Research Article

Synthesis, Characterization, and Physicochemical Studies of Mixed Ligand Complexes of Inner Transition Metals with Lansoprazole and Cytosine

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Few complexes of inner transition metals [Th(IV), Ce(IV), Nd(III), Gd(III)] have been synthesized by reacting their metal salts with lansoprazole, 2-[(3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylsulfonyl]-1H-benzoimidazole and cytosine. All the complexes were synthesized in ethanolic medium. They yield percentage ranges from 80 to 90%. The complexes are coloured solids. The complexes were characterized through elemental analyses, conductance measurements, and spectroscopic methods (FT IR, FAB Mass, 1H NMR and UV). An IR spectrum indicates that the ligand behaves as bidentate ligands. The metal complexes have been screened for their antifungal activity towards Aspergillus niger fungi. The interaction of inner transition metals with lansoprazole, in presence of cytosine, has also been investigated potentiometrically at two different temperatures 26 ± 1°C and 36 ± 1°C and at 0.1 M (KNO3) ionic strength. The stability constants of ternary complexes indicate the stability order as Th(IV) < Ce(IV) < Gd(III) < Nd(III). Log K values obtained are positive and suggest greater stabilization of ternary complexes. The values of thermodynamic parameters (free energy (ΔG), enthalpy (ΔH), and entropy (ΔS)) are also calculated.

1. Introduction

Inner transition metal complexes are of continuing interest mainly due to their structural and catalytical properties and their application in diagnostic pharmaceutical and laser technology [1–3]. They have been found to exhibit anticancer and fungicidal properties also [4].

Investigations are going on the formation of metal complexes with benzimidazole ring containing ligands because benzimidazole and its derivatives play an important role in analysis and in several biological reactions [5]. Considering the importance of drugs and their complexes it has been desired to synthesize and characterize some ternary complexes of inner transition metal [Th(IV), Ce(IV), Gd(III), Nd(III)] with a Benzimidazole derivative, lansoprazole, and cytosine. Lansoprazole being an antiulcer drug reduces gastric acid secretion and has successfully been used to heal and relieve symptoms of gastric or duodenal ulcers and gastroesophageal reflux [6–9].

As the interaction of metal ions with nucleobases is of great interest because of their relevance to the essential, medical or toxic bioactivity of metal, where nucleobase molecule can coordinate as exogenous ligands in metalloproteins, function as cofactors in the enzymatic systems. Thus, cytosine is selected as the secondary ligand for the formation of ternary complexes. Its chemical name is 4-amino-1H-pyrimidine-2 one [10].

2. Experimental

All the chemicals used throughout the course of experiments were either of BDH or E merck quality. Spectroscopic grade solvents were employed for recording the spectra.

2.1. Preparation of the Complexes. The solid complexes were prepared by mixing the aqueous solution of metal salts [Th(NO3)4·4H2O, Ce(NO3)2·xH2O, Nd(NO3)3·6H2O, Gd(NO3)3·6H2O] with an ethanolic solution of lansoprazole and cytosine in molar ratio 1 : 1 : 1. The resulting mixtures were then refluxed for 4-5 hours to give the precipitate. After cooling at room temperature the solid complexes were filtered as fine precipitates. These precipitates were washed...
twice with water. Then they were dried and stored in a desiccators containing dry calcium chloride. The compounds obtained were stable coloured solids.

2.2. Physical Measurement. The melting point was recorded on Labotche instrument. Elemental analysis was performed on a Carlo Erba mod 1108 elemental analyzer. The Mass spectra was done on a Jeol SX-102 spectrometer using argon as the FAB gas Elico and SL191 double beam uv-vis spectrophotometer is used for recording uv-vis spectra. The antifungal activity is studied by paper disk method and data was recorded after 48 hours of incubation.

2.2.2. Stability of Complexes. The metal-ligand-ligand ratio was confirmed by conductometric titration method.

2.2.2.1. Ligand-Metal Ratio. The metal-ligand-ligand ratio was confirmed by conductometric titration method.

2.2.2.2. Stability of Complexes. Stepwise and overall proton ligand stability constants were computed by Bjerrum clavin pH titration technique as adapted by Irving and Rossotti. The extension of this titration technique to ternary system, as suggested by Chidambaram and Bhattacharya [11] has been applied to determine the stability constants of 1 : 1 : 1 ternary complexes at 26 ± 1°C and 36 ± 1°C.

