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Polydentate ligand construction: intramolecular condensation reactions in the synthesis of imine-containing ligands †

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Intramolecular condensation reactions between coordinated polyamines and 2-ketoacids have been examined as part of a route to the synthesis of polydentate amino acid complexes. Imine-containing products have been isolated, and eight of these have been characterised by X-ray crystallographic techniques. In most cases, only a single product is isolated from these reactions. This selectivity can be attributed largely to the geometric constraints that are placed on a system by formation of the imine group. Reaction between a coordinated primary amine and a 2-ketoacid ligand appears to be a quite general route to polydentate iminoacid complexes.

Introduction

Photodecarboxylation reactions of amino acids coordinated to cobalt(III) have been shown to give rise to metallacyclic products.[1,2] We would like to be able to study the chemistry of the resulting metallacyclic systems in detail, but, unfortunately, the complexes have not proven sufficiently stable for this to be feasible.

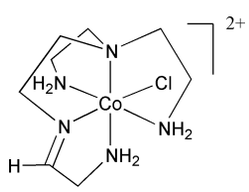
We, and others, have shown recently that incorporation of the initial amino acid fragment into a polydentate ligand leads to metallacycles of enhanced stability being produced in the photolysis reactions.[2g,j] We have therefore undertaken a series of studies with the aim of synthesising cobalt(III) complexes of polydentate amino acids. These complexes would be good candidates for the photochemical preparation of cobalt complexes containing relatively stable three-membered Co–N–C metallacycles.

One of the synthetic routes to the polydentate complexes involves the synthesis of imino acid complexes *via* intramolecular condensation reactions between a polyamine ligand and a keto acid ligand such as pyruvate. Borohydride reduction of the resulting imino acid complexes should produce the related amino acid compounds that are required for the photochemical studies. This paper details the progress we have made in the study of the first step in the synthetic route, preparation of the imino acid complexes.

Condensation reactions between carbonyl-containing ligands and amine ligands are the key steps in a well-established route to the synthesis of complexes of polydentate ligands.[3] In most cases, this has involved the use of aminocarbonyl ligands, but coordinated pyruvate has been condensed with an ammine ligand (rather than a polyamine) to make an imino acid complex.[4] This paper represents an extension of that work, as we explore the generality of the reaction through the use of complexes of a number of different polyamine ligands in reactions with pyruvate, 2-ketoglutarate and, in one case, with phenylpyruvate. ‡ We have also examined two closely related reactions of pyridine-2-carboxaldehyde.

One of the key reasons for using intramolecular condensation reactions for the synthesis of polydentate ligands is that high regioselectivities can be obtained. Such selectivity would be highly desirable in our systems, in order to reduce the number of isomers that might be produced. In a number of cases that appear in the literature, the observed regioselectivity can be attributed to the differences between the acidities of protons on the coordinated primary amines that are available to react with the carbonyl group, an idea that was put forward by Golding *et al.*[3a]

In the synthesis of *mf(f)*-[Co(trenenim)Cl]$^{2+}$, (**1**),§ the condensation occurred only with the primary amine *trans* to the chloride ligand (and not with the other two primary amine groups that are coordinated *trans* to one another).[3a] The protons on the coordinated amine *trans* to the chloride ligand are more acidic than those on the other coordinated primary amines. The nucleophile resulting from this deprotonation will therefore have a greater opportunity to trap the carbonyl group.



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We have shown recently that the preferred planarity of the resulting imine group should prevent the formation of some stereoisomers in our systems, as the imine donor and the two

† Electronic supplementary information (ESI) available: separation of [Co(tetraen)Cl]$^{2+}$ isomers. See http://www.rsc.org/suppdata/dt/b1/b111556a/

‡ Abbreviations for the ligands formed during these reactions are constructed from the accepted single letter abbreviation for the related amino acid (*e.g.* A = alanine, E = glutamic acid, F = phenylalanine), 'im' to indicate that the residue is at the imine oxidation level, followed by the accepted abbreviation for the polyamine to which the residue is attached. Thus, a single pyruvate condensation with coordinated trien gives Aimtrien products, and a double condensation would give Aim2trien products. Picolyl derivatives are formed in the same way using 'p'.

§ The conventions introduced by Hartshorn and House (*J. Chem. Soc., Dalton Trans.*, 1998, 2577–2588) are used to describe the wrapping of polydentate ligands around metal ions in this paper. The descriptors that define the wrapping of polydentate ligands around an octahedral metal are given as prefixes. The descriptors *m* and *f* indicate meridional and facial ligand segments respectively, while a and s (as subscripts) indicate the location of substituents on coordinating atoms (*anti* or *syn* to other donor atoms of the polydentate ligand).

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adjacent donor atoms must be part of a meridional ligand fragment (when 5-membered chelate rings are being considered).[5]

On the other hand, that study revealed also that in the conditions under which these reactions are typically performed, the polyamine ligand can undergo rearrangements around the cobalt(III) centre. These reactions may involve simple epimerisation of coordinated nitrogen atoms, or changes in the relative locations of donor atoms around the central metal ion.

Thus, the number of stereoisomers that might be produced in such a system may be limited by geometrical constraints associated with imine planarity, but not necessarily by the locations of donor atoms in the starting complex. One of the goals of this work was to establish the degree to which these competing factors influence the chemistry of the system.

Experimental

Materials and methods

Dowex 50WX2-400 and SP Sephadex C25 ion exchange resins were obtained from Sigma-Aldrich. Column dimensions are given as height × diameter. Concentration of solutions by removal of solvent was carried out at reduced pressure in a Büchi rotary evaporator equipped with a water aspirator and water bath (<40 °C).

All reagents were of reagent grade or better and were used without further purification, unless otherwise stated.

ff-[Co(trien)Cl_2]Cl,[6] *cis*-[Co(en)$_2Cl_2$]Cl and *trans*-[Co(en)$_2$-Cl_2]Cl[7] were prepared according to literature methods.

f(m)m-[Co(trenen)Cl]$^{2+}$ ¶ was prepared according to the literature method[3] and isolated as the $[ZnCl_4]^{2-}$ salt by addition of 1.01 equivalents of $ZnCl_2$ dissolved in a small portion of aqueous hydrochloric acid (1 M) to solutions of the [Co(trenen)Cl]Cl_2 salt. The solution was taken to dryness on a rotary evaporator at 40 °C and the resulting red powder washed thoroughly with methanol.

