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Coordination Possibility of Uracil and Applications of Some of Its Complexes: A Review

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ABSTRACT

Investigations about the way transition metal cations interacting with biological molecules are essential for a better assessment of the role and effects of metal ions in biological systems. Uracil is a base with ability to coordinate to the metal ion through any of the two nitrogen atoms, and the two carbonyl oxygens of the pyrimidine ring.This paper reviewsthe coordination tendency of uracil, its derivatives and biological uses of some complexes of uracil and its derivatives. The structural reviews of metal complexes of uracil and its derivatives as single ligand and mixed ligand showed that in most complexes of uracil and its derivatives, the ligands act as bidentate where O(4) and N(3) are favourable sites for cation binding. The involvement of O(4) as unidentate is observed in a Cu (II) complex of uracil derivative while involvement of N(1),N(3) as unidentatewas also observed in organometallic complexes of uracil derivatives and in the Cd^{2+} complex of 2-thiouracil, carbonyl sulphur is preferred to carbonyl oxygen. Some of these complexes showed significant biological activities.

Key words: Uracil, bidentate, pyrimidine, unidentate, organometallic,ligand.

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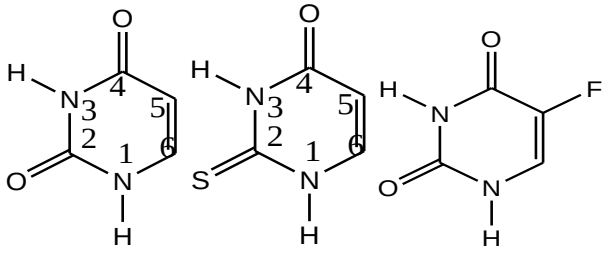
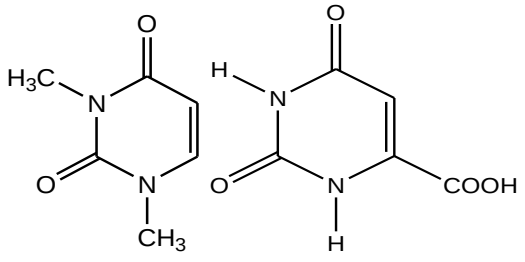
INTRODUCTION

Coordination chemistry is undoubtedly the most active research area in inorganic chemistry. Several thousands of coordination complexes have been synthesized and investigated during the past few decades. Ever since the importance of coordination phenomenon in biological processes was realized, lot of metal containing macromolecules have been synthesized and studied to understand the role of these ligands in biological systems, and they also contribute to the development of new metal-based chemotherapeutic agents. These have resulted in the emergence of an important branch of inorganic chemistry viz. bioinorganic chemistry because in several cases, the metal chelates have been found to be more antimicrobial than the chelating agents themselves.[1]The importance of pyrimidine derivatives arises from their biological, medicinal and agricultural applications.[2-4]Metal complexes of pyrimidine have been extensively studied in recent years owing to their great variety of biological activity ranging from antimalarial, antibacterial, antitumoral, antiviral activities etc.[5,6]

Uracil is naturally occurring pyrimidine derivative found in nucleic acids.[7]It is a pyrimidine base which consists of four different binding sites, and belongs to a group of the most important pyrimidines that played a fundamental role in the structure and function of enzymes and drugs.Uracil was used to synthesis antibacterial [8] and antitumor agents.[9] Some of the derivatives of uracil exhibit significant pharmacological activity and have been used as antitumor, antibacterial, and antiviral drugs.[10]The interaction of metal ions with nucleobases is of great interest because of their relevance to the essential, medical or toxic bioactivity of metal, where nucleobase molecule can coordinate as exogenous ligands in metalloproteins, functions as cofactors in the enzymatic systems and construct important cell structures e.g. RNA.[8] Therefore, this paper is aimed at reviewing the way of interaction of uracil and its derivatives with metal ions, and the applications of some of these complexes.



