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NICKEL (II) AND COBALT (II) COMPLEXES OF ORTHO-PHTHALALDEHYDE SEMICARBAZONE, SYNTHESIS, STRUCTURAL AND ANTIMICROBIAL ACTIVITY

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ABSTRACT

Schiff bases are the most widely used organic compounds. They have been shown to exhibit a broad range of biological activities, including; antifungal, antibacterial, anti-malarial, anti-proliferative, anti-inflammatory, antiviral and antipyretic properties. In this study the Schiff base ortho- phthalaldehyde semicarbazone was prepared as a new multi-dentate complexing agent, by condensing ortho-phthalaldehyde with semicarbazide hydrochloride in 2:1 molar ratio respectively in ethanolic medium. This ligand was used to synthesize metal complexes of Ni (II) and Co (II) in 1:1 molar ratio using ethanol as a solvent. Characterization and structure elucidation of the ligand and its corresponding metal complexes have been investigated on the basis of molar conductance, UV and IR spectral studies. An in vitro antimicrobial investigation was also carried out for the free ligand and its metal complexes against four bacteria; *Bacillus subtitles*, *Staphylococcus aureus* (Gram-positive), *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-negative) and one Fungi; *Candida albicans*, to assess their antimicrobial properties by disc diffusion technique. Antimicrobial activity of the prepared complexes showed higher activity than the free ligand.

Keywords: Semicarbazone, ortho-phthalaldehyde, Schiff bases, metal complexes, antimicrobial activities.

1. INTRODUCTION

Semicarbazones are a class of compounds having the structure [$R_2C=NNHCONH_2$] formally derived from aldehyde or ketones with semicarbazide to form semicarbazones in the solid state, predominantly exist in the keto-form, whereas in solution state they exhibit a keto-enol tautomerism [1]. They are classified as imines derivatives because they are formed from the reaction of an aldehydes or ketones with the terminal -NH_2 group of semicarbazide, which behaves very similarly to primary amines, semicarbazones uesd as spectrophotometric agents as well for the analysis of metal ions and are frequently used in the qualitative organic analysis of carbonyl compounds [2]. Furthermore, bearing in mind that many semicarbazones form stable colored metal Complexes [3]. Semicarbazones can act as neutral ligand in their keto forms coordinated to metal ions via azomethine N and carbamoyl O, while the deprotonated enolic form appears to serve monoanionic (N,O) binding pattern. When a coordinating functional group (X) is additionally present in the semicarbazone compounds, more diversified

binding modes can occur, typically tridentate (X, N, O) coordination can be found in their metal complexes, which provides a stronger metal binding ability to the ligands [4]. Semicarbazones are well known due to their biological activities, which are considered related to their ability to form chelates with metals [5]. The influence of certain metals on the biological activity of these compounds and their intrinsic chemical interest as multidentate ligands has prompted a considerable increase in the study of their coordination behavior. Semicarbazones have a great interest because of their chemistry and biological activities for the treatment of various human ailments, semicarbazones have proved the efficiency in combating various diseases. It is of great interest because of their potentially beneficial biological activities such as antinociceptive, anticonvulsant, antiarrhythmic, insulinmimic, uterotrophic, antiviral, antimalarial, antitubercular, cytotoxic, antibacterial, antifungal activities and antioxidant agents [6-9].

Ortho-phthalaldehyde (OPA) is a benzene ring based structure, OPA has been approved for antimicrobial pesticide use (indoor only) by the U.S.EPA and for disinfecting medical devices by the U.S.FDA, and used of measurement for cholesterol in plasma and tissue based on detection of free and esterified cholesterol following thin-layer chromatographic separation, as well used in diagnostic for urea nitrogen test system, intermediate in the synthesis of pharmaceuticals, medicines, and other organic compounds, OPA also inhibited enzyme function in bacteria (alpha amylase from *Bacillus Subtillis*) and fungi (glutathione reductase from yeast) [10]. Previous studies showed that OPA is effective against glutaraldehyde (GTA) resistant mycobacteria and that it's a viable alterinative to GTA for high level disinfection [11]. The efficacy of OPA was tested against *Pseudomonas aeruginosa*, *Mycobacterium chelonae* and a GTA - resistant *mycobacterial strain Mycobacterium Chelonae* (Epping), using a quantitative suspension test, quantitative carrier test and using bacteria grown as sedimentation biofilms. OPA (0.5 % W/V) was shown to be an effective high - level disinfectant against *M. chelonae* (Epping) and *P. aeruginosa*. OPA is react strongly with amino acids, particularly at low PH which means that the cell is unable to undertake most, if not all of its metabolic and other functions. It's thought that OPA cross - links the outer membrane of Gram - negative bacteria to a lesser extent than that of GTA, this reduced cross - linking ability would be thought to reduce the antimicrobial activity of OPA, however this is compensated for by the lipophilic nature of the biocide, which enhances its uptake within the lipi - rich of mycobacteria, including GTA resistant mycobacteria. The reduced cross - linking of OPA at the cell surface allows OPA to penetrate the cell membrane un - hindered. OPA at 0.45% (W/V) was first shown to effectively disinfect endoscopes in 1994, producing a $\geq$ 5 log reduction in bacterial counts, within 5 minutes. Since then, there have been other studies confirming the antimicrobial efficacy of this aldehyde against a wide range of bacteria including mycobacteria and spores [12]. The rapid mycobactericidal effect of OPA probably arises from its more efficient penetraion a cross biological membranes [13].

