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A NEW APPROACH TO THE SYNTHESIS OF 'CHIRAL' GLYCINE

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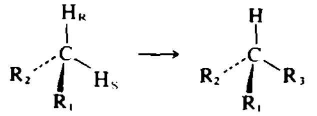
Abstract—The stereospecific coordination of N-benzylglycinate ion in ΛR-(N-benzylglycinato)*bis*(ethylenediamine) cobalt(III) chloride has been determined by X-ray crystallographic analysis, rotatory dispersion and ^1H NMR spectroscopy. The chiral glycinato-N and Co centres influence the relative rates of exchange of the diastereotopic glycine methylene protons in basic solution (pH 10·5 with Na_3PO_4 in D_2O) and a synthesis supposedly of S-(N-benzyl)-2-^2H glycinate ion (~80% optical purity) has been achieved.

Many enzymatic reactions are known which involve one of the enantiotopic H atoms of a methylene group in a prochiral substrate.[1a] One type of reaction in this group is the following exchange process:

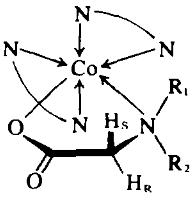


N.B. the priority of R_1 is arbitrarily taken to be higher than that of R_2.

Enzymes are chiral reagents and such reactions are usually accomplished with high stereoselectivity[1b,1c] (i.e. the reacting hydrogen above will be *either* H_R *or* H_S and the product will be either the R or S enantiomer: for a rare exception see below). The stereochemistry of a particular case can be defined using a substrate stereospecifically labelled with an isotope of hydrogen. For example, the synthesis of δ-aminolaevulinic acid (δ-ALA) from glycine and succinyl coenzyme A is catalysed by the enzyme δ-ALA synthetase and the coenzyme pyridoxal phosphate. It is believed[2a] that the imine (**1**) formed from glycine and pyridoxal phosphate loses an H atom to produce carbanion (**2**), which attacks succinyl coenzyme A to give δ-ALA after elimination of coenzyme A, decarboxylation and release of pyridoxal phosphate (*see* Scheme 1). The relevant part of this sequence in the present context is the removal of a proton from inime (**1**). Using (R)- and (S)-2-^3H-glycine it has been shown[2a,b] that the pro-R H-atom of imine (**1**) is removed preferentially. The 2-^3H-glycines used were prepared[2b] by a stereoselective exchange at the methylene hydrogens of glycine, catalysed by serine hydroxymethyltransferase. Four other enzymatic reactions studied in which glycine is generated or utilised also occur stereoselectively with respect to the methylene hydrogens.†,‡,§ However, aminomalonate decarboxylase from rat liver produces equal amounts of (R) and (S)-2-^3H-glycine from aminomalonate in tritiated water.[3d]

The commonly observed high stereoselectivity in enzymatic reactions involving enantiotopic groups has proved difficult to match with chiral reagents derived from relatively small molecules.[1c] We now describe a method for achieving a chemical synthesis of 2-^3H-glycine (containing an excess of the S isomer) which entails preferential exchange at one of the diastereotopic methylene hydrogens of glycine in a chiral complex of cobalt. This method resembles one[2b] of the enzymatic methods for preparing enantiomers of 2-^3H-glycine. A preliminary communication has appeared.[4]

Our synthesis depends for its selectivity on the stereospecific chelation of N-benzylglycine to a *bis*-(ethylenediamine)cobalt(III) template. Two sets of diastereoisomers are possible arising from chiral centers at cobalt (Λ or Δ) and nitrogen (R or S). One set is shown below:



ΛR isomer: R_1 = H, R_2 = CH_2Ph
ΛS isomer: R_1 = CH_2Ph, R_2 = H
$\left(\begin{smallmatrix}N\\N\end{smallmatrix}\right.$ = ethylenediamine

The other set contains the catoptric (mirror image) arrangement of all chelates about the metal ion. A consideration of non-bonding interactions, especially those between benzylic protons and protons of the adjacent ethylenediamine chelate, leads to the expectation that ΛR will be more stable than ΛS. This is primarily because the bulky benzyl group abuts on the chelate in the ΛS form, whereas a large part of this interaction can be avoided in the ΛR ion.

In the ΛR (or ΛS) form the methylene hydrogens of the glycinate group are diastereotopic and should have different reactivities with either a chiral or achiral reagent.[1b] The prospect of a selective base-catalysed deuteration at this site arises because the hydrogen (pro-S in ΛR)*trans* to the benzyl group might exchange preferentially leading to an excess of (S)-2-^2H-N-benzylglycinate over the R isomer. This paper examines the specificity of co-

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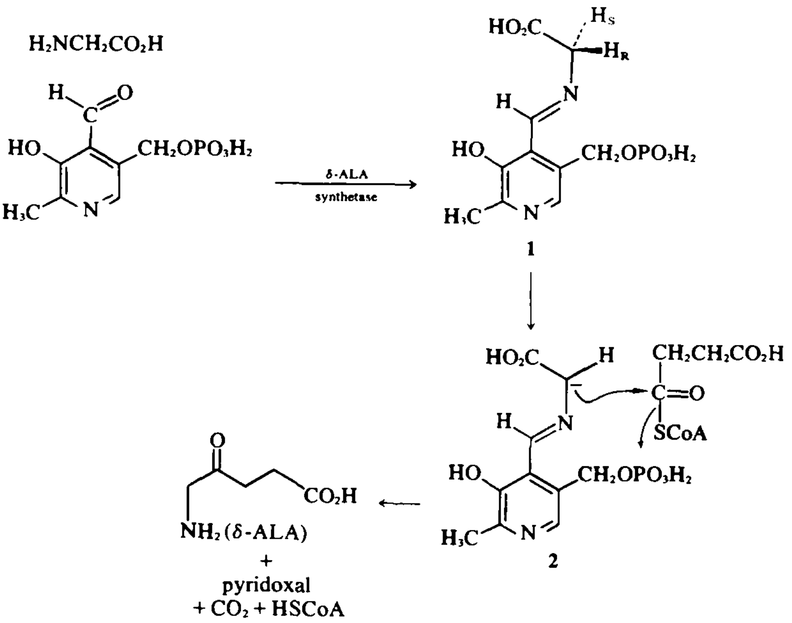
†It has been shown[3a] that an L-specific transaminase converts glyoxylate and L-aspartate in tritiated water to (R)-2-^3H-glycine (see also ref. 3*c*); and also that serine hydroxymethyltransferase in tritiated water produces (S)-2-^3H-glycine from L-serine.[3b]

‡L-aspartate decarboxylase catalyses stereospecific decarboxylation of aminomalonate in tritiated water to (S)-2-^3H-glycine.[3c]

§For the assignment of absolute configuration to enzymically prepared 2-^3H-glycines it has been assumed[2,3] that D-aminoacid oxidase selectively removes the pro-S hydrogen from glycine (i.e. the methylene hydrogen corresponding to the α-H of D-aminoacids).



