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X-ray structural studies on metal complexes with nucleotides and pyridoxal-amino acid Schiff bases. Models for platinum binding to DNA and pyridoxal catalyzed reactions

M DAMODARA POOJARY, S P SUDHAKARA RAO and H MANOHAR

Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560012, India

Abstract. X-ray structural studies on metal complexes with nucleotides and with pyridoxal-amino acid Schiff bases are briefly reviewed. The results with ternary metal nucleotide complexes show that the oxopurine nucleotides coordinate to the metal ion through the N(7) atoms of the bases in *cis* position. The relevance of this mode of binding is discussed in terms of the possible mechanism of action of the novel platinum drugs. On the basis of the studies on metal pyridoxal-amino acid Schiff base complexes, the variations in stereochemistry of the ligands in different metal complexes have been related to the catalytic activity of various metal ions in pyridoxal-catalyzed nonenzymatic reactions.

Keywords. X-ray crystallography; metal-nucleotide complexes; metal-Schiff base complexes; pyridoxal-amino acid Schiff bases; Pt(II)-DNA interaction.

1. Introduction

Metal ion complex formation is one of the prominent interactions in biological systems. Groups like nucleotides and pyridoxal-amino acid Schiff bases are important biological entities and their interactions with metal ions are a fertile field of research activity. We have initiated work on structural studies of ternary metal nucleotide complexes and metal complexes with pyridoxal-amino acid Schiff bases. In this paper, our recent results, as well as earlier work in this area, are briefly reviewed.

2. Models for platinum binding to DNA

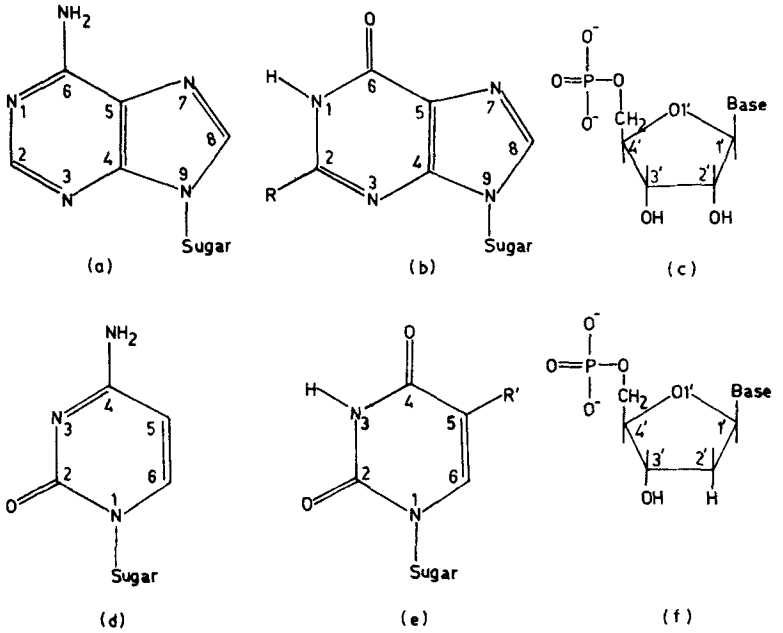
2.1 *Role of metal ions in the biochemistry of nucleic acids*

It is well-known that metal ions play an important role in the biochemistry of nucleic acids (Eichhorn 1973). For example, the transfer of ATP phosphoryl, which is an enzymatic process essentially requires the presence of metal ions. Even the non-enzymatic transphosphorylation, which occurs between ATP and the orthophosphate ion, is catalysed by metal ions, notably Mn^{2+}, Cd^{2+}, Ca^{2+}. Similarly the cleavage of pyrophosphate from four deoxyribonucleotide triphosphates, dATP, dCTP, dGTP, dTTP, involved in the DNA-polymerase reaction, together with the formation of phosphodiester linkage requires the presence of divalent metal ions, mainly Mg^{2+}. It was also discovered that the transition metal ions like Fe^{2+} and Cu^{2+} are components of tobacco mosaic virus DNA, and they are strongly bound to the ligating sites in the nucleic acid. More recent investigations have shown that Zn^{2+} is essential for the activity of

Escherchia coli polymerase 1. Moreover the *in vivo* role of metal ions in nucleic acid chemistry—DNA replication, transcription and translation; DNA denaturation and renaturation; RNA conformational properties; depolymerization of RNA; enzyme-metal-nucleic acid ternary species has been well recognised (Eichhorn 1973). Furthermore, the clinical success of certain transition metal complexes, *e.g.* *cis*-$[Pt(NH_3)_2Cl_2]$ (Rosenberg *et al* 1969) and the speculation that these complexes may act by crosslinking DNA *in vivo* has promoted research activity in this area. Also the unique properties of metals are used as probes for nucleic acid chemistry, for structural investigations and for isolation of these biologically important molecules (Eichhorn 1973; Marzilli 1977; Hodgson 1977).

