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Current Challenges for Modeling Enzyme Active Sites by Biomimetic Synthetic Diiron Complexes

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This tutorial review describes recent progress in modeling the active sites of carboxylate-rich non-heme diiron enzymes that activate dioxygen to carry out several key reactions in nature. The chemistry of soluble methane monoxygenase, which catalyzes the selective oxidation of methane to methanol, is of particular interest for (bio)technological applications. Novel synthetic diiron complexes that mimic structural, and, to a lesser extent, functional features of these diiron enzymes are discussed. The chemistry of the enzymes is also briefly summarized. A particular focus of this review is on models that mimic characteristics of the diiron systems that were previously not emphasized, including systems that contain (i) aqua ligands, (ii) different substrates tethered to the ligand framework, (iii) dendrimers attached to carboxylates to mimic the protein environment, and (iv) two N-donors in a syn-orientation with respect to the iron-iron vector, and (v) a N-rich ligand environment capable of accessing oxygenated high-valent diiron intermediates.

1 Introduction.

Biology has adopted geologically abundant iron with its inherent electronic properties, including Lewis acidity and accessible redox states for selective O2 binding and/or activation, in heme and non-heme enzymes. A subfamily of non-heme enzymes contains a carboxylate-bridged non-heme diiron active site, which is responsible for many different biochemical O2 utilization pathways including (i) biomineralization of iron as an oxide in ferritin (Ft); (ii) DNA biosynthesis via the generation of an essential tyrosyl radical in the ribonucleotide reductase subunit B2 (RNR-B2),3 (iii) fatty acid desaturation in Δ1 stearoyl-acyl carrier protein desaturase (Δ1D),4 (iv) regulation of cell proliferation via the biosynthesis of hypusine in human deoxyhypusine hydroxylase (hDOHH),5 and (v) hydrocarbon oxidation in the hydroxylase components of bacterial multicompartment monooxygenases (BMMs).6 Enzymes belonging to the BMM family include soluble methane monoxygenase (sMMO),7,8 toluene/o-xylene monooxygenase (ToMO),9 and phenol hydroxylase (PH).10 The chemistry in these non-heme diiron enzymes occurs at a common structural motif, a diiron active site that is embedded in a four-helix bundle of an α-helical protein. Each diiron center is coordinated by four carboxylates from glutamate or aspartate residues and two imidazoles from histidine side chains that are bound in a syn-disposition to the diiron vector.

Hemerythrin, responsible for reversible O2 binding in marine invertebrates,1 myo-inositol oxygenase, which catalyzes the ring-opening glycol cleavage of myo-inositol by a radical O2 activation pathway,11 and flavo-diiron proteins, which function as O2− and/or NO-scavenging reductases,13 are some additional members of the extended family of carboxylate-bridged diiron enzymes, but they contain more than two histidine residues per diiron center.

Of special interest is to create synthetic analogs of the BMMs because several biological reactions catalyzed by these enzymes are of potential technological relevance. An example is the activation/utilization of petrochemical hydrocarbons. The carboxylate-rich diiron motif of the enzyme active site has often been considered as a template for achieving comparable chemistry and efficiency in biomimetic chemistry.13 An excellent example is the conversion of the simplest and least reactive of the saturated hydrocarbons, methane, into methanol, a liquid fuel. Such a chemical transformation would allow for the exploitation of vast natural gas resources in remote areas, often found alongside crude oil or as methane clathrates in deep-sea water and permafrost regions, and its use as a safe and transportable fuel, methanol. Natural gas is an energy-rich and low-cost chemical feedstock and it has a lower carbon footprint (CO2 emission) than coal and oil when burnt as a fuel. Today, methanol is produced from methane in an energy-intensive and costly process by the intermediate production of synthesis gas, which involves complete dehydrogenation of methane, on a large scale by the petroleum industry (eqs. 1 and 2).14-16

\[
\begin{align*}
\text{Industrial CH}_4/\text{OH production} & \\
\text{CH}_4 + \text{H}_2\text{O} & \xrightarrow{700-900 \text{°C} \atop \text{40 bar}} \text{CO} + 3\text{H}_2 \\
\text{CO} + 2\text{H}_2 & \xrightarrow{200-400 \text{°C} \atop \text{60350 bar}} \text{CH}_3\text{OH} \\
\text{biological CH}_3\text{OH production (MMOH)} & \\
\text{CH}_4 + \text{O}_2 + 2\text{H}^+ & \xrightarrow{25 \text{°C} \atop \text{1 bar}} \text{CH}_3\text{OH} + \text{H}_2\text{O} 
\end{align*}
\]

Methanotrophic micro-organisms rely on methane as their only carbon and energy source. These aerobic proteobacteria contain the sophisticated enzyme machinery of sMMO to hydroxylate the nonpolar and strong C−H bond (ΔH°C−H = 414 kJ mol\(^{-1}\)) in CH4 using O2, protons, and electrons in the first step of methane metabolism under mild conditions (eq. 3).17,18 The diiron active site of the hydroxylase component of the enzyme, MMOH, is an attractive target for biomimetic synthetic chemists, having the potential for achieving hydrocarbon oxidation catalysis such as methane hydroxylation. In this review, we present enzymatic features that facilitate methane hydroxylation as a guide to, and for comparison with current, strategies for the preparation of MMOH model complexes.
2 Bacterial Multicomponent Monoxygenases.

