Stereoselective Synthesis of Coordinated Penicilloates

Neville J. Curtis,[a] Anders Hammershøi,[b,c] Louisette M. Nicolas,[a] Alan M. Sargeson[a] and Kenneth J. Watson[d]

[a]Research School of Chemistry, Australian National University, G.P.O. Box 4, Canberra, A.C.T. 2601, Australia, [b]Chemistry Department, Royal Veterinary and Agricultural University, Thorvaldsensvej 40, DK-1871 Frederiksberg C, [c]Chemistry Department I (Inorganic Chemistry), University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark and [d]The Crystallographic Centre, University of Western Australia, Nedlands, Perth, W.A. 6009, Australia
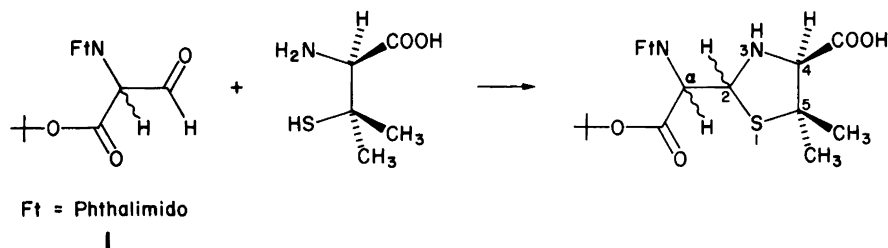
Protection of the amino acid function of C-formylglycine (abbreviated: C-formyl-glyOH) by synthesis from the chiral bis(ethylenediamine)glycinatocobalt(III) ion is described. The $\Delta(-)_{589}$-[Co(en)$_2$$C$-formylglycinato]$^{2+}$ complex, **2**, condenses in aqueous pyridine buffer with (S)-penicillamine to give largely the ($2S,4S,\alpha S$) (C) and ($2S,4S,\alpha R$) (B) isomers of the corresponding Co(III) complexes of the coordinated penicilloates. The stereochemistry of these isomers was elucidated by X-ray crystallography. Isomer C, $\Delta(2S,4S,\alpha S)-(C_{12}H_{28}O_4N_6SCo \cdot ClO_4 \cdot 3H_2O)$: space group $P2_12_12_1$; $a = 18.478(6)$, $b = 12.698(3)$, $c = 9.889(4)$ Å, $Z = 4$, 2308 independent reflections $[F^2 \geqq 3.0(F^2)]$, residual $R_1 = 0.045$. Isomer B, $\Delta(2S,4S,\alpha R)-(C_{12}H_{28}O_4N_6SCo \cdot ClO_4 \cdot 2H_2O)$: space group $P2_12_12_1$; $a = 15.865$ (6), $b = 13.142(4)$, $c = 10.683(4)$ Å, $Z = 4$, 4400 independent reflections $[F^2 \geqq 3.0$ $(F^2)]$, residual $R_1 = 0.070$. With the condensation reaction in Me$_2$SO or DMF solutions, all four possible isomeric ($4S$) penicilloato complexes were observed. In DCl solution, each isomer undergoes a rearrangement to give an equilibrium mixture with its C-2 epimer. The condensation in 0.1 M DCl leads stereoselectively to the ($2S,4S,\alpha S$) (C) isomer as the initial product, which subsequently epimerises. The mechanisms of the condensation and epimerisation reactions are discussed.

The first total synthesis of the penicillin nucleus was achieved in the 1950's by Sheehan and co-workers.[1-3] Germane to the successful synthesis was the attainment of the correct stereochemistry at C-2 and C-α during the thiazolidine condensation (Scheme 1). In Sheehan's work, the reaction of the protected C-formylglycine **1** with (S)-penicillamine afforded largely two of the possible four diastereoisomers,* isolated in 54 % total yield, which were efficiently separated on the basis of their different solubilities in water–alcohol mixtures. One diastereoisomer was found to have the naturally occurring configuration,

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*In accordance with Chemical Abstracts usage, these penicilloic acids are treated as derivatives of 2-thiazolidineacetic acid and are numbered as in Scheme 1.

($2R,4S,\alpha R$), whilst the other was subsequently[4] shown to be ($2S,4S,\alpha S$).

Protected C-formylglycines such as **1**, apart from their use as precursors in penicilloic acid synthesis, have potential in the preparation of α,β-diaminoacids as well as the derived β-lactam compounds. Analogues of **1** have now been prepared in which protection of both the amine and carboxylate functions is achieved by coordination to a substitution-inert tetraaminecobalt(III) moiety. The preparation of tris(2-aminoethyl)-amine complexes of this type, via Vilsmeier-Haack formylation of the chelated glycinato complex, has previously been reported.[5,6] However, for this system, which is achiral with respect to the disposition of chelate rings, the reaction with (S)-penicillamine in Me$_2$SO or aqueous solution

Ft = Phthalimido

I

Scheme 1.

exhibited little stereoselectivity.[7] The possibility exists that the use of a chiral ligating system about Co^{3+} could lead to asymmetric induction in the reaction with (S)-penicillamine, and for this reason the enantiomers of the bis(ethylenediamine)(C-formylglycinato)cobalt(III) ion, Δ- and Λ-**2,** have been synthesised. In this paper we report the preparation of these potentially useful chiral synthons, their reactions with (S)-penicillamine, akin to that described in Scheme 1, the stereochemical course of the reaction and the solution properties of the derived complexes.

Experimental

Absorption spectra and optical rotations were monitored with a Cary 14 spectrophotometer and a Perkin-Elmer P22 spectropolarimeter (±0.002°), respectively, for the latter in 1 dm quartz cells. All listed values of specific ($[α]_λ$) and molar ($[M]_λ$) rotations are at 25.0±0.1 °C in units of deg ml g^{-1} dm^{-1} and deg M^{-1} m^{-1}, respectively. IR spectra (KBr disks) were recorded on a Perkin-Elmer 683 spectrophotometer. NMR spectra were recorded with a Bruker CXP 200 (^{1}H) or a Jeol JNM-FX 200 instrument (^{1}H, ^{13}C) using sodium 3-(trimethylsilyl)propanesulfonate (NaTPS) (^{1}H) or 1,4-dioxane (^{13}C) as internal standards. Unless otherwise stated, D_2O was used as solvent and chemical shifts δ (positive downfield) are given in ppm relative to 1,4-dioxane (^{13}C) or Me_4Si (^{1}H), taking δ for NaTPS as −0.02.

The ion-exchange resins employed, AG 50W-X2 (cation) and Dowex 1-X8 (anion), were both 200–400 mesh (Bio-Rad). Dimensions of resin columns are given as diameter × length. All routine evaporation of solvents was carried out at reduced pressure (~20 torr) on a Büchi rotary evaporator using a water aspirator and water bath (45 °C).

All chemicals were of analytical grade. Commercial HO_3SCF_3 (3M Co.) was distilled before use. S-penicillamine was purchased as natural D-penicillamine.

[Co(en)₂glyO](ClO₄)₂. Portions of [Co(en)₂-CO₃]Cl[8] (138 g, 0.50 mol) were carefully added to ice-cold 4 M $HClO_4$ (325 ml) with stirring and the ice-cooled mixture was purged with N_2 for 1 h. Glycine (41 g, 0.50 mol) followed by NaOH solution (32 g, 0.80 mol in 150 ml of water) were added to the reaction mixture and the resulting solution was heated on a steam-bath for 2 h. To the hot, orange-coloured solution was added $NaClO_4 \cdot H_2O$ (150 g) with stirring and the mixture was left at 0 °C overnight to crystallize. The orange crystals were collected and washed with ethanol and ether. Yield 184 g (81.5 %).

[Co(en)₂glyO]Cl₂. Crude [Co(en)₂glyO](ClO₄)₂ (184 g, 0.4 mol), dissolved in water, was sorbed on an AG 50W-X2 column (8×20 cm) in the H⁺ form. The column was washed with 0.5 M HCl to remove two minor purple impurities and the main (orange) band was eluted with 2 M HCl. This fraction was concentrated to 180 ml whence crystals started to form. The precipitation was completed by gradual addition of ethanol (200 ml) with stirring. The solid product was collected, washed with ethanol–water (2:1, v/v), ethanol and then ether. Yield 115 g (97 %).

