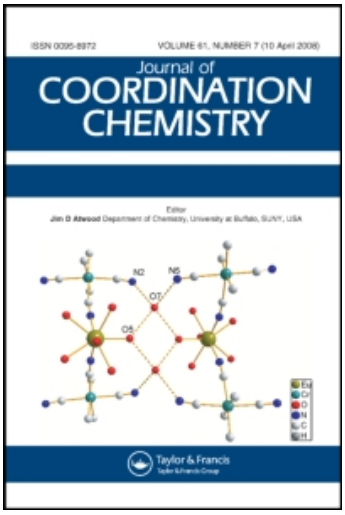


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# A convenient resolution of pipecolic acid using a metal complex as the chiral auxiliary

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Optically pure enantiomers of pipecolic acid are conveniently prepared in high yield by reacting the racemate with Λ-β-[Co(*R*,*R*-picchxn)$Cl_2$]$^+$ (picchxn = *N*,*N*′-di(2-picolyl)1,2-diaminocyclohexane) and crystallization of pure internal diastereoisomers as perchlorate salts. Subsequent reactions give the free acid of either hand. The stereochemical course of the resolution is established unambiguously by a single-crystal X-ray analysis of one intermediate and a combination of CD and $^1$H NMR measurements.

*Keywords*: Pipecolic acid; Resolution; Internal diastereoisomer; X-ray structure

## 1. Introduction

A resolution of pipecolic acid has been reported previously [1] and involves the repeated recrystallization of a diastereoisomeric tartrate salt followed by isolation of the free acid. However, the procedure results in poor yields of the enantiomers. In studies of chiral Co(III) complexes of ligands based on *N*,*N*′-di(2-picolyl)-1,2-diaminoethane [2], we have shown that coordination of aminoacids in ternary complexes of the type Λ-β-[Co(*R**, *R**-picchxn)(aminoacidate)]$^{n+}$ (picchxn = *N*,*N*′-di(2-picolyl)-1,2-diaminocyclohexane) is effective for resolutions of a variety of substrates [3]. We have extended these studies to provide a convenient, high-yield resolution of pipecolic acid, as reported below.

## 2. Experimental

Electronic absorption and CD spectra of aqueous solutions were recorded using a Perkin–Elmer Lambda 5 spectrophotometer and a CNRS-Jobin Yvon

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Dichrographe III, respectively. $^1$H NMR spectra of dmso-$d_6$ solutions were measured with a Bruker WM 360 MHz spectrometer, using TMS as internal standard.

