

Synthesis, Characterization, Electrochemistry and Antimicrobial Activity of Zinc(II) Complexes of some Hydrazone Schiff Bases

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ABSTRACT A series of hydrazone Schiff bases and their zinc(II) complexes have been synthesized, characterized and evaluated for antimicrobial activity. The new zinc(II) complexes have been prepared in ethanol media by a template condensation of hydrazides, with either ketone or aldehyde and zinc(II) acetate in the presence of triethylamine. The IR, ¹H and ¹³C NMR data indicate that the hydrazone ligands are coordinated to zinc metal. The cyclic voltammetry of these zinc complexes exhibited irreversible oxidation peaks. The electro-oxidation of Zn₂(Clhaptch)₂(py)₂ displayed a diffusion-controlled one electron transfer reaction process. The anti-microbial activity of the ligands and complexes were evaluated by plate diffusion method against some gram-positive bacteria, gram-negative bacteria and two fungi. There was growth inhibition exhibited by ligands and zinc(II) complexes against tested bacteria and fungi.

ABSTRAK Beberapa bes Schiff hydrazone dan kompleks logam zink(II) telah disintesis, dicirikan dan aktiviti anti-mikrobialnya telah dikaji. Kompleks zink(II) telah disediakan dalam etanol melalui kondensasi templat beberapa jenis hidrazida dengan keton atau aldehid beserta dengan zink(II) asetat dengan mencampurkan sedikit trietilamina. Data IR, NMR ¹H dan ¹³C menunjukkan ligan hidrazon berkoordinat tridentate kepada zink melalui kumpulan CN, CO dan kumpulan OH fenolik. Voltammetri siklik kompleks zink(II) menunjukkan puncak pengoksidaan tak berbalik. Pengoksidaan-elektro Zn₂(Clhaptch)₂(py)₂ menunjukkan proses pembauran tindak balas satu elektron. Aktiviti anti-mikrobial ligan (ligand) dan kompleks zink(II) diuji dengan beberapa bakteria gram-positif dan gram-negatif dan juga dua fungi. Didapati ligan dan kompleks zink(II) telah membantutkan pertumbuhan bakteria dan fungi ini.

(Hydrazone Schiff bases, zinc(II) complexes, cyclic voltammetry, anti-microbial activity)

INTRODUCTION

In recent years, chemistry of Schiff bases has been intensively investigated due to their coordination properties and diverse biological applications. Schiff bases derived from hydrazides play an important role in developing coordination chemistry related to magnetism, molecular architectures, anti-bacterial, anti-tumoral and anti-viral [1-3].

Hence, we extend the chemistry of the hydrazones by synthesizing some hydrazone Schiff bases such as 5-chloro-2-hydroxyphenylethylidene benzoylhydrazone (H₂ClHpbh), 5-chloro-2-hydroxyphenylethylidene thiophene-2-carboxylic hydrazone (H₂Clhaptch) and 3-methyl-thiophene-2-methylidene furoic-2-carboxylic hydrazone (HMetfh) (Figure 1).

