Bioinorganic Chemistry: a personal perspective*

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Bioinorganic Chemistry is an interdisciplinary field of science which draws on the strengths of the disciplines of Inorganic Chemistry and Biological Sciences and requires the application of advanced physical and theoretical methodologies. The articles in this special volume illustrate the state of knowledge in five topics, each of considerable current interest and development: oxomolybdenum and oxotungsten enzymes; small molecule activation by metalloproteins; biomineralisation; mixed-valence metal clusters in biology; and metals in medicine.

This special volume of *Dalton Transactions* is comprised of the presentations given at the Dalton Discussion No. 2. This meeting follows the successful inaugural Dalton Discussion meeting on the theme of 'Clusters', held at Southampton University, 3rd–5th January 1996.[1] The format for these meetings involves a series of keynote lectures, presented by leading scientists of international standing, plus a larger number of other speakers, invited to deliver a short lecture based on an article submitted prior to the meeting. All presenters are required to produce a contribution to *Dalton Transactions,* which is refereed in the manner and to the standards normally required by the journal. These articles are made available to all participants prior to the meeting. The subsequent publication serves as a permanent record of the meeting and a valuable reference source on the particular topics covered. The nature of Dalton Discussions is still evolving but it is already clear that they will become important events in the scientific calendar of the Royal Society of Chemistry and will lead to influential issues of *Dalton Transactions*.

Bioinorganic Chemistry is experiencing rapid and sustainable development with many fundamental academic challenges and strategically important problems being addressed. The field derives considerable stimulus from the synergy arising from the interdisciplinary approach to the search for new knowledge which draws on the expertise available from the Chemical and Biological Sciences and uses the power of advanced physical and theoretical methodologies. The resolution available from structural methods, particularly state-of-the-art protein crystallography and NMR techniques allows the structure and function of biological systems to be clearly elucidated in chemical terms. Also, a detailed understanding of a biological system and the identification of its unique features require complementary information from relevant chemical systems. Furthermore, an important practical consideration is that the spectroscopic techniques used to probe metal centres in biological systems need to be calibrated by parallel investigations of well defined and relevant chemical analogues.

Dalton Discussion No. 2 was organised along the lines of its predecessor. Five themes were chosen from the many possible within Bioinorganic Chemistry and, for each, two keynote speakers were selected on the basis of the significant contributions they and their research group have made to advance the state of knowledge of the particular topic. The themes and keynote lecturers were:

Oxomolybdenum and oxotungsten enzymes – D. C. Rees and E. I. Stiefel
Small molecule activation by metalloproteins – A. M. Valentine and L. Que Jr.
Biomineralisation – G. A. Ozin and S. Mann
Mixed-valence clusters in biology – D. Gatteschi and G. Blondin
Metals in medicine – J. Reedijk and B. Lippert

Eight of these keynote lectures are reported as Perspectives, one as a Paper and the other as a Communication; the shorter presentations are reported as 18 Papers and one Communication. An especially pleasing aspect of the meeting was the relatively large number of presentations given by younger scientists. The meeting received further and significant impetus from some 48 poster contributions which gave an excellent focus for extensive informal discussions.

Each of the sessions was chaired by one (or in one case two) authorities in the field who ensured that a lively and focused discussion followed each of the presentations with contributions from the 135 participants drawn from 14 different countries. The key elements of the discussions are reported herein in the format adopted for the first Dalton Discussion meeting.[1] The task of providing a detailed overview, reporting all of the views and comments expressed during the meeting, as a supplement to this excellent collection of articles, is not feasible without significantly delaying the publication time of this issue. Therefore, what follows is a personal perspective on each of the five themes, concentrating on important issues which emerged during the meeting.

Oxomolybdenum and Oxotungsten Enzymes

D. C. Rees presented an excellent review of his important protein crystallographic contributions[2] which, together with other such structural studies, have transformed the status of this topic. In particular, the results of this research have conclusively defined the nature of the special pterin [2-amino-4(1*H*)-pteridinone] (molybdopterin, Fig. 1) bound to Mo and W in these enzymes and unambiguously determined the metal:pterin ratio.

