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Synthesis, Characterization and Spectral Studies of Samarium Complex with Gliclazide- an Oral Antidiabetic Drug

Bal Krishan*, Neeti Rathor*, Vibha Agrawal** and S.A. Iqbal***

**Department of Chemistry, Saifia Science College, Bhopal, (M.P.) India.*
*** Department of Chemistry, Gyan Ganga Institute of Technology & Management, Bhopal, (M.P.) India.*
****Department of Chemistry, Cresent College of Technology, Bhopal, (M.P.) India.*

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ABSTRACT: The present work describes synthesis, characterization and spectral studies of samarium 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 $(C_{15}H_{20}N_3O_3S)_2Sm.\ 2H_2O$. Structure of complex was assigned octahedral, supported by IR, ^{1}H-NMR and Mass studies. Structure (I) is proposed for complex.

Keywords: Gliclazide, antidiabetic drug, complex, IR, NMR and Mass spectra.

I. INTRODUCTION

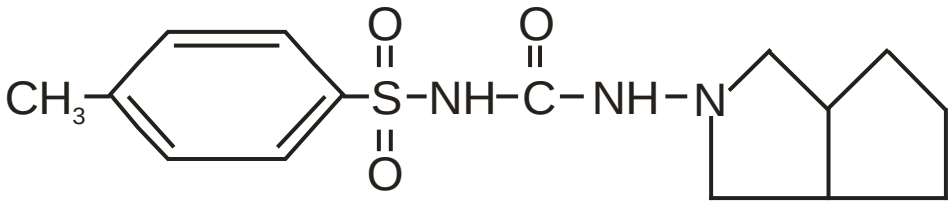
Metal ions are required for many critical functions in humans. Scarcity of some metal ions can leads to disease [1]. Well – known example can leads to pernicious anemia resulting from iron deficiency; growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper 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 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]; Bloomgarden [3]; 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 a chelate is the characteristic aspects of their chemistry.

In recent years much attention is given to the use of sulphonyl-urea because of their high complexing nature with essential metals. Sulphonyl-urea are effective for non- insulin dependent *Diabetes mellitus*. Sadilot and Phatak [2], 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 sulphonyl-urea with lighter transition metals has been studied in detail by Yoshinaga and Yamamotto [5, 6], Iqbal *at.el*., [7, 10, 11, 26] and other author synthesis the complexs of various metals with compound. A perusal of available literature shows that systematic study of complexation of samarium with gliclazide is relatively scanty. It is interesting to have an insite into the synthesis of samarium complex with gliclazide and to diagnose various structural aspects of the isolated complex.

Here the synthesis and characterization of samarium with gliclazide have been described



Structure of Gliclazide

II. EXPERIMENT

A. Ligand-Metal Ratio

(i) 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 samarium trioxide at 30±1°C. Results were plotted in the form of a graph which indicate ligand metal ratio as 2 :1 (L_2M).

(ii) Formation of 2:1 (L_2M) ratio was further confirmed by Job's method [8] of continuous variation as modified by Turner and Anderson [9] (Table-1) spectrophotometric studies were conducted using absorbance as index property, from these values the stability constant (log k) and free energy change (-ΔF), were also calculated (Irving and Rossotti [20, 21]) Tables 1, and fig. 1 given for gliclazide-samarium complex.

B. Synthesis of Complexes

The chemicals used in this synthesis were all of analaR grade Hi-media. A weighed quantity of Gliclazide (2 mole) (supplied by Zim lab.Nagpur) was dissolved separately in minimum quantity of 90% ethanol. The samarium solution was prepared by dissolving (1 mole) 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 hours and on cooling the complexes separated out. Which were filtered off, washed well with ethanol and finally dried in vacuum and weighed.

Table 1. Gliclazide With Samarium Oxide.

Gliclazide - 0.002M, 0.005M, Samarium trioxide – 0.002M, 0.005M, Solvent: 90% Ethyl alcohol, Temperature- 30±1°C, Wavelength: 480 nm, pH: 6.2.

