The combination of transition metal ions and hydrogen-bonding interactions

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This feature article presents an overview of the types of hydrogen bonding interactions involving metal complexes and their functional effects. It shows with recent examples why hydrogen bonds have become a crucial functional and structural element in modern inorganic chemistry. The relevance of this combination in tackling current chemistry challenges such as energy production and the development of new materials and more effective catalysts, sensors and medicines is illustrated.

Introduction

Essentially all metal complexes have groups capable of forming hydrogen bonds. The properties of hydrogen bonds make these interactions useful for many purposes.[1] For example, the strength of hydrogen bonds ranges from that of weak covalent bonds and that of strong intermolecular interactions. Hydrogen bonds are stronger when the X–H···Y angle (X = hydrogen-bond donor, Y = hydrogen-bond acceptor) is close to linearity meaning that, like chemical bonds and in contrast to other intermolecular interactions, they have predictable directional preferences. Hydrogen bonds are also capable of polarizing the covalent bonds of the hydrogen-bond donor and acceptor groups, and hence affect their reactivity and properties;[1a–c] a well-known example is water. They show an ability to link small and large molecules; remarkable examples include the double helical structures of DNA and RNA macromolecules.[1d] Hydrogen-bonding interactions can regulate proton[1e] and electron transfer events,[1f] and proton-coupled electron transfer (PCET)[1g] which are ubiquitous processes of fundamental importance in chemistry and biology *e.g.* in photosynthesis.

Exploiting the combined properties of metals and hydrogen bonds is common in the chemistry of biological species. For instance, the active sites of metalloenzymes generally exhibit many hydrogen-bonding interactions, which fine-tune or enhance the properties of these natural metal complexes.[2] It is interesting that transition metals and their primary coordination sphere exert a very diverse influence over hydrogen bonds, extending the properties and nature of these interactions.[3] As a result, the combination of transition metals and hydrogen-bonding interactions has become increasingly important in several areas of chemistry.

There is an interest in creating metals with hydrogen-bonding features as a way to test and improve our understanding of how metalloenzymes work under physiological conditions. Because nature exploits this combination to accomplish very important, challenging chemistry, metal complexes with built-in hydrogen-bonding groups are also important for practical purposes. For example, they could lead to complexes that provide us with energy for the future, new materials, new transformations and more effective catalysis and medicines (*vide infra*).

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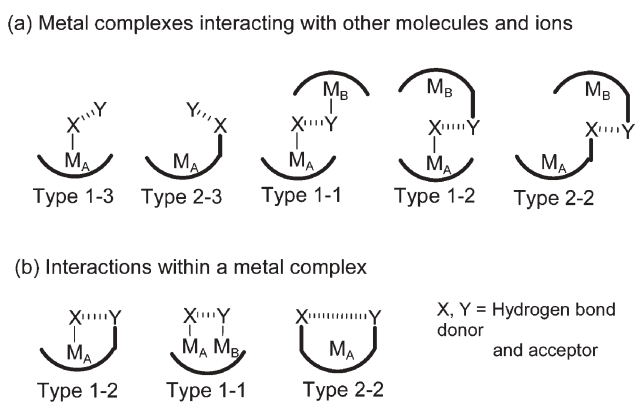
Dr Juan C. Mareque Rivas was born in Santiago de Compostela, Spain in 1972. He obtained his BSc from the University of Santiago de Compostela (1995) and his PhD at the University of Missouri in St. Louis under the supervision of Prof. Lee Brammer. Following two years of postdoctoral work at the Massachusetts Institute of Technology with Prof. Stephen Lippard, in 2000 he took up a Lectureship at the University of Edinburgh, where he is now a Senior Lecturer. His research interests span many areas of inorganic, biological and supramolecular chemistry, with special emphasis on using molecular recognition and hydrogen-bonding interactions as a way to enhance the properties of metal complexes.

These aspects are illustrated in this article with a selection of metal complexes where hydrogen bonding has been shown to exert effects which are both of fundamental and practical importance.

As a way of structuring this article, we have decided to discuss separately hydrogen bonding between metal complexes with other molecules or ions, and hydrogen bonds within a metal complex. In addition we differentiate hydrogen-bonding interactions in terms of the location of the donor and acceptor atoms relative to the metal; that is, directly bonded, part of a metal-bound ligand and external to the metal complex.

Types of interactions

Since there are many different types of hydrogen-bonding interactions occurring in transition metal complexes, a convenient way of classifying them is in terms of the position of the hydrogen-bonding groups relative to the metal. Using this criterion, it is possible to characterize three different kinds of hydrogen-bond donors and acceptors: metal-bound (1), part of a metal-bound ligand (2), and external to the complex (3). When the metal is coordinated to the hydrogen-bond donor/acceptor, it exerts a strong electronic effect upon the interaction. In such case, one can expect a strong mutual influence between the metal and the interaction formed. If the donor or acceptor is part of a metal-bound ligand the metal can exert both a direct and indirect effect upon hydrogen-bond formation. The metal directly influences a hydrogen bond if there is electronic communication between the metal and hydrogen-bonding groups, and indirectly if the geometry of the complex orients the hydrogen-bonding group(s). From combining these three types of donors and acceptors, a hydrogen bond in a metal complex can be formed in five ways: types 1–1, 1–2, 1–3, 2–2 and 2–3 (Scheme 1). These five combinations can lead to external (or intermolecular) hydrogen bonding when the hydrogen-bond donor and acceptor are part of different molecules, or internal (intramolecular) hydrogen bonds if the interaction occurs within a metal complex. The former types of interactions are particularly relevant to supramolecular chemistry aspects, whereas the latter are more relevant to the chemistry of the individual molecule.



Scheme 1 Types of hydrogen bonding involving metal complexes.

Interactions between metal complexes and other molecules or ions

The interaction of a metal complex with external, non-metal containing molecules or ions can occur through two types of hydrogen bonding: types 2–3 and 1–3. In type 2–3, a metal-bound ligand serves as hydrogen-bond donor or acceptor to external molecules or ions, whereas in type 1–3 it is a metal-bound atom which serves as hydrogen-bond donor or acceptor to the external molecules or ions. On the other hand, a metal complex can be involved in hydrogen bonding with other metal complexes through type 1–1, 1–2 and 2–2 interactions.

Generally, as a result of the positive charge of the metal, coordinated ligands with protons become more acidic leading to stronger hydrogen bonds. This is widely important for instance in aqueous chemistry in which water acts as a ligand. In addition, the geometry of the ligand and complex can also exert an effect upon the interaction by positioning the hydrogen-bonding groups. In turn, these interactions have been shown to affect and enhance the chemistry of the metal complexes involved in aspects of fundamental and practical importance in diverse areas.

Host–guest chemistry

In simple terms a host–guest complex involves a molecule (a 'host') binding another molecule (a 'guest'). Metal complexes can act as both the host and the guest through the involvement of type 2–3 hydrogen bonds. For example, Bondy, Gale and Loeb have created metal complex receptors **1** (Fig. 1) where the geometric preferences and charge of Pt^{II} are exploited to allow two urea functionalities to form hydrogen-bonding interactions with a range of anions (Cl^-, Br^-, I^-, $H_2PO_4^-$ and SO_4^{2-}) which are so captured above or below the square plane of the complex despite not being coordinated to the Pt^{II} centre.[4]

Metal complexes with hydrogen-bonding features have been applied to metal recovery processes for extractive metallurgy. For example, ditopic ligands with separated metal cation and SO_4^{2-} binding sites have been developed. The prototypes, **2** (Fig. 1), developed by Tasker and co-workers, are based upon tetradentate H_2salen-type molecules bearing tertiary amine groups in the ligand periphery, which upon metal binding, deliver two protons to the amine functionalities providing outer-sphere SO_4^{2-} binding sites.[5] These studies have

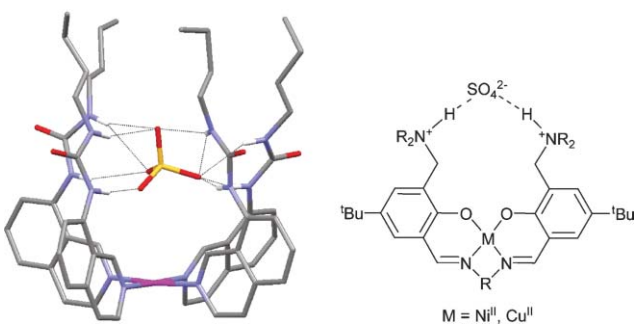


Fig. 1 X-Ray crystal structure of receptor **1** sulfate complex (*left*), and proposed sulfate binding to receptors **2** (*right*).

