

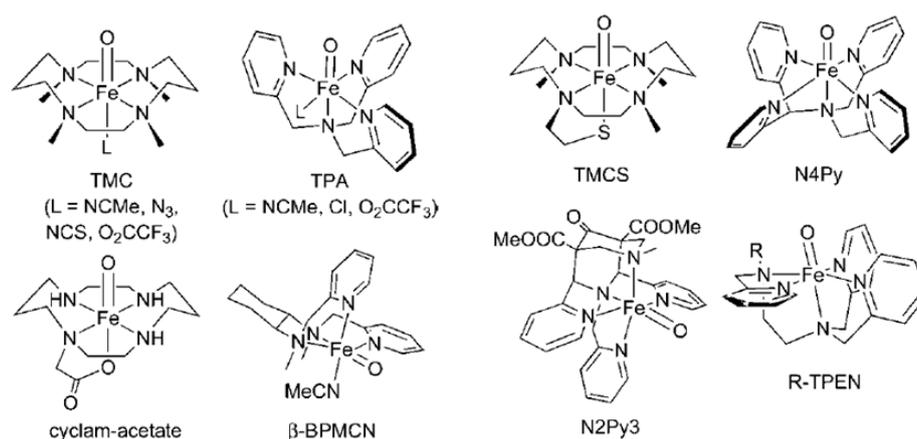
## From Low Spin to High Spin: Iron Opens Up to High Activity

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Proteins containing non-heme iron cofactors are widely found in nature. They exhibit many different functions, including activation of dioxygen and oxidation of a large number of substrates.<sup>1</sup> High-valent  $\text{Fe}^{\text{IV}}=\text{O}$  intermediates have been proposed as the active oxidants in a broad range of mononuclear non-heme iron monooxygenases. Four enzymes containing these high-valent species have been spectroscopically characterized recently, and it has been found that all of them have a high-spin ( $S=2$ )  $\text{Fe}^{\text{IV}}=\text{O}$  intermediates.<sup>2</sup> In contrast, synthetic models of non-heme iron monooxygenases prepared until very recently are all low spin ( $S=1$ ) at the iron centers, resulting from a ground state with two unpaired electrons (Figure 1). Furthermore, there is also typically a very low-lying excited state with quintet spin. The proximity of these two states makes it difficult to understand the mechanisms of these oxidation reactions.<sup>3</sup>

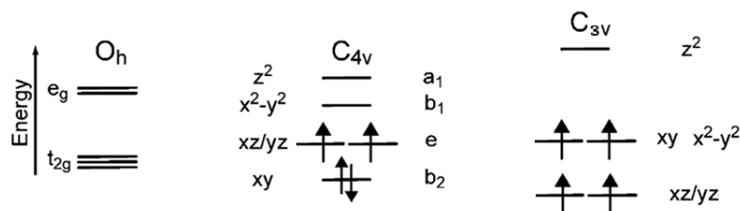


**Figure 1.** Selected  $\text{Fe}^{\text{IV}}=\text{O}$  complexes.<sup>3</sup>

Compared to nonheme iron monooxygenases, synthetic non-heme model complexes have thus far shown poor reactivity towards C–H bond activation. It has been a long-standing question whether this sluggishness in reactivity is due to the spin state of the iron center or the presence of the bulky ligands which are typically used to stabilize the highly reactive  $\text{Fe}^{\text{IV}}=\text{O}$  species. Additionally, it remains to be seen whether the high spin  $\text{Fe}^{\text{IV}}=\text{O}$  state is intrinsically more reactive than the low spin state. Theoretical calculation suggests that the answer is yes, but until recently there is no clear experimental evidence to support this prediction.<sup>4</sup> Obtaining an answer to this question might provide an explanation for the puzzling observation that Nature has only selected enzymes that use a high spin state intermediate.

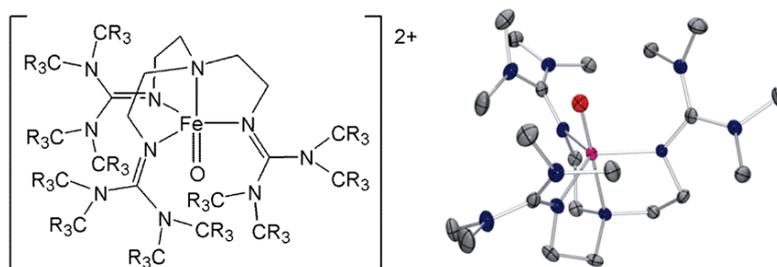
Consideration of the crystal-field splitting diagram for an octahedral oxoiron(IV) complex reveals that the spin state is determined by the energy gap between the  $d_{xy}$  and the  $d_{x^2-y^2}$  orbitals.<sup>5</sup> In the  $S=1$  complexes reported thus far, this energy gap is larger than the spin-pairing energy. Therefore, weakening the strength of the equatorial ligand field is one

