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Reaction of Formaldehyde with *mer*-(Ethylenediamine)(glycylglycinato)nitrocobalt(III). Crystal Structure of *mer*-(Ethylenediamine)[*N*-((5,6-dihydro-5,5-bis(hydroxymethyl)-1,3-oxazin-4-yl)carbonyl)glycinato]nitrocobalt(III) Trihydrate

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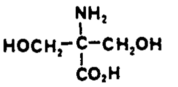
Three new compounds result from the reaction of *mer*-[Co($NH_2CH_2CONCH_2CO_2$)NO_2(en)] with formaldehyde in alkaline aqueous solution: *mer*-(ethylenediamine)[*N*-((5,6-dihydro-5,5-bis(hydroxymethyl)-1,3-oxazin-4-yl)carbonyl)glycinato]nitrocobalt(III) trihydrate (*mer*-[Co{$(CH_2OH)_2\overline{CCH_2OCH_2N{=}C}CONCH_2CO_2$}$NO_2$(en)]·$3H_2O$), *mer*-(ethylenediamine)[*N*-(((methylimino)methyl)carbonyl)glycinato]nitrocobalt(III) (*mer*-[Co($CH_3N{=}CHCONCH_2CO_2$)NO_2(en)]), and *mer*-(ethylenediamine)(*N*-methylideneglycylglycinato)nitrocobalt(III) (*mer*-[Co($CH_2{=}NCH_2CONCH_2CO_2$)NO_2(en)]). They were separated by adsorption chromatography on a cationic exchanger, in the hydrogen form, and characterized by elemental analysis, electronic spectroscopy, and ^1H and ^{13}C NMR spectroscopy. The structure of *mer*-[Co{$(CH_2OH)_2\overline{CCH_2OCH_2N{=}C}CONCH_2CO_2$}$NO_2$(en)]·$3H_2O$ was determined by X-ray crystallography. It crystallizes in the monoclinic space group $P2_1/n$ in a unit cell of dimensions $a = 8.843$ (1) Å, $b = 26.809$ (2) Å, $c = 8.910$ (1) Å, $\beta = 115.91$ (2)°, $V = 1899.9$ Å^3, and $\rho_{calcd} = 1.62$ g cm^{-3}, with $Z = 4$. Refinement converged to $R = 0.031$ for 3260 independent observed ($I/\sigma(I) > 3$) reflections. The 1,3-oxazine derivative is tridentate, coordinated through carboxylato oxygen, peptide nitrogen, and imino nitrogen atoms. The equatorially disposed ligand forms with cobalt three fused rings, two five-membered chelates, and one six-membered heterocyclic ring.

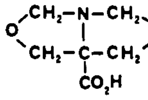
Introduction

Base-catalyzed condensation of formaldehyde with glycine coordinated to Co(III) results in the formation of the corresponding complex of α-(hydroxymethyl)serine (I).[2,3] On the other



$$HOCH_2-\overset{\displaystyle NH_2}{\underset{\displaystyle CO_2H}{C}}-CH_2OH$$

I

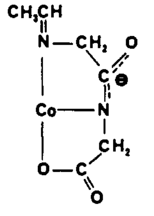


II

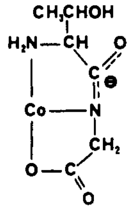
hand, for bis(glycinato)copper(II) the condensation of aldehyde at the α-carbon is preceded by condensation at the amino group, followed by cyclization to give a complex containing oxazolidine-type rings (II). The latter yields α-(hydroxymethyl)serine under acidic conditions.[3-5]

It has also been reported that the aldol condensation of formaldehyde with the bis(glycylglycinato)cobaltate(III) ion yields the bis(glycylserinato)cobaltate(III) ion;[6] i.e., the reaction is confined to the C-terminal amino acid residue, reflecting the pattern of selectivity found for H-D exchange in (dipeptidato)cobalt(III) complexes.[6-8] Conversion of glycylglycine into glycylserine has been confirmed by chromatographic analysis of the amino acids obtained upon hydrolysis of the liberated peptide.

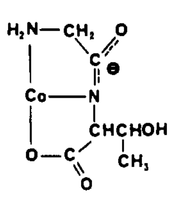
Intermediate formation of imine derivatives of glycylglycine has been assumed as an explanation for the formation of serylglycine instead of glycylserine[9] when glycylglycine itself reacts with formaldehyde in the presence of copper(II).[10] This assumption is based on the fact that metal complexes of salicylidene derivatives of dipeptides, in contrast to simple dipeptide complexes, show activation of the N-terminal amino acid residue.[9] Moreover, from the base-catalyzed reaction of acetaldehyde with *mer*-[Co(glygly)L(en)] complexes (L = NO_2^-, NCS^-, CN^-) we have isolated such imine derivatives.[11,12] Namely, the glycylglycinato ligand in all the investigated complexes is converted into its corresponding *N*-ethylideneglycylglycinato complex (III), as well



III



IV



V

as a mixture of diastereomeric threonyl- and allothreonylglycinato complexes (IV), and not to glycylthreoninato complexes (V), as was reported for the reaction of acetaldehyde with [Co(glygly)$(NH_3)_3$]$^+$, [Co(glygly)(dien)]$^+$,[8] and [Co(glygly)$_2$]$^-$ [6] ions.

