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NMR and Crystallographic Studies of Zn(II) Complexes with Thiazolidine-4-carboxylic Acid and Thiazolidine-2-carboxylic Acid

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^{13}C NMR studies in aqueous solutions have shown that Zn(II) ions form with thiazolidine-4-carboxylic and thiazolidine-2-carboxylic acids 1:2 complexes with the metal ion bound *via* N amino and O carboxylate donors. Crystals of the complex [Zn(thiazolidine-4-carboxylic)$_2$(H$_2$O)$_2$] are monoclinic, space group $P2_1$, with a = 6.156(2), b = 20.808(5), c = 6.020(2) Å, β = 111.32(5)° and Z = 2. The structure was solved by the heavy atom method and refined by full-matrix least-squares calculations to a final R = 0.056 for 1012 counter reflections. The zinc atom is octahedrally coordinated by two thiazolidine-4-carboxylic chelate (O, N) ligands and two water molecules in *cis* positions. The five-membered chelate rings exist in envelope-like conformations. The absolute configurations of the ligands were assigned as (C(4)R, NR) with reference to the known R configuration of the thiazolidine-4-carboxylic ligand.

Introduction

Gosálvez *et al.* [1–3] have reported that thiazolidine-4-carboxylic acid (thiaproline) is able to induce the restoration of 'contact inhibition' to tumor cells. Thiaproline was also selected as the possible chelate of a metal from a protein complex in the plasma membrane which could be the cause of contractile microfilaments [1, 2]. These suggestions inspired the chemical studies on the binding possibilities of thiaproline.

Recent potentiometric studies [4] suggest that the binding site is a nitrogen donor for Zn(II), Mn(II), Ni(II) and Co(II) having some carboxylate involvement as appropriate.

A crystallographic study [5] of the Cu(II) thiaproline complex has shown that nitrogen and carboxylate donors are indeed involved in metal ion binding but that the ligand molecule undergoes an oxidation process.

In this communication we present ^{13}C NMR and crystallographic results for the Zn(II) thiaproline system as well as the ^{13}C NMR results for Zn(II)–thiazolidine-2-carboxylic acid complexes. The anticancer activity of the latter ligand was tested on human uterine cancer cells in tissue culture. It shows only a slight regression effect on cell growth (15% compared to thiaproline activity) and no morphological reversion activity.

Experimental

L-thiazolidine-4-carboxylic acid was used as obtained from Merck. DL-thiazolidine-2-carboxylic acid was synthesized from cisteamine and glyoxalic acid. $Zn(NO_3)_2 \cdot 6H_2O$ was used as a metal ion source. ^{13}C NMR spectra were recorded on a JEOL JNM PS-100 spectrometer with dioxane as internal standard for the solutions with 0.1 M l^{-1} of ligand in D_2O and 2:1 ligand to metal molar ratio. Spectra could be measured up to pH 6.2 at which precipitation occurred. The precipitate corresponds to a Zn(thiaproline)$_2 \cdot 2H_2O$ complex: *Anal.* Found 4.9 (H), 27.2 (C), 7.9 (N), 17.3 (S); calc. 4.4 (H), 26.3 (C), 7.7 (N), 17.5 (S). The washed precipitate was dissolved in a large amount of warm water. The crystals obtained from this solution were analyzed by the X-ray method.

Results and Discussion

^{13}C *NMR*

The carbon chemical shift variation of thiaproline carboxylate upon Zn(II) ion coordination is only slight at pH below 3.5, pK_{COOH} = 1.7 (Table I). Since the other carbons are not affected it seems evident that the Zn(II)–carboxylate interaction is not very effective at a lower pH region, *i.e.* the monodentate complex is a minor species in solution [6]. The increase of pH above 4 $pK_{NH_2^+}$ = 6.1 causes distinct chemical shift variations of C_2 and C_4 as well as of the carboxylate carbons (Table I). At pH 5.1–5.2 the carbon chemical shift changes upon metal ion coordination are equal to 3.6 (COO$^-$), 1.5 (C_2) and 0.4 ppm (C_4) downfield (Table I). This result strongly suggests that Zn(II) binds nitrogen and carboxylate donors and that the involvement of carboxylate is much more effective when the metal forms a chelate (NH, COO$^-$) complex.

