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Synthesis, Characterization, Enzyme Inhibition and Antioxidant Activity of Nickel^{II} Complex of a Schiff Base

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Abstract – A novel active Ni^{II} complex of the Schiff base ligand ((E)-methyl-6-benzyl-2-(2-hydroxy-3-methoxybenzylideneamino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate) has been synthesized. FT-IR, UV-Vis, NMR, microanalysis, mass spectroscopy and physical studies (TGA, molar conductivity, melting point) were used to characterize the newly prepared Ni^{II} complex. Various characterization data suggested that the Schiff base ligand, coordinated by the nitrogen atom of the azomethine, the oxygen atom of the carbonyl and the oxygen atom of the hydroxyl group. Then, deprotonation with metal ions in a molar ratio of 1:1, has the general formula $[LNiCl(H_2O)_2]\cdot H_2O$. The low molar conductivity values confirmed the non-electrolytic structure of the Ni^{II} complex. Thermal decomposition of the Ni^{II} complex was shown to yield a metal oxide and OCH_3 as residue. The octahedral geometry of the Ni^{II} complex was confirmed by microanalysis, mass spectroscopy, UV-Vis, magnetic susceptibility and FT-IR spectroscopy. The Ni^{II} complex was evaluated for its in vitro antioxidant activity by DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity and CUPRAC (cupric ion reduction capacity) in vitro bioanalytical methods. According to the CUPRAC method, the synthesized Ni^{II} complex was found to have potent antioxidant activity. In contrast to standard antioxidants, the Ni^{II} complex did not scavenge DPPH radical solution.

Keywords – Antioxidant Activity, Schiff Base, DPPH, Ni Complex, Enzyme Inhibition

I. INTRODUCTION

Schiff bases are one of the most recently studied basic compounds and are generally obtained by condensation of a carbonyl and a primary amine under basic conditions. Schiff bases could coordinate with metal ions to stabilize the ligand in different oxidation states. In the development of coordination chemistry, transition metal complexes containing Schiff bases have played an important role. Metal complexes of S-, N- and O-chelating ligands have attracted a great deal of attention due to their interesting physico-chemical properties, their distinct biological activities and their use as models for the active sites of metalloenzymes. The Schiff base is used as a biological model to recognize the structure, shape and biological reaction processes of biomolecules. It is also used as a catalyst in many reactions [1-3].

Coordinating complexes, chirality, flexibility, reactivity, structural diversity, easy to obtain and environmentally friendly, etc. Because of their many properties, they are an important class of inorganic compounds that play an important role in medicinal chemistry.

Recently, transition metal coordination compounds have been the focus of much research. These compounds are found in electron-rich building blocks such as nucleic acids, proteins, enzymes and carbohydrates. They are therefore necessary for a wide range of biological processes.

The need to synthesize less toxic drugs for biological systems has therefore stimulated research into metal ion-based drugs. The use of transition metal compounds based on Schiff base ligands are a good argument for research in bioinorganic chemistry. Chelation, chemical sensors, structural modifications, reactivity, etc. belong to the Schiff base ligands. Due to their many properties, they form the backbone of many fields. These include analytical, biological, organic and inorganic industries. Properties such as the activity of the ligands, the behavior of the unit groups, the solubility, the cell permeability and the enzymatic activity increased with the formation of complexes with transition metal ions [3-5]. Due to their wide range of pharmacological activities, such as anti-inflammatory, antibacterial, analgesic, anti-tuberculosis, antioxidant, anthelmintic and anticancer, Schiff base complexes have been the most extensively studied in the medical and pharmaceutical fields [2,5].

Herein, synthesis of Ni^{II} metal ion chelate with Schiff base [6] are reported and structurally characterized on the basis of analytical, physical and spectral data. The metal chelate were studied for antioxidant and enzyme inhibition activities. It was found that, the Ni^{II} complex showed significant biological activity.

II. MATERIALS AND METHOD

Elemental analysis of the synthesized compounds was performed using an ELEMENTAR Vario EL III CHNS analyzer. A Perkin Elmer 65 FT-IR spectrophotometer with KBr pellets was used to record infrared spectra for each compound. UV-visible spectra were measured in the wavelength range 200-800 nm using a Shimadzu UV-1800 spectrophotometer. Mass spectrometric analysis was performed on a SCIEX Triple TOF 5600 spectrometer using acetonitrile as solvent. The $Hg[Co(SCN)_4]$ calibrant was used to record the magnetic moments of the complex on a Gouy balance. The conductivity of the complexes was measured with the Jenway 4010 conductivity meter in 10^{-3} M in DMF. Thermogravimetric analysis was performed at a heating rate of 10 °C/min. rate using alumina as standard on a Perkin Elmer Diamond TG/DTA thermogravimetric analyzer in a high purity argon atmosphere at a flow rate of 20 mL/min. All the chemicals used in the present work were of analytical grade.

