

Synthesis and Structural Investigations and Antitumor Activity of Co-Ordination Compounds of Palladium (II) With Uracil and Substituted Uracils

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Abstract - A new series of mixed ligand co-ordination compound of Palladium having square planer stereochemistry, around the metal ion with the general formula, [PdL₂Cl₂] where L= uracil and substituted uracils has been isolated in the solid state by the interaction of with the aforesaid ligands. The synthesized co-ordination compounds have been characterized by elemental analysis, electrical conductance, magnetic measurements, molecular weight determination, electron spin resonance, infra red spectral measurements and NMR studies. A square planer structure has been proposed for square planer complexes. It is observed that the synthesized compounds are light brown or brown in colour, they are non hygroscopic, they are soluble in DMF, DMSO, slightly soluble in acetonitrile and sparingly soluble in other solvents, they are thermally stable and do not decomposed up to 2600C, all the compounds have d8 configuration and all the complexes have anti tumor activity.

Key words - Substituted uracils, Co-ordination compound, Uracil, palladium

I. INTRODUCTION

Uracil 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 and substituted uracils 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, platinum and 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 complexes. The structure, vibrational spectra, UV-VIS spectra and NMR spectra of uracil and its derivatives organic compound complexes.

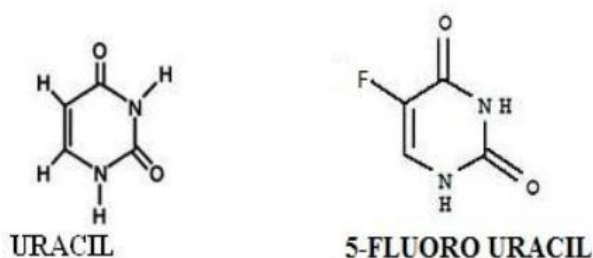


Fig-1

II. STRUCTURE AND PHYSICAL PROPERTIES

In solid state, uracil exists as the dioxo tautomer (**fig-II**), which has been shown with the aid of refined X-ray analyses from which the position of hydrogen atoms were directly determined. Uracil crystallizes in the space group P21/a.

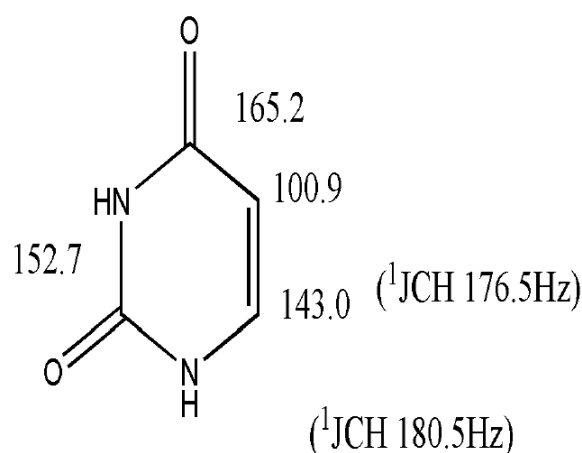


Fig: 2

The following list shows some parameters for the monoclinic cell.

$$\begin{aligned} a &= 11.938 \pm 0.001 \text{ \AA} \\ b &= 12.376 \pm 0.009 \text{ \AA} \\ c &= 3.6552 \pm 0.003 \text{ \AA} \\ d &= 120054' \pm 0.4' \\ 1(\text{Mo Ka}) &= 0.71069 \text{ \AA} \end{aligned}$$

This dioxo form is further supported by other spectroscopic data. For instance, UV-(3) indicate that the same tautomer predominate in solution(1).

In ¹H NMR spectroscopy (solvent D₂O), 5-H and 6-H form a quadrouplet centered at δ 5.71 and 7.60, respectively, with a coupling constant of J = 8 Hz (63 M I). As the chemical shift of C-5 and C-6, ¹³C-NMR spectroscopy reveal the 5,6 double bond is highly polarized as expected for a heterocyclic enamino carbonyl compound.

The ^{15}N NMR data also support the dioxo structure, although all spectra are complicated by extensive, long range ^{15}N coupling and the low solubility of the material in most solvents. The mass spectrum (MS) 70 eV of uracil shows a molecular ion at m/z 112, which expels HNCO (43 mass units) and produces peak at m/z 69 ($\text{C}_3\text{H}_3\text{NO}^+$) and a metastable peak at m/z 42.5 (4). The additional fragmentation processes have been studied in detail. Protonation/deprotonation sites have been discussed [5].