Much effort has been spent to understand the mechanistic details by which BMMs achieve their biological transformations, including detailed structural, spectroscopic, and kinetic studies.7,19,20 We focus in this section on the sMMO system, because it is well-studied and can convert methane into methanol.7 Methane hydroxylation also occurs in particulate MMO (pMMO), a membrane-bound copper-containing MMO from methanotrophic bacteria that is beyond the scope of this review.21,22

Dioxygen activation and CH₂ oxidation in sMMO involves a complex multi-component protein system. The three components (Figure 1) are (i) a hydroxylase (MMOH), (ii) an NADH oxidoreductase (MMOR), and (iii) a regulatory protein (MMOB). The hydroxylase is a 251 kDa heart-shaped heterodimer consisting of two αβγ protomers with an almost entirely α-helical secondary structure. The hydroxylating diiron active site is embedded in a four-helix bundle in each of two identical α-subunits. MMOH is only active in the presence of a protein cofactor, MMOB, which forms a specific complex with MMOH that indirectly affects the structure and reactivity of the diiron site. The required electron equivalents are transferred to MMOH from MMOR, which contains a bound flavin adenine dinucleotide (FAD) and a [2Fe-2S]-ferredoxin (Fd) cofactor.7 In this multicomponent system, four substrates, namely the hydrocarbon, dioxygen, electrons, and protons, are transported selectively and separately (to avoid quenching of the high-valent state by electrons) to the diiron active site by biologically well-engineered substrate tunnels or pockets.20

Figures 1 and 2

Figure 1. The multicomponent enzyme system of sMMO from Methylococcus capsulatus (Bath) consists of a hydroxylase (MMOH, pdb reference 1MTY), an oxidoreductase (MMOR; consisting of FAD domain, 1TVC, and [2Fe2S]-Fd domain, 1QJ4), and a regulatory (binding) protein (MMOB, 1CKV). The ribbon diagram presentation of MMOH is based on X-ray coordinates and those of MMOB and the two truncated MMOR fragments, on NMR structures.

Although all components of sMMO are required for CH₄ oxidation, O₂ activation and C–H bond functionalization occur at the diiron site of MMOH, which is the central catalytic of the enzyme system. The diiron site can be accessed in the following three O₂-free high-spin oxidation states: Fe₄[FeIII] (MMOHox), Fe₃[FeII] (MMOHred), and Fe₂[FeII] (MMOHred), but only the last, diiron(H), state can react directly with O₂. Thus, before MMOH reacts with O₂, the resting, oxidized di(µ-hydroxy)(µ-carboxylato)diiron(III) species, MMOHox, must be activated by a two-electron reduction with NADH via MMOR to form MMOHred (Figure 2, Scheme 1). Reduction occurs simultaneously with a carboxylate shift of a terminally coordinated semi-bridging glutamate (E243) residue in MMOHox, resulting in protonation and displacement of both bridging hydroxide ions and formation of a µ-η¹:η¹'-bridging glutamate with a concomitant decrease in Fe–Fe distance from ca. 3.3 Å (in Fe₂[FeII]) to ca. 3.0–3.1 Å (in Fe₃[FeII]).

Figure 2. The inactive (resting state) diiron(III) site of MMOH (left) is activated by two-electron reduction and a carboxylate shift of E243 to the diiron(II) state (MMOHred), which can then react with O₂ in the presence of MMOR to form high-valent diiron-oxo species. Ball and stick structures of MMOHred and MMOHox adopted from D. A. Kopp, S. J. Lippard Curr. Opin. Chem. Biol. 2002, 6, 568-576.

The dioxygen activation pathway has been studied extensively in MMOH from M. capsulatus Bath (Mc) and M. trichosporium OB3b (Mb). Kinetic analyses in both systems have revealed a minimum of four oxygenated intermediates in a multi-step reaction pathway. The detailed proposed mechanism for O₂ activation and substrate oxidation in Mc is illustrated in Scheme 1. Dioxygen reacts with the reduced, diiron active site of MMOHred to form intermediate P*, presumably by intermediate formation of a spectroscopically silent and/or very short-lived superoxoiron(III,II) species analogous to superoxioiron(III) units in the oxidation of reduced heme proteins and synthetic iron porphyrin complexes.24 Experimental evidence for a superoxo species in MMOH has not been obtained, however. Intermediate P* is the precursor to the peroxodiiron(III) species, MMOHperox, having optical spectroscopic features (720 nm, ε ≈ 1250 M⁻¹ cm⁻¹ and 420 nm, ε ≈ 3500 M⁻¹ cm⁻¹) nearly identical to those of this intermediate, suggesting that they have very similar oxygenated diiron core structures. MMOHperox is tentatively assigned as a cis-µ-1,2-peroxodiiron(III) species and it features peroxo ligand-to-iron(III) charge transfer (LMCT) bands centered at 720 nm (ε ≈ 1350 M⁻¹ cm⁻¹) and 420 nm (ε ≈ 3880 M⁻¹ cm⁻¹) and Mössbauer parameters of δ = 0.66 mm s⁻¹ and ΔE₀ = 1.51 mm s⁻¹, characteristic of two antiferromagnetically coupled iron atoms.7,25

MMOHperox is competent for oxidation of electron-rich hydrocarbons, such as diethyl ether and propylene, but not CH₄.26,27 Following O–O bond cleavage, MMOHperox converts to a high-valent iron species, the methane-oxidizing intermediate Q.7,19,25,28,29 The mechanism of this step is not well understood, however, and it is still under debate whether the O–O bond is cleaved homolytically or heterolytically.25 A di(µ-oxo)diiron(IV) “diamond core” structure with a short Fe–Fe distance of 2.46 Å was derived by EXAFS spectroscopy for intermediate Q, which has intense optical absorption bands at 420 nm (ε ≈ 7200 M⁻¹ cm⁻¹) and 350 nm (ε ≈ 3600 M⁻¹ cm⁻¹).30 pH dependence studies demonstrated that proton transfer is necessary for conversion of H₆perox to Q.25,31 The
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origin of the protons is most likely an active site water molecule, because there are no suitable amino acids within reasonable proton-transfer distance to the diiron site.

**Scheme 1.** Catalytic cycle of O$_2$ activation and CH$_4$ hydroxylation in sMMO. The oxidized diiron(III) state (MMOH$_{ox}$) is activated via two-electron reduction by MMOR (R, red circle) to a diiron(II) state (MMOH$_{red}$), which reacts in the presence of MMOB (B, blue circle) with oxygen to form intermediate P*, presumably via a superoxo species. Intermediate P* then transforms via proton transfer (PT) into MMOH$_{peroxo}$, which can either decay to MMOH$_{ox}$ via oxidation of electrophilic substrates RH (e.g. ethers), or form the diiron(IV) intermediate Q, which is responsible for CH$_4$ hydroxylation. In the absence of CH$_4$, intermediate Q decays slowly to intermediate Q*, which is not on the methanation pathway, and then to MMOH$_{ox}$. The bridging glutamates (E144 and E243) are also shown. Characteristic physical parameters of the intermediates can be found in the text.

