CHAPTER I

General introduction.

Aims and objectives of the work

This treatise is concerned with the coordination Chemistry of molybdenum and dioxouranium (VI) [i.e., the uranyl ion, UO_2^{2+}] with pterin and aldimine ligands containing a few selected α – amino acids.

For molybdenum, the study involves both the pterin and aldimine ligands whereas for the uranyl ion, only the aldimine ligands have been used. Coordination Chemistry of molybdenum with pterin ligands constitutes the subject matter of the initial part of this work. The relevant new compounds involve the commonly accessible oxidation states of molybdenum, i.e., VI, V and IV ; several of them possess the attribute of an oxometal entity, i.e., a multiply bonded oxygen atom stabilizing the high charge (VI, V) on the molybdenum atom. In the higher oxidation states, different types of oxomolybdenum entities have been characterized structurally [19, 55].

In the last two Chapters of this thesis, coordination Chemistry of $(Mo^{V}_2O_3)^{4+}$ and UO_2^{2+} entities with aldimine ligands are discussed, especially their reactivity aspects and analyzing the relevant data in the light of stereochemical influences. In fact studies on coordination compounds of aldimine derivatives of amino acids constitute an important area of bioinorganic chemistry, due to their relevance to a diverse series of reactions in amino acid metabolism [22, 74]. The salicylideneamino chirality rule is helpful for assigning the absolute configuration / conformation of an entire set of chiral primary amines including α – amino acids, by CD spectroscopy [79]. Necessary attention has also been paid to the NMR studies on conformation analysis of pyridoxal Schiff bases of α – amino acids [93]. As delineated here in the relevant Chapters, the present aldimine ligands containing α – amino acids help to elicit valuable inferences regarding structure – reactivity / property correlation of the pertinent $(Mo^{V}_2O_3)^{4+}$ - and UO_2^{2+} - complexes.

In the introductory part of each of the subsequent chapters (e.g., Chapters II to V) the aims and objectives of that particular chapter are stated. In this Chapter the overall background about different aspects of this work is outlined.

Molybdenum containing enzymes catalyze a wide range of reactions in carbon, sulphur and nitrogen metabolism. Apart from nitrogenase (with a multinuclear active site), the other class of enzymes (nearly 50 such enzymes contain molybdenum in their active sites) generally function catalytically to transfer an oxygen atom either to or from a physiological acceptor / donor molecule [1, 2, 26, 187, 189]. In general, these enzymes utilize water as the ultimate source or sink of oxygen in the overall catalytic reaction (equation 1) and the reaction is coupled to electron transfer between substrate X / XO, on Fe – S centre, heme or flavin.

$$X + H_2O \rightleftharpoons XO + 2H^+ + 2e^- \quad \text{------ (1)}$$

Considering the metal centre the overall reaction can be represented by equation 2.

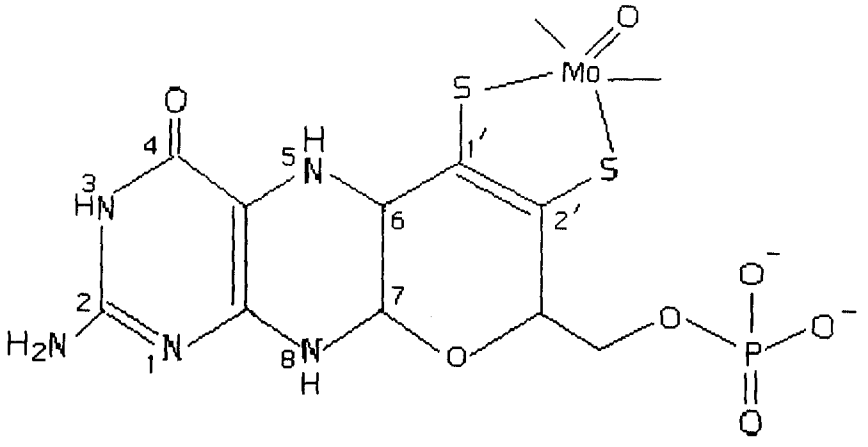
$$X + H_2O + Mo^{VI} \rightleftharpoons Mo^{IV} + XO + 2H^+ \quad \text{------ (2)}$$

