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Metal complex amino acid synthons: syntheses, structures and stereoselective reactions of (iminoacetato)cobalt(III) complexes

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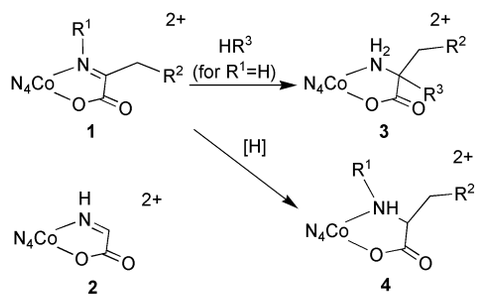
Amino acid anions (AAO^-) chelated to cobalt(III) in $[(en)_2Co(AAO)](O_3SCF_3)_2$ (AA = Gly, Sar, Ala and Glu) were selectively oxidized to their imine derivatives by a new general procedure utilizing PBr_3 and *N*-bromosuccinimide in dmf. The new iminoacetato complexes, Λ- and Δ-$[(en)_2Co(O_2CCH{=}NH)](O_3SCF_3)_2$, constitute chiral glycine equivalents which can serve as synthons for stereoselective α-amino acid synthesis. In alkaline EtOH, quantitative addition of $CH_2(COMe)_2$, $CH_2(CO_2Et)_2$ or $MeCOCH_2CO_2Et$ to the imine of the iminoacetate ligand initially produced both diastereomers of the product α-amino acid cobalt(III) complexes. However, subsequent crystallization-induced asymmetric transformations in the heterogeneous reaction mixtures led to better than 90% excess of a single diastereomer after five days, and the diastereopure product triflate salts were obtained after recrystallization. Both enantiomers of isotopically substituted (3-^{13}C, 98%)aspartic acid were produced by facile synthesis from Δ-$[(en)_2Co(O_2CCH{=}NH)](O_3SCF_3)_2$ and diethyl (2-^{13}C)malonate. The new *N*-methyliminoacetato complex, *rac*-$[(en)_2Co(O_2CCH{=}NMe)](O_3SCF_3)_2$, also yielded to imine addition reactions providing a route to the α-*N*-methylamino acid subclass. The molecular structures of the new imine complexes, Λ-$(+)_{578}$-$[(en)_2Co(O_2CCH{=}NH)]Br_2{\cdot}H_2O$ and *rac*-$[(en)_2Co(O_2CCH{=}NMe)]S_2O_6{\cdot}1.5H_2O$, and the diethyl carboxy-aspartate addition product, $(\Lambda S,\Delta R)$-$[(en)_2Co\{O_2CCH(CH(CO_2Et)_2)NH_2\}](ClO_4)_2$, were determined by X-ray crystallography.

Introduction

The biological importance of chiral α-amino acids, natural and unnatural, motivates a continued search for improved synthetic avenues to these compounds. Conceptually, one of the most direct and general approaches for the synthesis of α-amino acids is homologation of glycine equivalents *via* C–C bond formation at the α-position. Glycine equivalents which offer various degrees of nucleophilic or electrophilic reactivity at the α-C atom have been developed.[1] These synthons include protected iminoacetates[2] which allow homologation by nucleophilic addition at the imine-C atom. However, the iminoacetate anion and iminoacetic acid are highly unstable species,[3] and regular organic routes for the production and elaboration of the iminoacetate entity, and similar synthons, rely critically on the presence and effective removal of different standard protecting and activating groups at various stages of a synthesis.[1] A promising alternative approach makes use of the ability of a single metal centre to simultaneously activate and protect even multifunctional organic substrates.[4] Thus, 2-iminocarboxylates have been stabilized to hydrolysis and rupture to varying degrees by chelation to Fe(II),[5] Cu(II),[6] Pd(II),[7–8] Mo(II),[9] Ru(II),[10–16] Co(III),[10,12,17–28] Rh(III)[8,10] and Ir(III).[10–12] Even so, activation of the imine moiety is evident in some instances and further modification of the organic ligand in a controlled fashion is feasible. In addition, the inherent chirality of many substitutionally inert octahedral complexes with chelate ligands may render ligand modification reactions stereoselective. Charged products resulting from such ligand reactions may be readily purified and even resolved by aqueous ion-exchange chromatography or by simple crystallization procedures. Cobalt(III) complexes with chelate carboxylate- and amine-donor ligands, especially, combine all these properties and, eventually, enable facile liberation of the product ligands by mild controlled reductions to the labile cobalt(II) state.[26] The rich chemistry developed with amine cobalt(III) complexes of 2-iminopropanoate, $[N_4Co\{O_2CC(Me){=}NH\}]^{2+}$ [**1** (R^1,R^2 = H), Scheme 1], and higher



Scheme 1

homologues illustrates how the metal is capable of modifying the reactivity of a chelated organic substrate to such a degree that it becomes a useful starting point for further organic synthesis.[17–32] However, this development has not embraced the simplest 2-iminocarboxylate, and chiral (iminoacetato)-cobalt(III) complexes (**2**) have remained elusive until now. Also, with other metals only a few examples of iminoacetato complexes are reported.[8,9,14,16,17]

Hitherto, cobalt(III) complexes which have qualified as chiral glycine equivalents incorporate chelated glycinate or N-substituted glycinate derivatives. Procedures for elaboration at the α-C atom in such systems have relied on initial carbanion formation at this atom, aided by the ligand N,O-chelation

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to the positively charged metal centre. Deprotonation can be effected by base[4] or, spontaneously, by activation through *in situ* glycyl halide formation.[33–35] The nucleophilic reactivity of such carbanions towards aldehydes[4] and more powerful electrophiles[23–25,33–35] is well described. However, attempted alkylation reactions with alkyl halides (or equivalents) have not been successful, and this limits such strategies for amino acid synthesis.

By comparison, the electrophilic reactivity of readily produced chelate 2-iminocarboxylato cobalt(III) complexes[17–28] make them more useful starting points for asymmetric syntheses of amino acids. For example, in the (2-iminopropanoato)-cobalt(III) complexes, $[N_4Co\{O_2CC(Me)=NH\}]^{2+}$ [**1** (R^1,R^2 = H)], and higher 2-iminocarboxylato homologues [**1** (R^1 = H)] both the imine-N atom and β-C centre can be deprotonated and used as nucleophiles.[17–19,21,26,31,32] Furthermore, the imine-C atom of **1** (R^1 = H) is susceptible to nucleophiles, or the imine may be reduced to produce the derivative amino acid anions **3** and **4** (Scheme 1), respectively.[17,19,22,26,27,29,30] These capabilities are the basis for the synthetic potential of such imine systems.

Chiral 2-iminocarboxylato cobalt(III) complexes have been obtained from appropriate amino acid precursor complexes by β-elimination,[21] oxidative decarboxylation[27] or oxidation reactions using permanganate[28] or thionyl chloride (in dmf).[23–25] However, (iminoacetato)cobalt(III) complexes (**2**) were not attainable by these procedures. For example, thionyl chloride oxidation of chelated glycine led to oxidation beyond the imine level[23,35] and decarboxylation of the 2-iminomalonato complex, $[(H_3N)_4Co\{O_2CC(CO_2H)=NH\}]^{2+}$, only produced the achiral iminoacetato complex, $[(H_3N)_4Co(O_2CCH=NH)]^{2+}$, in low yield.[17] This paper now reports the synthesis and reactivity of chiral complexes incorporating the iminoacetate ligand and some derivatives. A preliminary account of some of the work has appeared previously.[36]

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 25 °C. Within experimental error all listed values for specific rotations ([*a*], in units of 10^{-1} deg cm^2 g^{-1}) of chiral products did not change on further recrystallization of the product, and this was taken as evidence of optical purity. ^{1}H and ^{13}C NMR spectra were recorded in D_2O on a modified (250 MHz) Bruker HX-270 spectrometer using sodium 3-(trimethylsilyl)propanesulfonate (^{1}H) or 1,4-dioxane (^{13}C, δ = 69.14 ppm relative to Me_4Si) as internal standards. For ^{1}H NMR spectra, only signals associated with non-exchangeable protons are quoted. 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.* 45 °C). Drying *in vacuo* was accomplished over P_4O_{10}. HO_3SCF_3 (3M Comp.) was used as supplied and $NaO_3SCF_3{\cdot}H_2O$ synthesized according to a published procedure.[38] Λ-(+)$_{578}$- and Δ-(−)$_{578}$-[(en)$_2$Co(GlyO)](O$_3$SCF$_3$)$_2$·*n*HO$_3$SCF$_3$ were synthesized as described[34] and used as the analyzed salt mixtures containing residual amounts of HO_3SCF_3; *rac*-[(en)$_2$Co(GlyO)](O$_3$SCF$_3$)$_2$·0.2HO$_3$SCF$_3$ was obtained similarly from *rac*-[(en)$_2$Co(GlyO)]Cl$_2$.[34] Commercial (analytical grade) dmf and absolute EtOH were dried over 3 Å molecular sieves. Diethyl (2-^{13}C, 98%)malonate was obtained from Cambridge Isotope Laboratories, MA, USA.

Synthesis of 2-iminocarboxylato complexes

***rac*-[(en)$_2$Co(O$_2$CCH=NH)]Br$_2$.** A solution of *rac*-[(en)$_2$-Co(GlyO)](O$_3$SCF$_3$)$_2$·0.2HO$_3$SCF$_3$ (32.3 g, 56 mmol) and *N*-bromosuccinimide (13.0 g, 73 mmol) in dry dmf (200 ml) was cooled to ≤−3 °C (ice/salt mixture) in a flask fitted with a $CaCl_2$ drying tube. With stirring and continued cooling, PBr_3 (5.8 g, 21 mmol) was slowly added over 50 min. The coagulated mixture was left without cooling for 1 h before it was mixed with a solution of LiBr (2.0 g, 23 mmol) in water (3.0 ml, 0.17 mol). After cooling in ice, the separated orange solid was collected, washed with EtOH and Et_2O and dried before it was dissolved in hot 0.1 M HBr (90 ml, 50 °C). Addition of LiBr (10 g) and EtOH (80 ml) followed by cooling (5 °C) produced large orange crystals (17.3 g, 75%) which were collected, washed with 50% EtOH, 99% EtOH and Et_2O and dried *in vacuo* (Found: Co, 14.2; C, 17.8; H, 4.2; N, 16.8; Br, 38.3. $CoC_6H_{18}N_5O_2Br_2$ requires Co, 14.34; C, 17.53; H, 4.41; N, 17.04; Br, 38.88%); δ_H (1 mM DCl) 7.97 (s, C*H*), 5.7–4.2 (br, N*H*$_2$) and 3.0–2.6 (br, C*H*$_2$); δ_C (1 mM DCl) 179.7 (*C*H), 175.7 (*C*O$_2$), 48.5, 47.9, 47.2 and 46.6 (*C*H$_2$).

