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SYNTHESIS OF COBALT(II), NICKEL(II), COPPER(II) AND ZINC(II) COMPLEXES OF(1-(3-FURAN-2-YL)-3-OXO-1-PHENYLPROPYL)SEMICARBAZIDE AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

The present study deals with the structure and antimicrobial properties of some complexes of Co(II), Ni(II), Cu(II), Zn(II) with a new Mannich base (1-(3-furan-2-yl)-3-oxo-1-phenyl propyl) semicarbazide (FBSC). The ligand and the complexes have been characterized by various physico-chemical techniques such as elemental analysis, molar conductance, magnetic susceptibility measurements, infrared and electronic spectra. Based on these data, we propose tetrahedral geometry for Co(II) and Zn(II), square planar geometry for Ni(II) and octahedral geometry for Cu(II) complexes. Antibacterial activities of the ligand and its complexes were tested against some selected bacteria.

Key words: Mannich base, Semicarbazide, Spectral Studies, Geometry, Antibacterial Activity.

INTRODUCTION

Mannich base complexes have remained an important and popular area of research due to their simple synthesis, adaptability, and diverse range of application. From the survey of existing literature, it appears that metal complexes of Mannich base play a vital role in the development of coordination chemistry [1-5]. To our knowledge, Mannich reaction is a three- component condensation reaction consisting of active hydrogen containing compound, aldehyde and secondary amine. Much work has been done so far on isolation of solid complexes of different aromatic aldehydes or ketones and semicarbazones with transition metals [6-8]. A search through the literature reveals that no work has been done on the condensation of 2-Furyl methyl ketone, benzaldehyde and semicarbazide. It is interesting to note that NH- amides also behave as an amine reactant and several reports are available to support this reference [9]. Literature survey reveals that 2-Furyl methyl ketone

derivatives and amide moieties have widely been used for various biological activities [10-12]. It is well known from the literature that in the semicarbazide ligand system, dicoordination takes place via the N and O of semicarbazide. The proposed structure of the synthesized Mannich base is given in Figure 1.

MATERIALS AND METHODS

Experimental

All the reagents used for the preparation of the ligand and complexes were Merck products. Spectroscopic grade solvents were used for the spectral and cyclic voltammetric measurements. The carbon, hydrogen and nitrogen contents in each sample were done at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow. The ¹HNMR and ¹³CNMR spectra of the samples were measured in Bruker 300 MHz Instrument using DMSO as solvent. Mass spectra

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were recorded on a JEOL-8X102. The IR spectra were recorded with KBr pellets using FT-IR Shimadzu Instrument. Molar conductivity was measured using 10^{-3} M solution of complexes in DMSO on Systronic Conductivity Bridge. UV-Visible spectra of the complexes were recorded on Perkin Elmer Lambda EZ201 spectrometer in DMSO solutions. Electrochemical measurements were carried out with electrochemical analyzer mode BAS-27 voltammogram. Magnetic susceptibility was measured with Gouy balance. Nutrient agar was used for testing the susceptibility of microorganisms to antimicrobial agents using the *Disc-diffusion* technique. *Ciprofloxacin* was used as standard for antibacterial activity and *Nystatin* for antifungal activity.

Synthesis of Mannich base

Semicarbazide 2.78 mL (0.025mol) was dissolved in water. To this solution 2-Furylmethylketone 2.75 mL (0.025mol) was added drop wise with constant stirring. After 10 minutes, benzaldehyde 2.65 mL (0.025 mol) was added in drops and the reaction mixture was kept in an ice bath that was placed over a magnetic stirrer and stirred for half an hour. Compound formed was filtered and then recrystallised from ethanol. Purity of the compound was checked by TLC and the melting point of the compound was determined in an open capillary tube and was uncorrected. Yield: 65%, M.P: 222 °C.

General synthesis of metal complexes

The Mannich base (dissolved in CHCl_3) and the metal chlorides, MCl_2 [where $\text{M}=\text{Cu(II)}$, Ni(II) , Co(II) , Zn(II)] dissolved in methanol were mixed in 1:1 molar ratio. The reaction mixture was stirred under ice bath maintained at $5\text{--}10^\circ\text{C}$ for 1 hour. The bluish green colored precipitate obtained was filtered and then dried in vacuum. The proposed structure of the complexes is given in Figure 2.

