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Harnessing the active site triad: merging hemilability, proton responsivity, and ligand-based redox-activity

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Abstract

Metalloenzymes catalyze many important reactions by managing the proton and electron flux at the enzyme active site. The motifs utilized to facilitate these transformations include hemilabile, redox-active, and so called proton responsive sites. Given the importance of incorporating and understanding these motifs in the area of coordination chemistry and catalysis, we highlight recent milestones in the field. Work incorporating the triad of hemilability, redox-activity, and proton responsivity into single ligand scaffolds will be described.

Introduction

The most important chemical reactions that occur in Nature are carried out by metalloenzymes. The active site, in conjunction with the secondary and outer sphere(s) of these enzymes provide a tuneable environment capable of performing a vast number of recalcitrant reactions. For example, the nitrogenase enzyme can catalyse the six proton, six electron conversion of dinitrogen to ammonia at atmospheric conditions, while the industrial production of ammonia *via* the Haber–Bosch process requires high temperatures and pressure, resulting in the consumption of 2% of global energy¹ and is a major contributor of annual global CO₂ emissions.² Three key features allowing for the tunability of metalloenzymes^{3–8} are redox-activity, hemilability, and proton responsivity, where proton-responsivity is defined here as the ability to accept or donate a proton. Nature often couples proton responsivity and redox-activity, preferring the more efficient proton coupled electron transfer (PCET)^{5,6} to transferring each moiety separately. The function of hemilability in both biological and synthetic systems^{9–15} is primarily to stabilize otherwise unfavorable intermediates by filling a vacant coordination site. This variable binding motif can be found stabilizing resting states,¹⁶ actively participating in catalytic cycles,^{4,17} or stabilizing high energy intermediates in enzymes and catalysts.^{18–21}

A classic example where the triad of hemilability, proton responsivity, and ligand-based redox-activity are incorporated into a single active site is in galactose oxidase. Galactose oxidase (Fig. 1, left) is a fungal enzyme that oxidizes primary alcohols to aldehydes, coupled with a reduction of dioxygen to hydrogen peroxide.^{3,17} The alcohol oxidation undergoes a

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Conflicts of interest

There are no conflicts to declare.

proton transfer, followed by a hydrogen atom transfer and a single electron transfer. The axial tyrosine, Tyr495, displays both hemilability and proton responsivity, by accepting a proton from the alcohol then dissociating from the copper (Fig. 1, right). The copper(I) center of the reduced enzyme has been shown to be three coordinate by XAS,²² illustrating the importance of hemilability, providing favourable coordination depending on the oxidation state of the copper. The equatorial Tyr 272 exists as a radical in the resting state.²³ A hydrogen atom is transferred from the substrate to this Tyr-Cys residue, forming a ketyl radical as the rate limiting step. This is followed by a single electron transfer to the copper, forming the aldehyde (Fig. 1, right).¹⁷

There are numerous, elegant reports of synthetic systems that draw inspiration from Nature, either to help understand complex chemistry utilizing simpler models (bioinspired),^{24,25} or to copy useful functionalities of biological systems like enzymes (biomimetic). These systems have been reviewed in detail^{26,27} and are outside of the scope of this article. However, some notable, recent examples incorporating some of the motifs described above are shown in Fig. 2. These include the stabilization of metastable Mn-peroxo species *via* the open coordination sites provided by the hemilabile N4S ligand platform¹⁸ ($\text{S}^{\text{Me}_2}\text{N}_4(6\text{-Me-DPEN})$) (**A**, Fig. 2), and the reported catalytic reduction ($\text{TON} = 3.5$) of NO_3^- to NO^{28} *via* diphenylhydrazine on the bioinspired, proton-responsive Fe-trispyrrole platform (**B**, Fig. 2). Other prominent advances are the reported deoxygenation of NO_3^- to NO on the proton responsive bispyrazol-pyridine scaffold (**C**, Fig. 2);²⁹ the proton-switchable, bifunctional isoindoline ligand scaffold capable of facilitating hydroborations; (**D**, Fig. 2)¹⁹ and the polymerization of lactides facilitated by hemilability in the pyridinediiminine (PDI) ligand.¹⁴ Lastly, the resurgence in metallocrown ethers as switchable catalysts has recently been reviewed.¹⁵

Two out of three motifs

Studies that incorporate the triad of redox-activity, hemitability, and proton responsivity, all in a single ligand scaffold, are exceedingly limited.^{30,31} However, recent noteworthy advances in proton and electron flux management by incorporation of two of the three motifs into single ligand scaffolds have been made. Hydrogen-atom noninnocence of ligand scaffolds^{32,33} can be an effective method of moving both protons and electrons (as an H atom).³⁴ We are choosing to focus here on work involving proton-responsivity in terms of proton donors/acceptors in the secondary coordination sphere.

