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SYNTHESIS AND STRUCTURAL INVESTIGATIONS OF CO-ORDINATION COMPOUNDS OF PALLADIUM (II) WITH URACIL AND 5-METHYL URACIL

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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, [PdL_2Cl_2] where L= uracil and 5-methyl uracil 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 planner structure has been proposed for square planner complexes. It is observed that:

(i) The synthesized compounds are light brown or brown in colour.

(ii) They are non hygroscopic.

(iii) They are soluble in DMF, DMSO, slightly soluble in acetonitrile and sparingly soluble in other solvents.

(iv) They are thermally stable and do not decomposed up to 260^0C.

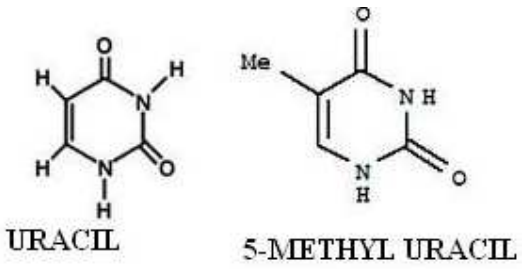
(v) All the compounds have d^8 configuration.

(vi) All the complexes have anti tumor activity.

Key words: 5-methyl uracil, Co-ordination chemistry, Uracil, palladium.

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 5-methyl uracil 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

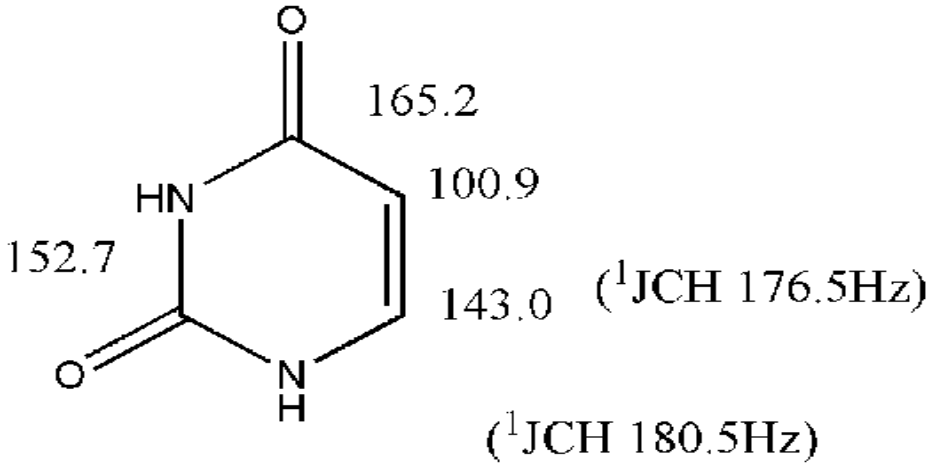
investigated, perhaps because of their widespread catalytic activity, their relatively inert character, anti cancerous activity and usual facile synthesis of their complexes. **Fig-I.**



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

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 . The following list shows some parameters for the monoclinic cell. **(Fig-II).**



a = 11.938 ± 0.001Å

b = 12.376 ± 0.009Å

c = 3.6552 ± 0.003Å

d = 120054′ ± 0.4′

1(Mo Ka) = 0.71069Å

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 D_2O), 5-H and 6-H form a quadrouplet centerdat d 5.71 and 7.60, respectively, with a coupling constant of J = 8 Hz (63 M I)

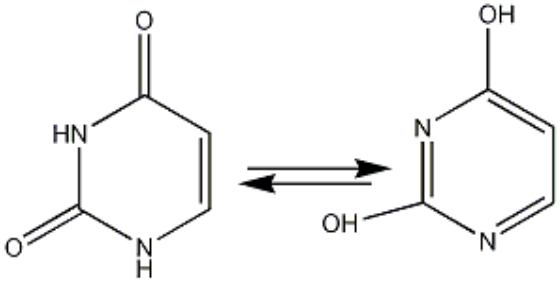
As the chemical shift of C-5 and C-6, ^{13} C-NMR spectroscopy reveal the 5, 6 double bond is highly polarized as expected for a hetrocyclic enamino carbonyl compound.