Hydroxylation presumably occurs by a mechanism whereby intermediate Q abstracts a hydrogen atom from CH$_4$ with concomitant electron transfer to an iron atom followed by recombination of the bound methyl radical with a bridging oxygen atom as a second electron transfers to the other iron atom. The cycle completes upon release of methanol from the hydrophobic substrate-binding pocket and formation of the resting-state MMOH$_{ox}$, thereby completing the catalytic cycle. Rate-limiting in this reaction is presumably product release, as demonstrated for the hydroxylation of nitrobenzene. In the absence of hydrocarbon substrate, intermediate Q gradually decays to intermediate Q*, which does not react with methane, to form the resting state of the enzyme, MMOH$_{ox}$. The structure of Q* has not yet been elucidated. Its optical spectrum contains an absorption band centered around 420 nm and a broad shoulder at 455 nm.

Studies of the hydroxylase component of ToMO (ToMOH) revealed that reaction of the reduced form of the enzyme with O$_2$ results in the formation of a putative peroxydiiron(III) species that is responsible for hydrocarbon oxidation. There is no evidence for a high-valent, Q-type intermediate in this system. In contrast to the MMOH$_{peroxo}$ species, the oxygenated intermediate in ToMOH has distinctive Mössbauer parameters of $\delta = 0.54$ mm s$^{-1}$ and $\Delta E_Q = 0.67$ mm s$^{-1}$, and it lacks an observable UV-vis absorption band. The intermediate has an isomer shift that lies within the range of peroxydiiron(III) species. The quadrupole splitting parameter, however, is more than 0.3 mm s$^{-1}$ smaller. This EPR-silent intermediate was tentatively assigned as a peroxydiiron(III) species having a different coordination mode and/or protonation state than peroxydiiron(III) species typically observed in non-heme diiron enzymes. An oxygenated intermediate formed by the hydroxylase of PH (PHH) has nearly identical spectroscopic features, implying a structure related to that of ToMOH.

Dioxygen activation in other non-heme diiron enzymes, such as ferritin, RNR-R2, D$_{3}$D, and human deoxyhypusine hydroxylase, occurs by formation of a peroxo(diiron(III)) species. Spectroscopic studies of these peroxo intermediates revealed Mössbauer parameters $\delta = 0.55$–0.68 mm s$^{-1}$ and $\Delta E_Q > 0.9$ mm s$^{-1}$ and optical bands similar to those of MMOH$_{peroxo}$. For these enzymes, a cis-$\mu$-1,2-peroxo binding mode is suggested.

RNR-R2 is the only non-heme diiron enzyme besides sMMO where a high valent iron center has been observed on the pathway of O$_2$ activation, as shown in Scheme 2. The reduced diiron(II) species, R$_2$$^{red}$, reacts with O$_2$ to form a peroxydiiron(III) species. R$_2$$^{peroxo}$ then transforms to the mixed-valent diiron(III,IV) intermediate X, which abstracts an electron from a neighboring tyrosine residue involved in the reduction of ribonucleotides to deoxyribonucleotides.

**Scheme 2.** Catalytic cycle of O$_2$ activation and tyrosyl radical formation in RNR-R2. The diiron(II) species reacts with O$_2$ to form the peroxydiiron intermediate R$_2$$^{peroxo}$, which oxidizes a tryptophan residue (Trp48) to form intermediate X. This Fe$_2$Fe$^{V}$O$_2$ species then generates a tyrosine (Tyr122) radical and restores the resting diiron(II) state, which can be activated again by a two-electron reduction to form R$_2$$^{red}$. Dioxygen binding in MMOH most likely occurs by substitution of a weakly coordinating, bridging water molecule distal to the syn-histidines. This site directly faces a hydrophobic substrate-binding cavity with a volume of approximately 185 Å$^3$ adjacent to the diiron center, which favors the binding of hydrophobic guests, such as methane and O$_2$. Product molecules like MeOH are released from the active site upon reduction of MMOH$_{ox}$. Furthermore, in order for chemistry to occur at the diiron center, electrons, protons, dioxygen, and hydrocarbon substrates all need to be provided through processes that are tightly regulated. Such regulation is finely tuned by the tertiary structure of the MMOH/MMO complex.

Although many structural and mechanistic details about sMMO have been clarified, providing information that forms the basis for the assembly of corroborative and functional biomimetic compounds, there is another important consideration to be taken into account in the design of future biomimetic catalysts. X-ray crystal structures of MMOH$_{red}$ and, have been solved and are used to help design biomimetic target constructs, but it must be remembered that the enzyme has diminished activity in the absence of MMOB. Thus, MMOB is presumably not only responsible for modulating the MMOH tertiary structure to control access of substrates to the active site, but it may also affect the first coordination sphere of the diiron center. The geometry of MMOH$_{red}$ and, in particular, its diiron active site that reacts with O$_2$ may differ from that seen in any of the known crystal structures.
3 Biomimetic Carboxylate-rich Diiron Complexes

3.1 Classical biomimetic MMOH systems containing bulky mononuclear building blocks. Iron carboxylate complexes are kinetically labile and have a strong tendency to form polymeric species in the absence of steric shielding. In order to isolate discrete diiron complexes, carboxylates with a finely tuned degree of steric bulk must be used. Bulky ligands result in mononuclear complexes and too little steric constraint results in formation of oligo- and polynuclear iron species (Figure 3). StERICly open carboxylates (e.g., OCAr = benzoate) can only be incorporated into discrete structures as bridging ligands when they co-coordinate with other, sterically demanding ligands (e.g., in [Fe2(dien)(OCAr)](BF4)2; Ph-dienn = 2,6-bis[3-[1-(methyl-4,5-diphenylimidazolyl)]-methyl]-4-methylphenolate), preventing their use in carboxylate-rich diiron systems. One example of a polyiron(II) species is [Fe6(O2CCF3)3(OH2CCF3)2] (O2CCF3 = trifluoroacetate), which has bridging trifluoroacetate ligands arranged in a windmill configuration.\(^1\) The asymmetric 2-biphenylcarboxylate ligand (OCAribp) provides sufficient steric bulk to avoid polymerization and maintains the ability to assemble the discrete planar tetra-, linear tri-, and paddlewheel diiron species [Fe2(OCAribp)]n (n = 2–4), depending on experimental conditions and the donor L.\(^18\)

