



Synthesis, Characterization and Spectral Studies of Gold Complex with Gliclazide, An Oral Antidiabetic Allopathic Drug

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ABSTRACT

Synthesis, characterization and spectral studies of gold complex with gliclazide, an oral antidiabetic drug have been studied. The conductometric titration using monovariation method indicate that complexes are non-ionic and L_2M type. Analytical data agrees with the molecular formula $(C_{15}H_{20}N_3O_3S)_2Au$. Structure of complex was assigned tetrahedral, supported by IR, ¹H-NMR, X-Ray and Mass studies. Structure (II) is proposed for complex.

Key words: Gliclazide, antidiabetic drug, complex, IR, NMR. Mass, X-Ray.

INTRODUCTION

Metal ion are required for many critical function in humans. Scarcity of some metal ions can leads to disease¹. Well – known example can leads to pernicious anemia resulting from iron deficiency; growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. The ability to recognize, to understand at the molecular level, and to the diseases caused by inadequate metal- ion function constitutes an important aspect of medicinal bioinorganic chemistry. Understanding the biochemistry and molecular biology of natural detoxification mechanisms and designing and applying ion -specific chelating agents to treat metal over -loads are the two components of a second major aspect of the new science that is evolving at

the interface of bioinorganic chemistry and medicine.

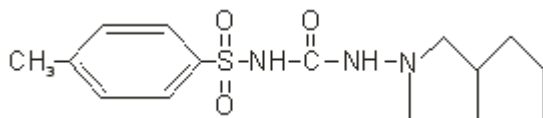
Diabetes is a deceptive disease and if not detected in early stage may cause even death. It is considered hereditary but actual genetic disorder is still a mystery. Several million people are suffering from this disease all over the world [Sadilot and Phatak,²; Bloomgarden³, ; Sanger and Thompson,⁴]. Zinc- insulin was discovered as early as in 1921 and later it proved to be a very efficacious medicine in the treatment of diabetes mellitus. To avoid the daily pricks of hypodermic syringe, oral hypoglycemic agents were discovered which has revolutionized the treatment of diabetes .It is worthwhile to mention here that the majority of the essential metallic elements of biological importance are transition metals, whose ability to form

coordination complexes and chelates is the characteristic aspects of their chemistry.

In recent years much attention is given to the use of sulphonylureas because of their high complexing nature with essential metals. Sulphonylureas are effective for non- insulin dependent *diabetes mellitus*, [Sadilol and Phatak², Bioomgarden,³ Sanger and Thompson,⁴]. These compounds are completely absorbed on oral administration. They are metabolized by liver and are excreted predominantly through urine.

Complexation of sulphonylureas with lighter transition metals has been studied in detail by Yoshinaga and Yamamoto⁵⁻⁶, [Iqbal *et al.*,]^{7,10-11,26} and other author synthesis the complexes of various metals with compound³⁰⁻³⁷. A perusal of available literature shows that systematic study of complexation of gold with gliclazide is relatively scanty. It is interesting to have an insite in to the synthesis of vanadium complex with gliclazide and to diagnose various structural aspects of the isolated complex

Here the synthesis and characterization of gold with gliclazide have been described.



Scheme 1: Structure of Gliclazide

EXPERIMENTAL

Ligand-Metal Ratio

- Pure Gliclazide m.p. 180°C (Lit. 179.5-180.5), 0.005 M, were diluted to 100 mL as required and titrated conductometrically against gold chloride at 30±1°C. Results were plotted in the form of a graph which indicate ligand metal ratio as 2:1 (L₂M).
- Formation of 2:1 (L₂M) ratio was further confirmed by Job's method⁸ of continuous variation as modified by Turner and Anderson⁹(Table-1) spectrophotometric studies were conducted using absorbance as index property, from these values the

stability constant (log k) and free energy change (-DF), were also calculated (Irving and Rossotti³⁸⁻³⁹) Tables 1, and fig. 1 given for Gliclazide -Gold complex.

