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Role of metal-oxo complexes in the cleavage of C–H bonds^a

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Abstract

The functionalization of C–H bonds has yet to achieve widespread use in synthetic chemistry in part because of the lack of synthetic reagents that function in the presence of other functional groups. These problems have been overcome in enzymes, which have metal-oxo active sites that efficiently and selectively cleave C–H bonds. How high-energy metal-oxo transient species can perform such difficult transformations with high fidelity is discussed in this tutorial review. Highlighted are the relationships between redox potentials and metal-oxo basicity on C–H bond activation, as seen in a series of bioinspired manganese-oxo complexes.

Introduction

The functionalization of C–H bonds is one of the most difficult transformations in synthetic chemistry, even though it has been studied for over 100 years. There are several reasons why this type of reaction has been under-utilized in chemical synthesis, the most commonly cited being the general thermodynamic stability of C–H bonds.¹ This stability has led to the use of reagents that are highly oxidizing, nonselective, and often incompatible with other functional groups. Although notable advances have been reported,² the use of reagents to functionalize C–H bonds usually occur early within a multi-step synthesis in order to avoid complications. In addition, many of these reagents contain expensive and toxic metal ions, whose cost and environmental incompatibilities would limit their use. Therefore the development of new reagents that can target specific C–H bonds, but are less oxidizing, is currently an important area in chemical sciences.

Directly linked to the quest for new reagents for C–H functionalization are investigations into the chemistry of metal complexes with dioxygen, a connection arising from the prevalence of metal-containing oxygenases that selectively cleave C–H bonds.³ These metalloproteins contain one or more metal ions within their active sites that first bind and activate dioxygen, initially producing what are believed to be high valent metal-oxo species, which then cleave C–H bonds of substrates.⁴ The identity of the metal-oxo species, the mechanistic steps leading to their formation, and subsequent reactivity are in many cases still the subject of intense studies. However some systems have been sufficiently investigated to give important insights into the nature of the active species and how they may react. The most often cited examples are the cytochrome P450s (P450s), whose hydroxylase component contains an iron-thiolate heme center that reacts with dioxygen to produce Compound I (Figure 1a).⁵ Note that Compound I is formally an Fe^V=O complex but spectroscopic measurements suggest that it is best described as an Fe^{IV}=O(radical).^{5,6} The fate of Compound I is still debated yet the “rebound” route (Figure 1b) is often used to

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explain how it reacts with substrates: Compound I homolytically cleaves a C–H bond from a substrate affording a carbon-based radical and an $\text{Fe}^{\text{IV}}\text{--OH}$ species (Compound II) that recombine to produce the oxidized substrate (Figure 1b).

As work on P450s continues, several non-heme enzymes have been discovered that also functionalize C–H bonds of external substrates. The picture that emerges from structural, physical, and biochemical studies is one of complicated active site structures, containing metal ion(s) that support the binding of dioxygen and substrates. The details of the O_2 activation processes are still unknown for most systems but some studies have revealed that metal-oxo species also have a dominant role in the cleavage of C–H bonds. For example, methane monooxygenases (MMOs) are oxidoreductase enzymes found in methanotrophic bacteria that convert methane to methanol.⁷ There are two forms of this enzyme, both of which activate dioxygen to form putative metal-oxo species: 1) particulate MMO (pMMO) contains a diiron active site whose competent oxidant is compound Q, proposed to have a $[\text{Fe}^{\text{IV}}(\text{O})]_2$ core structure (Figure 1c) and 2) soluble MMO (sMMO) whose active site components are still debated but postulated to have a dicopper-oxo motif. MMOs are selective for the oxidation of methane, which is surprising because methane contains the most stable C–H bonds, with a homolytic C–H bond dissociation energy (BDE_{CH}) of 104 kcal/mol.⁸ Proteins with single metal ion active sites are also known, which selectively cleave C–H bonds, as shown in Figure 1d for the non-heme iron enzyme taurine D monooxygenase.⁹ Similar to the P450s, these systems are proposed to activate dioxygen to produce a high valent metaloxo center that then oxidizes substrates through a C–H bond cleavage step.

The fact that metalloproteins make use of high valent metal-oxo species is somewhat puzzling because it is not known how such energetic intermediates can exist within an active site without causing harmful damage to the protein. The potential reactivity with several amino acid residues would result in irreversible oxidation and loss of activity. Self-destruction via intramolecular oxidation is also a problem with synthetic systems and is the major reason there are few synthetic catalysts that utilize dioxygen as the terminal oxidant. Of course, if these obstacles could be overcome, cheaper and more environmentally beneficial catalysts for the functionalization of C–H bonds could be developed. This review will examine ideas of how to design metal complexes that bind and activate dioxygen to form reactive metal-oxo complexes. Moreover, the importance of the ancillary ligands in control of the microenvironment in which the metal-oxo unit resides will be described.

