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Chiral Metal Complexes.
18.* A Highly Stereoselective Synthesis of Alanine

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Abstract

The complex Λ-β_1-[Co(R,R-picchxn)(AMMAH)]$(ClO_4)_2\cdot4\frac{1}{2}H_2O$, where R,R-picchxn is N,N′-di(2-picolyl)-1R,2R-diaminocyclohexane and $AMMAH_2$ is 2-amino-2-methylpropandioic acid has been prepared stereospecifically from the reaction of Λ-β-[Co(R,R-picchxn)Cl_2]$^+$ and $AMMAH_2$ is aqueous solution. Decarboxylation of the complex in aqueous HCl under a variety of conditions always gave the mixture of diastereoisomers containing R-alanine and S-alanine in the same ratio, Λ-β_1-[Co(R,R-picchxn)(R-ala)]$^{2+}$: Λ-β_1-[Co(R,R-picchxn)(S-ala)]$^{2+}$ = 89 ± 0.5: 11 ± 0.5. The optical yield of alanine is the highest ever achieved in this kind of reaction.

Introduction

We recently reported [1] that the complex† Λ-β-[Co(R,R-picchxn)Cl_2]$ClO_4\cdot\frac{1}{2}H_2O$ forms stereospecifically and that, furthermore, only Λ-β isomers are obtained upon substitution of the dichloro-complex with a variety of other ligands. With S-amino acids both β_1 and β_2 diastereomers are obtained, but the yield of β_2 species is much lower than that of the β_1 complexes. Since the optically active tetradentate when coordinated to the Co(III) ion thus gives an apparently stereospecific chiral framework, under a variety of reaction conditions, it seemed an ideal species to investigate with respect to its facility for stereospecifically catalysing reactions in the remaining positions of the coordination sphere. The geometry of the Co(III) complex is not maintained for Cr(III) for which a Δ-α-isomer of R,R-picchxn has been characterized [2, 3]. On the basis that the complex [Co(R,R-picchxn)XY]$^{n+}$ retains the basic framework of the related complexes Δ, Λ-[Ru(diimine)$_2$XY]$^{n+}$ with respect to sterically discriminating interactions [4] it was decided to investigate the reaction of Λ-β_2-[Co(R,R-picchxn)(AMMAH)]$^{2+}$ in acid solution to yield complexes containing R- or S-alanine [5, 7]. We find that the decarboxylation reaction in aqueous HCl under a variety of conditions proceeds to yield analine with a higher induction of optical activity than has hitherto been observed for any related complexes or reactions.

Experimental

Λ-β-[Co(R,R-picchxn)Cl_2]$ClO_4\cdot\frac{1}{2}H_2O$, Λ-β-[Co(R,R-picchxn)(S-ala)]$(ClO_4)_2\cdot3H_2O$ and Λ-β_1-[Co(R,R-picchxn)(R-ala)]$(ClO_4)_2\cdot3H_2O$ were synthesised using previously published procedures [1]. The method of Thanassi [8] was used to prepare α-amino-α-methylmalonic acid, $AMMAH_2$.

Λ-β_1-[Co(R,R-picchxn)(AMMAH)]$(ClO_4)_2\cdot4\frac{1}{2}H_2O$

A solution of Λ-β-[Co(R,R-picchxn)Cl_2]$ClO_4\cdot\frac{1}{2}H_2O$ (0.5 g, 0.93 mmol) in 20 cm^3 H_2O was added to a solution of $AMMAH_2$ (0.62 g, 4.65 mmol) in 10 cm^3 H_2O. The pH of the resulting mixture was adjusted to 8.0 with dilute aqueous NaOH, and the solution was stirred at room temperature overnight. After five fold dilution with water, the reaction mixture was applied to a Sephadex® CM C-25 ion exchange column (35 × 1.5 cm) in the Na^+ cycle. The column was washed with 20 cm^3 H_2O and developed with 1% (w/w) aqueous $NaClO_4$. A broad orange band developed, and this was collected in 20 cm^3 fractions. CD and electronic spectral measurements gave identical results for all fractions, which were combined and reduced to a volume of 20 cm^3 at 30 °C using a rotary evaporator. The deep-orange solu-

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†R,R-picchxn = N,N′-di(2-picolyl)-1R,2R-diaminocyclohexane, diimine = 1,10-phenanthroline, 2,2′-bipyridyl, alaH = alanine, $AMMAH_2$ = 2-amino-2-methylpropandioic acid (α-amino-α-methylmalonic acid), S,S-pyht = 1,7-bis(2S-pyrrolidyl)-2,6-diazaheptane.

