3. Characterisation studies of gel grown folic acid crystals.

Prasanna S., Bijini B.R., Deepa M., Rajendra Babu K. and C.M.K. Nair


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1. Thermal and dielectric studies of Pyridine-3-carboxylic acid single crystal grown in gel.

Prasanna S., Bijini B.R., Deepa M., Rajendra Babu K. and C.M.K. Nair

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2. Crystal structure and characterisation of single crystals of sodium salicylate complex of the antimalarial drug quinine.

Prasanna S., Deepa M., Rajendra Babu K. and C.M.K. Nair

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CHAPTER 1

Introduction

1.1 Crystals

1.2 Organometallic compounds in drug research

1.3 Metal-organic frameworks as potential drug carriers

1.4 Polymorphism

1.4.1 Polymorphism and lattice energy compensation

1.4.2 Polymorphism in drugs

1.5 Pharmaceutical co-crystals

1.6 Vitamins

1.6.1 Vitamin B complex

1.6.1.1 Thiamine (vitamin B$_1$, anti beriberi substance)

1.6.1.2 Thiamine and its complexes - an overview

1.6.1.3 Nicotinic acid (niacin)

1.6.1.4 Nicotinic acid and its complexes - A brief literature survey

1.6.1.5 Folic acid (vitamin B$_9$)

1.6.1.6 Folic acid and its complexes - A general survey of recent studies

1.7 Alkaloids

1.7.1 Quinine (C$_{20}$H$_{24}$N$_2$O$_2$)

1.7.2 Quinine and its complexes - A review of recent literature

1.8 Motivation for the present work
CHAPTER 1

Introduction

1.1 Crystals

Crystals are the backbone of modern technologies. The involvement of crystals extends to fields such as nonlinear optical activity, electrical conductivity, ferromagnetism, and pharmaceutical technology. The molecular ordering in crystals determines the macroscopic properties of a given solid. Hence the determination of crystal structure and packing of molecules in crystal lattices are important in revealing the physical properties of materials in solid state.

Crystals are really "windows on the world of atoms" (Raymo 1991). Crystal structure analysis is the method of choice for structure determination across the complete chemical spectrum, from inorganics through organics and metal organics to proteins and viruses. The result provides precise experimental data on molecular geometry, conformation and higher order features in macromolecules. Moreover, since crystal structures comprise of infinite symmetric molecular arrays, they are unique in providing direct experimental observations of intermolecular interactions, yielding the geometries and motifs formed by hydrogen bonds and other nonbonded interactions, which are fundamental to our understanding of both protein - ligand interactions and properties of pharmaceutical materials in solid form (Groom and Allen 2010). Precise information about molecular structure and intermolecular interactions is essential in the development of new active pharmaceutical ingredients (API). Knowledge of solid-state properties like polymorphism, size and morphology, amorphous structure, salt/polymorph selection, solvates and co-crystals etc are essential for the design and production of pharmaceutical materials (Khankari and Grant 1995, Hancock et al. 1997, Brittain 1999, Yu 2001, Vippagunta et al. 2001, Crowder et al. 2002, 2003, Singhal and Curatolo 2004, Hilden 2004, Kaushal et al. 2004, Hilfiker 2005). Development of an undesirable crystal form may result in production failures and product performance problems (Stahl and Wermuth 2002). Moreover, changes in crystal structure can change the way in which the drug is
absorbed and accessed by the body (Peterson et al. 2006). The chemical and molecular structure of a drug profoundly affects the stability, ease of manufacture and its biopharmaceutical performance. Generally drug molecules have complex chemical structures with multifunctional groups and conformations (Morissette et al. 2003).

1.2 Organometallic compounds in drug research

Organometallic compounds were used in medicine for centuries without much knowledge about their design or molecular basis of their mechanism of action. Metals easily lose electrons from their elemental or metallic state to form positively charged ions which tend to be soluble in biological fluids. Though metal ions are electron deficient, most of the biological molecules like proteins and DNA are electron rich. The attraction of these positive charges leads the metal ions to bond and react with the biological molecules. The same principle is applicable for the affinity of metal ions to small molecules such as oxygen, which are crucial to life. For example hemoglobin, an iron containing protein transport oxygen to body tissues by binding it with the iron atom. Thus a multitude of chemical reactions necessary for life can be facilitated through the incorporation of metals such as copper, zinc, iron, manganese etc to metalloenzymes. Metal coordination to biologically important molecules can be used to enhance their activity and overcome resistance (Tandon 2010).