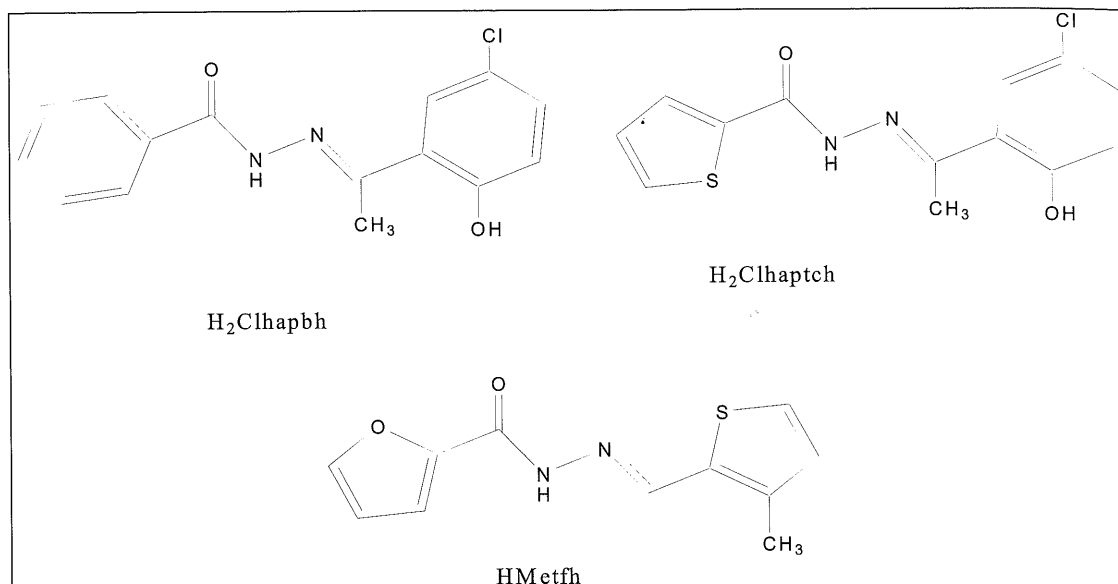


Figure 1. Schiff base ligands

Coordination of these ligands to zinc metal is the subject of our considerable interest as the metal appears in some metalloenzymes such as in human carboanhydrase and carboxypeptidase [4]. The zinc complexes of the hydrazone ligands provide an opportunity to study the effect of the coordinated ligand to the metal on spectroscopy, electrochemistry and molecular structures of the complexes.

EXPERIMENTAL

Materials

Benzhydrazide, furoic acid hydrazide, thiophene carboxylic hydrazide, 2-hydroxyacetophenone, 2-methylthiophene carboxaldehyde and 5-chloro, 2-hydroxyacetophenone, zinc(II) acetate, ethanol, diethylether were used without further purification. DMSO was pre-dried over activated molecular sieve before use in electrochemistry study.

Physical measurements

Carbon, hydrogen and nitrogen analyses were carried out at the Faculty of Science and Technology, Universiti Kebangsaan Malaysia. The UV-vis and IR spectra were recorded using Shimadzu 1600 spectrometer and Perkin Elmer RX1 spectrometer as KBr disks in the range of (370-4000 cm^{-1}), respectively. ^1H and ^{13}C NMR spectra were recorded on Lambda JEOL 400 MHz FT-NMR spectrometer. Cyclic voltammetry (CV) was performed on Basic Autolab with potentiostat/galvanostat PGSTAT 30 at platinum

electrode as the working as well as counter electrode in DMSO using $[\text{NBu}_4]\text{BF}_4$ as the supporting electrolyte. The saturated calomel electrode (SCE) was used as the reference electrode.

Synthesis of ligands

The typical procedure used for the preparation of Schiff base ligands is as follows: A solution of 0.1 mol aromatic hydrazide in 50 cm^3 ethanol was added slowly to a 0.1 mol ethanolic solution of aromatic ketone or aldehyde.

Synthesis of complexes

The metal complexes were prepared by mixing a solution of zinc(II) acetate in ethanol with the solution of hydrazide and the corresponding ketone or aldehyde in a 1:2:2 molar ratio with stirring and refluxing for 5 hours. The products formed were filtered and recrystallized from either pyridine- or DMSO-ethanol mixture.

Anti-microbial activity tests

The anti-microbial activity of the ligands and complexes was determined by plate diffusion method [5]. *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, *Candida albicans* and *Saccharomyces cerevisiae* were used to investigate the bacteriological and antifungal activities of the ligands and their transition metal complexes. The bacteria were grown on nutrient agar incubated at 37 °C while the fungi were grown on Sabouraud agar at 37°C. The ligands and

complexes were dissolved in DMSO and concentrations of 3 mgmL⁻¹ and 5 mgmL⁻¹ were tested in triplicate plates. Chloramphenicol at 3 mgmL⁻¹ was used as control.

