

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

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ABSTRACT: To determine the effects of metal complexes Ni(II), Co(II) and Zn(II) have been synthesized with Gliclazide that is (N-(hexahydrocyclopenta[C]-pyrrol-2(1H)-ylcarbonyl-4-methylbenzene sulphonamide is a second generation sulphonyl-urea drug. Gliclazide works in several different ways, but its primary function is to increase insulin Sensitivity, improve glucose clearance and reduce the amount of hepatic glucose produced. Analytical data and stoichiometry suggest ligand metal ratio of 2:1 for Ni(II), Co(II) and Zn(II) complexes. The metal ligand behaves as a O donor. Infrared spectral studies confirm the co-ordination of sulphonyl oxygen on one side and enolic oxygen attached from other side with the metal ion. From the magnetic data and IR spectra, on the basis of electronic spectral value the complexes are proposed to have the geometrical structure of complex is octahedral Ni(II), Co(II) and tetrahedral structure of Zn(II). The complex has been formulated as $[\text{Ni}(\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2(\text{H}_2\text{O})_2]$, $[\text{Co}(\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2(\text{H}_2\text{O})_2]$ and $[\text{Zn}(\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2]$.

KEYWORDS: Gliclazide drug, Complexes, Synthesis, Ligand, Stoichiometry.

1. INTRODUCTION

A available literature shows that systematic study on complexation of metals with sulphonyl urea is carried out by Suman Malik and co-workers. The therapeutic value of organometallics is well known. Most of organometallics compounds and co-ordination compounds are used in the treatment of several fatal diseases in human and other animal system, e.g. organovanadium [1] and mercury [2] as diuretic, organoselenium in the treatment of cancer [3] organozinc [4] in the treatment of skin cancer, organogallium, platinum and palladium as antitumor [5], organobismuth in trypanosome infection [6] etc. In all these cases, work is largely focused on elucidating the mechanism of action of those complexes.

Gliclazide (GLZ), a sulphonylurea, is used to treat non-insulin dependent diabetes mellitus (NIDDM). Its primary mode of action is to increase insulin secretion by pancreatic β cells. It also a variety of other effects on the cells; such as a reduction in hepatic glucose production, improved glucose turnover, a reduction in platelet aggregation and a free radical scavenging effect.

The treatment of NIDDM generally focuses on the reduction of blood glucose levels. Increased blood glucose, which is caused by defective insulin secretion and decreased insulin sensitivity, is the hallmark of diabetes. There is a multitude of complications involved with this disease; kidney failure, micro- and macrovascular disease, retinopathy and atherosclerosis. Gliclazide is an antidiabetic drug and it contains have the metal complexes a chelate ring frequency at $627 \pm 5 \text{ cm}^{-1}$. The present paper describes the synthesis and characterization of Ni(II), Co(II) and Zn(II) Complexes of GLZ.

However, in this work we prepared chelates of Ni(II), Co(II) and Zn(II) transition metals with GLZ drug molecule. The solid chelates are characterized using different physico-chemical methods like elemental analyses (C,H,N,S and metal content), IR spectra. The structure of GLZ drug is given in Fig. 1

International Journal of Innovative Research in Science, Engineering and Technology

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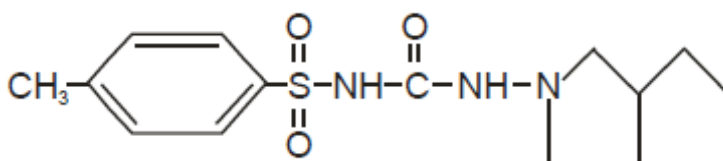


Fig. 1: Structure of Gliclazide

II. RELATED WORK

Iqbal *et al.*, [7] worked on synthesis, characterization and spectral studies of metal complexes of glimepiride, an oral anti-diabetic drug. Hiromura *et al.*, [8] worked on action mechanism of metallo-allixin complexes as anti-diabetic agents. Chouhan *et al.*, [9] reported the X-ray diffraction and thermal characterization study of Sm(III) complex of sulphonylurea glipizide: An oral anti-diabetic drug. Kamran *et al.*, [10] further study reveals that the synthesis and characterization of Glibenclamide complexes of Magnesium, Chromium, Cobalt, Nickel, Zinc and cadmium salts Glibenclamide is the commonly used hypoglycemia agent in NIDDM.

