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ORIGINAL RESEARCH PAPER

SYNTHESIS, CRYSTAL STRUCTURE AND ANTITUMOR ACTIVITY OF A Zn(II) COMPLEX WITH 1,2-PHENYLENEDIOXYDIACETIC ACID

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Abstract: A novel Zn(II) complex, $[Zn(L)(H_2O)_3]\cdot 2H_2O$, has been obtained by reaction of $Zn(OAc)_2\cdot 2H_2O$ with 1,2-phenylenedioxydiacetic acid in CH_3OH/H_2O. It was characterized by elemental analysis, IR and X-ray single crystal diffraction analysis. The crystal of the title complex belongs to monoclinic, space group *C2/c* with a = 29.283(7) Å, b = 6.7305(15) Å, c = 17.243(3) Å, β = 109.25(3)º, V = 3208.4(12) Å^3, Z = 8, Dc = 1.621 mg·m^{-3}, μ = 1.590 mm^{-1}, F(000) = 1576, and final R_1 = 0.1284, ωR_2 = 0.3895. X-ray analysis reveals that the Zn(II) center is seven-coordination with a O_7 distorted pengonal bipyramidal coordination environment. The Zn(II) complex molecules form 1D chain structure by the hydrogen bonds and π-π stacking interactions. The antitumor activity of 1,2-phenylenedioxydiacetic acid ligand and its Zn(II) complex against human intestinal adenocarcinoma *HCT-8* cells, lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells line have been investigated.

Keywords: *antitumor activity, crystal structure, 1,2-phenylenedioxydiacetic acid, synthesis, Zn(II) complex*

INTRODUCTION

Metal complexes of multidentate ligands have received considerable attention over the past two decades [1 - 5]. This may be attributed to unusual structural features in the resultant metal complexes and their biological activities. Some of the metal complexes have antitumor properties [6], antioxidative activities [7], electronic and photophysical properties [8]. As part of our group to explore the synthesis and property of metals complex, we have been exploring the preparation of metal-organic hybrid materials by combining metal ions and organic ligands [9 - 12]. In this paper, A novel Zn(II) complex has been obtained and characterized by elemental analysis, IR, UV spectra, molar conductivity and X-ray single crystal diffraction analysis. The antitumor activity of 1,2-phenylenedioxydiacetic acid ligand and its Zn(II) complex against human intestinal adenocarcinoma *HCT-8* cells, lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells line have been investigated.

EXPERIMENTAL

Materials and methods

The following A. R. grade chemicals and other solvents were used for the preparation of the studied compound without further purifications: $Zn(OAc)_2{\cdot}2H_2O$, 1,2-phenylenedioxydiacetic acid, sodium hydroxide.
Elemental analysis (C, H, N) was carried out on a Elementar Vario III EL elemental analyzer. The FT-IR spectra were obtained on a Nicolet AVATAR 360 FTIR spectrometer with KBr pellets in the range of 4,000 cm^{-1}-400 cm^{-1}. The crystal data was collected on a Bruker smart CCD Area Detector.

Synthesis of the Zn(II) complex

A solution of 1,2-phenylenedioxydiacetic acid (1.0 mmol, 0.226 g) and sodium hydroxide (2.0 mmol 0.080 g) in 10 mL CH_3OH/H_2O (v:v = 1:1) was stirred at room temperature. Then 0.5 mmol (0.109 g) of $Zn(OAc)_2{\cdot}2H_2O$ was added to the above solution. The mixture was continuously stirred for 3 h at refluxing temperature. The mixture was cooled at room temperature, and the resulting solution was filtered. The colourless crystals were obtained after the filtrate was kept in air for several days (52% yield). The results of the elemental analysis and IR data of Zn(II) complex are listed in Table 1.

Table 1. *Results of the elemental analysis and IR data*

Chemical formula	Elemental analysis (%)				IR ν_{max} (cm^{-1})	
	C		H		ν(O-H)	$\nu(COO^-)$
	calc.	found	calc.	found		
$C_{10}H_{18}ZnO_{11}$	31.61	31.38	4.74	4.43	3438	1629

X-ray Crystallography

A colourless block single crystal with dimensions of 0.22 × 0.20 × 0.16 mm was selected for measurement. Diffraction data of the single crystal were collected by φ~ω scan mode using a graphite-monochromatic Mo $K\alpha$ radiation (λ = 0.71073 Å) at 293(2) K on a Bruker Smart Apex CCD diffractometer. A total of 14480 reflections were collected in the range 3.12-27.48°, of which 3631 were unique (R_{int} = 0.0450) and 3203 were observed with $I>2\sigma(I)$. The data were corrected for *Lp* factors. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2. The structure was solved by direct methods [13] using SHELXL-97 and expanded using Fourier techniques. All of the non-hydrogen atoms and hydrogen atoms were refined anisotropically and isotropically, respectively. Molecular graphics were drawn with the program package SHELXTL-97 crystallographic software package [14]. The most relevant crystal data for Zn(II) complex are quoted in Table 2, and selected bond lengths and angles are listed in Table 3 and Table 4.

