Stereospecific Effects in Cobalt(III)–Triethylenetramine-*N*-methyl-(*S*)-alanine Complexes

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Summary Three interconvertible isomers of β_2-[Co(trien)-*N*-Me-(*S*)-Ala]$^{2+}$ have been identified and their rates of isomerisation and relative stabilities have been measured.

THE formation of D(+)$_{589}$-β_2-(*SSS*)-[Co trien(*S*)-Pro]$^{2+}$† and L(−)$_{589}$-β_2-(*RRS*)-[Co trien(*S*)-Pro]$^{2+}$ (trien = 1,4,7,10 tetra-azadecane) from β_2-[Co trien(OH)(OH$_2$)]$^{2+}$ and *S*-proline is kinetically controlled and approximately equal amounts of both isomers appear.[1] However, the relative stabilities of the two forms was not established in basic solutions since cleavage of the amino-acid moiety preceded interconversion.[1] The slow rate for interconversion was attributed to the requirement that in the intermediate the asymmetric N and C centres on proline both need to be deprotonated before mutarotation is permitted. This arises because the N and C atoms are coupled by a 5-membered ring. However, in the analogous *N*-methyl-*S*-alanine complexes the possibility of observing interconversion is enhanced since inversion at the asymmetric N and C centres can be substantially independent.

In the reaction of *N*-methyl-*S*-alanine with β-[Co trien (OH)(H$_2$O)]$^{2+}$, three [Co trien*N*-Me-(*S*)-Ala]$^{2+}$ species were detected by ^{1}H n.m.r. spectroscopy (Figure 1c). Two of these isomers have been isolated by fractional crystallization and their ^{1}H n.m.r., o.r.d., and c.d. and spectra are presented (Figures 1a, 1b, 2, and 3). The ^{1}H n.m.r. signals of major interest are those about 2 p.p.m. corresponding to the C-methyl doublets and those about 3 p.p.m. corresponding to the N-methyl doublets and those about 3 p.p.m. corresponding to the N-methyl doublets. It is evident from the o.r.d. and c.d. spectra of these two complexes that they are catoptric‡ with respect to the configuration about each cobalt ion. However, all attempts to purify the remaining isomer by the use of fractional crystallization, ion exchange, paper chromatography, and resolving agents have been unsuccessful.

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† The nomenclature β_1, β_2 is given in ref. 2. *R* and *S* (IUPAC) refer to the chiral sec-N-centres in the order "angular" trien,[3] 'planar ' trien,[3] amino-acid and also to the chiral C-centre in the amino-acid.

‡ "Mirror image": Shorter Oxford Dictionary.

There is a close correspondence between the spectral properties of the isolated isomers and the complexes L(−)$_{589}$-β_2-(RRS)-[Co trien)(NMe-Gly)]$^{2+}$,[2] L(−)$_{589}$$\beta_2$-($RRS$)-[Co trien($S$)-Pro]$^{2+}$ and D(+)$_{589}$-β_2-(SSS)-[Co trien) (S)-Pro]$^{2+}$.[1,2] Further, Dreiding models indicate that in the β_1-[Co trien(N-Me-(S)-Ala]$^{2+}$ isomers there would be very large steric interactions between the N-methyl group and the trien ligand. We conclude therefore that the N-methyl-S-alanine complexes have the β_2 configuration.

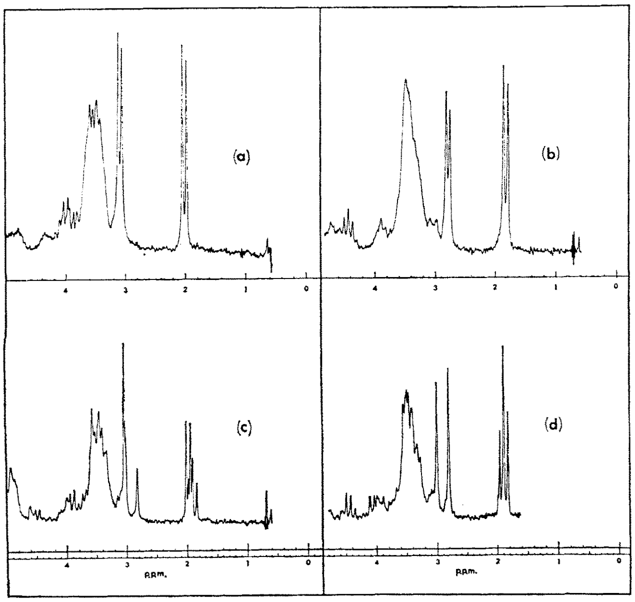

FIGURE 1. 100 MHz ^{1}H *n.m.r. spectra of* β_2-[Co trien(N-Me-Ala)]$^{2+}$ *isomers* (*external* Me$_4$Si).

