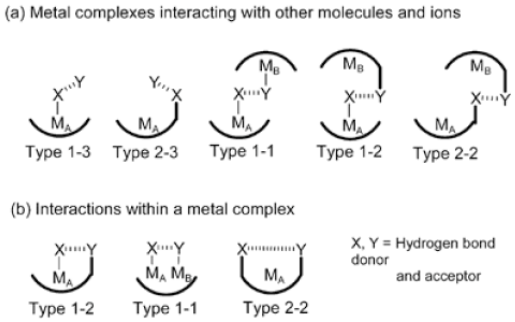
The Combination of Transition Metal Ions and Hydrogen-bonding Interactions in Bioinorganic Chemistry

Lanyu Lei Literature Seminar December 4, 2007

Many metal complexes have groups capable of forming hydrogen bonds, whose strength ranges widely and can be as strong as 155 kJ/mol.[1,2] The combined properties of metals and hydrogen bonds have been exploited extensively in the chemistry of biological systems. For example, the positive charge of the metal increases the acidity of coordinated ligands that bear protons, leading to stronger hydrogen bonds.[3] In turn the hydrogen bonds around the active sites of metalloenzymes can fine-tune or enhance the catalytic acitivity.[4-11]

Hydrogen bond donors and acceptors fall into three types: metal-bound (1), ligand based (2), and external to the complex (3). By 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).[2]



Scheme 1 Types of hydrogen bonding involving metal complexes.

To undertand the mechanism of proton coupled electron transfer (PCET), which is a fundamental function of many enzymes in biology, Nocera and coworkers carried out a comparative study of electron transfer through an asymmetric interface formed from a 1:1 association of an amidinium to a carboxylate via two hydrogen bonds. The rate of electron transfer through the donor-amidinium-carboxylate-acceptor assembly is ~40 times slower than that for the pair when the interface is switched to donor-carboxylate-amidinium-acceptor, inferring that the type of hydrogen bonding bridge significantly influences the kinetics of proton coupled electron transfer. [4]

Another important function of hydrogen bonding in metalloenzymes is orienting substrates in an appropriate way to enhance catalytic activity or achieve high catalytic regio- and stereoselectivities. A remarkable example is the dimanganese catalyst developed by Crabtree and coworkers.[4] This dimanganese complex, $[H_2O(L)Mn(\mu\text{-}O)_2Mn(L)OH_2](NO_3)_3$ (L is 2,2':6',2"-terpyridine) is modified by introducing a ligand-based hydrogen bonding group (–COOH) at an appropriate position on L to achieve molecular recognition. Oxidation of ibuprofen can occur at either of two benzylic sites, but owing to its bonding interactions with –COOH group on the catalyst (**Fig. 1**), only one of these two sites is oxidized on the Mn complex with a regioselectivity as high as >98％.

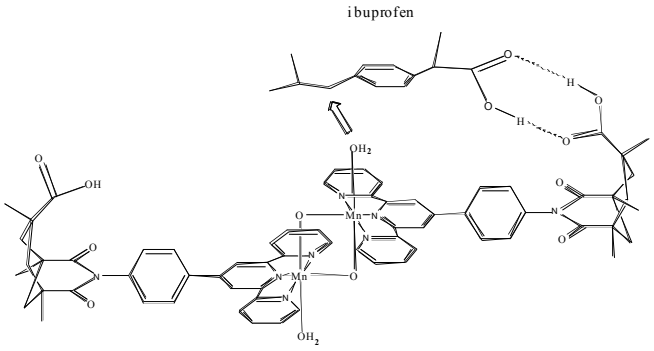


Fig. 1 Type 2-3 H-bonding positioning an ibuprofen molecule for selective C-H bond oxygenation by a dimanganese catalyst

Hydrogen bonding with external molecules or ions can also influence chemistry at metal sites. For instance, a key feature of zinc-containing enzymes such as metallonucleases, proteases and carbonic anhydrases is the protonation state of the aqua/hydroxo ligand: [ZnOH] vs $[Zn\text{-}OH_2]^+$. The Zn–O bond in $[Tp^{But},Me]$-ZnOH is lengthened through a hydrogen bonding interaction with a $(C_6F_5)_3B(OH_2)$ molecule to form $\{[Tp^{But},Me]Zn\text{-}(OH_2)\}[HOB(C_6F_5)_3]$. This hydrogen bonding interaction is suggested to be analogous to that between the aqua ligand and Thr-199 at the active site of carbonic anhydrase.[5]

A challenge in investigating catalytic mechanism of metalloproteins is to isolate and characterize the catalytically active species or intermediates. Metal complexes with hydrogen bonding groups have been extremely useful in meeting this challenge by mimicking the protein framework and protecting the active site from the surrounding environment. For instance, Masuda and coworkers have reported that the stability imparted by hydrogen bonding allowed the isolation and first spectroscopic and structural characterization of a mononuclear copper-hydroperoxo species, which is a postulated intermediate and/or active species in catalytic oxygenation reactions.[6] Their later work has shown that the thermal stability of (μ-peroxo)dicopper complexes can be regulated with intramolecular hydrogen bonding interactions.[7] By employing a tris(2-pyridylmethyl)amine (TPA) ligand with attached pivalamido and amino groups, they obtained hydroperoxo and alkylperoxo species that showed high thermal stability.

In recent years much attention has been given to the design of synthetic metallonucleases for the cleavage of RNA or DNA due to their potential applications as therapeutic agents. Mareque-Rivas has quantified the relative contributions of hydrogen bonding, the hydrophobic environment and coordinating groups to the acidity of the zinc(II)-water group and found that the hydrogen bonding is far more important than the other two factors.[2] They successfully synthesized both mononuclear[8a),b)] and dinuclear Zn(II) complexes[10c)] that are remarkably active for phosphodiester cleavage by introducing type 1-2 hydrogen bonding interactions.

Metal complexes with type 2-2 or type 1-1 hydrogen bonding groups have also been studied in the context of dioxygen activation and hydrolysis reactions. Monometallic Zn(II) complexes of terpyridine-based ligands developed by Anslyn and co-workers bearing ammonium and guanidinium groups capable of hydrogen bonding to a phosphodiester accelerate the hydrolysis of the RNA dimer adenylyl phosphoadenine (ApA) by as much as 3300-fold compared to the parent complex without the hydrogen bonding groups.[9] A possible

reason for the enhanced reactivity is 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.

An example of the application of the type 1-1 interaction can be found in 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. $[M(H_3O_2)M]^{2+}$ cores have been proposed to be active species of some multinuclear metalloenzymes and 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 $[Zn–OH–Zn]^{3+}$ unit.[10]

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