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Synthesis, Characterization, and Biological Evaluation of Some 3d-Metal Complexes of Schiff Base Derived from Sulfonamide Drug

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ABSTRACT:

A sulfonamide based novel acyclic bidentate compartmental ligand E-4-(((1H-indol-3-yl)methylene)amino)-N-(pyridine-2-yl) benzene sulfonamide was prepared by condensation of Indole-3-carbaldehyde with sulphapyridine in equimolar ratio in ethanol. The reaction of metal chlorides (Mn(II), Co(II), and Cu(II)) with the newly synthesized ligand in methanol results the formation of deep colored metal complexes with the formula $[ML_2]Cl_2$ (M=Mn, Co, and Cu). The free ligand and its metal complexes were characterized by elemental analyses, conductometric measurements, IR, UV-Vis, 1H and $^{13}CNMR$ and EI Mass spectrometric techniques. The physical measurements and FTIR spectral data showed that most of the complexes contain octahedral coordinated to the central ion (II). The antibacterial activity of the ligand and its complexes was done by well diffusion method using DMSO as inert solvent and the test solution was diffused into the plate and affected the growth of the incubated microorganisms such as staphylococcus aureus, E.coli, Bacillus, and Aspergillus Niger. The values of zone of inhibition were found out at 37 °C for a period of 24 h. It has been found that all the complexes have higher activity than the free ligand and the standard.

Key Words: Schiff base, Sulfonamide, ulfapyridine, Antimicrobial activity

1. INTRODUCTION

The presence of exocyclic nitrogen and Sulphur atoms in the structure of Schiff bases gives mutative ability to coordination sites to link directly with the transition metal ions [1].The sulfa drugs, first effective chemotherapeutic agents are widely used for the cure of bacterial infection in humans. Sulphanilamide is found to be active against several types of bacteria and hence used in

the treatment of diseases like pneumonia, gonorrhoea, meningitis, tonsillitis, sinus infections [2] etc. The sulfonamides constitute an important class of drugs, with several types possessing a host of biological properties including antibacterial, anti-carbonic anhydrase [3], diuretic [4], hypoglycemic [5], antithyroid [6], and antiprotons activities [7]. Sulphonamides inhibit growth of bacterial cell by blocking the synthesis of an essential vitamin called

folic acids. Azomethine ligands involving sulfapyridine ring have attracted the chemists to prepare novel metal chelate due to their importance in antimicrobial, anti-inflammatory, and anti-HIV applications [8,9]. Due to the growing interest of metal chelates involving heterocyclic rings, here we report the synthesis and characterization of some first row transition metal complexes with new Schiff base derived from condensation of Indole-3-carbaldehyde and sulfapyridine.

2. MATERIALS AND METHOD

All chemicals were obtained commercially and used without further purification. To prepare the complexes under study appropriate chlorides, $MCl_2 \cdot 4H_2O$ ($M=Mn$), $MCl_2 \cdot 6H_2O$ ($M=Co$), $CuCl_2 \cdot 2H_2O$ from Sigma Aldrich Chemie (Germany) and Merck were used, which were of p.a. purity. Infrared spectra for all the complexes and ligands were recorded on a JASCO FT-IR-410 ($4000-400\text{ cm}^{-1}$) spectrophotometer. Potassium bromide disc was employed for sample preparation. Cyclic voltammetric measurements were carried out on a Bio-Analytical System (BAS) model CV-50W electrochemical analyzer. The three-electrode cell comprised a reference Ag/AgCl, counter electrode as platinum wire and working glassy carbon (GC) electrodes with surface area of 0.07 cm^2 . Electronic absorption spectral measurements were recorded in solution using JASCO V-550 UV-Vis spectrophotometer. Nuclear magnetic resonance spectroscopic measurements were made on a Perkin-Elmer 300 MHz spectrometer. Deuterated organic

solvents along with tetramethylsilane (TMS) as the internal standard were used. For in vitro antimicrobial assay, nutrient liquid medium, a Mueller–Hinton broth was purchased from Liofilchem (Italy), while a Sabouraud dextrose broth was from Torlak (Belgrade, Serbia). Antibiotics, tetracycline and amphotericin B were obtained from Sigma Chemicals Co. (St. Louis, MO, USA).

