Research Article

Synthesis, Structural Investigations and Antibacterial Activity of Co-Ordination Compounds of Palladium (II) With Uracil-4 Carboxylic Acid

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ABSTRACT

A new series of mixed ligand co-ordination compound of Palladium having square planner stereochemistry, around the metal ion with the general Formula, $[PdLCl_2]$ where L= uracil -4-carboxylic acid has been isolated in the solid state by the interaction of with the aforesaid ligand. The synthesized co-ordination compound has been characterized by elemental analysis, electrical conductance, magnetic measurements, molecular weight determination, electron spin resonance, infra red spectral measurements and NMR studies. A square planner structure has been proposed for square planner complex. It is observed that:

(i) The synthesized compound is yellow in colour.
(ii) It is non hygroscopic.
(iii) It is soluble in DMF, DMSO, slightly soluble in acetonitrile and sparingly soluble in other solvents.
(iv) It is thermally stable and does not decomposed up to 260^0C.
(v) The compound has d^8 configuration.
(vi)The complex has anti tumor activity.

Keywords: Co-ordination chemistry, Uracil-4 –carboxylic acid, palladium, Anti tumor activity magnetic measurements, molecular weight determination.

I. INTRODUCTION

Uracil-4 –carboxylic acid represents one of the most active classes of compounds possessing wide spectrum of antitumor activities. The recent interest in the preparation and structural investigation of palladium (II) complexes with uracil-4-carboxylic acid can be attributed in part to the importance of these compounds as catalyst, anticancerous drugs and biologically active compounds. Although several other transition metals are now very important as laboratory and industrial catalysts, palladium continue to be widely investigated, perhaps because of their widespread catalytic activity, their relatively inert character, anti cancerous activity and usual facile synthesis of their complex.

1.1Uracils as Active Principles

2,4 (1H, 3H)- Pyrimidinedione normally called by the trivial name Uracil has been known since 1900 when it was first isolated by hydrolysis from materials containing ribonucleic acids , such as yeast , wheat germs .Thymine was found much earlier from bovinethymus (1) . In 1901 , the constitution of uracil was estabilished by Emil Fisher (2); however, 6- methyl uracil was made early as 1885(3).

No exhaustive and detailed review on uracils , their syntheses, structure, or their utility in heterocyclic chemistry exists. Uracils have represented, for more than 90 years , a class of compounds that continually attract organic chemist , biochemists, medicinal chemists and photo biologists Uracils were detected as constituents of ribonucleic acids, from which they were prepared by hydrolysis. Nucleosides derived from uracil are called uridine, pseudouridine, and uridine phosphate respectively. Recently, uracil moieties were detected in the antibiotic Tunicamycin (6).The biosynthesis of uracil proceeds via decarboxylation of orotidin-5-phosphate , which is formed from carbonyl phosphate and aspartate via orotate after

nucleosidation with 5- phosphoribosyl-1-di phosphate. Uracil can also be generated from cytosine by Oxidative deamination using sodium hydrogen sulfite.

Several uracil derivatives have been developed as drugs .Thus, methylthiouracil and propylthiouracil are thyroid inhibitors; Bucolome is an antinflammatory; and Uramustine (Uracil mustard) , Fluorouracil, and its masked compounds are anticancer agents . Aminometradine and Amisometradine are used clinically as diuretics , and Urapidil and Ketanserin are used as antihypertensives. Uracil nucleosides, the uridines and their derivatives, play a decisive role as biologically and Pharmacologically active principles .

For example , idoxuridine(7), trifluridine (7), and edoxuridine(7) show antiviral activity as an antimetabolite of thymidine; Cytarabine is used for the clinical treatment of leukemia.Naturally occurring hetrocondensed uracils derivatives are shown in Scheme 8. Methylxanthines, e.g., Caffine(8), theophylline (8), and theobromine (8) show various Pharmacological activities. Riboflavine (VitaminB_2) acts as a coenzyme in bio-redox reactions (9).Uric acid is a metabolite of purine nucleoside (10).Toxoflavin (11) and fervenuline (11) are antibiotics.

Fig-I

As this chapter involves the synthesis of complex with uracil-4- carboxylic acid based organic compounds, it would be appropriate to discuss here the structure, vibrational spectra, UV-VIS spectra and NMR spectra of uracil.

