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Condensation Reactions of Cobalt Amino Acid Complexes with Formaldehyde: Preparation and Crystal Structures of Cobalt Complexes Containing New Hexadentate, Pendant-Arm Macrocyclic and Acyclic Ligands

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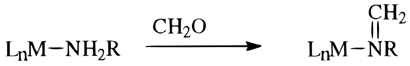
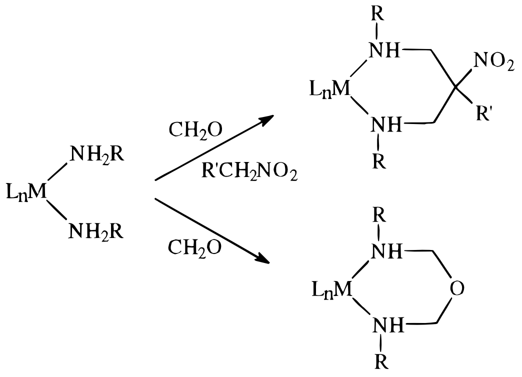
The reaction of cobalt(III) complexes α-*cis*-$[Co(EDDA)L]^+$ containing both amino acid (EDDA, ethylenediamine-*N,N′*-diacetate) and bidentate amine ligands (L = en, ethylenediamine; Men, *N*-methylethylenediamine; BEE, *N,N′*-diethylethylenediamine; DEE, *N,N*-diethylethylenediamine) with formaldehyde under basic conditions has been investigated. For L = en, the product is $[Co(L^1)]^+$, which contains a macrocyclic ligand (L^1 = 1,4-bis(carboxymethyl)-6,13-dioxacyclam) formed by linking the primary nitrogens on the en ligand with the secondary nitrogens on the EDDA ligand through two CH_2OCH_2 bridges. For L = Men and DEE, which each contain only one primary nitrogen, the reaction gives complexes $[Co(L^2)]^+$ and $[Co(L^3)]^+$ bearing hexadentate acyclic ligands (L^2 = 1,4-bis(carboxymethyl)-11-ethyl-6-oxa-1,4,8,11-tetraazatridecane; L^3 = 1,4-bis(carboxymethyl)-6-oxa-1,4,8,11-tetraazadodecane) each resulting from formation of one new CH_2OCH_2 linkage. All complexes have been characterized by ^1H and ^{13}C NMR, IR, and UV−visible spectroscopy and cyclic voltammetry. The X-ray crystal structures of $[Co(L^1)]Cl{\cdot}3H_2O$ and $[Co(L^3)]PF_6{\cdot}NH_4PF_6{\cdot}H_2O$ have been determined. $[Co(L^1)]Cl{\cdot}3H_2O$ is monoclinic, $P2_1/n$, with $a = 14.792(3)$ Å, $b = 7.766(1)$ Å, $c = 16.520(4)$ Å, $\beta = 99.54(2)°$, $V = 1871.5(6)$ Å^3, $Z = 4$, $R = 0.042$. $[Co(L^3)]PF_6{\cdot}NH_4PF_6{\cdot}H_2O$ is monoclinic, $P2_1/n$, with $a = 13.353(6)$ Å, $b = 11.595(2)$ Å, $c = 16.900(5)$ Å, $\beta = 95.59(3)°$, $V = 2604(2)$ Å^3, $Z = 4$, $R = 0.107$.

Introduction

Metal-mediated template reactions of coordinated amines with aldehydes are an important area in coordination chemistry.[1] In the case of primary amines, the condensation product can be a coordinated imine, which, while itself a reactive group, has under some conditions been isolated (eq 1). A subset of this type of reaction involves the reaction of formaldehyde with coordinated primary amines in the presence of an additional coupling agent such as a nitroalkane or an amine, leading to the linkage of two coordinated ligands through a newly created bridge formed from intermediate imine fragments (eq 2).[2] In a very few examples, formaldehyde alone has been shown to be sufficient as the coupling agent, linking two amines through an ether bridge, and it is this type of reaction that is relevant to the work to be presented here (eq 3).[3,4]



$$L_nM{-}NH_2R \xrightarrow{CH_2O} L_nM{-}\overset{\overset{\displaystyle CH_2}{\|}}{N}R \qquad (1)$$



(2)

(3)

In just one example involving amino acid rather than amine ligands, the nitrogen atoms of two amino acid ligands coordinated to copper are linked through a three-carbon bridge formed from formaldehyde and nitroethane.[5,6] As outlined above, the condensations of coordinated amines with aldehydes result in reaction at nitrogen. In contrast, the corresponding reactions of chelated α-amino acids largely involve activation of the α-carbon atom, giving hydroxyalkyl derivatives as shown by a number of studies on Cu(II) and Co(III) amino acid complexes.[7] In copper complexes, reaction at the coordinated nitrogen to give *N*-α-hydroxyalkyl or imine intermediates is believed to occur prior to reaction at the α-carbon.[8,9] For cobalt, there is as yet no direct evidence that activation at nitrogen prior to reaction at the α-carbon is required.[7,9]

The chemistry described in this paper features two new aspects. First, bridge formation utilizing formaldehyde alone has been reported for coupling reactions between two coordinated amines on cobalt(III)[3] and copper(II),[4] but it has never been observed for the correponding reaction involving two coordinated amino acids or between coordinated amino acid and amine ligands. It is this last combination that will be explored

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(1) Black, D. St. C. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1987; Vol. 1, Chapter 7.4, p 415; Vol. 6, Chapter 61.1, p 155.

(2) Comba, P.; Curtis, N. F.; Lawrance, G. A.; Sargeson, A. M.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1986**, *25*, 4260.

(3) Geue, R. J.; Snow, M. R.; Springborg, J.; Herlt, A. J.; Sargeson, A. M.; Taylor, D. *J. Chem. Soc., Chem. Commun.* **1976**, 285.

(4) Lawrance, G. A.; Maeder, M.; O'Leary, M. A.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1991**, *44*, 1227.

(5) Comba, P.; Hambley, T. W.; Lawrance, G. A.; Martin, L. L.; Renold, P.; Várnagy, K. *J. Chem. Soc., Dalton Trans.* **1991**, 277.

(6) Balla, J.; Bernhardt, P. V.; Buglyo, P.; Comba, P.; Hambley, T. W.; Schmidlin, R.; Stebler, S.; Várnagy, K. *J. Chem. Soc., Dalton Trans.* **1993**, 1143.

(7) Hay, R. W. In *Rections of Coordinated Ligands*; Braterman, P. S., Ed.; Plenum: New York, 1989; Vol. 2, p 223.

(8) Phipps, D. A. *Inorg. Chim. Acta* **1978**, *27*, L103.

(9) Casella, L.; Pasini, A.; Ugo, R.; Visca, M. *J. Chem. Soc., Dalton Trans.* **1980**, 1655.

below, the use of formaldehyde for coupling of the coordinated amino acid EDDA (*N,N′*-ethylenediaminediacetate) with coordinated diamines, in particular ethylenediamine and its derivatives.[10] Second, the products of this chemistry involve reaction at the EDDA nitrogen atoms, in contrast to the alkylation at the α-carbon reported previously for the reactions of formaldehyde with coordinated amino acids.

