 60/40 in the *Δ*-β_2-[Co(*N*-Me-ala)(trien)]$^{2+}$ system. Further, the *Δ*-[Co(*N*-Me-ala)$(en)_2$]$^{2+}$ system gave an improved ratio *Δ*-*R*/*Δ*-*S*=80/20.[6] The strain energy minimization study on the *Δ*-[Co(*N*-Me-ala)$(en)_2$]$^{2+}$ and *Δ*-β_2-[Co(*N*-Me-ala)(trien)]$^{2+}$ isomers correctly predicted the stability order and the energy difference among the diastereomers.[3]

In order to obtain further information about the asymmetric transformation of *N*-methylalaninate, a few chiral derivatives of triethylenetetramine (=trien) and 3,7-diazanonane-1,9-diamine (=2,3,2-tet) were employed for quadridentate ligand (=N_4), and *Λ*-β_2-[Co(*N*-Me-(*S*)- and -(*R*)-ala)(N_4)]$^{2+}$ complexes were prepared. The structure and abbreviations for these tetramines are summarized in Table 1. The epimerization of the amino acidato complexes were accomplished in basic solution. Each equilibrated mixture contained three isomers *Λ*-β_2-(*R*)-*S*, *Λ*-β_2-(*R*)-*R*, and *Λ*-β_2-(*S*)-*R*, as shown in Fig. 1. The isomer ratios for *Λ*-*S*/*Λ*-*R* were obtained, and the results are discussed in relation to the prediction of strain energy minimization calculations.

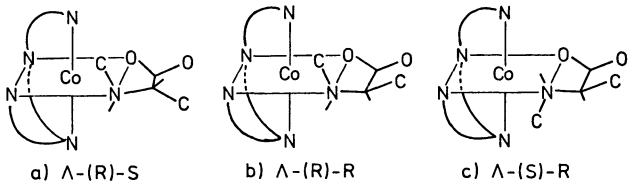
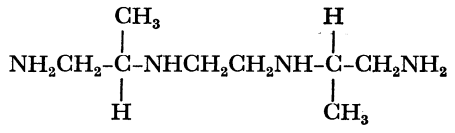
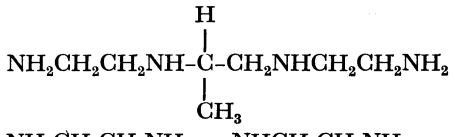
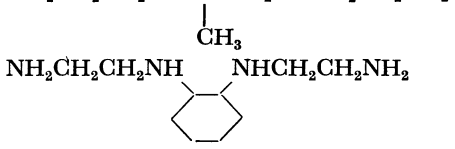
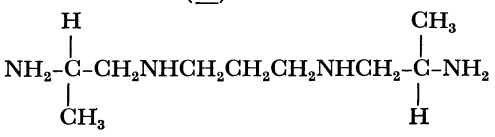
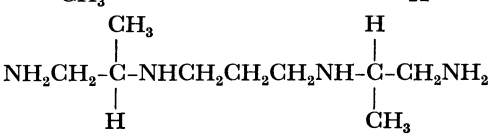


Fig. 1. Possible structures of the *Λ*-β_2-[Co(*N*-Me-ala)(N_4)]$^{2+}$ cations; (a) *Λ*-(*R*)-*S*, (b) *Λ*-(*R*)-*R*, and (c) *Λ*-(*S*)-*R*.

Experimental

All material used were of reagent grade. The ligands 2(*S*),7(*S*)-dimethyl-3,6-diazaoctane-1,8-diamine (=3(*S*)8(*S*)-dimetrien),[13] 5(*R*)-methyl-1,4,7,10-tetraazadecane (=5(*R*)-metrien),[14] *N*,*N*′-bis(2-aminoethyl)-1(*R*),2(*R*)-cyclohexanedi-

Table 1. Abbrebiation and structure of quadridentate ligands

Structure	Abbreviation
	3(*S*)8(*S*)-dimetrien
	5(*R*)-metrien
	(*R*)-baetchxn
	2(*S*)10(*S*)-Me_2-2,3,2-tet
	3(*S*)9(*S*)-Me_2-2,3,2-tet

amine (=(*R*)-baetchxn),[9] 2(*S*),10(*S*)-4,8-diazaundecane-2,10-diamine (=2(*S*)10(*S*)-Me_2-2,3,2-tet),[15] and 2(*S*),8(*S*)-dimethyl-3,7-diazanonane-1,9-diamine (=3(*S*)9(*S*)-Me_2-2,3,2-tet)[1] were prepared by the methods described previously. The dichlorocobalt(III) complexes (*trans*-[$CoCl_2$(3(*S*)8(*S*)-dimetrien)]ClO_4,[16] *Λ*-*β*-[$CoCl_2$(5(*R*)-metrien)]$Cl\cdot 0.5H_2O$,[14] *Λ*-*β*-[$CoCl_2$((*R*)-baetchxn)]$Cl\cdot 0.5H_2O$,[14] *trans*-[$CoCl_2$(2(*S*)-10(*S*)-Me_2-2,3,2-tet)]ClO_4,[1] and *trans*-[$CoCl_2$-(3(*S*)9(*S*)-Me_2-2,3,2-tet)]ClO_4[1]) were prepared according to the methods reported previously. *N*-Methyl-(*S*)-alanine and *N*-methyl-(*R*)-alanine were synthesized by the method of Quitt, *et al.*,[17] using (*S*)- and (*R*)-alanine, respectively.