C–H Bond Functionalization: The pK_a Effect

The rebound mechanism for the hydroxylation of a C–H bond depicted in Figure 1a implies that the metal-oxo unit, generated after O_2 activation, is a strong oxidant. The oxidizing strength of compounds is normally correlated with redox potential, with stronger oxidants having higher redox potentials. Thus species such as the cerium(IV) and silver(I) ions, whose redox potentials are 1.52 and 0.68 V vs NHE, are used as reagents to oxidize substrates (Figure 2a).¹⁰ However redox potential is not the only parameter that needs to be considered for the functionalization of C–H bonds. Mayer has used thermodynamic cycles to evaluate C–H bond cleavage by metal-oxo complexes:¹¹ this method was pioneered by Bordwell¹² and Tilset¹³ to determine the BDE of organic compounds in the condensed phase. Mayer's approach analyses the BDE_{OH} of metal-hydroxo complexes formed from the initial cleavage event (e.g., Compound II in Figure 1a). There is a direct thermodynamic connection to C–H functionalization: the energy for homolytic C–H bond cleavage must be comparable to that produced in forming the MO–H bond.

Thermodynamic cycles arise from equation 1,

$$\text{BDE}_{\text{OH}} = 23.06 - E^\circ + 1.37 - \text{p}K_a + C \quad (1)$$

where C is a constant that corrects for the properties of the hydrogen atom in solution and depends on solvent and the redox potential reference. Note that BDE values determined by this method are estimates (10% error) and it is assumed that there is negligible change in entropy during the homolytic C–H cleave and transfer steps. The BDEs determined by this approach are thus enthalpic quantities, even though equation 1 uses the free energy terms of redox potentials and $\text{p}K_a$. Figure 2b shows a typical cycle (or square scheme) derived from equation 1, illustrating the dependence of redox potentials and $\text{p}K_a$ on the BDE_{OH} . The critical feature of this analysis is the inclusion of the $\text{p}K_a$ values for the metal–hydroxo species, the conjugate acid of the metal–oxo unit, and thus a gauge of the basicity of the oxo ligand. Furthermore, this analysis shows that the basicity of the oxo ligand affects the reactivity of metal–oxo complexes and provides another tunable parameter that can influence the cleavage of C–H bonds.

The importance of this effect is shown graphically in Figure 2c for the homolytic cleavage of a C–H bond in methane. At low $\text{p}K_a$ values (less than 10), redox potentials of greater than +1.5 V vs NHE are needed to react with C–H bonds: these potentials are far too large to be compatible with a protein active site. Similarly, synthetic metal–oxo systems would not tolerate this condition, with the most likely outcome being irreversible destruction of the ancillary ligands in the complex. As the basicity of the oxo ligand increases (higher $\text{p}K_a$ values of the conjugate metal–hydroxo species) there is a decrease in the required redox potential to cleave this C–H bond—at $\text{p}K_a$ values of greater than 20 the redox potential drops to a more manageable value of 0.50 V vs NHE.

Green suggested that a correlation between redox potentials and $\text{p}K_a$ values can explain how proteins utilize high energy metal–oxo intermediates in the functionalization of C–H bonds.¹⁴ His argument centers on the one-electron reduced oxo species in Figure 2b, referred to as Compound II: he contends that the much lower than expected redox potential in Compound I is compensated by the high basicity of the oxo ligand in Compound I. Support for this premise has come from the Mn^{V} –oxo complexes prepared by Goldberg that cleave C–H bonds in a diverse group of substrates.¹⁵ In one complex, a $\text{p}K_a$ value of 15 (CH_3CN) has been estimated for a Mn^{IV} –OH complex, the conjugate acid of the Mn^{IV} –oxo, which is touted to compensate for the modest one-electron reduction potential measured for the parent Mn^{V} –oxo (+0.24 V vs NHE). Similar findings have been reported by Nam and Que for Fe^{IV} =O complexes.¹⁶

C–H Bond Cleavage with Low Potential Manganese-Oxo Complexes

My group has been investigating C–H bond functionalization using metal–oxo and metal–hydroxo complexes that were prepared via the activation of dioxygen or deprotonation of water (Figure 3a).¹⁷ Notice that each anion contains an intramolecular hydrogen bonding network that we have found assists in the stabilization of complexes with terminal oxo or hydroxo ligands. The tripodal compound H_6buea utilizes urea groups that serve two functions: 1) deprotonation of one NH group (alpha to the ethyl group) per arm affords a tri-anion ligand that binds a single metal ion and 2) metal ion binding produces a cavity formed whose scaffolding is provided by the remaining parts of the urea group. The rigidity of the cavity and preferred conformation of the urea groups installs three intramolecular hydrogen bond donors within the interior of the cavity, well positioned to interact with moieties (oxo ligands) bonded to the metal center. One of the distinguishing features of this system is the ability to prepare and characterize monomeric $\text{Fe}^{\text{III/IV}}$ –oxo, $\text{Mn}^{\text{III/IV}}$ –oxo and their corresponding $\text{M}^{\text{II/III}}$ –OH complexes. Note that the inner urea groups within cavities serve