Λ(+)₅₈₉- and Δ(−)₅₈₉-[Co(en)₂glyO](O₃SCF₃)₂ · HO₃SCF₃. [Co(en)₂glyO]Cl₂ (48 g, 0.15 mol) was dissolved in 1 l of water and the solution passed down a column (6×20 cm) of Dowex 1-X8 anion-exchange resin in the acetate form. The eluate

was concentrated to 200 ml and 46 g (0.075 mol) of disodium bis((+)$_{589}$-tartrato)diantimonate dihydrate (Na$_2$[Sb$_2$((+)$_{589}$-tart)$_2$]·2H$_2$O) was added. The resulting solution was left to crystallize at 20°C overnight. The orange crystals were isolated, washed with water, methanol–water (1:1, *v/v*), methanol and then ether (55 g, Fraction A). The combined filtrates were concentrated to 50 ml and a further 46 g of Na$_2$[Sb$_2$((+)$_{589}$-tart)$_2$]·2H$_2$O was added. Heating on a steam-bath effected dissolution and initiated the formation of orange crystals. The mixture was cooled in ice and after crystallization was complete, the solid product was collected, washed with ethanol (4–5 times) and ether (38 g, Fraction B). Fraction A, comprising the diastereoisomer Δ(−)$_{589}$-[Co(en)$_2$glyO][Sb$_2$((+)$_{589}$-tart)$_2$]·4H$_2$O, was recrystallized repeatedly (usually twice) from boiling water (ca. 1.5 l) until the specific rotations became constant: [α]$_{589}$ −83, [α]$_{546}$ −264, [α]$_{470}$ 849 (0.05 %, in H$_2$O). Fraction B, comprising Λ(+)$_{589}$-[Co(en)$_2$glyO][Sb$_2$((+)$_{589}$-tart)$_2$]·4H$_2$O, was similarly recrystallized from boiling water (ca. 0.8 l) until the specific rotations became constant: [α]$_{589}$ 284, [α]$_{546}$ 508, [α]$_{470}$ −496 (0.05 %, in H$_2$O).

In separate experiments, each of the diastereoisomers (65 g) was dissolved in water (10–15 l) and sorbed on a column (7×13 cm) of AG 50W-X2 resin in the Na$^+$ form. The column was washed with 1 l of water, followed by 1 l of 0.5 M HCl. The complex was eluted with 2 M HCl and the eluate was carefully evaporated to dryness. The amorphous residue was treated with trifluoromethanesulfonic acid (80 ml), causing the complex to dissolve with evolution of HCl gas. This process was facilitated by the use of a rotatory evaporator. Following the gas evolution, a homogeneous solution was obtained which was poured into vigorously stirred ether (1 l). After ¹/₂ h of vigorous stirring, the solid, hygroscopic product was collected, washed with ether (3–5 times), rapidly sucked dry on the filter and finally dried *in vacuo* over P$_4$O$_{10}$. Yield of each chiral [Co(en)$_2$glyO](O$_3$SCF$_3$)$_2$·HO$_3$SCF$_3$ salt ~60 g. Anal. Calcd. for CoC$_9$H$_{21}$F$_9$N$_5$O$_{11}$S$_3$: Co 8.40, S 13.71. Found: Co 8.0, S 13.9.

Λ(+)$_{589}$- and *Δ(−)$_{589}$-[Co(en)$_2$C-formylglyO]Cl$_2$·HCl·2H$_2$O.* The procedure was identical for each of the enantiomers. Chiral [Co(en)$_2$glyO](O$_3$SCF$_3$)$_2$·HO$_3$SCF$_3$ (22 g) was dissolved

in dry *N,N*-dimethylformamide (150 ml). The solution was stirred and cooled in an ice/salt cooling mixture and POCl$_3$ (25 ml) was added dropwise over 20 min. After stirring for 2 h at room temperature the reaction mixture was poured into iced water (2 l) and the resultant solution sorbed on a column (7×10 cm) of AG 50W-X2 resin. The column was washed with water (1 l) and 2 M HCl (~2 l) to remove a minor purple band. The remaining orange-coloured band was eluted with 4 M HCl and the eluate evaporated to dryness. The residue was cautiously (HCl gas evolution!) treated with 96 % sulfuric acid (60 ml) followed, upon completion of the gas evolution, by water (3 ml). The mixture was stirred overnight and was then poured into ice-water (4 l). The resulting solution was sorbed on a column (7×10 cm) of AG 50W-X2 resin which was then washed with water (0.5 l) and 1 M HCl (1 l). Using 2 M HCl the major orange-coloured band was eluted (a minor band remained on the column) and the eluate was concentrated to ~15 ml whence crystallization commenced. This process was completed by addition of acetone (100 ml) and the product was collected, washed with acetone and dried in the air; (12 g, 90 %). Anal. Calcd. for CoC$_7$H$_{20}$Cl$_2$N$_5$O$_3$·HCl·2H$_2$O: Co 13.88, C 19.80, H 5.93, N 16.49, Cl 25.05. Found [Δ(−)$_{589}$ isomer]: Co 13.2, C 19.8, H 5.9, N 16.4, Cl 25.4. ε$_{max}^{487}$ 98, ε$_{max}^{334}$ 116 M^{-1} cm^{-1} (0.10 M Cl). Specific rotations (0.03 %, in 0.10 M HCl; Λ(+)$_{589}$ form): [α]$_{589}$ 420, [α]$_{578}$ 535, [α]$_{546}$ 845, [α]$_{473}^{max}$ −1410, [α]$_{436}$ −1030, [α]$_{365}$ −1000. ¹H NMR (D$_2$O): δ 2.5–3.1 (br, H$_2$NC*H*$_2$C*H*$_2$NH$_2$), 5.47 (s, C*H*(OH)$_2$), 7.59 (s, C*H*O), 4–6 (br, N*H*$_2$); ratio of C*H*(OH)$_2$ to C*H*O: ~20:1. ¹³C NMR (CF$_3$SO$_3$H): δ 113.0 (*C*OO), 95.0 (*C*HO), 37.6, (*C*HCHO), −22.1, −22.9, −23.7, −24.5 (en *C*H$_2$); (D$_2$O): δ 116.4/116.2 (*C*OO), 87.9 (*C*HO), 42.1 (*C*HCH(OH)$_2$), 21.3/21.1 (*C*H(OH)$_2$), −20.9, −21.1, −21.4, −22.0, −22.3, −22.8, −23.3 (en *C*H$_2$).

For one of the isomers [Λ(+)$_{589}$-form], optical purity was ascertained through conversion to the derived serinato complexes by reduction with tetrahydridoborate(III) ion.[6] The isomer (0.25 g) was dissolved in phosphate buffer (0.25 M, pH 7.0, 30 ml) and NaBH$_4$ (0.5 g) was cautiously added in portions (H$_2$ evolution!). The resulting solution was diluted three-fold and sorbed on a column (3×20 cm) of AG 50W-X2 resin in the Na$^+$ form. Elution with the phosphate buffer separated two major orange-coloured bands (a mi-

nor third band remained at the top of the column) and the eluates of these (diluted three-fold) were each sorbed on a column (3×4 cm) of the same resin. After washing with 1 M HCl (0.1 l) to remove Na$^+$ the complexes were eluted in each case with 3 M HCl and the resultant eluates evaporated to dryness. The products were taken up in water and their visible and rotatory dispersion spectra recorded. The maxima of these spectra agreed (to within ±2%) with those of the optically pure $\Lambda(+)_{589}$-[Co(en)$_2$S-serO]$^{2+}$ (first band) and $\Lambda(+)_{589}$-[Co(en)$_2$R-serO]$^{2+}$ (second band) complexes.[9,10]

Δ-[Co(en)$_2$(2S,4S,αR)-penicilloato]ClO$_4$·2H$_2$O (Isomer B) and Δ-[Co(en)$_2$(2S,4S,αS)-penicilloato]ClO$_4$·3H$_2$O (Isomer C). To a solution of $\Delta(-)_{589}$-[Co(en)$_2$C-formylglyO]Cl$_2$·2H$_2$O (1.05 g, 2.5 mmol), NaClO$_4$·H$_2$O (1.05 g, 7.5 mmol) and (S)-penicillamine (0.41 g, 2.7 mmol) in water (5 ml) was added pyridine (0.4 ml, 5 mmol). Upon standing at 20 °C, well-formed orange-red crystals deposited and after 48 h the reaction mixture was warmed to 30 °C, filtered, and the filtrate set aside. The collected crystals were washed with water (2×20 ml) followed by ethanol, and dried in the air. Yield of Δ-[Co(en)$_2$-(2S,4S,αR)-penicilloato]ClO$_4$·2H$_2$O 0.69 g (50%). Anal. Calcd. for CoC$_{12}$H$_{28}$Cl-N$_6$O$_8$S·2H$_2$O: Co 10.78, C 26.36, H 5.90, Cl 6.48, N 15.37, S 5.86. Found: Co 10.5, C 26.1, H 5.8, Cl 6.8, N 15.1, S 5.4.

The filtrate obtained above was kept for a further 24 h at 20 °C to separate crystals of the (2S,4S,αS) isomer (C). These were collected and washed with ethanol (2×20 ml) and ether; (0.23 g, 17%). Anal. Calcd. for CoC$_{12}$H$_{28}$Cl-N$_6$O$_8$S·3H$_2$O: Co 10.43, C 25.52, H 6.07, Cl 6.28, N 14.88, S 5.68. Found: Co 10.8, C 25.8, H 6.2, Cl 6.5, N 14.9, S 5.4.

