

Short communication

Synthesis and crystal structure of some transition metal complexes with a novel bis-Schiff base ligand and their antitumor activities

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Abstract

Mononuclear complex of Zn(II) with a new bis-Schiff base ligand derived from 2,3-butanedione and thiosemicarbazide, [Zn(II)L·H₂O]·2DMF [L = (2E,2'E)-2,2'-(butane-2,3-diylidene)bis(hydrazinecarbothioamide)], and other transition metal ions [Cu(II), Mn(II), Co(II), Ni(II)] complexes have been prepared. The Zn(II) complex has been structurally characterized by X-ray crystallography. Among the five complexes, the Cu(II) complex has the novel highest antitumor activity.

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1. Introduction

Transition metal complexes of bis(thiosemicarbazone) ligands have been studied for nearly 50 years [1–3] and continued to attract attention, since Domagk first reported the antitumor activity of thiosemicarbazone [4–6]. The potential biological activity of compounds containing sulfur and nitrogen may be responsible for this increased interest. In particular bis(thiosemicarbazone) complexes of copper(II) have been known for sometime to be antitumor agents [7–8]. Many efforts have been made to establish further metal-containing cytostatics, however, without great success. Only little is known about the antitumor efficacy of elements such as zinc, nickel, manganese, or cobalt [9]. Recently, we studied the coordination properties of bis(thiosemicarbazone) ligand, **L**, towards various transition metal ions.

The Schiff base ligand, **L**, synthesized by condensing 2,3-butanedione with thiosemicarbazide, on refluxing with copper acetate, zinc acetate, manganese acetate, cobalt acetate and nickel acetate in ethanol yielded corresponding complexes, respectively. On the basis of elemental analysis, the metal to

ligand stoichiometry of 1:1 has been proposed for these complexes. The proposed structure for these complexes has the support of IR and UV spectra. A strong band in the Schiff bases at 1595 cm⁻¹ region underwent a shift of 4–33 cm⁻¹ in complexes confirming the formation of co-ordinate bond from azomethine nitrogen to metal ion. From the analytical data and infrared studies, it has been concluded that the ligand has linked through mercapto sulfur and co-ordinated through azomethine nitrogen behaving as a tetradentate ligand (Fig. 1). The complexes along with their characteristics are recorded in Table 1, their UV spectra in Table 2, their IR spectra in Table 3, ¹H NMR chemistry shift of the ligand in Table 4, and thermal analysis data of the complexes in Table 5.

The crystal structure of Zn complex is illustrated in Fig. 2. The central Zn ion is surrounded by two nitrogen atoms (N4 and N3) with Zn–N distances of 2.124 and 2.1437 Å, two sulfur atoms (S2 and S1) with Zn–S distances of 2.3552 and 2.3808 Å, and one oxygen atom (O1) with Zn–O distance of 2.054 Å. The zinc(II) ion is well described as having a square-pyramidal configuration with N4, N3, S2 and S1 in the equatorial plane and an apical Zn–O distance of 2.054 Å. Fig. 3 shows that N–H...O and O–H...O hydrogen bonds connect the adjacent complex forming a 1D supramolecular structure along the diagonal between *b* and *c* axis.

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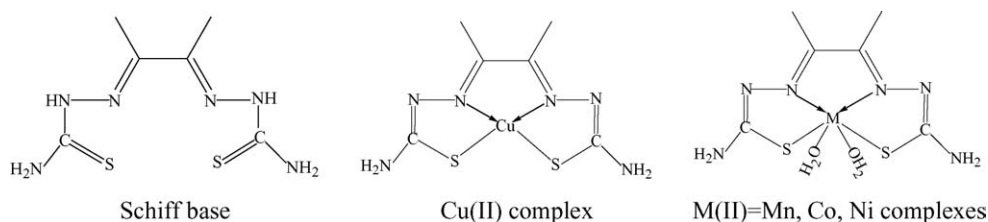


Fig. 1. Structures of Schiff bases and its transition metal complexes.