The ^{15}N NMR data also support the dioxo structure, although all spectra are complicated by extensive, long range ^{15}NH coupling and the low solubility of the material in most solvents .The mass spectrum (MS) 70 eVof uracil shows a molecular ion at m/z 112, which expels HNCO (43 mass units) and produces peak at m/z 69 ($C_3H_3NO^+$) 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].

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

Fig -3



2,4 (1H,3H)-Pyrimidinedione 2,4 Dihydoxypyrimidine

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.

Uracil Syntheses

The classical and primary synthetic route to uracil from Formal acetic acid (made insitu 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 chloro acetic 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 in to uracil. Some more recent uracil syntheses start with propanoic acid and urea in PPA (or conc. sulfuric acid and benzene as solvent.

A broad choice of hetrocondensed uracils is easily and generally accessible from heterocyclic β- enamino esters and isocynates. The mixed urea intermediate is smoothly cyclized with 5% aq.NaOH; the whole procedure cab 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 di imidazole , 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, lactums, and thio lactones, and heterocyclic β-enamino esters, especially .The later 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].

Experimental

(a)Materials employed

Uracil and 5-methyl 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:

(i) Carbon, hydrogen, nitrogen and oxygen present in the investigated complexes were estimated micro analytically.

(ii) 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 60^0C-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.

Preparation of the complexes:

(a)Preparation of [Pd (Uracil)$_2$Cl$_2$]:

Palladium (II) complex with uracil were 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.

Preparation of [Pd (5 – methyl Uracil)$_2$ Cl$_2$]:

A mixture of $PdCl_2$ (500mg) and ligand 5-Methyl Uracil (1gm) in water and methanol (50ml) was refluxed at 80^0C 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:

$$[Pd(Cl)_2] + 2L \xrightarrow[H_2O]{CH_3OH} [Pd(L_2)(Cl)_2]$$

Where L = Uracil and 5-Methyl Uracil

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 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 d^8 metal ion complexes. The ^{1}H 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 $[ML_2Cl_2]$ and $[ML_2Cl_2]$ 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 $^1A_{2g} \longleftarrow {}^1A_{1g}$, $^1B_{1g} \longleftarrow {}^1A_{1g}$ $^1E_g \longleftarrow {}^1A_{1g}$ transitions, respectively. The analytical and physical data of the ligand and its metal complexes are given in **table 1.** 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-I: Analytical Data of the Complexes.

Sl.No.	Compound	% Pd Found (Calc.)	% C Found (Calc.)	% H Found (Calc.)	% N Found (Calc.)	% Cl Found (Calc.)
1	**$[Pd(Uracil)_2Cl_2]$**	26.52 (26.40)	23.91 (23.80)	1.99 (1.94)	13.94 (13.97)	17.20 (17.59)
2	**$[Pd(5\text{-}MethylUracil)_2Cl_2]$**	24.34 (24.56)	21.94 (21.46)	1.37 (1.36)	12.80 (12.81)	16.23 (16.26)

Table-II: Colour & % yield of the complexes.

Sl.No.	Compound	Colour	Decomposition	% Yield
1	$[Pd(Uracil)_2Cl_2]$	Light yellow	$< 250^0C$	65
2	$[Pd(5\text{-methylUracil})_2Cl_2]$	Brown	$< 250^0C$	75

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 $[Pd(5\text{-Methyl Uracil})Cl_2]$ are zero. Hence, all the complexes are evident from their diamagnetic nature.

(b)-Conductance Measurement: The Analytical and physical data of the ligand and its metal complexes are given in **table 1.** 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 complexes.

(c)-Infrared Spectra Measurement: The IR spectra of synthesized complexes containing coordinated uracil and 5-methyl uracil are presented in **Table -III** respectively. 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.

Table-III Important IR spectral bands and their assignments.

Compound	ν (c=o)(cm^{-}	$\nu_{NH(\beta)(cm-1)}$	$\nu_{NH(\gamma)(cm-1)}$	$\nu_{C\ NH2(cm-^{1})}$	Ring(cm-1)
$[Pd(Uracil)_2Cl_2]$	1640	1550	825	-	1640
$[Pd(5\text{-methylUracil})_2Cl_2]$	1640	1545	807	-	1630

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