Preparation of the ligand

E-4-(((1H-indol-3-yl)methylene)amino)-N-(pyridine-2-yl)benzenesulfonamide was prepared by the condensation of Indole-3-carbaldehyde with sulphapyridine in equimolar ratio in ethanol. The contents were refluxed for 10 hrs and the solid which separated out was filtered off recrystallized in ethanol and dried in vacuo. A pale orange coloured solid mass separated out on cooling is filtered, washed and dried over anhydrous $CaCl_2$ in a desiccator. The purity of the ligand was checked by melting point, TLC and spectral data. The ligand is insoluble in some common organic solvents viz. acetone, benzene and soluble in polar solvents viz. DMF, DMSO. The physical properties and microanalysis of this E-4-(((1H-indol-3-yl)methylene)amino)-N-(pyridine-2-yl)benzenesulfonamide are recorded in Table 1.

Synthesis of metal complexes

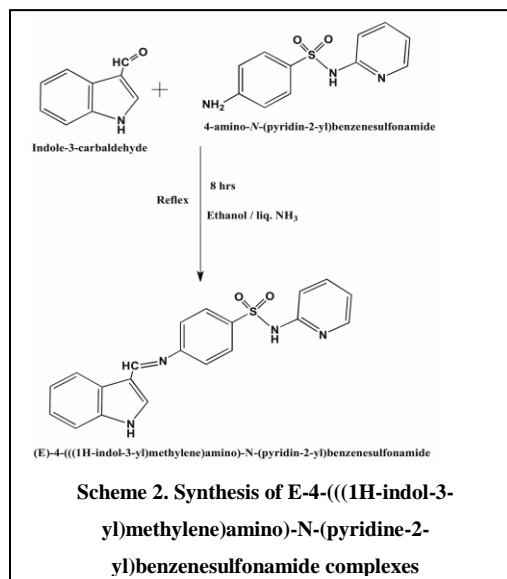
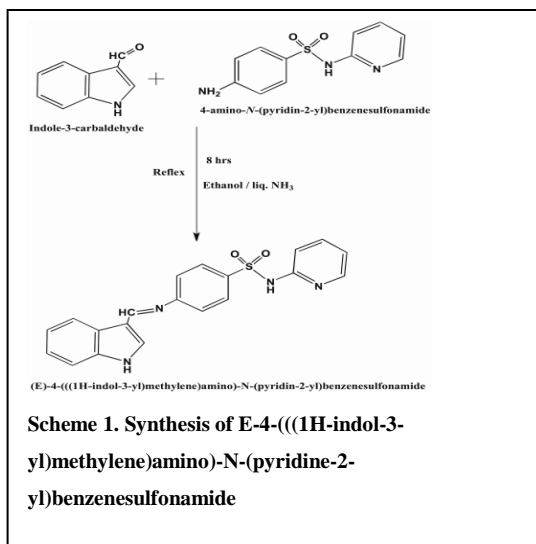
Equimolar and bimolar synthesis of the metal acetate with the E-4-(((1H-indol-3-yl)methylene)amino)-N-(pyridine-2-yl)benzenesulfonamide was carried out in ethanol. The mixture was refluxed for 10 hrs and then cooled to room temperature. The solvent was removed, residue dried and

finally the complexes recrystallized in ethanol. The important properties and physical data of the complexes are recorded in Table 1.

The resulting mixture was then refluxed in a water bath for 6 hours. The complexes obtained in each case were cooled, filtered and washed with ethanol several times to remove any excess of the ligand. Finally the complexes were washed with anhydrous diethylether and dried in a desiccator. All the complexes are stable, non-hygroscopic and coloured solids. The results of the elemental analysis (Table 1) of the Schiff base and their complexes are in good agreement with those calculated for the suggested formula and agree with a 1:2 metal to ligand stoichiometry for all the complexes.