Table 1
Data of color, elemental analysis and molar conductivity of the complexes

Complex	Color	Data of mature (data of theory) (%)			Λ_m (S cm ⁻² mol ⁻¹)
		C	H	N	
ZnL·H ₂ O	Yellow	22.95 (22.97)	3.83 (3.86)	26.81 (26.79)	4.04
CuL	Brown	24.53 (24.49)	3.36 (3.40)	28.50 (28.58)	14.5
MnL·2H ₂ O	Light yellow	22.40 (22.43)	4.36 (4.39)	26.72 (26.16)	1.83
CoL·2H ₂ O	Dark brown	22.43 (22.15)	4.56 (4.34)	25.81 (25.84)	8.62
NiL·2H ₂ O	Dark green	22.14 (22.17)	4.32 (4.34)	25.89 (25.86)	1.39

Table 2
UV spectra of the ligand and the complexes (nm)

Compound	L ₁	ZnL·H ₂ O	CuL	MnL·2-H ₂ O	CoL·2-H ₂ O	NiL·2H ₂ O
Bands (nm)	330	295	303	310	308	315

Table 3
IR spectra of the ligand and the complexes (cm⁻¹)

Compound	ν_{N-H}	$\nu_{C=N}$	$\nu_{C=S}$
L ₁	3411, 3254	1595	1642
ZnL·H ₂ O	3452, 3322	1599	—
CuL	3408, 3285	1628	—
MnL·2H ₂ O	3416, 3284	1627	—
CoL·2H ₂ O	3422, 3297	1616	—
NiL·2H ₂ O	3413, 3291	1631	—

Table 4
¹H NMR chemistry shift of the ligand (ppm) (solvent/DMSO-d₆)

Ligand	δ	δ	δ
L ₁	2.16 (s, 6H, CH ₃)	10.17 (s, 2H, NH)	8.37 (s, 2H, NH ₂), 7.83 (s, 2H, NH ₂)

The possible structures of complexes of Cu(II), Mn(II), Co (II) and Ni(II) ions are presumed by element analysis. The Cu (II) complex contains one chelating ligand **L** with a ratio of 1:1, and no H₂O or solvent, so it is a planar structure. Each complex of Mn(II), Co(II) or Ni(II) ion contains one molecule of **L** and two H₂O, and their coordination polyhedron is an octahedron.

Table 5
Thermal analysis data of the complexes

Complex	Dehydration temperature (°C)	Process	%H ₂ O calc.	Loss found	Decomposed (°C)			Process	Residue
					t1	t2	t3		
MnL·2H ₂ O	120	Endothermic	5.90	6.04	250	486	554	Exothermic	MnO
CoL·2H ₂ O	84	Endothermic	5.82	5.93	250	449	535	Exothermic	CoO
NiL·2H ₂ O	65	Endothermic	5.82	5.89	285	490	575	Exothermic	NiO

2. Experimental

The compounds gave satisfactory elemental analyses. The IR spectra were recorded on a Perkin–Elmer FTIR in KBr.

3. General procedure for the preparation of Schiff base and its transition metal complexes

An EtOH solution (25 ml) of 2,3-butanedione (5 mmol) was added dropwise to the solution (15 ml) of thiosemicarbazide (10 mmol) with stirring at ca. 70 °C for 8 h. The light yellow precipitates was removed by filtration and recrystallized from 1:1 (v/v) MeOH/EtOH solution. Then a mixture of the ligand (5 mmol) and transition metal (II) acetate (5 mmol) in EtOH (80 ml) was stirred at ca. 65 °C for 6 h to give the desired complexes. The Zn complex was dissolved in DMF, and ether evaporated slowly into the DMF solution to afford almost quantitatively orange crystal of mononuclear complex at ambient temperature after several days [1].