### 2.1. *Resolution*

$\Lambda$-$\beta$-[Co(*R*,*R*-picchxn)$Cl_2$]$ClO_4 \cdot 5H_2O$ was prepared as previously described [4]. The resolution of pipecolic acid (pipH) was effected as follows. $\Lambda$-$\beta$-[Co(*R*,*R*-picchxn)$Cl_2$]$ClO_4 \cdot 5H_2O$ (1 g, 1.87 mmol) was dissolved at room temperature in water (30 $cm^3$) at 60°C and to the solution was added *R*,*S*-pipecolic acid (1.29 g, 10 mmol). The solution was stirred and the pH adjusted by adding 1.0 M aqueous NaOH (1 $cm^3$). After stirring and heating at 60°C for 1 h, the reaction mixture was cooled to room temperature, diluted to 155 $cm^3$ with water and applied to a Sephadex® column (30 × 2 cm) in the $H^+$ form. The column was eluted with 0.2 M aqueous NaCl, when three bands developed, a faint reddish orange band and two intense orange ones. These were collected in fractions and measurements of optical density *versus* CD were used to establish the fact that only one isomer was present in each band. Addition of solid $NaClO_4$ to combined fractions gave crystalline solids from each of the three bands. The first (yield 10.1%, based on Co) proved to be $\Lambda$-$\beta_1$-[Co(*R*,*R*-picchxn)(*R*-pip)]$(ClO_4)_2 \cdot 3H_2O$ (**1**). Anal. Calcd (%): C, 39.1; H, 5.6; N, 9.5. Found: C, 39.0; H, 5.0; N, 9.2. Electronic spectrum, CD ($\lambda$/nm, $\varepsilon$ or $\Delta\varepsilon$ $dm^2\,mol^{-1}$): 492, 3270; 359, 3890; 468, +65.0; 356, −27.1. Characteristic $^1$H NMR data ($\delta$, ppm): 7.86, d, H(114), 8.33, t, H(113), 7.83, t, H(112), 8.44, d, H(111), 7.70, d, H(124), 8.18, t, H(123), 7.58, t, H(122), 7.09, d, H(121); $J_{113,114}$ 7.7, $J_{112,113}$ 7.2, $J_{111,112}$5.5, $J_{123,124}$ 7.4, $J_{122,123}$ 7.5, $J_{121,122}$ 5.7 Hz (the hydrogen atom numbering scheme, here and below, refers to the carbon atom to which the hydrogen is attached as shown in figure 1). The second eluted isomer (yield 40.6%) gave $\Lambda$-$\beta_2$-[Co(*R*,*R*-picchxn)(*S*-pip)]$(ClO_4)_2 \cdot H_2O$ (**2**). Anal. Calcd: C, 41.2; H, 5.2; N, 10.0. Found: C, 41.0; H, 5.2; N, 9.9. Electronic spectrum, CD: 490, 1930; 354, 2070; 543, −8.4; 494, +27.0. $^1$H NMR data: 7.85, d, H(114), 8.34, t, H(113), 7.85, t, H(112), 8.86, d, H(111), 7.71, d, H(124), 8.20, t, H(123), 7.59, t, H(122), 7.23, d, H(121); $J_{113,114}$ 7.6, $J_{112,113}$ 7.8, $J_{111,112}$ 5.6, $J_{123,124}$ 7.8, $J_{122,123}$ 8.1, $J_{121,122}$ 5.9 Hz. The third eluted species, yield 4.8%, gave $\Lambda$-$\beta_1$-[Co(*R*,*R*-picchxn)(*S*-pip)]$(ClO_4)_2$ (**3**). Anal. Calcd: C, 42.2; H, 5.0; N, 10.3. Found: C, 42.5; H, 5.1; N, 10.4. Electronic spectrum, CD: 496, 2660; 359, 2560; 514, +32.0; 390, +2.7. $^1$H NMR data: 7.96, d, H(114), 8.43, t, H(113), 7.96, t, H(112), 8.35, d, H(111), 7.72, d, H(124), 8.15, t, H(123), 7.51, t, H(122), 6.90, d, H(121); $J_{113,114}$ 7.8, $J_{112,113}$ 7.8, $J_{111,112}$ 5.7, $J_{123,124}$ 7.9, $J_{122,123}$ 7.5, $J_{121,122}$ 5.7 Hz.

Optically pure pipecolic acid was isolated from the appropriate diastereoisomeric salt by the following method. A potential difference of −1 V was applied for 5 h to a solution of the complex (0.5 g) in 0.1 M aqueous HCl (150 $cm^3$) using an EG&G Prinston Applied Research 365 potentiostat operating with a mercury working electrode and a Pt counter electrode. The resulting yellow solution was diluted with water and applied to CM-Sephadex column (50 × 2 cm) in the $Na^+$ cycle. The free amino acid was eluted with water, which was removed *in vacuo* at 40°C to give the solid product in 95% yield after collection at the pump, washing with ice-cold water and air-drying; the *S*-$(-)_D$-pipecolic acid (from both isolated isomers) had $[\alpha]_D^{25} = -24.4°$ (*c* 3.0, $H_2O$); lit. [1] (for the *R*-$(+)_D$-isomer): $[\alpha]_D^{23} = +24.6°$ (*c* 3.35, $H_2O$), $[\alpha]_D^{19} = +26.2°$ (*c* 3.106, $H_2O$). *R*-$(-)_D$-pipecolic acid had $[\alpha]_D^{25} = -24.1°$ (*c* 3.0, $H_2O$).

