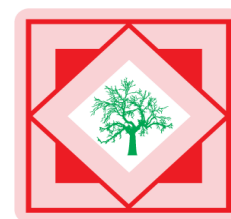




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Der Pharmacia Sinica, 2011, 2 (4):112-116



Der Pharmacia Sinica

ISSN: 0976-8688

CODEN (USA): PSHIBD

Complexation Behavior of a Proton Pump Inhibitor with Bivalent Metal Ions

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ABSTRACTS

Benzimidazoles act as good ligand to transition metal ions and they exhibit several coordination modes. The synthesis of hetero-chelates of the type $ML_2 \cdot 2H_2O$ has been reported here. The metal complex of Co(II) and Ni(II) Complexes have been synthesized with 6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1H-benzo[d]imidazole (Pantoprazole). Pantoprazole is a proton pump inhibitor (PPI) drug that inhibits gastric acid secretion. Proton pump inhibitors (or PPI) are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. Conductometric titrations have suggested metal-ligand ratio of 1:2 for both Co(II) and Ni(II) complexes. The ligand behaves as a bidentate with N, O donor atoms. Complexes have been synthesized and characterized by elemental analysis, UV-visible and IR spectral studies.

Key Word: Complex, Pantoprazole, Co(II), IR, PPIs.

INTRODUCTION

The literature reveals that a large number of drugs have been used to synthesize the complex with many metals with a view to enhance their therapeutic action.[1,2]. PPI drugs are among the most widely selling drugs in the world and are generally considered safe and effective[3,4]. The vast majority of these drugs are benzimidazole derivatives. Benzimidazole derivatives constitute an important class of heterocyclic compounds for their versatile pharmacological activities[5] such as antibacterial, antifungal, antihelmintic, antiallergic, antineoplastic, local analgesic, antihistaminic, antiulcer activities[6,7,8]. Pantoprazole, which contains benzimidazole and pyridine, is the best selling antiulcer drug now-a-days[9].

Compounds used as medicines are overwhelmingly organic compounds including small organic molecules and biopolymers. However, inorganic compounds and metal-containing compounds

have been found to be useful as drugs. For example, the cis-platin series of platinum-containing complexes have found used as anti-cancer agents[10].

Many drugs possess modified toxicological and pharmacological properties when they are in the form of metal complexes[11]. Complexation with Ni(II) resulted in improved antimicrobial profile of the drug while Mn(II) and Cu(II) metal complexes modulated oxidative burst response of phagocytes and unlike enoxacin could have potential to be anti-inflammatory, as they suppressed the production of reactive oxygen species[12,13]. Here in this paper we are describing synthesis and characterization of Cobalt (II) complexe with pantoprazole, (6-(difluoromethoxy)-2[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1*H* benzo[d]imidazole).

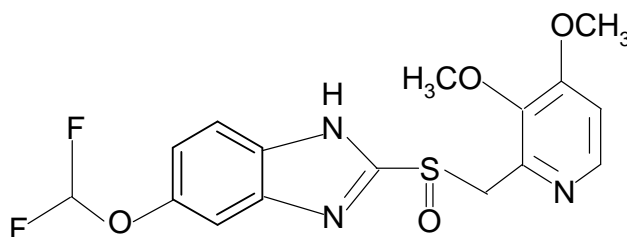


Fig.1. Structure of Pantoprazole

MATERIALS AND METHODS

(a) Reagents and Instruments:

All chemicals and solvents used were of analytical grade. Pure sample of Pantoprazole, molecular formula $C_{16}H_{15}F_2N_3O_4S$ and molecular weight 383.37, was obtained from Cornileus Pharmaceutics (P) Ltd. Metal salt $CoCl_2 \cdot 6H_2O$ and $NiCl_2 \cdot 6H_2O$ used were of Merck chemicals.

Elemental analysis (C, H, N and S) were carried out using micro analytical technique on C,H,N,S,O Elemental analyzer at SAIF, IIT Bombay. IR and electronic spectra of the complex were obtained from DST-FIST Instrumentation Laboratory of Sadhu Vaswani College, Bairagarh, Bhopal. Electronic spectra were recorded in the range 200-800nm on Perkin Elmer UV-visible spectrophotometer. Infrared spectra were recorded as KBr pellets in the range 4000-400 cm^{-1} on Perkin Elmer FTIR spectrophotometer. Melting point were recorded using melting point apparatus and found to be 180 $^{\circ}C$ for Co(II) and 200 $^{\circ}C$ for Ni(II) complex.