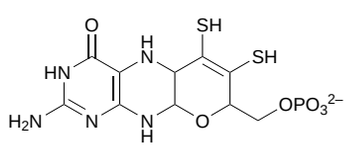

Fig. 1 Structure of molybdopterin[2]

The chemistry of the molybdenum-containing enzymes was placed in an admirably clear Perspective[3] by E. I. Stiefel on the basis of the protein crystallographic studies accomplished for representatives of the oxomolybdoenzymes and the nitrogenases. For the former group of enzymes, the information now available indicates that the 'molybdenum cofactor' should now

* Based on the presentations given at Dalton Discussion No. 2, 2nd–5th September 1997, University of East Anglia, UK.

be viewed as a generic term for a family of prosthetic groups. The variations include: (*i*) one or two molecules of the pterin bound to the Mo; (*ii*) the presence or absence of a nucleotide appended to the phosphate of the pterin; (*iii*) variation in the co-ordination chemistry at the metal.

An important aspect of these presentations and the subsequent discussion was the requirement to integrate the protein crystallographic studies with spectroscopic investigations of these systems. This is essential. Firstly, because of the limitations in the precision of the measurements, especially in respect of the identification of the non-protein and non-pterin ligands of the Mo and W centres. Secondly, the current nature of X-ray crystallography is such that ambiguities over the oxidation level of the metal centre during the experiment arise and the precision of the structural data is insufficient to resolve questions regarding oxidation levels of the pyrazine, pyran and dithiolene rings of the metal–pterin assembly. Thirdly, there is a fundamental need to fully characterise the chemical state and the homogeneity of the enzyme studied by protein crystallography. These problems are highlighted by the three different structures of native dimethyl sulfoxide reductase, each with the protein and pterin structures invariant but with significantly different Mo centres. Also, sulfite oxidase which has been characterised spectroscopically as the prototypical *cis*-$Mo^{VI}O_2$ centre but protein crystallography has identified a mono-oxo centre!

The discussion concentrated upon several chemical aspects of the protein crystallographic results. The special ligand for the metals in these enzymes has the same conformation in all structures so far determined, as would be expected if there is a common, genetically controlled, pathway for the biosynthesis of molybdopterin. A nucleotide is appended to the molybdopterin in some, but not all, of these enzymes; whilst this serves to anchor the centre within the protein, it is interesting to speculate whether the nucleotide has another role. The molybdopterin supplies the dithiolene (ene-dithiolate) group which co-ordinates to the Mo or W and the question arises as to whether the redox properties of the metal centre are coupled in any way to those of the pyrazine ring. One intriguing possibility is that the pyran ring could open, leading to unsaturation of the pyrazine ring which would be conjugated to the dithiolene ring.[3] The 'non-innocent' nature of the dithiolene ligands is well established (see Fig. 2) and the challenge still exists for chemists to

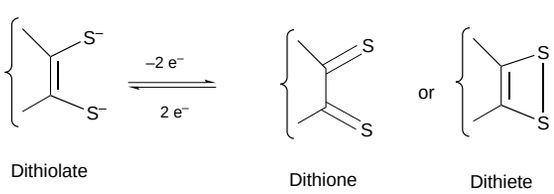

Fig. 2 Redox activity of an ene-dithiolate (dithiolene) ligand[3]

understand the electronic structure of dithiolenes, especially, as the protein crystallographic and resonance-Raman studies of the oxomolybdoenzymes have identified different types of dithiolene groups. Of course, the redox chemistry of sulfur (and selenium) is rich and the coupling of the metal-based and chalcogenide-based redox chemistry has been elegantly developed by Stiefel[3] and this behaviour is likely to be a feature of the reactivity of the metal centres in the oxomolybdenum and oxotungsten enzymes.

These keynote lectures were complemented by four other presentations. One was concerned with the synthesis of $[Mo^{IV}O(dithiolene)_2]^{2-}$ complexes[4] and another with the mechanism of O-atom transfer between such systems and their *cis*-$Mo^{VI}O_2$ counterparts.[5] The nature of the intermediate(s) formed in the O-atom transfer reactions of chemical systems, and how these might relate to the natural systems, was discussed. The advances made in the theoretical treatment of transition-metal centres in proteins is now starting to have a major impact in Bioinorganic Chemistry and this has been used to good effect for some molybdenum centres including xanthine oxidase.[6] The need to integrate the results of these calculations with experimental data, *e.g.* EPR parameters, was stressed during discussion.

Major advances have been achieved in defining the structure of molybdate- and tungstate-binding proteins.[7] The anions are embedded in the protein matrix by a set of hydrogen-bonding interactions. The structure of the *Azotobacter vinelandii* periplasmic molybdate-binding protein is very similar to that of the sulfate-binding protein of *Salmonella typhimurium*. This raises the question of the basis of the anion selectivity. The discussion considered MoO_4^{2-}, WO_4^{2-}, SO_4^{2-} and PO_4^{3-} and how the 'venus-fly trap' binding proteins might discriminate between them; is it on the basis of size, the electrostatic potential on the surface of the tetrahedron, the pK_b of the anion, or a combination of these factors? Also, the mechanism for release of the anions is unclear.

