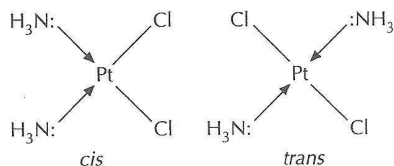




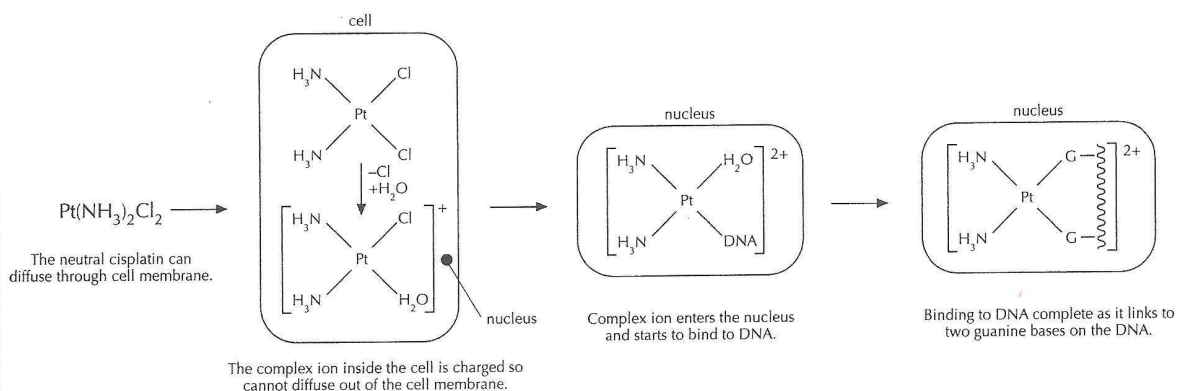
Importance of stereochemistry in drug design and action (1)

GEOMETRIC ISOMERISM

Geometric isomerism can exist in inorganic compounds as well as in organic compounds, e.g. the square planar compounds of diamminedichloroplatinum(II) can exist in both *cis*- and *trans*- forms.



The *cis*- form (known as cisplatin) is highly effective in the treatment of testicular and ovarian cancers as well as other forms of cancer. Transplatin is not an effective anti-cancer drug. Cisplatin has no overall charge so can diffuse through the cancer cell membrane. Inside the cell it exchanges a chloride ion for a molecule of water to form $[\text{Pt}(\text{NH}_3)_2\text{Cl}(\text{H}_2\text{O})]^+$. This complex ion enters the cell nucleus, where it binds to the DNA by exchanging another chloride ion to form $[\text{Pt}(\text{NH}_3)_2(\text{DNA})(\text{H}_2\text{O})]^{2+}$. This alters the cancer cell's DNA, so that when the cell tries to replicate it cannot be copied correctly and the cell dies.



CHIRALITY

Asymmetric or chiral carbon atoms form two different optically active forms. Because of their different stereochemistry the two enantiomers can behave in totally different ways in the body. It is now realized that one of the enantiomers of thalidomide gives the benefits associated with the drug and it is the other enantiomer that is thought to be responsible for causing the fetal deformities. When new drugs are synthesized nowadays the pharmacological activity of both forms is studied separately.

It can be difficult to prepare just one of the isomers and often a racemic mixture (50:50 mixture of both isomers) is prepared first and then separated. A new technique using **chiral auxiliaries** now makes it possible to synthesize just the desired isomer. Attaching an auxiliary, which is itself optically active, to the starting material creates the stereochemical conditions necessary for the reaction to form only one enantiomer. After the desired product has been formed the auxiliary is removed and recycled.

One drug for which this technique has been used to great effect is the anti-cancer drug taxol. Although it does occur naturally in yew trees the commercial semi-synthesis of taxol provides the necessary quantity to meet the demand.

Use of a chiral auxiliary

