Asian Journal of Chemistry Vol. 22, No. 6 (2010), 4671-4674

Synthesis and Characterization of Complexes of Some Bivalent Metal Ions with Omeprazole

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The Hg(II) and Mn(II) complexes have been synthesized with 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl sulfinyl]-1*H*-benzimidazole (omeprazole). Omeprazole is a proton pump inhibitor (PPI). Analytical data and stochiometry suggest ligand metal ratio of 2:1 for both Hg(II) and Mn(II) complexes. The ligand behaves as a bidentate N, O donors. The complexes have been synthesized and characterized by elemental analysis, magnetic susceptibility and infrared spectrum studies. The complexes have been formulated as $(C_{17}H_{19}N_3O_3S)_2Hg$ and $(C_{17}H_{19}N_3O_3S)_2Mn{\cdot}2H_2O$.

Key Words: Complex, Omeprazole, Synthesis, Ligand, Stochiometry.

INTRODUCTION

The therapeutic activity of coordination compounds has been evaluated extensively[1,2]. Some important examples of inorganic based drugs are metallocene antitumor complexes[3], gold antiarthritic compounds[4], lithium antidipressants[5], *etc*. In all these cases, work is largely focused on elucidating the mechanism of action of these complexes. Investigations are going on the formation of metal complex with benzimidazole ring containing ligands because benzimidazole and its derivatives play an important role in analysis and in several biological reactions. Benzimidazole derivatives exhibit antibacterial, antihelmintic and insecticidal activities[6-8]. Omeprazole is an antiulerative drug and it contains benzimidazole ring. The present paper describes the synthesis and characterization of Hg(II) and Mn(II) complexes with 5-methoxy-2[(4methoxy-3,5 dimethyl-2-pyridinyl)methylsulfinyl]-1*H*-benzimidazole (Fig. 1).

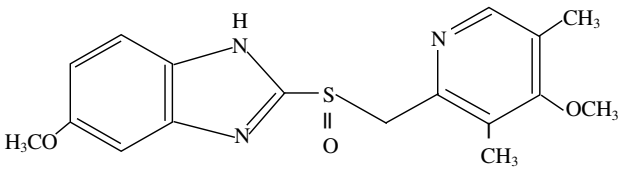

Fig. 1. Structure of omeprazole

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EXPERIMENTAL

All chemicals used were of analytical grade. Pure sample of omeprazole (m.f. $C_{17}H_{19}N_3O_3S$, m.w. 345.42) was obtained from Aristo Pharmaceuticals Ltd. Mandideep, Bhopal. Metal salt $MnCl_2 \cdot 7H_2O$ and $HgCl_2$ were of Merck chemicals. The solvents used were distilled water and methanol. Metal-ligand ratio was calculated using systronics digital conductivity meter, IR spectra were obtained from CDRI, Lucknow (in the range of 4000-400 cm^{-1}). Magnetic susceptibility measurements were received from CAT indore using vibrating sample magnetometer nitrogen was determined by the Dumas method and sulphur was estimated by the Messenger's method. The elemental microanalyses of C, H and N for ligand were carried out with Thomas and Coleman Analyzer Carlo Erba 7106.

Ligand-metal ratio: To confirm the ligand-metal ratio, conductometric titrations using monovariation method were carried out at 21 ºC. 0.01 M solution of omeprazole drug was prepared in 70:30 mixture of methanol and water. Similarly, solutions of metal salts $MnCl_2 \cdot 7H_2O$ and $HgCl_2$ were prepared in the same solvent of 0.02 M concentration. 20 mL of ligand was diluted to 200 mL with the same solvent. The ligand was 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 using Job's method[9] of continuous variation modified by Turner and Anderson[10].

Synthesis of complexes: Complexes were synthesized by mixing the solutions (70 % methanol) metal salt solutions with that of ligand in 1:2 molar ratios, respectively and refluxing the mixture for 3.5 h. The light pink precipitate of $Mn(Om)_2 \cdot 2H_2O$ and white precipitate of $Hg(Om)_2$ formed were filtered, washed with mixture of methanol and distilled water (70:30) and dried. Carbon, hydrogen, nitrogen, metal and water were estimated micro analytically at CDRI, Lucknow.

RESULTS AND DISCUSSION

The synthesized complexes are stable solids, being soluble in DMF and DMSO and insoluble in all other organic solvents. Analytical data (Table-1) and conductometric studies suggest 2:1 [L:M] ratio. Measured conductance values of these complexes are too low to account for their electrolytic behaviour. The magnetic studies indicate that the Mn complex is paramagnetic nature with magnetic moment of 5.3 B.M. while Hg complex is diamagnetic (Table-2).

Infrared spectral studies: The IR spectra[11-14] of ligand and complexes have been recorded and the probable assignments are given in the Table-3. The IR spectra of the complexes indicate that the ligand behaves as a donor coordinating to the metal *via* C=N and sulphonic acid group. The shift of the ν(C=N) and ν(S=O) by 10-15 cm^{-1} in the complexes indicate that these groups are involved in the complexation.