The chemistry discussed here will focus on cobalt(III) complexes containing EDDA and a coordinated diamine. Cobalt complexes of this type have been described, and reports have focused on investigations of structure, spectroscopy, stereochemistry, and ligand substitution rate studies.[11] However, very little reaction chemistry has been described, and certainly reactions of coordinated ligands such as those to be described below are hitherto unknown for this class of complexes. We have prepared both known and new examples of cobalt(III) EDDA diamine complexes, and for all complexes full spectroscopic characterization will be presented. The use of these complexes as precursors for the formaldehyde condensation reactions will be detailed. These reactions link the amino acid and amine nitrogen atoms through three-atom ether bridges, forming new hexadentate, pendant-arm macrocyclic and acyclic ligands.

Experimental Section

Materials and Measurements. Ethylenediamine-*N,N′*-diacetic acid (EDDA, Aldrich), *N,N′*-diethylethylenediamine (BEE, Aldrich), *N*-methylethylenediamine (Men, Aldrich), *N,N*-diethylethylenediamine (DEE, Sigma), and all other reagent grade chemicals were used without further purification. α-*cis*-[Co(EDDA)(en)]Cl,[12] β-*cis*-[Co(EDDA)(en)]Cl,[13] α-*cis*-[Co(EDDA)(H_2O)$_2$]ClO_4,[12] and K{α-*cis*-[Co(EDDA)(NO_2)$_2$]}[14] were prepared using published procedures. Sephadex-SP C-25 ion exchange resin (Pharmacia) was used in all cases where the experimental procedure required the purification of crude reaction mixtures. All chromatography columns were prepared by washing with water and then either 1 mol L^{-1} HCl (to convert to H^+ form) or 1 mol L^{-1} NaCl (to convert to Na^+ form). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker AM 400 spectrometer, operating at 400.1 and 100.6 MHz, respectively. All spectra were recorded in D_2O, except where noted. Either TSP-d_4 (3-(trimethylsilyl)propionic-*2,2,3,3*-d_4 acid, sodium salt) or DSS (3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt) was used as the internal reference for spectra recorded in D_2O, but all data have been referenced to TSP-d_4 as 0.0 ppm, where DSS is 0.162 ppm vs TSP ($^{13}C\{^1H\}$ spectra) and 0.18 ppm vs TSP (^1H spectra). Infrared spectra were recorded as Nujol mulls between KBr plates on a Digilab FTS-7 FTIR spectrometer. Ultraviolet−visible (UV−vis) spectra were recorded on a Shimadzu UV-2100 spectrometer using as solvent a phosphate buffer solution (pH 7) prepared from 0.1 mol L^{-1} potassium dihydrogen phosphate and 0.1 mol L^{-1} NaOH. Cyclic voltammograms and Osteryoung square wave voltammograms were recorded using a BAS 100A electrochemical analyzer. The BAS-supplied electrodes used were glassy carbon (working electrode), platinum wire (counter electrode), and Ag/AgCl gel (reference electrode). The Ag/AgCl gel reference electrode was determined to be 39 mV negative of the saturated calomel electrode (SCE). The solvent employed was phosphate buffer solution (pH 7) prepared from 0.1 mol L^{-1} potassium dihydrogen phosphate and 0.1 mol L^{-1} NaOH. Microanalyses were carried out at the University of Otago by Dr. R. G. Cunninghame and associates and are gratefully acknowledged.

Safety Note. Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with great caution.

[Co(EDDA)(BEE)]ClO_4·H_2O. α-*cis*-[Co(EDDA)(H_2O)$_2$]ClO_4 (0.400 g, 1 mmol) was dissolved in water (6 mL) to which *N,N′*-diethylethylenediamine (0.128 g, 1 mmol) and activated charcoal (0.100 g) were added. The reaction mixture is stirred at room temperature for 1.5 h. The activated charcoal was removed by filtration through Celite, and the filtrate was diluted to 75 mL and then loaded onto a column (11 cm × 2.5 cm) of Sephadex-SP C-25 ion exchange resin (Na^+ form). The column was washed with water, removing a purple compound, probably [Co(EDDA)(H_2O)(OH)]. The product was eluted with 0.1 mol L^{-1} $NaClO_4$, and two bands were observed. The first and major band was collected, concentrated on a rotary evaporator, and refrigerated for 48 h, forming dark red crystals of the α-*cis* isomer. These were filtered off and washed with ethanol and diethyl ether (0.286 g, 56%). The second, minor band was not collected. Anal. Calcd for $C_{12}H_{26}ClCoN_4O_8$·H_2O: C, 30.88; H, 6.05; N, 12.00; Cl, 7.59. Found: C, 30.88; H, 5.76; N, 12.00; Cl, 7.57. UV−vis: λ_{max} (ϵ) 543 (113); 376 (130) nm.

[Co(EDDA)(DEE)]ClO_4. The α-*cis* isomer was prepared and purified as described for the BEE analog, using α-*cis*-[Co(EDDA)(H_2O)$_2$]ClO_4 (0.400 g, 1 mmol) dissolved in water (6 mL), activated charcoal (0.100 g), *N,N*-diethylethylenediamine (0.128 g, 1 mmol), and a reaction time of 1.5 h. The desired product was eluted with 0.1 M $NaClO_4$, and two bands were collected. The larger, faster moving red-violet band gave purple crystals of the α-*cis* isomer (0.227 g, 47%). Anal. Calcd for $C_{12}H_{26}N_4O_8ClCo$: C, 32.12; H, 5.84; N, 12.49. Found: C, 31.87; H, 6.01; N, 12.75. UV−vis: λ_{max} (ϵ) 554 (1120); 381 (144) nm.

The solvent was removed from the second band on a rotary evaporator, and the resulting mixture of crystalline $NaClO_4$ and a pink solid, the β-*cis* isomer, was dried over silica gel before being characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy.

[Co(EDDA)(Men)]ClO_4. The α-*cis* isomer was prepared and purified as described for the BEE analog, using α-*cis*-[Co(EDDA)(H_2O)$_2$]ClO_4 (0.200 g, 0.5 mmol) dissolved in water (10 mL), activated charcoal (0.050 g), *N*-methylethylenediamine (0.040 g, 0.54 mmol), and a reaction time of 2 h. The elution with 0.1 M $NaClO_4$ resulted in the removal of two bands. The larger, faster moving dark pink band crystallized to form the α-*cis* isomer as a pink solid (0.138 g, 63%). Anal. Calcd for $C_9H_{20}ClCoN_4O_8$: C, 26.58; H, 4.96; N, 13.78. Found: C, 26.25; H, 5.23; N, 13.70. UV−vis: λ_{max} (ϵ) 433 (105); 366 (127) nm.

The solvent was removed from the second, much smaller pale pink band. The resulting mixture of crystalline $NaClO_4$ and a pink solid, the β-*cis* isomer, was dried over silica gel before being characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy.

[Co(L^1)]Cl·3H_2O. α-*cis*-[Co (EDDA)(en)]Cl (0.200 g, 0.6 mmol) was dissolved in water (10 mL), and 40% w/v aqueous formaldehyde (0.91 mL, 12 mmol) was added. Sufficient 1 M KOH was then added to adjust the reaction mixture to pH 12. After stirring at room temperature for 12 h the reaction was quenched by the addition of 1 mol L^{-1} HCl, resulting in a solution of pH 6. After dilution to 100 mL, the crude product was loaded onto a column (11 cm × 2.5 cm) of Sephadex-SP C-25 ion exchange resin (H^+ form). Upon elution with 0.1 mol L^{-1} HCl, three bands were observed. Two small, pale pink bands remained close to the origin. The faster moving dark pink band, which contained the desired product, was collected and concentrated to a small volume. KCl was precipitated from solution by the dropwise addition of acetone and was removed by filtration. Refrigeration of the filtrate resulted in the formation of dark pink crystals, which were filtered off and washed with ethanol and diethyl ether (0.116 g, 51%). Anal. Calcd for $C_{12}H_{22}ClCoN_4O_6$·3H_2O: C, 30.88; H, 6.05; N, 12.00. Found: C, 30.67; H, 5.88; N, 11.89. UV−vis: λ_{max} (ϵ) 523 (94); 365 (126) nm.