Table 2. *Crystallographic data for the title compound*

Formula	$C_{10}H_{18}O_{11}Zn$
Formula weight	379.62
Cell setting	Monoclinic
Space group	*C2/c*
a (Å)	29.283(7)
b (Å)	6.7305(15)
c (Å)	17.243(3)
β (°)	109.25(3)
Volume (Å^3)	3208.4(12)
Z	8
Dc(Mg m^{-3})	1.621
μ (mm^{-1})	1.590
Crystal size (mm)	0.22×0.20×0.16
Radiation (Å)	0.71073
Theta min–max (°)	3.12-27.48
Tot., uniq. data, R(int)	14480, 3631, 0.0450
Observed data [I > 2 sigma(I)]	3203
F (000)	1576
Goodness-of-fit on F^2	3.276
R_1 [I > 2 sigma(I)]	0.1284
ωR_2 [I > 2 sigma(I)]	0.3895
R_1 (all data)	0.1352
ωR_2 (all data)	0.3981
Min. and max. resd. dens. [e/Å^3]	5.319 -0.753

Table 3. *Selected bond lengths (Å) for the title compound*

Bond	Distance	Bond	Distance
Zn1-O8	2.031(6)	Zn1-O10	2.055(5)
Zn1-O7	2.065(6)	Zn1-O2	2.110(5)
Zn1-O4	2.163(5)	Zn1-O6	2.463(5)
Zn1-O1	2.480(6)	C10-O5	1.271(8)
C3-O8	1.261(8)	C2-O6	1.373(8)
C9-O6	1.405(8)	C4-O10	1.243(7)
C2-O8	1.242(9)	C1-O1	1.354(9)
C7-O1	1.417(9)		

Table 4. *Selected angles (°) for the title compound*

Angle	(°)	Angle	(°)
O8-Zn1-O10	166.1(2)	O8-Zn1-O7	92.0(2)
O7-Zn1-O10	100.9(2)	O8-Zn1-O2	95.6(2)
O2-Zn1-O10	91.3(2)	O7-Zn1-O2	82.2(2)
O8-Zn1-O4	90.4(2)	O4-Zn1-O10	86.39(19)
O7-Zn1-O4	81.7(2)	O2-Zn1-O4	163.0(2)
O8-Zn1-O6	85.5(2)	O6-Zn1-O10	80.75(18)
O7-Zn1-O6	149.3(2)	O2-Zn1-O6	128.52(19)
O4-Zn1-O6	67.67(18)	O8-Zn1-O1	84.5(2)
O10-Zn1-O1	87.0(2)	O7-Zn1-O1	149.3(2)
O2-Zn1-O1	67.9(2)	O4-Zn1-O1	128.65(19)
O6-Zn1-O1	61.00(18)		

Antitumor activity

Human intestinal adenocarcinoma *HCT-8* cells, human lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells were propagated continuously in culture and grown in RPMI 1640 medium with 10 % inactivated fetal calf serum and antibiotics. Cell harvested from exponential phase were seeded equivalently into 96 well plates and incubated for 24 h and then compounds studied were added in a concentration gradient. The final concentrations were maintained at c /(μg·mL^{-1}) 5, 10, 20, 30, 40, 60 respectively. The plates were maintained at 37°C in a humidified 5% CO_2 - 90% N_2 - 5% O_2 atmosphere and incubated for 48 h, the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) solution was added following the procedure referred to [15]. The measurements of absorption of the solution concerned with the number of live cells were performed on spectrophotometer at 570 nm.

RESULTS AND DISCUSSION

IR spectra

The IR spectrum of Zn(II) complex is shown in Figure 1. The ν_{as}(COOH) and ν_{s}(COOH) vibrations of free ligand are at 1666 and 1457 cm^{-1}. In the Zn(II) complex, they appear at 1629 and 1435 cm^{-1}. Which can be explained that the oxygen atoms of COO^{-} group take part in coordination with Zn(II) ions and the $\Delta\nu(\nu_{as}(COOH) - \nu_{s}(COOH))$ is 194 cm^{-1}, indicating that the carboxylates are unidentate coordinated with Zn(II) atoms. The broad peak at 3438 cm^{-1} is ascribed to the O-H stretching vibrations of the coordinated and uncoordinated water. The result of IR is in accordance with the results of X-ray single crystal diffraction analysis.