II.EXPERIMENTAL

1.2MATERIALS AND METHODS

Uracil was procured from Aldrich Chemical Company, U.S.A. and used as such. Distilled water used in all the operations. Carbon, hydrogen, nitrogen and oxygen present in the investigated complexes were estimated micro analytically.

For the estimation of Palladium as Palladium 1, 2, 3 benzotriazole, the synthesized compound solution were mixed with 10ml of 2M. acetic acid-sodium acetate buffer and 5ml of 4% EDTA solution.. Then 2.5 % acetic acid, was added with shaking. Digest the solution between 60^0C-90^0C, are 20 minutes. The resulting precipitate was filtered (G 3), washed several times with very dilute HCl (1:100), finally with distilled water and dried to a constant weight at 110^0C.

Conductance's were measured in analytical grade dimethyl sulphoxide (DMSO) and dimethyl formamide (DMF) using dip type cell on Toshniwal Conductivity Bridge at the department of chemistry, Atarra P.G. College , Atarra.

Magnetic susceptibility measurement was made at room temperature by Gouy method. A magnetic field strength of 8500 gauss was employed. The apparatus was calibrated using cobalt mercury thiocyanate Hg [Co $(NCS)_4$]. The diamagnetic correction was computed using Pascal's constant. For calculation of effective magnetic moments, following equation has been used.

Effective magnetic moments (μeff) = 2.84 (x_m^{corr} .T)$^{1/2}$

Where T = temperature in absolute scale , and

x_m^{corr} = corrected molar susceptibility.

Infrared spectra (4000-450cm^{-1}) of the uncoordinated ligands and the synthesized complex was recorded in nujol mulls supported between KBr pellets on Perkin Elmer (RXI) spectrometer (at Sophisticated analytical instrument facility, Central Drug Research Institute, Lucknow).

UV-VIS specta of the the uncoordinated ligand and the synthesized complex was recorded in Perkin Elmer lambda15 UV-VIS spectrophotometerranging from (260-700nm) (at Sophisticated analytical instrument facility, Central Drug Research Institute , Lucknow).

NMR spectra of the uncoordinated ligands and the synthesized complex was recorded on Brucker DRX-300MHz FT NMR using DMSO as solvent.

Molecular weight determination of the synthesized complex was made by Rast's method.

III. PREPARATION OF THE COMPLEX

1.3PREPARATION OF [Pd (URACIL 4-CARBOXYLIC ACID)Cl_2]

Palladium (II) complex with uracil -4 carboxylic acid was prepared by mixing 0.1 N HCl solution of $PdCl_2$ with methanolic solution of the uracil (0.112mol) and heating the reaction mixture was refluxed on a water bath for 2 hours .The complex precipitated out in neutral medium on cooling .It was filtered ,washed several times with hot methanol and dried in vacuo over fused calcium chloride.

1.4Properties

It has also been observed that due to the participation of carbonyl groups in complexation the bands in the 1500-1800 cm^{-1} region shifted to a lower frequency .Moreover it has been reported that the carbonyl at C(4) has a greater affinity to get coordinated to the metal ion. The uracil spectrum showed a doublet peak at 1710 & 1695 cm^{-1} .In the metal complexes , the former band is shifted to ca. 1670 cm^{-1} .In the complexes , the hafnium (IV) ion displaced the proton at N(3), similar to the complexes reported earlier and consequently the υ (C-N) stretching frequency also perturbed. It shifted from 1390 in the ligand to 1350 cm^{-1} in the complexes.Thus, the uracil moiety acted as a bidentate group , being chelated to the Pd (II) ion through carbonyl at C(4) & deprotonated N (3).

The uracil ligand showed two absorption bands at 260 (log ϵ 4.0) & 220 nm (log ϵ 1.5) . The former was attributed to the π-π* transition of the carbonyl group , while the later to the corresponding transition n of N ═ C ┈ O chromophore. One complexation the absorption due to carbonyl group shifted to 270 nm (log ϵ 5.2) ,indicating the involvement of carbonyl oxygen in complexation. The N ═ C ═ O chromophore in the metal complexes absorbed at ca. 226 nm ((log ϵ 4.5) .All the complexes are diamagnetic as expected for square planner d8 metal ion complex.