Small Molecule Activation by Metalloproteins

An especially important aspect of Bioinorganic Chemistry is the catalyses which are accomplished by metalloenzymes, particularly as many of these transformations are difficult to duplicate outside of the natural system. Metalloenzymes can activate chemical bonds which are inert and control the subsequent transformation to achieve an elegant specificity. These capabilities represent intriguing aspects of the structure and function of the active site of the soluble methane monooxygenase (sMMO) from *Methylococcus capsulatus* (Bath).[8] This enzyme is comprised of three proteins with the catalytic site of the hydroxylase involving a non-heme diiron centre. The carboxylate-bridged diiron centres in sMMO activate dioxygen and methane to accomplish, under ambient conditions, a reaction which can only be duplicated industrially at high temperature and pressure. Thanks to the achievements of several research groups, the sequence of events in the catalytic cycle for sMMO is (Fig. 3) well defined.

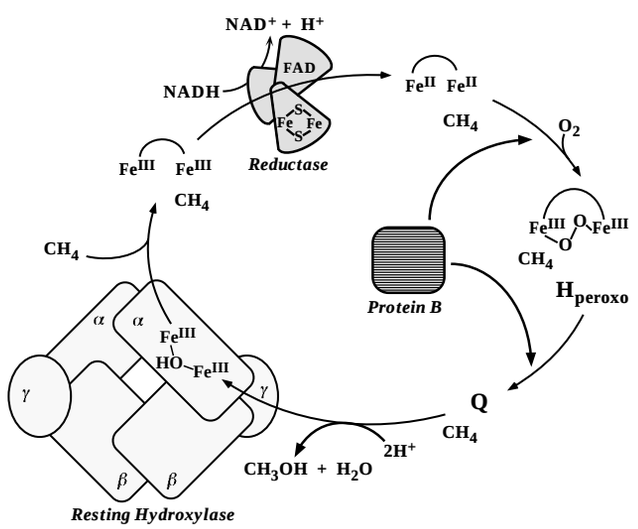

Fig. 3 Catalytic cycle for sMMO from *M. capsulatus* (Bath) showing observed intermediates[8]

The discussion, following the accomplished keynote lecture of A. M. Valentine,[8] concentrated upon the chemistry of the intermediates in the catalytic cycle of sMMO. This considered the spectroscopic information available for the transient species with reference to the protein crystallographic results of Rosenzweig, Lippard *et al.* which have provided a clear view of the molecular architecture of this protein. The enzyme possesses a hydrophobic pocket adjacent to the catalytic site for substrate

binding prior to reaction with O_2 at the diiron centre. How O_2 binds to the diiron centre and the nature of the peroxo intermediate which converts spontaneously to a bright yellow intermediate (Q), remain to be established. Intermediate Q is generally considered to react with CH_4 to form CH_3OH and, although some spectroscopic characterisation of Q has been achieved, the nature of this centre has not been defined and thus the essence of the catalytic action remains elusive. Some important distinctions between sMMO and the Cu-dependent, membrane-bound methane monooxygenase were elaborated during the discussion. Oxidation of NH_3 is accomplished reasonably readily by the Cu enzyme but not by sMMO and this could be because the former enzyme may involve a different type of pocket for initial substrate binding. The presence of Cu suppresses the biosynthesis of sMMO and there is clearly gene regulation of this process; however, this does not appear to involve stimulation of the biosynthesis by the presence of CH_4.

The awareness of the presence of carboxylate-bridged, non-heme, diiron centres as a common structural motif for several metalloproteins that bind and/or activate dioxygen (Fig. 4) has stimulated important developments in related co-ordination chemistry.[9]

