Conference paper

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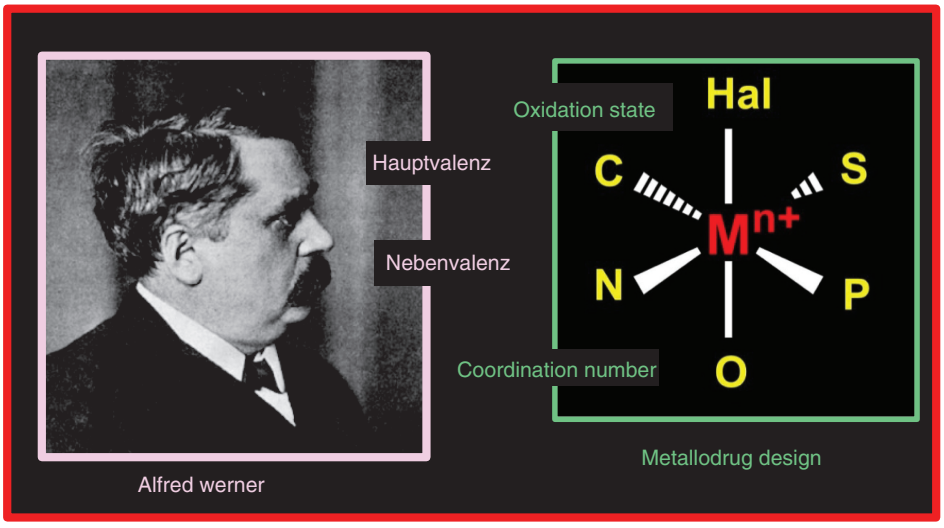
100 years of metal coordination chemistry: from Alfred Werner to anticancer metallodrugs



Abstract: Alfred Werner was awarded the Nobel Prize in Chemistry just over 100 years ago. We recall briefly the era in which he was working, his co-workers, and the equipment he used in his laboratories. His ideas were ground breaking: not only does a metal ion have a primary valency ("hauptvalenz", now the oxidation state), but also a secondary valency, the coordination number ("nebenvalenz"). At that time some refused to accept this idea, but he realised that his new thinking would open up new areas of research. Indeed it did. We illustrate this for the emerging field of medicinal metal coordination chemistry, the design of metal-based therapeutic and diagnostic agents. The biological activity of metal complexes depends intimately not only on the metal and its oxidation state, but also on the type and number of coordinated ligands, and the coordination geometry. This provides a rich platform in pharmacological space for structural and electronic diversity. It is necessary to control both the thermodynamics (strengths of metal-ligand bonds) and kinetics of ligand substitution reactions to provide complexes with defined mechanisms of action. Outer-sphere interactions can also play a major role in target recognition. Our current interest is focussed especially on relatively inert metal complexes which were very familiar to Werner (Ru^{II}, Os^{II}, Rh^{III}, Ir^{III}, Pt^{II}, Pt^{IV}).

Keywords: Alfred Werner, bioinorganic chemistry, coordination chemistry, IUPAC Congress-44, medicinal chemistry; metal complexes.

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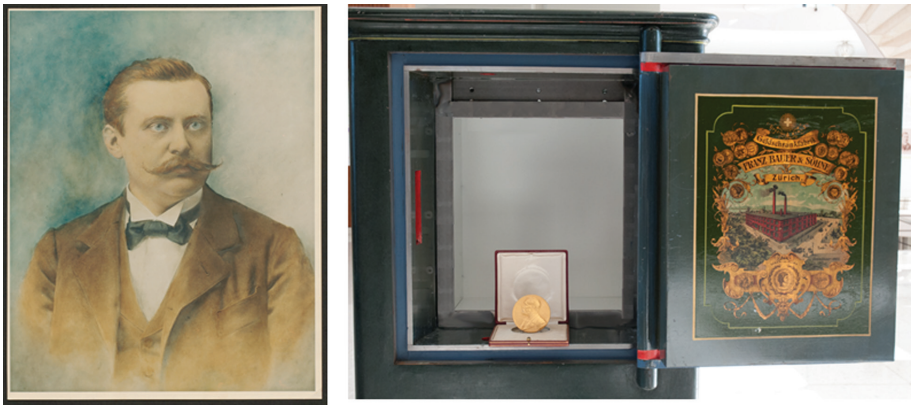

Fig. 1 Alfred Werner and his Nobel Prize medal. Acknowledgement: Nachlass Alfred Werner, Zentralbibliothek der Universität Zürich.

Introduction

Alfred Werner (1866–1919) was a child of the Industrial Revolution. His scientific heritage helped to shape Chemistry as we know it today [1, 2], not only because he was awarded in 1913 the Nobel Prize in Chemistry (Fig. 1) "*in recognition of his work on the linkage of atoms in molecules by which he has thrown new light on earlier investigations and opened up new fields of research especially in inorganic chemistry*", but also because – as pointed out in 1966 by Leopold Horner *"making full use of his ideas will be a task for generations*."

