$[Pt(NH_3)_2(pyrimidine)]X_n$ (where X = $CH_3CO_2^-$, Cl^-, etc.) are known to have the therapeutic activity against some cancers. Some Pt(IV) complexes like *cis*-$[Pt(NH_3)_2Cl_4]$, $[Pt(en)Cl_4]$ are also known to have the anticancer activity.

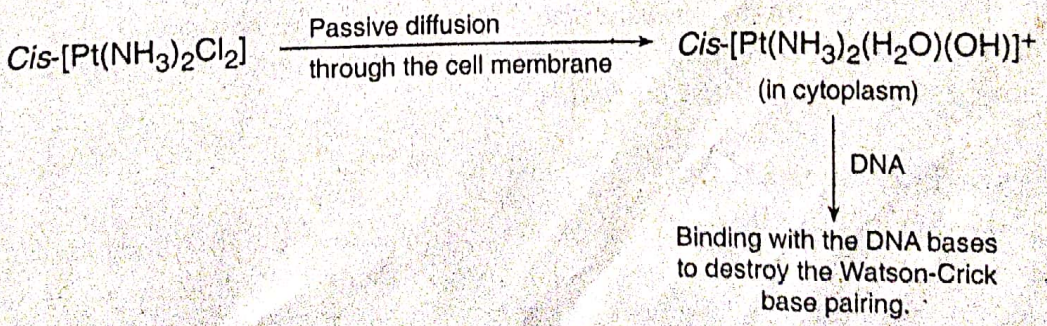
12.19.2 Toxic Effects of Anticancer Pt-Complexes

Platinum is not biologically involved and the living system does not have any efficient mechanism to cope with the toxic effects of Pt-complexes. Pt(II) being soft can interact like other heavy metals, with the soft and border line sites (*e.g.* —SH, $—NH_2$, etc.) of different enzymes. However, the toxicity (measured by LD_{50}) largely depends on the nature of amine and acido ligands present in the Pt(II) complex.

The major toxic effects of *cis*-platin and related compounds include *nephrotoxicity* (*i.e.* kidney damage probably due to inactivation of the enzymes through the binding with the —SH groups), vomiting, loss of appetite (*i.e. anorexia*), etc. However the nephrotoxicity can be largely mitigated by administering large quantities of water by intravenous injection to the patients together with an osmotic diuretic like D-mannitol. The *hydration therapy* can flush out the heavy metal complex to ameliorate the kidney toxicity. From the principle of HSAB theory, it is expected that the —SH groups of the enzymes can be protected by using some *competitive rescue agents* like diethyldithiocarbamate, etc. having soft sulfur sites. To manage the symptoms of nausea and vomiting, the antiemetic agents can be administered.

12.19.3 Mechanism of Anticancer Activity of *cis*-DDP

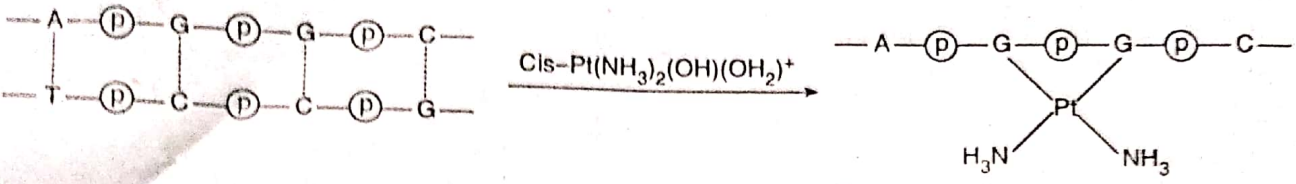
It is established that binding of *cis*-DDP, *i.e. cis*-platin, with the DNA bases destroys the double helix DNA structure. The main target is the DNA. The *cis*-platin, to interact with the DNA bases, should hydrolyse at the right place after the passive diffusion through the membrane. If it hydrolyses in the blood stream before it reaches the target site within the cells, it will react with the *nonspecific target* site available to it. The compound is both thermodynamically and kinetically stable with respect to hydrolysis in blood where the concentration of Cl^- is fairly high (*i.e.* 0.1 M). After entering through the cell membrane, it hydrolyses in cytoplasm where the concentration of Cl^- is very low (*ca.* 4 mM). The hydrolysed products are kinetically activated to interact with the DNA bases.