A. *Synthesis and Characterization of Ni^{II} Complex*

Schiff base metal complexes were synthesized by direct reaction between $NiCl_2{\cdot}6H_2O$ (0.24g; 1.0 mmol) and Schiff base ligand (0.44g, 1.0 mmol) in hot ethanolic solution in 1:1 molar ratio with catalytic amount of triethylamine. The resulting mixture was refluxed for about 7 h. The mixture was cooled to room temperature and the precipitate formed. The precipitate was filtered and washed several times with di ethyl ether to obtain the complexes. The product was then recrystallized from a methanol-chloroform mixture.

$[NiLCl(H_2O)_2]H_2O$. Dark brown powder, Yield: 78%, M.p.: >300 °C. Anal. Calc. for $C_{24}H_{30}N_2O_7SNiCl$ (584.36 g/mol): C, 49.32; H, 5.13; N, 4.79; S, 5.48. Found: C, 50.00; H, 5.15; N, 4.80; S, 5.50%. FT-IR Data (KBr, cm^{-1}): 3387 ($-OH/H_2O)_{br}$, 3146, 3058 (Ar. –CH), 2948 (Alip. –CH), 1654 (C=O), 1607 (CH=N), 1583, 1542, 1485 (Ar. C=C), 1149 (C–O), 855 (H_2O), 780 (C–S–C), 567, 535 (M–O), 497, 463 (M–N). UV-Vis. ($\lambda_{max,}$ nm): 225, 235, 245, 257, 268, 275, 287, 298, 300, 306, 317, 331, 349, 369, 377, 395, 404, 410, 416, 436, 445, 467, 482, 494, 521, 535, 543, 550. ESI-MS (*m/z*): 585.36 (calc.), 585.60 (found) $[M+H]^+$. μ_{eff} (B.M.): 3.10. Molar conductance: 15.50 Ω^{-1} cm^2 mol^{-1}.

B. *Antioxidant Methods*

DPPH (1,1-Diphenyl-2-picrylhydrazyl) free radical scavenging activity and CUPRAC (cupric ions reducing capacity) in vitro bioanalytical methods were used to evaluate the antioxidant activity of the synthesized Ni^{II} complex [7,8].

C. *Acetylcholineesterase Enzyme Activity*

AChE activity of the Ni^{II} complex was determined according to a slight modification of the Ellman method [9]. Tacrine was used as a standard inhibitor of AChE enzyme.

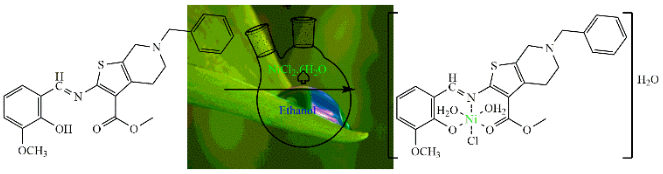

Fig. 1. Structure of the ligand and its Ni^{II} complex

III. RESULTS AND DISCUSSION

The unique infrared bands of the Schiff base in the ground state (4000-450 cm^{-1}, KBr) in comparison to the Ni^{II} complex provided valuable information about the binding sites of the important groups that were changed, especially the Schiff base.

The IR spectrum of Schiff base ligand showed peak at 3428 cm^{-1} assigned to ν(OH) phenolic group. Disappearance of this peak in chelate spectra suggests deprotonation of -OH (phenolic) group and coordination to metal by deprotonated -OH (phenolic) group. In addition, the ν(C-O) stretching band observed at 1164 cm^{-1} in the free ligand appeared in the region of 1149 cm^{-1} for the Ni complex, suggesting coordination through the phenolic oxygen atom to the metal ion. This is further supported by the peak that performed at 567, 535 cm^{-1} which is assigned to the ν(Ni-O) stretching [10-13]. The IR spectrum of Schiff base ligand showed strong peak at 1601 cm^{-1} which is ascribed to the azomethine ν(CH=N) group vibration. In metal chelates, this band is changed to higher frequencies at 1607 cm^{-1}, indicating coordination of the imine nitrogen atom to the metal ion. This is further confirmed by appearance of IR bands at 497, 463 cm^{-1} in the metal chelates assigned to ν(Ni–N) stretch [6, 10-13]. The OH stretching band observed in the spectra of chelates around 3387 cm^{-1} and 855 cm^{-1} is attributed to presence of water of coordination and water or hydration.

The electronic absorption spectra of the Schiff base ligand and its Ni^{II} complex were performed in ethanol solution in the range of 200 - 800 nm. The UV-Vis spectrum of the ligand showed absorption bands in the range of 215 to 404 nm. These bands were due to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions of electrons on the benzene rings and the azomethine chromophores. These bands displayed a red shift upon complexation owing to the contribution of the nitrogen electron pair coordinated to the metal ion. The Ni^{II} complex, probably due to the charge transfer (CT) transitions, confirmed bands in the range of 410-550 nm [14].

