Short Communication

Chiral metal complexes Part 39*. Resolution of α-methyltryptophane via coordination to an optically active metal complex

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Interest in the synthesis and resolution of α-alkylamino acids is increasing as the search for novel peptide pharmaceuticals continues [2]. To date, large-scale syntheses of optically pure α-alkylamino acids or resolution of their racemates has proved difficult [3, 4]. Enzymatic resolution is more restricted than for normal α-amino acids and resolution by chemical means has assumed a greater importance for such compounds. Earlier reported resolutions of *N*-acyl-α-methylamino acids involved fractional crystallization as salts of optically active α-phenylethylamine [5] or cinchonidine [6]. More recently, ligand exchange HPLC techniques have been employed to resolve a number of α-alkylamino acids, including α-methyltryptophane (α-Me-trpH) [7, 8].

The [Co(*R*,*R*-picchxn)]$^{3+}$ complex nucleus (*R*,*R*-picchxn = *N*,*N'*-di(2-picolyl)-1*R*,2*R*-diaminocyclohexane) has been successfully used as a coordinating chiral auxiliary for the resolution of proline, pipecolic acid and α-amino acids with normal aliphatic side chains [9]. This prompted an investigation of its use for the resolution of α-methyltryptophane. The separation of isomers of Λ-β$_1$-[Co(*R*,*R*-picchxn)(*R* or *S*-α-Me-trp)]$^{2+}$, and subsequent recovery of the free, optically pure amino acids, is described below.

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Experimental

Electronic and CD spectra were recorded using a Perkin-Elmer Lambda 5 spectrophotometer and a Jobin-Yvon Dichrographe III, respectively. High-resolution 360 MHz ^{1}H NMR spectra were recorded at 21 °C using a Bruker WM 360 spectrometer with TMS as internal standard in dmso-d_6. Optical rotations were measured using an Optical Activity A10 automatic polarimeter. Elemental analyses were carried out by Mrs A. Dams of the School of Chemistry and Applied Chemistry, Cardiff.

Synthesis and separation of the isomers Λ-β$_1$-[Co(R,R-picchxn)(R-α-Me-trp)]$^{2+}$ and Λ-β$_1$-[Co(R,R-picchxn)(S-α-Me-trp)]$^{2+}$

During all manipulations, care was taken to exclude light in order to avoid undesired photochemical decompositions. The racemic α-Me-trpH used was kindly supplied by Dr K. R. N. Rao of Jones Chromatography, Hengoed, South Wales.

To a stirred suspension of Λ-β-[Co(*R*,*R*-picchxn)Cl$_2$]ClO$_4$·0.5H$_2$O [10] (2.00 g, 3.74 mmol) in water (100 cm^3) was added *rac*-α-Me-trpH (2.48 g, 2.45 mol equiv.). The mixture was warmed at 50 °C until all solids had dissolved, was cooled to room temperature and aqueous NaOH (1 M) was added to give a pH of 6.5. The solution was then warmed at 45–50 °C for 4 h, during which time an orange crystalline solid, **1**, separated. This was collected at the pump, washed with ice-cold water, and air dried. Yield 1.20 g (42%, based on Co). The crystals proved to be suitable for X-ray investigation, and were shown (*vide infra*) to consist of Λ-β$_1$-[Co(*R*,*R*-picchxn)(*S*-α-Me-trp)](ClO$_4$)$_2$. *Anal.* Calc. for $C_{30}H_{37}N_6O_{10}Cl_2Co$: C, 46.7; H, 4.8; N, 10.9. Found: C, 46.7; H, 4.9; N, 10.7%. Spectroscopic data: λ_{max} 490 nm, $\epsilon = 248$ M^{-1} cm^{-1}, $\Delta\epsilon_{485} = +2.65$ M^{-1} cm^{-1} (extremum).

The filtrate from the above was diluted two-fold and applied to a CM-Sephadex column (100 × 1.8 cm) in the H$^+$ cycle. Elution with 0.2 M aqueous NaCl gave two orange bands, which were each collected in fractions. Electronic absorption and CD measurements showed that the faster moving band contained one isomer. These fractions were combined, excess sodium perchlorate was added, and the volume was reduced until

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a second crystalline orange compound, **2**, separated. The solid was isolated as above. Yield 0.24 g (23%, based on Co). *Anal.* Calc. for $C_{30}H_{47}N_6O_{15}Cl_2Co$ (Λ-β_1-[Co(*R*,*R*-picchxn)(*R*-α-Me-trp)]$(ClO_4)_2 \cdot 5H_2O$): C, 41.8; H, 5.5; N, 9.8. Found: C, 41.8; H, 4.6; N, 9.6%. The low hydrogen analysis is associated with loss of H_2O prior to combustion. Spectroscopic data: $\lambda_{max} = 482$, 350 nm; $\epsilon = 217$, 284 M^{-1} cm^{-1}, respectively; $\Delta\epsilon_{490,380} = +2.51$, $+0.59$ M^{-1} cm^{-1}, respectively (extrema).