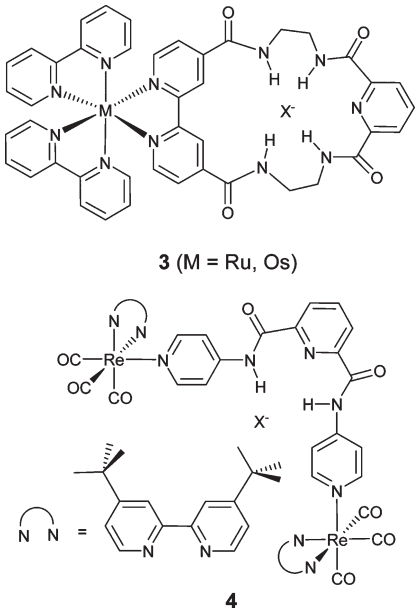


Fig. 2 Representative anion luminescent sensors exploiting type 2–3 hydrogen bonding.

established that incorporation of Ni^{II} or Cu^{II} into the salen $N_2O_2^{2-}$ coordination site templates the pendant dialkylammonium groups to facilitate binding of SO_4^{2-} through type 2–3 hydrogen bonding.

By taking advantage of the photophysical properties of the metal, Lees, Beer and others have created luminescent metal-complex receptors such as **3** and **4** (Fig. 2).[6] These receptors can detect anions held in the proximity of the metal due to quenching of their luminescence upon anion binding. There are also redox sensors in which the anion is held by type 2–3 hydrogen bonds (Fig. 3). Recently, some of these receptors have been immobilised onto gold electrode surfaces using self-assembled monolayers (SAMs) **5**. These SAMs provide improved anion-sensing properties, due to the increased preorganization of the molecule on the surface.[7] Astruc *et al.*

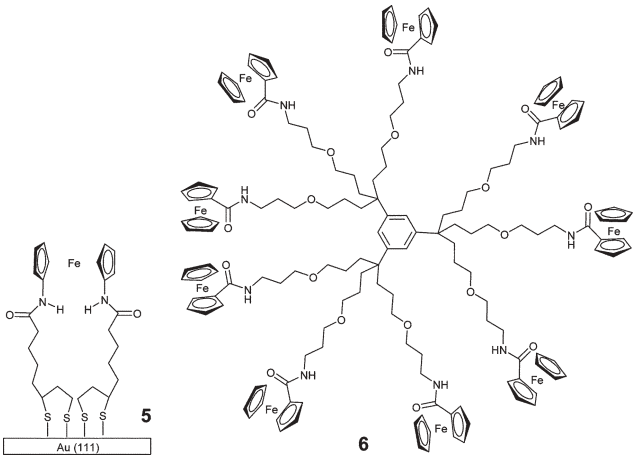


Fig. 3 Redox sensors exploiting hydrogen bonding (type 2–3).

have incorporated similar receptors into dendrimers **6**. An important feature of these dendrimers is that the perturbation of the redox potential caused by the anion increases as size of the dendrimer increases.[8]

It is also possible to take advantage of the redox behaviour of the metal complex to control binding of external molecules by affecting the strength of hydrogen bonding. For example, Astruc *et al.* have immobilised amidoferrocenyl moieties on gold colloidal nanoparticles such as **7** and **8** and found a striking 6000-fold enhancement of $H_2PO_4^-$ binding upon oxidation of the ferrocene (Fig. 4).[9] This is due to the stronger type 2–3 hydrogen bonding obtained by increasing the charge of the metallocene centre, which makes the amide N–H more acidic.

In the examples described above, the metal complex acts as the receptor for external ions. However, there are also receptors for metal complexes exploiting type 2–3 hydrogen bonding. For example, polyammonium aza-crown receptors such as **9** have the ability to bind anionic metal-cyanide complexes (Fig. 5).[10] In some cases, these hydrogen-bonding interactions prevent the escape of the CN^- ligands upon

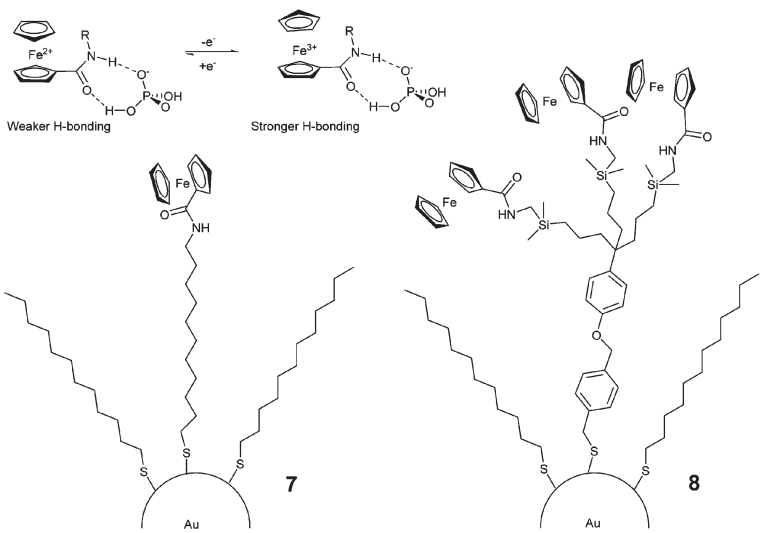


Fig. 4 Schematic representation of redox-controlled binding of $H_2PO_4^-$ to gold colloids by influencing type 2–3 hydrogen bonding.

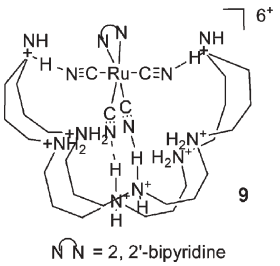


Fig. 5 Proposed H bond-mediated binding between a polyammonium aza-crown receptor and a photoactive metal–cyanide complex guest.

excitation in the metal d–d absorption bands, and in others increase the reduction potential of the complex allowing otherwise unfavourable electron transfer processes.[11]

Although there are more host–guest complexes assembled by type 2–3 hydrogen bonds, there are also some exploiting type 1–3 hydrogen bonding. For example, García-España and co-workers have shown that polyammonium aza-crown receptors have the ability to bind $[PtCl_4]^{2-}$ anions.[12]

Bioinorganic chemistry

Many proteins and enzymes derive their functions from coupled transport of both proton and electron equivalents, making proton coupled electron transfer (PCET) fundamental in biology. Important examples include the photoinduced oxidation of water to oxygen by photosystem II and the reduction of oxygen to water by cytochrome C oxidase. Despite the importance of PCET events, the mechanistic details of how the electron transfer couples to the proton motion are not particularly well-understood. Because hydrogen bonds involve protic groups, metal complexes with hydrogen-bonding groups have been synthesised and studied in the context of investigating PCET processes.[13] These metal complexes have been proven invaluable to understand the mechanism(s) of PCET. Many of these elegant mechanistic studies have been approached by Nocera and co-workers as shown in Fig. 6 with **10**. In this approach, PCET is photoinitiated between a donor (metal complex) and acceptor connected by a hydrogen-bonding interface. The hydrogen-bonding interfaces investigated include symmetric dicarboxylic acid and asymmetric amidinium–carboxylate cyclic linkages, showing that the type of hydrogen-bonding bridge significantly influences the kinetics of electron transfer and the ability to study the accompanying proton motion.[13b]

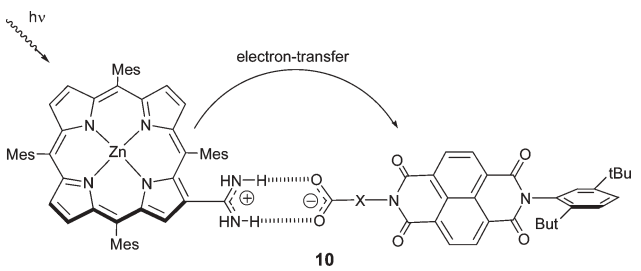


Fig. 6 Proton-coupled electron transfer across type 2–3 hydrogen bonding.

