Synthesis, characterization and spectroscopic studies of pyrazinamide metal complexes

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Abstract The present paper deals with the synthesis and characterization of Schiff base complexes of pyrazinamide an antitubercular drug. Metals selected for complexation are copper, silver, gold, zinc, mercury, iron and cobalt. The complexes have been suitably synthesized and isolated in pure powdered form. Analytical data agrees with the compositions M(L), M(L)₂ and M(L)₂·2H₂O, respectively where M = Ag, M’ = Cu, Au, Zn and Hg and M” = Fe and Co, ligand metal ratios were also confirmed by monovariation method and Job’s method of continuous variation. Molar conductance values suggest the non ionic nature of the complexes. The tentative structure assigned to the complexes on the basis of stoichiometry and analytical data were further supported by spectral studies viz; IR, NMR, magnetic susceptibility and electronic spectra. A preliminary attempt has also been made to compare the potencies of metal complexes with parent drug. The Cu and Ag complexes are giving encouraging results. Particle size studies further suggest that the drug molecule undergoes reduction in size on complexation.

1. Introduction

Schiff base ligands are excellent coordinating molecules and can exhibit variety in the structure of their metal complexes (Cukurovali et al., 2001). Literature reveals that Schiff base complexes have a very special role in the development of inorganic chemistry (Sreenivasulu and Hussain Reddy, 1993; Sami and Jejukar, 1993). Schiff base metal complexes have been the subject of intensive research due to their novel properties and their industrial and biological importance. They are found to have a number of pharmacological applications (Mahindra et al., 1983; Parihari and Patel, 1998; Joshi et al., 2006; Chandra and Kumar, 2007; Lutfullah et al., 2007;
Patel et al., 2008). It has been reported that certain Schiff bases exhibit antitubercular activities (Kumar et al., 1990). Thus looking to the importance of Schiff bases with essential metals in the form of coordination compounds for the successful treatment of various diseases and in continuation of our work (Iqbal and Deshavi, 1988; Iqbal and Manke, 1992; Iqbal and Qureshi, 1985, 1987, 1990, 1998; Iqbal et al., 1991, 2002), we have undertaken the synthesis of Schiff base of antitubercular drug pyrazinamide and its metal complexes.

2. Experimental

Pure sample of pyrazinamide having molecular formula C\textsubscript{5}H\textsubscript{5}N\textsubscript{3}O was procured from Dr. Reddy’s Laboratories, Hyderabad and was used as such for the synthesis of ligand.

Metal salts used were all of AR grade. Solvents used were ethanol, acetone, double distilled water and DMSO. Elemental analyses (CHN) were carried out on a Carlo Erba 1106 Thomas and Coleman Analyzer. Conductivity measurements were carried out on Sytronics digital direct reading conductivity meter using conductivity cell having cell constant 1.0. The IR spectra of the ligand and its complexes were recorded in KBr pellets with a Perkin–Elmer spectrophotometer in the 400–500 cm\textsuperscript{-1} range. The UV visible spectra were recorded on a Lambda Perkin–Elmer spectrophotometer in DMSO while magnetic susceptibility measurements were done in a vibrating sample magnetometer at room temperature. The \textsuperscript{1}H NMR spectra of ligand and its Hg(II) and Zn(II) complexes were run in DMSO-d\textsubscript{6} on a Joel-FX-100 spectrometer using TMS as an internal standard. Metals were estimated by using standard methods (Vogel, 1959; Kohlhoff and Stegar, 1947; Coratt, 1955).

2.1. Synthesis of the ligand (pyrazinamide–salicylaldimine, PZM–SA)

Equimolar solution of pure drug pyrazinamide and salicylaldehyde were prepared separately in aqueous ethanol (1:1) and refluxed for 3 h in a round bottom flask attached with Liebig’s condensor. The resulting solution was cooled. Light yellow precipitate was collected by filtration, washed with absolute alcohol, dried in vacuo (yield 34% m.p. 194 °C).

2.2. Ligand metal ratio and stoichiometry

About 20 ml of ligand (PZM-SA) was diluted to 200 ml using 50% aqueous acetone and titrated against metals using monovariation method. On plotting graphs, results indicate the formation of (2:1) complexes of ligand with Cu, Au, Zn, Hg, Fe and Co while 1:1 complex with silver. Formation of 2:1 and 1:1 (L:M) complexes were further confirmed by Job’s method (Job, 1928) of continuous variation as modified by Turner and Anderson (1949). Stability constant and free energy change were also calculated.

2.3. Synthesis of complexes

About 2 mol of ligand (PZM-SA) and 1 mol of metal salt (except Ag, where one mole ligand and one mole salt were taken), were dissolved separately in aqueous acetone. Both the solutions were mixed slowly with continuous stirring. The mixture was refluxed for 3–4 h whereby the metal complex was precipitated. After cooling, the precipitate was filtered, washed with acetone and dried in vacuo (yield – 12.5 g, 48.38%).

