PERSPECTIVE

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Ligand design in coordination chemistry: approaches to new catalysts, new materials, and a more sustainable environment

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An overview of ligand design in the field of coordination chemistry is presented in a perspective format. Four major areas in coordination chemistry, where design and synthesis of ligands are crucial, are reviewed. We show that for successes in research leading towards new catalysts, new materials, insight is biocatalysis and for a sustainable environment, controlled ligand design is a crucial element.

Introduction

Coordination chemistry, by its very nature, deals with metals and ligands. Metals are known to have preferences for certain ligands and for certain geometries. Ligands can be as simple as ammonia molecules with one lone pair of electrons that bind monofunctionally to a metal ion. Ligands can also be larger and more complex, like monoatomic bridging ligands, such as chloride ions, or polyatomic with multiple bridges, such as the 1,2,4-triazolate anion.[1] Ligands can be designed with a variety of steric and electronic constraints, but with the introduction of supramolecular aspects, new avenues have been opened, towards combinations of coordination with stacking, hydrogen bonds, clusters and other bi- and multifunctionalities.[2,3] In certain cases the ligands are formed only, or preferentially, when the metal ion to which it binds is present already. Classical

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Paul Walton received his BSc and PhD from Nottingham University and from 1991–1993 was NATO postdoctoral fellow, University of California at Berkeley. He then moved to the University of York and is currently Professor of Bioinorganic Chemistry. His research interests are in designing, preparing and characterising new metal complexes which have unusual properties because of their structure, whilst at the same time discovering more about the role of structure in proteins and catalysts; this incorporates research into modelling of metalloenzymes, ultra-high stability metal-ion chelation and novel catalysts.

Michael Ward did his BA and PhD in Cambridge, where he worked with Professor Ed Constable on double helicate complexes. After post-doctoral work with Professor Jean-Pierre Sauvage in Strasbourg, he joined the School of Chemistry in Bristol as a new lecturer in 1990 where he is now Professor of Inorganic Chemistry. His research interests cover numerous aspects of coordination and supramolecular chemistry. He will be moving to a new post at the University of Sheffield this summer.

Left to right: **Kees Elsevier, Paul Walton, Jan Reedijk and Michael Ward**

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cases are the so-called Schiff-base couplings;[4] in other cases rather unique ligands can be formed only when the metal is present.[5,6]

Although ligand design nowadays plays a major role in almost all sub-areas of coordination chemistry, we have decided to concentrate in the present *Dalton Discussion* conference (DD5) and this *Dalton Transactions* issue on 4 major themes, each of which will be detailed below. Of course one could think of many other areas where ligand design is extremely important, such as in Analytical Chemistry, and in Medicinal Chemistry, where the ligands such as those for Pt, Ru and Au determine the therapeutic or diagnostic properties of the coordination complexes. Given the limited size of the conference, these latter topics were not to be addressed, but a few will be briefly mentioned at the end of this perspective paper.

Ligand design for new materials and devices

The role of coordination complexes in materials chemistry is currently growing at an enormous rate. This is a reflection of the fact that, as the syntheses become better understood and more routine, it becomes possible for the chemistry community to turn its attention to what can be done with the wide range of ligands and complexes whose syntheses have been developed. If we look at the recent development of organometallic chemistry, for example, the evolution from exploratory synthesis to applications and devices (catalysis, functional polymers, opto-electronics) is obvious. Coordination chemistry is following the same path, with the basic electronic, spectroscopic, magnetic, and structural properties of complexes being exploited for new materials and devices.

It would be helpful at this point to define what is meant by a 'material' and a 'device' in the context of coordination chemistry. Generally a 'material' can be considered as something whose properties arise from co-operative interactions between the components of the bulk assembly and are not exhibited by the individual molecules. Examples of this include the molecular superconductors based on stacked planar metal-dithiolene complexes, and thermotropic metallomesogens, both of which are examples of materials based on discrete molecules in which the bulk property depends on the precise ordering of molecules with respect to one another in the condensed phase.[7] Many other examples of coordination complexes as materials are based on infinite polymeric structures rather than molecular structures. These include one-, two- and three-dimensional magnetic materials in which paramagnetic centres are linked by short bridging ligands such as cyanide, azide or oxalate;[8] and mesoporous solids based on coordination network polymers which form zeolite-like structures with cavities which can reversibly bind various small molecules as guests.[9,10]

The term 'device' in this context is rather more nebulous and often refers to any potentially applicable property of a complex. It is not limited to bulk (material) properties but also encompasses exploitation of purely molecular properties such as redox and optical behaviour (this latter category includes absorption and luminescence properties, as well as non-linear optical properties such as frequency doubling and tripling, and saturable or reverse saturable absorption), and molecular magnetism (as in the well-known single-molecule magnets).[11,12] The field of non-linear optics illustrates how 'molecular' and 'materials' properties combine. Many organometallic and coordination complexes have a particular combination of structure and electronic properties, which gives them a significant first hyperpolarisability,[13–15] essential for observing frequency doubling (an important property which has applications in fields as diverse as telecommunications networks and military night-vision equipment). However, the bulk expression of this molecular property requires the molecules to be oriented in a polar space group such that their individual dipoles do not cancel out, and observation of bulk second-order NLO effects therefore relies on a *combination* of molecular and material properties.

However, one defines materials and devices (and the overlap between them means that it is appropriate to consider them together) the element of ligand design is of fundamental importance. The whole point of using coordination complexes is to exploit the properties of the metal ion, and—particularly for d-block metals—the basic redox, spectroscopic and magnetic properties of the metal are determined by the ligand set. Even in simple mononuclear complexes the ligand can contribute significantly to the optical properties of the complexes *via* metal-to-ligand and ligand-to-metal charge-transfer processes, which can yield useful properties such as luminescence (*e.g.* the well-known Ru(II) and Os(II) polypyridines) and non-linear optical effects. In 'molecular' materials the ligands play an important role in controlling the packing of molecules which is crucial for the bulk properties. In polynuclear and polymeric systems, however, the ligands fulfil several functions simultaneously. In addition to providing the ligand field which controls the basic properties of each metal centre, and possibly also participating in electronic transitions, bridging ligands control the all-important inter-metallic electronic and magnetic interactions by determining the separation between metal centres and their mutual orientation, as well as providing the orbital pathway through which the interactions are propagated. Any or all of these factors can be influenced by modifying the ligands, which provides enormous scope for using ligand design as a tool for the preparation of coordination complexes with properties appropriate for use in materials and devices. A few recent examples, which show how careful ligand design has contributed to the properties of the complexes, are now presented.

In the field of non-linear optics, many molecules have been prepared for second-order NLO behaviour in which donor and acceptor components are connected by a long, conjugated bridge.[13–15] This results in a polarisable donor–bridge–acceptor assembly which shows a substantial degree of charge-transfer behaviour in the lowest energy electronic transition. This basic design principle is widely accepted as being essential for preparation of molecules showing good second-order NLO properties, and it has been implicitly assumed that 'longer is better' as regards the length of the bridge. Coe and co-workers have recently challenged this principle by preparing and studying a series of complexes (Fig. 1) in which a ruthenium(II)-ammine p-donor is attached to a pyridine ligand which contains an organic p-acceptor attached to it by a polyene spacer whose length was varied.[16]

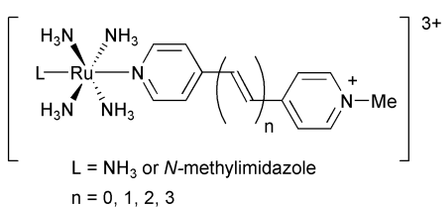

Fig. 1 Series of donor–acceptor complexes to probe effect of ligand length on second-order NLO behaviour.