as permanent H-bond donors that strongly interact with oxygen-containing ligands.¹⁸ This set of complexes allows us to fully probe the reactivity of the metaloxo complexes with external substrates having relatively weak C–H bonds. We cannot only follow the formation of organic products (which is the norm in this field) but we can also examine the inorganic products, specifically the formation of the metal-hydroxo complexes, which should be the metal-containing product formed immediately after the cleavage event (Figure 3b). This approach provides important mechanistic information that could lead to the production of efficient reagents and catalysts that utilize dioxygen.

We followed the thermodynamic approach outlined in Figure 2b to develop two cycles that allowed us to determine the BDE_{OH} for the two relevant MnO–H complexes, $[Mn^{II}H_3buea(OH)]^{2-}$ and $[Mn^{III}H_3buea(OH)]^-$ (Figure 4).^{19,20} These complexes have BDE_{OH} of 77 kcal/mol and 89 kcal/mole respectively, indicating that $[Mn^{IV}H_3buea(O)]^-$ has a stronger thermodynamic driving force for the cleavage of C–H bonds. Note also that pK_a values of 28.3 measured for $[Mn^{III}H_3buea(OH)]^{2-}$ and ~15 estimated for $[Mn^{IV}H_3buea(OH)]^-$ show the high basicity of the terminal oxo ligands in their respective conjugate bases, $[Mn^{III}H_3buea(O)]^{2-}$ and $[Mn^{IV}H_3buea(O)]^-$. Furthermore, the redox potentials for the one-electron reduction of $[Mn^{IV}H_3buea(O)]^-$ is –1.0 V vs $[Cp_2Fe]^+ / [Cp_2Fe]$ (–0.30 V vs NHE) and that of $[Mn^{III}H_3buea(O)]^{2-}$ is less than –1.3 V vs NHE. These redox potentials are usually associated with reducing agents (Figure 1c) and not complexes that oxidize organic substrates. Nevertheless, our findings showed that these complexes can indeed homolytically cleave C–H bonds, producing oxidized substrates. We used simple external substrates with varied BDE_{CH} to test the reactivity of our Mn–oxo: the results from this study confirmed that our predictions from the thermodynamic analyses were correct. For example, treating $[Mn^{III}H_3buea(O)]^{2-}$ with cyclohexadiene produced benzene and $[Mn^{II}H_3buea(OH)]^{2-}$ in yields of greater than 95%.

The ability of the low-potential $[Mn^{III}H_3buea(O)]^{2-}$ and $[Mn^{IV}H_3buea(O)]^-$ complexes to cleave C–H bonds was at first puzzling but only because we initially only considered their redox potentials. However, it became increasingly apparent that the strong basicity of the oxo ligands could be the key parameter in the observed reactivity of these complexes. One supporting piece of evidence came from the differing reactivities of the Mn–oxo complexes with phenols: treating $[Mn^{IV}H_3buea(O)]^-$ with 2,4,6-tri-*tert*-butylphenol resulted in the formation of the corresponding phenoxyl radical and $[Mn^{III}H_3buea(OH)]^-$, a process consistent with the homolytic cleavage of the phenolic O–H bond. In contrast, the phenolate anion and $[Mn^{III}H_3buea(OH)]^-$ were produced via simple acid-base chemistry when the same substrate was allowed to react with $[Mn^{III}H_3buea(O)]^{2-}$, a complex with a significantly more basic oxo ligand.

We gained further insights into the role of the metal-oxo units in $[Mn^{III}H_3buea(O)]^{2-}$ and $[Mn^{IV}H_3buea(O)]^-$ by performing a comparative kinetic study on the conversion of 9,10-dihydroanthracene (DHA) to anthracene (Figure 5).²⁰ To our surprise the $[Mn^{III}H_3buea(O)]^{2-}$ complex, the system with the lower driving force for C–H bond cleavage (by 12 kcal/mol), had the larger corrected second-order rate constant by over an order of magnitude! Our kinetic studies at 20°C found a $k^{Mn(III)-O}$ of 0.48(4) M^{–1}s^{–1}, while a $k^{Mn(IV)-O}$ of 0.026(2) was obtained for $[Mn^{IV}H_3buea(O)]^-$. The two C–H bond cleavage reactions have other differences: 1) large, but significantly different, primary kinetic isotope effects of 2.6 for $[Mn^{III}H_3buea(O)]^{2-}$ and 6.8 for $[Mn^{IV}H_3buea(O)]^-$ and 2) a difference of 35 eu in the entropies of activation for the two processes ($\Delta S^\ddagger = -14(6)$ eu for $[Mn^{III}H_3buea(O)]^{2-}$ and $\Delta S^\ddagger = -49(4)$ eu for $[Mn^{IV}H_3buea(O)]^-$). These additional findings suggested that the two manganese-oxo complexes were reacting with DHA via different mechanisms, which is directly linked to the basicity of the oxo ligands. We propose that $[Mn^{IV}H_3buea(O)]^-$ reacts with DHA by a proton-coupled electron (PCET) route (Figure 6a),