S. No.	Metal: Ligand Ratio	Absorbance		Corrected Absorbance	
		0.002M	0.005M	0.002M	0.005M
1	0:12	0.015	0.019	0.00	0.00
2	1:11	0.042	0.056	0.027	0.037
3	10:2	0.087	0.103	0.072	0.084
4	9:3	0.141	0.193	0.126	0.174
5	8:4	0.188	0.235	0.173	0.216
6	7:5	0.146	0.198	0.131	0.178
7	6:6	0.114	0.178	0.099	0.156
8	5:7	0.071	0.139	0.056	0.116
9	4:8	0.048	0.087	0.033	0.064
10	3:9	0.035	0.056	0.020	0.032
11	2:10	0.029	0.042	0.014	0.018
12	1:11	0.024	0.034	0.010	0.010
13	1:12	0.015	0.026	0.00	0.00

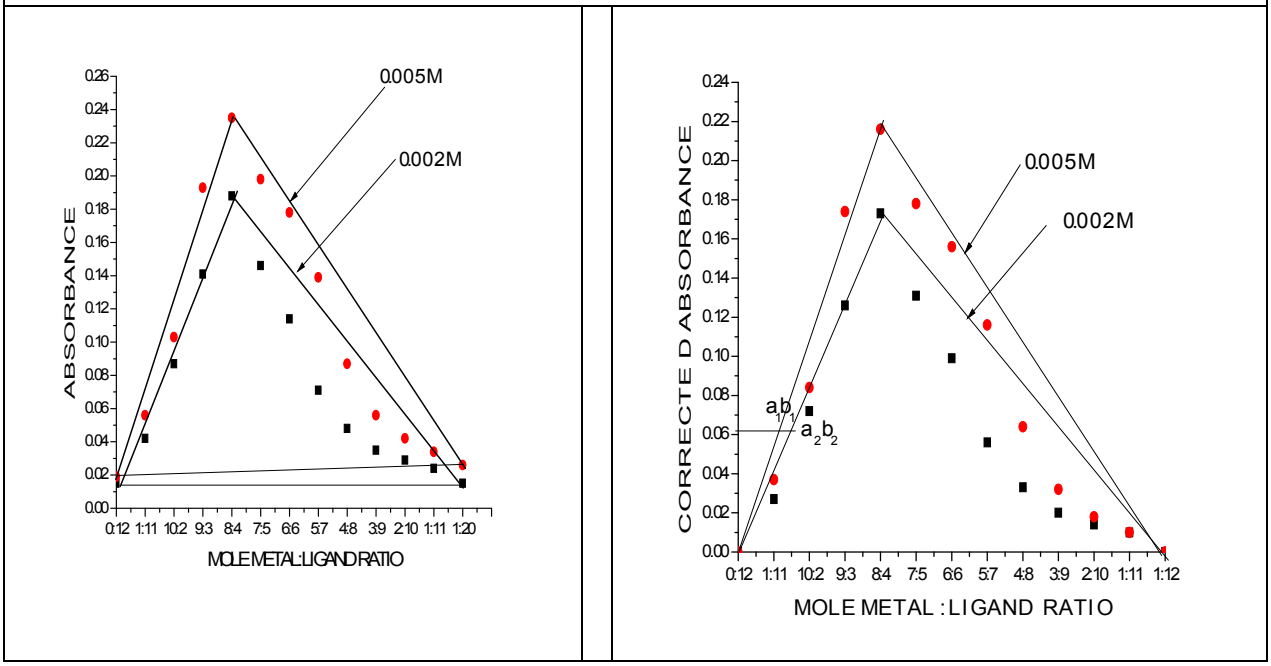
The elemental analyses of the isolated complexes were carried out using coleman analyzer at the departmental micro analytical laboratory CDRI Lucknow.

The IR spectrum of the ligand as well as of the complex was recorded on Perkin Elemer Spectrometer (I.I.T Bombay) and ^{1}H-NMR spectra of the ligand and isolated complex was recorded on a Bruker DRX-300 Spectrometer and d_6-DMSO was used as a solvent. IR and ^{1}H-NMR spectrums recorded in CDRI, Lucknow and IIT Bombay. India

From stoichoimetry and analytical data, the composition of the complex comes out to be $(C_{15}H_{20}N_3O_3S)_2Sm.2H_2O$, which favour 2:1 ($L_2M$) ratio. The tentative structure (I) assigned to complex on the basis of analytical data and IR, NMR and Mass studies.

JOB'S METHOD OF CONTINUOUS VARIATION (MODIFIED BY TURNER AND ANDERSON).

