SYNTHESIS AND PHYSIOCHEMICAL STUDIES OF NEWLY FORMED COMPLEXES OF INNER TRANSITION METALS WITH 1,5-DIHYDRO-4H-PYRAZOLO [3,4-D]-PYRIMIDIN-6-ONE

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ABSTRACT:

Complexes of La(III) and Pr(III) were synthesized by using tridentate ligand 1,5-DIHYDRO-4H-PYRAZOLO [3,4-D]-PYRIMIDIN-6-ONE having the general formula ML_3. The complexes were characterized by IR, UV, elemental analysis, TGA, magnetic moment, conductivity etc. The conductivity data suggests their electrolytic nature. Spectral studies and magnetic susceptibility measurements revealed an octahedral geometry for all the complexes. The ligand and it's complexes were screened for their antimicrobial activity against E. Coli, S. Aureus, A. Niger, Alternaria.

Keywords : 1,5-dihydro-4H-pyrazolo [3,4-d]-pyrimidin-6-one,Alloprinol,La,Pr

INTRODUCTION :

The family of purinic type heterocycles, their structural analogues and isomers are relevant in biochemical and pharmacological processes[1], and its coordination chemistry is a topic of present-day research[2]. The specific role that several transitional metals play in the nucleic acid processes have prompted several research groups to study the bonding behavior of these heterocycles in metal-heterocycle reactions[3]. Within the class of these heterocycles Pyrazolo[3,4-d]-pyrimidin-6-one (allopurinol) is interesting ligand from very different points of view.

Erich and Hänggi[4] study the thermal behaviour of metal compounds of the naturally occurring oxopurines hypoxanthine, xanthine and uric acid and of the synthetic pyrazolo pyrimidines allopurinol and alloxanthine. Hypoxanthine (1,7-dihydro-6H-purin-6-one) formed by degradation of nucleic acids, is oxidized by the molybdenum-and iron-containing enzyme xanthine oxidase via xanthine to uric acid, which subsequently is released from the active site of the enzyme[5]. Disturbances in purine metabolism result in an increase of the uric acid level and in the deposition of sodium hydrogenurate monohydrate crystals in joints. This disease, known as gout, is clinically treated by the drug allopurinol (pyrazolo[3,4-d]pyrimidin-6-one),which is a substrate for xanthine oxidase[6]. Alloxanthine (pyrazolo[3,4-d]primidin-2,6-dione), the enzymatic oxidation

product of the drug allopurinol, inactivates xanthine oxidase by irreversible coordination to the reduced form of the molybdenum centre of the enzyme[7].

The metal coordination capability of allopurinol lies in great measure both in the existence of several electron donor atoms and their disposition in the framework. Many metal complexes involving allopurinol as an uncharged (neutral) ligand and metals, such as Zn(II), Co(II), Ni(II), etc. have been reported in the literature[8-9]. Generally, a monodentate metal co-ordination through the pyrazole nitrogen atom N(8) has been generally observed, whereas a monodentate N(9) co-ordination of neutral allopurinol has been only reported for a rhodium carbonyl compound[10]. Under acidic conditions N(9) coordination of allopurinolium cation has been observed and a copper complex, having a chlorine-bridge polymeric chain structure, has been evidenced[11].

Recently interest in the trend of metal drug complexes, has increased in order to achieve an enhanced therapeutic effect in combination with decreased toxicity. It has been found that platinum or palladium complexes of purine derivatives show enhanced activity with respect to free ligand[12]. It has attracted lots of attention because of its potential role in tissue and vascular injuries, as well as in inflammatory diseases and chronic heart failure[13-14]. The production of reactive oxygen species (ROS) by XO and its damaging consequences has prompted investigations into the ability of some compounds to control and/or inhibit the enzyme activity or to scavenge the free radicals produced[15-16].

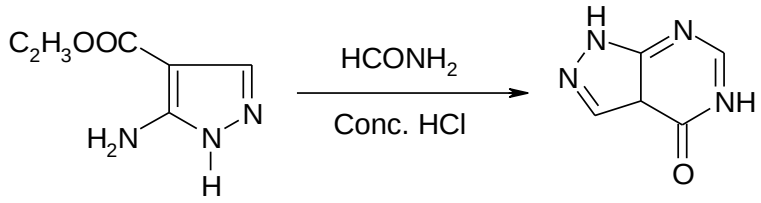
Allopurinol[Pyrazolo[3,4-d]-pyrimidin-6-one] a purine analogue was the first XO inhibitor approved by the FDA in 1966 and has been the cornerstone of the clinical management of gout and conditions associated with hyperuricemia for several decades.