Uracil Thiouracil5-Florouracil



1,3-dimethyluracil Uracil-4-carboxylic acid

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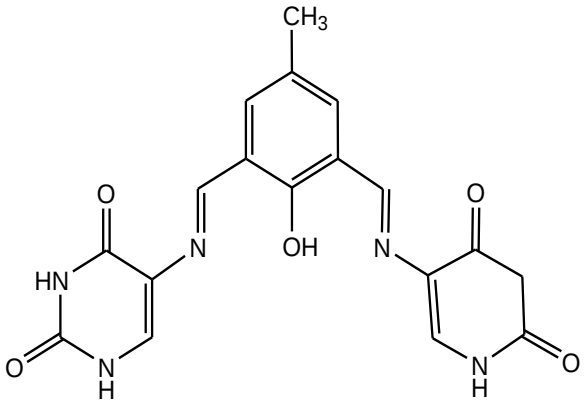

Schiff base ligand of 5-aminouracil reported by Huesco-Urenaet. al.[11]

Fig. 1 :Structures of uracil and some of it derivatives

INTERACTIONS OF URACIL AND ITS DERIVATIVES WITH METALS

Some metal complexes of uracil and its derivatives have been prepared either as single ligand or in mixed ligand complexes.Krishan et al.[12] synthesized Fe (III) and Cr (III) complexes of uracil of type [M(Uracil)$(H_2O)_2$-(OH)Cl];M-CrIII or FeIII and characterized by elemental analysis,UV-Visible, magnetic measurement, electron spin resonance and infrared spectra measurement. The μ_{eff} values, electronic spectral bands and e.s.r. spectra suggested a polymeric six coordinate spin-free octahedral stereochemistry for the Cr (III) and Fe (III) complexes with uracil coordinating to the metal ions through the O atom of C(4) and the N atom of N(1).

The Pd complexes of uracil and uracil derivatives of the type [Pd(Uracil)$_2$Cl$_2$],[Pd(Uracil4-Carboxylic Acid)Cl$_2$]and[Pd(4-Amino Uracil)Cl$_2$] were synthesized and characterized by elemental analysis, electrical conductance, magnetic measurements, molecular weight determination, electron spin resonance, infra red spectral measurements and NMR studies. Square planar structures were proposed for the complexes with the ligands coordinating through O and N donor atoms. But in the complexes of uracil and uracil 4 carboxylic acid, cyclic N donor atom is involved in coordination.[13]

Wang et al.[14] investigated the interaction of Cd^{2+} with uracil, 2-thiouracil, 4-thiouracil and 2,4-dithiouracil by the density functional theory (DFT) calculations and reported that uracil and 2-thiouracil coordinated through N, O and N,S atoms respectively.Polymeric mixed ligand complexes of the type [MCl(ur)(Bh)$(H_2O)]_n$and [M(ur)(Inh)$(H_2O)_2]_n$, where, M = Co(II), Ni(II), Cu(II) and Zn(II), Ur = uracil, Bh = benzoic acid hydrazide and Inh = isonicotinic acid hydrazide, have been prepared and characterized by elemental analysis, magnetic susceptibility measurements, thermogravimetric analysis (TGA), electronic, IR and ESR spectral studies. IR studies suggested that uracil behaves as monobasic bidentate ligand bonding through N(1) and C(4)=O.[15]

Some mixed ligand complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) with Adenine-uracil base pair have been prepared and characterized by their elemental analysis, infrared, UV-visible, magnetic measurement and powder X-ray diffraction studies. It was reported that C(2) =O group of uracil was involved in metal coordination and directly enhances the proton donor ability at the N(3) atom which formed hydrogen bonding with N(1) of adenine[16]. Bran *et al*.[17] synthesized bis-(1,3-dimethyluracil)-dichlorocopper(II) complex by direct reaction between a hot saturated solution of copper (II) chloride in ethanol and hot solution of 1,3-dimethyl in ethyl acetate. Crystals were formed after slow evaporation of clear solution and subjected to IR, elemental analysis and X-ray analysis. X-ray structure determination showed that uracil coordinated to the metal via the C(4)=O atom.

The complex of Fe(III) with uracil and complexes of Thiouracil and 5-(phenylazo) thiouracil with Co(II), Ni(II) and Cu(II) were synthesized and characterized by elemental analyses, IR, electronic spectra, magnetic susceptibility, DTA, and Mossbauer spectra. In the uracil-metal complex, uracil acts as a bidentate ligand through O(4) and N(3) atoms, and in the thiouracil and 5-(phenylazo)thiouracil complexes, the two ligands also acted as bidentate ligands coordinating through O and N(3) atoms.[18] Parthasarah*et al.*[19] synthesized some novel onelectrolytic complexes of uracil of type $[ML_2(H_2O)_2]$ where M = Mn, Fe, Co, Ni, or Cu; L = $C_4H_3N_2O_2$, in its anionic form by heating to reflux a methanolicsolution of uracil and a metalsalt at pHca. 7.5. Electronic spectra indicated the hexacoordination of the metal ion in all the complexes while infrared spectra of all the complexes indicated the chelation of the uracil through C(2)=O and N(3).