Although the importance of metal ions in nucleic acid processes is well established their mechanism of action is little understood. As these processes are selective in nature, the interaction of inorganic species with nucleic acids has also to take place through selective coordination. The polynucleotides offer three major ligating sites to metal ions: (i) the heterocyclic ring nitrogen atoms, especially N(1) and N(7) of purines and N(3) of pyrimidines, and the exocyclic functional groups of purine and pyrimidine bases; (ii) the phosphate oxygens of phosphodiester linkages; (iii) the ribose moiety. A knowledge of the metal ion binding sites for each of these component nucleotides (chart I), therefore, is of great value in assessing how the metal ions might interact with nucleic acids.

This led several workers to investigate metal complexes of nucleic acids and their



a) Adenosine
b) R=NH_2 Ganosine
R=H, Inosine
f) Deoxyribonucleotide
c) Ribonucleotide
d) Cytidine
e) R'=H, Uridine
R'=CH_3, Thymidine

Chart 1.

constituents: nucleotides, nucleosides and bases, while earlier studies in this direction carried out in solution and using spectroscopic methods are significant, more experimental data are necessary to determine with certainty the mode of binding of metals and their effects on the structure and conformations of nucleic acids. Among the various physical techniques suitable for studying substances in the crystalline state, x-ray diffraction has proved to be a powerful tool to elucidate the structure of complexes formed by transition metal ions with nucleic acid constituents. A great wealth of information regarding binding sites, conformations, packing, hydrogen bonding, etc. has been accumulated in nucleic acid constituents in their complexes (Hodgson 1977; Marzilli 1977; Marzilli and Kistenmacher 1977; Gellert and Bau 1979; Swaminathan and Sundaralingam 1979; Aoki 1981).

As mentioned earlier, the mixed ligand complexes have been recognised as the low-molecular weight representatives for the active catalytic centres occurring *in vivo*. A ternary complex involving a metal ion, a nucleotide and a secondary ligand such as 2-2′-bipyridine can mimic enzyme-metal ion-substrate interactions in biological systems (Naumann and Sigel 1974). Moreover it has been suggested that in solution, in the presence of a π-aromatic amine, metal-nucleotide interaction takes place predominantly through phosphate oxygens, while the base of the nucleotide does not take part in coordination (Naumann and Sigel 1974; Sigel 1975; Mitchell and Sigel 1978). This observation is attributed to the discriminating qualities of π-aromatic amines to the metal ions, which in turn is one of the tools employed by nature to achieve selectivity. Hence one is tempted to predict that much of the specificity and many of the properties so far only associated with metal ion complexation in macromolecular biological systems are inherent already in relatively simple ternary systems.

On the other hand, an entirely different binding mode has been observed in some ternary platinum oxopurine nucleotide complexes (Aoki 1981). The nucleotides coordinate to the metal ion in *cis* position through the N(7) atoms of the purine bases. Such a type of binding has been observed (Poojary and Manohar 1982, 1983) in ternary Co^{3+}, Ni^{2+} and Cu^{2+} oxopurine complexes. The importance of these compounds as models for platinum binding to DNA is discussed below.

2.2 *Anti-cancer activity of cis-DDP*

Since the discovery of the anti-tumour activity of *cis*-$[Pt(NH_3)_2Cl_2]$ (*cis*-DDP) (Rosenberg *et al* 1969), considerable research has been focussed on elucidating the mechanism of activity of these drugs. The following common features which link structure to reactivity have emerged from these studies (Rosenberg 1980): (i) The complexes have both inert and labile ligands and only the latter ligands undergo labilization quickly in reactions with biological molecules. (ii) The exchangeable leaving groups should be in the *cis* configuration. (iii) The complexes should be neutral. (iv) The geometry of the complexes is either square planar or octahedral. (v) Two *cis* monodentate or one bidentate leaving groups are required. (vi) The leaving ability of these labile groups should be moderate. (vii) The leaving groups should be separated approximately by 3·4 Å.