Λ-(+)$_{578}$- and Δ-(−)$_{578}$-[(en)$_2$Co(O$_2$CCH=NH)]Br$_2$. Each enantiomer was synthesized analogously to the racemate above (80% yield) from Λ-(+)$_{578}$- and Δ-(−)$_{578}$-[(en)$_2$Co(GlyO)]-(O$_3$SCF$_3$)$_2$·1.4HO$_3$SCF$_3$, respectively.

Λ-(+)$_{578}$ isomer. [*a*]$_\lambda$ (λ/nm), 0.03% in 0.1 M HBr: 516 (578), 867 (546), −1050 (436) and −975 (364); CD, λ_{max}/nm ($\Delta\varepsilon_{max}$/m^2 mol^{-1}) in 0.1 M HBr: 500 (0.255); (Found: Co, 14.2; C, 17.2; H, 4.5; N, 16.7; Br, 38.3%); λ_{max}/nm (ε_{max}/m^2 mol^{-1}) in 1.2 M $HClO_4$: 482 (10.3) and 304 (75.0); δ_C (1 mM DCl) identical to the racemate.

Δ-(−)$_{578}$ isomer. [*a*]$_\lambda$ (λ/nm), 0.03% in 0.1 M HBr: −512 (578), −858 (546), 1054 (436) and 985 (364); CD, λ_{max}/nm ($\Delta\varepsilon$)$_{max}$/m^2 mol^{-1}) in 0.1 M HBr: 500 (−0.25); (Found: Co, 14.2; C, 17.2; H, 4.6; N, 16.7; Br, 38.5%); δ_C (1 mM DCl) identical to the racemate.

Λ-(+)$_{578}$-[(en)$_2$Co(O$_2$CCH=NH)]Br$_2$·H$_2$O. Crystals for X-ray crystallography were grown from a solution of the anhydrous salt (0.5 g) in 1 M HBr (6 ml, 50 °C) and EtOH (6 ml). After washing with EtOH and Et_2O, the isolated and air dried crystals constituted the monohydrate salt (Found: Co, 13.7; C, 16.6; H, 4.8; N, 16.3; Br, 37.2. $CoC_6H_{20}N_5O_3Br_2$ requires Co, 13.74; C, 16.80; H, 4.70; N, 16.32; Br, 37.25%).

***rac*-[(en)$_2$Co(O$_2$CCH=NH)](O$_3$SCF$_3$)$_2$.** Anhydrous HO_3SCF_3 (25 ml) was slowly added to solid *rac*-[(en)$_2$Co(O$_2$CCH=NH)]Br$_2$ (10.0 g, 24.3 mmol) which gradually dissolved with HBr gas evolution. This process was completed in a vacuum (rotary evaporator) before the homogeneous dark red solution was slowly poured into vigorously stirred Et_2O (0.40 l). The suspended (hygroscopic) orange powder was collected, washed with Et_2O and dried *in vacuo* before it was dissolved in absolute EtOH (60 ml) and the solution heated to boiling for 5 min to initiate crystallization. After cooling in ice, the separated crystalline product (12 g, 88%) was collected, washed with EtOH, Et_2O and dried *in vacuo* (Found: C, 17.8; H, 3.4; N, 12.6. $CoC_8H_{18}F_6N_5O_8S_2$ requires C, 17.49; H, 3.30; N, 12.75%).

Λ-(+)$_{578}$- and Δ-(−)$_{578}$-[(en)$_2$Co(O$_2$CCH=NH)](O$_3$SCF$_3$)$_2$·0.5EtOH. Each enantiomer was synthesized analogously to the racemate above from Λ-(+)$_{578}$- and Δ-(−)$_{578}$-[(en)$_2$Co(O$_2$CCH=NH)]Br$_2$, respectively.

Λ-(+)$_{578}$ isomer. (Found: C, 19.3; H, 3.7; N, 11.8. $CoC_9H_{21}F_6N_5O_{8.5}S_2$ requires C, 18.89; H, 3.70; N, 12.24%).

Λ-(−)$_{578}$ isomer. (Found: C, 19.4; H, 3.7; N, 11.8%).

***rac*-[(en)$_2$Co(O$_2$CCH=NMe)]Br$_2$.** PBr_3 (0.7 g, 2.6 mmol) was added to a solution of [(en)$_2$Co(SarO)](O$_3$SCF$_3$)$_2$·H$_2$O·0.5HO$_3$SCF$_3$[35] (4.2 g, 6.7 mmol) and *N*-bromosuccinimide

(1.6 g, 8.8 mmol) in dry dmf (30 ml). The stoppered reaction mixture was stirred for 5 min when crystallization began. After 20 min without stirring, LiBr (0.2 g, 2.2 mmol) and water (0.14 g) were added and the mixture left for 1 h with occasional gentle swirling to separate the orange solid. This was collected, washed with EtOH and Et_2O and dried on the frit. Dissolution in water (28 ml, 50 °C), gradual addition of LiBr (1.5 g, 17 mmol) and EtOH (*ca.* 12 ml) followed by cooling to 5 °C, overnight, gave large red crystals which were collected, washed with EtOH and Et_2O and dried in the air (2.6 g, 90%) (Found: Co, 13.7; C, 19.3; H, 4.9; N, 16.0; Br, 38.3. $CoC_7H_{20}N_5O_2Br_2$ requires Co, 13.87; C, 19.78; H, 4.74; N, 16.48; Br, 37.60%); δ_H 7.86 (C*H*), 5.8–4.9 (br, NH_2), 3.74 (CH_3) and 3.0–2.7 (br, CH_2); δ_C 175.7 (*C*H), 175.1 (*C*O_2), 48.6 (*C*H_3), 48.4, 47.8, 47.2 and 46.3 (*C*H_2).

***rac*-[(en)$_2$Co(O_2CCH=NMe)]S_2O_6·1.5H_2O.** A solution of [(en)$_2$Co(O_2CCH=NMe)]Br_2 (0.20 g, 0.5 mmol) and $Na_2S_2O_6$·H_2O (2.42 g, 10 mmol) in hot water (27 ml, 55 °C) was slowly cooled to 5 °C. The separated orange crystals (0.15 g, 75%) were collected, washed with EtOH and Et_2O and dried in the air (Found: Co, 13.3; C, 18.5; H, 4.7; N, 15.3; S, 13.3. $CoC_7H_{20}N_5O_8S_2$·1.5H_2O requires Co, 13.03; C, 18.59; H, 5.12; N, 15.48; S, 14.18%); λ_{max}/nm (ε_{max}/m^2 mol^{-1}): 483 (10.9), 300 (82.5). A representative single crystal was selected for X-ray crystallographic analysis.

***rac*-[(en)$_2$Co(O_2CC(Me)=NH)]Cl_2·2H_2O.** PBr_3 (1.18 g, 4.4 mmol) was added to a stirred solution of [(en)$_2$Co(*S*-AlaO)](O_3SCF_3)$_2$ [23] (4.3 g, 6.6 mmol) and *N*-bromosuccinimide (1.75 g, 9.8 mmol) in dry dmf (35 ml). The stoppered reaction mixture was stirred for 1 d before it was diluted tenfold (water) and passed through an AG 50W-X2 column (3.5 × 13 cm, H^+ form). After washing with water (0.2 l) an orange band containing the product and some unreacted starting complex was eluted with 2 M HCl and the eluate evaporated to dryness. The residue was dissolved in 1 M HCl (2 ml) and the imine product crystallized by gradual addition of EtOH (3 ml). The separated crystals (1.9 g, 76%) were collected, washed with EtOH and Et_2O and dried in the air (Found: C, 22.8; H, 6.1; N, 18.5. Calc. for $CoC_7H_{20}N_5O_2Cl_2$·2H_2O: C, 22.59; H, 6.50; N, 18.82%); δ_H 3.1–2.6 (br, CH_2) and 2.52 (CH_3); δ_C 188.4 (*C*CH_3), 175.5 (*C*O_2), 48.4, 47.8, 47.1, 46.5 (*C*H_2) and 24.4 (*C*H_3).

***rac*-[(en)$_2$Co(O_2CC($CH_2CH_2CO_2H$)=NH)](ClO_4)$_2$.** PBr_3 (0.31 g, 1.2 mmol) was added to a stirring solution of Λ,Δ-[(en)$_2$Co{*S*-Glu(OH)O-*N*,*O*^{1}}](O_3SCF_3)$_2$ [23] (1.00 g, 1.55 mmol) and *N*-bromosuccinimide (0.62 g, 3.5 mmol) in dry dmf (6 ml). After 15 min of stirring in a stoppered vessel, the reaction mixture was diluted tenfold (water) and adsorbed on an AG 50W-X2 column (3.5 × 12 cm, H^+ form) as an orange-coloured band. After washing with water, elution with 0.5–3.0 M HCl separated three bands. The eluate of the major orange-coloured (second) band was evaporated to dryness and the residue dissolved in water (2 ml) followed by addition of $NaClO_4$·H_2O (2.0 g, 16 mmol) and EtOH (2 ml). After 7 d, the separated large red crystals (0.30 g) were collected, washed with EtOH and Et_2O (Found: Co, 11.3; C, 20.7; H, 4.0; N, 13.0. Calc. for $CoC_9H_{22}N_5O_{12}Cl_2$: Co, 10.9; C, 20.70; H, 4.25; N, 13.41%); λ_{max}/nm (ε_{max}/m^2 mol^{-1}, in 0.1 M $HClO_4$): 478 (10.2), 297 (96.1), 217 (21.2 × 10^2); δ_H 3.08, 2.92 (2 × t, β- and γ-CH_2) and 2.8–2.6 (br, en-CH_2); δ_C 189.4 (N=*C*), 178.4 (*C*O_2H), 175.1 (*C*O_2Co), 48.3, 47.8, 47.3, 46.6 (en-*C*H_2), 33.0 and 31.6 (β- and γ-*C*H_2).