(b) Ligand-Metal ratio:

Before the synthesis of complexes, we need to confirm metal-ligand ratio by conductometric titration method. 0.01 M solution of pantoprazole drug was prepared in 80:20 mixture of ethanol and distilled water. Similarly, solution of metal salts $CoCl_2 \cdot 6H_2O$ and $NiCl_2 \cdot 6H_2O$ were prepared in the same solvent of 0.02 M concentration. 20 ml of ligand solution was diluted to 200 ml. The ligand was titrated against metal salt solutions and conductance was recorded after each addition of metal salt solution. From the graph between corrected conductance and volume of titrant added, it was concluded that the complex formation has taken place in the ratio of 1:2 (metal-ligand).

(c) Synthesis of complex:

After finding out the ligand-metal ratio, the solutions of ligand and metal salts were prepared in this ratio in 80:20 ethanol-water mixture. After mixing, the resulting mixture was refluxed for three hours after adjusting the pH and, there after, the solution was kept for a few days. A pink crystalline complex of cobalt and pistal green complex of nickel were separated that were washed with ethanol, filtered, dried, weighed and melting point were recorded.

RESULTS AND DISCUSSION

The synthesized complexes are stable solid towards air and moisture with high decomposition temperature. The metal complexes are insoluble in common organic solvents like benzene, chloroform, carbon tetrachloride, hexane, methanol, ethanol, acetone etc and soluble in DMF and DMSO. The analytical data (Table 1) of the metal complexes clearly shows the 1:2 metal to ligand stoichiometry.

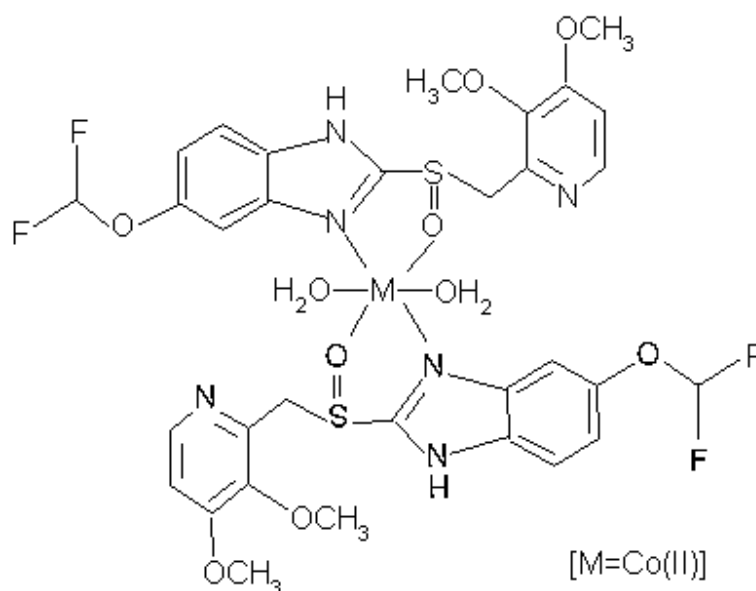


Fig. 2. Structure of Pantoprazole -Co complex

Infrared spectral studies: The Infrared spectra[14-18] of the ligand PPZ and the complexes have been recorded and the probable assignments are given here. The IR spectra of the complexes indicates that the ligand behaves as a donor coordinating to the metal via C=N and sulphonic acid group. The shift of the $\nu(\text{C}=\text{N})$ and $\nu(\text{S}=\text{O})$ by 10-15 cm^{-1} in the complexes indicates that these group are involved in the complexation. In the ligand, the band appearing at 3500 cm^{-1} due to NH stretching remains almost unchanged at 3505 cm^{-1} in the complex and the band $\nu(\text{C}=\text{N})$ in the ligand at 1589 cm^{-1} is shifted to 1573 cm^{-1} in Co-complex and 1570 cm^{-1} in Ni-complex. This confirms the coordination through the azomethine nitrogen atom. The IR band at 1039 cm^{-1} in the ligand due to aromatic sulfoxide stretching is shifted to 1024 cm^{-1} in the Co-complex and 1035 cm^{-1} in the Ni-complex indicating the involvement of oxygen of sufoxide in complex formation. Band appearing in the region 3631 cm^{-1} may be assigned to coordinated water molecules in Co-complex and 3610 cm^{-1} in Ni-complex. The appearance of band in far-IR

region at 460 cm^{-1} in the Co-complex and at 462 cm^{-1} in the Ni-complex may be assignable to M-N frequency. Additional band in the complex in the region 687 cm^{-1} in Co-complex and at 622 cm^{-1} in Ni-complex compared with IR spectra of free ligand have tentatively been assigned to M-O frequency.