GLICLAZIDE WITH SAMARIUM OXIDE



(a) **(b)**

Fig.1. Gliclazide with samarium complex.

III. RESULT AND DISCUSSION

Table 2. Pysico-chemical characteristics of gliclazide complex with samarium.

S. No.	Complexes	Colour	Yield (%)	m.p.°C	–ΔF	Log K	Molar conductance $\Omega^{-1}cm^{-1}mole^{-1}$
1.	$(C_{15}H_{20}N_3O_3S)_2Sm.2H_2O$ Mol. Wt=832.18	Pale Yellow	41.83	210	16.00	11.50	38.0

S.No.	Formula of complexes	Molecular weight (g/mole)	C%	H%	N%	S%	Water	Metal (%)
1.	$(C_{15}H_{20}N_3O_3S)_2Sm.2H_2O$	832.18	43.31 (41.86)	5.29 (5.42)	10.10 (11.40)	7.69 (8.68)	4.33 (4.88)	18.08 (17.58)

A. Infra-red Spectra Studies

The IR spectra of ligand and isolated complex (Fig. 2) were recorded within the range 4000-400 cm^{-1}. Assignments of the infrared spectral bands are based on literature. IR spectrum shows important bands due to ν(M-O) 400-600 cm^{-1}, ν(Ar-S) 700-800 cm^{-1}, ν(-S-N) 1085±20 cm^{-1}, ν(SO_2-N) 1120±20 cm^{-1}, ν(C-N) 1210±20 cm^{-1}, ν(S = O) 1340±20 cm^{-1}, ν(C = O) 1920 cm^{-1} (present only in pure drug and there is a variation in complex indicates that M-O linkage), 1600 cm^{-1} vs and 3607 cm^{-1} (coordinate H_2O molecule present only complex), ν(NH-stretch) 3260±20 cm^{-1}. The proposed structure for the isolated complex is also supported by IR absorption, Rao [12], Bellamy [13], Weissberger [14].

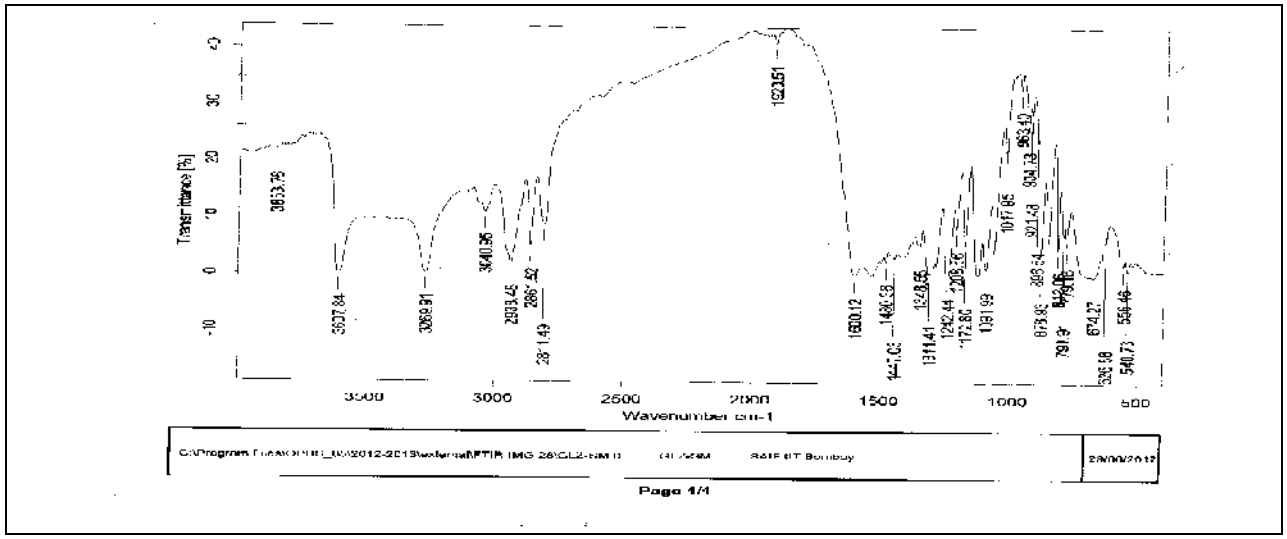


Fig. 2. IR Spectra of Gliclazide-Samarium complex.