The preparation of diiron complexes containing the m-terphenylcarboxylate ligands 2,6-di(p-mesityl)benzoate (OCArMes) and 2,6-di(p-tolyl)benzoate (OCArTol) having the general formula [Fe2(OCAr)](L)2 marked a considerable breakthrough in MMOH diiron core modeling.\(^19\) These compounds not only represent the first coordination sphere of the MMOH active site stoichiometrically, but also recapitulate important aspects of MMOH chemistry, like the carboxylate shift, formation of high valent diiron species upon reaction with O2, and encapsulation of the diiron core with a hydrophobic shell allowing for mimicking of the protein interior.\(^21\)

Diiron complexes with four OCArTol carboxylates and different ligands L were isolated either as doubly (windmill), triply, or quadruply (paddlewheel) bridged iron complexes in the solid state.\(^24\) Moreover, an equilibrium between doubly- and quadruply-bridged species in solution was found by variable-temperature solution \(^1\)H NMR spectroscopic studies of [Fe2(OCAr)4(dppm)(THF)], \(^1\)HCAr = 2,6-di(p-fluorophenyl)benzoate, thereby simulating an important feature of the MMOH active site – the carboxylate shift.\(^23\) This ability can be attributed to the rotational flexibility of the carboxylate ligand. Triply bridged diiron species are possible intermediates in this equilibrium. Triptycene carboxylates (OCArCtPr) only support paddlewheel complexes due to the interlocking geometry of the triptycene units, and no windmill structures have yet been isolated. The bulky OCArMes carboxylate, on the other hand, exclusively facilitates the formation of a doubly bridged diiron compound,\(^25\) e.g., [Fe2(OCArMes)]2(OCArMes)(MeCN)]2, which dissociates into mononuclear species upon addition of various pyridine donors. A further increase in steric bulk, as in 2,6-di(4-tolyl-butylphenyl)benzoate (OCAr4tBuPh), affords only mononuclear iron complexes.\(^26\)

A short Fe–Fe distance may be crucial for O2 activation in MMOHred (see above), and metal-metal distances in diiron(II) models usually vary between 2.7 and 4.4 Å. The actual value depends on the number of bridging ligands (Figure 3), but exceptions have recently been reported. The windmill complexes [Fe2(μ-OCAr)][OCAr]2(NH2(CH2)3CH2)] (OCAr = 2,6-di(3,5-dimethylphenyl)benzoate),\(^45\) [Fe2(μ-OCAr)][OCAr]2(NH2(CH2)3CH2)] and [Fe2(μ-OCAr)][OCAr]2(NH2(CH2)3CH2)] (OCAr = asymmetric 3,5-dimethyl-1,1’3’1”-terphenyl-2’-carboxylate)\(^46\) feature very short windmill Fe–Fe distances, between 3.25 and 3.46 Å, comparable to those found in MMOHred. In diiron complexes with mixed carboxylates, [Fe2(μ-OCAr)[OCAr]2(Py)]2 (Py = Fe–Fe = 4.0 Å), the bridging 2,6-di(p-tolyl)benzoate prevents shortening of the Fe–Fe distances.\(^46\) Thus, the shortening of the metal-metal distance compared to analogous OCArTol complexes is presumably due to diminished steric repulsion of the flanking methyl groups in the bridging OCArTol and OCAr(Tol) ligands. The induction of bulky N-donors in [Fe2(μ-OCAr)(N)]2(L)2] complexes, which cannot convert into the more open windmill configuration (see above), results in elongated Fe–Fe distances for paddlewheel diiron complexes, e.g., [Fe2(μ-OCAr)(N)]2(2-PPh)2] with Fe–Fe = 3.0 Å.\(^47\)

Diiron(II) complexes of the type [Fe2(μ-OCAr)[OCAr]2(L)]2 (L = 4-BuPy) or Py) form a deep green solution upon reaction with O2 at −78 °C in CH2Cl2 or toluene.\(^20\) The closed paddlewheel complex is in equilibrium with the corresponding open windmill complex, which can react quickly with O2. Detailed analyses of the oxygenated product confirmed the presence of an equal mixture of the quadruply bridged diiron(II,III), and a high-valent diiron(III,IV) species.\(^49\)\(^50\)

| Figure 3. The nuclearity of carboxylate-rich iron complexes is sterically controlled. Sterically highly demanding ligands like OCArTol form monoiron complexes, [Fe2], whereas sterically open ligands like OCAribp form polymeric species, [Fe2]. Reversible cluster interconversions occur between windmill, [Fe2(bam)]; and paddlewheel, [Fe2(p)]; complexes (presumably via a triply bridged species, [Fe2(p)]; with OCArTol] and between triiron, [Fe3], and tetrairon, [Fe4]; complexes, with OCAribp. Interconversions must occur via carboxylate shifts (see text). |
The proposed reaction pathway is depicted in Scheme 3. A peroxy species forms by exposing the diiron(II) complex to O₂, which may convert to a high-valent diiron(IV) species. The latter acts as one-electron oxidant toward the diiron(II) starting material, which leads to the simultaneous formation of a 1:1 mixture of two mixed-valent species with S = 1/2 (Fe²⁺Fe⁴⁺) and S = 9/2 (Fe⁴⁺Fe²⁺), as demonstrated by EPR spectroscopy. The diiron(III,IV) species effects the one-electron oxidation of substituted phenol substrates. This process closely resembles the mechanism in RNR-R2, in which the diiron(III,IV) intermediate X oxidizes a neighboring tyrosine residue.  