3. Results and Discussion

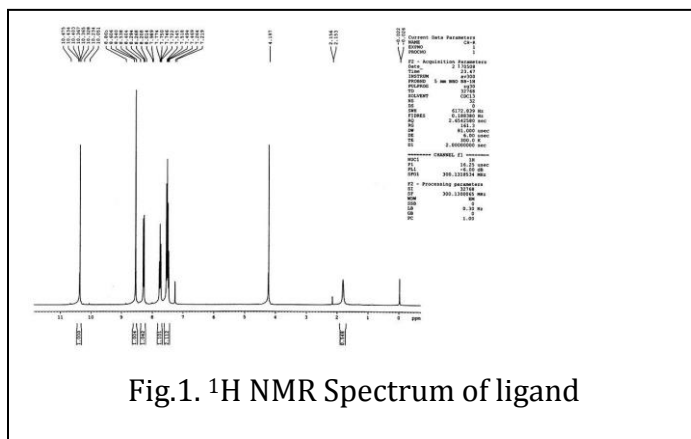
The results of the elemental analysis of the compounds listed in (Table 1) reveals the formation of 1:2 metal – ligand complexes of the type ML_2 . All the complexes are coloured, non-hygroscopic, amorphous, air and photo sensitive powders. Most of the complexes are insoluble in common organic solvents but are soluble in coordinating solvent like DMSO and acetonitrile. The probable reaction pathways are given in Scheme-1 and 2.



¹H & ¹³C NMR Spectra

The ¹H NMR Spectra of Schiff base and its complexes were recorded in DMSO (d₆). The azomethine proton (-CH=N-) in Schiff base appeared at $\delta = 8.9$ ppm has been shifted to downfield in metal complexes. This confirms the coordination by azomethine nitrogen. The aromatic protons in Schiff base appeared in the range at δ 6.55 to 7.86 ppm and metal complexes in the range δ 6.39 to 8.61 ppm. The proton of the -NH group of the ligand gives a signal at δ 10.20 ppm.

The conclusions drawn from the UV, IR, and ¹H NMR spectra are concurrent with the ¹³C NMR spectral data regarding the confirmation of the proposed structure. The signals due to the carbon atoms attached to



the thionic and azomethine groups in the ligand appear at 176.20 ppm and 164.25 ppm, respectively.

IR spectra

The IR spectra of the ligand displays two sharp bands around $3450 - 3300 \text{ cm}^{-1}$ and $3550 - 3400 \text{ cm}^{-1}$, assignable to ν_{sym} and ν_{asym} vibrations of the NH_2 group respectively (Fig.3). Furthermore, strong bands at 3250 cm^{-1} due to $\nu(\text{NH})$ vibrations are observed. These bands disappear in the complex. A sharp and strong band at 1625 cm^{-1} is due to the azomethine group of the ligand. In the IR spectrum of the complex

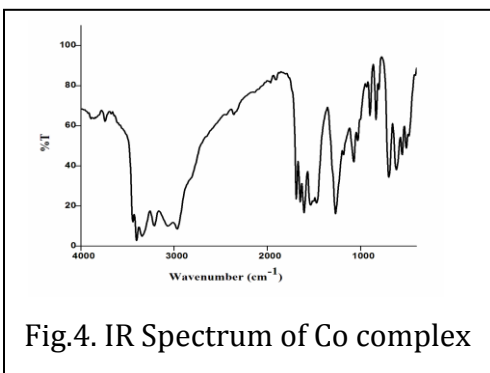


Fig.4. IR Spectrum of Co complex

this showed a lower shift of the order 20 cm^{-1} indicating the coordination of the azomethine nitrogen to the metal atom (Fig.4). One strong band located at 1050 cm^{-1} in the ligand was attributed to $\nu_{\text{C}=\text{S}}$ moiety, which disappears in the case of complexes. This contention is further confirmed by the presence of $\nu_{\text{M-N}}$ and $\nu_{\text{M-Cl}}$ bands at $(510-565)$ and $(438-448) \text{ cm}^{-1}$ in the far IR frequency region of the complexes.