Δ-[Co(en)$_2$(2S,4S,αS)-penicilloato](ClO$_4$)$_2$·H$_2$O. A solution was prepared as described in the preceding preparation except that 0.2 ml of pyridine was used. After 48 h at 20 °C orange crystals of the title complex (0.46 g) were collected by filtration. To the filtrate was added a solution of NaClO$_4$·H$_2$O (4 g) in water (2 ml) and the mixture was left for a further 4 d, when another 0.72 g of product was obtained. Total yield 1.18 g (75%). Anal. Calcd. for CoC$_{12}$H$_{29}$Cl$_2$N$_6$O$_{12}$S· H$_2$O: Co 9.36, C 22.90, H 4.97, Cl 11.27, N

13.35. Found: Co 9.4, C 22.8, H 4.9, Cl 11.7, N 13.3.

Protonation of Δ-[Co(en)$_2$(2S,4S,αR)-penicilloato](ClO$_4$)·3H$_2$O (0.5 g) in 15 ml of 0.1 M HClO$_4$ containing 30 ml of methanol led to pink needles of the corresponding diperchlorate salt after 3 d at 5 °C. A further quantity was obtained on prolonged standing at −20 °C (total ~0.4 g).

Condensations in Me$_2$SO and HCONMe$_2$. A solution of $\Delta(-)_{589}$-[Co(en)$_2$C-formylglyO]Cl$_2$· HCl·2H$_2$O (0.6 g, 1.4 mmol) and (S)-penicillamine (0.28 g, 1.85 mmol) in Me$_2$SO or HCONMe$_2$ (15 ml) was kept for 5 d at 20 °C. The complexes present in the resultant deep-red solution were precipitated by the addition of 20 ml of EtOH followed by 200 ml of ether. The precipitate was collected and dried over P$_4$O$_{10}$. Diastereoisomer ratios in the products were determined by integration of the signals for the *gem*-dimethyl region in the ^{1}H NMR spectra (0.1 M DCl).

The presence of small quantities of water (5–20%) or 1 equivalent of pyridine in the Me$_2$SO reaction mixture did not alter the isomeric ratios appreciably.

NMR experiments. A solution in 1 ml D$_2$O was made containing 212 mg of $\Delta(-)_{589}$- or $\Lambda(+)_{589}$-[Co(en)$_2$C-formylglyO]Cl$_2$·HCl·2H$_2$O, 82 mg of (S)-penicillamine (1.1 eq.) and 0.04 ml of pyridine. For the high-pH solutions a buffer of 1 M pyridine/0.1 M DCl was used as solvent; this results in a 5:2 ratio of pyridine:DCl. A buffer of 1 M pyridine/0.5 M DCl gives a 3:2 ratio. A low-pH experiment was performed in the absence of pyridine using 0.1 M DCl as solvent. Epimerisation experiments were carried out on approximately 2–5 mg of the appropriate isomer dissolved in the relevant solvent.

Crystal structure determination. A summary of the crystal, experimental and structure refinement data is given in Table 1. Single crystals of both the isomer C and isomer B complex perchlorate salts were of rhombic habit. All X-ray diffraction data were measured using a Syntex *P*2$_1$ four-circle diffractometer with graphite-monochromated Mo*K*α radiation. Unit cell dimensions for each compound were determined from a least-squares fit to the 2θ-values of 14 reflections. Intensities were measured at room temperature

Table 1. Crystal, experimental and refinement data.

Compound name	Isomer C, Δ-(2S,4S,αS)	Isomer B, Δ-(2S,4S,αR)
Formula	$C_{12}H_{28}O_4N_6SCo \cdot ClO_4 \cdot 3H_2O$	$C_{12}H_{28}O_4N_6SCo \cdot ClO_4 \cdot 2H_2O$
Formula weight	564.88	546.86
Space group	Orthorhombic $P2_12_12_1$	Orthorhombic $P2_12_12_1$
a/Å	18.478(6)	15.865(6)
b/Å	12.698(3)	13.142(4)
c/Å	9.889(4)	10.683(4)
U/Å^3	2320(2)	2227(2)
No. of formula units per cell, Z	4	4
Calculated density, D_c/g cm^{-3}	1.617(2)	1.631(2)
Linear absorption coefficient, μ/cm^{-1} [λMo$K\alpha$ = 0.71069Å]	10.4	10.7
Crystal dimensions/mm	0.18×0.27×0.23	0.13×0.18×0.22
Diffractometer	Syntex $P2_1$	Syntex $P2_1$
Monochromator	Graphite	Graphite
Scan type	ω–2θ	ω–2θ
Scan speed; min., max./° s^{-1}	0.081, 0.488	0.081, 0.488
Number of scans per measurement	1	1
Scan range ($a+b$ tan θ); a, b	2.3, 0.7	2.3, 0.7
Diffraction range; min., max./°	2.0, 50.0	2.0, 65.0
Number of intensities measured	4664	4599
Number of independent observations	2308	4400
Refinement type	Blocked matrix	Blocked matrix
Number of variables (final model)	291	281
Least-squares weighting	Unit	Unit
Final R factor	0.045	0.070
Isotropic extinction parameter, r*	3(1)×10^{-4}	Not refined

$^aR = \Sigma|k|F_o| - |F_c||/\Sigma k|F_o|$ summed over all independent observations, where F_o and F_c are the observed and calculated structure factors, respectively, and k is the data scale-factor. ^{b}Ref. 11.

in the ω–2θ scanning mode. Background was measured at each end of each intensity scan. Crystal orientation was checked periodically during data collection; the intensities of three standard reflections in each data set, monitored every 100 intensity measurements, did not vary systematically and the maximum random fluctuation was ±2.5%. After each set of intensity data had been checked for gross systematic errors, Lorentz and polarization factors, but not absorption corrections ($\mu \sim 10.5$ cm^{-1}), were applied and symmetry-equivalent reflections were averaged to yield sets of structure amplitudes used in the subsequent analyses.

Each structure was solved by the heavy-atom method and increasingly detailed structural models were refined by least-squares techniques. For isomer C, in the crystals of which the perchlorate ions are well ordered, the positions of the oxygen atoms of three water molecules of crystallization

and of all the hydrogen atoms were located on a difference map. The perchlorate ions in crystals of isomer B exhibit very large thermal vibration amplitudes (or are somewhat disordered). As a consequence it was not possible to determine the coordinates of the hydrogen atoms of the *gem*-dimethyl groups or of the two water molecules of crystallization, the oxygens of which were located on a difference map. However, the positions of all the other hydrogen atoms could be inferred from geometrical considerations (the bond length to hydrogen was taken as 0.88 Å).

In the final refinement cycles (blocked matrix), the coordinates and anisotropic temperature factors of all non-hydrogen atoms, a scale-factor and, for isomer C, an isotropic extinction parameter were varied. The contributions from the hydrogen atoms, each of which was assigned an isotropic temperature factor slightly greater than the equivalent isotropic factor for the atom to

40

which it was bonded, were included but none of their parameters was refined. All observations were included (no "less-thans" cut-off) with equal weight.

Owing to the large thermal motion of the perchlorate ions and water molecules in the isomer B crystals the final structure for isomer C is considered to be significantly the more accurate.

The absolute configuration of each complex was determined from anomalous dispersion effects exhibited by the X-ray diffraction data.

Atomic scattering factors for the non-hydrogen atoms were computed from numerical Hartree-Fock wave functions[12] and were corrected for anomalous dispersion.[13] The atomic scattering factor of Stewart, Davidson and Simpson[14] was used for hydrogen. Computations were performed with The XRAY System,[15] modified locally for the Perkin-Elmer 3240 computer.

Results

$\Lambda(+)_{589}$- and $\Delta(-)_{589}$-[Co(en)$_2$C-formylglyO]$^{2+}$. The racemic [Co(en)$_2$glyO]$^{2+}$ complex was obtained from [Co(en)$_2$CO$_3$]Cl[8] in a facile synthesis. The procedure for the subsequent resolution employing [Sb$_2$((+)$_{589}$-tart)$_2$]$^{2-}$ as the resolving agent has been reported previously with sparse experimental detail,[16,17] and a more detailed report has therefore been given here. Introduction of a formyl group on the methylene carbon atom of the chelated glycinate ligand to yield the $\Lambda(+)_{589}$- or $\Delta(-)_{589}$-[Co(en)$_2$C-formylglyO]$^{2+}$ complexes was achieved (via the Vilsmeier-Haack reaction) in essentially the same manner as described for the similar, but achiral [Co(tren)glyO]$^{2+}$ complex.[5,6]