The First Industrial Revolution from about 1760 to around 1840, a period of transition to new manufacturing processes, evolved into the Second Industrial Revolution in the transition years between 1840 and 1870 with the large scale manufacture of machine tools and use of machinery in steam-powered factories. It was in the 1820s that Justus Freiherr von Liebig established the world's first major School of Chemistry (at the University of Giessen, Germany) and initiated the chemical fertiliser industry.

This time of dramatic evolution has led to the World as we know it today, a world in which Technology and Science not only accompany us, but inspire and drive the scientific progress and social evolution of Humankind. It is clear that the Industrial Revolution, as previously the Renaissance period, has deeply changed our perception of the world and of our own identity. This industrial golden age was accompanied and supported by great minds in a range of artistic, philosophical, and scientific domains. Such a relationship between an

Fig. 2 Alfred Werner and his research group in 1911. Acknowledgement: Nachlass Alfred Werner, Zentralbibliothek der Universität Zürich.

age of progress and the emergence of intellectual leaders can create a dynamic environment and a blast of creation that lasts for centuries.

Beyond this scientific inheritance, Alfred Werner's personality also reflects the societal challenges which accompanied the transitional and (R)evolutionary time. For instance, the picture of Alfred Werner and co-workers in 1911 shown in Fig. 2 strikingly highlights one of the current societal challenges in modern science, namely that of enhancing the role of women in science (three women out of 17 people can be seen on this picture). Very unusually at the beginning of the 20th century, Werner's research group was not only international, one of the reasons for the success of the best research groups in our current time, but was also marked by its high proportion of women students. Alfred Werner supervised 230 doctoral students, 22 women among them. Today at our own institution, The University of Warwick, for example, about one-third of our PhD students are women. Interestingly, 1911 is also the year when Marie Curie won the Nobel Prize in Chemistry (after having shared the 1903 Nobel Prize in Physics with her husband). The greatness of scientific research such as that of Werner relies not only on his/her brightness, intellectual vision and capability for innovation (Fig. 3), but also on the ability of society to allow and enhance such greatness. There is no doubt that Alfred Werner is a typical example and a direct product from the golden age that was the end of the 19th and beginning of the 20th century, a golden age that he also helped to build, and which has had a major impact, producing many benefits we share today.

In this article, we focus on the impact of Werner's ideas and discoveries in metal coordination chemistry on modern medicinal inorganic chemistry. This review does not aim to be comprehensive and is restricted largely to examples of precious metal coordination complexes (Pt, Ru, Os and Ir). We attempt to illustrate how vibrant the field of medicinal inorganic chemistry is, and to relate recent fundamental advances to the pioneering work of Alfred Werner.

Medicinal inorganic chemistry in a nutshell

Metal ions possess inherent properties such as preferred oxidation states and ligand geometries, but the overall reactivity of a metal complex also depends on the types and number of ligands and on the environment. Such variety and complexity makes inorganic chemistry an inexhaustible source of reactions that provide not only a huge reservoir (library, Fig. 4) of molecules and complex-ions, but also presents a number of challenges to be overcome. Reduction and oxidation of the metal ion, or the bound ligands, ligand substitution, and (covalent and non-covalent) reactions of the ligands at sites remote from the metal, are all potential reactions that may induce changes in the chemical and physical properties of metal complexes. Figure 5 lists some features of metals and metal complexes that can be used in the design of such compounds for controlling their reactivity and tuning their properties.

Alfred Werner's contribution to the elucidation of the features shown in Fig. 5 was essential. The modern IUPAC definition of valence is for instance is very similar to Werner's definition of *Hauptvalenz*:

> "*The maximum number of univalent atoms (originally hydrogen or chlorine atoms) that may combine with an atom of the element under consideration, or with a fragment, or for which an atom of this element can be substituted*" (http://goldbook.iupac.org/V06588.html).

Fig. 3 Some of the vessels (including platinum crucibles) used for synthesis in Werner's laboratory. We thank Professor Roger Alberto for his assistance with this photograph.

Fig. 4 Some of the transition metal complexes synthesis by Werner and his co-workers. Their beautiful colours have long since made them attractive for study and are often useful for characterisation, including identification of coordination geometries, and distinction between isomers. Acknowledgement: Nachlass Alfred Werner, Zentralbibliothek der Universität Zürich.

The introduction by Werner of *Nebenvalenz* introduced the concept of coordination number and spatial arrangement of the ligands for a given metal centre. By extending isomer-counting methods [3] and by postulating that the *Nebenvalenz* is directed towards fixed positions in space, in the same way as the four valences of carbon are orientated in a tetrahedral geometry, Werner confirmed both the hexagonal planar structure of benzene and the octahedral geometry of the six ligands in six-coordinate cobalt(III) complexes.