These data on comparison with the spectrum

of the ligand suggested that the azomethine nitrogen and amino nitrogen atom of the ligand are involved in coordination with the metal ion.

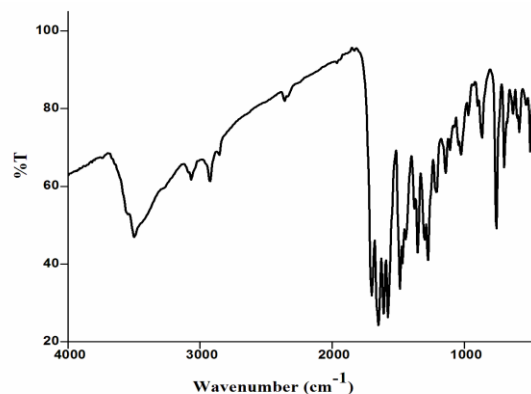


Fig.3. IR Spectrum of ligand

UV spectra

The electronic spectra of the sulphonamide imine and its 2: 1 metal complexes have been recorded. The spectrum of the ligand shows a broad band at 372nm which can be assigned to the $n-\pi^*$ transitions of the azomethine group (Fig.5). This band shows a blue shift in the metal complexes appearing at 351, 353, 356, and 361 nm, due to the polarization within the $>\text{C}=\text{N}$ chromophore caused by the formation of covalent metal-nitrogen bond. The K band $\pi-\pi^*$ showed a red shift due to the overlap of the central metal d-orbital with the p-orbital of the donor atom which causes an increase in conjugation and the B-bands undergo a hypsochromic shift in the complexes.

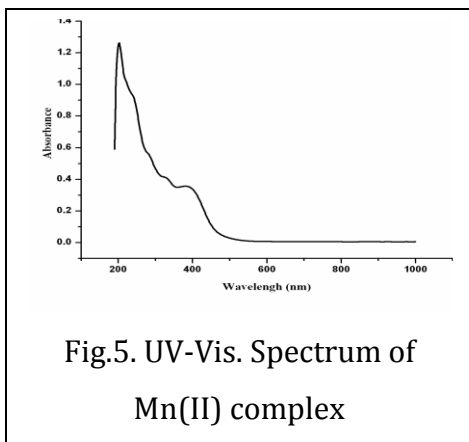


Fig.5. UV-Vis. Spectrum of Mn(II) complex

FAB-Mass Spectral studies of Schiff bases

The FAB mass spectra of E-4-(((1H-indol-3-yl)methylene)amino)-N-(pyridine-2-yl)benzenesulfonamide have been depicted in (Fig.6). The spectrum of the ligand showed a molecular ion peak at $m/z = 389$ which is equivalent to its molecular weight. In addition, the fragment peaks at $m/z = 83.9$, 155 and 110 are due to the cleavage of C_3H_2NS , $C_6H_5NO_2S$ and C_5H_4NS respectively. In case of ligand showed the molecular ion peak at $m/z = 389$ ascribed to $C_{19}H_{15}N_3O_2S_2$. The peaks at 248 and 63 are assigned to the cleavage of C_6H_6 and SO_2 respectively. All these fragmentation patterns are well observed in the FAB mass spectra.

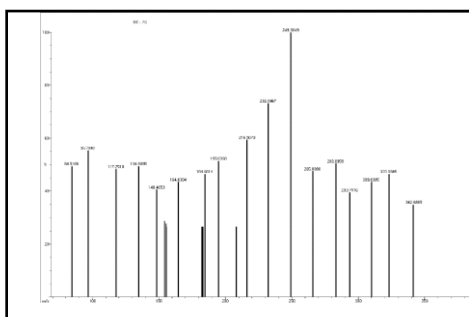


Fig. 6. Mass spectrum of ligand E-4-(((1H-indol-3-yl)methylene)amino)-N-(pyridine-2-yl)benzenesulfonamide

Electrochemical Studies

The electrochemical behavior of mononuclear Copper(II) Schiff base complexes were investigated by cyclic voltammetry techniques. Glossy carbon was used as the working electrode and potentials are reported versus Ag/AgCl reference electrode.

