Oxford Cambridge and RSA

Tuesday 13 October 2020 – Morning

A Level Chemistry B (Salters)

H433/02 Scientific literacy in chemistry Advanced

Notice Article

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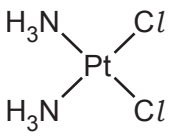
Platinum metal complexes in medicine

Adapted from an article in Chemistry World, 13 MARCH 2018, by Joseph Clarke.

The history of the surprisingly simple metal complex that is still the gold – or should that be platinum? – standard in cancer drugs.

This is the story of cisplatin, from the accidental discovery of its anti-tumour properties in 1965 to the related generations of platinum-based derivatives. It tells how one simple metal complex revolutionised the treatment of cancer in the latter half of the 20th century.

The original: Cisplatin



Cisplatin is an example of a metal complex. The name combines its stereoisomeric geometry, *cis*-, and the platinum metal at the heart of the complex, *-platin*. Its formula is cis-$PtCl_2(NH_3)_2$, with the platinum metal centre bonded to four ligands: two ammonia (NH_3) and two chloride (Cl^-) groups. What makes cisplatin special is the platinum metal, which enforces the adoption of a square planar geometry, meaning all four ligands are in the same plane as the metal centre. There are two possible stereoisomers that a $PtCl_2(NH_3)_2$ complex can adopt, cis and trans, which differ according to the geometric arrangement of the four ligands. Later investigations would show that the cis configuration is essential for the anti-tumour activity.

Cisplatin dates back to 1845, when it was originally known as Peyrone's chloride. The discovery of its anti-tumour properties was one of the greatest accidental discoveries in modern science.
In the early 1960s, physicist-turned-biologist Barnett Rosenberg at Michigan State University hypothesised that applied electric or magnetic fields might affect cell division. He tested the effect of an electric field on the growth of Escherichia coli bacteria. Luckily for him – and humanity – he used platinum electrodes. After turning on the field, Rosenberg noticed something odd about the bacteria. They were around 300 times longer than expected. The bacteria elongation was found to be caused, not by the presence of the field, but by the presence of two platinum-based complexes which had prevented bacterial cell division. One of which later became known as cisplatin.

Barnett Rosenberg and his colleagues showed for the first time that platinum-containing drugs disrupted cell division and could possibly be used in the treatment of certain types of cancer. If cisplatin inhibited cell division seen in the bacteria, would it have a similar effect on tumour cells? Rosenberg set about testing his hypothesis. Results published in Nature in 1969 showed that cisplatin caused marked tumour regression in mice. The first steps towards an effective metal-based treatment for cancer had begun.

The story of cisplatin continued through the 1970s, with the drug entering clinical trials in 1971 before being made commercially available in 1978. As with any pharmaceutical discovery, shortcomings had to be addressed relating to how the drug was administered, but this was a major advance in a field that saw survival rates of many cancers increase. Typically prescribed for ovarian, lung and stomach cancer, it was actually in the treatment of testicular cancer that survival rates saw the largest improvement, from 10% to upwards of 85%. Cisplatin is still used, both as an anti-cancer treatment, and as the 'gold standard' of cancer drugs against which all newly proposed drugs are measured.
The advent of more powerful research-enabling technologies and the scientific community's increased knowledge of cellular processes have resulted in refined understanding of the mechanisms behind cisplatin's anti-tumour properties. Following an intravenous injection of cisplatin – which is the only way to administer the treatment – cisplatin is transported around the body in its neutral, relatively unreactive form.

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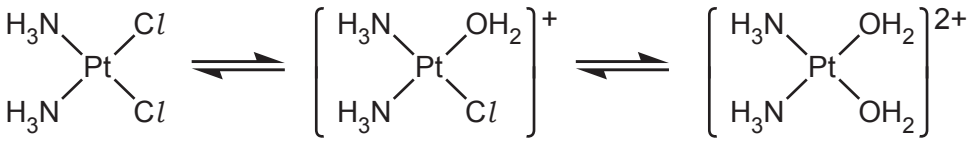
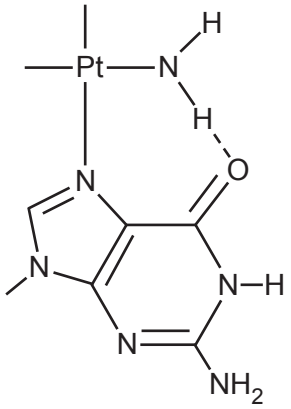
For cisplatin to be reactive, it first must be activated. Following entry into a cell, this is achieved through water replacing its chloride ligands.



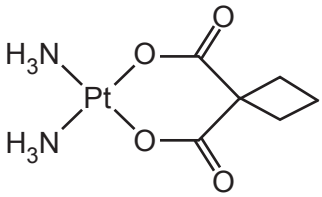
The complex becomes positively charged, which facilitates the interaction with the negatively charged DNA backbone. This leads to covalent binding with specific sites on the DNA base pairs through an exchange of the weakly bound water ligands. There are several possible methods of binding, forming complexes known as cisplatin–DNA adducts that distort the helical structure. It is this irreversible binding to DNA that is thought to disrupt the normally routine DNA repair and cell division cycle, leading to controlled cell death, known as apoptosis.