4. Cytotoxicity assay

The cytotoxicity was in five kinds of cells line (HL-60, Spsa-1, Tb, MGC, K562). Cells were cultured at 37 °C under a humidified atmosphere of 5% CO₂ in RPMI 1640 medium supplemented with 10% fetal serum and dispersed in replicate 96-well plates with 1 × 10⁴ cells per well. Compounds were then added. After 48 h exposure to the toxins, cell viability was determined by the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) colorimetric assay by measur-

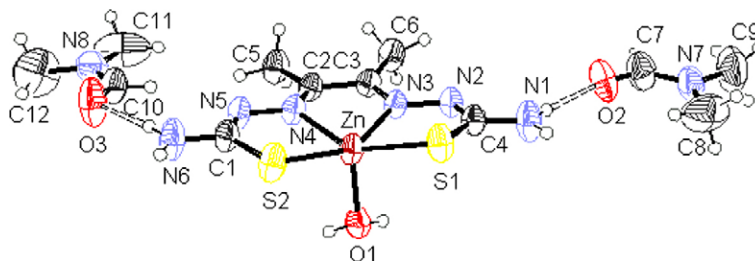


Fig. 2. Crystal structure of $[\text{Zn(II)L}\cdot\text{H}_2\text{O}]\cdot 2\text{DMF}$. One DMF (C10, C11, C12, N8, O3) is disorder.

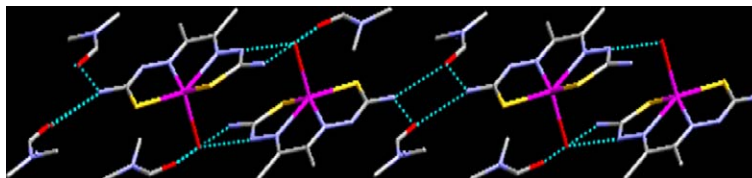


Fig. 3. 1D supramolecular structure of $[\text{Zn(II)L}\cdot\text{H}_2\text{O}]\cdot 2\text{DMF}$ along the diagonal between b and c axis in the crystal.

Table 6
Antitumor activities data of the compounds

Compounds	HL-60 IC-50 (μM)	Spca-1 IC-50 (μM)	Tb IC-50 (μM)	MGC IC-50 (μM)	K562 IC-50 (μM)
L	37.25	> 100 ^a	72.86	> 100 ^a	> 100 ^a
L·Zn	32.59	32.7	26.21	32.89	28.06
L·Cu	1.01	5.167	7.18	9.06	9.917
L·Mn	39.20	> 100 ^a	> 100 ^a	> 100 ^a	> 100 ^a
L·Co	> 40 ^a	> 100 ^a	69.47	> 100 ^a	> 100 ^a
L·Ni	> 40 ^a	67.6	> 100 ^a	> 100 ^a	> 100 ^a

Antitumor activities are expressed as IC_{50} (50% inhibitory concentration) in five kinds of cells (HL-60, Spca-1, Tb, MGC, K562). Data are average data of triplicate assay.

^a When the inhibition was below 50% at the highest test concentration.

ing the absorbance at 570 nm with an ESILA reader. Each test was performed in triplicate. From the data in Table 6, it can be inferred that the Schiff base ligand **L** and its Cu, Zn, Mn, Co and Ni complexes all have antitumor activities in a way, but its copper(II) complex is substantially more active than the ligand and other compounds reported before [10–11].

Crystal data: $\text{C}_{12}\text{H}_{26}\text{N}_8\text{O}_3\text{S}_2\text{Zn}$, $M = 459.90$, triclinic, crystal dimensions $0.56 \times 0.30 \times 0.20$ mm, space group $P-1$, $a = 8.947(1)$, $b = 11.007(2)$, $c = 11.568(2)$ Å, $\alpha = 75.11(1)$, $\beta = 89.61(1)$, $\gamma = 75.12(1)$, $\lambda = 0.71073$ Å, $T = 291(2)$ K, $U = 1058.8(3)$ Å³, $Z = 2$, $D_c = 1.442$ g cm⁻³, $\mu = 1.385$ mm⁻¹, $F(000) = 480$; 4117 reflections measured, 3711 unique ($R_{\text{int}} = 0.0125$), 297 refined parameters, transmission factors 0.5110 to 0.7692. The final discrepancy factors were $wR_2 = 0.0746$, $R_1 = 0.0297$, goodness-of-fit $S = 0.997$ on F^2 , largest difference peak and hole 0.258 and -0.198 eÅ⁻³. CCDC reference number 214456.

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