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Spectroscopy Characterization and Synthesyzation of Metal Complexes of Antiulcerative drugs

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ABSTRACT: Few complexes of Transition metals have been synthesized by reacting their metal salts with Rabeprazole. Transition metal complexes of Ni (II), Co (II) and Zn (II) have been synthesized with Rabeprazole i.e. 2-([4-(3-methoxypropoxy)-3-methylpyridin-2-yl] methylsulfinyl)-1H- benzimidazole](L) which is an anti-ulcerative drug. From elemental analysis, the complexes have been formulated as ML_2 for Zn (II) complex and $ML_2.2H_2O$ for Ni (II) and Co (II) complexes. The ligand behaves as O, N donor and forms coordinate bonds through C = N and S = O groups. IR, NMR, Magnetic susceptibility, UV-Visible spectral studies suggest that Ni (II) and Co (II) complexes possess octahedral geometry whereas Zn (II) complexs exhibit tetrahedral geometry. Ligand and their metal complexes have been screened for their antibacterial activities against bacteria *Escherichia coli* and *Staphylococci aureus*. The result obtained is compared with that of parent drug. The result reveals that the metal chelates showed resistance as compared with parent drug.

Key Words: Metal Complex, Rabeprazole (RAB), Synthesis, (L) Ligand, Stochiometry, Proton pump inhibitors (PPIs).

I. INTRODUCTION

Metal complexes play an important role in biological activity of drugs. Physico-chemical property helpful in biological activity. Physiological activity and commercial applications of many benzimidazole derivatives have received much attention. Benzimidazole and its derivatives have different activities as they can act as bacteriostats or bactericides, fungicides, anticarcinogens, etc [1-5]. This ring system is present in numerous antiparasitic, antihelmintic and anti-inflammatory drugs [6], for example, Rabeprazole, Omeprazole, Pantoprazole, and Lansoprazole. which contain benzimidazole and pyridine are the best selling antiulcer drugs now a days [7]. In many cases metal complexes of drugs are more potent than the parent drug. Rabeprazole (RAB) is a very common PPI [8]. PPIs have demonstrated gastric acid suppression superior to that of histamine H2-receptor blockers. The literature reveals that a large number of drugs have been used to synthesize the complexes with many metals with a view to enhance their therapeutic action [9]. Considering the importance of drugs and their complexes it has been desired to synthesize and characterize some transition metal complexes of Rabeprazole with transition metals like Zn(II)), Ni(II) and Co(II). Transition metal complexes are of continuing interest mainly due to their structural and catalytical properties and their application in diagnostic pharmaceutical and laser technology.

II. EXPERIMENTAL

All chemicals used were of Analytical Grade or S.M. grade. Pure sample of Rabeprazole (molecular formula $C_{18}H_{21}N_3O_3S$ with molecular weight 359.450) was obtained from Dr. Reddy's Laboratories LTD, India. Metal salts $CoCl_2.6H_2O$, $NiCl_2.4H_2O$ and $ZnCl_2$ were of Merck Chemicals. The ligand as well as metal complexes were analyzed by standard methods. The solvents used were Millipore water and methanol.

Metal-ligand ratio was calculated using Systronics digital conductivity meter, IR Spectra were obtained from Department of Pharmacy, RGPV, Bhopal (Instrument used: Perkin Elmer FTIR Spectrophotometer in the range of 4000-400 cm1). Magnetic susceptibility measurements were received from CAT Indore (Instrument used-Vibrating Sample Magnetometer). Nitrogen was determined by the Dumas method and sulphur was estimated by the Messenger's method.

Electronic Spectra were obtained from Food and Drug Department, Bhopal. ESR spectra were obtained from IIT, Powai, Mumbai. Elemental analysis of C,H,N was were obtained from RRL, Bhopal.

The Mass spectra were obtained from DRDE, Gwalior. Spectra of isolate complex for NMR spectra were recorded on TC & HRD Division DRDE, Gwalior. Bacteriological studies of various compounds were obtained from Department of Microbiology, Rajiv Gandhi College, Bhopal. Elemental analysis of C,H,N was were obtained from RRL, Bhopal.