Carbon is the most important element in the drug design. It can generate inert covalent bonds with connectivities two to four and coordination geometry, linear to trigonal and planar to tetrahedral. Even though based on carbon atoms, an incredible number of different molecules can be prepared, the binding geometry obtainable are limited. On the other hand metal ions can form either labile or inert bonds with coordination number ranging from one to twelve with a fairly large number of coordination spheres. Thus metal ions can be used as new scaffolds to construct therapeutic molecules better than carbon based compounds (Tandon 2010).

1.3 Metal-organic frameworks as potential drug carriers

Metal-organic frameworks (MOFs) can be considered as relatively new nanoporous crystalline material family, synthesized through coordination assisted self-assemblies of metal connecting points and organic bridging ligands (Fig.1.1). They are
also known as coordination polymers or coordination networks. Because of their large porosity with tunable pore sizes, shapes and functionalities, they have wide applications in the field like nonlinear optics, gas storage, catalysis and chemical sensing. Recent reports suggest that the use of MOFs as potential drug carriers in drug delivery systems can effect a controlled localized delivery of drugs which improve the efficiency of the treatment and reduce side effects (Huxford et al. 2010).

Fig. 1.1 Formation of MOFs by coordination-directed self-assembly processes and the loading of drugs into MOFs via physical encapsulation. (Courtesy : Current Opinion in Chemical Biology, 2010, 14:262-268)

MOF materials can be prepared in nano size to form nanoscale metal-organic frameworks (NMOFs) and are potential nanocarriers for delivering therapeutic agents to targeted areas of the body. They can control drug release with their large surface areas, high porosity, and presence of functional groups to interact with loaded drug moieties.

1.4 Polymorphism

The existence of a chemical compound in more than one unique crystalline form is termed as polymorphism and it leads to different physicochemical properties. Polymorphism implies that free energy differences between various forms are small (0.5-4 kcal mol⁻¹) and the kinetic factors are important during crystal nucleation and growth (Yu et al. 2000, Nangia 2007). Polymorphs are ideal systems to study the energy relationship between crystal and molecular structure with a minimum number of variables because the differences arise only due to molecular conformation, hydrogen
bonding and crystal packing effects and not due to different chemical species (Blagden and Davey 2003).

Polymorphs are classified into two (a) concomitant polymorphs (b) conformational polymorphs. The concomitant polymorphs crystallize simultaneously from the same solvent and crystallization flask under identical crystal growth conditions. They can be considered as supramolecular isomers in a chemical reaction. Conformational polymorphism occurs for those molecules which can adopt more than one conformation under the given crystallization condition.

1.4.1 Polymorphism and lattice energy compensation

A molecule is defined by the parameters such as bond distances, bond angles and torsion angles. Because of high bond energies (80 to 200 kcal mol\(^{-1}\)) of covalent bonds, structural changes do not occur due to its stretching or compression. A change in bond length by 0.03Å to 0.05Å causes energy compensation of the order of 0.3 kcal mol\(^{-1}\) for a single bond while the values for double and triple bonds are of the order of 0.6 to 1.0 kcal mol\(^{-1}\). Distortion of bond angle by 6 to 10° has also the same energy penalty as for the change in bond distances of the above order. Single bond torsions have energy requirements of 0.5 to 3.0 kcal mol\(^{-1}\), which can be as high as 8 to 10 kcal mol\(^{-1}\) due to steric factors and hindered rotations (Buttar et al. 1998).

The energy scale of hydrogen bonds are found to be of the order of 4.0 to 10.0 kcal mol\(^{-1}\) for O-H--O and N-H--O bonds, 1.0 to 4.0 kcal mol\(^{-1}\) for C-H--O interactions and 0.5 to 1.0 kcal mol\(^{-1}\) for van der Waals interactions at ambient temperature (Desiraju and Steiner 1999). Thus the bond torsion changes that determine molecular shape are of comparable energy to intermolecular interactions that direct crystal packing. Hence it is possible that stronger interactions and better crystal packing stabilize a metastable molecular conformation whereas a stable molecular conformation may be involved in weaker hydrogen bonds and/ or inefficient packing (Nangia 2007).