Formation of IV, instead of V, results from the fact that the first step in a base-catalyzed reaction of aldehyde with glycylglycine coordinated to Co(III) takes place on the amino group, giving rise to the complex III in which the N-terminal CH_2 group is activated for the reaction with aldehyde.

These results led to reinvestigation of the behavior of the [Co(glygly)$(NH_3)_3$]$^+$, [Co(glygly)(dien)]$^+$, and [Co(glygly)$_2$]$^-$ ions in alkaline solution in the presence of acetaldehyde.[13] The ^1H NMR spectra have shown that reversible formation of the Schiff base complexes (III) also occurs with these Co(III) dipeptide complexes and that, for example, the major product of the reaction of [Co(glygly)$_2$]$^-$ with acetaldehyde at pH 11 is, in fact, the corresponding threonylglycinato complex (IV) and not the glycylthreoninato complex (V) as was reported earlier.[6]

The present study shows that the aldol condensation of formaldehyde with cobalt chelated by glycylglycine produces a complex

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Table I. Absorption Maxima (nm) and log ε Values of the Synthesized Complexes

no.	compd	λ_1	log ϵ_1	λ_2	log ϵ_2
1	*mer*-$[Co(NH_2CH_2CONCH_2CO_2)NO_2(en)]$	476	2.40	329	2.95
2	*mer*-$[Co\{(CH_2OH)_2\overline{CCH_2OCH_2N{=}C}CONCH_2CO_2\}NO_2(en)]$	471	2.64	328	3.40
3	*mer*-$[Co(CH_3N{=}CHCONCH_2CO_2)NO_2(en)]$	470	2.55	331	3.34
4	*mer*-$[Co(CH_2{=}NCH_2CONCH_2CO_2)NO_2(en)]$	470	2.58	331	3.21

Table II. ^{13}C NMR Data for the Obtained Compounds[a]

no.	compd	N–CH_2	C–CH_2	CO	COO^-	CH_2(en)	C=N	others	
1	$[Co(NH_2CH_2CONCH_2CO_2)NO_2(en)]$	48.9 (t)	49.4 (t)	179.2 (s)	187.6 (s)	45.3 (t)			
						44.6 (t)			
2	$[Co\{(CH_2OH)_2\overline{CCH_2OCH_2N{=}C}CONCH_2CO_2\}NO_2(en)]$		50.0 (t)	182.9 (s)	187.3 (s)	45.9 (t)	170.0 (s)	NCH_2O	80.9 (t)
						45.7 (t)		CCH_2O	67.4 (t)
								C[b]	51.2 (s)
								CH_2OH	62.6 (t)
									62.4 (t)
3	$[Co(CH_3\text{-}N{=}CHCONCH_2CO_2)NO_2(en)]$		49.9 (t)	170.3 (s)	187.3 (s)	45.5 (t)	175.9 (d)	CH_3–N	46.2 (q)
						46.1 (t)			
4	$[Co(CH_2{=}NCH_2CONCH_2CO_2)NO_2(en)]$	66.3 (t)	50.3 (t)	175.5 (s)	188.0 (s)	45.7 (t)	174.7 (t)		
						44.9 (t)			

[a] Taken in D_2O solutions. δ values in ppm relative to $SiMe_4$, with dioxane as internal reference. Line shape is given in parentheses for the proton-coupled spectra. s = singlet, d = doublet, t = triplet, and q = quartet. [b] Quaternary carbon.

of an entirely new ligand, *N*-((5,6-dihydro-5,5-bis(hydroxymethyl)-1,3-oxazin-4-yl)carbonyl)glycinato, in addition to tautomeric forms of dipeptidato ligand Schiff base complexes.

Experimental Section

Reaction of *mer*-$[Co(NH_2CH_2CONCH_2CO_2)NO_2(en)]$ with Formaldehyde. To a solution of *mer*-$[Co(NH_2CH_2CONCH_2CO_2)NO_2(en)]$[14] (**1**) (2.06 g, 7 mmol) in 200 mL of water were added (24 mL, 0.28 mol) of 36% aqueous formaldehyde and sufficient 0.1 M sodium hydroxide to adjust the reaction mixture pH to 11. The resulting solution was allowed to stand at room temperature for 8 h (maintaining pH = 11 by periodic addition of the NaOH solution). It was then neutralized with 0.1 M hydrochloric acid and evaporated on a rotary evaporator (40 °C) to a volume of 15 mL and left at room temperature for 24 h. The separated organic byproducts were removed by filtration and the filtrate was poured onto a Dowex 50W-X8 (200–400 mesh) cation-exchange column (8-cm length and 3-cm o.d.), in the hydrogen form. Elution with distilled water (at a rate of 8 mL/min) formed four zones on the column.

The first zone, which contained *mer*-$[Co\{(CH_2OH)_2\overline{CCH_2OCH_2N{=}C}CONCH_2CO_2\}NO_2(en)]\cdot 3H_2O$ (**2**), came off the column about 5 min after the solvent front and was completely eluted within 5 additional min. The eluate was reduced to 2 mL on a rotary evaporator (40 °C), and the precipitated organic products were removed by filtration. The filtrate, to which 2 mL of ethanol was added, was left in a refrigerator overnight. The orange crystals of **2** (0.05 g, 2%) were isolated by filtration and recrystallized from H_2O/EtOH. Anal. Calcd for $C_{11}H_{20}CoN_5O_6\cdot 3H_2O$: C, 30.63; H, 6.08; N, 16.24. Found: C, 30.46; H, 6.30; N, 15.98.

