

MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF ISONIAZID Mn(II) AND Ni(II) COMPLEXES

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Abstract: In this work, metal complexes of the type, $[M(\text{INH})_2(\text{H}_2\text{O})_2](\text{NO}_3)_2$, where M = Mn(II), Ni(II) and INH = isoniazid, have been synthesized and characterized by melting point, conductometric measurements, TGA, UV-Vis, IR studies. Both the complexes adopt octahedral geometry around the metal ion. The molar conductance of one milli-molar solution of the complexes measured in DMF indicates that the metal complexes are 1:2 electrolyte. The thermal analysis suggests that the complexes contain water molecules because metal oxide is left as residue.

Keywords: Isoniazid, TGA, DSC

Introduction

The complex formation has played a vital role in the field of medicinal and biological sciences.[1] The literature survey reveals that over the last decade there has been tremendous attention towards studies on metal complex formation using drugs as ligands [2-4]. The goal of this work is to know the proper mechanism of action of drugs and lower side effects. The stability constants of metal complexes with drugs are useful to know the proper dose of drug and their effect with all other components of blood stream as well as to measure the strength of metal ligand bonds. The studies of complex equilibria of metal ion with drugs are useful in elucidating the mechanism of action of drugs. The role of transition metal ions and their complexes are involved in metabolism, transportation and catalytic processes in the systems.[5] Organic synthesis, especially diversity-oriented synthesis may likely to play a vital role in drug discovery in the future. However, the manufacture of fine chemicals and pharmaceuticals through traditional processing generates a lot of waste, the bulk of which consists of by-products and inorganic salts. Hence, for cleaner productions, waste minimization is essential which can be achieved by newer techniques. Microwave assisted organic synthesis offers a cleaner and greener route, since higher yields are obtained in few minutes leading to minimization of wastes. In recent years, there has been considerable interest in the chemistry of hydrazine compounds because of their potential pharmacological applications[6] and biological activities[7]. Hydrazine derivatives have been used in many drug formulations, as they possess antitubercular antihypertensive and antidepressant properties. In this work, a heteroaroyl derivative of hydrazine, i.e. pyridine-4-carbonylhydrazine, commonly called isonicotinic acid hydrazide or isoniazid(INH) will be used. Isoniazid is a remarkably effective drug and is now considered one of the primary drug for the chemotherapy of tuberculosis[8]. Therefore, the interest in coordination chemistry of novel ligand containing isoniazid moiety is primarily because its binding with the metal ion offers many binding sites and structural novelties and metal ion incorporation into the drug-based compound may increase its potency.

This work is mostly concerned with the design and synthesis of metal complexes of isoniazid. The work is inherently multidisciplinary and will involve exposure to both advanced organic and inorganic synthetic techniques.

The mode of bonding of the central metal ion to the ligand will be explored by IR, UV/Vis, TGA and conductivity measurements.

Experimental

Isoniazid (INH) (Fluka) and metal nitrates (BDH) were used as received. The IR spectra ($4000-600\text{ cm}^{-1}$) were recorded on a RXI FT-IR spectrometer as KBr discs. The conductivity measurements were carried out with a CM-82T Elico conductivity bridge in DMF. The electronic spectra were recorded on a Cintra 5GBC spectrophotometer. The TGA and DSC were performed using a SDT Q600 thermogravimetric analyzer. The experiments were done in nitrogen atmospheres using calcinated Al_2O_3 as reference material. The weight of the sample taken was 8 mg and the heating rate was kept at 5°C min^{-1} .

Synthesis of Mn(II) complex

A mixture of isoniazid, (4-pyridine-4-carbohydrazide), (2.74 g, 0.02 mole) and Mn(II) nitrate (1.79 g, 0.01 mole) will be taken in Erlenmayer flask and mixed thoroughly in 100 mL methanol solvent. The mixture will be irradiated under microwave for few minutes at 500 W power with intermittent radiation of few sec interval. The crude light brown product formed after 2-3 hours were collected by filtration. The product was washed several times with methanol and dried over anhydrous calcium chloride in a desiccator. Yield 2.87 g (61%).

Synthesis of Ni(II) complex

A mixture of isoniazid, (4-pyridine-4-carbohydrazide), (2.74 g, 0.02 mole) and cobalt (II) nitrate (1.83 g, 0.01 mole) will be taken in Erlenmayer flask and mixed thoroughly in 100 mL methanol solvent. The mixture will be irradiated under microwave for few minutes at 500 W power with intermittent radiation of few sec interval. The crude green product formed after 2-3 hours were collected by filtration. The product was washed several times with methanol and dried over anhydrous calcium chloride in a desiccator. Yield 3.28 g (69%).