WARNING! Perchlorates may be explosive and should be handled accordingly.

Products of imine addition reactions

Asymmetric transformation of imine addition reaction products. Experiments were performed in order to follow the change with time of relative product diastereomer distributions in ethanolic reaction mixtures of [(en)$_2$Co(O_2CCH=NH)](O_3SCF_3)$_2$ complex, addition reagent and excess Na_2CO_3. Addition reagents were pentane-2,4-dione, diethyl malonate or ethyl 3-oxo-butyrate. In each experiment, a suspension of *rac*-[(en)$_2$Co(O_2CCH=NH)](O_3SCF_3)$_2$ or Λ-(+)$_{578}$-[(en)$_2$Co(O_2CCH=NH)](O_3SCF_3)$_2$·0.5EtOH (1.0 mmol) and the addition reagent (1.2 mmol) in dry EtOH (4 ml) was stirred in a closed vial before anhydrous Na_2CO_3 (0.6 mmol) was added and the vial closed with a septum. The mixture was continuously stirred at *ca.* 20 °C for 5 d while 0.1 ml samples were withdrawn (syringe) at suitable intervals. Vigorous stirring was applied during sampling in order that samples would represent the heterogeneous reaction mixture at the time of sampling. Quenching was performed by mixing the sample with 0.2 M HCl (1 ml) followed by dilution with water before chromatographic analysis (FPLC equipment (Pharmacia); Mono-S HR 5/5 cation exchange column; gradient elution using 0.167 M Na_2Hcitrate/Na_3citrate buffer; detection: 280 or 254 nm). Chromatograms revealed only two almost completely separated peaks identifiable as the two product diastereomers of the reaction in question. Peak areas were evaluated by a standard procedure assuming the molar absorption coefficients of diastereomers to be essentially equal.

(ΛS,ΔR)-[(en)$_2$Co{O_2CCH[CH(COMe)$_2$]NH_2}](O_3SCF_3)$_2$. Acetylacetone (1.6 g, 16 mmol) followed by anhydrous Na_2CO_3 (0.60 g, 5.7 mmol) were added to a stirred solution of *rac*-[(en)$_2$Co(O_2CCH=NH)](O_3SCF_3)$_2$ (5.5 g, 10 mmol) in dry EtOH (40 ml). After 5 d in a closed vessel at 20 °C the suspension was mixed with a solution of anhydrous HO_3SCF_3 (2.0 g, 13.3 mmol) in dry EtOH (10 ml) and then stirred for 20 min. After dilution with water (0.3 l) the mixture was evaporated to dryness and the residue dissolved in boiling water (60 ml). Dropwise addition of a 50% NaO_3SCF_3 solution (10 ml) followed by cooling to 20 °C resulted in orange crystals (5 g) which were collected, washed with ice-cold 7% NaO_3SCF_3 solution (3 × 10 ml), EtOH and Et_2O and dried *in vacuo*. A second crop (1 g, total yield: 6 g, 92%) was obtained after concentrating the combined mother liquor and aqueous washings to 30 ml, heating to boiling and cooling (Found: Co, 9.1; C, 24.1; H, 3.8; N, 10.6; S, 10.0. $CoC_{13}H_{26}N_5O_{10}S_2F_6$ requires Co, 9.07; C, 24.04; H, 4.04; N, 10.78; S, 9.87%); δ_C 209.5, 209.1 (2 × *C*O), 185.5 (*C*O_2Co) 122.2 (q, *C*F_3), 58.6 (α-*C*H) 48.1, 47.5, 47.4, 46.2 (4 × *C*H_2) 33.6 and 32.6 (2 × *C*H_3).

(ΛS,ΔR)-[(en)$_2$Co{O_2CCH[CH(COMe)$_2$]NH_2}](ClO_4)$_2$. Saturated $NaClO_4$ (3 ml) was added to a solution of (Λ*S*,Δ*R*)-[(en)$_2$Co{O_2CCH[CH(COMe)$_2$]NH_2}](O_3SCF_3)$_2$ (0.78 g, 1.2 mmol) in water (1 ml) in a glass centrifuge tube. Cooling in ice for 1 h induced crystallization, and after centrifugation the mother liquor was removed by decantation. The solid crystalline product was washed with saturated $NaClO_4$ solution (2 × 2 ml) before it was dissolved in hot water (6 ml) and the solution filtered through a microfilter (0.45 μm, Millipore). Saturated $NaClO_4$ solution (2 ml) was added to the filtrate followed by cooling to 5 °C to produce large orange–red crystals (0.48 g, 75%) which were collected and washed with ice-cold water (2 × 0.5 ml) and dried on filter paper (Found: Co, 10.7; C, 24.0; H, 4.6; N, 12.6; Cl, 12.3. $CoC_{11}H_{26}N_5O_{12}Cl_2$ requires Co, 10.71; C, 24.01; H, 4.76; N, 12.73; Cl, 12.89%); δ_C 209.5, 209.4 (2 × *C*O), 185.4 (*C*O_2Co) 58.4 (α-*C*H), 48.0, 47.5, 47.4, 46.1 (4 × *C*H_2), 33.5 and 32.5 (2 × *C*H_3).

WARNING! Perchlorates may be explosive and should be handled accordingly.

(ΛS)-(+)$_{578}$-[(en)$_2$Co{O_2CCH[CH(COMe)$_2$]NH_2}](O_3SCF_3)$_2$·0.5NaO_3SCF_3. Λ-(+)$_{578}$-[(en)$_2$Co(O_2CCH=NH)](O_3SCF_3)$_2$·0.5EtOH (2.75 g, 10 mmol), pentane-2,4-dione (0.8 g, 8 mmol), anhydrous Na_2CO_3 (0.30 g, 2.8 mmol) in dry MeOH (20 ml) were treated as above. The solid residue from evaporation of the diluted reaction mixture was recrystallized by dissolution in boiling water (15 ml), addition of a boiling 50% NaO_3SCF_3 solution (20 ml) and slow cooling to 4 °C. The

crystals (2.6 g, 74%) were collected, washed with 30% NaO_3SCF_3 solution (2 × 5 ml), EtOH and Et_2O and dried *in vacuo*; $[\alpha]_\lambda$ (λ/nm), 0.1% in 0.1 M HCl: 329 (578), 544 (546), −750 (436), −495 (364); (Found: Co, 8.1; C, 22.1; H, 3.3; N, 9.5; S, 10.9. $CoC_{13.5}H_{26}N_5O_{11.5}S_{2.5}F_{7.5}Na_{0.5}$ requires Co, 8.14; C, 22.05; H, 3.56; N, 9.52; S, 10.80%); δ_C identical to racemate, above.

(ΛS,ΔR)-[(en)$_2$Co{O$_2$CCH[CH(CO$_2$Et)$_2$]NH$_2$}](O$_3$SCF$_3$)$_2$. Was synthesized by an addition reaction akin to that described above for (ΛS,ΔR)-[(en)$_2$Co{O$_2$CCH[CH(COMe)$_2$]NH$_2$}](O$_3$SCF$_3$)$_2$ (reaction time: 5 d) but using diethyl malonate (2.00 g, 12.5 mmol) *in lieu* of pentane-2,4-dione. The solid residue obtained from evaporation of the diluted reaction mixture was recrystallized by dissolution in boiling water (80 ml) followed by dropwise addition of a 50% NaO_3SCF_3 solution (5 ml) and isolation of the resulting crystals (6.3 g, 88%) as above (Found: Co, 8.4; C, 25.6; H, 4.2; N, 9.7; S, 8.6. $CoC_{15}H_{30}N_5O_{12}S_2F_6$ requires Co, 8.31; C, 25.39; H, 4.26; N, 9.87; S, 9.04%); δ_C 185.0 (*C*O$_2$Co), 171.4, 170.6 (2 × *C*O$_2$Et), 122.2 (q, *C*F$_3$), 66.4 (2 × *C*H$_2$CH$_3$), 58.6 (α-*C*H), 56.1 (b, weak, β-*C*D), 48.0, 47.5, 47.4, 46.1 (4 × en-*C*H$_2$) and 15.7 (2 × *C*H$_3$).

(ΛS,ΔR)-[(en)$_2$Co{O$_2$CCH[CH(CO$_2$Et)$_2$]NH$_2$}](ClO$_4$)$_2$. Representative crystals for an X-ray crystallographic determination were grown in a microfiltered (0.45 μm, Millipore) solution of (ΛS,ΔR)-[(en)$_2$Co{O$_2$CCH[CH(CO$_2$Et)$_2$]NH$_2$}](O$_3$SCF$_3$)$_2$ (0.15 g) and $NaClO_4 \cdot H_2O$ (0.6 g) in water (20 ml) which evaporated slowly at 20 °C. The large orange crystals were collected and dried between filter papers (Found: Co, 9.8; C, 25.7; H, 4.8; N, 11.3. $CoC_{13}H_{30}N_5O_{14}Cl_2$ requires Co, 9.66; C, 25.59; H, 4.95; N, 11.48%).

WARNING! Perchlorates may be explosive and should be handled accordingly.