The enzymes are referred to as oxotransferases when the substrate is transformed by primary oxygen atom transfer and as hydroxylases when bound or unbound water or hydroxide is directly involved in the substrate transformation reaction. Among others, the oxidation of sulphite to sulphate and the reduction of DMSO to DMS (dimethyl sulphide) can be viewed as oxygen atom (= O, oxo group) transfer reaction. Members of the xanthine oxidase family catalyze the oxidative hydroxylation of a diverse range of aldehydes and aromatic heterocycles in reactions that necessarily involve the cleavage of a C – H bond, e.g., conversion of xanthine to uric acid.

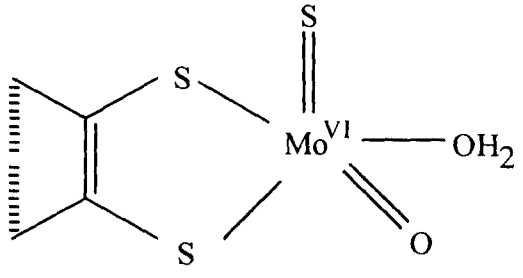
The term "oxotransferase" is not universally accepted and the nomenclature remains an active area of discussion [187]. Majority of these enzymes possess a Mo = O unit in their active sites ; however, some of them do not catalyze oxygen atom transfer (e.g., polysulphide reductase and possibly formate dehydrogenase) and others do not possess a Mo = O unit.

Hill [187] has classified molybdenum enzymes into three families based upon their protein sequences and the structures of their oxidized active sites ; each family is named as per its most prominent member, e.g., xanthine oxidase, sulphite oxidase and DMSO reductase families. Scheme (I – 2) shows outlines of their active sites in the oxidized (Mo^{VI}) and reduced (Mo^{IV}) sites. For the DMSO reductase family of enzymes, the Mo(IV) centre in the reduced form is devoid [189] of any terminal oxo (=O) group. In all

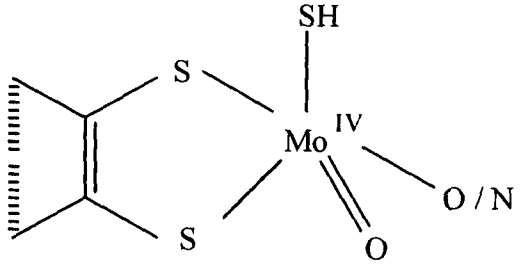
three families, additional ligands [2, 189] are present in the molybdenum coordination sphere which make the metal, minimally, five coordinate. In spite of the above differences with respect to their active sites, enzymes of this type are characterized by a pterin cofactor having a basic structure as per Scheme (I – 1).



Scheme (I – 1): Pyranopterin dithiolate – molybdenum coordination [189]



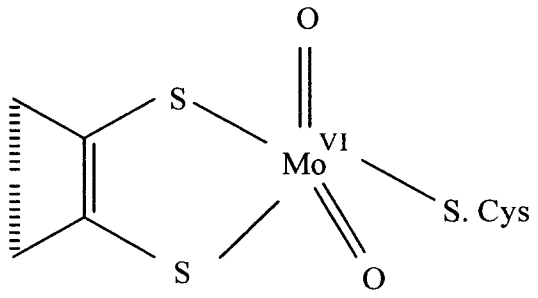
(oxidized form)