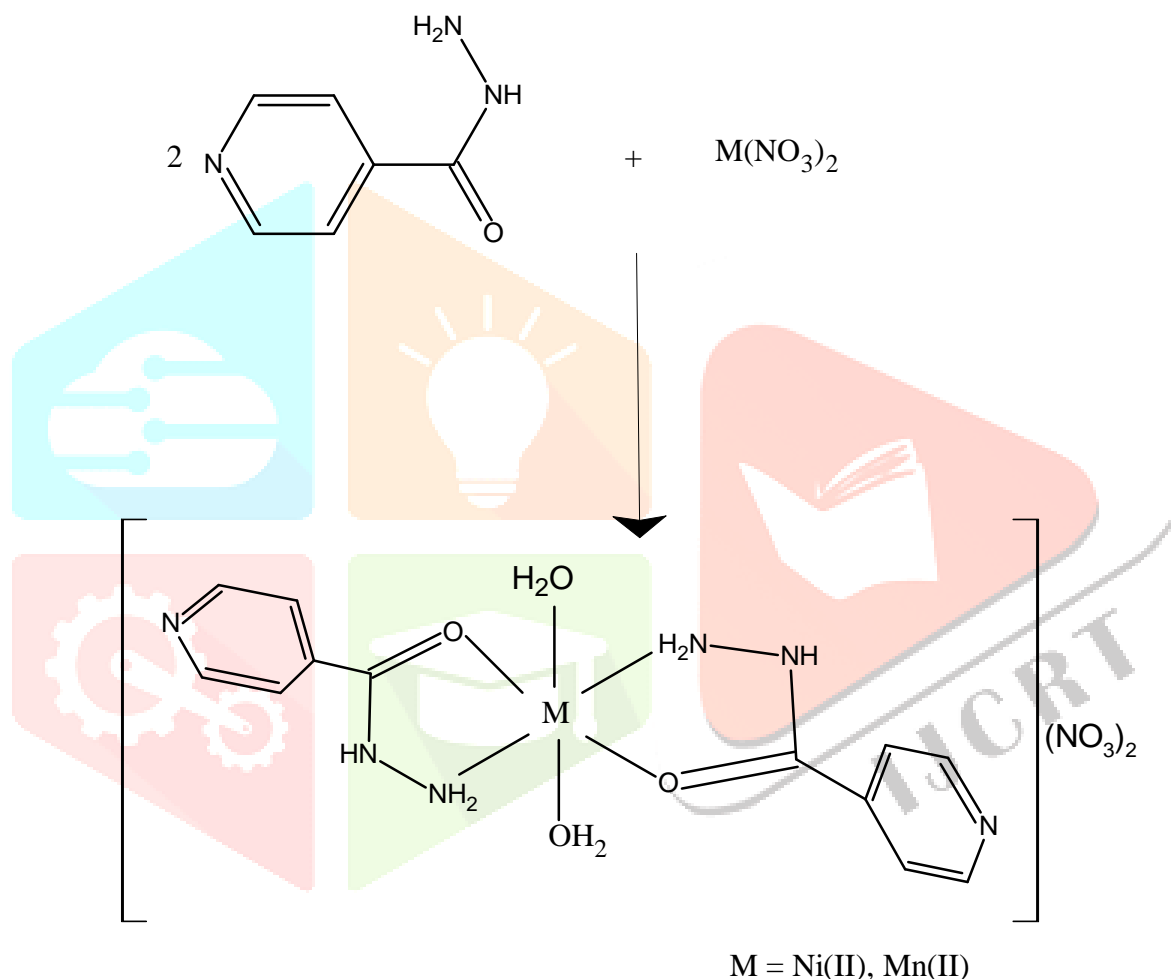


Fig.1 Synthesis of $[M(INH)_2(H_2O)_2](NO_3)_2$

Table 1. Analytical data, melting points, and colours of complexes

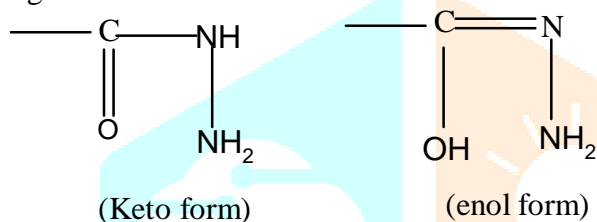
Compounds (formula weight)	Colour	M.P. (°C)	Yield (%)	Molar conductance ($\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$) DMF
Isoniazid(INH)	White	171	-	28
$[Mn(INH)_2(H_2O)_2](NO_3)_2$	Light brown	335	61	112
$[Ni(INH)_2(H_2O)_2](NO_3)_2$	Green	220	69	120