The octahedral geometry of the Ni^{II} complex is confirmed by the magnetic moment measurement of 3.10 B.M. [15].

The thermal properties of the complex were investigated using TGA in the range 50-1000°C. This method is also used to gain an idea of the coordinated water molecules that are present, either inside or outside of the coordination sphere. The Ni^{II} complex was exhibited to decompose in four steps. The first step, with a weight loss of 14.28% (calcd. 15.31%), indicated the loss of coordinated and hydrated water molecules and chloride in the temperature range of 50-210 °C. The second step took place at the temperature range of 210-400 °C, which suggested the removal of $C_{14}H_{1}1O$ having weight loss of 33.59% (calcd. 33.40%). The third step took place at the temperature range of 400-435 °C, which suggested the elimination of $C_7H_{10}N_2SO$ having weight loss of 28.22% (calcd. 29.10%). In the last step, the weight loss of 4.22% (calcd. 4.11%) at temperature range 435-480 °C suggested the loss of C_2 and leaving behind the residue of metal oxide and OCH_3 as final product [16].

A. *Antioxidant Results*

The synthesized Ni^{II} complex was found to be quite potent activity according to the CUPRAC method. The reducing activity of the Ni complex was found to be more effective than ascorbic acid and α-tocopherol standard antioxidant compounds (Fig. 2).

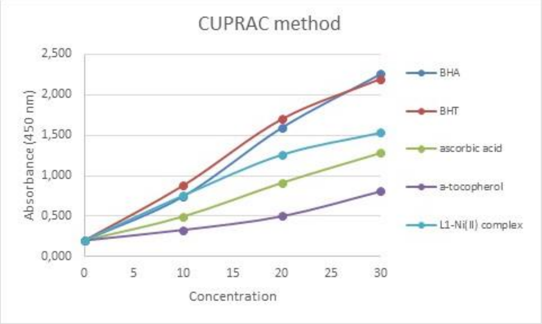

Fig. 2. CUPRAC reducing antioxidant activity of the Ni^{II} complex

On the other hand, Ni^{II} complex did not scavenge DPPH radical solution compared to the standard antioxidants. The absorbance of the radical was not reduced with increasing concentration of the complex sample (Fig. 3).

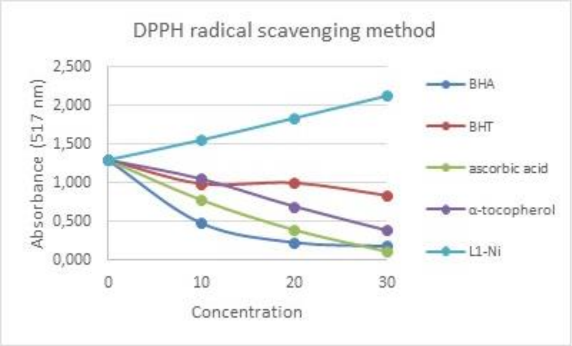

Fig. 3. DPPH radical scavenging activity of the Ni^{II} complex

B. *Acetylcholineesterase Enzyme Activity*

AChE enzyme activity was inhibited by the Ni(II) complex solution. Tacrine was used as a standard inhibitor of AChE enzyme. The inhibition potential of the Ni^{II} complex was found to be higher than the standard tacrine compound. According to the results, 52.7% of the AChE activity was inhibited by the standard tacrine, whereas 63.6% the AChE activity was inhibited by the Ni^{II} complex at 5 μM concentration (Fig. 4).

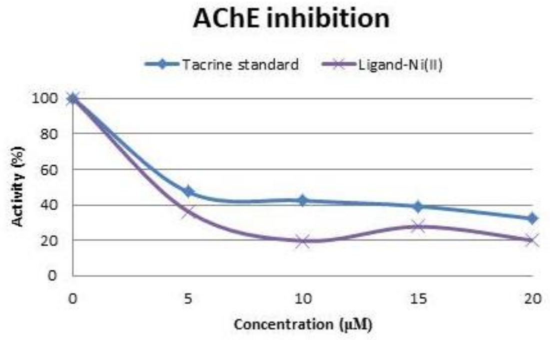

Fig. 4. AChE inhibitory activity of the Ni^{II} complex

IV. CONCLISION

This study, it can be concluded that the Schiff base and Ni^{II} complex have been synthesized and characterized used by a variety of physico-chemical techniques. The ligand is monobasic. It is three dentate coordinated through the N of the imine and the O of the carbonyl and phenolic group. From the above spectral study, the Ni^{II} complex has an octahedral geometry. Ni^{II} complexes was found to be more stable than the Schiff base by thermogravimetric analysis.

The antioxidant and enzyme inhibition activities of these compounds were also investigated. The complex exhibited very good reducing antioxidant activity in the CUPRAC method. It was observed that the AChE inhibitory activity of the Ni^{II} complex was more effective than the standard tacrine compound.

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