III. URACILS 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 established by Emil Fisher (2); however, 6-methyl uracil was made early as 1885(3).

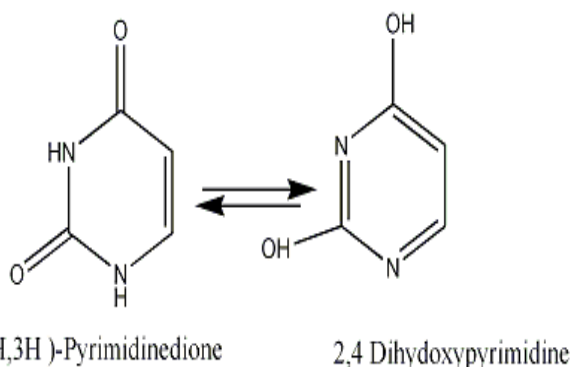


Fig -3

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 chemists, biochemists, medicinal chemists and photobiologists. 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-diphosphate. 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 anti-inflammatory; 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., Caffeine(8), theophylline (8), and theobromine (8) show various pharmacological activities. Riboflavine (VitaminB2) acts as a coenzyme in bio-redox reactions (9). Uric acid is a metabolite of purine nucleoside (10). Toxoflavin (11) and ferveruline (11) are antibiotics.

IV. URACIL SYNTHESSES

The classical and primary synthetic route to uracil from formal acetic acid (made in situ from malic acid) and urea in sulphuric acid is still important(12). Some alternative syntheses use malic acid, urea, and PPA(13) or maleic/fumaric acid, urea, and poly phosphonic acid (PPA) (13). The reaction of formyl acetate with thiourea is convenient for the synthesis of 2-thio uracil. Another main synthesis involves the reaction of ureas with β -keto esters diketene or acid anhydride. Orotic acids are synthesized from oxaloacetate and ureas in the presence of hydrogen chloride via ring transformation of hydantoin into the uracil ring system.

Treatment of the easily obtainable 2-thio uracil with chloroacetic acid followed by acid hydrolysis or by oxidation with dimethyl sulphoxide (DMSO) in conc. sulphuric acid are alternative pathways. 1,3-dimethyluracil is transformed with urea in ethanolic sodium ethoxide into uracil. Some more recent uracil syntheses start with propanoic acid and urea in PPA (or conc. sulphuric acid and benzene as solvent).

A broad choice of hetrocondensed uracils is easily and generally accessible from heterocyclic β -enamino esters and isocyanates. The mixed urea intermediate is smoothly cyclized with 5% aq. NaOH; the whole procedure can be carried out in a one step reaction, when pyridine serves as solvent and base catalyst for the ring closure.

The condensation of urea with protected β -keto esters gives 6- or 5, 6-(di) substituted uracils by means of retro Diels Alder splitting, nonbornene condensed tricyclic dihydrouracils, accessible from aminononbornene carboxylic acid and 1,1-carbonyl diimidazole, afford, upon heating, uracils in good yield. Substituted uracils are obtained from imido esters, isocyanates, and malononitrile. Similarly N-substituted N-cyanoacetyl ureas cyclize in an alkaline medium. Hetrocondensed uracils are easily accessible from acyl lactones, lactams, and thio lactones, and heterocyclic β -enamino esters, especially. The latter gives a broad range of novel types of condensed systems. With the aid of the hexamethyldisilazane trimethylchlorosilane (HMDS/TMSCl) technique or the use of NaOH and halosugars, respectively,

simple approaches have been developed to obtain unusual nucleosides[10].

V. EXPERIMENT

a. Materials employed

uracil and 5-fluoro uracil were procured from Aldrich Chemical Company , U.S.A. and used as such. Distilled water used in all the operations.

b. Analysis of the constituent elements

- (1) Carbon, hydrogen, nitrogen and oxygen present in the investigated complexes were estimated micro analytically.
- (2) Estimation of Palladium: 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^oC-90^oC, 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^oC.

