PART B

LANTHANIDE(III) OXO PYRIDINIUM, DIPICOLINATE
COMPLEXES- STUDIES ON ANTICANCER ACTIVITY OF
GADOLINIUM DIPICOLINATE
4.1 Lanthanide Oxo-pyridinium or Hydroxy-pyridine Complexes

Lanthanide metal ions are hard acids and are known to form complexes with numerous ligands, mostly with hard donor centres like oxygen or nitrogen. The normal oxidation state of lanthanides is $+3$ [Note: Bismuth also has a stable $+3$ oxidation state, see Chapter 1]. The coordination number in most cases is more than six and the geometry around the metal centre is difficult to predict a priori. Lanthanide complexes with $O$-donor ligands are more numerous than those with other donor atoms and hence lanthanides are called ‘oxophilic’. The compounds 2-hydroxy pyridine (2-HOPy) (4.1) and 4-hydroxy pyridine (4-HOPy) (4.2) constitute an interesting set of ligands because the coordination can occur via the nitrogen or oxygen subsequent to the proton shift to nitrogen or by complete deprotonation in the presence of a base (Scheme 4.1). 4-Hydroxypyridine is also bioactive and is known to inhibit photosystem II in plants; some of its derivatives act as vasodilators. In the case of deprotonated 2-hydroxypyridine, both chelation and bridging are possible while for deprotonated 4-hydroxypyridine, only bridging mode is possible. Several of these have been realized synthetically but interestingly it is also possible to have $O$-coordination or covalent bond formation via forms 4.1’ or 4.2’. The different structural types are exemplified by compounds 4.3-4.7 [Fig. 4.1]\(^3\) and also in the trinuclear clusters $[\text{Fe}_3(\mu_3-\text{O})(\mu_2-\text{CH}_3\text{COO})_6(\text{C}_9\text{H}_8\text{NO})_2(\text{H}_2\text{O})]\text{ClO}_4\cdot n\text{H}_2\text{O}$ (n = 3, 4; $C_9H_8NO = 2$-pyridone). Compound 4.4 represents $O$-coordination after proton shift. The palladium and platinum complexes 4.4a-b as well as the iron complex 4.6 of 4-hydroxypyridine are assigned $N$-coordination while the X-ray structure of compound 4.7 shows $O$-coordination; the deprotonated ligand shows both $N$- and $O$-coordination in the tin complex 4.5. Some complexes of lanthanides including those of dysprosium and gadolinium with $O$-coordination are also known.\(^1\)
Das and coworkers have made an interesting observation on water clusters that involves the loss/gain (from atmospheric water vapour) of water molecules in several transition metal complexes of 2-hydroxy pyridine. Among them, the Fe₃ cluster-containing compound [Fe₃(μ₃-O)(μ₂-CH₃COO)_6(C₆H₆NO)₂(H₂O)]ClO₄·4H₂O is having 2-pyridone ligands coordinating through neutral oxo donor atoms to two Fe(III) centres.
4.1.1 4-Hydroxy pyridine or 4-pyridone-heterometallic complexes

Reaction of Cu(OAc)$_2$, 4-(1H)-pyridone and Dy(III) or Gd(III) nitrate in MeOH results in the formation of the heterometallic complexes [Cu$_2$LnL$_2$(OH)$_4$(NO$_3$)$_4$ xH$_2$O], [Ln = Dy (4.8) or Gd (4.9), L = 4-(1H)-pyridone].$^{14}$ Reaction of Cu(OH)$_2$ with 4-(1H)-pyridone and Dy(NO$_3$)$_3$ in DMF results in the formation of the heterometallic compound [Cu$_2$DyL$_2$(OH)$_4$(NO$_3$)$_2$(DMF)] (4.10). Due to the poor solubility in organic solvents, single crystals were not obtained. On the basis of the physico-chemical studies, different structures are tentatively proposed. It seems that lanthanide ions are coordinated to eight oxygen atoms, two from deprotonated 4-pyridone units, two from neutral pyridone ligands, two from a bidentate nitrate anion and two from hydroxyl anions. However, no conclusion could be made as to which structure is correct, since molar conductivity measurements are unattainable due to the insolubility of these complexes.