RESULTS AND DISCUSSION

Mn(II) and Ni(II) complexes are highly soluble in DMF and DMSO. The molar conductance measured in DMF indicated that the metal complexes are 1:2 electrolyte.[8] (Table 1) Further, the conductivity was measured in the same solution after 24 hours and no major changes were observed showing the stability of the complexes in DMF. The melting points of both the synthesized complexes are found to be higher than their parent ligand (INH) suggesting the formation of complexes.

FT-IR Spectra

According to bibliographic reports [9], the isoniazid spectrum presents two bands at 3312 and 3118 cm^{-1} corresponding to asymmetric and symmetric stretching of NH_2 group. It is shifted to lower wave number by about 100 cm^{-1} after coordination of the metal ions with NH_2 group of isoniazid. (Figure 2) However, the band assigned as $\nu(\text{N-H})$ appearing at 3114 cm^{-1} in isoniazid doesn't shift in the complex showing that this group does not participate in the coordination. On the other hand, isoniazid spectrum shows one band at 1670 cm^{-1} assigned as $\nu(\text{C=O})$. In the Mn(II) and Ni(II) complexes this band shifted to 1652 cm^{-1} and 1660 cm^{-1} respectively showing the metal coordination through this group. This behaviour permits to propose that isoniazid acts as a bidentate ligand coordinating through the $-\text{NH}_2$ and the C=O group. Besides the broad band at 3378 cm^{-1} and 3402 cm^{-1} in Mn(II) and Ni(II) complexes respectively confirm the presence of water molecules in the complex. Further a shift to lower value in the $\nu(\text{C-N})$ band observed at 1490 cm^{-1} in the INH spectrum by about 80 cm^{-1} in the spectra of its complexes indicates the preference of the keto form to the enol form of the ligand for coordination.



The band at 1570-1530 cm^{-1} and 1080-1010 cm^{-1} are assigned to $\nu(\text{C=C})$ and $\nu(\text{C=N})$ of pyridine ring respectively. Upon coordination, these bands remain unchanged. This reveals that the non-involvement of pyridine nitrogen in complex formation. Since only one absorption band at 1387 cm^{-1} and 1402 cm^{-1} for Mn(II) and Ni(II) complex respectively has been observed, it is suggested that the nitrate group is not bonded to the metal.

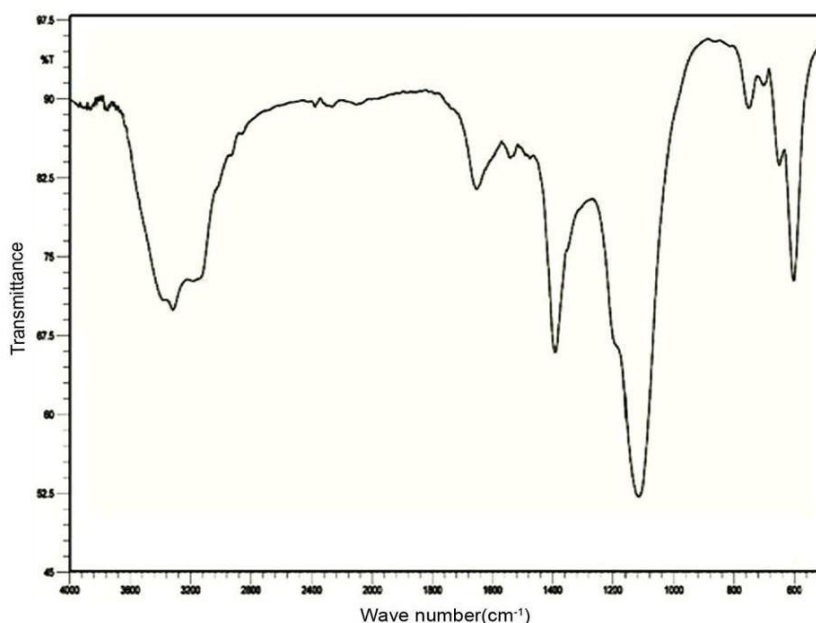


Fig.2 IR spectrum of $[\text{Mn}(\text{INH})_2(\text{H}_2\text{O})_2](\text{NO}_3)_2$