INVITRO ANTIBACTERIAL AND ANTIFUNGAL ASSAY

The biological activities of synthesized Mannich base and its Co(II) , Ni(II) , Cu(II) and Zn(II) complexes have been studied for their antibacterial and antifungal activities by *Disc diffusion* test using Nutrient agar (NA) and Sabouraud Dextrose Agar (SDA). The antibacterial and antifungal activities were done at $10\mu\text{g/mL}$ concentrations in DMSO solvent using bacteria (*S.aureus*, *B.substillis*, *E.coli* and *P.aeruginosa*) and fungi (*C.albicans*, *A.niger*) at the minimum inhibitory concentration (MIC) method. These bacterial strains were incubated for 24h at 37°C and fungi strains were incubated for 48h at 37°C . Standard antibacterial (*ciprofloxacin*) and antifungal drug (*Nystatin*) were used for comparison under similar conditions. Activity was determined by measuring the diameter of the zone showing complete inhibition (mm).

RESULTS AND DISCUSSION

The elemental analyses show 1:1 (metal: ligand) stoichiometry for all the complexes. The analytical data of ligand and the complexes are given in Table 1. They correspond well with the general formula ML where $\text{M}=\text{Cu(II)}$, Ni(II) , Co(II) , and Zn(II) ; $\text{L}=(\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3)$. The presence of chlorides is evident from Volhard's test. The low conductance of the chelates supports the non-electrolytic nature of the metal complexes.

IR SPECTRA

In order to study the binding mode of the Mannich base to the metal ion in the complexes, the IR spectrum of the free ligand (Mannich base) was compared with the spectra of the complexes. It is observed that the band appearing at 1689cm^{-1} due to $\nu_{(\text{C}=\text{O})}$ in the ligand spectrum is shifted to a lower side by $30\text{--}40\text{cm}^{-1}$ in the spectra of the complexes indicating the involvement of carbonyl oxygen in coordination. The IR spectra of free ligands exist in $\nu_{(\text{N-H})}$ absorption band at 3291cm^{-1} , $\nu_{(\text{C}=\text{N})}$ band and at 1644cm^{-1} , indicating that the ligand probably exist in equilibrium with tautomeric enol form. By the loss of proton the enolic form may act as a slightly charged ligand. The bands appearing in the spectra of the ligands $1689, 1644, 105\text{cm}^{-1}$ are attributed [13] to $\nu_{(\text{C}=\text{O})}$, $\nu_{(\text{C}=\text{N})}$ and $\nu_{(\text{N-N})}$ modes respectively. The two strong bands observed at 692 and 759 are assigned to furan ring deformation modes. In the case of $[\text{M(L)Cl}_2]$ complexes [where $\text{M}=\text{Ni(II)}$, $\text{L}=\text{FBSC}$] the amide band shifts to lower frequency in the spectra of these complexes. The $\nu_{(\text{C}=\text{N})}$ shifts to lower frequency ($\Delta=10\text{cm}^{-1}$) and $\nu_{(\text{N-N})}$ to higher ($\Delta=20\text{cm}^{-1}$) frequencies. The non-ligand bands [14] occurring at 656 and 494 are assigned to $\nu_{(\text{M-O})}$ and $\nu_{(\text{M-N})}$ modes respectively. The presence of coordinated water molecules in Cu(II) complex is determined by the appearance of bands at $3200\text{--}3600$ and a peak at 926cm^{-1} assignable to the $-\text{OH}$ stretching and rocking of water molecules.

MANGNETIC MOMENT AND UV-VISIBLE SPECTRA

Electronic spectra and magnetic measurements were recorded in order to obtain information about the geometry of the complexes. The μ_{eff} (1.6BM) value of the Cu(II) represents an octahedral geometry of the ligand around the central metal ion. The four coordinated Co(II) complexes shows μ_{eff} value of 3.9BM which indicates the presence of three unpaired electrons, supporting tetrahedral geometry. The observed zero magnetic moment value confirms the square planar environment for the Ni(II) . The Zn(II) complexes are found to be diamagnetic as expected for d^{10} configuration.

The electronic spectra of the ligand and its complexes were recorded in DMSO solution. The Cu(II) ion with d^9 coordination in a complex can be either octahedral or tetrahedral or rarely square planar. The octahedral coordinated Cu(II) ion has the ground state ${}^2\text{E}_g$ ($t_{2g}^6 e_g^3$). The only excited state should then be ${}^2\text{T}_{2g}$ (t_{2g}^5).