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tion was placed in a vacuum desiccator over silica gel and allowed to evaporate slowly at room temperature. Deep-orange coloured crystals were deposited over a few days. These were collected at the pump, washed sparingly with ice cold water, and dried under suction. [Yield: 0.23 g. *Anal.* Found: C, 34.3; H, 5.0; N, 8.5; H_2O, 12.0%. Calc. for $C_{22}H_{39}N_5O_{16.5}Cl_2$-Co: C, 34.4; H, 5.1; N, 9.1; H_2O, 12.6%]. Electronic spectral data (λ in nm) are $\epsilon_{480} = 2250$, $\epsilon_{345} = 1820$ $dm^2\ mol^{-1}$. CD spectral data are $\Delta\epsilon_{490} = +21.4$, $\Delta\epsilon_{386} = +1.6$, $\Delta\epsilon_{353} = -3.9$, $\Delta\epsilon_{292} = +9.7$ $dm^2\ mol^{-1}$.

Decarboxylation Experiments

A 0.1 g portion of Λ-β_1-[Co(*R*,*R*-picchxn)-(AMMAH)]$(ClO_4)_2 \cdot 4½H_2O$ was dissolved in 75 cm^3 of aqueous HCl of the desired concentration (1.0 or 0.1 mol dm^{-3}) and the reaction mixture was heated at 70 °C for 2 hours. After cooling the solution to room temperature, its pH was adjusted to 7.0 with dilute aqueous NaOH, and the solution evaporated to dryness under reduced pressure at 30 °C. The orange product was extracted with absolute MeOH and the undissolved NaCl collected at the pump and washed with more MeOH. This desalting procedure was repeated twice, after evaporation of the filtrate. The resulting orange solid was dissolved in 10 cm^3 H_2O and applied to a Sephadex® CM C-25 cation exchange column (20 × 1 cm) in the Na^+ cycle. The column was washed with water and the mixture of orange isomers was eluted using 1% (w/w) aqueous $NaClO_4$. The *entire* orange band was collected and evaporated to dryness on a rotary evaporator at 30 °C. The *entire* solid product was dissolved in dmso-d_6 and ^1H NMR spectra of this solution were measured in order to find the ratio of Λ-β_1-[Co(*R*,*R*-picchxn)-(*R*,*S*-ala)]$^{2+}$ diastereoisomers present. Separate experiments using identical procedures to the above, as well as others, in which the reaction mixture was maintained at 70 °C during six hours, gave the same measured ratio of diastereomers.

Analyses were carried out by Mrs. A. Dams in the Department of Chemistry, Cardiff. Water of hydration analyses were determined thermogravimetrically using a Stanton Redcroft TG 750 temperature-programmed balance. CD and electronic spectral measurements were made using a Jobin-Yvon CNRS Dichrographe III and a Beckman DK 2A spectrophotometer, respectively. 360 MHz ^1H NMR spectra were recorded at 298 K using a Bruker WM 360 spectrometer with TMS as internal standard.

Results and Discussion

Only one diastereoisomer, Λ-β_1-[Co(*R*,*R*-picchxn)-(AMMAH)]$(ClO_4)_2 \cdot 4½H_2O$, was isolated from the reaction mixture of Λ-β-[Co(*R*,*R*-picchxn)Cl_2]$^+$ and $AMMAH_2$. Furthermore, we have been able to show that under the reaction conditions employed, it forms stereospecifically; the reaction solution from which

TABLE I. Selected 360 MHz ^1H NMR Data[a] for the Complexes Λ-β-[Co(*R*,*R*-picchxn)(aa)]$^{n+}$, in dmso-d_6 at 298 K.