The *fff*, *ffm*$_s$ and *ffm*$_a$ isomers of [Co(tetraen)Cl]$^{2+}$ ‖ were prepared from method C of House and Garner[8] on a 10 mmol scale and separated by an adaptation of the method of Yoshikawa *et al*[9] (see ESI). The reagent grade tetraen ligand was found to contain too many impurities, so recrystallized tetraen·5HCl was used, following neutralisation with NaOH. The dichloride salts were obtained as the $[ZnCl_4]^{2-}$ salts by the addition of a 1.01 equimolar amount of $ZnCl_2$ dissolved in a small amount of aqueous hydrochloric acid (1.0 M) to solutions of the [Co(tetraen)Cl]Cl_2 complexes in aqueous hydrochloric acid (1.0 M). The solutions were taken to dryness on a rotary evaporator at 40 °C. The red powders produced were washed thoroughly with methanol to remove any remaining $ZnCl_2$.

f(m)m-[Co(pimtren)Cl]$(ClO_4)_2$ was prepared according to the literature method.[10]

Measurements

^{13}C NMR spectra were recorded on a Varian VXR300 spectrometer using 1,4-dioxane (δ 67.19 ppm) as an internal standard and dilute DCl (~0.01 M, 99% D) as the solvent. Infra-red spectra were run on a Shimadzu FTIR-8201PC using KBr disks. A Hewlett Packard 8452A spectrophotometer was used to record the UV-visible spectra in 1 mM HCl, and the data are reported as λ_{max}/nm (ε_{max}/M^{-1} cm^{-1}). Elemental analyses were performed by the University of Otago Microanalytical Service.

Syntheses

***mffm*$_a$-[Co(Aimtetraen)]$ZnCl_4$.** *ffm*$_s$-[Co(tetraen)Cl]$ZnCl_4$ (1.23 g, 2.5 mmol), pyruvic acid (0.48 g, 5.5 mmol), 2,6-lutidine (0.29 g, 2.75 mmol) and 225 mL of methanol were heated at reflux for 48 h. An orange precipitate developed during this time. The solution was cooled to room temperature, and then at −10 °C. The orange product was filtered off and dried under suction. Yield: 1.23 g (93%). Anal. calcd. for $C_{11}H_{24}Cl_4$-CoN_5O_2Zn·0.5CH_3OH: C, 25.56; H, 4.85; N, 12.96%. Found: C, 25.68; H, 4.85; N, 13.15%. Absorption spectrum λ_{max} (ε_{max}): 466 nm (228 M^{-1} cm^{-1}). IR: 1693, 1585 cm^{-1}. ^{13}C{^{1}H} NMR (ppm): 181.8 (C=N), 173.4 (COOM), 57.1, 54.6, 54.2, 53.3, 52.6, 50.8, 50.4, 48.8 (CH_2NH_2), 19.2 (CH_3). Use of *ffm*$_a$-[Co(tetraen)Cl]$ZnCl_4$ and *fff*-[Co(tetraen)Cl]$ZnCl_4$ in this reaction resulted in the same product being isolated, in similar yields.

***mmf(f)*-[Co(Aimtrenen)]$ZnCl_4$.** *f(m)m*-[Co(trenen)Cl]$ZnCl_4$ (0.49 g, 1 mmol), pyruvic acid (0.18 g, 2 mmol), triethylamine (0.11 g, 1.1 mmol) and 90 mL of methanol were heated at reflux for 48 h. The solution, containing an orange/tan-coloured precipitate, was cooled at −10 °C, and filtered under suction. The resulting solid was dried under vacuum over P_2O_5. Yield: 0.46 g (87%). Anal. calcd. for $C_{11}H_{24}Cl_4CoN_5O_2Zn$·0.75$CH_3OH$: C, 25.73; H, 4.96; N, 12.77%. Found: C, 25.33; H, 5.00; N, 12.40%. Absorption spectrum λ_{max} (ε_{max}): 458 nm (296 M^{-1} cm^{-1}). IR: 1686 cm^{-1}. ^{13}C{^{1}H} NMR (ppm): 181.1 (C=N), 173.3 (COOM), 63.2, 62.2, 62.0 (CH_2N), 57.8 (CH_2N=C), 52.2, 51.7 (CH_2NH), 46.3, 46.2 (CH_2NH_2), 18.5 (CH_3).

***mff*-[Co(Aimtrien)Cl]Cl.** *ff*-[Co(trien)Cl_2]Cl (1.56 g, 5 mmol), pyruvic acid (0.48 g, 5.5 mmol), 2,6-lutidine (0.60 g, 5.6 mmol) and 200 mL of methanol were heated at reflux for 12 h. The solution was stood at room temperature for 24 h, during which time a carmine precipitate crystallized on the flask walls. The solution was filtered under suction to give a carmine crystalline powder. Yield: 0.61 g (35%). Anal. calcd. for $C_9H_{19}Cl_2CoN_4O_2$: C, 31.32; H, 5.55; N, 16.23%. Found: C, 31.39; H, 5.58; N, 16.27%. Absorption spectrum λ_{max} (ε_{max}): 487 nm (193 M^{-1} cm^{-1}). IR: 1674, 1597 cm^{-1}. ^{13}C{^{1}H} NMR (ppm): 180.0 (C=N), 174.3 (COOM), 57.5, 56.4, 55.7, 54.8, 53.5 (CH_2NH, CH_2N=C), 45.1 (CH_2NH_2), 19.1 (CH_3).