In anhydrous CF$_3$SO$_3$H medium the ^{13}C NMR spectrum indicates that the [Co(en)$_2$C-formylglyO]$^{2+}$ ion is present as the free aldehyde. How-

ever, in D$_2$O solution both the ^{1}H and ^{13}C NMR spectra are consistent with the aldehyde being present almost entirely in hydrated form, the free aldehyde now constituting $\leq 5\%$ (based on the ^{1}H NMR integration). This is consistent with previous observations for the [Co(tren)C-formylglyO]$^{2+}$ system. In the present system, which contains two chiral centres (the metal centre and the methine carbon centre of the amino acid chelate), the ^{13}C NMR spectrum in D$_2$O reflects the presence of both diastereoisomeric forms (~1:1) of the hydrated aldehyde complex, since all the expected resonances appear as double peaks with a pair separation of $\Delta\delta \leq 0.2$ ppm. Such doubling is not seen in the ^{13}C spectrum in CF$_3$SO$_3$H, in spite of the fact that two diastereoisomeric forms of the non-hydrated [Co(en)$_2$C-formylglyO]$^{2+}$ ion (for the Δ complex: αR–Δ–2 and αS–Δ–2) would also be expected. It seems highly unlikely that one diastereoisomer should dominate entirely over the other in this case since no such high degree of stereoselectivity has so far been seen in closely related systems with even more bulky substituents. The simplicity of the ^{13}C NMR spectrum in CF$_3$SO$_3$H may therefore be rationalized in terms of an interconversion process (illustrated here for the αR–Δ and αS–Δ forms) which is rapid on the NMR time-scale. Such fast interconversion could occur via a planar enol (3) species (Scheme 2), produced by protonation of the carbonyl oxygen and loss of a proton at the strongly activated methine centre. The single observed signal would imply that the aldehyde forms are dominant and that the enol 3 is, on average, a relatively minor and short-lived component. Strong evidence that deprotonation at the "inner" methine (α) carbon atom occurs readily is provided by the ^{1}H NMR data in D$_2$O. Whereas the resonance attributable to the $-CH(OH)_2$
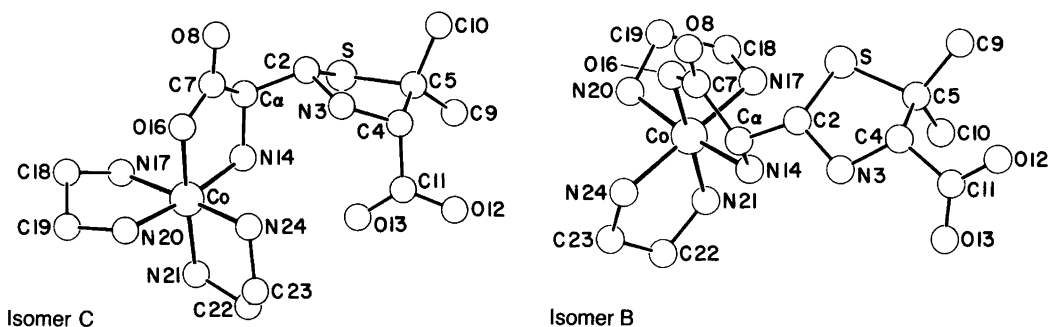

αR – Δ – 2 Δ – 3 αS – Δ – 2
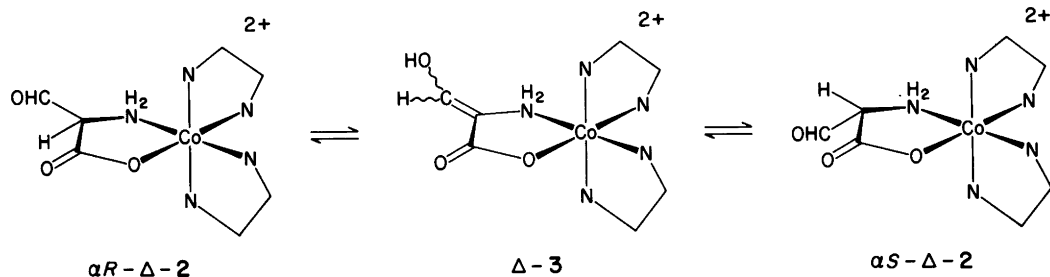
Scheme 2.

Fig. 1. Molecular geometry and atom numbering in Δ-[Co(en)₂(2*S*,4*S*,α*S*)-penicilloato]⁺ (Isomer C) and Δ-[Co(en)₂(2*S*,4*S*,α*R*)-penicilloato]⁺ (Isomer B). Hydrogen atoms have been omitted for clarity.

Table 2. Atomic fractional coordinates of non-hydrogen atoms for Δ-[Co(en)₂(2*S*,4*S*,α*R*)-penicilloato]ClO₄ · 2H₂O (isomer B) and Δ-[Co(en)₂(2*S*,4*S*,α*S*)-penicilloato]ClO₄ · 3H₂O (isomer C).

	Isomer B			Isomer C		
Atom	x/a	y/b	z/c	x/a	y/b	z/c
S1	0.0527(1)	−0.0940(1)	−0.0318(1)	0.2693(1)	0.2580(1)	0.3110(2)
C2	0.1496(4)	−0.1288(4)	0.0582(5)	0.2541(3)	0.1907(4)	0.4709(7)
N3	0.1225(3)	−0.1595(4)	0.1822(4)	0.3046(3)	0.2368(4)	0.5699(5)
C4	0.0439(3)	−0.2168(4)	0.1646(5)	0.3390(3)	0.3356(5)	0.5246(7)
C5	−0.0186(4)	−0.1498(5)	0.0862(5)	0.2966(3)	0.3782(5)	0.4019(7)
Cα	0.2149(4)	−0.0439(4)	0.0523(5)	0.2689(3)	0.0732(5)	0.4524(5)
C7	0.2418(4)	−0.0292(4)	−0.0850(5)	0.2492(3)	0.0137(5)	0.5848(6)
O8	0.2566(4)	−0.1027(3)	−0.1491(5)	0.1911(2)	0.0343(3)	0.6421(5)
C9	−0.0854(5)	−0.2146(6)	0.0181(8)	0.3398(4)	0.4456(6)	0.3007(8)
C10	−0.0592(5)	−0.0646(6)	0.1642(7)	0.2299(4)	0.4409(6)	0.4469(9)
C11	0.0051(4)	−0.2557(5)	0.2881(6)	0.4199(3)	0.3213(5)	0.4955(7)
O12	−0.0519(3)	−0.3218(4)	0.2762(4)	0.4563(3)	0.4053(4)	0.5069(7)
O13	0.0304(4)	−0.2211(5)	0.3875(4)	0.4430(2)	0.2335(4)	0.4622(6)
N14	0.1851(3)	0.0566(3)	0.1042(4)	0.3454(2)	0.0512(4)	0.4164(5)
Co15	0.2202(0)	0.1678(1)	−0.0079(1)	0.3816(0)	−0.0662(1)	0.5252(1)
O16	0.2447(3)	0.0636(3)	−0.1246(4)	0.2938(2)	−0.0548(3)	0.6271(4)
N17	0.1041(3)	0.1800(4)	−0.0763(5)	0.3357(3)	−0.1680(4)	0.4006(5)
C18	0.0996(4)	0.2679(6)	−0.1615(7)	0.3224(3)	−0.2672(5)	0.4762(7)
C19	0.1822(5)	0.2738(6)	−0.2319(6)	0.3873(4)	−0.2884(5)	0.5627(7)
N20	0.2521(3)	0.2660(4)	−0.1396(5)	0.4047(3)	−0.1902(4)	0.6380(5)
N21	0.1983(3)	0.2736(4)	0.1159(5)	0.4745(3)	−0.0702(4)	0.4305(5)
C22	0.2735(6)	0.3019(7)	0.1885(9)	0.5250(5)	0.0079(5)	0.4926(7)
C23	0.3487(6)	0.2658(8)	0.1319(11)	0.5080(4)	0.0194(6)	0.6412(8)
N24	0.3359(3)	0.1690(5)	0.0598(5)	0.4287(3)	0.0283(4)	0.6526(5)
Cl25	0.3307(2)	0.4593(2)	0.4765(3)	0.1169(1)	−0.2391(1)	0.4056(2)
O26	0.3830(5)	0.5247(6)	0.5465(8)	0.1619(3)	−0.1486(4)	0.3878(6)
O27	0.2625(6)	0.5124(6)	0.4296(12)	0.0587(3)	−0.2352(5)	0.3085(6)
O28	0.3044(8)	0.3728(7)	0.5255(17)	0.0867(4)	−0.2426(6)	0.5398(6)
O29	0.3852(8)	0.4288(16)	0.3792(13)	0.1582(3)	−0.3314(4)	0.3801(8)
O30	0.0635(4)	0.0271(5)	0.4173(7)	0.5179(3)	0.5526(4)	0.3306(5)
O31	0.0717(5)	0.0333(17)	0.6811(7)	0.5934(2)	0.4069(4)	0.5900(5)
O32				0.5575(4)	0.2393(5)	0.2774(6)

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methine proton in D_2O appears as a sharp singlet, we find no sign of the "inner" methine proton, the implication being that this has exchanged with solvent D^+. This exchange process would be expected to be more strongly activated for the free aldehyde than for the hydrated form.

When treated with $NaBH_4$ at pH 7, the $\Lambda(+)_{589}$-[Co(en)$_2$C-formylglyO]$^{2+}$ ion produced a 1:1 mixture of the serinato complexes $\Lambda(+)_{589}$[Co(en)$_2$S-serO]$^{2+}$ and $\Lambda(+)_{589}$-[Co(en)$_2$ R-serO]$^{2+}$. Each isomer was optically pure ($\pm 2\%$), which established that the synthesis of the [Co(en)$_2$C-formylglyO]$^{2+}$ complex from [Co(en)$_2$glyO]$^{2+}$ proceeds with retention of configuration.

Table 3. Bond distances (Å) and angles (°) for isomer C and isomer B. Estimated standard deviations in units of the last significant digit are given in parentheses.