The pioneering work by Alfred Werner on the structure of metal complexes has provided a basis for inorganic chemists to understand that metallodrugs can provide unique mechanisms of drug action based on the choice of the metal, its oxidation state, the types and number of coordinated ligands and the coordination geometry. We have recently surveyed [4] metal compounds, metal-chelating agents (metalloenzyme inhibitors) or other agents which interfere with metabolic pathways, including metal complexes currently undergoing clinical trials both for therapy and diagnosis. Moreover, inorganic medicinal chemistry can make use of both non-essential as well as essential elements for the design of drugs and diagnostic agents (Fig. 6).

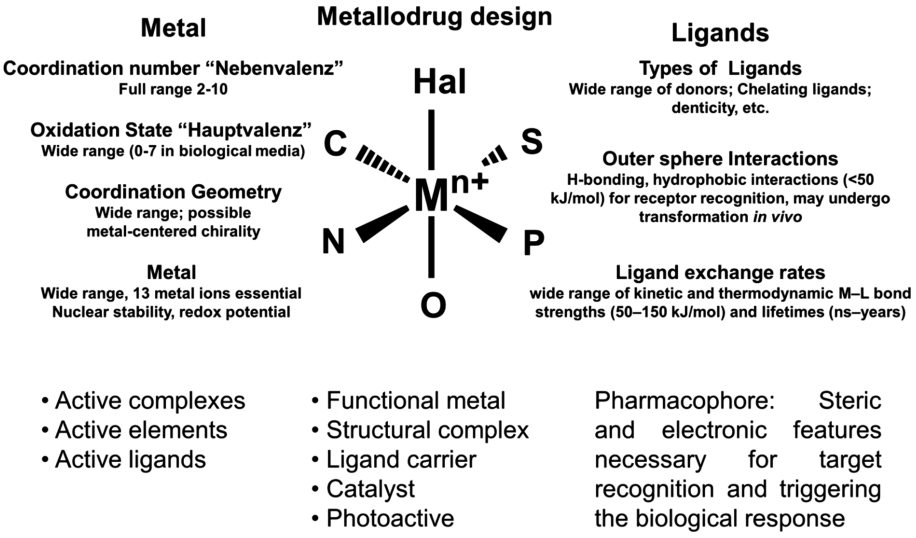

Fig. 5 A metal coordination complex and some of the features which can be used in the design of metallodrugs (and diagnostic agents).

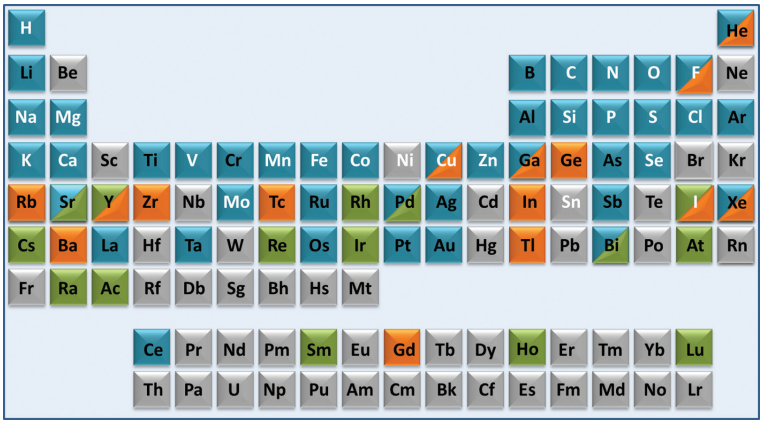

Fig. 6 A medical periodic table showing essential elements for man (symbols in white font), medical radioisotopes (green fill), and elements currently used in therapy (blue fill) or diagnosis (orange fill). There are other ways to colour-code the entries but for simplicity we have used only 2 fill colours per element which are therefore illustrative and not comprehensive. Colours mainly highlight elements/compounds which are clinically approved or on current clinical trials (e.g., as listed on http://www.clinicaltrials.gov/). Some entries for implants are included (e.g., Ti, Ta). Reproduced with permission from reference [4] (Copyright 2013, Royal Society of Chemistry Publishing).

Medicinal inorganic chemistry has been stimulated recently in particular by the success of platinum anticancer drugs (used as a component of nearly 50% of all cancer chemotherapy treatments), by the use of gadolinium(III) complexes as MRI contrast agents (about 20 million doses administered per year), and of the radionuclide 99m-technetium radiopharmaceuticals for γ-ray imaging (used in about 20 million radiodiagnostic procedures each year). However, the involvement of metals in many other diseases and conditions is of current interest in relation to their causes, their treatment or detection, including neurodegeneration, microbial and parasitic (and other neglected tropical diseases) infections and inflammation [5–8]. In the following sections, we will restrict the discussion to examples of precious metal anticancer drug candidates based on Pt, Ru, Os, and Ir.