4.1.2 4-Pyridone- complexes with Gadolinium and Dysprosium

Goodgame et al reported the synthesis and crystal structures of [DyL$_4$(NO$_3$)$_2$](NO$_3$) (4.11) and [GdL(NO$_3$)$_3$(H$_2$O)].CH$_3$OH (4.12) [L = 4-(1H)-pyridone].$^{12}$ In compound 4.11, the dysprosium ion is eight-coordinate with a distorted dodecahedral coordination geometry. All four pyridone nitrogen atoms are involved in intermolecular hydrogen-bonding. The X-ray structural analysis of gadolinium complex (4.12) shows that this compound has a structure quite different from that of the dysprosium complex 4.11. In 4.12, dimers are formed in which pairs of Gd(III) ions are linked by two nitrate bridges. Each bridging nitrate binds in bidentate fashion to one Gd(III), but one of the coordinated nitrate oxygen atoms additionally adopts a binucleating role and bonds to the second Gd(III) ion, thus producing a Gd$_2$O$_2$ ring. Each gadolinium ion is further bonded to two pairs of oxygen atoms from bidentate but nonbridging nitrate groups, one pyridone oxygen atom and a water molecule. Each Gd(III) is thus nine-coordinate. All the available hydrogen bonding donors are involved in intermolecular bonding interactions.
4.2 Lanthanide Pyridine-2,6-dicarboxylic Acid Complexes

Among the O,N-ligands, pyridine carboxylic acids are very well known to coordinate to metals in a chelate fashion to form stable complexes. These carboxylic acids are biocompatible, soluble in water (most of them) and not so expensive. Pyridine-2,6-dicarboxylic acid (4.13) is a ligand with 5-coordinating centres. Various coordination modes of this ligand are shown in Figure 4.2.

![Figure 4.2. Various coordination modes observed in metal complexes of pyridine-2,6-dicarboxylic acid.](image)

Bharadwaj and coworkers reported the synthesis of linear coordination polymers with lanthanides and pyridine-2,6-dicarboxylic acid under hydrothermal conditions. [Pr(pdc)(pdcH2H2O)0.4H2O (4.14) [Ce(pdc)(pdcH2H2O)0.4H2O (4.15) are the two structures in which hexameric water clusters join these linear chains through bonding to the metal ions (Fig. 4.3). Other coordinated water and the carboxylate oxygen form an intricate array of hydrogen bonding resulting in a 3D network where each metal ion shows 9-coordination with an approximate $D_3$ symmetry. The structure of each metal organic framework (MOF) consists of linear chains of M(III) ions where each metal ion shows 9-coordination binding two pdc$^{2-}$ ligands, one bridging carboxylate O atom from a neighbour and two water molecules.
Brouca-Cabarrecq and coworkers reported the synthesis of three lanthanide dipicolinates of the formula \((\text{CN}_3\text{H}_6)_3[\text{La(C}_7\text{H}_3\text{NO}_4)_3] \cdot 3\text{H}_2\text{O}\) (4.16) \((\text{C}_4\text{N}_2\text{H}_12)_1.5[\text{Ce(C}_7\text{H}_3\text{NO}_4)_3] \cdot 7\text{H}_2\text{O}\) (4.17) and \([\text{Eu(C}_7\text{H}_4\text{NO}_4)_3]_2 \cdot 2.5\text{H}_2\text{O}\) (4.18).  

Three complexes are zero dimensional structures with lanthanides being linked through dipicolinate groups. Each lanthanide is surrounded by three dipicolinic groups in the usual tridentate mode: two oxygen atoms pertaining to the two carboxylate functions and one nitrogen atom chelate the central Ln(III) (Fig. 4.4). In compounds 4.16 and 4.17, each dipicolinate is nonprotonated and charge balance is maintained by the presence of guanidinium and piperazinium cations. In the structure of 4.18, the three-dipicolinic groups surrounding each Eu(III) are either unprotonated or one- and two-times protonated and so the entity is neutral.
Guerriero et al reported the synthesis of lanthanide dipicolinates of the formula Na$_3$[Ln (pdc)$_3$] $n$H$_2$O and [Ln(pdc)(Hpdc)] $m$H$_2$O ($n = 5-10$; $m = 5-8$) by the reaction of Ln(NO$_3$)$_3$ $n$H$_2$O [Ln = La, Gd, Dy] and pyridine-2,6-dicarboxylic acid [H$_2$pdc] in the presence of sodium hydroxide.\textsuperscript{18} In each asymmetric unit, two dipicolinate ions are chelated to the metal ion through the nitrogen and two carboxylate oxygens and one of them links a further Ln(III) ion by a multidentate bridging bond with one remaining carboxylate oxygen. Sobolev and coworkers reported europium dipicolinate compound of the formula (C$_8$H$_{20}$N)$_3$[Eu-(C$_7$H$_3$NO$_4$)$_3$].4H$_2$O (4.19) as a tetraethylammonium salt. Eu(III) is bound with nine-coordination to six O- and three N-donor atoms of the ligands. Water molecules within the lattice are found sufficiently close to the uncoordinated dipicolinate O atoms to justify the postulation of hydrogen-bonding interactions.\textsuperscript{19a} Extensive hydrogen-bonding interactions between the NH groups of the cations and the carboxylate O atoms of the anions in these salts may explain both the high lattice energy, which is reflected in low solubility, and the luminescence quenching.\textsuperscript{19b}