To confirm the ligand-metal ratio, conductometric titrations using monovariation method were carried out 26°C. 0.01 M solution of Rabeprazole drug was prepared in 20 : 80 mixture of methanol and water. Similarly, a solution of metal salts $CoCl_2.6H_2O$, $NiCl_2.4H_2O$ and $ZnCl_2$ were prepared in same solvent of 0.02 M concentration. 20 ml of ligand was diluted to 200ml and titrated against metal salt solution using monovariation method.

Conductance was recorded after each addition. Graph is plotted between corrected conductance and volume of metal salt added. From the equivalence point in the graph it has been concluded that the complex formation has taken place in the ratio of 2:1 (L:M). Stability constants and free energy changes were also calculated by Bjerrum Calving pH titration technique as adopted by Irving and Rossotti [10-11]. Conductometric studies of the metal-drug equilibria in solution utilising Nair and Pande's monovariation method indicated formation of complexes in these systems with metal-RAB molar ratio method.

The complexes were synthesized by mixing the metal salt solutions with that of ligand respectively and refluxing the mixture at low temperature for two hours. The mixtures were refluxed and the solutions were kept for few days. A green colored crystalline complex of $(RAB)_2Co.2H_2O$,brown colored crystalline complex of $(RAB)_2Ni.2H_2O$ and white crystalline complex of $(RAB)_2Zn$ formed were filtered, washed with mixture of methanol and distilled water (20:80) and dried. Elemental analysis of C, H, N was were obtained from RRL, Bhopal.

III. RESULTS AND DISCUSSION

The characterization of their molecular structure was made by elemental analysers conductivity and spectroscopy studies. The compounds prepare were colourful , soluble in Millipore water. The reaction of the Transition metal ions with RAB afforded in good yield (80-90%) of stable solid compound. The synthesized complexes are stable solids. Analytical data suggest 2:1 [L: M] ratio. The magnetic studies indicate that the ligand-Co and ligand-Ni complex to be paramagnetic with magnetic moment of 4.77 B.M and 3.16 B.M while Zn complex is diamagnetic.

Table 1. Analytical data of Complexes.

S. No.	Composition of Complex (m-wt.)	Color	Yield %	m.p.	Metal (%) Found (Cal)	Molar conductance ($ohm^{-1}cm^2mol^{-1}$)	Magnetic Moment (B.M.)
1	$C18H21N_3O_3S$ (359.45)	White		98^0C	_	_	_
2	$(C_{16}H_{14}N_3O_3S)_2$ Zn (784.24)	White	31	111^0C	8.35 (8.55)	9.36	_
3	$(C_{16}H_{14}N_3O_3S)_2Co.2H_2O$ (813. 849)	Green	23	127^0C	7.26 (7.14)	11.10	4.77
4	$(C_{16}H_{14}N_3O_3S)_2Ni.2H_2O$ (813. 606)	Brown	44	107^0C	7.22 (7.17)	12.4	3.16

Infrared Spectra Study

The IR spectra [12-15] of ligand and complexes have been recorded.The IR spectra of the complexes indicate that the ligand behaves as a bidentate and metal co-ordinate via C = N and sulphonic acid group.The shift of the *ν*C = N and *ν*S = O by 10-15cm^{-1} in the complexes indicating that these groups are involved in the complexation.In the ligand band appearing at 3456 cm^{-1} due to NH stretching remain unaffected in the complexes. The band due to *ν*C = N in the ligand at 1590 cm^{-1} is shifted to lower wave number at 1590-1576 cm^{-1} in the complexes confirm the coordination through the

azomethine nitrogen atom.