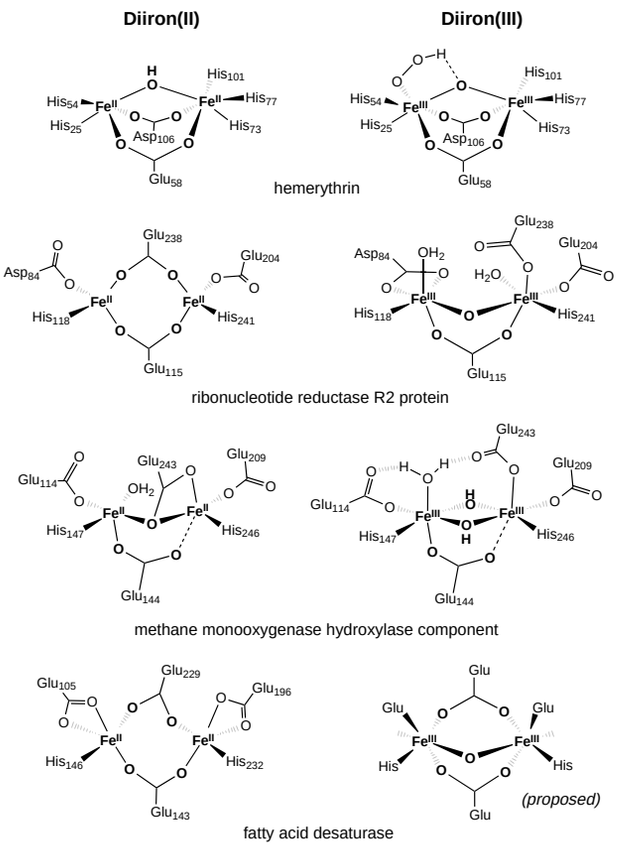

Fig. 4 Non-heme diiron active sites of several important metalloproteins[9]

Not only have the spectroscopic studies of the chemical systems been vital for the interpretation of spectra recorded for the natural systems but also this chemistry has been influential in considerations of the structure and properties of the reactive centres of the metalloproteins. This last point is especially true for the compounds obtained by reacting diiron centres with O_2 and Que *et al.* have made important progress by identifying the Fe_2O_2 'diamond core' in chemical systems. This is a well characterised type of centre as Mn_2O_2 and Cu_2O_2 (of course, the analogous Fe_2S_2 moiety is the building block of Fe–S clusters), and the proposition that $M_2(\mu\text{-}O)_2$ moieties are common to metalloproteins which activate or produce O_2 has considerable attractions. Rapid freeze–quench ^{57}Fe Mössbauer and Fe K-edge EXAFS studies of sMMO have shown that the intermediate Q is a diiron(IV) species with an unusually short Fe···Fe separation of 2.5 Å and one short (1.8 Å) Fe–O bond per Fe, in addition to four Fe–O/N bonds that average 2.04 Å. An asymmetric $Fe_2(\mu\text{-}O)_2$ diamond core would be consistent with these data. How this centre hydroxylates CH_4 is still a matter of speculation.

The knowledge gained from metalloenzymes which activate small molecules has greatly stimulated co-ordination chemistry. Novel developments in the synthesis of iron(III)–metal(II) complexes as structural models of the active centre of purple acid phosphatases have been accomplished.[10] A $Cu^{II}N_5$ centre, which can be oxidised electrochemically to give Cu^{II} adjacent to an aryl radical cation, is of relevance to galactose oxidase; the results obtained suggest that π-stacking interactions do not contribute to stabilisation of the radical cation.[11] An extensive series of electrochemical studies of the oxidation and protonation of a bridging amide ligand at a dinuclear metal–sulfur site has been accomplished.[12] These results clearly demonstrate that an amide ligand, which is believed to be an intermediate in biological nitrogen fixation, can be protonated to NH_3 at a dinuclear, sulfur co-ordinated, metal site. In the discussion, it was pointed out that the role of the sulfur could be important in such reactions, *e.g.* for H^+ binding.

Biomineralisation

Biomineralisation centres on the idea that an organic matrix controls the nucleation, growth and form of inorganic materials, and it is this process that creates hierarchical composite structures with unusual chemical and physical properties. The meeting was treated to two impressive keynote lectures by G. A. Ozin[13] and S. Mann.[14] These showed the beautiful morphology which can be obtained for inorganic materials formed in the presence of a suitable organic template and the advances made in mimicking these processes. The challenges to understand and fully replicate the biological processes are considerable but the returns will be immensely valuable if it proves possible to reproduce the elegant connection of form to function achieved by Nature.

