Metallodrugs

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Activating Platinum Anticancer Complexes with Visible Light**

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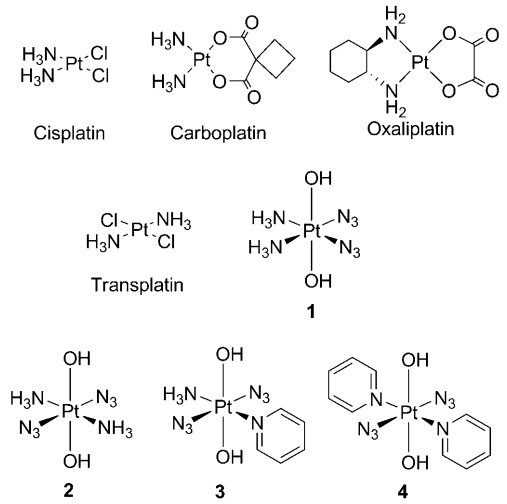
The platinum anticancer drugs cisplatin, carboplatin, and oxaliplatin are currently very successful in the clinic: they are used to treat 40–80% of all cancer patients. The sales of



oxaliplatin alone are expected to reach US$3 billion in total within the next 2 years. Despite this success, there are good reasons to attempt to improve their design. These existing platinum drugs are not active against all types of cancer, they can have adverse side effects, and resistance to therapy can develop. If relatively nontoxic platinum complexes could be designed that could be selectively activated in tumor cells, they might find widespread use in the clinic. The report by Sadler and co-workers[1] of complexes with these characteristics is therefore notable.

Cisplatin kills cells by binding to GG sequences in DNA, kinking the DNA, and triggering apoptosis. Carboplatin and oxaliplatin can form similar lesions, except that the latter has a 1,2-diaminocyclohexane ligand in place of two NH_3 ligands. This different ligand arrangement distorts the DNA structure differently and affects recognition by mismatch-repair and damage-recognition proteins.[2] The type of nitrogen ligand on Pt can therefore affect the activity of the complex.

Platinum(IV) complexes are known to be less reactive and less toxic than Pt^{II} complexes, so Sadler and co-workers based their design on Pt^{IV} prodrugs. To enable light activation, they incorporated azido ligands so as to introduce intense ligand-to-metal charge-transfer absorption bands. Early attempts by Bednarski and co-workers[3] to achieve this aim by using iodido ligands were promising but resulted in complexes which reacted too readily with glutathione (GSH), the abundant intracellular reducing agent, and so were not dark-stable. The *cis*-diazido Pt^{IV} complex **1** is dark-stable and forms Pt^{II}–GG cross-links similar to cisplatin on DNA, but only when irradiated with light by a mechanism involving electron transfer from N_3^- to Pt^{IV} and the formation of N_2. If **1** is merely a prodrug for cisplatin, then the *trans* complex **2** might be expected to be inactive, as is transplatin itself. However, this is not the case. When irradiated with UVA light **2** is as active as cisplatin under conditions which might be used for photochemotherapy (short treatment and irradiation times of less than 1 h). Moreover, when the geometry is changed from *cis* to *trans*, the ligand-to-metal charge-transfer (LMCT) band is shifted to a longer wavelength.[4] Short-wavelength UVA light (365 nm) penetrates tissues to a depth of approximately 1 mm and could be useful for surface cancers, such as bladder and oesophageal cancer, but visible light penetrates more deeply (e.g. green to 3 mm and red to 5 mm).