The proton ligand stability constant of the drug lansoprazole and cytosine has been calculated at 26 ± 1°C and 36 ± 1°C and at 0.1 M (KNO₃) ionic concentration, utilizing the Irving Rossotti pH titration technique [12].

2.3. Thermodynamic Parameters. Thermodynamic parameters computed for the complexation reactions studied in this investigation are free energy (ΔG), enthalpy (ΔH), and entropy (ΔS) changes [13].

The reaction will go in the direction written, when ΔG is negative. These have been calculated using the Vant Hoff isotherm, Vant Hoff equation, and the Gibbs-Helmholtz equations, respectively, at 26°C and 36°C and at ionic strength of 0.1 M with KNO₃:

$$\Delta G = -2.303 RT \log_{10} K, $$

$$\Delta H = 4.576 \frac{T_1 \times T_2}{T_2 - T_1} \log_{10} K, $$

$$\Delta S = \frac{\Delta H - \Delta G}{\Delta T}. $$

3. Result and Discussion

3.1. Stability of Complexes. The Δ log K values obtained in the present study (recorded in Table 1) are positive indicating greater stabilization (greater degree of chelation) of ternary complexes.

The stability order obtained in the present investigation is shown below:

$$(\text{M-LANSO-CYTO})$$

$$(\text{Th} < \text{Ce} < \text{Gd} < \text{Nd}) \quad \text{at} \ 26 \pm 1°C,\ (1)$$

$$\text{Th} < \text{Ce} < \text{Gd} < \text{Nd} \quad \text{at} \ 36 \pm 1°C.\ (2)$$

3.2. Thermodynamic Parameters. The values of changes in free energy (ΔG), enthalpy (ΔH), and entropy (ΔS) recorded in Table 2, accompanying the formations of the ternary complexes, using the standard equations are as in [14]. The negative values of ΔG show that the driving tendency of the complexation reaction is from left to right and the reaction tends to proceed spontaneously.

4. Analytical Data of Complexes

The reaction of the inner transition metal with lansoprazole and cytosine was afforded in good yield (85–90%) of stable solid compound. The compounds prepared were coloured, soluble in ethanol, 1, 4 dioxane, DMF, DMSO and
insoluble in water. The characterization of their molecular structure was made by elemental analysers conductivity and spectroscopy studies. The studied complexes of inner transition metal showed 1 : 1 : 1 (M : LANSO : CYTO) composition as indicated from elemental analyser and exhibited corresponding conductivities suggesting 1 : 1 : 1 electrolytic behaviour. The analytical data including yield percentage of the complexes are recorded in Table 3.

5. Elemental Analysis

The result of elemental analysis is recorded in Table 4.

5.1. FT IR Spectra. The relevant vibration bands of the free ligand and the complexes are in the region 4000–400 cm\(^{-1}\) [15, 16]. The characteristic frequencies of the ligands and metal complexes are given in Table 5. In case of Lanso molecule the N–H (aromatic sec. amine) stretching occurs also reported. Hence in these complexes cytosine also acts as a bidentate ligand coordinating through the nitrogen at N(3) and the oxygen of C=O. Additional bands in the complex in the region 740–765 cm\(^{-1}\) compared with IR spectra of free ligand have tentatively been assigned to M–O frequency and new band appearing at 1380–1390 cm\(^{-1}\) in the complexes might be due to chelate ring formation in the complexes. The appearance of strong band at ~820 cm\(^{-1}\) and ~3380 cm\(^{-1}\) in the spectra of all the ternary complexes indicates the presence of coordinated water.

5.2. Mass Spectra. In the present investigations, the mass spectrum of the lansoprazole shows the formation of molecular ion peak at M/Z 344 corresponding to the total molecular weight of the ligand. Data on the molecular weight of complexes are present in table along with the values calculated on the basis of established molecular formulae of the complexes as shown in Table 6.

5.3. \(^{1}\)H NMR Spectra. To confirm the coordination of the ligands to the metal ion the complexes, \(^{1}\)H NMR spectra were recorded for the ligands and its inner transition metal complexes. The important chemical shifts for the ligands and the complexes are given in the Table 7. The \(^{1}\)H NMR spectra of the ligand have the expected characteristic signals. The CH\(_3\) proton shows singlet at \(\delta 2.16\) and O–CH\(_3\) proton at \(\delta 3.69\) ppm and the peak observed at \(\delta 4.71\) is attributed to CH\(_2\) protons. In addition multiplet peak at \(\delta 6.8–8.2\) may be due to aromatic protons and peak at \(\delta 13.2\) is observed due to NH proton of benzmimidazole ring.