	Λ-β_1-[CoL[b](R-AMMA)]$^+$	Λ-β_1-[CoL(*R*-ala)]$^{2+}$	Λ-β_1-[CoL(*S*-ala)]$^{2+}$
H(12)[c]	7.882	7.926	7.911
H(13)	8.302	8.366	8.352
H(14)	7.856	7.881	7.889
H(15)	8.213	8.278	8.225
H(42)	7.743	7.761	7.764
H(43)	8.133	8.183	8.176
H(44)	7.525	7.567	7.561
H(45)	7.044	7.082	7.035
$J_{12,13}$	7.31	8.02	7.86
$J_{13,14}$	8.19	6.61	7.66
$J_{14,15}$	5.37	5.48	5.66
$J_{42,43}$	7.69	7.76	7.67
$J_{43,44}$	7.87	7.88	7.74
$J_{44,45}$	5.49	5.69	5.69
H(N2)	6.756	7.536	6.789
H(N3)	11.091	6.926	6.866
H_α[d]		3.190	3.759
CH_3[d]	1.162	1.277	1.063
J_{CH_3,H_α}[d]		6.80	7.18
N*H*[d]	5.853	5.382	6.050
N*H*′[d]	4.895	4.877	4.789

[a] Chemical shifts are ±0.002 ppm, coupling constants ±0.02 Hz. [b] L = *R*,*R*-picchxn. [c] Numbering scheme is shown in (**I**). [d] Amino acidate resonances and coupling constants.

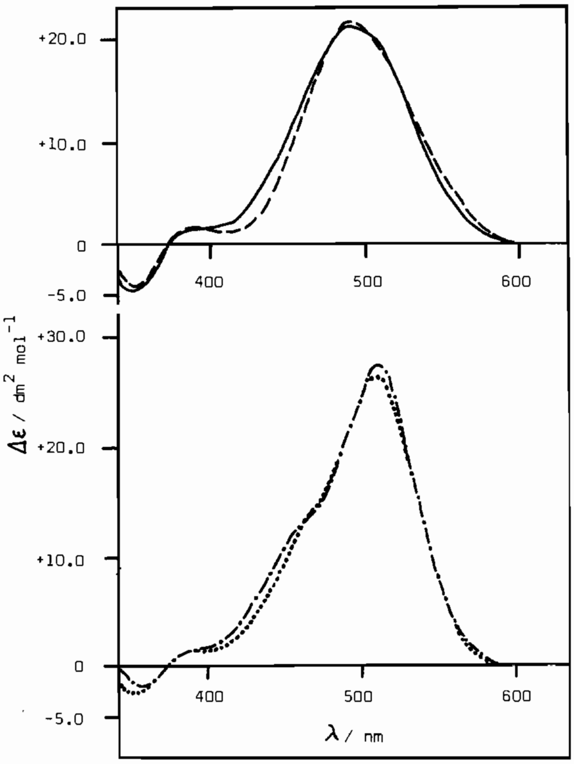
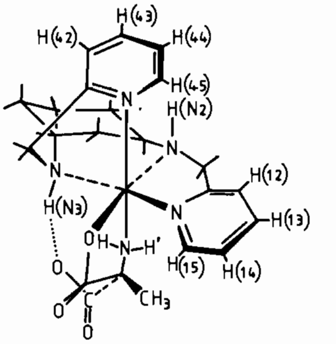


Fig. 1. CD spectra of (———): Λ-β_1-[Co(*R*,*R*-picchxn)(*S*-ala)]$^{2+}$; (— — —): Λ-β_1-[Co(*R*,*R*-picchxn)(*R*-AMMA)]$^+$; (— · —): Λ-β_1-[Co(*R*,*R*-picchxn)(*R*-ala)]$^{2+}$; (·······): The mixture of Λ-β_1-[Co(*R*,*R*-picchxn)(*R*,*S*-ala)]$^{2+}$ diastereomers from the decarboxylation. All spectra are recorded in H_2O at 298 K.