(e_g)⁴, the energy difference being 10Dq. The Cu(II) complex under the present study exhibits a broad band in the region 13790cm⁻¹. The broadness of the band may be due to John-Teller distortion [15,16]. These observations indicate that the complexes have distorted octahedral structure. Co(II) complex displays a band at 15834cm⁻¹ which is assigned to ⁴A₂→⁴T₁ for tetrahedral geometry [17]. The Ni(II) complex is diamagnetic suggesting a square planar geometry [18]. It shows a broad band at 16611cm⁻¹ which is assigned to ¹A_{1g}→¹B_{1g}. No transition was observed in the visible region for the Zn(II) complex consistent with the d¹⁰ configuration of the Zn²⁺ ion. This complex is also found to be diamagnetic as expected for the d¹⁰ configuration.

ESR, ¹H-NMR and ¹³C-NMR SPECTRA

The EPR spectrum of the Cu(II) complex shows $g_{\parallel} > g > 2.0023$ and a g value within the range of 2.08-4.49 which are consistent with the d_{x²-y²} ground state in an octahedral geometry.

Evidence for the bonding mode of ligand is also provided by the ¹H-NMR spectra of the Mannich base and the diamagnetic Zn(II) complex, which were recorded in CDCl₃. The ¹HNMR spectrum of the ligand shows the following resonance signals: Signals due to aromatic protons appear at 7.57-7.66 δ. The N-H proton chemical shift occurs at 7.3 δ which gives rise to weak doublet. The ¹HNMR spectrum of Zinc(II)chloro complexes of FBSC

has been recorded in DMSO-d₆ and compared with the free ligand. Upon coordination the downfield shifting of the amide N-H proton signal in the complex has been observed which may be due to the deshielding of N-H proton adjacent to C=O group. This further confirms the participation of C=O group in coordination. The signals due to the protons of furan ring and free-NH₂ of the ligand remain unchanged in the complex indicating the non-involvement of oxygen and nitrogen atom in coordination.

The [13] C-NMR spectrum of the ligand shown signal at 173 ppm is for 2-furyl methyl ketone, 134 ppm for aromatic CH-carbon and 150 ppm for amide C=O carbon respectively.

CYCLIC VOLTAMMETRY

The CV is the most versatile electroanalytical technique for the study of electroactive species. The redox properties of copper(II) complex have been studied by cyclic voltammetry experiments using glass carbon working electrode in DMSO solvent at scan rate 100 mVs⁻¹. The Cyclic voltammogram of the copper complex in DMSO solution recorded over a potential range -0.4V to -1.1V shows two quasi-reversible peaks, one at cathodic direction and another at anodic direction. The quasi-reversible reduction peak at -0.92V due to the formation of Cu(II)/Cu(I) while the other quasi-reversible oxidation peak at -0.56V is due to formation of Cu(I)/Cu(II).

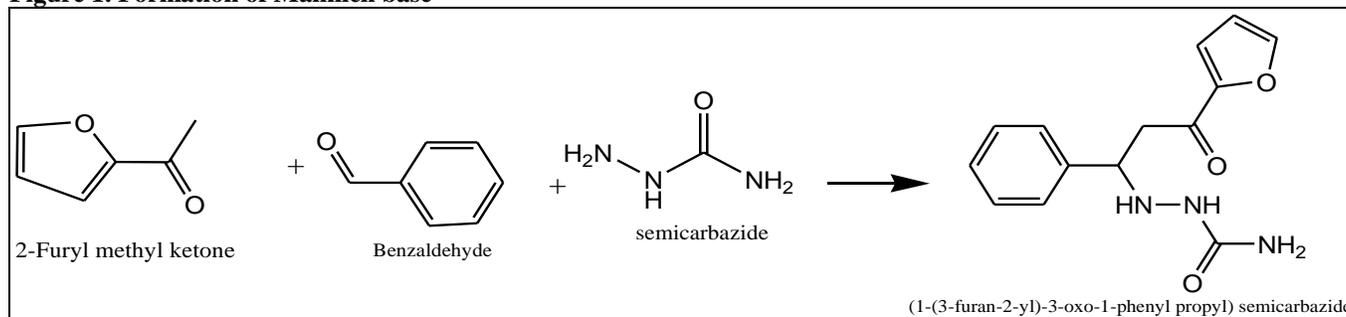
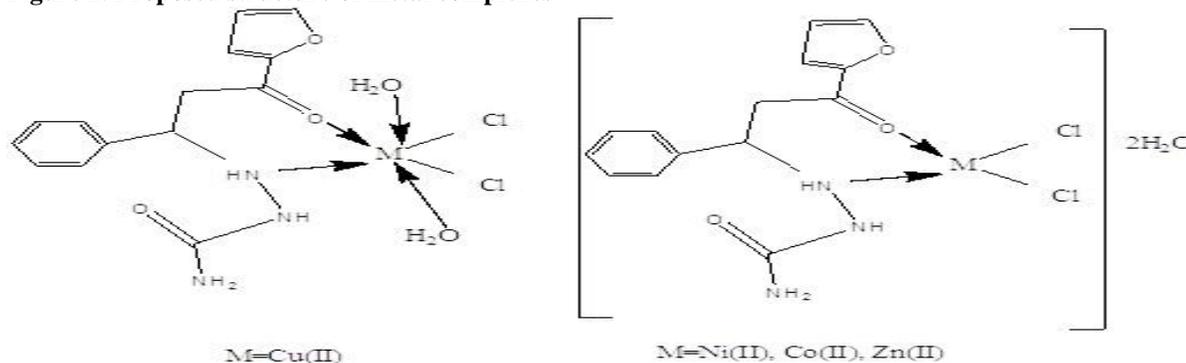
Table 1. Physical characterization, Analytical, Molar conductance, Magnetic susceptibility data