1.4.2 Polymorphism in drugs

Investigation of polymorphic forms of API is important in many aspects. The pharmaceutical companies are forced to take patents of all possible polymorphic forms of the API that they invent, before somebody else finds a non-infringing polymorph or
hydrate showing bio-equivalence with the parent drug form. It was observed that the accidental crystallization to the polymorphic forms of some drugs in use have caused toxic effects, eg. the Norvir accident of HIV-1 protease inhibitor occurred at Abbott laboratories in 1998, and it necessitated the knowledge of the complete physical landscape of the drug before clinical trials (Bauer et al. 2001). Also prolonged storage of the drug can result in phase transition followed by polymorphic changes. (Bastin et al. 2000, Rodriguez-Spong et al. 2004).

1.5. Pharmaceutical co-crystals

Co-crystals are crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions. In such crystals the constituent molecules are bound together mainly by hydrogen bonds (Jones et al. 2006, Vishweshwar et al. 2006). Co-crystals are now widely used in pharmaceutical industry to enhance and optimize drug properties by changing the molecular interactions and composition of pharmaceutical materials (Mirza et al. 2008). Co-crystals can also be used to determine absolute stereochemistry of oils and viscous liquids (Eccles et al. 2011).

1.6. Vitamins

Vitamins are naturally occurring organic compounds found in natural foods or synthesized in body, essential for the normal growth, reproduction and maintenance of the body. Although they themselves supply very little energy, they play an important role in several energy transformation reactions in the body (Satoskar et al. 2005).

In 1912 Funk (Piro et al. 2010) found that there are some compounds in the food which prevent beriberi, scurvy, pellagra, rickets etc. All these compounds contain nitrogen. Because of their vital function and basic nature, he called them as ‘vitamine’. But later, as it was found that all such other compounds do not contain nitrogen and therefore the term ‘vitamine’ was modified as ‘vitamin’. Vitamins are classified as fat soluble (A,D,E and K) and water soluble ( C and B complex – B1, B2, B6, niacin, pantothenic acid, biotin, lipoic acid, folic acid, B12 and inositol).

1.6.1 Vitamin B complex

The B complex vitamins play an important role in many functions including the production of healthy red blood cells and synthesis of DNA. This complex includes all
the water soluble vitamins except vitamin C. They are found in yeast, liver, rice polishing etc. Because of their water solubility they are lost during cooking, while washing the material before cooking and draining the water after cooking. Vitamin B₁ is destroyed by heat and most of the other compounds are stable to heat. All the members of the B complex including B₁ and B₁₂ form coenzymes or prosthetic groups of different enzymes. Another similarity among B complex vitamins is that all of them contain nitrogen.

1.6.1.1 Thiamine (vitamin B₁, anti beriberi substance)

Thiamine (C₁₂H₁₇N₄O₅S⁻) is one of the largest known vitamins. Chemically it consists of a pyrimidine ring and a thiazole ring system joined by a methylene bridge (Fig. 1.2). It is generally prepared as chloride hydrochloride.

![Fig. 1.2 Molecular structure of thiamine hydrochloride](image)

Thiamine is soluble in water (1gm/ml) and 95% ethanol (1gm/100ml) but not in fat solvents. It is resistant to heat (boiling or acute cleaving) in solutions below pH 3.5 but becomes inactive above pH 5.5 owing to hydrolysis. It forms a number of salts and esters of which the most important ester is thiamine pyrophosphate (TPP or cocarboxylase). TPP is formed by the phosphorylation of the vitamin under the influence of an ATP (Adenosine triphosphate) dependent thiamine diphosphotransferase present in brain and liver.

Thiamine is essential for normal functioning of the intestine, cardiovascular and nervous systems (Schellenberger and Schowen 1988). It is also required for proper circulation, blood formation, and metabolism of carbohydrates. It is a precursor to several neurotransmitters including Gamma-amino-butryric acid (GABA). GABA is a chemical that affects nervous system and prevents neurons from over firing, thus calming the brain.
Due to its high water solubility, it is excreted through urine and its storage is limited and hence must be provided regularly.

Deficiency of this vitamin leads to disruption of carbohydrate metabolism viz., accumulation of pyruvic acid and α-keto acids in blood. Its deficiency also affects the peripheral nervous system, the gastro intestinal tract and the cardiovascular system. Prolonged deficiency of thiamine in man leads to the condition known as beriberi.

1.6.1.2 Thiamine and its complexes - an overview

Thiamine can form complexes with metals and halides. The reports on the crystal structures of these complexes are very few. The first reported X-ray structure of a thiamine complex is that of thiamine hydrochloride (Kraut and Reed 1962). The crystal structure and physicochemical properties of a polymorph of the complex- thiamine hydrochloride hemihydrates was reported by Watanabe et al. (1979). Clemente et al. (1988) has reported the crystal and molecular structure of thiamine monochloride with F conformation.