the crystals of the complex perchlorate were removed (it is very soluble in H_2O) had the same maxima and null dichroic points in its CD spectrum as the isolated solid. The reaction of the cobalt(III) complex proceeds with retention of absolute configuration as evidenced by the CD spectrum (Fig. 1) [7, 9], and the 360 MHz ^{1}H NMR spectrum of the complex, recorded in dmso-d_6, shows that it adopts the β_1 geometry by virtue of the chemical shifts observed in the aromatic region of the spectrum when compared with related complexes [1]. NMR spectral data are listed in Table I and the spectrum is shown in Fig. 2. This technique provides unequivocal evidence that only one diastereoisomer is present. One singlet due to the $AMMAH_2$ methyl resonance is observed at δ 1.162, and a unique set of pyridyl proton resonances are evident. The question then remains as to the mode of coordination of the α-amino-α-methylmalonate ligand. Two sets of NMR evidence indicate that this group adopts the *pro-S* configuration*, in the sense that if the uncoordinated carboxyl group is replaced by a hydrogen atom, then S-alanine results.

The *pro-S* complex, Λ-β_1-[Co(*R*,*R*-picchxn)(*R*-AMMA)]$^+$, depicted in (I), has the amino acid methyl group lying in such a position as to experience some shielding from the adjacent pyridyl ring. Thus it would be expected to be observed in the ^{1}H NMR spectrum as slightly higher field than in the alternative *pro-R* arrangement. In dmso-d_6 the methyl resonance of Λ-β_1-[Co(*R*,*R*-picchxn)(*S*-ala)]$^{2+}$ (Table I) is found at δ 1.063 compared with the *R*-alanine analogue at δ 1.277 [1]. This pattern of chemical shifts is found in a number of closely related alanine complexes of Co(III) with *R*,*R*-picchxn and *R*-picpn (2,5-diaza-3*R*-methyl-1,6-di(2-pyridyl)hexane) [1, 11, 12]. Λ-β_1 complexes of *S*-alaH dissolved in both D_2O and dmso-d_6 have the alanine methyl resonance between δ 1.06 and δ 1.21. Complexes in which this group does not experience a shielding effect by the adjacent pyridyl ring, such as Λ-β_1 complexes of *R*-ala Λ-β_2 complexes of *S*-ala and Δ-β_1 complexes of *S*-ala all show this resonance between δ 1.28 and δ 1.51.



I

Secondly, we note that only in the *pro-S* configuration can the uncoordinated carboxyl group hydrogen bond to the adjacent amine hydrogen atom of the tetradentate, as shown in (I). This three-point mode of attachment has been shown by crystal structure studies to occur in Λ-β_2-[{(2*S*,9*S*)-2,9-diamino-4,7-diazadecane}(α-amino-α-methyl malonato) cobalt(III)] [6], and in the related complex (citrato)(1,4,7,10-tetraazadecane)cobalt(III) [13]. In the 360 MHz ^{1}H NMR spectrum of the complex in dmso-d_6, one of the tetradentate amine proton resonances is found at unusually low field (δ 11.1) for this type of complex [1, 12]. However, this would be entirely expected if the particular proton were to be involved in hydrogen bonding to the uncoordinated carboxylic group of the amino acidate. Molecular models show that this hydrogen bond may form with no strain imposed on the complex, although it should be noted that the species isolated in the solid state is fully protonated.

In addition, it should be noted from Fig. 1 that the CD spectrum of the complex is very similar to that of Λ-β_1-[Co(*R*,*R*-picchxn)(*S*-ala)]$^{2+}$ as contrasted with the CD spectrum of the analogous *R*-alaH dia-

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*Because of the mode of coordination of the α-amino-α-methylmalonate ligand, the *pro-S* form has absolute configuration *R* [10].