In case of ternary complexes of lansoprazole-cytosine, the chemical shifts occur at low field; that is, deshielding of proton occurs in methylene group proving the involvement of electron of S=O in bonding. Signals observed in the complexes at region of \(\delta 8.18–8\) due to the azomethine proton have either remained unaffected or shifted slightly to higher field with reference to those of the parent ligand, and the

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**Table 3: Analytical data of synthesized mixed ligand complexes of M-Lanso-Cyto.**

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Complex</th>
<th>Color</th>
<th>Melting point</th>
<th>Molar conductance ((\text{cm}^2 \text{mol}^{-1} \text{S} \text{cm} \text{mol}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Th-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>Light brown</td>
<td>322°C</td>
<td>96.1</td>
</tr>
<tr>
<td>2</td>
<td>[Ce-Lanso-Cyto-4H(_2)O]SO(_4)(_2)_xH(_2)O</td>
<td>Light brown</td>
<td>319°C</td>
<td>89.6</td>
</tr>
<tr>
<td>3</td>
<td>[Gd-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>Orange</td>
<td>300°C</td>
<td>94.2</td>
</tr>
<tr>
<td>4</td>
<td>[Nd-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>Black</td>
<td>320°C</td>
<td>80.2</td>
</tr>
<tr>
<td>5</td>
<td>[Sm-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>Black</td>
<td>319°C</td>
<td>79.2</td>
</tr>
<tr>
<td>6</td>
<td>[Ytt-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>Black</td>
<td>315°C</td>
<td>83.2</td>
</tr>
</tbody>
</table>

**Table 4: Elemental analysis of mixed ligand complexes of Lanso and Cyto.**

<table>
<thead>
<tr>
<th>Metal complex</th>
<th>Found mass (calculated mass %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>[Th-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>30.26 (30.6)</td>
</tr>
<tr>
<td>[Ce-Lanso-Cyto-4H(_2)O]SO(_4)(_2)_xH(_2)O</td>
<td>33.99 (34.6)</td>
</tr>
<tr>
<td>[Gd-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>34.13 (33.8)</td>
</tr>
<tr>
<td>[Nd-Lanso-Cyto-4H(_2)O]NO(_3)(_2)_xH(_2)O</td>
<td>34.23 (34.4)</td>
</tr>
</tbody>
</table>

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**Table 5: IR bands of mixed ligand complexes of M-Lanso-CYTO.**

<table>
<thead>
<tr>
<th>Metal complexes</th>
<th>( \nu (S=O) \text{ cm}^{-1} )</th>
<th>( \nu (C=N) \text{ cm}^{-1} )</th>
<th>( \nu (C=O) \text{ cm}^{-1} )</th>
<th>( \nu (C-N) \text{ RING cm}^{-1} )</th>
<th>( \nu (\text{M-O}) )</th>
<th>( \nu (\text{coordinated H}_2\text{O}) \text{ cm}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanso</td>
<td>1090</td>
<td>1590</td>
<td>547</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cyto</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1700</td>
<td>1276</td>
<td>--</td>
</tr>
<tr>
<td>([\text{Th-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot\text{xH}_2\text{O})</td>
<td>1077 (s)</td>
<td>1578 (s)</td>
<td>529</td>
<td>1636</td>
<td>1240 (m)</td>
<td>759</td>
</tr>
<tr>
<td>([\text{Ce-Lanso-Cyto-4H}_2\text{O}]\text{SO}_4\cdot\text{xH}_2\text{O})</td>
<td>1079</td>
<td>1550 (w)</td>
<td>525</td>
<td>1637</td>
<td>1232 (s)</td>
<td>745</td>
</tr>
<tr>
<td>([\text{Gd-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot\text{xH}_2\text{O})</td>
<td>1038 (s)</td>
<td>1573 (s)</td>
<td>520</td>
<td>1637 (s)</td>
<td>1255 (s)</td>
<td>764</td>
</tr>
<tr>
<td>([\text{Nd-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot\text{xH}_2\text{O})</td>
<td>1052 (w)</td>
<td>1554 (s)</td>
<td>520/576</td>
<td>1633 (s)</td>
<td>1242 (m)</td>
<td>740</td>
</tr>
<tr>
<td>([\text{Sm-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot\text{xH}_2\text{O})</td>
<td>1080</td>
<td>1560 (s)</td>
<td>520</td>
<td>1632 (s)</td>
<td>1250</td>
<td>740</td>
</tr>
</tbody>
</table>