It was found unexpectedly that adding additional –C=C– units to the bridging group resulted not in a steady increase in β (the first hyperpolarisability) but in an initial increase and then a tailing off of β as further –C=C– units were incorporated into the chain. The commonly-assumed 'longer is better' design principle, therefore, needs to be treated with caution and this piece of ligand design has significant implications for the development of future NLO chromophores.

The field of metallo-organic compounds for NLO has taken a significant new direction recently with the proposal by Zyss and Ledoux that *octupolar* species should also display

substantial second-order NLO properties.[17] Purely octupolar molecules (belonging to the space groups D_{2d}, D_3, D_{3h} and T_d) have no dipolar character, which means that the likelihood of molecules crystallising in a centrosymmetric space group (in which adjacent dipoles are opposed, destroying the bulk NLO effect) is much reduced.

Accordingly several groups, most notably that of Le Bozec, have studied the second-order NLO properties of octupolar metal complexes such as $[M(bpy)_3]^{2+}$ derivatives (D_3 symmetry; M = Ru, Fe, Zn *etc.*) and found that, with careful choice of substituents on the bpy ligands, the complexes exhibit first-order hyperpolarisability values comparable to the best dipolar systems[18] (Fig. 2). The ligands contain electron-rich units (the substituted phenyl groups) connected to π-acceptor pyridine units by a conjugated linker and are accordingly dipolar. By using a bipyridine unit as the electron-accepting component, two or three of these dipolar units can be assembled into the necessary octupolar array by using an octahedral or tetrahedral metal ion respectively. The ligands accordingly contain two important design elements, *viz.* the charge-transfer character which provides a dipole, and the correct complementarity with the metal template to generate the octupole. Incorporation of several octahedral $[M(bpy)_3]^{2+}$ units of this sort into oligomeric or dendrimeric systems has also been accomplished, and remarkably there is good evidence that adjacent complex units align with one another for steric reasons, giving a reinforcement of the β value for the ensemble above what was expected for randomly-oriented octupolar chromophores.[19] The NLO properties of these assemblies therefore arise from a combination of the inherent molecular properties of the chromophores, and a co-operative effect characteristic of the bulk material which allows adjacent chromophores to be aligned.

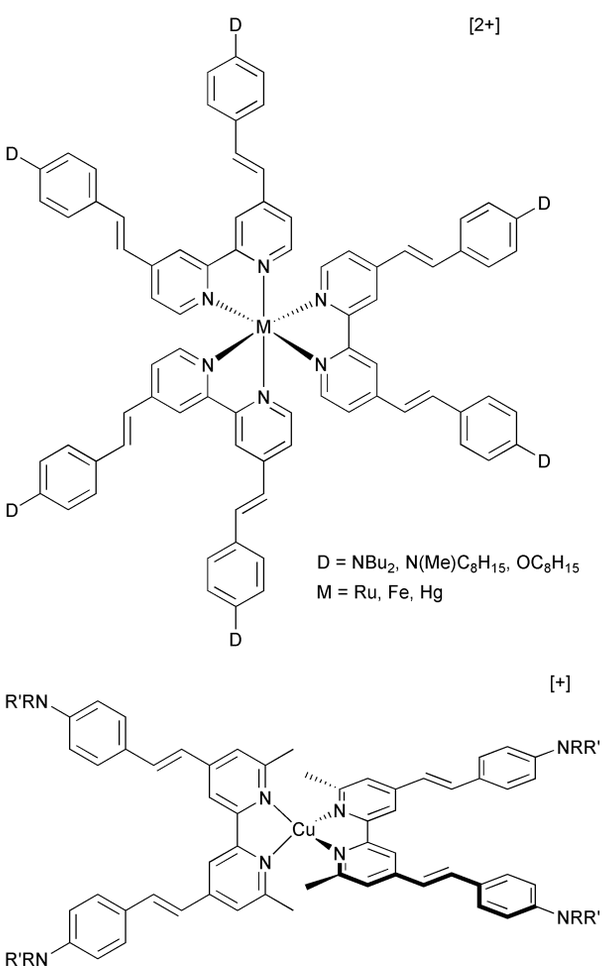

Fig. 2 Octopolar complexes for second-order NLO studies based on assemblies of donor-substituted bipyridyl ligands.

In the field of molecular magnetism it has been demonstrated recently by McCleverty and Ward how the topology of the bridging ligand which connects two paramagnetic fragments can control the sign of the spin–spin exchange coupling between them.[20] It has long been known in the realm of organic polyradicals that a *meta*-phenylene spacer separating two unpaired spins results in ferromagnetic exchange between them, whereas a *para*-phenylene spacer results in spin-pairing. In the same way, *meta*-substituted bridging ligands such as 1,3-dihydroxybenzene afford ferromagnetic coupling between two oxo-Mo(v) units, but *para*-substituted bridging ligands such as 1,4-dihydroxybenzene in contrast give antiferromagnetic coupling; this can be considered to arise from a 'spin-polarisation' mechanism involving alternation of induced spins on the connecting pathway. This principle has been applied to linear and triangular trinuclear complexes (Fig. 3).

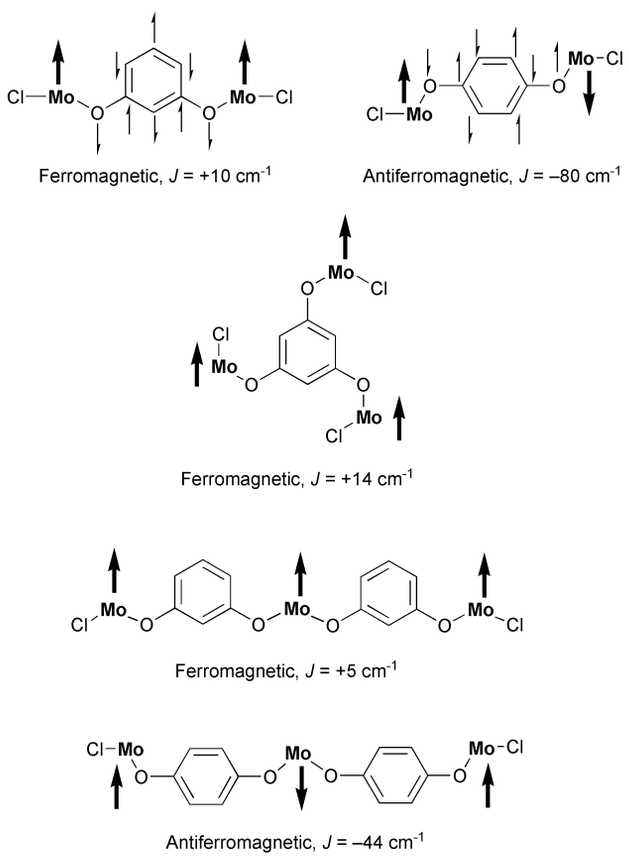

Fig. 3 Control of magnetic exchange in dinuclear and trinuclear Mo(v) complexes according to the topology of the bridging ligand [**Mo** = [Mo(O)(TpMe,Me)]2+]. The large arrows denote the unpaired electrons on the metal ions; the small ones in the first two examples denote the pattern of induced spins on the diamagnetic atoms of the bridging ligands.