III. EXPERIMENTAL

All chemicals used were of the analytical reagent grade (AR), and highest purity available. Pure sample of gliclazide C₁₅H₂₁N₃O₃S, m.w. 323.42 was obtained from Rinilifescience pvt. Ltd. Indore, metal salt NiCl₂.6H₂O, CoCl₂.6H₂O and ZnCl₂ was of Merck chemicals. The solvents used were distilled water and ethanol. Metal-ligand ratio was calculated using Systronics digital conductivity meter, the elemental microanalyses of C, H, N and S for ligand was carried out with Thomas and Coleman Analyzer Carlo Erba.

Ligand- metal ratio

To confirm the ligand- metal ratio, conductometric titrations using Monovariation method were carried out at 28°C. 0.01M solution of GLZ drug was prepared in ethanol. Similarly, solutions of metal salts NiCl₂.6H₂O, CoCl₂.6H₂O and ZnCl₂ were prepared in the same solvent of 0.02M 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 [11] of continuous variation modified by Turner and Anderson [12].

Synthesis of complex

Complex was synthesized by mixing the solution (ethanol) metal salt solutions with that of ligand in 1:2 molar ratios, respectively and refluxing the mixture for 3.5 to 4 h. The light green precipitate of [Ni(C₁₅H₂₁N₃O₃S)₂(H₂O)₂], pale pink precipitate of [Co(C₁₅H₂₁N₃O₃S)₂(H₂O)₂] and white precipitate of [Zn(C₁₅H₂₁N₃O₃S)₂] formed was filtered, washed with ethanol, dried and weighed, melting point of the complex was recorded.

IV. RESULTS AND DISCUSSION

The synthesized complex is 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 the complex are too low to account for their electrolytic behavior. The magnetic studies indicate that the Ni(II), Co(II) complexes are octahedral and Zn(II) tetrahedral structure (Table-2).

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Infrared spectral studies

The IR Spectra (13-16) of ligand and complex have been recorded and the probable assignments are given in (Table-3).

TABLE -1 Analytical data of Complex

| Composition of Complex (m.w.) | Color | Yield (%) | M.P. (°C) | Elemental analyses (%) : Found (calculated) | | | | | |
|--|-----------|-----------|-----------|---|----------------|------------------|----------------|----------------|------------------|
| | | | | C | H | N | M | S | H ₂ O |
| C ₁₅ H ₂₁ N ₃ O ₃ S (323.41) | White | - | 182 | 55.70 (55.94) | 6.54 (6.76) | 12.99 (12.94) | - | 9.92 (9.96) | - |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Ni.2H ₂ O (741.562) | Green | 75 | 205 | 48.58 (48.67) | 5.70 (5.79) | 11.32 (11.45) | 7.91 (7.98) | 8.65 (8.69) | 4.85 (4.96) |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Co.2H ₂ O (741.802) | Pale Pink | 56 | 230 | 48.57 (48.63) | 5.70 (5.79) | 11.33 (11.28) | 7.94 (8.02) | 8.65 (8.73) | 4.85 (4.97) |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Zn (712.21) | White | 55 | 220 | 50.58 (50.92) | 5.94 (6.23) | 11.80 (11.87) | 9.23 (9.02) | 9.00 (9.43) | - |

TABLE -2

Stability Constant, Free Energy Change, Molar Conductance and Magnetic-Moment data of Complex

| Composition of Complex | Stability Constant logK(L/mol) | Free energy change - ΔF (Kcal/mol) | Molar conductance (ohm ⁻¹ cm ² mol ⁻¹) | Magnetic moment (B.M.) |
|---|--------------------------------|------------------------------------|--|------------------------|
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Ni.2H ₂ O | 12.1264 | 15.2145 | 10.8 | 2.78 |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Co.2H ₂ O | 11.5654 | 15.9301 | 12.3 | 4.60 |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Zn | 12.1139 | 16.6304 | 13.25 | Diamagnetic |