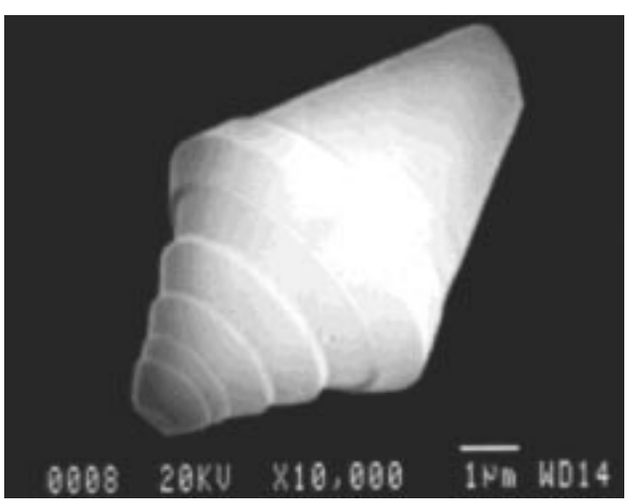

Fig. 5 A scanning electron microscopy image of a high curvature mesoporous synthetic silicate[13]

Ozin described the mineralisation of silicate and phosphate in liquid-crystal phases to create morphologies with 'natural' forms.[13] Many illustrations were given of the formation of silicates, to produce fascinating morphologies (see Fig. 5) using simple, well-defined procedures in which the aggregation occurs in surfactant micelles. Much of the subsequent discussion centred on the chemistry of the control of the deposition of the Si–O aggregate within the surfactant micelle, especially the pH at the surface of the Si–O aggregate and how to measure this.

The use of electric fields, kinetic isotope effects, the presence of particular anions, and variation in the nature of the silicon-containing species were all discussed as further possible ways of controlling the morphology. Mann emphasized that the interplay between the intrinsic molecular forces of inorganic precipitation and the extrinsic field, arising from longer-range cellular activity and organisation, is pivotal in explaining the extraordinary complex form of biominerals (see Fig. 6).[14] The reaction space can control the shape of the mineral, *e.g.* curved rods of SiO_2 can be produced in a curved vesicle and a network of vesicles can give a honeycombed array. However, it is important to note that the reaction space may not be static and there is a general need to study the dynamics of biomineralisation processes. The role of trace elements in the control of morphology may be important but, from studies of chemical systems, these effects relate to the symmetry of the unit cell and the growth of a particular face (or faces); Nature has developed the means of overruling the morphology of the unit cell.

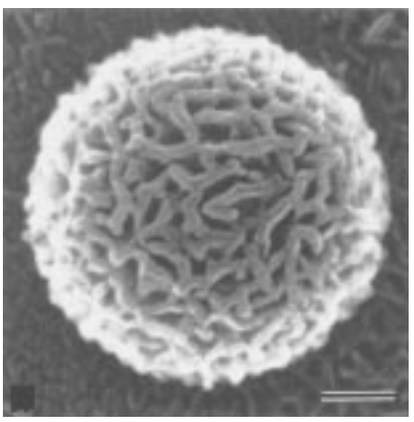

Fig. 6 Hollow spherical shell of calcium carbonate (aragonite) formed by synthesising a cellular mineralised film on polymer microspheres (scale bar = 200 nm)[14]

Biomimetic inorganic materials chemistry aims to exploit the principles of biomineralisation to control crystal morphology and synthesise novel materials. Whilst this is typically demonstrated for compounds of the s- and p-block elements, the principles are quite general. The meeting heard of the influences of amphiphiles on the crystallisation of $CuSO_4 \cdot 5H_2O$[15] and the control over magnetite crystal morphology exerted by the oxalate template. The stabilisation of an intermediate new synthetic iron oxyhydroxy oxalate phase has enabled the action of oxalate in directing this crystal growth to be clearly discerned.[16]

Ferritins are vital Fe^{III} storage proteins and a major challenge is to understand the mechanism of the oxidative uptake of Fe^{II} *via* the dinuclear centres which have been identified in subunits of the protein shell. New spectroscopic studies have identified a transient blue species.[17] The chemical nature of this species is intriguing and site-directed mutagenesis experiments indicate that it is not an iron–tyrosinate complex; could it be an Fe^{III}_2–peroxo moiety? The important inter-relationships between Cu and Fe metabolism continue to attract much attention but the chemistry of these connections remains difficult to define. One potentially important aspect of this inter-relationship is the influence of Cu^{II} on the rate of aerobic oxidative uptake of Fe^{II} by horse spleen apoferritin.[18] Since commercial ferritin contains copper, this must be removed in experimental work, so that a controlled addition of Cu^{II} can be achieved. It is not clear where the Cu^{II} binds; one possibility is the formation of dinuclear Fe · · · Cu centres in the transport channels.