***mffm*-[Co(Aim2trien)]$_2ZnCl_4$.** *ff*-[Co(trien)Cl_2]Cl (0.78 g, 2.5 mmol), pyruvic acid (0.88 g, 10 mmol), 2,6-lutidine (1.07 g, 10 mmol) and 400 mL of methanol were heated at reflux for 24 h. Methanolic $ZnCl_2$ {$ZnCl_2$ (0.34 g, 2.5 mmol) in 5 mL of methanol} was added dropwise to the hot solution. The solution was cooled at room temperature for 16 h, during which time an orange precipitate formed. The reaction mixture was reduced in volume to 100 mL on a rotary evaporator at 40 °C, cooled at −10 °C and filtered under suction to give an orange crystalline powder. Yield: 0.97 g (86%). Anal. calcd. for $C_{12}H_{20}Cl_2CoN_4O_4Zn_{0.5}$·$CH_3OH$: C, 32.61; H, 5.05; N, 11.70%. Found: C, 32.52; H, 4.92; N, 11.86%. Absorption spectrum λ_{max} (ε_{max}): 458 nm (350 M^{-1} cm^{-1}). IR: 1680, 1659 cm^{-1}. ^{13}C{^{1}H} NMR (ppm): 180.8 (C=N), 173.8 (COOM), 55.9, 54.9, 53.7 (CH_2NH, CH_2N=C), 19.1 (CH_3).

***m*-[Co(Aimen)$_2$]Cl.** *cis*-[Co(en)$_2Cl_2$]Cl (1.43 g, 5.0 mmol), pyruvic acid (1.77 g, 20.0 mmol), triethylamine (1.52 g, 15.0 mmol) and 650 mL of methanol were heated at reflux for 6 h. An orange precipitate was evident in the solution. The reaction mixture was reduced in volume to 50 mL on a rotary evaporator at 40 °C, cooled at 0 °C, filtered under suction and the orange precipitate obtained dried under vacuum over P_2O_5. Yield: 1.26 g (71%). A small sample was recrystallized as the $[ZnCl_4]^{2-}$ complex from aqueous HCl (1 M) and $ZnCl_2$ (0.5 equiv.). Anal. calcd. for $C_{10}H_{18}Cl_2CoN_4O_4Zn_{0.5}$·0.5$H_2O$: C, 27.94; H, 4.46; N, 13.04%. Found: C, 27.97; H, 4.54; N, 13.08%. Absorption spectrum λ_{max} (ε_{max}): 462 nm (290 M^{-1} cm^{-1}). IR: 1674, 1643 cm^{-1}. ^{13}C{^{1}H} NMR (ppm): 180.5 (C=N), 174.3 (COOM), 54.8 (CH_2-

¶ trenen = 3-(2-aminoethyl)-3,6-diazaoctane-1,8-diamine.
‖ tetraen = 3,6,9-triazaundecane-1,11-diamine.

N=C), 46.3 (CH_2NH_2), 19.0 (CH_3). Use of *trans*-[Co(en)$_2$Cl$_2$]Cl in this reaction resulted in the same product being isolated, in a similar yield.

***mffm$_a$*-[Co(Eimtetraen)]ZnCl$_4$.** *ffm$_s$*-[Co(tetraen)Cl]Cl$_2$ (0.355 g, 1 mmol), α-ketoglutaric acid (0.292 g, 2 mmol), LiOH (0.048 g, 2 mmol) and 50 mL of methanol were heated at reflux for 24 h. Methanolic $ZnCl_2$ {$ZnCl_2$ (0.136 g, 1 mmol) in 5 mL of methanol} was added dropwise to the hot solution, which was heated at reflux for a further 30 min. The solution was cooled to room temperature, followed by further cooling at 0 °C. The orange precipitate was filtered off under suction, washed with a small amount of acetone and dried under vacuum over P_2O_5. Yield: 0.44 g (76%). A small sample was recrystallized from aqueous HCl (1 M). Anal. calcd. for $C_{13}H_{26}Cl_4CoN_5O_4Zn\cdot 2H_2O$: C, 25.24; H, 4.89; N, 11.32%. Found: C, 25.57; H, 4.70; N, 11.44%. Absorption spectrum λ_{max} (ε_{max}): 464 nm (225 M^{-1} cm^{-1}). IR: 1720, 1666, 1593 cm^{-1}. $^{13}C\{^1H\}$ NMR (ppm): 183.0 (C=N), 176.9 (COOH), 172.7 (COOM), 57.1, 54.6, 54.2, 53.3, 52.8, 50.8, 50.4 (CH_2N, CH_2NH), 48.8 (CH_2NH_2), 30.6, 28.4 (sidechain CH_2).

***mffm*-[Co(Eim2trien)]$_2$ZnCl$_4$.** *ff*-[Co(trien)Cl$_2$]Cl (0.31 g, 1 mmol), α-ketoglutaric acid (0.73 g, 5 mmol), LiOH (0.12 g, 5 mmol) and 250 mL of methanol were heated at reflux for 18 h. Methanolic $ZnCl_2$ {$ZnCl_2$ (0.20 g, 1.5 mmol) in 10 mL of methanol} was added dropwise to the hot solution. The turbid solution was cooled to room temperature and the volume reduced to 25 mL on a rotary evaporator at 40 °C. The reaction mixture was cooled at 0 °C, filtered under suction and the precipitate obtained washed with acetone. The orange product is hygroscopic. Yield: 0.39 g (69%). Absorption spectrum (λ_{max}): 456 nm. $^{13}C\{^1H\}$ NMR (ppm): 181.8 (C=N), 176.5 (COOH), 173.0 (COOM), 56.1, 55.1, 54.1 (CH_2N, CH_2NH), 30.3, 28.2 (pendant CH_2).

