International Journal of Theoretical & Applied Sciences, **4**(2): 164-169 (2012)

ISSN No. (Print): 0975-1718
ISSN No. (Online): 2249-3247

Synthesis, Spectral Studies of Fe(II) Complex with Gliclazide, an Oral Antidiabetic Drugs

Bal Krishan Sharma [*] ***Vibha Agrawal*** [*] ***and S.A. Iqbal*** [**]

Department of Chemistry,
** Gyan Ganga Institute of Technology, Bhopal, (MP)*
***Cresent College of Technology, Nabi Bagh, Karond, Bhopal, (MP)*

(Received 05 November, 2012, Accepted 12 December, 2012)

ABSTRACT: Synthesis, characterization by spectroscopic studies of Fe(II)) with Gliclazide, an oral antidiabetic allopathic drugs have been studied. The conductometric titration using monovariation method indicates that complexes are non-ionic and L_2M type. Analytical data agrees with the molecular formula $(C_{15}H_{21}N_3O_3S)_2Fe.2H_2O$ of complexes for Gliclazide, structure of complexes was assigned octahedral supported by IR, and ^{1}H-NMR studies and propose structure (I) for complexes.

Keywords: Gliclazide, oral anti diabetic drugs, complexes, IR, NMR.

I. INTRODUCTION

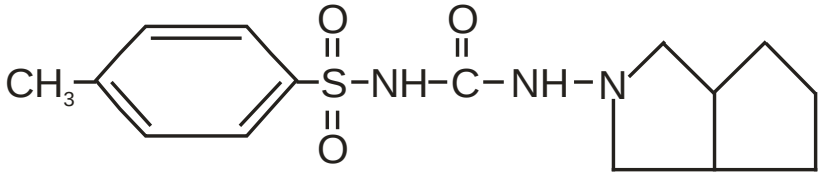
Metal ions are required for many critical function in human. Scarcity of some metal ions can leads to disease. Well known example can leads to pernicious anemia resulting from iron deficiency; growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. 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 [1]; Bloomgarden [2], Sanger and Thompson, 1953) [3]. 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 are 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 (Sadilot and Phatak, 1992 [1]; Bloomgarden, 1999; [2] Sanger and Thompson,1953) [3]. 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 Yamamotto [4], Iqbal *at.el*. [5-9]. A perusal of available literature shows that systematic study of complexation of iron with Gliclazide is relatively scanty. It is interesting to have an insite in to the synthesis of iron complex with Gliclazide and to diagnose various structural aspects of the isolated complex. Here the synthesis and characterization of iron with Gliclazide have been described.

Structure of Gliclazide



II. EXPERIMENTAL

A. Ligand-Metal Ratio

(a) Pure Gliclazide m.p. 180°C (Lit. 179.5-180.5), 0.005 M, pure were diluted to 100ml. and titrated conductometrically against ferrous sulphate at 30±1°C. Results were plotted in the form of graph which indicates ligand metal ratio as 2:1 (L_2M).

(b) Formation of 2:1 (L_2M) ratio was also confirmed by Job's method of continuous variation as modified by Turner and Anderson (Table 1), Absorbance as index property, from these values the stability constant (logk) and free energy change (-ΔF), were also calculated (Irving and Rossotti (1953, 1954) [10-11], Table 1, and Fig. 1 given only for Gliclazide iron complex.

B. Synthesis of Complexes

The chemicals used in this synthesis were all of analytical grade. A weighed quantity of Gliclazide, was dissolved separately in minimum quantity of 90% ethanol. The Ferrous Sulphate solution was prepared by dissolving them separately in the same solvent. Ligand solution was added slowly with stirring into the solution metallic salt of room temperature, maintain the pH between 6.0 to 6.5 by adding dilute NaOH solution. On refluxing the mixture for 3-4 hours 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.

The IR spectrum of the ligands as well as of the complexes was recorded on Perkin Elemer Spectrometer (I.I.T BOMBAY) and ^{1}H-NMR spectra of the ligand and isolated complexes were 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, India (Fig. 2, 3).

From stoichiometric [19-20] and analytical data, the composition of the complex comes out to be $(C_{15}H_{20}N_3O_3S)_2 \cdot Fe \cdot 2H_2O$ for which favors 2:1 (L_2M) ratio. The tentative structure (I) assigned to complexes on the basis of analytical data, IR and NMR.

Table 1. Gliclazide with Ferrous Sulphate (Jobs Method).

