Chiral Metal Complexes. 28*. A Stereoselective Synthesis of Proline

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Abstract

The complex Λ-β_2-[Co(*R*,*R*-picchxn)(dehydropro)]$^{2+}$, where *R*,*R*-picchxn is *N*,*N'*-di(2-picolyl)-1*R*,2*R*-diaminocyclohexane and dehydropro is the anion of 1,2-dehydroproline may be synthesised quantitatively from Λ-β-[Co(*R*,*R*-picchxn)Cl_2]$^+$ and 5-amino-2-oxopentanoic acid in aqueous solution at room temperature. This ternary complex may in turn be reduced to Λ-β_2-[Co(*R*,*R*-picchxn)(*R*,*S*-pro)]$^{2+}$ (where pro is the anion of proline) in high yield by the use of aqueous sodium borohydride (also at room temperature) and the diastereoisomeric products separated quantitatively using chromatographic techniques. At 298.2 K the ratio of *R*-proline:*S*-proline produced is equal to 84:16 ± 2. Using this method, it is possible to stereoselectively synthesise 4- and 5-substituted diastereoisomers based on proline, in general.

Introduction

Over the last few years we have been exploring the causes and effects of chiral discriminations in certain octahedral complexes of d^6-metal ions [2, 3]. Recently we have reported a series of reactions to produce α-aminoacidates in high optical yield [4]. Chirality transfer may be brought about in many ways in the kinds of complexes employed. Accordingly, we have embarked on a series of studies involving the reactions of prochiral and achiral substrates coordinated to Co(III) in ternary complexes which also contain a chiral tetradentate based upon 2,5-diaza-1,6-di(2-pyridyl)-hexane. The aim of this work is to develop novel and efficient routes to one- and two-centre chiral molecules with a high degree of functionality.

Sargeson *et al.* [5–7] have reported extensively on intramolecular imine formation in complexes of Co(III), and more particularly, have developed a biomimetic synthesis of proline and 2-cyclopropylglycine via the reaction of 5-bromo-2-oxopentanoic acid with the aquapentaamminecobalt(III) ion [8]. This work prompted us to examine a related system employing 5-amino-2-oxopentanoic acid hydrochloride, which may be conveniently prepared at large scale, as starting material.

We wish to report here a highly efficient and stereoselective synthesis of *R*- or *S*-proline from 5-amino-2-oxopentanoic acid using the optically active complex Λ-β-dichloro{*N*,*N'*-di(2-picolyl)-1*R*,2*R*-diaminocyclohexane}cobalt(III), Λ-β-[Co(*R*,*R*-picchxn)Cl_2]$^+$, or its enantiomer.

Experimental

R,*R*-picchxn was synthesised according to a published procedure [9], as was 5-amino-2-oxopentanoic acid hydrochloride [10].

The precursor complex Λ-β-[Co(*R*,*R*-picchxn)Cl_2]$ClO_4 \cdot 0.5H_2O$ was synthesised according to the following procedure which gives a considerably higher yield. $Na_3[Co(CO_3)_3] \cdot 3H_2O$ [11] (75 g, 0.207 mol) was added in portions to *R*,*R*-picchxn·4HCl (102 g, 0.231 mol) which had been dissolved in H_2O (350 cm^3) heated to 90 °C. Conc. HCl (39.4 cm^3) was then added dropwise, followed by conc. $HClO_4$ (29 cm^3). The reaction mixture was evaporated slowly on a steam bath. During this process an oily scum formed, and it was dispersed continuously by the addition of a few drops of water from time to time. When the total volume had reduced to 200 cm^3 and purple crystals of the product had formed, the mixture was cooled to room temperature, allowed to stand overnight, and the purple crystalline product was collected at the pump. This was washed with H_2O (3 × 20 cm^3) and diethyl ether (3 × 20 cm^3), sucked dry and finally dried in a desiccator over silica gel to give 87.3 g (77% yield based on Co) of the desired product Λ-β-[Co(*R*,*R*-picchxn)Cl_2]$ClO_4 \cdot 0.5H_2O$.