Platinum complexes

Alfred Werner devoted specific effort to investigations of the chemistry of platinum complexes and published 14 papers on this topic between 1896 and 1920 [9–22]. However, his interest in platinum(II) and platinum(IV) complexes spans more work than these 14 specific articles, and can be dated back to 1893 and publication of the first article on his co-ordination theory "Beitrag zur Konstitution anorganischer Verbindungen" [23]. Alfred Werner's research on the platinum metals was comprehensively reviewed by George B. Kauffman in 1997 [24]. A particularly essential piece of research from Werner in the context of this review on bioinorganic chemistry is the disproof of the Blomstrand-Jøsrgensen chain theory for formulation of the isomers *cis*- and *trans*-$[PtCl_2(NH_3)_2]$. *Cis*-$[PtCl_2(NH_3)_2]$ was first described by Michele Peyrone in 1844 (Peyrone's salt) [25]. Peyrone prepared the compound soon after moving to Liebig's laboratory at the University of Giessen from Dumas' laboratory in Paris. Peyrone was later to become an ardent defender of Liebig's belief that plants can absorb ammonia and other nutrients from the soil that led to the concept of fertilisers and a revolution in agricultural practices.

In 1893, Werner claimed that the four ligands in the cisplatin and transplatin molecules, at that time known as platosemidiammine and platosammine chlorides, respectively, are directly bound to the metal which adopts square-planar configurations rather than polymeric-type chain structures [23]. The isomerism [which results in powders of different colours – yellow (*cis*) and white (*trans)*] was assumed by Werner to be due to the *cis* and *trans* positions of the ammonia and chlorido ligands. This assumption of square-planar arrangements B_2C_2 of molecules and ions around a central atom was not only a breakthrough in the

comprehension of the geometry and structure of inorganic compounds and formation of isomers, but has also allowed advances in understanding the reactivity of such complexes. For instance, based on the square-planar geometry, Werner was able to explain the reactivity of the ammonia complexes with pyridine, and the formation of the *cis*- and *trans*-$[Pt(NH_3)_2(pyridine)_2]Cl_2$ [23]. Such an innovative concept was subsequently supported experimentally by conductivity measurements of *cis*- and *trans*-$[PtCl_2(NH_3)_2]$, carried out in collaboration with his former student Arturo Miolati [26].

The discovery of the antiproliferative property of cisplatin by Rosenberg, Van Camp, and Kigras in 1965 [27] led to the clinical success of this compound as an anticancer drug. Following this success, more than 4000 platinum compounds have been tested as potential anticancer drugs, leading to the worldwide approval for use in the clinic of two other platinum(II) complexes – carboplatin and oxaliplatin approved by the FDA in 1989 and 2002, respectively. Carboplatin and oxaliplatin are both 'blockbuster' drugs (http://www.businessdictionary.com/definition/blockbuster-drug.html) that generated $128 M and $1862 M of annual sales in 2011 (http://www.evaluategroup.com/View/437--1003-modData/generic_name/carboplatin). A schematic representation of the effect and resistance mechanisms for platinum in cells is shown in Fig. 7.

A striking feature of the scheme in Fig. 7 is the number of cancer cell resistance mechanisms towards platinum complexes that have been identified, including reduced uptake or increased efflux, complexation to sulfur ligands such as metallothionein or glutathione, or excision of Pt from DNA and repair of the damage. Side-effects may also accompany the treatment of cancer with platinum(II) complexes. Hence there is a need to design alternative metal-based anticancer drugs which can overcome the problems of resistance and side effects.

In his paper published in 1893 [23], Werner also argued that platinum(IV) complexes have an octahedral configuration. Octahedral low-spin $5d^6$ Pt^{IV} complexes are well known to be relatively inert towards ligand substitution, but can be activated chemically by reduction [28–30]. They are less susceptible to substitution reactions than square-planar platinum(II) complexes and so as drugs are likely to undergo fewer reactions en route to the tumour. This may result in fewer undesired side-effects and reduced drug loss due to deactivation compared to platinum(II) complexes. Another advantage of Pt^{IV} complexes is often their higher aqueous solubility [31]. Hence, Pt^{IV} complexes have potential advantages over Pt^{II} as anticancer prodrugs [32–35], although reliance on activation by reduction may mean that their activity is less predictable since this will depend on the natural abundance and local concentrations of reductants such as thiols (e.g., glutathione) and ascorbate. In general, tumours are relatively hypoxic and provide a reductive microenvironment which may allow for the selective activation of metal pro-drugs such as those containing Pt^{IV} [36, 37].