However due to lack of free radical scavenging activity against superoxide anions produced, use of allopurinol is associated with side effects that include allergy, hypersensitivity reactions, gastrointestinal upset, skin rashes and acute interstitial nephritis. Therefore there is a need for the development of novel compounds with better safety profiles that could be used to relieve associated side effects. Alterations of XO activity by various metals have also been probed with mixed results of either stimulation or inhibition, depending on the metal[17].

For the last few years the interest has been increased to study the reaction between metal ions and biologically active compounds. This may due to the fact that some of the complexes show different activities than the drug allopurinol itself[18-20]. Allopurinol is also known as lopurin, zyloprim, antisuril etc. molecular formula $C_5H_4N_4O$ molecular wt.136.11 a xanthine oxidase inhibitor that decreases uric acid production. It also acts as an antimetabolite on some simple organisms. It has 4-nitrogen hetero atoms in the ring system. Nitrogen contains lone pair electrons which can be used for the bonding purpose. Succinic acid form strong binary complexes with metal in allopurinol[21-26].

SYNTHESIS OF PYRAZOLO[3,4-D]-PYRIMIDIN-6-ONE:

Pyrazolo[3,4-d]-pyrimidin-6-one (B) is prepared by a mixture of 28 gm of A compound, 112 ml of formamide, at 15 ml concentrated hydrochloric acid was heated with stirring at temperature of 170^0C in the reaction mixture for 8 hours. After cooling, 100 ml of water was added, and the mixture was filtered. The substance is Pyrazolo[3,4-d]-pyrimidin-6-one (yield = 60%).



(A)

(B) Allopurinol

EXPERIMENTAL :

1. Characterization of Ligand :

Mol. Formula : $C_5H_4N_4O$

Mol. Wt : 136.11

Yield : 70%

Color : Off white

M.P. : >300^0C

Solubility : Ethanol, Methanol, DMF, DMSO.

IUPAC name : 1H-Pyrazol[3,4-d]pyrimidin-4-ol

Pyrazolo[3,4-d]-pyrimidin-6-one

1,5-dihydro-4H-pyrazolo [3,4-d]-pyrimidin-6-one

1H-pyrazolo[3,4-d]-pyrimidin-6-one

Other name : Zyloric, Zyloprim, Milurit, Uridocid, Uriprim, Foligan,Allopurinol

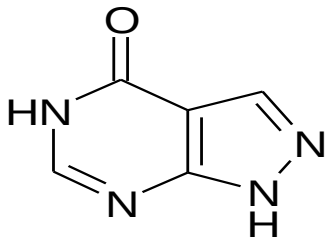


Figure No. 2

Characterization of Pyrazolo[3,4-d]-pyrimidin-6-one is carried out by elemental analysis, IR, UV, NMR.

SYNTHESIS OF PYRAZOLO[3,4-D]-PYRIMIDIN-6-ONE-LANTHANIDE(III)CHLORIDE COMPLEXES :

1) Preparation of Lanthanum-(III) Chloride – Pyrazolo[3,4-D]-Pyrimidin-6-one complex :

To a hot methanolic solution (20ml) of the Allopurinol (0.02 mol), solution (10ml) of methanolic solution Lanthanum(III) chlorides hydrated [($LaCl_3$)7H_2O)] (0.01 mol) was added with constant stirring. The pH of the reaction mixture was adjusted to 7-8 by adding 10% alcoholic ammonia solution and refluxed for about 4-5hr. The precipitated solid metal complex cooled at room temperature and was filtered off and washed with methanol, petroleum ether and dried in vacuum desiccators. Light brown coloured fine crystals of complexes were obtained. Checked the purity by TLC and melting point (yield= 50 %).

Preparation of Praseodymium (III) Chloride- Pyrazolo[3,4-D]-Pyrimidin-6-one complex:

To a hot solution of Pyrazolo[3,4-d]-pyrimidin-6-one (0.272gm in methanol) a methanolic solution of Praseodymium (III) Chloride (0.247 gm) added drop wise. The 1: 2 reaction mixture was stirred for 4-5 hr. After leaving the solution to cool at room temperature, maintain PH at 7-8 and fine crystals obtained. The precipitate was filtered, washed absolute ethanol and dried in vacuo (Yield : 50 %).