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TABLE I. ^{13}C NMR Data for Thiaproline, Thiazolidine-2-carboxylic Acid and their Complexes with Zn(II).

Compound	pH	C_{COO^-}	C_2	C_4	C_5
thiaproline	1.0	170.5	49.3	63.2	32.9
	2.5	172.6	49.6	64.7	33.8
	4.5	172.7	49.4	64.7	33.8
	5.2	173.1	49.7	64.9	34.0
thiaproline + Zn 2:1 molar ratio	1.0	170.6	49.3	63.0	32.9
	3.2	173.0	49.6	64.7	33.9
	4.5	174.5	50.3	65.0	34.2
	5.1	176.7	51.2	65.3	34.4
thiazolidine-2-carboxylic acid	2.5	172.5	63.0	50.2	30.4
	3.5	172.5	63.2	50.0	30.3
	4.5	172.6	63.2	50.2	30.4
	5.5	173.1	63.6	50.4	30.8
thiazolidine-2-carboxylic acid + Zn 2:1 molar ratio	2.5	172.6	63.0	50.2	30.4
	3.5	173.2	63.5	50.4	30.9
	4.3	175.4	64.6	51.0	32.3

Similar results were obtained for Zn(II)–thiazolidine-2-carboxylate acid solutions (Table I). In the latter case the chemical variations upon metal ion binding at pH 4.3–4.5 are equal to 2.8 (COO^-), 1.4 (C_2) and 0.8 ppm (C_4) downfield. The conclusions obtained for the Zn(II)–thiaproline system agree well with the potentiometric results reported by D. R.Williams *et al.* [4].

Crystal Data

$Zn(C_4H_5NO_2S)_2(H_2O)_2$, $C_8H_{14}ZnN_2O_6S_2$, M = 727.7, monoclinic, a = 6.156(2), b = 20.808(5), c = 6.020(2) Å, β = 111.32(5)°, V = 718.4 Å^3, space group $P2_1$, Z = 2, D_c = 1.68 g cm^{-3}, $F(000)$ = 372.

The intensities of 1076 reflections ($4° < 2\theta < 125°$) were recorded on a Syntex $P2_1$ diffractometer using CuK_α radiation ($\mu_{CuK\alpha}$ = 52.8 cm^{-1}) and $\theta/2\theta$ scan. The structure was solved by the heavy atom method and refined by a full-matrix least-squares procedure with anisotropic thermal parameters for all non-hydrogen atoms. The structure was refined to R = 0.056 for 1012 significant reflections for which $F > 3.92\sigma(F)$. The coordinates of the H atoms and their isotropic thermal factor (B = 6.0 Å^2) were not refined. Scattering factors for neutral atoms were taken from International Tables for X-ray Crystallography [7].

The final positional and isotropic thermal parameters are listed in Table II.

Description of the Structure

A perspective view of the complex molecule showing the atom-numbering scheme is given in Fig. 1.

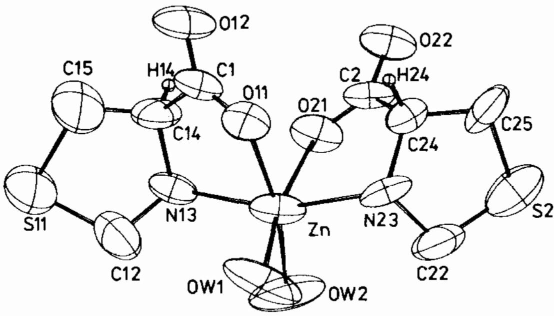

Fig. 1. Perspective view of the Zn(thiaproline)$_2$(H$_2$O)$_2$ complex.