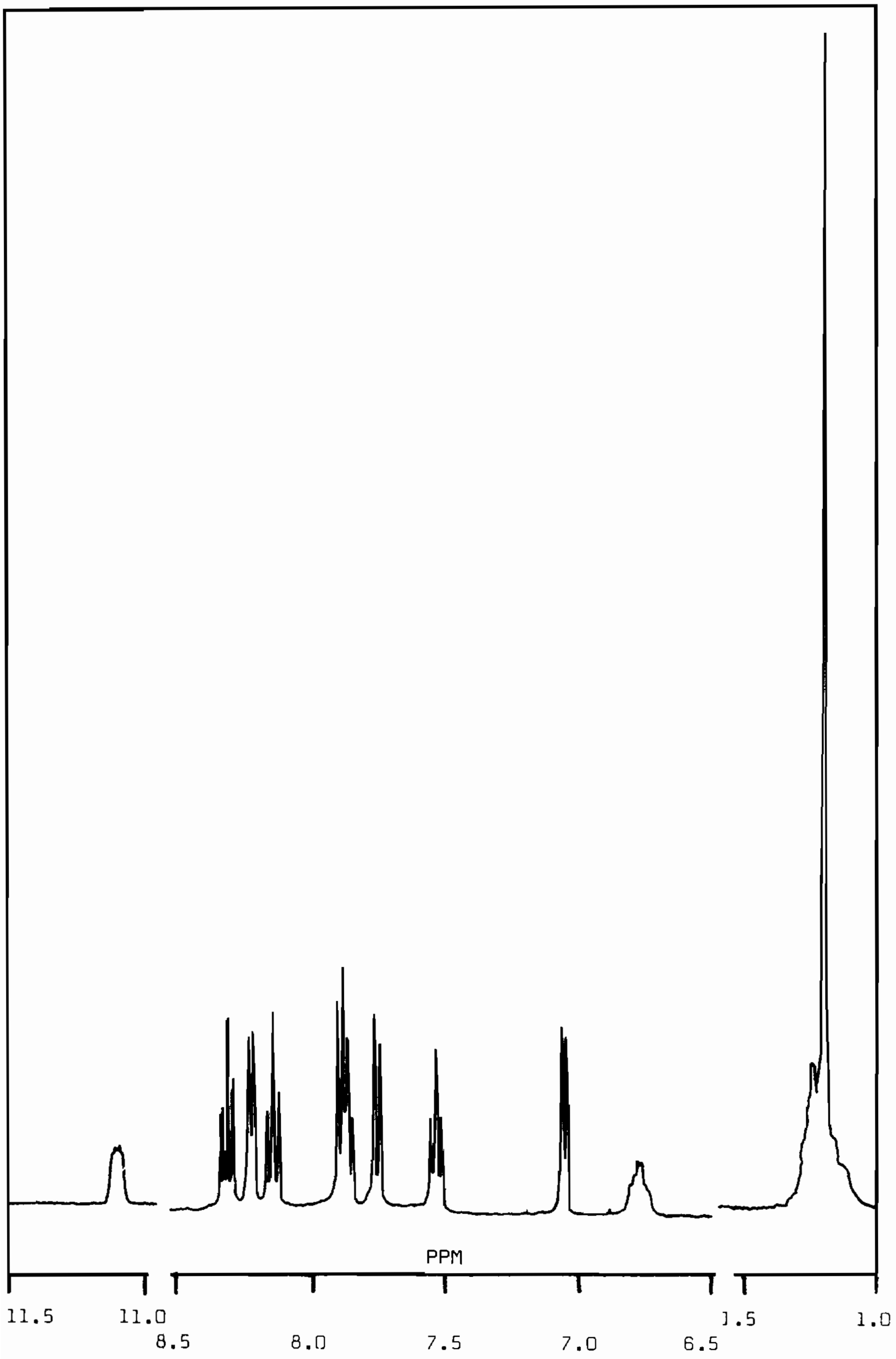


Fig. 2. 2.360 MHz ^{1}H NMR spectrum of Λ-β_1-[Co(R,R-picchxn)(R-AMMAH)]$(ClO_4)_2$ in dmso-d_6 at 298 K, with particular reference to the aromatic and -CH_3 regions.

stereoisomer. This pattern of results is exactly analogous to that found for Λ-β_2-[Co{(2S,9S)-2,9-diamino-4,7-diazadecane}(AMMA)]$^+$. For this latter complex, in which the α-amino-α-methylmalonate ligand has been shown crystallographically to coordinate in the *pro-R* configuration [6], its CD spectrum is very similar to those of corresponding R-aminoacidate complexes rather than those containing S-amino acidate ligands. Thus we conclude that the isomer we isolate in our system is that shown in (**I**),

Λ-β_1-[Co(*R*,*R*-picchxn)(*R*-AMMA)]$^+$, or in the solid state, its conjugate acid perchlorate salt.