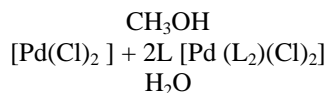
VI. PREPARATION OF THE COMPLEXES

a. Preparation of [Pd (Uracil)₂Cl₂]:

Palladium (II) complex with uracil were prepared by mixing 0.1 N HCl solution of PdCl₂ 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.

b. Preparation of Substituted Uracils such as [Pd (5 – fluoro Uracil)₂ Cl₂]

A mixture of PdCl₂ (500mg) and ligand 5-fluoroUracil (1gm) in water and methanol (50ml) was refluxed at 800C 6-7 hours until it become a clear yellowish colour solution. This volume was reduced to 5ml and treated with methanol. The resulting gray white crystals were collected and washed well with ethanol and acetone. The analytical data is given in the table 3.4 The General reaction for the preparation of coordination compound of palladium is as follows:



Where L = uracil and 5-fluoro uracil.

VII. PHYSICAL MEASUREMENTS

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 ν (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 planer d⁸ metal ion complexes. The ¹H NMR signal of uracil 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.

All the complexes are light brown or brown in colour and stable towards air and moisture. They decompose at higher temperatures. They are insoluble in water and common organic solvents but soluble in DMF, DMSO, and Dioxane. The general formulas for the complexes are [ML₂Cl₂] and [ML₂Cl₂] respectively. Where M = Pd, L = ligand. The electronic spectra of Pd (II) complexes exhibit three bands in the ranges 17391-1754325000-27777 and 31250-32258 cm⁻¹ where are assigned to ¹A_{2g} ← ¹A_{1g} ← ¹B_{1g} ← ¹A_{1g} ← ¹E_g ← ¹A_{1g} transitions, respectively. The analytical and physical data of the ligand and its metal complexes are given in table 1.

TABLE 1 THE ANALYTICAL AND PHYSICAL DATA OF THE LIGAND AND ITS METAL COMPLEXES

S N	Compound	% Pd Found (Calc.)	% C Found (Calc.)	% H Found (Calc.)	% N Found (Calc.)	% Cl Found (Calc.)	% F Found (Calc.)
1	[Pd(Uracil) ₂ Cl ₂]	26.52 (26.40)	23.91 (23.80)	1.99 (1.94)	13.94 (13.97)	17.20 (17.59)	-
2	[Pd(5-fluoroUracil) ₂ Cl ₂]	24.79 (24.63)	27.93 (27.80)	2.79 (2.64)	13.03 (13.13)	16.53 (16.56)	-

The complexes are non hygroscopic and stable towards moisture .They are insoluble in water and organic solvents but soluble in DMF, DMSO. The colour of all these complexes is shown in table 2.

TABLE-2 COLOUR & % YIELD OF THE COMPLEXES

SN	Compound	Colour	Decomposition	% Yield
1	[Pd(Uracil) ₂ Cl ₂]	Light yellow	< 2500C	65
2	[Pd(5-FluoroUracil) ₂ Cl ₂]	Brown	< 2500C	70

VIII. RESULT AND DISCUSSION

a. Magnetic Measurement

The magnetic values of the synthesized complexes measured at room temperature. An observation shows that the magnetic moment values of the complexes $[Pd(Uracil)_2Cl_2]$ and $[Pd(5-fluoro\ Uracil)Cl_2]$ are zero. Hence, all the complexes are evident from their diamagnetic nature.

b. Conductance Measurement

The value of molar conductance are in the range $0.05_2-0.058\ \Omega^{-1}\ cm^{-1}\ mol^{-1}$ suggesting non electrolyte nature of the synthesized complexes.

c. Infrared Spectra Measurement

The IR spectra of synthesized complexes containing coordinated uracil and 5-fluoro uracil are presented in Table - 3 respectively.

Compound	ν (C=O)(cm^{-1})	ν NH(β)(cm^{-1})	ν NH(γ)(cm^{-1})	ν C NH2(cm^{-1})	Ring(cm^{-1})
$[Pd(Uracil)_2Cl_2]$	1640	1550	825	-	1640
$[Pd(5-FluoroUracil)_2Cl_2]$	1640	1545	807	-	1630

The ligand Uracil 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 complexes of uracil, 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.

IX. ACKNOWLEDGEMENT

Dr.Anshu is grateful to the Department of chemistry Atarra P.G.College Atarra Banda. The authors wish to thank CDRI, Lucknow, India, for providing Analytical data and Dr .Dinesh Chandra Gupta for kind cooperation.

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