3. Results and discussion

The colour, melting point, yield percentage, stability constant, free energy change and molar conductance of the complexes are summarized in Table 1. The analytical data of the complexes summarized in Table 2, correspond with the general formulæ M(L), (M(L)\textsubscript{2} and M\textsuperscript{0}(L)\textsubscript{2}. H\textsubscript{2}O where M = Ag, M\textsuperscript{+} = Cu, Zn, Hg and M\textsuperscript{0} = Co, Fe. The complexes are soluble in DMSO 2:1 (L:M) stoichiometry for Cu, Zn, Hg, Fe and Co complexes and 1:1 (L:M) stoichiometry for Ag complexes was confirmed by Job’s method of continuous variation modified by Turner and Anderson. The complexes are thermally stable as evident from the stability constant value. The molar conductance values of the complexes (9.8–15.0 Ω\textsuperscript{-1} cm\textsuperscript{2} mol\textsuperscript{-1}) indicate their non electrolytic nature (Geary, 1971; Sreenivasulu and Hussain Reddy, 1994).

The reactions for the formation of the ligand and their metal complexes are shown below.

\begin{align*}
L + M\text{NO}_3^- & \xrightarrow{\text{Aqueous acetone, Reflux}} M(L) + HNO_3 \quad (1) \\
2L + M'^{+}\text{Cl}_2 & \xrightarrow{\text{Aqueous acetone, Reflux}} M'^{+}(L)\textsubscript{2} + 2HCl \quad (2) \\
2L + M'^{+}\text{Cl}_2\cdot2H_2O & \xrightarrow{\text{Aqueous acetone, Reflux}} M'^{+}(L)\textsubscript{2}\cdot2H_2O \cdot 2HCl_2 \quad (3)
\end{align*}

where M = Ag, M' = Cu, Zn, Hg, M'' = Co, Fe.

3.1. Spectral studies of PZM–SA and its complexes

3.1.1. IR spectra

The relevant spectral bands and their assignments are recorded in Table 3. Few important absorption bands are discussed here.

The molecule of PZM–SA consists of salicyl group, (C\textsubscript{6}H\textsubscript{4}OH\textsubscript{CH}=–) and pyrazine carboxylamide group (C\textsubscript{5}H\textsubscript{5}N\textsubscript{3}O). A band between 1659 and 1715 cm\textsuperscript{-1} has been observed in the case of ligand and complexes which is assignable to \textsuperscript{C}=\textsuperscript{O} group (Elba et al., 1997). The frequency due to pyrazine ring appears at 1160 ± 10 cm\textsuperscript{-1} and it remains unchanged on complexation indicating the non involvement of pyrazine ring in complexation (Rao, 1963). \textsuperscript{N}– frequency both in the case of ligand as well as complex is observed in the range of 870 ± 5 cm\textsuperscript{-1} (Bellamy, 1954). Chelate ring frequency is observed in all the complexes except ligand at 1380 ± 5 cm\textsuperscript{-1} (Weissberger, 1956). The presence of sharp band in the region 517–542 cm\textsuperscript{-1} in the spectra of all the complexes assigned to v(M–N) mode, bands further support to the involvement of nitrogen atom in coordination (Mahanan, 2004).

M–O frequency is observed in the range of 660 ± 10 cm\textsuperscript{-1} in all the complexes which is in agreement with the observation of previous workers [loc.cit].

The frequency in the range of 3410 ± 5 cm\textsuperscript{-1} has been observed in the case of Fe and Co complexes which may be assigned to water of coordination [loc.cit].
3.2. Electronic spectra and magnetic moments

The electronic spectra in DMSO and magnetic moments are given in Table 4.

The electronic spectra of copper(II) complexes exhibit three bands. The band at 27027 cm⁻¹ for (L)₂Cu can be attributed to charge transfer. The other bands found at 18195 and 15120 cm⁻¹ are assigned to 2A₁g → 2B₁g and 2E₁g → 2B₁g. These are characteristics of square planar geometry around copper(II) ion. The observed magnetic moment value is 1.82 BM suggesting a square planar (Bhaskare and Hankare, 1995; Nishat et al., 2003) environment for Cu(II) ion.

Table 4: Electronic spectral bands, magnetic moment values and possible assignment of Cu(II), Zn(II), Hg(II) and Co(II) complexes of PZM–SA.

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<tr>
<th>Compound/molecular formula</th>
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<td>Charge transfer</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>Tetrahedral</td>
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<tr>
<td>(L)₂Hg</td>
<td>Diamagnetic</td>
<td>–</td>
<td>–</td>
<td>Tetrahedral</td>
</tr>
<tr>
<td>(L)₂Co(H₂O)₂</td>
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<td>20410 15780 12180</td>
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No transitions were observed in the visible region for Zn(II) and Hg(II) complexes of ligand PZM–SA consistent with d^10 configuration for Zn(II) and Hg(II) ion Mahapatra et al., 1993 indicating tetrahedral geometry.

