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NOVEL *N,N'*-METHYLENE-BRIDGED METAL(II) COMPLEXES OF *N,N'*-METHYLENEDI(4-HYDROXY-L-PROLINE) OBTAINED FROM THE CONDENSATION OF BIS(4-HYDROXY-L-PROLINATO)METAL(II) WITH FORMALDEHYDE

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Abstract—The condensation of bis(4-hydroxy-L-prolinato)metal(II) (metal = zinc, cobalt, copper, nickel) with formaldehyde led to the formation of the respective metal(II) complexes of *N, N'*-methylenedi(4-hydroxy-L-proline), $M^{II}[My(OH-Pro)_2]$, each of which possesses an *N, N'*-methylene bridge linking the coordinated 4-hydroxy-L-proline ligands. Such linkage is without precedent in the products of the reactions of chelated amino acids with aldehydes.

Although extensive studies have been carried out on the reactions of formaldehyde with chelated α- and β-amino acids,[1–8] no such reactions involving a coordinated cyclic amino acid with an aldehyde leading to the successful isolation of products have been reported.

In this paper we present for the first time the condensation reactions of formaldehyde with the coordinated cyclic amino acid, 4-hydroxy-L-proline, which lead to the formation of novel metal(II) complexes of *N,N'*-methylenedi(4-hydroxy-L-proline), $M^{II}[My(OH-Pro)_2]$, in which the amino nitrogen atoms of the cyclic amino acid are linked by a methylene bridge.

The X-ray structural determinations of M^{II}

$[My(OH-Pro)_2]$ (M = Zn, Co) have been performed and the results are discussed herein.

EXPERIMENTAL

Preparation of bis(4-hydroxy-L-prolinato)metal(II), $M^{II}(OH-Pro)_2$

The $M^{II}(OH-Pro)_2$ complexes were prepared according to procedures similar to those described previously.[9,10]

Preparation of $M^{II}[My(OH-Pro)_2]$

The preparation of $Zn^{II}[My(OH-Pro)_2]$ is given as a typical preparative procedure.

A reaction mixture consisting of $Zn(OH-Pro)_2$ (1.0 g, 0.003 mol) and 10 cm³ of a 37% w/v solution of formaldehyde (0.12 mol) was stirred thoroughly.

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The resultant colourless solution (pH 5.5) was allowed to evaporate slowly at room temperature, whence colourless crystals appeared after 2 weeks. These were filtered and washed with ethanol and finally dried *in vacuo* for 5 h. Yield 0.3 g (27%). Found: C, 35.3; H, 5.3; N, 7.4. Calc. for $C_{11}H_{16}N_2O_6Zn \cdot 2H_2O$: C, 35.4; H, 5.4; N, 7.5%.

The other $M^{II}[My(OH\text{-}Pro)_2]$ (M = Co, Cu, Ni) complexes were prepared in a manner similar to that for $Zn^{II}[My(OH\text{-}Pro)_2]$.

X-ray structure determination

X-ray measurements were performed at room temperature on single crystals of $Zn^{II}[My(OH\text{-}Pro)_2]$ and $Co^{II}[My(OH\text{-}Pro)_2]$ respectively using

diffractometers which employed graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å). Crystal data, data collection and details of structure refinement for both crystals are summarized in Table 1.

The observed systematic absences of both crystals were consistent with the space group $P3_221$. The intensities of the reflections showed no significant change over the duration of the data collection. Lorentz and polarization corrections were applied. The $Zn^{II}[My(OH\text{-}Pro)_2]$ and $Co^{II}[My(OH\text{-}Pro)_2]$ structures were solved using Siemens SHELXTL PLUS (PC Version)[11] and direct methods,[12] respectively, and were refined by the full-matrix least-squares technique. In the refinement, all non-hydrogen atoms were assigned anisotropic thermal par-

Table 1. Crystal data, data collection and details of structure refinement for M^{II} [My(OH-Pro)$_2$] (M = Zn, Co)