The inertness of Pt^{IV} has recently been exploited in our laboratory for the development photo-activated chemotherapeutic agents. In 2003, we developed a general method for the photoactivation of Pt^{IV}-diazido complexes containing a variety of monodentate and chelated diamine ligands that allows the site-specific delivery of a wide range of Pt^{II}-diamine drugs, and thus the possibility of a strong reduction of the unwanted

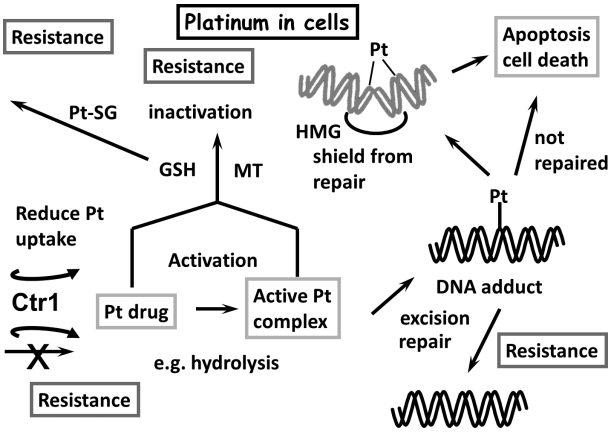

Fig. 7 A schematic representation of cellular processes involving the anticancer drug cisplatin, including resistance mechanisms cells which can make the drug ineffective.

side-effects often associated with platinum chemotherapy [38]. This proof-of-concept work was followed by a number of reports highlighting the promise of this strategy. For instance, the complex *trans, trans, trans*-$[Pt(N_3)_2(OH)_2(NH_3)(pyridine)]$ contains an octahedral Pt^{IV} centre with almost linear azido ligands, and is remarkably stable in the dark and in the presence of millimolar concentrations of glutathione. The complex readily undergoes photoinduced ligand substitution and photoreduction reactions. Its photoactivation in cells results in high toxicity (13–80 × more cytotoxic than cisplatin, and *ca.* 15 × more cytotoxic towards cisplatin-resistant human ovarian cancer cells) [39]. It is notable that this is a *trans* diam(m)ine Pt^{II} complex and that *trans* diam(m)ine Pt^{II} complexes were long thought to be inactive as anticancer agents since early studies demonstrated the inactivity of transplatin, *trans*-$[PtCl_2(NH_3)_2]$. Since then, some examples of active *trans* diam(m)ine Pt^{II} complexes have been reported [40–44].

In 2009, the photocytotoxicity of a series of anticancer *trans*-dihydroxido $[Pt(N_3)_2(OH)_2(NH_3)(X)]$ (X = alkyl or aryl amine) platinum(IV) diazido complexes was examined and the influence of *cis-trans* isomerism investigated. This study showed that *trans* isomers of complexes containing aliphatic or aromatic amines are more photocytotoxic than their *cis* isomers [45]. The following year, the novel platinum(IV) diazido complex *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(pyridine)_2]$ was synthesised. It is stable in aqueous solution and also towards glutathione (GSH, the tripeptide γ-*L*-Glu-*L*-Cys-Gly, a reductant that protects cells from reactive oxygen species (ROS), and plays a major role in intracellular drug metabolism, especially in detoxification and deactivation of platinum anticancer drugs [46]). This bis-pyridine complex can be photoactivated with low doses, not only of UVA, but also of visible blue and green light to give potent antiproliferative activity, and exhibits strong cytotoxic effects in a number of cell lines at micromolar doses [47]. Figure 8 illustrates the dramatic increases in activity towards ketatinocytes and ovarian cancer cells on changing the geometry of the amine ligands from *cis* to *trans* and the ammonia ligands to pyridines. Figure 8 also illustrates the greatly enhanced potency of the photoactivated Pt^{IV} complexes compared to cisplatin used under the same conditions (short cell treatment time of about 1 hour, and low irradiation dose – typical of procedures which might be used in the clinic).

The unusual photobiological properties of photoactivatable Pt^{IV} diazido complexes have been further investigated. They can kill human cancer cells by an apoptosis-independent mechanism [48]. Rapid photoreduction (UVA/blue) without amine loss, absence of cross-resistance to cisplatin, potency in ovarian cancer cells and oesophageal cells both *in vitro* and in a xenograft cancer model [48], and strong DNA interactions (e.g., mono- and bi-functional DNA lesions, preference for G and C, large DNA unwinding angles, high percentage of interstrand cross links) have been demonstrated [49]. The influence of the *N*-donor monodentate