Liu et al reported the structural details of samarium dipicolinate compound of the formula [Sm(C$_7$H$_3$O$_4$)(C$_7$H$_4$O$_4$)(H$_2$O)$_2$] 4H$_2$O (4.20) in which pyridine-2,6-dicarboxylate ligand chelates to the Sm(III) and also bridges to the neighbouring Sm ions to form infinite chains along the c axis.\textsuperscript{20} The asymmetric unit of (4.20) is composed of one Sm(III) ion, one Pydc$^-$, one Pydc$^{2-}$ ligand, two coordinated water molecules and four water molecules of crystallization. Atom Sm1 is coordinated by pydc$^-$ (atoms O1, N1 and O3), pydc$^{2-}$ (O6, N2 and O7), and two aqua ligands (O9 and O10); the Sm atom is also bonded to one bridging O5 atom from a neighbouring pydc$^{2-}$ ligand, giving an overall nine-coordination [Fig. 4.5 (Top)]. The pydc$^{2-}$ group chelates to the Sm(III) ion and bridges to the neighbouring Sm(III)' ion, forming an infinite chain along the c axis [Fig. 4.5 (Bottom)]. Two neighbouring chains are linked to form a ladder-like band through O—H…O hydrogen bonds. The ladder-like bands form a layer structure parallel to (100) plane by hydrogen bonds with the uncoordinated water molecules, and adjacent layers are linked together through hydrogen bonds, resulting in a three-dimensional framework.
4.3 Lanthanide-Transition Metal Heterometallic Pyridine-2,6-dicarboxylic acid Complexes

A significant number of three-dimensional (3D) coordination polymers with well-defined pores find applications in catalysis, gas storage, chemical separation, and ion exchange.21-24 Zhao et al. reported coordination polymers \{[Ln(dipic)\textsubscript{3}Mn\textsubscript{1.5}(H\textsubscript{2}O)\textsubscript{3}]\cdot nH\textsubscript{2}O\}\textsubscript{∞} \ [Ln = Pr, n = 2 (4.21); Ln = Gd, n = 3.5 (4.22); Ln = Er, n = 3 (4.23) through hydrothermal synthesis.25 All these polymers crystallized in the hexagonal crystal system and the crystal structure is built up of two distinct types of building blocks, Ln(dipic)\textsubscript{3} and MnO\textsubscript{4}(H\textsubscript{2}O)\textsubscript{2} (Fig. 4.6). The Ln(III) ion is coordinated by three tridentate (ONO) dipic anions, for which each carboxy group coordinates through one oxygen atom. Three N atoms and six O atoms complete the coordination sphere of the Ln(III) centre, which conforms most closely to a tricapped trigonal prism. The coordination geometry around Mn(II) centre is a slightly distorted octahedron, the equatorial plane of which comprises
four O atoms from the carboxy groups of the 2,6-dipicolinate molecules that are chelated to four neighboring Ln(III) centres; two water molecules occupy the remaining apical coordinate sites. There are three crystallographically independent 2,6-dipicolinate moieties in the structure, each with the same coordination mode, i.e. chelation to one Ln(III) ion and linkage to two Mn(II) ions. One oxygen atom from a carboxyl group bonds to a Ln(III) centre and the other oxygen atom bonds to a Mn(II) centre; thus each Ln(III) centre has six Mn(II) ions as the nearest metal centres, while the Mn(II) centre has four Ln(III) ions in its vicinity (Fig. 4.6), as is consistent with the Mn:Ln molar ratio.