![Scheme 3](Image)

Scheme 3. Formation of a high-valent Fe²⁺Fe⁴⁺-peroxo intermediate upon oxygenation of carboxylate-rich diiron(II) of [Fe₂(μ-O₂CR)₃(L)₂] type complexes at -78 °C in CH₂Cl₂ or toluene.

Oxygenation reactions with [Fe₂(μ-O₂CPhₓMesₙ)₂(O₂C-C₆H₄Mes)₂(MeCN)₂] at low temperatures yielded a purple-colored intermediate, which was spectroscopically assigned as a symmetrically bridged peroxy species. The quadruply bridged diiron(II) complex with benzyl-substituted benzoate ligands dxICO₂⁻, [Fe₂(μ-O₂CDx)(py)₂], reacts with O₂ to generate an asymmetrically bound peroxy species. One possible structure based on spectroscopic analysis is depicted in Scheme 3.  

### 3.2 Considerations and strategies for modeling advanced features of the MMOH active site.  

An intrinsic difficulty in the understanding and, even more, modeling carboxylate-bridged diiron protein systems is that, although the active sites are largely conserved, they promote a variety of different reactions with O₂. Thus, subtle changes in the coordination number, carboxylate binding mode, ligation by water or hydroxide, active site hydrophobicity, ligand protonation states including those of intermediates, e.g., peroxy vs. hydroperoxy, as well as electronic and structural contributions from the surrounding protein environment, play various roles in tuning the functional properties in these versatile enzymes. The grand challenge to the synthetic chemist lies in the preparation of model compounds that mimic the steric and electronic effects of the second or even third coordination sphere as defined by the polypeptide environment in the enzymes sufficiently to allow for functional biomimetic compounds with the desired catalytic properties.

Although successful strategies for the assembly of first coordination shell MMOH model complexes containing two Fe(II) ions, two bridging and one terminal carboxylates, as well as one imidazole per iron, have been developed during the last two decades (see above), they do not mimic environmental effects imposed by the surrounding protein. Small differences in peripheral amino acid composition are not only responsible for altered substrate access to the active site, but also influence the reactivity at the diiron center. Incorporation of some of the effects induced by the protein environment in an enzyme structure, which have been largely neglected in MMOH models mainly due to synthetic complexity, has become of increasing interest. In the following sections, new approaches to model more complex features of the MMOH active site are summarized. In particular, we cover (i) the effect of water coordinated to the diiron site, (ii) incorporation of substrates tethered to the ligand framework, (iii) synthesis of model complexes with two N-donors in syn-disposition with respect to the diiron bond, (iv) strategies for assembling complexes with a hydrophobic substrate access route, and (v) encapsulation of the diiron complexes within dendrimer ligand sheaths to mimic the protein scaffold.

#### 3.2.1 The effect of water coordinated to the diiron site.

The diiron complexes [Fe₂(μ-O₂CR)₃(L)₂] (R = Ar₄⁺) exist in solution as an equilibrium between paddlewheel and windmill isomers. The addition of water shifts this equilibrium quantitatively to the windmill species as a result of H₂O-induced carboxylate shifts. The use of electron-poor N-donor ligands L, such as 4-cyan- and 4-acetylpyridine, facilitates measurement of the kinetics of these water-induced conversions and subsequent oxygenations by stopped-flow electronic absorption spectroscopy utilizing the visible Fe→L charge-transfer (MLCT) band. The rate of oxygenation increases by approximately an order of magnitude in the presence of water when compared to the reactivity of the corresponding anhydrous diiron(II) analogs (Scheme 4). The oxygenation acceleration of the aquated windmill complex compared to the anhydrous species presumably originates from conversion to the active windmill form, which has more open access to the diiron site for O₂ attack. Thus, the open windmill configuration is crucial for the O₂-reactivity of carboxylate-rich diiron complexes.

![Scheme 4](Image)

Scheme 4. Addition of water to [Fe₂(μ-O₂CR)₃(4-RPy)₂] (R = CN, acetyl) results in a windmill [Fe₂(μ-O₂CR)₃(μ-O₂CR)₃(L)₂(L)₂] complex, which reacts more rapidly with dioxygen than the non-aquated paddlewheel and windmill mixture.

#### 3.2.2 Incorporation of substrates tethered to the ligand framework.

The ability of an oxygenated diiron species to transfer an O-atom is often determined by examining its reaction toward external substrates. This chemistry has not yet been achieved satisfactorily with synthetic carboxylate-rich diiron complexes, possibly due to (i) restricted access of the substrate due to steric encumbrance by the ligand framework, (ii) quenching of the reactive species by an intermolecular
electron-transfer (ET) pathway; and/or (iii) slow substrate diffusion to the short-lived high-valent oxo-diiron species.

To circumvent these potential problems, substrates can be tethered to ancillary neutral donor ligands L bound to the diiron site.55 The diiron(II) complex [Fe₂(μ-O₂Car)(3)]

O

reacts with O₂ to afford benzaldehyde via intramolecular benzyl oxidation followed by oxidative N-dealkylation (Scheme 5A).56 A detailed investigation of the mechanism of this reaction, including a Hammett analysis and the measurement of kinetic isotope effects, suggests that it proceeds by one-electron oxidation of the amine nitrogen atom, followed by α-H atom abstraction and subsequent oxygen rebound.57 This study was extended to include benzyl- and ethyl-substituted pyridines and anilines, which upon incorporation into carboxylate-rich diiron systems and subsequent exposure to O₂ yield alcohols for benzyl C-H bonds and a mixture of alcohols and ketones for the less reactive ethyl group (Scheme 5B). When steric factors are held constant, more electron-donating carboxylate and pyridine ligands increase the amount of oxidized product compared to their more electron-deficient counterparts, suggesting the need to stabilize an electrophilic intermediate to perform these transformations.45,58

Scheme 5. Oxidation of various substrates tethered to coordinated amine or pyridine ligands in carboxylate-rich [Fe₂(μ-CN)(L)₂] complexes. (A and B) C-H bond activation, (C) catalytic oxidation of 2-PyPPh₂ and (D) Fe-S distance dependent sulfoxidation; R = phenyl (Fe-S distance 2.66 Å), mesityl (Fe-S = 3.20 Å) and 2,4,6-trisopropylphenyl (Fe-S = 4.03 Å).