The crystal and molecular structure of thiamine iodide hydroiodide was determined and reported in 1976 (Lee and Richardson, 1976). The protonated thiamine bromide hemihydrates was crystallised and its structure was compared with that of protonated thiamine chloride monohydrate and protonated thiamine iodide (Thompson and Richardson 1977). The crystal structure of thiamine iodide sesquihydrate as a host-guest model was reported in 1993 (Haihu and Zhang 1993). The molecule has a F conformation with a disordered hydroxyethyl side chain. The thiazolium ring of one of the two molecules found in the asymmetric unit is found to connect with the pyrimidine ring of the other, by an iodine ion or a water molecule. In this structure, the thiamine molecules self associate to form a pipe like polymeric structure, in which the four thiamine hosts surround an iodide guest and hold it through hydrogen bonds and electrostatic interactions.

The infra red spectrum of the zwitterionic zinc complex of thiamine was studied at room temperature at various pressures and it was inferred that it retained its S conformation even at high pressure (Butler et al. 1995). Casas et al. (1996) has observed a competition between water molecule and chloride ion for coordination to diorganotin
dihalides in the crystal structure of the salts [Hthiamine][SnMe₂(H₂O)Cl₃]Cl and [Hthiamine][SnPh₂Cl₄]H₂O. Properties and structural characterization of the complex of thiamine with antimony trichloride, 2[C₁₂H₁₆N₄O₅][Sb₂Cl₁₀] was investigated by Hursthouse et al. (1996). Kinetic studies and mechanism of the reversible ring opening of thiamine and related thiazolium ions in aqueous solution was carried out by Carmichael et al. (1997). In another work, X-ray diffraction studies of the complexes of an antagonist of thiamine-oxythiamine were carried out by Hu et al. (1999 b).

The crystal structure of Cd(II), Hg(II), and Pt(II) complexes of 2-(α-hydroxybenzyl) thiamine was determined and observed that despite different shape and sizes of metal coordination units, all the metal ions are bounded to N(I) of the pyrimidine ring (Hu et al. 1999 a). Casas et al. (2006) had determined the structure of zinc (II), cadmium (II) and mercury (II) complexes of oxythiamine and these were characterised by mass spectrometry, and IR in the solid state and by NMR spectroscopy in hexadeuterated dimethylsulfoxide.

Raman and surface - enhanced Raman study of thiamine at different pH values were studied for evidencing the protonated and unprotonated thiamine molecular species in aqueous solution (Leopold et al. 2005). A crystalline solid solution of thiamine with 5-fluorouracil in which the two crystallographically independent sites were occupied by either a thiamine or a fluorouracil molecule, was synthesized by Barnett et al (2006). A kinetic and mechanistic investigation of ruthenium(III)-catalyzed oxidative cleavage of thiamine hydrochloride with N-bromosuccinamide in presence of hydrochloric acid medium was carried out by Mohana and Ramya (2009). Jain et al. (2011) had synthesized some transition metal complexes containing thiazole moiety using microwave techniques and studied its spectral and thermal characteristics.

1.6.1.3 Nicotinic acid (niacin)

Nicotinic acid has two faces of physiological action, first one as the vitamin and the second one as the broad spectrum antihyperlipidemic drug. Nicotinic acid (pyridine-3-carboxylic acid, Pellagra preventive factor (PPF) or vitamin B₃, (C₆H₅NO₂) was synthesized first time by Huber in 1867 as reported by Shibata etal. (2000). It is an indispensible nutrient for humans and animals and has been widely used as an additive in
food, forage and cosmetics. It acts as coenzyme and takes part in various oxidation-reduction reactions essential for tissue respiration (Gilman et al. 1980). It is usually a member of most of the antilipidemic drug regime because of its broad spectrum and relative safety (Chaudhuri 1997). It has several important pharmacological applications, particularly in the treatment of hypercholesterolemia and atherosclerosis (Carlson 2005). In tissues it occurs primarily as the amide (nicotinamide) which is the physiologically active compound.

Nicotinic acid occurs as a white crystalline powder. It has a solubility of 1 in 60 in water at room temperature and is freely soluble in boiling water, alcohol, alkali hydroxides and carbonates. Nicotinic acid sublimates at 236°C without melting (Menon et al. 2002). The molecular structure of nicotinic acid is given in fig. 1.3.