RESULT AND DISCUSSION :

Physical and analytical parameters :

Analytical data as well as physical parameters of the ligand and complexes are presented in the table No. 1. The metal complexes formed by Pyrazolo[3,4-d]-pyrimidin-6-one ligand possess blackish–brown colors. Complexes are insoluble organic solvents where as they are sparingly soluble in DMSO/DMF solvents. Decomposition points of the all complexes are relatively high (>300^{0}C), indicating good thermal stability at

normal conditions. On the basis of TGA measurements and elemental analysis complexes are assigned with empirical formula and metal ligand ratio is 1:2.

Table No. 1 : Physical and analytical data

Compound	Molecular Formula	Formula Wt	Yield (%)	Color	M.P. ^{0}C	M : L ratio
ALP	$C_5H_3N_4O$	136.11	60	White	>300	-
$[La(ALP)_2]3H_2O.3Cl$	$C_{10}H_{12}N_8O_5Cl_3La$	571.47	50	Light brown	>300	1 : 2
$[Pr(ALP)_2]3H_2O.3Cl$	$C_{10}H_{12}N_8O_5Cl_3Pr$	573.47	50	Blakish brown	>300	1 : 2

Compound	M.F.	Elemental Analysis % found (calculated)					
		C	H	N	O	Cl	M
ALP	$C_5H_3N_4O$	44.50 (44.08)	2.80 (2.20)	41.65 (41.14)	12.10 (11.75)	- -	- -
$[La(ALP)_2]3H_2O.3Cl$	$C_{10}H_{12}N_8O_5Cl_3La$	13.50 (20.99)	2.70 (2.09)	20.60 (19.59)	12.35 (13.99)	17.60 (18.60)	25.00 (24.30)
$[Pr(ALP)_2]3H_2O.3Cl$	$C_{10}H_{12}N_8O_5Cl_3Pr$	21.60 (20.92)	3.70 (2.09)	20.25 (19.52)	14.45 (13.94)	19.20 (18.53)	23.40 (24.56)

INFRARED SPECTROSCOPY :

Infra red spectrum of the ligand Pyrazolo[3,4-d]-pyrimidin-6-one exhibits strong asymmetric stretching at 3122 cm^{-1} for υ NH, at 1704 cm^{-1} for υ C=0, and at 1591 cm^{-1} for υ C-N (ring)[27-29]. On complexation, υ NH band has disappeared, the absence of a weak broad band in 3200-3400 cm^{-1} region, in the spectra of the metal complexes suggests deprotonation[30] υ C=0 and υ C=N have shifted to lower wave number. The IR spectrum of the complexes showed a sharp band near 1591 cm^{-1}, which may be due to azomethine linkage which was shifted to lower frequencies 1498-1548 cm^{-1} in the metal complexes, indicating co-ordination of the metal ions through the azomethine linkage. The C=O bands observed at 1704 cm^{-1} in ligand and in the metal complexes 1676-1693 cm^{-1}.

It indicates the coordination of C=O group with metals. Deprotonation of –NH moiety due to involvement in coordination[31], bonding via ketone[32-34] may be responsible for observed shifts. This has been supported by the appearance of new vibrations υ M–O and υ M-N that are absent in free ligand[35-37]. The appearance of the M – N bands at 447 cm^{-1}, 433 $cm^{-1}$and the M–O bands at 605 cm^{-1} and 605 cm^{-1}in the complexes indicate that Pyrazolo[3,4-d]-pyrimidin-6-one – metal ions coordinated through an O and a N atom. The absorption bands at 3406 $cm^{-1}$and 3404 cm^{-1}show the presence of water molecule in the complexes.

Thus the ligand Pyrazolo[3,4-d]-pyrimidin-6-one exhibits tridentate behavior and coordinates to the metal through secondary amine, keto and azomethine group. Significant changes of wave numbers involved in coordination of ligand Pyrazolo[3,4-d]-pyrimidin-6-one and metal complexes are shown in table 3.

Table No. 3 : Infra Red Spectral Data

Compound	ν NH	ν C=O	ν C = N	ν M – N	ν M – O	ν H_2O
ALP	3124	1704	1591	-	-	-
$[La(ALP)_2]3H_2O.3Cl$	-	1693	1548	447	605	3406
$[Pr(ALP)_2]3H_2O.3Cl$	-	1676	1516	433	605	3404

ELECTRONIC SPECTRA:

The electronic absorption spectra of metal complexes were recorded in DMSO in the range 200-800 nm. The electronic spectrum of free pyrazolo[3,4-d]-pyrimidin-6-one ligand showed one band around 262 nm, characteristic of $\pi - \pi^*$. In metal complexes, this band is shifted to a longer and shorter wavelength.

