

## SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME METAL IONS WITH 2-THIOACETIC-5-PHENYL-1,3,4-OXADIAZOLE

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### Abstract

New metal complexes of the ligand 2-thioacetic-5-phenyl-1,3,4-oxadiazole with the metal ions Ni(II), Cu(II), Zn(II), Cd(II) and Sn(II) were prepared in alcoholic medium. The prepared complexes were characterized by FTIR Spectroscopy, electronic spectroscopy, mass spectroscopy <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, magnetic susceptibility and conductivity measurements. From the spectral measurements, monomer structures for the complexes were proposed. Square planar geometry was proposed for the copper complex. The other complexes were proposed to be tetrahedral. Preliminary *in vitro* tests for antimicrobial activity show that all prepared compounds display good activity to *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*.

**Keywords:** carboxylate, 1,3,4-oxadiazole, metal complexes, antimicrobial activity.

### Introduction

Increasing physiological importance of Oxygen donor organic compounds and active role played by coordination certain metal ions to them have interested use in synthesizing and studying structural aspects of metal complexes with some oxygen, sulphur and nitrogen donor ligands [1-3]. 1,3,4-Oxadiazoles are a class of heterocycles which have attracted significant interest in medicinal chemistry and they have a wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, and antihypertensive[4,5]. The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bio-active class of heterocyclic.

The wide range of application of the ligand and its metal complexes aroused our interest to prepare a new series of some metal complexes.

### Experimental

#### Synthesis of 2-thioacetic -5-phenyl-1,3,4-oxadiazole

A mixture of ethyl benzoate (0.1 mole) and hydrazine hydrate (0.1 mole) was refluxed for

two hours, ethanol (50 ml) was added and refluxed for (5) hours. The precipitate benzoyl hydrazine which separated on cooling was filtered and washed with cold methanol. To a solution of benzoyl hydrazine (0.02 mole) in ethanol (100ml) at (0°C) were added carbon disulfide (0.04mol) and potassium hydroxide (0.02 mole) the mixture was refluxed for (7) hours .the solvent was evaporated and the residue dissolved in water and acidified with dilute hydrochloric acid. The precipitate was filtered and crystallized from (ethanol) to give 2-mercapto-5-phenyl 1,3,4-oxadiazole which react with one equivalent of chloroacetic acid in presence of KOH as a basic media to give 2-thioacetic-5-phenyl-1,3,4-oxadiazole Figure (1). The final product was recrystallized from methanol.

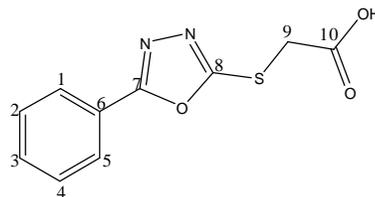


Figure (1).

### Preparation of Complexes

Addition of ethanol solution of the suitable metal salt (Nickel acetate tetrahydrate, Tin chloride, Copper acetate, Cadmium acetate dihydrate and Zinc acetate dihydrate) to an ethanol solution of 2-thioacetic-5-phenyl-1,3,4-oxadiazole (HL) in 2:1 (ligand : metal) molar ratios was carried out. After reflux for half an hour, crystalline colored precipitates formed at room temperature. The rustling solids were filtered off, washed with distilled water, dried and recrystallized from ethanol and dried at 50 °C. Table (1) shows the melting point of the prepared compounds.

### Instrumentation

Elemental C, H, N and S analysis were carried out on a Fison EA 1108 analyzer, the FTIR spectra in the range (4000-200)  $\text{cm}^{-1}$  cut were recorded as CsI disc on FTIR.8300 Shimadzu Spectrophotometer, uv-visible spectra were measured using Shimadzu Uv-vis. 160 A-Ultra-violet Spectrophotometer in the range (200-1000) nm. The magnetic susceptibility values of the prepared complexes were obtained at room temperature using Magnetic Susceptibility Balance of Bruke Magnet B.M.6, Atomic absorption

measurements of the prepared complexes were obtained using Shimadzu 680cc-flame. The  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance spectra were recorded on a jeol 400 MHz spectrometer in deuterated DMSO, relative to the internal standard tetramethylsilane (TMS). Mass spectra were recorded on a Micromass UK PLATFORM II LC-MS spectrometer. Melting points were recorded on a hot stage Gallen Kamp melting point apparatus.