The second zone came off the column about 5 min after the first zone was completely eluted. It was eluted within 20 min and found to contain *mer*-$[Co(CH_3N{=}CHCONCH_2CO_2)NO_2(en)]$ (**3**). The eluate was concentrated on a rotary evaporator (40 °C) to a volume of 2 mL, ethanol (~1 mL) was added, and the solution was left at room temperature for 24 h. The resultant orange crystals of **3** (0.1 g, 5%) were isolated by filtration and recrystallized from H_2O/EtOH. Anal. Calcd for $C_7H_{14}CoN_5O_5$: C, 27.37; H, 4.59; N, 22.80. Found: C, 27.12; H, 4.25; N, 22.70.

Forty minutes after complete elution of the second zone the third zone came off the column, and this was found to contain *mer*-$[Co(CH_2{=}NCH_2CONCH_2CO_2)NO_2(en)]$ (**4**). This zone was completely eluted within about 60 min. The eluate was reduced on a rotary evaporator (40 °C) to a volume of 2 mL, ethanol (~1 mL) was added, and the solution was left at room temperature for 24 h. By this time complex **4** (0.2 g, 10%) crystallized from the solution in the form of orange crystals. Anal. Calcd for $C_7H_{14}CoN_5O_5$: C, 27.37; H, 4.59; N, 22.80. Found: C, 27.49; H, 4.74; N, 23.13.

The fourth zone came off the column about 1 h after complete elution of the third zone; it was found to contain the starting substance.

Physical Measurements. Electronic spectra in the visible and ultraviolet regions were recorded on a Varian Super Scan 3 ultraviolet spectrophotometer. Visible spectra were taken with aqueous solutions having concentrations of 2×10^{-3} mol dm^{-3}, whereas solutions having concentrations of 2×10^{-4} mol dm^{-3} were used for recording the ultraviolet spectra. The length of the cell was 0.5 cm. Absorption maxima and log ε values are given in Table I. ^1H NMR spectra were recorded at 300 MHz on a General Electric QE-300 spectrometer, in D_2O, using DSS as the internal standard. $^{13}C\{^1H\}$ and ^{13}C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer, in D_2O. Chemical shifts are given with reference to TMS, using dioxane (δ 67.7) as the internal standard.

Crystal Data. The orange, prismatic crystals of *mer*-$[Co\{(CH_2OH)_2\overline{CCH_2OCH_2N{=}C}CONCH_2CO_2\}NO_2(en)]\cdot 3H_2O$ (**2**), $C_{11}H_{26}CoN_5O_{11}$, fw 463.29, belong to the monoclinic system, with a = 8.843 (1) Å, b = 26.809 (2) Å, c = 8.910 (1) Å, β = 115.91 (2)°, V = 1899.9 Å^3, space group $P2_1/c$, Z = 4, ρ_{calcd} = 1.62 g cm^{-3}, Mo Kα radiation, λ = 0.71073 Å, and μ(Mo Kα) = 9.6 cm^{-1}.

Data Collection. A crystal of approximate dimensions 0.52 × 0.36 × 0.20 mm was mounted on an Enraf-Nonius CAD4 diffractometer, equipped with a graphite-crystal, incident-beam monochromator. The unit cell dimensions were determined by a least-squares treatment of 25 high-angle reflections. The data were collected by using the $\theta/2\theta$ scan technique. The scan rate varied from 1 to 7° min^{-1} with scan widths of $0.8 + 0.35 \tan \theta$. A total of 4352 reflections in the range $2 < \theta < 27°$ were collected, of which 4019 were unique and not systematically absent. Three standard reflections were measured every 60 min of exposure time to monitor the stability of the crystal and of the experimental conditions: no significant variation was observed. The orientation of the crystal was checked by measuring 2 reflections every 200 reflections. The raw intensity data were corrected for Lorentz-polarization effects but not for absorption. The intensities of the 366 equivalent reflections were averaged; the agreement factor for the averaging was 1.2% based on intensity.

Structure Solution and Refinement. The structure was solved by standard Patterson and Fourier methods and refined by full-matrix least-squares calculations. The function minimized was $\sum w(|F_o| - |F_c|)^2$, and weight w was defined as 1.0 for all the observed reflections. Scattering factors were taken from the literature, and contribution of the real and imaginary parts of the anomalous dispersion was taken into account.[15] Only 3260 reflections having intensities greater than $3.0\sigma(I)$ were used in the refinement. A secondary extinction correction was applied.[16] The final coefficient was 6×10^{-7}.