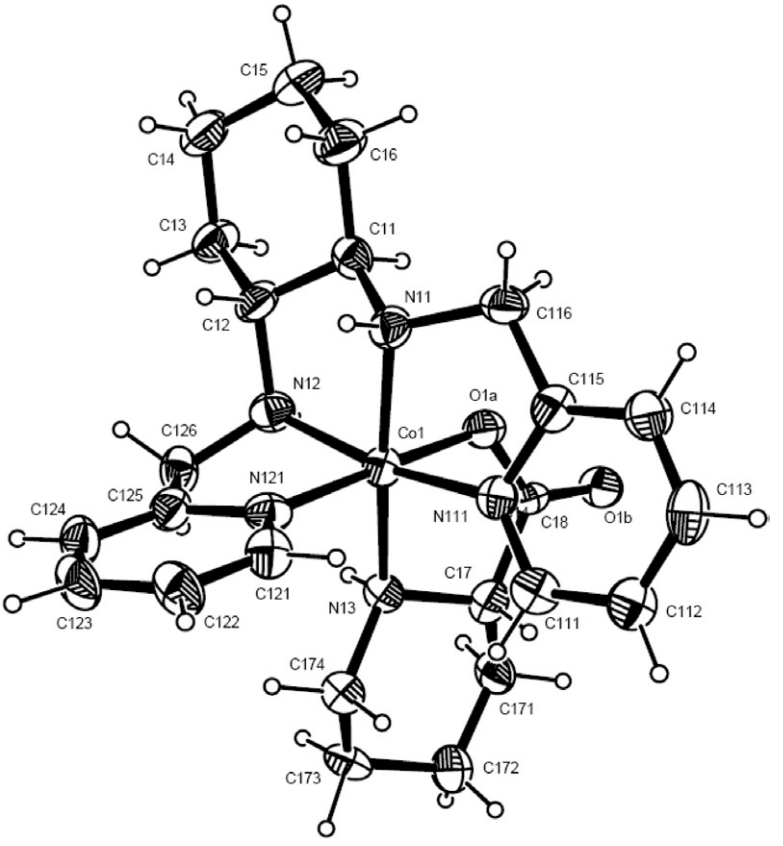


Figure 1. A perspective view of the complex cation Λ-$\beta_2$-[Co(*R*,*R*-picchxn)(*S*-pip)]$^+$ showing the atom numbering scheme for the non-hydrogen atoms. Only the Co(1) cation is shown.



### 2.2. *Crystal structure of Λ-β$_2$-[Co(R,R-picchxn)(S-pip)](ClO$_4$)$_2$·0.5H$_2$O (2)*

Unit cell parameters were refined *via* a least-squares fit to diffractometer data. The crystal used for data collection was $0.30 \times 0.15 \times 0.10\,\text{mm}^3$ in size. Intensity data were collected on an Enraf-Nonius FAST area detector diffractometer in the range $3.40^\circ < \theta < 25.05^\circ$ at 278 K using graphite-monochromatized Mo-K$\alpha$ radiation with omega scan increments of 0.3°. Data integration and correction for Lorentz and polarization effects was performed using documented procedures [6]; absorption corrections were not applied due to the size of the crystal. A total of 20336 measured reflections was merged to give 9313 unique reflections of which 7320 had $I > 2\sigma(I)$, and these were used for the structure determination. The structure was solved by the heavy atom method and difference Fourier techniques and refined by full-matrix least-squares techniques [7] in which the function $\Sigma w(F_o^2 - F_c^2)^2$ was minimized. Scattering factors used were those given by Sheldrick [7]. The weight for each reflection in the final cycles of refinement is given by $w = 1/[\sigma^2(F_o)^2 + (0.0253P)^2]$ where $P = (\max(F_o^2,0) + F_c^2)/3$, as defined by SHELXL-97 [7]. This weighting scheme gives a uniform analysis of variance in terms of $F_c^2$. The initial isotropic refinement converged to a conventional $R$ factor ($R_1$) of 0.070 but showed some evidence for slight disorder within the

perchlorate anions. Anisotropic refinement of the structure, excluding hydrogen atoms and with SHELXL restraints applied to the oxygen atoms of the perchlorate anions to maintain tetrahedral geometry, then proceeded smoothly to an $R_1$ of 0.056. All complex cation hydrogen atoms were then positioned using the appropriate geometry and relevant C–H and N–H bond lengths, where the accuracy of these hydrogen positions was confirmed by a subsequent difference synthesis. Refinement was continued with hydrogen atoms riding on the atoms to which they were bonded, with fixed isotropic thermal parameters, and with anisotropic temperature factors for all other atoms except for the oxygen atoms of the two partially occupied lattice water molecules which were held isotropic. The refinement process was considered complete when the minimization factor changed by <0.1% and a final difference map showed no residual electron density greater than $|0.5|\,e\,Å^{-3}$. The final $R_1$ value was 0.053 for 7320 reflections with $I > 2\sigma(I)$. The final weighted $R_w$ $[=\{\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2\}^{1/2}]$ was 0.1380 for all 9313 data. Full details concerning crystal data and structure refinement parameters are given in table 1.



