Introduction

Proline (1) and derivatives play essential roles in chemistry and biology. Chiral proline and analogues constitute archetypal agents in enantioselective organocatalysis. Prolyl segments within peptide strands impose rigid constraints on the peptide secondary structure, and in this respect proline is unique among the proteinogenic amino acids. Synthetic studies have focussed on extending proline entities in order to create “proline chimeras” that mimic other peptidal amino acids with respect to side chain while retaining the conformational rigidity of the prolyl segment. This prospect has sparked interest in producing proline derivatives stereoselectively by elaboration from the α-C centre. However, modification at this, the sole stereogenic centre of proline, without loss of chirality is not straightforward. In 1981, Seebach et al. devised an elegant strategy which permitted α-alkylation of (S)-proline (1) to be conducted enantioselectively with a number of electrophilic reactants (Scheme 1). The strategy relied on temporary incorporation of an auxiliary, stereogenic centre via formation of a bicyclic acetal (2) by condensation with pivaldehyde. The auxiliary stereogenic centre arose diastereoselectively at C-2 of the so formed 2-(tert-butyl)oxazolidin-5-one ring. Alkylation at the α-C centre of the lithium enolate intermediate 3 to give 4 also proceeded diastereoselectively. The inherent stereogenicity of the α-C centre in 1 was lost in the deprotonation step providing 3, but the auxiliary stereocentre upheld an asymmetric environment for the alkylation step to yield 4 stereoselectively. Hydrolytic removal of the auxiliary centre provided 5. This, overall, stereoretentive sequence (Scheme 1) constitutes a seminal example of the application of the
principle of Self-Regeneration of Stereocentres (SRS), due to Seebach.⁴,⁷

Throughout the reaction sequence of Scheme 1 the N centre was not configurationally fixed. However, if (S)-proline was chelated to a metal centre (6), the configuration of the N centre (S₃) will be tied to that of the α-C centre (S₆), since the pyrrolidine ring only resides on one side of the pseudo plane defined by the chelate ring, a general feature of all reported structures of proline chelates at cobalt(m).⁸–¹² In this respect the stereochemical characteristics of fragment 6 resemble those of 2 (Scheme 1). In both instances the amine and carboxylate groups are incorporated into a five-membered ring of a bicyclic system, and the absolute configuration of the parent (single) stereogenic centre of (S)-proline determines the configuration of the new stereocentre. Due to this similarity, proline chelates (6) may be anticipated to behave analogously to 3 with respect to stereopreferences. However, for such selectivity to operate in the case of 6 the coordinated amine would need to remain configurationally intact in the course of any reaction sequence aimed at modifying the α-C centre. Therefore, the amine should neither dissociate nor deprotonate at any point, since either event could facilitate loss of chirality by inversion, thus obviating the prospect of selectivity. These restrictions may be met by employing a substitutionally inert metal centre and applying conditions that suppress deprotonation at the amine-N-relative to the α-C centre. In general, bidentate coordination of an amino acid to a cationic metal centre invariably serves to activate both of these centres, with the amine usually the most acidic, primarily due to the direct binding to the metal.¹³ However, enhanced activation of the α-C proton(s) of amino acid chelates by acid halide formation has been implicated for a number of cobalt(m) systems in reactions effecting, overall, formylation,¹⁴–¹⁷ oxidative imine formation¹⁸–²³ or oxidation²⁴,²⁵ of the amino acid chelate. These reactions were typically carried out in DMF with POCl₃, SOCl₂ or PBr₃ as reagents, and were all interpreted as proceeding via initial conversion of the cobalt(m)-bound amino acidate to the derivative acid halide, thus enhancing activation at the α-C centre.¹⁴–²⁴ However, the extent of concomitant activation of the neighbouring amine has not been elucidated. Clearly, simultaneous deprotonation at both sites would seem unlikely.