Three species were detected in the slower moving band. Their further identification was not attempted.

Recovery of S-α-Me-trp

Method A

A procedure similar to that of Yoshikawa and coworkers [11] was used. The least soluble diastereoisomer, **1**, (0.4 g) was dissolved in 0.1 M aqueous Na_2CO_3 (50 cm^3) and the solution heated at 50 °C for 3 h to yield a deep purple solution. This was applied to a CM-Sephadex column (70×1.8 cm) in the Na^+ cycle and the frec amino acid was eluted with H_2O. Removal of the solvent gave an off-white solid which was laevorotatory at the Na-D line, but which was contaminated by small amounts of unidentified decomposition products, as revealed by a ^1H NMR spectrum.

Method B

In this method, the pure amino acid enantiomers were recovered after electrolytic reduction of the complexes. A potential difference of -1 V was applied for 5 h to a solution of **1** (0.5 g) in 0.1 M HCl (150 cm^3) using an EG&G Princeton Applied Research 363 potentiostat operating with a mercury working electrode and a Pt counter electrode. The resulting yellow solution was diluted with water and chromatographed as above. Removal of most of the solvent gave pure *S*-α-Me-trpH, which was collected at the pump, washed with ice-cold water and air dried (yield 90%); $[\alpha]_D = -10.3°$ (20 °C, $c = 0.9$, H_2O); lit. [12]: $[\alpha]_D = -10.6°$ (20 °C, $c = 0.9$, H_2O). Treatment of **2** in the same way gave pure *R*-α-Me-trpH; $[a]_D = +10.2°$ (20 °C, $c = 0.9$, H_2O).

Crystal and molecular structure of Δ-β₁-[Co(R,R-picchxn)(S-α-Me-trp)](ClO₄)₂

Crystal data

$C_{30}H_{37}N_6O_{10}Cl_2Co$, $M_r = 771.5$, monoclinic, $a = 12.089(4)$, $b = 11.5450(3)$, $c = 12.493(3)$ Å, $\beta = 113.87(2)°$ $U = 1594.5$ Å^3, $Z = 2$, $D_c = 1.607$, $F(000) = 800$, μ(Mo Kα) = 8.0 cm^{-1}, space group $P2_1$ (No. 4).

Unit cell data were initially determined from precession photographs using Mo Kα radiation. Accurate cell parameters were obtained from a least-squares fit to diffractometer data. The crystal used for data collection had dimensions 0.24×0.22×0.21 mm. Intensities were collected at -120 °C on a Nicolet XRD-P3 four-circle diffractometer [13] in the range $3 < 2\theta < 50°$ using graphite-monochromatized Mo Kα radiation. Intensities were corrected empirically for absorption ($t_{max} = 0.812$, $t_{min} = 0.737$), and for Lorentz and polarization effects. Of the 2949 reflections measured, 2092 gave counts

TABLE 1. Final atomic coordinates (fractional ×10⁴) for non-hydrogen atoms with e.s.d.s in parentheses for Λ-β₁-[Co(*R*,*R*-picchxn)(*S*-α-Me-trp)](ClO₄)₂