[(en)$_2$Co{O$_2$CCH[CH(CO$_2$Et)(COMe)]NH$_2$}](O$_3$SCF$_3$)$_2$. (Single diastereomer or mixture of (Λ2*S*3*S*,Δ2*R*3*R*) and (Λ2*S*3*R*,Δ2*R*3*S*) diastereomers, see Discussion section). Was synthesized in a similar manner to that described above for (ΛS,ΔR)-[(en)$_2$Co{O$_2$CCH[CH(COMe)$_2$]NH$_2$}](O$_3$SCF$_3$)$_2$ using ethyl 3-oxobutyrate (0.8 g, 6.2 mmol) *in lieu* of pentane-2,4-dione. The solid residue from evaporation of the diluted reaction mixture was recrystallized from boiling water (50 ml) by dropwise addition of a 50% NaO_3SCF_3 solution (5 ml) and isolation of the product (2.8 g, 82%) as above (Found: Co, 8.6; C, 24.9; H, 3.9; N, 10.2; S, 8.0. $CoC_{14}H_{28}N_5O_{11}S_2F_6$ requires Co, 8.67; C, 24.75; H, 4.15; N, 10.31; S, 9.44%); δ_C (Consistent with a mixture of two diastereomers in almost equal proportion): 209.4, 207.9 (*C*OCH$_3$); 185.9, 185.7 (*C*O$_2$Co); 171.7, 170.7 (*C*O$_2$Et); 124.7, 119.7 (*C*F$_3$); 66.34, 66.26 (*C*H$_2$CH$_3$); 58.3, 58.2 (α-*C*H); 47.7, 47.1 (double int.), 45.8 (4 × en-*C*H$_2$); 32.7, 32.5 (CO*C*H$_3$); 15.71, 15.67 (CH$_2$*C*H$_3$).

(ΛS,ΔR)-[(en)$_2$Co{O$_2$CCH(C$_5$H$_8$N$_2$)NH$_2$}]Cl$_3$·2H$_2$O. A solution of (ΛS,ΔR)-[(en)$_2$Co{O$_2$CCH[CH(COMe)$_2$]NH$_2$}](O$_3$SCF$_3$)$_2$ (1.30 g, 2.0 mmol), hydrazine monohydrate (0.15 g, 3.0 mmol) and hydrazinium monochloride (0.21 g, 3.0 mmol) in water (10 ml) was left stirring overnight. After acidification (5 ml 2 M HCl) and dilution with water to 0.2 l, the resulting solution was passed through a column of AG 50W-X2 resin (3 × 10 cm). Elution with 1–2 M HCl revealed a minor leading band followed by a major orange band. The eluate of the latter was evaporated to dryness and the residue triturated under EtOH (50 ml) before the solid material was collected and recrystallized from hot water to yield large orange crystals (0.73 g, 76%) which were washed with EtOH and Et_2O (Found: Co, 12.0; C, 26.9; H, 6.5; N, 20.0; Cl, 22.2. $CoC_{11}H_{31}N_7O_4Cl_3$ requires Co, 12.01; C, 26.92; H, 6.37; N, 19.98; Cl, 21.67%); δ_C 184.0 (*C*O$_2$Co), 148.0 (2 × *C*CH$_3$), 116.5 (tert. *C*), 53.5 (α-*C*H), 48.1, 47.7, 47.2, 47.0 (4 × en-*C*H$_2$) and 12.9 (2 × *C*H$_3$).

Isotopically substituted aspartic acid

(ΔR)-(−)$_{578}$-[(en)$_2$Co{(3-^{13}C)Asp(OH)O}]Cl$_2$·0.5EtOH·1.5H$_2$O and (ΔS)-(−)$_{578}$-[(en)$_2$Co{(3-^{13}C)Asp(OH)O}]Cl$_2$·0.5EtOH·0.5H$_2$O. To a stirred solution of Δ-(−)$_{578}$-[(en)$_2$Co(O$_2$CCH=NH)](O$_3$SCF$_3$)$_2$·0.5EtOH (1.94 g, 3.4 mmol) and diethyl (2-^{13}C, 98%)malonate (0.5 g, 3.1 mmol) in dry EtOH (20 ml) was added anhydrous Na_2CO_3 (0.22 g, 2.1 mmol). The reaction vessel was fitted with a $CaCl_2$-drying tube and left with stirring for 1 h. After acidification with HO_3SCF_3 (0.4 ml, 4.4 mmol) in EtOH (7 ml) the reaction mixture was diluted with water (0.2 l) and the solution evaporated to dryness. The orange residue was taken up in 4 M H_2SO_4 (70 ml) and the solution gently refluxed for 2 h before it was diluted with water (1.5 l) and passed down an AG 50W-X2 column (7 × 10 cm). After washing with water (0.2 l) and 0.5 M HCl (0.2 l) all the orange complex was eluted with 3 M HCl and the eluate evaporated to dryness. The residue was dissolved in water (10 ml) and the solution re-evaporated to dryness. This residue was dissolved in water (0.1 l) and sorbed as an orange band on a Na^+-form AG50W-X2 column (7 × 40 cm). Elution with 0.15 M trisodium citrate developed two well-separated, equally sized bands. The eluates of each band (*ca.* 0.6 l) were treated identically and separately. After acidification with 12 M HCl (25 ml) and dilution to 1.3 l with water, desalting was effected on an AG 50 W-X2 column (3 × 12 cm) by elution with 1–2 M HCl. Each eluate was evaporated to dryness, the residue dissolved in water (10 ml) and re-evaporated to dryness before it was triturated under absolute EtOH (25 ml) and Et_2O (10 ml). The resulting powdery products were collected, washed with EtOH and Et_2O and dried *in vacuo*.

(ΔR)-(−)$_{578}$-[(en)$_2$Co{(3-^{13}C)Asp(OH)O}]Cl$_2$·0.5EtOH·1.5H$_2$O (1st band, 0.47 g).[37] δ_C 187.1 (*C*O$_2$Co), 177.5 [d, *J*(CC) 54.4 Hz, *C*O$_2$H], 56.5 [d, *J*(CC) 38.9 Hz, α-*C*H], 48.2, 47.5, 47.4, 46.0 (en-*C*H$_2$) and 39.1 (m + s, enriched, β-*C*H$_2$).

(ΔS)-(−)$_{578}$-[(en)$_2$Co{(3-^{13}C)Asp(OH)O}]Cl$_2$·0.5EtOH·0.5H$_2$O (2nd band, 0.52 g).[37] δ_C 187.1 (*C*O$_2$Co), 177.7 [d, *J*(CC) 54.4 Hz, *C*O$_2$H], 56.0 [d, *J*(CC) 38.6 Hz, α-*C*H], 47.9, 47.5, 47.2, 46.6 (en-*C*H$_2$) and 38.9 (m + s, enriched, β-*C*H$_2$).

(*R*)-(3-^{13}C, 98%)Aspartic acid. To a rapidly stirring solution of (ΔR)-(−)$_{578}$-[(en)$_2$Co{(3-^{13}C)Asp(OH)O}]Cl$_2$·0.5EtOH·1.5H$_2$O (0.52 g, 1.4 mmol) in 0.5 M HCl (20 ml) was added zinc powder (0.31 g, 4.7 mmol). After 60 s, unreacted zinc was removed by filtration and washed with water. All filtrate was passed down an AG 50W-X2 column (3 × 15 cm) developing a narrow pink band. After washing with water (0.25 l) the column was eluted with 0.5 M HCl and the effluent solution passed through a 1 dm quartz cell and monitored polarimetrically at 364 nm. The optically active (colourless) eluate fraction (*ca.* 0.1 l, α_{max} −0.7°) was collected and evaporated to dryness. The solid residue was dissolved in water (10 ml), re-evaporated and recrystallized from boiling water (4 ml) by addition of boiling EtOH (16 ml) and slow cooling to 5 °C. The collected colourless crystals were washed with EtOH and Et_2O and dried *in vacuo*. The mother liquor was reduced to half volume yielding further crystals which were combined with the first batch to give (*R*)-(3-^{13}C, 98%) aspartic acid (95 mg, 50%); $[\alpha]_\lambda$ (λ/nm), 0.16% in 5 M HCl: −54 (436), −86 (364), −138 (313) [commercial D-aspartic acid, 0.16% in 5 M HCl: −51 (436), −84 (364), −133 (313)] (Found: C, 35.9; H, 5.2; N, 10.3 %; M^+ 134. $^{13}CC_3H_7NO_4$ requires C, 35.83 (corrected for enriched isotope); H, 5.26; N, 10.45 %); δ_C (D_2O/DCl) 175.5 [d, *J*(CC) 55.7 Hz, β-*C*O$_2$], 173.0 (α-*C*O$_2$), 51.8 [d, *J*(CC) 37.7 Hz, *C*H], 36.2 (m + s, enriched, *C*H$_2$); *m*/*z* (5 M TCA in glycerol)) 135 (MH^+, 97.7%), 134 (2.3%).

(*S*)-(3-^{13}C, 98%)Aspartic acid. Obtained from (ΔS)-(−)$_{578}$-[(en)$_2$Co{(3-^{13}C)Asp(OH)O}]Cl$_2$·0.5EtOH·0.5H$_2$O (0.52 g, 1.4 mmol) as described above for the (2*R*) enantiomer (107 mg, 57%); $[\alpha]_\lambda$ (λ/nm), 0.16 % in 5 M HCl: 52 (436), 85 (364), 134 (313); (Found: C, 35.8; H, 5.2; N, 10.3%); δ_C (D_2O/DCl) identical to (*R*) enantiomer; *m*/*z* (5 M TCA in glycerol) 135 (MH^+, 97.5%), 134 (2.5%).

Table 1 Summary of crystallographic data

Compound	Λ-[**9**]Br_2·H_2O	[**10**]S_2O_6·1.5H_2O	(Δ*S*,Δ*R*)-[**22**]$(ClO_4)_2$
Empirical formula	$C_6H_{20}N_5O_3Br_2Co$	$C_7H_{23}N_5O_{9.5}S_2Co$	$C_{13}H_{30}N_5O_{14}C_{l2}Co$
Formula weight	429.0	452.4	610.3
Crystal system	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_1/n$	$Pca2_1$
a/Å	8.1300(2)	7.3390(2)	23.9830(2)
b/Å	8.3730(3)	16.3540(3)	8.8240(6)
c/Å	20.9660(6)	14.3640(3)	22.0290(4)
β/°		92.7780(16)	
V/Å^3	1427.21(7)	1721.97(7)	4661.9(3)
Z	4	4	8
μ(Mo-Kα)/mm^{-1}	6.807	1.295	1.045
Crystal size/mm^3	0.34 × 0.23 × 0.14	0.22 × 0.17 × 0.16	0.44 × 0.12 × 0.06
Measured reflections	30189	57596	83343
Independent reflections	6211	7557	17496
R_{int}	0.0445	0.0372	0.0527
Observed reflections[a]/parameters	5893/203	6691/283	15541/812
R^a	0.0436	0.0368	0.0403
$wR(F^2)$	0.1149	0.0951	0.1011

[a] $F^2 > 2\sigma(F^2)$.