	Zn^{II} complex	Co^{II} complex
Diffractometer	Siemens P4	Huber
Crystal shape	Hexagonal plate	Cuboidal
Size (mm)	$0.3 \times 0.3 \times 0.4$	$0.6 \times 0.6 \times 0.6$
Formula	$C_{11}H_{16}N_2O_6Zn \cdot 2H_2O$	$C_{11}H_{16}N_2O_6Co \cdot 2H_2O$
Formula weight	373.7	367.2
Crystal system	Trigonal	Trigonal
Space group	$P3_221$	$P3_221$
Unit cell dimensions		
a (Å)	7.774(3)	7.8020(10)
c (Å)	21.797(10)	21.849(5)
V (Å^3)	1140.8(8)	1151.8(3)
Z	3	3
D_c (g cm^{-3})	1.632	1.588
$F(000)$	582	573
Absorption coefficient (mm^{-1})	1.656	1.159
2θ range (°)	3.0–55.0	3.0–70.0
Scan type	2θ–θ	ω
Scan range, ω (°)	2.00 plus K_α separation	0.20
Range of h, k, l	-8 to 0; 0–10; 0–28	-12 to 10; 0–10; -35 to 35
Standard reflections	2 every 200 reflections	1 every 50 reflections
Total no. of reflections	954	3964
No. of unique reflections,	954	1993
R_{int} (%)	0.00	2.74
No. of observed reflections	917	1906
Criterion for observed reflections	$F > 4.0 \, \sigma \, (F)$	$F > 4.0 \, \sigma \, (F)$
Weighting scheme	$w^{-1} = \sigma^2(F) + 0.0011F^2$	$w^{-1} = \sigma^2(F) + 0.0038F^2$
Parameters refined	118	112
Value of R	0.066	0.038
Value of R_w	0.093	0.040
Largest and mean Δ/σ	0.275, 0.038	0.931, 0.054

ameters. Selected bond lengths and angles are
shown in Table 2, while lists of atomic coordinates,
thermal parameters and observed and calculated
structure factors have been deposited as sup-
plementary material with the Editor, from whom
copies are available on request.

The molecular structure of $Zn^{II}[My(OH-Pro)_2]$
(Fig. 1) was drawn with ORTEP.[13]

RESULTS AND DISCUSSION

The molecular structure of $Zn^{II}[My(OH-Pro)_2]$
(Fig. 1) establishes the coordination of two cyclic
4-hydroxy-L-proline molecules to the central zinc
atom via the amino nitrogen and carboxylato oxy-
gen atoms of the cyclic amino acid moieties, which
in turn are linked by a single methylene bridge
across their respective nitrogen atoms.

The presence of the methylene bridge gives rise
to two types of chelate ring in the complex, one of
which is the five-membered ring formed by Zn(1),
O(2), C(5), C(1) and N(1), while the other is a four-
membered ring comprising Zn(1), N(1), C(6) and
N(1A) such that N(1) and N(1A) are equidistant
from a mirror plane passing through Zn(1) and
C(6).

In the molecule, the zinc atom exists in a distorted
octahedral geometry defined by the ZnN_2O_2 atoms
of the chelated N,N'-methylenedi(4-hydroxy-L-
proline), as well as two water molecules. The
greatest deviations from ideal octahedral angles
are found for the N(1)—Zn(1)—N(1A), O(4)—

Zn(1)—N(1) [also O(4A)—Zn(1)—N(1A)] and
N(1)—Zn(1)—O(4A) [also O(4)—Zn(1)—N(1A)]
angles of 63.5(3)°, 101.8° and 160.9(2)°, respec-
tively.

The reduced N(1)—Zn(1)—N(1A) angle (less
than 90°) reflects the restricted bite distance of the
methylene bridged chelating ligand [cf. the cor-
responding N(1)—Zn(1)—N(1A) angle of 115.0(1)°
in bis(L-prolinato)zinc(II)[14]. This unique meth-
ylene bridge pulls the N(1) and N(1A) atoms closer
together [N(1)—N(1A) distance, 2.410 Å] to the
extent of lengthening the Zn(1)—N(1) and
Zn(1)—N(1A) bonds [2.283(6) and 2.283(6) Å,
respectively], which are much longer than the aver-
age Zn—N length (2.06 Å) of unbridged zinc-coor-
dinated amino acids.[14,15]

However, the bond distances and angles of
each chelated 4-hydroxy-L-proline moiety are
comparable with those of the free molecule and
those of copper(II) complexes of 4-hydroxy-L-
proline.[16–18]

As the molecular structure of Co^{II} [My(OH-
Pro)_2] is isostructural with that of the zinc(II) ana-
logue, it is not shown here.