Tethered thiol, sulfide, sulfoxide, and phosphine moieties on pyridine ligands also serve as substrates for oxidation at O₂-activated carboxylate-bridged diiron(II) centers, particularly when bound in a position ortho to the N-atom of the pyridine ring (Scheme 5C and 5D).59 Oxidation of [Fe₂(μ-O₂Car)(2)](O₂Car)(2)(2-Ph₂PPy)] in the presence of excess 2-Ph₂PPy in CH₂Cl₂ catalytically converts the phosphate to its oxide (17 turnovers) with formation of [Fe₂(μ-OH)₂(μ-O₂Car)(2)](O₂Car)(2)(2-Ph₂P(O-Py)], which contains the biologically relevant [Fe₂(μ-OH)₂(μ-O₂Car)] core.59 The extent of substrate oxidation depends mainly on the proximity of the substrate to the diiron center. Either no or very little oxidation occurs when the substrate moiety is installed in the meta or para position of the pyridine ligand. Moreover, when the iron-sulfur distance in a series of [Fe₂(μ-O₂Car)(3)](picSR)+ complexes was systematically elongated by increasing the steric bulk on R from phenyl to mesityl and 2,4,6-trisopropylphenyl, the sulfoxidation yield upon exposure to O₂ at room temperature in toluene substantially diminished (Scheme 5D).58

3.2.3 Mimicking the protein backbone with dendrimer encapsulation of a carboxylate-bridged diiron center.

Significant advances have been made in the synthesis of catalytically active diiron complexes as biomimetic analogs of enzymes.60 Dendrimers have highly branched and organized three-dimensional structures that facilitate the encapsulation of reactive metalloenzymes. Similar to the protein scaffold in a metalloenzyme, dendritic shielding creates a distinct microenvironment around the active core, which protects it from unwanted side reactions and controls its reactivity. Dendritically functionalized ligands have been explored extensively to model heme enzymes61,62 and were recently applied toward understanding non-heme diiron systems. The first dendrimer-derived mimic of a non-heme diiron enzyme contained a triazacyclononane ligand bearing poly(benzylether) dendritic substituents (1,17).63 The resulting mononuclear iron(II) starting material reacted upon oxygenation to form an oxo-bridged diiron(III) complex, assigned as [Fe₂(μ-O)(μ-OAc)(L₁TACN)]⁺.65 Photoirradiation of this complex led to 2-electron reduction and subsequent oxidation to the diiron(III) complex in the presence of dioxygen.


In order to prevent deleterious intermolecular electron transfer reactions, as observed in compounds with m-terphenyl carboxylate ligands (see above), and to restrict access of solvent molecules to the active site, the basic structure of these ligands was extended with third-generation dendritic poly(benzylether) units.60 The dendrimer-appended carboxylate, O₂C[G-3], facilitated the synthesis of doubly bridged diiron(II) complexes having the general formula [Fe₂(μ-O₂C[-G3])₂(O₂C[-G3])₂(4-RPy)₃] (R = cyano, pyrrolidino). The dendritic hydrophobic shield diminished gas permeability, which resulted in a 300-fold decrease in reaction rate compared with those of the unsubstituted m-terphenyl carboxylate-based complexes (Scheme 6).63

Unlike the parent compounds, the dendrimer complexes stabilized a new intermediate upon oxygenation, which Mössbauer, UV-vis, EPR, and X-ray absorption spectroscopic studies suggest to be a superoxo(dendrimer) complex. This
intermediate was stable at temperatures below -5 °C, a result that reflects the value of the protective shell of the dendrimer.

### 3.2.4 Modeling the syn-histidine disposition in MMOH

Despite the large number of model compounds, a structural characteristic that none of the aforementioned ligand motifs can rigidly enforce is the syn-disposition of the nitrogen donors with respect to the diiron vector present in these carboxylate-bridged non-heme diiron enzymes. The significance of this stereochemical feature is uncertain, but it is likely that nature did not choose this stereochemistry arbitrarily and that it plays a role in dioxygen activation. DFT studies of intermediate Q of MMOH suggest that a stereoelectronic effect is derived from this configuration, which helps to control the reactivity of this key intermediate. For this reason, dinucleating ligands that enforce the desired coordination mode were designed and synthesized. A requirement of such ligands is that the linker must fix the N-donor groups at the proper distance and orientation while being sufficiently flexible to accommodate different Fe–Fe distances. In addition, the resulting metal complexes should have a carboxylate-rich coordination environment and withstand bimolecular decomposition, oligomerization, or ligand oxidation by high-valent iron-oxo intermediates.

To address these challenges, a series of ligands with a 1,2-diethynylbenzene (DEB) linker connecting two heterocycles such as pyridines, quinolines, or imidazoles were prepared.87-89 The facile functionalization of the pyridine substituent allowed the synthesis of a series of ligands with the 1,2-bis(pyridin-3-yl)ethynylbenzene moiety (Figure 4A).88,89 This type of ligand has proved to be a useful template for preparing dimetallic complexes with a syn N-donor configuration. The structures of several such diiron complexes were recently determined by X-ray crystallography, and interesting structural features were noted upon inspection of dimetallic compounds with this ligand scaffold. The complexes revealed M–M distances that range from 3.11 to 5.17 Å (Chart 1), suggesting that this seemingly rigid linker is flexible enough to accommodate changes in the Fe–Fe distance upon reaction with dioxygen.87,70,71

Additionally, the diethynylbenzene backbone provides a pocket in which a bridging oxo-group can be accommodated, as may occur in intermediate Q of MMOH. Finally, functionalization of the pyridine moiety can provide additional protection from bimolecular decomposition, formation of polymers, or head-to-head ligand dimerization as observed with PIC2DET in [Fe2(µ-OTf)2(PIC2DET)]2+ (Chart 1).