Sadhna*et al*.[20] synthesized some mixed complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) ions by performing the reaction of their metal nitrates, 5FU and Hm in aqueous ethanol medium at suitable pH. The isolated solid complexes were characterized by infra red spectral, magnetic susceptibility, elemental analysis, uv/vis spectra and X-ray analysis. It was reported that 5-fluorouracil coordinated to metal ion through N(3). Complexes of two dimensional coordination polymer, $M(6AU)_2Ni(CN)_4$(M= Mn, Co, Ni and Cd; 6AU = 6-aminouracil) were synthesized and characterized using FT-IR, FT-Raman and far-IR spectra. It was reported that 6-aminouracil coordinated through only pyrimidine ring N atom forming octahedral geometry.[21] Some mixed ligand complexes of Th(II),Ce(II) andGd(II) metals with uracil and omeprazone of type $[M(Ome)(ura).4H_2O)]SO_4.xH_2O$ were synthesized and characterized through elemental analyses, conductance measurements,spectroscopy (FT-IR, Mass, ^{1}H NMR and U.V). An IR spectrum indicated that uracil ligand behaves as bidentate in the complexes binding through its C (2) =O and N (3).[22]

The complexes of 5-Fluorouracil (5-FU)(A) in the presence of some amino acid moieties (B) [B =alanine (ala) and phenylalanine (pal)] with some metal ions namely Ni(II), Cu(II) and Zn(II)of MAB type mixed ligand complexes were synthesized and characterized by elemental, spectral (vibrational, electronic, ^{1}H NMR and ESR) data as well as by magnetic moment values and conductivity measurements. Magnetic moment values as well as the electronic spectra indicated that 5-FU coordinates with the metal ion in a bidentate manner through the C(4) = O and N (3) atoms.[23] Margaret and Keith synthesized complexes ofuracil Mn(II), Co(II), Ni(II),

Cu(II), Zn(II), and Cd(II) using the chlorides, bromides, iodides, nitrates, and perchlorates.From the results of Infra Red spectra, elemental analysis and UV-Visible, uracil ligand in the complexes coordinated to the metal ions through the carbonyl groups.[24]

Asit and Shipra isolated mixed ligand oxoand peroxo complexes of vanadium (V), $M[VO(O_2)L_2].nH_2O$ where M = K or NH4, HL = uracil, n = 1 or 2,from aqueous methanolicmedium. The complexes were characterised by elemental analysis, conductance, TGA, UV-Visible, IR and NMR spectral studies. From the results, it was reported that Uracil ligand acted as chelate coordinating through their oxygen at C(2) and nitrogen at N(3).[25] Organometallic complexes of Uracil have been synthesized by the reaction of either $W(CO)_5THF$ or $W(CO)_5MeOH$ with the tetraethylammonium salt of the deprotonated monoanion of dihydrouracil (**1**) and 5-methyluracil (**2**), and 6-methyluracil (**3**). The complexes were all characterized in solution by IR and ^{13}C NMR spectroscopy, and some selected ones in the solid-state by X-ray crystallography. The structures of complexes **1** and **3** consist of octahedrally coordinated anions of pentacarbonyltungstenuracilate, where the uracilate ligand is bound to the metal center by the N(3) atom of the pyrimidine ring, and the tetraethylammoniumcation for charge balance and in the anion of complex **2**, the uracilate ligand was bounded to the $W(CO)_5$ fragment by the N(1) atom of the pyrimidine ring.[26]