Building on the previously reported trispyrrole tripodal system, ($\text{tris}(5\text{-cycloiminopyrrol-2-ylmethyl})\text{amine} = \text{H}_3[\text{N}(\text{pi}^{\text{Cy}})_3]$),²⁸ the bispyrrole-trispyridine, 2,2',2'-methylbis-pyridyl-6-(2,2',2'-methylbis-5-cyclohexyliminopyrrol)-pyridine ($\text{Py}_2\text{Py}(\text{pi}^{\text{Cy}})_2$), hybrid was recently designed to contain ligand-based redox-active functionalities in conjunction with hydrogen bond (H-bond) donors in the secondary coordination sphere³⁵ ($[\mathbf{1}]^+$, Fig. 3). This compound mimics the short lived intermediate in the nonheme iron 2-oxoglutarate enzymes.³⁶ $[\mathbf{1}]^+$ was shown to be proton responsive, with deprotonation forcing tautomerization. Additionally, the compound was evaluated in both the stepwise addition/removal of a proton and an electron separately; or together as an H atom. To verify that the compound was behaving as an iron nonheme 2-oxoglutarate enzyme mimic it was then used to hydroxylate

Gomberg's dimer, corroborating the likely mechanism the enzyme uses for hydroxylation (Scheme 1, bottom).

An example of systems that demonstrate both hemilability and proton responsivity are the PN-ligands shown in Scheme 2. Depending on the protonation state of the ligand, the ligands can exist as either the neutral bidentate PN-system, or as the anionic tridentate PNC-system. The PONC_{Ph} nickel containing compound **2** is active for the C–H functionalization of arenes (Scheme 2, top), which is postulated to involve a nickel metallocycle.^{37,38} By including the arene in the ligand as a hemilabile arm, this intermediate was trapped.³⁹ Additionally, the 2-di(*tert*-butylphosphinomethyl)-6-phenylpyridine ligand scaffold metallated with rhodium (complex **3**) was able to generate H_2 and CO_2 from formic acid.⁴⁰ The catalytic cycle invokes proton responsivity in the hemilabile arene ring (Scheme 2, bottom). This proof of principle revealed the importance of the bifunctionality of the ligand scaffold and metal, achieving a modest TOF (169 h^{-1}).

A hemilabile ligand that is able to incorporate ligand-based redox-activity is the pyridinediimine (PDI) system shown in Scheme 3. Merging both motifs is not only useful in studying reaction intermediates, but can also play a key role in catalysis. The manganese complex of the phosphine functionalized PDI ligand (Ph_2PPrPDI) (**4**, Scheme 3) is a highly active catalyst for the hydrosilylation of carbonyls and carboxylates.^{20,41,42} TOFs of up to 4900 min^{-1} with a turn over number (TON) of 31 000 were reported. The hemilabile nature of the phosphine arms stabilize the active sites where both substrate and hydride can bind. These sites allow for access to the metal center where the oxidative addition of the Si–H reagent can occur, while also allowing enough space for the reversible coordination to the carbonyl bond of the second substrate. In the postulated mechanism, the substrate is thought to insert into the Mn–H bond of **5** (Scheme 3), followed by reductive elimination to regenerate the starting material (which is once again stabilized by the hemilabile phosphine arms). Additionally, the redox non-innocent nature of the PDI ligand scaffold allows for the storage of multiple electron equivalents. In the proposed catalytic cycle, the metal center does not cycle oxidation states; the electrons are instead shuttled to and from the ligand for storage through oxidative addition and reductive elimination.

