SYNTHESIS, SPECTRAL CHARACTERIZATION AND STUDY OF PALLADIUM COMPLEX OF GLICLAZIDE

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ABSTRACT*: The present work describes the synthesis and spectral characterization of Pd(II) with Gliclazide,an antidiabetic drug. Analytical data agree with the molecular formula of the complex [Pd($C_{15}H_{21}N_3O_3S)_2$]. Geometry of this complex assigned is assumed to be four coordinated square planar. This structure is supported by IR, ^{1}H-NMR and ^{13}C-NMR, atomic absorption and electronic spectroscopy. Elemental analyses (CHNS and Metal) and magnetic susceptibility measurement are also conducted to verify the geometry of the Pd(II)-(GCZ) complex.*

Keywords: Gliclazide; Sulphonylurea; Diabetes; Complex; Palladium

INTRODUCTION

Gliclazide (GCZ) is an important member of hypoglycemic sulphonylureas (SUs) drugs. These are very effective for non-insulin dependent Diabetes mellitus [1-3] and are absolutely absorbed by oral administration. They undergo metabolism by lever and are excreted primarily through urine. Diabetes is a deceiving disease and if not diagnosis earlier it may causes even death. Several millions peoples have been suffered from this disease in the world [4-6].

Much attention is being given to the use of sulphonylureas (SUs) because of their high complexation ability with transition metals. These metals exhibit different oxidation states and can interact with a number of donor ligands. Transition metals have therefore a prominent place within biomedical chemistry. Researchers have shown momentous development in consumption of transition metal complexes as drugs for the treatment of various human diseases. This potential of transition metals has started the progress of metal based drugs, which are found to be more potent and less toxic as compared to the free ligand[7-12].

In 1960 "anti-tumor" action of an inorganic complex cis-"[Pt(NH3)2Cl2]" "(cis-diammine-dichloroplatinum (II)(cisplatin)" was revealed. Platinum (II) complexes has been found to be very effective hemotherapeutic agent for treating various types of cancers[13]

Gold (I) thiomalate and gold (I) thioglucose complexes have been effectively used since long for the management of "rheumatoid arthritis" [14-16].Some complexes of "anti-inflammatory" drugs containing "carboxylate ligands" have given away promise results[13].

Anti-tumor activity of Pd(II) complexes found to be comparable to that of cisplatin. The nature of the leaving ligands in palladium (II) complexes is a most important factor to determine its potential [17]. Further, synthesis and characterization of palladium complex with tolbutamide (a sulphonylurea drug) have been described [18]. Determination of gliclazide in biological fluids through ternary complex formation with palladium (II) have been carried out[19]

On the basis of above discussion and potential of the palladium metal for complex formation with a sulphonylurea drug motivated us to take over the synthesis and structural characterization of palladium complex with Gliclazide (GCZ), a hypoglycemic sulphonylurea drug.

MATERIAL AND METHOD

All chemicals utilized in the experiments were of analytical grade imported from "Merck, Germany" Fluka, Switzerland and "BDH Chemicals England". Pure drug compound "Gliclazide"was obtained from "E.Merck Co Germany".

"IR spectra (in KBr)" were taken out on "Shimadzu FTIR 4200 infrared spectrophotometer".

^{1}H-NMR and ^{13}C-NMR "(in DMSO-d_6)" spectra were recorded on "Bruker 14.1T NMR spectrometer" that operates at 600 MHz frequency . Analysis of elements was conducted on"CHNS analyzer "Exeter Analytical CE-440".

Analysis of metal in this complex was carried out on "atomic absorption spectrophotometer model AA-680" operational with "GFA-4B Graphite Furnace Atomizer" with "ASA Arsenic analyzer"by applying an accepted procedure [20].

"Melting point apparatus", "Mel-Temp MP-D", "Mitamura Rikon Kogyo Japan" was used to determine the melting point and decomposition points of complex and ligand drug itself. "Sealed capillary tube" process was adapted to do this.