[Co(L^2)]ClO_4·H_2O. α-*cis*-[Co(EDDA)(Men)]ClO_4 (0.050 g, 0.1 mmol) was dissolved in water (10 mL), and 40% w/v aqueous formaldehyde (0.13 mL, 1.7 mmol) was added. Sufficient 1 KOH was then added to adjust the reaction mixture to pH 12. After stirring at room temperature for 12 h the reaction was quenched by the addition of 1 mol L^{-1} HCl, which adjusted the solution to pH 6. The crude product was diluted to 50 mL with water and loaded onto a column (12 cm × 1 cm) of Sephadex-SP C-25 ion exchange resin (Na^+ form). Elution

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(10) Abbreviations: EDDA, *N,N′*-ethylenediaminediacetate; en, ethylenediamine; Men, *N*-methylethylenediamine; BEE, *N,N′*-diethylethylenediamine; DEE, *N,N*-diethylethylenediamine; L^1, 1,4-bis(carboxymethyl)-6,13-dioxacyclam; L^2, 1,4-bis(carboxymethyl)-11-ethyl-6-oxa-1,4,8,11-tetraazatridecane; L^3, 1,4-bis(carboxymethyl)-6-oxa-1,4,8,11-tetraazadodecane.

(11) Radanović, D. J. *Coord. Chem. Rev.* **1984**, *54*, 159.

(12) Kuroda, K.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1034.

(13) Halloran, L. J.; Gillie, A. L.; Legg, J. I. *Inorg. Synth.* **1978**, *18*, 103.

(14) Jordan, W. T.; Froebe, L. R. *Inorg. Synth.* **1978**, *18*, 96.

Table 1. Crystallographic Data for $[Co(L^1)]Cl\cdot 3H_2O$ and $[Co(L^3)]PF_6\cdot NH_4PF_6\cdot H_2O$

	$[Co(L^1)]Cl\cdot 3H_2O$	$[Co(L^3)]PF_6\cdot NH_4PF_6\cdot H_2O$
formula	$C_{12}H_{28}ClCoN_4O_9$	$C_{14}H_{34}CoF_{12}N_5O_6P_2$
M_r	466.761	717.312
space group	$P2_1/n$ (No. 21)	$P2_1/n$ (No. 21)
a/Å	14.792(3)	13.353(6)
b/Å	7.766(1)	11.595(2)
c/Å	16.520(4)	16.900(5)
α/deg	90.0	90.0
β/deg	99.54(2)	95.59(3)
γ/deg	90.0	90.0
V/Å^3	1871.5(6)	2604(2)
ρ_{calcd}/(g cm^{-3})	1.656	1.809
Z	4	4
T/°C	22	23
λ/Å	0.710 69	0.710 69
μ/mm^{-1}	1.119	0.909
R^a [F^2, $I > 2\sigma(I)$]	0.042	0.084
$R_w{}^b$ [F^2, $I > 2\sigma(I)$]	0.112	0.251

^{a} $R = \sum||F_o| - |F_c||/\sum|F_o|$. ^{b} $R_w = \{\sum|w(F_o{}^2 - F_c{}^2)^2|/\sum|w(F_o{}^2)^2|\}^{1/2}$.

with 0.1 mol L^{-1} $NaClO_4$ removed one band only, which contained the desired product. This was concentrated to a small volume, and ethanol was added dropwise to the pink solution to effect crystallization. Refrigeration resulted in the formation of dark pink crystals, which were washed with ethanol and diethyl ether (0.039 g, 68%). The product was recrystallized from warm water. Yield: 0.024 g. Anal. Calcd for $C_{11}H_{22}ClCoN_4O_9\cdot H_2O$: C, 28.31; H, 5.18; N, 12.00; Cl, 7.60. Found: C, 28.35; H, 5.03; N, 11.87; Cl, 7.89. UV−vis: λ_{max} (ϵ) 531 (99); 369 (119) nm.

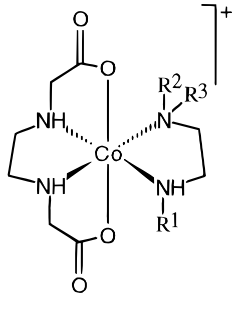
$[Co(L^3)]PF_6\cdot 2H_2O$. α-*cis*-[Co(EDDA)(DEE)]ClO_4 (0.223 g, 0.5 mmol) was dissolved in water (25 mL), and 40% w/v aqueous formaldehyde (0.64 mL) was added. Sufficient 1 mol L^{-1} KOH was then added to adjust the reaction mixture to pH 12. After stirring at room temperature for 12 h the reaction was quenched by the addition of 1 mol L^{-1} HCl, which adjusted the solution to pH 6. The crude product was diluted to 1000 mL with water and loaded onto a column (11 cm × 2.5 cm) of Sephadex-SP C-25 ion exchange resin (Na^+ form). Washing with water prior to elution removed a purple compound, probably $[Co(EDDA)(OH)(H_2O)]$. Elution with 0.1 mol L^{-1} $NaClO_4$ removed one band only, which contained the desired product. This band was concentrated, and excess solid NH_4PF_6 was added to the solution. After cooling, the purple solid which formed was washed with a small amount of acetone (0.083 g, 23%). Anal. Calcd for $C_{14}H_{28}CoF_6N_4O_5P\cdot NH_4PF_6\cdot 2H_2O$: C, 22.87; H, 4.93; N, 9.52. Found: C, 22.35; H, 4.63; N, 9.37. UV−vis: λ_{max} (ϵ) 538 (103), 382 (120) nm.

X-ray Crystal Structure Determinations. Crystals suitable for intensity data collection were mounted on glass fibers and positioned on a Nonius CAD-4 diffractometer. Unit cell dimensions were derived from least squares fits to the observed setting angles of 25 reflections distributed throughout reciprocal space, using monochromated Mo Kα radiation at ambient temperature. Intensity data collection employed the $2\theta/\omega$ technique with a total peak/background count time of 2:1. Reflections were counted for 60 s or until $\sigma(I)/I$ was 0.02. Crystal alignment and decomposition were monitored throughout data collection by measuring three standard reflections every 100 measurements; no statistically significant variation was observed. The data were corrected for Lorentz and polarization effects. Absorption corrections were applied using DIFABS[15] for $[Co(L^1)]Cl\cdot 3H_2O$ and ψ scans[16] for $[Co(L^3)]PF_6\cdot NH_4PF_6\cdot H_2O$, and equivalent reflections were averaged. Details of crystal data and intensity data collection parameters are summarized in Table 1 and fully described in the Supporting Information.