Crystallography

Single crystal structure determinations were performed for Λ-(+)$_{578}$-[$(en)_2Co(O_2CCH{=}NH)$]Br_2·H_2O (= Λ-[**9**]Br_2·H_2O), *rac*-[$(en)_2Co(O_2CCH{=}NMe)$]S_2O_6·1.5H_2O (= [**10**]S_2O_6·1.5H_2O) and (Δ*S*,Δ*R*)-[$(en)_2Co\{O_2CCH[CH(CO_2Et)_2]NH_2\}$]$(ClO_4)_2$ (= (Δ*S*,Δ*R*)-[**22**]$(ClO_4)_2$). Data were collected[39] at *T* = 122(1) K with Mo-Kα radiation (λ = 0.71073 Å) on a Nonius Kappa-CCD diffractometer employing ω and Φ scan modes to θ_{max} = 35.0° (all octants). Unit cell parameters were obtained from φ/χ-scan data and refined in DIRAX.[40] The data were integrated with Eval CCD[41] and numerical absorption corrections[42] performed within the maXus suite.[43] The structures were solved with SIR97[44] followed by full-matrix least-squares refinement on F^2 with SHELXL97[45] including all independent reflections and treating all non-hydrogen atoms anisotropically. Hydrogen atoms were identified in the difference electron density maps (except for the H atoms of crystal water molecules). They were included in the refinement with isotropic displacement parameters constrained to $1.2U_{eq}$ of the bonded non-hydrogen atom ($1.5U_{eq}$ for Me groups). For [**10**]S_2O_6·1.5H_2O, all H-atom positions were refined independently. For Λ-[**9**]Br_2·H_2O and (Δ*S*,Δ*R*)-[**22**]$(ClO_4)_2$ the C–H distances of CH_2 groups and N–H distances of NH_2 groups were each restrained to be equal within 0.02 Å. Bond distances to H atoms in NH and CH groups were restrained to 0.91(1) and 0.97(1) Å, respectively. The structure of [**10**]S_2O_6·1.5H_2O had disordered water molecules distributed over three different sites. The population parameters for O atoms at each of these sites were refined independently giving a total crystal water content of 1.48(3) in agreement with the microanalysis results. The absolute configuration of Λ-[**9**]Br_2·H_2O was ascertained by the Flack parameter.[46] The structure of (Δ*S*,Δ*R*)-[**22**]$(ClO_4)_2$ was refined in the space group $Pca2_1$ assuming an inversion-twinned specimen. This precluded determination of the absolute structure but not of relative stereochemistry. A symmetry check[47] indicated a 96% fit for the space group *Pbca* but analysis of the diffraction pattern and systematic absences excluded this possibility. Further crystal data and details relating to data collection and refinement appear in Table 1.

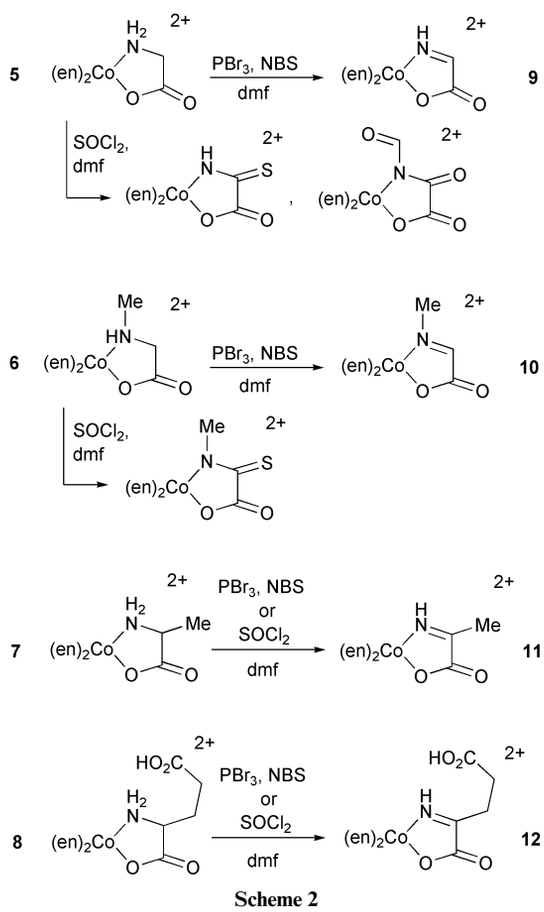
CCDC reference numbers 180573–180575.

See http://www.rsc.org/suppdata/dt/b2/b202090d/ for crystallographic data in CIF or other electronic format.

Results and discussion

2-Iminocarboxylate complexes

The chelated amino acid anions (AAO^-) of Gly, Sar, Ala and Glu were selectively oxidized to their imine derivatives by the reaction of PBr_3 and *N*-bromosuccinimide (NBS)[49] with the triflate salt of the appropriate (amino acidato)bis(ethane-1,2-diamine)cobalt(III) complex, $[(en)_2Co(AAO)](O_3SCF_3)_2$·*n*$HO_3SCF_3$, in dmf (Scheme 2). Thus, the synthetically useful



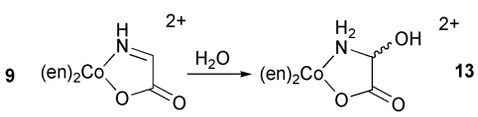
Scheme 2

iminoacetato (**9**) and *N*-methyliminoacetato (**10**) complexes were here obtained directly and simply for the first time and their chemical structures verified by X-ray crystallographic analyses. Earlier, the Ala (**7**) and Glu (**8**) complexes were also transformed into their imine derivatives (**11**, **12**) by a similar oxidative procedure utilizing $SOCl_2$ *in lieu* of the PBr_3/NBS combination in dmf.[23] However, with the Gly (**5**) and Sar (**6**) complexes the $SOCl_2$ procedure only gave carboxamide

products, thus evincing oxidation beyond the imine level in these instances.[35]

During the PBr_3/NBS oxidations of **5**, as racemate and enantiomer, the crude iminoacetato products, *rac*-, Λ- or Δ-[**9**] dibromides, separated from the dmf reaction mixture in each instance, enabling isolation by simple filtration. The same advantage also applied in the oxidation of the racemic Sar complex (**6**) to the *N*-methyliminoacetato product, *rac*-[**10**]Br_2. Clearly, this one-pot procedure constitutes a remarkably simple route to these complexes, and the crude products recrystallized from 1 M HBr below 50 °C in good yield.

For the iminoacetato complex, *rac*-[**9**]Br_2, recrystallization attempts involving temperatures higher than 50 °C typically resulted in mixed products due to partial conversion by hydration. In addition to **9**, these mixtures comprised comparable proportions of another complex which from the ^{13}C NMR evidence was consistent with the 2-hydroxyglycinato complex, **13** (Scheme 3). Thus, apart from all the signals of **9** and additional signals (δ_C 40–50 ppm) ascribed to ethane-1,2-diamine ligands, the ^{13}C NMR spectrum of the mixed product in DCl/D_2O exhibited pairs of signals which are attributed to the carboxylate-C (δ_C 183.4, 183.3) and methine-C (δ_C 80.8, 80.5) atoms of the putative 2-hydroxyglycinate ligand. The proposed structure of **13** sustains two stereogenic centres, and the pairwise grouping of the ^{13}C signals is consistent with a mixture of diastereomers. Attempts to isolate **13** as a pure salt were not successful, nor was this complex observed to revert to the iminoacetato complex (**9**) at any pH. Evidently, the present system strongly favours the hydrated species in both acid and base. This is unusual for such coordinated hemi-aminals which would be expected to eliminate readily in both situations. Fortunately, the hydration reaction (**9** ⟶ **13**) was suppressed in acid and lower-temperature conditions.

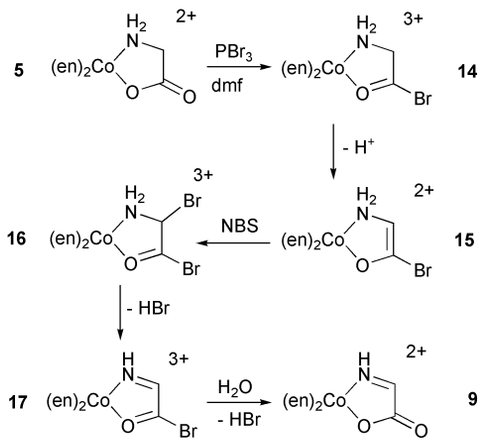


Scheme 3

In keeping with these results, the iminoacetato complex **9** spontaneously transformed ($t_{1/2}$ < 3 min, 25 °C) into the hydrated product **13** at pH 7 in water, apparently reaching an equilibrium (ratio: [**13**]/[**9**] ≈ 6, from ^1H NMR spectroscopy). Signals due to both **9** and **13** were still discernible in the ^{13}C NMR spectrum recorded after 3 d, but decomposition was also evident with the formation of a massive brown precipitate accumulating after 6 d. When a freshly prepared solution of [**9**]Br_2 in D_2O was adjusted to pD 9.2 (boric acid/sodium borate buffer) the initial ^{13}C NMR signals due to **9** and **13** vanished almost immediately, and a brown precipitate formed within a day. By comparison, the *N*-methyliminoacetato complex (**10**) remained unchanged in water at pH 7 for at least 1 h, akin to the reported higher stability of the 2-iminopropanoato type complexes (**1**), for example **11** and **12**.[17–28]

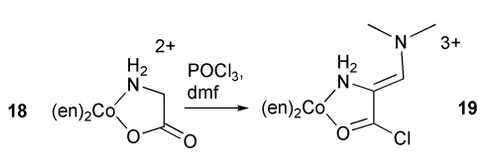
The low-field region of the ^{13}C NMR spectrum of the 2-iminopropanoato complex, [**11**]$Cl_2 \cdot 2H_2O$, in D_2O exhibited resonances at δ_C 188 and 176 ppm, attributed originally to the carboxylate-C and imine-C atoms, respectively.[21,23] However, this assignment is now revised by correlation with the unambiguous assignments attained for the new complexes described here, [**9**]Br_2 [δ_C 180 (N=*C*H), 176 (*C*O_2)] and [**10**]Br_2 [δ_C 176 (N=*C*H), 175 (*C*O_2)], in which the imine-C atoms were readily distinguished from those of the carboxylate group by the APT technique. The carboxylate resonances of the precursor complex ions, **5** to **8**, all fall within the δ_C 188–185 range. Clearly, the carboxylate signals of both the iminoacetato and *N*-methyliminoacetato ligands in **9** and **10** appear *ca.* 10 ppm upfield relative to the related signals of the parent Gly (**5**) and Sar (**6**) complexes, respectively. A similar relationship would be expected to hold between the 2-iminopropanoato complex (**11**) and its parent Ala complex (**7**). Therefore, consistency dictates that the lowfield signal (δ_C 188) of **11** be allocated to the imine-C and the upfield signal (δ_C 176) to the carboxylate, contrary to the assignments made earlier for this[21,23] and a number of homologous systems.[26] The larger deshielding observed for the imine-C in the 2-iminopropanoato complex (**11**) compared with a H-substituted imine-C atom in the imino- and *N*-methyliminoacetato complexes (**9** and **10**) also complies with general expectation.