| Compound | Colour | Found/Calculated | | | | | M.Wt | Yield % | Λ-m Mho cm ² mol ⁻¹ | μ-eff B.M |
|---|-----------------|------------------|------------------|----------------|------------------|------------------|------|---------|---|-----------|
| | | M% | C% | H% | N% | Cl% | | | | |
| FBSC C ₁₄ H ₁₅ N ₃ O ₃ | Colourless | - | 61.53 (61.54) | 5.53 (5.49) | 15.38 (15.39) | - | 273 | 63 | - | - |
| Cu(II) Complex | Bluish green | 14.03 (14.05) | 36.97 (36.98) | 4.23 (4.26) | 11.35 (11.37) | 15.59 (15.61) | 449 | 55 | 4 | 1.6 |
| Co(II) Complex | Pink | 14.47 (14.49) | 40.58 (40.56) | 3.66 (3.69) | 12.46 (12.42) | 17.19 (17.17) | 410 | 60 | 1.8 | 3.9 |
| Ni(II) Complex | Green | 14.42 (14.41) | 40.52 (40.50) | 3.58 (3.52) | 12.41 (12.39) | 17.12 (17.10) | 409 | 58 | 2.7 | - |
| Zn(II) Complex | Colourless | 15.66 (15.69) | 40.02 (40.08) | 3.61 (3.68) | 12.28 (12.30) | 16.86 (16.82) | 415 | 59 | 1.6 | - |

Table 2. Antimicrobial Activities of Metal Complexes of FBSC

| Compound | <i>Bacillus subtilis</i> | <i>Staphylococcus aureus</i> | <i>Escherichia Coli</i> | <i>Pseudomonas aeruginosa</i> | <i>Candida albicans</i> | <i>Aspergillus niger</i> |
|----------------|--------------------------|------------------------------|-------------------------|-------------------------------|-------------------------|--------------------------|
| FBSC | 20 | 20 | 17 | 18 | 11 | 14 |
| Cu(II) complex | 18 | 20 | 16 | 16 | 12 | 13 |
| Co(II) complex | 18 | 22 | 16 | 17 | 12 | 12 |
| Ni(II) complex | 18 | 20 | 18 | 17 | 12 | 15 |
| Zn(II) complex | 20 | 21 | 22 | 18 | 11 | 17 |
| Standard | 30* | 23* | 31* | 30* | 33** | 32** |
| Solvent(DMSO) | NI | NI | NI | NI | NI | NI |

NI=No Inhibition *Ciprofloxacin**Nystatin

Figure 1. Formation of Mannich base**Figure 2. Proposed structure of metal complexes****IN VITRO ANTIBACTERIAL ASSAY**

For in vitro antimicrobial activity, the synthesized compounds were tested against the bacteria *Bacillus Subtillis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* and fungi *Candida albicans* and *Aspergillus niger* [19,20]. The minimum inhibitory concentration (MIC) values of the investigated compounds with the standard drugs are presented in Table 2.

CONCLUSION

Antimicrobial activity of metal chelates can be explained on the basis of coordination theory [21]. On

chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π electrons over the whole chelate ring and enhances the presentation of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganism. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism.

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