The IR band at 1012 cm^{-1} in ligand is due to aromatic sulfoxide stretching in Co-complex and Ni-complex shifted to 1023 cm^{-1} and 1021 cm^{-1} respectively and complex at 1026 cm^{-1} indicates the involvement of oxygen of sulfoxide in complex formation. In Co and Ni complexes, band appeared at region 3654-3619 cm^{-1} is due to coordinated water molecules. The appearance of bands in the far IR region at 429-409 cm^{-1} in the complexes may be assignable to M-N frequency. Additional bands in the complexes in the region 615-608cm^{-1} compared with IR spectra of free ligand have tentatively been assigned to M-O frequency and new band appeared at 1380-1390 cm^{-1} in complexes might be due to chelate ring formation in the complex.

NMR Spectra

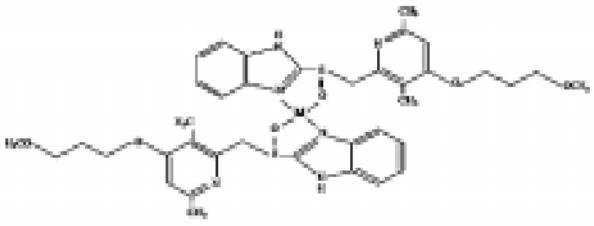
The ^{1}H NMR spectra of the ligand has the expected characteristic signals. The CH_3 proton shows singlet at δ 2.2 and O-CH_3 proton at δ 3.7ppm the doublet peak observed at δ4.36 and 4.66 ppm is attributed to CH_2 protons. In addition multiplet peak at δ 6.9-8.3 may be due to aromatic protons and peak at δ 13.2 is observed due to NH proton of benzimidazole ring. Signals observed in the complexes at region of δ 8.18-8.23 due to the azomethine proton are either remained unaffected or shifted slightly to higher field with reference to those of the parent ligand and the position of signal due to NH proton remain unaffected in the complexes. The aromatic protons show down field shifts in the complexes. These observations support the assigned structure to the complex.

Electronic spectra and magnetic susceptibility data

The spectra of Co(II) complex of Rabeprazole show three bands at 8900 cm^{-1}, 18000 cm^{-1} and 22000 cm^{-1} respectively corresponding to the following transitions $^{4}T_{2g}(F)$ $\nu\nu^{4}T_{1g}(F)$ (ν_1), $^{4}A_{2g}$ (F) $\nu\nu^{4}T_{1g}(F)$ (ν_2) and $^{4}T_{1g}(P)$ $\nu^{4}T_{1g}(F)$ (ν_3) which indicate octahedral geometry of the complex. The proposed geometry is further confirmed by high μ_{eff} value in the range [17-18] 4.89-5.24 B.M. The electronic spectra of Ni(II) complex display three absorption bands at 8333 cm^{-1}, 13700 cm^{-1} and 24640 cm^{-1} which may be assigned to $^{3}T_{2g}(F)^{3}A_{2g}$ (F) (ν_1), $^{3}T_{1g}(F)$ (ν_2) and $^{3}T_{1g}(P)$ ν $^{3}A_{2g}$ (F) (ν_3) transitions indicating octahedral geometry of the complex. The geometry of Ni (II) complex is further confirmed [16-17] by the high μ_{eff} value in the range 3.09-3.20 B.M. As expected Zn(II) complex is diamagnetic. The complex is suggested to be tetra coordinated probably having tetrahedral geometry based on analytical, I.R. and conductance data.

Antimicrobial activity

The antimicrobial activity of the ligand, metal salts and complexes were evaluated by the disc diffusion technique [19] against bacteria *Escherichia coli* and *Staphylococci aureus*. A 1mg/ML solution in DMF was used. The standard used was gentamycin sulphate 1mg/ML and solvent control was used to know the activity of the solvent.The Co(II) , Ni(II) and Zn(II) complexes show significant activity against bacteria *Escherichia coli* and *Staphylococci aureus* compared to ligand . The Ni(II) complex show is less active than the ligand in *Escherichia coli*. In view of the forgoing discussions, the high melting points and insolubility in common organic solvents we have assigned following probable structure to the Co, Ni and Zn complexes of Rabeprazole.



Structure for Rabeprazole-M (II) Complex.

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