RESULTS AND DISCUSSION

The zinc(II) complexes are light-yellow in colour, non-hygroscopic and stable in air. They are insoluble or sparingly soluble in common organic solvents and quite soluble in DMSO and pyridine. All the complexes melt over 250°C. The elemental analysis is shown in Table 1 and they are satisfactorily characterized.

IR Spectra

The $\nu(\text{N-H})$ bands of the free ligands disappear in the spectra of the complexes, supporting deprotonation of the ligands upon complex formation (Table 2). The carbonyl bands, $\nu(\text{C=O})$ of the non-coordinated ligands also disappear in the spectra of the complexes, indicating destruction of the keto group presumably *via* enolisation and bonding of the ligand through the resulting enolate oxygen [6].

The strong bands around 1600 cm⁻¹ are assigned to the imine, (C=N) groups. In the metal complexes, these stretching bands have shifted to lower frequencies, due to the lowering of the C=N bond order as a result of zinc-nitrogen bond formation. The shift of the $\nu(\text{N-N})$ to higher wave numbers further supports coordination of the ligand to the metal via the azomethine nitrogen atom. The $\nu(\text{C-OH})$ bands of the phenol in the zinc(II) complexes have disappeared indicating coordination of phenolic OH to the metal center. The new bands at *ca.* 590 and 430 cm⁻¹ are tentatively assigned to $\nu(\text{M-O})$ and $\nu(\text{M-N})$ bands respectively [7].

NMR Spectra

The ¹H NMR spectra of the zinc(II) complexes do not exhibit the NH proton signal, lending further support to the infrared evidence that the

hydrazone ligand coordinates to the metal center in its deprotonated form (Table 3). The phenolic $\delta(\text{OH})$ proton signal peak has disappeared in the ¹H NMR spectra of zinc(II) complex and indicates that the ligand is coordinated to zinc metal *via* phenolic oxygen. The ¹³C{¹H} NMR spectra show that the (C=O) and (C=N) signals have shifted to downfield region indicating participation of these groups in chelate formation.

UV-vis of ligands and complexes

The UV-vis spectra of the ligands in DMSO exhibit strong absorption bands between 267 to 285 nm. In order to help in qualitative assignment of these bands, semi empirical CI calculations at PM3 and ZINDO/S levels were carried out (Table 4).

For ligand H₂ClHpbb, two peaks are assigned as a mixture of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$. The peak at 336 nm, the π orbitals covers the hydrazone part of the molecule into the phenyl ring, with the lone pair of electrons on the C=O oxygen. The 287 nm peak could be due to the lone pair of electrons on the oxygen of C=O and N as well as π on the C=N-N chain.

The peak at 260 nm for H₂Clhaptch is assigned to $\pi \rightarrow \pi^*$ transition involving the π on the thiophene ring and lone pair electrons on the oxygen of C=O. The π^* involves the same thiophene ring. Both the peaks for HMetfh are assigned to $\pi \rightarrow \pi^*$ transitions. Both involve π transition on the furan ring.

Upon complexation, all the ligand peaks, except for Zn(Metfh)₂(DMSO) are hypsochromically shifted, or at least remain as they are for the ligands. Nevertheless, it is still thought that the peaks still involve $\pi \rightarrow \pi^*$. The 399 nm peaks however, could be due to $\pi \rightarrow \pi^*$ which is of different nature to the $\pi \rightarrow \pi^*$ transition of the ligand.