The strategy for the synthesis of chelated 2-iminocarboxylates was based on a modified Hell–Volhard–Zelinskii reaction.[49] The general mechanism, depicted in Scheme 4, is assumed to involve initial acyl bromide formation which enhances the acidity at the α-C atom allowing α-bromination by NBS and, subsequently, facile loss of HBr. Compared with the standard organic, *i.e.* non-coordinated, situation spontaneous proton loss at the α-C atom is here facilitated by the cationic nature of the complex (**14**), and the carbanionic ligand of **15** then readily captures Br^+ from NBS. The acidity of the proposed N,O-coordinated α-amino-α-bromoacetyl bromide intermediate **16** would also be enhanced and loss of H^+ from the N site promotes elimination of HBr with formation of the 2-iminoacyl bromide **17**. Finally, this hydrolyses to the imino acidate complex, **9**.



Scheme 4

The proposed initial acyl halide formation (⟶ **14**) is implicated by circumstantial evidence. Firstly, the overall reaction of Scheme 4 does not proceed in the absence of PBr_3. Secondly, for reactions of the same or similar complexes in dmf with other acid halides, acyl halide formation has been implicated. Thus, the mechanism of Scheme 4 is analogous to that suggested for related imine forming reactions involving $SOCl_2$ in dmf.[23–25] There, initial acyl halide formation was also invoked as a prerequisite for activation of the α-C centre towards proton loss. However, the $SOCl_2$–dmf reagent mixture did not selectively oxidize the methylene group of Gly, nor of Sar, to the imine but gave only products at the higher carboxamide oxidation level.[35] For the Vilsmeier–Haack-type reaction of the $[(tren)Co(GlyO)]^{2+}$ complex (**18**) involving $POCl_3$ in dmf as reagent, a stable intermediate dimethyliminoacrylyl chloride complex (**19**) was isolated and identified crystallographically (Scheme 5).[33] The presence of the acyl chloride moiety in this product is compelling evidence for the initial acyl halide formation with such reagents.



Scheme 5

In a simple diagnostic test, the acid halides $SOCl_2$ and $POCl_3$ in dmf have been shown to labilise the α-proton of such chelated amino acids through acyl halide formation.[23] Treatment of a 1 : 1 mixture of the diastereomeric valinato complexes (Λ*S*)- and (Δ*S*)-[$(en)_2$Co(ValO)]$(O_3SCF_3)_2$ in dmf with each of the acid halides, above, shifted the diastereomer distribution in favour of the more stable (Λ*S*,Δ*R*) over the less stable (Λ*R*,Δ*S*) diastereomer. This epimerization reaction results from deprotonation followed by inversion and reprotonation at the α-C centre due to activating acyl halide formation. Subsequent hydrolysis traps the equilibrium mixture as the chelate amino acid diastereomers.[23] Similar observations but somewhat weaker activation apply for ester formation.[50] In the current study, using PBr_3 *in lieu* of $SOCl_2$ or $POCl_3$, the same epimerization reaction of the valinato complex system was observed. All these results support the assertion that PBr_3 is able to effect acyl bromide formation with the present amino acidate complexes in dmf (Scheme 4).

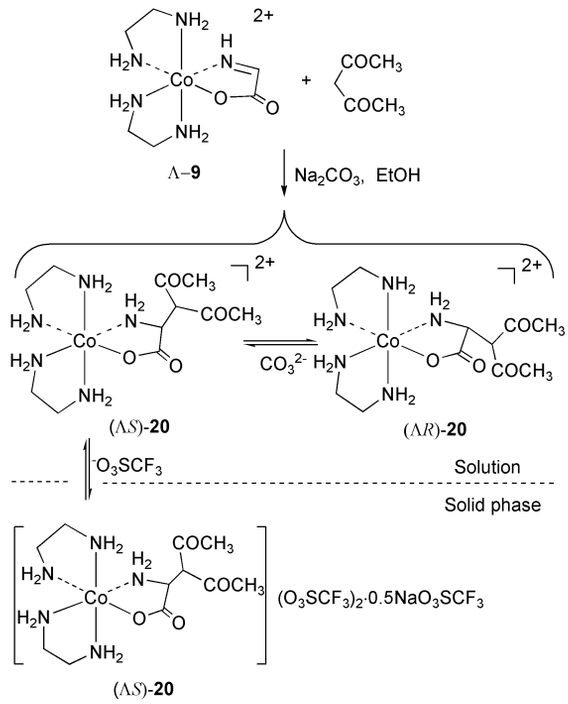
The procedure using the PBr_3/NBS combination in dmf[49] has provided the iminoacetato (**9**) and *N*-methyliminoacetato (**10**) complexes for the first time. In this respect, this new procedure is more selective than the similar procedure using $SOCl_2$ in dmf. The latter method readily produced the 2-iminocarboxylato complexes (**11**, **12**) from the complexes of Ala (**7**), Glu (**8**) and a range of other amino acids, all carrying alkyl substituents at the α-C atoms.[23–25] However, for the Gly (**5**) and Sar (**6**) complexes, bearing no α-C substituents, the $SOCl_2$–dmf oxidation of the α-methylene groups did not stop selectively at the imine but continued to the higher carboxamide level.[35] Thus, the electrophilic $SOCl_2$–dmf reagent combines acid halide reactivity with up to four-electron oxidative capacity. By contrast, in the PBr_3–NBS–dmf system PBr_3 serves solely as an acid halide and NBS cleanly provides the Br^+ ion (for NBS the dominant pathway in non-basic conditions is atom transfer).[51]

At this point some amino acids, for example Asp and Asn, have so far failed to yield dominant 2-iminocarboxylato derivatives by both methods. The β-C proton may also be activated leading to numerous products. Clearly, more research is required to unravel and control such reactivity.

Imine addition and asymmetric transformation reactions

Despite the propensity for hydration in neutral and alkaline aqueous conditions (Scheme 3) the imine-C of the iminoacetato complex (**9**) readily yielded to addition reactions involving carbanionic nucleophiles. Furthermore, unexpectedly high levels of stereoselectivity were achieved with the chiral templates in these reactions.

Two diastereomers can arise from addition at the imine-C of **9** (Scheme 6). From earlier experience with closely related systems, detectable amounts of both diastereomers would be expected.[26] For shorter reaction times (0.5 h) this expectation was borne out by the present systems. However, if reaction mixtures were left longer, a growing proportion of one diastereomer was observed in the product mixture. Thus, after a suspension of *rac*-[**9**]$(O_3SCF_3)_2$, pentane-2,4-dione and Na_2CO_3 in EtOH had been left stirring for 5 d, a single (racemic) diastereomer was obtained in 92% yield and was identified as (Λ*S*,Δ*R*)-[**20**]$(O_3SCF_3)_2$ by X-ray crystallographic analysis of the perchlorate salt.[36] The increase with time of the diastereomeric excess (de) in the product mixture was evaluated chromatographically but on a smaller scale (Fig. 1). After 0.5 h of reaction, samples representing the entire heterogeneous reaction mixture were collected at intervals, quenched with acid, diluted with water and chromatographed. The chromatograms revealed only peaks due to the two diastereomers (Λ*S*,Δ*R*) and (Λ*R*,Δ*S*), and de values were obtained from peak areas. The addition reaction, *per se*, was clearly over within 30 min providing a (heterogeneous) mixture of the two diastereomers in comparable proportions. However, the amount of the (Λ*S*,Δ*R*)



Scheme 6

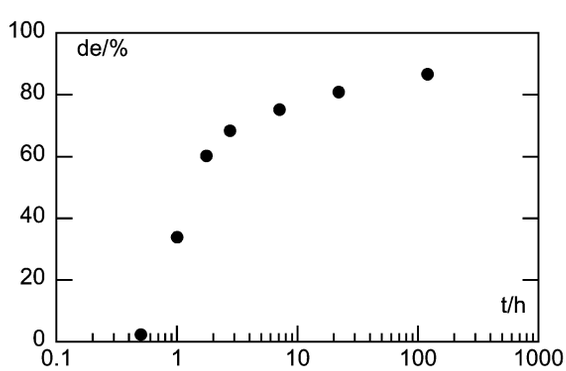


Fig. 1 Diastereomeric composition with time of stirred heterogeneous reaction mixture from reaction of *rac*-[$(en)_2$Co(O_2CCH=NH)]$(O_3SCF_3)_2$ in EtOH with pentane-2,4-dione in the presence of Na_2CO_3. The diastereomeric excess (de) signifies excess of the (Λ*S*,Δ*R*)-**20** diastereomer over the (Λ*R*,Δ*S*)-**20** diastereomer.

diastereomer grew with time at the expense of the (Λ*R*,Δ*S*) diastereomer, and even after 1 d (81% de) the system was largely depleted of the latter. The same pattern was observed when starting with the chiral Λ-$(+)_{578}$-[**9**]$(O_3SCF_3)_2$·0.5EtOH reactant, *in lieu* of *rac*-[**9**]$(O_3SCF_3)_2$, leading to 94% de after 6 d. On a larger scale, enantiopure (Λ*S*)-$(+)_{578}$-[**20**]$(O_3SCF_3)_2$·$0.5NaO_3SCF_3$ was obtained in 74% isolated yield from reaction of Λ-$(+)_{578}$-[**9**]$(O_3SCF_3)_2$·0.5EtOH with pentane-2,4-dione in EtOH in the presence of Na_2CO_3.