Λ-*β*$_2$-[*Co*(N-*Me*-(S)- *or* -(R)-*ala*) (3(S)8(S)-*dimetrien*)]*Cl*·$ClO_4\cdot 0.5H_2O$. *N*-Methyl-(*S*)-alanine (or *N*-methyl-(*R*)-alanine) (0.26 g) was added to 5 ml of hot water, followed by $LiOH\cdot H_2O$ (0.088 g). The mixture was warmed to 70 °C until the compound dissolved. To the resulting solution was added *trans*-[$CoCl_2$(3(*S*)8(*S*)-dimetrien)]ClO_4 (0.80 g). The mixture was warmed for 15 min on a water bath at 70 °C. Solid $LiClO_4\cdot 3H_2O$ (0.48 g) was added to the solution, and the mixture was cooled in a refrigerator overnight. The orange-red crystals were collected, washed with methanol and acetone, successively, and air dried. The porduct was recrystallized from hot water. Calcd for [Co-($C_4H_8NO_2$)($C_8H_{22}N_4$)]$Cl\cdot ClO_4\cdot 0.5H_2O$: C, 30.07; H, 6.30; N, 14.61%. Found: for *N*-Me-(*S*)-ala complex, C, 30.33; H, 6.42; N, 14.81%, and for *N*-Me-(*R*)-ala compex, C 29.76; H, 6.45; N, 14.84%.

Λ-*β*$_2$-[*Co*(N-*Me*-(S)-*ala*)(5(R)-*metrien*)]$(ClO_4)_2$ was prepared by the method described previously.[8]

Λ-*β*$_2$-[*Co*(N-*Me*-(R)-*ala*)(5(R)-*metrien*)]$I_2\cdot 5H_2O$ was prepared by the method used for the preparation of *Λ*-*β*$_2$-[Co(*N*-Me-(*S*)-ala)(5(*S*)-metrien)]$I_2\cdot 2H_2O$ except that *Λ*-*β*-[$CoCl_2$-(5(*R*)-metrien)]$Cl\cdot 0.5H_2O$ and *N*-methyl-(*R*)-alanine were employed in place of the corresponding 5(*S*)-metrien complex and *N*-methyl-(*S*)-alanine, respectively.

Calcd for [Co($C_4H_8NO_2$)($C_7H_{20}N_4$)]$I_2\cdot 5H_2O$: C, 19.86; H, 5.76; N, 10.73%. Found: C, 19.83; H, 6.08; N, 10.46%.

Λ-*β*$_2$-[*Co*(N-*Me*-(S)-*ala*)((R)-*baetchxn*)]$(ClO_4)_2$ and *Λ*-*β*$_2$-[*Co*(N-*Me*-(R)-*ala*)((R)-*baetchxn*)]$ZnCl_4$ were prepared according to the method described previously.[9]

Λ-*β*$_2$-[*Co*(N-*Me*-(S)- *or* -(R)-*ala*)(2(S)10(S)-*Me*$_2$-2,3,2-*tet*)]$(ClO_4)_2\cdot H_2O$ and *Λ*-*β*$_2$-[*Co*(N-*Me*-(S)- *or* -(R)-*ala*)-(3(S)9(S)-*Me*$_2$-2,3,2-*tet*)]$(ClO_4)_2\cdot H_2O$ were prepared by the method used for the preparation of the *Λ*-*β*$_2$-[Co((*S*)-ala)(*SS*-pyht)]$(ClO_4)_2\cdot 2H_2O$.[1] Calcd for [Co($C_4H_8NO_2$)-($C_9H_{24}N_4$)]$(ClO_4)_2\cdot H_2O$: C, 27.57; H, 6.05; N, 12.37%. Found: for *N*-methyl-(*S*)-ala complex with 2(*S*)10(*S*)-Me_2-2,3,2-tet, C, 27.14; H, 6.06; N, 12.02%; for *N*-methyl-(*R*)-ala complex with 2(*S*)10(*S*)-Me_2-2,3,2-tet, C, 27.53; H, 5.98; N, 12.13%; for *N*-methyl-(*S*)-ala complex with 3(*S*)9(*S*)-Me_2-2,3,2-tet, C, 27.31; H, 5.94; N, 12.13%; for *N*-methyl-(*R*)-ala complex with 3(*S*)9(*S*)-Me_2-2,3,2-tet, C, 27.65; H, 5.92; N, 12.37%.

Measurements. Visible absorption spectra were measured with a Shimadzu UV-210 spectrophotometer. Circular dichroism curves were obtained with a JASCO-J20 recording spectropolarimeter. Proton NMR (PMR) spectra (90 MHz) were obtained on a Hitachi R-40 spectrometer using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard reference. FT carbon-13 NMR (CMR) spectra were obtained at 25.03 MHz with broad-band proton decoupling on a JEOL PS-99.5 MHz spectrometer employing the solvent deuterium signal as an internal lock. A pulse angle of 45 ° was employed with no pulse delay. The ambient temperature was 39 °C. Me_4Si sealed in a capillary was used as an external reference.

The perchlorate salts were suspended in the solvent (D_2O) and treated with twice the molar amount of tetraphenylarsonium chloride. The white precipitates were removed by filtration, and the filtrates were employed for NMR measurements.

Measurements of Isomer Ratios for Epimerization Reactions. (i) *N*-Methylalaninato complexes with the trien derivatives: Weighed samples (25 mg) of the *N*-methyl-(*S*)- or -(*R*)-alaninatocobalt(III) complexes with the trien derivatives were dissolved in 25 ml of 0.02 mol/dm^3 Na_2CO_3+0.02 mol/dm^3 $NaHCO_3$ buffer (pH 10.1), and the solution was warmed at 40 °C for 25 h. The solution was poured on a small column of SP-Sephadex C25 cation-exchange resin in the sodium form. The complex was eluted with 0.1 mol/dm^3 NaCl. Two bands were collected. The first