"Absorption spectra" of metal complex and pure ligand were obtained through "Perkin-Elmer Lambda 20 spectrometer".

Magnetic moment, "μ_{eff}" of this complex was obtained by "Chyo Balance MSB-10" [20].

SYNTHESIS AND CHARACTERIZATION

Gliclazide

"IR: (KBr, cm^{-1}) 3375 (s, NH Amide.), 3210 (NH thionyl), 1704 (C=O), 1591 (C-N)" 1345, 1163 (SO_2). UV (λ_{max} DMSO, nm), (ε x 10^3): 3.86 (30674), 2.76 (36101), 3.21 (40000), 2.32 (45045). δ_H (DMSO-d_6);1.2-1.7 (m, Heterocyclic ring), 2.3 (s, CH_3), 7.4 (d, H^3, H^4), 7.6 (d, H^1, H^2), 8.1 (b, N^a–H) and 10.0 (b, N^b–H). δ_C (DMSO-d_6); 61.73 (C1), 21.08 (C11), 24.20 (C2, C3, C4), 127.54 (C9), 129.34 (C8), 137.42 (C10), 143.59 (C7), 152.07 (C6).

Palladium (II)-Gliclazide Complex

Ligand (GCZ) 1.34g (6 m mol) and "KOH" "0.336g(6 mmol)" dissolved in a 100 ml mixture of ethanol:acetone (1:1) by constant stirring under reflux. Palladium(II) acetate 0.67g(3 mmol) was added to the ligand solution, while stirring continuously. A yellow coloured solution was formed which started to change into yellow precipitate after ten minutes. The resulting mixture was refluxed for 1hour to complete the reaction and then cooled to room temperature. The yellow product formed was filtered, washed with

acetone, ethanol and then dried at room temperature. "Yield": 90%.

The product obtained is a yellow, "amorphous powder", mp 280-285°C (dec.). As melting of complex involves decomposition, therefore a weak molecular ion peak at low electron volts area is found at *m/z* 755.2. IR "(KBr, cm^{-1})" 3180 (s, N-H), 1660 (C=O), 1594 (C–N), 1357, 1150 (SO_2) and 520 (M-N). δ_H (DMSO-d_6);1.0-1.6 (m, Heterocyclic ring), 8.6 (s, N^a–H), 7.8 (d, H^1, H^2), 7.1 (d, H^3, H^4), 2.5 (s, CH_3) δ_C (DMSO-d_6); 21.11 (C11), 23.75 (C2, C3, C4), 30.28 (C5), 61.71 (C1), 127.34 (C9),129.53 (C8), 142.84 (C7), 160.38 (C6), while C_{10} has disappeared. UV (λ_{max} DMSO, nm), (ε x 10^3): 0.1 (15649), 0.08 (13157). *Anal. Calcd* for $[Pd(C_{15}H_{21}N_3O_5S)_2]$ C, 47.87; H, 5.57; N, 11.15; S, 8.49; M, 14.07; Found: C; 47.96, H; 5.37, N; 11.19, S; 8.53, M; 14.16.

RESULTS AND DISCUSSION

The complex of Pd(II), with gliclazide (GCZ) (**I**) ethanol/cetone solution and are characterized by their elemental analyses (C,H,N,S and metal) and different spectroscopic techniques like IR, ^{1}H-NMR and ^{13}C-NMR, atomic absorption and electronic spectroscopy. Magnetic susceptibility measurements for paramagnetic was also carried out.

Palladium(II)-Gliclazide Complex

Analysis of the elements in this complex adjusts nicely in the formula $[Pd(C_{15}H_{21}N_3O_3S)_2]$. For bidentate mode of ligand this indicates a four coordinated environment around the metal ion.