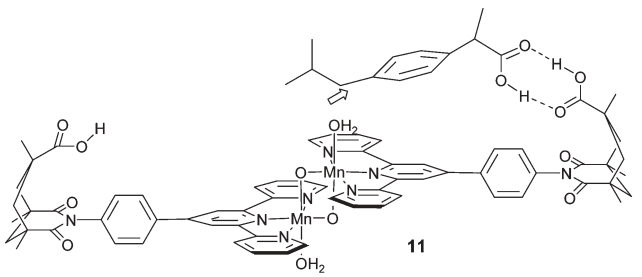


Fig. 7 Hydrogen bonding positioning an ibuprofen molecule for selective C–H bond oxygenation by a dimanganese catalyst.

One function of enzymes that has been rather elusive in models is the ability to orient substrates so that they can be transformed with high regio- and stereoselectivity. One of the few successful examples is a dimanganese catalyst **11** elegantly developed by Crabtree and co-workers (Fig. 7). This remarkable complex exploits hydrogen bonding between ligand-based hydrogen-bonding groups and the external ibuprofen substrate to achieve the long standing goal of selective oxygenation of saturated C–H bonds through a Mn–OH function.[14]

Hydrogen bonding with external molecules or ions can also influence chemistry at metal sites by affecting the bonding of functionally important metal–X units. For example, a key parameter in catalytic zinc sites such as those of metallonucleases, proteases and carbonic anhydrases is the bonding between Zn^{II} ions and water/hydroxide ions. Evidence of Zn–OH bond lengthening by hydrogen bonding with external molecules and ions is provided by monomeric [(L)Zn(OH)] complexes (L = tris(pyrazolyl)hydroborate, $Tp^{R,R'}$) and their interaction with $[(C_6F_5)_3B(OH_2)$.[15a]

In many metalloenzymes, chains of hydrogen-bonded water molecules provide a vehicle for functionally important proton transfers. Walton and co-workers have shown that hydrophobic ligands based on triaminocyclohexane can be used to form metal complexes with similar chains of hydrogen-bonded methanol molecules.[15b]

Medicinal chemistry

An area of intense research in medicinal chemistry is concerned with the rational design of antiviral agents to treat HIV. Macrocycles such as cyclams and bicyclams are of current medical interest because they exhibit strong anti-HIV activity. Clinically, the xylyl-bicyclam **12** is by far the most active and extensively studied cyclam. Zn^{II} binding to xylyl-bicyclam increases its anti-HIV activity. The anti-HIV activity is associated with the ability of the macrocycle to inhibit the virus entry into the cells of the immune system by specific binding to CXCR4 (receptor number 4 for natural chemotactic cytokine proteins containing a conserved Cys-X-Cys disulfide bond, mediators of white blood cell trafficking and activation), a G-protein-coupled, seven-helix transmembrane receptor. To this effect, type 1–3 hydrogen bonding interactions arising from the macrocycle Zn^{II} bound N–H groups are believed to play a key role. Sadler and co-workers have shown that these interactions cooperate with the Zn^{II} cation towards binding carboxylate ligands. From this result and molecular modelling it was then suggested that Glu288 of CXCR4 binds one

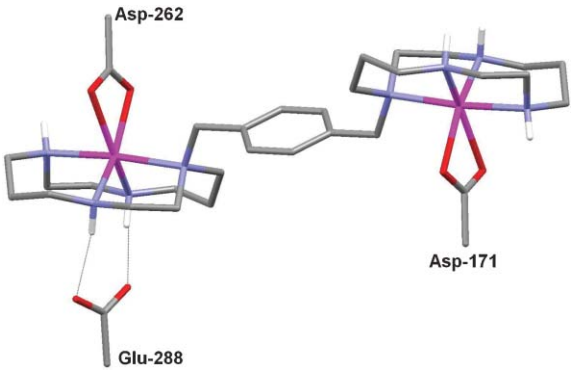


Fig. 8 Proposed binding of the dizinc(II) complex of the anti-HIV drug xylyl-bicyclam **12** to residues of the CXCR4 co-receptor.[16]

Zn^{II}-cyclam unit of Zn^{II}-xylyl-bicyclam with combined metal and hydrogen binding (Fig. 8).[16]

Another area of medicinal chemistry in which hydrogen bonding interactions to and from metal complexes play an important role is magnetic resonance imaging (MRI). MRI is one of the most important current tools in medical diagnosis. Consequently, the development of agents designed to enhance tissue differentiation has become a fertile area of medicinal chemistry. Most of these agents are lanthanide complexes with the ability to increase the image contrast between normal and diseased tissue and/or to provide dynamic tissue function. These contrast agents do this by enhancing the nuclear relaxation times of the water protons of the surrounding tissues through interactions between the metal ion unpaired electrons and proximate water molecules. This intrinsic property of the paramagnetic metal complex known as relaxivity is central to the performance of the contrast agent and it is expressed as the relaxation rate enhancement per millimolar concentration of the contrast agent. The relaxivity is commonly divided into two contributions: inner-sphere (due to protons of the water molecules directly coordinated to the metal) and outer-sphere (dipolar interactions through space with surrounding water molecules). However, this relatively simple relation has been recently modified with the introduction of a second coordination sphere component arising from water molecules held in the second coordination sphere of the paramagnetic metal ion by type 1–3 hydrogen-bonding interactions with hydrophilic groups of the ligand.[17a] The demonstration that the relaxivity due to water molecules in the second coordination sphere can be as much as 70% as the contribution from those in the inner coordination sphere has encouraged the rational design of contrast agents with hydrogen-bonding groups to bring closer and to interact more strongly with non-coordinated water molecules.[17b] These aspects have been explored with complexes of ligands bearing hydrogen-bonding arms such as phosphinate, phosphonate, carboxamide (Fig. 9) *etc.*[18]

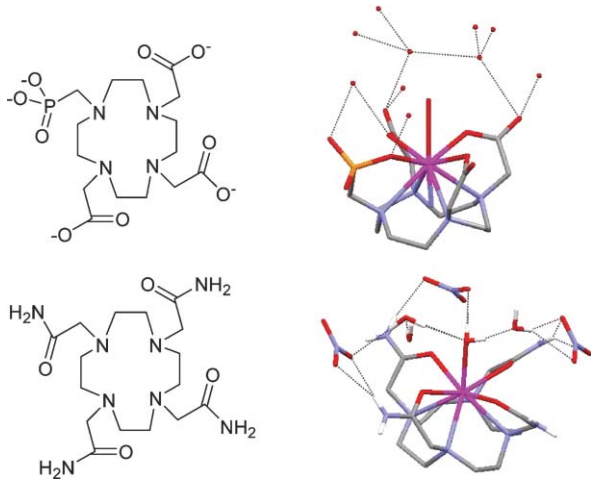


Fig. 9 Schematic representation of some of the ligands and hydrogen-bonding interactions involved in 'capturing' second-sphere water molecules in their lanthanide complexes.[18]

Photochemistry

The idea of using light energy absorbed by a photochemically active transition metal complex for important applications such as to drive endothermic reactions which could be used as a fuel source is a crucial concept in photochemistry. The underlying principle is that the chromophore absorbs a photon of light to enter a long-lived excited state and passes its energy on to the quencher *via* electron or energy transfer. Thus, the selection of suitable chromophore and quencher complexes together with the distance, medium and spatial orientation between them is the basis of this chemistry. Since in the photosynthetic reaction centre the components are not held together by covalent bonds between them, but by non-covalent interactions, the non-covalent association of chromophore-quencher systems has become an important tactic in modern transition metal photochemistry.[19] For the purposes of linking chromophore and quencher complexes as well as for mediating the energy or electron-transfer processes between them, hydrogen bonds are by far the most popular non-covalent interactions. The directionality and combined strength makes multiple hydrogen-bonding interactions ideal for precise and strong linkage between chromophore and quencher components. For example, Ward and co-workers has shown that it is possible to exploit Watson–Crick base pairing in pyridine-based ligands bearing cytosine and guanine nucleobases to achieve strong association in CH_2Cl_2 ($K_A > 5000\ dm^{-3}\ mol^{-1}$), and thereby light-induced energy transfer between ruthenium and osmium complexes of these ligands.[20] Comparison of the electron transfer rates determined on transition metal complexes with type 2–2 hydrogen bonding have shown that, at similar distances, electron transfer rates across hydrogen-bonding interfaces are similar to those observed in covalently bonded donor–acceptor complexes. A nice example is provided by complexes **13** where the Fe^{III}-porphyrin centre acts as an electron acceptor following excitation of the Zn^{II}-porphyrin centre (Fig. 10). Thus, the rate of electron transfer across the dicarboxylate double hydrogen-bonding interface occurs with $k_{ET} = 8.1 \times 10^9\ s^{-1}$, whereas across a saturated carbon covalent bridge of similar length with $k_{ET} = 4.3 \times 10^9\ s^{-1}$.[21a] In fact, in some ruthenium and/or osmium-bipyridine derivatives the rates of intermolecular electron transfer in these hydrogen-bonded complexes were shown to be only modestly slower than in the related, covalently-bonded complexes.[21b] More recently, Rebek, Martin and Guldi and co-workers have