Harnessing the triad

As stated above, systems that incorporate redox-activity, hemilability, and proton responsivity, all in single ligand scaffolds are rare. However, two recent ligand systems that intentionally integrate hemilability, proton responsivity and redox activity^{43–45} display some exciting chemistry pertinent to the topics of energy storage (from water) and nitrogen management. The first set of systems is based on the diiminopyrrole ligand scaffold 2,5-bis(*N*-cyclohexyl-1-(*p*-tolyl)methanimine) pyrrolide (Tol,CyDIPy). The palladium-chelated system (**6**, Fig. 4) utilizes the extended conjugation along the backbone and imine arms to allow for storage of electron equivalents in the ligand scaffold (as indicated by EPR). Another feature of the ligand system is the ability to protonate one imine arm at a time, facilitated by the variable binding around the metal center, with the binding to the palladium changing from κ^3 to κ^2 as the protonated arm is released from the metal. By storing both

protons and electrons in the same ligand scaffold the system is primed for PCET, however this reactivity has not yet been reported.

Replacing the imines in the diiminopyrrole system (Fig. 4, left), with hydrazono arms (Fig. 4, right) allow for varied binding (hemilability) and protonation states near the metal center. Again, the conjugated backbone allows for storage of electron equivalents, in the form of ligand-centered radicals. By incorporation of the triad into one ligand framework, a wide range of binding and redox states are available. Of particular note is the ability to homolytically cleave water and use/store the water as a hydroxide and a proton. The nickel complex **7** (Fig. 4 and Scheme 4) has been reacted with water in the presences of a variety of phosphines, demonstrating homolytic water splitting, as well as the ability to transfer the oxygen to substrate. The ligand system does unfortunately have a tendency to incorporate substrate into itself, including insertion of acetonitrile into a hydrazono arm, or the C–H activation of appended phenyl groups (Scheme 4). Catalytic turnover has not been reported with this system.

The second set of system(s) to fully harness the triad was recently reported by us. We have focused on tailoring the secondary coordinate on sphere of the PDI scaffold coordination sphere with pendant amines^{47–49} of varying pK_a and steric groups to tune the reactivity. This allowed us to induce both hemilability and proton responsivity, coupled with ligand-based redox sites in the highly versatile PDI platform. Using a diisopropylamine pendant group we were able to show protonation of the direduced dicarbonyl complex resulted in activity in the reduction of nitrate and nitrite to nitrosyl.⁴⁶ By tuning the sterics (and pK_a) of the pendant base(s) from diisopropylamine to pyrrolidine, hemilability was incorporated. Achievement of the triad resulted in 40-fold enhancements in the initial rate of nitrite reduction. The unique $\{\text{FeNO}\}^7$ mono-nitrosyl iron complex (MNIC) shown in the middle box of Scheme 5 was isolated as an intermediate on the nitrite reduction reaction coordinate, demonstrating the importance of incorporating hemilability, redox activity and proton responsivity into one complex.⁵⁰ This work provides important insight into the design of complexes responsible for the reduction of nitrate and nitrite.

Future frontiers and looking toward the tetrad

Incorporating the triad of proton responsivity, redox-activity and hemilability into single ligand scaffolds will unlock exciting chemistry in the future, particularly in the areas of energy, nitrogen recycling, small molecule activation, and catalysis. One of the more difficult aspects to intentionally design into the scaffold is hemilability. Attempts have been made to systematically design small ligand platforms containing hemilability,⁵¹ often concentrated around small modifications to a platform already known to be hemilabile. Furthermore, early systems were typically serendipitous.²¹ In addition, both sterics and electronics affect a platform's hemilabile binding affinity, and the delicate balance between the two must be considered (in addition to the individual metals used). Originally HSAB was used to describe the hemilabile binding of phosphine-amine and phosphine-ether ligands to a metal center,⁵² but in more complicated systems, such as pincer, tripodal, or scorpionate ligand scaffolds, this becomes inadequate to describe the full picture, proving difficult to predict or design. In these cases, sterics also play a large role, as well the

preferred geometry of the metal center within the range of anticipated redox states. That said, ligand scaffolds that incorporate the triad will continue to be designed to stabilize high energy intermediates while enabling the control of the proton/electron flux, through either PCET or the separate transfer of proton(s) and electron(s). The incorporation of all three aspects, when coupled with appropriate metal centers will allow for a wide range of chemistry, especially activation of small molecules.