When Λ-β_1-[Co(*R*,*R*-picchxn)(*R*-AMMAH)]$^{2+}$ is decarboxylated in hot aqueous 1.0 mol dm^{-3} HCl solution, negligible decomposition of the complex occurs. But a trace of a green unidentified complex is retained on the cation exchange column, and electronic spectra of the eluted alaninato complexes in solution indicate that >99% of the complex is recovered from the experiment.

The 360 MHz ^{1}H NMR spectrum of the mixture of Λ-β_1-[Co(*R*,*R*-picchxn)(*S*-ala)]$^{2+}$ and Λ-β_1-[Co(*R*,*R*-picchxn)(*R*-ala)]$^{2+}$ diastereoisomers formed is shown in Fig. 3, together with the pure individual complexes, for comparison. It is clear that the complex diastereomer containing *R*-alanine is formed in a far greater amount and integration of the appropriate pyridyl and amino acid methyl resonances show that the ratio of *R*-ala complex to *S*-ala complex is equal to 89:11. The CD spectrum of the mixture of dia-

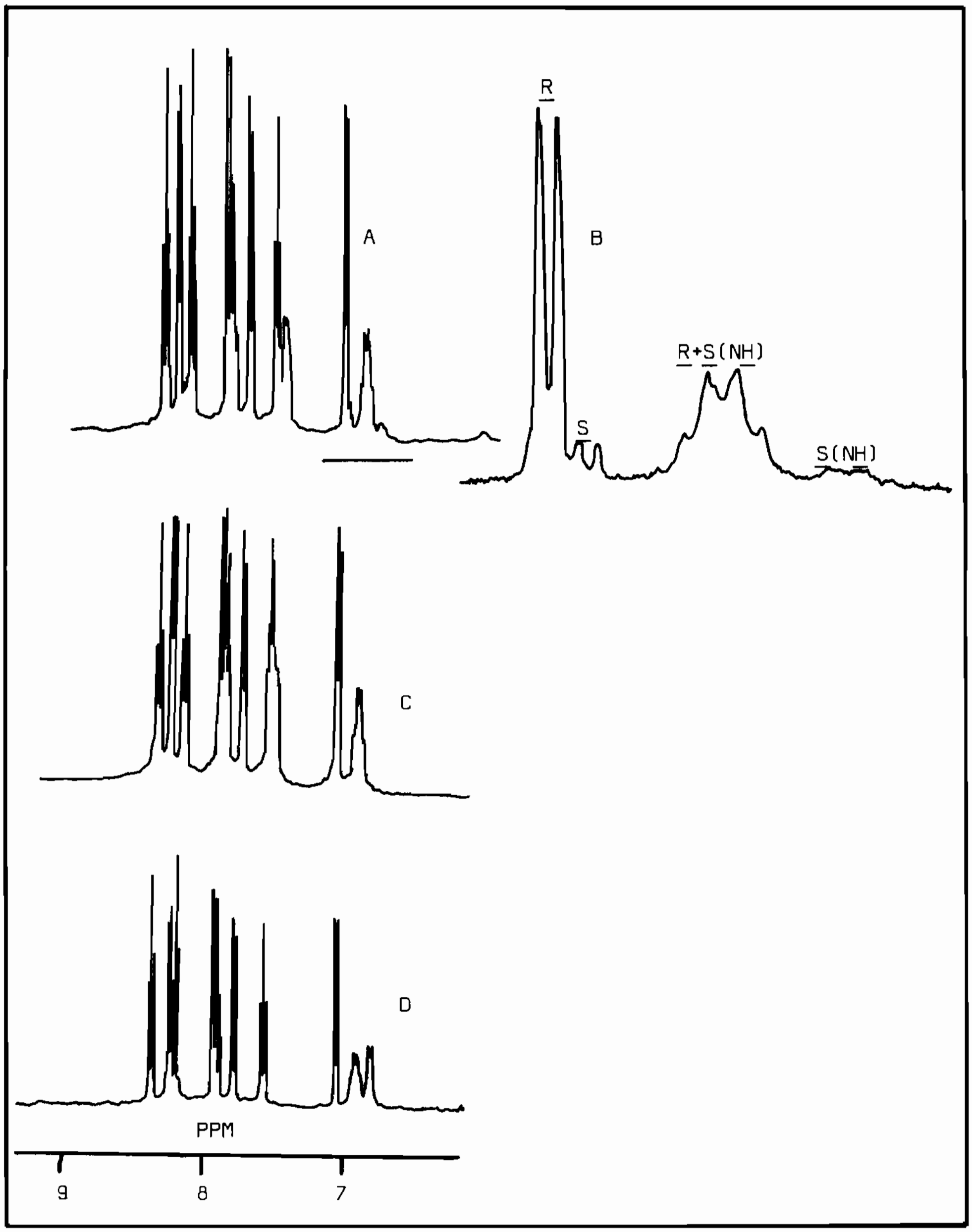
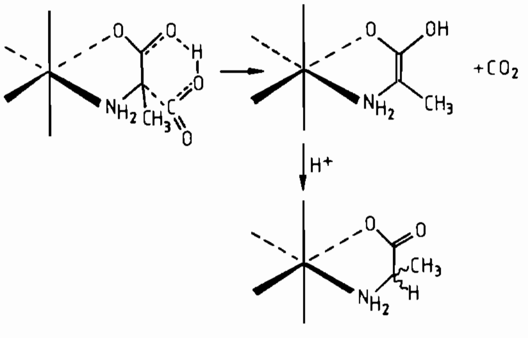