A. Distances

Bond	Isomer B	Isomer C
S1–C2	1.870(6)	1.818(7)
–C5	1.846(6)	1.842(7)
C2–N3	1.450(7)	1.474(8)
–Cα	1.524(8)	1.529(8)
N3–C4	1.469(7)	1.476(8)
C4–C5	1.568(8)	1.543(10)
–C11	1.543(8)	1.534(9)
C5–C9	1.542(10)	1.539(11)
–C10	1.537(10)	1.534(10)
Cα–C7	1.541(8)	1.554(8)
–N14	1.508(7)	1.483(7)
C7–O8	1.207(7)	1.243(7)
–O16	1.292(7)	1.269(7)
C11–O12	1.259(8)	1.265(8)
–O13	1.223(8)	1.238(8)
N14–Co	1.970(5)	1.957(5)
Co–O16	1.892(4)	1.916(4)
–N17	1.988(5)	1.977(5)
–N20	1.975(5)	1.976(5)
–N21	1.950(6)	1.956(5)
–N24	1.973(5)	1.945(5)
N17–C18	1.472(9)	1.485(8)
C18–C19	1.512(10)	1.497(10)
C19–N20	1.487(9)	1.487(8)
N21–C22	1.471(11)	1.494(8)
C22–C23	1.419(14)	1.510(11)
C23–N24	1.500(13)	1.475(8)
Cl25–O26	1.409(9)	1.429(6)
–O27	1.382(10)	1.442(6)
–O28	1.319(12)	1.440(6)
–O29	1.410(15)	1.421(6)

B. Angles

Angle	Isomer B	Isomer C
C2–S1–C5	93.1(3)	90.4(3)
S1–C2–N3	107.1(4)	107.1(4)
–Cα	111.0(4)	109.1(4)
N3–C2–Cα	116.3(5)	110.7(5)
C2–N3–C4	106.1(4)	114.1(5)
N3–C4–C5	108.5(5)	108.5(5)
–C11	113.5(4)	112.1(5)
C5–C4–C11	113.0(5)	112.9(5)
S1–C5–C4	101.6(4)	103.5(4)
–C9	108.5(4)	106.6(5)
–C10	109.7(5)	110.6(5)
C4–C5–C9	112.1(5)	116.3(6)
–C10	112.6(5)	111.2(6)
C9–C5–C10	111.7(5)	108.5(6)
C2–Cα–C7	108.6(4)	109.4(4)
–N14	114.4(5)	112.5(4)
C7–Cα–N14	109.1(4)	109.5(4)
C6–C7–O8	119.6(5)	119.0(5)
–O16	116.1(5)	117.3(5)
O8–C7–O16	124.3(5)	123.7(5)
C3–C11–O12	115.3(5)	113.7(6)
–O13	119.3(6)	119.4(6)
O12–C11–O13	125.4(6)	126.9(6)
C6–N14–Co	109.7(3)	109.7(3)
N14–Co–O16	85.5(2)	86.7(2)
–N17	91.2(2)	90.5(2)
–N20	172.0(2)	172.4(2)
–N21	93.8(2)	93.3(2)
–N24	92.6(2)	92.2(2)
O16–Co–N17	90.4(2)	90.8(2)
–N20	87.2(2)	86.9(2)
–N21	177.9(3)	175.7(2)
–N24	93.2(2)	89.5(2)
N17–Co–N20	85.6(2)	85.6(2)
–N21	91.6(2)	93.5(2)
–N24	174.9(2)	177.3(2)
N20–Co–N21	93.6(2)	93.5(2)
–N24	91.0(2)	91.7(2)
N21–Co–N24	84.9(2)	86.2(2)
C7–O16–Co	117.4(4)	115.3(4)
Co–N17–C18	109.5(4)	108.1(4)
N17–C18–C19	107.8(5)	108.0(5)
C18–C19–N20	108.2(5)	107.9(5)
Co–N20–C19	109.0(4)	109.8(4)
Co–N21–C22	113.2(5)	109.6(4)
N21–C22–C23	111.9(8)	109.5(5)
C22–C23–N24	112.9(8)	106.8(5)
Co–N24–C23	108.7(5)	110.4(4)
O26–Cl25–O27	110.2(5)	108.9(4)
–O28	120.1(8)	111.3(4)
–O29	101.8(8)	109.2(3)
O27–Cl25–O28	109.3(7)	109.0(4)
–O29	110.9(8)	108.1(4)
O28–Cl25–O29	104.0(11)	110.3(4)

Structural results. Two isomers of the cobalt(III) complexes with coordinated penicilloate were isolated as monoperchlorate salts suitable for X-ray crystallographic analyses. They are denoted isomers B and C in the Experimental and the structures of the cations are shown in Fig. 1. The absolute configurations of the chiral centres have been deduced by the anomalous dispersion method, from the known configuration of the (S)-penicillamine and from the rotatory dispersion of the (en)₂Co-aminoacidato complex. All three methods give consistent results for all the chiral centres. Table 2 gives the atomic fractional coordinates for non-hydrogen atoms and Table 3 gives bond lengths and angles for the two structures. Tables of atomic fractional coordinates for all atoms and tables of thermal parameters and structure factor amplitudes are available on request from one of the authors (A.H.).

¹H NMR spectra of the penicilloate diastereoisomers. Data for the ¹H NMR spectra due to the penicilloate ligands in the characterised $(2S,4S,\alpha R)$ (B) and $(2S,4S,\alpha S)$ (C) penicilloato complexes are given in Table 4. Also tabulated are the spectra of the other two diastereoisomers which are derived by epimerisation at the C-2 atom. Their syntheses and structural assignments will be reported later. Comparing the spectra of the neutral monoperchlorate salts in 0.1 M DCl/D₂O and in D₂O alone, it can be seen that the peak positions and the coupling constants are pH-dependent. For product identification purposes it is therefore necessary to record ¹H NMR spectra under standard conditions. The best comparisons were made using 0.1 M DCl in D₂O, where $[D^+] \gg [Co^{3+}]$. It was found most convenient to characterise the isomers by the *gem*-dimethyl sig-

nals (δ 1–2 ppm) for the pair of chemically inequivalent methyl groups in each diastereoisomer.

Assignments of the peaks in the spectra are straightforward. The singlets at $\delta \sim 4$ ppm are attributed to the C-4 protons, and the remaining doublets to the adjacent C-2 and C-α protons. In 0.1 M DCl, the signal at δ 4.29 (B) or 4.02 (C) was initially a multiplet but changed to a doublet during one day. A doublet was also observed immediately in neutral D₂O. The multiplet arises from coupling of the coordinated NH₂ protons with the chelate methine proton. Slow exchange of these NH₂ protons with D₂O leads to the doublet signal for the C-α hydrogens. The chemical shifts for the methine protons are consistent with those observed for the diastereoisomers of the analogous bis(ethylenediamine)alaninato complex,[18] which shows quartets for the methine hydrogen centered at about δ 3.9 ppm.

The remaining doublet of the penicilloato complexes is ascribed to the C-2 proton which is coupled to the C-α hydrogen.

Preparation and identification of penicilloato compexes. (a) Aqueous solution. The reaction of $\Delta(-)_{589}$-[Co(en)₂*C*-formylglyO]²⁺ with (S)-penicillamine in pyridine buffer (pH ~ 4–5) gave only two isolable diastereoisomers; these could be selectively precipitated as the 1+ or 2+ perchlorate salts, depending on reaction conditions. For instance, the reaction in the presence of 2 equiv. of pyridine (added to neutralise the HCl of crystallisation) and 3 equiv. of sodium perchlorate gave large, orange crystals of the $\Delta(-)_{589}$-[Co(en)₂$(2S,4S,\alpha R)$-penicilloato]ClO₄ · 2H₂O salt in 50 % yield. Upon standing, a second fine, orange precipitate of the $(2S,4S,\alpha S)$ isomer appeared, having the same constitution. At lower

Table 4. Selected ¹H NMR data for $\Delta(-)_{589}$-[Co(en)₂penicilloato]²⁺/³⁺ complex isomers.[a]

Solvent	Isomer		(CH₃)₂		C(4)H	C(α)H	C(2)H	J(H-α,H-2)
0.1 M DCl	(A)	$(2R,4S,\alpha R)$[b]	1.39	1.65	4.37	4.03	5.30	4 Hz
	(B)	$(2S,4S,\alpha R)$[c,d]	1.55	1.74	4.45	4.29	5.39	9 Hz
	(C)	$(2S,4S,\alpha S)$[c,d]	1.48	1.62	4.12	4.02	5.32	2 Hz
	(D)	$(2R,4S,\alpha S)$[e]	1.51	1.76	4.63	4.01	5.47	10 Hz
D₂O	(B)	$(2S,4S,\alpha R)$[c]	1.36	1.60	3.60	4.23	5.17	3 Hz
	(C)	$(2R,4S,\alpha S)$[c]	1.38	1.51	3.60	3.76	5.16	2 Hz

[a]Signals due to penicilloato ligands only. [b]Diperchlorate. [c]Monoperchlorate. [d]Spectrum identical to that for diperchlorate. [e]Deduced from epimerisation experiments.

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pH, in the presence of one equiv. of pyridine, only one isomer crystallised under similar conditions, in 75 % yield as a 2+ ion. This compound, whose ^{1}H NMR spectrum showed it to be the $(2S,4S,\alpha S)$ isomer, gave an IR spectrum containing a band at 1725 cm^{-1} consistent with a COOH

group. It also dissolved in water to give an acidic solution.

