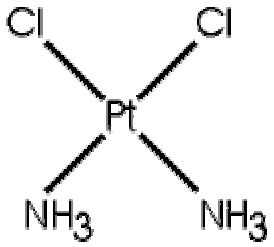
Platinum(II) Complexes & Cisplatin

Much of the current understanding of the unique properties of the current platinum drugs has come from studies with cisplatin. Several chemical requirements for the antitumor activity of platinum(II) complexes have since been established. These include the presence of either chloride, bromide, oxalate or malonate as leaving groups [a]. Complexes with more labile ligands, such as the nitrate ion, hydrolyse too rapidly to permit them to be useful *in vivo*, and other ligands, such as the cyanide ion, bind too tightly to platinum to be active. Only neutral platinum(II) complexes containing relatively inert carrier ligands, such as NH_3 groups are known to posses antitumour activity.



Cisplatin

Studies have shown that minor variations in the structure of these ligands can have a profound effect on the antitumour activity and toxicity of platinum complexes. Almost all trans-compounds tested are ineffective, while the cis-counterparts are quite the opposite. It appears that the cis-conformation is required for a complex to be an effective agent. Both cis- and trans- isomers exchange chloride ions for such nucleophilic groups as RS^-, $RSCH_3$, $R^1R^2R^3N$ and RNH_2 to form links that can be very stable.

The substitution of ligands of planar platinum(II) compounds, such as DDP ($[Pt(NH_3)_2Cl_2]$), may follow one of two pathways in aqueous solution. As shown on the right, a chloride ion may be replaced by water to produce a hydrated intermediate, the solvent molecule being subsequently eliminated by an incoming nucleophile. Alternatively, there may be direct replacement of the leaving group without the participation of the solvent. Since cisplatin is administered as an aqeuous solution, it is therefore, essential that ligand substitution be minimised before it reaches the tumour. This is achieved by using isotonic saline which has a relatively high chloride ion concentration, thus keeping the substitution equilibrium to the left:

$[Pt(NH_3)_2Cl_2] + 2H_2O$ <—> $[Pt(NH_3)_2(H_2O)_2]^{2+} + 2Cl^-$

This ensures that the "inactive" DDP complex will predominate, reducing the amount being converted to the "active" aqua form prior to administration. Once in the body, the high chloride ion concentrations present in blood plasma and extracellular fluid (>100mM), maintains the persistence of the electroneutral complex and prevents any premature activation or unwanted direct ligand

substitutions. Being uncharged, the molecule is able to cross cell membranes and thus into cancer cells. The relatively low chloride concentration of the cytosol (intracellular fluid), favours the formation of the active aquated species which goes onto to react with nucleophilic groups. Ligand replacement and chemical reactivity of both isomeric forms of DDP are very similar, however, biological activity is markedly different. The cis isomer has significant cytotoxic properties while the trans isomer does not. Clearly, this must be attributed to the difference in their conformation.

One of the most potent and widely used anticancer drugs in use today, cisplatin is a surprisingly simple and unique compound. It is unusual among modern pharmaceuticals in that it is an inorganic compound, possessing a metallic element whereas most drugs are purely organic such as paclitaxel (better known by its commercial name as taxol). Having been shown to possess antitumour activity since 1970, and used clinically for almost twenty years, cisplatin has picked up many names along the way. However, its formal name is *cis*-diamminedichloroplatinum(II), abbreviated to *cis*-DDP. This toxic substance exists simply as an electroneutral, four coordinate platinum complex. It has two chloride ion ligands situated adjacent to one another, and two remaining ammonia ligands likewise, in a square (tetragonal) planar structure.
The anticancer properties of cisplatin stem from the relative ease of substitution of the chlorine ligands with nucleophilic species like nucleic acid bases of a DNA strand. Before cisplatin binds to such nucleophiles, it is usually converted to the active form by aquation. Conversion occurs intracellularly as the lower chloride concentrations permit it. The resulting electrophile then goes onto bind to a variety of macromolecules displaying nucleophilic groups, which include DNA. It is now widely accepted that DNA is the primary target of cisplatin. This function is believed to be the largest contribution to its cytotoxicity.
On a simple level, cisplatin forms covalent bonds with nucleophilic sites on guanine present in all DNA. As cisplatin is a bifunctional agent, it is able to bind to two sites in a DNA strand. This results in the formation of inter- and intra-chain cross-linkings which interferes with cellular transcription and replication. Regulatory mechanisms detect the abnormal DNA and so activate a chain of responses to try and correct it. This, ultimately, causes cell death (apoptosis).
The success of cisplatin has been due to a large number of properties. [¤]
Cisplatin,

- Exhibits a wide spectrum of antitumour activity against drug-resistant as well as drug-sensitive tumours;
- Shows activity against slow-growing tumour as well as rapidly-growing tumours;
- Shows no strain or species specificity;
- Exhibits activity against viral-induced, chemical-induced, and transplantable tumours;
- Affects both solid and disseminated tumours.