Extension of this principle to infinite lattices (genuine 'materials') was accomplished by Lloret and co-workers,[21] who prepared and structurally characterised the complexes $[CoL_2(NCS)_2]_\infty$ (L = pyrimidine or pyrazine). These both consist of parallel two-dimensional sheets in which the square grid of metal ions in the sheet is connected by a *meta* linkage (pyrimidine) or a *para* linkage (pyrazine) with thiocyanate ligands in the axial positions (Fig. 4). In agreement with the structures of the bridging ligands, the pyrimidine-bridged complex displays ferromagnetic coupling at low temperatures to give a material displaying a magnetically ordered state below 8K which has the characteristics of a soft magnet. The pyrazine-bridged complex, however, displays antiferromagnetic coupling, with the susceptibility approaching zero at low temperatures, because of the alternation of spins throughout the lattice.

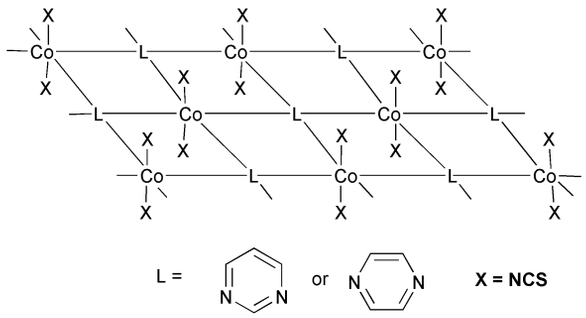

Fig. 4 Infinite two-dimensional lattices whose bulk magnetism can be controlled according to the topology of the bridging ligand.

Whilst the element of 'design' in these simple bridging ligands is limited, the nature of the ligand has a profound effect on the bulk magnetic behaviour and the correct choice of bridging ligand is crucial to achieve the desired effect. Shultz and co-workers prepared a series of ligands (Fig. 5) in which two or three *o*-semiquinone (sq) radical fragments are connected by a *meta*-phenylene spacer and are therefore ferromagnetically coupled to one another.[22,23]

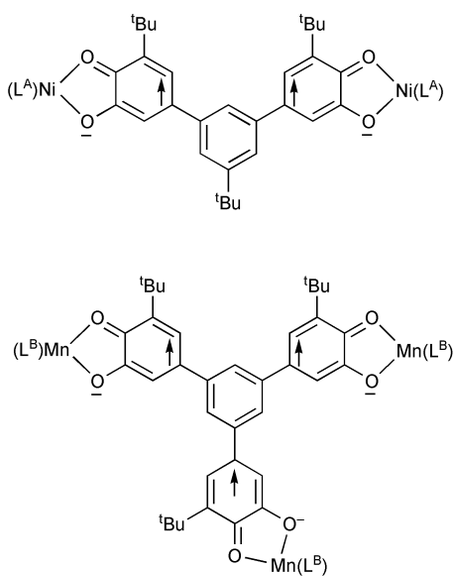

Fig. 5 Complexes in which ferromagnetic coupling within the bridging ligands is exploited to induce alignment of the metal spins to give complexes with high spin ground states (LA = D,L-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane; LB = TpCum,Me).

This effect has been exploited to enforce high-spin ground states in dinuclear and trinuclear complexes in which the semiquinone units are coordinated to paramagnetic metal ions such as Ni(II) and Mn(II). The exchange coupling between each metal ion and its associated paramagnetic metal ion is strong. The Ni(II)-sq coupling is ferromagnetic, such that each Ni(II)-sq unit can be considered as an $S = 3/2$ (quartet) fragment, and the Mn(II)-sq coupling is antiferromagnetic, such that each Mn(II)-sq unit can be considered as an $S = 2$ (quintet) fragment. At low temperatures, when the ferromagnetic coupling between the sq fragments within each ligand takes effect, this results in alignment of the spins of the M-sq units to give an $S = 3$ ground state for the dinuclear Ni(II) complex[22] and an $S = 6$ ground state for the trinuclear Mn(II) complex.[23] This elegant piece of ligand design, in which the ligands combine the disparate functions of bringing the metal centres together and controlling the magnetic exchange coupling between the M-sq units, therefore induces ferromagnetic coupling between two or three metal ions over distances where they would not normally interact with one another. The result is a new method of attaining high-spin ground states in metal complexes controlled by the topology of the bridging ligand.

Polymeric coordination networks have been of great interest in the last few years. In many cases mutual interpenetration of the polymer networks occurs, whereby the vertices of one network occupy the cavities of another. Such networks are structurally interesting but, since they do not contain large and accessible cavities, have no host-chemistry, although they may be of interest for their other intrinsic properties.

Thus, reaction of $Cd(ClO_4)_2$ with the achiral *trans*-pyridyl-ethenyl-benzoate in Fig. 6(a) affords a chiral two-dimensional network polymer $[Cd_3(\mu_3\text{-}OH)(py)_6(L)_3(ClO_4)_2]_8$, which contains $\{Cd_3(\mu_3\text{-}OH)\}$ units and is octupolar because of the threefold symmetry arising from coordination of three pyridine termini and three carboxylate termini of L to each $\{Cd_3(\mu_3\text{-}OH)\}$ unit. The non-symmetric nature of the bridging ligand also precludes the presence of inversion centres in the lattice. In consequence this material shows second-order non-linear optical activity, and was the first NLO-active bulk solid based on octupolar chromophoric units, an effect achieved through careful design of the simple bridging ligand.[24] Similarly, the chiral three-dimensional coordination polymer based on Zn^{2+} and the achiral ligand in Fig. 6(b) (the *cis*-isomer of the ligand in the previous example) contains two intersecting 6-fold helices, and has modest second-order non-linear optical activity which is allowed by the non-centrosymmetric structure.[25] In this case the helical chirality is induced by the slight skew in the ligand arising from steric interference between the primal phenyl and pyridyl rings which are *cis* to one another; again, a very simple design element has profound consequences for the structure and properties of the resultant coordination polymer.

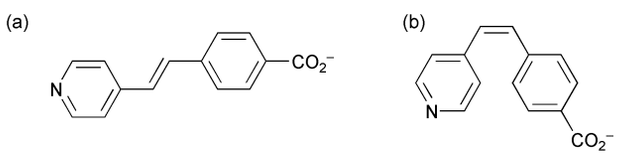

Fig. 6 Bridging ligands used to generate NLO-active coordination polymers.

If interpenetration of the networks does *not* occur then coordination polymers are of interest as materials for a quite different reason: they can exhibit 'zeolite-like' host–guest behaviour due to their nanoporous structure. Yaghi and co-workers have prepared an extensive series of nanoporous coordination polymers (described as 'metal-organic frameworks') in which the size, shape and arrangement of the pores is achieved by careful design of the poly-carboxylate ligands which bridge the metal centres.[26] These structures exploit the ability of some metal ions to form simple, highly symmetric clusters with carboxylates, such as the paddlewheel copper(II) acetate and the tetrahedral basic zinc(II) acetate structures. The combination of the symmetry properties of polycarboxylate ligands such as benzene-1,3,5-tricarboxylate (triangular) and adamantane-1,3,5,7-tetracarboxylate (tetrahedral), and those of the metal-carboxylate clusters which act as the points of connection for several ligands, allows precise design of a wide range of nanoporous three-dimensional networks with much higher effective surface areas than zeolites. Importantly, the structures do not collapse when the solvent molecules which occupy the pores or channels are removed, and the empty pores can bind reversibly a variety of organic solvent molecules or gas molecules.