Synthesis of Complexes

The chemicals used in this synthesis were all of analar grade Hi-media. A weighed quantity of gliclazide(2 mol) (supplied by Zim Laboratory, Nagpur) was dissolved separately in minimum quantity of 90% ethanol. The gold chloride solution was prepared by dissolving (1 mol) separately in the same solvent. Ligand solution was added slowly with stirring into the metallic salt solution at room temperature, maintain the pH between 6.0 to 6.5 by adding dilute NaOH solution. On refluxing the mixture for 3 h and on cooling the complexes separated out. Which were filtered off, washed well with ethanol and finally dried in vacuum and weighed.

The elemental analyses of the isolated complexes were carried out using coleman analyzer at the departmental micro analytical laboratory CDRI Lucknow, India.

The IR spectrum of the ligand as well as of the complex was recorded on Perkin Elemer Spectrometer(I.I.T Bombay) and ¹H-NMR spectra of the ligand and isolated complex was recorded on a Bruker DRX-300 Spectrometer and d₆-DMSO was used as a solvent. IR and ¹H-NMR spectrums recorded in CDRI, Lucknow and IIT Bombay, India and X-Ray diffractrogram from Punjab University, Chandigarh, India.

From stoichoimetry and analytical data, the composition of the complex comes out to be (C₁₅H₂₀N₃O₃S)₂.Au, which favours 2:1 (L₂M) ratio. The tentative structure(I) assigned to complex on the basis of analytical data and IR, NMR, Mass and X-ray.

RESULTS AND DISCUSSION

Infra-red Spectra Studies

The IR spectra of ligand and isolated complex was scanned within the range 4000-400 cm⁻¹. Assignments of the infrared spectral bands are based on literature (Table-3) IR spectrum shows

Table 1: gliclazide with gold(III)chloride (modified jobs method⁸)

Jobs method by spectrophotometrically					
Gliclazide-0.002M,0.005M			Gold(III) chloride-0.002M.0.005M		
Solvent: 90% Ethyl alcohol			Temperature: 30±1°C		
Wavelength: 660 nm			pH: 5.9		
S. No.	Mole Metal:Ligand	Absorbance		Corrected Abs.	Corrected Abs.
		0.002M	0.005M	0.002M	0.005M
1	0:12	0.01	0.015	0.00	0.00
2	1:11	0.119	0.253	0.109	0.233
3	2:10	0.283	0.423	0.261	0.402
4	3:9	0.464	0.611	0.449	0.586
5	4:8	0.725	0.925	0.710	0.895
6	5:7	0.701	0.849	0.682	0.712
7	6:6	0.593	0.693	0.478	0.633
8	7:5	0.474	0.613	0.459	0.504
9	8:4	0.422	0.563	0.405	0.503
10	9:3	0.332	0.442	0.312	0.362
11	10:2	0.098	0.397	0.078	0.322
12	11:1	0.053	0.243	0.032	0.163
13	12:0	0.023	0.085	0.00	0.00

Table 2: Pysico-chemical Characterstics of Gliclazide complex with Gold

S. No.	Complexes	Colour	Yield (%)	m.p. ° C	-ΔF	Log K	Molar conductance W ⁻¹ cm ⁻¹ mole ⁻¹
1.	(C ₁₅ H ₂₀ N ₃ O ₃ S) ₂ Au	Brown	36	183	16.66	11.97	33.6

Table 3: Elemental analysis of Gliclazide-Gold complex

S. No.	Formula of complexes	Molecular weight (g/mole)	C	H	N	S	Metal (%)
1.	(C ₁₅ H ₂₀ N ₃ O ₃ S) ₂ Au	842.45	42.76 (43.82)	4.75 (5.64)	9.57 (9.85)	7.60 (703)	23.48 24.96