All calculations were performed on a PDP-11/73 computer using the SDP/PDP package of programs and physical constants tabulated therein.[17]

The position of the Co atom was determined from a Patterson function, and those of the remaining atoms, including hydrogens, were de-

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Table III. Positional Parameters and Their Estimated Standard Deviations for $CoC_{11}H_{26}N_5O_{11}$ (**2**)[a]

atom	x	y	z	B, Å^2
Co	0.12425 (4)	0.08932 (1)	0.18551 (3)	1.615 (5)
O(1)	−0.0111 (2)	0.08473 (7)	−0.0493 (2)	2.27 (4)
O(2)	−0.2024 (2)	0.12559 (8)	−0.2643 (2)	3.02 (4)
O(3)	0.0159 (2)	0.22129 (7)	0.3122 (2)	2.35 (4)
O(4)	0.3713 (2)	0.08788 (7)	0.7098 (2)	2.52 (4)
O(5)	0.1675 (2)	0.18277 (7)	0.8444 (2)	2.77 (4)
O(6)	0.4149 (2)	0.23136 (8)	0.5440 (2)	3.13 (4)
O(7)	−0.1254 (4)	0.0235 (1)	0.1546 (4)	3.58 (7)
O(8)	−0.1119 (3)	0.0858 (1)	0.3149 (3)	3.67 (6)
O(7′)	−0.165 (1)	0.0369 (3)	0.1279 (9)	2.6 (1)*
O(8′)	−0.061 (1)	0.0690 (4)	0.360 (1)	3.3 (2)*
O(7″)	−0.209 (2)	0.0634 (8)	0.120 (2)	4.0 (4)*
O(8″)	−0.017 (2)	0.0414 (7)	0.371 (2)	2.9 (3)*
N(1)	0.0376 (2)	0.15346 (8)	0.1651 (2)	1.89 (4)
N(2)	0.2393 (2)	0.10819 (8)	0.4180 (2)	1.71 (4)
N(3)	0.2151 (3)	0.02210 (8)	0.1913 (2)	2.26 (4)
N(4)	0.3115 (2)	0.11148 (8)	0.1388 (2)	2.14 (4)
N(5)	−0.0579 (3)	0.06276 (9)	0.2254 (2)	2.58 (5)
C(1)	−0.1049 (3)	0.1231 (1)	−0.1143 (3)	2.14 (5)
C(2)	−0.0940 (3)	0.1660 (1)	0.0009 (3)	2.25 (5)
C(3)	0.0750 (3)	0.17978 (9)	0.3006 (3)	1.73 (4)
C(4)	0.2004 (3)	0.15115 (9)	0.4515 (2)	1.59 (4)
C(5)	0.2634 (2)	0.17132 (9)	0.6276 (2)	1.71 (4)
C(6)	0.4123 (3)	0.1395 (1)	0.7417 (3)	2.20 (5)
C(7)	0.3531 (3)	0.0745 (1)	0.5505 (3)	2.51 (5)
C(8)	0.3226 (3)	0.2258 (1)	0.6396 (3)	2.28 (5)
C(9)	0.1178 (3)	0.1666 (1)	0.6774 (3)	2.24 (5)
C(10)	0.3832 (3)	0.0250 (1)	0.1947 (3)	2.79 (6)
C(11)	0.3805 (3)	0.0683 (1)	0.0857 (3)	2.88 (6)
OW(1)	0.7566 (3)	0.04434 (8)	0.5324 (2)	3.94 (5)
OW(2)	0.5811 (3)	0.16562 (9)	0.4293 (2)	3.63 (5)
OW(3)	0.6648 (3)	0.2054 (1)	0.1920 (3)	5.59 (6)

[a] Starred B values are for atoms that were refined isotropically. B values for anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as $(4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$.

termined from difference electron density maps. Anisotropic temperature factors were used for all non-hydrogen atoms. The positional parameters of the hydrogen atoms of water molecules and hydroxyl groups were refined with fixed isotropic temperature factors. The remaining hydrogen atoms were included in the structural model in the calculated positions with C-H and N-H bonds of 0.95 Å and allowed to ride on the atoms to which they are bonded, with $U(H) = 1.2U$ of the corresponding atom. At the last stage of refinement in the difference Fourier map the four highest peaks of electron density of 0.95–1.24 e Å^{-3} were found in positions implying rotational disorder of the nitro group. Four oxygen atoms, corresponding to two other orientations of the nitro group, were included in the least-squares calculations, and their positional parameters and isotropic thermal parameters were refined. The occupancy factors for the three pairs of nitro oxygen atoms were first refined independently, then were manually reset to get total occupancy of 100%, and finally were fixed to values of 0.67, 0.22, and 0.11 for the three orientations of the nitro group, respectively. The refinement of 294 parameters converged at $R = 0.031$ and $R_w = 0.034$. In the final difference electron density syntheses values varied from −0.45 to 0.57 e Å^{-3}. Except for the largest positive peak situated 0.872 Å from OW(3) and indicating the disorder of OW(3) hydrogens, the others were randomly distributed. No effort was made to include this hydrogen atom in the least-squares calculations.

Atomic positions, along with their standard deviations as derived from the inverse matrix of the final cycle least-squares refinement, are given in Table III.

Results

Characterization of the Condensation Products. Three condensation products were obtained (Table I, **2**–**4**) from the reaction of *mer*-[Co($NH_2CH_2CONCH_2CO_2$)NO_2(en)] with formaldehyde. Since these complexes exhibit d–d electronic transitions in the regions in which the absorption maxima of the starting substance (**1**) also appear (Table I), it may be concluded that the chromophore CoN_5O remains unchanged in the course of the reaction.