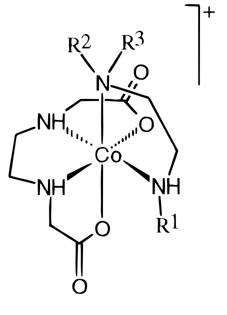
Structure Solution and Refinement. The structures were solved by Patterson and electron density syntheses. Refinement on F^2 employed SHELXL-93,[17] minimizing the function $\sum w||F_o|^2 - |F_c|^2|^2$. Atomic scattering factors were for neutral atoms.[18] After initial isotropic refinement, anisotropic thermal parameters were refined for all non-hydrogen atoms. For $[Co(L^1)]Cl\cdot 3H_2O$, hydrogen atoms were located from difference Fourier maps and refined individually; for $[Co(L^3)]PF_6\cdot NH_4PF_6\cdot H_2O$, hydrogen atoms were placed in calculated positions with an isotropic temperature factor set at 1.2 times that of the attached atom. In $[Co(L^3)]PF_6\cdot NH_4PF_6\cdot H_2O$, the fluorines of the PF_6 anions were disordered as is commonly observed. Weights used in the least squares refinement were $w = 1/[(\sigma^2(F_o)^2 + (aP)^2 + bP)]$ where $P = [(F_o)^2 + 2(F_c)^2]/3$, and the final values of a, b are 0.057, 1.71 and 0.154, 7.74 for $[Co(L^1)]Cl\cdot 3H_2O$ and $[Co(L^3)]PF_6\cdot NH_4PF_6\cdot H_2O$, respectively.

Results

The ethylenediamine complex α-*cis*-[Co(EDDA)(en)]Cl was prepared according to a published method[12] by oxidation of a cobalt(II) salt in the presence of the two chelating ligands $EDDA^{2-}$ and ethylenediamine and was isolated as the chloride salt rather than as the perchlorate salt which was reported in the literature. The diaqua complex α-*cis*-$[Co(EDDA)(H_2O)_2]ClO_4$, prepared from $H[Co(EDDA)Cl_2]$ upon sequential substitution of the chloride ligands by H_2O,[12] served as the precursor to a series of diamine complexes $[Co(EDDA)(L)]ClO_4$ (L = BEE, Men, DEE). Facile substitution of the two aqua ligands by the diamine was achieved by stirring the diaqua precursor together with the diamine in water in the presence of activated charcoal. The BEE and Men complexes had been reported previously, prepared by the direct oxidation route, and were characterized by elemental analysis and circular dichroism of the resolved complexes.[19] Careful chromatography of the reaction mixture on an ion exchange column with elution by aqueous $NaClO_4$ allowed separation and isolation of the perchlorate salts of both the α-cis isomer (the major product) and the β-cis isomer (the minor product) for all of the complexes, except where L = BEE, for which only the α-cis isomer was isolated. The α-cis isomers were fully characterized by elemental analysis, ^1H NMR, ^{13}C NMR, UV−visible, and IR spectroscopy, and cyclic voltammetry. The β-cis isomers were characterized by ^{13}C NMR and, for L = en and DEE, by ^1H NMR spectroscopy. For the symmetrical amines ethylenediamine and BEE the α-cis geometry and *RR* or *SS* configuration at the BEE nitrogen atoms were confirmed by the higher symmetry in the ^1H and ^{13}C NMR spectra.



α-*cis*-$[Co(EDDA)(L)]^+$



β-*cis*-$[Co(EDDA)(L)]^+$

R1	R2	R3	L
H	H	H	en
Me	Me	H	BEE
H	Me	H	Men
H	Et	Et	DEE

The reaction of α-*cis*-[Co(EDDA)(en)]Cl with excess aqueous formaldehyde at pH 12 resulted in a condensation reaction that

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(15) Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 158.

(16) North, A. C. T.; Phillips, D. C.; Mathews, F. S. *Acta Crystallogr.* **1968**, *A24*, 351.

(17) Sheldrick, G. M. Institut fur Anorganische Chemie, Universitat Gottingen, Germany, 1993.

(18) Atomic scattering factors from the following: *International Tables for Crystallography*; Kluwer Academic: Dordrecht, The Netherlands, 1992; Vol. C, Tables 4.2.6.8 and 6.1.1.4.

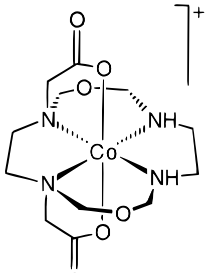
(19) Legg, I. J.; Douglas, B. E. *Inorg. Chem.* **1968**, *7*, 1452.

Table 2. Electrochemical Data

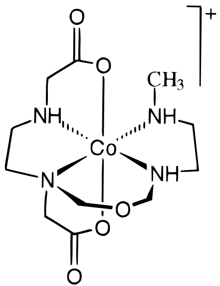
compound	sweep rate/(mV s^{-1})	E_{pc}/mV^a
α-*cis*-[Co(EDDA)(en)]Cl	20	−520
α-*cis*-[Co(EDDA)(BEE)]ClO_4	50	−420
α-*cis*-[Co(EDDA)(Men)]ClO_4	50	−560
α-*cis*-[Co(EDDA)(DEE)]ClO_4	50	−260
[Co(L^1)]Cl	20	−460
[Co(L^2)]ClO_4	20	−480

[a] Potential *vs* Ag/AgCl.

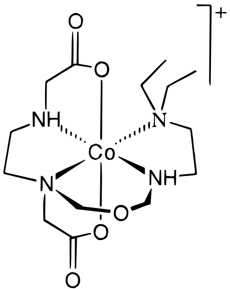
conserved the α-*cis* configuration of the EDDA fragment and formed two new ether ($-CH_2OCH_2-$) groups, each one linking a primary amine on the ethylenediamine ligand with a secondary amine on the EDDA ligand. The product, [Co(L^1)]Cl, contains a 14-membered macrocyclic derivative of 6,13-dioxacyclam in the equatorial plane with pendant acetato groups attached to two *cis* nitrogen atoms and coordinating to cobalt in the two axial sites. Similar condensation reactions using formaldehyde under basic conditions with α-*cis*-[Co(EDDA)(Men)]$^+$ and α-*cis*-[Co(EDDA)(DEE)]$^+$ gave complexes containing new hexadentate ligands, [Co(L^2)]$^+$ and [Co(L^3)]$^+$, respectively, which contain only one ether linkage between the single primary amine on the Men or DEE ligand and the adjacent secondary nitrogen on the EDDA ligand. In both cases, the α-*cis* configuration is retained in the new hexadentate ligands with the two acetato oxygen atoms *trans* and the four nitrogen donor atoms occupying the equatorial coordination sites. These three new complexes were characterized by elemental analysis and ^{1}H NMR, ^{13}C NMR, UV−visible, and IR spectroscopy. The formulation and geometry of two of the condensation products, [Co(L^1)]Cl and [Co(L^3)]PF_6, were confirmed by single-crystal X-ray structure determinations. Crystal data are given in Table 1.



[Co(L^1)]$^+$



[Co(L^2)]$^+$



[Co(L^3)]$^+$

Cyclic voltammetric measurements on each of the diamine complexes α-*cis*-[Co(EDDA)(L)]$^+$ (L = en, BEE, Men, DEE) and the acyclic hexadentate complex [Co(L^2)]ClO_4 showed essentially irreversible one-electron reduction in aqueous solution, with no reoxidation current (i_{pa}) observable. Cyclic voltammetry on [Co(L^1)]Cl in aqueous solution showed a reversible one-electron reduction, with $\Delta E_p = 69$ mV at a scan rate of 20 mV/s scan rate and a peak current ratio $i_{pc}/i_{pa} = 1$. Electrochemical data are given in Table 2.