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Δ-β₂-[Co(R, R-picchxn)(dehydropro)](ClO₄)₂·2H₂O

To an aqueous solution of 5-amino-2-oxo-pentanoic acid hydrochloride (4.19 g, 25 mmol, in 250 cm^3) was added 25 cm^3 of 1.0 M aqueous NaOH. The solution was stirred for 30 min at room temperature and then Λ-β-[Co(*R*,*R*-picchxn)Cl_2]ClO_4·0.5H_2O (2.675 g, 5 mmol) was added. Stirring was continued at room temperature for 48 h. Lithium perchlorate trihydrate (10 g) was added to the orange solution and the volume reduced to 50 cm^3 on a rotary evaporator at 30 °C. During this time a heavy powdery orange precipitate formed. The mixture was cooled overnight at 0 °C and the product was collected at the pump, washed with several portions of ice-cold H_2O, and then diethyl ether, and dissolved in the minimum volume of 50:50 (*v*:*v*) acetone/water. Selective evaporation of the acetone overnight gave a microcrystalline orange product which was isolated as above and dried over silica gel *in vacuo*. Yield: 2.73 (82% based on Co). This product proved to be perfectly satisfactory for use in further reactions. Feathery crystals of the diperchlorate salt are obtained by dissolving the product in water and evaporating the solution slowly over silica gel at slightly reduced pressure. *Anal.* Calc. for $C_{23}H_{34}N_5O_{12}Cl_2Co$: C, 39.3; H, 4.9; N, 10.0. Found: C, 39.5; H, 4.6; N, 10.0%.

In a separate experiment, on the same scale, the crude reaction mixture was diluted five-fold with H_2O and applied to a CM Sephadex® C-25 cation exchange column (40 × 2 cm) in the H^+ cycle. The column was eluted with 0.25 M aqueous NaCl solution and only one orange band developed. This was collected in fractions whose CD and electronic spectra showed that only one isomer was present in the band. No trace of any other isomer could be detected elsewhere on the column and thus the synthesis of this complex is stereospecific and essentially quantitative. Fractions containing the diastereoisomer were combined, excess $LiClO_4$ was added, and the volume reduced first using a rotary evaporator at 30 °C and then by slow evaporation over silica gel at room temperature. Fine orange crystals of the chloride perchlorate salt Λ-β₂-[Co(*R*,*R*-picchxn)(dehydropro)]$(ClO_4)Cl·H_2O$ were obtained. The crystal and molecular structure of this complex has been determined [12]. Identical CD, electronic, ^{13}C and ^1H NMR spectra are found for the two salts.

Reduction of Λ-β₂-[Co(R, R-picchxn)(dehydropro)]²⁺

Successful reduction of the dehydroproline complex and subsequent isolation of the resulting *R*- and *S*-proline diastereoisomers depends upon the careful preparation of the CM Sephadex® C-25 cation exchange resin used for absorption of the reaction products. The resin used was new, and was thoroughly washed with 2 M aqueous NaCl followed by water, and this washing procedure was repeated. Scrupulous elimination of any resin in the H^+ cycle is imperative in order to guard against decomposition of the product mixture.

The buffer solution employed was a 0.1 M aqueous solution of tris(hydroxymethyl)methylamine adjusted to pH 9.2 with 0.1 M aqueous HCl. The following describes a typical reduction procedure.

Λ-β₂-[Co(*R*,*R*-picchxn)(dehydropro)]$(ClO_4)_2$·$2H_2O$ (0.67 g, 0.95 mmol) was dissolved at 25 °C in 80 cm^3 H_2O with stirring and to the solution was added $NaBH_4$ (0.19 g, 5 mmol) dissolved in 50 cm^3 of pH 9.2 buffer. The colour of the solution changed rapidly from orange to the rose red of the proline complexes. After five min the reaction mixture was poured into 200 cm^3 of water and stirred with an excess of CM Sephadex® C-25 resin in the Na^+ cycle. After 30 seconds, the Sephadex® was filtered rapidly at the pump onto a fibreglass filter paper and washed with 1 dm^3 of water in portions to remove all traces of reductant. The rose red resin was then loaded on the top of a CM Sephadex® C-25 resin column (90 × 2 cm) in the Na^+ cycle. Two rose red bands developed, the faster moving one being considerably less intense in colour. The two bands separated completely, using 0.1 M aqueous $NaClO_4$ as eluant, and each was shown to contain a single diastereoisomer by CD and electronic spectral measurements of fractions collected from each band using an LKB Ultrovac® II fraction collector. Fractions from each band were thus combined and volumes greatly reduced using a rotary evaporator at 30 °C.

When the volume of the faster moving band's solution was reduced to *ca.* 25 cm^3, the remaining solution was left to evaporate slowly over silica gel in a desiccator at slightly reduced pressure. During several weeks, deep rose red prismatic crystals grew from solution, and these were collected at the pump, washed with small portions of ice-cold water and dried *in vacuo* over silica gel. Yield: 31 mg (5%). The complex proved to be Λ-β₂-[Co(*R*,*R*-picchxn)(*S*-pro)]$(ClO_4)_2$, a species which has been previously identified [9]. *Anal.* Calc. for $C_{23}H_{32}N_5O_{10}Cl_2Co$: C, 41.3; H, 4.8; N, 10.5. Found: C, 41.4; H, 5.0; N, 10.2%.