Turning now to the broad field of molecular 'devices', two recent examples illustrate how ligand design can be used to achieve quite sophisticated effects. The first is provided by the group of Fabbrizzi and co-workers and is a molecule in which a reversible on/off motion of a pendant arm, triggered by a pH change, is signalled by a change in luminescence from the dansyl reporter group (Fig. 7).[27] In acidic conditions, the Ni(II) centre in the tetra-aza macrocycle is octahedral with two water

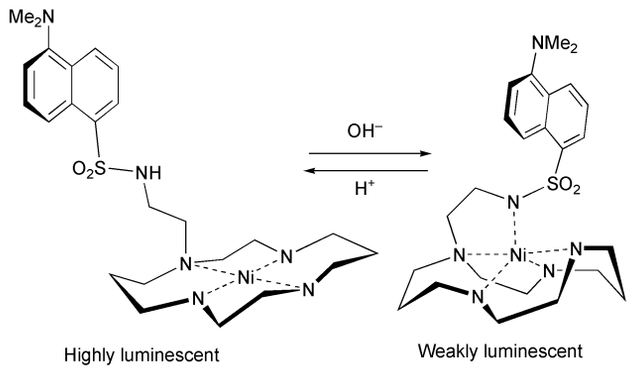

Fig. 7 A pH-induced intramolecular motion signalled by a luminescent reporter group.

molecules in the axial sites and the dansyl fluorophore is remote from the metal centre. As the pH is increased to 4.3, deprotonation of amide occurs and the N atom of the side chain coordinates to the Ni(II) centre, to give an irregular 5-coordinate geometry with the dansyl unit now in close proximity to the metal ion. The result is quenching of the characteristic dansyl luminescence at 510 nm by energy-transfer to the Ni(II). The reversible on/off motion of the arm is signalled by this reversible quenching and restoration of the luminescence. The ligand which makes this possible contains three components which have to act in concert: a macrocyclic site to accommodate the metal ion; an amide side-arm with an appropriate pK_a value which can coordinate to the metal ion only when deprotonated; and a luminescent unit which moves along with the side-arm and whose luminescence is capable of being quenched by the metal ion.

A rather different example, from Launay and co-workers, is a molecule in which ground state electron-transfer between two metal ions can be switched on/off by making a (reversible) structural change in the bridging ligand which mediates the electron transfer (Fig. 8).[28] This molecule is accordingly a model for a switch of electric current in a nanoscopic circuit. Given that electron transport between two metal electrodes across a single conjugated molecule which spans them has now been demonstrated,[29,30] the potential of switches of this sort for the further development of molecular electronic devices is clear. The complex contains two redox-active $[Ru(bipy)_2(NC)]^+$ units (where 'NC' denotes an anionic cyclometallating phenylpyridine ligand) connected by a dithienylethene spacer. The dithienylethene unit is photochromic and undergoes reversible interconversion between 'closed' and 'open' forms. Irradiation of the open dithienylethene unit in the UV region at 254 nm results in photocyclisation leading to formation of the closed form, which has a new low-energy electronic transition at 670 nm; irradiation into this band using red light re-opens the ring (Fig. 8).

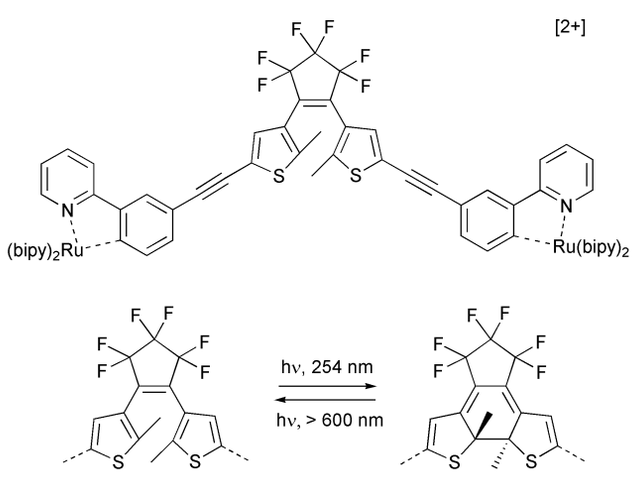

Fig. 8 Photochromic switching of long-distance inter-valence electron transfer.

One-electron chemical oxidation of the complex yields the Ru(II)–Ru(III) mixed-valence species in which optically-induced Ru(II)-to-Ru(III) (inter-valence) electron transfer can occur, and the resulting inter-valence charge transfer (IVCT) transition is used as a probe of the intermetallic electronic coupling. In the 'open' form no IVCT transition could be detected for the Ru(II)–Ru(III) complex, indicative of weak electronic coupling. In the closed form however an IVCT transition was apparent in the near-infrared region, from whose parameters an electronic coupling of 0.025 eV was derived. The reversible light-induced closure of the bridging ligand generates a bridging pathway which is more effective at mediating electron transfer than the open form, and accordingly genuine switching behaviour is demonstrated.

Overall it is clear that, as in other areas of coordination chemistry, ligand design is the key to preparing metal complexes which have useful properties and applications across the whole span of materials chemistry.

Ligand design and metal recovery

Metal recovery from waste and winning from ores is a very old process, and has not had a good reputation in the past when pyrometallurgical methods had to be used as no other methods were available. Such processes have been used in extractive metallurgy evolved over many centuries and they are based on the unit operations: *concentration, separation, and reduction.* In the case where a high purity metal is required also an additional, time-consuming and expensive *refining* step has to be applied.

The concentration and separation of base metals from ores and from leach solutions, such as Co, Ni, Cu and Zn, do present impressive technical challenges. For example, the production of 1 kg of electrical grade copper requires the processing of 800 kg of Copper ore.[31] The basic principles underlying the control of selectivity are charge of the ion, preferred coordination geometry, size of the cation, and the preference of certain metals for certain types of ligands, such as the HSAB principle.[32] Pre-concentration from acidic aqueous solutions is crucial in many of such cases.[33]

The gradual change from *pyro-* towards *hydro*-metallurgical processes for the recovery of transition metals, has clearly resulted in new sets of ligands that have been especially developed for selective metal coordination, in an efficient way. Clever design criteria for such special metal extractants are required, that not only deal with the metal-binding part of the ligand, but also with the hydrophobic groups of the ligand, influencing their solubility.

With the introduction of hydrometallurgy and the applications of methods like ion exchange and solvent extraction, the industry has become much cleaner, and much more sophisticated. This has resulted in the development of special, selective chelating ligands that meet the following criteria:

1. They are metal-specific,
2. They are air-stable,
3. They are hydrolytically stable, and
4. They are cheaply accessible.

Such ligands are either highly soluble in organic solvents, or can be easily attached to a solid, inert carrier, like silica or polystyrene.[33,34] In the first case they are used in commonly available, cheap solvents.[4,35,36]

Methodologies in separation technology that are frequently used to effect transfer of the desired metal from the aqueous (acidic) leach solution are based on equilibria between phases. To be mentioned are the liquid–liquid phase separations (selective solvent extraction) and the the liquid–solid phase separations (selective ion-exchange and specific chelating

resins). Details of the methodology will be presented in the paper by Tasker and co-workers.[31]

A high-boiling inert hydrocarbon is often used to extract metals. Such non-polar solvents help to assemble reaction species based on coordination, hydrogen-bonding and on ion-pair and ion-dipole interactions of dissolved species.

Some classical examples are shown below in Fig. 9.