Heating [Co(L^1)]$^+$ in 6 mol L^{-1} HCl for 1 h returned the complex unchanged, whereas heating the complex for 1 h in 32% aqueous ammonia gave the precursor complex α-*cis*-[Co(EDDA)(en)]$^+$, indicating that under basic conditions the formaldehyde condensation reaction is reversed and the ether bridges cleaved.

Discussion

Syntheses. The "direct" method of synthesis reported for the diamine (L) complexes [Co(EDDA)(L)]$^+$ (L = en, Men, and BEE)[12,19] involves air oxidation over 48 h of a cobalt(II) salt in the presence of the ligands EDDA^{2-} and L. We find the alternative synthesis *via* substitution of the two aqua ligands in the precursor α-*cis*-[Co(EDDA)(H_2O)$_2$]ClO_4 by the diamine ligand to be a useful general method, proceeding in 30 min to 2 h at room temperature using a charcoal catalyst. This contrasts with the original report of this method, which does not use charcoal and requires elevated temperatures.[20,21] We find the milder conditions using charcoal to be applicable for the synthesis of complexes when the free amine ligand is unstable.[22] The conversion of α-*cis* to *β-cis* isomers is favored at higher temperatures, so performing the reaction at room temperature results in higher yields of the desired α-*cis* isomers. A further advantage is the high overall yield, ranging from 47 to 63% of the α-cis isomers for L = BEE, Men, and DEE prepared by the substitution method, compared to 25% for L = en prepared by the direct oxidation method.

Treatment of α-*cis*-[Co(EDDA)(L)]$^+$ (L = en, Men, and DEE) in water containing an excess (*ca.* 20-fold) of aqueous formaldehyde at pH 12 for 12 h at room temperature produced, after quenching by acid and workup by ion exchange chromatography, the condensation products [Co(L^1)]Cl, [Co(L^2)]ClO_4, and [Co(L^3)]PF_6, respectively. The pH did not drop during the course of the reaction, indicating that there is no net OH^- consumption. The new complexes contain three-atom ether bridges (CH_2OCH_2) linking each primary amine on the diamine ligand to the adjacent, *cis*-coordinated secondary amine on the EDDA ligand. Since ethylenediamine contains two primary amines, two ether bridges are formed, giving a macrocyclic product. Men and DEE each contain only one primary amine, allowing only the formation of acyclic tetraamine chelating ligands as the condensation products.

Stereochemistry. The tetradentate ligand EDDA in [Co(EDDA)(L)]$^+$ (L = bidentate diamine) can coordinate to cobalt(III) in two geometries, the α-*cis* and *β-ci*s isomers (see sketch). In the former the two pendant acetate arms coordinate *trans*, whereas in the latter they adopt a *cis* configuration. Only the α-*cis* isomer was reported to be isolated from the preparation of [Co(EDDA)(en)]Cl by direct oxidation at room temperature,[12] while the *β-cis* isomer formed if the reaction was carried out at 100 °C.[21] The preparations of α-*cis*-[Co(EDDA)(L)]ClO_4 (L = BEE, Men, DEE) utilize the precursor α-*cis*-[Co(EDDA)(H_2O)$_2$]ClO_4 already in the α-*cis* configuration. Even so, some isomerization does occur during the course of the substitution reaction and small amounts of the *β-cis* isomers, sufficient for ^{1}H and ^{13}C NMR characterization, are separated from the reaction mixture by ion exchange chromatography and isolated, except where L = BEE.

Additional stereoisomers are possible for L = BEE and Men and for [Co(L^2)]ClO_4, arising from the fact that the secondary nitrogen centers (one nitrogen atom in Men and two nitrogen

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(20) Kuroda, K. *Chem. Lett.* **1972**, 197.
(21) Kuroda, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2176.
(22) Ware, D. C.; Tonei, D. M.; Palmer, H. R.; Brothers, P. J. To be published.

atoms in BEE) become chiral upon coordination. For the *β-cis* isomers where L = DEE and Men, further stereoisomers arise from the orientation of L (the primary nitrogen can be *cis* or *trans* to the EDDA oxygen). The cobalt complexes have overall Δ or Λ configurations, and this stereochemistry combined with *R* or *S* configurations at the secondary amine nitrogens gives rise to sets of diastereomers (where each diastereomer can exist as a pair of enantiomers). For the Men complexes two sets of diastereomers are possible for the α-*cis* geometry (Δ*R*/Λ*S* and Δ*S*/Λ*R*) and two for each of the the *β-cis* forms. Inspection of models indicates that one diastereomer might be expected to predominate on steric grounds. The NMR spectra of initially isolated samples of α-*cis*-[Co(EDDA)(L)]$^+$ (L = Men, BEE) show predominantly one diastereomer with minor amounts of another diastereomer. After one recrystallization, each of the α-*cis* complexes exists as a single diastereomer.

Each of α-*cis*-[Co(EDDA)(H$_2$O)$_2$]$^+$ and α-*cis*-[Co(EDDA)(en)]$^+$ exists as one pair of enantiomers, which have C_2 symmetry. C_2 symmetry is also possible for the α-*cis* BEE complex if the two nitrogen atoms are in the *RR* or *SS* configuration. This configuration is confirmed by the higher symmetry observed in the NMR spectra of this complex, although a small amount of a second diastereomer (*RS* configuration), which has lower, C_1 symmetry and gives rise to twice as many peaks, is observed in samples prior to recrystallization. The α-*cis* DEE complex exists as a single pair of enantiomers (Δ or Λ), and only one set of peaks is seen in the NMR spectrum. The α-*cis* isomers with unsymmetric diamines (L = Men, DEE) and all of the *β-cis* isomers of the diamine complexes have lower, C$_1$ symmetry.

The condensation products [Co(L^1)]Cl, [Co(L^2)]ClO$_4$, and [Co(L^3)]PF$_6$ retain the *trans* disposition of the pendant acetato groups, with the nitrogen donor atoms and new ether bridges occupying the equatorial plane, indicating that the stereochemistry of each precursor complex has been retained during the condensation reactions. The primary amines in the precursors become secondary amines in the products, thus creating new stereocenters. [Co(L^1)]Cl retains C_2 symmetry as evidenced by ^{1}H and ^{13}C NMR spectroscopy, showing that the configuration at the new secondary nitrogen atoms (derived from the ethylenediamine ligand) is exclusively *RR* or *SS*, and this is confirmed by the crystal structure. The *RR* or *SS* stereochemistry, combined with the chiral center at the cobalt atom, gives rise to the favorable chair conformation in the chelate rings of the macrocycle. The less favored skew conformation which would arise from *RS* or *SR* configurations at nitrogen does not form. The acyclic products [Co(L^2)]ClO$_4$ and [Co(L^3)]PF$_6$ retain C_1 symmetry.

NMR Spectroscopy. The lower symmetry (C_1) complexes show a unique resonance for every carbon atom in the molecule, while the higher symmetry (C_2) complexes show only half the number of resonances. The methylene (CH$_2$) groups give rise to AB quartets for the acetate arms (NCH$_2$CO$_2$) and ether bridges (NCH$_2$O) and complex multiplets for the CH$_2$ groups in the ethylene (NCH$_2$CH$_2$N) and ethyl fragments. Assignments were made utilizing 2D (COSY, XH CORR) experiments for selected complexes. Although low-field (60 MHz) ^{1}H NMR data are given in the literature for [Co(EDDA)(en)]$^+$,[21,23] the high-field ^{1}H and ^{13}C NMR data reported here allow more complete assignments of chemical shifts and coupling constants. NMR data have not previously been given for L = Men and BEE.

