Molecular Modeling and Biological Activity Studies of Schiff's Base Ligands and their Metal Complexes

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Abstract

Metal complexes of Schiff bases were synthesized and characterized by elemental analysis, spectral studies, conductance measurements and magnetic susceptibility. The Schiff bases and corresponding metal complexes are tested for their microbial activity against the bacterial species E.coli, S. Aureus and fungal species aspergillusterreus. The geometry identified with experimental results were further optimized and supported by molecular modeling studies.
KEYWORDS:molecular modeling, Schiff bases, metal complex esantibacterial, antifungal.

I.INTRODUCTION

Molecular modeling studies reproduce the stereochemistry and electronic structure of metal complexes in comparison with experimental studies. In the absence of x-ray crystal structure data, determiningthe 3-dimensional structures of the molecules cannot be entirely unambiguous. An alternative, Albeit approximate approach for obtaining the three dimensional structures of the compounds is obtained in the computational chemistry tools. The possible configurations for various metal complexes like Cu(II), Co(II), Zn(II), Cd(II), Ni(II), Fe(II), VO(IV) were evaluated using the semi empirical and the density functional theory calculations respectively.[1]
Metal complexes importance in biological process and their application in medicine was studied and reported earlier. Coordination complexes play an important role in human body function in which enzymes are activated by metal ions[2]. The role of metal ions in biological systems is evident in cell division, respiration, nitrogen fixation and photosynthesis[3].They play crucial role in living systems and they are essential for various biochemical operations and their arrival. A characteristic property of metals is to lose electrons easily to form positively charged ions which are soluble as proteins and DNA are electron rich and metal ions are electron deficient, the attraction of these opposite charges leads to an interaction in between these two.[4]The form of metal is always ionic but oxidation state can vary depending on biological needs. A large class of compounds showanti-bacterial effectiveness and several metal ions are known to act as antimicrobials.[5]

Earlier researchers studied molecular modeling and antibacterial activity of Schiff's base ligands[6-13] and their metal complexes against bacterial and fungal species. The extent of inhibition is observed to depend on the initial cell density and growth medium. It is known that chelation tends to increase the antibacterial activity of the ligand and metal complexes. The fungal activity[14] and bacterial activity[15,16] of ligands and metal ions like Mn(II) , Co(II) , Ni(II) ,Cu(II),Zn(II) complexes are very important in biological systems.

In the present paper molecular modeling and biological activity of the Schiff base ligands and metal complexes which are synthesized were The ligands 1-[5(1-{2-[-(5 acetyl-2,4-dihydroxy-phenyl)-ethylodeneamino]phenylimino}ethyl)-2,4-dihydroxy phenyl} ethanone**(ADPEPEDPE**) and [2-(2-(1-thiophene-2-yl) ethylidene) hydrazinyl] Benzoic

acid**(TEHBA) .**The systematic procedure involved in synthesis of ligands **ADPEPEDPE** and **TEHBA** and metal complexes of these Schiff bases are reported.[17,18]

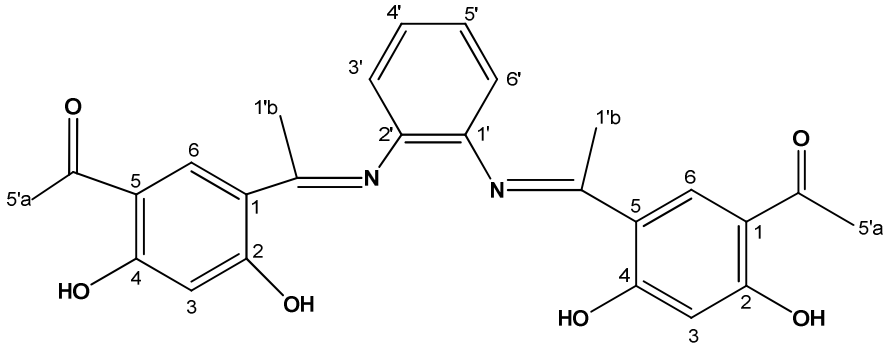


Fig 1: 1-[5-(1-{2-[1-(5-acetyl-2, 4-dihydroxy-phenyl)-ethylideneamino] phenylimino} ethyl)-2, 4 dihydroxy phenyl] ethanone (ADPEPEDPE)

Theligand1-[5-(1-{2-[1-(5-acetyl-2,4-dihydroxy-phenyl)-ethylideneamino] phenylimino} ethyl)-2, 4 dihydroxy phenyl] ethanone (ADPEPEDPE) was prepared by the condensation of 4,6- diacetyl resorcinol with o-phenylene diamine in the ratio 2:1 . The solution was refluxed for a period of three hours. Upon cooling overnight a yellow crystalline product was separated out. It was recrystallized from methanol, m.p. 202°C. (Yield 60%)