TABLE-1
ANALYTICAL DATA OF COMPLEXES

Composition of complex (m.w.)	Color	Yield (%)	m.p. (ºC)	Elemental analyses (%): found (calcd)			
				C	H	N	M
$C_{17}H_{19}N_3O_3S$ (345.42)	White		156	52.71	3.05	11.05	–
$(C_{17}H_{19}N_3O_3S)_2Hg$ (891.42)	White	30	210	45.81 (45.91)	4.29 (4.30)	9.42 (9.22)	22.50 (23.01)
$(C_{17}H_{19}N_3O_3S)_2Mn{\cdot}2H_2O$ (781.80)	Pink	28	190	52.23 (53.20)	4.89 (4.51)	10.74 (10.47)	7.02 (7.12)

TABLE-2
STABILITY CONSTANT, FREE ENERGY CHANGE, MOLAR CONDUCTANCE AND MAGNETIC- MOMENT DATA OF COMPLEXES

Composition of complex	Stability constant log K (L/mol)	Free energy change -ΔF (Kcal/mol)	Molar conductance (ohm^{-1} cm^2 mol^{-1})	Magnetic moment (B.M.)
$(C_{17}H_{19}N_3O_3S)_2Hg$	10.7471	14.9751	10.34	–
$(C_{17}H_{19}N_3O_3S)_2Mn{\cdot}2H_2O$	12.0880	17.0300	12.01	5.38

TABLE-3
IR ABSORPTION DATA OF THE COMPLEX

Ligand and complex	ν(N-H) (cm^{-1})	ν(C=N) (cm^{-1})	ν(S = O) (cm^{-1})	ν(M-N) (cm^{-1})	ν(M-O) (cm^{-1})	ν(H_2O) (cm^{-1})
$C_{17}H_{19}N_3O_3S$	3456	1590	1012	–	–	–
$(C_{17}H_{19}N_3O_3S)_2Mn{\cdot}2H_2O$	3452	1576	1019	409	610	3625
$(C_{17}H_{19}N_3O_3S)_2Hg$	3454	1582	1021	427	615	–

In the ligand the band appearing at 3456 cm^{-1} due to NH stretching remains unaffected in the complex. The band due to ν(C=N) in the ligand at 1590 cm^{-1} is shifted to lower wave number at 1576 cm^{-1} in Mn-complex and 1582 cm^{-1} in Hg-complex confirms the coordination through the azomethine nitrogen atom. The IR band at 1012 cm^{-1} in ligand is due to aromatic sulfoxide stretching in Mn-complex shifted to 1019 cm^{-1} and in Hg-complex at 1021 cm^{-1} indicates the involvement of oxygen of sulfoxide in complex formation. In Mn-complex, band appeared at region 3625 cm^{-1} may be assigned to coordinated water molecule. The appearance of bands in the far IR region at 429-409 cm^{-1} in the complex may be assignable to M-N frequency. Additional bands in the complex in the region 615-608 cm^{-1} compared with IR spectra of free ligand have tentatively been assigned to M-O frequency and new band appeared at 1380 cm^{-1} in complex might be due to chelate ring formation in the complex.

Electronic spectra and magnetic susceptibility data: The Mn(II) complex of omeprazole exhibits magnetic moment of 5.3 B.M. suggesting the formation of spin free complexes. This clearly agrees with the reported value of 5.30 B.M. for Mn(II) complexes[15]. The electronic spectra of the Mn(II) complex display three bands at 24,390; 22,220 and 16,666 cm^{-1} which can be assigned to $^4E_g(G) \leftarrow {}^6A_{1g}$, $^4T_{2g}(G)$

$\leftarrow {}^6A_{1g}$ and ${}^4T_{1g}(G) \leftarrow {}^6A_{1g}$ transitions, respectively suggesting an octahedral environment around the manganese ion.

As expected Hg(II) complex is diamagnetic. The complex is suggested to be tetra coordinated probably having tetrahedral geometry based on analytical, I.R. and conductance data. On the basis of above studies following structure may be assigned to the Mn and Hg complexes of omeprazole.

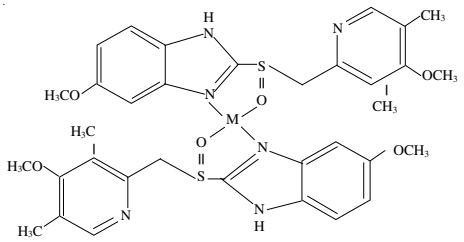

Fig. 2. Structure of omeprazole-Hg complex

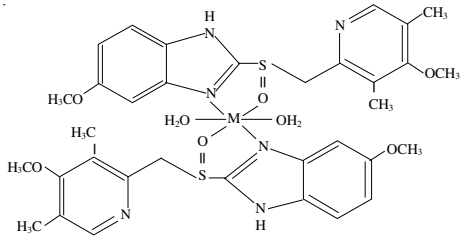

Fig. 3. Structure of omeprazole-Mn complex

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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(*Received*: 29 September 2009; *Accepted*: 17 February 2010) AJC-8459