The creation of a quaternary α-C centre by introduction of a formyl group is an obvious goal, generating the basis for further elaboration. So far, successful introduction of the formyl group at the α-C centre of a cobalt(m)-bound amino acidate is only reported with glycine (7). This was achieved by reaction with POCl₃ in DMF via a Vilsmeier–Haack-type reaction,²⁶ and results are summarised in Scheme 2 {L₄Co = p-Co(tren), t-Co(tren), Co(en)₂, cis-β₂-Co(trien) }.¹⁴–¹⁷,²⁷ The argued mechanism assumes initial formation of a glycyl chloride (8) which upon deprotonation at the α-C site is added to the N,N-dimethyl-chloromethyliminion ion (“Vilsmeier reagent”, generated in situ from reaction of POCl₃ with DMF) followed by elimination of HCl to produce the crystallographically verified 3-(dimethylamino)-2-aminocryl chloride complex, [L₄-Co = p-Co(tren)].¹⁴ The conjugationally stabilized ligand of 9 yielded to hydrolysis in strong aqueous acid, providing¹⁵,¹⁶ the aldehyde complex 11, which was distributed between its hydrated (12) and enol (10) forms in water in ca. 9 : 1 ratio {L₄ = (en)₂}.¹⁷ A published solid state structure has the aldehyde in the enol form [10, L₄Co = cis-β₂-Co(trien)].²⁷

In the sequence of Scheme 2 the site of reaction was the glycinate α-CH₂ group. However, if parallel chemistry was to be conducted with other α-amino acids (different from GlyO⁻) with the aim of converting an α-CH group into a quaternary centre, the extensive conjugation noted for 9 would not apply. Therefore, such parallel chemistry was intuitively viewed less feasible. However, in this paper we report the successful formylation of the α-C centres of the amino acidate ligands in (−)₅₇₆₆{[Co(tren)(S-AlaO)]}²⁻ and (+)₅₇₆₆{[Co(tren)(S-ProO)]}²⁺ producing the derivative aldehydes (hydrated form). While the (S)-alaninate complex resulted in a racemized product the reaction of the (S)-prolinato complex proceeded stereoselectively.

**Experimental**

**General**

Absorption spectra and optical rotations were monitored in water with a Lambda 17 spectrophotometer and a Perkin-Elmer P22 polarimeter (±0.002°), respectively; for the latter in 1 dm quartz cells at 23 °C. Within experimental error all listed values for specific rotations ([α] in units of 10⁻¹⁰ deg cm² g⁻¹) of chiral products did not change on further recrystallization of the product, and this was taken as evidence of optical purity.¹⁴¹⁷¹⁸¹⁹²⁰²¹²²²³ The ¹³C{¹H} NMR spectra were recorded in D₂O on a (500 MHz) Bruker spectrometer (with cryoprobe) using
1,4-dioxane ($^{13}$C, δ = 69.14 ppm relative to Me$_4$Si) as internal standard. When applicable, assignments of $^{13}$C resonances were made on the basis of the APT technique. The cation exchange resin AG 50W-X2 (Bio-Rad, 200–400 mesh) was used throughout and resin column dimensions are given as diameter × length. Routine concentration of solutions by removal of solvent was carried out at reduced pressure (ca. 20 Torr) in a Büchi rotary evaporator using a water aspirator and water bath (ca. 60 °C). Drying “in vacuo” was accomplished over P$_2$O$_5$.

Anhydrous CF$_3$SO$_2$H (3 M Comp.) was used as supplied.

$^{13}$p-[Co(tren)·(S-Ala)O]Cl$_2$·5H$_2$O (13[Cl$_2$·5H$_2$O]). To a solution of L-(S)-alanine (4.4 g, 50 mmol) and CoCl$_2$·6H$_2$O (11.9 g, 50 mmol) in water (0.2 l) was added tris(2-aminoethyl)-amine (7.3 g, 50 mmol) and activated charcoal (4.2 g, Norit W). The magnetically stirred mixture was heated (water bath) to ca. 70 °C and aerated for 2 h. After cooling and acidification with 1 M HCl (10 ml) the mixture was filtered through Kieselguhr and the dark orange-coloured filtrate evaporated to near dryness. The resulting viscous oil was taken up in hot water (25 ml) and ethanol (150 ml) was gradually added, leading to crystal formation. The resulting mixture was left at 5 °C, overnight, to complete crystallisation. The product of rac-p-[Co(tren)·(L-Ala)OCl]$_2$·2H$_2$O (11.9 g, 50 mmol) was slowly added POCl$_3$ (30 ml) over 0.5 h. The resulting orange powder (hygroscopic) was collected, washed with Et$_2$O and thoroughly dried in vacuo (19 g, 99%). (Found: C, 19.1; H, 3.6; N, 7.8. C$_{12}$H$_2$N$_2$O$_2$F$_2$S$_2$Co requires C, 25.4; H, 5.4; N, 14.86%).