The ligand [2-(2-(1-(thiophen-2-yl) ethylene) hydrazine] benzoic acid (TEHBA) was prepared by the condensation of hydrazine benzoic acid with 2-acetylthiophene in the ratio of 1:1 was added at room temperature. Then it was stirred and refluxed on water bath for one hour. When cooled to room temperature a yellow solid was precipitated. This is filtered and washed with n-hexane and dried. It is recrystallized from methanol, m.p 202^{0}C.Yield (65%).

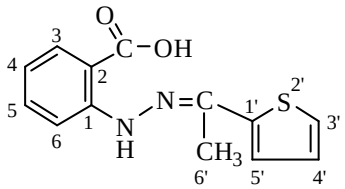


Fig2. Structure of [2-(2-(1-thiophene-2-yl) ethylene) hydrazine] Benzoic acid (TEHBA)

The metal chelates were prepared by refluxing the methanolic and aqueous solutions of metal chlorides of Mn^{+2},Co^{+2},Ni^{+2},Cu^{+2},Cd^{+2},$Fe^{+2}$and vandiumoxysulphate salt VO(IV)with ligands.

On the basisof the analytical data, IR spectral data , electronic spectral analysis, Magnetic moment data and also on the geometry of the ligand reported earlier it is proposed that Mn(II), Fe(II) and Ni(II) complexes have been assigned with an Octahedral stereochemistry. The Cu (II) and VO (IV) complexes have been proposed with a square pyramidal geometry. The Co (II) and Cd (II) complexes have been interpreted with a pseudo tetrahedral geometry. All geometries of metal complexes are supported by molecular modeling studies.

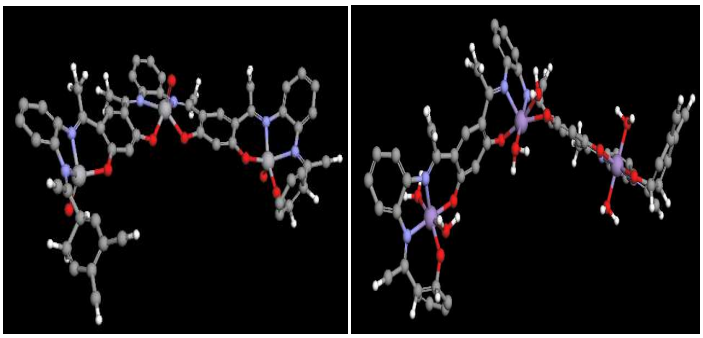
II.MATERIALS AND METHODS

2.1 Molecular modelling studies

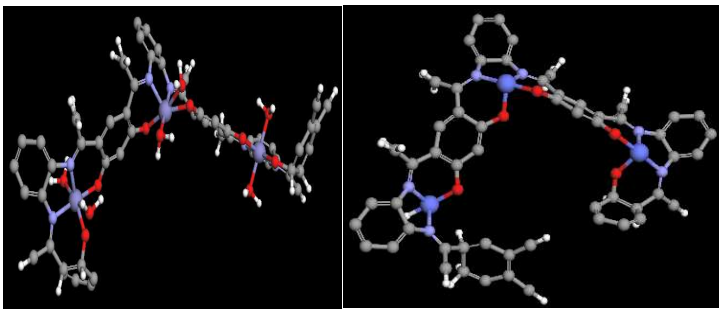
In the present study ARGUS Lab software was used for geometry optimization ARGUS Lab offers geometry optimization using MNDO[19], AM1[20,21] or PM3 semi empirical SCF (Self-consistent field) method procedure which is based on quantum chemistry principles where drastic simplifications are made in terms of evaluating integrals. PM3[12] is being the latest among the series at semi empirical methods it is expected to be the most reliable among them and hence we employed PM3 to estimate the relative energy differences and obtained the three dimensional geometries of metal complexes. The most probable geometry was assigned based on the minimum energy obtained by geometry optimization. The results obtained from molecular modeling studies are in accordance with experimental data. The position of the various atoms in the expected geometry was confirmed by stabilization energies obtained by computational analysis. Sometimes it was not represented in some of the figures as it is a 2D representation.

A molecular modeling[22] study provides information that is complementary to experimental data on the structures, properties and reactions of substances. The objective of theoretical molecular modeling of geometry optimization is to find the point at which the energy is minimum because this is where the molecule is most stable and most likely to be found in nature.