	x/a	*y/b*	*z/c*
Co	534.7(9)	0	3336.1(9)
N(11)	−1097(6)	−259(5)	2150(6)
N(21)	1310(7)	−1220(7)	2800(6)
N(1)	577(6)	1144(7)	2220(6)
N(2)	2257(6)	452(7)	4255(6)
N(3)	−163(6)	1025(7)	4169(6)
O(31)	389(6)	−1176(5)	4357(5)
O(32)	−569(6)	−1597(5)	5500(5)
C(31)	−187(8)	−886(8)	5009(8)
C(32)	−258(8)	408(8)	5205(8)
C(33)	−1438(8)	767(8)	5327(7)
C(34)	829(8)	698(9)	6315(8)
N(4)	−4196(7)	−268(7)	2821(7)
C(41)	−3286(9)	−401(8)	3903(9)
C(42)	−2571(9)	565(9)	4209(9)
C(43)	−3076(8)	1365(8)	3246(8)
C(44)	−2740(8)	2484(8)	3033(8)
C(45)	−3392(9)	2973(9)	1924(9)
C(46)	−4362(9)	2381(10)	1063(8)
C(47)	−4747(8)	1304(10)	1274(8)
C(48)	−4077(9)	813(9)	2367(9)
C(11)	−1759(8)	−1220(9)	2033(8)
C(12)	−2864(8)	−1362(8)	1061(8)
C(13)	−3276(9)	−483(9)	244(8)
C(14)	−2614(8)	518(8)	374(8)
C(15)	−1523(8)	598(8)	1337(8)
C(16)	−673(8)	1631(8)	1595(8)
C(1)	1547(8)	1989(8)	2794(8)
C(2)	2632(8)	1210(8)	3474(9)
C(3)	3798(8)	1917(9)	4136(8)
C(4)	4012(9)	2718(9)	3253(9)
C(5)	2948(9)	3507(9)	2632(9)
C(6)	1794(9)	2795(8)	1932(9)
C(21)	764(8)	−1962(8)	1877(8)
C(22)	1359(9)	−2914(9)	1728(9)
C(23)	2529(9)	−3119(9)	2473(9)
C(24)	3105(9)	−2374(9)	3403(9)
C(25)	2458(8)	−1439(9)	3550(8)
C(26)	2967(8)	−619(8)	4577(7)
Cl(1)	1483(2)	66(3)	−153(2)
O(1a)	1382(8)	−829(7)	−975(7)
O(1b)	1577(8)	1175(7)	−623(7)
O(1c)	395(5)	40(8)	92(5)
O(1d)	2510(6)	−129(9)	930(6)
Cl(2)	4320(2)	1397(2)	−2502(2)
O(2a)	4865(7)	529(7)	−2948(7)
O(2b)	3929(7)	928(7)	−1649(6)
O(2c)	5171(6)	2330(6)	−1985(6)
O(2d)	3289(6)	1858(6)	−3478(5)

for which $I > 3\sigma(I)$, and these were used for the structure determination.

The structure was solved by the heavy atom method and was refined by least-squares calculations in which the function minimized was $\Sigma w\Delta^2$, the weights employed being unity. After several cycles of refinement the positions of the hydrogen atoms were found by a difference synthesis. These were optimized assuming the appropriate geometries to which they were attached with C,N–H bond lengths of 1.0 Å and only their positional parameters were subsequently varied. Final refinement was carried out with anisotropic thermal parameters for all non-hydrogen atoms and terminated when the maximum shift in any parameter was less than 0.1σ. The final value for R was 0.042 and R' $\{=(\Sigma w(F_o - F_c)^2/\Sigma w|F_o|^2)^{0.5}\}$ was 0.047. A final difference Fourier map showed no electron density greater than |0.4| e Å^{-3}.

Calculations were carried out on a FACOM M350S computer using programs written by F.S.S. Neutral atom scattering factors with corrections for anomalous dispersion were taken from the International Tables for X-Ray Crystallography [14]. Final atomic positional parameters are given in Table 1 (see also 'Supplementary material').

Results and discussion

Crystal and molecular structure of Λ-β$_1$-[Co(R,R-picchxn)(S-α-Me-trp)](ClO$_4$)$_2$

A view [15] of the complex cation showing the atom labelling scheme is shown in Fig. 1. The most significant feature of the structure is that it unambiguously establishes the stereochemistry of the amino acid in **1**. This results from the fact that the absolute configuration of the complex Λ-β$_1$-[Co(*R*,*R*-picchxn)(*S*-α-Me-trp)]$^{2+}$ cation is certain since the *R* configuration holds for both asymmetric carbon atoms of the cyclohexane ring. Other stereochemical features are that the tetradentate adopts the β geometry with both secondary nitrogen atoms possessing the *S* configuration, and that the amino acid is coordinated to give the β$_1$ diastereoisomer. It is also worth noting that the non-coordinated indole ring of *S*-α-Me-trp lies parallel to one of the pyridine rings of the tetradentate (Fig. 1) and appears to be stabilized in this conformation by hydrophobic interactions. Resulting shielding effects observed in its ^{1}H NMR spectrum are of significance both with respect to this isomer and to the elucidation of the nature of **2**.