### Result and Discussion

All chemicals and reagents were of reagent-grade quality. 2-thioacetic acid-5-phenyl-1,3,4-oxadiazole was prepared by reaction one mole of 2-mercapto-5-phenyl 1,3,4-oxadiazole with one mole of chloroacetic acid in presence of KOH. The purity of the ligand and its complexes were checked by TLC using silica gel-G as adsorbent. Melting point, elemental analysis and ms-molecular peak masses of all the compounds studied are tabulated in Table (1). The data of CHNS and metal analysis were obtained using flame atomic absorption technique. The calculated values were in a good agreement with the experimental values.

*Table (1)*  
*Physical data for preparation ligand and the complexes.*

Compound	Melting point $^{\circ}\text{C}$	Found(Calcd.)%				M	m/e
		C	H	N	S		
HL	162-164	50.84(50.78)	3.41(3.57)	11.14(11.21)	13.17(13.69)	-	230.0
Ni(L) <sub>2</sub>	155-157	45.55(45.39)	2.52(2.61)	11.33(10.59)	12.31(12.12)	11.22(11.09)	527.9
Cu(L) <sub>2</sub>	152-153	45.14(44.98)	2.34(2.46)	11.10(10.49)	11.97(12.01)	11.45(11.90)	532.9
Zn(L) <sub>2</sub>	99-101	44.91(44.83)	2.27(2.63)	10.77(10.46)	12.83(11.97)	12.25(12.20)	533.9
Cd(L) <sub>2</sub>	111-113	41.15(41.21)	2.36(2.42)	9.83(9.61)	11.32(11.00)	19.23(19.29)	583.9
Sn(L) <sub>2</sub>	209-211	40.64(40.77)	2.64(2.40)	10.01(9.51)	11.19(10.88)	20.36(20.15)	589.9

### Infra-Red Spectroscopy

The FTIR spectrum for HL, shows a characteristic stretching absorption bands at 3468  $\text{cm}^{-1}$ , 1633  $\text{cm}^{-1}$ , 1351  $\text{cm}^{-1}$ , 1606  $\text{cm}^{-1}$ , 1187  $\text{cm}^{-1}$  and 1066  $\text{cm}^{-1}$  assigned to hydroxyl group,  $\nu(\text{COO})$  asym.,  $\nu(\text{COO})$  sym., C=N of the oxadiazole ring, asymmetrical C-O-C, symmetrical C-O-C stretching respectively. The COO stretching vibrations are important to predict the bonding mode of the ligand. The values of  $\Delta\nu$  [ $\Delta\nu = \nu$  asym.(COO) -  $\nu$  sym.(COO)] can be divided into 3 groups ; (a)

In compounds where  $\Delta\nu(\text{COO}) > 350 \text{ cm}^{-1}$ , the carboxylate group binds in a monodentate fashion. However, other very weak intra- and intermolecular interactions cannot be excluded. (b) When  $\Delta\nu(\text{COO}) < 200 \text{ cm}^{-1}$ , the carboxylate groups of these compounds can be considered to be bidentate. (c) In compounds where  $\Delta\nu(\text{COO}) > 200 \text{ cm}^{-1}$  and  $< 350 \text{ cm}^{-1}$  an intermediate state between monodentate and bidentate (anisobidentate) occurs. It has also been suggested that the  $\Delta\nu(\text{COO})$  value in

the chelating mode is less than the  $\Delta\nu$  (COO) in a bridging mode.