Studies on *cis*-DDP and its analogues clearly suggest that activity of these drugs depends on the *cis* oriented labile ligands in the coordination plane of platinum. In aqueous solution these labile ligands may be easily displaced, and it has been speculated that the resulting *cis* $(NH_3)_2Pt^{2+}$ moiety is the active species which interacts with

biological target molecule (Barton and Lippard 1980). Studies have also shown DNA as cellular target for *cis* DDP. In binding to DNA, *cis* DDP could block replication, which would suppress rapid growth of cancerous tissues.

2.3. *Possible mechanisms of action of cis-DDP*

A variety of structural models for the ligating site in DNA for *cis* DDP have been proposed. Studies have shown that N(7) nitrogen atom of purine and N(3) nitrogen atom of pyrimidines are the primary sites of coordination for the platinum atom. However, this unidentate coordination is not sufficient to explain the observed differences in activity of *cis* and *trans* isomers. Potentiometric studies (Macquet and Theophanides 1975) show that on binding of *cis* DDP to DNA both the chlorine ions are released, while the release of one chlorine ion is observed on binding of *trans* isomer. Thus N(7)–O(6) chelation was proposed on the basis of bifunctional mode of coordination. The *trans* isomer could not bind to these sites simultaneously. However, geometrical considerations required for such chelation have led many to suggest that such a structure is unlikely.

Other possible bifunctional coordination modes include the formation of either intra or interstrand crosslinks. The crosslinking of base residues on opposite strands of DNA would severely hinder replication. Even though interstrand crosslinking of DNA does occur in the presence of *cis* DDP, the frequency of this event is too low to account for its antitumour activity (Roberts and Thomson 1979). At present it appears more probable that the site of interaction involves an intrastrand crosslinking. The observation that the nonbonded distance between the chlorine ions in *cis* DDP is 3·4 Å, the base pair stacking distance suggests that intrastrand crosslinking is chemically more reasonable. Such a crosslink would necessarily result in an unstacking of bases. The base tilting required to accomplish this crosslink would lead to local denaturation. This intrastrand crosslink could be formed by platinum binding to N(7) nitrogen atoms of the adjacent guanine bases.

2.4 *Intrastrand crosslinking models*

Even though information about the binding of *cis* DDP to the polymer is scarce, some recent studies on monomers allow interesting speculations to be made. One increasingly mentioned mode of binding to the *cis* isomer is intrastrand crosslinking. Goodgame *et al* (1975) described a *cis*-$Pt(NH_3)_2^{2+}$ complex of 5′-IMP, *cis*-$[Pt(5'\text{-IMP})_2(NH_3)_2]^{2-}$, wherein Pt(II) binds through equatorial sites to two 5′-IMP ligands which are related by a crystallographic two-fold axis. Similar type of complexes were reported with different inert ligands like ethylenediamine and trimethylenediamine (Kistenmacher *et al* 1978; Bau and Gellert 1978; Kistenmacher *et al* 1979; Marzilli *et al* 1980). Most of these complexes are nonstoichiometric. All these structures bear a strong resemblance to the structure of monosodium salt of 5′-IMP (Rao and Sundaralingam 1969), where a water molecule lies on a crystallographic 2-fold axis and links, *via* hydrogen bonds, two symmetry-related nucleotides. In the isomorphous platinum complexes this water site is occupied by the Pt(II) moiety and the hydrogen bonding scheme present in the sodium salt is replaced by two *cis* coordination bonds. In terms of the possible effect on a polynucleotide structure due to intrastrand crosslinking, the structural similarities displayed by these 5′-IMP salts are particularly important. Chiang *et al* (1978) showed that there is a strong competition between the crystal packing forces

operative in the solid and the distortion of the basic structure due to the simultaneous binding of the two 5′-IMP bases by Pt(II) moiety. In fact if one assumes that the crystal packing forces operative in the 5′-IMP complexes approximate those found in the base-stacked polynucleotide, the above result suggests that intrastrand crosslinking by reagents such as *cis* DDP will place a significant strain on the conformational properties of the polynucleotide.