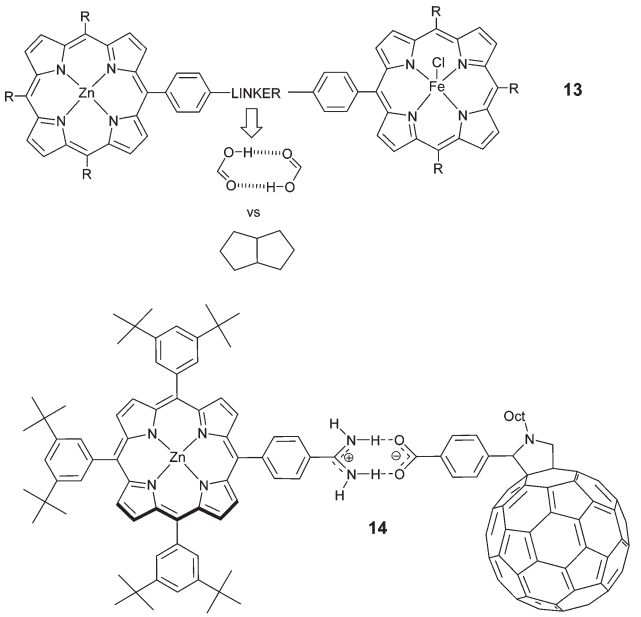


Fig. 10 Energy and electron transfer across hydrogen-bonding interactions (type 2–2 and 2–3).

exploited the selectivity and directionality of hydrogen bonds to facilitate a faster, more effective and longer-lived generation of radical ion pairs between a metalloporphyrin–C_{60} complex **14**, which is relevant to the development of efficient photovoltaic devices.[22]

The strong type 2–3 hydrogen bonding between $[Ru(bipy)(CN)_4]^{2-}$ and a polyammonium aza-crowns has been exploited as a way of linking photoactive compounds for a range of light-induced electron/energy transfer applications. For example, this tactic has been used to create an artificial antenna-energy trap complex resembling natural photosynthetic systems. The system contains four light-harvesting $[Ru(bipy_3)]^{2+}$ units and the $[Ru(bipy)(CN)_4]^{2-}$ complex as the energy trap, covalently and hydrogen bonded to a diprotonated cyclam core **15**, respectively (Fig. 11).[23] Using a similar tactic, Vögtle and co-workers created a supramolecular assembly that produces different optical outputs and behaves according to an XOR or an XNOR logic gate.[24] The system is based upon a dendrimer consisting of sixteen naphthalene units appended to a cyclam core **16**. Assembly and disassembly of the **16**–$[Ru(bipy)(CN)_4]^{2-}$ adducts is achieved upon protonation and addition of a base, respectively, and the optical outputs arise from naphthalene and Ru(bipy)-based emission. In the $\{\mathbf{16}(2H^+)\cdot[Ru(bipy)(CN)_4]^{2-}\}$ supramolecular complex, the naphthalene luminescence is quenched by very efficient energy transfer to the $[Ru(bipy)(CN)_4]^{2-}$ complex.

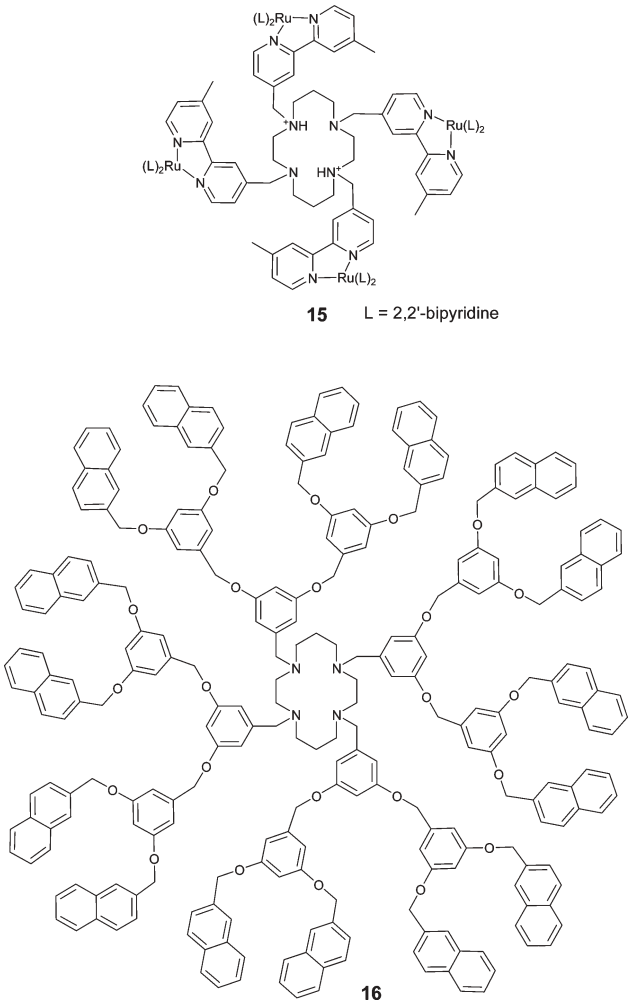


Fig. 11 Photoactive compounds exploiting strong type 2–3 hydrogen bonding with $[Ru(bipy)(CN)_4]^{2-}$.[23,24]

Organometallic chemistry

Counter ion effects resulting from ion-pairing are now recognised as very important in organometallic chemistry. In many cases ion pairing occurs through type 2–3 hydrogen bonding, and differences in their energy can lead to switching of reaction pathways in solution. For example, Crabtree and co-workers have shown that these interactions influence whether reaction of a metal hydride $[IrH_5(PPh_3)_2]$ with 2-pyridylmethylimidazolium salts gives a complex with chelating *N*-heterocyclic carbenes (NHCs) bound at C2 (normal binding mode) **17a** or C5 (abnormal) **17b** (Fig. 12).[25] This is important because NHCs have become universally useful ligands in organometallic chemistry. There are also very important examples of organometallic complexes exploiting type 2–3 hydrogen bonding relevant to catalysis. Complex **18** developed by Noyori and co-workers and some related MCp* systems **19** (M = Ru, Rh, Ir; Cp* = η^5-C_5Me_5; Fig. 12) are examples of organometallic catalysts exploiting hydrogen bonding. Thus, it is believed that these complexes transfer hydridic and acidic hydrogens *via* a concerted hydrogen transfer mechanism featuring hydrogen bonds.[26]

Solid-state chemistry

An important objective of solid-state chemistry is to control the arrangement of molecules and/or ions in the solid state, which is relevant to many disciplines and applications. A widely used strategy consists of using molecular tectons (building blocks) able to self-assemble based upon molecular recognition events.[27] The geometry, charge and properties of metal complexes make them attractive tectons. These can be

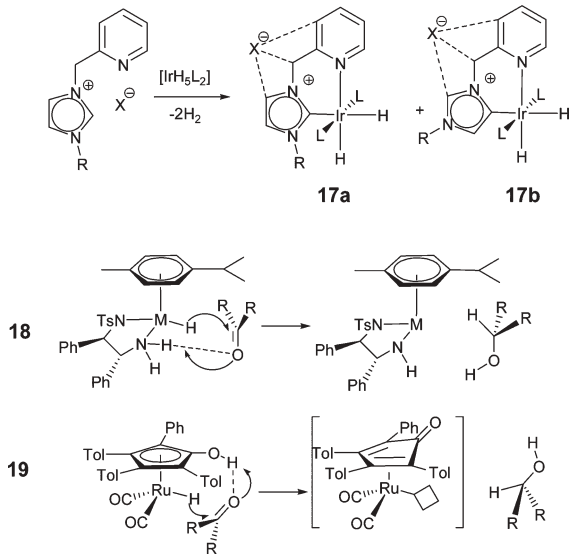


Fig. 12 H-Bonding regulating organometallic synthesis (**17**) and catalysis (**18**, **19**).