Scheme 1.

ordination of N-benzylglycine to *bis*(ethylenediamine) cobalt(III) ion, the absolute configuration of the derived complex and the selectivity of deuteration of the glycine methylene hydrogens in this complex.

RESULTS

Specificity of chelation of N-*benzylglycine.* The ^1H NMR spectrum of the [Co(en)$_2$(N-benzylglycinato)] $(CH_3SO_3)_2$† obtained as described in the experimental section is shown in Fig. 1a. It is characterised by the signal for the phenyl protons at δ 7·6 ppm, by the N-proton signals between δ 4·2 and 6·2, by the benzyl and glycine CH_2 multiplets from δ 3·2–4·4 and the ethylenediamine-CH_2 signals at δ 3·0 ppm (relative to DSS). The methyl signal of $CH_3SO_3^-$ occurs at δ 2·9. In D_2O the glycinato NH_2 protons exchange and the signal at δ 6·2 vanishes (Fig. 1b). Concomitantly, the complex ABX systems between δ 3·2 and 4·4 collapse to simple AB doublet pairs [$PhC\underline{H}_2$ *ca.* δ 4·0; $HNC\underline{H}_2CO_2$ *ca.* δ 3·5: these assignments are consistent with the relative positions of the corresponding signals in the free ligand (i.e. $PhC\underline{H}_2$ at lower field)]. In the presence of a trace of DCO_3^- the ethylenediamine NH protons also exchange rapidly (Fig. 1c). In more strongly basic media the AB doublet pair centred about δ 3·5 also collapses and this is attributed to the exchange of the glycinato methylene protons with D_2O. As expected, the AB system centred around δ 4·0 (assigned to the benzyl methylene protons) remains unaffected.

The AB doublet pairs arise from the diastereotopicity of both sets of methylene protons especially due to the influence of the nearby chiral N centre. NMR spectra of analogous complexes (chelated alanine, valine and N-methylalanine) have shown the sensitivity of the chemical shift of the α-H of these amino-acids for detecting diastereoisomers[8] arising from epimerisation at the N and C chiral centres. It is therefore expected that their presence would be most likely detected in this area of the ^1H NMR spectrum rather than in other regions of the spectrum.

In the spectrum shown in Fig. 1c there are small signals at δ 4·0, 3·66 and 3·58 which might be construed as arising from epimerisation at the N centre during deuteration of the N-proton site. This possibility was tested by treating the optically pure isomer with DCO_3^- in D_2O and then fractionally crystallising the product by adding HBr. The fractions obtained by this route had the same spectra as that shown in Fig. 1c. Moreover, after deuteration of the glycinate methylene protons these small signals remained. Clearly they cannot be due to glycinate methylene protons in a diastereoisomeric form and it is most unlikely that they are from impurities, considering the numerous recrystallisations effected on the racemic and then resolved complex. We conclude that the signals are due to an integral part of the complex, namely the ethylenediamine methylene protons.

It is concluded from the above data that coordination of N-benzylglycine to the *bis*(ethylenediamine) cobalt(III) moiety takes place stereospecifically. Additional support for this deduction comes from ion exchange chromatography on Sephadex SP25 using conditions which separate isomers analogous to those considered here.[9] The preparative sample ran as a single band and fractions treated under conditions desirable for epimerisation at the chiral N centre also eluted as a single fraction. Moreover the samples obtained by the fractionation described in the previous paragraph all had the same rotatory dispersion curves in dilute acid (Fig. 2), and a solution of the AR isomer in dilute base (pH 9 with NH_3) was restored to the same activity on acidification (Fig. 2). In dilute base proton exchange at the chiral N centre is fast and the conditions are suitable for epimerisation to occur rapidly. Finally the specificity was confirmed by an X-ray crystallographic analysis of a single crystal representative of the mass sample.

Solution and refinement. The structure was solved by conventional Patterson function and difference Fourier methods. The function $\Sigma\omega(|F_0| - |F_c|)^2$ was minimized in full matrix least squares refinements, where $|F_0|$ and $|F_c|$ are observed and calculated structure factor amplitudes and the weights, ω, were taken as $4F_o^2/\sigma^2(F_o^2)$. The atomic

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†en = ethylenediamine.

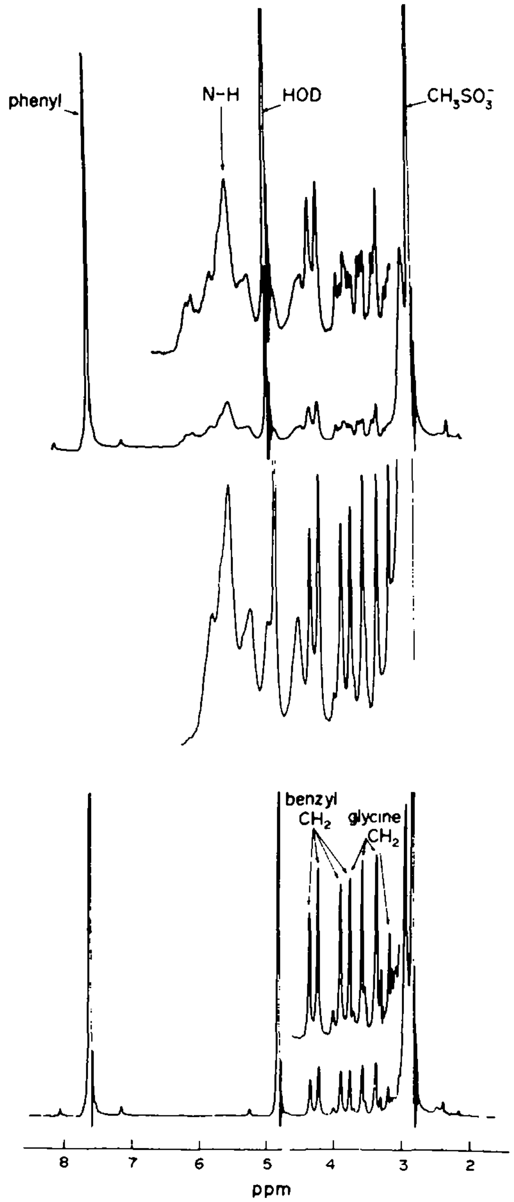

Fig. 1. ¹H NMR spectra of (N-benzylglycinato) *bis*(ethylene diamine) cobalt(III) methanesulfonate (0·2M) (a) in 0·1 MDCl, (b) in D_2O, (c) in 0·1M $NaDCO_3$, relative to sodium 2,2-dimethyl-2-silapentane-5-sulphonate (Jeol Minimar 100 MHz).