The course of the condensation reaction in 0.1 M DCl and in buffers consisting of 3:2 and 5:2 ratios of pyridine to DCl was also followed by NMR. The various diastereoisomers were readily identified (vide infra). In the pyridine buffers, signals for two isomers only were clearly visible, their NMR spectra matching those of the two complexes whose structures have been established. The condensation is pH-dependent. In the 5:2 pyridine/DCl buffer a ratio of 70:30 for the $(2S,4S,\alpha R)$ (B) to the $(2S,4S,\alpha S)$ (C) isomers was seen after 29 h, whilst in the 3:2 buffer the corresponding ratio was 35:65 after 50 h. Upon prolonged standing some Co(II) was produced, thereby broadening the peaks in the spectrum.

In 0.1 M DCl, ^{1}H NMR measurements (Fig. 2) showed the situation to be very different; only a trace of the $(2S,4S,\alpha R)$ isomer appeared, two major products again being formed. These are the $(2S,4S,\alpha S)$ isomer (C) and its acid epimerisation product, deduced to be the $(2R,4S,\alpha S)$ form (vide infra). Initially, the former isomer predominates, implying kinetic control of its formation; however, in time the latter isomer predominates. It is evident that in D$_2$O solution, the C-α proton is lost to solvent and replaced by deuterium.
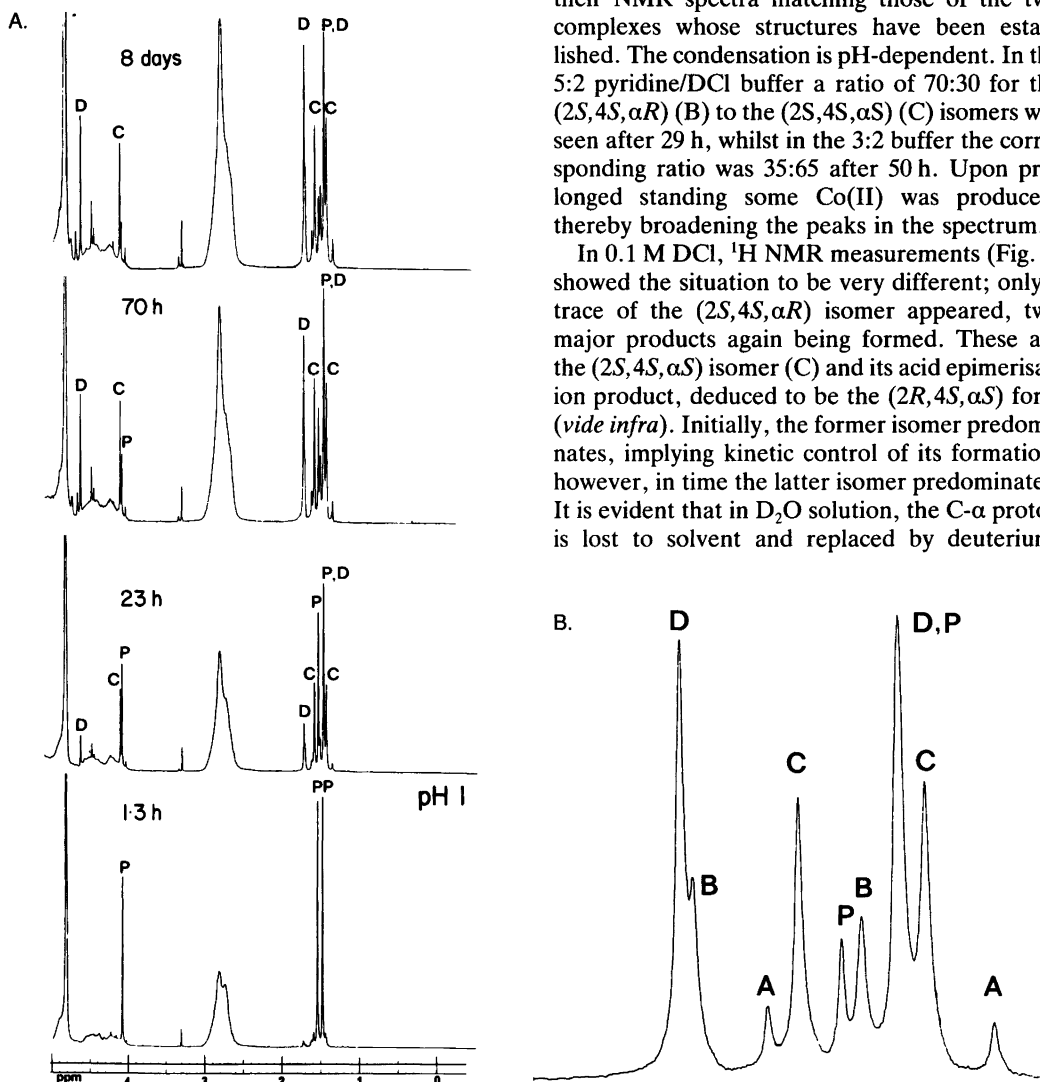
Fig. 2. (A) ^{1}H HMR spectra measured over a period of 8 days showing the course of the condensation of (S)-penicillamine with $\Delta(-)_{589}$-[Co(en)$_2$C-formylglyO]Cl$_2$ in 0.1 M DCl (details given in the experimental section). (B) Expansion of the gem-dimethyl region (1–2 ppm) for the spectrum obtained after 8 days. Abbreviations used are: P, (S)-penicillamine; A, the $(2R,4S,\alpha R)$-penicilloato isomer; B, the $(2S,4S,\alpha R)$ isomer; C, the $(2S,4S,\alpha S)$ isomer; D, the $(2R,4S,\alpha S)$ isomer.

However, the C-4 methine proton, which appears as a singlet, is clearly visible for the major isomers as well as for penicillamine. After 23 h, the signal for the (2S,4S,αS) isomer is growing at a faster rate than that for the (2R,4S,αS) form. After 70 h, however, the two species are present in roughly equal concentrations, and after 8 days the latter isomer is in excess. A similar effect is seen on examining the *gem*-dimethyl region. The spectrum for the methyl region after 8 days reveals, on expansion, the presence of all four isomers, although two of these are minor components.

The reaction of the $\Lambda(+)_{589}$-[Co(en)$_2$C-formylglyO]$^{2+}$ isomer was also studied, although in a much less thorough way. Interpretation of results is hampered by the fact that we were unable to isolate any isomerically pure samples. It should be stressed that without samples suitable for X-ray structure determination it is not possible to make stereochemical assignments readily. A ^{1}H NMR study of the condensation reaction in the

5:2 pyridine/DCl buffer system showed, however, the formation of only two major isomers.

(b) Me$_2$SO and HCONMe$_2$ solution. The $\Delta(-)_{589}$-[Co(en)$_2$C-formylglyO]Cl$_2$ · HCl · 2H$_2$O salt is sufficiently soluble in Me$_2$SO or HCONMe$_2$ to allow the condensation reaction to occur. Quenching of the reaction by addition of ether gave a powder which was a mixture of penicilloato complex isomers. ^{1}H NMR analysis of this powder in 0.1 M DCl showed that all four diastereoisomers were formed in both solvents and

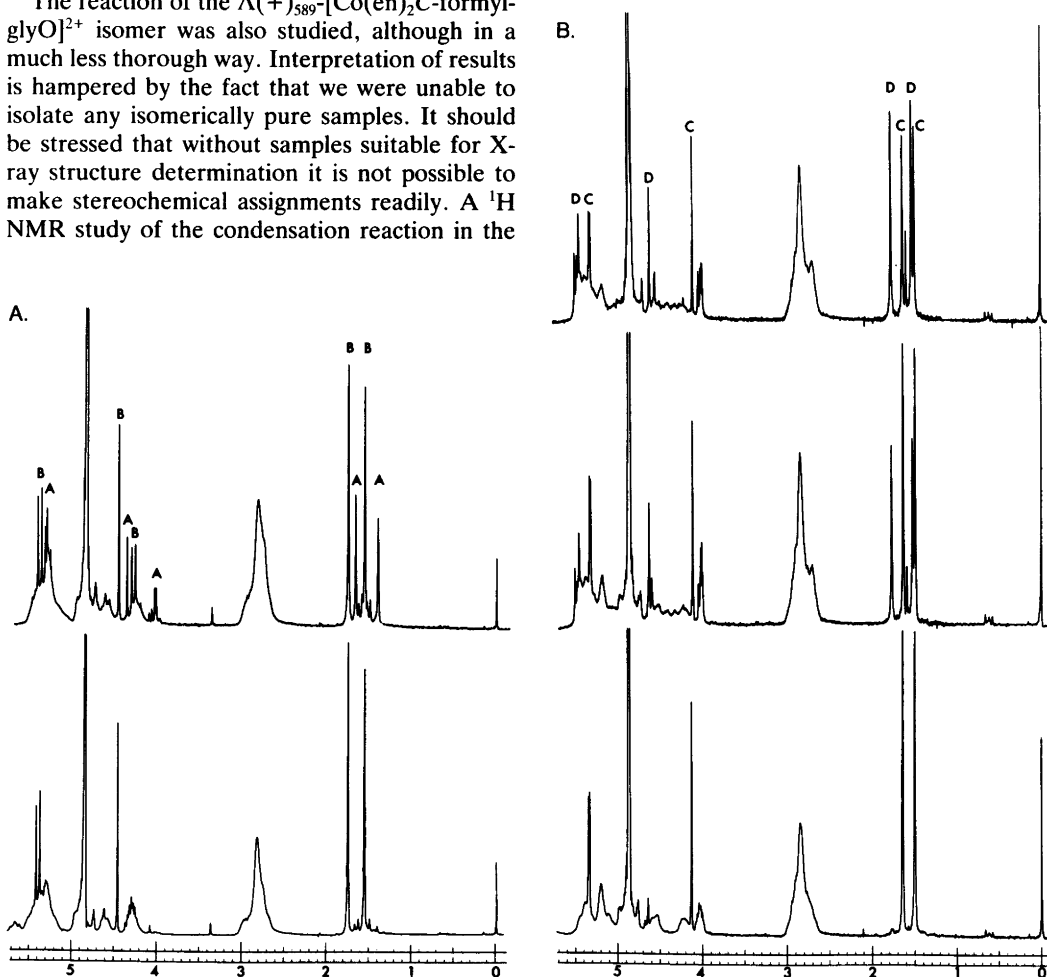*Fig. 3.* (A) ^{1}H HMR spectra of the (2S,4S,αR)-penicilloato complex (isomer B) immediately after dissolution (lower) and after 24 h (upper) showing the formation of the (2R,4S,αR) isomer (isomer A). (B) ^{1}H NMR spectra of the (2S,4S,αS)-penicilloato complex (C) immediately after dissolution (lower) and after 24 h (middle) and 46 h (upper), showing the formation of the (2R,4S,αS) isomer (isomer D).