Table 2. Electronic and circular dichroism spectral data

Complex	Absorption maxima/nm (ε/M^{-1} cm^{-1})	Circular dichroism maxima/nm ($\Delta\varepsilon$/M^{-1} cm^{-1})
Λ-β_2-[Co(3(*S*)8(*S*)-dimetrien)-(*N*-Me-(*R*)-ala)]Cl·ClO_4·0.5H_2O	488(170) 354(182)	513(1.22), 357(−0.05)
Λ-β_2-[Co(3(*S*)8(*S*)-dimetrien)-(*N*-Me-(*S*)-ala)]Cl·ClO_4·0.5H_2O	485(163) 350(167)	506(1.55), 374(−0.23)
Λ-β_2-[Co(5(*R*)-metrien)-(*N*-Me-(*R*)-ala)]I_2·5H_2O	493(159) 355(167)	485(1.83), 358(−0.17)
Λ-β_2-[Co(5(*R*)-metrien)-(*N*-Me-(*S*)-ala)]$(ClO_4)_2$[a]	488(144) 351(147)	500(2.42), 356(−0.22)
Λ-β_2-[Co((*R*)-baetchxn)-(*N*-Me-(*R*)-ala)]$ZnCl_4$[b]	494(173) 357(172)	482(1.41), 362(−0.14)
Λ-β_2-[Co((*R*)-baetchxn)-(*N*-Me-(*S*)-ala)]$(ClO_4)_2$[b]	492(148) 354(154)	500(1.65), 360(−0.11), 328(0.06)
Λ-β_2-[Co(2(*S*)10(*S*)-Me_2-2,3,2-tet)-(*N*-Me-(*R*)-ala)]$(ClO_4)_2$·H_2O	503(166) 357(160)	540(2.16), 482(−1.25), 367(0.32), 351(0.33)
Λ-β_2-[Co(2(*S*)10(*S*)-Me_2-2,3,2-tet)-(*N*-Me-(*S*)-ala)]$(ClO_4)_2$·H_2O	501(154) 358(146)	529(1.32), 469(−0.56), 360(−0.26)
Λ-β_2-[Co(3(*S*)9(*S*)-Me_2-2,3,2-tet)-(*N*-Me-(*R*)-ala)]$(ClO_4)_2$·H_2O	502(160) 356(159)	536(1.70), 479(−0.99), 383(0.13), 342(0.17)
Λ-β_2-[Co(3(*S*)9(*S*)-Me_2-2,3,2-tet)-(*N*-Me-(*S*)-ala)]$(ClO_4)_2$·H_2O	502(152) 358(146)	530(1.22), 472(−0.58). 364(−0.30)

a) Ref. 8. b) Ref. 9.

pink band (bottom of the column) moved at a rate consistent with a univalent cation was assumed to be a hydrolysis product. The second orange-red 2+ band (top) which was a mixture of Λ-β_2-(*N*-Me-(*R*)-ala)Co(III) and Λ-β_2-(*N*-Me-(*S*)-ala)Co(III) complexes was concentrated to near dryness with a rotary evaporator, and excess NaCl was filtered off. After removing most of NaCl by addition of methanol, final desalting was carried out by gel permiation chromatography on a column (2.5×40 cm) of SP-Sephadex G15. The solution was passed down the column and collected. The resuting solution was evaporated to an appropriate concentration, then the CD curves was obtained. The best fitted curve with the observed CD curve of the equilibrated mixture was calculated by mixing the authentic CD curves of corresponding (*R*)- and (*S*)-amino acidato complex (in H_2O) between 560 nm and 400 nm using least-squares method, and the isomer ratio (Λ-*S*/Λ-*R*) was obtained. The agreement between the observed and calculated curves was satisfactory. Attempts to separate the diastereomeric isomers, (*R*)- and (*S*)-amino acidato complexes, failed.

(ii) *N*-Methylalaninato complexes with the 2,3,2-tet derivatives: Weighed samples (100 mg) of the *N*-methyl-(*S*)- or -(*R*)-alaninatocobalt(III) complex with the 2,3,2-tet derivatives were dissolved in 100 ml of 0.02 mol/dm^3 Na_2CO_3+0.02 mol/dm^3 $NaHCO_3$ buffer, and the compound was equilibrated and desalted by the above-mentioned procedure. The resulting solution was loaded on a SP-Sephadex C25 cation-exchange resin (2.5×40 cm), and eluted with 0.1 mol/dm^3 sodium L-tartratoantimonate(III). Since the length of the column was not sufficient for the complete separation, the eluate was recycled by a rotary pump. After 5—6 cycles the complexes separated cleanly into two bands. The bands were washed with 500 ml of water, eluted with 0.1 mol/dm^3 NaCl, and evaporated to near dryness. After desalting by a similar procedure as above their absorption spectra and CD curves were obtained. The first minor (bottom) and second major band (top) were assigned to the *N*-methyl-(*R*)-alaninato and *N*-methyl-(*S*)-alaninato complexes, respectively. The isomer ratio was estimated spectrophotometrically. Attempts to separate chromatographically the cis and trans isomers of the *N*-methyl-(*R*)-alaninato complexes failed.

In both methods the isomer ratios were reproducible to better than within ±2%.

Strain Energy Minimization Calculations. The minimized strain energies of the complexes Λ-β_2-[Co(*N*-Me-(*R*)- and -(*S*)-ala)(2(*S*)10(*S*)-Me_2-2,3,2-tet)]$^{2+}$ were calculated by the method reported previously.[1] The starting models were generated from the Λ-β_2-[Co(ala)(2(*S*)10(*S*)-Me_2-2,3,2-tet)]$^{2+}$ cations.[1] Calculations were carried out on a HITAC 8700/8800 computer at the Computer Center of this University.

Results and Discussion

β_2-[Co(*N*-Methyl-(*S*)- or -(*R*)-alaninato)(N_4)]$^{2+}$ complexes were prepared from *trans*-[$CoCl_2(N_4)$]$^+$ complexes or Λ-β-[$CoCl_2(N_4)$]$^+$ complexes by the methods described previously.[1,8,9]

The absolute configuration for the complexes was assigned to the Λ configuration based on their circular dichroism spectra. The complexes prepared by the present methods were expected to have the β_2 configuration.[1,18] The electronic and circular dichroism spectral data of Λ-β_2-[Co(*N*-Me-(*S*)- and -(*R*)-ala)(N_4)]$^{2+}$ complexes are listed in Table 2.