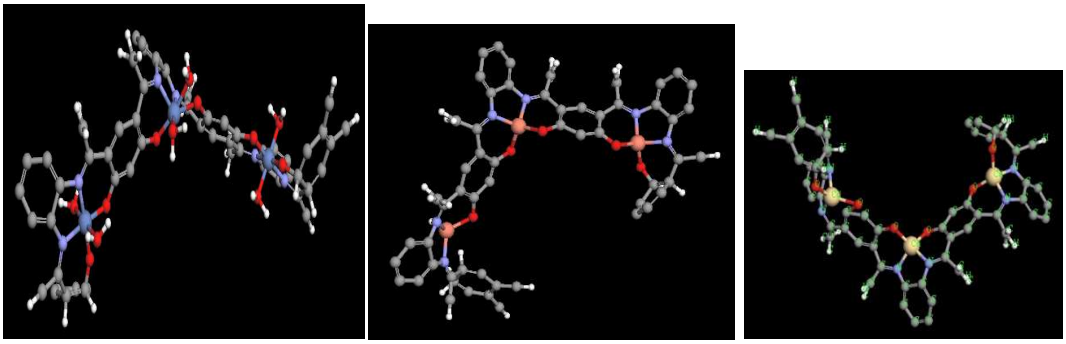
Figs. 3: Molecular Modeling of metal complexes of ligand ADPEPEDPE



VO (IV) - Square Pyramidal GeometryMn(II) – Octahedral Geometry

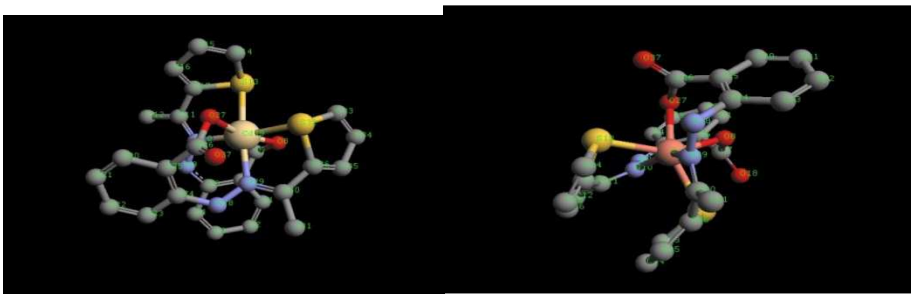


Fe (II) – Octahedral Geometry Co(II) – Tetrahedral Geometry



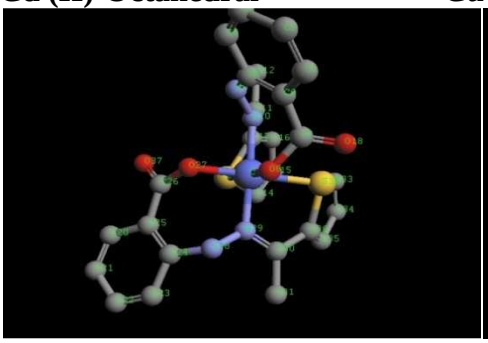
Ni (II) – Octahedral Geometry Cu(II) – Square Planar Geometry Cd (II) – Tetrahedral Geometry