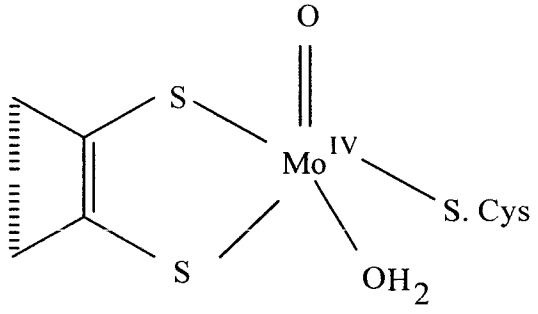
(reduced form)

The xanthine oxidase family (true hydroxylase)

Scheme (I – 2) ; continued below

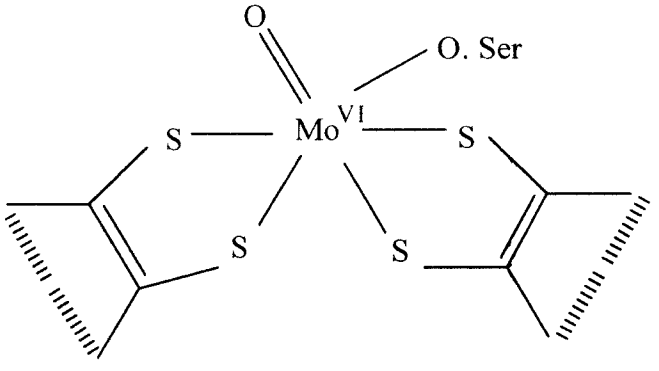


(oxidized form)



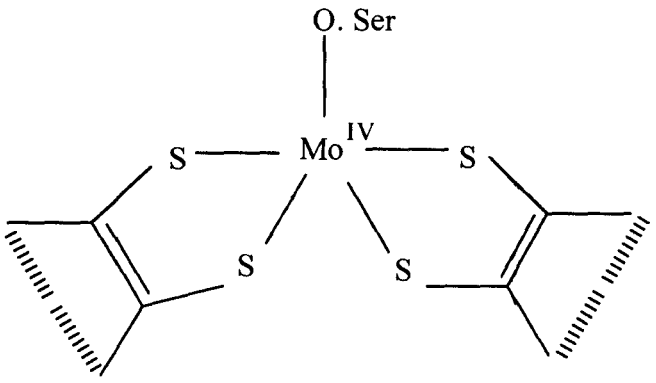
(reduced form)

The sulphite oxidase family



(oxidized form)

Scheme (I – 2) ; continued below



(reduced form)

The DMSO reductase family

Scheme (I – 2) [187, 189]

This pyranopterin structure has been established crystallographically in several cases [1, 2, 187 - 189]. The basic pterin ring structure and dithiolene side chain had been elucidated earlier by chemical analysis of the cofactor extracted from purified enzymes [187]. Presence of the pyran ring was established crystallographically [187 - 189]. According to a proposal put forward by Enemark and Garner [1(b)], scission / condensation of the pyran ring of pyranopterin is needed for a change in oxidation level of the pterin nucleus by two unit, which can be synchronized with the reaction scheme represented by equation (2).

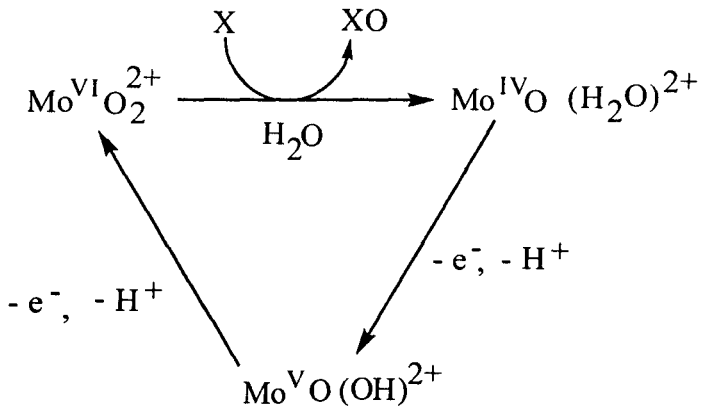
The choice of molybdenum by Nature for oxygen atom transfer activity of oxomolybdo-enzymes, is guided by several chemical reasons [19, 41, 52(b), 187, 189]. Molybdenum is widely available to biological systems due to the solubility of its high – valent oxides. Molybdenum is not as "oxophilic" as the early transition metals of groups IV and V. Its strong tendency to bind an oxo group is balanced by a capacity to lose a single oxygen atom easily. The redox potentials available to biological systems closely overlap with those of molybdenum that makes it the most preferred one among the group VI metals (Cr, Mo, W). Usually organisms find chromium too difficult to oxidize from the trivalent state and tungsten is not easily reduced from the hexavalent state. Perhaps it is one of the reasons that enzymes containing molybdenum at their active sites appear to be present in all forms of life, whereas well – characterized tungstoenzymes cover the