Table 4: Specific IR assignment of Gliclazide,and Gliclazide complexes with Au

Pure drug(Gliclazide)	Gliclazide-Au complex
632cm ⁻¹ s,668cm ⁻¹ vs,1087cm ⁻¹ vs	618cm ⁻¹ s ,672vs,1108cm ⁻¹ s,1187cm ⁻¹ s ,1620vs
1240cm ⁻¹ vs,1348cm ⁻¹ vs,1710cm ⁻¹ vs,2867cm ⁻¹	1340cm ⁻¹ s,1520cm ⁻¹ s 2857cm ⁻¹ 2924cm ⁻¹
1,2950cm ⁻¹ vs,3274cm ⁻¹ vs	3021cm ⁻¹ s,3670cm ⁻¹ m
Vs=very strong,s=strong,m=medium	Vs=very strong,s=strong,m=medium
W=weak	W=weak

important bands due to $\nu(\text{M-O})$ 400-600 cm^{-1} , $\nu(\text{Ar-S})$ 700-800 cm^{-1} , $\nu(\text{-S-N})$ 1085 \pm 20 cm^{-1} , $\nu(\text{SO}_2\text{-N})$ 1120 \pm 20 cm^{-1} , $\nu(\text{C-N})$ 1210 \pm 20 cm^{-1} , $\nu(\text{S=O})$ 1340 \pm 20 cm^{-1} , $\nu(\text{C=O})$ 1710 cm^{-1} (present only in pure drug and absent in complex), 1600 \pm 20 cm^{-1} vs (coordinate H_2O molecule present only complex), $\nu(\text{NH-stretch})$ 3274 \pm 20 cm^{-1} .

The proposed structure for the isolated complex is also supported by IR absorption, C.N.Rao¹², Bellamy¹³, Weissberger¹⁴.

¹H-NMR Studies

¹H-NMR spectral data are given in (Table-4). It was observed that the singlet due to the imide (NH) proton around (d8.033) in the spectrum of the ligand disappeared in the spectra of (NH) group in the complex molecule due to formation of M-O band. This also confirms the deprotonation of imide NH group through enolization (the appearance of >C=N stretching band observed in IR spectra)

Table 5: NMR-Assignments of Gliclazide-Gold complex

$(\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2$ pure drug Gliclazide	$(\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2\text{Au}$
δ 8.041 (s,1H,NHCo, $J=0.334\text{H}_z$), δ 7.817 (d,benzene $J=1\text{H}_z$), δ 7.395(d,benzene, $J=1\text{H}_z$), δ 6.28 (s, SO_2NH), δ 3.320 (NH-CO, $J=0.929\text{H}_z$), δ 2.901(s, CH_3 group attached to benzene, $J=2.160\text{H}_z$), δ 1.388 (s, CH_3 group, $J=2.955\text{H}_z$)	δ 8.033 (d,1H,NH-CO, $J=1.441\text{H}_z$), δ 7.806 (d,benzene, $J=4.987\text{H}_z$), δ 7.395 (s, $\text{SO}_2\text{-NH}$, $J=1\text{H}_z$), δ 3.504 (s,NH-CO-Au, $J=0.83\text{H}_z$), δ 2.618 (s, CH_3 -group attached to benzene, $J=13.395\text{H}_z$), δ 1.571 (q, CH_3 group, $J=5.50\text{H}_z$), δ 1.224 (CH_3 group, $J=1.165\text{Hz}$)

s=singlet, d=doublet, t=triplet, q=quartrate, m=multiplet

Table 6: Cell data and crystal parameter of GLZ-Au Complex

Fig.4: X-ray diffractogram of Gliclazide-Gold complex

$a(\text{\AA}) = 21.762$	Volume (abcsin b) $\text{\AA}^3 = 14065.307$
$b(\text{\AA}) = 23.4271$	$c(\text{\AA}) = 27.274$
Dobs = 3.36041 g/cm^3	Dcal = 3.35724 g/cm^3
Standard deviation = 0.0026%	Crystal system = orthorhombic
$\alpha=90^\circ$, $\beta=89.2$, $\gamma=90^\circ$	Porosity(%) = 2.361
Density = 0.059845 g/cm^3	Particle size = 10.91microns
Space group = Pm	