Table 1. Elemental analysis of the ligands and complexes [% found (theory)]

COMPOUNDS	%C	%H	%N
H ₂ ClHpbh	62.1(62.4)	3.4(4.5)	11.5(9.7)
H ₂ Clhaptch	52.6(53.1)	3.2(3.4)	9.0(9.5)
HMetfh	52.5(52.4)	4.6(4.8)	11.4(11.1)
Zn ₂ (hapbh) ₂ (DMSO) ₂	52.3(51.5)	4.9(4.8)	6.2(7.1)
Zn ₂ (ClHpbh) ₂ (DMSO) ₂	46.9(47.4)	3.9(4.2)	6.9(6.5)
Zn ₂ (Clhaptch) ₂ (py) ₂	49.6(49.1)	3.2(3.9)	9.9(9.5)
Zn(Metfh) ₂ DMSO	46.9(47.1)	4.2(4.3)	10.4(9.2)

Table 2. Selected IR bands for ligands and complexes in cm⁻¹

COMPOUNDS	OH OF H ₂ O	OH OF PHOH	N-H	C=O	C=N	C-OH	N-N	M-O	M-N
H ₂ ClHpbh	-	3062	3226	1647	1607	1288	1025	-	-
H ₂ Clhaptch	3458	-	3306	1643	1600	1290	1030	-	-
HMetfh	-	-	3225	1648	1602	-	950	-	-
Zn ₂ (hapbh) ₂ (DMSO) ₂	3431	-	-	-	1590	-	1082	590	437
Zn ₂ (ClHpbh) ₂ (DMSO) ₂	3413	-	-	-	1593	-	1066	598	475
Zn ₂ (Clhaptch) ₂ (py) ₂	-	-	-	-	1601	-	1161	585	439
Zn(Metfh) ₂ -DMSO	-	-	-	-	1601	-	957	622	424

Table 3. ¹H and ¹³C{¹H} n.m.r. spectra of ligands and complexes (δ, ppm)

COMPOUNDS	OH PHOH	NH	CH ₃	C=O	C=N	C-O	CH ₃
H ₂ ClHpbh	13.45	11.43	2.49	164.51	156.68	157.43	14.15
H ₂ Clhaptch	13.30	11.39	2.50	158.90	156.74	157.40	14.30
HMetfh	-	11.75	2.28	153.8	146.65	-	-
Zn ₂ (hapbh) ₂ (DMSO) ₂	-	-	2.66	167.78	161.74	136.92	16.19
Zn ₂ (ClHpbh) ₂ (DMSO) ₂	-	-	2.61	167.78	160.38	136.75	15.61
Zn ₂ (Clhaptch) ₂ (py) ₂	-	-	-	166.60	160.22	136.75	18.64
Zn(Metfh) ₂ -DMSO	-	7.84	2.34	-	164.2	-	-

Table 4. Assignments of UV-vis spectra of ligands and complexes

COMPOUNDS	PEAK I (nm)	ASSIGNMENT	PEAK II (nm)	ASSIGNMENT
H ₂ ClHpbh	287	Mixed π → π*, n → π*	336	Mixed π → π*, n → π*
H ₂ Clhaptch	260	Mixed π → π*, n → π*	312	π → π*
HMetfh	267	π → π*	334	π → π*
Zn ₂ (hapbh) ₂ (DMSO) ₂	266	π → π*	315	π → π*
Zn ₂ (ClHpbh) ₂ (DMSO) ₂	269	π → π*	317	π → π*
Zn ₂ (Clhaptch) ₂ (py) ₂	-	-	312	π → π*
Zn(Metfh) ₂ -DMSO	289	π → π*	399	π → π*

Table 5. Cyclic voltammetry data for the ligands and complexes at 25 mVs⁻¹ scan rate

COMPOUNDS	OXIDATION EA(MV)	REDUCTION EC(MV)	ΔE (MV)	IA (MA)	IC (MA)	IA/IC
H ₂ ClHpbh		-750 irrev				
H ₂ Clhaptch	-640	-880	240	8.2	1.94	0.42
HMetfh	-	-				
Zn ₂ (ClHpbh) ₂ (DMSO) ₂		-1480 irrev				
Zn ₂ (Clhaptch) ₂ (py) ₂	850 irrev					
Zn(Metfh) ₂ DMSO	1010 irrev					

Electrochemical studies of ligands and complexes

The cyclic voltammogram of H₂ClHpbh indicates quasi-reversible process with oxidation peak at – 880 mV and reduction at –640 mV (Figure 2).