In fact, although *trans*-diamine complexes were not thought to be active on account of the inactivity of transplatin, in the last few years many active *trans* complexes have been discovered by the research groups of Farrell, Natile, Navarro-Ranninger, Gibson, and others.[5] Indeed, *trans*-[$PtCl_2$((*E*)-imino ether)$_2$] complexes can be more active than their *cis* isomers, and *trans*-diamine complexes can have quite different properties to those of *cis* complexes. For example, complexes such as *trans*-[Pt(acetate)$_2$(pyridine)$_2$] are relatively inert towards hydrolysis and yet cytotoxic to cisplatin- and oxaliplatin-resistant cancer cells.[6]

The potency of **2** as a photoactivated agent can be greatly increased by replacing one of the NH_3 ligands with pyridine: complex **3** attacks DNA rapidly and causes lesions which are different from those caused by cisplatin, and more difficult to

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repair.[7] Although promising, **3** was only active against cancer cells when UVA radiation was used, and not longer-wavelength visible light. The introduction of a second pyridine ligand to give the all-*trans* complex **4** has now produced the required breakthrough. Complex **4** can be activated in cells by UVA, blue, and green light, and is potently phototoxic at low light doses towards a number of human cancer cell lines, including parental (A2780) and cisplatin-resistant (A2780CIS) ovarian carcinoma, oesophageal adenocarcinoma (OE19), and hepatoma (HepG2) cells. Oesophageal cancer (eighth highest in incidence and increasing in Western populations), for example, might be a good candidate for such photochemotherapy.

It will now be interesting to determine whether these diazido complexes are active in vivo. The necessary experiments will be challenging, since drug administration and distribution must be synchronized with irradiation.

Interestingly, Sadler and co-workers have made use of the quadrupolar nucleus ^{14}N to explore the photodecomposition pathways of these diazido complexes by NMR spectroscopy. Depending on the conditions, they observed N_2 formation, azide release, and Pt^{II} products. More commonly for Pt amine anticancer complexes, ^{15}N NMR spectroscopy, with $I = 1/2$ for ^{15}N, is used.[8] However, with no coupled protons, it is very difficult to observe ^{15}N peaks for azido ligands. Photoactivation may give rise to some unusual reactive intermediates which attack biomolecules in cells. For example, in the presence of thioethers, nitrenes can be trapped.[9]

DFT calculations also provide insight into the photodecomposition pathways.[1] Singlet and triplet excited states have dissociative character, with an elongation of bonds to both ammine and pyridine ligands in the triplet excited state. Importantly, the calculations suggest the presence of weak absorption bands in the visible region of the spectrum of **4**. Perhaps this characteristic explains how activation with visible light can occur beyond the tail of the major UV LMCT band.

Not only does platinum hold promise for photochemotherapy, but a range of other transition-metal complexes, including polyazaaromatic Ru^{II} and polypyridyl Rh^{III} complexes that can oxidize DNA when excited, are being explored in various laboratories.[10a] Interestingly, like **4**, methylated derivatives of *cis*-$[Rh(phen)_2Cl_2]Cl$ (phen = 1,10-phenanthroline) can be activated by photoexcitation at wavelengths at which there is no apparent absorption (> 500 nm) as a result of the direct population of weakly absorbing triplet metal-centered (^{3}MC) states.[10b] Some complexes can cause DNA cleavage through the production of reactive oxygen species, such as $^1O_2$ and hydroxyl radicals. A potential advantage of complex **4** is that its mechanism of action does not appear to require O_2, which can be relatively deficient in tumor tissues.

Overcoming cisplatin resistance is an important goal. The recent introduction by Farrell and co-workers of multinuclear Pt complexes that can form new types of cross-links on DNA may provide another promising approach.[11] Apart from the use of directed light, there are other ways of trying to improve the delivery and targeting of Pt drugs. For example, Lippard and co-workers have used single-walled carbon nanotubes labeled with folate as a homing device bound to Pt^{IV}, which is subsequently reduced (by GSH) to active Pt^{II} in the cell, as well as platinum(IV)-encapsulated prostate-specific membrane antigen (PSMA) targeted nanoparticles.[12]

In three years' time, none of the three current major platinum anticancer drugs, cisplatin, carboplatin, or oxaliplatin, will be patent-protected worldwide. The time is therefore ripe for novel platinum therapies to emerge: perhaps photoactivated platinum could be one of them.

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