rac-p-[Co(tren)·(Ala(CH(OH)$_2$)O)]SO$_2$·2H$_2$O (17[SO$_2$·2H$_2$O]). To a continuously stirred and cooled (ice bath) solution of p-[Co(tren)·(S-Ala)O]Cl$_2$·5H$_2$O (7.9 g, 10 mmol) in dry DMF (50 ml) was slowly added POC$_3$I (30 ml) over 0.5 h. The reaction mixture was left with rapid stirring and gradually heated to 40 °C over 1 h when it became darker in colour. The reaction mixture was immediately poured into iced water (0.5 l) and the resulting orange-coloured solution adsorbed on a column of AG 50W-X2 cation exchange resin (H$^+$-form, 6.5 × 20 cm). After washing with water the orange band was eluted with a gradient of 1–3 M HCl and the eluate concentrated to near dryness. The residue was taken up in water (30 ml) followed by addition of Na$_2$SO$_4$·10H$_2$O (3.9 g, 12 mmol) and gradual addition of acetone (35 ml) with cooling in ice. The orange-red crystals were collected, washed with acetone, Et$_2$O and dried in the air (3.9 g, 80%). (Found: C, 25.6; H, 6.4; N, 14.7. C$_{10}$H$_{30}$N$_5$O$_7$SCo requires C, 25.48; H, 6.42; N, 14.86%); δ$_C$ (126 MHz, D$_2$O) 187.6 (COO), 93.1 (CH(OH)$_2$), 68.5 (CH$_3$), 64.0, 63.5, 61.1 [N(CH$_2$)$_3$], 47.9, 47.3, 46.8 [N(CH$_2$CH$_2$)$_2$], 23.4 (CH$_3$); [α]$_{D}$ 0, [α]$_{D}$ 46.0.

rac-p-[Co(tren)[Ala(CH(OH)$_2$)O]]$_2$H$_2$O (17[Cl$_2$·1.5H$_2$O]). A mixture of rac-p-[Co(tren)(Ala(CH$_2$OH)$_2$)O]SO$_2$·2H$_2$O (0.14 g, 0.30 mmol) and KI (0.21 g, 1.3 mmol) was suspended and dissolved in water (1 ml) by gentle heating. The resulting solution was left at 5 °C, whereby large orange-red, needle-shaped crystals formed. (Found: C, 19.1; H, 4.6; N 11.2. C$_{16}$H$_{38}$N$_5$O$_3$I$_2$Co requires C, 19.65; H, 4.62; N, 11.46%).

(+)p-[Co(tren)((S$_2$-S$_2$)-Pro)]Cl$_2$-1.5H$_2$O (18[Cl$_2$·1.5H$_2$O]). To a solution of (+)-3-proline (3.45 g, 30.0 mmol) and Co(NO$_3$)$_2$·6H$_2$O (8.73 g, 30.0 mmol) in water (100 ml) was added tris(2-aminoethyl)amine (4.39 g, 30.0 mmol) and activated charcoal catalyst (1.4 g, Norit W). The mixture was constantly aerated and stirred while maintaining the temperature at ca. 70 °C for 4 h. After cooling and acidification (3 M HCl, 5 ml) the reaction mixture was filtered through Kieselguhr, and the orange-coloured filtrate was sorbed on a column of AG 50W-X2 cation exchange resin (6.5 × 20 cm). After washing with water the single orange band was eluted with 0.5–3.0 M HCl and the eluate concentrated to almost dryness. The resulting syrupy residue was taken up in water (12 ml) followed by gradual addition of abs. EtOH (100 ml) leading to separation of orange crystals, which after cooling in ice were collected, washed with abs. EtOH, Et$_2$O and air dried (9.85 g, 79%). (Found: C, 31.7; H, 6.9; N, 16.5. C$_{12}$H$_{28}$N$_5$O$_5$I$_2$Co requires C, 31.67; H, 7.01; N, 16.78%); δ$_C$ (126 MHz, D$_2$O) 188.0 (COO), 67.9 (CH), 64.33, 64.28, 61.4 [N(CH$_2$)$_3$], 54.1 (NCH$_3$), 48.0, 47.4, 47.3 [N(CH$_2$CH$_2$)$_2$], 31.6, 29.1 (CH$_3$CH$_2$CH$_2$). [α]$_{D}$ 50.0, [α]$_{D}$ 115; λ$_{max}$(H$_2$O)/nm 476 (ε/dm$^3$ mol$^{-1}$ cm$^{-1}$) and 345 (122).