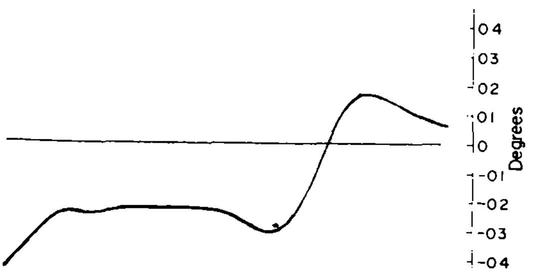

Fig. 2. Rotatory Dispersion Curves of ΛR-[Co(en)$_2$(N-benzylglycinato)]Br_2 (0·625 M × 10^{-3}) in (a) H_2O, (b) 0·05 M $HClO_4$, (c) H_2O brought to pH 9·5 with NH_3, (d) solution (c) reacidified after 0·5 hr to 0·05 M $HClO_4$ (Spectropolarimeter P22) (note all four curves coincide).

scattering factors for Co, Cl, N and C were taken from Cromer and Waber;[10] those for H from Stewart *et al.*[11] The effects of anomalous dispersion were included in F_c, with the values of $\Delta f'$ and $\Delta f''$ for Co and Cl^- taken from Cromer's tabulation.[12] Initial least squares refinement with all atoms isotropic gave $R_1 = 0{\cdot}11$, $R\omega = 0{\cdot}13$ where $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R\omega = (\Sigma\omega||F_o| - (F_c))^2/\Sigma\omega|F_o|^2)^{1/2}$.

A difference Fourier synthesis indicated that the cobalt and chlorine atoms were vibrating anisotropically. The absolute configuration of the complex was therefore determined with these latter three atoms allowed anisotropic temperature factors and the remainder isotropic. With the initial data set of 1048 reflections, two catoptric models constructed by changing the sign of the z coordinate of the atoms were refined to convergence. For the correct model Rω, R, were 0·077, 0·087 compared with 0·079, 0·089 for the opposite configuration. An examination of structure factors indicated that although the data set contained some errors, a consistent trend was evident for all Bijvoet pairs with significantly different F_c's (Table 1). Hamilton's R factor test[13] indicates greater than 99·5% probability of correctness for the final assignment of a Λ(R) configuration.

A difference map, based on the final data set, showed that the terminal oxygen atom (O1) of the glycinato ligand, which had a relatively high temperature factor, was vibrating anisotropically; other atoms had residual density wells and peaks around them, but the size of data set limited further parameterisation. With these 113 variables, the refinement converged with $R_1 = 0{\cdot}053$, $R\omega = 0{\cdot}049$. Only three of the 23 possible hydrogen atoms could be located in the subsequent difference Fourier. For the last cycles, the hydrogen atoms were included without refinement in their calculated positions (d(N–H) = 0·87 Å, d(C–H) = 0·95 Å, H–N–H = H–C–H = 109·5°; B = 5·5 Å for aliphatic carbons, 7·5 Å for phenyl carbons C9-C13). The structure refinement converged to R_1 0·051, Rω 0·048, with maximum final shift/error of 0·07. Several correlations around 0·35 were observed, notably between the coordinates of the atoms in the carboxylate part of the glycinato ring.

The average values of the minimized function over ranges on $|F_o|$ and $\lambda^{-1} \sin\theta$ indicated that the experimen-

Table 1. Structure factor amplitudes[a] for some Bivjöet pairs in ΛR-[Co(en)$_2$(N-benzylglycinato)]Cl_2

Reflections		Observed[b]		Calculated[a]	
hkℓ	$hk\bar{\ell}$	hkℓ	$hk\bar{\ell}$	hkℓ	$hk\bar{\ell}$
2,2,1	2,2,-1	50.7	53.1	45.0	48.9
1,2,2	1,2,-2	81.0	85.4	77.9	79.2
2,1,2	2,1,-2	64.2	66.1	62.1	65.7
5,1,1	5,1,-1	24.1	22.7	19.9	17.9
1,8,2	1,8,-2	33.5	39.7	36.5	38.4
4,5,2	4,5,-2	62.7	60.5	63.2	60.5
2,11,2	2,11,-2	22.2	27.7	21.7	24.7
3,1,2,	3,1,-2	55.1	51.0	51.4	54.2[c]

[a] During refinement (see text), the table contains reflections with significantly different $|F_c|$ values ~2.0 on Table scale

[b] Esd's for $|F_o|$ values ~2.0 on the Table scale.

[c] Only reflection observed with sign of effect reversed

Table 2. Positional and thermal parameters for ΛR-[Co(en)$_2$(N-benzylglycinato)]Cl$_2$

Atom	x	y	z	β_{11}^{a}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Co	.1773(2)	3496(1)	.7865(5)	.0058(3)	0015(1)	.0106(9)	-.0000(1)	.0039(5)	.0001(3)
Cℓ1	.1567(5)	4781(2)	.2902(11)	0116(7)	0020(1)	.0244(22)	- 0011(3)	- 0033(13)	.0019(5)
Cℓ2	3851(4)	2696(2)	2086(11)	.0059(5)	.0027(1)	0196(24)	0010(2)	.0038(10)	0002(6)
O1	.062(1)	.2747(6)	1.281(3)	.008(1)	.0025(4)	.018(6)	-.0019(6)	-.000(3)	-.001(1)