thermophilic bacteria and hyperthermophilic archaea [81]. Of course, the emergence of molybdenum and tungsten isoenzymes [189] adds a new dimension to this area of Chemistry / bioinorganic Chemistry. Available data shows that oxo transfer from substrate to metal ($M^{IV} \rightarrow MO^{VI}$) is faster with tungsten and that to substrate from metal ($MO^{VI} \rightarrow M^{IV}$) is faster with molybdenum. The results indicate a kinetic metal effect on direct oxo transfer for isoenzymes, provided the catalytic sites are isostructural.

The biochemical transformation involving the above enzymes are redox reactions and many involve at least formal oxygen atom transfer process. The one – and two – electron transfer capability associated with Mo / W (in the oxidation states VI, V, IV) and the ability to couple ion (H^+ or O^{2-}) transfer with electron transfer may be crucial to the chemical role played by these metals in enzymes.

Apart from the oxygen atom transfer formulation, the alternative mechanistic possibility involving electron / proton transfer process with a water molecule added or subtracted, depends on the possibility that incorporates the known effect of metal oxidation state on the pk_a of coordinated ligands [19, 41]. Oxidation of a metal ion makes it electron poor resulting in a pull of electron density from any coordinated heteroatom, A. If A is protonated, this flow of electron density increases the proton acidity of the AH group (i.e., lowers the pk_a). Conversely, reduction of the metal pushes electron density back onto A and increases its basicity (raises the pk_a). As the magnitude of this dependence may be as great as 8 pk_a units per unit oxidation state change, a Mo^{VI} / Mo^{IV} redox cycle could vary ligand acidity by 16 pk_a units or approximately the difference between a strong acid and water [41]. Thus the electron transfer at molybdenum cofactor may be intimately coupled to proton transfer in the same direction. A proposal for a coupled proton / electron transfer mechanism for the oxidation of xanthine by xanthine oxidase [with oxosulphido core at the metal centre, Scheme (I – 2)] involves two electron transfer to the metal (($Mo^{VI} \rightarrow Mo^{IV}$); the increase in pk_a at the sulphido ligands (= S) causing proton transfer to sulphur to be coupled to the electron transfer process.

Two unit change of oxidation state at the metal centre [in case of xanthine oxidase, the cis – dioxo core is replaced by a oxosulphido core] is associated with the gain or loss of an oxygen atom (or, oxo group, = O) as shown below [26].



Now the reactivity aspect of other metal – oxygen cores in Nature may be compared with that of molybdenum, e.g., oxygen evolution capability versus oxygen atom transfer activity respectively, in terms of their redox potential values.

The production of molecular oxygen in photosynthesis is assisted by a manganese enzyme, probably containing four atoms of manganese [193]. During the redox reactions the manganese centres shuttle between two oxidation states with each manganese atom increasing (and subsequently decreasing) its oxidation state by one unit, but it is not known with absolute certainty what these oxidation states are. In the reduced form the oxidation states may be as low as three Mn (II) and one Mn (III), but they are more likely to be three Mn (III) and one Mn (IV). In the lower oxidation states [e.g., Mn (II)], the affinity for oxygen is quite low.