(+)p-[Co(tren)((S$_2$-S$_2$)-ProO)]Cl$_2$-1.5H$_2$O (18[H$_2$O]$_2$(HOEt$_2$)(O$_3$SCF$_3$)$_7$(5.23 g, 2.91 mmol) in dry DMF (25 ml) was slowly added tris(2-aminoethyl)amine (4.39 g, 30.0 mmol) and activated charcoal catalyst (1.4 g, Norit W). The mixture was constantly aerated and stirred while maintaining the temperature at 70 °C, whereby large orange-red, needle-shaped crystals formed. (Found: C, 23.80; H, 7.54; N, 15.42%). C$_{10}$H$_{34}$N$_5$O$_7$Cl$_2$Co requires C, 23.6; H, 7.1; N, 15.2. C$_{10}$H$_{30}$N$_5$O$_7$SCo requires C, 25.48; H, 6.42; N, 14.7. C$_{10}$H$_{30}$N$_5$O$_7$SCo requires C, 23.6; H, 7.1; N, 15.2. C$_{10}$H$_{30}$N$_5$O$_7$SCo requires C, 23.6; H, 7.1; N, 15.2.

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A single band was eluted with 1–3 M HCl and the eluate was concentrated to near dryness. The residue was taken up in water (10 ml) followed by addition of acetone (30 ml) and cooling in ice. The massive orange-red crystals (2.53 g, 92%) were collected, washed with gradually increasing concentrations of acetone and dried in the air. The product was recrystallized in the same manner using water (12 ml) and acetone (35 ml) to yield large orange-red crystals which were collected as above (2.20 g, 80%). (Found: C, 31.0; H, 6.7; N 14.9). To a solution adsorbed on a column of AG 50W-X2 cation exchange resin (0.2 M, pH 6.86, 60 ml) of -[Co(tren)\{(S)-3-(dihydroxymethyl)alaninato- and (S)-prolinato\}Cl2·2H2O] with stirring, NaBH4 (1.0 g, 26 mmol) was slowly added, initiating slow deposition of crystals. After stirring overnight, the large crystals were collected, washed with EtOH, Et2O and air-dried (1.11 g, 78%). (Found: C, 31.5; H, 7.07; N, 15.35%). C12H32N5O5Cl2Co requires C, 31.59; H, 7.0; N, 15.2. C12H32Cl2CoN5O6 requires C, 30.52; H, 6.83; N, 14.83%);

### Crystallography

Adequate crystals of rac-p-[Co(tren)[(R)-CH(OH)]2O]Cl2·2H2O ([17]Cl2·H2O), (+)578-[Co(tren)[(RC)-Pro(CH(OH))]2O]Cl2·2H2O ([22]Cl2·H2O) and (+)578-[Co(tren)[(RC)-Pro(CH(OH))]2O]Cl2·2H2O were selected and each mounted on a glass fiber or nylon loop attached to a copper pin and placed in the N2 stream of a Bruker D8 Venture diffractometer. Data were collected using Mo-Kα radiation (\(\lambda = 0.71073 \text{ Å}\)). Details of the crystal structure determination and refinement are given in Table 1. The structures were solved using the charge-flipping method (olex2.solve) and refined using the program packages SHELXL and Olex2.