[Co(Fimtetraen)]ZnCl$_4$. *ffm$_s$*-[Co(tetraen)Cl]Cl$_2$ (0.355 g, 1 mmol), phenylpyruvic acid (0.25 g, 1.5 mmol), 2,6-lutidine (0.16 g, 1.5 mmol) and 150 mL of methanol were heated at reflux for 24 h. An orange film developed on the inside wall of the flask and the solution turned orange during this time. The mixture was cooled to room temperature. The volume was made up to 500 mL with 0.1 M HCl. The mixture was loaded onto a Dowex column (H+ form, 12 × 7 cm) and the column was prewashed with 0.1 M HCl. Two bands developed on elution with 0.5 M and then 1 M HCl. The first band was red and proved to be starting material. The orange second band was collected and taken to dryness on a rotary evaporator. The orange residue was taken up in methanol (100 ml) and a small amount of brown material removed by filtration. Two equivalents of $ZnCl_2$ were added as a methanolic solution (25 mL) to give an orange precipitate. The volume was reduced to 40 mL and the solution was then cooled to 0 °C. Filtration gave an orange solid. Yield: 0.29 g (48%). A small sample was recrystallised by slow evaporation from aqueous HCl (3 M). Anal. calcd. for $C_{17}H_{28}Cl_4CoN_5O_2Zn\cdot H_2O$: C, 33.01; H, 4.89; N, 11.32%. Found: C, 33.26; H, 4.80; N, 11.22%. Absorption spectrum λ_{max} (ε_{max}): 466 nm (250 M^{-1} cm^{-1}). IR: 1674 cm^{-1}. $^{13}C\{^1H\}$ NMR (ppm): 182.0 (C=N), 172.9 (COOH), 133.1, 130.1, 129.9, 128.7 (phenyl), 57.1, 54.6, 54.5, 54.1, 53.2, 50.7, 50.3, 48.9 (CH_2N, CH_2NH), 38.5 (sidechain CH_2).

[Co(pimtetraen)](ZnCl$_4$)Cl. *ffm$_s$*-[Co(tetraen)Cl]ZnCl$_4$ (0.49 g, 1 mmol), pyridine-2-carboxyaldehyde (0.54 g, 5 mmol) and 90 mL of methanol were heated at reflux for 60 h. An orange/brown precipitate was evident and increased in quantity when methanolic $ZnCl_2$/LiCl {$ZnCl_2$ (0.14 g, 1 mmol) and LiCl (0.04 g, 1 mmol) in 10 mL of methanol} was added dropwise, resulting in further precipitation. The solution was cooled to room temperature, the product filtered off under suction, washed with acetone and dried under vacuum over P_2O_5. Yield: 0.52 g (80%). The crude material was found to contain at least two isomers by $^{13}C\{^1H\}$ NMR. The major isomer was recrystallized from the crude material by slow evaporation of an aqueous HCl (1 M) solution. Yellow/brown crystals grew from the slowly evaporating solution. Major isomer: Anal. calcd. for $C_{14}H_{26}Cl_5CoN_6Zn$: C, 28.99; H, 4.52; N, 14.49%. Found: C, 28.87; H, 4.57; N, 14.45%. Absorption spectrum λ_{max} (ε_{max}): 458 nm (251 M^{-1} cm^{-1}). IR: 1645, 1638, 1617, 1607 cm^{-1}. $^{13}C\{^1H\}$ NMR (ppm): 175.8 (py-CH=N), 158.8 (quaternary C), 153.4, 143.8, 132.3, 131.3 (4 tertiary py C's), 58.9, 58.2, 58.0, 55.9, 54.8, 53.1, 53.0, 47.6 (CH_2NH_2).

Crystal structure determinations

The X-ray data were collected on a Siemens P4 four circle diffractometer, using a Siemens SMART 1K CCD area detector and irradiating the samples with graphite monochromated Mo-Kα(λ = 0.71073 Å) X-rays. The crystals were mounted 5.5 cm from the detector. The data were collected by the SMART program[11] and processed with the help of SAINT,[12] applying Lorentz and polarisation corrections to the diffraction spots (integrated 3 dimensionally). SADABS[13] was used to scale the diffraction data, apply empirical absorption corrections and to apply decay corrections where required. The structures were refined by direct methods using the SHELXTL program.[14] Hydrogen atoms were calculated at ideal positions and refined using a riding model.

Crystallographic data are shown in Table 1.

***mffm$_a$*-[Co(Aimtetraen)ZnCl$_4$.** Crystals of *mffm$_a$*-[Co(Aimtetraen)]ZnCl$_4$ (orange blocks) were grown by vapour diffusion of acetone into a solution of *mffm$_a$*-[Co(Aimtetraen)]ZnCl$_4$ in aqueous hydrochloric acid (0.1 M).

***mmf(f)*-[Co(Aimtrenen)]ZnCl$_4$·H$_2$O.** Crystals of *mmf(f)*-[Co(Aimtrenen)]ZnCl$_4$·H$_2$O (orange rods) were grown by vapour diffusion of acetone into a solution of *mmf(f)*-[Co(Aimtrenen)]ZnCl$_4$ in aqueous hydrochloric acid (0.1 M).

***mff*-[Co(Aimtrien)Cl]Cl.** Crystals of *mff*-[Co(Aimtrien)Cl]Cl (red plates) were grown by vapour diffusion of acetone into a solution of *mff*-[Co(Aimtrien)Cl]Cl an aqueous hydrochloric acid (0.1 M).

***mffm*-[Co(Aim2trien)]$_2$ZnCl$_4$.** Crystals of *mffm*-[Co(Aim2trien)]$_2$ZnCl$_4$ (orange blocks) were grown by vapour diffusion of methanol into a solution of *mffm*-[Co(Aim2trien)]$_2$ZnCl$_4$ in aqueous hydrochloric acid (0.01 M).

***m*-[Co(Aimen)$_2$]$_2$ZnCl$_4$.** Crystals of *m*-[Co(Aimen)$_2$]$_2$ZnCl$_4$ (orange blocks) were grown by slow evaporation of an aqueous solution of *m*-[Co(Aimen)$_2$]Cl and 0.5 equivalents $ZnCl_2$.

***mffm$_a$*-[Co(Eimtetraen)]ZnCl$_4$·2H$_2$O.** Crystals of *mffm$_a$*-[Co(Eimtetraen)]ZnCl$_4$ (orange needles) were grown by slow evaporation of a solution of *mffm$_a$*-[Co(Eimtetraen)]ZnCl$_4$ in aqueous hydrochloric acid (1.0 M).

***m$_a$ffm*-[Co(pimtetraen)](ZnCl$_4$)Cl.** Crystals of *m$_a$ffm*-[Co(pimtetraen)](ZnCl$_4$)Cl (yellow/brown blocks) were grown by slow evaporation of a solution of crude [Co(pimtetraen)](ZnCl$_4$)Cl in aqueous hydrochloric acid (1.0 M).