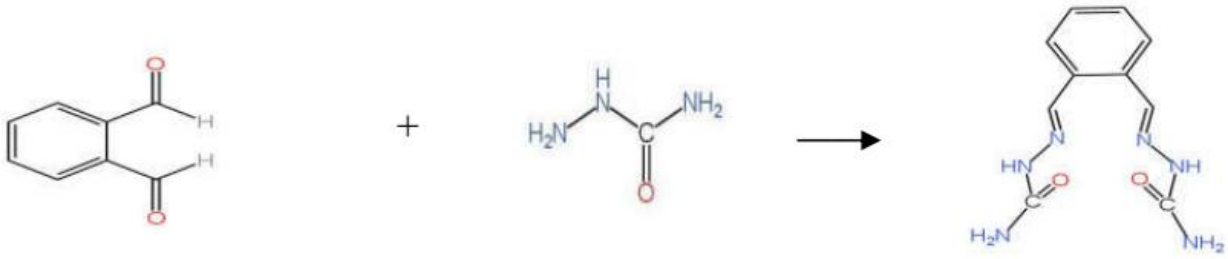
The biological activity of ortho - phthalaldehyde semicarbazone - metal complexes has not been widely reported. Given the potential biological activity of semicarbazone and ortho-phthalaldehyde and the involvement of metal ions in antimicrobial activity. This study concentrates on the synthesis and biological activity of ortho-phthalaldehyde semicarbazone ligand and its metal complexes.

2.1. Chemicals

Semicarbazidehydrochloride, Nickel chloride hexahydrate, Cobalt chloride hexahydrate, Ortho-phthalaldehyde and Ethanol.

2.2. Synthesis of ligand

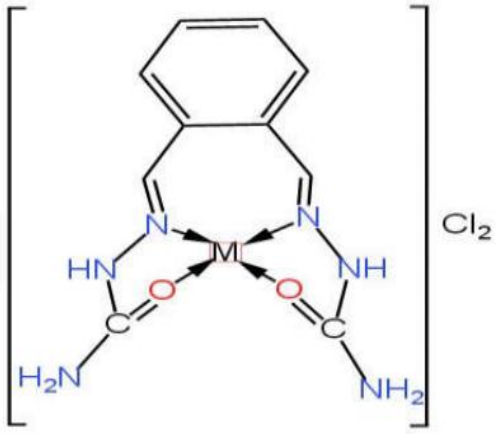
The synthesis of ortho-phthalaldehyde bis (semicarbazone) was based on condensation reaction: an ethanolic solution (20ml) of ortho-phthalaldehyde (0.0005mol, 0.06707g) and (20ml) of semicarbazide hydrochloride (0.001mol, 0.11153g) were mixed together and refluxed at 68°C for 3h. The solution was allowed to cool at room temperature and left for slow solvent evaporation. After several days orange crystals were obtained. The crystals were separated, washed with cold ethanol, and dried, Scheme 1.



Scheme1. Synthesis of ortho-phthalaldehyde semicarbazone ligand

2.3. Synthesis of metal complexes

The prepared ligand (0.0005mol, 0.124115g) was dissolved in (20ml) of ethanol and (0.0005mol) of metal salts Ni(II) or Co(II) in (20ml) of ethanol was added to the previous solution, were mixed und and refluxed for 3h at 68°C. After cooling to room temperature. The precipitate was filtered, washed with cold ethanol and dried. The desired complexes was shown figure 1.



Where; M = Ni (II) or Co (II)

Figure 1. Suggested structure of ortho-phthalaldehyde semicarbazone metal complexes

2.4. IR spectral analysis

The appropriate weight of the ligand and its metal complexes were mixed with potassium bromide and grind to form KBr disk and the infrared (IR) spectrum record within the range 400-4000cm^{-1}.

2.5. UV-Vis spectral analysis

A solutions with a concentration of (1×10^{-3} mol.L^{-}) for the ligand and the complexes were prepared. The absorbance spectra were recorded in the visible and ultraviolet region with 200-800 nm using ethanol as a reference solution.