### Results and discussion

The chiral (S)-alaninato- and (S)-prolinato cobalt(II) complexes were each formylated at their α-methylene centres in a Vilsmeier–Haack-type reaction, essentially as done before at the α-methylene group of the analogous glycinato complexes. However, in the present study quaternary carbon centres were created, and the products, rac-p-[Co(tren)\{(R)-CH(OH)]2O\}]Cl2·2H2O ([17]Cl2·H2O) and (+)578-p-[Co(tren)[(RC)-Pro(CH(OH))]2O]Cl2·2H2O ([22]Cl2·H2O), were each isolated in their hydrated, i.e. α-(dihydroxymethyl) forms, and

### Table 1: Summary of crystallographic data

| Compound reference | [17]Cl2·H2O | [22]Cl2·H2O | [23]Cl2·H2O |
|--------------------|------------|------------|------------|
| Empirical formula  | C10H22CoI2N5O6 | C12H32Cl2CoN5O6 | C12H32Cl2CoN5O6 |
| M                  | 611.11     | 472.26     | 456.25     |
| Crystal system     | Monoclinic | Orthorhombic | Orthorhombic |
| Space group        | P21/211   | P221/221   | P221/221   |
| a/Å                | 21.619(3) | 9.6314(6)  | 8.9450(3)  |
| b/Å                | 9.0014(10)| 13.5664(6) | 12.4236(4) |
| c/Å                | 22.283(3) | 14.7998(8) | 17.4130(1) |
| α/°                | 90         | 90         | 90         |
| β/°                | 117.732(6)| 14.7998(8) | 14.7998(8) |
| γ/°                | 90         | 90         | 90         |
| Unit cell volume/Å³ | 3838.1(8) | 1933.8(2)  | 1935.1(1)  |
| Temperature/K      | 298(1)    | 122(1)     | 122(1)     |
| Z                  | 8          | 4          | 4          |
| Refl. measured     | 35227      | 14308      | 30215      |
| Independ. refl.    | 6799       | 4259       | 5425       |
| Observed refl. (I > 2σ(I)) | 5152 | 3991 | 4854 |
| Parameters         | 427        | 281        | 233        |
| Rint               | 0.051      | 0.0366     | 0.050      |
| R1 (I > 2σ(I))     | 0.0550     | 0.0269     | 0.0271     |
| wR2 (I > 2σ(I))    | 0.1316     | 0.0617     | 0.0556     |
| R1 (all data)      | 0.0765     | 0.0309     | 0.0356     |
| wR2 (I) (all data) | 0.1443     | 0.0662     | 0.0585     |
| S                  | 8.014      | 4.143      | 1.043      |
| Δρmax, Δρmin (e Å⁻³) | 1.31, -0.71 | 0.63, -0.37 | 0.63, -0.37 |
| Flack parameter    | —          | 0.010(13)  | 0.006(6)   |
| CCDC number        | 1411924    | 1411925    | 1411926    |
their structures verified by X-ray crystallography. While the
formylation of the chiral alaninato complex (13) gave racemic
17, the formylation of the chiral prolinato complex (18) pro-
duced the chiral α-formyl (R)-prolinato complex (22) in 85%
enantiomeric excess (ee).

Synthesis and characterisation
The two precursor complexes were readily produced in a “one-
pot” procedure comprising aeration of a solution of cobalt(ii)
salt, tris(2-aminoethyl)amine (tren) and α-amino acid in water
in the presence of activated-charcoal catalyst. Enantiopure prod-
cuts, (−)-578−[Co(tren)](S-Alo)[Cl2·5H2O] and (+)-578−[Co(tren)-
(Sc,Sn)-ProO)]Cl2·1.5H2O, respectively, were isolated in good
yields. Usual cobalt(ii) behaviour predicts activated charcoal to
catalyse the equilibration of coordination isomers.31,12 Here, the
p isomer was the sole geometrical isomer observed in both
instances.33,34 This isomer has the carboxylate group co-
ordinated trans to a primary amine of the tren ligand in the
complex,35 and the same single product geometry was observed
in similar syntheses of the homologous glycino-, ornithinato-
and sarcosinato complexes.33,36,37 These concur-
ing results corroborate the suggestion that this facile strategy
is generally applicable for the directed, stereoselective syn-
thesis of p-[CoαN(tren)[amino acidato]]3− complexes, obviating
earlier (non-stereoselective) methods based on substitution of
ligands of a suitable cobalt(ii) complex [[Co(tren)Cl2]Cl,38,39
[Co(tren)(OH2)(OH)][ClO4]2 or [Co(tren)(OH2)(OH)][ClO4]3,40
[Co(tren)(ClO4)4]0 or [Co(tren)(OH2)(OH)][ClO4]2.41,42