Prasad and Rajasekharan reported the heterometallic coordination polymers of dipicolinic acid (dipicH₂) containing Ce(IV) and Zn/Cd cations namely [Zn(H₂O)₄Ce(dipic)₃] 8H₂O (4.24), [Zn-(CH₃OH)₂(H₂O)₂Ce(dipic)₃]·3H₂O (4.25), [Zn(CH₃CH₂OH)(H₂O)₃Ce(dipic)₃] 2CH₃CH₂OH·2H₂O (4.26), [Cd(H₂O)₄Ce(dipic)₃]·[Ce-(dipic)(dipicH)₂]·24H₂O (4.27), [Cd(CH₃OH)₂(H₂O)₂Ce(dipic)₃] 3H₂O (4.28), and [Cd(H₂O)₄Ce(dipic)₃] 3H₂O (4.29). In compound 4.24, Ce(IV) is nine coordinate with a distorted tricapped trigonal prismatic geometry and Zn(II) has a distorted octahedral geometry. The polymeric chain is made up of alternating units of [Ce(dipic)₃]²⁻ and two crystallographically unique [Zn(H₂O)₄]²⁺ groups, situated on inversion centres and linked on either side by coordination through carbonyl oxygen atoms of two different dipicolinate ligands. Structure of [Zn-(CH₃OH)₂(H₂O)₂Ce(dipic)₃]·3H₂O (4.25) is similar to 4.24 except that only one unique Zn(II) ion situated on an

![Figure 4.6. Diagram showing the two building units with atom labels of the Mn–Ln series [cf. ref. 25].](image-url)
inversion centre with two of the four coordinated water molecules replaced by methanol molecules. Compound $[\text{Zn(CH}_3\text{CH}_2\text{OH})(\text{H}_2\text{O})_3\text{Ce(dipic)}_3]$ CH$_3$CH$_2$OH·2H$_2$O (4.26) differs from 4.24 and 4.25 in having two different zinc coordination polyhedra, one having four water molecules as terminal ligands and the other with two water molecules and two ethanol molecules. The polymeric part in $[\text{Cd(H}_2\text{O})_4\text{Ce-(dipic)}_3]$ (4.27) is exactly similar to the chain in compound (4.24) except that Cd replaces Zn. The main difference is the presence of a free $[\text{Ce(dipic)}_2(\text{dipicH}_2)]$ molecule and 24 lattice–water molecules. The structure of $[\text{Cd(CH}_3\text{OH})_2(\text{H}_2\text{O})_2\text{Ce(dipic)}_3]$ 3H$_2$O (4.28) is very similar to that of 4.25 with Zn replaced by Cd. The coordination environment in compound $[\text{Cd(H}_2\text{O})_4\text{Ce(dipic)}_3]$ 3H$_2$O (4.29) is similar to that of 4.25 and 4.27. The difference is only in the number of lattice–water molecules.26

4.4 Medicinal Importance of Lanthanide Compounds

Biomedical inorganic chemistry is an important area of chemistry. It offers the potential for the design of novel therapeutic and diagnostic agents and hence for the treatment and understanding of diseases which are currently intractable.27-30 Many biological properties of the lanthanides are a function of their similarity to calcium.31,32 One of the major physiological effects of the Ln(III) is to block both voltage operated and receptor operated calcium channels.33 The Ln(III) can block the Na$^+$/Ca$^{2+}$ synaptic plasma membrane exchange and inhibit skeletal, smooth and cardiac muscle contraction by blocking the Ca$^{2+}$-ATPase in the sarcoplasmic reticulum of muscle. The Ln(III) ions themselves are unable to cross cell membranes but act by blocking the exterior face of the calcium channel. Despite this difficulty, the Ln(III) have been used as biochemical probes to study calcium transport in mitochondria and other organelles. They can substitute for calcium in proteins,32 though it should be noted that the Ln(III) can also substitute for other metal ions such as Mg(II), Fe(III) and Mn(II). Calcium dependent enzymes can either be inhibited by lanthanides or in some cases be activated to a similar or greater extent than by calcium. Generally the lanthanides are non-toxic, primarily because they cannot cross cell membranes and are therefore not absorbed if ingested orally. However, they are toxic if administered by the intravenous route where upon they can gain access to cells expressing calcium channels. Chelate such as Gd(DTPA), which is used as an NMR contrast imaging agent, is 50 times less toxic than GdCl$_3$
on a molar basis. It is rapidly cleared with a plasma half-life of 20 minutes and within 3 hours over 80% is excreted in the urine. This is in contrast to GdCl$_3$ where only 2% is excreted after 7 days. This emphasizes two important points when considering metal toxicity and pharmacology. The first is that the biochemical and physiological effects are dependent upon the chemical form and speciation of the metal, e.g. oxidation state, salt or complex. The second, more general, point is that toxicity is dependent upon the route of exposure.$^{34}$

