Synthesis, Spectral, SEM, Antibacterial and Antifungal Activity Studies on Some Co(II), Ni(II) and Cu(II) Complexes of New Schiff Base, 4-\{(E)-[(2-hydroxynaphthalen-1-yl)methylidene]amino\}-N-(5-methyl-1,3,4-thiazol-2-yl)benzenesulfonamide

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Summary: A novel group of Co(II), Ni(II) and Cu(II) complexes of the species, [M(L)AcO(H₂O)]nH₂O [n= 1, 2 and 3] were synthesized by the coaction of Schiff base ligand, (LH) 4-\{(E)-[(2-hydroxynaphthalen-1-yl)methylidene]amino\}-N-(5-methyl-1,3,4-thiazol-2-yl)benzenesulfonamide, derived from the concentration of 2-hydroxynaphthalene-1-carbaldehyde and sulfathiazole. Schiff base and its Co(II), Ni(II) and Cu(II) complexes were characterized by different spectroscopic tools (IR, ¹H-NMR, ¹³C-NMR, UV, SEM, TGA, CV) and magnetic moment. Magnetic moments and Electronic spectra of the Co(II), Ni(II) and Cu(II) complexes indicate that the geometries of the metal centers are octahedral. The metal-ligand ratios of complexes are 1:1 according to the elemental analyses results. Schiff base ligand and its Co(II), Ni(II) and Cu(II) complexes were tested for their antibacterial and antifungal activities by the (MIC) method. The antimicrobial activity studies have been undertaken and results are discussed.

Keywords: Antimicrobial activity; Metal Chelating Activity; Sulfa drug; Coordination compounds.

Introduction

Schiff bases are a significant class of chelating ingredients in coordination chemistry because of their ability to form stable complexes with different transition metals. These ligands are able to coordinate metals owing to another group and imine nitrogen, usually dependent to the aldehyde [1, 2].

Several Schiff Base ligands and their metal complexes were studied in the past because of their broad applicability [1-4]. Furthermore this ligand and their complexes play a key role in our understanding of the coordination chemistry of transition metal ions [5]. There is significant interest in the chemistry of transition metal complexes of ligand containing sulfur, oxygen and nitrogen donor atoms due to the carsinostatic, antitumor, antibacterial antifungal and antiviral activity and their industrial uses of complexes derived from them [6]. Supplement, the existence of oxygen and nitrogen donor atoms in the complexes provides this compound effective and hydrolysis, reduction, stereospecific catalysts for oxidation and other transformation of inorganic and organic chemistry and they also show biological activity [6]. It is known to increase the efficacy of some drugs when administered as metal complexes [6-7].

Recently, studies on sulfonamides and their transition metal complexes have increased due to their potential applications in chemistry, biology and medicine. [10-17].

Significant biological activity of metal complexes of sulfa drug-derived Schiff bases showed great interest in coordination chemistry [12]. Antioxidants against oxidative damage are important inhibitors. Antioxidant supplements are used to help reduce the oxidative damage of the human body from free radicals and active oxygen species [18].

In this study, we report the synthesis and characterization of complexes with Schiff base ligand. LH and its Co(II), Ni(II) and Cu(II) complexes have been characterized by Infrared, proton-NMR, carbon-NMR spectra, elemental analyses, electronic spectra, magnetic susceptibility measurements, thermo gravimetric analyses, scanning electron microscope and cyclic voltammetry. In addition, antifungal and antibacterial activities and minimum inhibitory concentration values of the compounds have been reported.

Experimental

Materials and Physical measurements

C, H and N contents were determined on an Exeter Analytical Inc. CHN Analyzer (Model LECO-932). ¹H and ¹³C NMR spectra were recorded in
DMSO-\textit{d}_6 on a BRUKER GmbH Dpx-400 MHz High Performance Digital FT-NMR multinuclear spectrometer. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded in KBr on a Mattson 1000 FT-IR spectrophotometer in the 4000-400 cm\textsuperscript{-1} region. Magnetic Susceptibilities were recorded on a Sherwood Scientific Magnetic Susceptibility Balance at room temperature. UV-visible spectra of the Schiff bases were carried out in DMSO solution in the range 200-1100 nm on a Shimadzu spectrophotometer, Pharmaspec. UV-1700 model. The cyclic voltammetry evaluations were recorded in DMSO at room temperature and 0.1 M TBAPF\textsubscript{6} were used as supporting electrolyte. The Scanning Electron Microscope images were carried out on JEOL JSM-6510LV. TGA graphs were stabled on a Shimadzu TG-50 thermo balance.