X-ray Crystallography. The cations of [Co(L^1)]Cl·3H$_2$O and [Co(L^3)]PF$_6$·NH$_4$PF$_6$·H$_2$O are shown in Figures 1 and 2, respectively. We recently reported the complex [Co(1,4-bcc)]$^+$, which contains a macrocyclic ligand very closely related to that in [Co(L^1)]$^+$, but with CH$_2$ groups in place of the ether oxygens, thus existing as a cyclam ligand with pendant carboxymethyl groups on adjacent nitrogen atoms.[24] The structures of the two cations are very similar, with the macrocycles both adopting the *trans*-III conformation commonly observed in cyclam complexes.[25] The average tertiary N−Co bond lengths (1.976 Å for [Co(L^1)]$^+$ and 1.977 Å for [Co(1,4-bcc)]$^+$) are the same, while the average secondary N−Co bond lengths of 1.948 and 1.961 Å, respectively, are slightly shorter in [Co(L^1)]$^+$. Very similar bond angles are observed in the two complexes, with

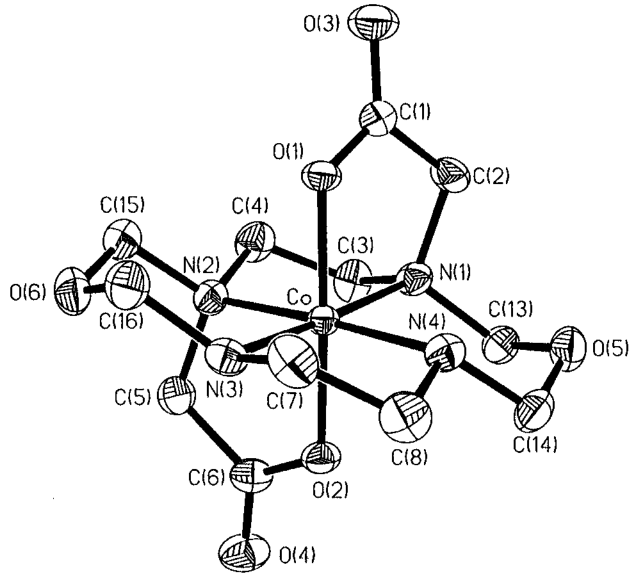

Figure 1. ORTEP view and atomic labeling scheme of the [Co(L^1)]$^+$ cation. Selected bond lengths (Å): Co−O(1), 1.888(2); Co−O(2), 1.897(3); Co−N(1), 1.977(3); Co−N(2), 1.975(3); Co−N(3), 1.947(3); Co−N(4), 1.949(3).

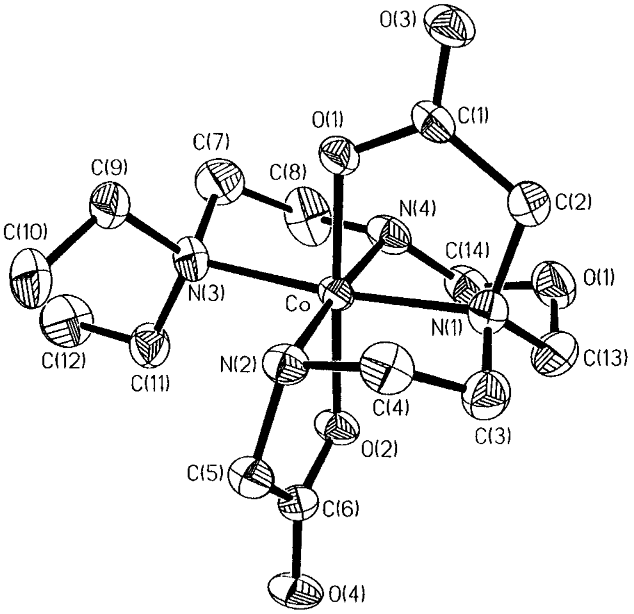

Figure 2. ORTEP view and atomic labeling scheme of the [Co(L^3)]$^+$ cation. Selected bond lengths (Å): Co−O(1), 1.883(3); Co−O(2), 1.890(3); Co−N(1), 2.003(4); Co−N(2), 1.971(3); Co−N(3), 2.082(4); Co−N(4), 1.961(3).

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(23) Legg, I. J.; Cooke, D. W. *Inorg. Chem.* **1965**, *4*, 1576.

(24) Ware, D. C.; Tonei, D. M.; Baker, L.-J.; Brothers, P. J.; Clark, G. R. *Chem. Commun.* **1996**, 1303.

(25) Restivo, R. J.; Ferguson, G.; Hay, R. W.; Piplani, D. P. *J. Chem. Soc., Dalton Trans.* **1978**, 1131.

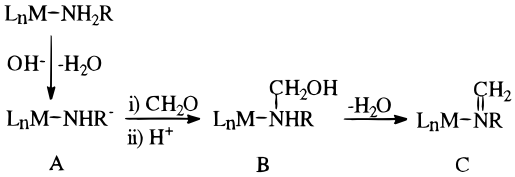
N−Co−N angles within the five- and six-membered chelate rings close to 87° and 92°, respectively. The EDDA ligand in α-*cis*-[Co(EDDA)(en)]$^+$, the precursor to [Co(L^1)]$^+$, has an average N−Co bond distance of 1.979 Å,[26] very similar to the corresponding N−Co distances in [Co(L^1)]$^+$ and [Co(1,4−bcc)]$^+$,[24] although these complexes contain tertiary nitrogen donors whereas the EDDA ligand in α-*cis*-[Co(EDDA)(en)]$^+$ contains secondary nitrogen donors. In α-*cis*-[Co(EDDA)(en)]$^+$ the primary N−Co bond distances involving the ethylenediamine ligand, averaging 1.931 Å, are shorter than the corresponding secondary N−Co distance in [Co(L^1)]$^+$. The N−Co−N angles in the five-membered chelate rings in [Co(EDDA)(en)]$^+$ are the same as those in [Co(L^1)]$^+$, but the N−Co−N angles between the EDDA and en ligands are wider in [Co(EDDA)(en)]$^+$ because they are not constrained to a chelate ring. Overall, the close similarity between the structures of [Co(EDDA)(en)]$^+$ and [Co(L^1)]$^+$ shows that no strain has been induced in the structure of the latter by the formation of the ether bridges.

The complex [Co(α-$HOCH_2$-serine)(6,13-dioxacyclam)]$^{2+}$ contains the same macrocycle as [Co(L^1)]$^+$, but minus the pendant carboxymethyl arms and with the macrocycle in a folded conformation.[3] This macrocycle contains four secondary nitrogen donors, and in this case the different coordination geometry results in a slightly longer average N−Co bond length (1.976 Å) than the secondary nitrogen donors in [Co(L^1)]$^+$ (1.948 Å).

The new acyclic hexadentate ligand in [Co(L^3)]$^+$ shows, on average, longer N−Co bond lengths than its macrocyclic counterpart, [Co(L^1)]$^+$. In particular, the tertiary N−Co distances are quite long (2.003(4) Å to the carboxymethyl-substituted nitrogen and 2.082(4) to the NEt_2 group). The latter distance approaches the tertiary N−Co distance in [Co(Meacac)$_2$(DCE)]ClO_4 of 2.092(4) Å, which is believed to be one of the longest such bond lengths reported (DCE = *N*,*N*-bis(2-chloroethyl)ethylenediamine).[27] The N−Co−N angle which is not part of a chelate ring in [Co(L^3)]$^+$ shows a considerably wider bond angle of 97.41(14)°, reflecting the steric effect of the two bulky ethyl substituents on the adjacent tertiary nitrogen.

