Study of some biorelevant complexes of manganese(II) with active imines

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Some new manganese(II) complexes of biologically relevant ligands, hydrazinecarboxamide and hydrazinecarboxalamide of 5-nitro-indol-2,3-dione and 6-nitro-indol-2,3-dione of the composition \([\text{MnCl}(\text{N}^\text{X})\text{H}_2\text{O}]\) and \([\text{Mn}(\text{N}^\text{X})\text{I}]\) have been isolated, where \(\text{N}^\text{X} = \text{donor system of the ligand and X is oxygen or sulphur. The complexes have been characterized by the elemental analysis, molar conductance, magnetic measurements, molecular weight determinations, IR and ESR spectral studies. On the basis of spectroscopic studies, it has been inferred that the manganese(II) complexes are consistent with the tetrahedral geometry. The magnetic measurements reveal that the manganese(II) complexes are high spin in nature. All the ligands and their corresponding complexes have been screened for their antifungal and antibacterial activities.

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The coordination chemistry of transition metals and their derivatives has received much attention in the recent years primarily because of their biological importance. The metal thiosemicarbazone compounds are emerging as a new class of experimental anticancer chemotherapeutic agents which exhibit inhibitory activity against most of the cancers through inhibition of a crucial enzyme obligatory for DNA biosynthesis and cell division. The complexes of manganese play an important role in photochemical reaction. Nitrogen, oxygen and sulfur donor ligands possess a range of biological applications like antitumour, antiviral, antibacterial, antimalarial and antifungal activities. Manganese ethylene bisdithiocarbamate is known to exhibit antifungal activity and has been successfully used against a wide variety of diseases, particularly of vegetables and fruits. Manganese complexes of some thiosemicarbazones are potent antileukemic agents. In view of this and our interest in biologically active coordination compounds of Mn(II), we report herein the reactions of \(\text{MnCl}_2\cdot 4\text{H}_2\text{O}\) with various active imines.

Materials and Methods

All the reagents were dried and distilled before use. The hydrazinecarboxamide and hydrazinecarboxalamide of 5-nitro-indol-2,3-dione and 6-nitro-indol-2,3-dione were prepared by the condensation of ethanolic solution of 5-nitro-indol-2,3-dione and 6-nitro-indol-2,3-dione with aqueous solutions of semicarbazide hydrochloride (in the presence of sodium acetate) and thiosemicarbazide respectively in 1:1 molar ratio. The resulting mixture was boiled under reflux for 30-40 min. On cooling, the crystals separated out which were recrystallised using the same solvent and finally dried in vacuo. These were characterized and analysed before use (Fig. 1).

Synthesis of isonitrosoacetanilide

To a solution of chloral hydrate (0.11 mol, 18.12 g) in water (250 mL) were successively added \(\text{Na}_2\text{SO}_4\) (120 g), a solution of appropriate aniline (0.01 mol) in HCl (5.5 mL) and finally a solution of hydroxyamine hydrochloride (0.33 mol, 22.0 g) in water. The reaction mixture was heated at such a rate that vigorous boiling started in 45 min. The boiling was continued for further 10 min. The reaction mixture was cooled when appropriate precipitate separated out. These were filtered and recrystallised from ethanol. The resulting product is isonitrosoacetanilide (Fig. 2).

Synthesis of 5/6-nitro-indol-2,3-dione

Isonitrosoacetanilide (0.05 mol) was added to conc. sulphuric acid (50 mL) in about 30 min with constant stirring. After the addition was complete, the reaction
Here \( X = \text{Oxygen and Sulphur} \)
\( X = O \ (L^1) \), \( X = S \ (L^2) \)

\[ \begin{align*}
\text{Fig. 1} & \quad \text{Structures of the ligands.}
\end{align*} \]

\[ \begin{align*}
\text{Fig. 2} & \quad \text{Synthesis of isonitrosoacetanilide.}
\end{align*} \]

\[ \begin{align*}
\text{Fig. 3} & \quad \text{Synthetic routes of 5/6-nitro-indol-2,3-dione.}
\end{align*} \]

For the preparation of manganese(II) complexes equimolar and bimolar reactions of \( \text{MnCl}_2 \cdot 4\text{H}_2\text{O} \) with ligands were carried out in dry methanol. The reaction mixture was refluxed for 10-15 h and then cooled at room temperature. The solvent was removed and residue was dried in vacuo after being repeatedly washed with dry cyclohexane. Finally, the complexes were recrystallized in methanol. The important properties and physical data of the complexes are reported in Table 1.