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that the reaction was substantially complete within five days at 20 °C. Apart from those signals due to the (2S,4S,αS) and (2S,4S,αR) isomers, another two pairs of signals were visible in the *gem*-dimethyl region. Fractional crystallisation of the products from the reaction mixture in Me₂SO lead to reasonably pure samples of a new isomer (A), as well as the (2S,4S,αR) (B) form isolated as the monoperchlorate salt. This preparation, however, was difficult to reproduce.

Isomer interconversion. The stereochemical rearrangements of the diastereoisomers under a variety of conditions were studied using ¹H NMR spectroscopy. In neutral, unbuffered solution, the (2S,4S,αS) (C) and (2S,4S,αR) (B) isomers were stable for at least two days and no sign of change was observed. At higher pH the solutions darken rapidly and considerable decomposition occurs. In 0.1 M DCl solution, however, the isomers rearrange. Fig. 3A shows the ¹H NMR spectrum of the (2S,4S,αR) isomer a few minutes after dissolution in this solvent and after standing for 24 h at 20 °C. In the latter spectrum, signals due to two species are visible, viz. those for the (2S,4S,αR) (B) isomer and signals due to another species (A). The latter has a distinct spectrum which is still characteristic of a penicilloate isomer: Thus, in the methyl region another pair of peaks has appeared while in the downfield region a singlet due to the C-4 proton, as well as two doublets with small coupling constants, due to the C-2 and C-α protons, are present. Integration of the signals revealed that the reaction proceeded to give an equilibrium ratio of the

(2S,4S,αR) (B) isomer to the A isomer of about 70:30. The equilibrium was established more rapidly in 1 M DCl, the ratio being around 80:20. The new isomer (A) has the same spectrum, under identical solvent conditions, as isomer A isolated from the reaction in Me₂SO. A sample of this compound, when dissolved in 0.1 M DCl, isomerises to the same equilibrium mixture as the (2S,4S,αR) isomer under the same conditions.

Similarly, the (2S,4S,αS) (C) diastereoisomer also isomerises in acid (Fig. 3B) to give an equilibrium mixture (ca. 60:40 in favor of the new isomer D). In this reaction mixture the doublet signals for the C-α protons are superimposed, whereas the remaining signals are separated. In 1 M DCl, the equilibrium was attained more rapidly and lay almost entirely in favor of isomer (D). This new isomer had a ¹H NMR spectrum identical to that for the remaining diastereoisomer formed in the condensation in Me₂SO or HCONMe₂.

Both the (2S,4S,αR) (B) isomer and the isomer generated in acidic conditions (A) decompose in acid, on a much slower time scale, to give some free penicillamine, some of the (2S,4S,αS) (C) isomer and isomer D (*vide infra*).

During the course of all the reactions in acidic D₂O, neither the C-2 nor the C-α protons exchange with deuterons. Their signals remain as doublets.

Discussion

The mechanism of thiazolidine formation by the condensation of cysteine with formaldehyde has
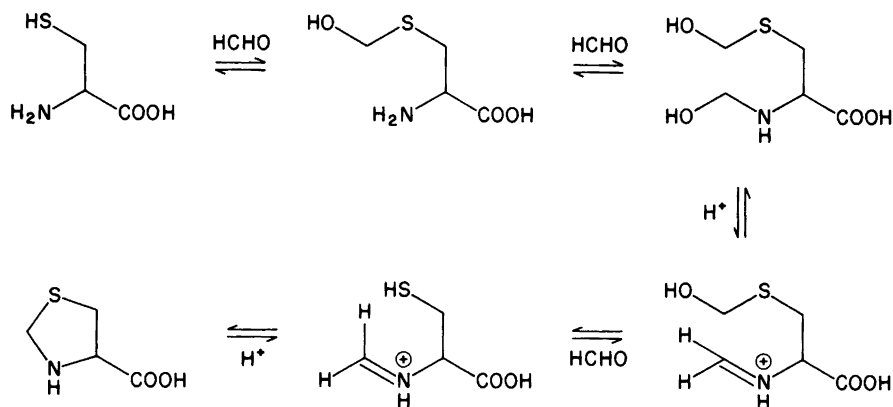
Scheme 3.

been well studied.[19] In acidic solution, and in the absence of a large excess of aldehyde, the equilibria which lead to ring closure may be summarised[19] as in Scheme 3. The equilibrium constant for the formation of thiazolidine-4-carboxylic acid from cysteine and formaldehyde is large,[20] and by analogy it is to be expected that the condensation of 2 (Scheme 2) with penicillamine will also be thermodynamically favorable. The inclusion of the *gem*-dimethyl group in the five-membered ring will serve to increase the rate of cyclization via the Thorpe-Ingold effect.[21] A mechanism similar to that depicted in Scheme 3, in which penicillamine replaces cysteine and 2 replaces formaldehyde, may be applied to the formation of the penicilloato complexes in the present study.

Although, in general, short-chain and electron-deficient aldehydes exist to a large extent as the hydrates in aqueous solution, the active species is undoubtedly the unhydrated free carbonyl form.[22] In acidic solution, the rate-determining step for the synthesis of thiazolidine-4-carboxylic acid is the formation of the carbinolamine by reaction of the amine with the aldehyde, rather than the subsequent dehydration or cyclisation steps.[19] The thiol is more reactive than the amine towards the aldehyde but the reverse reaction is sufficiently fast to allow access to the free thiol for cyclisation. Dehydration of the carbinolamine is expected to be general acid-catalyzed and not rate-determining[19] at pH < 6. Reaction via attack of thiol on the iminium ion is preferred to nucleophilic displacement of hydroxide ion or water from the carbinolamine and is analogous to other reactions of the iminium group. Cyclisation via the attack of amine on the thionium ion ($R_2C = S^+ - R'$) may also be considered, although this would seem unlikely[19] as a route because of the inferior stability of the thionium ion relative to the iminium ion.

For the condensations leading to the penicilloato complexes of this study we propose a general mechanism involving an iminium intermediate. Here, the mechanism (Scheme 4) is argued for the specific case involving the Δ-[Co(en)$_2$-(αR)-*C*-formylglyO]$^{2+}$ ion as a reagent to give the (αS,4S)-penicilloato isomers 6 and 7. As discussed above, the *C*-formylglycinato complex exists in solution as an equilibrium mixture of the αR and αS isomers. However, the argument would be completely parallel for the situation

starting with the Δ-[Co(en)$_2$(αS)-*C*-formylglyO]$^{2+}$ isomer. Depending on the face at which the sulfur atom attacks the iminium double bond in 5, the 2R (6) or 2S (7) isomers may arise. This mechanism is consistent with the results of the isomerisation experiments starting with authentic (2S,4S,αR) (B) and (2S,4S,αS) (C) diastereoisomers in 0.1 M DCl solution. Each of these complexes isomerises to give an equilibrium mixture containing itself and one other diastereoisomer. These isomerisations proceed with retention of the C-α and C-2 hydrogen atoms, both of which are seen throughout by their doublets in the ¹H NMR spectra. Isomerizations in acidic solution therefore occur about the C-2 centre. It is difficult to see how the configurations about C-α and C-4 centres could invert without the loss (and hence exchange) of a proton. By implication, the logical mechanism for inversion at C-2 without loss of its proton is via the imine 5, involving ring opening and ring closing with breaking of the C(2)-S bond. The results preclude isomerization through dissociation to penicillamine and the formylglycine complex followed by reformation, a situation which would lead to C-α proton exchange. Furthermore, the (2S,4S,αR) and (2S,4S,αS) isomers do not interconvert in acid, which is also consistent with a stable configuration at the C-α atom. A mechanism involving the formation of an enamine intermediate through loss of the C-α proton is also excluded. If inversion at the C-4 centre had occurred, more isomers would have been evident.

