

Mixed Ligand Copper (II) Complex with Isoniazid and Pyrazinamide

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Abstract: The fact that the pharmacological action of certain drugs was due to the formation of chelates with essential or trace metal ions of biological significance prompted many research workers all over the world to investigate the structural features of the metal chelates of drug substances both in solid state and in solution. So it was considered interesting and useful to study the metal complexes of drugs using various physico-chemical methods.

It is proposed to study the metal binding characteristics of some selected pharmaceuticals mentioned below.

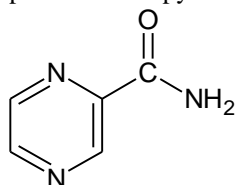
Isoniazid, a common anti-tuberculosis drug, was shown to form complexes with metal ions like, Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} .⁽¹⁾ Isoniazid was shown to form both 1:1 and 1:2 complexes with copper, binding through oxygen and amino nitrogen.⁽²⁻³⁾

Pyrazinamide, another anti-tuberculosis drug was reported to form metal complexes of the type $MX_2 \cdot 4L$ where $M = Co(II)$, $Ni(II)$, $Cu(II)$ and $X = Cl^{-}$, Br^{-} , I^{-} . Besides thermal and spectral studies of these complexes, ESR spectral study was also made for the copper complex.⁽⁴⁾ Nickel was also shown to form neutral 1:2 complex with pyrazinamide.

Keyword: Isoniazid,Pyrazinamide

I. Introduction

Pyrazinamide occurs as a white crystalline powder, practically insoluble in water, slightly soluble in acetone, alcohol and chloroform. The combination of pyrazinamide with other anti-tubercular drugs such as isoniazid is highly effective. The pKa value for pyrazinamide is 0.5.⁽⁵⁾



($C_5H_5N_3O$)

MW 123.12

Experimental procedure

Instrumentation

For thermogravimetric analysis: Stanton Redcroft STA780 Apratus was used.

For IR spectra: Nujol mull SP1200 was used

For Magnetic susceptibility Measurement: Cahn2000 magnetic balance(faraday) was used, using $Hg[Co(NCS)_4]$ as calibrent.

Material used

All metal salts used in synthesizing complexes were available commercially and their purity was 99 percent or above

Isoniazid (Wilson Laboratories, Bombay), Pyrazinamide (Wilson Laboratories, Bombay),

Common organic solvent:

Distilled water.Sodium hydroxide solution,Dimethylsolfoxide

Preparation of Mixed Ligand Copper(II) Complexes of Isoniazid and pyrazinamide:

Equimolar quantities of isoniazid and pyrazinamide (2.5 mmol) were dissolved in water (30 ml) and the pH of the solution was adjusted to 6.6 by adding dilute sodium hydroxide solution. This ligand solution was then added slowly to an aqueous solution (5 ml) of copper(II) chloride (1.25 mmol) with continuous stirring. The stirring was continued for two hours and the resultant solution was allowed to stand overnight. A reddish orange coloured precipitate formed was filtered, washed with water and then dried in a vacuum desiccator.

II. Results And Discussion

The copper(II) complex was found to be decomposing at 120°C and the measurement of conductivity on the millimolar solution in dimethylsulfoxide showed that the complex is neutral. The elemental analyses of the complex for copper, carbon, hydrogen and nitrogen yielded results which were found to be useful in deducing the molecular formula for the brownish orange coloured copper(II) compound (see Table 1).

Magnetic Susceptibility

The effective magnetic moment, μ_{eff} calculated for the copper(II) complex from the measured magnetic susceptibility at room temperature is 1.68 BM. This lesser value of magnetic moment than that of the spin-only magnetic moment for one unpaired electron system (1.73 BM) showed the nature of magnetism in the copper(II) complex as temperature and field dependent.⁽⁵⁾ This kind of magnetic behaviour is due to interaction between single unpaired electrons on the separate copper(II) ions, the magnitude of which must be comparable to that of thermal energy KT (ca. 200 cm^{-1}). The subnormal magnetic moment of 1.68 BM (at room temperature) suggests that the structure of this copper(II) complex of isoniazid and pyrazinamide could be polymeric.

Table 1: Physical and Analytical Data of the Complex, [Cu(INA) (PZA-H) (OH)]H₂O

Description	Results
Colour	Brownish Orange
Decomposition temperature (°C)	120
Elemental analysis Found (calculated) %	
Copper	17.22 (17.76)
Carbon	36.95 (36.91)
Hydrogen	3.73 (3.91)
Nitrogen	23.85 (23.49)
Magnetic moment, μ in BM	1.68
Molar conductivity, ΛM ($\text{ohm}^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$)	Neutral (in DMSO)
Electronic Spectral Analysis Diffuse Reflectance Wavelength (cm^{-1})	40,000 32,258 (Charge transfer band)

Electronic Spectral Study

The diffuse reflectance spectrum of the copper(II) complex showed two absorptions (40,000 and 32,260 cm^{-1}) in the ultraviolet region corresponding to charge transfer between the metal and the ligands. Any absorption in the visible region might have been obscured by charge transfer band.⁽⁶⁾

Infrared Spectral Study

Infrared spectra were recorded for isoniazid, pyrazinamide and the copper(II) complex as nujol mull in the region 4000–400 cm^{-1} .