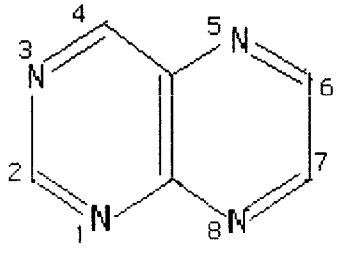
Oxygen evolution by catalase tekes place due to high potential of the [$Fe^{V}O$ + H_2O_2] system.

The biochemical significance of the above statements may be summarized as follows : the oxo groups of manganese and iron are strongly oxidizing and can take part in oxygen evolution ; the oxomolybdenum systems operate at low redox potential and cannot evolve oxygen, but can take part in oxo (= O) group transfer Chemistry [52 (b)]. Vanadium can hold one oxo – group in $(V^{IV}O)^{2+}$ at low potential, but it is then only a one – electron reactant and cannot carry out the molybdenum type reactions. The tungstoenzymes function at a lower potential range (under anaerobic conditions at ~ 100 °C) as compared to oxomolybdoenzymes operating in a wider potential range at lower

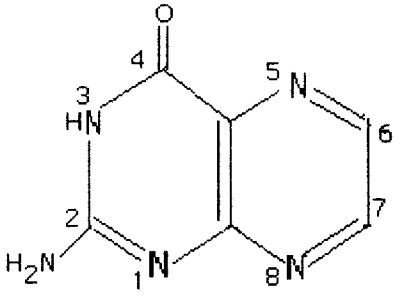
temperature. Most likely stronger π – interactions confer greater thermal stability on the tungsten centres in the corresponding class of enzymes ; besides this, greater stability of the higher oxidation states make the tungsten centre more air – sensitive and hence the need of anaerobic conditions for their operation.

Aims and objectives of the work :

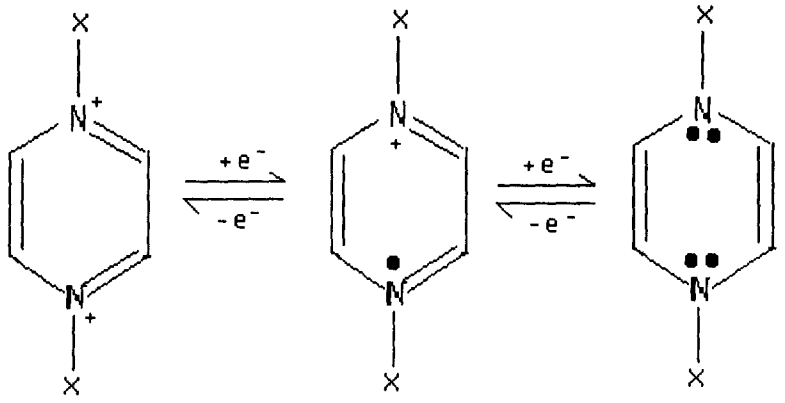
The term "pteridine" was introduced by Wieland for the fused ring system of pyrimidine and pyrazine rings and is related to the first isolation of such compounds from



natural sources like the pigments of butterfly wings [84] [(b)]. Pterins (2-amino-4-oxopteridines) represent a system of heterocycles with unique structure and Nature has



selected them (especially, the 6-substituted variety) for a wide range of biological functions including the essential components of a large number of metal (e.g., Fe, Mo, W) containing enzymes [26, 82, 187, 189, 194]. The well – known ability of pterins to act as redox partners in biological redox systems is intimately connected with the ability of the



pyrazine moiety (of the pterin ring) to exist in different oxidation states [4], thereby exhibiting multiple redox activity like the redox capabilities of the transition metal counterparts in the metalloenzymes stated above.

These facts have inspired symbiotic developments in the coordination Chemistry of pterin ligands and the assignment of oxidation states of both the metal and ligand centres in the new complexes along with their electronic structures is an involved task [3, 20, 119].