The ^1H NMR signal of uracil-4- carboxylic acid appeared at δ 6.37 (1H , d , H(5), τ 6.0 Hz) & 7.95(1H , d , H(5) , τ 6.0 Hz), which remained un effected on complexation. The cyclopentadienyl group showed signal at δ 6.9-7.0 (m , 10H) in the metal complexes.

The complex is yellow in colour and stable towards air and moisture. They decompose at higher temperatures. It is insoluble in water and common organic solvents but soluble in DMF, DMSO, and Dioxane. The general formula for the complex is [$MLCl_2$] respectively.Where M = Pd , L = ligandThe electronic spectra of Pd (II) complex exhibit three bands in the ranges 17391-17543, 25000-27777 and 31250-32258 cm^{-1} where are assigned to $^1A_{2g} \longleftarrow {}^1A_{1g}$, $^1B_{1g} \longleftarrow {}^1A_{1g}$ $^1A_{1g} \longleftarrow {}^1E_g \longleftarrow {}^1A_{1g}$ transitions, respectively.

The analytical and physical data of the ligand and its metal complexes are given in **table I.**

The complexe is non hygroscopic and stable towards moisture. It is insoluble in water and organic solvents but soluble in DMF, DMSO. The colour of the complex is shown in **table II.**

IV. RESULT AND DISCUSSION

The magnetic values of the synthesized complex measured at room temperature. An observation shows that the magnetic moment values of the complexe [Pd(uracil-4- carboxylic acid)Cl_2] is zero.Hence, the complex is evident from their diamagnetic nature.The Analytical and physical data of the ligand and its metal complex is given in table I. The value of molar conductance are in the range 0.052-0.058 $Ω^{-1}$ cm^{-1} mol^{-1} suggesting non electrolyte nature of the synthesized complex.The IR spectra of synthesized complex containing coordinated uracil-4-carboxylic aciod, is presented in Table -III respectively.

The ligand uracil-4- carboxylic acid possesses 3 possible donar sites; two cyclic nitrogen and one ketonic group in the ring respectively. Further the cyclic nitrogen involved in coordination through the nitrogen atom. Co-ordination through N in the cyclic nitrogen group amino group invariable result in the increase in at least 40 cm^{-1}. In the complex of uracil-4-carboxylic acid, studied here the IR frequency of cyclic nitrogen ring is essentially changed, thereby , suggesting

the cyclic nitrogen of this ligand has been participate in the coordination. The presence of a Broad band at 505-530 cm^{-1} in the synthesized compounds is due to Pd-N.

V.CONCLUSION

The complex has anti tumor activity. Filamentous growth in bacteria is indicative of the ability of an agent to react with DNA, giving selective inhibition of DNA synthesis but no accompanying effect on other biosynthetic pathways. Induction of bacteriophage from lysogenic bacteria an mutogenicity of some active complex is also important evidence for direct DNA attack. Biochemical studies on cells in culture have shown that cis[Pd (uracil-4- carboxylic acid) Cl_2] selectively and persistently inhibits the rate of DNA synthesis as compared to RNA and protein synthesis .It is postulated that the primary chemical lesion in the DNA, inhibiting it as a template for replication. Studies on cis and trans isomer of [Pd (uracil-4- carboxylic acid) Cl_2] on cells in vitro showed that trans binds to cell macromolecules as effectively as cis . There are more palladium moieties bound per molecule of DNA than to either RNA orbitals protein. Interstand cross-linking has been demonstrated to occur for Pd compounds, but to a much lesser extent than for alkylating agents. The balance of evidence highly favours the proposal that this form of binding to DNA is not an important cytotoxic events . Linking between bases on the same strand has been circulating white Blood cells, although this is lower than that for most other anti tumor drugs. Other side effects include nausea, vomiting, and high frequency hearing loss (ototoxicity). Peripheral neuropathy has been observed on repeated treatment.

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VI.ACKNOWLEDGEMENT

Dr. Anshu is grateful to the Department of chemistry Atarra P.G.Colllege Atarra Banda. The author wish to thank CDRI, Lucknow, India, for providing Analytical data and Dr .Dinesh Chandra Gupta Professor Atarra P. G. College Atarra (Banda) for kind supervision and valuable time. I also thankful to Dr. A. C. Nigam, Dr. G. Gupta for review my work.