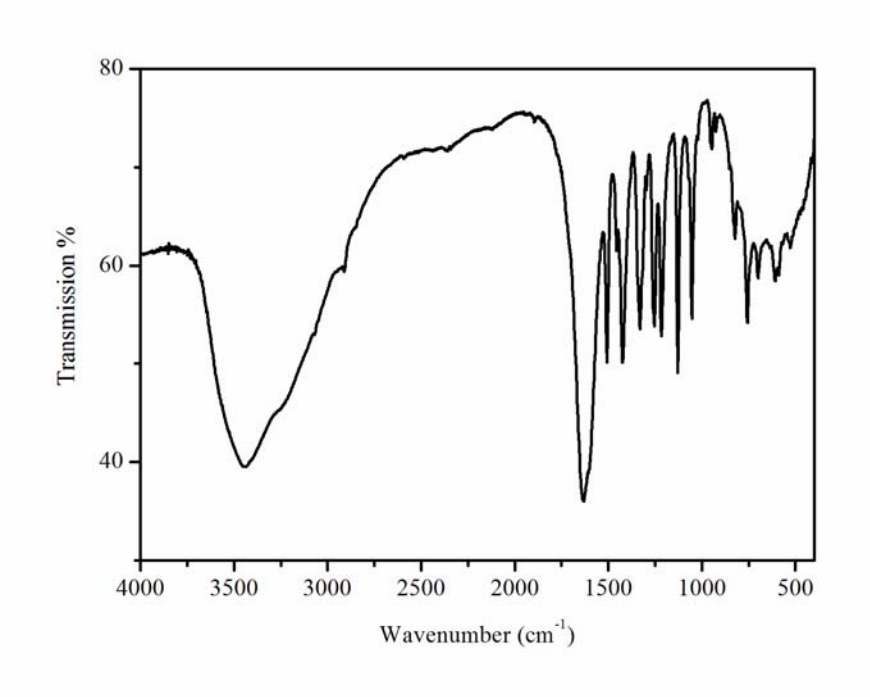

Figure 1. *The IR spectrum of Zn(II) complex*

Structure Description

The crystal structure of the Zn(II) complex is revealed in Figure 2. The molecular packing arrangement is shown in Figure 3.

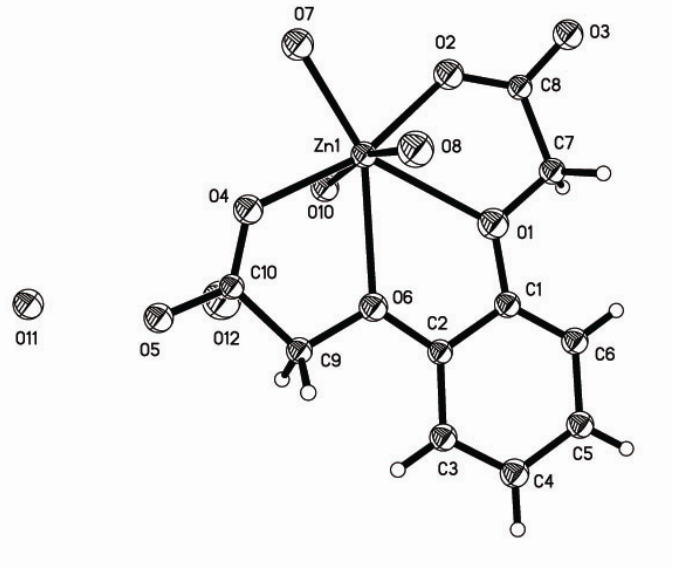

Figure 2. *Molecular structure of the Zn(II) complex, where the thermal ellipsoids were drawn at 30% possibility*

As shown in Figure 2, in the crystal structure, the Zn(II) ion is seven-coordination by four oxygen atoms (O1, O2, O4, O6) from 1,2-phenylenedioxydiacetic acid ligand, three oxygen atoms (O7, O8, O10) from the coordinated water molecule, forming up a distorted pengonal bipyramidal coordination environment. The distances of the Zn-O bonds are in the range of 2.031(6)-2.480(6) Å, and the distances of Zn-O are comparable with that observed in other Zn complexes [16, 17].