2θ	I/I_0	$D_{(\text{Obs})}$	$D_{(\text{Cal})}$	h	k	l
26.5255	100	3.36041	3.35724	1	6	4
30.3724	40.21	2.94300	2.93864	-1	2	9
34.9471	63.10	2.56752	2.56734	-3	1	10
43.9242	31.47	2.06137	2.06019	8	3	8
51.9526	29.96	1.75867	1.35806	-8	11	8

Table 7: Mass Spectrum assignment of GLZ-Au Complex

m/z 840 due to $[\text{Au}(\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2]^+$ or $(\text{ML}_2)^+$. Molecular ion peak (m^+); m/z 447 due to $[\text{C}_{18}\text{H}_{30}\text{N}_4\text{O}_7\text{S}]^+$ radical ion, m/z 324 due to $[\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3\text{S}]^+$ base peak ion 100% relative abundance, m/z 386 due to $[\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_6\text{S}]^+$ Fragment ion, m/z 273 due to $[\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_7]^+$ radical ion.

Job's Method of continuous variation

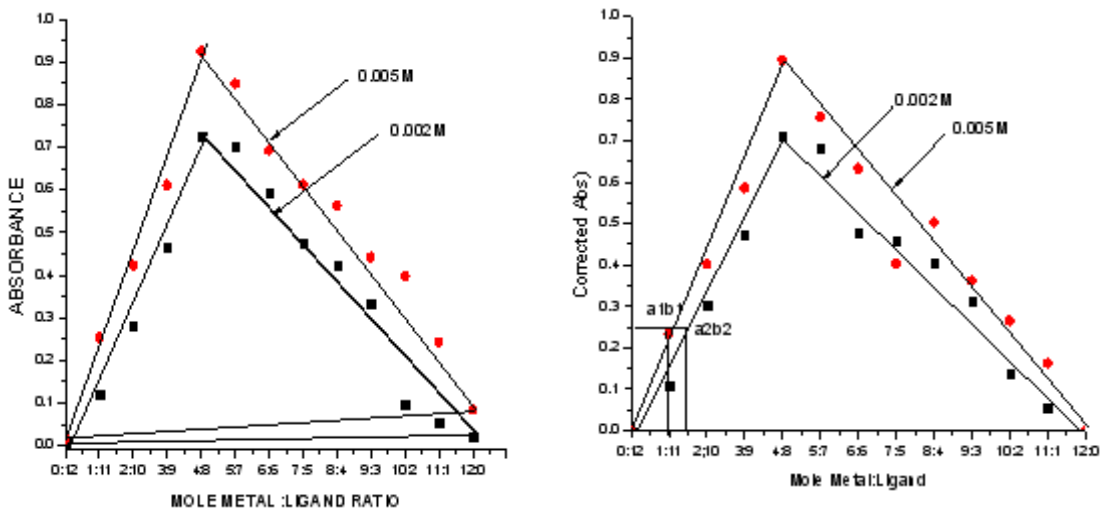


Fig. 1: Gliclazide with gold chloride

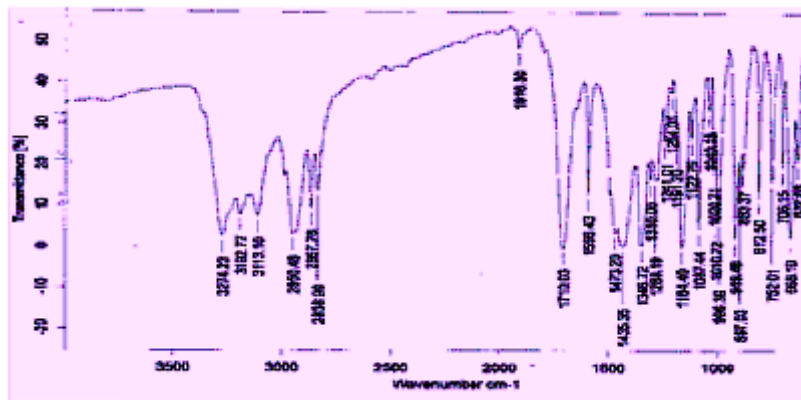


Fig. 2: IR Spectra of Gliclazide

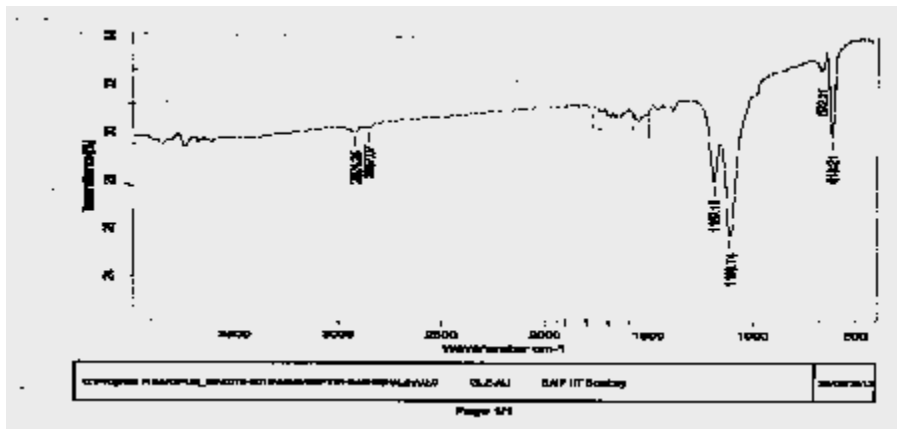


Fig. 3: IR Spectra of Gliclazide-Gold complex

Other features of NMR spectrum were the aromatic presence of unresolved multiplet suggestive protons. Slichter¹⁵, Akit¹⁶, Siewers¹⁷, Jacob and Iqbal¹⁸, Afridi¹⁹,