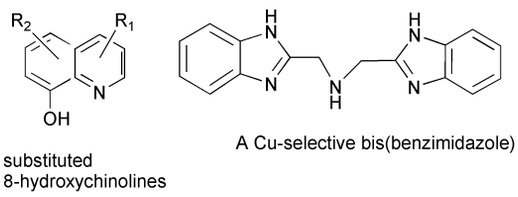

Fig. 9 Examples of chelating ligands as used in selective ion exchangers (right; R_1, R_2 = attached to a solid carrier) or solvent extraction reagents (left; R = hydrophobic tail).

Crucial for any commercial exploitation of organic metal-binding reagents in metal recovery is that they are inexpensive and not harmful when used on a large scale. A well-known and very successful base-metal recovery process involving solvent is copper production (over 25% of all Cu in the world is produced using this process).[38] The best ligand here appears to be a group of ligands containing a phenol and an oxim group. Here the square planar Cu(II) is strongly chelated, the intramolecular hydrogen bonding provides a strong further stabilization, and the variety of R tails can take care for the solubility in a specific organic medium and for stability down to pH of 1.5 (see Fig. 10).

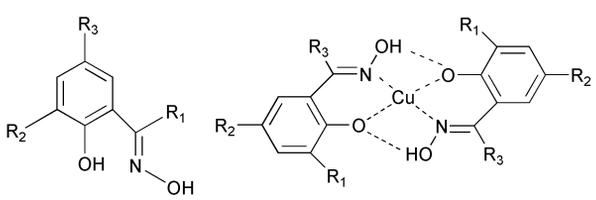

Fig. 10 Phenolic oxime ligand group (left) and its Cu complex (right), used on a large scale for Cu recovery.

Considerable research and effort is known for developing a process route for the recovery of cobalt from acidic leach solutions. The majority of this effort has been directed at selective recovery of cobalt from acid solutions. An economic solution for the efficient, but non-selective extraction of cobalt from leach solution is not yet known.

In conventional copper leach systems a great variety of other metals, some of which are quite expensive, is present and not extracted. Iron is the most frequently occurring, but is has also been observed that cobalt levels may reach a constant concentration of the order of ~100 ppm and this amount is worthwhile to recover. The winning of nickel is discussed in detail in the paper by Tasker and co-workers.[31] Improvements on many other metal-winning systems have started or are ongoing on the road towards a more sustainable industrial environment for one of the oldest chemical processes.

Ligand design and homogeneous catalysis

During the last decades, an increasing effort has been devoted to the design of ligands and metal complexes aimed at homogeneous catalytic conversions. Design has been primarily focused on the ligands, since the reactivity, selectivity and stability of transition metal compounds in homogeneous catalytic reactions are highly dependent on the ligand environment, in fact, of course, on the interplay between the metal, ligand(s) and reagents involved. One can distinguish a number of different, complementary approaches in ligand design. Many of these rely on (i) experience and insight, sometimes based on knowledge of the mechanism, (ii) molecular modeling, (iii) fast screening methods and (iv) serendipity. Although the latter no doubt continues to contribute to the plethora of new ligands and catalysts appearing in the open and patent literature on an almost daily basis, the former two approaches will be mainly dealt with here. Only a restricted number of topics and areas can be mentioned in this introduction, so biased choices have been made.

Chelate effects on rates and selectivity have traditionally been studied in terms of Tolman parameters and more recently by using the concept of the "natural bite angle" and "flexibility range" for didentate phosphanes.[39] Following arguments by Hoffmann, ligands with a tendency to enlarge the P–M–P angle could assist in reaching a situation resembling the transition state and hence accelerate migration reactions. Indeed, early proof of this principle was given by the dramatic effect of the chelate bite angle on the selectivity of rhodium-catalyzed hydroformylation of alkenes[40] and on insertion reactions of CO and alkene into (diphosphane)palladium–carbon bonds.[41,42] Rigid backbones that enforce constraints concerning the coordination angles were developed, for didentate phosphanes as pioneered by Venanzi (transphos, Fig. 11),[43] which later appeared to be rather flexible and also allows *cis*-geometries. In fact, only a limited number of ligands enforcing the *trans*-geometry are known.[44] Very recently, a truly *trans*-spanning ligand (SPANphos) has been designed and synthesized, allowing one to evaluate processes by rigorously excluding the intermediate formation of *cis*-species.[45]

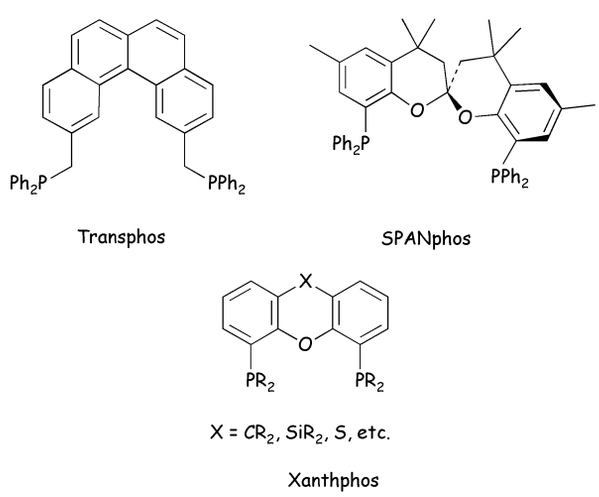

Fig. 11 Examples of ligands with large bite-angles.

An important class of (modeled) rigid ligands concerns the xanthphos type ligands developed by Van Leeuwen *et al.*,[46–48] which have bite angles between 102 and 131°. These impose, for instance, the intermediacy of bis-equatorial $HRh(CO)_2$-(xanthphos) species,[49] which are crucial for an increased n/i ratio of product aldehydes in the hydroformylation of alkenes. They also result in improved activity of nickel-catalyzed hydrocyanation.[46]

Rigidity and bulk imposed by *nitrogen* ligands have also been the subject of many studies, especially the class of (rigid) α-diimine ligands such as bian.[50] The palladium(bian) system allowed for the first time the isolation of consecutive compounds along the reaction coordinate of alternating CO-alkene oligomerization[51] and they are amenable to very selective homogeneous *cis*-hydrogenation of alkynes.[52] Similar ligands impose regioselectivity in palladium-catalyzed cross-coupling involving allylic substrates.[53]

Hemilabile (hybrid) ligands have been designed and used in catalysis.[54–56] Usually, such ligands contain two or more different donor atoms, but also symmetric didentate ligands are

known to behave as hemilabile ligands.[57] Ni-complexes with P,O chelates based on those employed in the SHOP process for ethylene oligomerization have enjoyed renewed interest (Fig. 12). Especially compounds with large groups near the oxygen atom give rise to very active catalysts, which is believed to be a result of protection of the otherwise relatively exposed oxygen donor.[58]

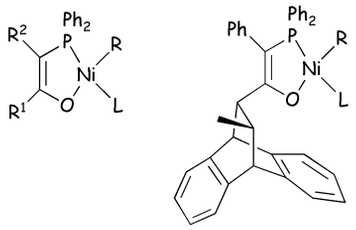

Fig. 12 Ni-chelates with hemilabile P,O-ligands.