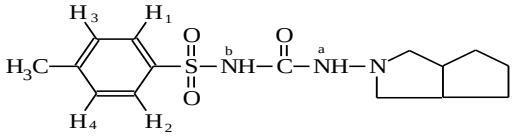
IR spectrum of this complex shows that the band due to N – H stretch of (–SO_2NHCO–) moiety of ligand at 3210 cm^{-1}, has shifted a little to 3180 cm^{-1}. This shows the least involvement of N–H group in coordination. Pd(II) may be bonded through some other nitrogen atom of the ligand. The $\nu_{asy}(SO_2)$ (1345 cm^{-1}) and $\nu_{sym}(SO_2)$ at 1163 cm^{-1} in ligand is shifted to 1357 cm^{-1} and 1150 cm^{-1} respectively. This negligible shift indicates that SO_2 group is not involved in coordination in this complex. C–N stretching (1591 cm^{-1}) in ligand has transferred to 1594 cm^{-1} and (C=O) stretch in ligand (1704 cm^{-1}) has transferred to 1660 cm^{-1} in Pd(II)-GCZ complex. A new peak due to M–N stretching is observed at 520 cm^{-1}. A broad peak between 3365 cm^{-1} and 3610 cm^{-1} is due to presence of water. These observations suggest that ligand coordinates with metal through carbonyl oxygen and one of the nitrogen atom of the GCZ molecule in ligand **(III).**

The ^{1}H NMR spectrum of the ligand shows two distinct peaks at 7.4 and 7.6 ppm due to aromatic ring protons. A little upfield shift in the aromatic protons is observed only if the complexation occurs through N^b–H protons. In case of Pd(II)-GCZ complex no shift in aromatic protons was observed and N^b–H protons appeared as an intense peak towards upfield position (8.6 ppm) compared to the free ligand. On the other hand, the cyclohexyl ring protons are slightly shifted toward the upfield position. This observation suggests that Pd(II) binds the ligand through C=O group of –SO_2NHCO– moiety and heterocyclic ring nitrogen atom.

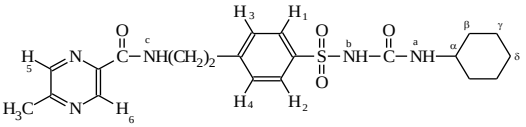
The ^{13}C NMR spectrum of Pd-GCZ complex indicates a downfield shift in C=O resonance (160.386 ppm) compared to the ligand (152.079 ppm). In case of binding through ^{b}N-H and C=O groups the signals due to carbon atoms of heterocyclic ring (C^1-C^5) should slightly shift toward the upfield position, but this is not observed in this complex. The signal due to C^1, C^5 attached directly to the nitrogen of heterocyclic ring appeared downfield at 61.736 ppm in ligand, experienced a marked shift of about18 ppm in this complex and resonate downfield at 79.234 ppm. These observations provide an evidence that ligand has coordinated to Pd(II) through nitrogen of the heterocyclic ring and carbonyl C=O of the –SO_2NHCO– group.

Absorption spectrum of Pd(II)-GCZ complex exhibits a broad band at 15,649 (ε = 110 L mol^{-1} cm^{-1}) and a shoulder band at 13,157 cm^{-1} (ε = 80 L mol^{-1} cm^{-1}). A number of bands in between 36000 cm^{-1} to 47000 cm^{-1} range are observed in the spectrum. Among these the most intense band is observed at 36,449 cm^{-1} (ε = 5990 L mol^{-1} cm^{-1}) which is a charge transfer band extending toward the visible region.