Scheme 12.9.3.1 : *Anticancer activity of cis-platin.*

Binding of *cis*-platin with the DNA bases can occur in three possible ways : *intrastrand linking* in which the platinum centre bridges the two adjacent guanine bases on a single DNA-chain; *interstrand cross-linking* in which the platinum centre bridges the DNA bases on the opposite strands of DNA; and a *bidentate chelation* by a single base like guanine. Among the purine bases, Pt(II) preferably binds with the N(7) of guanine; and among the pyrimidine bases, Pt(II) preferably

interacts with the N(3) of cytosine. The guanine base can also act as a bidentate ligand through the N(7) and the exocyclic O(6) sites. The *cis*-isomer can bind the groups about 300 pm apart (called *bite distance*). Among the different possibilities, *the major route involves the intrastrand linking* by two adjacent guanine bases from a single DNA chain. This mode of binding of *cis*-platin with the DNA strand can destroy the Watson-Crick base pairing mechanism of the DNA helix. This explains the anticancer activity of *cis*-platin. Destruction of Watson-Crick base pairing *by interstrand cross-linking is the minor route* (*ca.* 1% of total reaction).



Scheme 12.19.3.2 : *Intrastrand linking by* cis*-platin with DNA*
(G = guanine, C = cytosine, A = adenine, T = thymine, p = phosphate)

The intrastrand linking with the adjacent guanine bases sharply changes the angle between the planes of the base molecules formerly parallel planes. Thus the axis of the helix kinks by a large angle (40-60°, estimated) and this sharp *kink angle* essentially prevents (sterically) the *DNA polymerase enzyme*, which generally moves along a strand assembling its compliment (Sec. 6.14). The body's DNA repair mechanism is highly sophisticated. If this DNA repair mechanism can suitably '*program around the Pt-kink*', then the therapeutic activity of *cis*-platin will decrease. It is believed that the *cis-platin kink* in DNA effectively blocks the *DNA damage recognition protein* which is an important component of the overall DNA repair mechanism system.

DNA has been identified as the target of *cis*-platin drug and DNA–*cis*-platin interaction introduces a distortion in the double helix structure of DNA. Now, there have been some strong evidences that there are some cellular proteins that also bind specifically to the *cis*-platin–DNA adducts. Such proteins probably help the drug to show its cytotoxic effects.

Nature can develop resistance against the cis-platin drug. It is established that the *cis*-platin treated cells develop an increased concentration of —SH group containing species like glutathione (having —SH group) which is a tripeptide containing cysteine. These S-sites bind strongly with the Pt(II) centre to prevent the binding of DNA bases with the Pt(II)-centre. Moreover, *the DNA repair mechanism may increase its efficiency to eliminate Pt(II) from DNA to develop a resistance against cis-platin.*

12.19.4 Nonactivity of *trans*-DDP

The nonactivity of *trans*-DDP can be explained by considering the thermodynamic and kinetic properties of the complex. In the *cis*-complex, replacement of the Cl^- ions by chelation is thermodynamically favoured more than in the case of *trans*-complex where the *chelate effect* is not possible. The *trans*-isomer is *kinetically more labile* (*trans* effect) than the *cis*-isomer, and consequently the *trans*-isomer undergoes *rapid and nonspecific exchange reactions* with the different nucleophiles coming from different amino acid residues prior to binding with the DNA sites. It explains its toxicity. On the other hand, the *cis*-isomer being kinetically less labile does not experience any nonspecific substitution reaction before reaching the target. In fact, the corresponding Ni(II) and Pd(II) complexes are inactive because of their enhanced lability. The lability order is : Ni(II) >> Pd(II) >> Pt(II).