Figs. 4: Molecular Modeling of metal complexes of ligand TEHBA

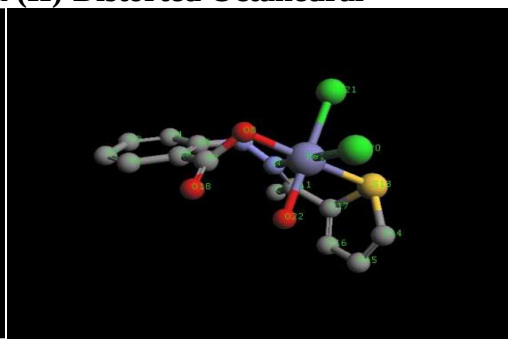


Cd (II)-Octahedral

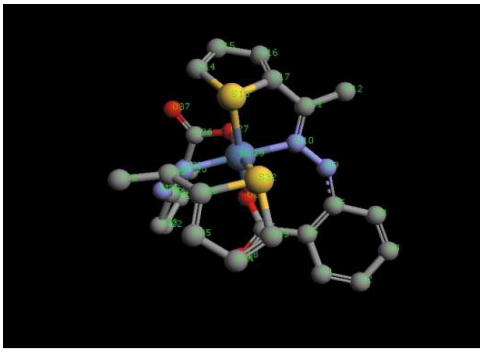
Cu (II)-Distorted Octahedral



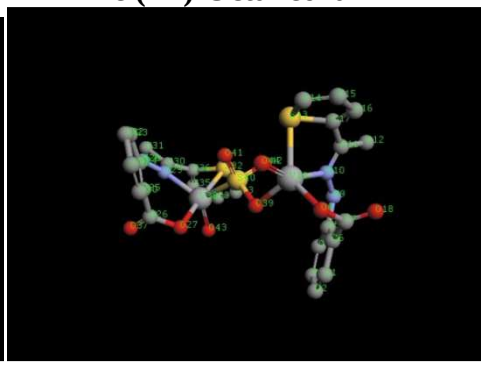
Co (II)-Octahedral



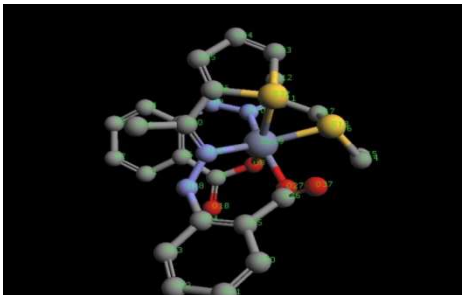
Fe (III)-Octahedral



Ni (II)-Octahedral



VO(IV)-Square pyramidal



Zn (II)-Octahedral

Metal complexes will adapt different geometries depending on the co-ordination number and the number of possible coordinating sties available on the ligand. Geometrical approximations for different possible structures of Schiff base metal complexes of VO (IV), Mn (II), Fe (II), Co (II), Ni (II), Cu(II), Cd(II), are considered initially and tried to optimize the geometry with least energy by performing a series of alterations on the molecule until the energy of the molecule has reached the minimum. The most probable geometry is assigned based on the minimum energy obtained by geometry optimization (Fig 3&4).

2.2. Biological activity

Materials obtained:

1. Ligands & their Metal Complexes
2. Test cultures:

Pure cultures of the following microorganisms were used for screening the antimicrobial properties of ligands and their metal complexes

a) Staphylococcus aureus(NCIM No: 2079)
b) Escherichia coli(NCIM No: 2803 (Strain CR-63) Wild type)
c) Aspergillus terreus

The pure cultures of these microorganisms were obtained from National Collection of Industrial Microorganisms (NCIM), NCL, India. The cultures were maintained on Nutrient Agar and Potato Dextrose Agar (HI Media, India) slopes at 4^0C and sub-cultured before use.

3. Culture media:

a) Nutrient broth
b) Nutrient agar
c) Potato Dextrose Agar

Methods followed:

a)Biological Activity of Metal Complexes against Bacteria

Agar well diffusion method[23]for screening the antibacterial activity

In vitro antibacterial activity was studied against two bacterial strains using Agar well diffusion method. In this method the antimicrobials present in the metal complexes are allowed to diffuse out into the medium and interact in a plate freshly seeded with the test organisms. The Nutrient agar plates were seeded with the overnight broth culture of each test organism ($1.5x10^8$/ CFU/ml). Wells were prepared in seeded agar plates with 6mm diameter and 100 µl of each compound (125µg/µl concentration) was introduced in each well. The solvent used for preparing metal complexes was DMSO. Solvent control well was run for every assay. All the inoculated plates were incubated at 37^0C for 24 hours in the incubator. The antimicrobial spectrum of the compounds was determined in terms of diameter of inhibition zones. A zone of inhibition of 12mm (millimeter) or above was considered as

sensitive and less than 12mm as resistant. The entire experiment was carried out under strict aseptic conditions. The samples were run in triplicates and each result is a mean of the three values obtained.

b) Biological Activity of Metal Complexes against Fungi

The fungal activity has been studied by taking the solutions of ligand and its complexes formed in DMSO with 100 µg/ml concentrations. The complexes and ligand dissolved in DMSO (100 µ g/ml) were added to a potato dextrose agar (PDA) and were then poured into sterile petri dishes (9 cm. in diameter) and were left to solidify. Using a cork borer (6mm in diameter), Aspergillus terreus spores were suspended on the medium at the centre. Finally the dishes were incubated at 27°C for 72 hours and the treated petri dishes were compared with controlled petri plates. Clear inhibition was noticed with the ligand and complexes where the DMSO solutions were added. This experiment was carried out in triplicates. The percentage inhibition of the Fungi was calculated by the following equation and moderate effectiveness is exhibited.

$$\% \text{ inhibition} = \frac{100\ (C - T)}{C}$$

Where C is the diameter (mm) in controlled plates after 72 hrs.and T is the diameter in mm in treated plates after 72 hrs.