S. No.	Metal: Ligand ratio	Absorbance	
		0.002M	0.005M
1	0:12	0.012	0.019
2	1:11	0.045	0.065
3	2:10	0.085	0.117
4	3:9	0.110	0.142
5	4:8	0.178	0.211
6	5:7	0.156	0.172
7	6:6	0.135	0.156
8	7:5	0.127	0.142
9	8:4	0.121	0.139
10	9:3	0.098	0.109
11	10:2	0.065	0.095
12	11:1	0.048	0.072
13	12:0	0.040	0.052

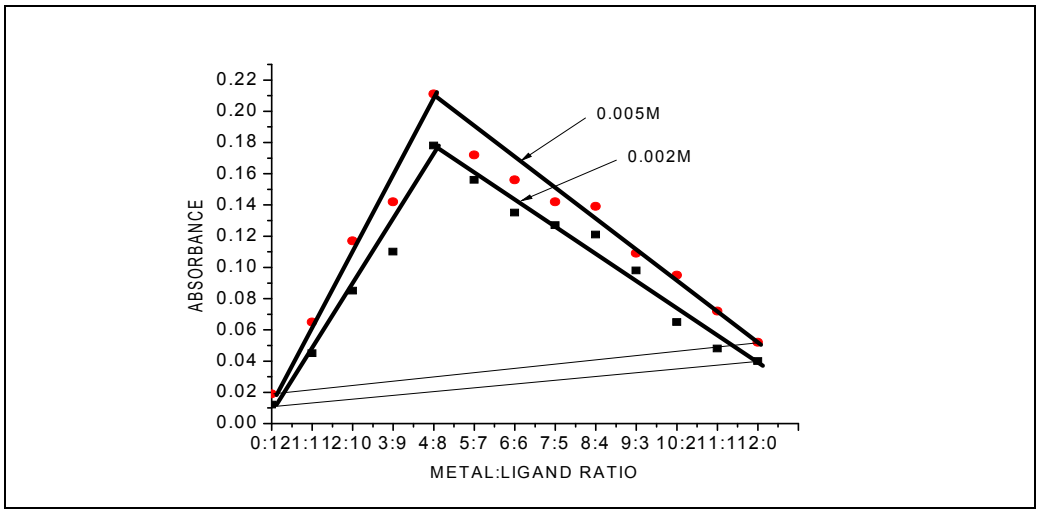


Fig. 1. Method of Continuous Variation (Job's Method).

III. RESULT AND DISCUSSION

A*. Infra-red Spectra Studies*

The IR spectra of ligand and isolated complexes were scanned within the range 4000-400 cm^{-1}. Assignments of the infrared spectral bands are based on literature (Table 4) 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) 1140 ± 20 cm^{-1}, ν(C-N) 12320 ± 20 cm^{-1}, ν(S = O) 1340 ± 20 cm^{-1}, ν(C = O) 1710 cm^{-1}(present only in pure drug and absent in complex),1600cm^{-1} vs (coordinate H_2O molecule present only complex), ν(NH-stretch) 3274 ± 20 cm^{-1}. The proposed structure for the isolated complexes is also supported by IR absorption Nakamotto (1963) [12] C.N.R. (1963) [13], Bellamy (1964) [14], Weissberger (1956) [15].

B*. ^{1}H-NMR Studies*

^{1}H-NMR spectral data are given in Table 5. It was observed that the singlet due to the imide (NH) proton is around (δ8.74) in the spectrum of the ligand which disappeared in the spectra of complex molecule and formation of M-O band. This also confirms the deprotonation of aimide NH group through enolization as the appearance of >C=N stretching band observed in IR spectra.

Table 2. Pysico-chemical Characteristics of Gliclazide complexes with Fe.

S. No.	Complexes	Colour	Yield (%)	m.p.°C	Molar conductance Ω^{-1}cm^{-1} mole^{-1}
1.	$(C_{15}H_{21}N_3O_3S)_2Fe2H_2O$	Light Brown	64.50	180	34.1

Table 3. Elemental analysis of Gliclazide-Fe complexes.

S. No.	Formula of complexes	Molecular weight (g/mole)	% Analysis(found) Calculated					Metal (%)
			C	H	N	O	S	M
1.	$(C_{15}H_{21}N_3O_3S)_2Fe2H_2O$	736.67	48.86 (47.82)	5.97 (5.64)	11.40 (11.85)	13.84 (13.55)	8.68 (9.03)	7.99 (7.75)
Free Energy Change –ΔF K. Cal./mole			**Log K**					
-14.79			10.86					

Other features of NMR spectrum were the aromatic presence of unresolved multiplet suggestive protons. Slichter, [16], Akit [17], Siewers [18], Jacob and Iqbal (2010a, 2011b) [7], Afridi [6].

Table 4. Specific IR assignment of Gliclazide and Gliclazide complexes with Fe(II).