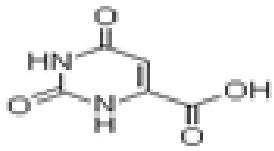

Fig 1: Uracil-4-carboxylic acid

Table 1: Analytical Data of the Complex

S. No	Compound	% Pd Found (Calc.)	% C Found (Calc.)	% H Found (Calc.)	% N Found (Calc.)	% Cl Found (Calc.)
1	[Pd(Uracil4-Carboxylic Acid)Cl_2]	31.01 (31.90)	16.87 (17.99)	1.20 (1.21)	8.01 (8.39)	21.02 (21.29)

Table 2: Colour and % yield of the complex

S. No	Compound	Colour	Decomposition	% Yield
1	[Pd(Uracil4-Carboxylic Acid)Cl_2]	Yellow	< 250^0C	67

Table 3: Important IR spectral bands and their assignments

S. No	Compound	v (c=o)(cm^{-1})	$v_{NH(\beta)(cm-1)}$	$v_{NH(\gamma)(cm-1)}$	v_M	$_C$(cm)
1	[Pd(Uracil4-Carboxylic Acid)Cl_2]	1640	1545	807	-	1630

VII.REFERENCES

1. Blitz H, Slotta and Prakt KJ. Chem. 1926;113:233.
2. Chipen GI and BOlkadere RP.Chem Abstr. 1969;70:115078u.
3. Rupe H. (a) with Labhardt H, Ber dtsch. Chem.Ges. 1900;33:233. (b) with Metz G. 1903;36:1092. (c) Rupe H, Hubner A, Helv. Chim. Acta. 1927;10: 846.
4. Netherlands Pat . (a) 6.406, 077 (1964) (b)6,409, 120 (1965); (c) 6, 501, 015 (1965); (d) 6, 501,053,(1665); (e) 6, 504, 121, (1965); (I) 6, 510, 485, (1966); (g) 301,383 (1965) [Chem.Abstr.64 (1966) 8196].
5. Kroger, C.F. (a)Freiberg ,W.Z. Chem.5 (1965) 381; (b) with Mietohen , R. 7 (1967) 184; (c) with Franck , H.Angew.Chem (Int Edn.) 4(1965)434, 879; (d) with Schoknecht , G. and Beyer H. Chem. Ber.97 (9164) 398 ; (e) Hummel, L., Mietscher , M. and Beyer H.98 (1965) 3025; (f) with Mietchen ,R. 100 (1967) 2250; (g) with Etzold, G. and Beyer, H. (with Busse. G.) Justus Liebigs Annlin Chem. 664 (1963) 156.
6. Belg, Pat. (a) 611,906 (1962) ; (b) 621, 842 (1963); (c) 630, 494 (1963); (d) 671, 402 (1966).
7. Dimroth, O. (a) Justus Liebigs Annln Chem. 335 (1904) 1 ; (b) with Eberhardt, E. 335 (19040 86 ; (c) 364 (1909) 183; (d) with Aicklin , H. and Merckle, E. 373 (1910) 352.
8. Scarpati, R. Sica , D. and Lionetti . A. Gazz. Chim. ital.93 (1963) 90.
9. Daeniker , H.H. and Druey, J.Helv. Chim. Acta 45 (1962) 2441.
10. Anschutz, R. (a) Justus Liebigs Annln Chem. 294 (1897) 219. (b) with Schwickerath , K. 284 (1895) 9 ; (c) with Montfort, W.F.284 (1895) 8 , 19.

11. Balaban, I.E. (a) with Pyman , F.L .J. Chem. Soc. 121 (1922) (1922) 947; (b) with Pyman , F.L.125 (1924) 1564; (c) with King, (1927) 1858; (d) (1930); (e) with Pyman, F.L. (1930)397 ; (f) (1932) 2423.
12. Cohen, A., King, H. and Strangeways, W.I.J.Chem. Soc.(1931).3043.Heath, H., Lawson A and Rimington C.(a) J Chem Soc. 1951;2215:.2217