combined with organic molecules leading to networks glued by charge-assisted type 1–3 hydrogen bonds. An elegant example illustrating this strategy is provided by the combination of $Au(CN)_2^-$ with bis-amidinium dications which affords crystals with photoluminescent properties dependent upon the Au···Au separation dictated by N–H···NC–Au hydrogen bonding (Fig. 13).[28] Metal complexes in which the geometric preferences of the metal(s) and the structure of the ligand are used to orient the hydrogen-bonding groups has led to supramolecular structures ranging in complexity;[29] chains, squares, 'honeycomb' networks *etc.*, held together by type 2–2 hydrogen bonding. Some of these supramolecular solids have the ability to trap molecules and ions due to hydrogen-bonding interactions, and they exhibit novel optical and/or magnetic properties.[30]

Recent impressive studies have shown that reversible solid-state reactions involving the elimination/uptake of water and HCl from crystalline solids proceeds *via* type 1–3

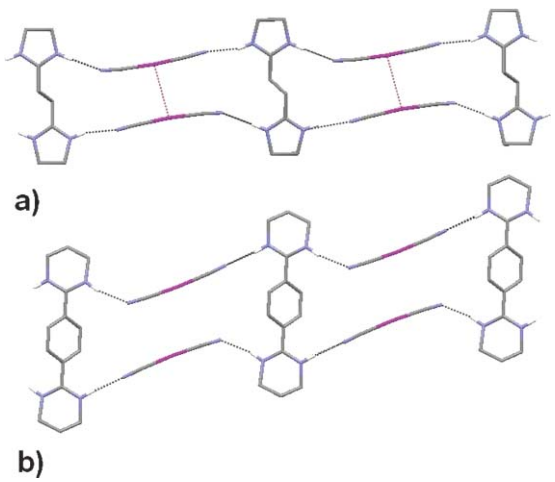


Fig. 13 Arrangement of $[Au(CN)_2]^-$ anions and bis-amidinium dications directed by N–H···NC–Au type 1–3 H-bonds leads to crystals with shorter (a) and longer (b) Au–Au distances and different luminescent properties.

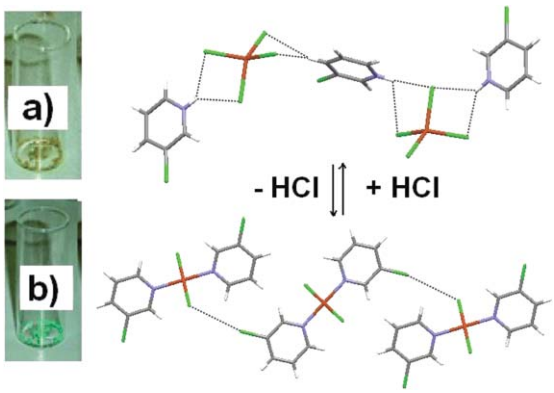


Fig. 14 Elimination/uptake of HCl from a crystalline solid through cleavage/formation of type 1–3 hydrogen-bonding interactions.

hydrogen-bonded precursors. For example, Brammer and co-workers have shown that (3-halopyridinium)$_2$[$CuCl_4$] salts form one-dimensional networks propagated *via* bifurcated N–H···Cl_2Cu hydrogen bond (Fig. 14(a)). This crystalline solid eliminates HCl through cleavage of these hydrogen-bonding interactions and formation of Cu–N bonds, yielding crystals of formula [$CuCl_2$(3-halopyridine)$_2$], and a colour change (Fig. 14).[31a] This process is reversible, with the salt reformed upon exposure to HCl. Orpen and co-workers have shown that a similar reaction occurs upon heating [4-picolinium]$_2$[MCl_4] salts (M = Pt, Pd), in this case to form sequentially [4-picolinium][$PtCl_3$(4-picoline)] and [$PtCl_2$(4-picoline)$_2$] with release of one and two equivalents of HCl respectively.[31b] In some cases, crystalline materials held together by type 2–2 hydrogen bonding can be converted into materials with type 2–3 hydrogen bonding by mechanochemical processes. These solid state reactions are attractive from an environmental point of view because they allow the formation of pure materials without the use of solvents. A beautiful example was reported by Braga *et al.*[32] In this study it was shown that [Fe(η^5-$C_5H_4COOH)_2$] forms O–H···O hydrogen-bonding networks using the carboxylic acid functions, and that upon manual grinding of this organometallic solid with a range of solid diamine organic bases (*e.g.* DABCO) [DABCO-H][Fe(η^5-C_5H_4COOH)(η^5-C_5H_4COO)] is formed, which exhibits O–H···N hydrogen bonding. Real and co-workers has reported that in crystals of [Fe(pmd)(OH_2){$M(CN)_2$}]·H_2O (M = Ag, Au) there are Fe–OH_2···N(pmd)–M hydrogen bonds (type 1–2), which are replaced by Fe–pmd–M bonding, when this compound is heated in the temperature range 345–399 K (M = Ag) and 323–382 K (M = Au). This induces expansion/contraction of the nanoporous structure and alters the spin-crossover behaviour of these materials without affecting their crystallinity.[33]

Interactions within a metal complex

There are many examples of hydrogen bonds in which a metal-bound atom serves as hydrogen-bond donor or acceptor to interact intra-molecularly with a ligand-based hydrogen donor or acceptor within a metal complex (type 1–2 interaction). There are also numerous examples of ligand-based hydrogen-bonding groups interacting intramoleculary (type 2–2). In

some dinuclear complexes a metal-bound atom from each metal serves as the hydrogen-bond donor and acceptor (type 1–1). Recent studies have shown that the importance of these interactions in bioinorganic, host–guest, medicinal and organometallic chemistry is significant.

Bioinorganic chemistry

In synthetic modelling chemistry, it is important to be able to isolate and characterise catalytically active or intermediate functions related to the chemistry of metalloproteins. Generally, this is challenging because model complexes do not have the large protein framework protecting the metal site from the surrounding environment. However, metal complexes with hydrogen-bonding groups have been extremely useful for this purpose (Fig. 15).

In the context of dioxygen activation Masuda and co-workers have shown that {6-Y–TPA–M} (M = Cu, Fe; Y = NH^tCOBu, $NHCH_2{}^tBu$, and NH_2) form hydroperoxo and alkylperoxo species that are thermally more stable than those of tris(2-pyridylmethyl)amine (TPA).[34a] The stability imparted by hydrogen bonding allowed the isolation and first spectroscopic and structural characterisation of a mononuclear copper-hydroperoxo species **20**,[34b] which are postulated intermediates and/or active species in catalytic oxygenation reactions. Metal-oxo species are another important type of intermediate/catalytically active functional groups in dioxygen activation chemistry. Borovik and co-workers have shown that Fe^{II} and Mn^{II} complexes of tris[(*N′-tert*-butylureayl)-*N*-ethylene]amine (H_6buea) and related ligands activate O_2, yielding structurally characterized M^{III} (M = Fe and Mn) complexes with terminal oxo ligands with internal N–H···O hydrogen bonds **21**.[2a,35a] These metal-oxo complexes exhibit unusual spectroscopic, structural and bonding properties, supporting the important possibility that hydrogen bonds can be used to regulate their function. Moreover, it has been found that there is a correlation between the number of hydrogen-bond donors provided by these ligands and the dioxygen binding/activation chemistry of their metal complexes.[35b] Studies by Berreau and co-workers have shown that hydrogen-bonding groups can enhance the hydrolytic stability of zinc-alkoxide species **22**.[36] This is relevant to the zinc-catalysed oxidation of alcohols to aldehydes or ketones by the enzyme liver alcohol dehydrogenase (LADH). In LADH it is proposed that the zinc-bound alkoxide is hydrogen bonded to a serine residue (Ser48) and that this interaction may be functionally important. The zinc-alkoxide is generated by displacement of a zinc-bound water and seems to be the active moiety for hydride transfer to NAD^+ to form NADH and the product aldehyde or ketone. In the context of modelling the chemistry of Zn^{II} metalloenzymes, we have shown that intramolecular N–H···OH–Zn hydrogen bonding stabilises and facilitates the generation of Zn–OH units using $[(L)ZnOH]^+$ complexes (L = TPA derivative with 6-amino or 6-neopentylamino groups) **23** (Fig. 15).[37]