Atom	x	y	z	B(Å)^2	Atom	x	y	z	B(Å)^2
O2	116(1)	3403(6)	1 056(2)	3.9(4)	C5	.141(1)	2408(8)	.979(3)	1.5(4)
N1	.039(1)	.3356(7)	651(3)	3.8(5)	C6	.109(2)	2879(9)	1.106(4)	1.6(5)
N2	133(1)	.4300(6)	801(3)	3.1(4)	C7	237(2)	230(1)	.645(4)	5 1(7)
N3	.317(2)	3711(7)	914(3)	4.3(5)	C8	.241(2)	.1652(7)	.668(3)	1 4(5)
N4	.244(1)	.3625(7)	517(2)	3 1(4)	C9	316(2)	137(1)	763(4)	6 5(6)
N5	.205(1)	2651(7)	.799(3)	4.8(5)	C10	.321(2)	076(1)	.784(4)	6 4(6)
C1	-.021(3)	.386(1)	.667(6)	9.6(9)	C11	.240(3)	047(1)	682(5)	6.2(7)
C2	021(2)	437(1)	.766(5)	6 6(7)	C12	162(2)	.072(1)	.587(5)	7 3(7)
C3	.396(2)	3654(8)	744(4)	4 6(6)	C13	162(2)	135(1)	.581(4)	5.8(7)
C4	353(2)	3889(9)	.547(4)	3.7(6)					

tal weights were adequate. The final difference Fourier map contained peaks and troughs of the order of 0·3 e/Å^3; the highest 25 peaks were within 1·9 Å of final heavy atom positions. The final atomic positional and thermal parameters are recorded in Table 2. Table 3 lists the root mean square components of thermal displacement. A copy of the values of |F$_o$| can be obtained from the authors.

Description of the structure. The crystal contains discrete ΛR-[Co(en)$_2$(N-benzylglycinato)]$^{2+}$ cations (Fig. 3) and Cl$^-$ anions held together by a network of N–H...Cl and N–H...O H-bonds: there are also some short C–H...Cl contacts (Fig. 4). Table 4 lists the intramolecular dimensions for the cation. The structure confirms the prediction made in the Introduction concerning the relative stability of the diastereoisomers namely that ΛR or ΔS would be the most stable species. It also assigns the absolute configuration of the ligands about the cobalt atom which is consistent with that deduced from the rotatory dispersion curve[14] (Fig. 2). The mean Co–N and C–N bond lengths, 1·966(28) and 1·48(5) respectively are normal for Co(III) structures.[15,16] The C–C mean bond lengths are 1·46(4) and 1·36(6) respectively for the aliphatic and aromatic carbons. Here the estimated standard deviations[17] reflect the large variation in bond lengths within the cation: the weighted means 1·47(2) and 1·35(3) Å respectively are not significantly shorter than usual values of 1·50[15,16] and 1·395[19] Å respectively. The C7-C8 distance also appears normal.[17] The glycinato ring bond lengths are similar to other structures[18] except for the rather long C6–O1 terminal CO bond. This could be the effect of the short hydrogen gond involving the nitrogen (N1) protons of an adjacent cation (the first listed in Table 5).

Table 3. Root mean square component of thermal displacement along principal axis of vibration for atoms vibrating anisotropically in ΛR-[Co(en)$_2$(N-benzylglycinato)]Cl$_2$

Atom	Smallest	Middle	Largest Components
Co	0 121(9)	0.199(4)	0.234(5)
Cℓ1	0.197(11)	0 234(11)	0.323(10)
Cℓ2	0.164(14)	0.231(11)	0 284(8)
O1	0.19(3)	0.21(3)	0 31(2)

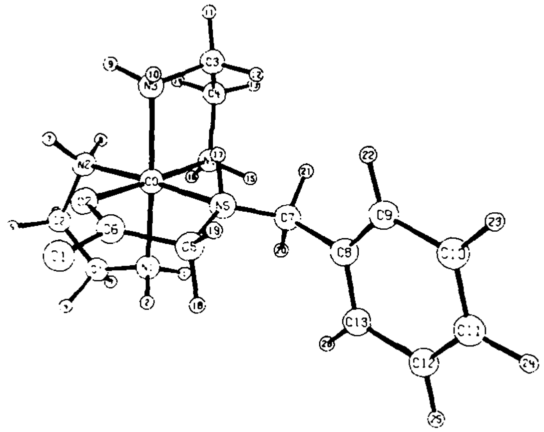

Fig. 3. Crystal structure of ΛR-[Co(en)$_2$(N-benzylglycinato)]$^{2+}$ ion.

Mean planes calculated for the complex are listed in Table 6. The glycinato ring is slightly buckled at the N atom N5, which is 0·3 Å out ot the plane (plane 4, Table 6). The best plane through any set of atoms of the glycinato ring involves the atoms O1, O2, C5 and C6 (plane 1, Table 6) with mean deviation out-of-plane 0·01 Å. This compares

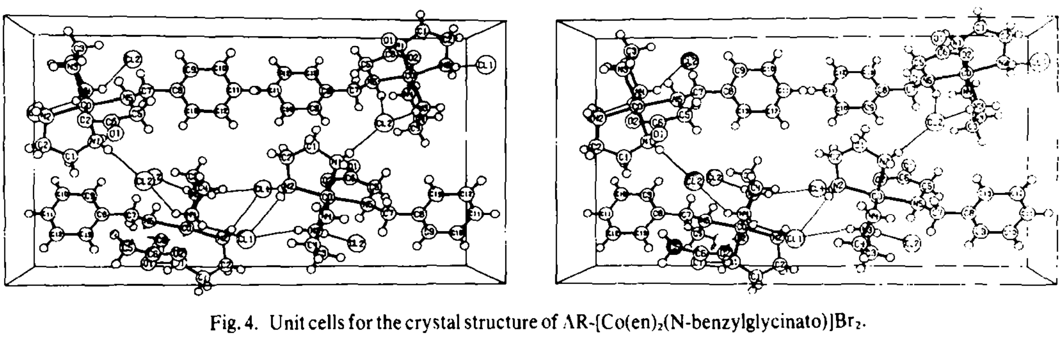

Fig. 4. Unit cells for the crystal structure of ΛR-[Co(en)$_2$(N-benzylglycinato)]Br$_2$.