These observations may be rationalized in the following way. In aqueous base, 2-aminocarboxylato complexes of the present kind ([$(en)_2$Co(AAO)]$^{2+}$) epimerize *via* base-catalyzed removal of the α-proton with second-order rate constants of $k \approx 10^{-2}$ M^{-1} s^{-1} (25 °C) but resulting in diastereomer ratios of only 1–2 at equilibrium.[37] In the present reaction mixtures (EtOH, saturated with Na_2CO_3) similar optical lability appears to obtain combined with selective crystallization. All the evidence is consistent with the situation illustrated in Scheme 6. Both diastereomers of **20** are initially formed in comparable amounts by the base-catalyzed addition reaction, but the (Λ*S*)-[**20**]$(O_3SCF_3)_2$·$0.5NaO_3SCF_3$ salt is the less soluble diastereomer in the conditions and, therefore, accumulates by crystallization. The diminution of this diastereomer in solution leads to further base-catalyzed epimerization of the more soluble

diastereomer and further separation of the less soluble component. The process effectively transforms the more soluble (Λ*R*) into the less soluble (Λ*S*) diastereomer until the former is largely exhausted. The overall situation (Scheme 6) constitutes a clear case of crystallization-induced asymmetric transformation[52] which Kuhn originally termed "asymmetric transformation of the second kind".[53] In the present case the optically labile component is crystallized with an achiral counterion, whereas most other known cases of crystallization-induced asymmetric transformations involving salts depend on a chiral counterion.[52]

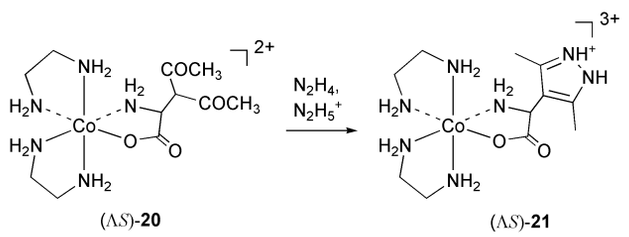
Similar asymmetric transformations and steric preferences were also observed for the other adducts arising from addition reactions of *rac*-[**9**]$(O_3SCF_3)_2$ with diethyl malonate (90% de, 6 d) and ethyl 3-oxo-butyrate (99% de, 5 d) as reagents in EtOH with Na_2CO_3 as basic catalyst. These reagents were chosen with regard to their ease of deprotonation relative to the imine of **9** (pK_a 10–11, in water; estimated).[17] The synthesis should be optimal when the acidity of the reagent is somewhat greater than that of the chelate imine. If too basic conditions are required for deprotonation of the addition reagent, opposing deactivation of the imine may result due to its deprotonation. The resulting dominant diastereomer (racemic) of the diethyl malonate adduct, (Λ*S*,Δ*R*)-[$(en)_2Co\{O_2CCH[CH(CO_2Et)_2]NH_2\}$]$(O_3SCF_3)_2$, was obtained diastereopure by recrystallization. Its relative configuration, established by X-ray crystallography, corresponds to that of the pentane-2,4-dione adduct.

The structure of the product arising from addition of ethyl 3-oxo-butyrate to **9** sustains three stereogenic centres (metal, α-C and β-C) which allow altogether four diastereomers for the isolated product, [$(en)_2Co\{O_2CCH[CH(CO_2Et)(COMe)]NH_2\}$]$(O_3SCF_3)_2$. However, the ^{13}C NMR spectrum (in D_2O and 0.2 M DCl) of the product milked by the crystallization process (5 d) is consistent with a mixture of only two diastereomers in almost equal proportions. Thus, no more than double the number of resonances expected for a single diastereomer were discernible in the spectra, implying that the absolute configurations of two of the three stereogenic centres are fixed relative to each other. Apparent doubling of ^{13}C resonances was evident for all signals of the amino acidate ligand but not for all signals of the ethane-1,2-diamine ligands. These observations imply that the configurations of the metal and α-C centres are fixed relative to each other. Qualitatively, the relative configuration of these centres would be expected to be the same as that determined for the preferred diastereomers of both the pentane-2,4-dione and diethyl malonate adducts, namely (Λ*S*,Δ*R*). Therefore, the ethyl 3-oxo-butyrate adduct is here tentatively assigned as a mixture of the racemic diastereomers, (Λ2*S*3*S*,Δ2*R*3*R*)- and (Λ2*S*3*R*,Δ2*R*3*S*)-[$(en)_2Co\{O_2CCH[CH(CO_2Et)(COMe)]NH_2\}$]$(O_3SCF_3)_2$. This is consistent with the situation that the configuration about the metal and the α-C atom are controlled as for the first two examples but that the configuration about the β-C atom is not controlled. In all three adducts, the β-C protons would readily exchange with solvent protons. Thus, in the ^{13}C NMR spectra of each adduct in D_2O, the expected β-C signals were weak or absent, consistent with partial and complete deuteration. Such proton exchange at a stereogenic β-C centre would also be accompanied by some inversion of this centre, and for the ethyl 3-oxo-butyrate adduct would lead to the epimerized equilibrium mixture implied by the ^{13}C NMR spectra — even in 0.2 M DCl, presumably due to the effect of acid catalysis. It is not clear whether the selectively crystallized ethyl 3-oxo-butyrate adduct constitutes a diastereomeric mixture or a single diastereomer which epimerizes upon dissolution. Analytical ion-exchange chromatography of the product in water revealed only a single band. However, in the conditions of the chromatographic experiment (sodium citrate buffer, pH 5) rapid interconversion between the relevant diastereomers could result in these eluting together.

All three addition products displayed parallel asymmetric transformation behaviour. For at least two of these adducts analogous diastereomer configurations crystallized preferentially in all cases, chiral and racemic, and this apparent generality may also embrace other related systems.

Imine addition reactions of the iminoacetato complex (**9**) inherently give α-amino acid products. With the *N*-methyliminoacetato complex (**10**, Scheme 2) also available, the important subclass of α-(*N*-methylamino) acids[54] would be equally accessible. Only the synthesis of racemic **10** by the NBS/PBr_3 oxidation of *rac*-[$(en)_2Co(SarO)$]$(O_3SCF_3)_2\cdot H_2O\cdot 0.5HO_3SCF_3$[35] was included here. However, for asymmetric synthesis both enantiomers of **10** would be easily obtained from the corresponding chiral precursor complexes.[55] In preliminary studies, *rac*-**10** participated in addition reactions with the nitromethane and pentane-2,4-dione reagents. This contrasts with the corresponding 2-(methylimino)propanoato complex, $[(en)_2Co\{O_2CC(Me)=N(Me)\}]^{2+}$, which has been found not to react.[26]

These synthons and products described above provide routes to many other derivative syntheses. For example, reaction of N_2H_4 with (Λ*S*)-[**20**]$(O_3SCF_3)_2\cdot 0.5NaO_3SCF_3$ yielded the 2-(3,5-dimethyl-4-pyrazolyl)glycinato complex, (Λ,2*S*)-**21**, stereoretentively (Scheme 7). Facile production of isotopically modified aspartic acid was also achieved, as outlined below.



(Λ*S*)-**20** (Λ*S*)-**21**

Scheme 7

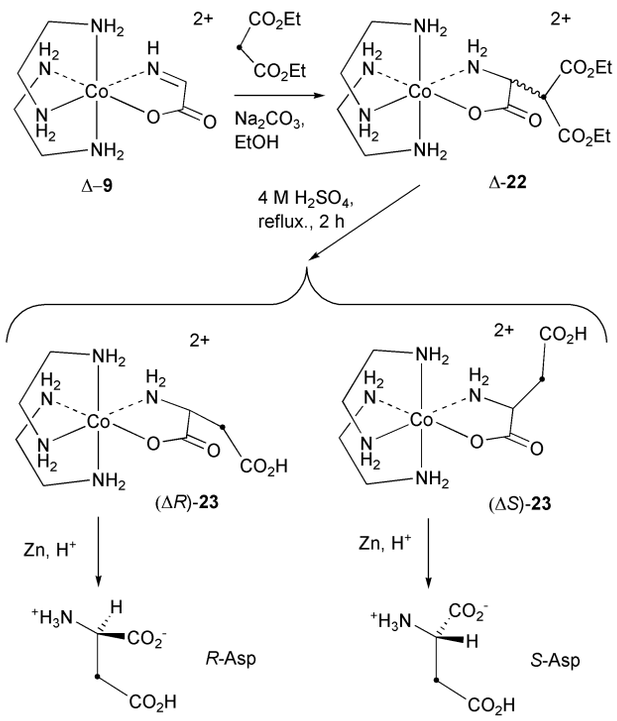
^{13}C-Substituted aspartic acid enantiomers

The ready addition of diethyl malonate to the iminoacetate ligand of **9** permits facile synthesis of ^{13}C-substituted aspartic acid enantiomers using chiral **9** and ^{13}C-substituted malonate ester (Scheme 8). This was exemplified by the synthesis of both enantiomers of (3-^{13}C)aspartic acid. Addition of diethyl (2-^{13}C, 98%)malonate to Δ-**9** followed by ester hydrolysis and monodecarboxylation at the β-C centre (of **22**) provided the isotopically substituted aspartato complex diastereomers (Δ,2*R*)- and (Δ,2*S*)-**23** in almost equal proportions, and these were readily separated by ion exchange chromatography.[37] With the absolute configuration of the chiral precursor Δ-**9** retained in **23**, this separation of diastereomers entails separation of the (3-^{13}C)aspartate enantiomers, and each was subsequently isolated upon liberation by reduction of the robust cobalt(III) to the labile cobalt(II) state.