The solution containing the second rose red diastereoisomer to be eluted from the column was concentrated to *ca.* 75 cm^3 and then evaporated *in vacuo* over silica gel at room temperature. Fine deep rose red crystals formed over several weeks and these, which proved to consist of Λ-β₂-[Co(*R*,*R*-picchxn)(*R*-pro)]$(ClO_4)_2$, were isolated in the same way as the *S*-pro complex. Yield: 326 mg (51%). *Anal.* Found: C, 41.3; H, 4.7; N, 10.5%. The *S*-pro diastereoisomer perchlorate is considerably more soluble in H_2O than is the *R*-pro diastereoisomer perchlorate.

The actual ratio of the two proline diastereoisomers produced during the reduction of the 1,2-dehydroproline complex, rather than the ratio based

TABLE I. Electronic and CD Spectral Data for the Complexes[a]

Complex	λ (nm)	ε	Δε
Λ-β_2-[Co(*R*,*R*-picchxn)(dehydropro)]$^{2+}$	468	2160	
	346	3200	
	541		−2.3
	482		+28.7
	361		−9.3
Λ-β_2-[Co(*R*,*R*-picchxn)(*R*-pro)]$^{2+}$	498	2080	
	359	2172	
	555		−0.6
	497		+14.1
	360		−2.0
Λ-β_2-[Co(*R*,*R*-picchxn)(*S*-pro)]$^{2+}$	492	1910	
	358	2120	
	553[b]		−16.8
	499[b]		+39.7
	373[b]		−18.5

[a]Recorded in H_2O at 298.2 K; concentrations approximately 1 mg cm^{-3}. ε and Δε given in units of dm^2 mol^{-1}. [b]Data re-determined. Values in ref. 9 are incorrect because of spectrophotometer calibration. We correct that error here.

on isolated solid products (this being influenced by solubility phenomena and mechanical losses) was estimated by taking the eluant containing the entire yield of each diastereoisomer, making it up to known volume and measuring the solution absorbance at 495 nm. Concentrations could then be simply computed by the use of the known extinction coefficients of the *R*,*S*-proline diastereoisomers obtained from samples of the pure complexes. A series of reduction experiments at 25 °C gave the ratio of *S*-pro:*R*-pro complexes formed as 16:84 ± 2. Total yields of products (based on 100% conversion of the 1,2-dehydroproline complex) varied from 85–95% in a series of six reductions.

Analyses were carried out by Mrs A. Dams of the Department of Chemistry, University College Cardiff, and the analytical service run by the City University, University of London. Electronic and CD spectra were recorded using a Perkin-Elmer Lambda 5 spectrophotometer and a Jobin-Yvon CNRS Dichrographe III, respectively. All ^1H and ^{13}C NMR spectra were recorded on a Bruker WM 360 instrument at 360 MHz (^1H) and 80.5 MHz (^{13}C) in DMSO-d_6 or D_2O with TMS or TSS as internal standards. Assignments of ^{13}C spectra were somewhat facilitated by the use of DEPT acquisition routines. All spectra were measured at 25 °C.

Results and Discussion

Electronic together with CD, ^1H and ^{13}C NMR spectral data for the complexes are listed in Tables I, II and III, respectively. Absolute configurations are assigned on the basis of CD spectral measurements as confirmed by X-ray crystallographic studies of related complexes [2, 4, 9, and refs. therein]. Indeed, the nature of each diastereoisomer reported here has been established crystallographically [12] and the above data is listed for comparative purposes and in conjunction with related studies of more highly substituted prolines (*vide infra*). Atomic numbering schemes for the ^1H and ^{13}C NMR spectra are shown in Figs. 1 and 2, respectively. A few points concerning the NMR spectra are worth elaborating. ^1H NMR spectra of the β_2-*S*-pro complex are identical to those reported previously [9], in the same solvent. Isomerisation at the proline nitrogen is not observed upon exchange in D_2O, and so the diastereoisomeric difference in the two proline products must arise in

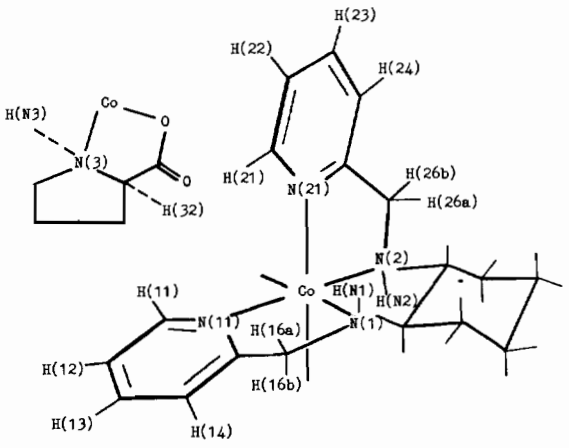

Fig. 1. Numbering scheme for ^1H NMR data.