Electrochemistry. Cyclic voltammetry of the diamine complexes [Co(EDDA)(L)]$^+$ and the acyclic product of the condensation reaction, [Co(L^2)]$^+$, in aqueous solution displayed completely irreversible behavior. In contrast, the macrocyclic product, [Co(L^1)]$^+$, exhibits reversible electrochemical behavior (Table 2). Irreversible electrochemical reduction of Co(III) complexes in aqueous media is generally ascribed to rapid aquation reactions on the labile Co(II) center following electron transfer. Some improvement in reversibility is seen in nonaqueous solution or when excess ligand is present, consistent with inhibition of ligand displacement from Co(II). For the macrocyclic complex, [Co(L^1)]Cl, the encapsulating nature of the ligand leads to significant kinetic stabilization of the Co(II) form giving rise to the chemically reversible electrochemistry observed. This phenomenon has been observed for other Co(III) encapsulated complexes, for example, the closely related macrocyclic complex Co(1,4-bcc)]$^+$.[24] The macrocyclic effect is important in the kinetic stabilization of Co(II), as shown by the comparison between the electrochemical behavior of [Co(L^1)]$^+$ and [Co(L^2)]$^+$. Both complexes contain hexadentate ligands with the same arrangement of donor atoms and similar ligand backbones. The key difference is that the macrocyclic complex [Co(L^1)]$^+$ shows reversible one-electron reduction, whereas [Co(L^2)]$^+$, which contains an acyclic ligand, is irreversibly reduced to Co(II) under the same conditions.

Condensation Reactions. Examples of metal-mediated template reactions involving coupling of coordinated amines using formaldehyde and a second linking agent such as nitroalkanes or amines are well-known and are believed to involve the transformation of coordinated amine nitrogen centers into carbinolamine and imine intermediates (eq 4).[28] The involvement of intermediate imine complexes has been established through, for example, the extensive chemistry of cobalt(III) cage complexes formed from formaldehyde condensations on coordinated chelating amines.[29] Formation of a coordinated imine (**C** in eq 4) is only possible at a primary amine. A secondary amine can form a carbinolamine (**B**) while a tertiary amine cannot undergo the initial deprotonation step to form **A**. These general types of reactions have been studied for both labile metals like Cu(II)[2,30] and inert metal centers, in particular Co(III).[31] In the latter case the reaction is constrained to take place in the metal coordination sphere, whereas in the former the possibility of ligand dissociation during the course of the reaction exists.



$$L_nM{-}NH_2R \xrightarrow[-H_2O]{OH^-} L_nM{-}NHR^- \xrightarrow[\text{ii) } H^+]{\text{i) } CH_2O} L_nM{-}\overset{CH_2OH}{N}HR \xrightarrow{-H_2O} L_nM{-}\overset{CH_2}{\overset{\|}{N}}R \quad (4)$$

The corresponding reactivity of coordinated amino acids shows some differences from that of coordinated simple amines. Upon coordination to a metal, the α-carbon atoms of amino acids are activated toward attack on electrophiles.[7] When the electrophile is formaldehyde, the products are α-hydroxymethyl amino acid derivatives (**G** in Scheme 1).[8] For copper, initial reaction of the NH_2 group to form an imine (**D**) may further enhance the reactivity of the α-carbon (**E**). Evidence for imine formation at copper(II) comes from intramolecular cyclization reactions between adjacent hydroxymethyl and imine groups leading to oxazolidine ring formation (**F**).[32] On the other hand, in the corresponding reactions of cobalt amino acid complexes there is no direct evidence that prior condensation of formaldehyde at nitrogen is required for alkylation at the α-carbon.[7,9]

In the condensation reactions reported here the coupling agent is formaldehyde alone, and the result is a three-atom ether bridge (CH_2OCH_2) formed between *cis* primary and secondary amine centers in the precursor complexes. The formaldehyde condensation reactions in aqueous base were successful for α-*cis*-[Co(EDDA)(L)]$^+$ (L = en, Men, and DEE) giving [Co(L^1)]Cl, [Co(L^2)]ClO_4, and [Co(L^3)]PF_6, respectively. However, treatment of α-*cis*-[Co(EDDA)(BEE)]$^+$ or α-*cis*-K[Co(EDDA)(NO_2)$_2$] with formaldehyde under the same conditions yielded only unchanged starting material after acidification during workup. Neither of these complexes contains a primary amine. The presence of at least one nitrogen donor which is a primary

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(26) Das, K.; Sinha, U. C.; Phulambrikar, A.; Chatterjee, C.; Bohra, R. *Acta Crystallogr.* **1989**, *C45*, 398.

(27) Ware, D. C.; Clark, G. R.; Denny, W. A. *Acta Crystallogr.* **1997**, *C53*, 1058.

(28) Gainsford, A. R.; Pizer, R. D.; Sargeson, A. M.; Whimp, P. O. *J. Am. Chem. Soc.* **1981**, *103*, 792.

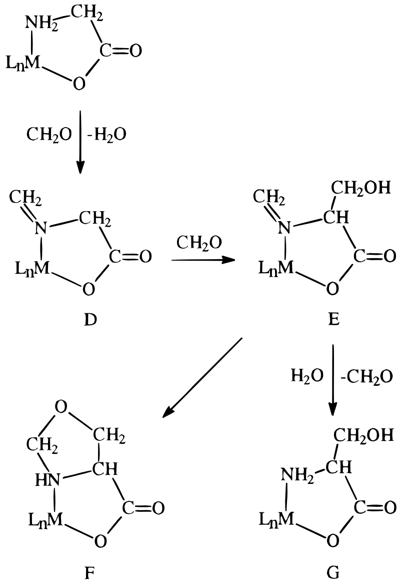
(29) Sargeson, A. M. *Pure Appl. Chem.* **1984**, *56*, 1603. Sargeson, A. M. *Pure Appl. Chem.* **1986**, *58*, 1511.

(30) Lawrance, G. A.; Skelton, B. W.; White, A. H.; Wilkes, E. N. *Aust. J. Chem.* **1991**, *44*, 1511 and references therein.

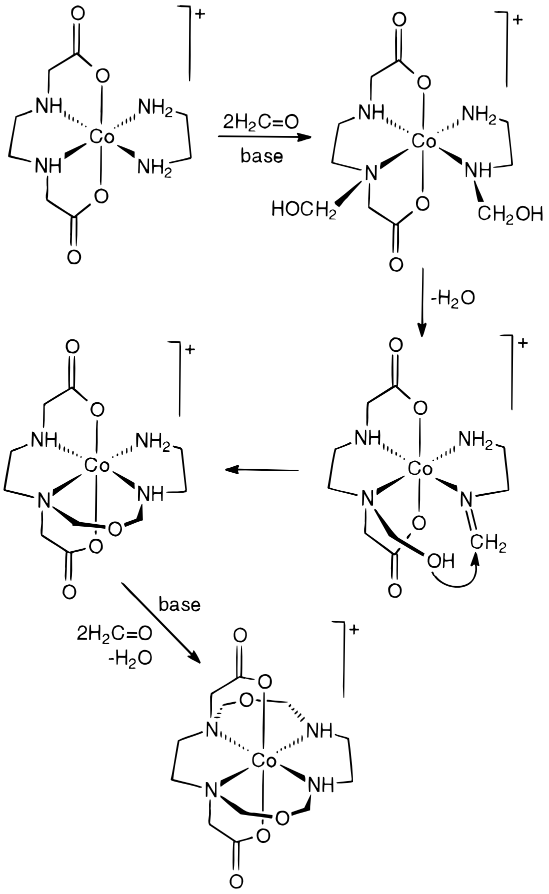
(31) (a) Creaser, I. I.; Geue, R. J.; Harrofield, J. M.; Herlt, A. J.; Sargeson, A. M.; Snow, M. R.; Springborg, J. *J. Am. Chem. Soc.* **1982**, *104*, 6016. (b) Geue, R. J.; Hambley, T. W.; Harrofield, J. M.; Sargeson, A. M.; Snow, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 5478.