## 3. Results and discussion

The structure and absolute configuration of Λ-$\beta_2$-[Co(*R*,*R*-picchxn)(*S*-pip)] $(ClO_4)_2 \cdot 0.5H_2O$ (**2**) was unequivocally established by single-crystal X-ray crystallography. The natures of the other diastereoisomeric salts were unambiguously deduced from nmr and CD measurements.

Table 1. Crystal data and structure refinement for **2**.

| | |
|---|---|
| Empirical formula | $2 \times C_{24}H_{35}Cl_2CoN_5O_{10.50}$ |
| Formula weight | 691.40 |
| Temperature (K) | 293(2) |
| Wavelength (Å) | 0.71073 |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions | |
| *a* (Å) | 10.534(5) |
| *b* (Å) | 16.830(3) |
| *c* (Å) | 34.074(4) |
| *V* (Å$^3$) | 6041(3) |
| *Z* | 8 |
| Density (calculated) (Mg m$^{-3}$) | 1.520 |
| Absorption coefficient (mm$^{-1}$) | 0.808 |
| *F*(000) | 2872 |
| Crystal size (mm$^3$) | $0.40 \times 0.0.20 \times 0.10$ |
| $\theta$ range for data collection (°) | 3.40–25.05 |
| Index ranges | $-11 \le h \le 8$, $-18 \le k \le 18$, $-37 \le l \le 38$ |
| Reflections collected | 20336 |
| Independent reflections | 9313 [$R$(int) = 0.0528] |
| Completeness to $\theta = 25.05°$ | 89.1% |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 9313/41/766 |
| Goodness-of-fit on $F^2$ | 0.846 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1 = 0.0528$, $wR_2 = 0.1317$ |
| $R$ indices (all data) | $R_1 = 0.0592$, $wR_2 = 0.1380$ |
| Absolute structure parameter | −0.026(18) |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.455 and −0.289 |

The crystal structure analysis of Λ-$\beta_2$-[Co(*R*,*R*-picchxn)(*S*-pip)]$(ClO_4)_2 \cdot 0.5H_2O$ revealed that there are two crystallographically independent but structurally identical complex cations located within the asymmetric unit. A perspective drawing of one of these molecular cations showing the atom labelling scheme is shown in figure 1. Table 2 gives selected bond lengths and angles for the coordination spheres of the two crystallographically independent complex cations. Examination of bond lengths and angles (see Supplementary data) does not reveal any anomaly. In the crystal lattice, the perchlorate groups are generally constrained and a weak hydrogen bonding network links two of the perchlorate ions and one of the water molecules (OW1) to the complex cations; the complex cations are also linked by further weak hydrogen bonds and a summary of the hydrogen bond contacts are given in table 3. It may be noted that in the final refinement stages it was evident that many of the perchlorate oxygen atoms had significant anisotropic thermal vibration, which might indicate slight disorder of the anions within the structure.

Although single crystal structure analyses of Λ-$\beta_1$-[Co(*R*,*R*-picchxn)(*R*-pip)]$(ClO_4)_2 \cdot 3H_2O$ (**1**) and Λ-$\beta_1$-[Co(*R*,*R*-picchxn)(*S*-pip)]$(ClO_4)_2$ (**3**) are not available, a combination of CD and NMR data served to establish their identities. In particular, the dominant sign of the visible CD transitions is positive, and thus both have absolute configuration Λ with respect to the metal centre. $^1$H NMR for the aromatic rings proves the $\beta$ disposition of the tetradentate and the chemical shifts of the H(111) proton serve to distinguish between $\beta_1$ and $\beta_2$ isomers, in line with previous studies of closely related species [3–5]. The small negative CD peak at lower energy in the CD of **2** is consistent with previous observations of Λ-$\beta_2$ isomers and the bimodal visible CD spectrum of **3** has been found for other Λ-$\beta_1$-[Co(*R*,*R*-picchxn)]$^{n+}$ complexes with *R*-aminoacidates. Particular attention is drawn to the fact that in **2**, the sole Λ-$\beta_2$ diastereoisomer isolated, H(111) is observed in the $^1$H NMR spectrum at significantly