There have been efforts to create $[M(H_3O_2)M]^{2+}$ cores in which a metal-bound water molecule is hydrogen bonded to an adjacent metal-hydroxide (type 1–1 interaction). $[M(H_3O_2)M]^{2+}$ cores have been proposed to be active species of some multinuclear metalloenzymes. This motif is believed to be important in the generation/activation of the nucleophile in hydrolysis reactions. Meyer and co-workers have exploited pyrazolate-based bridging ligands to create these functions and found that the reactivity of these hydrogen-bonded $[Zn(H_3O_2)Zn]^{2+}$ cores is enhanced compared to that of the more frequently observed $[Zn–OH–Zn]^{3+}$ function.[38]

Hydrogen bonding can also affect the chemistry of metalloenzymes by tuning their redox properties. For example, we have shown that N–H hydrogen-bond donors affect the redox potentials of not only redox-active metals but also substrates. For example, Zn^{II} complexes of ligands derived from TPA with 6-amino hydrogen-bonding groups bind 3,5-di-*tert*-butyl-1,2-benzocatecholate ($DTBC^{2-}$) through metal coordination bonds and N–H···O hydrogen bonding.[39a] These type 1–2 hydrogen bonds shift the $DTBC^{2-}$/$DTBSQ^{\cdot-}$ redox couple by as much as 270 mV. Using the same ligands we have shown that the $Cu^{II/I}$ redox potential is increased by 180 mV by intramolecular N–H···Cl–Cu hydrogen bonding.[39b]

A key aspect of synthetic bioinorganic chemistry is to be able to reproduce the important functional properties of metalloenzymes for practical purposes. The fixation and transformation of CO_2 by metal complexes is a long standing topic of considerable current importance for a number of reasons. Excess CO_2 is an atmospheric pollutant responsible for global warming and climate changes, and therefore it is desirable to find efficient solutions for its recovery. CO_2 is also an attractive C1 feedstock for the preparation of useful carbon-containing compounds. Moreover, the activation and reversible hydration of CO_2 to hydrogen carbonate is a physiologically important process. In some very interesting recent reports, the groups of Berreau and Masuda have shown that M–OH species (M = Cd, Zn) stabilised by type 1–2 hydrogen bonding react with CO_2 to form M–CO_3 units.[40] In some cases the process has been found to be reversible, and it seems that hydrogen-bonding interactions between the

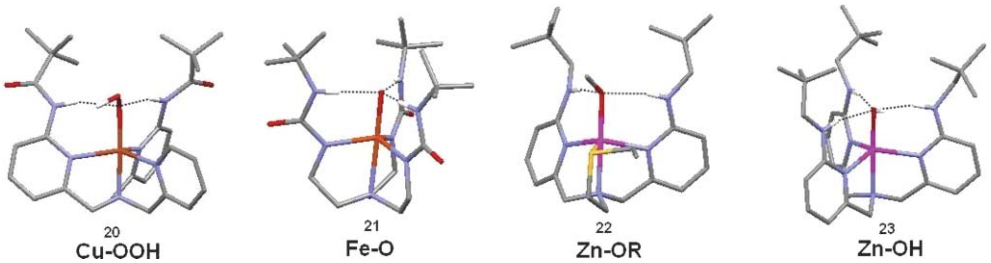


Fig. 15 Biomimetic metal complex intermediates stabilised by hydrogen-bonding interactions (type 1–2).

metal-bound carbonate and ligand based N–H groups may be implicated in this behaviour.

The development of effective, functional synthetic metalloenzyme analogues has been and continues to be a key objective of synthetic bioinorganic chemistry. It is therefore important to examine the extent to which hydrogen bonding features can enhance catalysis.

Several of the most effective transition metal catalysts for hydrolysis of phosphate esters exhibit type 1–2 hydrogen-bonding features (Fig. 16). These interactions have been shown to have the following functions. Chin and co-workers have shown with {(2,9-diamino-*o*-phenanthroline)Cu}$^{2+}$ **24** that these interactions facilitate deprotonation of the copper-bound water at lower pH values and lead to faster hydrolysis of 2′,3′-cyclic adenosine monophosphate.[41] More recently, these effects have been observed for more biologically relevant Zn^{II} complexes **25** and **26**.[42] We have shown that in water, ligands derived from TPA with 6-amino and 6-neopentylamino groups afford stable monometallic zinc complexes such as **26**, in which zinc–water units are up to 2 pK_a units more acidic than in [(TPA)Zn(OH$_2$)]$^{2+}$.[42b] Importantly, these monometallic Zn^{II} complexes are considerably more efficient (*ca.* 10^4-fold) at catalysing hydrolysis of 2-hydroxypropyl-*p*-nitrophenyl phosphate (HPNP) than the TPA complex which lacks the hydrogen-bonding groups.[42c] In fact the catalytic activity of this monometallic complex is comparable to that of the most efficient diZn^{II} complex reported to date, and several orders of magnitude better than any monometallic transition metal complex lacking hydrogen-bonding groups. Moreover, we have shown that the rate enhancement caused by multiple hydrogen-bonding groups in these and related monometallic Zn^{II} complexes is of the same magnitude as that of the metal itself.[42c,43a] The most effective biologically relevant synthetic catalyst created to date for hydrolysis of natural and artificial phosphate esters is **27**.[43b] This catalyst has two Zn^{II} ions and four amino hydrogen-bonding groups that work cooperatively to make the catalyst extraordinarily active.

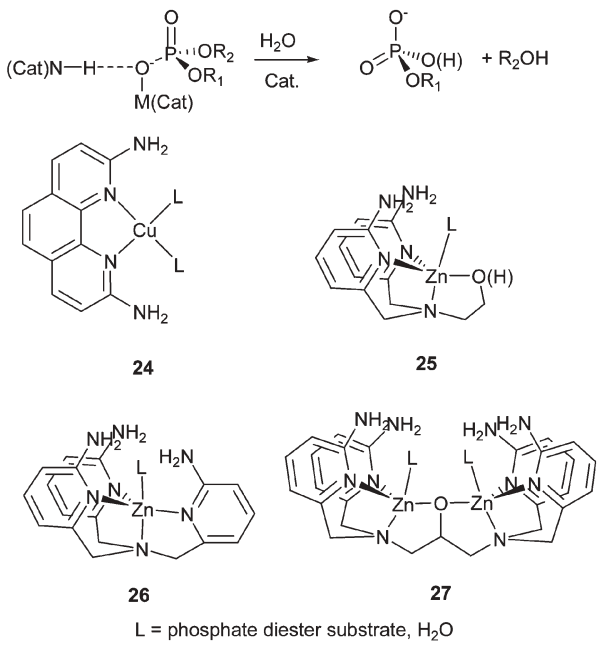


Fig. 16 Exceptionally effective catalysts for hydrolysis of phosphodiesters exploiting type 1–2 hydrogen-bonding interactions.

Like type 1–2 hydrogen bonding, metal complexes with type 2–2 hydrogen-bonding groups have been studied in the context of dioxygen activation chemistry and hydrolysis reactions, leading to metal complexes with enhanced properties.

Nocera and co-workers have developed porphyrin-based ligand platforms for catalytically activating dioxygen and water by PCET. Probably the best molecular construct consists of a xanthene anchor that ''hangs'' a hydrogen-bond group over a redox-active metalloporphyrin, hence they have been designated Hangman porphyrins (HPX).[13,44] The HPX construct allows exquisite control over the nature of the hydrogen-bonding group in terms of proton donating ability and arrangement in relation to the metalloporphyrin redox site. The HPX platform has provided the first model of a redox-active site displaying a monomeric porphyrin ligated Fe^{III}–hydroxide with a structurally well-defined proton transfer network involving a structured water molecule (Fig. 17).[44a] Similar structural motifs are present in heme monoxygenases with postulated roles of fine tuning the redox potential of the heme and/or providing a proton transfer relay during catalysis. The HPX platform is also unique in that with iron it can catalyse dismutation of H_2O_2 to water and oxygen, whereas with manganese it catalyses epoxidation reactions.[44b] It was found that the HPX platform leads to the most effective catalysts for these chemistries when the pK_a of the hanging group is acidic, *ca.* <5.[44c] These studies have suggested that the HPX scaffold stabilises binding of the oxidant by hydrogen bonding and following proton delivery to the putative metal–hydroperoxide it promotes heterolytic O–O bond cleavage to produce catalytically active high-valent metal-oxo species.[44b] However, it is important to note that the hydrogen-bonded network enforced by the HPX platform is not sufficient in itself to stabilize a monomeric Fe^{III}–OH porphyrin function, for this, incorporation of peripheral aryl groups with suitable stereoelectronic properties is also important.[44d]

In the context of catalysts for hydrolysis reactions, monometallic Zn^{II} complexes of terpyridine-based ligands **28** developed by Anslyn and co-workers (Fig. 18), ammonium and guanidinium groups capable of hydrogen bonding to a phosphodiester impart rate enhancements as large as 3300-fold compared to the parent complex without the functional

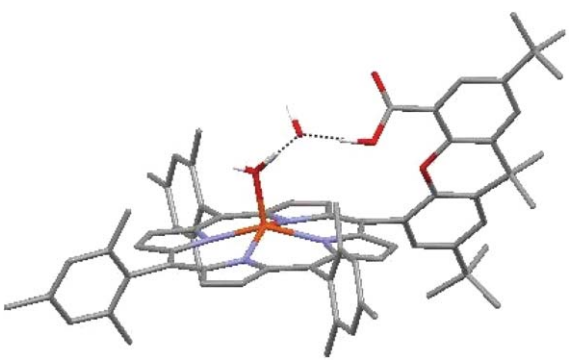


Fig. 17 Porphyrin-based metal complex for dioxygen activation.