***f(m)m*-[Co(pimtren)Cl](ClO$_4$)$_2$.** Crystals of *f(m)m*-[Co(pimtren)Cl](ClO$_4$)$_2$ (red blocks) were grown by vapour diffusion of acetone into a solution of *f(m)m*- [Co(pimtren)Cl](ClO$_4$)$_2$ in aqueous hydrochloric acid (1 mM).

CCDC reference numbers 176555–176562.

See http://www.rsc.org/suppdata/dt/b1/b111556a/ for crystallographic data in CIF or other electronic format.

Table 1 Crystallographic data

Compound	*mffm*$_a$-[Co(Aimtetraen)]-$ZnCl_4$	*mmf(f)*-[Co(Aimtrenen)]-$ZnCl_4 \cdot H_2O$	*mff*-[Co(Aimtrien)Cl]-Cl	*mffm*-[Co(Aim2trien)]$_2$-$ZnCl_4$	*m*-[Co(Aimen)$_2$]$_2$-$ZnCl_4$	*mffm*$_a$-[Co(Eimtetraen)]-$ZnCl_4$	*m*$_a$*ffm*-[Co(pimtetraen)]-$(ZnCl_4)Cl$	*f(m)m*-[Co(pimtren)Cl]-$(ClO_4)_2$
Formula	$C_{11}H_{24}Cl_4CoN_5O_2Zn$	$C_{11}H_{26}Cl_4CoN_5O_3Zn$	$C_9H_{19}Cl_2CoN_4O_2$	$C_{24}H_{40}Cl_4Co_2N_8O_8Zn$	$C_{10}H_{18}Cl_2CoN_4O_5Zn$	$C_{13}H_{30}Cl_4CoN_5O_6Zn$	$C_{14}H_{26}Cl_5CoN_6Zn$	$C_{12}H_{22}Cl_3CoN_5O_9$
M	524.45	542.47	345.11	893.67	436.80	618.54	579.96	545.63
Crystal system	Monoclinic	Monoclinic	Monoclinic	Tetragonal	Monoclinic	Orthorhombic	Triclinic	Triclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$	$I4_1/a$	$P2_1/c$	$Pna2_1$	$P\bar{1}$	$P\bar{1}$
a/Å	8.927(3)	7.933(3)	8.966(4)	10.797(3)	12.501(3)	14.131(5)	8.627(2)	8.235(3)
b/Å	15.035(5)	22.849(10)	14.474(7)	10.797(3)	19.753(4)	9.479(3)	9.318(2)	9.612(3)
c/Å	14.714(5)	11.323(5)	10.343(5)	30.419(12)	14.227(3)	17.514(6)	14.226(4)	14.315(5)
α/°							82.903(3)	93.980(5)
β/°	104.915(4)	90.984(7)	98.319(7)		111.397(7)		75.790(3)	94.152(5)
γ/°							84.019(4)	112.341(5)
V/Å^3	1908.3(10)	2052.2(15)	1328.0(11)	3546(2)	3270.9(12)	2345.9(14)	1096.8(5)	1039.5(6)
Z	4	4	4	4	4	4	2	2
T/K	163(2)	163(2)	163(2)	163(2)	163(2)	168(2)	163(2)	163(2)
μ/mm^{-1}	2.701	2.518	1.694	1.952	2.119	2.224	2.472	1.267
Reflections collected	23538	23646	16417	22282	41392	26513	13500	13220
Independent reflections	3883	3626	2690	1824	6690	4746	4374	4200
Observed reflections	3644	2586	2351	1575	5742	4547	4227	3826
Parameters refined	217	227	177	108	406	301	244	321
$R[I > 2\sigma(I)]$	0.026	0.028	0.027	0.021	0.032	0.028	0.026	0.032
$Rw[I > 2\sigma(I)]$	0.064	0.054	0.071	0.057	0.090	0.074	0.067	0.086

Results and discussion

In a typical reaction, a cobalt(III) complex containing a polyamine ligand and at least one relatively labile ligand was heated in methanol with a 2-ketoacid and sufficient base to ensure that the carboxylic acid group is deprotonated. The products that were isolated contained new polydentate ligands that result from the condensation of a primary amine donor atom with the ketone of the 2-ketoacid.

The products have been characterised by ^{13}C NMR spectroscopy, UV-vis spectrometry, elemental analysis and, in many cases, by single crystal X-ray crystallography. ^{1}H NMR spectroscopy was not particularly useful in characterising these compounds, as the methylene region of the spectra was rather congested. The complexes had relatively high solubilities in water, which meant that ^{13}C NMR spectra could be collected over quite short periods of time. These spectra revealed a significant amount of information about the product complexes. For example, the additional resonances at low field, and the reduction in the number of resonances in the 45–50 ppm range (which are assigned to carbon atoms adjacent to coordinated primary amines), were characteristic of the formation of the imine complexes. The number of resonances in the methylene and other regions of the ^{13}C NMR spectrum could be used, in some cases, to identify whether one or two such condensation reactions had occurred on a complex and to provide information on the symmetry elements that may be present in the molecule. On occasion, coincidence of resonances was observed in the methylene region of the ^{13}C NMR spectrum.

The X-ray structure determinations confirmed those structural assignments that had been made on the basis of the spectroscopic data and, in some cases, notably those of the tetraen-derived complexes, they were vital to determining the precise way in which the polydentate ligand was wrapped around the metal ion. For example, such determinations allow the configurations of coordinated secondary amines to be established unequivocally. The structures were all approximately octahedral, with the deviations being unremarkable for systems containing chelate rings of this kind.

The imine bonds in these structures were found to fall in the range 1.267(3)–1.287(5) Å, with the bulk of them being near the middle of this range, clearly distinguishing them from other kinds of C–N bonds in the structures (amines 1.458–1.53 Å, pyridines 1.342–1.367 Å). The bonds between the cobalt atom and the imine nitrogen atom were always shorter than those between the metal and the other nitrogen donor atoms. Typically, they were approximately 0.05 Å shorter than the next smallest Co–N bond (the errors on each bond were 0.003 Å or less).