The complex Zn₂(Clhpbh)₂(DMSO)₂ reduces irreversibly at 1480 mV while Zn₂(Clhaptch)₂(py)₂ shows an oxidation peak at 850 mV and there was no reduction peak when the scan was reversed at various scan rates 10, 25, 100, 200, and 400 mV s⁻¹ (Figure 3). The current I_p was found to be proportional to the square root of the scan rates, indicating that the electro-oxidation of Zn₂(Clhaptch)₂(py)₂ was a diffusion controlled reaction [8]. By solving the expression below, values of n, number of electrons involved in redox activity is equal to one. Thus the results shows that the electro-oxidation of Zn₂(Clhaptch)₂(py)₂ was a diffusion controlled, one electron transfer reaction.

$$I_p = \frac{nFAD}{\pi} \frac{1}{t^{1/2}} \frac{c}{t^{1/2}}$$

Structure of Zinc (II) complexes

The structure of Zn₂(Clhaptch)₂(py)₂ (Figure 4) shows coordination of pyridine when the crude

product was recrystallized from pyridine. The molecule is dimeric *via* phenolic oxygen bridges [9].

This is an example of coordination DMSO solvent molecule to zinc atom when the initial complex was recrystallized from DMSO (Figure 5). The Schiff base ligand coordinated bidentatically to the metal *via* (C=O) and (C=N) bonds while the DMSO molecule through the oxygen atom forming a five coordinated complex [10].

Antibacterial activity of ligands and complexes

Table 6 below shows the anti-bacterial activity of the ligands and complexes studied. The free ligands H₂ClHpbh only showed some inhibition towards the growth of all bacteria tested.

Most of the zinc(II) complexes exhibited better anti-bacterial activity than the hydrazone ligands especially towards *E. coli*. The monomer Zn(Metfh)₂.DMSO complex has the highest activity against gram-positive bacteria *S. aureus*. Polarizing effect of the zinc atoms may have increased this biological activity.