In the face of climate change brought on by the burning of fossil fuels there is a pressing, urgent need for alternative fuels.⁵³ Water oxidation is a route to provide alternative fuel sources to fossil fuels.⁵⁴ There is a wealth of redox active synthetic systems for this purpose⁵⁵ and turning to Nature will help provide solutions to this issue. As shown in Fig. 5, the Mn_4CaO_5 cluster of photosystem II utilizes the triad described above to catalyze the oxidation of water into oxygen and protons.⁵⁶ This reaction uses cycling oxidation states,⁵⁷ extensive hydrogen bonding networks^{58,59} to shuttle protons, redox active residues, and conformation changes (hemilability)^{60,61} to catalyze this difficult reaction.

Recent advances on incorporating aspects of the OEC have focused on synthetic manganese-oxo clusters incorporating redox innocent metals, coordination environment, and structural changes on the oxygen evolving reaction.^{62,63} By studying how each of these factors affect the rate of oxygen transfer in these synthetic systems, greater insight can be applied to build mimics that would allow for water oxidation at mild conditions. Other successful systems have incorporated both redox activity and proton responsivity.^{64,65} However, there has yet to be systems to include all three aspects of the triad. As the field continues to grow, the addition of hemilability into synthetic systems may offer improvements. Homogeneous catalysts are prone to degradation in the harsh conditions needed for water oxidation⁵⁵ and hemilability may be applied here to stabilize resting states, control reactivity, and increase proton responsivity.

Lastly, the role of the calcium ion in the OEC has been studied extensively.⁶⁶ It is thought to play a role in the tuning of (a) the redox potential of the Mn_4CaO_5 cluster; (b) the $\text{p}K_a$ of bound water; or both. In this context, the redox innocent ion can be thought of as a fourth motif in ligand design and incorporating redox innocent ions into ligand scaffolds is an area of intense investigation.^{67–76} However, ligand scaffolds containing redox innocent ions in conjunction with the triad (*i.e.* the tetrad) achieved by the OEC have not been reported to date. One can imagine that these scaffolds will bring new, fascinating discoveries with them, vital in our quest to mimic Nature.

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Fig. 1. Pymol illustration (PDB entry 1GOF) of the active site of galactose oxidase (left) and the rate limiting step of the proposed mechanism of aldehyde formation (right). The proton responsive (blue, right), hemilabile (blue, right), and ligand-based redox active (green, right) are shown.

Fig. 2.
Notable recent complexes demonstrating bioinspired motifs.

Fig. 3. Iron complexes of the bispyrrole-trispyridine hybrid ligand, $\text{Py}_2\text{Py}(\text{pi}^{\text{Cy}})_2$ demonstrating ligand-based redox sites and H-bonding (proton responsive) sites.

Fig. 4. The palladium diiminopyrrole ^{Tol,Cy}DIPy (**6**, left) and nickel dihydrazonopyrrole 2,5-bis((2-phenylhydrazono)(*p*-tolyl)methyl)-pyrrole (**7**, right) systems that demonstrate the triad of hemilability, proton responsivity, and ligand-based redox activity.

Fig. 5.
Pymol illustration (PDB entry 3WU2, left) and chemdraw (right) of the OEC of
Photosystem II. The proton responsive, redox-active, and hemilabile sites are highlighted.

Scheme 1.

Reaction of $[1]^{2+}$ with Gomberg's dimer (top) and the proposed mechanism of 2-oxoglutarate (bottom).

Scheme 2.

Reactions involving the nickel 2-phosphinito-6-phenyl-pyridine (PONC_{Ph}) (top) and the rhodium 2-di(*tert*-butylphosphinomethyl)-6-phenylpyridine (bottom) systems, demonstrating ligand hemilability and proton responsivity in single ligand scaffolds.

Scheme 3.

Hydrosilylation by the Mn(Ph₂PPrPDI) system illustrating ligand-based redox-activity merged with hemilability.

Scheme 4.
Reaction of **7** with water.

Scheme 5.

Nitrite reduction on the $\text{Fe}(\text{Pyrr})\text{PDI}$ system that illustrates the triad of hemilability, proton responsivity, and ligand-based redox activity. The structure of the $\{\text{FeNO}\}^7 \text{ MNIC}$ intermediate is shown in the middle box.