All the platinum-5′-IMP complexes discussed above are 1 : 2 complexes. The binding of metal to the oxopurine nucleotides in *cis* position has also been displayed by 1 : 1 ternary metal-nucleotide complexes containing ethylenediamine and metal ions like Co(III) and Ni(II) (Poojary and Manohar 1982). Again these complexes are isomorphous among themselves and isostructural with platinum complexes and sodium salts of oxopurine nucleotides. For comparison, structures of the sodium salt, the platinum and cobalt 5′-IMP complexes are given in figure 1. The geometry of the nucleotides around Pt(II) and Co(III) is the same. An interesting feature of the Co(III) and Ni(II) complexes is that the ethylenediamine molecule has been displaced from the metal centre, to which the nucleotides coordinate. This results in one metal ion interacting only with ethylenediamines and the other with nucleotides. The remaining octahedral coordination sites are occupied by waters. Both the metal ions lie on different two-fold

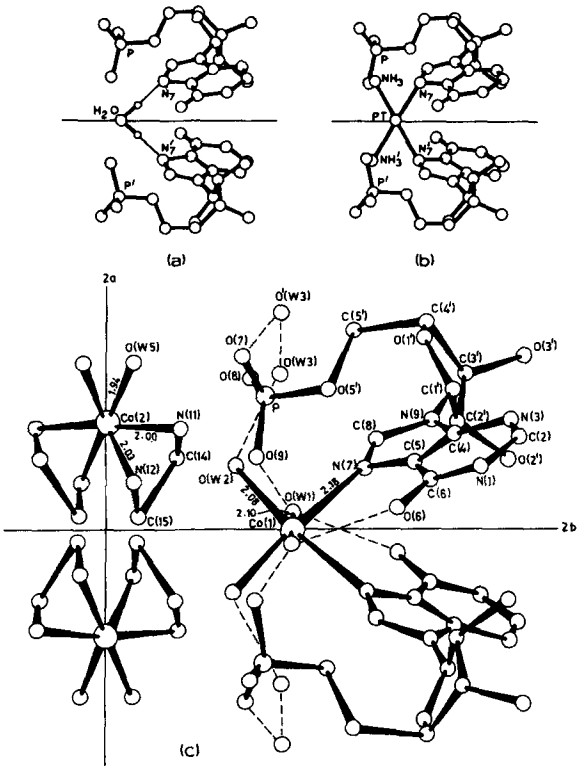


Figure 1. A comparison of structures of (**a**) monosodium salt of 5′-IMPH, (**b**) $[Pt(5'\text{-}IMP)_2(NH_3)_2]^{2-}$ and (**c**) $[Co(5'\text{-}IMP)(en)(H_2O)_3]^{+}$. Horizontal and vertical lines represent two-fold rotation axes. Broken lines indicate hydrogen bonds. (Figures **1**(**a**) and (**b**) are reprinted with permission from Chiang *et al* 1978; Figure **1**(**c**) with permission from Poojary and Manohar 1982).

axes. Chlorine ions which neutralize the charge in the Co(III) complex are disordered in the vacant site between the molecules. The ethylenediamine molecules are also disordered.

The 5′-GMP complexes of Co(III) and Ni(II), like the 5′-IMP complexes, are based on the sodium salt of 5′-GMP (Katti *et al* 1981). In the sodium salt of 5′-GMP, a sodium ion links the two nucleotide moieties. This sodium ion is replaced by the metal ions Co(III) and Ni(II). Recently a similar binding has been observed (Poojary and Manohar 1983) in a ternary Cu-5′-IMP complex, containing imidazole groups. This complex is isomorphous with *cis* $[Pt(5'\text{-IMP})(NH_3)_2]^{2-}$. The imidazole moieties are in *cis* position with a partial occupancy of 0·4, while for the rest of the time these sites are replaced by waters. The *cis* binding of nucleotides to Cu(II) ion in the presence of a π-aromatic amine (imidazole) is at variance with the results of crystallographic studies on ternary complexes containing other π-aromatic amines (Aoki 1981) and contrary to the conclusions derived from solution studies mentioned earlier.