The quinoline-based ligand Et2BCQEBet (1,2-bis(3-ethyl-8-carboxylate-quinoline)-benzene ethyl ester), afforded a diiron(II) complex, [Fe2(Et2BCQEBet)(µ-O2CPh)µ-O2CPh]2+, with three bridging carboxylates.90 Another carboxylate-rich but heterodinuclear complex, [NaFe(PIC2DET)(µ-O2CPh)µ-O2CPh]2+, was isolated.91 The labile sodium ion could be replaced by tritation with a ferrous salt, resulting in a diiron complex. It has been observed by crystallographic analysis of various X-ray crystal structures that the position of Fe2 is more flexible and distorted than Fe1 in MMOH (Figure 2). Thus, this model system simulates the lability of one iron atom in MMOH (see above).

The more recently introduced BPG-DE2+ ligand affords three oxo-bridged diiron(III) complexes, [Fe2(µ-O)(H2O)2-BPG-DE2](ClO4)2, [Fe2(µ-O)(µ-O2CPh2)2-BPG-DE2](ClO4)2, and [Fe2(µ-O)(µ-O2CPh)2(BPG-DE2)](ClO4)2, which form a

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**Figure 4.** General synthetic pathway via Pd-catalyzed cross-coupling reactions to (A) syn N-donor,87 and (B) C-clamp ligands.69 (C) Energy-minimized structure of [Fe2(BPGEt)(PICMe2)]2 [DEB(terphCO)2]1 displaying the substrate-access cavity (adapted from ref. 69).

**Table 1.** Structures of complexes (from left to right): [Fe2(µ-O)(µ-O2CPh)2(BPG-DE2)], [NaFe(PIC2DET)(µ-O2CPh)µ-O2CPh], [Fe2(µ-O2CPh)2(BPGEt)(PIC2DET)]2+, and comparison of the M–M distances in these compounds.

<table>
<thead>
<tr>
<th>M–M (Å)</th>
<th>3.11</th>
<th>3.18</th>
<th>3.58</th>
<th>5.17</th>
</tr>
</thead>
</table>

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**3.2.5 Toward modeling the hydrophobic substrate pocket with C-clamp ligands.** The work on syn N-donor ligands was further expanded for the synthesis of diiron complexes having specific hydrophobic cavities to allow for substrate access to the diiron site. This feature is of special interest considering the importance of instantaneous access of a substrate to a short-lived high-valent diiron intermediate. In MMOH, methane resides in a hydrophobic cavity at the active site at the time of formation of intermediate Q. Molecular recognition plays an important role in selective C–H activation of small molecules.74 C-clamp ligands as potential chelate hosts capable of binding a guest molecule in their endo-dicarboxylate pockets have been prepared with a flexible aromatic diaimine linker75 and with a sterically more constraining ligand having a diethyl benzene backbone (Figure 4B).69 The syn N-donor ligand provides a platform to which a C-clamp ligand, with two bridging, endo-oriented carboxylate groups, can bind in such a manner that a cavity is
formed. A space-filling diagram of the energy-optimized structure of a diiron complex containing a C-clamp and syn N-donor ligand is shown in Figure 4C. This in silico model features a hydrophobic substrate-access cavity as well as two N-donors in syn-disposition.

4 Bioinspired, N-rich MMOH model complexes.

The first carboxylate-bridged diiron complexes were reported in the early 1980s using nitrogen-rich capping ligands and bridging carboxylates (Chart 2) as models for met-hemerythrin. Although many models containing a N-rich structural motif have been published subsequently, these diiron complexes do not strictly resemble the coordination stoichiometry and environment of carboxylate-bridged non-heme diiron enzymes involved in oxidation chemistry. The lack of a carboxylate-rich ligand environment typically results in diiron intermediates and compounds having different electronic spin states than those in the biological systems. Thus, their UV-vis and Mössbauer spectroscopic properties often differ significantly from those in the enzymes and the oxidative strength towards substrates is greatly diminished. However, to some surprise, the only high-valent intermediate similar to intermediate Q, and the cleavage of strong C–H and O–H bonds in external substrates, have been achieved with such N-rich ligand systems. These bioinspired, rather then biomimetic, transformations fully justify the introduction of this alternative ligand set, without diminishing the ultimate goal of achieving the chemistry with a more relevant donor atom set. In the following sections we describe a few selected oxygenated diiron intermediates in model compounds containing a nitrogen-rich environment, which are of potential relevance to the active site of sMMO and related enzymes.

![Chart 2. Commonly used classical N-rich capping ligands for the assembly of diiron complexes (top) and ligands used to study peroxo complexes in Scheme 7 and 8.](image)

4.1 Superoxodiron(II,III) model intermediates. A superoxo intermediate has been observed only in a carboxylate-rich system in which the diiron core was embedded within a dendritic ligand sheath (see above). Reaction of [Fe₂(µ-OH)₂(6-Me₂-TPA)]₂⁺, where 6-Me₂-TPA is tris(6-methyl-2-pyridylmethyl)amine, with O₂ at −80 °C gave rise to an end-on bound µ-hydroperoxodiron(II,III) complex and a µ-hydroperoxodiron(III,III) species, as revealed by resonance Raman spectroscopy and kinetic studies (Scheme 7). These intermediates are precursors to a (µ-oxo)(µ-peroxo)diron(III) species, which forms by warming the reaction mixture to −60 °C. In contrast to the peroxo species, which is inert toward 2,4-di-tert-butyphenol (DTBP), the superoxo intermediate readily performs a one-electron oxidation on this substrate, a result suggesting that metal-superoxo species may play a previously unanticipated role as oxidants in metalloenzymes.