^{1}H NMR studies

Characteristic ^{1}H NMR data for **1** and **2** are given in Table 2. The aromatic regions of the spectra are well-resolved and all resonances may be unambiguously identified, in accordance with previously established criteria [10, 16–18]. In particular, the positions of the H(15) and H(25) resonances confirm that both **1** and **2** are β$_1$ isomers. Thus it is established that **2** contains the complex cation Λ-β$_1$-[Co(*R*,*R*-picchxn)(*R*-α-Me-trp)]$^{2+}$, further evidenced by the subsequent isolation of the *R*-amino acid from it.

Certain of the amino acid resonances provide additional support for the assignment of stereochemistry for **2**. In **1**, the pyrrole C*H* singlet at 6.73 ppm is shielded with respect to its position in **2** (7.79 ppm), presumably because of its proximity to the pyridine ring involved with stacking in the solid state. Consistent with this is the fact that the reverse holds for the C*H*$_3$ resonances. The singlet in **2** (0.86 ppm) is considerably more shielded than in **1** (1.55 ppm), again due to differences in the relative proximities of the pyridine rings in both isomers. In this, the NMR behaviour exactly parallels that of related β$_1$ complexes of *R*,*S*-alanine [8, 16–18], whose absolute configurations were readily assigned on the basis of the same relative ^{1}H NMR shielding effects.

The use of the Λ-β-[Co(*R*,*R*-picchxn)]$^{3+}$ nucleus as a chiral auxiliary again is successful in this example

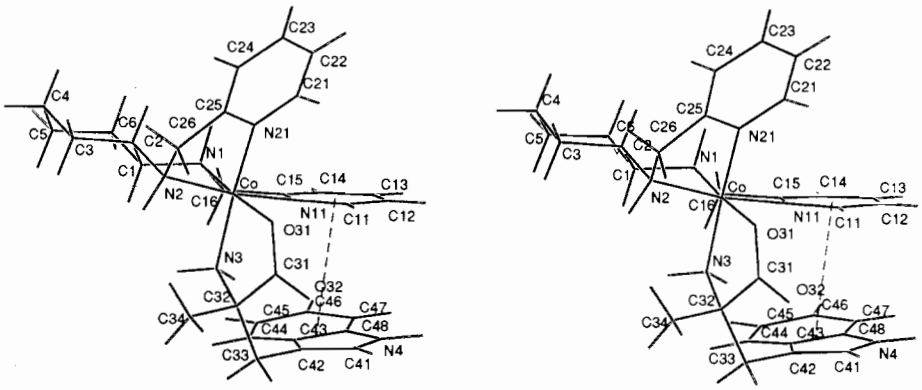

Fig. 1. A stereo view [15] of the complex cation of Λ-β$_1$-[Co(*R*,*R*-picchxn)(*S*-α-Me-trp)](ClO$_4$)$_2$ showing the atom labelling scheme.

TABLE 2. Characteristic ^{1}H NMR data for the complexes (at 21 °C in dmso-d_6, δ in ppm relative to TMS as internal standard)

	1	2
H(12)	7.55d[c]	7.94d
H(13)	8.21t	8.37t
H(14)	7.56t	7.48t
H(15)	6.90d	6.96d
H(22)	7.56d	7.48d
H(23)	8.18t	8.09t
H(24)	7.78t	7.92t
H(25)	8.15d	8.22d
Pyrrole C*H*[a,b]	6.73s	7.79s
Benzene C*H*[a,b]	7.34d	7.68d
	7.27d	7.55d
	7.06t	7.18t
	6.95t	7.02t
C*H*$_3$[a]	1.55s	0.86s

[a]Amino acid resonances. [b]Of indole ring. [c]Symbols: d = doublet, t = triplet, s = singlet.

and shows that its application is not confined to the resolution of unsubstituted amino acids. Other α-alkyl-substituted analogues have not been studied, but the successful resolution reported above suggests that the system is sufficiently flexible to accommodate such species. Indeed, the *S* enantiomer would be readily accessible in larger quantities via the formation of the comparatively insoluble Λ-β_1-[Co(*R*,*R*-picchxn)(*S*-α-Me-trp)]$(ClO_4)_2$ salt, since *R*,*R*-picchxn may be obtained from inexpensive chiral starting materials.

Supplementary material

Lists of observed and calculated structure factors, anisotropic thermal parameters, hydrogen atom positions, hydrogen bonding parameters in the crystal, and a comprehensive table of bond lengths and angles, are available from the authors on request.

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