The observed magnetic moment value of the cobalt(II) complex is in the range expected for three unpaired electrons. The electronic spectra shows three bands at 20410, 15780 and 12180 cm\(^{-1}\) which can reasonable be assigned to the \(4T_{1g}(P) \rightarrow 4T_{1g}(F), 4A_{2g}(F) \rightarrow 4T_{1g}(F), 4T_{2g}(P) \rightarrow 4T_{1g}(F)\) transitions, respectively. These transitions are characteristics of compounds with an octahedral geometry of the Co(II) ion Sharma et al., 1997; Figgis and Nyholm, 1954.

3.3. \(^1\)H NMR spectra

The \(^1\)H NMR spectra of ligand and its metal complexes were recorded in DMSO-\(d_6\). The ligand (PZM–SA) shows a group of multiple signals at \(\delta(8.2–8.9)\) ppm corresponding to aromatic protons (Larkem et al., 2004). A signal of \((9.2)\) ppm in ligand can be assigned to phenolic –OH proton (Sallam and Orabi, 2004). –CH proton of azomethine group in ligand shows a peak at \(\delta(7.8)\) ppm (loc.cit).

In the mercury and zinc complexes of PZM–SA, aromatic proton signals appear in the range of \(\delta(8.2–8.86)\) ppm due to different environment of protons (Mansingh and Dash, 1995). The azomethine proton appeared as a singlet in the range \(\delta(7.86–7.90)\) ppm, the low field shifting (high \(\delta\) value) of azomethine protons confirms the coordination of the metals with azomethine group.

3.4. Particle size

The particle size of drug and its metal complexes have been studied by Laser Diffraction Particle Size Analyzer. The instrument used was CILAS 1064 L/D model in the range of 0.04–500 \(\mu m\). The particle size of pyrazinamide was found to be 161.33 \(\mu m\) while the particle size of all the complexes except Cu (170.61 \(\mu m\)) were found to be less than 40 nm. Thus we conclude that the size of the particles get reduced after complexation.

3.5. Antitubercular activity

The results of antitubercular activity are tabulated in Table 5. The pure drug pyrazinamide and its metal complexes were tested against the bacteria “\textit{Mycobacterium tuberculosis}” in vitro in order to compare the antitubercular activity of the parent drug PZM with various metal complexes. The bacterial growth was determined by turbidity measurements (spectrophotometric method) (Aneja, 2009; Syre et al., 2003). The results indicate that the complexes of pyrazinamide inhibit the growth of bacteria to a greater extent than the pyrazinamide alone.

On the basis of above studies the following structures have been proposed for the metal complexes of pyrazinamide.

![PZM-SA-M Complex (M = Ag)](image)

![PZM-SA-M Complex (M = Cu, Zn, Hg, Au)](image)

| Table 5 | Bacterial growth inhibition in terms of optical density by PZM and its metal complexes (spectrophotometric method). |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days/\(\mu\)M–concentration | Controlled plate | PZM | (PZM)–Cu | (PZM)–Zn |
| | \(0.2\) | \(0.4\) | \(0.6\) | \(0.8\) | \(1\) | \(0.2\) | \(0.4\) | \(0.6\) | \(0.8\) | \(1\) | \(0.2\) | \(0.4\) | \(0.6\) | \(0.8\) | \(1\) |
| 0 | 0.02 | 0.015 | 0.013 | 0.015 | 0.01 | 0.011 | – | – | – | – | 0.01 | 0.01 | 0.007 | 0.007 | 0.009 |
| 1 | 0.1 | 0.018 | 0.02 | 0.02 | 0.016 | 0.016 | 0.017 | – | – | – | 0.011 | 0.011 | 0.009 | 0.008 | 0.01 |
| 2 | 0.17 | 0.13 | 0.16 | 0.04 | 0.1 | 0.03 | 0.001 | – | – | – | 0.042 | 0.03 | 0.01 | 0.01 | 0.01 |
| 3 | 0.21 | 0.18 | 0.18 | 0.11 | 0.14 | 0.06 | 0.01 | – | – | – | 0.13 | 0.04 | 0.011 | 0.011 | 0.01 |
| 4 | 0.29 | 0.24 | 0.2 | 0.16 | 0.19 | 0.11 | 0.01 | – | – | – | 0.17 | 0.1 | 0.03 | 0.024 | 0.019 |
| 5 | 0.36 | 0.3 | 0.26 | 0.2 | 0.22 | 0.18 | 0.011 | – | – | – | 0.19 | 0.14 | 0.1 | 0.029 | 0.02 |
| 6 | 0.4 | 0.39 | 0.31 | 0.25 | 0.25 | 0.21 | 0.011 | – | – | – | 0.19 | 0.15 | 0.12 | 0.1 | – |
| 7 | 0.5 | 0.4 | 0.33 | 0.29 | 0.25 | 0.23 | 0.011 | – | – | – | 0.2 | 0.15 | 0.13 | 0.1 | – |

P. Budhani et al.
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References