**Preparation of 4-{[(E)-\{2-hydroxynaphthalen-1-yl\}methylidene}amino\}-N-(5-methyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide (LH)**

The Schiff base, (LH) was synthesized by reacting 75 ml absolute ethanol solution of 2-hydroxynaphthalene-1-carbaldehyde (0.861 g, 5.0 mmol) with 25 ml absolute ethanol solution of sulfathiadiazole (1.352 g, 5.0 mmol) in a round bottom flask. The reaction mixture was refluxed for 6 h. In these reactions p-toluen sulfonic acid was used as catalyst. The product was filtered on a Büchner funnel and washed several times with ethanol. The pure compound dried in a desiccator over anhydrous calcium chloride at room temperature.

For LH; IR (KBr, \textit{v}, cm\textsuperscript{-1}): 3248 (O-H), 3068 (C-H\textit{a}), 3064 (C-H\textit{a}), 1616 (C=N), 1440 (C-O), 1389 (O=S=O\textit{trans}), 1140 (C-O\textit{trans}), 1024, 512, 256, 128, 64, 32, 16, 8, 4, 2, and 1 \textmu g/mL on the microorganisms at the concentrations studied. Stock solutions were prepared in DMSO having no effect on the microorganisms at the concentrations studied. Further dilutions were done at the required quantities of test compounds and the control drugs were dissolved in absolute dimethylsulfoxide (DMSO). Antimicrobial activities of compounds were determined using the broth dilution method proposed by the National Committee for Clinical Laboratory Standards (CLSI). MIC, which is the lowest concentration of a compound that completely inhibits microbial growth, was determined by a standard broth dilution technique adapted from the CLSI. As quality control strains 1 gram positive bacterium and 1 gram-negative bacterium were used. Tested microorganisms are gram-positive Staphylococcus aureus ATCC 6538P, Bacillus subtilis ATCC 6633, gram-negative Escherichia coli ATCC 25922, Salmonella typhimurium NRRL B 4420, and the yeast like fungi; Candida glabrata ATCC 66032 and Candida tropicalis ATCC 13803. Ampicillin (Mustafa Nevzat) and Fluconazole (Pfizer) were used as antibiotic.
reference for bacteria and yeast, respectively (obtained from Department of Biology, Fatih University, Turkey).

**Antibacterial and Antifungal Assays**

Bacterial cultures were obtained in Mueller-Hinton broth (Difco) for all the bacterial strains after 24 h of incubation at 37 ± 0.1 °C. Yeasts were propagated in Sabouraud dextrose broth (Difco) after incubation for 24 h at 25 ± 0.1 °C. Testing was carried out in Mueller-Hinton broth and Sabouraud dextrose broth at pH 7.4 for bacteria and yeast, respectively. The final inoculum size for bacteria and fungi was 105 CFU/mL. Test compounds were dissolved in DMSO at an initial concentration of 1024 µg/mL and then serially diluted in culture medium to 1 µg/mL. A set of tubes containing only inoculated broth was kept as control. Antimicrobial activity was determined after incubation for 24 h at 37 °C for bacteria and after incubation for 48 h at 25 °C for the yeasts. MIC was defined as the lowest concentration of the compounds that inhibited the visible growth of a microorganism. Each experiment in the antibacterial and antifungal assays was replicated two times to define the MIC values.

**Result and Discussion**

The physical properties and analytical data of the metal complexes reveal that the reactions between the metal (II) acetate and ligand are carried out with a molar ratio of 1:1 (M:L). In all the metal complexes, LH behaves as a ligand and coordinates thanks to carboxyl oxygen and azomethine nitrogen atoms. The two water molecules and acetate atoms also occupy the two sites of each metal giving an out of order octahedral geometry for metal complexes. These reactions are given in Scheme-1. Analytic data with Schiff base ligand and some physical properties of metal complexes are summarized in Table-1.

Metal complexes are intensely tinted solids and are thermally stable up to 280 °C. They are insoluble in water and chloroform, methanol, ethanol, cyclohexane, benzene, diethyl ether and acetone but are soluble in dimethyl sulfoxide and dimethyl formamide.