As described in the Introduction, only one isomer was anticipated for Λ-β_2-[Co(*N*-Me-(*S*)-ala)(N_4)]$^{2+}$ complexes, in which the *N*-methyl group was trans

TABLE 3. ASSIGNMENT OF PROTON RESONANCE SHIFTS[a] OF *N*-METHYLALANINATE MOIETIES

	C-CH_3	N-CH_3
Λ-β_2-[Co(*N*-Me-(*S*)-ala)-(3(*S*)8(*S*)-dimetrien)]$^{2+}$	1.54	2.54
Λ-β_2-[Co(*N*-Me-(*R*)-ala)-(3(*S*)8(*S*)-dimetrien)]$^{2+}$	1.41 unobsd.	2.36 2.58
Λ-β_2-[Co(*N*-Me-(*S*)-ala)-(5(*R*)-metrien)]$^{2+}$ [b]	1.53	2.61
Λ-β_2-[Co(*N*-Me-(*R*)-ala)-(5(*R*)-metrien)]$^{2+}$ [b]	1.42 1.50	2.38 2.58
Λ-β_2-[Co(*N*-Me-(*S*)-ala)-((*R*)-baetchxn)]$^{2+}$ [c]	1.50	2.58
Λ-β_2-[Co(*N*-Me-(*R*)-ala)-((*R*)-baetchxn)]$^{2+}$ [c]	1.43 1.51	2.40 2.57
Λ-β_2-[Co(*N*-Me-(*S*)-ala)-(2(*S*)10(*S*)-Me_2-2,3,2-tet)]$^{2+}$	1.47	2.42
Λ-β_2-[Co(*N*-Me-(*R*)-ala)-(2(*S*)10(*S*)-Me_2-2,3,2-tet)]$^{2+}$	1.45 1.52	2.45
Λ-β_2-[Co(*N*-Me-(*S*)-ala)-(3(*S*)9(*S*)-Me_2-2-3,2-tet)]$^{2+}$	1.46	2.37
Λ-β_2-[Co(*N*-Me-(*R*)-ala)-(2(*S*)9(*S*)-Me_2-2,3,2-tet)]$^{2+}$	1.43 1.48	2.39

a) ppm from DSS. b) Ref. 8. c) Ref. 9.

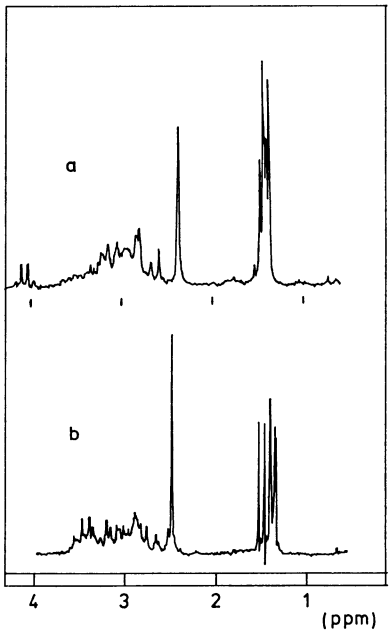


Fig. 2. PMR spectra of Λ-β_2-[Co(*N*-Me-ala)(3(*S*)8(*S*)-dimetrien)]$^{2+}$ ions in D_2O; (a) *N*-Me-(*R*)-ala and (b) *N*-Me-(*S*)-ala.

to the *C*-methyl group in the *N*-methylalaninate (=Λ-β_2-(*R*)-*S*). The PMR spectra of Λ-β_2-[Co(*N*-Me-(*S*)-ala)(N_4)]$^{2+}$ in D_2O exhibited a doublet at about 1.5 ppm and a singlet at 2.4—2.6 ppm arising from the *C*-methyl and *N*-methyl groups, respectively (Table 3 and Figs. 2b and 3a). These spectra are similar to those of other Λ-β_2 isomers of *N*-methyl-(*S*)-alaninato complexes with trien[7] and trien derivatives.[8,9] The ^{13}C-NMR spectrum of the Λ-β_2-[Co(*N*-Me-(*S*)-ala)-(3(*S*)9(*S*)-Me_2-2,3,2-tet)]$^{2+}$ complex exhibited twelve signals with one broad peak corresponding to two carbons, which was consistent with the number of the carbons expected for one kind of the isomer (Fig. 4b).

On the other hand, the presence of two isomers for Λ-β_2-[Co(*N*-Me-(*R*)-ala)(N_4)]$^{2+}$ has been reported.[3,7-9] The PMR spectrum of the *N*-methyl-(*R*)-alaninato complex with 3(*S*)8(*S*)-dimetrien showed two *N*-methyl resonances at 2.36 and 2.58 ppm, which were assigned to those of the *N*-methyl groups of the Λ-β_2-(*R*)-*R* and Λ-β_2-(*S*)-*R* complexes, respectively (Table 3 and Fig. 2a). The isomer ratio for Λ-β_2-(*R*)-*R*/Λ-β_2-(*S*)-*R* at equilibrium (pH 7) was estimated as about 3/1. This value is in contrast to those in the corresponding *N*-methyl-(*R*)-alaninato complexes with other tetramines, in which the isomer ratios for Λ-β_2-(*R*)-*R*/Λ-β_2-(*S*)-*R* were close to 1/1.[7-9] An X-ray structure analysis of the Λ-[$CoCO_3$(3(*S*)8(*S*)-dimetrien)]$^+$ ion[19] revealed that the apical five-membered chelate ring of the tetramine has the λ conformation with an axial *C*-methyl group in the crystal. If the apical chelate ring of the *N*-methylalaninato complex takes similarly the λ conformation, severe nonbonded repulsions will occur between the *N*-methyl group and the axial *C*-methyl group. Actually, the conformer