The precursor complex chlorides were converted to their
DMF-soluble triflate salts, (−)-578−[Co(tren)](S-Alo)[H2O]-
(O3SCF3)3 and (+)-578−[Co(tren)][(Sc,Sn)-ProO]]H2O],(HOEt2)-
(O3SCF3)7, and each subjected to Vilsmeier–Haack-formylation
in DMF followed by chromatographic workup and crystalli-
zation of products. Thereby, the chiral (S)-alaninato complex
(13) was converted to the racemic α-(dihydroxymethyl)
product, rac-p-[Co(tren)][Ala(CH(OH)2)O]SO4·2H2O (17),
whereas the chiral (S)-prolinato complex (18) gave the product
enantiomorph (+)-578−[Co(tren)][(Sc,Sn)-ProO][CH(OH)2]O)]Cl2·2H2O
(22) in 85% ee (in eluate after chromatography), but recrystall-
ization afforded enantiopure product in 80% yield. The 13C
NMR spectra (in D2O) of both formyl complexes (17, 22)
revealed the hydrated, α-(dihydroxymethyl) forms of the crys-
tallized products to also persist in aqueous solution. With
NaBH4 in water (pH 6.9) the α-formyl-prolinato complex (22)
was selectively reduced to the derivative alcohol complex (+)-578−
p-[Co(tren)][(Sc,Sn)-ProO][CH2OH]O)]Cl2·2H2O ([23]Cl2·2H2O).

Structures
A number of prolinato cobalt(ii) complexes are reported
before.8–12,43,44 In all instances for which a crystal structure
was also reported, the five-membered pyrrolidine ring was
found to reside in a cisoid fashion on the same side of the
plane defined by the proline chelate ring.8–12 Thereby, the
configurations of the α-C- and sec.-amine-N atoms of chelated
prolinate are mutually interlocked. Thus, in the published12
structure of chiral p-[Co(tren)][(Sc,Sn)-ProO]I2·H2O ([18]I2·H2O)
the absolute configurations of these centres are Sc,Sn, and

![Fig. 1](https://example.com/image1.png)
**Fig. 1** A view of the molecular structure of one of the two crystallo-
graphically independent but structurally similar complex ions of
[17]I2·H2O showing the atom-labelling scheme for selected atoms. Dis-
placement ellipsoids are drawn at the 30% probability level and H atoms
are shown as small spheres of arbitrary radii.

![Fig. 2](https://example.com/image2.png)
**Fig. 2** A view of the molecular structure of the complex cation of [22]
Cl2·2H2O showing the atom-labelling scheme for selected atoms. Dis-
placement ellipsoids are drawn at the 50% probability level and H atoms
are shown as small spheres of arbitrary radii.

inspection of a molecular model reveals the alternative trans-
oid disposition (S*(C),R*, relative configuration) to be more
strained, relatively.

Here, crystal structure determinations were undertaken of
product complexes rac-p-[Co(tren)][Ala(CH(OH)2)O]I2·H2O ([17]-
I2·H2O), (+)-578−[Co(tren)][(Sc,Sn)-ProO][CH(OH)2]O)]Cl2·2H2O
([22]Cl2·2H2O) and (+)-578−[Co(tren)][(Sc,Sn)-ProO][CH2OH]O)]-
Cl2·2H2O ([23]Cl2·2H2O), and the complex cations of each
structure are depicted in Fig. 1–3. The monoclinic crystal of
racemic [17]I2·H2O contains two formula units per asymmetric
unit, but since the two crystallographically independent
complex ions are structurally very similar, only one of these is
depicted in Fig. 1. Selected bonding parameters for all three
structures appear in Table 2. Since all corresponding values
of the two crystallographically independent complex cations
of [17]I2·H2O are similar within a few standard deviations, only
averaged values are given in Table 2 for this compound.
the complex. Nevertheless, in 22 the pyrrolidine ring adopts the envelope conformation with the flap oriented towards the complex core. This orientation contrasts with the conformation in the structure of 23 and in other structures of prolinato cobalt(II) complexes which all have the flap pointing away from the complex centre.8–12