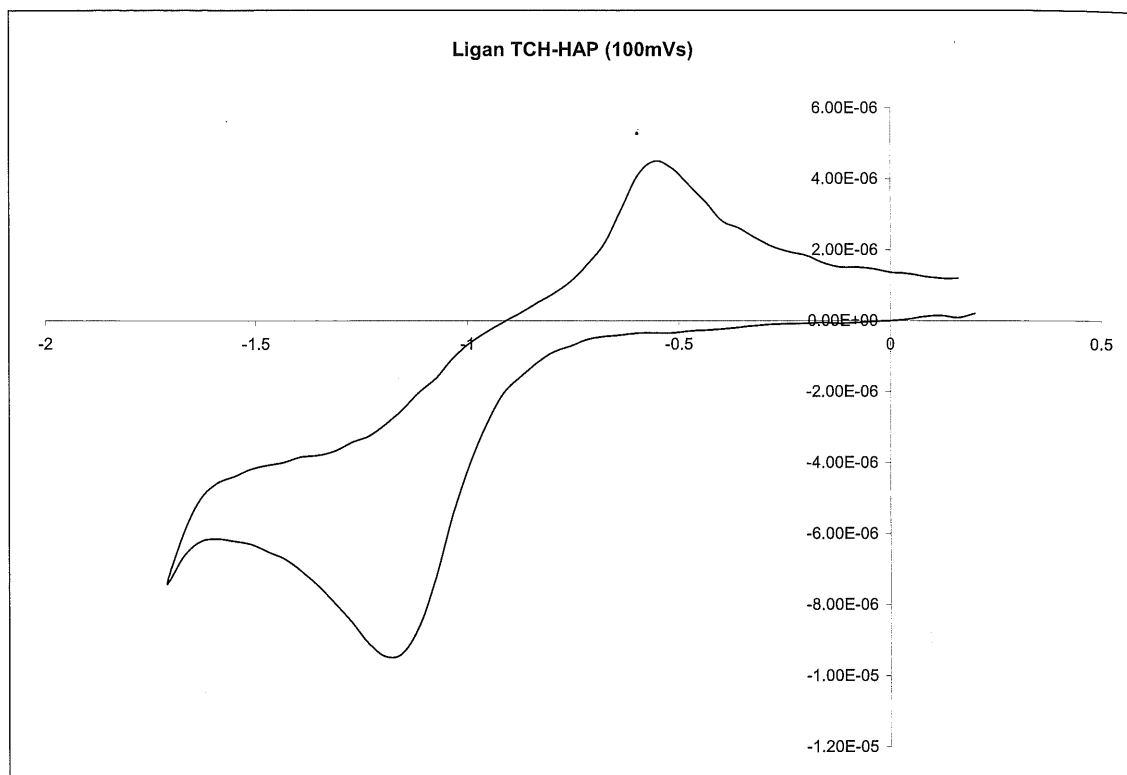


Figure 2. Cyclic voltammogram of ligand $H_2Clhaptch$ at scan rate 0.1 Vs^{-1}

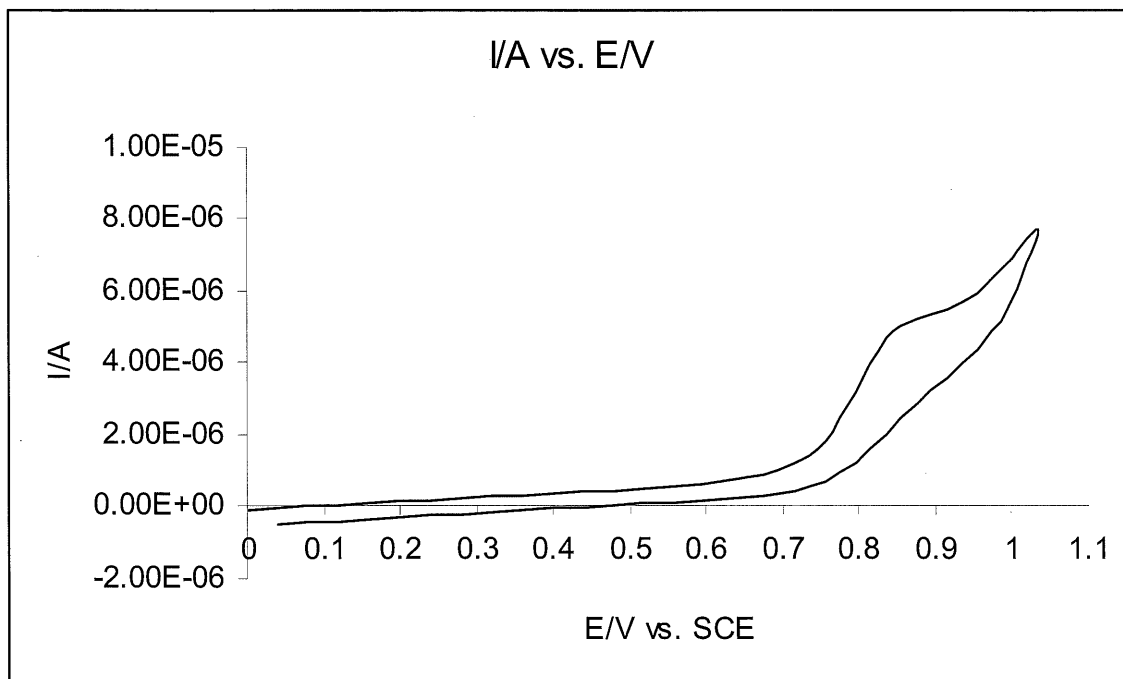


Figure 3. Cyclic voltammetry of $Zn_2(Clhaptch)_2(py)_2$ 10 mg with 0.2 g TBATFB in 25 ml DMSO, at 50 mV s^{-1} , at 28°C