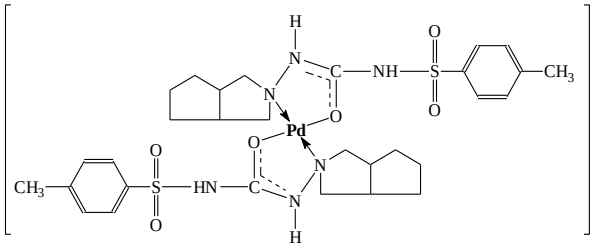
The majority of Pd (II) complexes are four coordinated and square planar which exhibit a band between 15.000 cm^{-1} to 20,800 cm^{-1} (ε = 10-100 L mol^{-1} cm^{-1}) in visible region resolvable into at least two components. Weaker bands are observed on the low energy side of this absorption, whilst several intense bands are observed on the high energy side in UV region. The most intense and highest energy d-d transition band can be ascribed to $^1A_{1g} \rightarrow {}^1E_g$ transition in the Pd(II) complexes. In the observed spectrum of Pd(II)-GCZ complex the highest energy broad band at 15,649 cm^{-1} (ε = 110 L mol^{-1} cm^{-1}) is assigned to the transition. $^1A_{1g} \rightarrow {}^1E_g$. Thus Pd(II) complex may therefore be assumed to be four coordinated square planar species as shown in (**III**)



(I)



(II)



(III)

CONCLUSION:

Analytical and spectral investigation of Pd(II)-Gliclazide complex associates with the proposed structures. It is one of the few Pd (II) complexes synthesized with sulphonyl urea drug. It can be utilized as a compelling and alluring metal based medication. A thorough examination can see if the complex is secured to use as Metal Based Drugs for non-insulin dependent diabetes mellitus (NIDDM).

ACKNOWLEDGEMENT

We highly appreciate the help and cooperation granted by "Midwest Micro Lab Indianapolis" U.S.A, "Geo-Science Laboratories" Islamabad and "Queen Marry Westfield college London" for the analysis of this complex.

REFERENCES

[1] Baena, M. I., Márquez, M. C., Matres V., Botella, J., Ventosa, A. *Curr.Microbiol*. 53, 491-495 (2006).

[2] Oladipo, M. A. & Olaoye, O. J. *Inter. J. of Res. in Pharm. and Biomed. Sci.*. **4**(4),1160-1171 (2013).

[3[Huang, R., Wallqvist, A., Covell, G. *Biochemical pharmacology.*, **69**, 1009-1039 (2005)

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

[5] Bloomgarden, Z.T., *Diabetes Care*., (22), 1–117 (1999)

[6] Sanger, F., Thompson, E.O.L., *Ibid*., **53**, 535, 366 (1953)

[7] C.F. Meares and T.G. Wensel, *Acc. Chem. Res.*, **17**, 202 (1984).

[8] M. Coughlan, Palladium and Palladium-Containing Enzymes, Oxford:Pergamon Press (1980).

[9] S.M. Hinton and D. Dean, *Crit. Rev. Microbiol.*, **17**, 169 (1990).

[10] E.I. Sitefel, *Prog. Inorg. Chem.*, **22**, 1 (1977).

[11] H. Irving and H.S. Rossotti, *J. Chem. Soc.*, 2904 (1954); 3397 (1953);1176 (1955).

[12] H.H. Willard, L.L. Merritt Jr. and J.A. Dean, Instrumental Methods of Analysis, Van Nostrand Co, New York, edn. 5 (1974).

[13] Jamieson ER, Lippard SJ *Chem. Re.,*. **99**, 2467-2498(1999)

[14] Shaw III, C.F., *Chem. Rev.*, **99**, 2589 (1999)

[15] Best, S. L., Sadler, P. *J. Gold Bull.*, **29**, 7 (1996).

[16] Ahmad, S.,*Coord. Chem. Rev.*, ***248***, 231(2004).

[17] Jahromi E. Z. , Divsalar A., Saboury A. A. at.al. *Journal of the Iranian Chemical Society*., 5 (13), 967–989 (2016)

[18] Jacobi,G. Aftab Iqbal S., and Elmossalamy E.H. *Asian Journal of Chemistry*., 2(23), 573-576 (2011)

[19] El-Enary N, *Farmaco* Jan;59(1), 63-9(2004)

[20] Figgis B.N, Lewis J, In *Progress in Inorganic Chemistry* Vol. 6, Lippard S.J. Ed.; Interscience Publications: New York, 37 (1964)