![Fig. 1.3 Molecular structure of nicotinic acid](image)

Nicotinamide is one of the most stable vitamins as it is resistant to heat, light, oxidation, alkali etc. In tissues, it is present largely as the nicotinamide adenine dinucleotide (NAD⁺, DPN⁺ or coenzyme II) (Menon et al. 2002). Deficiency of this vitamin gives rise to pellagra (Jingyan et al. 2008).

1.6.1.4 Nicotinic acid and its complexes - A brief literature survey

As a part of the physicochemical research on vitamins, the optical properties and preliminary X-ray investigation (unit cell parameters and space group) of nicotinic acid and nicotinamide and the crystal structure of nicotinic acid were reported by Wright and Kino (1950,1953). The absorption spectra of pyridine monocarboxylic acids in water and ethanol solutions in the near ultraviolet range were investigated (Stephenson and Sponer...
Crystal structures of hydrated lanthanide (III) nicotinates- \( \text{La}_2(\text{C}_6\text{H}_4\text{NO}_2)_{6}(\text{H}_2\text{O})_{4} \) and \( \text{Sm}_2((\text{C}_6\text{H}_4\text{NO}_2)_{6}(\text{H}_2\text{O})_{4}) \) - were reported by Moore et al. (1972) and they also made a comparison of magnetic moments at 23K with room temperature values. The thermal decomposition of ammonium salts of nicotinic acid and its analogs in liquid phase was investigated (Frenkel et al. 1995). Synthesis, X-ray structure and magnetic properties of three dimensional manganese(II) coordination polymers based on m-pyridine carboxylates were reported (Lin et al. 2000). These complexes are found to be the examples of one dimensional Heisenberg antiferromagnetic chains. Abinitio molecular orbital vibrational analysis of SERS of nicotinic acid species were carried out and its comparison with the experimental values were reported (Sala et al. 2001). Chapman et al. (2001) had synthesised, copper (II) pyridine carboxylate crystals and investigated the X-ray structures and magnetic properties of the coordination networks.

Synthesis and crystal structures of four metal- organic coordination networks of cadmium(II) thiocyanate and nicotinic acid derivatives with hydrogen bonds were reported (Yang et al. 2001). Li et al. (2001) has tried a potentially powerful tool -the tethered agonist approach- in mapping ion channel proteins towards a structural model for the agonist binding site of the nicotinic acetylcholine receptor. Synthesis, structure determination and X-ray photoelectron spectroscopic characterisation of polymeric silver(I) nicotinic acid complex, \( \text{H}[\text{Ag(py-3-CO}_2)_2] \), was reported by Olovkall et al. (2001). The TGA/DTA study of the sublimation of nicotinic acid was carried out and using the Langmuir equation the vapor pressure curves were constructed (Menon et al. 2002). A three dimensional hydrogen bond network of Zinc (II) complex of isonicotinic acid was synthesized and its crystal structure was reported (Liang and Jia-Jeng 2001). Vibrational spectra of alkaline metal complexes of nicotinic, benzoic and salicylic acids were used to trace out the binding modes and bite sites of the coordination by Lewandowski et al. (2002). Koczon et al. (2003) has reported the experimental and theoretical IR and Raman spectral analysis of picolinic, nicotinic and isonicotinic acids. Based on the nicotinato tecton, a tube-and-ladder like copper(II) coordination polymers were constructed and studied its magnetic properties (Madalan et al. 2005). Synthesis and crystal structure of cadmium(II) and silver(I) complex of isonicotinic acid having
excellent fluorescence property was reported by Yuan and Liu (2006). Two lead-carboxylate complexes based on nicotinic acid N-oxide were synthesized and its structure was determined along with its luminescent properties (Zhao et al. 2007).