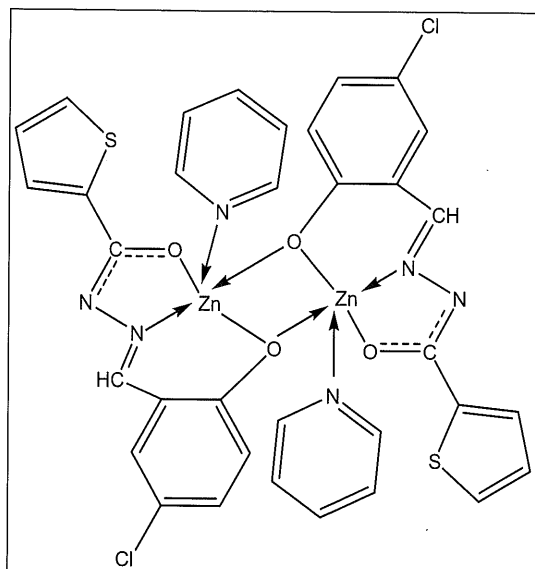


Figure 4. Structure of $[Zn_2(Clhaptch)_2(py)_2]$

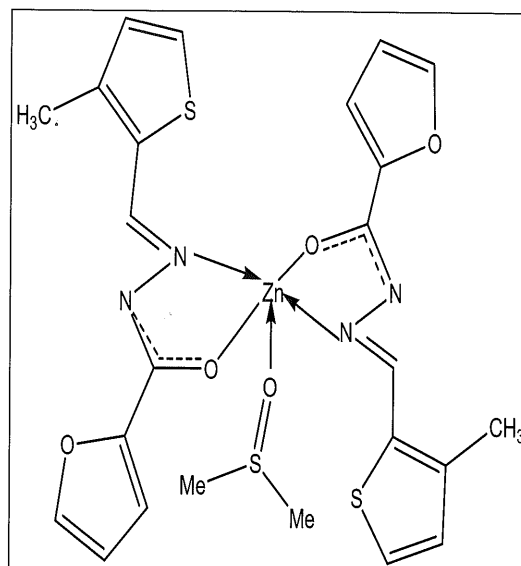


Figure 5. Structure of $Zn(Metfh)_2.DMSO$

Table 6. Anti-bacterial and anti-fungal activity data of ligands and Zn (II) complexes

COMPOUND	<i>B. cereus</i>	<i>B. subtilis</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>P. vulgaris</i>
H ₂ ClHpbh	6.2	-	-	9.3	10.3
H ₂ Clhaptch	-	-	-	-	-
HMetfh	-	-	-	-	-
Zn ₂ (hapbh) ₂ (DMSO) ₂	16.5	15.3	-	9.3	11.2
Zn ₂ (ClHpbh) ₂ (DMSO) ₂	10.3	12.3	19.6	26.5	13.7
Zn ₂ (Clhaptch) ₂ (py) ₂	10.2	11.3	18.5	17.4	-
Zn(Metfh) ₂ .DMSO	16.5	19.7	21.0	18.3	-
Chloramphenicol	30.0	32.0	29.0	30.0	31.0

- : no zone of inhibition
- Inactive : zone of inhibition less than 9 mm diameter
- Partially active : zone of inhibition within 9 – 12 mm diameter
- Active : zone of inhibition within 13 – 18 mm diameter
- Very active : zone of inhibition greater than 18 mm diameter

CONCLUSIONS

The Schiff base, (H₂ClHpbh) coordinates to the zinc metal in a tridentate manner *via* CN, CO and phenolic OH while the ligands (H₂Clhaptch) and (HMetfh) are bidentate NO-type. Coordinated ligands as well as coordinated solvent molecules of metal complexes displayed a variety of geometries.

Cyclic voltammetry of the zinc complexes exhibited irreversible one-electron oxidation and the electrochemistry data may have some correlations with the antimicrobial activity.

The zinc(II) complexes generally showed better anti-bacterial activity than the hydrazone ligands especially towards *E. coli*. The monomer Zn(Metfh)₂.DMSO complex has the highest activity against gram-positive bacteria *S. aureus*.

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