To explain the ineffectiveness of the *trans*-isomer, some explanations at the molecular level are available. The *trans*-isomer can bind with the groups about 450 pm apart and the groups approach from the *trans*-directions. In an intrastrand cross link formation, its geometry will not allow it to bind with the adjacent bases and at least one G-C pair will separate the binding sites. In such cases, the predicted *bend angle* is relatively small (~15°, estimated). In fact, if the Pt(II)-centre binds with a single base (as a monodentate one), practically no bending occurs and consequently DNA synthesis is not prevented. The *trans*-isomer cannot also effectively block the *DNA damage recognition protein*. Thus the DNA repair mechanism can effectively knock out the bound *trans*-isomer.

Here it is interesting to note that Au(III) (d^8 system) can form *isostructural complexes* with Pt(II), but the Au(III) complexes are not active as anticancer drugs. This arises due to the facts : *Au(III) is highly oxidising* to oxidise different biomolecules having —SH groups and other oxidisable functional groups; aqua complexes of Au(III) are *highly acidic*; Au(III) complexes readily respond to ligand substitution reactions; $Au(NH_3)_2X_2^+$ being charged faces an electrostatic barrier to enter into the cell and *cis*-$Au(NH_3)_2X_2^+$ is not characterised.

12.20 ANTICANCER ACTIVITY OF OTHER METAL COMPLEXES

Several metallocenes and their halides like $(C_5H_5)_2TiX_2$ (X = Cl, Br,), $(C_5H_5)_2MCl_2$ (M = V, Nb, Mo), $(C_5H_5)_2Fe^+$, etc. (Fig. 12.20.1) are found to show an anticancer activity against some types of experimental animal tumors. Some of these metallocenes, X_2Cp_2M ($Cp^- = C_5H_5^- = \eta^5$–cyclopentadienyl ion) have entered into the *Phase II clinical trial*. These are less toxic than the anticancer platinum complexes. In contrast to the Pt-complexes, the metallocene halides undergo hydrolysis rapidly to produce the oxo-bridged and aqua complexes which interact with the phosphate groups of DNA rather than with the DNA bases. However, softer metal centres like Mo in Cl_2Cp_2Mo may interact simultaneously with the heterocyclic nitrogen and phosphate group of DNA to inhibit the DNA synthesis. The actual mode of interaction of these metallocenes with the DNA is not yet clearly understood. It is believed that besides the covalent interaction, ferrocenium ion may noncovalently (*i.e.* intercalation, groove binding, *etc*, *cf*. Sec. 2.5) interact with the DNA to inhibit the DNA synthesis. Thus the mechanism of drug action of these compounds is different compared with that of Pt-complexes.

Several gold-phosphine complexes are known to have anticancer activity. The diphosphine bridged complex, $[ClAu(PPh_2CH_2CH_2PPh_2)AuCl]$ is an important example in this group. Different Sn(IV)-complexes having the general formula, $R_2L_2SnX_2$ (R = alkyl or phenyl; L_2 = py_2 or bipy or phen; X_2 = two *cis*-coordinated halides or pseudohalides acting as leaving groups) are quite active against different types of experimental tumors. Their mechanism of action is probably comparable with that of *cis*-platin.

$Ga(NO_3)_3$ shows activity against some types of cancer. Several ruthenium complexes like *cis*-$[RuCl_2(DMSO)_4]$, $[Ru(NH_3)_5(Asc)]^+$ (Asc = ascorbate dianion), *fac*-$[Ru(NH_3)_3Cl_3]$ are known to have anticancer activity due to binding with DNA. Some Rh(III) complexes like *trans*-$[RhL_4X_2]Y$ (L = py or substituted py), *trans*-$[RhL_2X_2]Y$ (L = bipy or phen or en), X = Cl, Br; Y = Cl, Br, NO_3, etc. are well known for their anticancer activity. The dimeric compound, $Rh_2(RCO_2)_4$ is also active against the mice tumors. The *bis*(thiosemicarbazone) complexes of Cu(II) show also anticancer activity. Fe(II) can potentiate the anticancer activity of bleomycin (an anticancer antibiotic).