(a) D(+)$_{589}$-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *in* 0·01 N-DCl. (b) L(−)$_{589}$-β-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *in* 0·01 N-CDl. (c) L(−)$_{589}$-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *isomers in neutral* D$_2$O *after equilibration at pH* 12. (d) L(−)$_{589}$-β_2-[Co trien(N-Me-Ala)]$^{2+}$ *isomers after equilibration in* D$_2$O *at pH* 7.

All three isomers were interconvertible and the equilibria and rates of equilibration were measured. Two distinct equilibria were studied in different pH ranges. At pH = 6·5, (27°) L(−)$_{589}$-β_2-[Co trien(N-Me-(S)-Ala)]$^{2+}$ mutarotates with retention of configuration about the cobalt centre with a rate constant $k = 6{\cdot}4 \times 10^{-4}$ sec.$^{-1}$. The ^{1}H n.m.r., o.r.d., and c.d. spectra of the equilibrium solution are shown in Figures (1d, 2, and 3) and clearly differ from those of the reactant. In this pH region the N-CH$_3$ signals collapse to a singlet since the N-proton exchanges with D$_2$O. The peaks at 3·00, 1·96, and 1·89 p.p.m. correspond with the N-CH$_3$ singlet and the C-CH$_3$ doublet, respectively, of the isomer which has not yet been purified, and the rate constant in this pH region indicates that the change is due to mutarotation at an N-centre.[3,4]

At higher pH values (0·01M[OH$^-$]) L(−)$_{589}$-β_2-[Co trien-(N-Me-(S)-Ala)]$^{2+}$ mutarotates further, also with retention about the cobalt centre, with a rate constant $k = 3{\cdot}1 \times 10^{-3}$ sec.$^{-1}$ (27°). The ^{1}H n.m.r. spectrum for the equilibrium is shown in Figure 1c. The o.r.d. curves (at $5 \times t_{\frac{1}{2}}$) showed evidence of some base hydrolysis of the amino-acid moiety. The rate of mutarotation observed in this pH region is consistent with proton exchange at the asymmetric C centre[5] and deuteriation was observed during

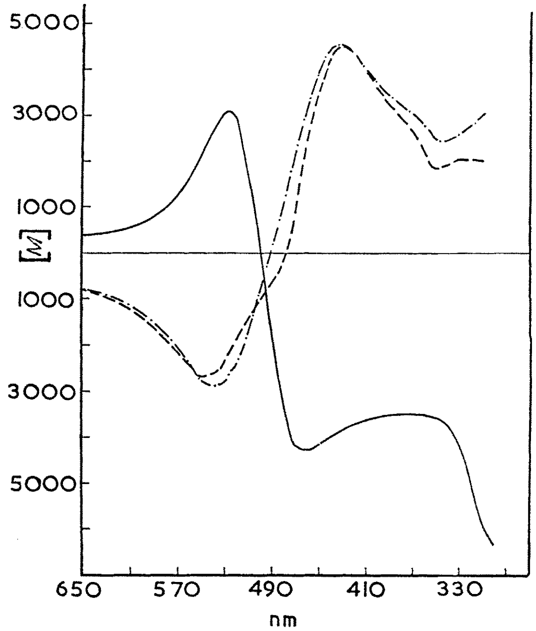

FIGURE 2. *O.r.d. spectra of* β_2-[Co trien(N-Me-Ala)]$^{2+}$ *isomers*: (———)D(+)$_{589}$-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *in* 0·1 N-HClO$_4$. (— — —) L(−)$_{589}$-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *in* 0·1 N-HClO$_4$. (— · —) L(−)$_{589}$-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *isomers in* H$_2$O *after equilibration at pH* 7.

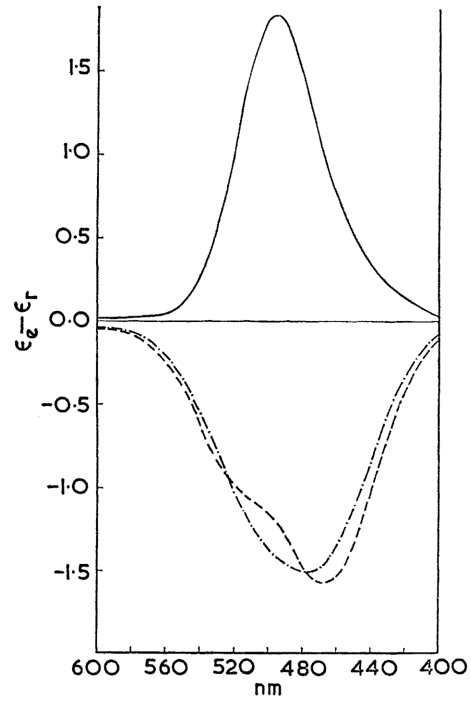

FIGURE 3. *C.d. spectra of* β_2-[Co trien(N-Me-Ala)]$^{2+}$ *isomers*: (———) D(+)$_{589}$-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *in* 0·1 N-HClO$_4$. (- - -)L(−)-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *in* 0·1 N-HClO$_4$. (— · —) L(−)$_{589}$-β_2-{Co trien[N-Me-(S)-Ala]}$^{2+}$ *isomers in* H$_2$O *after equilibration at pH* 7.