The disappearance of the hydrogen from hydroxyl group on complexation indicate the complexation is through the oxygen atom. Stretching of metal-oxygen bands of the complexes appeared in low frequency region[6] (497-472)  $\text{cm}^{-1}$ . The IR data of the ligand and complexes are shown in Table (2).

**Table (2)**  
**Characteristic absorption bands of 2-thioacetic acid-5-phenyl-1,3,4-oxadiazole and its complexes.**

Compound	$\nu(\text{O-H})$	$\nu(\text{COO})$ asym	$\nu(\text{COO})$ sym
HL	3468	1633	1351
Ni(L) <sub>2</sub>	-	1593	1347
Cu(L) <sub>2</sub>	-	1589	1348
Zn(L) <sub>2</sub>	-	1591	1348
Cd(L) <sub>2</sub>	-	1590	1349
Sn(L) <sub>2</sub>	-	1599	1344

#### Ultraviolet-Visible Spectroscopy

The ultraviolet visible electronic spectrum of the 2-thioacetic acid-5-phenyl-1,3,4-oxadiazole in ethanol solvent was recorded in Table(3), a band at the wavelength (205 nm), this transition may be attributed to  $\pi \rightarrow \pi^*$  electronic transition. And the other band appearing at 276 nm could be assigned to  $n \rightarrow \pi^*$  electronic transition. The electronic spectra of 2-thioacetic acid-5-phenyl-1,3,4-oxadiazole complexes show, as expected, different absorptions from that of the free ligand. In complexes these bands was shifted to higher wavelength than the corresponding bands in the ligand, which appears in the wavelength range between 390 to 410 nm.

The ligand field electronic transitions between the metal d orbital appear in Ni(II) and Cu(II) bands located in the visible region at 424 nm. for Ni(L)<sub>2</sub> assigned to the transition  ${}^3T_{1g} \rightarrow {}^3T_{1g(p)}$  and 695 nm. for Cu(L)<sub>2</sub> assigned to the transitions  ${}^2E_g \rightarrow {}^2T_{2g}$ . The other complexes were diamagnetic as expected for  $d^{10}$  ions, so that no (d-d) transition can be expected in the visible region [7].

**Table (3)**  
**Electronic spectra for 2-thioacetic acid-5-phenyl-1,3,4-oxadiazole and its complexes in ethanol solvent.**

Compound	Color	Absorption Bands (nm)	Assigned Transition
HL	White	205	$\pi \rightarrow \pi^*$
		276	$n \rightarrow \pi^*$
Ni(L) <sub>2</sub>	Pale green	206	$\pi \rightarrow \pi^*$
		249	$n \rightarrow \pi^*$
		424	${}^3T_{1g} \rightarrow {}^3T_{1g(p)}$
Cu(L) <sub>2</sub>	Green	228	$\pi \rightarrow \pi^*$
		261	$n \rightarrow \pi^*$
		695	${}^2E_g \rightarrow {}^2T_{2g}$
Zn(L) <sub>2</sub>	White	230	$\pi \rightarrow \pi^*$
		257	$n \rightarrow \pi^*$
Cd(L) <sub>2</sub>	White	223	$\pi \rightarrow \pi^*$
		301	$n \rightarrow \pi^*$
Sn(L) <sub>2</sub>	White	224	$\pi \rightarrow \pi^*$
		277	$n \rightarrow \pi^*$

#### Magnetic susceptibility and conductivity measurements

The experimental magnetic moment for each metal complexes listed in Table (4). Magnetic measurements are widely used in studying transition metal complexes. The magnetic properties are due to the presence of unpaired electrons in the partially filled d-orbital in the outer shell of these elements. These magnetic measurements give an idea about the electronic state of the metal ion in the complex. The magnetic moment for Ni(II) in any complex is approximately 2.49 B.M., this value refers to a high spin tetrahedral structure, while the value of Cu(II) is approximately 1.67 B.M. led to suggest the square planar structure[7] which can become in a good agreement with the data of electronic transitions. Other complexes have no magnetic moment because its diamagnetic. Molar conductivity measurement in DMF solvent at 25 °C showed that all the prepared complexes were non-electrolyte Table (4).