All three structures are dominated by extensive hydrogen-bonding networks. A common feature is a strong intramolecular hydrogen-bond interaction between a coordinated amine and one O atom of the α-(dihydroxymethyl) or α-hydroxymethyl groups [N2⋯O3: 2.799 (13) Å in 17, 2.865 (3) Å in 22 and 2.791 (3) Å in 23], a general feature in related structures.33,37,45

**Stereoselectivity**

The contrasting stereochemical outcomes of the formylation reactions of the two amino acide complexes of this study provide important mechanistic insight. A mechanistic proposal for the formylation (accompanied by racemization) of the (5)-alaninato complex (13) is depicted in Scheme 3, and the mechanism is argued on the background of the parallel reaction of the analogous glycinate system (Scheme 2).14–17 Thus, with POCI3 the (5)-alaninato complex 13 is converted to the triply charged acid-chloride complex 14, which after proton loss and electronic readjustment provides enolate complex 15. This would be stabilized, relatively, due to the overall lower charge and electronic delocalization of the ligand with negative charge shifted towards the metal ion. The planarity of the

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**Table 2**

Selected bond distances (Å) and angles (°)

| Compound | [17]Cl2·H2O | [22]Cl2·2H2O | [23]Cl2·2H2O |
|-----------|-------------|-------------|-------------|
| Co-N1     | 1.938       | 1.956(2)    | 1.945(2)    |
| Co-N2     | 1.948       | 1.969(2)    | 1.971(2)    |
| Co-N3     | 1.934       | 1.940(2)    | 1.943(2)    |
| Co-N4     | 1.944       | 1.971(2)    | 1.957(2)    |
| Co-N5     | 1.952       | 1.973(2)    | 1.977(2)    |
| Co-O1     | 1.885       | 1.902(2)    | 1.906(2)    |
| N1-Co-N2  | 86.1        | 85.0(1)     | 86.2(1)     |
| N1-Co-N3  | 87.9        | 86.9(1)     | 87.9(1)     |
| N1-Co-N4  | 86.2        | 86.5(1)     | 86.5(1)     |
| O1-Co-N5  | 85.3        | 86.0(1)     | 85.9(1)     |
| N2-Co-N3  | 92.5        | 91.7(1)     | 92.0(1)     |
| N3-Co-N4  | 91.8        | 92.3(1)     | 91.6(1)     |
| N4-Co-O1  | 86.7        | 87.1(1)     | 87.0(1)     |
| O1-Co-N2  | 89.1        | 88.8(1)     | 89.3(1)     |
| N4-Co-N5  | 94.8        | 97.6(1)     | 96.5(1)     |
| N2-Co-N5  | 92.8        | 90.7(1)     | 91.3(1)     |
| N1-Co-N5  | 177.3       | 175.6(1)    | 176.8(1)    |
| N2-Co-N4  | 171.1       | 170.4(1)    | 171.1(1)    |
| N3-Co-O1  | 178.4       | 179.4(1)    | 178.6(1)    |
| Co-N5-C12 | 120.1(2)    | 119.8(2)    |             |
| Co-N5-C8  | 111.8       | 110.1(1)    | 109.8(1)    |
| Co-O1-C7  | 116.6       | 117.1(2)    | 116.5(1)    |

*Averages.*
enolate ligand renders 15 achiral, and any reaction which restores sp\(^3\)-hybridization at the \(\alpha\)-C atom would result in racemic product mixtures. Here, addition to the imine of the Vilsmeier reagent followed by elimination of Cl\(^-\) produces 16, which after hydrolysis of the iminium- and acid chloride functionalities provides the racemic \(\alpha\)-(dihydroxymethyl)alaninato complex 17. Once formed, the quaternary \(\alpha\)-C centre of this product is configurationally locked. Thus, while enantiomers of the related \(\alpha\)-formyl-glycinato system may interconvert via an enol intermediate (10, Scheme 2),\(^{17,27}\) such path is clearly not available to the \(\alpha\)-formyl-alaninato complex (17).