B. ^{1}H-NMR Studies

^{1}H-NMR spectral data are given in (Table 4) and a spectrum is given in fig.3. It was observed that the singlet due to the imide (NH) proton around (δ8.033) 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 aimide NH group through enolization (the appearance of >C=N stretching band observed in IR spectra). Other features of NMR spectrum were the aromatic presence of unresolved multiplet suggestive protons. Slichter [15], Akit [16], Siewers [17], Jacob and Iqbal [18], Afridi [19],

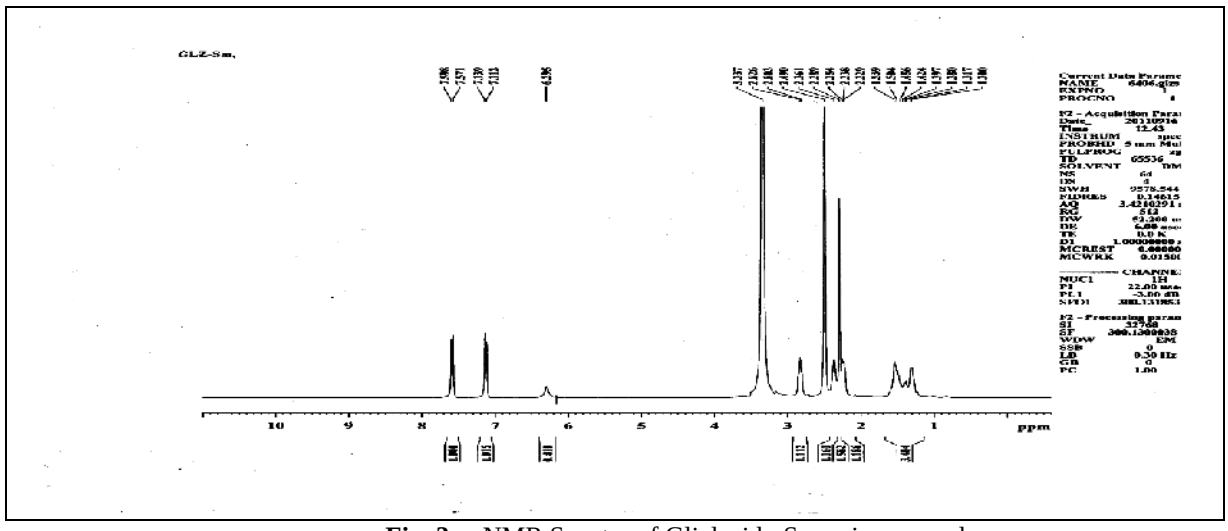


Fig. 3. NMR Spectra of Gliclazide-Samarium complex.

Table 4. NMR-Assignments of Gliclazide-Samarium complex.

$(C_{15}H_{21}N_3O_3S)_2$ pure drug gliclazide	$(C_{15}H_{20}N_3O_3S)_2Sm.2H_2O$
δ8.041 (s,1H,NHCo, J=0.334H_z), δ7.817 (d, benzene J=1H_z), δ7.395 (d, benzene, J=1H_z), δ6.28 (s,SO_2NH), δ3.320 (NH-CO, J=0.929H_z), δ2.901(s,CH_3 group attached to benzene, J=2.160 H_z), δ1.388 (s,CH_3 group, J=2.955H_z	δ7.598 (d, benzene, J=1H_z), δ6.295 (s, SO_2-NH, J=0.410H_z), δ3.337 (s due to solvent, J=0.83H_z), δ2.803 (d, CH_3-group attached to benzene, J=1.112H_z), δ1.539 (q, pyrrolyl ring , J=1.186H_z), δ1.300 (m CH_3 group, J=3.404H_z)

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

C. Mass spectrophotometric studies

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 pattern [22, 23]. Now days, chemist have 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 values [24, 25]. 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 samarium complex of gliclazide and assignment are m/z 824 may be due to $[Sm(C_{15}H_{20}N_3O_3S)_2(H_2O)_2]^{+\cdot}$ Or $(ML_2{\cdot}2H_2O)^{+\cdot}$ Molecular ion peak ($m^{+\cdot}$); m/z 324 due to $(C_{15}H_{21}N_3O_3S)^{+\cdot}$ Base peak ion 100% relative abundance, m/z 386 due to $[C_{15}H_{22}N_4O_6S]^{+\cdot}$ fragment ion m/z 408 due to $[C_{13}H_{20}N_4O_7S_2]^{+\cdot}$ Fragment ion and spectra is given Fig. 4.