mutarotation. Also the new ^{1}H n.m.r. signals observed coincide with those of the D(+)$_{589}$-β_2-[Co trien(*N*-Me-(*S*)-Ala)]$^{2+}$ ion (Figure 1a). We suggest therefore that the second mutarotation corresponds to inversion at the asymmetric C centre leading to L(−)$_{589}$-β_2-[Co trien(*N*-Me-(*R*)-Ala)]$^{2+}$ the enantiomer of the isolated D(+)$_{589}$-β_2-isomer.

Two possibilities exist for mutarotation at the *N*-centre. Either inversion occurs at the *N*-methyl group or at the sec-N centre which couples the trien chelate rings in the same plane. In the complexes [Co en$_2$(*N*-Me-Gly)]$^{2+}$,[6,7] β_2-[Co trien(*N*-Me-Gly)]$^{2+}$,[2] and {Co en$_2$[*N*-Me-(*S*)-Ala]}$^{2+}$ [8] mutarotation at the *N*-methyl centre was excluded ($< 2\%$). This result was attributed to unfavourable steric interactions between the methyl group and the adjacent Co–en-type chelate ring for the less stable form. We conclude therefore that in the [Co trien(*N*-Me-Ala)]$^{2+}$ complexes the mutarotation observed at pH = 6·5 is associated with N-inversion and conformational interchange in the trien ligand (Figure 4).

The most stable configuration for the β-trien topology is that shown for the L(−)$_{589}$-β_2-(*RRS*)-[Co trien(*N*-Me-(*R*)-Ala)]$^{2+}$ ion. This conclusion has been reached from a study of numerous β-trien complexes and is supported by several structural analyses.[1–3,9,10]

The most stable configuration for the *N*-methyl-(*S*)-alanine moiety should be that where the methyl groups are *trans* to each other. This analysis requires L(−)$_{589}$-β_2-(*RRS*)-{Co trien[*N*-Me-(*R*)-Ala]}$^{2+}$ to be more stable than L(−)$_{589}$-β_2-(*RRS*)-{Co trien([*N*-Me-(*S*)-Ala]}$^{2+}$ where the methyl group are now *cis* to each other. The equilibrium results support this conclusion and the ^{1}H n.m.r. spectra (Figure 1c) indicate that L(−)$_{589}$$\beta_2$-(*RRS*)-{Co trien[*N*-Me-(*R*)-Ala]}$^{2+}$ is approximately three times more stable than the other two isomers respectively. However, the arguments concerning the stability of the two forms of the β trien topology would require L(−)$_{589}$-β_2-(*RRS*)-{Co trien[*N*-Me-(*S*)-Ala]}$^{2+}$ to be more stable than L(−)$_{589}$-β_2-(*RSS*)-{Co trien[*N*-Me-(*S*)-Ala]}$^{2+}$ and the equilibrium results imply that these two isomers have nearly the same stability in solution. The reasons for this departure from the general stability relationship found for the β-trien configuration may be associated with the additional instability factor introduce by the *cis*-methyl groups.

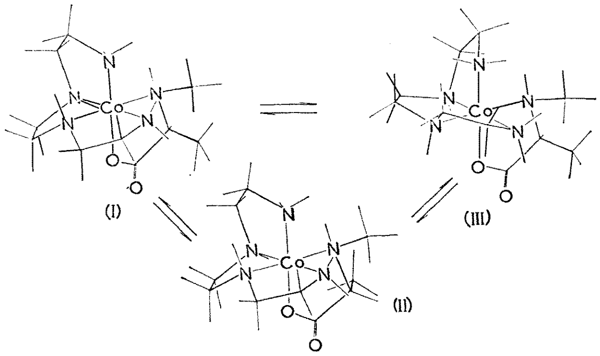

FIGURE 4. *Equilibrium and structural relationships between* L(−)$_{589}$-β_2-[Co trien(*N*-Me-Ala)]$^{2+}$ *isomers*: (I) L(−)$_{589}$-β_2-*RRS*-{Co trien[*N*-Me-(*R*)-Ala]}$^{2+}$ *ion*; (II) L(−)$_{589}$-β_2-*RRS*-{Co trien-[*N*-Me-(*S*)-Ala]}$^{2+}$ *ion*; (III) L(−)$_{589}$-β_2-*RSS*-{Co trien[*N*-Me-(*R*)-Ala]}$^{2+}$ *ion.*

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