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"Medicinal Applications of Coordination Chemistry"

BY CHRIS J. JONES (University of Birmingham and The University of Manchester, U.K.) AND JOHN R. THORNBACK (MassTag Technologies Ltd., U.K.), Royal Society of Chemistry, Cambridge, U.K., 2007, *xii* + 354 pages, ISBN 978-0-85404-596-9, £89.95, U.S.$169.00

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Inorganic compounds have been used in medicine for thousands of years, often without a known molecular basis for their mechanism of action, and with little attempt to design them. The design of coordination (metal) complexes is not an easy task. The organic chemist often deals with diamagnetic compounds which are both kinetically and thermodynamically stable, and benefits from the use of well developed speciation techniques, especially ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. For metal compounds the situation is more complicated. Ligand substitution and redox reactions can be facile, can occur over very wide timescales, and are not so easily followed by conventional techniques, especially under physiologically relevant conditions (for instance, at micromolar concentrations). But the challenge is real and worth exploring. We need new drugs with novel mechanisms of action. Inorganic chemistry offers that possibility.

Platinum Anticancer Drugs

Two areas of work have highlighted the potential of inorganic chemistry in recent years: the platinum anticancer field and gadolinium compounds, used as contrast agents in magnetic resonance imaging (MRI). Both of these are well covered in this new book. Platinum commands about forty pages. This is warranted. Platinum compounds are now the world's best-selling anticancer drugs – they have billion-dollar sales each year. If you are not familiar with atomic structure, types of chemical bonds, oxidation states, coordination geometries, isomerism, electronic structure and magnetism, then there are some one hundred pages (just over a quarter of the book) of introduction to help you, including the background on square-planar platinum complexes needed to understand the mechanism of action of the first platinum complex to be approved for clinical use: cisplatin (*cis*-diamminedichloroplatinum(II)).

The section on platinum, like the others, is in general well illustrated with line diagrams of chemical structures, and gives a good coverage of new developments, such as active *trans* complexes and potent di- and tri-Pt anticancer complexes, such as BBR3464. Not quite so good are some of the (grayscale) views of structures of DNA, proteins and their adducts, e.g. Figures 10 and 11 in Chapter 4. There is an omission concerning an intriguing feature of the structure of the adduct between guanine-guanine platinated DNA and the protein HMG1A, which is the intercalation of a protein phenylalanine side chain between the platinated guanine bases on DNA. Such an adduct probably plays a crucial role in the mechanism of action of cisplatin. But this feature is not shown in the picture on page 254; Figure 1 of this review shows an alternative view (1).

Diagnostic Imaging

It is a tribute to clever coordination chemistry that gram quantities of potentially toxic gadolinium ions can be safely injected into a patient undergoing an MRI scan, in fact into millions of patients each year. The Gd^{3+} ion binds strongly to multidentate chelated ligands, while still having sufficient room in its coordination sphere to bind and relax water. Much elegant research is being undertaken to optimise this effect: investigating the choice of the ligand donors, the size of the

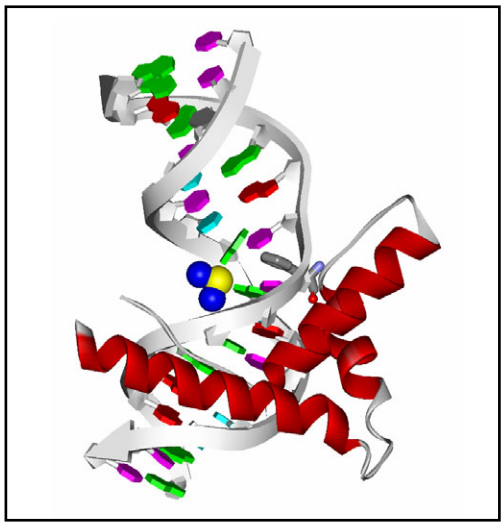

Fig. 1 The insertion (intercalation) of phenylalanine-37 side-chain (grey) from the HMG protein into the hydrophobic lesion on DNA created by a cisplatin intrastrand crosslink between two adjacent guanine bases (based on the Protein Data Bank (PDB) entry 1ckt (1)). Colour key: Yellow = platinum; Dark blue = N of NH_3; Red helices = HMG protein; DNA bases: Green = guanine, G; Purple = cytosine, C; Red = adenine, A; Cyan = thymine, T

complex, control of rotation, water exchange rates, targeting and so on. These features are well described in thirty pages of Chapter 3, which also deals with radiopharmaceuticals, another area of much commercial interest. Much attention is deservedly focused on ^{99m}Tc, the short-lived (6 h half-life) technetium isotope-of-choice for many diagnostic imaging procedures, with its wide range of oxidation states and potential for being targeted with the right choice of ligands.

Other Metals

Coverage of other precious metals includes gold, ruthenium (currently two complexes in clinical anticancer trials), palladium (much more kinetically labile than platinum, currently the subject of research) and rhodium (anticancer potential). Surprisingly, silver is not dealt with, even though it is a very effective antibacterial agent. Washing machines containing slow-release silver are even being sold these days, to sterilise clothes as you wash them (see Samsung's SilverCare Washing Machine!). Gold drugs have been used for the treatment of difficult cases of rheumatoid arthritis for over seventy years: gold is transported by albumin in the blood by binding to the thiol at cysteine-34. This is depicted in Figure 18 on page 288, but in fact the thiol group is partially buried in a crevice and not totally exposed on the surface of the protein as the figure suggests.

Other topics covered include chelation therapy (for iron in thalassaemia, copper in Wilson's disease), vanadium as an insulin mimetic and superoxide dismutase mimics. A final chapter on design emphasises the need to control both the thermodynamics and kinetics of the reactions of metal complexes in biological (physiological) systems, in order to make real progress in this field. I missed bismuth (antiulcer drugs), antimony (antiparasitic) and arsenic (mentioned in passing, now a first-line treatment for certain types of leukaemia). Three elements with poor NMR nuclei! Missing too, except as a passing mention, is lithium for treatment of bipolar disorder (taken by more than 1 in every 1000 of the U.K. population).

Concluding Remarks

It is fortunate that the authors included a disclaimer on page *vii* that their information must not be relied upon to guide clinical decisions, since it says on page 11 that Phase I clinical trials involve 'healthy volunteers'. This is not usually the case with anticancer drugs, many of which are known to be cytotoxic. For these, Phase I (which is mainly concerned with establishing a safe dose for administration) involves patients who have not responded to other treatments.

This book will serve a useful role in teaching inorganic chemistry to both undergraduate and postgraduate students. The topic helps to 'bring inorganic chemistry to life', and in my experience does arouse their curiosity at all levels. It will be a useful addition to libraries, or if you shop around on the web, perhaps affordable for your own personal bookshelves.

Reference

1 U.-M. Ohndorf, M. A. Rould, Q. He, C. O. Pabo and S. J. Lippard, *Nature*, 1999, **399**, (6737), 708