TABLE -3 IR Absorption data of the Complex

| Composition of Complex | ν (N-H) (cm ⁻¹) | ν (C=O) (cm ⁻¹) | ν (S=O) (cm ⁻¹) | ν (SO ₂ N) (cm ⁻¹) | ν (M-O) (cm ⁻¹) | ν (H ₂ O) (cm ⁻¹) |
|---|-----------------------------|-----------------------------|-----------------------------|---|-----------------------------|--|
| (C ₁₅ H ₂₁ N ₃ O ₃ S) | 3379 | 1770 | 1382 | 1287 | - | - |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Ni.2H ₂ O | 3360 | 1709 | 1343 | 1286 | 629 | 3440 |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Co.2H ₂ O | 3300 | 1764 | 1310 | 1243 | 667 | 3468 |
| (C ₁₅ H ₂₁ N ₃ O ₃ S) ₂ Zn | 3322 | 1761 | 1308 | 1222 | 644 | - |

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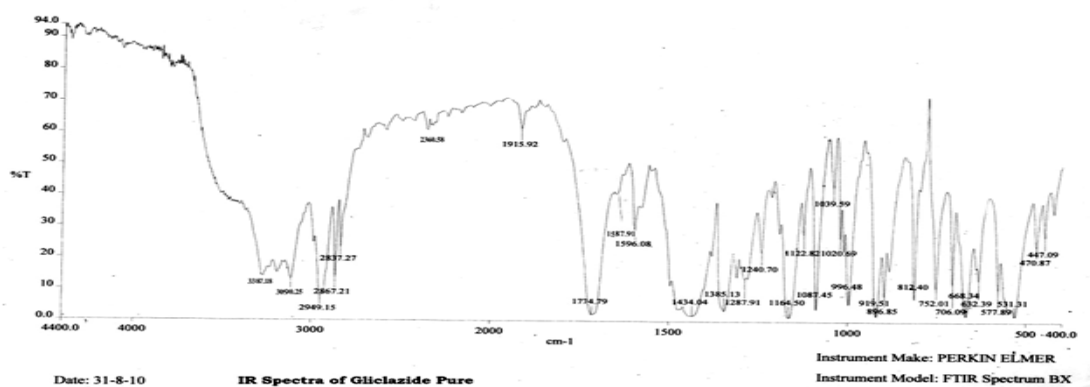


Fig. 2 IR Spectra of Pure Gliclazide

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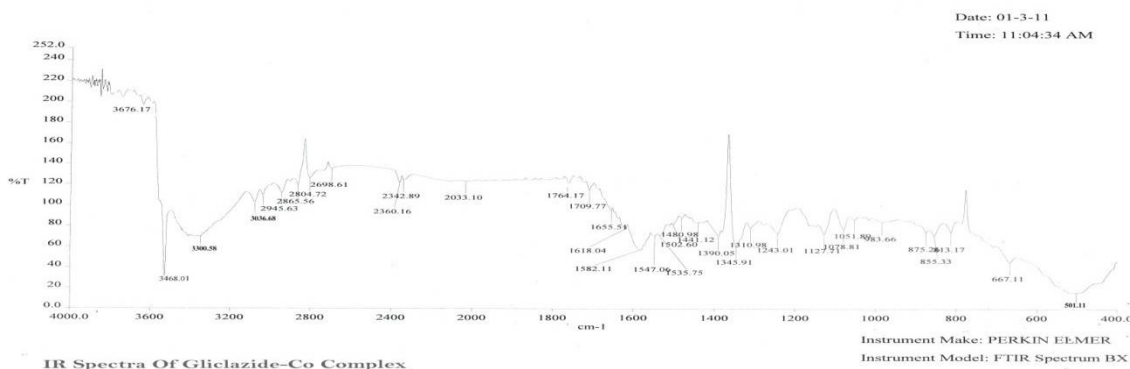


Fig. 3 IR Spectra of Gliclazide – Co Complex

The IR spectra of the complex indicate 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 $10\text{-}15\text{ cm}^{-1}$ in the complex indicate that these groups are involved in the complexation.