Marcin and Winiarski, (2006) have investigated the X-ray photoelectron spectroscopy (XPS) of magnesium nicotinate and its derivatives. Cyclic voltammetric response of nicotinic acid and nicotinamide on a polycrystalline gold electrode was investigated and inferred that the oxidation occurred at almost same potential but their reduction did at different peak potentials (Wang et al. 2006). Nicotinamide-acetyl salicylato complexes of Co(II), Ni(II), Cu(II) and Zn(II) were synthesized and their characteristics as well as magnetic and thermal properties were studied. The thermal study revealed that the final products of all the decomposed crystals are the respective metal oxides (Kose et al. 2007). Synthesis, crystal structure and luminescent properties of two lead carboxylate complexes based on nicotinic acid were carried out by Zhao et al. (2007). A new one dimensional Mn(II) complex with mixed pyridine and sulfonate carboxylates was reported (Li et al. 2007). Three manganese (II) complexes have been prepared from in situ metal/ligand solution reactions with 2-mercaptanonicotinic acid (Xiao et al. 2008). Quantum chemical studies on nicotinato lead(II) complex, [ Pb(II)(C₅H₄NCOO)₂ ], has been carried out and the results showed that the lead(II) ion adopts 2-coordinate geometry which is same as its crystal structure. Atomic charge distribution of this complex indicates that during the formation, each nicotinic acid ion transfers their negative charges to central lead (II) ion (Zhao et al. 2008).

The hydrothermal synthesis and crystal structure of a poly-cationic chain of [Nd(C₆NO₂H₂)₃(H₂O)₂]n[ZnCl₄].nCl.2.5nH₂O was reported (Chen et al. 2008). Di et al. (2008) had synthesized the coordination compound Cd(HNic)₂ Cl₂ (S) and its thermal characteristics have been studied. Six lanthanide complexes with nicotinate and isonicotinate ligands were synthesized and their crystal structure and luminescence properties were studied (Jia et al. 2008). Jingyan et al. (2008) had investigated the thermal behavior of nicotinic acid using TG, FT-IR and TG/DSC-FTIR. They also calculated the kinetic parameters using master plots method. The porphyrin nicotinic acid
binary compounds have been synthesized and different substituent effects on spectral and electrochemical properties were studied by Wang et al. (2009).

Interaction of Nickel (II) ions with nicotinamide and nicotinic acid in aqueous solution were examined by potentiometric, dc polarographic and spectroscopic techniques and their electro chemical parameters were determined (Urbanska and Podsiadly 2009). Polynuclear lanthanide hydroxide complexes were synthesized by controlled hydrolytic method using nicotinic acid as the ancillary ligand and determined the crystal structure (Kong et al. 2009). Shahverdizadeh et al. (2008) has determined the crystal structure of $[\text{Pb}(\mu_3-\text{Nic})_2]_n$ in which the lead(II) ion is eight coordinated and the direction of Pb-N and Pb-O bonds showed that the coordination is holodirected.

The biological activities - antimicrobial and superoxide dismutase activities - of copper complex of pyridine derivatives were studied by Suksrichavalit et al. (2009). They also studied the infrared spectrum of the complexes and geometrically optimized the structures. Lanthanide nicotinic / isonicotinic complexes were synthesised and their structure and photophysical properties were studied with UV-Vis absorbance spectra, low temperature phosphorescence spectra, quantum yield, excitation and emission spectra. (Chen and Fukuzum 2009). They inferred that the factors like type of metal centers and organic ligands, the extent of conjugation of the complex and the coordinated water molecules can affect the photoluminescent properties. The standard molar enthalpies of formation and sublimation of crystalline nicotinic acid was determined by Goncalves et al. (2010). They concluded that the energetics of crystalline materials are sensitive to a multitude of structural factors that are normally difficult to control. Wang et al. (2010) had synthesized and elucidated the crystal structure of silver(I) complex $[\text{Ag}(\text{AMP})(\text{NA})]_n\cdot\text{H}_2\text{O}$. In this pyridine-3-carboxylate bridged polynuclear silver (I) complex, the silver atom is in a distorted triangular geometry and the crystal is stabilized by intermolecular hydrogen bonds. A hybrid inorganic-organic polymeric frame work formed by lead (II) pyridine carboxylate was synthesized and characterized by Rana et al. (2011). They also investigated the luminescent and thermal properties of the complex and demonstrated the existence of inter ligand and metal to ligand charge transfer transitions through emission study.
1.6.1.5 Folic acid (vitamin B₉)