Table 4. Final bond lengths and angles for ΛR-[Co(en)$_2$(N benzylglycinato)]Cl$_2$

Atoms	Distance[a]	Atoms	Distance[a]
Co - N1	1.967(17)	N4 - C4	1.50(3)
Co - N2	1.929(14)	N5 - C5	1.53(3)
Co - N3	1.997(19)	N5 - C7	1.35(3)
Co - N4	1.971(17)	C1 - C2	1.43(3)
Co - N5	1 975(16)	C3 - C4	1.50(3)
Co - O2	1.938(15)	C5 - C6	1.42(3)
O1 - C6	1.32(2)	C7 - C8	1.50(2)
O2 - C6	1.25(2)	C8 - C9	1 30(2)
N1 - C1	1.39(3)	C8 - C13	1.34(2)
N2 - C2	1.43(3)	C9 - C10	1.41(3)
N3 - C3	1.50(3)	C11- C12	1 29(3)
		C12- C13	1.45(3)

Atoms			Angle (°)	Atoms			Angle (°)
N1	Co	N2	85.9(6)	Co	N5	C5	107(1)
		N3	174.9(7)	Co	N5	C7	127(2)
		N4	89.7(7)	C5	N5	C7	120(3)
		N5	90.8(7)	Co	O2	C6	112(1)
		O2	92.5(7)	N1	C1	C2	121(3)
N2	Co	N3	89.5(6)	N3	C3	C4	111(2)
		N4	91.3(7)	N5	C5	C6	109(2)
		N5	171.8(8)	O2	C6	C5	124(2)
		O2	86.9(7)	N5	C7	C8	122(2)
				C7	C8	C9	125(2)
N3	Co	N4	88.1(8)	C7	C8	C13	117(2)
		N5	94.0(7)	C13	C8	C9	118(2)
		O2	89.6(7)	C8	C9	C10	125(2)
N4	Co	N5	96.3(8)	C9	C10	C11	113(3)
		O2	177.1(7)	C10	C11	C12	126(3)
N5	Co	O2	85.7(7)	C11	C12	C13	117(3)
O2	C6	O1	119(2)	C12	C13	C8	121(2)
Co	N1	C1	108(2)				
	N2	C2	112(1)				
	N3	C3	104(1)				
	N4	C4	109(1)				

Atoms	Angle(°)
b	
Co-N1-C1-C2	0.8(3.8)
N1-C1-C2-N2	11.8(4.3)
Co-N2-C2-C1	-18.5(3.1)
Co-N3-C3-C4	41.2(1.8)
N3-C4-C4-N4	-49.6(2.1)
Co-N4-C4-C3	32.2(1.8)
Co-N5-C5-C6	-16 1(1.9)
N5-C6-C5-O2	11.8(2.8)
Co-O2-C6-C5	-0.6(2.6)
Co-O2-C6-O1	-175.9(1.5)
N5-C7-C8-C9	-77 9(3.3)
C7-C8-C9-C10	-179 3(2.6)

[a] Numbers in brackets are estimated standard deviations in least significant digits quoted, calculated from the final least-squares variance-covariance matrix.

[b] The dihedral angle A-B-C-D is defined as the angle between the planes comprising atoms A,B,C and B,C,D with the normal sign convention.

with mean deviation out-of-plane for atoms of the phenyl ring (plane 1, Table 6) of 0·01 Å. The benzyl carbon, C7, also cannot be described as significantly out of the phenyl plane (0·06 Å, 2σ) on the basis of this experimental data set.

Table 5. Possible hydrogen bonds in ΛR-[Co(en)$_2$(N-benzylglycinato)]Cl$_2$

Number	Atoms (A-H. .B)	D(H. B)Å	D(A.. B)Å	Symmetry Operations[a]
1.	N1-H1. .O1	1 99	2 81	1″
2	N3-H10 Cℓ2	2 31	3 14	1′
3	N1-H2 Cℓ2	2.38	3 22	2
4	N4-H16 Cℓ1	2 41	3 23	1
5.	N2-H7 ..Cℓ1	2.51	3 37	1′
6	C4-H14.. Cℓ1	2 58	3 45	3
7	C5-H18 . Cℓ2	2.63	3 44	2
8	N4-H15 Cℓ2	2 68	3 43	1
9	N2-H8 Cℓ1	2.74	3.40	3
10	N2-H8 Cℓ1	2 88	3 54	1
11	N3-H9.. Cℓ1	2.89	3.57	3

Atoms	Angles(°)	Atoms	Angle(°)
Co-N1...O1	112	Co-N2.. Cℓ1	112
C1-N1 O1	122	C2-N2. .Cℓ1	134
C6-O1 H1	126	N2-H7 Cℓ1	170
N1-H1...O1	156	N4-C4 Cℓ1	113
Co-N3.. Cℓ2	108	C3-C4 Cℓ1	86
C3-N3.. Cℓ2	102	C4-H14. Cℓ1	147
N3-H10. Cℓ2	162	C6-C5 Cℓ2	90
Co-N1 Cℓ2	121	N5-C5. .Cℓ2	104
C1-N1. Cℓ2	106	C5-H15...Cℓ2	143
N1-H2. Cℓ2	163	Co-N2...Cℓ1	110
Co-N4 . Cℓ1	113	N2-H8...Cℓ1	131
C4-N4. Cℓ1	92	C2-N2 Cℓ1	103
N4-H16. Cℓ1	154	Co-N2. Cℓ1	102
		C2-N2 .Cℓ1	84
		N2-H8 Cℓ1	134
		Co-N3...Cℓ1	103
		C3-N3...Cℓ1	82
		N3-H9...Cℓ1	137

[a] Symmetry operations to bring atom B into contact with A-H are:

1 x, y, z

1′ $x, y, 1 + z$

1″ $x, y, 1 - z$

2 $x - \frac{1}{2}, \frac{1}{2} - y, 1 - z$

3 $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$

In order to assess the distortions in the molecule, strain energy minimization calculations on this and related molecules have been carried out.[18]† The significant distortions arising in these calculations are the opening of the angles Co–N5–C7 and C5–N5–C7, 127(2)° and 120(3)° respectively. The opening of the Co–N5–C7 angle is apparently caused by non-bonded repulsions of the benzyl methylene protons (on C7) and ethylenediamine protons on N4 and N1. (H15... H21... H1... H20). This is confirmed by a recent neutron study of Δ-β_1-[(Co(trien)glyO)]I$_2$.0·5H$_2$O[19] which shows that the Co–N–H angle is not inherently widened in glycinato rings. According to these calculations, other distortions in the crystal structure are either within experimental errors or are dependent on packing forces.

The H-bonds that contribute significantly to the packing are indicated in the stereo view of the contents of the unit cell viewed down the short c axis (Fig. 4), with the appropriate intermolecular distances and angles tabulated in Table 4. Although the longer bonds noted in this table exceed the van der Waal's criteria suggested by Hamilton and Ibers[20] by up to 0·2 Å, the geometrical requirements outlined by these authors and further developed by Baur[21] are satisfied for all eleven contacts. Even though the shorter hydrogen bonds (the first five in Table 5) are sufficient to describe a complete three-dimensional network, the remaining interactions presumably provide further cohesion to the packing . A good example of this cohesion lies in the hydrogen bonding of *both* independent Cl atoms to hydrogens on nitrogen N4 (Table 5). The

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†By modifications to the force field and the same method used in Ref. 18; only two phenyl group orientations were considered (see Table 8).