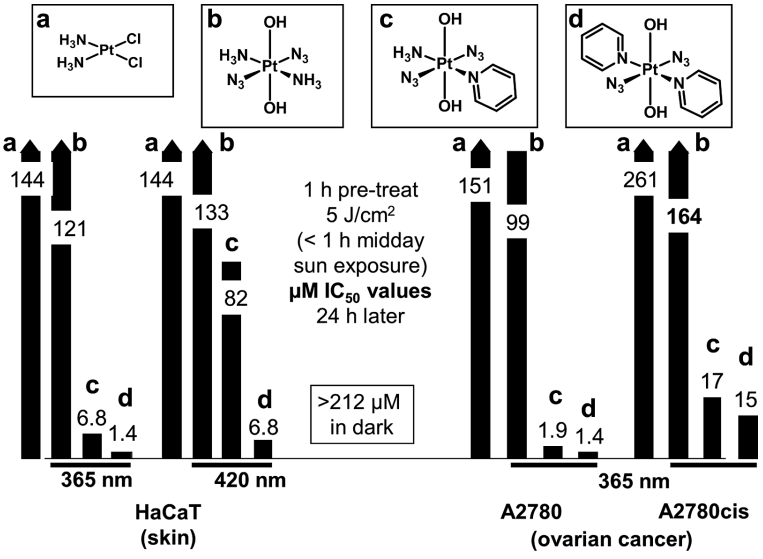

Fig. 8 Photoactivation of platinum(IV) complexes and comparison of their cytotoxic effects with cisplatin. The enhanced effect on photocytoxicity of introducing pyridine ligands is evident.

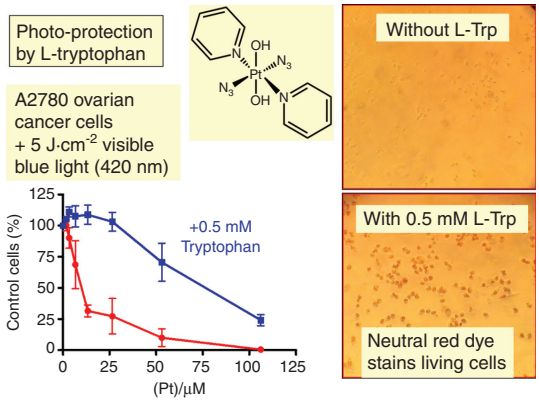

Fig. 9 Photo-protection of Pt^{IV} prodrug photo-irradiated living cells by addition of L-tryptophan. Adapted from ref. [51].

ligand L (pyridine *vs.* piperidine) on the chemical, DNA binding and cytotoxic properties of light activated *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(NH_3)(L)]$ was also investigated. The nature of the heterocyclic nitrogen ligand, its basicity and lipophilicity, have a subtle influence on both the phototoxicity and photobiochemistry of this class of photo-chemotherapeutic agents.

Recently, combined theoretical and computational molecular modeling and extensive experimental studies have been used to study possible DNA distortions induced by the major photoproduct of the platinum(IV) prodrug *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(pyridine)_2]$ as an interstrand cross-link of *trans*-$\{Pt(pyridine)_2\}^{2+}$ to guanine N7 positions on each DNA strand [50]. Such cross-links offer possibilities for specific protein–DNA interactions and suggest possible mechanisms to explain the high potency of this photoactivated complex.

Photoactivation of *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(pyridine)_2]$ can lead to the generation of azidyl radicals which can be trapped by the spin-trap DMPO and detected by electron paramagnetic resonance (EPR) [51]. The photocytotoxicity of *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(pyridine)_2]$ can be modulated by low doses (500 μM) of the amino acid *L*-tryptophan that can quench azidyl radicals. This opens up new perspectives for controlling the activity of photo-chemotherapeutic azido Pt^{IV} drugs. The photo-protection by *L*-Trp of photo-irradiated cells is shown in Fig. 9. This study also suggests that the high potency of such photoactive platinum complexes may arise from their dual attack on cancer cells by radicals and Pt^{II} photoproducts.

Ruthenium, osmium, and iridium complexes

Despite the clinical success of platinum(II) metallodrugs and the clinical potential of platinum(IV) drug candidates, their limitations have led to intense research on metallodrugs containing other metals. Among them, ruthenium and osmium compounds are promising. Ruthenium complexes have raised considerable expectations for the treatment of cancer since the beginning of the 1990s [52, 53]. Today, two ruthenium(III)-based anticancer drugs have successfully completed phase I clinical trials [54, 55]: imidazolium-*trans*-dimethylsulfoxide-imidazole-tetrachloridoruthenate (NAMI-A) and imidazolium-*trans*-bis(1H-indazole)-tetrachloridoruthenate (KP1019). Organometallic arene Ru^{II} complexes such as $[(\eta^6\text{-biphenyl})Ru(en)Cl]^+$ (en = ethylenediamine) [52] (**11**) and $[(\eta^6\text{-}p\text{-cymene})Ru(PTA)Cl_2]$ [56] (*p*-cymene = *para*-cymene and PTA = 1,3,5-triaza-7-phosphaadamantane) (**12**) have also been widely studied, and several others also show promise [57–76]. Recently, different groups have investigated the chemical and biological activity of analogous half-sandwich arene osmium complexes [77–85]. Osmium, the heavier congener of ruthenium and a third row transition metal, commonly exhibits slower kinetics than ruthenium, and is often considered to be relatively inert. However, it is apparent that it is possible to tune the biochemical reactivity of arene osmium(II) complexes through understanding their aqueous solution chemistry [86, 87].