Pure drug(Gliclazide)	**Gliclazide-iron complex**
632cm^{-1}s, 668cm^{-1} vs,1087cm^{-1}vs 1240cm^{-1}vs,1348cm^{-1}vs, 1710cm^{-1}vs, 2867cm^{-1}, 2950cm^{-1}vs, 3274 cm^{-1}vs, Vs = very strong, s = strong, m = medium W = weak	549cm^{-1} s ,1122cm^{-1}s,1216cm^{-1}vs 1337cm^{-1} s,1524cm^{-1}s 2947cm^{-1}m 3021cm^{-1}s,3674cm^{-1}m Vs = very strong, s = strong, m = medium W = weak

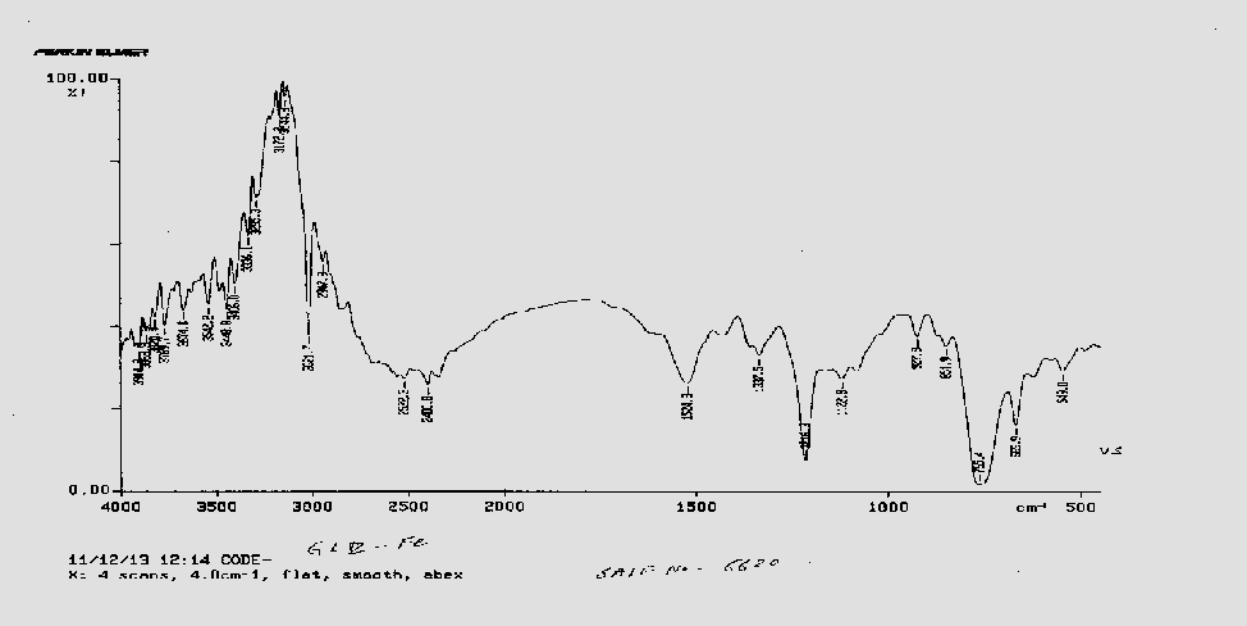


Fig. 2. IR Spectra of Gliclazide-iron complex.

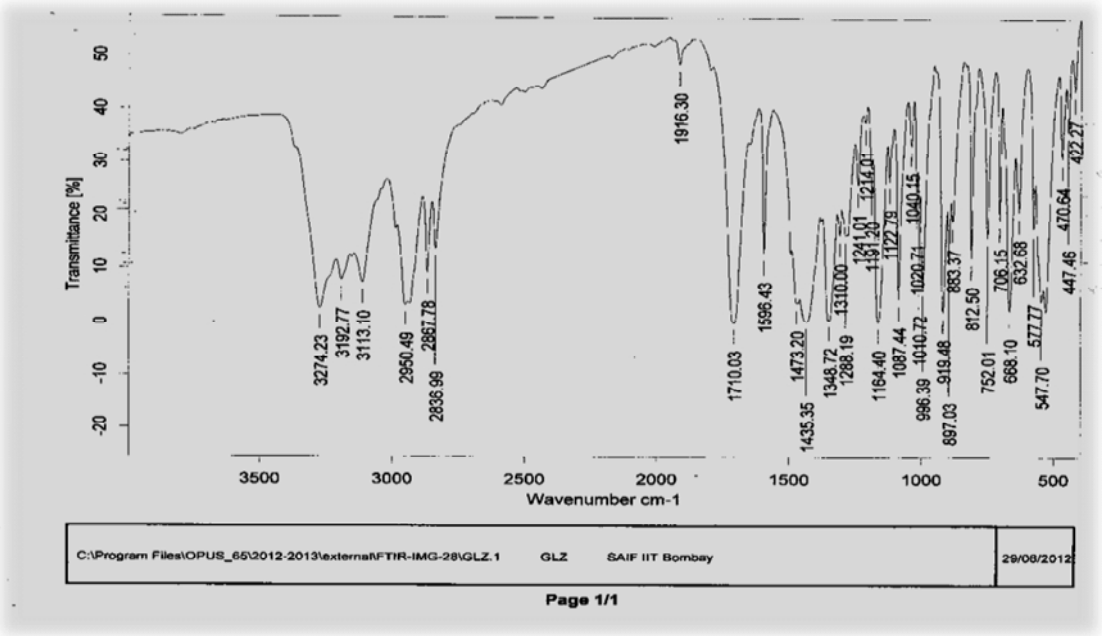
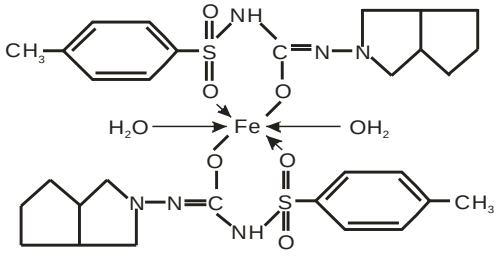