strategy to obtain S=2 complexes. Indeed, the complex  $[\text{Fe}^{\text{IV}}=\text{O}(\text{H}_2\text{O})_5]^{2+}$ , which is generated by treating  $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})_6]^{2+}$  with ozone in acidic aqueous solution, has a high spin state, with S=2.<sup>6</sup> However, this complex is very unstable, with a  $t_{1/2}$  value of only 7 s at 25°C.<sup>7</sup>



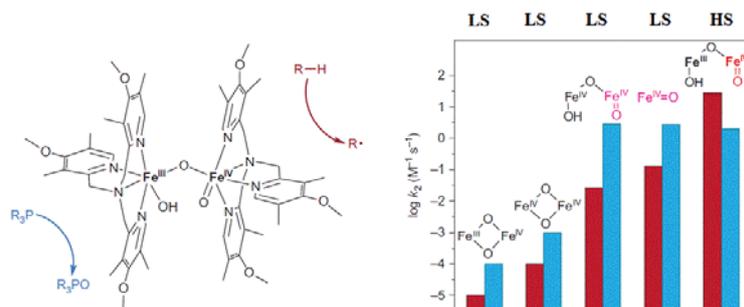
**Figure 2.** Ligand field splitting diagram of d orbitals.<sup>5</sup>

An alternative approach is to adopt a trigonal bipyramidal (TBP) geometry, where the  $d_{xy}$  and  $d_{x^2-y^2}$  orbitals would become degenerate (Figure 2). Thus, a tetradentate tripodal ligand with sufficient steric constraints to enforce local  $C_{3v}$  symmetry at the iron(II) center could afford a trigonal bipyramidal  $\text{Fe}^{\text{IV}}=\text{O}$  complex with an S=2 ground state (upon introduction of an axial oxo ligand). Using this strategy, Que and coworkers successfully synthesized the first high spin nonheme  $\text{Fe}^{\text{IV}}=\text{O}$  with the tripodal ligand “TMG<sub>3</sub>tren” (Figure 3). This high spin  $\text{Fe}^{\text{IV}}=\text{O}$  species has been fully characterized with Mössbauer, XANES and resonance Raman spectroscopy.<sup>8</sup> Later, they studied the self-decay pathway of this new  $\text{Fe}^{\text{IV}}=\text{O}$  species and reported its x-ray crystal structure.<sup>9</sup> Borovik and coworkers also reported a high spin nonheme  $\text{Fe}^{\text{IV}}=\text{O}$  species with a similar tripodal ligand. The  $\text{Fe}^{\text{IV}}=\text{O}$  unit bond length for this compound is 1.680(1) Å, which is the longest distance yet reported for a monomeric  $\text{Fe}^{\text{IV}}=\text{O}$  complex.<sup>10</sup>



**Figure 3.** First synthetic model of high spin nonheme  $\text{Fe}^{\text{IV}}=\text{O}$  species and its crystal structure.<sup>9</sup>

Münck, Que and coworkers reported the conversion of a synthetic complex with a valence-delocalized  $[\text{Fe}^{3.5}(\mu\text{-O})_2\text{Fe}^{3.5}]^{3+}$  diamond core into a complex with a valence-localized  $[\text{HO}-\text{Fe}^{\text{III}}-\text{O}-\text{Fe}^{\text{IV}}=\text{O}]^{2+}$  open core, with a consequent million-fold increase in C–H bond cleavage activity.<sup>11</sup> This activity enhancement results from three factors: the formation of a terminal  $\text{Fe}^{\text{IV}}=\text{O}$  moiety, the conversion of the low-spin (S=1)  $\text{Fe}^{\text{IV}}=\text{O}$  centre to a high-spin (S=2) center, and the concentration of the oxidizing capability to the active terminal  $\text{Fe}^{\text{IV}}=\text{O}$  moiety.



**Figure 4.** Million-fold activation of the high spin  $[\text{Fe}_2(\mu\text{-O})_2]$  diamond core for C–H bond cleavage.<sup>11</sup>

Recent studies are the first time providing conclusive experimental evidence to support the theoretical prediction that the high-spin state is more reactive. These findings will help our understanding of many enzymes and spur the development of more efficient C-H functionalization catalysts.

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