TABLE II. Characteristic ^{1}H NMR Data for the Complexes[a]

δ or J	Complex[b]		
	A	B	C[c]
H(14)	7.85(d)	7.82(d)	7.87(d)
H(13)	8.30(t)	8.30(t)	8.34(t)
H(12)	7.74(6)	7.79(t)	7.88(t)
H(11)	8.20(d)	8.76(d)	8.88(d)
H(24)	7.70(d)	7.75(d)	7.62(d)
H(23)	8.22(t)	8.20(t)	8.15(t)
H(22)	7.59(t)	7.61(t)	7.56(t)
H(21)	7.23(d)	7.40(d)	7.21(d)
$J_{13,14}$	7.6	8.1	7.9
$J_{12,13}$	7.6	9.4	8.6
$J_{11,12}$	5.6	5.7	5.5
$J_{23,24}$	7.8	7.7	7.7
$J_{22,23}$	7.4	7.3	7.3
$J_{21,22}$	5.7	5.7	5.8
H(N1)	8.20(b, m)	8.11(m)	7.99(m)
H(N2)	7.51(b, d)	7.14(b, s)	6.94(b, s)
H(16a)	[d]	4.35	4.43
H(16b)	[d]	4.62	4.53
H(26a)	[d]	4.23	4.22
H(26b)	[d]	4.93	4.84
$J_{16a,N1}$	[e]	4.8	5.1
$J_{16b,N1}$	[e]	9.4	8.8
$J_{26a,N2}$	[e]	~0	~0
$J_{26b,N2}$	[e]	4.4	4.8
$J_{16a,16b}$	[e]	16.2	16.4
$J_{26a,26b}$	[e]	18.0	18.6
H(3)		6.05(m)	7.20(m)
H(32)		4.10(m)	3.71(m)

[a]Recorded in DMSO-d_6 at 25 °C. Chemical shifts relative to TMS as internal standard ±0.01 ppm, coupling constants ±0.1 Hz; d = doublet, t = triplet, m = multiplet, b = broad. [b]A: Λ-β_2-[Co(*R*,*R*-picchxn)(dehydropro)]$^{2+}$; B: Λ-β_2-[Co(*R*,*R*-picchxn)(*R*-pro)]$^{2+}$; C: Λ-β_2-[Co(*R*,*R*-picchxn)(*S*-pro)]$^{2+}$. [c]Data in D_2O are given in ref. 9. [d]Two multiplets are observed at δ 4.37 (2H) and δ 4.55 (2H) and are 'deceptively simple'. [e]Not determined.

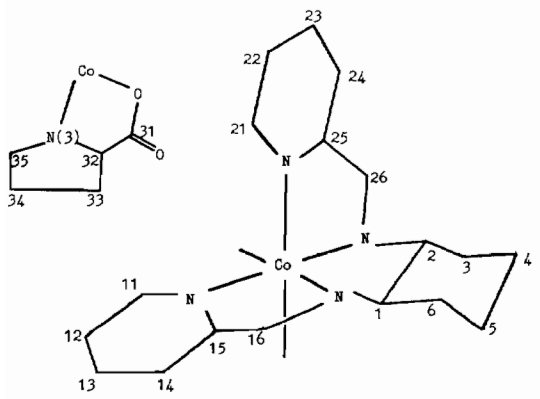

Fig. 2. Numbering scheme for ^{13}C NMR data.