The ^{1}H NMR spectrum of compound **4**, which, according to the elemental analysis, contains one condensed unit of formaldehyde, (Figure 1) shows a very low field AB quartet (δ 7.5 ppm, $\Delta\delta_{AB}$ 0.23 ppm, $J = 8$ Hz) attributable to *N*-methylidene protons. The ^{13}C NMR spectrum of this product (Table II) shows a low-field resonance at 174.7 ppm (a triplet in the absence of proton decoupling) assignable to the $H_2C{=}N-$ group. Since the introduced imino group shifts the signal of the N-terminal CH_2 protons of the dipeptidato ligand (δ 4.4 ppm AB quartet, $\Delta\delta_{AB}$ 0.15 ppm, $J = 19.5$ Hz) about 1 ppm downfield relative to the same methylene of the starting complex (δ 3.4 ppm AB quartet, $\Delta\delta_{AB}$ 0.09 ppm, $J = 18$ Hz), it may be concluded that the imine is formed on the glycylglycine chelate rather than on an ethylenediamine amino group. This conclusion is supported by the fact that the shifts of the ethylenediamine CH_2 groups, in comparison to those of the starting material, are negligible. Additionally, the resonance for the methylene carbon α to the imino group is shifted downfield by about 17 ppm with respect to the resonance of this carbon when it is α to the amino group.

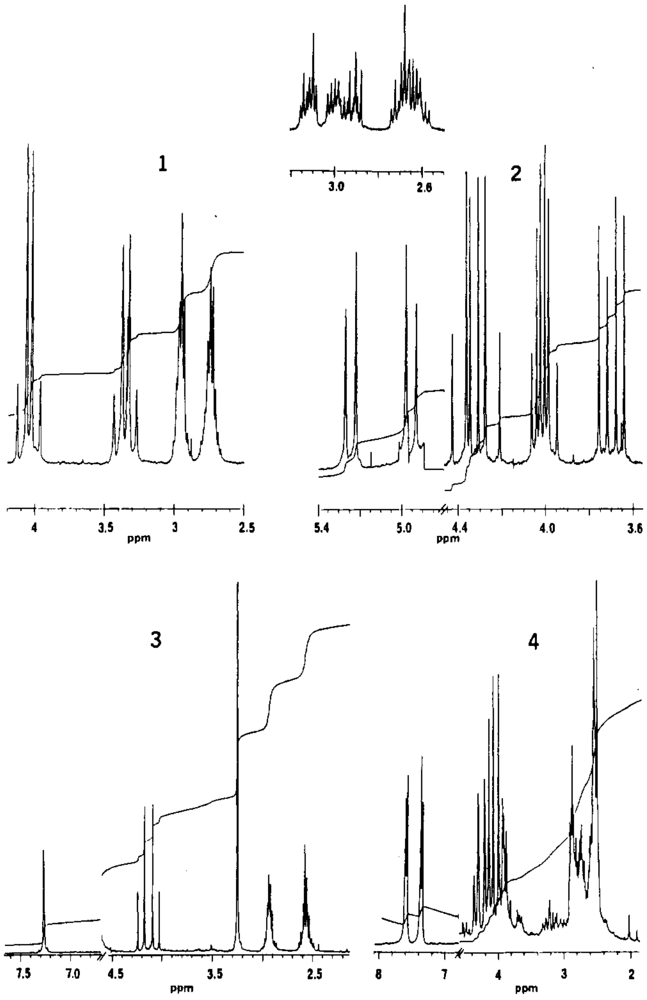

Figure 1. 300-MHz ^{1}H NMR spectra of *mer*-[Co($NH_2CH_2CONCH_2CO_2$)NO_2(en)] (**1**) and its reaction products with formaldehyde (**2**–**4**).

The elemental analysis of **3** also indicated one unit of condensed formaldehyde. Inspection of its ^{1}H and ^{13}C NMR spectra provide convincing evidence that **3** contains a tautomer of *N*-methylideneglycylglycine, i.e. compound **4**. Thus, the resonances of the $CH_2{=}N{-}CH_2-$ group in the spectra of complex **4** are replaced by the resonances of the $CH_3{-}N{=}CH-$ group in the spectra of **3**. The ^{1}H NMR spectrum of this complex shows a methyl doublet resonance (δ 3.4 ppm, $J \leq 2$ Hz), which is ascribed to a methyl group attached to the imine nitrogen that exhibits a small long-range coupling with a proton on the imino carbon. Also the spectrum shows a resonance for one proton attached to the imino carbon (δ 7.3 ppm, quartet, $J \leq 2$ Hz). A well-resolved AB quartet at δ 4.3 ppm (Δδ 0.13 ppm, $J = 19.8$ Hz) and complex signals around δ 2.6 and 2.9 ppm are ascribed to the dipeptidate C-terminal methylene and ethylenediamine methylene groups,

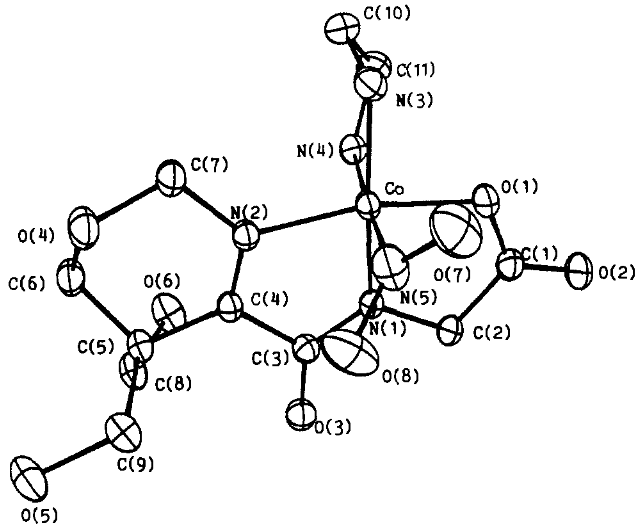

Figure 2. Perspective view of the *mer*-[Co{$(CH_2OH)_2\overline{CCH_2OCH_2N{=}C}CONCH_2CO_2$}$NO_2$(en)] (**2**) molecule, showing the atom-numbering scheme. Only the most occupied position of the nitro oxygen atoms is presented. The hydrogen atoms are omitted for clarity.

respectively. The relative intensities of the NMR signals are in agreement with these assignments. In the ^{13}C NMR spectrum the signals at δ 175.9 and 46.2 ppm are ascribed to imine and methyl carbons, respectively, since in the ^{13}C off-resonance-decoupled spectrum they appear as a doublet and quartet, respectively.