By analogy with the stepwise processes that have been been examined for related reactions with aminocarbonyl compounds,[3] we propose that the reactions described herein proceed *via* initial ligand exchange. The carboxylate group of the 2-ketoacid substitutes for the labile ligand (either directly or with a solvent-bound intermediate), and then a subsequent reaction between the ketone of the new ligand and the coordinated primary amine would give rise to the imine-containing products.

This subsequent reaction actually consists of several steps, deprotonation of the coordinated amine, nucleophilic attack by the deprotonated amine on the ketone and dehydration of the resulting carbinolamine to give the final imine. Detailed study of an aminocarbonyl-containing system showed that this final step appears to occur only when the imine nitrogen atom and the adjacent donor atoms form part of a meridional ligand fragment (at least when 5-membered chelate rings are being considered).[5] Indeed, it was seen that if the intermediate carbinolamine is not able to dehydrate for this reason, the polyamine wrapping around the metal ion will rearrange in order to allow the dehydration to occur.

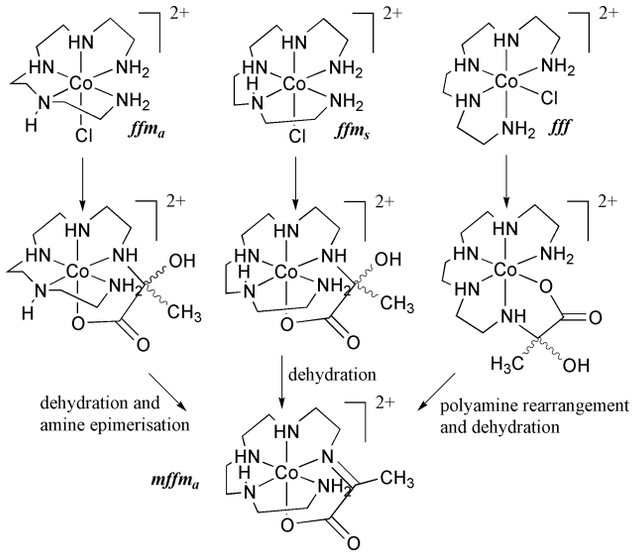

Fig. 1 Possible routes to the common product from reactions of the $[Co(tetraen)Cl]^{2+}$ stereoisomers.

Three isomeric polyamine complexes, *fff*-, ffm_s- and ffm_a-$[Co(tetraen)Cl]^{2+}$, were subjected separately to reaction with pyruvate. It can be seen in Fig. 1 that when the chloride ligand is replaced by pyruvate, the *ffm* isomers can form a carbinolamine that is part of a meridional ligand fragment, which means it can then dehydrate directly to give an imine. In the case of the *fff* isomer, the pyruvate could react to give a carbinolamine, but the subsequent dehydration cannot occur immediately because the imine donor will not be at the centre of a meridional ligand fragment. The polyamine ligand wrapping would have to be altered in order to allow the dehydration to occur.

We expected, based on the earlier studies, that the polyamine portion of the ligand would rearrange in such a way as to allow the dehydration to occur. Indeed, all three complexes give the same product, shown in Fig. 2 (structure 1); that which has the same polyamine wrapping as the ffm_s starting material.

It is not especially surprising that the same *mffm* wrapping is observed for all three isomers reacting with pyruvate, and for all the other condensation reactions of the $[Co(tetraen)Cl]^{2+}$ ion. If the first three donor atoms of a linear hexadentate ligand are restricted to a meridional arrangement (in this case because of the presence of the imine group), then the *mffm* wrapping is the only one that will allow all six donor atoms to be coordinated to an octahedral metal atom.

In the basic conditions under which the reaction is conducted, it is also not surprising that epimerisation of meridional secondary amine donor atoms can occur during the reactions, thus the ffm_s-derived product (the $mffm_a$ complex) can be formed from the ffm_a starting material.** The factors influencing the configuration at the meridional secondary nitrogen donor atom are clearly rather subtle, as the opposite configuration (m_affm) is observed to be the major product from the condensation reaction with pyridine-2-carboxaldehyde. In this latter case, it is possible that steric interactions between the pyridine ring and the methylene groups of the polyamine ligand lead to the opposite configuration at the meridional nitrogen donor atom being preferred.

** The hydrogen atom on the secondary nitrogen atom is defined as being *syn* or *anti* to the donor atom that is considered first in the wrapping description of the polydentate ligand. The attachment of an additional donor atom of higher rank (a carboxylate oxygen atom) during the condensation reaction results in a change in the end from which the wrapping description is begun. This, in turn, gives a different representation for an unchanged configuration around the meridional nitrogen atom. In the case of the pyridine-2-carboxaldehyde condensation reactions, the ligand wrapping description still begins at the amine end of the ligand.