In the ligand the band appearing at 3357 cm^{-1} due to NH stretching remains unaffected in the complex. The band due to $\nu(\text{C}=\text{N})$ in the ligand at 1596 cm^{-1} is shifted to lower wave number at 1570 cm^{-1} in Ni Complex, in Co complex shifted to wave number at 1535 cm^{-1} and Zn complex shifted to wave number at 1531 cm^{-1} . Confirm the Coordination through the oxygen atom. The IR band $\nu(\text{S}=\text{O})$ stretching at 1087 cm^{-1} in ligand is due to aromatic sulfoxide stretching in Ni complex shifted to 1014 cm^{-1} in Co complex 1087 cm^{-1} and Zn complex 1092 cm^{-1} indicates the involvement of oxygen of sulfoxide in complex formation. In IR band $\nu(\text{S}=\text{O})$ stretching six membered heterocyclic ring enolic structure in ligand modified on complexation in Ni complex shifted to 1343 cm^{-1} , Co complex shifted to 1310 cm^{-1} and Zn complex shifted to 1308 cm^{-1} . In Ni complex, band appeared at region 3440 cm^{-1} , Co complex 3468 cm^{-1} may be assigned to coordinated water molecule. Aromatic ring vibration in Ni 852 cm^{-1} , Co 855 cm^{-1} and SO_2N frequency indicate in 1286 cm^{-1} , 1243 cm^{-1} and 1222 cm^{-1} . Additional bands in the complex in the region 632 cm^{-1} , Ni complex 629 cm^{-1} , Co complex 667 cm^{-1} and Zn complex 644 cm^{-1} compared with IR spectra of free ligand

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have tentatively been assigned to M-O frequency and new band appeared at 508 cm^{-1} in complex might be due to chelate ring formation in the complex.

Electronic spectra and magnetic susceptibility data:-

The electronic spectra of Ni (II) complexes exhibit a two broad, band in reason 10197 cm^{-1} and 23100 cm^{-1} . The bands observed are assigned to the transition $3T_2g(F) \leftarrow 3A_2g(F)$ and $3T_1g(P) \leftarrow 3A_2g(P)$ respectively, suggesting the presence of Ni (II) complex expected octahedral geometry [17-19]. It is further supported by the high μ_{eff} value in the range 2.78 B.M. The electronic spectra of Co (II) complexes exhibit a two broad, band in reason 10189 and 14832 cm^{-1} . The bands observed are assigned to the transition $4T_2g(F) \leftarrow 4T_1g(A)$ and $4A_2g(F) \leftarrow 4T_1g(F)$ respectively, suggesting the presence of Co (II) complex expected octahedral geometry. It is further supported by the high μ_{eff} value in the range 4.60 B.M. Zn(II) complex is diamagnetic in nature. The zinc complex is suggested to be tetra-coordinated probably having tetrahedral geometry [20]

V. CONCLUSION

The Ni(II), Co(II) and Zn(II) complexes of Gliclazide were synthesized and characterized by elemental and spectral analysis . The magnetic studies and electronic spectra indicate that the Ni(II) and Co(II) complexes possess octahedral and Zn(II)complex tetrahedral geometry. Proposed structure of metal complexes are as under:

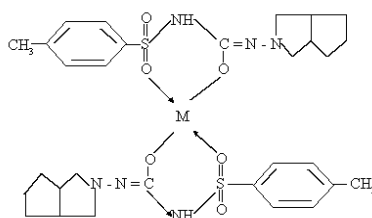


Fig. 5 (M=Zn)

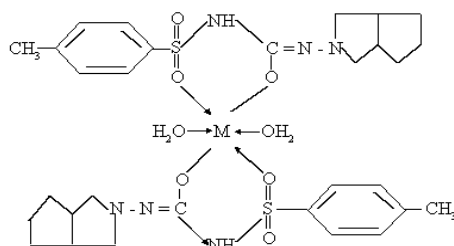


Fig.6 (M=Co or Ni)

ACKNOWLEDGEMENT

The authors are thankful to Principal, Sadhu Vaswani Autonomous College, Bairagarh, Bhopal 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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