Humic acids are ubiquitous in soils and serve to bind metals with an extraordinary capacity and tenacity. This behaviour is important, not only to agriculture but also for soil remediation and water quality. The meeting heard of progress made in understanding the chemistry of these systems; there is no evidence for the formation of metal clusters or aggregates within the organic matrix.[19] The question of pH control of metal binding was raised and whether metals migrate from one site to another.

Mixed-valence Metal Clusters in Biology

Mixed-valence transition-metal clusters are vital for the function of many metalloenzymes and redox active metalloproteins. These allow multi-electron catalyses to be controlled and facilitate electron transfer over long distances since electrons can (generally) move freely within the cluster. The challenges of (amongst other things): defining the electronic and magnetic structures of mixed-valence clusters; the coupling of electronic and vibrational motions; the degree of electronic delocalisation; and spin-dependent electronic delocalisation are considerable. An armoury of sophisticated methodologies (calibrated by studies on suitable, structurally characterised, chemical systems) has been successfully employed to analyse and determine the electronic and magnetic structures of these centres.

Mixed-valence chemistry is particularly rich for manganese, with the oxygen evolving complex (OEC) of Photosystem II being the most enigmatic case. The theoretical basis for describing mixed-valence in metal clusters derives from the classical treatments of chemical and mineralogical systems. D. Gatteshi authoritatively showed that the magnetic coupling between mixed-valence centres provides a useful tool for investigating the structure of the arrangement; the coupling can be assessed both by direct magnetisation measurements and from indirect spectroscopic measurements. This point of view was clearly justified by a review of the magnetic interactions between pairs of Mn ions, concentrating on the spin-dependent electron transfer in Mn^{III}–Mn^{IV} pairs which originates the ferromagnetic double exchange, and then extending the perspective to larger clusters comprising 4–12 Mn centres.[20] The larger arrays of Mn centres are being investigated as possible candidates for single-molecule magnets (Fig. 7), especially because these systems display thermally assisted quantum tunnelling. The prospect of the controlled incorporation of other metals into the Mn_{12} structure to achieve a variation in magnetic properties was considered during the discussion.

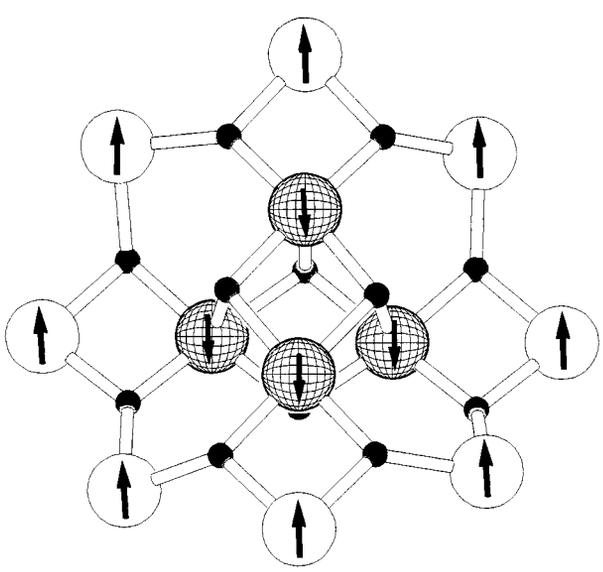

Fig. 7 Representation of the spin structure of the core of $[Mn_{12}O_{12}(O_2CCH_3)_{16}(H_2O)_4]$[20]

Inorganic systems which involve four Mn centres in close proximity have potential relevance to the OEC of Photosystem II; a wide range of such systems has attracted attention as the structure of the natural system is not yet established. Although

crystals of Photosystem II have been obtained, the resolution of the diffraction patterns (>4 Å) is not sufficient to provide information at atomic resolution and so the nature of the Mn centre is being elucidated spectroscopically, principally from EPR and X-ray absorption studies. G. Blondin presented the results of an elegant study, whereby γ-irradiation of a dimethylformamide solution of $[Mn^{IV}_4O_6(bipy)_6]^{4+}$ (bipy = 2,2′-bipyridine) (Fig. 8) at 77 K, has produced the first example of a