Folic acid (Pteroyl glutamic acid, C₁₉H₁₉N₇O₆ – (FA)), is a yellowish or orange crystalline powder, known as vitamin B₉ in which the pteroic acid and glutamic acid are connected through an amide linkage (Fig. 1.4). It is present in the liver and kidney of human beings. It is found in spinach, mushrooms, yeast, and green leaves and is used in the treatment of megaloblastic anaemia. It functions to transfer one carbon units such as methyl and formyl groups to various substrates in enzymatic reactions in the synthesis of DNA, RNA and protein components (Keating 2009). FA is vitally important for normal fetal development during pregnancy (Hutto 1997, Lucock 2000, Picciano 2003, Pitkin 2007). Maternal FA deficiency causes pregnancy complications such as preeclampsia and higher incidence of fetal neural tube defects (Bonechi et al. 2004). Persons with deficiency of this vitamin are more prone to risk of cancer. Its deficiency also results in DNA strand break, DNA hypomethylation and abnormal gene expression (Wainfan and Poirier 1992, Pogribny et al. 1995). FA is used to induce acute renal failure in animals to study the mechanism of renal failure and the effect of drugs in acute renal failure (Wan 2006). Crystallization of folic acid in renal tubules causes intratubular obstruction which results in acute renal failure (Schaefer et al. 2002, Cheng et al. 2005). Folic acid induced renal damage is associated with the rapid appearance of folic acid crystals within renal tubules. This is followed by acute tubular necrosis, epithelial regeneration and cortical scarring (Fink et al. 1987).

![Fig. 1.4 Molecular structure of Folic acid](image-url)
Folic acid is a potential agent for cancer prevention by free radical scavenging and antioxidant activity and also functions as a tumour targeting ligand in cancer therapy (Jennings 1995, Mason and Levesque 1996, Lai et al. 2009).

1.6.1.6 Folic acid and its complexes - A general survey of recent studies

A detailed study of folic acid and its metal complexes have been started only very recently. Vora et al. (2002, 2004) have investigated the degradative processes which folic acid undergoes during thermal stress. They also identified the decomposition products using various analytical techniques such as infrared spectroscopy, mass spectroscopy and X-ray diffraction and suggested that the glutamic acid degrades first and the vitamin degrades ultimately to carbon residue. The conformational information of folic acid in solution was investigated through NMR spectroscopy and elucidated its accurate structure from molecular mechanics and molecular dynamic calculations (Bonechi et al. 2004). The design and synthesis of folic acid targeted tetraphenylporphyrin as novel photosensitizers were reported (Scheider et al. 2005).

Hameed et al. (2009) had synthesized and studied the spectroscopic and thermal characteristics of copper (II) and iron (III) complex of folic acid. Folic acid dimethyl ester benzenesilicate was hydrogenated homogeneously in a diasterioselective reaction with daniphos ligands and its crystal structure was determined (Braun et al. 2006). Layered double hydroxides of metals with folic acid and its derivatives were synthesized as efficient drug reservoirs and carriers (Choy et al. 2004, Qin et al. 2008).

The fluorescence spectroscopic behavior of folic acid in bicationic, cationic, neutral and anionic forms was studied in detail (Tyagi and Penzkofer 2010). They also investigated the thermal stability and compared the calculated absolute absorption cross-section with fluorescence excitation spectra. Some transition metal complexes of folic acid were synthesized and characterized by elemental analysis, infrared as well as electronic spectra, thermogravimetric and conductivity measurements (El-Wahed et al. 2008).

The use of folic acid in targeting drug delivery systems depends on its pH sensitivity. A study of folic acid functionalized microgels was reported by Saez-Martinez et al. (2008). They suggested that the folate complexes were formed by 2:1 molar ratio
Alkaloids are the organic products of natural or synthetic origin which are basic in nature and contain one or more nitrogen atoms, normally heterocyclic in nature, and possess specific physiological actions on human or animal body when used in small quantities (Kokate et al. 2003). Alkaloids are potent therapeutic compounds and have been manufactured as various allopathic drugs, including the pain-killer morphine and the anti-malarial quinine. Derived from amino acids, alkaloids represent a varied and complex class of nitrogenous crystalline or oily compounds. The major structural difference between alkaloids and other natural products such as flavanoids and terpenes is the presence of nitrogen atom. This group also includes some related compounds with neutral and even weakly acidic properties (Manske 1965). Also some synthetic compounds of similar structure are attributed to alkaloids. In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulfur and more rarely other elements such as chlorine, bromine, and phosphorus.

Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants, and animals and are part of the group of natural products (also called secondary metabolites). Many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications, as recreational drugs or in entheogenic rituals. Examples are the local anaesthetic and stimulant cocaine, the stimulant caffeine, nicotine, the analgesic morphine, or the antimalarial drug quinine.