- \( \nu \) denotes stretching frequency.
- \( \nu \) (Bending) denotes bending frequency.
- \( \nu \) (S=O) refers to the stretching frequency of the S=O bond.
- \( \nu (\text{C=N}) \) refers to the stretching frequency of the C=N bond.
- \( \nu (\text{C=O}) \) refers to the stretching frequency of the C=O bond.
- \( \nu (\text{C-N}) \text{ RING} \) refers to the stretching frequency of the C-N ring.
- \( \nu (\text{M-O}) \) refers to the stretching frequency of the metal-oxygen bond.
- \( \nu (\text{coordinated H}_2\text{O}) \text{ cm}^{-1} \) refers to the stretching frequency of the coordinated water molecule.
Table 6: Mass spectra of mixed ligand complexes of Lanso and Cyto.

<table>
<thead>
<tr>
<th>Metal complex</th>
<th>Structure</th>
<th>Spectral mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Th·Lanso·Cyto·4H₂O]NO₃·xH₂O</td>
<td>1:1:1:4H₂O</td>
<td>793</td>
</tr>
<tr>
<td>[Ce·Lanso·Cyto·4H₂O]SO₄·xH₂O</td>
<td>1:1:1:4H₂O</td>
<td>706</td>
</tr>
<tr>
<td>[Gd·Lanso·Cyto·4H₂O]NO₃·xH₂O</td>
<td>1:1:1:4H₂O</td>
<td>703</td>
</tr>
<tr>
<td>[Nd·Lanso·Cyto·4H₂O]NO₃·xH₂O</td>
<td>1:1:1:4H₂O</td>
<td>701</td>
</tr>
</tbody>
</table>

![Proposed Scheme and Structure of representative ternary complex (M-Lanso-cyto).](image)

5.4. Electronic Spectra. Typical spectral data of the metal salts, ligand and ternary complexes of inner transition metal complexes have been investigated in ethyl alcohol and are shown in Tables 8(a) and 8(b). The electronic spectra of the lansoprazole display absorption bands at 219, 301 which is assigned to n-\(\pi^*\) and \(\pi-\pi^*\) transition, respectively. The electronic spectra of the complexes show a shift towards lower frequency. This shift was attributed to the effects of the crystal field upon the inter electronic repulsion between the 4f electrons.

Some red shift or nephelauxetic effect is observed in the alcohol solutions of these complexes. This red shift is usually accepted as evidence of a higher degree of covalency than the presence of aqua compounds [13, 19]. In all the complexes, marked enhancement in the intensity of the bond has been observed. This red shift of the hypersensitive bands has been utilized to calculate the nephelauxetic effect (\(\beta\)) in these chelate complexes. From the \(\beta\) values the covalence factors (\(b^{1/2}\)), Sinha parameter (\(\delta\%\)) (metal-ligand covalency percent), and the covalency angular overlap parameter (\(\eta\)) have been calculated using the following expressions [20]:

\[
b^{1/2} = \frac{1}{2} \left[ (1 - \beta)^{1/2} \right],
\]

\[
\delta (\%) = \left[ \frac{(1 - \beta)}{\beta} \right] \times 100,
\]

\[
\eta = \left[ \frac{(1 - \beta)^{1/2}}{\beta^{1/2}} \right].
\]

The positive values for \((1 - \beta)\) and \(\delta\%\) in these coordination compounds suggest that the bonding between metal and ligand is covalent compared with the bonding between the metal and an aqua ion. The values of parameter of bonding (\(b^{1/2}\)) and angular overlap parameter (\(\eta\)) were found to be positive, indicating covalent bonding. The mechanism of the formation and structure of representative ternary complex can be given in Figure 1.

6. Antifungal Activity

The antifungal activity of the ligand, metal salts and the corresponding complexes was assayed simultaneously against
Table 7: $^1$H NMR signals of the ligands and mixed ligand complexes of M-Lanso-Cyto.