Table 6. Mean planes in ΛR-[Co(en)$_2$(N-benzylglycinato)]Cl$_2$

No.	Atoms in Plane (distance Å)	Other Atoms (distance Å)	Equation Coefficients[a] A	B	C	D
1.	C8(0.01), C9(0.01), C10(-.03) C11(0.02), C12(0.00), C13(-.02)	C7(.06) N5(-1.03)	.5348	-.0332	-.8443	-2.2176
2.	O1, O2, C6	Co(0.13), C5(0.10) N5(-.10), C7(,	-.8832	-.0613	-.4650	-4.9720
3.	O1(0.01), O2(0.01), C5(0.01), C6(-.02)	N5(-.22), Co(.08) C7(-.11)	-.8987	-.0272	-.4378	-4.5474
4	Co(0.02), O1(0.03), O2(-.01), C6(-.03)	C5(-.02), N5(-.27) C7(-.18)	-.9079	-.0323	-.4180	-4.4414
5.	Co, N1, N2	C1(-.21) C2(-.36)	.4237	.1734	-.8890	-2.2435
6.	Co, N3, N4	C3(.44) C4(-.20)	.2838	-.9585	-.0263	-7.2035

[a] Method of B. M. Blow, *Acta Cryst.* 13, 168 (1960) the planes have the equation

AX + BY + CZ = D where X(Å) is measured along the *a* axis,

Y(Å) is measured in the (*a*,*b*) plane and

Z(Å) is measured along the *c* axis.

major linking of the structure in the c axis direction appears to be the N1–H... O1 inter-cation bond; this may be the reason for the abnormally long C6–O1 bond observed for the cation.

Strain energy minimisation. The calculations referred to in the structural section comprise the application of a general force field to the assembly of atoms coupled with a minimisation technique which produces a structure of minimum energy.[18]* The force field includes terms for bond length deformations, bond angles variations, non-bonded interactions, torsional interactions and out of plane deformations for the glycinato ring. The procedure has been widely tested for molecules of this type and reproduces the structural features formed in crystals, including large deformations, with compelling accuracy.[18] It has also gauged the relative stability of the isomers correctly, but the quantitative agreement here has been less accurate.[18] Part of the problem comes from the equation of the observed free-energy difference with the calculated strain energy difference, when more properly the enthalpy change should be compared. Clearly the calculations take no account of solvation effects. In this context we can have confidence in the calculations as an indication of relative stability without being certain of the magnitude.

Table 7. Calculated final positional parameters for hydrogen atoms ΛR-[Co(en)$_2$(N-benzylglycinato)]Cl$_2$

Atom	x	y	z
H1	.050	.327	.523
H2	.006	.307	712
H3	-.047	.396	.537
H4	-.086	.376	.736
H5	-.014	441	.895
H6	.009	.469	685
H7	.148	.442	.928
H8	.173	.450	718
H9	316	.407	.960
H10	.333	.349	1.017
H11	462	.386	.774
H12	.414	.326	.721
H13	.399	.381	.434
H14	.346	.431	.557
H15	.252	330	.450
H16	.205	386	.440
H17	.264	.281	.851
H18	.083	.220	.924
H19	.186	.213	1.054
H20	.189	.239	536
H21	.307	.243	.603
H22	.372	.159	.824
H23	.376	.055	860
H24	.241	.006	680
H25	.107	.047	526
H26	.105	.155	.513

The present calculations were performed using the force field described in previous publications.[18] Only two orientations of the phenyl group were considered* and the computations have restricted value because of this and because the non-bonded functions for the atoms in the aromatic ring are the same as those used for the saturated C and H atoms. The results of the strain energy calculations are given in Table 8. For the orientation of the phenyl group (N_5–C_7–C_8–C_9 −60°) closest to that found in the crystal (−77°), the calculations indicate that the ΛR_1 isomer is more stable than the ΛS_1 isomer in agreement

Table 8. Strain energies[a] for the minimised structure of ΛR- and ΛS-[Co(en)$_2$(N-benzylglycinato)]$^{2+}$ ions (kcal/mole)

	ΛR_1	ΛS_1	ΛR_2	ΛS_2
Bond Deformations	0.89	0.98	0.97	1.06
Angle Deformations	4.20	3.78	4.80	3.97
Non-Bonded Interactions	-4.71	-4.18	-4.01	-3.73
Torsional Interactions	2.77	4.15	4.35	4.70
Glycinato out-of-plane Deformations	0.00	0.01	0.02	0.02
Total S.E.	3.15	4.74	6.13	6.02

for 1068 interactions

[a] The subscripts ΛR_1, ΛR_2 etc. refer to two orientations of the phenyl group

(1) dihedral angle N_5-C_7-C_8-C_9 -60°

(2) dihedral angle N_5-C_7-C_8-C_9 -120°

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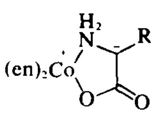
*By modifications to the force field and the same method used in Ref. 18; only two phenyl group orientations were considered (see Table 8).

with the chemistry and the crystallography. Significant interactions occur between the methylene group and the adjacent chelates. However for the ΛR_1 and ΛS_1 isomers the non-bonded interactions between the atoms in the aromatic ring and the remainder contribute little to the strain energy. It follows that the approximations used in the force field for these atoms are not especially significant. The major differences for ΛR_1 and ΛS_1 come from torsional interactions with significant contributions from bond angle deformation and non-bonded interactions. The result is not especially surprising when it is seen that the energies required to deform the torsional angles are less than those for corresponding deformations in bond angles.

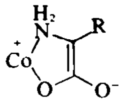
For the other orientations of the phenyl group the strain energy is higher overall for both isomers and clearly these are not favoured structures.

Synthesis of chiral N-*benzylglycine*. The deuteration of chelated N-benzylglycine was carried out in D_2O containing PO_4^{3-} ion as a means of controlling the pH at 10·5. The results are depicted in Fig. 5. Numerous variations in conditions and buffers did not improve the specificity. Clearly the glycine protons exchange with D_2O. The methylene doublet pairs centred about δ3·52 and δ3·12 collapse and a singlet at δ3·16 grows rapidly. This occurs by a base-catalysed removal of a proton from the chelated methylene moiety to give a chelated carbanion[8] which then captures D^+ from D_2O with a marked preference for one side of the chelate relative to the other. Previous studies[8] on analogous systems have indicated that the chelated carbanion moiety shown below should be effectively planar with respect to reprotonation.