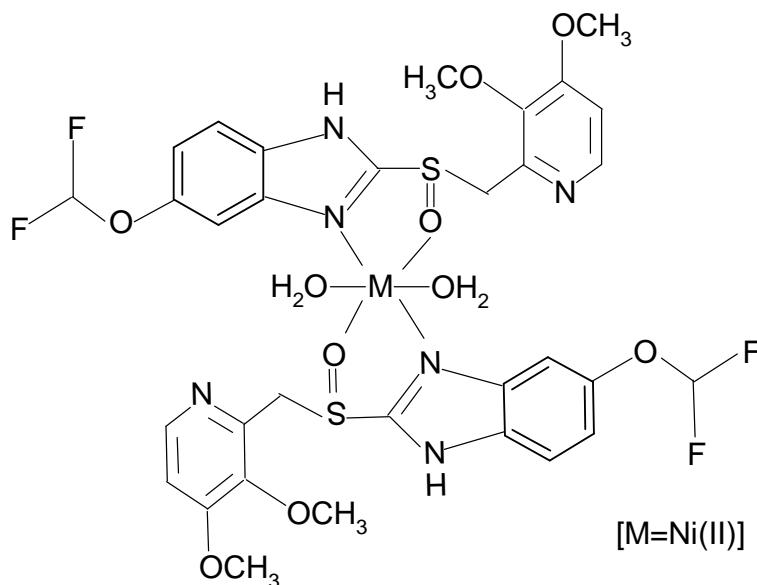


Fig. 2. Structure of Pantoprazole -Ni complex

Electronic spectra: The electronic spectra of the Co(II) complex displays two bands at 17762 cm^{-1} (ν_1) and 15385 cm^{-1} (ν_2) which can be assigned to ${}^4T_{2g}(G) \leftarrow {}^6A_{1g}$ and ${}^4T_{1g}(G) \leftarrow {}^6A_{1g}$ transitions, respectively, suggesting an octahedral environment around the cobalt ion. Electronic spectra of the Ni(II) complex displays three bands at 9134 cm^{-1} (ν_1), 20000 cm^{-1} (ν_1) and 25773 cm^{-1} (ν_1) which can be assigned to ${}^3T_{2g}(F) \leftarrow {}^3A_{2g}(F)$, ${}^3T_{1g}(F) \leftarrow {}^3A_{2g}(F)$ and ${}^3T_{1g}(F) \leftarrow {}^3A_{2g}(F)$ transitions, respectively suggesting an octahedral environment around the nickel ion.

Table-1. Analytical data of the ligand and complex

| Composition of complex (m.wt.) | color | yield (%) | m.p. ($^{\circ}\text{C}$) | Elemental analyses(%):found (calcd) | | | |
|---|--------------|-----------|-----------------------------|-------------------------------------|----------------|------------------|----------------|
| | | | | C | H | N | M |
| $\text{C}_{16}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_4\text{S}$ (383.34) | white | - | 140 | 50.12 | 3.94 | 10.96 | - |
| $(\text{C}_{16}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_4\text{S})_2\text{Co} \cdot 2\text{H}_2\text{O}$ | pink | 38 | 180 | 50.71 (50.12) | 3.73 (3.94) | 10.48 (10.96) | 7.58 (7.68) |
| $(\text{C}_{16}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_4\text{S})_2\text{Ni} \cdot 2\text{H}_2\text{O}$ | Pistal Green | 35 | 200 | 44.83 (44.65) | 3.78 (3.57) | 8.72 (9.76) | 6.70 (6.81) |

CONCLUSION

From the analytical and spectral data, it can be concluded that the synthesized complexes are stable with probably octahedral environment around it.

Acknowledgements

The authors are thankful to Principal, Sadhu Vaswani College, Bairagarh for providing necessary facilities for research work; DST for granting FIST program to the college and UGC for sanctioning UGC Research Award to Dr. Suman Malik, one of the co-authors.

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