The zinc atom is coordinated by two thiazolidine-4-carboxylate ligands in bidentate fashion through the N amino and O carboxyl atoms forming a five-membered chelate ring. Octahedral coordination is completed by two water molecules in *cis* positions. Bond distances and angles in the coordination polyhedron are given in Table III. The Zn–O-(carboxyl) distances 2.137 and 2.172(8) Å , agree well with those observed in the literature for octahedral Zn–O geometry [8]. The Zn–O water and Zn–N distances are also comparable with the values found in related complexes [9, 10]. Although the coordination about the zinc atom may be considered to be approximately octahedral, extensive deviations from the ideal angles are present (O_{water}–Zn–N 103.1(4)°, N(13)–Zn–N(23) 160.9(4)°). The bite angles of the chelate rings O(11)–Zn–N(13) [78.1(4)°] and O(21)–Zn–N(23) [77.4(4)°] deviate significantly from 90°. The chelate ring 'bite', O(11)····N(13) and O(21)····N(23) of 2.702(13)

TABLE II. Positional Parameters and B_{eq} (A)^2 Values for the Non-H Atoms with e.s.d.s in Parentheses.

	x	y	z	$B_{eq/iso}$^{a}
Zn	−0.0531(2)	−0.3400	−0.2735(2)	4.5(1)
S(11)	−0.1632(14)	−0.1194(3)	−0.2120(8)	10.7(7)
S(21)	−0.1459(15)	−0.5545(3)	−0.3434(12)	12.9(9)
O(11)	−0.1514(15)	−0.3024(5)	−0.6269(13)	5.2(7)
O(12)	−0.4271(16)	−0.2417(6)	−0.8819(14)	6.7(10)
O(21)	−0.4058(12)	−0.3763(5)	−0.3661(14)	5.2(7)
O(22)	−0.6622(14)	−0.4376(6)	−0.6268(15)	5.9(8)
OW(1)	0.2959(13)	−0.3230(8)	−0.2017(17)	9.5(15)
OW(2)	0.0260(16)	−0.3564(8)	0.0865(13)	8.6(13)
N(13)	−0.1846(17)	−0.2466(6)	−0.2352(15)	4.7(9)
N(23)	−0.0305(16)	−0.4335(6)	−0.4090(16)	5.0(9)
C(12)	−0.0088(31)	−0.1964(8)	−0.1340(28)	6.9(15)
C(14)	−0.3471(26)	−0.2253(9)	−0.4727(22)	6.2(13)
C(15)	−0.3356(54)	−0.1546(11)	−0.5014(31)	12.3(32)
C(1)	−0.3011(19)	−0.2596(7)	−0.6753(18)	4.8(11)
C(22)	0.0288(29)	−0.4856(9)	−0.2174(28)	7.0(16)
C(24)	−0.2661(21)	−0.4507(7)	−0.5980(20)	4.5(10)
C(25)	−0.2832(35)	−0.5222(8)	−0.6444(31)	8.1(19)
C(2)	−0.4609(18)	−0.4199(7)	−0.5244(18)	4.6(10)
H(14)	−0.511	−0.241	−0.483	6.0
H(24)	−0.288	−0.431	−0.757	6.0

$^a B_{eq} = 1/3 \Sigma B_{ii}$.

TABLE III. Bond Distances (A) and Angles (°) with e.s.d.s in Parentheses.

Zn–N(13)	2.149(12)	Zn–O(11)	2.137(8)	Zn–OW(1)	2.063(10)
Zn–N(23)	2.134(12)	Zn–O(21)	2.172(8)	Zn–OW(2)	2.070(8)