The above facts have motivated the present synthetic work on new coordination compounds of molybdenum with the pterin ligands stated in the preface. Out of them the 2-pivaloylamino derivative of 7-acetonyl-xanthopterin has been characterized using X-ray crystal structure determination. A new Schiff base ligand, [H_3(pte$_2$ – tsc)] has been synthesized by condensing 7-acetonyl-xanthopterin with thiosemicarbazide.

In many cases the complex formation process between the molybdenum starting material and the pterin ligand is accompanied by a redox reaction and due attention has been given in assigning the oxidation states of the metal centres in the resulting complexes. The results are expected to serve as bench mark data for understanding the roles of different components of pterin – containing biological systems and possible cooperativity between formally metal – based and pterin – based redox systems [119]. Furthermore, this effort will help to correlate the information obtained from chemical and electrochemical studies with the inferences derived from different spectroscopic methods [34, 110, 127, 179, 180]. It has been pointed out in the subsequent Chapters

that some of the new Mo(IV) – pterin complexes are devoid of terminal oxo (= O) group, just like the Mo(IV) centres of the DMSO reductase family in the reduced state [187, 189]. Some parallel examples exist with dithiolenes and a few NS ligands [19, 191]. The reason for this must lie in the ability of these ligands to act as strong σ – and π – donors while keeping sufficient π – acceptor quality to prevent complete charge transfer from ligand to metal. Some of the present physicochemical and spectroscopic data support this flexible redox property of the present ligands.

The new compounds have been characterized through physicochemical, spectroscopic data and their reactivities towards suitable substrates have been studied. Purity of the ligands and the new complex compounds reported here have been checked through TLC and their chemical compositions have been established through elemental analysis, mass spectral data (as well as the assignment of characteristic fragment through computer simulation) and different spectroscopic data. In several cases, the CHEM3D models have been obtained through molecular mechanics (MM2) calculations ; the optimized bond lengths (Å) and bond angles (deg) data so obtained, show good agreement with the literature X-ray structural data of related systems. The spectroscopic data are consistent with the CHEM3D models. Reactivity studies (both kinetic and stoichiometric aspects) of these compounds represent an important facet of this work.

Tables A & B below compare the bond angles and bond lengths data of [H_2(2-piv-pte$_2$)] derived from CHEM3D optimized computational model (MM2) and from single crystal X – ray diffraction method (shown in Chapter – III). The data derived from optimized computational model showing agreement with the X – ray structural data verifies the applicability of such an approach to molybdenum – pterin system or to the systems closely related to this, and provides with a suitable frame work for discussion on their spectroscopic, reactivity and other relevant aspects [85, 111]. This view is further substantiated by a comparative study of some vital optimized bond lengths (Å) of the CHEM3D model of some molybdenum – pterin complexes, showing good agreement with the corresponding X – ray structural data of several pterin compounds reported by different authors [88(a)].

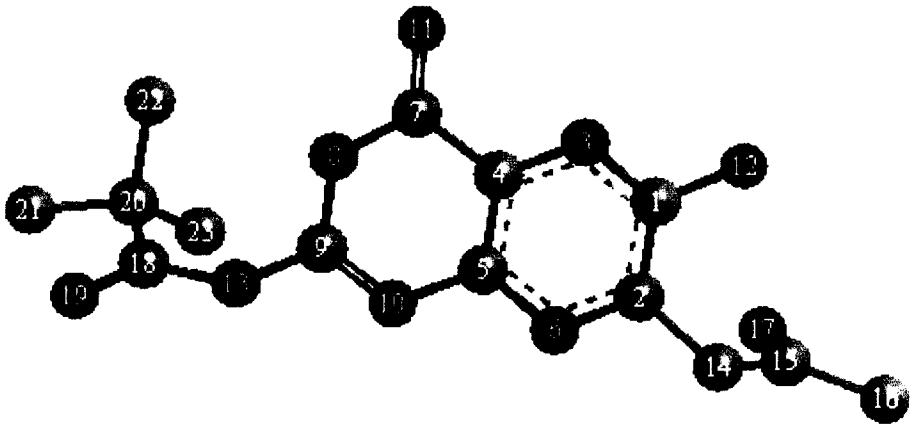


Fig.(I – 1): The optimized geometry (CHEM3D model obtained through MM2 calculations) of $[H_2(2\text{-piv-pte}_2)]$ with a steric energy of -2.35 Kcal mol^{-1}. Its numbering system is set by the software used [87] and is different from that in different Schemes.