a proposal based in the large part on the substantial difference between the pK_a values for the C–H bonds in DHA and $[Mn^{IV}H_3buea(OH)]$ ($\Delta pK_a \sim 15$). This PCET route requires the approach of the substrate to the metal-oxo complexes, producing an ordered transition state, which agrees with the $\Delta S^\ddagger$ of $-49(4)$ eu measured for this process. A ΔpK_a of 2 is estimated between DHA and $[Mn^{III}H_3buea(OH)]^-$, a difference small enough to suggest a two-step mechanism, in which proton transfer precedes electron transfer (PT-ET, Figure 6b)). This mechanism requires that proton transfer is the rate-limiting step because of the observed primary kinetic isotope effect of 2.6. Moreover, the mechanism would produce a less ordered transition state (and a more positive value for $\Delta S^\ddagger$) because greater charge-delocalization would occur, a result of less ordered solvent molecules.

Conclusions

We have studied homolytic C–H bond cleavage using an unusual set of manganese-oxo complexes in order to understand some of the fundamental requirements needed to ultimately develop efficient and selective catalysts. We have found that the basicity of the oxo ligand is crucial in oxidation of simple substrates and our results highlight how low-potential metal complexes can serve as reagents to cleave relatively strong C–H bonds. In addition, the observed rate acceleration found for the Mn^{III} -oxo complex can also be understood within the context of oxo ligand basicity: these results suggest that faster rates may be obtained by matching the acid/base properties of the C–H bonds with those of the metal-oxo unit. Our complexes appear to be extreme examples from the standpoint of having highly basic oxo ligands that compensate for very low redox potentials. In other systems, the interplay between these two parameters may not be so drastic: for instance, it is unlikely that oxo ligands as basic as those in $[Mn^{IV/III}H_3buea(O)]^{-2-}$ can exist in metalloproteins. Nevertheless, our results show that even moderately basic oxo ligands can sufficiently reduce the redox potentials to achieve C–H bond cleavage without damaging a protein active site. Moreover, our findings can be applied to other systems, most notably metal-nitrenes complexes, which should have similar properties to those found in our metal-oxo systems. As more information on these types of reactions is obtained the commonality between reagents that functionalize C–H bonds will be clearer.

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Fig. 1.

(a) Proposed structure of Compound I in cytochrome P450, (b) possible reaction sequence for C–H bond functional by cytochrome P450, (c) proposed reaction sequence for C–H bond activation in non-heme monooxygenases, (d) proposed active site of compound Q in pMMO. Atom legend for the structure in 1A: carbon atoms (grey), sulfur atoms (yellow), nitrogen atoms (blue), oxygen atoms (red), iron atoms (orange).

Fig. 2.

(a) comparison of redox potentials for some common chemicals¹⁰ to low-potential manganese-oxo complexes (highlighted in orange), (b) square scheme illustrating the thermodynamic components that contribute to MO–H bond energies, (c) plot of redox potential versus pK_a values need to cleave the C–H bond in methane (see equation 1).

Fig. 3. (a) Structures of bioinspired iron and manganese complexes with terminal oxo and hydroxo ligands, (b) reaction wheel highlighting the C–H bond reactivity of $[\text{Mn}^{\text{III}}\text{H}_3\text{buea}(\text{O})]^{2-}$.

Fig. 4. Thermodynamic square schemes used to determine the BDE_{OH} in $[\text{Mn}^{\text{III}}\text{H}_3\text{buea}(\text{O})]^{2-}$ and $[\text{Mn}^{\text{IV}}\text{H}_3\text{buea}(\text{O})]^{-}$.

Fig. 5. Plots of rate data for reaction of 9,10-dihydroanthracene with $[\text{Mn}^{\text{III}}\text{H}_3\text{buea}(\text{O})]^{2-}$ (●) and $[\text{Mn}^{\text{IV}}\text{H}_3\text{buea}(\text{O})]^{-}$ (■).

Fig. 6. Proposed mechanism for C–H bond activation of (a) $[\text{Mn}^{\text{IV}}\text{H}_3\text{buea}(\text{O})]^-$ and (b) $[\text{Mn}^{\text{III}}\text{H}_3\text{buea}(\text{O})]^{2-}$ with 9,10-dihydroanthracene.