Oxoiron (IV) Complexes

Comparison of Fe^{IV}=O Heme and Non-heme Species: Electronic Structures, Bonding, and Reactivities**

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Mononuclear non-heme iron enzymes catalyze a variety of essential biological reactions that require the binding and activation of dioxygen;[1,2] their reactivity is as extensive as that of heme enzymes.[3] In both heme and non-heme enzymatic cycles, a high-valent oxoiron species is often invoked as the key active oxidizing species.

In many heme systems and biomimetic porphyrin model complexes oxoiron(IV) porphyrin cation radical (the so-called compound I in biological systems) and oxoiron(IV) porphyrin (compound II in biological systems) species, both with an Fe–O $S=1$ unit, are found to be important intermediates and are well studied and characterized by experimental and theoretical techniques.[4–7]

In mononuclear non-heme enzymes, a high-valent oxoiron(IV) ($S=2$) intermediate is often evoked, but has only recently been reported[8] and initially characterized.[9,10] There are also numerous theoretical studies on putative mononuclear non-heme Fe^{IV}=O ($S=2$) enzyme intermediates.[11–13] However, the coordination environment of these enzyme intermediates is not known and thus a direct correlation to calculations is not accessible.

The only structurally characterized mononuclear non-heme Fe^{IV}=O species are biomimetic model complexes with an $S=1$ ground state,[14,15] some of which exhibit C–H bond cleavage and oxidation reactivity similar to mononuclear non-heme iron enzymes.[16] Spectroscopic studies and experimentally calibrated density functional theory (DFT) calculations on the structurally defined complex provide a detailed description of the electronic structure and Fe–O bonding.[17]

While the oxoiron intermediates in heme and mononuclear non-heme enzymes and model complexes have been characterized experimentally and theoretically, we present herein the first comparison between oxoiron(IV) species in heme and non-heme environments. We will a) show that the electronic structures and Fe–O bonding in Fe^{IV}=O ($S=1$) heme and non-heme complexes are in fact very similar, b) provide an explanation for this, focusing on the effects of the Fe–O bond on the porphyrin π system, and c) evaluate the relative reactivities of the heme and non-heme oxoiron(IV) complexes for hydrogen-atom abstraction reactions.

Unrestricted DFT calculations using the Amsterdam density functional (ADF)[18] program package (see Supporting Information for detailed computational methodology) were carried out on an $[Fe^{IV}(O)(Por)(NCMe)]$ (Por = unsubstituted porphyrin ring) $S=1$ complex. Acetonitrile was chosen as the axial ligand[19] to correspond with the $[Fe^{IV}(O)(TMC)(NCMe)]^{2+}$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) non-heme model complex.

The geometric and electronic structure description of the heme Fe^{IV}=O (Figure 1a) agrees well with other results on heme Fe^{IV}=O species.[20–23] The Fe–O bond is short (1.65 Å, Table 1) and the $(d_{xy})^2(d_{xz}/d_{yz})^2$ electronic configuration is as expected. The two unpaired electrons are distributed across the Fe–O unit with little delocalization onto the porphyrin ring. The strong Fe–O π bonds are formed by overlap of the $Fe(d_{xz}/d_{yz})$ and $O(p_x/p_y)$ orbitals (Figure 1b) with a large contribution from the oxygen p orbitals (43%, Table 1).

This Fe^{IV}=O heme complex is compared to the well-characterized non-heme $[Fe^{IV}(O)(TMC)(NCMe)]^{2+}$ model complex[14,17] (Figure 1c), using the same computational methodology. A comparison of the key parameters describing the electronic structure and bonding (Table 1) shows that the heme and non-heme complexes are very similar, with almost identical Fe–O bond lengths and bond strengths (reflected by the vibrational frequencies) and comparable frontier molecular orbitals (FMOs).[24] According to these calculations, both heme and non-heme Fe^{IV}=O systems have very similar electronic structures and strong and very covalent oxo-to-iron π-donor and σ-donor bonds.