Table A : Comparison of CHEM3D bond lengths & single crystal X – ray bond lengths of 2 – pivaloylamino – 7 – acetonylxanthopterin $[H_2(2\text{-piv-pte}_2)]$:

Atoms	CHEM3D Bond Distances(Å)	X – ray Bond Distances(Å)	Atoms	CHEM3D Bond Distances(Å)	X – ray Bond Distances(Å)
C(4)-N(3)	1.35	1.38	C(1)-O(12)	1.31	1.22
C(7)-O(11)	1.22	1.22	C(2)-C(14)	1.32	1.37
C(5)-N(10)	1.42	1.34	N(6)-C(2)	1.32	1.35
C(5)-N(6)	1.35	1.39	C(20)-C(22)	1.52	1. 48
C(1)-C(2)	1.42	1.48	C(20)-C(23)	1.52	1.51
C(4)-C(7)	1.48	1.44	C(20)-C(18)	1.52	1.48
C(4)-C(5)	1.40	1.37	N(13)-C(18)	1.37	1.40
C(7)-N(8)	1.37	1.39	C(15)-O(17)	1.21	1.23
C(9)-N(13)	1.35	1.36	C(15)-C(16)	1.51	1.53
C(9)-N(10)	1.28	1.33	C(14)-C(15)	1.51	1.42
N(8)-C(9)	1.45	1.36	C(20)-C(21)	1.53	1.50
N(3)-C(1)	1.44	1.36	C(18)-O(19)	1.21	1.21

Table B : Comparison of CHEM3D bond angles & single crystal X – ray bond angles of 2 – pivaloylamino – 7 – acetonylxanthopterin [H_2(2-piv-pte$_2$)] :

Angle Atoms	CHEM3D Bond Angles (degree)	X – ray Bond Angles (degree)
C(14)-C(2)-N(6)	120.3	123.5
N(6)-C(2)-C(1)	122.4	119.5
C(9)-N(8)-C(7)	126.6	123.4
N(13)-C(9)-N(10)	120.7	116.9
N(8)-C(9)-N(10)	119.3	123.2
C(5)-N(6)-C(2)	119.9	122.9
C(9)-N(10)-C(5)	118.1	115.2
C(1)-N(3)-C(4)	117.2	122.6
N(8)-C(7)-C(4)	114.4	113.5
N(6)-C(5)-C(4)	120.3	117.2
N(3)-C(4)-C(7)	121.7	119.6
N(3)-C(4)-C(5)	121.2	121.9
C(5)-C(4)-C(7)	119.1	118.5

Just as X – ray structural data of a compound correspond to its thermodynamically most stable form, the optimized geometries (obtained through MM2 calculations) of the present compounds correspond to their lowest steric energies. However, in solution intrinsic relative stability of different forms (e.g., tautomers, conformers, etc.,) of a compound are determined by different factors, e.g., hydrogen bonding and other intermolecular interactions, which can easily outweigh the small intrinsic energy barriers, leading to their labile equilibrium in solution [4, 117]. As far as the pterin compounds are concerned the roles of hydrogen bonding and tautomerism are well – documented [6(c), 20(a), 84, 118].