Fig. 3. IR Spectra of Gliclazide.

Table 5. [1] H - NMR-Assignments of Gliclazide-iron complex.

Assignment :$(C_{15}H_{21}N_3O_3S)_2$ pure drug Gliclazide	Assignment: $(C_{15}H_{21}N_3O_3S)_2Fe2H_2O$ Complexes
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 s = singlet, d = doublet, t = triplet, q = quartrate, m = multiplet	δ9.579 (s, H, Coordinated H_2O, J = 1H_z), δ7.829 (d,1H,NHCO, J = 2.78H_z), δ7.709 (s, benzene, J = 1.63H_z), δ7.130 (s, So_2 -NH, J = 2.99H_z), δ3.020 (s, NH-CO-Fe, J = 1.34H_z), δ2.982 (s, CH_3 group attached to benzene, J = 9.50H_z), δ1.798 (q,CH_3 group, J = 58.28H_z), δ1.141 (t, CH_3-group, J = 1.48H_z)

Structure (I)



ACKNOWLEDGEMENT

The author is thankful to the principal of Saifia Science College, Bhopal and Principal, of Cresent College of Technology, Bhopal for providing all necessary facilities and IIT, BOMBAY for providing IR spectra.

REFERENCES

[1]. Sadilot, S.M., Pathak, R.B. *J. Diabet. Assoc. India*, **32**(4): (1992).

[2]. Bloomgarden, Z.N. American Diabetes Association Consensus Statement on pharmacologic treatment, *Diabetes Care*, 22 SIS117(1999).

[3]. Sanger, Thompson, E.O.L., *Ibid*., **53**: 535,366, (1951).

[4]. Yoshinaga, I**.,** Yamamotto, Y., *Endocrinologie (Gen)*, **50**: 3(1966a).

[5]. Iqbal, S.A., *Acta. Clin. Indica*, **12**C(1): 15-16(1986).

[6]**.** Farhana, Afridi, Iqbal, S.A., and Javed, Hasan. *Orient. J. Chem*., **22**(1): 195-197(2010).

[7]. George Jacob, Syed Aftab Iqbal and E.H. El-Mossalamy *Asian J. Chem*., **23**(2): 573-576 (2011).

[8]. Iqbal,S.A.,Qureshi,R. *Asian J. Expt. Sci.*, **1**: 68-70 (1985).

[9]. Iqbal, S.A., Desnavi, *Asmi, Ibid.*, **5**(2): 194-195(1989).

[10]. Irving, H., Rossotti, H.S., *J. Chem. Soc*., 3397(1953).

[11]. Irving, H., Rossotti, H.S., *J. Soc.*, 2904,(1954).

[12]. Nakamoto, K.,"*Infrared spectra of inorganic and coordination compounds" John Willey and Sons,* New York. (1963).

[13]. Rao, C.N.R Chemical Applications of Infra-red spectroscopy, Academic press NY. (1963).

[14]. Bellamy L.J. The Infra-red spectra of complex molecules.Matheun and co. Ltd. London (1964)

[15]. Weissberger, A. Chem. Application of spectroscopy", Vol. **XI** Inter Science Publ. New York. (1956).

[16]. Slichter, C.P. Principles of magnetic resonance, Harper and Row (1963).

[17]. Akit, J.W. NMR and chemistry an introduction to nuclear magnetic resonance spectroscopy, Champan and Hall, (1973).

[18]. Siewers, R.E. Nuclear magnetic resonance shift reagents academic, New York (1973).

[19]. Job, P., *Ann. Clin*, **113**: 10(1928).

[20]. Terner, S.E. and Anderson, R.C., *J Am. Chem. Soc*., **912**: 71(1949).