Progress in co-polymerization and polymerization has gained a lot of impetus from the reports of highly active late transition metal complexes with α-diimine ligands by Brookhart *et al.*[59,60] Their steric and electronic properties can be easily and effectively adjusted by modification of the substituents on the imino carbon and nitrogen atoms, thus influencing the rate of chain propagation relative to chain transfer and termination. The subject has been recently reviewed.[61] Cationic palladium-(diphosphane) and palladium(α-diimine) systems are active in alternating CO-alkene co-polymerization,[62] whereas the palladium and nickel(α-diimine) complexes with MAO are tunable for oligomerization and polymerization of alkenes (Fig. 13). The palladium catalysts usually lead to more branched, high molecular weight polymers under circumstances comparable to those for nickel analogs. Whereas the nickel systems do not generally polymerize in a living fashion, the palladium analogue does, giving rise to narrow polydispersities.[63]

Ring-opening co-polymerization of methylenecyclopropanes with CO was reported to be effectively catalyzed by neutral and cationic Pd(α-diimine) catalysts.[64,65] The mechanism for growth was proposed to proceed *via* π-allyl-palladium complexes arising from regiospecific ring-opening of the monomer. Similar complexes may produce polyketone.[66]

Apart from highly active cationic nickel catalysts, also neutral bis(phosphanyl)amine type systems have been developed by Pringle *et al.*,[67] which exhibit unexpectedly high activity in ethylene polymerization.

An enormous growth in catalyst design for single-site polymerization catalysts based on these principles has been triggered.[68] For instance, transition metal catalysts with tridentate bis(imino)pyridine ligands as non-metallocene ethylene polymerization were designed by Gibson *et al.*[69,70] and Brookhart *et al.*[60] Iron and cobalt pre-catalysts have received attention in this context (Fig. 14); diiminato ligands were employed as logical extension[58,71,72] and formation of the catalyst as well as the initiation of the polymerization have been studied. Metallocene catalysts, especially of group 4, continue to receive interest and new ligands have been designed for more unusual polymers, such as stereo-block and hemi-isotactic polypropene.[73,74]

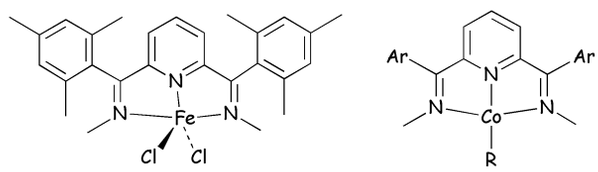

Fig. 14 Transition metal complexes with tridentate N-ligands for polymerization.

Metallacycles have received renewed attention because of their involvement in activation of C–H bonds, for instance palladium(*o*-tolylphosphane) compounds and their relevance to catalysis (Fig. 15).[75] Arylimines have been revisited in this context and new cyclopalladated imine complexes appeared to be exceptional catalysts for the Heck arylation.[76,77]

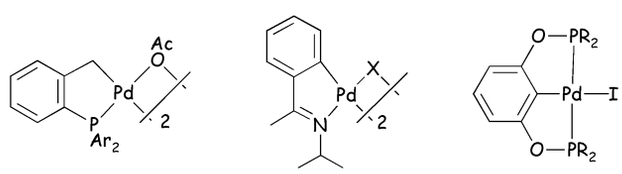

Fig. 15 Metallacyclic compounds as precatalysts for C–H activation and Heck reactions.

In the area of enantioselective catalysis, monodentate chiral ligands are back on track after having been disregarded for a long time. In this context, the recent successful use of chiral phosphoramidite ligands derived from 2,2′-binaphthol, specifically as their copper and zinc complexes in enantioselective conjugate addition reactions,[78] should be mentioned.

Carbenes, especially *N*-heterocyclic carbenes (NHCs), have found universal application in organometallic chemistry and homogeneous catalysis.[79]

Particularly the introduction of NHCs in second-generation Grubbs catalysts has boosted ruthenium-catalyzed metathesis and related reactions.[80,81] Several tailored compounds, such as NHCs with tethered N- and P-donor functionalities have

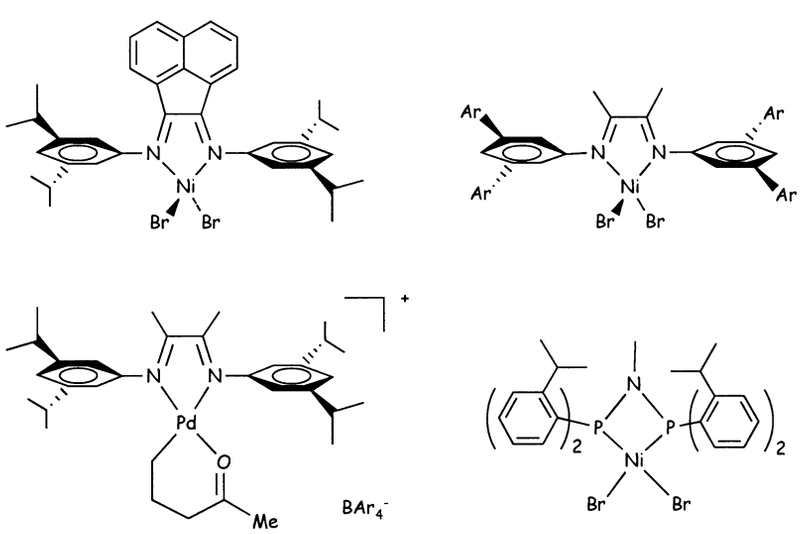

Fig. 13 Typical late-TM complexes with didentate ligands for polymerization.

recently been employed (Fig. 16).[82–84] In other cases, NHCs have been used as substitutes for phosphane in catalysis. Novel platinum compounds are capable of activation of imidazolium C–H bonds, generating hydridoPt^{II} carbene[85] and hydridoPt^{IV} carbene compounds.[86]

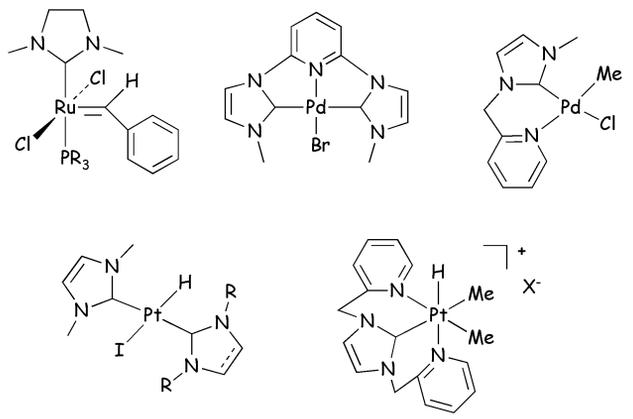

Fig. 16 Various TM-carbene species for metathesis, C–H activation, *etc*.

Computing power has increased to the point that even "first-principle" methods for transition metal compounds no longer pose severe constraints in computational chemistry. Apart from elucidating structural features and catalytic pathways, novel routes may also be discovered.[87] Seminal early contributions concerning methodology, involving also the heavier metals, have been made by the groups of Baerends and Ziegler *et al*.[88,89] Advances in the field of heterogeneous[90] and homogeneous catalysis[91,92] were subsequently developed.

Herrmann *et al.* have shown that a number of conformations can be found for large and flexible ligands (*e.g.* BISBI),[93,94] each corresponding to a local minimum in the potential energy curve, emphasizing the point that one should carefully locate the global energy minimum to establish the natural bite angle.[87] Following Casey's concept,[39] Van Leeuwen *et al.*[95] have successfully designed a number of rigid diphosphane ligands,[47,48] as has been mentioned above (xanthphos type; see Fig. 11).