A perusal of the tables comparing optimized bond lengths and bond angles of the free ligands and that of the complexes derived from these (presented in the successive Chapters) reveals that the pterin ring is attached to the Mo atom through the O(4) and N(5) atoms [Scheme (II – 1) / Scheme (III – 1)] resulting from the anion formation involving the amide function in positions 3, 4 and the vinylogous amide in position 5 including the adjacent side – chain [i.e., the proton from C(1′) is located at N(5)] [89, 123]. The amide function in position 7, 8 is not involved in complex formation, as reflected by the bond length data (Å) of the ligands and complexes, for the C(6) – C(7) – N(8) region [3(b), 20(a)].

The overall bond lengths of the free ligand [Tables (II – 2), (II – 6), (III – 8) & (IV – 2) and Scheme (II -1) & (III – 1)] are in good agreement with the existing literature [88(a)]. The only exception to this reasonable agreement between the computed bond length data (Å) and the literature X – ray data, is the N(8) – C(7) distance ; this is due to the presence of vinylogous amide in position 5 including the adjacent side – chain [89, 121].

^{1}H NMR data (1D and 2D) of ribavirin in DMSO – d_6 show that restricted rotation around a C – N bond can make even the two primary amide NH protons non – equivalent on the NMR time – scale [14, 115, 116]. ^{1}H NMR data (both 1D and 2D) of the compounds, in DMSO – d_6 (δ in ppm versus TMS) reflect this aspect. ^{1}H NMR spectra of the OH(4), NH(5) and NH(8) protons [Scheme (II – 1) or Scheme (III – 1)] of the pterin ligand in DMSO – d_6 appeared in the range of δ, (10 – 13.5) as broad singlets but they disappear when the NMR spectrum is recorded afresh in CD_3OD indicating their exchangeable nature [16, 118].

Due to interplay of the foregoing factors determining intrinsic relative stabilities of the different forms in solution, of the pterin compounds also exhibits more than one type of NMR signal for most of its ligand protons.

Importance of the study on coordination Chemistry of the two oxocations [e.g., $(Mo^{V}_2O_3)^{4+}$ and $(U^{VI}O_2)^{2+}$] with aldimine ligands may be stated here briefly. While the importance of aldimine derivatives of α – amino acids as ligands, has been stated at the outset, details regarding them (i.e., their schematic structures, methods of preparation, etc.) have been given in appropriate chapters.

There are different possibilities of Mo = O_t distortional isomers of the $(Mo^V_2O_3)^{4+}$ core by rotations around the linear Mo – O_b – Mo bridge [19, 165]; structurally characterized species of this type usually possess cis – or trans – terminal oxygens and are diamagnetic due to coupling of the Mo^V, d^1 – electrons through the three centre bond. For a skew arrangement of the two Mo = O bonds these two d – electrons are unlikely to overlap significantly, leading to a triplet (S = 1) ground state [19, 164]. It will be worthwhile to study the physicochemical property and reactivity aspects of $(Mo^V_2O_3)^{4+}$ - complexes with aldimine ligands with possibilities of distortional isomers / rotamers involving different arrangements of Mo = O_t bonds with respect to the Mo – O_b – Mo bridge.

The UO_2^{2+} ion is one of the most stable dioxo cations known, being able to maintain its identity over a wide range of chemical situations. The metal centre of this linear entity, can accomodate 4 to 6 ligand donor atoms in its equatorial plane [165]. Its versatile complex forming ability is reflected in its rich coordination Chemistry with a wide variety of ligands as well as rapid growth of literature on different facets of its Chemistry / coordination Chemistry till date with a promise for interesting future developments [105, 166 – 174, 177– 179, 182 – 187].

They cover wide areas ranging from synthesis of novel coordination compounds to the interesting reactivity aspects as well as studies on different physicochemical, spectroscopic properties and electronic structure.

Here the attention is focused on the redox activity of several uranyl complexes towards Na_2SO_3. The chiral aldimine ligands help to follow the effect of stereochemical factors on the electron transfer process. One of the pertinent uranyl complexes has been characterized through X-ray crystallography.