Fig. 3. Aromatic regions of the 360 MHz ^{1}H NMR spectra of the diastereoisomers in dmso-d_6 at 298 K. A: Mixture of Λ-β_1-[Co(*R*,*R*-picchxn)(*R*,*S*-ala)]$^{2+}$ isomers from a typical decarboxylation experiment; B: Expanded region of the underlined portion of spectrum A, indicating the relative amounts of diastereomers containing *R*-ala(*R*) and *S*-ala(*S*); C, D: Λ-β_1-[Co(*R*,*R*-picchxn)-(*R*-ala)]$^{2+}$ and Λ-β_1-[Co(*R*,*R*-picchxn)(*S*-ala)]$^{2+}$, respectively.

stereoisomers obtained is also given in Fig. 1 and this too shows the preponderance of the isomer containing *R*-alanine. This experiment was repeated three times and the same ratio was obtained, *viz.* 89 ± 0.5: 11 ± 0.5. Furthermore, the same ratio is found for decarboxylations of the same starting complex under the same conditions maintained at 70 °C for six hours and in 0.1 mol dm^{-3} aqueous HCl at 70 °C for six hours. The degree of steric induction observed in the reaction is the largest so far recorded for alanine in like reactions involving complexes of other linear tetradentate ligands, [5–7, 14].

It is of interest that the *pro-S* α-amino-α-methylmalonate complex precursor yields the *R*-alaninato complex predominantly. The α-carbon atom of the precursor thus inverts its absolution configuration during the decarboxylation. This phenomenon has been noted previously in a number of similar reactions of α-amino-α-methylmalonate [6, 7, 10] although it is not generally found for related complexes of other α-amino-α-alkyl (or aryl) malonate ligands. The one exception to this observation concerns the complex Λ-β_2-$[Co(S,S\text{-pyht})(AMMA)]^+$. However, it was found using NMR techniques that this complex was in fact a mixture of the *pro-R* and *pro-S* diastereomers [7].

The mechanism of the decarboxylation was thought by Job and Bruice [10] to proceed via the cyclized intermediate as shown in (**II**). However, Yamaguchi *et al.* [7] have shown that in some systems the decarboxylation occurs in a direction opposite to that of the epimerization reaction in basic solution used to establish the chiral discrimination energies between pairs of *R* and *S*-amino acidate diastereoisomers. This fact in conjunction with that involving different isomer distributions dependant upon the solvent chosen for the decarboxylation, led to the conclusion that solvation effects are important and that the detailed mechanism is somewhat more complicated than was originally envisaged.



II

For our complexes, it has proved fruitless to attempt to measure the equilibrium distribution of *S*- and *R*-alaninato diastereoisomers by base-catalysed epimerization of a coordinated amino acid because of rapid decomposition of the isomers. However, we note that we obtain the same ratio of diastereoisomers (and thus the same stereoselectivity) under a variety of reaction conditions. This points to the probability that the results reflect thermodynamic rather than kinetic discriminations. We are pursuing our studies on this and related complexes with a view to establishing their synthetic potential.

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