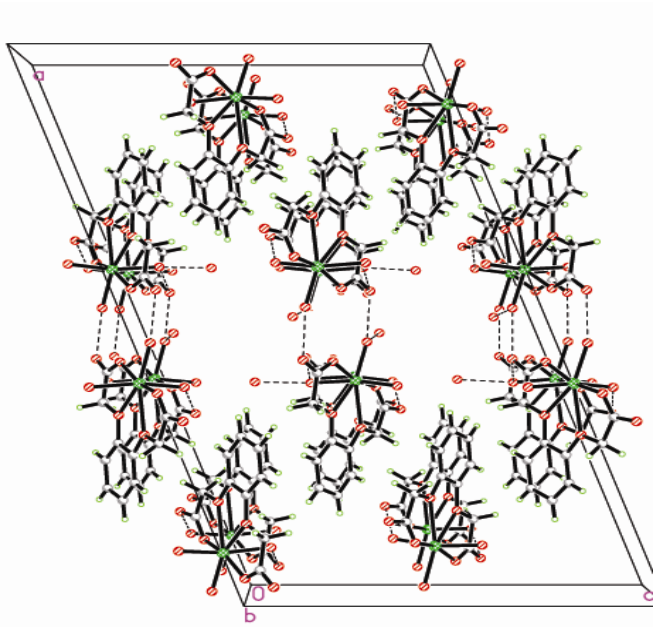

Figure 3. *Molecular packing of the Zn(II) complex*

The complex forms one dimensional chain structure along by the hydrogen bonds and π-π stacking interactions (Figure 4).

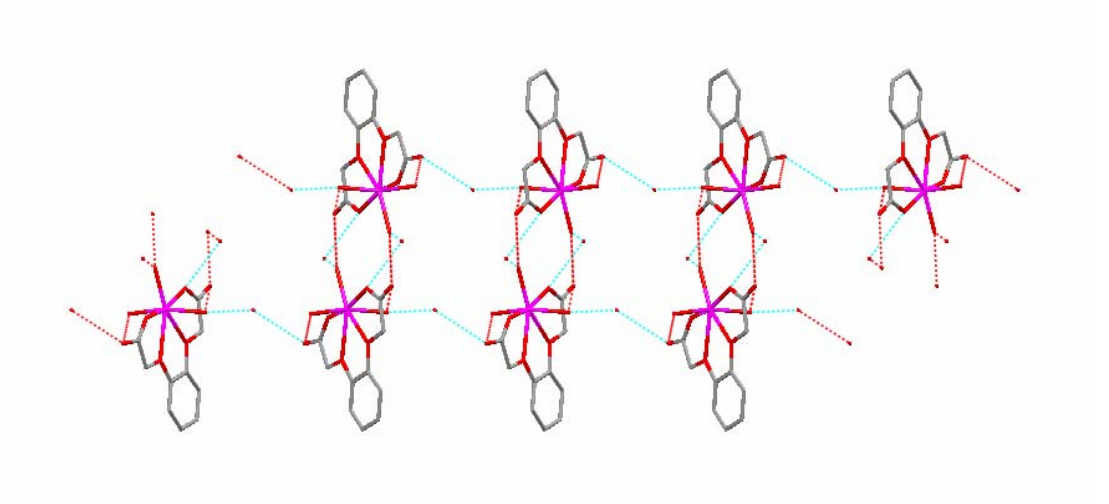

Figure 4. *One dimensional chain structure of the Zn(II) complex*

Antitumor activity

The data of antitumor activities of Zn(II) complex and 1,2-phenylenedioxydiacetic acid are given in Table 5. The concentration of DMSO was controlled under 1 % to assure not to affect the results. It can be seen that both Zn(II) complex and 1,2-phenylenedioxydiacetic acid exhibit cytotoxic effect against human intestinal adenocarcinoma *HCT-8* cells and human lung adenocarcinoma *HCT-116* cells. However, the antitumor effect of 1,2-phenylenedioxydiacetic acid is better than that of Zn(II) complex. 1,2-Phenylenedioxydiacetic acid has stronger cytotoxicity against human lung adenocarcinoma *A549* cells with lower IC_{50} (7±2.3 $\mu g \cdot mL^{-1}$), however, Zn(II) complex does not have effect.

Table 5. *Antitumor activities of Zn(II) complex and 1,2-phenylenedioxydiacetic acid ligand*

Compound	IC_{50} $\mu g \cdot mL^{-1}$		
	HCT-8	***HCT-116***	***A549***
1,2-phenylenedioxydiacetic acid	11±1.3	14±1.6	7±2.3
Zn(II) complex	22±1.9	17±1.1	----

---- no antitumor activity

CONCLUSIONS

In summary, a novel Zn(II) complex has been obtained and characterized. The results show that Zn(II) center is seven-coordination with a O_7 distorted pengonal bipyramidal coordination environment. The Zn(II) complex molecules form 1D chain structure by the interaction of hydrogen bonds and π-π stacking. The antitumor activity of 1,2-phenylenedioxydiacetic acid ligand and its Zn(II) coordination polymer against

human intestinal adenocarcinoma *HCT-8* cells, lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells line have been investigated.

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