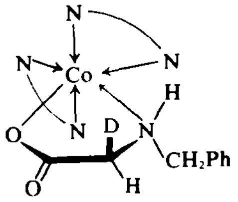


(e.g. R = CH_3)

The planar conformation is probably stabilised by the conjugative interaction shown below:



However, in the present case, there is a bulky substituent on the glycinate N which not only preserves the configuration at this chiral N centre but also directs the entry of the D_2O molecule which delivers D^+. It is likely that D_2O approaches the carbanion most easily from the side of the chelate *trans* to the N-benzyl substituent to give the deuterated species depicted below. i.e. chelated (S)N-benzyl-2-^{2}H-glycine.



This point has not been rigorously established (note that studies of the structure and stability of $[(en)_2Co(N\text{-methylalaninato})]^{2+}$ ions[22,23] show that their most stable configuration has the methyl groups *trans* to each other).

The degree of specificity in the C-deuteration process is difficult to quantify because of the residual signal at δ3·46, but is is clear that the low field proton signal is vanishing *ca.* 4–5 fold faster than the high field signal. The last spectrum in Fig. 5 indicates that *ca.* 40% of the product is doubly deuterated (CD_2) and of the forms containing CHD (*ca.* 60%) about 80% is one enantiomer-probably (S)-2-^{2}H-N-benzylglycine. To our knowledge a stereoselective non-enzymatic synthesis of labelled glycines has not otherwise been achieved.

We have not yet converted the deuterated complex to free deuterated glycine. We presume that the latter can be obtained after removing N-benzylglycine from the cobalt centre by reduction (e.g. with V^{2+} in acidic solution). N-benzylglycine could be separated from ethylenediamine and metal ions by ion exchange chromatography and then converted to 2-^{2}H-glycine by hydrogenolysis ($Pd/C/H_2$). All of this chemistry could be conducted under acidic conditions to preclude exchange at the glycinate methylene group. Before attempting this

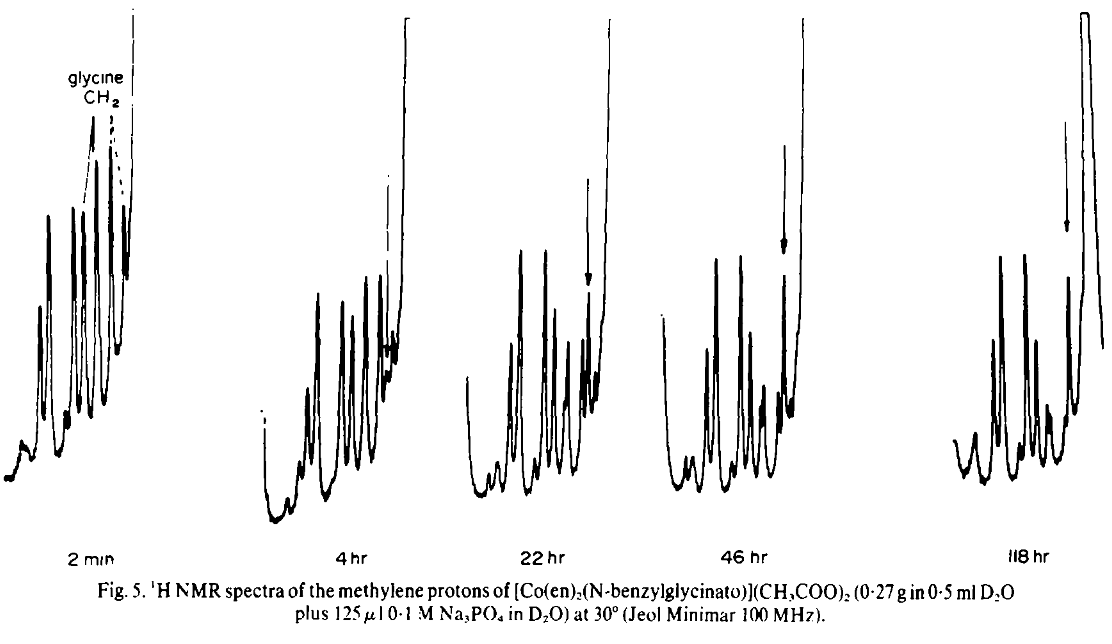


Fig. 5. ^{1}H NMR spectra of the methylene protons of $[Co(en)_2(N\text{-benzylglycinato})](CH_3COO)_2$ (0·27 g in 0·5 ml D_2O plus 125 μl 0·1 M Na_3PO_4 in D_2O) at 30° (Jeol Minimar 100 MHz).

sequence we hope to be able to improve the stereoselectivity of the exchange by making sensible modifications to the N-benzyl group of a (glycinato)*bis*(ethylenediamine)cobalt complex.

EXPERIMENTAL

N-Benzylglycine hydrochloride was prepared as described.[5]

Synthesis of (N-*benzylglycinato*) *bis*(*ethylenediamine*)*cobalt*-(*III*) *bromide.* *trans*-$[Co(en)_2Br_2]Br$ (4·2 g) and N-benzylglycine·HCl (2·0 g) were added to MeOH (120 ml) containing LiOH (0·84 g) and the mixture refluxed for 30 min. The colour changes from green to violet and the red complex crystallises. It was collected after cooling the soln (2·6 g) and recrystallised from water (60°) by cooling and adding NaBr (3 g). (Found: Co, 12·1; C, 31·15; H, 5·4; N, 13·7; Br, 31·7. Calc. for $Co\,C_{13}H_{26}N_5O_2Br_2$: Co, 11·71; C, 31·03; H, 5·21; N, 13·92; Br, 31·77%). The bromide salt was converted to the perchlorate with $AgClO_4$ in water and recrystallised from water with $NaClO_4$. (Found: C, 28·5; H, 4·8; N, 12·8. Calc. for $Co\,C_{13}H_{26}N_5O_{10}Cl_2$: C, 28·80; H, 4·83; N, 12·92%). The acetate salt was prepared similarly. The methane sulfonate salt was prepared by passing a soln of the perchlorate through an anion exchange column saturated with $CH_3SO_3^-$ and evaporating the soln to near dryness when the complex crystallised. The salt was deuterated at the N centres in D_2O, recovered and analysed. (Found: C, 33·2; N, 13·1. Calc. for $CoC_{15}H_{23}D_9N_5S_2O_8$: C, 33·20; N, 12·90%).

