

## Cisplatin and drug design

***Education in Chemistry***

September 2021

<https://rsc.li/36BWN2u>

**This resource reviews the action of cisplatin as an anticancer drug and explores the properties of transition metal complexes.**

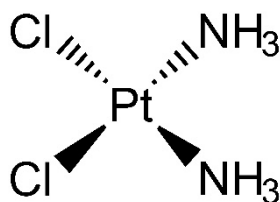
Part 1 – exploring the structure of cisplatin using transition metal chemistry.

Part 2 – exploring the mechanism of cisplatin as an anticancer drug.

Part 3 – exploring other drugs in the platin family.

## Part 1: exploring the structure of cisplatin

Cisplatin contains a central Pt ion with four ligands. The two chloride ligands can undergo ligand substitution to allow cisplatin to bind to a guanine base on DNA. This property is fundamental to the mechanism of its function as an anticancer drug.



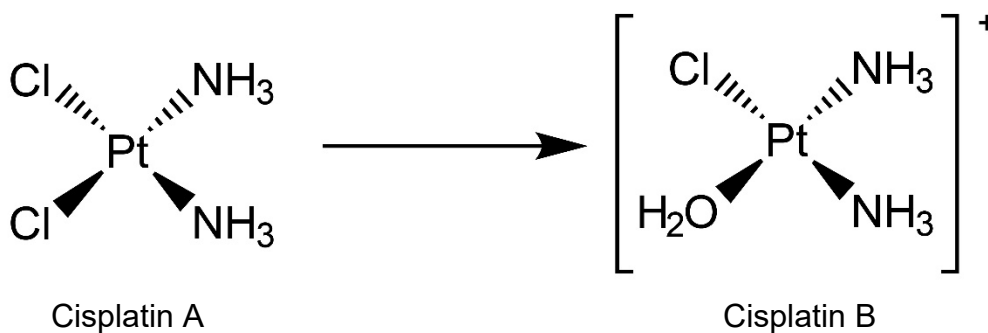
1. Cisplatin fact file. Fill in the boxes.

Central metal ion	
Coordination number	
Shape	
Ligands present	
Angle	
Overall charge of complex ion	

2. Why is cisplatin a neutral complex ion?
3. What property do both the Cl<sup>-</sup> ion and the N in the NH<sub>3</sub> have that enables them to bond to the central Pt ion?
4. Explain how the Cl<sup>-</sup> ion and NH<sub>3</sub> act as a ligand.

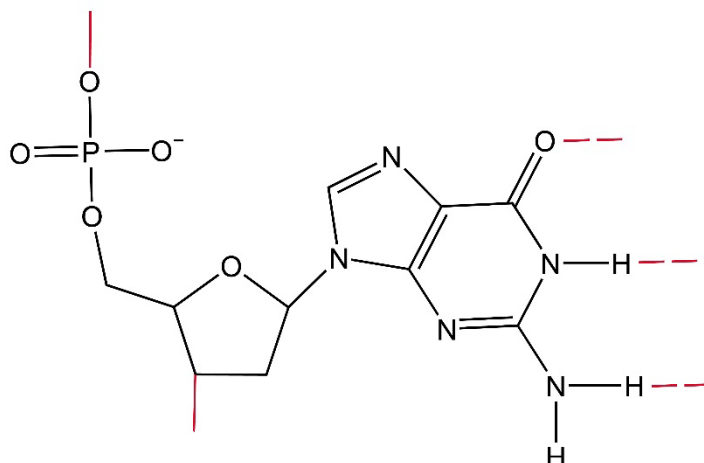
## Part 2: exploring the mechanism of cisplatin as an anticancer drug

1. When cisplatin is absorbed into the human body, it undergoes a ligand substitution reaction. A chloride ligand can be substituted for a water molecule.