In La(III)chloride complex, two bands at 270 nm and 229 nm assigned to the presence of n – π*, π – π* transition respectively. The Pr(III) chloride complex displays one bands at 584 nm due to LMCT respectively. The intensity of the bands indicate the presence of octahedral geometry.

Table No. 4 : Electronic Spectral Data

Complex	Absorbance nm	ν / cm^{-1}	Assign-ment	Molar Conductance $\Omega^{-1}cm^2 mol^{-1}$	Magnetic Moment (BM)	Geometry
ALP	262	38167	π - π*	–	–	–
La-ALP	270, 229	37037, 43668	n - π* π - π*	122	Diamagnetic (–)	Octahedral
Ce-ALP	420, 352	23809, 28409	LMCT, n - π*	135	Paramagnetic (2.10)	Octahedral
Pr-ALP	584	17123	LMCT	107	Paramagnetic (3.14)	Octahedral

SUMMARY AND CONCLUSION :

1. The ligand pyrazolo[3,4-d]-pyrimidin-6-one forms six membered metal chelates with inner transition metal ions viz of La(III), Pr(III) with Coordination number six for all complexes. Ligand behaves as tridentate in nature.

2. Decomposition points of the complexes are relatively high suggesting good thermal stability at room temperature.

3. Complexes are insoluble in common organic solvents, sparingly soluble in DMSO/DMF. Molar conductivities of the complexes in DMSO are medium suggesting that they are good electrolytes. All complexes shows 1:2 M:L ratios.

4. Electronic spectra and molar absorbity values of the chelates support octahedral geometry for all complexes.

5. Study of Infra red spectra and NMR spectra of the ligand and complexes reveals that the ligand pyrazolo[3,4-d]-pyrimidin-6-one coordinates to metal ions through azomethine nitrogen, keto oxygen and coordinated water molecules. Presence of metal-oxygen and metal nitrogen vibrations confirms this type bonding in complexes.

6. Magnetic susceptibility values indicates diamagnetic and paramagnetic nature of complexes.

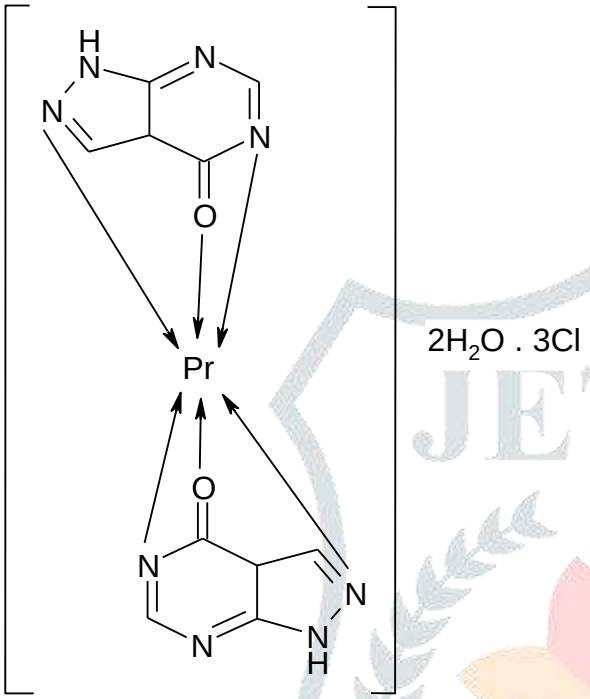
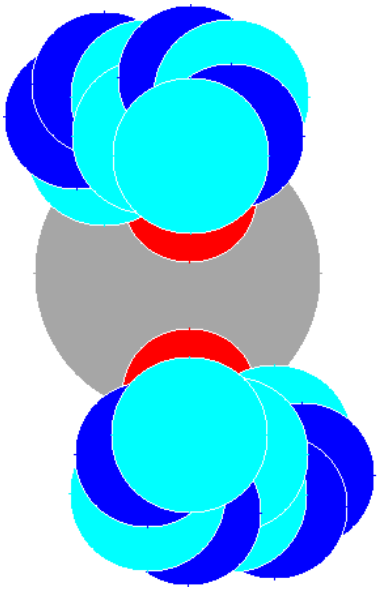


Figure No. 29 : Structure of [Pr(ALP)$_2$]3H$_2$O.3Cl complex



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