ΛR-[Co(*en*)$_2$(N-*benzylglycinato*)] *complexes*: rac-[Co(en)$_2$(N-benzylglycinato)]Br$_2$ (20 g) was treated with silver acetate (13 g) in water (100 ml) and shaken vigorously for 10 min. After filtration, the soln was treated with tartaric acid (11 g) partially neutralised with LiOH (1·7 g in 20 ml H_2O). The soln was allowed to stand for 12 h and the flocculent diastereoisomer was collected (14 g) and recrystallised to constant rotation. The least soluble diastereoisomer was then dissolved in the minimum amount of water and treated with excess NaBr to crystallise the complex bromide. $[\alpha]_{550}+520°$, $[\alpha]_{495}-880°$ (5·0 mg/10 ml H_2O gave $\alpha_{550}+0{\cdot}260°$ and $\alpha_{495}-0{\cdot}440°$ in a 5 cm cell). Recrystallisation of the bromide to constant rotation gave $[\alpha]_{550}+550°$, $[M]^{20}_{500}+2770$ deg. $M^{-1}\,m^{-1}$, $[\alpha]^{20}_{495}-926°$, $[M]^{20}_{495}-4660$ deg. $M^{-1}\,m^{-1}$. (Found: C, 30·6; H, 5·3; N, 13·7. Calc. for $Co\,C_{13}H_{26}N_5O_2Br_2$: C, 31·03; H, 5·21; N, 13·92%). The resolved bromide salt was converted to the chloride with AgCl and crystallised from water then from basic D_2O to deuterate the N centres and the glycine methylene region. (Found: Co, 14·3; C, 36·63; H + D, 8·6; N, 16·46; Cl, 17·2. Calc. for Co $C_{13}H_{15}D_{11}O_2N_2Cl_2$: Co, 13·86; C, 36·71; H + D, 8·74; N, 16·47; Cl, 16·68%). Crystals from this sample were used for the crystallography.

Crystallography of ΛR-[Co(*en*)$_2$(N-benzylglycinato)]Cl$_2$. Preliminary precession photographs taken with Ni-filtered Cu radiation indicated the crystals were orthorhombic. The conditions limiting possible reflections amongst all recorded spectra (h00, absent for h = 2n + 1; 0k0, absent for k = 2n + 1; 00l, absent for l = 2n + 1) are uniquely consistent with space group $P2_12_12_1$. Unit cell dimensions at 24 ± 2° were obtained by the least-squares procedure described below. A density of 1·53 (±0·03) g cm^{-3} was obtained by flotation in chloroform-carbon tetrachloride. This implied one independent molecule per unit cell.

Crystal data.† $CoC_{13}N_5O_2D_{11}H_{15}Cl_2$, molecular weight 425·2, orthorhombic with $a = 12{\cdot}508(5)$, $b = 22{\cdot}970(10)$, $c = 6{\cdot}544(3)$; $V = 1880$ Å^3; $D_{obs} = 1{\cdot}53$ (±0·03) g cm^{-2}; $Z = 4$, $D_{calc} = 1{\cdot}50$ g cm^{-3} $\mu(MoK\alpha) = 12{\cdot}5$ cm^{-1}.

Diffraction data were collected on a typical crystal plate of dimensions 0·35 × 0·18 × 0·028 mm; the boundary faces were (001), $(\bar{1}0\bar{3})$, (010), $(0\bar{1}0)$, (100) and $(\bar{1}00)$. This crystal, which was the best available, had a few very small fragments on its surface. It was mounted on a Hilger and Watts computer-controlled four-circle diffractometer with the c* crystal axis deliberately offset by about 10° in both arcs from coincidence with the goniometer head axis. Some difficulty was experienced in locating suitably intense high angle reflections for allignment and cell refinement. Eventually 11 reflections were accurately centred using a 3·5 mm diameter receiving aperture. The setting angles of these reflections were the data used for a least-squares refinement[6] of all parameters and crystal orientation, in which the wavelength of the $MoK\alpha_1$ radiation was taken as 0·70930 Å. The mosaicity of the crystal, determined by open counter ω scans at a take-off angle of 3°, was satisfactory: the crystal shape gave a substantial variation (0·15° to 0·4°) for strong low angle reflections corresponding to the crystal shape.

The intensity data were collected with Zr-filtered $MoK\alpha$ radiation at a take-off angle of 3°, using a 1·0 mm beam collimator. The circular receiving aperture, positioned 23 cm from the crystal was 5 mm in diameter. Data were collected by the θ-2θ scan technique. A symmetric scan of 1·20° (or 1·40°) in 2θ centred on the calculated peak position ($\lambda\,Mo(K\bar{\alpha}) = 0{\cdot}7107$ Å) consisted of 60 (or 70) steps of one second duration. Stationary-crystal, stationary counter background counts of 15 seconds were measured at each end of the scan range. Attenuation was not required as the intensity of the diffracted beam did not exceed 7000 counts/sec for any reflection.

A unique octant (h > k > l > 0) of reciprocal space up to a 2θ limit of 38° was recorded (1062 reflections); then a quadrant containing the Bijvoet pairs (hkl and hk$\bar{l}$) from 2θ of 4° to 31° was collected. Beyond 2θ of 38°, little data could be observed above background. The total number of reflections measured (2027, including standards) therefore contained suitable data for internal consistency checks as well as the Bijvoet pairs needed for the absolute configuration determination. Three reflections monitored at regular intervals showed a systematic fall in intensity to about 88% of their initial values at the end of data collection. All intensities were rescaled using linear interpolation between their nearest standard measurements.

Data processing included the application of Lorentz polarisation corrections and the calculations of $\sigma(I)$ with the value of p, the uncertainty factor, selected as 0·05.[7] After averaging reflections that had been measured more than once, and removing the Friedel equivalents, the data set consisted of 637 reflections from a total of 1048 reflections measured with $F^2 > \sigma(F^2)$. An absorption correction was then applied‡ using Gaussian integration (4^3 grid points) with transmission factors ranging from 0·82 to 0·96. The data was reprocessed following structure solution eliminating reflections suffering presumably from fragments on the crystal surface ($|F_0| \gg |F_c|$, checked by disagreement between equivalent reflections) and those with $F^2 < 1{\cdot}5\sigma(F^2)$. The final data set consisted of 520 independent reflections.

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†Here, and throughout the crystallography section, the uncertainties given in parentheses are estimated standard deviations in the least significant digit quoted.

‡Programmes used in this analysis come from the University of Canterbury: see K. Emerson, P. R. Ireland and Ward T. Robinson, *Inorg. Chem.* 9, 436 (1970) and the Australian National University: local versions of Busing and Levy's ORFLS and ORFE and Johnson's ORTEP written by J. D. Bell for the UNIVAC 1108 computer.

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