1.7.1 Quinine (C_{20}H_{24}N_{2}O_{2})

The bark of the cinchona tree is the source of a variety of alkaloids. Cinchona alkaloids have well known antimalarial activity. There are more than thirty different alkaloids of similar molecular framework in cinchona bark of which the most biologically active are quinine, quinidine, cinchonine and cinchonidine. Quinine is used in the anti-
malaria medication and quinidine calms the heart in tachycardia and arrhythmia. It has also antimuscarinic and alpha-adrenoceptor blocking properties. The molecular structure of these alkaloids is depicted in fig. 1.5. They are used in organic chemistry as organocatalysts in asymmetric synthesis.

Fig. 1.5 Molecular structures of (a) Cinchona alkaloids and (b) Quinine

Cinchonine and cinchonidine (stereoisomers with R = vinyl, R' = hydrogen)
Quinine and quinidine (stereoisomers with R = vinyl, R' = methoxy)
Dihydroquinidine & dihydroquinine (stereoisomers with R = ethyl, R' = methoxy)

1.7.2 Quinine and its complexes - A review of recent literature

The crystal structure of quininium salicylate monohydrate in which the hydrogen bonds link quininium cation, salicylate anion and water molecules to form an eleven membered ring was reported by Oleksyn (1993). This structure has been compared with the salt-bridge clusters observed in myoglobin. The potential energy surface of quinine has been investigated using the molecular mechanics and quantum mechanical semiempirical AM1 and PM3 methods (Silva et al. 1997). An organic salt quininium (R) -mandelate with incommensurately modulated structure in (3+1) dimensional space was reported by Schonleber and Chapuis (2004).

Rey et al. (2006) had isolated and characterised three copper(II) complexes of quinuclidine [Cu(C7H13N)2(OH2)CL]Cl.2H2O, quinine [Cu(C20H23O2N2)(OH2)2]ClO4 and hydroquinidine [Cu(C20H23O2N2)(OH2)Cl2]Cl.1/2H2O. The binding sites of these complexes were determined by FT-IR and EPR spectroscopy and thermal analysis. Both
bidentate and monodentate coordination of the ligand with copper (II) ion were observed for these complexes.

A polymeric zinc (II) complex of quinine was synthesized and its crystal structure was reported (Obaleye et al. 2007). The complex was characterized by FT-IR and elemental analysis. Structural investigation of trichloro-cobalt(II) complexes of equinquine, epiquinidine and epidihydrocinchonine were carried out and showed that in the absence of crystallizing solvent molecules, the chlorine atoms can act as proton accepters in intramolecular hydrogen bonds with an adjacent alkaloid molecule (Tesarowicz et al. 2007). Infrared absorption, vibrational and electronic and circular dichroism (VCD and ECD) studies of complexes of carbamoylated quinine and quinidine with N-blocked amino acids were conducted and established the leading role of selectors in the formation of selactands-selector complexes (Julinek et al. 2009).

The simultaneous FT-IR spectroscopic determination of two stereoisomers, quinidine and quinine using chemometric multivariate methods were done by Wahbi et al. (2008). Alumsa et al. (2011) had designed and synthesized a series of quinine analogs containing the quinine pharmacophore without some specific functional groups. They calculated the physicochemical characteristics of these materials and found that the structural alterations do not change these values much.

1.8 Motivation for the present work

Most of the active pharmaceutical ingredients exist in crystalline form. Hence the determination of the crystal and molecular structure of such materials will facilitate the research and development of new drugs. The changes in crystal structure can alter the way in which the drug is absorbed by the body. The chemical and physical structure of a drug profoundly affects the solubility, stability, ease of manufacture and its biopharmaceutical performance. The variation in physical properties and biological activities with changes in crystal structure of biologically important molecules and their complexes motivated us to perform the present work.

All the crystals except thiamine iodide hydroiodide were grown by gel method. Literature survey reveals that almost all the crystals of the previously reported compounds of the ligands considered in this work are synthesized hydrothermally at
elevated temperatures. Hence an attempt has been made to grow crystals of certain vitamins and alkaloids and their new complexes at ambient temperature. Sodium metasilicate gel is an apt medium for growing crystals of biologically important molecules at ambient temperature since its viscous nature provides simulation of biological fluids. This method provides a convenient technique to assess the various factors like pH, temperature, additives and external forces that alter the growth parameters such as nucleation time, morphology and growth rate of crystals.

The physical properties of the grown crystals such as thermal and dielectric properties were studied and the polarisability was calculated by various methods. These studies may help in revealing their various biopharmaceutical properties.