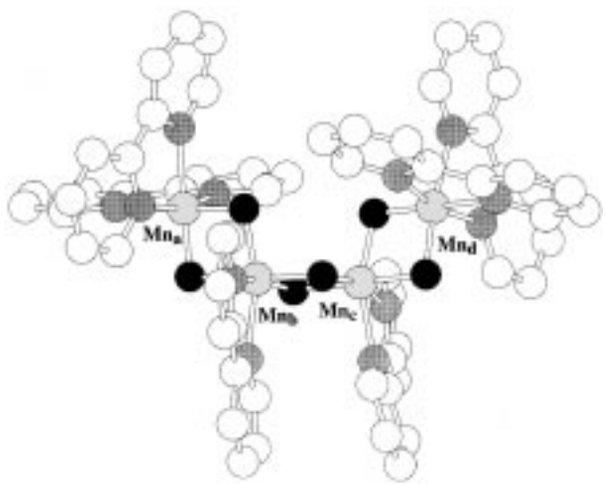

Fig. 8 Structure of $[Mn^{IV}_4O_6(bipy)_6]^{4+}$ [21]

mixed-valence tetranuclear centre containing Mn^{III} and Mn^{IV} centres which exhibits an $S = \frac{1}{2}$ ground state. The analysis of the EPR signal of $[Mn_4O_6(bipy)_6]^{3+}$ has contributed to an improved understanding of that observed for the S_2 state of the OEC.[21]

As was pointed out during the discussion, this EPR-active species should be structurally characterised, by Mn K-edge X-ray absorption spectroscopy *in situ* linked to the isolation and the determination of the crystal structure. The meeting also learned of the progress made in calibrating the Mn K-edge EXAFS of the OEC by parallel studies on chemical systems, notably one containing alkali- and alkaline-earth-metal cations in a crown ether moiety adjacent to a dinuclear manganese centre.[22]

Copper is used widely in biology because of its facile Cu^{II}–Cu^{I} redox chemistry which becomes intriguing when two, or more, Cu centres are in close proximity. The novel, binuclear Cu_A centres of cytochrome c oxidase and N_2O reductase, with equivalent Cu atoms in the mixed-valence Cu^{II}–Cu^{I} oxidation state has set challenges to understand the electronic structure of these centres, including the pathway for exchange, and to synthesise chemical systems with similar properties. Fully delocalised class III mixed-valence dicopper co-ordination complexes containing a $Cu^{II}Cu^{I}$ core are comparatively rare. However, an octaazacryptate ligand will encapsulate such a centre; UV/VIS and MCD measurements, linked to theoretical calculations, have successfully determined the electronic structure of this centre.[23] A new trinuclear Cu^{II} assembly has been synthesised and structurally characterised, the spectroscopic properties of which may have relevance to those of the trinuclear copper active sites of ascorbate oxidase and laccase. One possible extension of this chemistry is the interaction of the complex with DNA, for which it shows a high affinity.[24]

Metals in Medicine

The use of inorganic-based systems, as pharmaceuticals and agents which aid medical diagnosis is rapidly developing, as are the techniques to probe the metabolism and mode of action of these metal complexes. These studies, together with complementary chemical developments, are leading to an improved understanding of the biological behaviour of the complexes and the design and development of new variants. These developments are important for metal anti-cancer complexes, in order to circumvent cell resistance and to produce agents with an improved efficacy and minimal undesirable side effects. The majority of studies have concentrated on Pt^{II} compounds, following the initial discovery and widespread clinical use of 'cisplatin', *cis*-$[PtCl_2(NH_3)_2]$, and its second and third generation successors. Although Pd^{II} compounds, with their similar chemistry, might also appear attractive, the rates of ligand exchange for Pt^{II} complexes (min/h) are compatible with the time-scale of drug administration and delivery whilst those of the Pd^{II} systems (10^3–10^5 times faster) are not.

Platinum anti-cancer drugs are believed to exert their therapeutic action through interactions with DNA, the ultimate target being the N^7 of guanine. We do not know how the Pt species reaches the DNA, especially as Pt^{II} complexes are known to react rapidly with sulfur-donor ligands, such as cysteine and methionine which are present within a cell. Thus, as brought out in the discussion, metallothionines could scavenge platinum anti-cancer drugs. J. Reedijk clearly showed that the nucleopeptide Met-d(TpG) (5′-*O*-methioninate-*N*-ylcarbonylthymidine 2′-deoxyguanosine monophosphate) (see Fig. 9), containing a methionine moiety covalently linked to a TpG dinucleotide, reacts with platinum complexes. The initial binding gives Pt^{II}←S co-ordination: for [Pt(dien)Cl]Cl (dien = diethylenetriamine), this is subsequently substituted by the N^7 atom of guanine; in the case of the cisplatin analogue $[Pt(en)Cl_2]$ (en = ethane-1,2-diamine), the formation of a stable *S*,*N*-chelate occurs.[25]