**Infrared spectra**

LH showed the absence of characteristic bands of the carbonyl group of 2-hydroxynaphthalene-1-carbaldehyde moiety and the amino group of sulfathidiadiazole of starting materials and the aspect of a novel strong intensity band at 1616 cm⁻¹ characteristic of υ(C=N), azomethine group approve the formation of moved ligand structure [19]. Moreover, existence of medium density bands at 1440, 3070 and 1598 cm⁻¹ may reasonable be assigned to υ(C-O) stretching vibration of hydroxynaphthalene, υ(C-H) aromatic stretching vibrations and υ(C=N) group of benzenesulfonamide moiety, respectively [20,21]. However, a comparison of IR spectra of the Co(II), Ni(II) and Cu(II) metal complexes with the LH revealed a positive shift in the υ(C-O) and υ(C=N) stretching mode suggesting the coordination of ligand piece of oxygen and azomethine nitrogen of hydroxynaphthalene piece [22,23]. The bands in the range between 569 cm⁻¹ to 591 cm⁻¹ and 475 cm⁻¹ to 481 cm⁻¹ may be due to metal-oxygen and metal-nitrogen stretching vibration of cobalt(II), nickel(II) and copper(II) complexes respectively [24]. Co(II), Ni(II) and Cu(II) complexes show broad band in the region 3330 cm⁻¹ to 3352 cm⁻¹ along with other medium intensity bands in the region 829-835 cm⁻¹ and 627-634 cm⁻¹ may be assigned to υ(OH) and υ(H₂O) of coordinated water molecules. [25,26]. Also in the infrared spectrum of the LH (O=S=O)ₜₚ and (O=S=O)ₚₚ stretching vibrations was observed about at 1389 and 1140 cm⁻¹ respectively. The shoulder at 1580-1588 cm⁻¹ in the Co(II), Ni(II) and Cu(II) complexes may be imputed to the (C=O)₀ₚₚ [27]. Coordination of water molecules is required to account for the octahedral stereochemistry of metal complexes [28,29].

**Proton and Carbon NMR spectra**

NMR spectra of Schiff base were recorded in DMSO-d₆. The Schiff base ligand exhibited a signal due to all expected protons in the expected region and was found from the integration curve equivalent to the total number of protons removed from the proposed structure. These were compared with the reported signals of known analogous compounds and also provided further support for the new ligand compositions as well as the complexes proposed by IR and elemental analysis data. All protons enter resonance in suitable positions, ie OH group in LH gives a large singlet at 14.04 ppm, singlet at 8.92 ppm (CH=N), aromatic ring linked to 7.02-7.45 ppm sulfapyridine, aromatic protons of hydroxynaphthalene ring at 7.50-8.52 ppm, and 2.52 ppm for the methyl group. More detailed information on the structure of LH is provided by ¹³C-NMR spectral data. The carbon atoms for LH were observed at 171.55 (CH=N), 164.63 (C-OH), 157.40 (C-N=CH), 155.20 (S=CO-NH), 153.35 (S-C(CH₃)), 139.55 (C-S=O), 138.28-113.00 (Ar-C), 109.44 (C-CH=N), 16.55 (CH₃) ppm respectively. The results confirmed the proposed structure of the Schiff base ligand [30, 31].
As known, magnetic susceptibility measurements ensure knowledge concerning the structure of the metal complexes. The synthesized complexes are proposed to have the general structural formulas shown in Scheme 1. All complexes are paramagnetic. The magnetic moments are in the range of 3.80, 2.65 and 1.75 B.M for Co(II), Ni(II) and Cu(II) complexes, respectively [32].

Electronic Spectra

Electronic spectra of complexes were taken in dimethylformamide solution. The electronic spectrum of the cobalt(II) complexes shows d-d transition bands at 9530 cm⁻¹, 19780 cm⁻¹ and 27670 cm⁻¹. The first two bands correspond to the 4T₁̄g (F) → 4T₂̅g (F) ν₁ and 4T₁̄g (F) → 4T₁̄g (P) ν₃ transitions, respectively. These bands are the characteristics of high spin octahedral cobalt(II) complexes. However, due to its proximity to strong υ₃ transitions, band υ₂ is not observed. The electronic spectra of the nickel(II) complexes show d-d transition bands at 11160 cm⁻¹, 17420 cm⁻¹ and 23500 cm⁻¹. These passages belong to 3A₂g → 3T₂̅g (F) ν₁, 3A₂g → 3T₁̄g (F) ν₂ and 3A₂g → 3T₁̄g (P) ν₃, respectively. These passages reveal that the nickel complexes have an octahedral geometry and D₄h symmetry. For copper(II) complexes with D₄h, three spins were allowed transitions: ²B₁g → ²A₁g ν₁, ²B₁g → ²B₂g (F) ν₂ and ²B₁g → ²Eg ν₃. Two bands were observed in the electronic spectrum of the copper(II) complex at 605 and 650 nm, respectively [33,34]. The electronic spectra were given in Fig 1.