3. Model compounds for pyridoxal catalyzed reactions

3.1 *Role of metal ions*

Enzymes dependent on pyridoxal phosphate (PLP) (the cofactor form of vitamin B_6) catalyze a variety of metabolic reactions of amino acids such as decarboxylation, transamination, racemization and carbon-carbon bond cleavage. Many nonenzymatic model reactions also proceed by similar mechanisms in the presence of pyridoxal (PL) and a suitable metal ion (Holm 1973). A general theory on the mechanism of nonenzymatic reactions essentially involves the following steps: (i) Formation of a Schiff base with subsequent labilization of bonds attached to the α-carbon atom due to electron displacement from the α-carbon atom to the electronegative ring nitrogen through a conjugated system of double bonds, (ii) Release of H^+, $COOH^+$ or R^+ from the α-carbon atom depending upon their orientation with respect to the extended π-system (aldimine plane) to produce a transitional Schiff base, (iii) Localization of the lone pair of electrons of the heterocyclic nitrogen and subsequent protonation either at the α-carbon atom for racemization and decarboxylation or at the formyl carbon for transamination, (iv) Hydrolysis of the carbon-nitrogen bond to give the products.

The mechanism for the first stage of transamination reaction is given in chart 2. The imines **2** and **4** have been detected spectrophotometrically, but direct evidence supporting the existence of intermediate **3** is lacking. It has been suggested that the role of the metal ion is to stabilize the imines **2** and **4** through chelation in a tridentate fashion, which provides a planar conjugated system via **3** and increases the inductive effect away from the α-carbon atom (Metzler and Snell 1952). Thus, it is now believed that the metal ion serves as a trap for the preformed Schiff base.

It is of interest to note that different metal ions have varied catalytic influence. The efficiency towards PL transamination was found to be in the order $Co^{2+} < Ni^{2+} < Zn^{2+} < Fe^{3+} < Fe^{2+} < Al^{3+} < Cu^{2+}$, from the investigation of the influence of metal ions on the rate of the transamination of pyridoxamine with α-ketoglutarate (Longenecker and Snell 1957). As it is conjectured that the metal ion has no kinetic role in the Schiff base formation, apparently the cause for varied catalytic influence of different metal ions lies in the stereochemistry of metal-Schiff base complex. From pH-metric titrations (Christensen 1957), the expected downward shift in the pK value

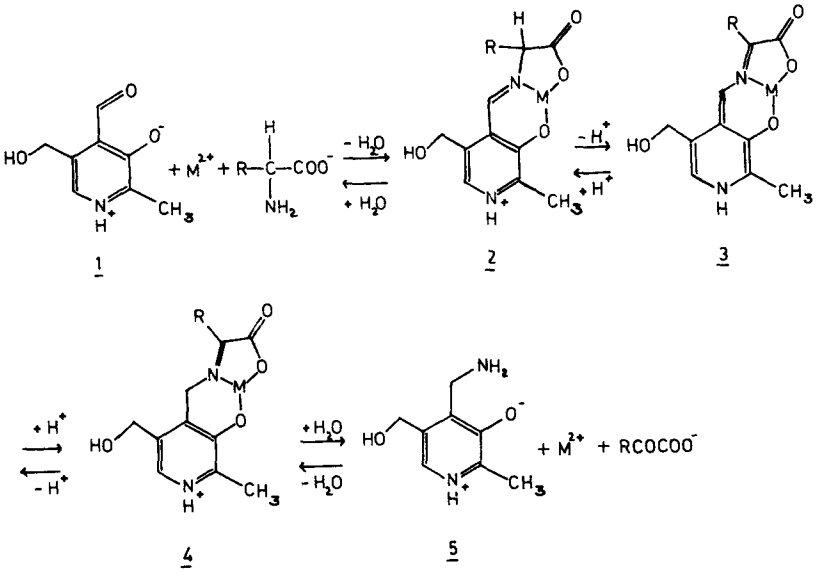


Chart 2.

of the pyridine nitrogen in Ni(II), Mn(II) and Zn(II) chelates was not observed and this result was attributed mainly to an unstable metal-phenolic oxygen bond in solution. But in the solid state, the crystal structures of [Mn(PL-DL-valine)$_2$] (Willstadter *et al* 1963), [Ni(PL-DL-valine)$_2$] (Capasso *et al* 1974) and [Zn(PL-L-valine)$_2$] (Capasso *et al* 1974) have shown that metal-phenolic oxygen bond is equally as strong as other metal-donor bonds. Capasso *et al* (1974) speculated that the puckering of the chelated Schiff bases could play a decisive role in catalytic activity. In [Ni(PL-glycine)$_2$] and [Cu(PLP-glycine) (H_2O)] complexes also contrasting features have been observed with respect to the stereochemistry (*vide infra*), but not in relation to the strength of the metal-donor bonds (Rao and Manohar 1983).