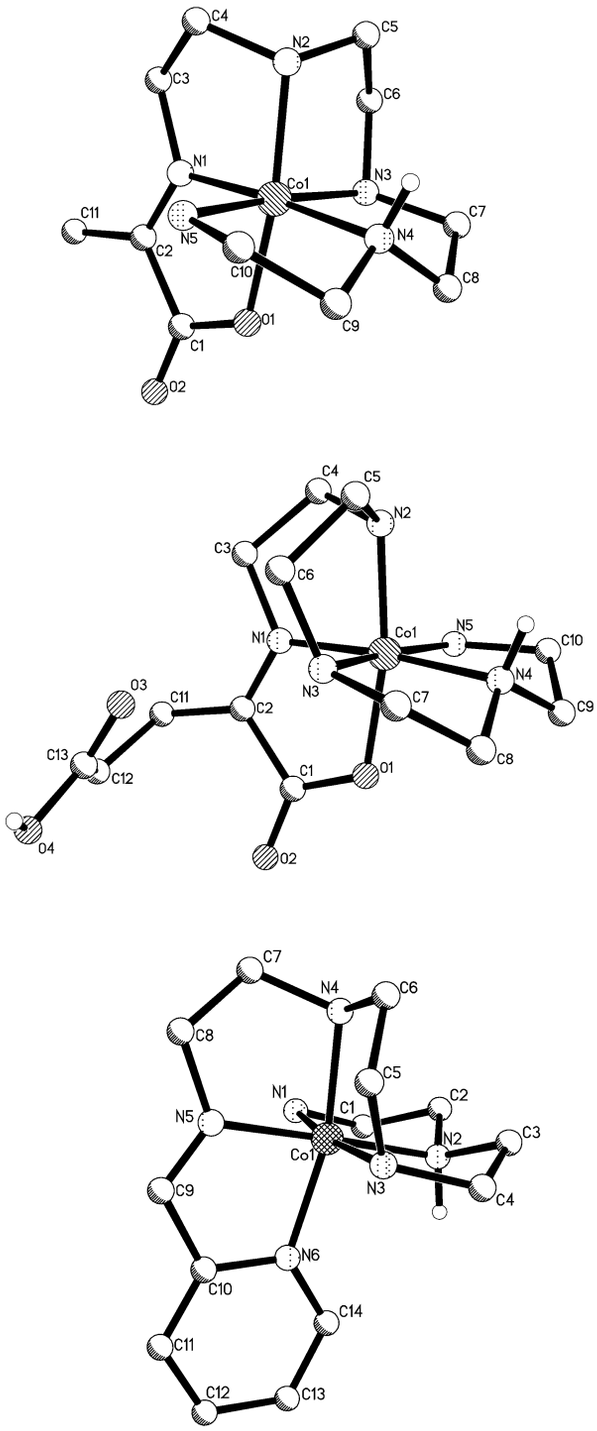

Fig. 2 X-Ray structures determined for the products of intramolecular condensation reactions between coordinated tetraen and pyruvate (top), 2-ketoglutarate (middle), and pyridine-2-carboxaldehyde (bottom). Most hydrogen atoms have been omitted for clarity.

The observed isomerisation of the tetraen complexes during the reactions with pyruvate indicated that it may not be worthwhile attempting to separate isomers of starting materials prior to attempting these kinds of reactions. The mixture of isomers could therefore be used in subsequent reactions of carbonyl-containing ligands with coordinated tetraen.

The results of X-ray studies on the compounds produced in these reactions are shown in Fig. 2. X-ray data was not obtained for the $[Co(Fimtetraen)]^{2+}$ complex, so we are unable to unequivocally assign the wrapping of the polyamine portion of the ligand in this molecule. However, there was a high degree of similarity between the ^{13}C NMR data obtained for this complex and those from the other two keto-acid-derived complexes, and significant differences from the data obtained for the pyridine-2-carboxaldehyde-derived complex. We believe, therefore, that the polyamine wrapping is the same in all of the iminoacid-tetraen complexes.

Only in the condensation reaction with pyridine-2-carboxaldehyde was a mixture of condensation products observed, perhaps reflecting a balance between a preference for the *ffm*$_s$-based wrapping, shown in all other cases, and the consequences of additional steric interactions that may be present in the pyridine system.

The case of $[Co(trenen)Cl]^{2+}$ is rather interesting in the context of the regiochemistry of these reactions. Here, only one product is isolated from the condensation reaction with pyruvate (Fig. 3). It is clearly the product that would result from

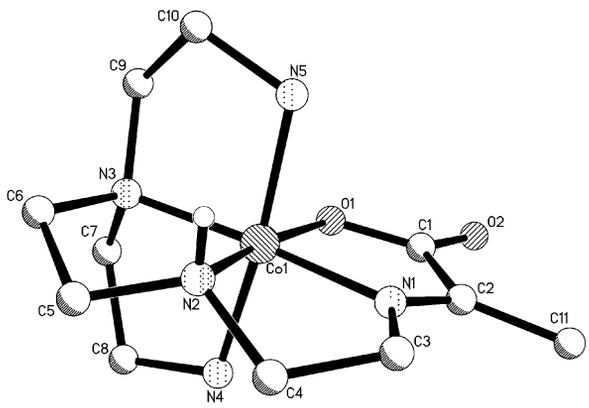

Fig. 3 The X-ray structure determined for the product of an intramolecular condensation reaction between coordinated trenen and pyruvate. Most hydrogen atoms have been omitted for clarity.

replacement of the chloride ligand by pyruvate and then condensation with the primary amine at the end of the longest of the three arms. The interest here lies in the fact that if the pyruvate does replace the chloride ligand, then why should it not be able to react with one of the two short arms instead? Clearly, such an intermediate carbinolamine could not dehydrate until the ligand had rearranged, but this kind of reaction has been seen in other cases (*e.g.* that of *fff*-$[Co(tetraen)Cl]^{2+}$, discussed above).

The relative acidity of protons on coordinated amines has been identified as a significant factor in determining the likely site of such condensation reactions, but, in this case, all three primary amine groups are coordinated *trans* to amine donors. This means that, while their acidities will not necessarily be identical, they are unlikely to be very different. Indeed, the increased acidity of coordinated amines in these kinds of systems has been correlated with shorter cobalt(III)–nitrogen bond lengths, and the bond lengths to the relevant amines in closely related structures are all rather close to one another.[15]

One possibility is that this selectivity may result from steric interactions between the coordinated pyruvate and parts of the polyamine ligand. Reaction with the short-arm amines may require the pyruvate to adopt a position in which there are significant steric interactions with the rest of the complex (possibly between the pyruvate methyl group and the methylene groups of the long arm of the polyamine ligand). Reaction with the long arm, on the other hand, would not require the coordinated pyruvate ligand to be particularly close to any other part of the molecule.

An alternative rationalisation for the selectivity of the condensation reaction with $[Co(trenen)Cl]^{2+}$ relies on the possibility that, during such a reaction, carbinolamine formation might be reversible, but that imine formation is not (due to the high stability of the resulting complex). In such circumstances, any

carbinolamines formed from reaction with the short arm of the trenen ligand may be in equilibrium with uncyclised material. They are unable to undergo immediate dehydration because the geometric constraints enforced by imine formation are incompatible with the ligand wrapping, and the process of ligand rearrangement that would allow subsequent dehydration to occur is a comparatively slow process. Reaction between coordinated pyruvate and the long arm of the trenen ligand is a competing process and, since this can be followed rapidly by the irreversible dehydration reaction that leads to the imine, essentially all of the material would follow this path.

This latter explanation for the selectivity may have important implications for predicting regioselectivity in some systems. If potential amine condensation sites have approximately the same acidity, those which allow immediate dehydration to give the imine (without ligand rearrangement) will be favoured over those which do not.