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>kind of proton Lanso</th>
<th>[Th-Lanso-Cyto-4H$_2$O]NO$_3$ $\cdot$ xH$_2$O</th>
<th>[Ce-Lanso-Cyto-4H$_2$O]SO$_4$ $\cdot$ xH$_2$O</th>
<th>[Gd-Lanso-Cyto-4H$_2$O]NO$_3$ $\cdot$ xH$_2$O</th>
<th>[Nd-Lanso-Cyto-4H$_2$O]NO$_3$ $\cdot$ xH$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aromatic benzimidazole 7.35–7.63</td>
<td>7.33–7.69</td>
<td>7.25–7.70</td>
<td>7.38–7.64</td>
<td>7.1</td>
</tr>
<tr>
<td>2(a)</td>
<td>Aromatic pyridine 8.18</td>
<td>8.20</td>
<td>8.30</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>(b)</td>
<td>Aromatic pyridine 6.98</td>
<td>6.90</td>
<td>6.94</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>3(a)</td>
<td>Methylene-CH$_2$ 4.81</td>
<td>4.7 (sharp)</td>
<td>4.7 (sharp)</td>
<td>4.7 (sharp)</td>
<td>4.6 (sharp)</td>
</tr>
<tr>
<td>4</td>
<td>Methyl-CH$_3$ 2.20</td>
<td>2.26</td>
<td>2.24</td>
<td>2.3</td>
<td>2.39</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>N(1)–H 10.7</td>
<td>10.52</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Table 8: (a) Electronic spectral data of mixed ligand complexes of Lanso-Cyto. (b) Electronic spectral data and related bonding parameter of ternary complexes of Lanso-Cyto.

(a) Serial no. | Metals complexes | $\lambda_{\text{max}}$ (nm) | ABS | $\varepsilon_{\text{max}}$ (Lmol$^{-1}$cm$^{-1}$) | Assignment
---|---|---|---|---|---
1 | $[\text{Th-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot x\text{H}_2\text{O}$ | 221 | 0.2057 | 2057 | n-$\pi^*$
2 | $[\text{Ce-Lanso-Cyto-4H}_2\text{O}]\text{SO}_4\cdot x\text{H}_2\text{O}$ | 218 | 0.4268 | 4268 | n-$\pi^*$
3 | $[\text{Gd-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot x\text{H}_2\text{O}$ | 225 | 0.7008 | 7008 | n-$\pi^*$

(b) Serial no. | Complex | Lanthanide salts (cm$^{-1}$) | Complex band (cm$^{-1}$) | $\beta$ | $1-\beta$ | $b^{1/2}$ | $\delta$% | $\eta$
---|---|---|---|---|---|---|---|---
1 | $[\text{Th-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot x\text{H}_2\text{O}$ | 47619 | 44248 | 0.9292 | 0.0708 | 0.1330 | 7.6194 | 0.03475
2 | $[\text{Ce-Lanso-Cyto-4H}_2\text{O}]\text{SO}_4\cdot x\text{H}_2\text{O}$ | 47169 | 45455 | 0.96366 | 0.03634 | 0.09531 | 3.77103 | 0.01800
3 | $[\text{Gd-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot x\text{H}_2\text{O}$ | 47846 | 45248 | 0.94570 | 0.0543 | 0.1165 | 5.7417 | 0.05438
4 | $[\text{Nd-Lanso-Cyto-4H}_2\text{O}]\text{NO}_3\cdot x\text{H}_2\text{O}$ | 47169 | 45454 | 0.96364 | 0.03636 | 0.09534 | 3.7737 | 0.01801
Aspergillus niger fungus by paper disk method [21] at room temperature. The pure metal salts, and lansoprazole drug showed activity in Aspergillus niger. The zones of inhibition against microorganism were measured (in cm) after 48 hours of incubation as shown in Table 9. The mixed ligand complexes showed higher inhibition zone as compared to parent drug.

### 7. Conclusion

The studied ternary complexes of inner transition metals showed 1:1:1 (M:LANSO:CYTO) composition as indicated from elemental analyser and exhibited corresponding conductivities suggesting 1:1:1 electrolytic behaviour. The IR data reveals that all the ligands function as bidentate ligands. Lansoprazole molecules chelate with the metal ions using their C=O group and S=O group and the cytosine acts as a chelating ligand binding through its N(3) and the oxygen of C=O. The 1H NMR spectra of nonequivalent proton of M-Hsal-M(Lanso)2(Cyto)4H2O where X is SO2− or NO3−. The result of antifungal activity indicates that the complexes are more active than free ligand (lansoprazole drug). The possible general structure of these representative ternary complexes is shown in Figure 1.

### Acknowledgments

The authors are thankful to the Chemistry Department for providing all laboratory facilities. They are grateful to Mr. Chowdary of Nosch Labs, Hyderabad, for providing pure powdered lansoprazole. Director of CDRI Lucknow for mass spectrum, NMR, the elemental analysis is also acknowledged. authors are also thankful to the Director of MPCST Bhopal for providing UV spectra and antimicrobial study. Cali Labs for IR spectroscopy is also acknowledged.

### References