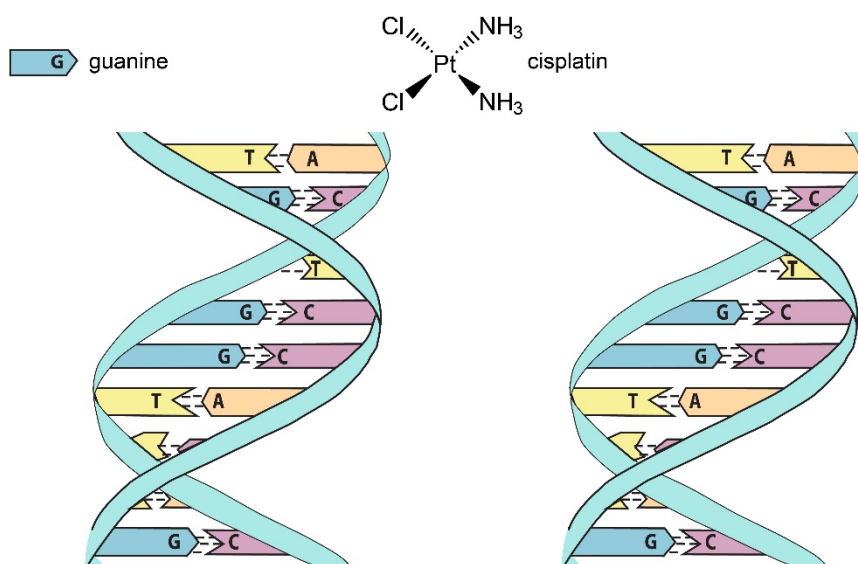
- a) Write a chemical equation to show this reaction.
- b) Why does the exchange of a chloride ligand for water change the charge on the complex ion?

- c) The diagram below shows a nucleotide with a guanine base. Circle two atoms on the guanine that



cisplatin could bind to.

- d) Explain two possible ways that cisplatin B can bind to the guanine, using either the chloride ligand or the water ligand.
- Chloride
  - Water
2. There are two possible ways that cisplatin can bind to a DNA molecule, either to two different guanines on the same strand (intrastrand) or two different guanines on different strands (interstrand).
- a) Using the simplified DNA below, show two possible ways that cisplatin can bind by ligand substitution to a guanine base.

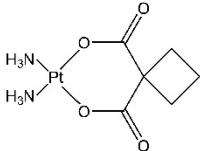
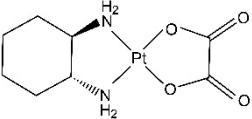
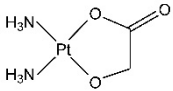
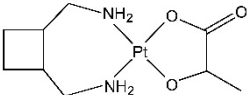
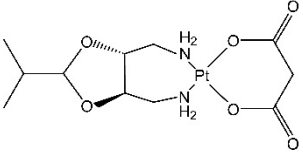
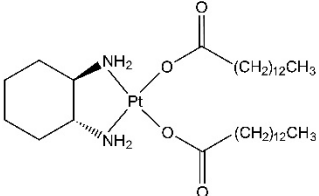


- b) Transplatin is a geometric stereoisomer of cisplatin and does not work as an anticancer drug. Explain why.
- c) Draw transplatin.

### Part 3: exploring other drugs in the platinum family

To find new drugs, chemists can take an existing drug and use computing iterations to find many different versions but with just a small change each time. These similar compounds could potentially have therapeutic effects using the same mechanism as the original and may have less side effects or, in the case of platins, kill different types of tumours.

- Other platinum molecules have also been shown to be successful as anticancer drugs. For each of the compounds below decide:
  - Which ligands, or ligand, will be substituted when binding to the guanine base and circle it.
  - If the ligand is monodentate (in which case there will be two ligands) or bidentate (two attachment points, in which case there will be only one ligand) and draw it showing the lone pair/s.

Compound	a) Circle the ligand(s) that will be substituted for the N of guanine	b) Draw the substituted ligand showing the lone pair/s
Carboplatin		
Oxaliplatin		
Nedaplatin		
Lobaplatin		
Heptaplatin		
Miriplatin		

2. Ligands have an order of stability. The more stable ligand will readily substitute the less stable one.



Using  $\text{NH}_3$  to represent the N on guanine:

- a) Identify one ligand that would not enable the cisplatin to bind to the N of guanine on DNA if it was present instead of the  $\text{Cl}^-$ .
  - b) Identify one ligand, if present instead of  $\text{Cl}^-$  on the cisplatin would still enable it to bind to the N of guanine on DNA.
3. All these drugs are toxic to humans because they are non-specific and will also prevent healthy cells from replicating. What precautions are taken by doctors to minimise this problem?
4. Side effects for a person on chemotherapy include feeling extreme tiredness and commonly their hair falls out. Using your knowledge of how platin drugs work, explain why a person might get these side effects.