Magnetic resonance imaging (MRI) has become an important technique in modern diagnostic medicine, providing high-quality three-dimensional images of soft tissue without the need for harmful ionizing radiation.$^{35}$ Gadolinium (III), with its high magnetic moment and long electron spin relaxation time, is an ideal candidate for such a proton relaxation agent and is the most widely used metal centre for such purposes.$^{36,37}$ Free Gd(III) is toxic (LD$_{50}$=0.2 mmolkg$^{-1}$ in mice)$^{38}$ and must therefore be administered in the form of stable chelate complexes that will prevent the release of the metal ion in vivo. For these reasons, the development of ligands that are suitable for production of high-relaxivity agents with favorable properties for imaging applications remains an important goal. Lanthanide complexes have found a role in cancer treatment as contrast imaging agents such as Gd(III)-DTPA which is commonly used for MRI imaging of tumors.$^{36,39-40}$ One group of lanthanide complexes that has progressed into clinical trials is the texaphyrins.$^{41}$ Recently a redox active gadolinium texaphyrin complex has entered phase III clinical trials for the treatment of brain metastases of lung cancer. The Gd-texaphyrin complex, motexafin gadolinium (MGd, Xcytrin; Fig. 4.7) has been investigated and exploited as a radio- and chemo-sensitizer for cancer treatment based on its unique redox properties. Using pulse radiolysis it was shown that MGd can accept electrons from radicals including O$_2$ and also aquated electrons in the medium, resulting in reduction of the MGd complex.$^{41}$
MGd contains the paramagnetic Gd ion in its central cavity and is detectable by magnetic resonance imaging (MRI). Pre-clinical studies have shown that MGd localizes to tumor cells and enhances the efficacy of radiation and chemotherapy in tissue culture and in animal tumor models. Lanthanides are able to inhibit calcium fluxes, required for cell cycle regulation, but they cannot substitute for calcium or other metal ions such as Mg(II), Fe(III) and Mn(II) in proteins, leading to the inhibition of their functions. The tumor-inhibiting activity of lanthanum is considerably enhanced by complexation with various ligands such as phenanthroline. The lanthanide complex tris(1,10-phenanthroline)tris(thiocyanato)lanthanum(III) (KP772; Figure 4.8) exerts potent activity against a wide range of tumor cell lines in vitro and a colon carcinoma xenograft model in vivo with properties comparable to cis-platin and methotrexate.

Figure 4.7. The structure of motexafin gadolinium (MGd, Xcytrin)

Figure 4.8. Structure of tris(1,10-phenanthroline)tris(thiocyanato-)lanthanum(III) (KP772).
4.5 Mixed Metal Pyrophosphates involving Lanthanides

Phosphate matrix is a good host for lasing ions both in crystalline and glassy states due to excellent transparency and good mechanical and thermal stabilities. They find applications in ultrafast switches and laser induced gratings. The luminescence properties of doped ions (M) depend on the ionic nature of M-O bond in the parent lattice. This is achieved in phosphates in which the strong covalency of P-O bond induces an ionic M-O bond. Such a covalent P-O network is present in layer like structures of pyrophosphates. Some pyrophosphates and their solid solutions are known to exhibit isotropic negative thermal expansion behaviour in the appropriate temperature intervals. There are only limited reports on mixed lanthanide-(other) metal pyrophosphates that may possess useful optical properties. In the present work, attempts to investigate this aspect are made.

OBJECTIVES OF THE PRESENT WORK - PART B

The main objective of this part of the present work is to develop lanthanide oxopyridinim and lanthanide dipicolinate chemistry. In addition, it was planned to explore mixed metal pyrophosphates. Specifically, it was intended to investigate the following:

(i) Synthesis and structural characterization of new crystalline lanthanide oxopyridinium complexes using lanthanide nitrates and 4-hydroxypyridine,

(ii) Synthesis and anticancer activity of new lanthanide dipicolinate complexes through a simple route (non- hydrothermal), and

(iii) Methods for the synthesis of lanthanide(III)-zinc(II) pyrophosphates Ln\(_{2/3}\)ZnP\(_2\)O\(_7\).