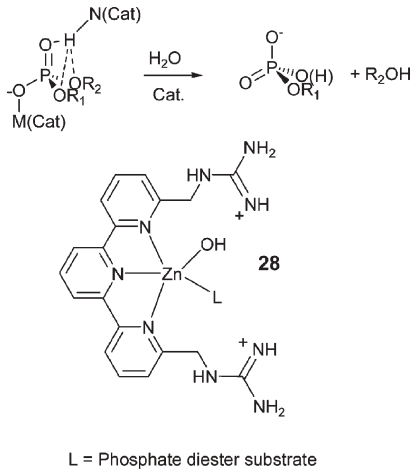


Fig. 18 Effective catalyst for phosphodiesters hydrolysis due to hydrogen-bonding interactions (type 2–2).

hydrogen-bonding features toward the hydrolysis of the RNA dimer adenylyl(3′ → 5′)phosphoadenine (ApA).[45] A possible reason for the enhanced reactivity has been proposed to be double activation of the phosphate by coordination to the zinc center and to one of the guanidinium fragments, followed by Zn−OH general-base-promoted delivery of the 2′-OH group.

Host–guest chemistry

An important challenge in host–guest chemistry is creating receptors that work effectively in water. Organic receptors equipped with acidic hydrogen atoms can provide efficient hosts for anions due to strong complementary hydrogen bonding in non-aqueous solutions.[46] These hydrogen bonds, however, are typically disrupted in water and as a result it is generally difficult to achieve strong binding of guest molecules with organic hosts. Recently, the combination of hydrogen bonding and metal coordination has been proven to be a very powerful strategy for effective host–guest chemistry in water (Fig. 19).[47] For example, cooperation of metal co-ordination and type-1–2 N–H···O–P hydrogen bonding have resulted in stronger phosphate ester binding to a monometallic inert Co^{III} complex **29** and labile Zn^{II} complexes **30**.[47a,b] The hydrogen-bonding groups, although neutral, are rigidly positioned and very close to the phosphate binding site, which allows the formation of the favourable six-membered ring intramolecular hydrogen bond. Similarly, the combination of metal binding, shape, charge and type 2–2 hydrogen bonding increased the affinity of inorganic tetrahedral anions to monometallic Cu^{II} host molecules **31**. Specifically, the binding constant of phosphate obtained, 2.5×10^4 M^{-1} is one of the largest binding constants of phosphate to a synthetic receptor in water at neutral pH.[47c]

Medicinal chemistry

Many DNA-binding agents are designed as potential anticancer drugs. The idea is that such molecules on binding to specific sequences or structures of DNA will modify in some way DNA functions such as replication and transcription killing tumour cells. For this, the combination of

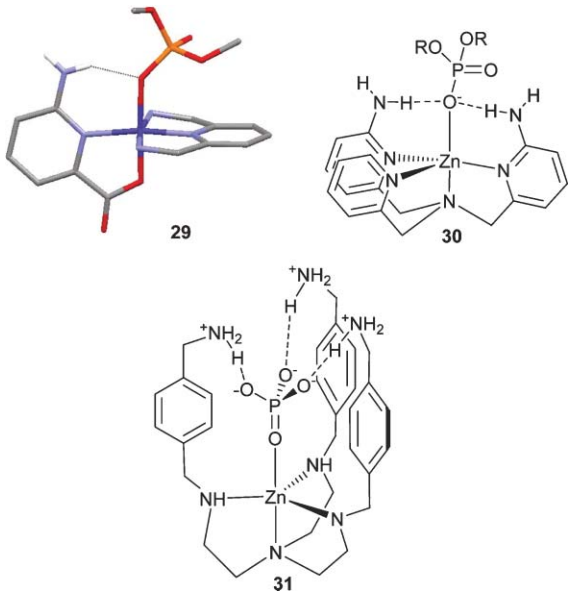


Fig. 19 Efficient metal complex hosts for anions based on type 1–2 and 2–2 hydrogen bonds.

metal-coordination and type 1–2 hydrogen bonding to DNA has been used to enhance affinity, kinetic and selectivity properties of the metallodrug. A consummate example is the anticancer drug *cis*-$[PtCl_2(NH_3)_2]$, often referred to as cisplatin, which preferentially binds guanine sites through N7 of the purine ring and forms N–H···O hydrogen-bonding interactions with the C6=O of guanidine; the latter feature is important at discriminating between adenine (A) and guanine (G) sites (Fig. 20).[48] Although cisplatin is one of the most important anticancer drugs, it has several side effects and resistance problems. Consequently, the design of novel anticancer drugs with improved properties is a fertile area of inorganic chemistry. Most of the newly developed metallodrugs exploit hydrogen-bonding interactions to direct DNA binding. These hydrogen-bonding interactions are of a diverse nature. Examples are provided by the series of organometallic ruthenium and cisplatin-like ethylendiamine complexes shown in Fig. 21. In the Ru^{II} arene anticancer complexes **32** the NH_2 groups of the ruthenium-bound ethylenediamine ligand form type 1–2 hydrogen-bonding interactions with nucleobases.[49] Sadler and co-workers have shown that these interactions play a key roles in favouring site-selective reactions of these ruthenium complexes with nucleobases.[49] For example, for guanine, N7 is the preferred binding site for ruthenium binding and X-ray crystallography suggests the formation of a strong

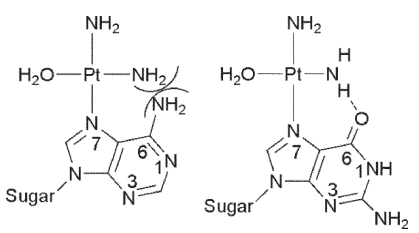


Fig. 20 Discrimination between adenine and guanine sites by cisplatin due to hydrogen-bond interactions.

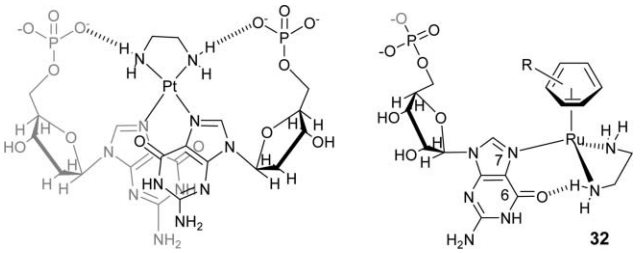
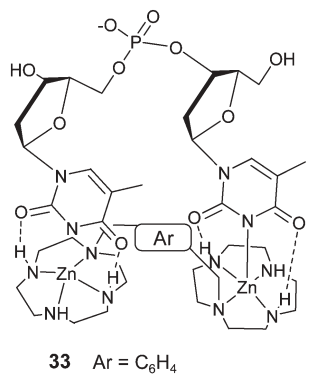


Fig. 21 Potentially important hydrogen-bonding interactions in DNA binding of second generation anti-cancer metallodrugs.