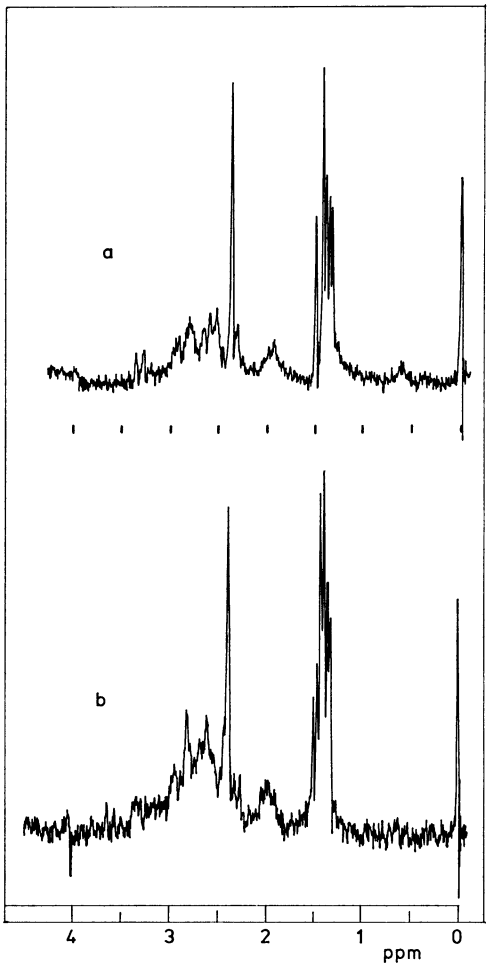


Fig. 3. PMR spectra of Λ-β_2-[Co(*N*-Me-ala)(3(*S*)9(*S*)-Me_2-2,3,2-tet)]$^{2+}$ ions in D_2O; (a) *N*-Me-(*S*)-ala and (b) *N*-Me-(*R*)-ala.

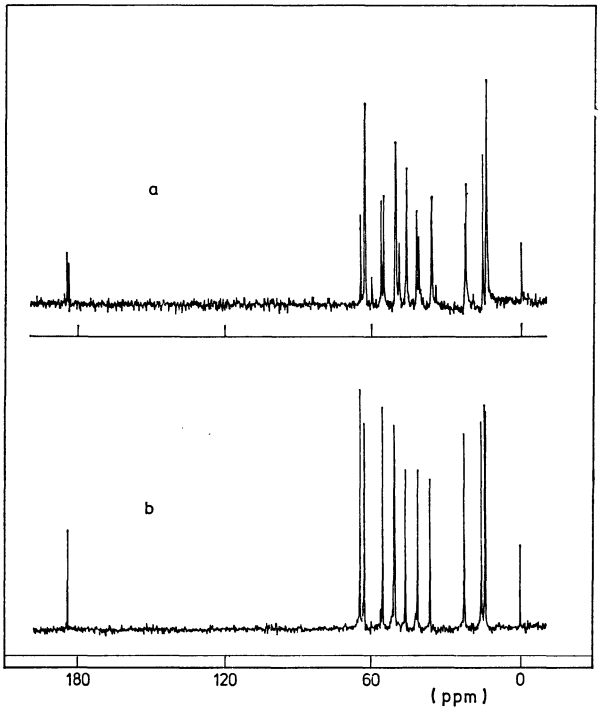


Fig. 4. CMR spectra of Λ-β_2-[Co(*N*-Me-ala)(3(*S*)9(*S*)-Me_2-2,3,2-tet)]$^{2+}$ ions in D_2O; (a) *N*-Me-(*R*)-ala and (b) *N*-Me-(*S*)-ala.

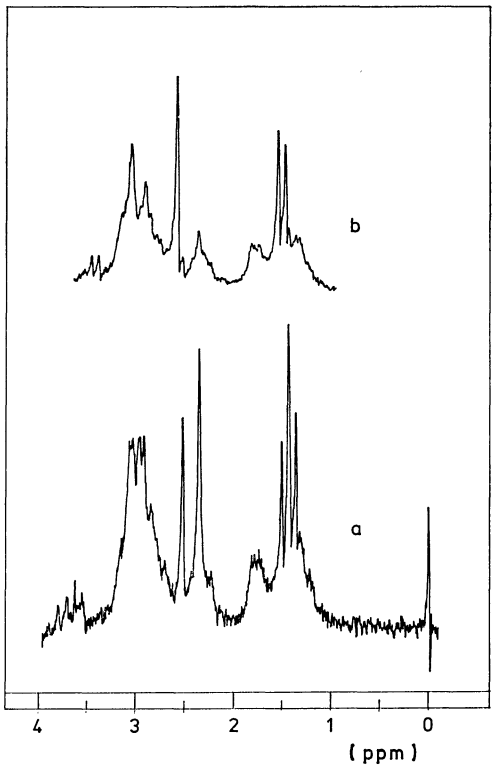


Fig. 5. PMR spectra of an equilibrated mixture of Λ-β_2-[Co(*N*-Me-(*R*)-ala)((*R*)-baetchxn)]$^{2+}$ ions; (a) equilibrated in D_2O (pD 7) and (b) equilibrated in H_2O (pH 10).

with the δ conformation with respect to the apical chelate ring will coexist in solution. It is probable that the steric repulsions between the *N*-methyl group and the axial *C*-methyl group in the apical chelate ring contribute properly to the destabilization of the Λ-β_2-(*S*)-*R* isomer in comparison with the Λ-β_2-(*R*)-*R* for the 3(*S*)8(*S*)-dimetrien complex.