**Table (4)**  
**Magnetic Moment, Conductivity measurements in DMF solvent.**

Symbol	Name	Conductivity $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$	Magnetic Moment (B.M)	Suggested Structure
HL	Potassium-2-thioacetic acid-5-phenyl-1,3,4-oxadiazole	-	-	-
Ni(L) <sub>2</sub>	Bis(2-thioacetic acid-5-phenyl-1,3,4-oxadiazole) nickel(II)	15	2.94	Tetrahedral
Cu (L) <sub>2</sub>	Bis(2-thioacetic acid-5-phenyl-1,3,4-oxadiazole)copper(II)	11	1.67	Square Planner
Zn(L) <sub>2</sub>	Bis(2-thioacetic acid-5-phenyl-1,3,4-oxadiazole) zinc(II)	12	0.00	Tetrahedral
Cd(H) <sub>2</sub>	Bis(2-thioacetic acid-5-phenyl-1,3,4-oxadiazole) cadmium(II)	8	0.00	Tetrahedral
Sn(H) <sub>2</sub>	Bis(2-thioacetic acid-5-phenyl-1,3,4-oxadiazole) tin(II)	10	0.00	Tetrahedral

### Nuclear magnetic resonance

The data of proton NMR of 2-thioacetic - 5-phenyl-1,3,4-oxadiazole and its complexes displayed good solubility in DMSO. The proton nuclear magnetic resonance spectral data gave additional support for the composition of the complexes. The observed changes are evidences of complexation had happened because the chemical shift of a compound is heavily depended on its electronic environment. The spectra also exhibit a singlet -OH peaks at 9.58 ppm due to hydroxyl group. The hydroxyl resonances is absent in the spectra of the complexes indicating deprotonation and coordination of Tin to the oxygen. The  $\delta$  7.59-7.96 ppm resonance signal protons of the aromatic ring shifted to the higher field upon complexation, while the downfield shift of the protons in C9 of the -CH<sub>2</sub> aliphatic group shifted from  $\delta$  3.88(in the free ligand to 3.30-3.35 (in the metal complexes). However, we have been able to detect all proton and carbon signals separately. <sup>1</sup>H NMR data for the ligand and the complexes are reported in Table (5).

**Table (5)**  
**<sup>1</sup>H NMR spectral data ( $\delta$ ,ppm) of the ligand and complexes**

* HL	Ni(L) <sub>2</sub>	Cu(L) <sub>2</sub>	Zn(L) <sub>2</sub>	Cd(L) <sub>2</sub>	Sn(L) <sub>2</sub>
1	7.96	7.97	7.95	7.94	7.95
2	7.94	7.65	7.66	7.67	7.68
3	7.59	7.59	7.59	7.58	7.57
4	7.94	7.64	7.66	7.67	7.68
5	7.96	7.97	7.95	7.94	7.954
9	3.88	3.30	3.32	3.33	3.35

\* H-atom attached to the C-atom numbered as  $\delta$ (<sup>1</sup>H).

The <sup>13</sup>C NMR of the ligand and its complexes are presented in Table (6). The C=O resonance group of the complexes at (169.70-170.77) ppm where shifted to higher field compared with the position in the free ligand which appeared at 168.69 ppm. It is most likely that shift is due to the decrease of electron density at carbon atoms when oxygen is bonded to metal ion.