2.6. Antimicrobial activity

2.6.1. Antifungal screening

Antifungal screenings of the prepared compounds was performed. Potato dextrose agar medium was prepared by using potato dextrose agar and distilled water. Appropriate amount of the compounds in DMSO was added to potato dextrose agar medium in order to get a concentration of 5% µg/mL of compound in the medium. The medium was poured into a set of two Petri plates under aseptic conditions in a laminar flow hood. When the medium in the plates was solidified, a mycelial disc of 0.5 cm in diameter was cut from the periphery of the seven days old culture and it was aseptically inoculated upside down in the center of the Petri plates. These treated Petri plates were incubated at 26±1 °C until fungal growth in the control Petri plates was almost complete. The mycelial growth of fungi (mm) in each Petri plate was measured [14].

2.6.2. Antibacterial screening

The paper disc diffusion method was used to screen the antibacterial activity of the prepared compounds and performed by using Mueller Hinton agar (MHA). The ligand and its complexes were carried out according to the National Committee for Clinical Laboratory Standards Guidelines. Bacterial suspension was diluted with sterile physiological solution to 108 cfu/mL (Turbidity = McFarland standard 0.5). One hundred microliters of bacterial suspension were swabbed uniformly on the surface of MHA and the inoculum was allowed to dry for 5 minutes. Sterilized filter paper discs (Whatman No. 1, 6 mm in diameter) were placed on the surface of the MHA and soaked with 20 µL of a solution of each sample. The inoculated plates were incubated at 37°C for 24 h in the inverted position. The diameters (mm) of the inhibition zones were measured [15].

3. RESULTS AND DISCUSSION

Table 1. Physical properties of ligand and its metal complexes

Compounds	M.wt	Colour	Appearance	Yield %	Molar Conductance (µS/cm)
Ligand (L)	248.23	Orange	Crystal	94.4	-
$[Ni(L)]Cl_2$	377.83	Green	Powder	75.8	69.8
$[Co(L)]Cl_2$	378.07	Violet	Powder	79.0	59.4

L= Ligand ($C_{10}H_{12}N_6O_2$) and M.wt=Molecular weight.

3.1. IR data of ligand and its metal complexes

The IR spectrum of the prepared compounds showed absorption peak at 1691cm^{-1} due to the vibration of C=O and note that the decrease of this absorption in the complex, indicating the metal bonding oxygen [16]. and the appearance of absorption peaks at 1573-1598cm^{-1} due to the stretching of the conjugate C=N, and the appearance of absorption peak at 3265cm^{-1} due to NH the and reduction of the absorption in the complex, indicating the association of the metal with the nitrogen and the emergence of absorption in the region 3427-3386cm^{-1} is due to the NH_2 group, and the appearance of absorption peaks in the region 659-657cm^{-1} and 565-538cm^{-1} due to the metal bonding with oxygen and nitrogen respectively [17].

Table 2. IR spectrum of the ligand and its metal complexes

Compounds	*v*(C=N)	*v*(NH)	*v*(NH_2)	*v*(C=O)	*v*(M-N)	*v*(M-O)
Ligand (L)	1598	3265	3421	1691	-	-
$[Ni(L)]Cl_2$	1579	3085	3427	1687	565	659
$[Co(L)]Cl_2$	1573	3083	3386	1637	538	657

Table 3. U.V spectrum of ligand and its metal complexes

S.No	Sample	Absorption bands n-π* in (nm)	Absorption bands π-π* in (nm)
1	Ligand (L)	636, 315	264
2	$[Ni(L)]Cl_2$	639	-
3	$[Co(L)]Cl_2$	398, 305	262

3.2. Antimicrobial activity

The synthesized compounds were screened in vitro for their antimicrobial activity against four pathogenic bacteria; *Bacillus subtitles*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and one fungus; *Candida albicans* at a concentration of 5% µg/mL with DMSO as the solvent. The results showed that the tested compounds possess high antimicrobial activity against most of the tested organisms, as shown in Table 4.

Table 4. Antimicrobial activity of the ligand and its metal complexes

S.No	Sample	Conc µg/mL	E.c	Ps.a	S.a	B.s	C.a
1	Ligand (L)	5%	14	14	14	12	17
2	$[Ni(L)]Cl_2$	5%	15	16	14	13	18
3	$[Co(L)]Cl_2$	5%	14	16	15	18	20

The results were expressed in terms of the diameter of the inhibition zone: < 9 mm, inactive; 9-12 mm, partially active; 13-18 mm, active; >18 mm, very active. Where Fungi; C.a = *Candida albcans*.
Gram negative bacteria; E.c = *Escherichia coli*, Ps.a = *Pseudomonas aeruginosa*. Gram positive bacteria; B.s = *Bacillus subtitles*, S.a = *Staphylococcus aureus.*

4. CONCLUSION

In This study we have synthesized biologically active semicarbazone ligand and its Ni (II) and Co (II) complexes. The synthesized ligands and its metal complexes were characterized and identified on the basis of physical and spectral data. Antimicrobial activities were found that metal complexes are more active than the free ligand indicated that the coordination increases their bioactivity. The more investigations are going on with this hope that some of these compounds may be used as antimicrobial agent.

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