In the mechanistic proposal above (Scheme 3) the identity of the acid halide 14 was inferred by analogy. Thus, the formation of a chelated acid halide (9, Scheme 2) from \(p\)-[Co(tren)] GlyO\(^2+\) and POCl\(_3\) in DMF has been verified crystallographically.\(^{14}\) Since 15 is achiral, re-protonation yields both enantiomers of 14 in equal proportion, and the reversible interconversion between 14 and 15 affects overall racemization of 14, even though this was not verified directly. However, the same effect of activation due to acid halide formation has been noted in a related system. Thus, SOCl\(_2\), POCl\(_3\) and PBr\(_3\) were each shown to induce epimerization at the \(\alpha\)-C centre of racemic product mixtures. Here, addition to the imine of the Vilsmeier reagent followed by elimination of Cl\(^-\) restores sp\(^3\)-hybridization at the \(\alpha\)-C atom would result in racemic product mixtures. Here, addition to the imine of the Vilsmeier reagent followed by elimination of Cl\(^-\) produces 16, which after hydrolysis of the iminium- and acid chloride functionalities provides the racemic \(\alpha\)-(dihydroxymethyl)alaninato complex 17. Once formed, the quaternary \(\alpha\)-C centre of this product is configurationally locked. Thus, while enantiomers of the related \(\alpha\)-formyl-glycinato system may interconvert via an enol intermediate (10, Scheme 2),\(^{17,27}\) such path is clearly not available to the \(\alpha\)-formyl-alaninato complex (17).

The pronounced stereoselectivity associated with the formation of a chelated acid halide (9, Scheme 2) from \(p\)-[Co(tren)] GlyO\(^2+\) and POCl\(_3\) in DMF has been verified crystallographically.\(^{14}\) Since 15 is achiral, re-protonation yields both enantiomers of 14 in equal proportion, and the reversible interconversion between 14 and 15 affects overall racemization of 14, even though this was not verified directly. However, the same effect of activation due to acid halide formation has been noted in a related system. Thus, SOCl\(_2\), POCl\(_3\) and PBr\(_3\) were each shown to induce epimerization at the \(\alpha\)-C centre of racemic product mixtures. Here, addition to the imine of the Vilsmeier reagent followed by elimination of Cl\(^-\) restores sp\(^3\)-hybridization at the \(\alpha\)-C atom would result in racemic product mixtures. Here, addition to the imine of the Vilsmeier reagent followed by elimination of Cl\(^-\) produces 16, which after hydrolysis of the iminium- and acid chloride functionalities provides the racemic \(\alpha\)-(dihydroxymethyl)alaninato complex 17. Once formed, the quaternary \(\alpha\)-C centre of this product is configurationally locked. Thus, while enantiomers of the related \(\alpha\)-formyl-glycinato system may interconvert via an enol intermediate (10, Scheme 2),\(^{17,27}\) such path is clearly not available to the \(\alpha\)-formyl-alaninato complex (17).

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Conclusions

The feasibility of conducting Vilsmeier–Haack-type formylation reactions at the α-C centre of a chelated amino acidate, hitherto only performed at the glycinate methylene group,14–17,27 has been expanded to also incorporate the methine groups of chelated alaninate and proline.

The highly stereoselective formylation reaction of chelated (S)-proline to give α-(R)-di(hydroxy)methyl proline (22) constitutes a novel and highly efficient example of the execution of the SRS principle.7 Here, the prolinato cobalt(n) system is unique in the sense that the combined exploitation of the activating and protecting effects of an inert metal centre, modulating the chemistry while directing the stereochemistry, has not been exemplified in this manner before. The formyl group thus introduced at the quaternary α-C centre of the chiral complex 22 makes this an ideal starting point, easily synthesized, for future controlled elaboration of the proline segment. In the complex, the amine and carboxylate functionalities remain protected by the coordination to the inert metal centre. However, product amino acids may be readily liberated at any time by gentle reduction to the labile cobalt(n) state, as demonstrated before.23,32,33

Further enhancement of the stereoselectivity, and fine-tuning of reactivity, may be envisaged by the introduction of suitable steric demands in the backbone ligand sphere. Investigations along these lines are currently being pursued.

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