3.2 *Stereochemistry of metal pyridoxal-amino acid complexes*

Because of the tridentate nature of the Schiff base ligand, complexes with 2:1 and 1:1 ligand metal stoichiometry can be formed. The heterocyclic nitrogen may be protonated according to the charge neutralization requirement. In 1:1 complexes, confined to copper(II) only, approximate square-pyramidal coordination geometry exists, in which three positions in the basal plane are occupied by the aldimine ligand. In [Cu(PL-DL-valine)] (Dawes *et al* 1982) the fourth basal position and the fifth apical position are occupied by a pyridine nitrogen and a hydroxymethyl oxygen respectively of different neighbouring molecules, whereas in [Cu(PLP-DL-phenylalanine) (H_2O)] (Bentley *et al* 1968) they are filled by a water molecule and phosphate oxygen of another molecule. In [Cu(PL-*o*-phospho-DL-threonine)] (Aoki and Yamazaki 1980) the phosphate oxygen from a neighbouring molecule acts as the fourth donor which results in a dimeric structure, the fifth being a water molecule. The copper complex with PL-L-histidine has recently been reported (Dawes and Waters 1982) to be trimeric with the histidine nitrogen of another ligand of the same trimer and a water molecule being in the fourth and fifth coordination positions respectively.

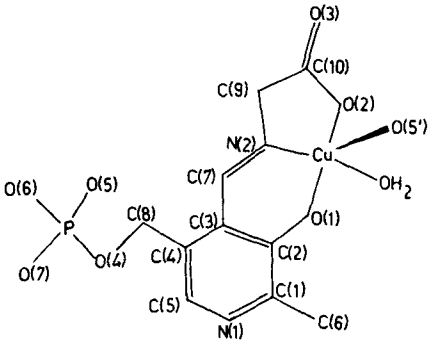


Figure 2. Structure of [Cu(PLP-glycine) (H_2O)] $3H_2O$ with atom numbering scheme.

In [Cu(PLP-glycine) (H_2O)] (Rao and Manohar 1983) a polymeric structure is observed, the axial site being occupied by a phosphate oxygen of a neighbouring molecule translated along *a* axis; a water molecule binds at the remaining equatorial site (figure 2). There are three more water molecules in the asymmetric unit which link the two polymeric chains through hydrogen bonds.

In 2:1 complexes, chelation takes place on an octahedral edge so that the two imine nitrogens are *trans* and the two phenolate and carboxylate oxygens are mutually *cis* to each other. From a structural point of view, such complexes are interesting in that the *bis* (tridentate) complexes have the *abf* structure for which two enantiomorphous forms *A* and *B* are possible (chart 3). The presence of an asymmetric centre in the condensed amino acid generates the diastereoisomeric species, $A(LL) \equiv B(DD)$, $A(DD) \equiv B(LL)$ and $A(DL) \equiv B(LD)$ where *A* and *B* stand for the two possible enantiomorphous forms of the complex, *D* and *L* refer to the configuration of the two Schiff base ligands.

However, it has been observed that either the enantiomorphous pair $A(LL)$, $B(DD)$ (or $A(DD)$, $B(LL)$) are present in the solid state as found in [Mn(PL-DL-valine)$_2$] (Willstadter *et al* 1963) and [Ni(PL-DL-valine)$_2$] (Capasso *et al* 1974) or only the $A(LL)$ diastereoisomer as observed in [Zn(PL-L-valine)$_2$] (Capasso *et al* 1974). The fact that complexes such as $A(DL)$ or $B(DL)$ are not formed, as expected, with racemic

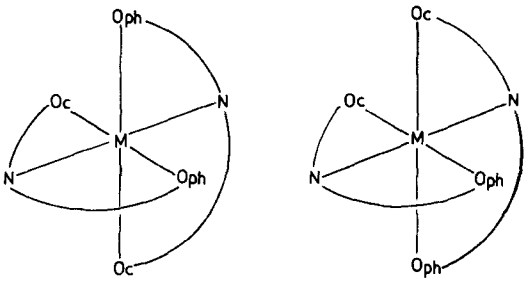


Chart 3. A B

Schiff bases with the same yield as *A*(*LL*) and *B*(*DD*) indicate that the formation of crystalline complexes is stereospecific. In [Ni(PL-glycine)$_2$] complex (Rao and Manohar 1983), only enantiomers *A* and *B* are present but not those arising from the chirality of the amino acid, as glycine is nonchiral.