IR Region 4000–3000 cm^{-1}

Vibrational absorptions at 3005, 3210, 3165 and 3105 cm^{-1} in the spectrum of isoniazid⁽⁷⁾ and at 3400 and 3180 cm^{-1} in the spectrum of pyrazinamide could be due to asymmetric and symmetric stretchings of NH and NH₂ groupings. The infrared spectrum of the copper(II) complex exhibited a strong absorption at 3445 cm^{-1} probably due to O–H stretching of water molecule along with that of N–H stretching at 3385, 3255 and 3130 cm^{-1} .^(8–10) The reduction in the number of vibrational bands corresponding to N–H stretching might be due to loss of NH protons on complex formation. The overall negative shift in energy with respect to these vibrational frequencies in the case of copper(II) complex indicates the bond formation between the metal and the ligands (isoniazid and pyrazinamide) through amide nitrogen atoms^(11–13) (see Table 2).

IR Region 2000–400 cm^{-1}

The carbonyl stretching vibrational bands at 1670 cm^{-1} (isoniazid) and 1720 cm^{-1} (pyrazinamide) have suffered only a slight negative shift (1660 and 1710 cm^{-1}) on complex formation. This suggests that the carbonyl groups might be free of metal binding in the copper(II) complex.

Table 2: Infrared Spectral Data of Isoniazid, Pyrazinamide and the Copper(II) Complex*

Assignment of vibrational bands	Isoniazid	Pyrazinamide	[Cu(INA)-(PZA-H)-(OH)] H ₂ O
ν_{O-H} (H ₂ O)	–	–	3450s
ν_{N-H}	3305s 3210s 3165s 3105s	3400s 3180s – –	3280s 3255b,s 3130b,s –
$\nu_{C=O}$	– 1670s	1720s –	1710s 1660s
$\delta_{NH_2} + \nu_{O-C-N}$	1635m	1610m	–
Amide II	1560s	1580s	1585s
ν_{O-C-N}	1380s	1380s	1400–1320b
NH	1225m 1200m	– –	– –
ν_{N-N}	1000m	–	960
Two adjacent ring C–H + δ_{NH} (out of plane)	890m –	780w –	875m 780w
Pyrazine ring out of plane deformation	–	435m	455m

* Spectra recorded in nujol; vibrational frequencies in cm^{-1} ; vibrational band description; b = broad, s = strong, medium = m and w = weak

Pyrazine ring vibrational bands at 1580, 1525, 620 and 435 cm^{-1} have suffered an overall positive shift ($1585, 1525, 640$ and 456 cm^{-1}) in the infrared spectrum of the copper(II) complex (Fig. 6.21). This indicates that the ring nitrogen has also taken part in the metal–ligand binding. Similar observations were made by Singh and Seth in the case of cobalt(II) and nickel(II) complexes of pyrazinamides⁽¹⁴⁾.

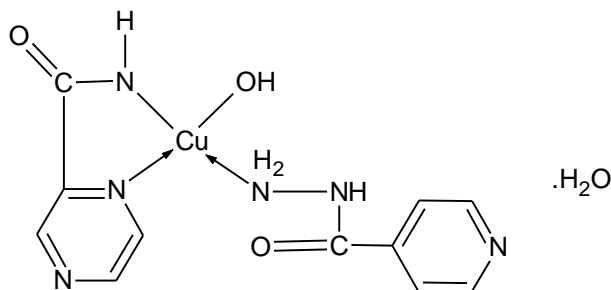
As both the ligands, isoniazid and pyrazinamide themselves have rich infrared absorptions in the region $600\text{--}400\text{ cm}^{-1}$, assignment of infrared peaks to M–N and M–O stretchings was found to be difficult.

Thermal Decomposition Study

The initial decomposition of the copper(II) complex of isoniazid and pyrazinamide has occurred at 120°C with the loss of one water molecule (5% by weight). Around 39% weight loss was recorded at 250°C probably due to loss of one more water molecule along with pyrazinamide moiety. Above 340°C , a further decrease in the weight of the sample was noticed.⁽¹⁵⁾ Approximately 35% weight loss at this stage could possibly be due to decomposition of isoniazid moiety. Between 520° and 570°C , there existed a constant weight residue which could possibly be cuprous oxide, Cu_2O accounting for 20% of the weight of the sample⁽¹⁶⁾

III. Conclusion

Based on these data of structural investigation on the copper(II) complex prepared, the following structure is suggested.



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