Complexes of 2-thiouracil and 6-methyl-2-uracil derivatives of tungsten carbonyl were synthesized from the reaction of photogenerated$W(CO)_5$(solvent) (solvent = MeOH or THF) and the corresponding $[Et_4N][$thiouracilate]. The crystal structure of the $[Et_4N][W(CO)_5$(2-thiouracilate)] derivative revealedthiouracilate coordinating to the tungsten center via the exocyclic sulfur atom.[27] New complex of rhenium(I) with 5-nitrosouracil derivative with formula $[ReCl(CO)_3(DANU)] \cdot CH_3CN$ (DANU=6-amino-1,3-dimethyl-5-nitrosouracil) has been synthesized and solved by X-ray diffraction. The coordination environment around the Re(I) may be described as a distorted octahedron in which the ligand behaves in a bidentate fashion through N(5) and O(4) atoms, making a five-membered chelate ring. The coordination sphere is completed with three carbonyl groups in *fac*-arrangement and one chlorine atom.[28] The crystal structure of the complex catena-bis(~-6-amino-3-methyl-5-nitrosouracilato-N^5,O^4,N^1,O)cadmium(II)has been determined. X-ray structure revealed the coordination of each ligand through O^2,O^4 and N^1 of the uracil ring and N.[5,29]

Complex formation of M^{2+} ions (M=Co, Ni, and Zn) with L = 6-chloromethyluracil, 5-hydroxymethyluracil, uracil, 6-methyluracil, and 6-umpm (dimethyl 6-uracilmethylphosphonate) has been studied by potentiometric titration. Potentiometric results indicated the coordination *via* N^3 of the ligands.[30] The coordination of $Me_2Sn(iv)^{2+}$ and $Me_3Sn(iv)^+$ to uracil and 5-fluorouracil has been investigated by means of potentiometric titration. It was reported that these ligands coordinated to dimethyltin(iv) through N.[3,31] George et al.[32] synthesized mixed ligand complex of 6-amino-1,3-dimethyl-5-nitrosouracil and 2,2′bipyridine of the type $[Cu(DANU)(bipy)\ EtoH]NO_3$. The compound was characterized by means of elemental analysis, TGA, Infra red, UV-Visible, ESR, magnetic measurements and single-crystal X-ray diffraction. It was revealed by the X-ray result that uracil derivative coordinated to metal ion through N atoms of nitroso and 6-amino groups.[32]

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Terron et al.[33] synthesized complexes of 5-chlorouracilate with Zn(II) of the type $[Zn(5\text{-chlorouracilato-N(1)})(NH_3))_3].(H_2O)_2$. It was reported that Zn(II) in the complex presents a tetrahedral co-ordination with three ammonia molecules and the N(1) of the corresponding uracilato moiety.[33]The synthesis and spectroscopic characterization of complexes of Ni(II), Cu(II), Zn(II) and Cd(II) containing hydrazones derived from 6-amino-5-formyl-1,3-dimethyluracil, nicotinicand isonicotinic acid hydrazides have been reported by Francisco et al. In all cases, The coordination of the organic ligandtakes place through the deprotonated N(6) atom from the 6-amino group, the N(51) azomethine atom and the O(52) oxygen from the hydrazide moiety, and experimental data indicated that no carbonyl oxygen atoms from the uracil ring were involved in the coordination to the metal.[34]Gamze et al have worked on the synthesis, spectroscopic and biological activity studies of Ni(II), Cu(II) and Co(II) complexes of Schiff baseligands derived from 5-aminouracil, 2-hydroxy-1-naphtaldehyde, 2,4-dihydroxybenzaldehyde and salicylaldehyde. It was reported that in Ni(II), Cu(II) and Co(II) complexes, ligands coordinated in bidentate fashion to Ni(II) and Co(II), but in a tridentate fashion to Cu(II) by coordinating to the carbonyl oxygen atom in the 4th position of uracil.[35]

Diyya et al. carried out research in aqueous medium to reveal the speciation and coordination tendencies of Glutamic Acid and Uracil Pb(II), Hg(II), Cd(II), Cu(II), Zn(II), Co(II) and Ni(II) ions complexes by potentiometric study.It was reported that uracil coordinated through C(2)O and N(3) to the metal ions.[36]

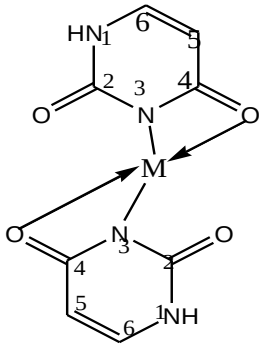

Fig 2 : Predominant binding sites for uracil ring

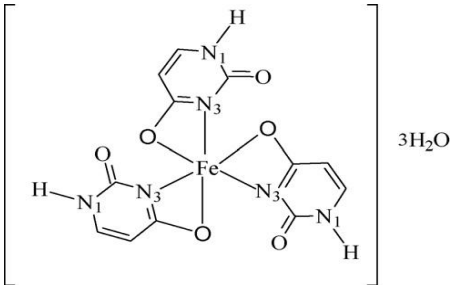

Fig. 3 : Suggested structure of the iron(III)–uracil complex.