Product **2** contains, according to the elemental analysis, five incorporated units of formaldehyde. Its ^1H and ^{13}C NMR spectra indicate that the ethylenediamine and C-terminal amino acid chelates remain intact during the course of its formation and that this product derives from the condensation of the aldehyde with the N-terminal amino acid residue. The ^{13}C NMR spectrum of this complex shows resonances at δ 45.7, 45.9, and 50.0 ppm due to the ethylenediamine and C-terminal methylene carbons, respectively. Their chemical shifts correspond to those found in the spectrum of the starting complex. Also, this spectrum shows that the resonance of the N-terminal methylene carbon is replaced by a very low field signal (δ 170.0 ppm), indicating that an imine is formed on the N-terminal amino acid chelate. In addition, this spectrum contains five signals at δ 51.2, 62.4, 62.6, 67.4, and 80.9 ppm originating from the newly introduced carbon atoms. The ^{13}C off-resonance-decoupled spectrum reveals that the resonance at δ 51.2 ppm arises from a quaternary carbon and the others arise from methylene carbons. Since the resonances at about δ 62 ppm correspond to the carbons of $-CH_2OH$ groups attached to carbon[3] and the resonances at δ 80.9 and 67.4 ppm can be attributed to methylene carbons attached to two and one heteroatom, respectively, we assumed that complex **2** contains a 1,3-oxazine derivative as the N-terminal chelate. Data obtained from its ^1H NMR spectrum are consistent with the proposed structure. This spectrum displays AB quartets at δ 5.1 ppm ($\Delta\delta_{AB}$ 0.28 ppm, J = 11.4 Hz), 4.0 ppm ($\Delta\delta_{AB}$ 0.07 ppm, J = 12 Hz), 3.9 ppm ($\Delta\delta_{AB}$ 0.06 ppm, J = 11.4 Hz), and 3.8 ppm ($\Delta\delta_{AB}$ 0.59 ppm, J = 11.4 Hz), which are ascribed to $N-CH_2-O$, $C-CH_2-O$, and the two $C-CH_2OH$ moieties, respectively. Complex signals around δ 3.0 and 2.6 ppm are ascribed to the ethylenediamine CH_2 groups, and an AB quartet at δ 4.3 ppm ($\Delta\delta_{AB}$ 0.14 ppm, J = 19.8 Hz) is due to the C-terminal CH_2 group.

Discussion

A central feature of the investigated condensation of formaldehyde with cobalt-chelated glycylglycine is formation of a complex with an entirely new ligand *N*-((5,6-dihydro-5,5-bis(hydroxymethyl)-1,3-oxazin-4-yl)carbonyl)glycine (**2**). In order to gain more conclusive support for the structure proposed on the basis of the spectral data and to better characterize this new ligand system, an X-ray crystal structure of complex **2** was undertaken.

Crystal Structure of Complex 2. The crystal structure of **2** consists of enantiomeric pairs of the complex molecules and molecules of water, joined together by O-H···O and N-H···O hydrogen bonds. An ORTEP drawing of the molecule with the atom-numbering scheme is given in Figure 2. Bond lengths and angles are listed in Tables IV and V, respectively.

The cobalt atom is surrounded by five nitrogen atoms and one oxygen atom, forming a distorted octahedron. The diamine ligand acts, as usual, as a bidentate ligand. The ligand, obtained by the condensation reaction of glycylglycine and formaldehyde, is coordinated through carboxylato oxygen and peptide and imino nitrogens in a meridional arrangement. The sixth coordination position is occupied by a nitro group.