We have also achieved condensation reactions in which two equivalents of keto acids have been condensed to form complexes containing two imino acid fragments. An excess of the keto acid is required for these reactions. If less than this excess is used, then a significant amount of the singly-condensed material is observed. In one case, such a complex has been isolated and fully characterised (Fig. 4). Double condensation

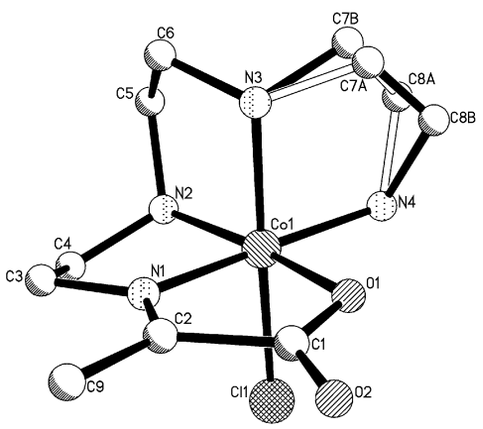

Fig. 4 The X-ray structure of the compound in which one equivalent of pyruvate has condensed with coordinated trien. Hydrogen atoms have been omitted. Disorder in one of the chelate rings has been modelled with C7 and C8 in two alternative positions.

products are shown in Fig. 5. Unfortunately, the double condensation product from the reaction of *ff*-$[Co(trien)Cl_2]^+$ with 2-ketoglutarate was not amenable to crystallisation, and the hygroscopic nature of the solid material that was isolated precluded elemental analysis. However, we are confident in our structural assignment of this material, based on the similarity of the ^{13}C NMR data to that obtained for the analogous material derived from reactions with pyruvate. Collectively, the products of these reactions demonstrate that it is possible to achieve these reactions at more than one site in the same molecule.

The presence of an imine group as the second donor in a linear hexadentate ligand is sufficient to restrict the number of possible ligand wrappings to one (as mentioned above). The second imine group in these double condensation products (in place of the secondary amine that was present in the tetraen cases) further limits the possible number of isomers in these systems. Indeed, the geometrical constraints ensure that only two stereoisomers exist for these double condensation products, and they are enantiomers. The same is true for the en-based condensation product. It appears, therefore, that while the polyamine backbone wrapping is not necessarily fixed during the reaction, the presence of imine can restrict the number of isomers that are produced.

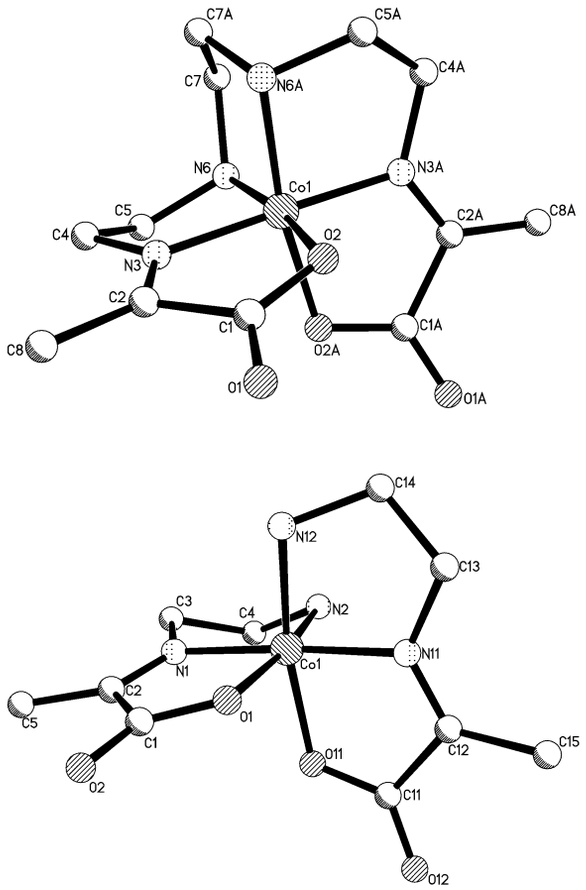

Fig. 5 X-Ray structures of compounds resulting from condensation of two equivalents of pyruvate with coordinated trien (top) and bis(en) units. Hydrogen atoms have been omitted for clarity.

The final structure that is included in this paper is that of the known compound, *f(m)m*-$[Co(pimtren)Cl](ClO_4)_2$.[10] This structure (Fig. 6) confirms the structural assignment that was made

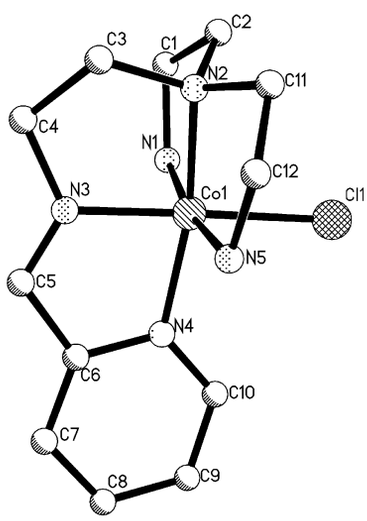

Fig. 6 The X-ray structure of the product from condensation of coordinated tren with pyridine-2-carboxaldehyde. Hydrogen atoms have been omitted for clarity.

for this compound and is consistent with the predictions for the location of the condensation reaction that can be made based on the acidity of the protons on the coordinated amines. The formation of this compound is strictly analogous to that of the *mf(f)*-[Co(trenenim)Cl] (**1**) complex discussed in the introduction.

Conclusion

Coordination of 2-ketoacids and then condensation with coordinated primary amines leads to production of new ligands with higher denticity. The geometrical constraints associated with the presence of the imine group restrict the number of wrappings that are available to the polydentate ligand, and the ability of the polyamine ligands to change wrapping around the central metal ion can actually facilitate the formation of a particular isomer. Indeed, it has become apparent from this study that such reactions can be performed with starting material that is a mixture of stereoisomers. However, if there are multiple possible condensation sites available to a coordinated keto acid, it appears possible that those in which an immediate dehydration can occur will be favoured.

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