The IR spectra of the copper(II) and nickel(II)
complexes resemble those of the zinc(II) and
cobalt(II) complexes;[19] hence the former two com-
plexes are postulated to have the same structures as
the latter two compounds. Such postulations are
well corroborated by the excellent agreement of the
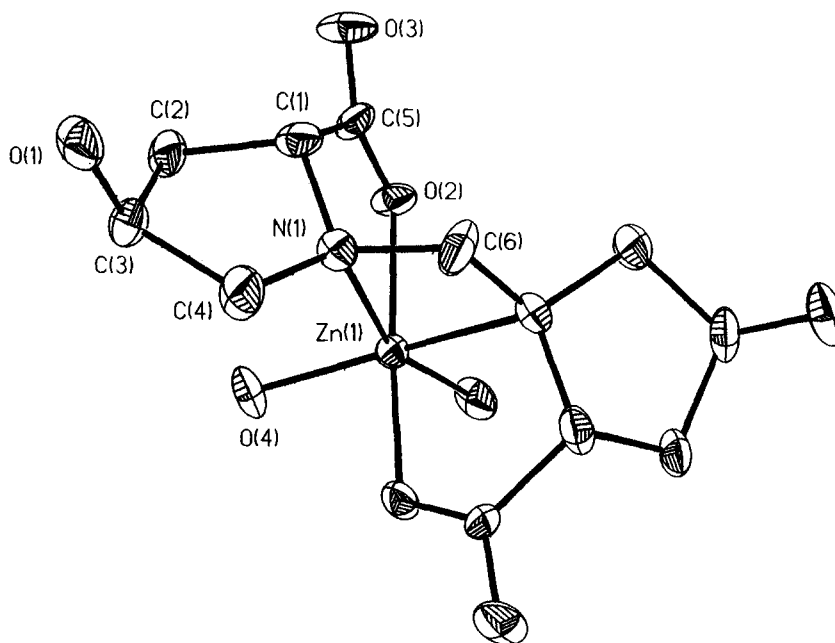microanalytical data with the proposed molecular
formulae.[19]

Fig. 1. The molecular structure of $Zn^{II}[My(OH-Pro)_2]$.

Table 2. Bond distances (Å) and angles (°) of $M^{II}[My(OH\text{-}Pro)_2]$ (M = Zn, Co)