On the basis of this analysis, it is possible to assign the stereochemistry of the acid epimerization products for which there are no crystal structures. The mechanism outlined in Scheme 4 implies that the isomerization is in fact an epimerisation at C-2 with the stereochemistry at C-α unchanged. It follows that the configuration of the isomer which is interconvertible with the (2S,4S,αR) (B) isomer in acidic solution is (2R,4S,αR) (A), i.e. the complex of the naturally occurring penicilloic acid anion. Similarly, the C-2 epimer of the (2S,4S,αS) (C) 7 form is the (2R,4S,αS) (D) 6 diastereoisomer. In this way, all four of the diastereoisomers were identified.

The condensation of Δ-[Co(en)$_2$C-formylglyO]$^{2+}$, 2, with (S)-penicillamine exhibits varying degrees of stereoselectivity under the different conditions. In 0.1 M DCl, the Δ-(2S,4S,αS) (C) 7 diastereoisomer is formed initially as a ki-

netically controlled product before subsequent isomerization to the Δ-(2R,4S,αS) (D) **6** form. Under these conditions only a little of the two diastereoisomers is formed. In decreasingly acidic conditions, the Δ-(2S,4S,αR) (B) isomer is formed in significant amounts. In aqueous pyridine/HCl buffers, only the (2S,4S,αS) (C) and (2S,4S,αR) (B) isomers are formed. No acid epi-

merisation products were observed under these last conditions. The change in the (2S,4S,αR)/ (2S,4S,αS) isomer ratio on going from 3:2 to 5:2 pyridine/DCl buffers (35/65 to 70/30) is quite substantial and the pH change is only ~0.3. It seems likely that this effect is associated with critical ionisation of the reactants. When the condensation is carried out in the presence of two equiv. of
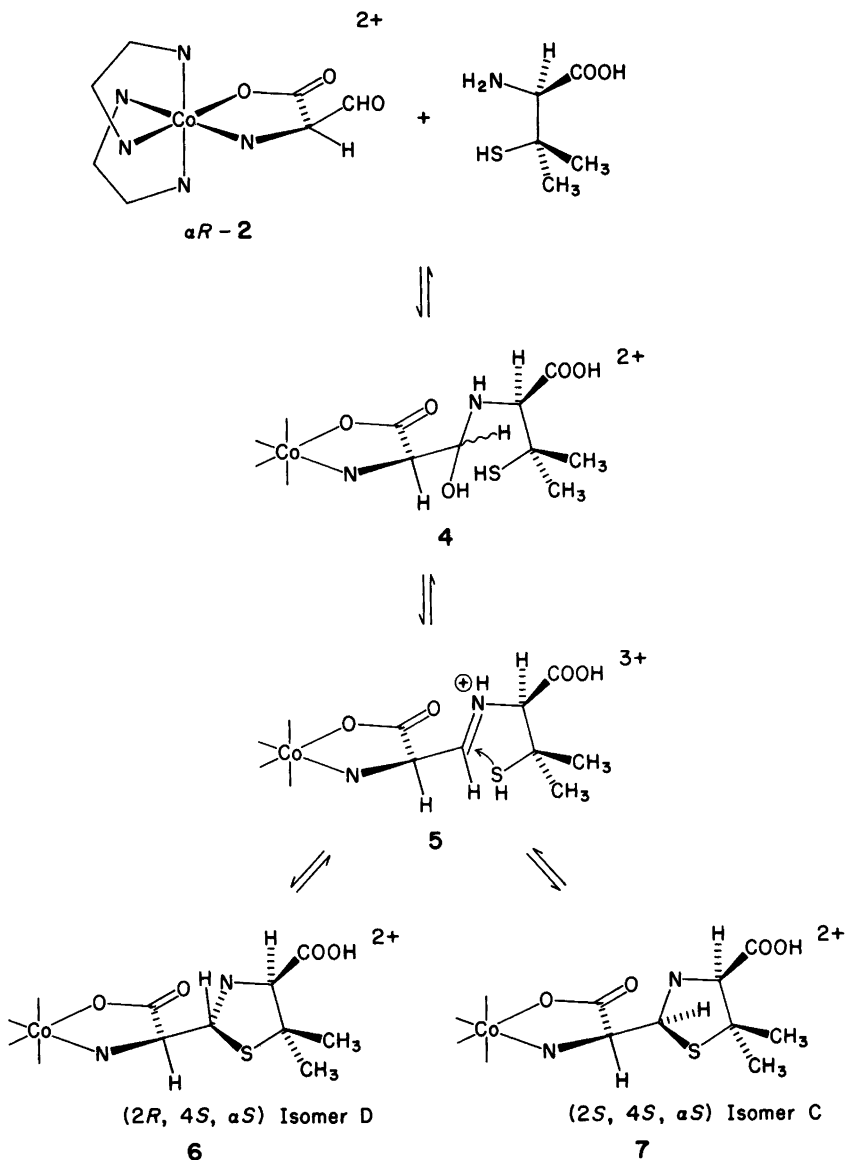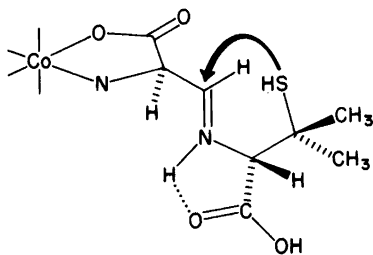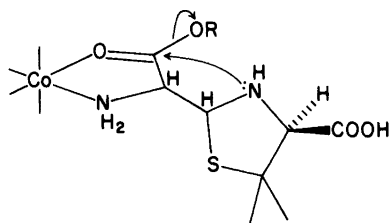

Scheme 4.

pyridine, the resulting penicilloato complexes crystallize as the monovalent (carboxylate) forms, whilst with one equivalent of base, the acid salts are obtained. In Me_2SO and $HCONMe_2$, the stereoselectivity is far less pronounced. The proportions of each isomer were approximately (Me_2SO reaction): A, 30; B, 10; C, 30; D, 30 % and ($HCONMe_2$ reaction): A, 20; B, 5; C, 35; D, 40 %.

Some discussion of the stereoselectivity seems warranted. Firstly, consider the thiazolidine formation, in particular the role of the asymmetric centre in (S)-penicillamine. This process is a 5-endocyclic ring closure,[23] argued to be "disfavoured" for a system composed entirely of first-row elements but "allowed" in this case since sulfur is involved.[24] Several models[25] are available for the prediction of the stereochemistry associated with addition to unsaturated carbon atoms, although as far as we are aware, thiazolidine formation has not been treated theoretically. The stereochemistry of the iminium group is important and it has been demonstrated[26] that in organic solvents, aldimines exist exclusively in the *E* rather than the *Z* configurations. Given that this stability also applies to the aqueous condensations, the preferred rotamer is as shown in Schemes 4 and 5. Addition of the S atom (Scheme 5) would occur below the plane to generate the observed (S) stereochemistry about the thiazolidine C-4 atom. H-bonding between the imine and the carboxylate group could also assist this specificity.

Accounting for the specificity at the chelate methine centre (α) is more difficult. The results imply the Δ-*R* configuration of the chelated *C*-formylglycine to be by far the more abundant and/or the more reactive one. Once the nucleophile has added at the carbonyl centre the chelate methine chiral centre (α) is fixed under the

Scheme 6.

acidic conditions. Neither this proton nor the thiazolidine ring protons exchange with water. However, not only is the formylglycine an α-stereogenic centre[27] labilized through the enol form, but under the acidic aqueous conditions roughly equal concentrations of the two diastereoisomeric hydrates occur. This is in keeping with observations on analogous amino acid systems.[28] Moreover, there seems to be no obvious reason why the addition of the nucleophile at the formyl group should be stereospecific. If anything, a specificity opposite to that observed would be expected. In these respects, the isomer distributions observed under higher pH conditions are more in keeping with the previous observations, but clearly we have no obvious explanation for the stereospecificity in acid nor the change in isomer distribution as the pH increases.

The variation in solubility of the isomers with protonation and with the anion leads to interesting possibilities for "milking" the reaction mixtures and for interconversion of B ($\Delta,2S,4S,\alpha R$) to A ($\Delta,2R,4S,\alpha R$), the naturally occurring form, and of C ($\Delta,2S,4S,\alpha S$) to D ($\Delta,2R,4S,\alpha S$). Appropriate solubilities of individual salts could well lead to stereoselectivity for the formation of the individual isomers. This aspect is currently being explored.

Finally, the issue of ring-closure to give the β-lactam, penicillamic acid, still needs to be addressed. An interesting opportunity arises here which is more difficult to organise in the regular organic chemistry. Generation of the chelate ester shown in Scheme 6 creates a very reactive amino acid ester ($\sim 10^6$ fold more reactive than the uncoordinated ester)[29] in the vicinity of an intramolecular nucleophile, in this case the N atom of the thiazolidine ring. The combination of the enhanced reactivity and the propinquity of the two reaction centres may be enough to generate the strained β-lactam.

Scheme 5.

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