In the PMR spectra of the *N*-methyl-(*R*)-alaninato complexes with the 2,3,2-tet derivatives the *N*-methyl resonance appeared as a singlet at about 2.4 ppm, while the PMR signals for the *C*-methyl group in the *N*-methyl-(*R*)-alaninate showed two kinds of doublets (Table 3 and Fig. 3b). This indicates that the chemical shift of the *N*-methyl signals of the Λ-(*R*)-*R* and Λ-(*S*)-*R* isomers are incidentally identical. The CMR spectrum of the Λ-β_2-[Co(*N*-Me-(*R*)-ala)(3(*S*)9(*S*)-Me_2-2,3,2-tet)]$^{2+}$ complex showed more complicated feature than that of the corresponding *N*-methyl-(*S*)-alaninato complex (Fig. 4a). Both signals at 184.4 and 185.0 ppm were assigned to the carboxyl carbon in the *N*-methyl-(*R*)-alaninate. It indicates the presence of the two species for the *N*-methyl-(*R*)-alaninato complex. The ratio of Λ-(*R*)-*R*/Λ-(*S*)-*R* at equilibrium (at pH 7) was estimated as about 1/1 from the CMR data.

It has been shown[6,7] that the epimerization at the C center of the *N*-methylalaninate ligand in the complexes occurs in basic aqueous solution. As Fig. 5 shows the PMR spectrum of the Λ-β_2-[Co(*N*-Me-(*R*)-ala)((*R*)-baetchxn)]$^{2+}$ at about pH 10 exhibited a new *C*-methyl doublet at 1.50 ppm and a new *N*-methyl singlet at 2.58 ppm. The equilibrated mixture should contain three isomers Λ-(*R*)-*S*, Λ-(*R*)-*R*, and Λ-(*S*)-*R*.[7-9] From the viewpoint of asymmetric transformation, the isomer ratios Λ-*S*/Λ-*R*, after the epimerization equilibria had been established, were obtained by CD measurements or by means of chromatographic separation. The electronic and CD spectra of the *N*-methyl-(*S*)-alaninato and the *N*-methyl-(*R*)-alaninato complexes, and the equilibrated mixture with 3(*S*)8(*S*)-dimetrien are shown in Fig. 6.

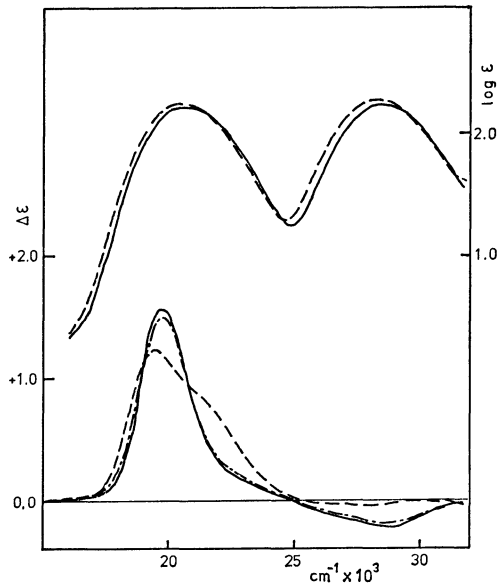


Fig. 6. Electronic absorption and CD spectra of Λ-β_2-[Co(*N*-Me-ala)(3(*S*)8(*S*)-dimetrien)]$^{2+}$ ions; (a) *N*-Me-(*S*)-ala (——), (b) *N*-Me-(*R*)-ala (— — —), (c) an equilibrated mixture (———).

TABLE 4. ISOMER RATIOS (Λ-S/Λ-R) OF Λ-β_2-[Co(amino acidato)(N_4)]$^{2+}$ a)

(N_4)	N-Me-ala	ala
	Λ-S/Λ-R	Λ-S/Λ-R
$(en)_2$	80/20[b]	50/50[d]
trien	60/40[c]	—
3(S)8(S)-dimetrien	85/15	50/50[e]
5(R)-metrien	76/24	—
(R)-baetchxn	88/12	—
2(S)10(S)-Me_2-2,3,2-tet	90/10	66/34[e]
3(S)9(S)-Me_2-2,3,2-tet	87/13	61/39[e]

a) At 40 °C, pH 10.1. b) Ref. 6. c) Ref. 7. d) Ref. 12. e) Ref. 1.

The isomer ratios for Λ-S/Λ-R are listed in Table 4. The isomer ratios for Λ-(R)-R/Λ-(S)-R at pH 10 were assumed to be the same as those at pH 7. The Λ-β_2-[Co(N-Me-ala)(N_4)]$^{2+}$ systems generally showed a considerable stereoselectivity on the epimerization. The degree of the stereoselectivity ranges from 85/15 to 90/10 ($\Delta G = -1.1 \sim -1.4$ kcal/mol) in this study except for the 5(R)-metrien complexes (76/24). These values are considerably larger than that for the [Co(N-Me-ala)(trien)]$^{2+}$ system (Λ-S/Λ-R=60/40),[7] and a little larger than for the [Co(N-Me-ala)$(en)_2$]$^{2+}$ system (80/20).[6]

As described in the Introduction, significant nonbonded repulsive interactions were anticipated in the Λ-R isomers between the N-methyl group and the adjacent chelate ring or alternatively between the N-methyl and the C-methyl groups in the N-methylalaninate. The effects of these two steric repulsions seem to be approximately equal, since the ratios for Λ-(R)-R/Λ-(S)-R are about 1/1 in all cases except for that of the 3(S)8(S)-dimetrien complexes. The observed thermodynamic preference of Λ-β_2-[Co(N-Me-(S)-ala)(N_4)]$^{2+}$ isomer over Λ-β_2-[Co(N-Me-(R)-ala)-(N_4)]$^{2+}$ isomer should be due to the absence of such steric disadvantage. The isomer ratio of the Λ-β_2-[Co(N-Me-ala)(5(R)-metrien)]$^{2+}$ complex is similar to that of the [Co(N-Me-ala)$(en)_2$]$^{2+}$ system, while those of the 3(S)8(S)-dimetrien or (R)-baetchxn complexes are considerably larger than that of the trien ones. Though the reason for these high selectivity with the substituted trien complexes is uncertain, it is probable that the relative stability is influenced by the C-methyl group substituted in the apical chelate ring of the 3(S)8(S)-dimetrien or by the increased rigidity due to the fused cyclohexane ring in the central chelate ring of the (R)-baetchxn.