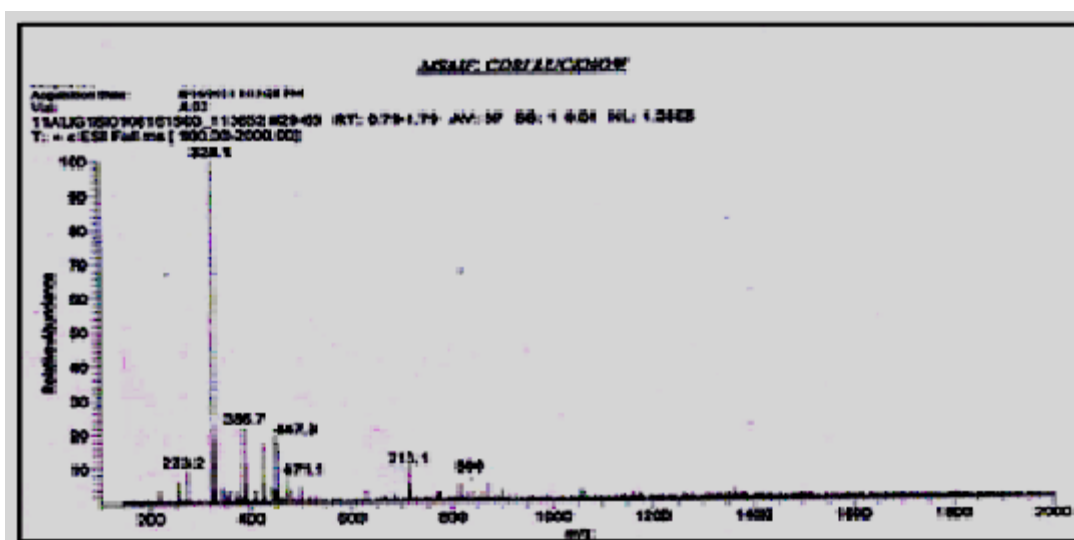
X-RAY diffraction studies

X-ray diffraction studies also confirm the complex and formation due to new bonds^{20-25,27-28}. The number of peaks in gliclazide are 22 while (GLZ)₂Au are 12 (Fig-6). Thus indicating that complex formed is a well kit one. All the reflections present are new ones and the patterns are fairly strong. On comparing the pattern obtained with available literature. It is evident that its pattern is not in good agreement with available information and thus confirms the formation of totally new complex. The X-ray pattern have been indexed by

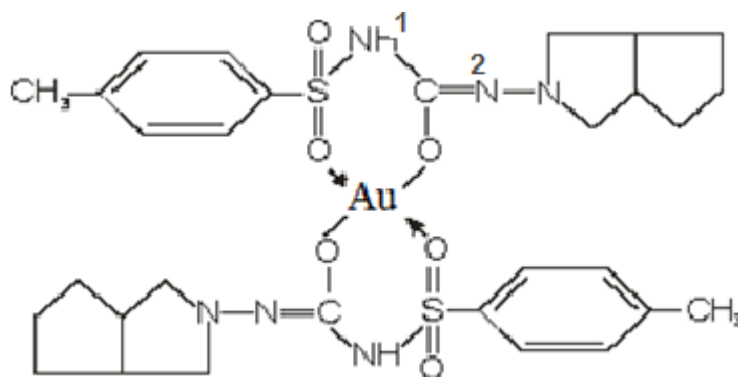
using computer software(FPSUIT 2.0V) and applying interactive trial and error method keeping in mind the characteristics of the various symmetry system, till a good fit was obtained between the observed and the calculated $\text{Sin}^2\theta$ value. The unit cell parameters were calculated from the indexed data, from cell data and crystal lattice parameters of (GLZ)₂Au, indicates complexes attributed to Monoclinic crystal system Table given below

Mass spectral studies of gliclazide-gold complex

Mass spectrophotometric studies gave useful information regarding the accurate determination of molecular weight and which provided information about the structure of compounds by examination of the fragmentation pattern⁴⁰⁻⁴¹. Now a days, chemist have



Mass Spectrum of GLZ-Au Complex



Structure 1:

enthusiastically embarrassed mass spectroscopy to identify and characterize molecule Mass spectrum of the compound is a plot which represents the intensities of the signals at various m/z value⁴²⁻⁴³. It is highly characteristic of the compound ,no two compounds can have similar mass spectra. It provides information regarding the molecular structure of organic and inorganic compounds. We have studied gold complex of gliclazide and assignment is given table-7

DISCUSSION

For supporting the proposed structure of gold-gliclazide complex, initially Jobs method of continuous variation as modified by Turner and Anderson was conducted which indicate 2:1 ligand:metal ratio of the complex , moreover stability constant and free energy change was also calculated .Analytical data agrees to the molecular formula $(C_{15}H_{20}N_3O_3S)_2Au (L_2M)$.

For determining the proposed structure on the basis of stoichiometry and analysis of the

complex. Advance spectroscopic methods like IR , ¹H-NMR , Mass were conducted which suggest the coordination of metal atom with enolic oxygen of the carbonyl group on one side and oxygen of the sulphonyl group from the other side .These observation were further supporting from the IR and NMR values of metal-oxygen and disappearance of M-H linkages in NMR. A detailed study of X-Ray also supports the complex formation and the various values like particle size , porosity , volume of unit cell , density as well as crystal system was evaluated and discussed .Moreover looking to the higher electronegativity of oxygen as compared to nitrogen, N² enolization is strongly supported.

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