[Ni(PL-*o*-phospho-DL-threonine) (H_2O)$_3$] (Aoki and Yamazaki 1980) is probably the only noncopper 1 : 1 transition metal pyridoxal-amino acid complex reported in the literature. For this complex, three octahedral coordination sites are occupied by the tridentate ligand and the remaining three by water molecules. The phosphate unit of the amino acid forms an intramolecular hydrogen bond with the axial water molecule.

Long *et al* (1980) reported a binuclear iron(III) complex, [Fe(N-(PL)$_2$ alanine) ClO_4]$_2$, with an unusual PL derivative. It is proposed that the ligand has resulted from the formation of Schiff base between PL and pyridoxamine and the subsequent nucleophilic attack of the Schiff-base imino group upon the α-keto carbon atom of pyruvic acid. In the dimer, two Fe(III) ions are bridged by two α-keto oxygens of pyruvic acid groups. Both Fe(III) ions have a highly distorted octahedral geometry with the other coordination sites of each ion being occupied by two phenolic oxygens, one carboxylate oxygen and one imine nitrogen.

3.3 *Reactivity*

It may be expected that the stereochemistry and ring strain of the Schiff base ligand could explain the rate and specificity of reactions, in particular, the lower and higher activities of the Ni(II) and Cu(II) chelates respectively. Mechanisms of pyridoxal-amino acid reactions postulated involve electron transfer via the extended π-orbital system. This requires the Schiff base ligand to be planar. However, it has been observed that in metal chelates the ligand itself is not planar and the distortion from planarity is mostly due to a rotation of carboxy group around the C(9)–C(10) bond (figure 2). This nonplanarity is more pronounced in Ni(II), Zn(II) and Mn(II) complexes than in Cu(II) chelates. For example, the dihedral angles between rings I and II and II and III (figure 3) are 4° and 0·7° respectively in [Cu(PLP-glycine) (H_2O)], whereas they are as high as 18·6° and 35.9° in [Ni(PL-glycine)$_2$] (Rao and Manohar 1983). These differences in ligand distortions may be attributed to the different metal-donor distances for different metals. Copper ion, having a mean metal-donor distance less than 2 Å

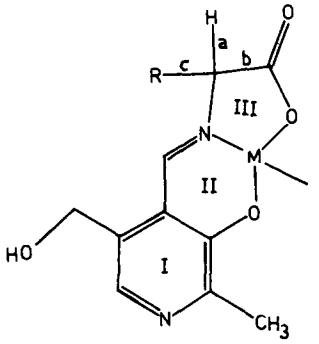


Figure 3. Metal-Schiff base complex showing the chelate rings and bonds around α-carbon atom.

occupies the center of a nearly planar tridentate ligand. The increased coordination bond lengths in the Mn(II), Ni(II) and Zn(II) complexes (2·00–2·15 Å) result in increased ring strain which determines the puckering of the chelated Schiff bases. Thus, the Schiff base ligated to the Cu(II) ion has the least distortion which is essential for facile electron transfer and this explains the higher activity of copper chelates.

The various reactions involving α-amino acids in model systems involve the formation of 1:1 and 2:1 aldimine complexes followed by the breaking of *a*, *b* or *c* bond in the condensed amino acid portion (figure 3). Dunathan's hypothesis (1966) states that the bond perpendicular to the extended π-system (which optimizes orbital interactions) is labilized most. Accordingly for [Ni(PL-*o*-phospho-DL-threonine)$(H_2O)_3$] and [Cu(PL-*o*-phospho-DL-threonine)], Aoki and Yamazaki (1980) considered the orientation of α-C-hydrogen atom and compared this to the relative activity. The α-C-hydrogen atom is positioned almost in the PL-aldimine plane, the torsion angles C(7)-N(2)-C(8)-H being 24° for the Ni complex and 33·5° for the Cu complex. This observation led them to rationalize that the Cu(II) ion under acidic conditions and the Ni(II) ion lack catalytic activity (for the β-elimination reaction).

Acknowledgement

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