O(11)–Zn–O(21)	88.7(3)	O(21)–Zn–N(23)	77.4(4)
O(11)–Zn–OW(1)	92.4(4)	OW(1)–Zn–OW(2)	88.7(5)
O(11)–Zn–OW(2)	167.5(4)	OW(1)–Zn–N(13)	103.1(4)
O(11)–Zn–N(13)	78.1(4)	OW(1)–Zn–N(23)	91.6(4)
O(11)–Zn–N(23)	89.3(4)	OW(2)–Zn–N(13)	89.5(4)
O(21)–Zn–OW(1)	169.0(4)	OW(2)–Zn–N(23)	103.1(4)
O(21)–Zn–OW(2)	92.5(4)	N(13)–Zn–N(23)	160.9(4)
O(21)–Zn–N(13)	87.8(4)		
O(11)–C(1)	1.238(17)	O(21)–C(2)	1.269(16)
O(12)–C(1)	1.259(14)	O(22)–C(2)	1.223(15)
C(1)–C(14)	1.525(19)	C(2)–C(24)	1.559(19)
C(14)–C(15)	1.487(28)	C(24)–C(25)	1.511(22)
C(14)–N(13)	1.484(16)	C(24)–N(23)	1.525(16)
C(15)–S(11)	1.831(20)	C(25)–S(21)	1.826(19)
S(11)–C(12)	1.835(18)	S(21)–C(22)	1.786(20)
C(12)–N(13)	1.469(21)	C(22)–N(23)	1.527(21)
O(11)–C(1)–O(12)	125.7(12)	O(21)–C(2)–O(22)	122.6(12)
O(11)–C(1)–C(14)	119.1(12)	O(21)–C(2)–C(24)	118.9(11)
O(12)–C(1)–C(14)	115.1(12)	O(22)–C(2)–C(24)	118.4(11)
C(1)–C(14)–N(13)	112.0(12)	C(2)–C(24)–N(23)	108.2(10)
C(1)–C(14)–C(15)	109.8(15)	C(2)–C(24)–C(25)	116.6(12)
N(13)–C(14)–C(15)	111.3(15)	N(23)–C(24)–C(25)	110.6(12)
N(13)–C(14)–H(14)	105.2(12)	N(23)–C(24)–H(24)	112.1(11)
C(15)–C(14)–H(14)	112.8(16)	C(25)–C(24)–H(24)	104.4(12)

(continued overleaf)

TABLE III. *(continued)*

C(14)–N(13)–C(12)	108.9(11)	C(24)–N(23)–C(22)	107.3(11)
N(13)–C(12)–S(11)	106.3(11)	N(23)–C(22)–S(21)	107.9(11)
C(12)–S(11)–C(15)	87.8(10)	C(22)–S(21)–C(25)	96.7(9)
S(11)–C(15)–C(14)	108.7(16)	S(21)–C(25)–C(24)	101.7(12)

TABLE IV. Least-squares Planes. Deviations (A) of Relevant Atoms from the Planes and Their e.s.d.s are given in Parentheses.

Plane 1 through O(11), C(1), C(14), N(13)
$0.7247X + 0.6891Y - 0.0087Z + 3.9811 = 0$
O(11) –0.006(10), C(1) 0.020(14), C(14) –0.025(17), N(13) 0.006(12), Zn –0.684(1), O(12) 0.053(12), H(14) –0.97

Plane 2 through Zn, O(21), C(2), C(24)
$-0.0234X + 0.6341Y - 0.7729Z + 3.3069 = 0$
Zn 0.0002(8), O(21) –0.032(9), C(2) 0.079(12), C(24) –0.040(12), N(23) –0.656(11), O(22) 0.313(10), H(24) 0.91

Plane 3 through S(11), N(13), C(14), C(15)
$0.9514X - 0.0200Y - 0.3072Z + 0.0956 = 0$
S(11) –0.004(8), N(13) 0.012(11), C(14) –0.045(16), C(15) 0.102(32), C(12) 0.636(19), C(1) 1.01(1)

Plane 4 through S(21), C(22), C(25), N(23)
$0.9027X - 0.3454Y - 0.2567Z - 4.3531 = 0$
S(21) –0.006(9), C(22) 0.039(19), C(25) 0.027(22), N(23) –0.010(11), C(24) –0.551(14), C(2) –2.106(12)

TABLE V. Torsion Angles (°) with e.s.d.s in Parentheses.

Zn–O(11)–C(1)–C(14)	17.2(12)	Zn–O(21)–C(2)–C(24)	11.0(12)
O(11)–C(1)–C(14)–N(13)	4.3(15)	O(21)–C(2)–C(24)–N(23)	15.5(14)
C(1)–C(14)–N(13)–Zn	–22.5(12)	C(2)–C(24)–N(23)–Zn	–33.7(11)
C(14)–N(13)–Zn–O(11)	23.5(7)	C(24)–N(23)–Zn–O(21)	30.8(7)
N(13)–Zn–O(11)–C(1)	–23.4(9)	N(23)–Zn–O(21)–C(2)	–24.0(9)
C(14)–C(15)–S(11)–C(12)	27.5(15)	C(24)–C(25)–S(21)–C(22)	–24.8(13)
C(15)–S(11)–C(12)–N(13)	–38.2(12)	C(25)–S(21)–C(22)–N(23)	3.6(12)
S(11)–C(12)–N(13)–C(14)	39.2(13)	S(21)–C(22)–N(23)–C(24)	19.0(13)
C(12)–N(13)–C(14)–C(15)	–18.9(17)	C(22)–N(23)–C(24)–C(25)	–40.1(16)
N(13)–C(14)–C(15)–S(11)	–10.1(16)	N(23)–C(24)–C(25)–S(21)	40.5(13)