Aspects involving design of ligands for heterogenization, aimed at catalyst-recycling, ranging from immobilization to encapsulated catalysts and dendrimers,[96–98] cannot be covered here. Also, the tuning of solubility of catalysts in, *e.g.*, fluorous,[99] supercritical[100] or ionic liquids[101,102] have seen remarkable progress, but can only be briefly mentioned.

The use of fast screening methods to discover new catalysts is one of the youngest fields of combinatorial chemistry. The application of combinatorial liquid- and solid-phase methods for the discovery and optimization of ligands and homogeneous catalysts is developing[103–107] and seems worthy of further investigations. High-throughput screening techniques for fast detection of activity and selectivity in catalytic reactions are still in their infancy. Despite the conceptual progress that has been made, problems seem to occur in establishing large libraries of ligands, which are the *conditio sine qua non* for real progress in this area. Combinatorial approaches are often hampered by the lack of suitable identification techniques, which may be the reason why ligand design for homogeneous catalysis by employing such techniques is lagging behind when compared to other fields. Nevertheless, several interesting approaches toward design and optimization of ligands by creating libraries and high-throughput catalyst screening have appeared. Examples (apart from the references given above) are enantioselective titanium-catalyzed additions to epoxides[108] and palladium-catalyzed allylic alkylation.[109]

Evolution-based principles for the selection of complex homogeneous enantioselective catalysts have been developed and, combined with modular construction of (chiral) ligands, hold much promise for the future of homogeneous catalysis.[110] Clearly, ligand design is one of the key activities when trying to establish new or better-performing homogeneous metal catalysts. A lot has been achieved and the pace of developments has appreciably increased over the last decade. Still, new venues and efforts in this area are needed.

Ligand design and biomimetics

In this area, a lot of inspiration comes from bioinorganic catalysis in enzymology.[111] For bioinorganic model complexes, the design and synthesis of the ligand is perhaps the single most important part of the whole modelling process. Fine positional control of the number and types of coordinating atoms is one of the keys in achieving a metal complex that mimics as closely as possible the coordination geometry and reactivity of the metal in the enzyme/protein. There are some impressive examples in the literature of this type of ligand synthesis, not least in the modelling of non-haem iron enzymes and models of the dioxygen evolving complex in photosystem II.

Despite the degree of sophistication, which can now be incorporated into biomimetic ligand design, there is a growing awareness amongst bioinorganic chemists of the need to incorporate into their model complexes mimics of not only the immediate metal coordination sphere, but also mimics of other features of the active site. These other features are often remote amino acid residues which have a key role to play in substrate recognition and in preventing product inhibition. It seems as if nearly all metalloenzymes have such features, which are often essential for catalytic activity. For example, the threonine-199 side chain in human carbonic anhydrase II. Model complexes based on this more encompassing view of the enzyme's active site can give remarkably powerful and effective mimics of the biological system; perhaps the most familiar example is Collman's and others picket fence porphyrins.[112] More recently also dioxygen binding to copper has become extreme important, as seen elsewhere in this issue.[113] Hereunder, several recent examples of model complexes are discussed. In each, the underlying modelling principle has been to incorporate some mimic of an active site feature(s) that is not part of the metal's immediate coordination sphere.

Models of zinc enzymes are a suitable starting point for the discussion, since they are the subject of many model complex studies. Of the zinc enzymes that are known, those that have received the most attention from a modelling point of view are *carbonic anhydrase* and *liver alcohol dehydrogenase*. *Carbonic anhydrase*, which catalyses the hydrolysis of carbon dioxide has been modelled extensively, with several examples of models where the immediate and secondary coordination spheres of the metal have been considered. Model complexes by Parkin *et al.* and Vahrenkamp *et al.* based on trispyrazolyl complexes of zinc, have incorporated a hydrophobic cavity *via* alkyl-substitution on the pyrazolyl rings (Fig. 17).[114–117] The cavity probably helps to stabilise the zinc-bound hydroxide anion, insofar as the cavity hinders the formation of bridged hydroxide dimers. The corresponding alkoxide complexes have also been prepared. Notably, the alkoxide complexes in the presence of water give an equilibrium mixture of the hydroxide and alkoxide complexes. Although the equilibrium favours the hydroxide, the fact that the alkoxide can be stabilised in such

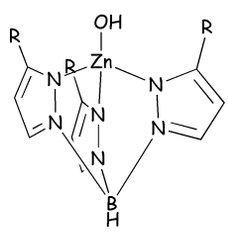

Fig. 17 Derivatised trispyrazolylborates. R = phenyl.

a fashion, presumably aided by the presence of a hydrophobic cavity around the coordinated alkoxide, indicates the influence of a cavity on the reactivity of a metal complex.

More recently, Reinaud *et al*,[118] incorporated imidazole ligands onto a *tert*-butylcalix[6]arene, such that the resulting zinc complex contained solvent molecules coordinated to the zinc within the hydrophobic cavity of the calixarene (Fig. 18).[119,120] This complex in which cyclodextrins were used to give the cavity was crystallised and its structure determined. The structure showed the presence of zinc-bound ethanol, with the ethanol inside the cavity of the calixarene. The resulting monomeric, cationic zinc ethoxide complex is a direct analogue of liver alcohol dehydrogenase.

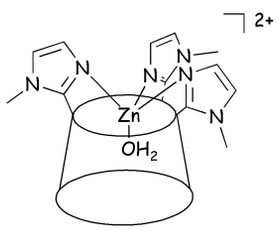

Fig. 18 Calixarene derivatized with imidazoles.

In a similar fashion, Vahrenkamp *et al.*[115] described the structure of a monomeric zinc-alkoxide complex in which the alkoxide rested in the cavity formed by phenyl substituents on a pyrazolylbis(thioimidazolyl)borate ligand (Fig. 19). In a closely related set of complexes, the role of a hydrophobic cavity is probably important in a zinc–methanol complex reported by Parkin *et al*.[117]

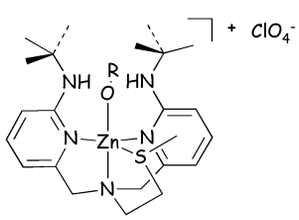

Fig. 19 A Zn complex with a hydrogen-bonding cavity.

The presence of a hydrophobic cavity around a free metal coordination site can also influence the degree of solvent association with the metal ion. Using a ligand system based on triaminocyclohexane, it was shown that chains of hydrogen-bonded methanol molecules which extend from the metal to the 'top' of the cavity could be prepared.[121] What is notable about such complexes is that they find direct analogues in the active sites of metalloenzymes, where chains of hydrogen-bonded water molecules are often a key part of proton-transfer pathways between metal-bound substrates (at the 'bottom' of active sites) to the surrounding solvent.

More recently, the incorporation of H-bond acceptors and donors as part of the ligand design have been shown to give metal complexes with very unusual reactivity. Berreau *et al.*[122] showed that dipyridyl–thiolate ligands with pendant amides acting as H-bond donors to an zinc bound alkoxide were effective models of liver alcohol dehydrogenase (Fig. 20).[119,120] The

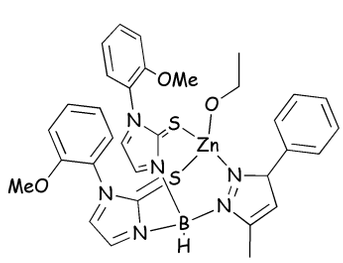

Fig. 20 Model complex of liver alcohol dehydrogenase.

complexes were effective to the extent that the alkoxide complex formed from the addition of methanol to the corresponding hydroxide complex; a similar reaction is seen in liver alcohol dehydrogenase. In comparison to the alkoxide complexes mentioned above, where the alkoxide is stabilised by a hydrophobic cavity only, the presence of a hydrogen bond significantly favours the formation of the alkoxide form over the hydroxide form of the complex. Since the catalytic cycle of liver alcohol dehydrogenase features the conversion of the hydroxide form of the enzyme to the ethoxide form, where the ethoxide form is stabilised by a hydrogen-bond from a nearby serine side chain, the analogous observation in a model system underlines the importance of hydrogen-bonding in influencing the reactivity of substrates bound to the metal ion.