Biological Activities

Antibacteria Activity

Uracil complexes of Th&Gd have been reported to show antibacterial activity against *E.Coli* and *Pseudomonasaeruginosa* bacteria than free ligand.[22] 5-fluoro uracil and its Ni(II),Cu(II), Zn(II)mixed ligand complexes with alanine and phenylalanine show antibacterial activity against*Bacillus subtilis*,*Staphylococcus saphyphiticus*,*Staphylococcus aureus*, *Escherichia coli*, and*Pseudomonas aeruginosa* than the free ligands.[23]

Antifungi Activity

5-fluorouracil mixed ligand complexes of Ni(II),Cu(II) and Zn(II) with alanine and phenylalanine showedantifungi activity against *Aspergillusniger*,*Enterobactersp.* and *Candida albicans*.[23]The ternary complexes of Th with Omeprazole and Uracil showed less inhibition zone but the complexes of Gd andCe showed higher inhibition zone against ***A.*** *niger* Culture . The results indicated that the complexes are more active than free ligands.[22]

Antitumor and Cytotoxic Avtivities

5-fluorouracil mixed ligand complexes of Co(II) and Zn(II)5-fluorouracil and histamine showed both significant *invivo* and *invitro* antitumor activity against Dalton's lymphoma tumour system and sarcoma-180system.[37]Ethylenediamineplatinum(II)Uracil Complex and Ethylenediamineplatinum(II) 5-Fluorouracil Complex showed antitumor activity against sarcoma-180 ascites in mice.[38] 5-bromouracil,5-chlorouracil and 5-florouracil mixed ligand complexes of Mn(II), Co(II), Cu(II) and Zn(II)with histidine showed significant antitumor activity against Dalton's lymphoma.[12] Cr(III) and Fe(III) complexes of uracil showed significant *in vivo* and *in vitro*antitumour activity against P815 murine mastocytoma and Al(III) complexes showed poor activity.[13] Mixed ligand transition metal (Mn, Cu, Ni) complexes of 5-iodouracil (5Iu) with 8-hydroxyquinoline or 8HQ and 5- nitrouracil (5Nu) with 8-hydroxyquinoline exerted significant cytotoxicity against HepG2, A-549, HuCCA-1 and MOLT-3 cell lines.The cytotoxicities of tested complexes against HepG2 cells showed their IC50 values lower than the reference drug. Cu complex of 5- nitrouracil (5Nu) with 8-hydroxyquinoline acted as the most potent and promising cytotoxic compound.[39]The complex $[ReCl(CO)_3(DANU)] \cdot CH_3CN$(DANU=6-amino-1,3-dimethyl-5-nitrosouracil) showedantiproliferative behavior against five human tumor cell lines (human breast cancer MCF-7 and EVSA-T, human neuroblastoma NB69, human glioma H4 and human bladder carcinoma cell line ECV).[40]

Insulin Mimic Activity

The potassium salt of mixed ligand vanadium complex of oxo,peroxo and uracil reduces the blood glucose level in Swiss Albino mice compared to that of potassium salt of oxo and peroxo complex of vanadium. The complex also readily oxidized cysteine to cystine in aqueous solution.[25]

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CONCLUSION

This review has summarized the coordinating sites and applications of some synthesized metal complexes of uracil and its derivatives. The structural reviews of metal complexes of uracil and its derivatives as single ligand and mixed ligand have produced a wealth of information regarding the nature of metal interactions with uracil and its derivatives. Spectrophotometer and X-ray analysis of the metal complexes of uracil and its derivatives have revealed the tendency of uracil and its derivatives to act as bidentate and unidentate agents both in binary and ternary complexes coordinating to metal through any of the ring carbonyl oxygen, nitrogen or carbonyl sulphur atoms. Some of these complexes of uracil have displayed diverse biological applications, therefore, they should be explored.

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