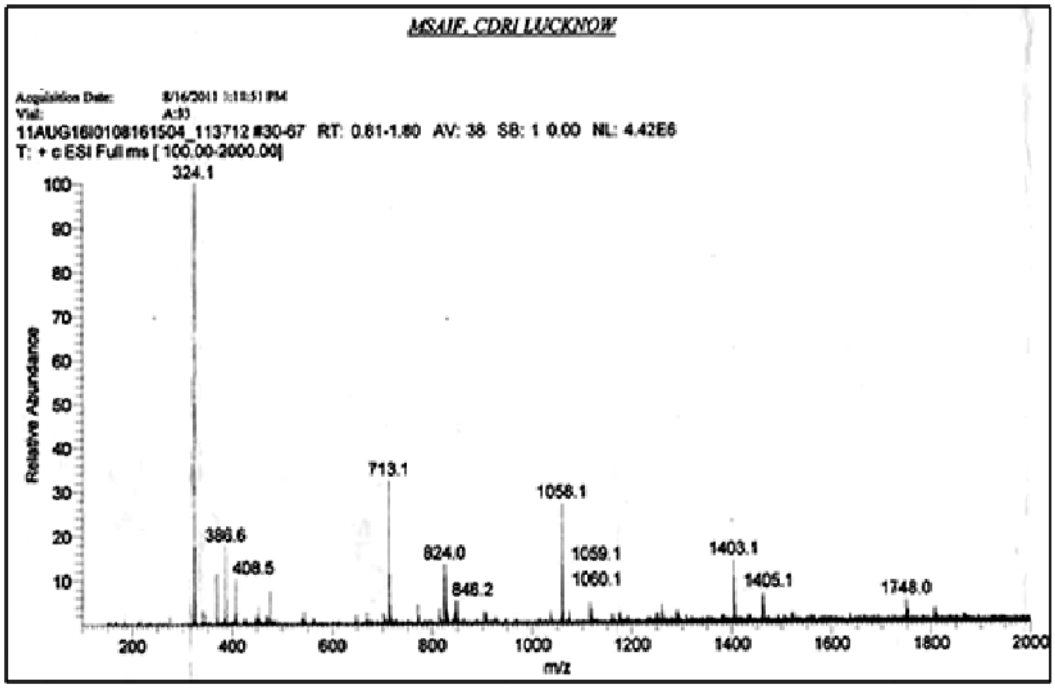
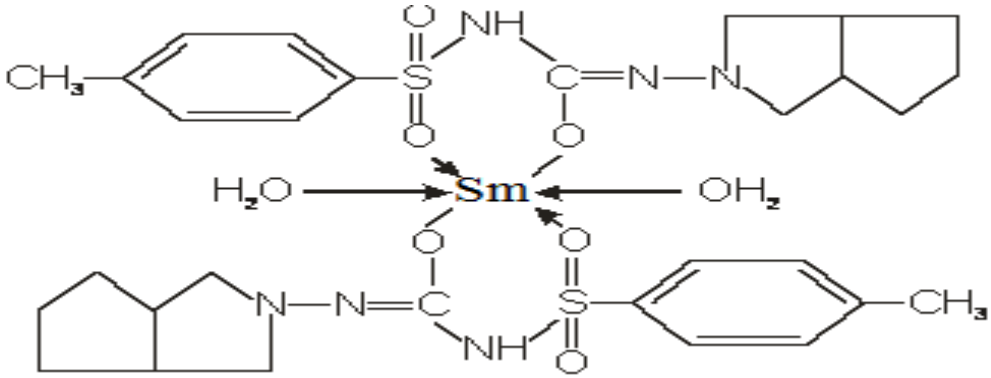


Fig. 4. Mass Spectra of gliclazide-Samarium Complex.



Structure (I)

For supporting the proposed structure of samarium-gliclazide complex, initially Job's 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 $(C_{15}H_{20}N_3O_3S)_2Sm.2H_2O$ (L_2M).

For determining the proposed structure on the basis of stoichiometry and analysis of the complex. Advance spectroscopic methods like IR, H^1-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. Moreover looking to the higher electronegativity of oxygen as compared to N^2 and to enolization is strongly supported.

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