Electronic Spectra

The electronic spectral bands have been recorded in DMF solvent. Three bands characteristic of octahedral nickel (II) ion are anticipated. In the present case the bands observed at 12431, 17614 and 25121 cm^{-1} have been assigned to ${}^3\text{T}_{2g}(\text{F}) \leftarrow {}^3\text{A}_{2g}(\text{F})$, ${}^3\text{T}_{1g}(\text{F}) \leftarrow {}^3\text{A}_{2g}(\text{F})$ and ${}^3\text{T}_{1g}(\text{P}) \leftarrow {}^3\text{A}_{2g}(\text{F})$ transitions. The electronic spectral bands suggest a distorted octahedral geometry for nickel (II) ion. The Three absorption bands have generally been observed for six coordinate Mn(II) complexes. In the present work also, three bands at 31005, 24126 and 21082 cm^{-1} corresponding to the transition ${}^4\text{T}_{1g}(\text{P}) \leftarrow {}^6\text{A}_{1g}$, ${}^4\text{E}_g(\text{G}) \leftarrow {}^6\text{A}_{1g}$ and ${}^4\text{T}_{2g}(\text{G}) \leftarrow {}^6\text{A}_{1g}$ which is consistent with an octahedral geometry for the Mn(II) ion.

TGA

Figure 3 shows the thermogravimetric curve for the Mn-INH complex, with three well defined weight losses. The first loss of about 15% occurs in the range 120-150 $^{\circ}\text{C}$ which correspond well to the removal of two coordinated water molecules. The other two mass losses occur in the ranges 250-380 $^{\circ}\text{C}$ and 550-625 $^{\circ}\text{C}$ which correspond to the decomposition of the ligand. The thermogravimetric curve shows a net weight loss of about 67%, with a final residue of 33% which is consistent with the formation of nickel oxide. Differential scanning calorimetry (DSC) analysis of the Ni-INH complex indicates the occurrence of one exothermic peak at 177.5 $^{\circ}\text{C}$ due probably to the removal of water molecules followed by three endothermic events with their maxima at 310, 575 and 348 $^{\circ}\text{C}$, which correspond likely to the melting of the complex and oxidation of the ligand leading to the formation of metal oxide.

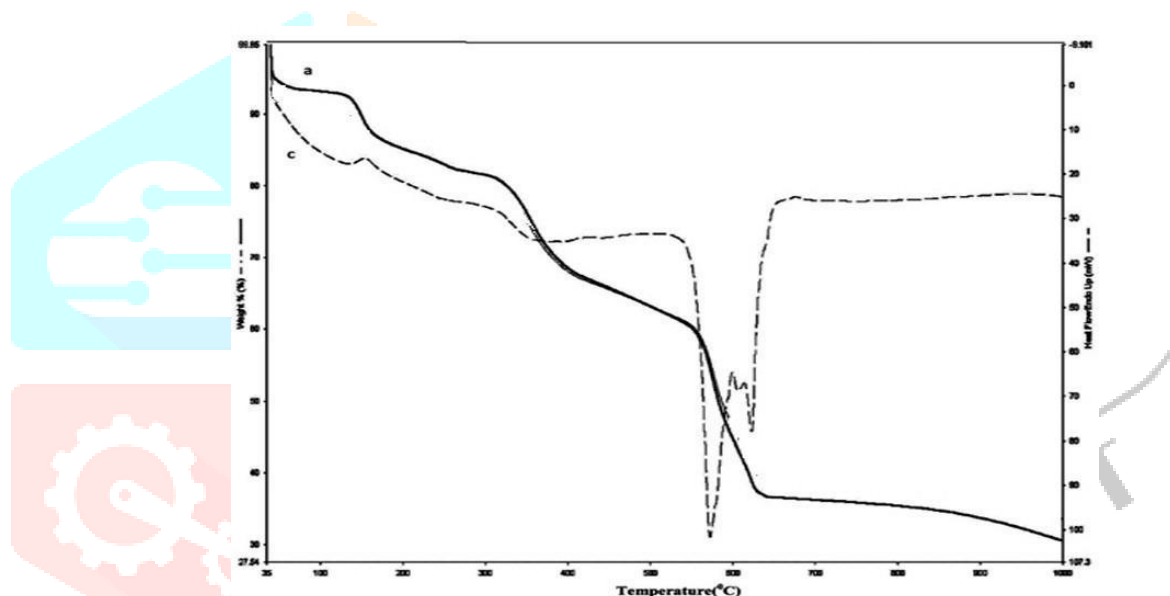


Fig.3. TGA and DSC of $\text{Ni}(\text{INH})_2(\text{H}_2\text{O})_2$

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