Zn^{II} complex			
Zn(1)—O(4)	2.039(5)	Zn(1)—N(1)	2.283(6)
Zn(1)—O(2)	2.027(7)	Zn(1)—O(4A)	2.039(5)
Zn(1)—N(1A)^a	2.283(6)	Zn(1)—O(2A)	2.027(7)
O(1)—C(3)	1.426(9)	N(1)—C(4)	1.478(9)
N(1)—C(1)	1.474(13)	N(1)—C(6)	1.466(9)
C(4)—C(3)	1.563(18)	C(3)—C(2)	1.501(12)
C(1)—C(2)	1.535(11)	C(1)—C(5)	1.507(9)
O(2)—C(5)	1.251(10)	C(5)—O(3)	1.269(13)
C(6)—N(1A)	1.466(9)		
O(4)—Zn(1)—N(1)	101.8(2)	O(4)—Zn(1)—O(2)	97.3(3)
N(1)—Zn(1)—O(2)	78.2(2)	O(4)—Zn(1)—O(4A)	95.0(3)
N(1)—Zn(1)—O(4A)	160.9(2)	O(2)—Zn(1)—O(4A)	90.7(2)
O(4)—Zn(1)—N(1A)	160.9(2)	N(1)—Zn(1)—N(1A)	63.5(3)
O(2)—Zn(1)—N(1A)	91.7(2)	O(4A)—Zn(1)—N(1A)	101.8(2)
O(4)—Zn(1)—O(2A)	90.7(2)	N(1)—Zn(1)—O(2A)	91.7(2)
O(2)—Zn(1)—O(2A)	168.2(3)	O(4A)—Zn(1)—O(2A)	97.3(3)
N(1A)—Zn(1)—O(2A)	78.2(2)	Zn(1)—N(1)—C(4)	122.5(5)
Zn(1)—N(1)—C(1)	105.1(4)	C(4)—N(1)—C(1)	107.1(8)
Zn(1)—N(1)—C(6)	93.2(5)	C(4)—N(1)—C(6)	113.5(7)
C(1)—N(1)—C(6)	115.2(5)	N(1)—C(4)—C(3)	106.4(9)
O(1)—C(3)—C(4)	109.2(7)	O(1)—C(3)—C(2)	113.2(8)
C(4)—C(3)—C(2)	104.9(7)	N(1)—C(1)—C(2)	103.8(6)
N(1)—C(1)—C(5)	111.9(7)	C(2)—C(1)—C(5)	113.6(7)
C(3)—C(2)—C(1)	104.7(8)	Zn(1)—O(2)—C(5)	119.2(5)
C(1)—C(5)—O(2)	119.7(8)	C(1)—C(5)—O(3)	117.4(7)
O(2)—C(5)—O(3)	122.6(6)	N(1)—C(6)—N(1A)	110.1(9)
Co^{II} complex			
Co(1)—O(2)	2.037(2)	Co(1)—O(4)	2.081(2)
Co(1)—N(1)	2.220(2)	Co(1)—O(2A)	2.037(2)
Co(1)—O(4A)	2.081(2)	Co(1)—N(1A)	2.220(2)
O(2)—C(5)	1.259(3)	O(3)—C(5)	1.250(3)
O(1)—C(4)	1.422(3)	C(5)—C(1)	1.527(2)
C(1)—C(2)	1.528(3)	C(1)—N(1)	1.482(4)
C(2)—C(3)	1.523(3)	C(3)—C(4)	1.528(5)
C(4)—N(1)	1.493(3)	N(1)—C(6)	1.470(3)
C(6)—N(1A)	1.470(3)		
O(2)—Co(1)—O(4)	95.5(1)	O(2)—Co(1)—N(1)	79.5(1)
O(4)—Co(1)—N(1)	102.9(1)	O(2)—Co(1)—O(2A)	171.7(1)
O(4)—Co(1)—O(2A)	90.3(1)	N(1)—Co(1)—O(2A)	93.5(1)
O(2)—Co(1)—O(4A)	90.3(1)	O(4)—Co(1)—O(4A)	90.6(1)
N(1)—Co(1)—O(4A)	163.7(1)	O(2A)—Co(1)—O(4A)	95.5(1)
O(2)—Co(1)—N(1A)	93.5(1)	O(4)—Co(1)—N(1A)	163.7(1)
N(1)—Co(1)—N(1A)	65.5(1)	O(2A)—Co(1)—N(1A)	79.5(1)
O(4A)—Co(1)—N(1A)	102.9(1)	Co(1)—O(2)—C(5)	118.4(1)
O(2)—C(5)—O(3)	123.6(2)	O(2)—C(5)—C(1)	118.8(2)
O(3)—C(5)—C(1)	117.6(2)	C(5)—C(1)—C(2)	111.9(2)
C(5)—C(1)—N(1)	112.0(2)	C(2)—C(1)—N(1)	103.2(2)
C(1)—C(2)—C(3)	104.2(2)	O(1)—C(3)—C(2)	113.2(2)
O(1)—C(3)—C(4)	111.1(2)	C(2)—C(3)—C(4)	104.7(2)
C(3)—C(4)—N(1)	107.1(3)	Co(1)—N(1)—C(1)	106.5(1)
Co(1)—N(1)—C(4)	122.1(1)	C(1)—N(1)—C(4)	106.7(2)
Co(1)—N(1)—C(6)	92.5(1)	C(1)—N(1)—C(6)	114.6(1)
C(4)—N(1)—C(6)	114.2(2)	N(1)—C(6)—N(1A)	109.5(2)

^{a} Atoms with labels ending in A are related by the symmetry operation y, x, $-z$.

The formation of the above $M^{II}[My(OH-Pro)_2]$ complexes with the attendant N,N'-methylene bridge is without precedent in the products of the reactions of chelated α- and β-amino acids with formaldehyde.[1-7]

The above reactions must involve the initial attack of formaldehyde on the amino nitrogen atom of the $M^{II}(OH-Pro)_2$ to yield the N-hydroxymethyl derivative. This is supported by mechanistic studies on the reactions of amino acid chelates with an aldehyde, where hydroxymethylation has been shown to occur readily.[20] Furthermore, preliminary studies have shown that aquabis(N-hydroxymethyl-L-prolinato)copper(II) has been isolated from the reaction of bis(L-prolinato)copper(II) with formaldehyde.[19] Condensation between the N-hydroxymethyl substituent and the amino nitrogen proton of the other coordinated 4-hydroxy-L-proline residue then yields the inter-ligand N,N'-methylene bridge.

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