Different mechanisms of action have been investigated for explaining the anticancer activity of arene ruthenium complexes. Among these, interactions between complexes containing reactive Ru-Cl bonds and nuclear DNA can occur, through their hydrolysis and the formation of intermediary aqua complexes able to ruthenate DNA specifically at guanine residues [88, 89]. Interestingly, the first article written by Werner on ruthenium complexes was part of his series "Zur Theorie der Hydrolyse" published in 1907 [15], and reported the behaviour of a bound hydroxido group. Thirteen years later, Werner published his second and last article about ruthenium complexes on the synthesis of hydroxonitrosylbis(ethylenediamine)ruthenium(III) compounds (general formula $[Ru(OH)NO(en)_2]X_2$, X being an halide and en = ethylenediamine) [22]. Interestingly, almost 80 years later, ethylenediamine arene ruthenium complexes have been shown to be a promising class of organometallic ruthenium anticancer drug candidates. A number of studies have demonstrated the *in vitro* and *in vivo* antitumoural activity of this type of complexes [90, 91]. Based on these promising results, we explored structurally related organometallics, particularly those containing phenylazopyridine ligands [92]. These complexes are of particular interest due to their synthetic versatility: modification of the phenylazopyridine ligand, arene, and the halide, all induce dramatic antitumoural modifications [93]. Figure 10 shows the impact of such chemical modifications on the antiproliferative activity of osmium(II) azopyridine arene complexes [81, 94].

Remarkably, the dimethylamino-phenylazopyridine osmium derivative is 10× more active than cisplatin in human ovarian cancer cells, and also shows high (nanomolar) potency in a wide range of cancer cell lines, as demonstrated with both a US National Cancer Institute (NCI) 60 human tumour cell line anticancer drug screen (NCI60), and an *in vivo* therapeutic study, showing reduction in colorectal tumour volume and low general toxicity (little body weight loss) for this compound [95].

Promising also as anticancer agents are organometallic half-sandwich 'piano-stool' Ir^{III} complexes [96]. Somewhat surprisingly, low-spin $5d^6$ Ir^{III} complexes can be quite labile and readily exchange ligands. Ir^{III} is not readily stabilised by arenes but is stabilised by cyclopentadienyl ligands, and especially by pentamethylcyclopentadienyl. Some complexes of these cyclopentadienyl complexes can accept hydride from coenzyme nicotinamide adenine dinucleotide (NADH) [97], and offer the possibility of killing cancer cells by redox modulation reactions. The prospect of these complexes acting as catalytic drugs in cells is an intruiging one [94].

Finally, we note that Werner's coordination theory was able to account for the chirality of metal complexes (Fig. 11) such as *cis*-$[Co(en)_2(NH_3)_2]$, which he resolved using (+)-bromocamphorsulfonate as a counterion [98].

Half-sandwich organometallic complexes can also be chiral, for example when the legs of the piano stool are non-equivalent ligands. Chirality can have a major influence on biological activity since many biological target sites are themselves chiral (DNA, proteins). We have resolved the enantiomers of the chiral iodide *p*-cymene Os^{II} iminopyridine complexes shown in Fig. 12 which contain chiral Os and chiral C centres [99].

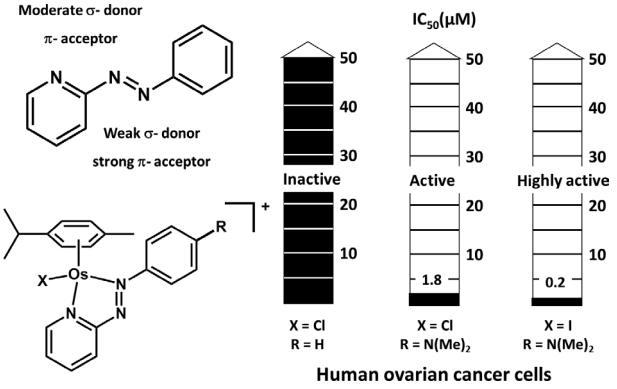

Fig. 10 Effect of the halido ligand and phenyl substituent on the activity of Os(II) phenylazopyridine arene complexes towards A2780 human ovarian cancer cells.