III. OBSERVATION & RESULTS:

Table 1: Antibacterial activity of metal complexes

Ligand	Compound	Zone of sensitivity (Diameter in mm)	
		Staph. Aureus	E.Coli
Ligand 1 ((**ADPEPEDPE**)	VO (IV)	R	R
	Mn (II)	R	R
	Fe (II)	4	4
	Co (II)	R	R
	Ni (II)	4	R
	Cu (II)	R	R
	Cd (II)	10	12
Ligand 2 **(TEHBA)**	Zn(II)	17	(R)
	Cu(II)	22	4 (non-significant)
	Co(II)	25	(R)
	Cd(II)	41	10 (non-significant)

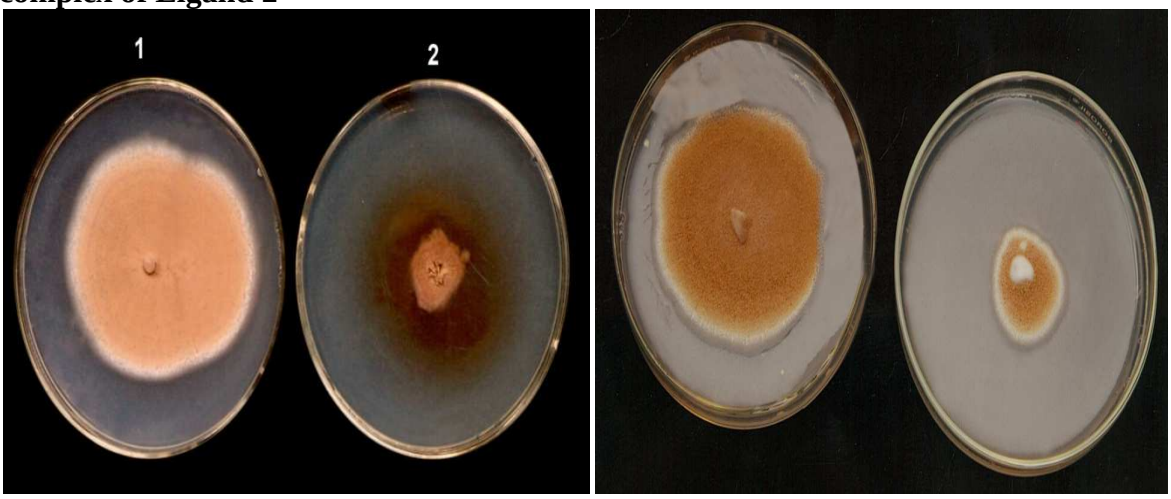
Fig.5: Bacterial Activity of Ligand 1 and its metal complexes

Fig.6: Bacterial Activity of Ligand 2 and its metal complexes

Table.2 Antifungal activity of the ligand and metal complexes

Ligand	Compound	%age inhibition with 100 µg/ml
Ligand 1 ((**ADPEPEDPE**)	VO(IV) complex	24
	Mn(II) complex	21
	Fe(II) complex	23
	Co(II) complex	59
	Ni(II) complex	22
	Cu(II) complex	69
	Cd(II) complex	62
Ligand 2 **(TEHBA)**	Ni(II) complex	21
	Cu(II) complex	24
	Cd(II) complex	23

Fig.7. Fungal Activity of Cu (II) complex of Ligand 1 **Fig. 8: Fungal Activity of Cd(II) complex of Ligand 2**



IV. CONCLUSION

On the basis of IR, UV, visible, magnetic data, analytical data, conductivity measurements, the Zn(II), Cd(II), Ni(II), Co(II), Fe(III), complexes have been assigned with octahedral stereochemistry. The VO(IV) complex has been interpreted to a square pyramidal disposition. The Cu(II) complex has been attributed to a tetragonally distorted octahedral geometry. Biological activity studies showed that ligand (TEHBA) and its metal complexes showed antibacterial activity only against gram positive bacteria Staphylococcus aureus, a bacterium which is drug resistant nosocomial agent in the order as Zn < Cu ~ Co <Cd (Fig. 5). metal complexes are found to be more potent antibacterial than the parent Schiff base

ligand.Antifungal activity was reported by ligand (ADPEPEDPE) and its metal complexes in the order of %age of inhibition : Cu(II) >Cd(II)>Co(II)>VO(IV)>Fe(II)>Ni(II)>Mn(II)>Ligand. Geometries of the metal complexes were supported by computational analysis. The results obtained from molecular modeling studies are in accordance with experimental data.

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