A cyclic voltammogram of Cu(II) complex (Fig. 7) displays a reduction peak at $E_{pc} = 821$ mV, with a corresponding oxidation peak at $E_{pa} = 608$ mV. The peak separation of this couple ΔE_p is 213 mV at 100 mVs^{-1} and increases with scan rate. The difference between forward and backward peak potential provide a rough evaluation of the degree of reversibility of electron transfer. The ratio of cathodic to anodic peak height was less than one (0.76). The separation in peak potentials increases at higher scan rates consistent with quasi reversibility of Cu (I)/ Cu (II) couple.

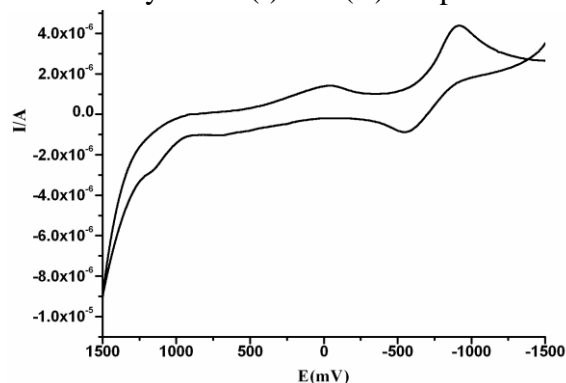
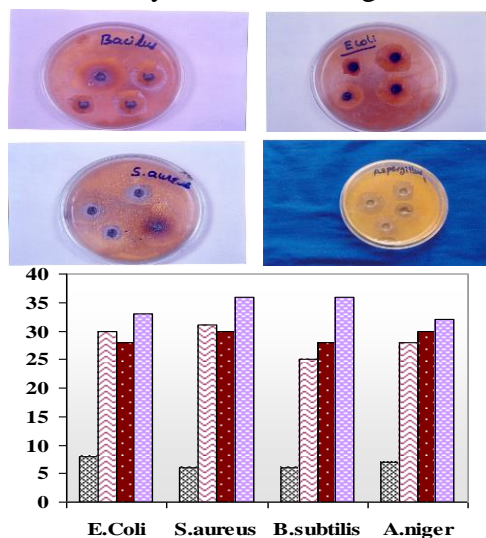


Fig.7. Cyclic Voltammogram of Cu complex

Biological activity

Antibacterial activity of the ligand and its complexes have been carried out against the Gram positive bacteria like *S.aureus*, *B.subtilis* and Gram negative bacteria such as *E.coli*, using Mueller-Hinton agar by

well-diffusion method using DMSO as solvent an Ampicillin standard. Antifungal activity of the ligand and its complexes have been carried out using the fungus such as A.Niger by well-diffusion technique, using DMSO as solvent potato dextrose agar medium are Amphotericin standard. The zones of inhibition values (fig.8) incubation period of 24 h at 35°C, the metal complexes have a higher activity than that of the free ligand and the standard. The increased activity of the metal chelates can be explained on the basis of Overtone's concept of cell permeability. Lipo solubility is an important factor which controls the antimicrobial activity. On chelation, the polarity of the ligand orbital and partial sharing of positive charge of metal ion with donor groups increases the delocalization of π -electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity enhances the penetration of the complexes into lipid membrane and blocks the metal binding sites on enzymes of microorganisms.



8. Antifungal activity of the ligand and its complexes

Conclusion

A Schiff base and its complexes derived from sulfonamide were successfully synthesized by the condensation reaction of the antibiotic with sulfapyridine and indol-3-carbaldedhyde and their structures were characterized by elemental and conductometric measurements, NMR and FTIR spectra. The coordination of the ligands with Co (II), Mn (II), and Cu (II), ions showed bidentate behavior with M: L mole ratio of 2:1. All complexes were of octahedral geometries. The biological activity of the prepared compounds was controlled by type of bacteria, functional groups of ligands and type of metal ion. The values of zone of inhibition were found out at 37 °C for a period of 24 h. It has been found that all the complexes have higher activity than the free ligand and the standard.

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