Cyclic Voltammetry

Schiff base ligand and electrochemical properties of metal complexes were investigated by cyclic voltammetry (CV). Cyclic voltammetry measurements were taken in dichloromethane solution at room temperature. 0.1 M TBAPF₆ was used as the supporting electrolyte. In the cathodic scan range, Ligand has two irreversible reduction peaks at about -1.20 and -1.45 V, which reflect the reduction of sulfoxide (S=O) and imine (-CH=N-), respectively. As the reduction potentials are sensitive to intramolecular and intermolecular electron transfer, the imine reduction peak is shifted to the potential below the ligand-bound metal unit ligand.
During anodic scan region an irreversible oxidation wave was observed. After attaching the metal unit on the Schiff base ligand, the oxidation potential was increased due to electron withdrawing ability of metal center (Fig. 2). A suitable HOMO-LUMO energy level is very important to use these molecules as active substances in different areas. The HOMO-LUMO energy levels were calculated using the start of the corresponding oxidation / reduction potentials against Fe/Fc\(^+\). HOMO-LUMO energy levels for ligand and metal complexes were calculated as -5.41 eV and -3.32 eV (for LH); -5.92 eV and -3.49 eV (for [Co(L)AcO(H\(_2\)O)\(_2\)]3H\(_2\)O); -5.94 eV and -3.52 eV (for [Ni(L)AcO(H\(_2\)O)\(_2\)]3H\(_2\)O); -6.02 eV and -3.57 eV (for [Cu(L)AcO(H\(_2\)O)\(_2\)]2H\(_2\)O). From the HOMO-LUMO levels, electrochemical band gap (\(E_g\)) of Schiff base ligand and its metal complexes were also calculated as 2.19 eV (for LH), 2.43 eV (for [Co(L)AcO(H\(_2\)O)\(_2\)]3H\(_2\)O), 2.42 eV (for [Ni(L)AcO(H\(_2\)O)\(_2\)]3H\(_2\)O) and 2.45 eV (for [Cu(L)AcO(H\(_2\)O)\(_2\)]2H\(_2\)O) [34]. All results were summarized in Table-2.

**SEM**

SEM analysis was performed to evaluate the facial morphology of LH and its complexes. (Fig. 3). SEM micrographs of LH and cobalt(II), nickel(II) and copper(II) complexes are markedly different due to coordination of metal ions with donor sites in the Schiff base ligand [35]. It has not been clarified in the SEM micrographs of the complexes that the surface morphology of cobalt(II), nickel(II) and copper(II) complexes has been modified by the exchange of metal ions. The micrograph of LH shows irregular thrombocyte structures of varying side dimensions with some scattered bars observed between them. Micrographs of the complexes of cobalt (II), nickel (II) and copper (II) have been superimposed on agglomerations of smaller and larger spherical particles of different sizes [35].

**Thermal studies**

The thermal behavior of the ligands and all the complexes were investigated using thermogravimetric techniques in the temperature range from ambient to 900 °C at a heating rate of 15°C/min. The decomposition temperature and the weight losses of the ligands and the complexes were calculated from TGA data (Fig. 4) (Table-3) [37]. The results were indicated indicate the loss of two lattice water molecules in the former step and coordinated water molecules in the latter [38-41].