![Scheme 7. Proposed mechanism of peroxo formation of diiron complexes with 6-Me₂-TPA (Chart 2) and reactivity with 2,4-di-tert-butyphenol (DTBP).](image)

4.2 Peroxodiron(III) model intermediates. The first intermediates that are spectroscopically observed after reaction of BMM₄ with O₂ are peroxo species, the most commonly observed intermediate in enzymatic as well as biomimetic diiron systems. Thus, detailed spectroscopic and structural information about peroxo intermediates is available. Most commonly, in synthetic models the peroxo ligand is bound in a cis-µ-1,2-fashion, with an Fe–O–O–Fe dihedral angle that depends on the nature of other bridging ligands. The value is close to 0° with a bridging phenoxide/alkoxide ligand and approximately 54° in the presence of carboxylate bridging ligands as was established by crystal structure analysis of some model compounds.

More recently, solid state structures of peroxodiron(III) complexes [Fe₂(µ-OH)₂(6-Me₂-TPA)₂(O)(O₂)]²⁻ and [Fe₂(µ-OH)₂(6-Me₂-TPA)₃(O)(O₂)]²⁻ (6-Me₂-TPA = tripodal-based ligand) have been determined (Scheme 8). Upon addition of acid to the (µ-oxo)(µ-peroxo)diron(III) species, protonation occurs at the oxo-bridge to form a (µ-hydroxo)(µ-peroxo)diron(III) intermediate. The study revealed that these two species have significantly different spectroscopic properties, with the oxo-bridged peroxo complex having a blue-shifted LMCT band in contrast to the hydroxo-bridged species. Studies of a related peroxodiron(III) complex, [Fe₂(µ-µ)(µ-OH)₃(H)₃]⁺ (L = tris(3,5-dimethyl-4-methoxy-2-methyl)amine), suggested that protonation of oxygenated intermediates plays an important role in the formation of intermediate Q and substantially influences the reactivity. In this system, rapid conversion of the peroxo species to a diiron(IV) intermediate was observed spectroscopically, the latter converts into a [µ-oxo]diiron(IV) species upon addition of acid.

By contrast, in the well-characterized N-rich (µ-oxo)/(µ-carboxylato)diron(III) synthetic complex, [Fe₂(µ-O)(µ-O₂CPh)₃(N-EtHPTB)]⁺, protonation occurs at the carboxylate rather than the peroxo ligand. This result suggests that a carboxylate-shift can be induced by protonation, which improves the electrophilicity of the diiron unit and substrate access to the diiron center. The resulting protonated carboxylate could contribute to the activation of the diiron(III) peroxo intermediate in a number of ways. It could form a hydrogen bond to one of the peroxo oxygen atoms, rendering it more electrophilic, or...
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More recently, \([\text{Fe}^{III}_{11}(\text{O}-\text{O})(\text{L})]^{2+}\) (\(L = N,N\)-bis-(3',5'-dimethyl-4-methoxypyridyl)-2'-methyl)-N-acetyl-1,2-diaminothene), which has a \((\mu\text{-oxo})\text{(μ-carboxamido)}\) diiron core and a relatively small Fe–O–Fe angle (approximately 130°), has been oxidized electrochemically to a low-spin diiron(IV) complex (Scheme 9). This species, which has the highest redox potential of the three diiron(IV) complexes reported so far, functions as a one-electron oxidant toward hydrocarbons having C–H bond activation energies as high as 100 kcal mol\(^{-1}\), but dehydrogenation of the substrate instead of hydroxylation occurs (Scheme 10). This high-valent diiron(IV) complex is a unique example of a complex that cleaves the strong O–H bonds of alcohols. The rate of cyclohexane oxidation for this system, however, is still orders of magnitude smaller than the rate of methane hydroxylation in intermediate Q, which in this case might be a result of the difference in iron spin states for these oxidants (see above).

**Scheme 9.** Comparison of C–H activation by mono- and diiron(IV) complexes with 3,5-Me\(_2\)-OMe\(_2\)-TPA ligand (adapted from ref. 76).

**Scheme 10.** Electrochemical generation of a diiron(IV) complex and its ability for C–H and O–H bond activation. The dinucleating ligand L is shown in the inset.

**5 Conclusions.**

Recent progress and attempts to mimic more closely the active sites and protein scaffolds of carboxylate-bridged non-heme diiron enzymes, MMOH in particular, are described in this review. Ligand design is the key factor for assembling diiron complexes with the desired steric and electronic properties. \(m\)-Terphenyl-based carboxylate ligands facilitate the synthesis of diiron complexes having the flexibility adequate to reproduce biological features such as the carboxylate shift and the proper substituents to enforce a hydrophobic ligand environment, but they cannot stabilize high-valent species at ambient temperature. Compounds with dendrimer-appended terphenyl carboxylates protect the diiron core in such a way that allows for the isolation of novel oxygenated diiron species. Although not strictly structurally biomimetic models, nitrogen-rich ligand systems have the ability to stabilize high-valent diiron species, but with the iron atoms in a low-spin rather than a high-spin state. This low-spin configuration is presumably a contributing factor for the lower reactivity of the oxygenated species and their non-biomimetic spectral properties. Syn N-donor ligands can afford diiron complexes that mimic not only the stoichiometry but also the geometry of the enzyme active sites with respect the syn dispositions of the two histidines. We await with interest the evolution of new strategies that allow access to model compounds that reproduce the geometric and electronic structural features as well as the functional dioxygen-activation chemistry of carboxylate-bridged non-heme diiron enzyme cores.
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Notes and references

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Biosketches

Dr Simone Friedle received her Diploma in chemistry (Dipl.-Chem.) from the University of Karlsruhe, Germany, conducting her diploma thesis research abroad in the group of Professor Richard R. Holm at Harvard University on metal dithiolene complexes. Her graduate work under the guidance of Professor Stephen J. Lippard involved modeling the active sites of non-heme diiron enzymes. At present, she is a postdoctoral fellow in the laboratory of Professor Samuel W. Thomas III at Tufts University investigating contact electrification of electrostatically responsive materials.

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This tutorial review describes recent progress in modeling features of the carboxylate-rich diiron active site of bacterial multicomponent monoxygenases with a particular focus on soluble methane monoxygenase, which is capable of hydroxylating methane under ambient conditions.