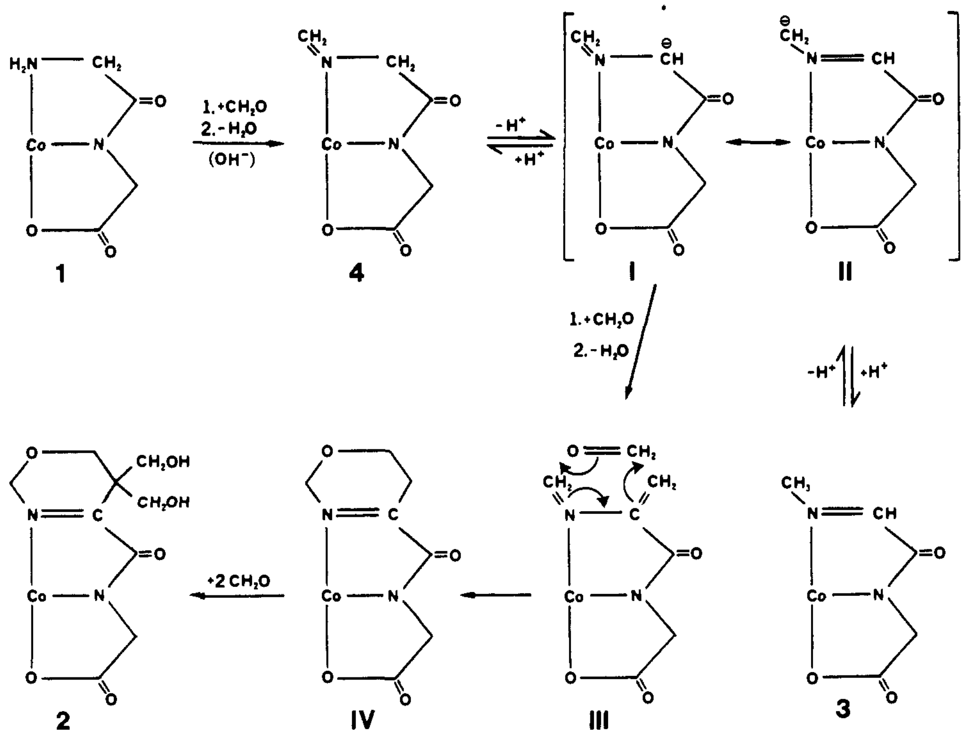

Figure 3. Proposed mechanism for the reaction of *mer*-[Co($NH_2CH_2CONCH_2CO_2$)NO_2(en)] with formaldehyde.

Table IV. Bond Distances (Å) for Complex **2**

Co–O(1)	1.907 (1)	O(8′)–N(5)	1.22 (2)
Co–N(1)	1.859 (2)	O(7″)–N(5)	1.25 (2)
Co–N(2)	1.934 (2)	O(8″)–N(5)	1.31 (3)
Co–N(3)	1.965 (3)	N(1)–C(2)	1.456 (3)
Co–N(4)	1.968 (2)	N(1)–C(3)	1.310 (3)
Co–N(5)	1.931 (2)	N(2)–C(4)	1.274 (3)
O(1)–C(1)	1.289 (4)	N(2)–C(7)	1.479 (4)
O(2)–C(1)	1.235 (2)	N(3)–C(10)	1.477 (4)
O(3)–C(3)	1.254 (2)	N(4)–C(11)	1.480 (4)
O(4)–C(6)	1.427 (4)	C(1)–C(2)	1.516 (5)
O(4)–C(7)	1.403 (3)	C(3)–C(4)	1.525 (4)
O(5)–C(9)	1.422 (3)	C(4)–C(5)	1.517 (4)
O(6)–C(8)	1.422 (3)	C(5)–C(6)	1.526 (3)
O(7)–N(5)	1.237 (4)	C(5)–C(8)	1.539 (4)
O(8)–N(5)	1.257 (3)	C(5)–C(9)	1.541 (4)
O(7′)–N(5)	1.191 (9)	C(10)–C(11)	1.507 (5)

Table V. Bond Angles (deg) for Complex **2**

O(1)–Co–N(1)	85.31 (4)	Co–N(5)–O(8″)	116.8 (6)
O(1)–Co–N(2)	167.5 (1)	O(7)–N(5)–O(8)	120.6 (4)
O(1)–Co–N(3)	91.32 (4)	O(7′)–N(5)–O(8′)	116.5 (7)
O(1)–Co–N(4)	88.30 (4)	O(7″)–N(5)–O(8″)	119.2 (8)
O(1)–Co–N(5)	90.21 (4)	Co–O(1)–C(1)	114.4 (1)
N(1)–Co–N(2)	82.2 (1)	C(6)–O(4)–C(7)	111.0 (2)
N(1)–Co–N(3)	175.9 (1)	O(1)–C(1)–O(2)	122.5 (3)
N(1)–Co–N(4)	92.8 (1)	O(1)–C(1)–C(2)	117.6 (2)
N(1)–Co–N(5)	91.0 (1)	O(2)–C(1)–C(2)	119.9 (3)
N(2)–Co–N(3)	101.2 (1)	N(1)–C(2)–C(1)	107.0 (2)
N(2)–Co–N(4)	92.86 (6)	O(3)–C(3)–N(1)	127.5 (2)
N(2)–Co–N(5)	89.44 (7)	O(3)–C(3)–C(4)	122.9 (2)
N(3)–Co–N(4)	84.8 (1)	N(1)–C(3)–C(4)	109.6 (2)
N(3)–Co–N(5)	91.2 (1)	N(2)–C(4)–C(3)	114.5 (2)
N(4)–Co–N(5)	175.8 (2)	N(2)–C(4)–C(5)	123.4 (2)
Co–N(1)–C(2)	115.3 (2)	C(3)–C(4)–C(5)	122.0 (3)
Co–N(1)–C(3)	118.8 (2)	C(4)–C(5)–C(6)	108.0 (3)
C(2)–N(1)–C(3)	124.8 (3)	C(4)–C(5)–C(8)	111.8 (2)
Co–N(2)–C(4)	114.7 (1)	C(4)–C(5)–C(9)	107.1 (1)
Co–N(2)–C(7)	123.5 (3)	C(6)–C(5)–C(8)	108.4 (2)
C(4)–N(2)–C(7)	121.6 (2)	C(6)–C(5)–C(9)	110.5 (2)
Co–N(3)–C(10)	110.4 (3)	C(8)–C(5)–C(9)	111.1 (3)
Co–N(4)–C(11)	109.6 (3)	O(4)–C(6)–C(5)	109.8 (2)
Co–N(5)–O(7)	118.3 (2)	O(4)–C(7)–N(2)	112.9 (3)
Co–N(5)–O(8)	120.9 (3)	O(6)–C(8)–C(5)	109.0 (3)
Co–N(5)–O(7′)	123.0 (4)	O(5)–C(9)–C(5)	111.2 (1)
Co–N(5)–O(8′)	120.4 (5)	N(3)–C(10)–C(11)	107.2 (2)
Co–N(5)–O(7″)	123.9 (6)	N(4)–C(11)–C(10)	106.8 (2)