The technique of strain energy minimization calculation was applied to the Λ-β_2-[Co(N-Me-(R)- and -(S)-ala)(2(S)10(S)-Me_2-2,3,2-tet)]$^{2+}$ complexes, the isomer ratio Λ-S/Λ-R in which was 90±2/10±2 ($\Delta G = -1.35 \pm 0.15$ kcal/mol). The 2,3,2-type tetramine ligands have the same geometrical structure in the cis configuration, while the *cis*-complexes with trien adopt two geometrical isomers.[20] Further, the conformation of 2,3,2-tet or its derivatives is assumed to be more rigid than that of trien series. Actually, a recent

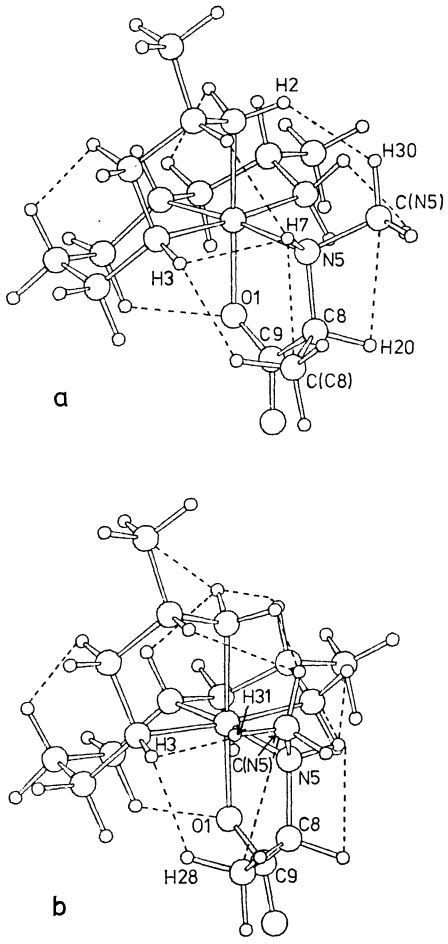


Fig. 7. Minimized structures for Λ-β_2-[Co(N-Me-(S)-ala)(2(S)10(S)-Me_2-2,3,2-tet)]$^{2+}$ ions; (a) Λ-(R)-S and (b) Λ-(S)-S. Dotted lines show interatomic repulsions greater than 0.3 kcal/mol.

X-ray analysis study revealed[21] that in the crystal of *cis*-β_2-[Co(gly)(trien)]$^{2+}$ two conformers coexist, the apical chelate rings of which have both the δ and λ conformations. On the other hand, the outer five-membered chelate rings of the methyl-substituted 2,3,2-tet employed in this study have the δ conformation due to the preference of the equatorial orientation of the C-methyl groups. Since the conformation and configuration of the 2,3,2-tet are thus fixed in the cis form, the stereoisomerism for the [Co(N-Me-ala)(2(S)10(S)-Me_2-2,3,2-tet)]$^{2+}$ system is simpler than the [Co(N-Me-ala)$(en)_2$]$^{2+}$ or the [Co(N-Me-ala)(trien)]$^{2+}$ systems.

The final minimized structures for the diastereomeric isomers are shown in Figs. 7 and 8, and the final energy terms are listed in Table 5. The most stable isomer is Λ-(R)-S with the N-methyl group trans to the C-methyl group, as shown in Fig. 7a. The calculated stability order, Λ-(R)-S, Λ-(S)-R, Λ-(R)-R, Λ-(S)-S is the same as that for the [Co(N-Me-ala)$(en)_2$]$^{2+}$ system. However, compared with the [Co(N-Me-ala)(trien)]$^{2+}$ system, the relative stabilities of the Λ-(S)-R with trans methyl groups and Λ-(R)-R with cis methyl groups are reversed (Table 6).

The starting models of the N-methylalaninate moiety was generated from both puckered and near-planar

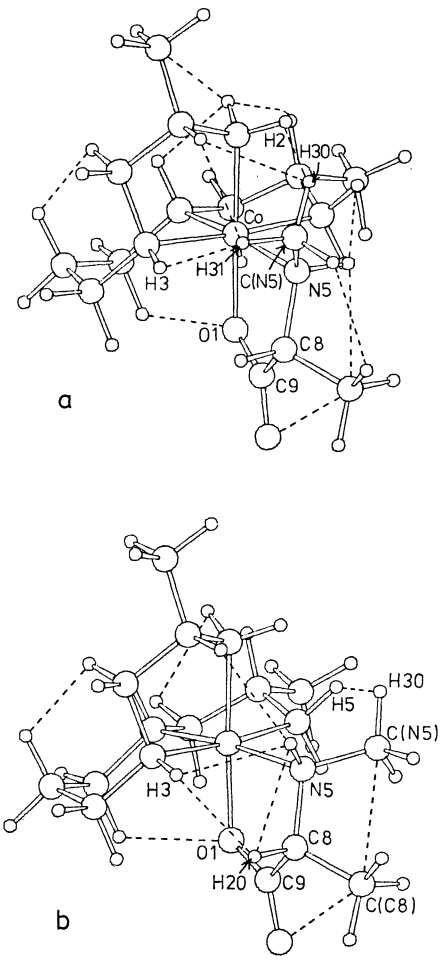


Fig. 8. Minimized structures for Λ-β_2-[Co(*N*-Me-(*R*)-ala)(2(*S*)10(*S*)-Me_2-2,3,2-tet)]$^{2+}$ ions; (a) Λ-(*S*)-*R* and (b) Λ-(*R*)-*R*. Dotted lines show interatomic repulsions greater than 0.3 kcal/mol.