Table 2. Selected bond lengths (Å) and angles (°) for (**2**).

| | | | |
|---|---|---|---|
| Co(1)–N(11) | 1.942(9) | Co(2)–N(21) | 1.907(12) |
| Co(1)–N(12) | 1.943(10) | Co(2)–N(22) | 1.913(11) |
| Co(1)–N(13) | 2.006(9) | Co(2)–N(23) | 1.979(11) |
| Co(1)–O(1A) | 1.893(9) | Co(2)–O(2A) | 1.870(8) |
| Co(1)–N(111) | 1.968(9) | Co(2)–N(211) | 1.943(10) |
| Co(1)–N(121) | 1.896(11) | Co(2)–N(221) | 1.945(9) |
| N(121)–Co(1)–O(1A) | 174.7(4) | N(221)–Co(2)–O(2A) | 173.9(4) |
| N(11)–Co(1)–N(13) | 169.8(4) | N(21)–Co(2)–N(23) | 168.4(4) |
| N(12)–Co(1)–N(111) | 167.9(4) | N(22)–Co(2)–N(211) | 166.5(5) |

Table 3. Hydrogen bonds for (**2**) (Å and °).

| D–H...A | d(D–H) | d(H...A) | d(D...A) | ∠(DHA) |
|---|---|---|---|---|
| N(13)–H(13)...O(14) | 0.91 | 2.10 | 2.995(14) | 169.7 |
| N(12)–H(12)...O(13) | 0.91 | 2.40 | 3.288(18) | 164.6 |
| N(12)–H(12)...O(14) | 0.91 | 2.44 | 3.180(16) | 138.7 |
| N(12)–H(12)...Cl(1) | 0.91 | 2.81 | 3.699(11) | 166.0 |
| N(11)–H(11)...OW1 | 0.91 | 2.14 | 2.99(2) | 154.7 |
| N(23)–H(23)...O(1B)$^{\#1}$ | 0.91 | 2.06 | 2.962(12) | 170.2 |
| N(21)–H(21)...O(41) | 0.91 | 2.17 | 3.05(2) | 162.2 |
| N(22)–H(22A)...O(1B)$^{\#1}$ | 0.91 | 2.14 | 2.904(12) | 140.8 |

Symmetry transformations used to generate equivalent atoms: $^{\#1}$ x−1, y, z.

lower field ($\delta$ 8.86 ppm) as compared to the two $\Lambda$-$\beta_1$ diastereoisomers **1** and **3** ($\delta$ 8.44 and 8.35 ppm, respectively), as a result of differential shielding effects involving orientations towards coordinated amine ($\beta_2$) and carboxylic acid ($\beta_1$) groups. Finally, it is noted that *R*-pipH was isolated from **3**.

Optically pure enantiomers of pipecolic acid were isolated using the method described in high yield. There is no ambiguity with respect to the hand of the aminoacid. This is reinforced by the single-crystal structure of the internal diastereoisomer $\Lambda$-$\beta_2$-[Co(*R*,*R*-picchxn)(*S*-pip)]$(ClO_4)_2 \cdot H_2O$, which determines the configuration of the aminoacid by virtue of the fact that the absolute configuration of the $\Lambda$*-$\beta$-[Co(*R**,*R**-picchxn)] fragment is well-established [2], in conjunction with related NMR and CD studies. The choice of hand of pipecolic acid desired is dictated merely by that of $\Lambda$*-$\beta$-[Co(*R**,*R**-picchxn)$Cl_2]^+$ and selection of the diastereoisomeric salt required, although smaller amounts of *R*-pipH as compared to *S*-pipH can be isolated by the use of the single starting chiral auxiliary $\Lambda$-$\beta$-[Co(*R*,*R*-picchxn)$Cl_2]^+$. The method described may well have general application for the resolution of aminoacids that are difficult to separate into their enantiomers, especially in the light of the fact that the system has been explored with a wide variety of such substrates [2].



## Supplementary material

CCDC 629262 contains crystallographic data for this article. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44(0)1223-336033; Email: deposit@ccdc.cam.ac.uk].

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