Kimura [123] reported the preparation of aza-macrocycle complexes of zinc, where the macrocycle contained a pendant amide group that had the potential to hydrogen-bond to a zinc-bound substrate. Whereas the presence of the amide group had an effect on the acidity of a coordinated water molecule—similar to the effect hydrogen-bonding within the active site of *carbonic anhydrase*—the conformational flexibility of the pendant alcohol meant that metal-bound substrates did not necessarily have to be hydrogen bonded to the alcohol. In this respect, if ligands are to mimic truly the hydrogen-bond donors that are seen in the active sites of metalloproteins, it is likely that the model complex will have to be stereochemically rigid enough such that the hydrogen-bonding groups are 'forced' to interact with the metal-bound substrate.

The influence of 'forced' hydrogen-bonding on metal coordination is perhaps no better demonstrated by a series of complexes reported by Borovik *et al*. They prepared an impressive range of manganese and iron-oxo complexes (Fig. 21).[124–128] The primary coordination sphere is completed by ureato donor groups, with the N–H group acting as hydrogen-bond donors to the coordinated oxo group. Notably, the terminal oxo is stabilised by the presence of hydrogen bonds, possibly similar to the stabilisation of terminal oxos in metalloproteins, including the oxygen evolving complex in photosystem II. These non-haem iron terminal oxo species have long-evaded bioinorganic modellers, presumably because of the importance of both hydrogen-bonding and steric-bulk in stabilising such species.

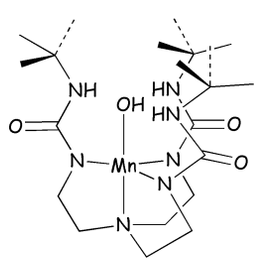

Fig. 21 Monomeric manganese–hydroxide complex, stabilised by internal hydrogen bonds.

The use of sterically bulky ligands to mimic the active site of metalloenzymes is, of course, not restricted to models of zinc enzymes. Generally, low valent metal complexes can be stabilised by the use of such ligands. A particularly striking example from bioinorganic model complexes comes from Lippard *et al.* and Que *et al.* who used sterically encumbered carboxylate ligands to give di-iron complexes that mimicked the chemistry of methane monooxygenase by oxidation of a C–H bond (Fig. 22).[129–131] The steric bulk of the carboxylate has a role in 'isolating' the metal centres and also allowing the stabilisation of unsaturated metal coordination geometries, similar to those seen in MMO itself. Moreover, hydrogen-bonds in the secondary coordination sphere of the iron atoms model closely hydrogen bonds seen in the active site of MMO. The bulk may also have a role in protecting the intermediate iron–dioxygen

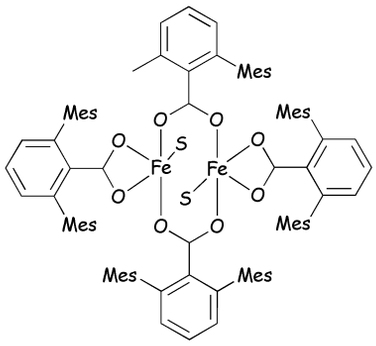

Fig. 22 Sterically-bulky ligands used in stabilisation of di-iron complexes. S = solvent.

complex from decomposition. Models which incorporate such steric bulk, and, as such, mimic the protein environment in the primary and secondary coordination spheres of the metal ions, hold much promise as potential functional model complexes of the oxygenating enzymes.

In models of copper enzymes the effect of steric bulk on the coordination mode of ligands to a metal ion is shown in the trispyrazolylborate copper complexes reported by Kitajima and Tolman.[132] Similar to the trispyrazolylborate complexes of Parkin *et al.*[117] and Vahrenkamp *et al.*[114–116] described above, it was shown the highly reactive copper species could be stabilised, such as copper-terminal hydroxide species, copper–peroxo species and copper alkyl–peroxide species could be stabilised.

Even from these few recent examples of model complexes there is little doubt of the need for bioinorganic model complexes to incorporate within their ligand design some features which mimic both the primary and secondary coordination spheres of the metal. Whereas this type of ligand design may present some considerable synthetic challenges, it is clear that it also holds considerable promise if functional model complexes are to be prepared.

Concluding remarks and outlook of the field

The brief overview given above of course is not complete, and basically has served to invite and encourage the reader to study the remaining papers of this Special Issue. In addition the authors would like to emphasize that a number of important non-covered areas deserve attention within this ligand-design theme. A few of these topics have to be mentioned, in particular:

1. Analytical chemistry, and chelating agents for detection and speciation, *e.g.* using very sensitive fluorescing probes.[133]

2. Metals in medicine, both as drugs and diagnostic agents. Examples of some of such ligands are given in Fig. 23.[134]

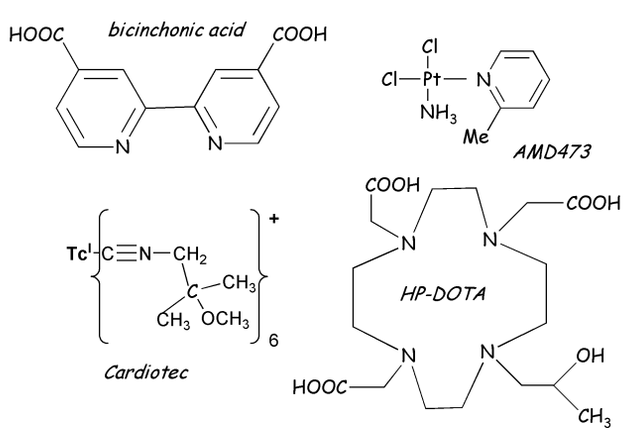

Fig. 23 Some examples of designed ligands in analytical chemistry and medicinal chemistry.

3. *De novo* synthesis of artificial peptides and proteins with specifically designed metal-binding properties.[135]

For further details the reader is referred to a specialized overview in the literature,[136] and an example of such a peptide is shown in Fig. 24. It is beyond any doubt that further developments in ligand design will lead to more sophisticated and constrained structures for all the applications mentioned above.

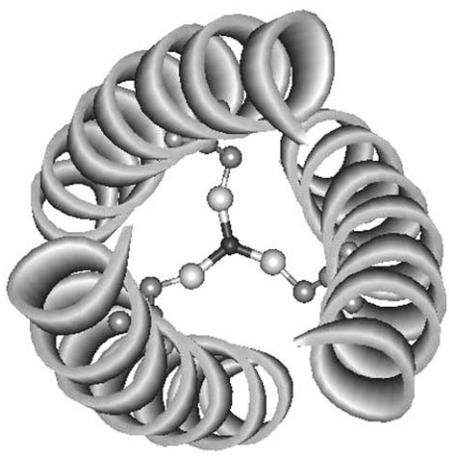

Fig. 24 An example of a polypeptide designed to bind metal ions in a trigonal geometry.

Acknowledgements

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