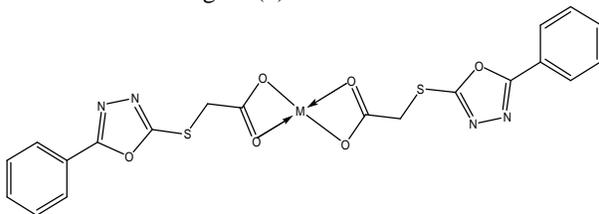
**Table (6)**  
**<sup>13</sup>C NMR spectral data ( $\delta$ ,ppm) of the ligand and complexes**

C-atom no	HL	Ni(L) <sub>2</sub>	Cu(L) <sub>2</sub>	Zn(L) <sub>2</sub>	Cd(L) <sub>2</sub>	Sn(L) <sub>2</sub>
1	126.31	126.35	126.37	126.33	126.34	126.18
2	129.42	129.48	129.47	129.44	129.47	129.43
3	131.87	131.87	131.85	131.81	131.71	131.71
4	129.42	129.48	129.47	129.44	129.47	129.43
5	126.31	126.35	126.37	126.33	126.34	126.18
6	123.12	122.13	122.26	122.23	122.35	122.35
7	164.43	164.44	164.43	164.44	164.44	164.44
8	164.6	164.61	164.62	164.64	164.47	164.43
9	39.69	39.92	39.92	39.67	39.55	39.51
10	168.15	169.70	170.11	170.19	170.77	170.74

### Study of complex formation in solution

Complexes of (HL) with metal ions were studied in solution using ethanol as a solvent, in order to determine [M/L] ratio in the complex follow Molar ratio method [9]. A series of solutions were prepared having a constant concentration (10<sup>-3</sup>M) of the metal ion and (L). The [M/L] ratio was determined from the relationship between the absorption of the absorbed light and the mole ratio of [M/L]. The results of complexes formation in solution. The results of complexes in ethanol, suggest that the metal to ligand ratio was [1/2] for all complexes which were similar to that obtained from solid state Study. On the basis of the

observed spectral evidence, the following structures square planar geometry for the copper complex. The other complexes were proposed to be tetrahedral Figure (2).



Where M = Ni(II), Cu(II), Zn(II), Cd(II) and Sn(II)

Figure (2).

### Biological Activity

With a view to explore the possibility of obtaining biologically useful complexes that contain 1,3,4- thiadiazole ring system, such biological activity prompt us to prepare some new series containing the above mentioned unite. The antimicrobial activity of these compounds was determined by the agar diffusion method [10] used were *Staphylococcus aureus*, *Escherishia coli*, *Pseudomonas aeruginosa* and *Cndida albicans*. In this method a standard 5mm diameter sterilized filter paper disc impregnated with the compound (1 mg per 1 ml of acetone) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 hours at 37 °C. The zone of inhibition formed was measured in mm and are represented by (+), (+ +) and (+ + +) depending upon the diameter and clarity, Table (7).

The preliminary screening result reveal that compound contained 2-thioacetic -5-phenyl-1,3,4-oxadiazole complexes exhibits highest antibacterial activity against *Escherishia coli*.

Table (7)  
Antibacterial activity of the prepared compounds.

Symbol	<i>Staphylococcus aureus</i>	<i>Escherishia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Cndida albicans</i>
HL	-	+	-	-
Ni(H) <sub>2</sub>	-	+++	+	+
Cu (H) <sub>2</sub>	+	+++	+	+
Zn(H) <sub>2</sub>	-	++	-	-
Cd(H) <sub>2</sub>	+	+++	-	+
Sn(H) <sub>2</sub>	+	+++	-	+

Note (-) = no inhibition, (+) = (5-10) mm, (+ +)=(11-20) mm, (+ + +) = more than (20)mm.

### Conclusion

The ligand 2-thioacetic-5-phenyl-1,3,4-oxadiazole was successfully synthesized. The ligand was treated to different metal ions salts to afford the corresponding complexes. It concluded that the ligand coordinated through carboxylate to the metal atom leading to the formation of four member ring chelate. Square planar geometry was proposed for the copper complex. The other complexes were proposed to be tetrahedral. Biological activity data have shown that the reported complexes have a significant antimicrobial activity against *Staphylococcus aureus*, *Escherishia coli*, *Pseudomonas aeruginosa* and *Cndida albicans*.

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