TABLE III. ^{13}C NMR Data for the Complexes[a]

δ	Complex[b]		
	A	B	C
C(31)	187.42	179.71	179.55
C(32)	166.33	63.85	62.85
C(15), C(25) [c]	164.46 162.58	165.05 162.59	164.97 163.12
C(11), C(21) [c]	151.90 151.37	152.16[d] 152.16[d]	151.93 150.68
C(13), C(23) [c]	141.11 140.61	141.24 140.47	141.02 139.83
C(14), C(24), C(12), C(22) [c]	126.78 125.74 124.29 122.68	125.45[d] 125.45[d] 123.79 123.01	126.14 124.96 123.36 122.94
C(2), C(1) [c]	69.66 64.21	70.27 65.05	71.52 63.71
C(35)	56.06	51.97	51.81
C(16), C(26) [c]	56.28 51.85	55.05 49.42	56.02 49.99
C(33), C(34), C(3), C(4), C(5), C(6) [c]	34.30 29.22 28.30 23.15 22.74 20.88	28.83 28.24 27.43 24.19 23.13 22.78	28.76 28.10 27.24 24.62 23.17 22.72

[a]In DMSO-d_6 at 25 °C. Chemical shifts relative to TMS as internal standard ±0.01 ppm. [b]As noted in Table II. [c]Resonances assigned in groups rather than individually. [d]These pairs resonate at the same frequency, within experimental error.

another way, since the ^{13}C NMR spectra in conjunction with other data shows unequivocally that both complexes do contain proline coordinated as a bidentate. The established criterion concerning the chemical shift of the *H*(11) proton [4, 9] which distinguishes β_2 from β_1 coordination in these kinds of complexes may be applied to both of the Λ-β_2-[Co(*R*,*R*-picchxn)(*R*,*S*-pro]$^{2+}$ isomers reported here. By virtue of elimination, therefore, the major isomer produced upon reduction of Λ-β_2-[Co(*R*,*R*-picchxn)-(dehydropro)]$^{2+}$ is the β_2-*R*-pro species.

This same criterion cannot be unequivocally applied to the ternary complex containing 1,2-dehydroproline because *H*(11) would be expected to be somewhat shielded by the imine function in the β_2 isomer and by the carboxyl group in the β_1 isomer. Analysis of the complex and its ^{13}C NMR spectrum, particularly with respect to the *C*(31) and *C*(32) chemical shifts, does establish the presence of 1,2-dehydroproline. Its electronic spectrum is characteristic of a β_2 species [4, 9], and it is most unlikely that a β_1-dehydropro complex would isomerise to β_2-*R*,*S*-pro diastereoisomers upon reduction under the conditions employed. We may therefore safely conclude that this complex has the Λ-β_2 geometry, and

this is in fact confirmed by our parallel crystallographic studies [12].

The reduction of the coordinated imine to produce the prolinato complexes is highly stereoselective. *R*-proline is produced in large excess using complexes containing *R*,*R*-picchxn. This result should be contrasted with the fact that while *S*-proline may be reacted with Λ-β-[Co(*R*,*R*-picchxn)-Cl_2]$^+$ to yield both β_1 and β_2 diastereoisomers, negligible ternary complex formation is found in analogous reactions involving *R*-proline under the usual conditions [9]. We have reconfirmed this finding and conclude that the patterns of isomer distribution found here and elsewhere must ultimately be due to kinetic effects, but the details of this phenomenon remain unclear. It is also worth pointing out the fact that reaction of Λ-β-[Co(*R*,*R*-picchxn)-Cl_2]$^+$ with 1,2-dehydroproline produces the Λ-β_2 diastereoisomer stereospecifically. Such a pattern of isomer distribution is markedly different to that found for *R*- and *S*-aminoacidates and α-substituted aminomalonic acids [4, 9] when β_1 diastereoisomers are found to form either stereospecifically or with great stereoselectivity. Just which discriminating interactions in the Λ-β_2-[Co(*R*,*R*-picchxn)(dehydropro)]$^{2+}$ complex give rise to the large excess of *R*-pro in the reduced products are hard to identify. Inspection of the structure of the imine complex and space-filling molecular models of it suggest however that hydride (or borohydride) approach to the imine carbon on the face that would yield *R*-pro is somewhat more favourable on steric grounds. This concerns the relative proximity to the imine carbon of the *H*(11) and *H*(N1) protons. Such differences are slight and it may well prove that transition state and solvation phenomena are the cause of the marked chiral induction in the proline product diastereoisomers.

The results of this study indicate that a judicious choice of the overall chiral framework in complexes of this kind effects a highly stereoseleective reduction of coordinated imine functions. In particular, proline may be produced with high enantiomeric excesses and applications for the incorporation of specific labels are obvious. Furthermore, the overall strategy employed here using 5-amino-2-oxopentanoic acid as a precursor may be elaborated to yield, stereospecifically, 4- and 5-substituted diastereoisomers of either *S*- or *R*-proline, the choice of hand being dictated merely by the choice of either *R*,*R*- or *S*,*S*-picchxn in the starting complex. We will report results of illustrative examples involving such systems in the near future.

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