Molecular weights were determined by the Rast Camphor Method. IR spectra were recorded on a
Table 1 — Analyses and physical properties of manganese(II) complexes

<table>
<thead>
<tr>
<th>Compound</th>
<th>M.pt (°C)</th>
<th>Colour</th>
<th>Mn (%)</th>
<th>N (%)</th>
<th>S (%)</th>
<th>Cl (%)</th>
<th>Found (Calc) %</th>
<th>M.W.</th>
</tr>
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<tbody>
<tr>
<td>L¹H</td>
<td>237</td>
<td>Light brown</td>
<td>-</td>
<td>28.01</td>
<td>-</td>
<td>-</td>
<td>(28.10)</td>
<td>242</td>
</tr>
<tr>
<td>L²H</td>
<td>232</td>
<td>Brown</td>
<td>-</td>
<td>26.22</td>
<td>11.24</td>
<td>-</td>
<td>(26.40)</td>
<td>259</td>
</tr>
<tr>
<td>[MnCl(L¹)H₂O]</td>
<td>182</td>
<td>Yellow</td>
<td>15.14</td>
<td>18.94</td>
<td>-</td>
<td>9.82</td>
<td>(15.40)</td>
<td>354</td>
</tr>
<tr>
<td>[MnL¹₂]</td>
<td>198</td>
<td>Yellow</td>
<td>9.56</td>
<td>25.11</td>
<td>-</td>
<td>-</td>
<td>(9.96)</td>
<td>496</td>
</tr>
<tr>
<td>[MnCl(L²)H₂O]</td>
<td>177</td>
<td>Orange</td>
<td>14.11</td>
<td>18.11</td>
<td>8.42</td>
<td>8.88</td>
<td>(14.74)</td>
<td>413</td>
</tr>
<tr>
<td>[MnL²₂]</td>
<td>210</td>
<td>Orange</td>
<td>9.76</td>
<td>23.98</td>
<td>10.76</td>
<td>-</td>
<td>(9.41)</td>
<td>620</td>
</tr>
<tr>
<td>L³H</td>
<td>232</td>
<td>Brown</td>
<td>-</td>
<td>27.86</td>
<td>-</td>
<td>-</td>
<td>(28.10)</td>
<td>250</td>
</tr>
<tr>
<td>L⁴H</td>
<td>221</td>
<td>Grey</td>
<td>-</td>
<td>26.16</td>
<td>12.24</td>
<td>-</td>
<td>(26.40)</td>
<td>263</td>
</tr>
<tr>
<td>[MnCl(L³)H₂O]</td>
<td>198</td>
<td>Dark brown</td>
<td>14.67</td>
<td>18.11</td>
<td>-</td>
<td>9.21</td>
<td>(15.40)</td>
<td>330</td>
</tr>
<tr>
<td>[Mn(L³)₂]</td>
<td>206</td>
<td>Dark brown</td>
<td>9.22</td>
<td>25.19</td>
<td>-</td>
<td>-</td>
<td>(9.96)</td>
<td>532</td>
</tr>
<tr>
<td>[Mn(L⁴)₂]</td>
<td>235</td>
<td>Yellow</td>
<td>8.67</td>
<td>23.48</td>
<td>10.84</td>
<td>-</td>
<td>(9.41)</td>
<td>597</td>
</tr>
</tbody>
</table>

Perkin-Elmer 577 Grating spectrophotometer. Electronic spectra of the complexes were recorded in DMF on a UV-160A Shimadzu spectrophotometer in the range 200-600 nm. ESR spectra were got recorded from IIT Madras, Chennai. Manganese was estimated complexometrically with EDTA using erichrome black-T as an indicator. Nitrogen and sulphur were estimated by the Kjeldahl's and Messengers methods, respectively.

**Antifungal activity**

The antifungal activity of all the ligands and their corresponding complexes was evaluated against *Alternaria alternata* and *Fusarium oxysporum* by the agar plate technique. The compounds were dissolved in 50, 100 and 200 ppm concentrations in methanol and then mixed with the medium. The linear growth of the fungus was obtained by measuring the diameter of the colony in petriplate after 96 h and percentage inhibition calculated as 100 (C-T)/C where C and T are the diameter of the fungus colony in the control and test plates respectively.

**Antimicrobial activity**

Antimicrobial activity was evaluated by the paper disc plate method. The nutrient agar medium (peptone, beef extract, NaCl and agar-agar) and 5 mm diameter paper disc of Whatman No.1 were used. The compounds were dissolved in methanol in 500 and 1000 ppm concentrations. The filter paper discs were soaked in different solutions of the compounds dried and then placed in the petriplates previously seeded with the test organisms. The plates were incubated for 20-30 h at 28±2°C and the inhibition zone around each disc was measured.