conformation.[3] Except for the Λ-(*R*)-*S* isomer the planar conformation was unstable. In the case of the Λ-(*R*)-*S* ion the planar form was a little more stable than the puckered one (8.56 kcal/mol). Normally, the puckered conformation with a pseudo-equatorial *C*-methyl group was stable for the alaninate. However, in the Λ-(*S*)-*S* isomer the puckered form with a pseudo-axial *C*-methyl group was much more stable than the pseudo-equatorial form (13.1 kcal/mol). The dihedral angles, ϕ(Co–N5–C8–C9), were 6.7° Λ-(*R*)-*S*, 27.3° Λ-(*S*)-*R*, 30.1° Λ-(*R*)-*R*, 18.8° Λ-(*S*)-*S*, and ϕ(N5–C8–C9–O1) were 3.0° Λ-(*R*)-*S*, 22.6° Λ-(*S*)-*R*, 26.7° Λ-(*R*)-*R*, 18.7° Λ-(*S*)-*S*.

The introduction of the *N*-methyl group to the alaninate moiety produces significant strains in the complex. The calculated strain energies of the corresponding alaninato complexes were *ca.* 4 kcal/mol more stable than the most stable isomer of the *N*-methylalaninato complex.[1] Comparisons of the strain energy contributions among the isomers of the Λ-β_2-[Co(*N*-Me-ala)(2(*S*)10(*S*)-Me_2-2,3,2-tet)]$^{2+}$ ions show that the difference derives mainly from the bond-angle deformations, torsional strain, and nonbonded interactions. The Λ-(*R*)-*S* isomer has the smallest strain energy contributions in the bond-angle deformations

Table 5. Final energy terms[a] for the four isomers of the *N*-methylalaninato complexes

	trans-N(*R*)-C(*S*)	*trans*-N(*S*)-C(*R*)	*cis*-N(*R*)-C(*R*)	*cis*-N(*S*)-C(*S*)
Bond deformations	1.61	1.59	1.76	1.64
Angle deformations	6.22	7.30	7.52	8.98
Torsional strain	3.58	2.86	2.80	3.23
Nonbonded interactions	−2.93	−2.57	−2.19	−2.54
Out-of-plane	0.0	0.0	0.0	0.0
Total strain energy	8.49	9.18	9.89	11.31
Energy differences	0.0	0.69	1.40	2.82

a) For the Λ-β_2-[Co(*N*-Me-ala)(2(*S*)10(*S*)-Me_2-2,3,2-tet)]$^{2+}$, (kcal/mol).

Table 6. Strain energy differences[a] for [Co(*N*-Me-ala)(N_4)]$^{2+}$ systems

(N_4)	Λ-(*R*)-*S* (*trans*)	Λ-(*S*)-*R* (*trans*)	Λ-(*R*)-*R* (*cis*)	Λ-(*S*)-*S* (*cis*)
$(en)_2$[b]	0.0	1.0	1.3	3.8
trien[b]	0.0	1.9	0.6	4.0
2(*S*)10(*S*)-Me_2-2,3,2-tet	0.0	0.7	1.4	2.8

a) kcal/mol. b) Ref. 3.

and nonbonded interactions, though the *N*-methyl-(*S*)-alaninate ring adopts a strained, near-planar, conformation: Torsional strain for N5–C8 bond is 1.5 kcal/mol Λ-(*R*)-*S*, 0.6 Λ-(*S*)-*R*, 0.8 Λ-(*R*)-*R* and 0.8 Λ-(*S*)-*S*. The strain due to the *N*-methyl group extends the Co–N5 bond (2.02 Å, 0.6 kcal/mol) in all isomers, and distorts the Co–N5–C(N5) angle, Λ-(*R*)-*S* 118° (0.6 kcal/mol), Λ-(*S*)-*R* 120° (1.0), Λ-(*R*)-*R* 115° (0.3), and Λ-(*S*)-*S* 122° (1.3). The *N*-methyl group causes significant nonbonded interactions in all four isomers. In the case that the *N*-methyl group has the *S* configuration, nonbonded interactions between the *N*-methylalaninate and the adjacent chelate ring are considerably large: the H2···H30 (2.16 Å, 0.5 kcal/mol) and H3···H31 (2.14 Å, 0.6) in the *N*-methyl-(*R*)-alaninato complex, and H3···H28 (2.09 Å, 0.7) and H3···H31 (2.14 Å, 0.6) in the *N*-methyl-(*S*)-alaninato complex. In the complexes with *N*(*R*)-methyl group close contacts arise between the N–H proton and the *N*-methylalaninate ring: the C(C8)···H7 (2.45 Å, 0.5 kcal/mol), C(N5)···H20 (2.42 Å, 0.6), H2···H30 (2.11 Å, 0.7), and H3···H7 (2.09 Å, 0.7) in the *N*-methyl-(*S*)-alaninato complex, and the C(C8)···C(N5) (2.80 Å, 0.7), H3···H20 (2.13 Å, 0.6), and H5···H30 (2.12 Å, 0.6) in the *N*-methyl-(*R*)-alaninato complex.

The stability order and the calculated strain energy differences are in good agreement with the experimental results, though the strain energy of the Λ-(*S*)-*R* isomer was underestimated. This result suggested that the main source of the destabilization of the Λ-β_2-[Co(*N*-Me-(*R*)-ala)(N_4)]$^{2+}$ ions and the absence of the Λ-(*S*)-*S* isomer was due mostly to serious intramolecular strain energy. From the viewpoint of asymmetric transformation, *N*-substitution of the alaninate results in a striking improvement of the chiral selectivity in the *N*-methylalaninato complexes, in comparison with that for the

corresponding alaninato complexes.[1)]

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