(32) Brush, J. R.; Magee, R. J.; O'Connor, M. J.; Teo, S. B.; Geue, R. J.; Snow, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 2034.

Scheme 1



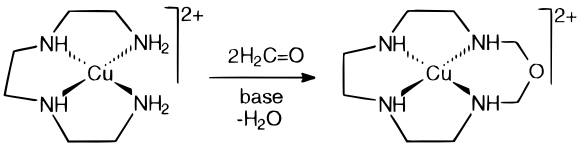
Scheme 2



amine is consistent with the requirement for an imine intermediate. Each ether bridge links a primary and secondary amine, indicating that only one imine intermediate is required per bridge. This parallels the formation of oxazolidine rings in primary amino acid complexes where the CH_2OCH_2 group links the α-carbon and adjacent NH_2 groups (Scheme 1). Heating [Co(L^1)]Cl in 6 mol L^{-1} HCl for 1 h returned the complex unchanged, whereas heating the same complex in 32% aqueous ammonia for 1 h returned the precusor complex α-*cis*-[Co(EDDA)(en)]$^+$, showing that the ether bridges are stable under acid conditions but their formation is reversed under basic conditions.

These observations are consistent with a mechanism (Scheme 2) involving formaldehyde attack at both primary and secondary coordinated amine centers to give carbinolamines. Where the original amine is a primary nitrogen, this may be followed by dehydration to give an imine, which is then attacked by the oxygen of a *cis* carbinolamine group leading to the ether bridge. Carbinolamine groups on pairs of adjacent secondary nitrogens do not lead to bridge formation, presumably because neither nitrogen center can undergo dehydration to form an imine. The reactions in this sequence are reversible under basic conditions, but quenching the reaction with acid retains the ether bridges which are stable at neutral and low pH.

There are few examples in the literature of condensation reactions leading to bridge formation which utilize formaldehyde alone under basic conditions. In a copper example, the same type of three-atom ether bridge is formed between the two primary nitrogen atoms in Cu(trien) and related derivatives, to give a 13-membered oxatetraaza macrocyclic complex (eq 5).[4] The example most closely related to the chemistry reported here is the reaction of [Co(en)$_2$(gly)]$^{2+}$ with formaldehyde and base, which gave two products (eq 6).[3] The first of these was [Co(α-(hydroxymethyl)serine)(en)$_2$]$^{2+}$, resulting from the addition of 2 equiv of formaldehyde at the α-carbon of the glycinato ligand, forming two hydroxymethyl groups at this position. In the second reaction product, [Co(α-(hydroxymethyl)serine)(6,13-dioxacyclam)]$^{2+}$, the two ethylenediamine ligands have also been linked by two three-atom ether bridges to form a 14-membered 6,13-dioxacyclam ligand,[3] the same macrocycle that is formed in [Co(L^1)]Cl. The dioxacyclam moiety occupies four equatorial sites in [Co(L^1)]Cl, and the remaining *trans* coordination sites are occupied by the oxygen donors from the pendant acetato side chains. In [Co(α-(hydroxymethyl)serine)(6,13-dioxacyclam)]$^{2+}$ the cyclam is in a folded configuration with the α-(hydroxymethyl)serine ligand occupying the *cis* coordination sites.[3]



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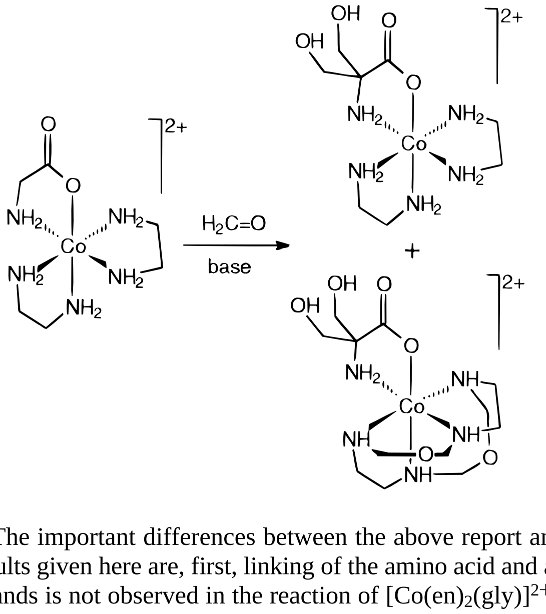

(6)

The important differences between the above report and the results given here are, first, linking of the amino acid and amine ligands is not observed in the reaction of [Co(en)$_2$(gly)]$^{2+}$ with formaldehyde and base, whereas the amino acid and amine ligands are linked in the reactions of the EDDA complexes under similar conditions. Second, α-hydroxymethyl formation resulting from reaction at the acetato methylene groups (the α-carbons) of the EDDA ligand is not observed. This fact can be interpreted as evidence for the requirement for imine formation at the amino acid nitrogen prior to alkylation at the α-carbon in cobalt complexes, for which there is support in the corresponding copper chemistry. The EDDA secondary nitrogens cannot form imines upon reaction with formaldehyde, and as a result, activation at the α-carbon does not occur. Third, the literature reports of formaldehyde condensation in both the Cu(II) and Co(III) complexes involve coupling of two primary amines,[3,4] whereas each of the new coupling reactions reported here occurs between a primary and a secondary amine, indicating that only a single imine intermediate is required per ether bridge formed, providing strong evidence for the proposed reaction sequence in Scheme 2.

In this report we have established that formaldehyde condensation reactions on coordinated amino acids can occur to give alkylation at nitrogen rather than at the α-carbon site. This different reactivity is ascribed to the presence of an amino acid ligand containing a secondary amine and hence the conclusion that imine formation is a prerequisite to reaction at the α-carbon atoms of amino acid ligands coordinated to cobalt(III). We have used this new reactivity for the synthesis of new ligands. The ligand synthesis is based on readily accessible precursor complexes and leads to higher denticity ligands incorporating functionalities already present in the coordinated amino acid precursor. The efficiency and stereospecificity of the reaction is dependent on the high degree of preorganization of the reactants in the coordination sphere of cobalt(III).

Acknowledgment. The authors are grateful to the University of Auckland Research Committee for financial support.

Supporting Information Available: Tables of ^{1}H and ^{13}C NMR data (4 pages). X-ray crystallographic files in CIF format for complexes $[Co(L^{1})]Cl\cdot 3H_2O$ and $[Co(L^{3})]PF_6\cdot NH_4PF_6\cdot H_2$ are available on the Internet only. Ordering and access information is given on any current masthead page. Structure factor tables are available from the authors.

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