**Results and Discussion**

The reactions of MnCl₂·4H₂O with 5-nitro-3-[indol]2-one and 6-nitro-3-[indol]2-one of carboxamide and carbothioamide have been carried out in unimolar and bimolar ratios in methanol. The
successive replacement of chloride resulted in the formation of products $[\text{MnCl}(N^\text{X})\text{H}_2\text{O}]$ and $[\text{Mn}(N^\text{X})_2]$ as shown below:

$$\text{MnCl}_2\cdot4\text{H}_2\text{O}+N^\text{X} \xrightarrow{\text{HCl} + 3\text{H}_2\text{O}} [\text{MnCl}(N^\text{X})\text{H}_2\text{O}]$$

(1:1)

$$\text{MnCl}_2\cdot4\text{H}_2\text{O}+2N^\text{X} \xrightarrow{2\text{HCl} + 4\text{H}_2\text{O}} [\text{Mn}(N^\text{X})_2]$$

(1:2)

where $N^\text{X}$ is the donor system of the ligand.

These reactions proceed easily and the resulting compounds are soluble in methanol, CHCl$_3$, DMF and DMSO. The magnetic moment values of the manganese(II) derivatives are 5.9±0.1 BM, suggesting a high spin state for these complexes with central manganese atom being surrounded by the tetra-coordinated environment.

**ESR spectra**

The ESR spectra of 1:1 and 1:2 complexes of manganese(II) were recorded at room temperature. These consist of a single broad peak in each case and from which the lande splitting factor ($g$ values) has been calculated. For the present complexes, the $g$ values lie in the range 1.978-1.982 indicating a tetracoordinated state of manganese in these complexes.

**IR spectra**

IR spectra of the ligands show medium intensity bands at 3300-3100 cm$^{-1}$ due to $\nu$NH vibrations. In the spectra of the metal complexes these bands disappear indicating deprotonation followed by coordination. A sharp band at ~1620 cm$^{-1}$ due to $\nu$C= N shifts slightly towards lower frequency (10-20 cm$^{-1}$) in the complexes indicating the coordination of azomethine nitrogen to the metal atom. Strong bands at 1682 cm$^{-1}$ ($L^{1}H$ and $L^{2}H$) and 1694 cm$^{-1}$ ($L^{2}H$ and $L^{4}H$) are due to $\nu$C=O and $\nu$C=S, respectively, in the case of the said ligands. These bands disappear in the case of complexes suggesting enolisation/thioenolization of the ligands and their chelation.
through the enolic oxygen and thiolic sulphur, respectively. The bands observed in the region 3430-
3350 cm\(^{-1}\) attributed to asymmetric and symmetric modes of the NH\(_2\) group remain at nearly the same position in the spectra of the complexes\(^{23}\). The aforesaid coordination pattern of the metal derivatives is further strengthened by the appearance of non-ligand bands in the spectra of metal complexes in the regions 490-450 cm\(^{-1}\), 420-370 cm\(^{-1}\), 340-290 cm\(^{-1}\) and 340-285 cm\(^{-1}\) due to \(\nu\)Mn-O, \(\nu\)Mn-N, \(\nu\)Mn-S and Mn-Cl vibrations, respectively. In the spectra of the 1:1 manganese complexes, a band observed at ca. 879 cm\(^{-1}\) can be assigned to the coordinated water molecule\(^{23}\). This band is absent in the spectra of the corresponding 1:2 complexes.

**UV spectra**

The UV spectra of the ligands and their complexes show bands at ca. 274 and 300 nm assignable to \(\pi-\pi^*\) electronic transitions within the benzene ring. Another band observed at ~370 nm in the spectra of the said ligands is due to \(n-\pi^*\) transitions of the azomethine (\(>\text{C}=\text{N}\)) group. However, in the spectra of the complexes, this band shifts to the lower wavelength due to the coordination of the azomethine nitrogen to the metal atom, indicating the delocalization of electronic charge within the chelate ring and thereby stabilizing the resulting complexes\(^{23}\). Based on these studies for the 1:1 and 1:2 manganese complexes, the tetrahedral geometry (Fig. 4) has been proposed.

**Antifungal and antibacterial activities**

The data for the antifungal and antibacterial activities of the ligands and their corresponding compounds against various fungi and bacteria have been recorded (Tables 2 and 3). The results point out that the compounds are inhibiting the growth of fungi and bacteria to a greater extent as the concentration is increased. The enhanced activity of metal chelates may be ascribed due to the increased lipophilic nature of these complexes arising due to chelation\(^{24}\). It is also noted that sulfur containing ligands as well as their complexes are more active than their oxygen containing counterparts. The toxicity increases as the concentration is increased. Mode of action of antimicrobials may involve various targets in microorganisms, e.g. interference with the cell wall synthesis, damage to the cytoplasmic membrane as a result of which cell permeability may be altered or they may disorganize the lipoprotein leading to the cell death\(^{25}\).

**References**