The ester hydrolysis and decarboxylation reaction conditions (4 M H_2SO_4, reflux, 2 h), alone, produced a diastereomeric mixture of **23**, primarily due to concomitant epimerization at the α-C centre. Thus, if diastereopure diethyl β-carboxyaspartato complex, (Λ*S*,Δ*R*)-[$(en)_2Co\{O_2CCH[CH(CO_2Et)_2]NH_2\}$]$(O_3SCF_3)_2$ [(Λ*S*,Δ*R*)-**22**], was subjected to the same conditions, a nearly 1 : 1 diastereomeric mixture of the (Λ*S*,Δ*R*)- and (Λ*R*,Δ*S*)-**23** complexes also ensued. Clearly, the reaction **22** ⟶ **23** is not stereoretentive with respect to the α-C centre,[56] and this obviates any need for production of diastereomerically pure **22** by the slow (5 d) asymmetric transformation reaction (*vide supra*) prior to conducting the hydrolysis and decarboxylation steps. The immediate products of the addition reaction, (Δ*R*)-**22** and (Δ*S*)-**22**, suffice for further reaction and, this way, the reaction time for the addition step may be reduced to < 1 h at which stage the addition reaction, *per se*, was over.

Table 2 Selected bond distances (Å)

			$(\Lambda S,\Delta R)$-[**22**]$(ClO_4)_2$	
	Λ-[**9**]$Br_2\cdot H_2O$	[**10**]$S_2O_6\cdot 1.5H_2O$	**22a**	**22b**
Co–N1	1.904(4)	1.951(2)	1.964(2)	1.961(2)
Co–O1	1.921(3)	1.905(2)	1.901(2)	1.901(2)
O1–C1	1.299(5)	1.282(2)	1.288(3)	1.287(3)
C1–O2	1.211(5)	1.235(2)	1.234(3)	1.236(3)
C1–C2	1.516(6)	1.498(2)	1.532(3)	1.532(3)
N1–C2	1.291(6)	1.279(2)	1.489(3)	1.489(3)
N1–C3	—	1.460(2)	—	—



Scheme 8

The overall method constitutes a convenient way of producing both enantiomers of isotopically substituted aspartic acid in good yield. Here, diethyl (2-^{13}C)malonate was used to produce both enantiomers of (3-^{13}C)aspartic acid for which no reported syntheses have appeared. With commercially available (1,3-$^{13}C_2$)- and (1,2,3-$^{13}C_3$)malonate esters, the chiral (4-^{13}C)- and (3,4-$^{13}C_2$)aspartic acid compounds, respectively, may be obtained by the same method. Also, the corresponding series of *N*-methyl aspartic acid derivatives may be produced from the *N*-methyliminoacetato complex **10** (*vide supra*).

Crystal structures

The complex cations of **9**, **10** and **22** as found in the crystal structures of Λ-$(+)_{578}$-[**9**]$Br_2\cdot H_2O$, *rac*-[**10**]$S_2O_6\cdot 1.5H_2O$ and $(\Lambda S,\Delta R)$-[**22**]$(ClO_4)_2$ are depicted in Figs. 2 and 3. The two independent cations of $(\Lambda S,\Delta R)$-[**22**]$(ClO_4)_2$ (Fig. 3) have essentially identical bond lengths and angles and in the crystal mainly differ with respect to the orientation of their ethoxy groups. Table 2 lists selected bond distances for the three compounds. Two chelating ethane-1,2-diamine ligands constitute a common feature of all three cations displaying almost identical conformational and geometrical characteristics over the structures with Co–N distances ranging from 1.948 to 1.971 Å, the longest being found in **22**. However, the cations are distinguished by their third chelating ligands which display significant differences within their common N1–C2–C1–O1 moiety. The Co–N1(imine) distance [1.904(4) Å] of the 2-iminoacetato complex (**9**) is very close to distances [1.905(10) and 1.890(3) Å] reported for other 2-iminocarboxylatocobalt(III) complexes.[20,26] Also, the significantly longer Co–N1 distance [1.951(2) Å] of the 2-(methylimino)acetato complex (**10**) confirms a trend set with other 2-(alkylimino)carboxylatocobalt(III) complexes for which Co(III)–N(alkylimine) distances of 1.939(3) and 1.933(7) Å have been reported.[18,26] The longer Co–N1 distances of the 2-(alkylimino)carboxylates seem to be accompanied by shorter Co–O1 distances [1.904(3)–1.909(4) Å][18,26] compared with the 2-iminocarboxylates [Co–O1 distances: 1.919(3)–1.922(7) Å].[20,26] In all instances, the imine N=C distances fall within a narrow range [1.279(2)–1.294(5) Å]. The variation in ligand geometry implies differences in the degree of conjugation between the two related ligands in **9** and **10**. Although the bond lengths in **10** suggest that the 2-(methylimino)acetate ligand is more conjugated it is less planar than the 2-iminoacetate ligand of **9**. Thus, the torsion angle O1–C1–C2–N1 is 1° in **9** and 6–7° in **10**. These variations seem to be caused by the steric effect of the methyl group.

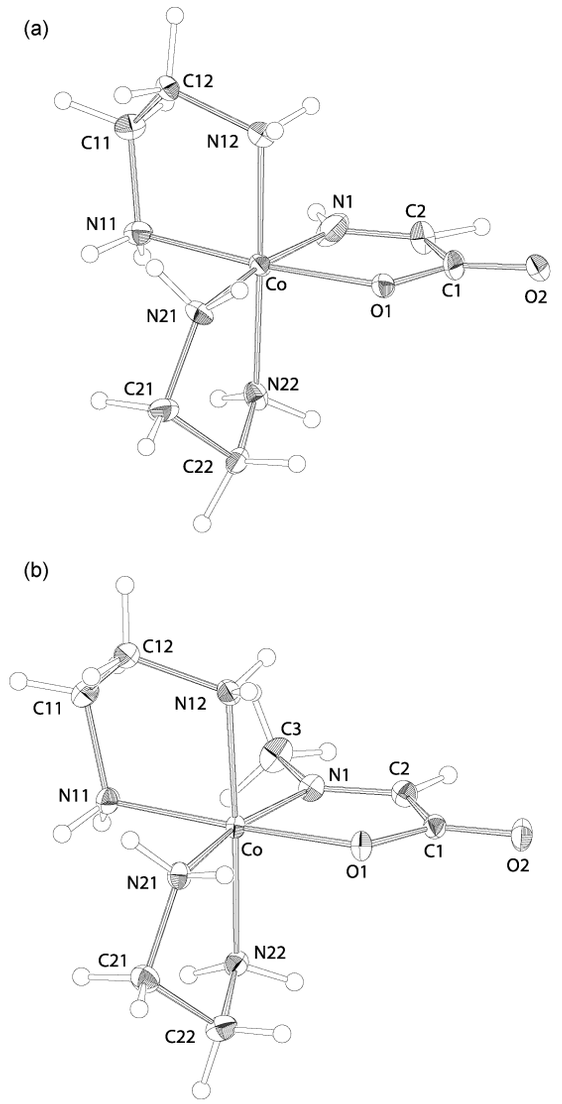


Fig. 2 The molecular structures and atomic numbering scheme of the complex ions Λ-$(+)_{578}$-$[(en)_2Co(O_2CCH{=}NH)]^{2+}$ (a) and *rac*-$[(en)_2Co(O_2CCH{=}NMe)]^{2+}$ (b) with 50% displacement ellipsoids.[48]

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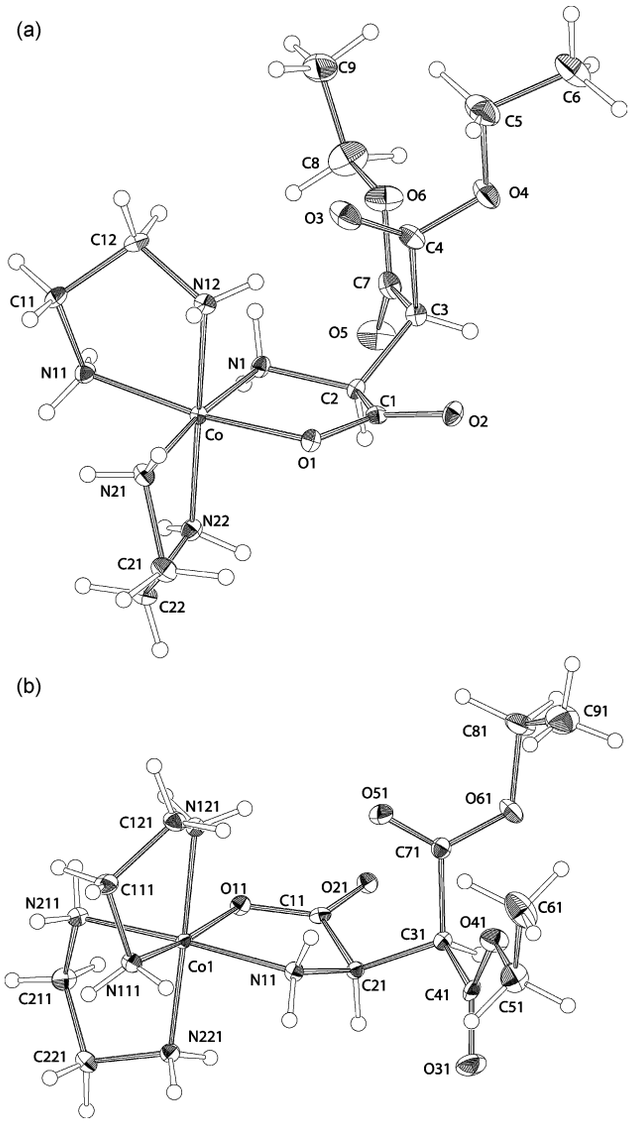

Fig. 3 The molecular structures and atomic numbering scheme of the independent cations of (Λ*S*,Δ*R*)-[(en)$_2$Co{O$_2$CCH(CH(CO$_2$Et)$_2$)-NH$_2$}](ClO$_4$)$_2$ with 50% displacement ellipsoids[48] shown as their (Λ*S*) (a) and (Δ*R*) (b) enantiomers, respectively.

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