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Reduction potential (V)</th>
<th>Oxidation potential (V)</th>
<th>HOMO (eV)</th>
<th>LUMO (eV)</th>
<th>(E_g)</th>
<th>Electrochemical band gap (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>(E_{\text{red}}) = -1.20</td>
<td>(E_{\text{ox}}) = 1.40</td>
<td>-5.51</td>
<td>-3.32</td>
<td>2.19</td>
<td></td>
</tr>
<tr>
<td>[Co(L)AcO(H(_2)O)(_2)]3H(_2)O</td>
<td>(E_{\text{red}}) = -1.45</td>
<td>(E_{\text{ox}}) = 1.74</td>
<td>-5.92</td>
<td>-3.49</td>
<td>2.43</td>
<td></td>
</tr>
<tr>
<td>[Ni(L)AcO(H(_2)O)(_2)]3H(_2)O</td>
<td>(E_{\text{red}}) = -1.07</td>
<td>(E_{\text{ox}}) = 1.55</td>
<td>-5.94</td>
<td>-3.52</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td>[Cu(L)AcO(H(_2)O)(_2)]2H(_2)O</td>
<td>(E_{\text{red}}) = -1.05</td>
<td>(E_{\text{ox}}) = 1.63</td>
<td>-6.02</td>
<td>-3.57</td>
<td>2.45</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 2: Cyclic voltammetry of the Schiff base ligand and its complexes (0.1 M TBAPF$_6$/DCM, scan rate of 100 mV s$^{-1}$ vs. Ag wire).

Fig. 3: SEM micrographs of the ligand and its complexes.
Fig. 4: TGA graphic of the ligand and its complexes.

Table 3: TGA results of metal complexes of Schiff base ligand.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Temperature Range (°C)</th>
<th>Mass Loss (%) Found (Calc.)</th>
<th>Casualties</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Co(L)AcO(H₂O)₂]₂H₂O</td>
<td>25-110</td>
<td>8.20 (8.55)</td>
<td>Lattice water</td>
</tr>
<tr>
<td>[Ni(L)AcO(H₂O)₃]H₂O</td>
<td>110-160</td>
<td>6.32 (5.70)</td>
<td>Coordinated water</td>
</tr>
<tr>
<td>[Cu(L)AcO(H₂O)₂]H₂O</td>
<td>25-116</td>
<td>9.48 (8.55)</td>
<td>Lattice water</td>
</tr>
<tr>
<td></td>
<td>116-156</td>
<td>5.90 (5.70)</td>
<td>Coordinated water</td>
</tr>
<tr>
<td></td>
<td>25-117</td>
<td>5.12 (5.82)</td>
<td>Lattice water</td>
</tr>
<tr>
<td></td>
<td>117-174</td>
<td>6.41 (5.82)</td>
<td>Coordinated water</td>
</tr>
</tbody>
</table>

Fig. 5: Comparison of MIC values of complexes (in μg/mL) against different bacterial species.
Biological Effects

We have designed and synthesized novel Schiff base ligand and its novel cobalt(II), nickel(II) and copper(II) complexes in order to Fig out their antimicrobial activities. The minimum inhibitory concentration of the synthesized compounds was determined against gram-positive Bacillus subtilis ATCC 6633, Staphylococcus aureus ATCC 6538P, gram-negative Salmonella typhimurium NRRL B 4420, Escherichia coli ATTC 25922, and yeast-like fungi Candida tropicalis ATCC 13803 and Candida glabrata ATCC 66032 using a standard broth dilution technique [42]. Antibacterial results demonstrate that metal complexes exhibit greater activity than ligands. Antibacterial results demonstrate that LH is more active when coordinated to metal ions. The main factor affecting antimicrobial activity appeared to be the structure of the tested compounds. The synthesized cobalt(II), nickel(II) and copper(II) complexes have similar inhibitory effects (moderate to high moderate MIC values of 32 and 256 μg / mL) on growth of strains tested (Fig. 5).

Conclusions

In this work, the synthesis and characterization of cobalt(II), nickel(II) and copper(II) complexes with a novel Schiff base ligand (2-hydroxynaphthalene-1-carbaldehyde and sulfonfthiadiazole) are described. The proposed structures for the complexes are the six-coordinate distorted octahedral geometry. Physical properties and analytical data studies have been proposed for complexes [Co(L)2(H2O)2]3H2O, [Ni(L)2(H2O)2]3H2O and [Cu(L)2(H2O)2]2H2O. The LH and its metal complexes have been synthesized and characterized by Infrared, proton-NMR, carbon-NMR spectra, elemental analyses, electronic spectra, magnetic susceptibility measurements, thermo gravimetric analyses, scanning electron microscope and cyclic voltammetry. The LH and [Co(L)2(H2O)2]3H2O, [Ni(L)2(H2O)2]3H2O and [Cu(L)2(H2O)2]2H2O complexes have been found to have showed strong antifungal and antibacterial activity against some bacterial strains.

References


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