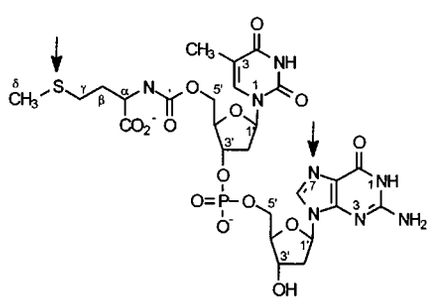

Fig. 9 Structure of the nucleopeptide Met-d(TpG); arrows indicate possible platinum binding sites [25]

The salt [Pt([^{15}N]dien)Cl]Cl, has been used extensively as a model for the first step in binding of platinum anti-tumour compounds to DNA, although the compound itself is inactive. New [^{1}H,^{15}N] NMR studies of the reactions of [Pt([^{15}N]dien)Cl]Cl have provided valuable spectroscopic correlations and have raised questions about the role of hydrolysis in the mechanism of binding of this complex to DNA bases.[26]

Our present understanding of basic principles of metal ion–nucleobase/nucleic acid interactions is clearly incomplete.

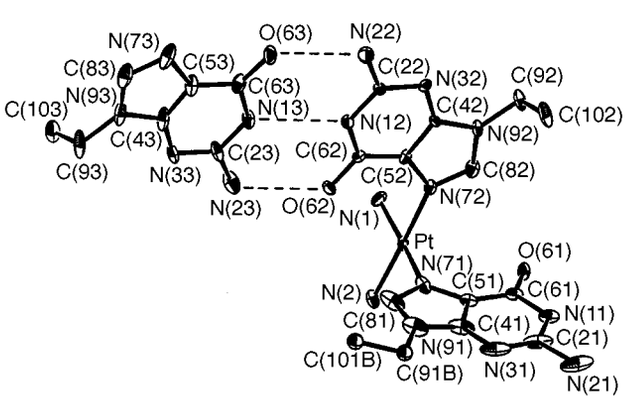

Fig. 10 Mispair between N^7 platinated, N^1 deprotonated guanine and neutral guanine, as found in *cis*-$[Pt(NH_3)_2(egua)_2]$·Hegua (Hegua = 9-ethylguanine) [27]

Despite a rapid increase in structural information derived from X-ray data and NMR work, and thermodynamic data (stability constants) of model systems, many essential features of the effects of metal ions on nucleic acids or their constituents are still poorly understood. Metal ions stabilise duplex, triplex and quadruplex DNA structures by relieving the repulsion between the negatively charged polynucleotide strands. The binding of metals to DNA profoundly changes the pK_a and chemistry of the nucleotide bases and, therefore, the base pair interactions. B. Lippert[27] provided an impressive and comprehensive survey of this field, demonstrating from an extensive range of structurally characterised chemical systems (*e.g.* Fig. 10) how the binding of Pt^{II} and other heavy, later transition-metal centres can lead to modifications to normal Watson–Crick or Hoogsteen base-pairing and produce mis-matches and/or other novel assemblies. This valuable information should form the basis of further studies to examine the reactivity of these systems, especially the ability of the metal to migrate from one Lewis base to another. Thus, as noted in discussion, an understanding of the dynamics of metal binding to sites on DNA is a vital aspect of understanding the role of metal-based anti-cancer agents.

A manganese cationic porphyrin covalently linked to the 5′ end of an antisense oligonucleotide has been shown to mediate sequence-specific oxidative lesions on an mRNA target when activated by $KHSO_5$;[28] this action may involve an Mn^{V}=O centre. The clinical use of the anthracycline antibiotic doxorubicin in cancer chemotherapy, although extensive, is limited by its severe negative side effects; complexation by metal ions is one of the many strategies used to reduce the toxicity of this drug. The interaction of $SnCl_4$ with doxorubicin has been followed spectroscopically and two sites for Sn^{IV} binding have been identified.[29] The nature of the interactions between this drug and metal ions normally present in humans still needs to be established.

Some stable metal chelates of polyfunctional macrocyclic ligands have considerable value for radiopharmaceutical and MRI applications. A new 18-membered hexaaza macrocyclic ligand with four pendant methylenephosphonates has been synthesised and characterised, and its properties, and those of its La^{III} complex, investigated; the ligand encapsulates the metal ion by providing 10 donor atoms.[30]

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