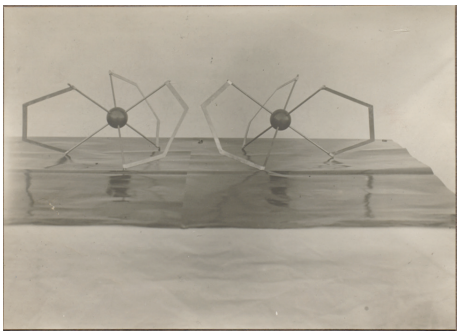

Fig. 11 Werner realised that *tris*-chelation of an octahedral metal ion by three bidentate ligands creates a chiral complex. His models show the mirror images. Acknowledgement: Nachlass Alfred Werner, Zentralbibliothek der Universität Zürich.

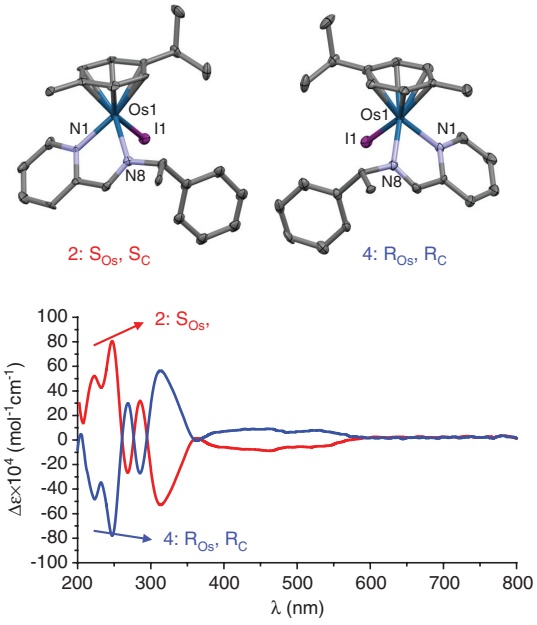

Fig. 12 X-ray crystal structures of enantiomeric *p*-cymene Os^{II} iminopyridine complexes and their CD spectra. Adapted from ref [99].

Interestingly, in this case the enantiomers showed little difference in their average IC_{50} values (7.6 μM for R_{Os},R_C and 9.6 μM for S_{Os},S_C) towards the 60 cancer cell lines in the NCI panel, consistent perhaps with a redox mechanism of action.

Conclusions

Alfred Werner's work on metal coordination complexes stemmed from his ability to visualise their structures in 3 dimensions. The practical demonstrations by him and his research group of the existence of both a primary valence (hauptvalenz, oxidation state), and a secondary valence (nebenvalenz, coordination number) of a metal ion were remarkable achievements considering the very limited range of analytical techniques which they had available. They were especially skilled in synthesis, crystallisation and observation (for example of the colours of complexes). Similar to the Impressionists who, for the first time in painting history, took their canvases outside of their workshops and painted landscapes, thus opening-up new artistic movements at the end of the 19th century, the work of Alfred Werner and other outstanding contemporary sci-

entists was born from the foundations of the Industrial Revolution, and has since fed the entire science of the 20th and early 21st centuries. Werner had the foresight (in his Nobel speech) to realise that his introduction of these new concepts in coordination chemistry would provide long-lasting "opportunities for the investigation of new fields in inorganic chemistry, which are promising".

We have tried to illustrate here with a few examples that this is the case for the field of medicinal inorganic chemistry, and in particular the design of precious metal complexes as anticancer drugs. The examples are taken largely from work carried out in our own laboratory but several recent reviews are available which cover the wider field, including the biochemistry of gold [100, 101], platinum [102–105], and other inorganic and organometallic complexes [55, 62, 74–76, 106–112], along with in-depth surveys of their potential mechanisms of action [100, 113–122].

The rich structural diversity of metal coordination complexes certainly presents an attractive platform for drug design. For example, an octahedral complex with six different ligands has 15 enantiomeric pairs. The significance of dynamic processes which metal complexes can undergo might have not been fully appreciated by Werner. He worked largely with relatively inert complexes that retained their ligands during purification processes, including many octahedral d^3 (e.g., Cr^{III}) and low-spin d^6 metal ions (e.g., Co^{III}, Rh^{III}, Ir^{III}, Pt^{IV}). However, it has become apparent in the last 40 years or so that even these metal ions can be rendered labile by the appropriate choice of ligands, especially carbon ligands such as arenes and cyclopentadienyls in organometallic complexes. The challenge for medicinal coordination chemistry is then to control ligand substitutions processes so that the active form of the metal complex (the pharmacophore – the metal ion plus ligands) reaches and attacks the target site.

The existence of Werner's coordination sphere therefore creates not only valuable pharmacological diversity, but also the problem of speciation as a result of ligand substitution (and perhaps redox reactions) in media where many other potential ligands are present. A major challenge now facing us is that of identifying species formed by metallodrugs in biological media, including cells and tissues. This is a very difficult task for which new methods are urgently needed.

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