N–H···O hydrogen bond between one N–H of the ruthenium bound ethylendiamine ligand and the G C6=O. Coordination of N1 is unfavourable as it would lead to the repulsive interaction between en and guanine NH_2 groups. Inosine (I), in contrast to guanine lacks the NH_2 groups and consequently, Ru–N7 and Ru–N1 adducts are formed. Applying this reasoning it is possible to explain the overall found binding preference order of the Ru(arene) for the different nucleobases; G(N7) > I(N7) > I(N1), T(N3) > C(N3) > A(N7), A(N1). Consequently, in competitive nucleobase reactions with these ruthenium complexes there is remarkable selectivity for G(N7) recognition.[49a,b] When the ethylendiamine ligand is replaced by hydrogen-bond acceptor ligands such as acetylacetonate, the ruthenium arene complex recognises A due to complementary interactions with the C6 NH_2 group.[49c]

Also important is Zn^{II}-acridinylmethylcyclen developed and studied by Kimura and co-workers. This complex recognises thymine and uracil nucleobases from the cooperation of metal coordination and hydrogen bonding.[50a] Similar binding features are responsible for the recognition of bis(Zn^{II}-cyclen) **33** (Fig. 22) and tris(Zn^{II}-cyclen) complexes of a dinucleotide, d(TpT), and a trinucleotide d(TpTpT), respectively.[50b] These properties have been shown to be of considerable and diverse biological and/or medicinal importance.[51] For example, these zinc complexes are capable of disrupting A–dT (or A–U) hydrogen bonds in double-stranded DNA (or RNA). One of the effects of disintegrating the A–T base pairs was that the separated A partners were made more susceptible to digestion by micrococcal nuclease, whereas the T sites were protected.[52a] Zn-acridinylmethylcyclen also binds selectively to the AT-rich DNA sequence located some 25–30 bases upstream from the transcriptional start sites, known as the TATA box region.[52b]



33 Ar = C_6H_4

Fig. 22 Recognition of a dinucleotide through type 2–2 hydrogen-bonding interactions.

This is important because some transcriptional factors such as TBP (TATA binding protein) must bind to the TATA box region for initiation of transcription. As a consequence, this complex was shown to inhibit the formation of the TBP–TATA complex and hence may have potential as small molecular genetic transcriptional regulation factor.

Because there is a direct correlation between the binding of the HIV-1 regulatory protein, Tat, to the U-rich bulge of a TAR (trans-activation response) element RNA and up-regulation of HIV-1 mRNA transcription, protection of the U-rich bulge provides a mechanism to inhibit transcription of the HIV-1 genome. Bis(Zn^{II}-cyclen) and tris(Zn^{II}-cyclen) have shown the ability to strongly protect the UUU bulge of the TAR element by cooperating zinc and hydrogen bonding, and as a result they have in vitro anti-HIV and anti-microbial activities.[52c] Bis(Zn^{II}-cyclen) complexes have been shown also to have the ability of protecting nucleic acids from photo-damage on exposure to UV radiation.[52d] This property is of significance because it is known that exposure of cellular nucleic acids to UV radiation leads to a variety of lesions, which can be carcinogenic, mutagenic or cytotoxic. In addition, lipophilic derivatives of monomeric and dimeric Zn^{II}-cyclen complexes have been shown to be selective and effective carriers of dT (or U) nucleotides.[52e] This is significant because a variety of nucleoside-based drugs such as AZT, 2′,3′-dideoxycytidine and 2′,3′-dideoxyadenosine are currently used in the treatment of AIDS as HIV reverse transcriptase inhibitors. Thus these zinc-cyclen complexes with cooperating zinc and N–H hydrogen-bonding groups as selective and effective nucleotide binding elements could prove to be useful for more effective drug administration.

Organometallic chemistry

Pioneering studies carried out by Crabtree and co-workers with 2-aminobenzoquinolate as a ligand showed the potential importance of type 1–2 hydrogen bonding in organometallic chemistry (Fig. 23). These studies revealed that ketones could be bound both by N–H···O hydrogen bonding and coordination to the metal more tightly than without the hydrogen-bonding groups. This holds the ketone in the benzoquinolate plane, leading to selective binding of 2-hexanone over 3-hexanone, non-existent when the NH_2 hydrogen-bonding group is absent.[53] The same ligand system was tested for dihydrogen activation, a potential first step in catalytic hydrogenation. The reaction of the metal complex with H_2 leads to a complex in which H_2 has been split heterolytically.[53b] In the absence of the NH_2 group a molecular hydrogen complex is formed. More recently, Grotjahn and Lev have shown that metal complexes with type 1–2 hydrogen bonding can provide exceptionally effective catalysts for the anti-Markovnikov hydration of terminal alkynes under neutral, mild conditions with low catalyst loading (Fig. 23).[54] For example, catalyst **34** has given an impressive rate acceleration of 2.4×10^{11} fold and changes in the selectivity by a factor of over 3×10^6 over the uncatalyzed reaction at neutral pH. It is impressive that these relatively simple organometallic complexes in which the metal and hydrogen bonds cooperate provide enzyme-like reaction rate acceleration and selectivity.

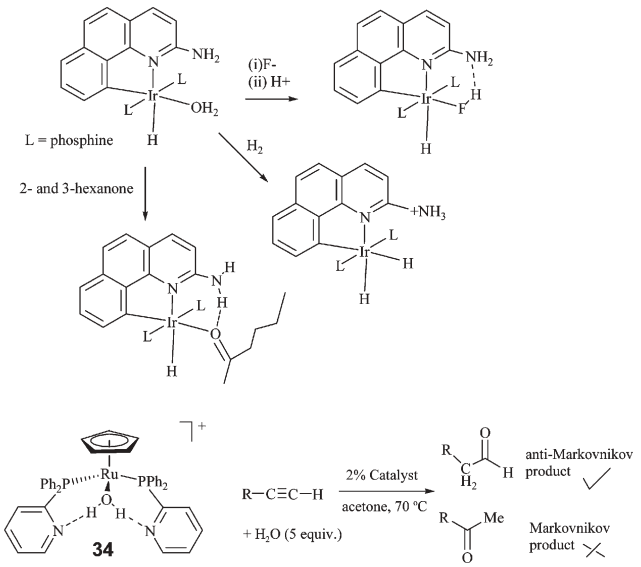


Fig. 23 Efficient organometallic catalysts based upon type 1–2 hydrogen-bonding interactions.

Conclusions and outlook

In conclusion, combining the properties of transition metals with those of hydrogen bonds has become widely important in inorganic chemistry. The past few years have provided striking examples of hydrogen bonding within a metal complex or between a metal complex and external molecules exerting important structural and functional effects in many areas, both by accident and by design.

From the preliminary work discussed in this review and related work it is clear that the study and use of hydrogen bonds as complementary interactions in inorganic chemistry has an undeniable potential and it is likely to grow.

Several of the most important current chemistry challenges provide timely opportunities for using the combined properties of transition metals and hydrogen bonds for practical purposes. For example, one approach to develop new materials for energy production and storage could be a biomimetic one, where light and catalysts are used to promote multielectron transfers coupled to proton transfer to form cheap carbon-neutral fuel molecules.[55] This review has shown that hydrogen-bonding interactions can be a suitable vehicle for this. In addition, hydrogen-bonding groups in the vicinity of transition metals may be useful to regulate the formation of H_2 and O_2 from water, and the oxidation of reduced fuel molecules such as methane with O_2. In medicinal chemistry, the design of effective agents to fight and diagnose serious conditions and diseases such as cancer and HIV will continue to attract major research efforts, and may benefit from the combination of metals and hydrogen bonding as shown in this article. The specific case of mimicking the effective phosphate ester cleaving chemistry of ribozymes with synthetic complexes could provide exciting opportunities in gene therapy. For example, recent advances in nanotechnology[56] should allow the incorporation of RNA cleaving agents that are both effective and selective into antisense, cell-permeating nanoparticles to target genes associated with cancer, Alzheimer's *etc.*. In the fields of nanotechnology and materials chemistry hydrogen bonds and transition metals are already essential structural and functional elements of many materials. However, improving our ability to predict and induce the formation and reactivity of solid structures of more complicated metal complexes may enable the construction of solids with more advanced properties and applications. Although organometallic chemistry has provided spectacular catalysts and chemistry without the use of hydrogen bonds, recent results suggest that hydrogen bonds have the potential to become important functional elements in organometallic chemistry. This may prove particularly important as water is becoming an important solvent in organometallic chemistry.[57] The increased demand for sensors for security and biological imaging applications provides additional opportunities for combining the properties of transition metals with those of hydrogen bonds. It is likely that the new sensors and devices will take further advantage of developments in other areas such as polymer, surface and combinatorial chemistry and of emerging nanotechnologies to enhance their selective, sensitivity and practical uses. In this context, sensing arrays that use new dendritic or polymeric structures, metal or semiconductor fluorescent nanoparticles[58] and SAMs[59] combining the properties of metals and hydrogen bonds could become important.

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