The structure of the new ligand is in accordance with that proposed on the basis of spectroscopic data. By condensation of five formaldehyde units to the N-terminal part of glycylglycine, a 1,3-oxazine derivative is formed, which contains a N=C double bond in the N-terminal amino acid chelate and a quaternary carbon atom to which two CH_2OH groups are attached. The equatorially disposed ligand with cobalt therefore consists of three fused rings, two five-membered chelates, and one six-membered heterocyclic ring. The configurations of the two CH_2OH groups with respect to the C(4)–C(5) bond are different: one is trans and the other is in a cis position.

The coordination geometry about cobalt conforms to those found in previously investigated (glycylglycinato)cobalt(III) complexes.[12,18–20] The usual geometry of the residue of the parent glycylglycinato fragment is not distorted by the formation of the C=N double bond and the presence of the 1,3-oxazine derivative. The bond distances and angles in the heterocyclic ring and CH_2OH groups have expected values. There is also nothing exceptional in the geometries of the ethylenediamine and nitro ligands.

The presence of three planar groups in the coordinated *N*-((5,6-dihydro-5,5-bis(hydroxymethyl)-1,3-oxazin-4-yl)carboxyl)glycinato ligand influences the pronounced planarity of the two fused chelate rings. The angle between mean planes of the chelates is 3.3 (7)°, and the maximum deviation from the plane containing all atoms of the glycylglycine fragment of the ligand is 0.08 Å. The 1,3-oxazine six-membered ring has a distorted half-chair conformation, with dominant rotational symmetry (C_2 axis intersecting the N(2)–C(4) and O(4)–C(6) bonds with $\Delta C_2 = 2.0°$[21]).

In the enantiomer that has the Δ absolute configuration, taking the rings of the ethylenediamine ligand and C-terminal amino carboxylato residue of parent glycylglycine as reference rings, the chirality of the ethylenediamine chelate is δ.[22]

The nitro oxygen atoms are statistically distributed in three positions with respective occupancies of 0.67, 0.22, and 0.11. The mean planes through the cobalt atom and the atoms of the corresponding orientation of the nitro group are inclined to each other at angles of 30.7, 105.0, and 135.7° and make angles of 38.3, 68.9, and 66.8°, respectively, with the principal axes of the complex.

In the structure there is an extensive network of hydrogen bonds. Each complex molecule is connected by N–H···O and O–H···O hydrogen bonds with three adjacent molecules and with each of the three molecules of water. The water molecules, acting as donors and acceptors for hydrogen bonds, also participate in joining the complex molecules and molecules of water in a three-dimensional network. The strongest hydrogen bond in the structure of 2.64 Å connects hydroxyl oxygen O(6) and water molecule OW(3). The hydrogen bonds involving water molecules as donor are in the range 2.74–2.93 Å, typical for crystalline hydrates. The existence of one bifurcated and one trifurcated hydrogen bond involving nitro oxygen atoms is in accordance with the observed rotational disorder of the nitro group.

Proposed Mechanism for the Condensation Reaction. Condensation of the coordinated amino groups with the aldehyde is believed to proceed through the deprotonated amine attacking the carbonyl groups to give the carbinolamine, which then eliminates water to give the imine.[23] Since the imine complex (**4**) is isolated, we assumed that the first step in the investigated base-catalyzed condensation reaction of coordinated glycylglycine with formaldehyde proceeds through this path (Figure 3, **1**–**4**). The newly formed *N*-methylidene group facilitates ionization of the C–H bond of the N-terminal methylene group and stabilizes by resonance the carbanion formed (I ↔ II). In the second step two competing processes are involved. In the first one, protonation occurs on either side of the imine nitrogen (I and II) and gives the products **3** and **4**. In the second process, alkylation of the carbanion, followed by dehydration, possibly leads to the formation of the α,β-unsaturated imine III (not isolated). The ease of H_2O elimination is probably related to the fact that the newly formed carbon–carbon double bond is stabilized by conjugation. The next step leading to **2** could be rationalized in terms of a [4 + 2] cycloaddition involving formaldehyde (dienophile) and imine III (1,3-heterodiene) to yield 1,3-oxazine compound IV (not isolated). The regioselectivity of the reaction is directed by the charge distribution in the reacting species. Subsequent alkylation of IV by 2 mol of formaldehyde at the carbon in the position α to the imino group, which should be activated toward alkylation,[24,25] affords the final product **2**.

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Supplementary Material Available: Listings of crystal and refinement data, anisotropic thermal parameters, hydrogen atom positions and thermal parameters, torsion angles, hydrogen bonds, and mean planes (6 pages); a listing of observed and calculated structure factor amplitudes (33 pages). Ordering information is given on any current masthead page.

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