The diagram shows a possible way in which a compound derived from cisplatin is thought to attach to a base in DNA.

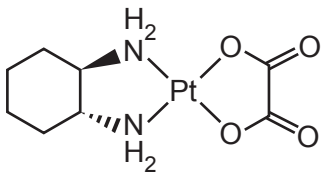


Side-effects and the second-generation platinum drugs.
Cisplatin is not a flawless medication. Early in clinical trials, side-effects became apparent. The most major of these was the toxicity, particularly damaging to the kidneys, gastrointestinal tract and nervous system. The cause is the indiscriminate nature in which cisplatin, and other platinum-based cancer treatments, target all cells, healthy and tumorous. Other problems with the administration of the drug meant that alternative cisplatin derivatives were sought.

The square-planar properties responsible for the directed DNA binding meant platinum metal complexes remained attractive. The task was to find a complex either as active as cisplatin while eliminating the most serious side-effects, or that had increased potency – a drug's effectiveness – allowing for a lower dose administration, effectively reducing the severity of the side-effects.
The second generation of platinum drugs, below, offered improved side-effects over cisplatin.



carboplatin



oxaliplatin

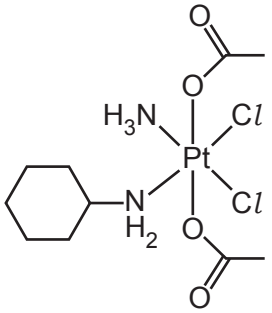
Thus began the renaissance of inorganic chemistry and decades of academic-industrial research in metallic chemistry. Multiple analogues of cisplatin were tested, whereby the ligands were altered and tested. The most successful of these was carboplatin, which gained FDA (Food and Drugs Administration) approval in 1989. Carboplatin offered a dramatic reduction in toxicity, but at a reduced activity.

Oxaliplatin was approved by the FDA in 2004. However, it is an inconvenient part of drug development that most platinum complexes screened end up not being developed.

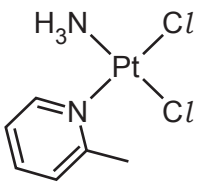
Resistance and the third generation of platinum drugs.
Following the development of carboplatin and its commercial availability, researchers' attention shifted to types of cancer that weren't so responsive to cisplatin. In addition, certain cancers that had previously been treated by cisplatin had developed cisplatin-resistance and the tumours had recurred. The search now began to identify a new platinum complex that could treat such cancers. Thus began the third generation of cisplatin drugs.

There are three major mechanisms by which a cell can be resistant to cisplatin. First, the mode of entry of cisplatin into a cell can be prevented or slowed. Alternatively, the modes of cell exit are accelerated, removing cisplatin before it can interact with a cell's DNA. Finally, the cancer cells themselves can evolve to improve the methods of DNA repair, meaning damage caused by cisplatin is repaired and cell apoptosis is not triggered. Owing to the similar mechanism of DNA binding between cisplatin and the second-generation platinum metal complexes, cell lines resistant to cisplatin were also resistant to drugs such as carboplatin. Thus, a platinum-based complex was sought with a different structure that would be active in cisplatin-resistant cells.

Two such third generation of platinum drugs that showed activity in cisplatin-resistant cells are known as satraplatin and picoplatin.



satraplatin



picoplatin

Satraplatin, with ethanoate ligands, was originally developed as an orally administered drug, more desirable than the intravenous injection necessary for cisplatin and carboplatin. More importantly, during clinical trials satraplatin was found to remain active in cells that had developed cisplatin-resistance. Satraplatin never made it to market, with the FDA putting its approval process on hold in 2007.
Picoplatin was the final platinum metal complex developed. It also showed activity in cisplatin-resistant cancers due to the steric bulk of an alternative nitrogen-based ligand. However, despite promising clinical trials, the drug never became commercially available.

The new renaissance of pharmaceutical research.
Platinum metal complexes were revolutionary innovations for an era when cancer research was in its early days. Cisplatin and its metal complex derivatives are still essential therapies to this day, being offered to patients around the world.

Other therapies will eventually surpass cisplatin as cancer treatment, because of their better targeting capabilities showing reduced side-effects, due to their increased specificity towards cancer cells. Innovative treatments such as antibody drug conjugates that deliver a cytotoxic treatment directly to a targeted cell and light-focused treatments involving bursts of directed lasers are some of the potential next-generation anti-cancer therapies. Shifting away from indiscriminately cytotoxic small-molecule treatments will reduce side effects benefitting the patient and may relegate cisplatin and its analogues to the past. But we should never forget the impact this one simple metal complex has had on modern medicine.

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