and 2.693(14) Å, respectively, are shorter than nonbite distances.

The five-membered chelate rings exist in envelope conformations with the Zn atom 0.684(1) Å from the O(11)C(1)C(14)N(13) plane (Table IV), and with N(23) deviating 0.656(11) Å from the mean plane defined by ZnO(21)C(2)C(24) respectively. The geometries of the chelate rings are very similar.

All bond distances and angles within sulfur containing rings fall within the expected range. This distribution of bond lengths is in good agreement with values obtained from the structure determination of thiazolidine-4-carboxylic [11] and its complexes with Cu [5] and Co [12]. The conformations of the ligand molecules are described by the torsion angles in Table V. The five-membered thiazolidine rings adopt an envelope conformation with the C(12) and C(24) atoms deviating 0.636(19) and –0.551(14) Å from the plane defined by the other four atoms. The assymetry parameters are C_s (C12) = 6.10 and C_s (C24) = 4.1° [13]. Atoms C(1) and C(2) are disposed *cis* with respect to C(12) and C(24), respectively. The carboxyl groups are planar, with N atoms 0.078(12) and 0.355(11) Å, respectively, out of this plane.

The thiazolidine-4-carboxylic ligand has a single asymmetric center at the C4 atom, but the coordination introduces a chiral center at the N atom. In this complex both asymmetric centers of the bound ligands have the same C(4)R, NR configurations, which is consistent with the known C(4)R configuration of L-thiaproline.

It should be mentioned, however, that photographic examinations of all studied crystals exhibit additional, relatively weak and diffused layers of reflections, giving a 6-fold extension of the *c* axis as a result. This indicates modulated structures which were the cause of relatively high values for the temperature coefficients and the standard deviations.

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References

1 M. Gosálvez, *Abstract, Proc. AACR New Orleans, 20,* 17 (1979).

2 M. Gosálvez, L. Pecci and C. Vivero, *Biochem. Soc. Trans., 6,* 659 (1978).

3 A. Burgarolas and M. Gosálvez, *Lancet, 1,* 68 (1980) and references therein.

4 Z. X. Huang, P. M. May, D. R. Williams and M. Gosálvez, *Inorg. Chim. Acta, 56,* 41 (1981).

5 F. Bigoli, M. Lanfranchi, E. Leporati and M. A. Pellinghelli, *Cryst. Struct. Comm., 9,* 1255 (1980).

6 H. Sigel and R. B. Martin, *Chem. Rev., 82,* 385 (1982).

7 'International Tables for X-ray Crystallography', Vol. IV, Kynoch Press, Birmingham (1974).

8 J. N. van Niekerk, F. R. L. Schoening and J. H. Talbot, *Acta Cryst., 6,* 720 (1953).

9 G. Smith, E. J. O'Reilly, C. H. L. Kennard, K. Stadnicka and B. Oleksyn, *Inorg. Chim. Acta, 47,* 111 (1981).

10 A. Karpides, *Acta Cryst., C39,* 1541 (1983).

11 K. K. Chacko, S. Swaminathan and S. K. Bhattacharjee, in 'Biomolecular Structure, Conformation, Function and Evolution', ed. R. Srinivasan, Pergamon Press, Oxford and New York, vol. 1, p. 621, 1980.

12 G. J. Gainsford, W. G. Jackson, A. M. Sargeson and A. D. Watson, *Aust. J. Chem., 33,* 1213 (1980).

13 W. L. Duax, C. M. Weeks and D. C. Rohrer, in 'Topics in Stereochemistry', ed. N. L. Allinger and E. L. Eliel, Wiley, New York, p. 271, 1976.