Key experimental parameters of heme and non-heme Fe^{IV}=O complexes are also similar (Table 2). The Fe–O bond lengths of compound II of horseradish peroxidase, measured by extended X-ray absorption fine structure spectroscopy (EXAFS), are comparable to the X-ray structure bond length of the non-heme $[Fe^{IV}(O)(TMC)(NCMe)]^{2+}$ model complex, despite having different *trans* axial ligands. The Fe–O vibrational frequencies, a measure of bond strength, are somewhat dependent on the nature of the *trans* axial ligand, but very

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[**] This research was supported by the National Institutes of Health (GM-40392). A.D. was supported by an Evelyn Laing McBain Stanford Graduate Fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200462182

Table 1: Key computational results of heme and non-heme Fe^{IV}=O and Fe^{III}–OH complexes.[a]

System	r(Fe–O) [Å]	ν(Fe–O) [cm^{-1}][b]	Spin density Fe	Spin density O	β d_{yz}(π*) [%] Fe(d)	β d_{yz}(π*) [%] O(p)	β d_{yz}(π*) [%] L(eq)	β d_{xz}(π*) [%] Fe(d)	β d_{xz}(π*) [%] O(p)	β d_{xz}(π*) [%] L(eq)	β d_{z^2}(σ*) [%] Fe(d)	β d_{z^2}(σ*) [%] O(p)	β d_{z^2}(σ*) [%] L(eq)
Fe^{IV}=O													
L(eq) = Por	1.65	849	1.13	0.90	49	43	4	49	43	4	55	24	13
L(eq) = TMC	1.65	846	1.31	0.77	53	37	5	54	36	5	56	22	15
Fe^{III}–OH													
L(eq) = Por	1.81	633	0.83	0.23	74	4	18	55	22	17	–[c]	15[c]	–[c]
L(eq) = TMC	1.82	615	0.93	0.16	85	4	3	72	17	3	66	11	15

[a] All structures fully optimized in adf/tzp, all with NCMe axial ligation. [b] From g98/BP86/lanl2dz calculation, for details see Supporting Information. [c] Weaker Fe–O bond causes d_{z^2} and $d_{x^2-y^2}$ to mix, Fe and Por contributions cannot be separated.

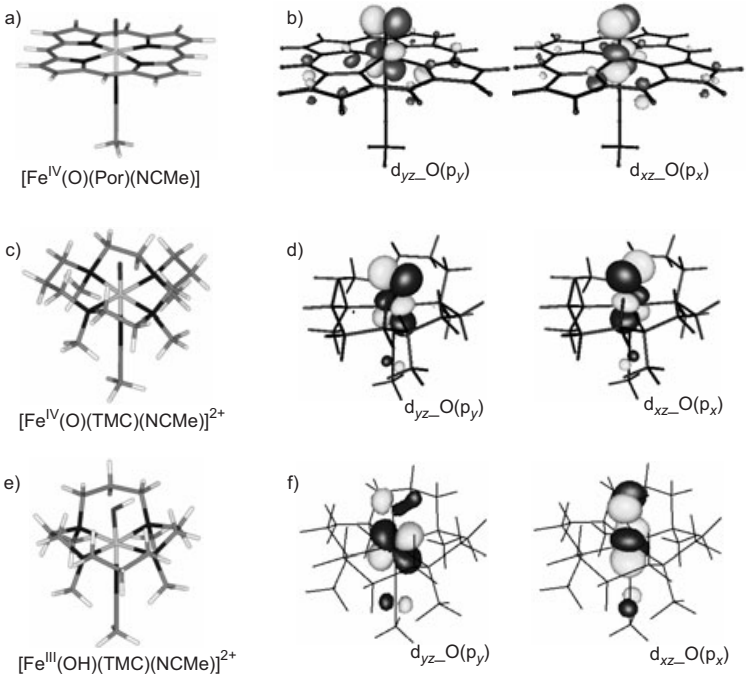

Figure 1. Optimized structures (a, c, e) and isosurfaces (b, d, f) of the Fe–O π* orbitals of Fe^{IV}=O and Fe^{III}–OH complexes.

Table 2: Comparison of experimental and theoretical parameters of non-heme and heme Fe^{IV}=O enzyme intermediates and model complexes.

	r(Fe-O) [Å] heme	r(Fe-O) [Å] non-heme[a]	ν(Fe-O) [cm^{-1}] heme	ν(Fe-O) [cm^{-1}] non-heme[a]
experimental data[b]	1.64(3)[d] [35] 1.704(10)[d] [37] 1.69[d] [39]	1.646(3)[e] [14]	807[f] [36] 814[d] [38] 843[g] [25]	834[e] [14]
calculations[c]	1.66[d] 1.65[e]	1.65[d] 1.65[e]	803[d] 849[e]	819[d] 846[e]

[a] TMC as equatorial ligand. [b] No structural data (X-ray or EXAFS) available on heme model complexes (compound II), EXAFS data of enzyme intermediates shown. [c] All theoretical values from this study. [d] Imidazole as axial ligand. [e] NCMe as axial ligand. [f] 1-Me-imidazole as axial ligand. [g] No axial ligand (five coordinate).

similar for heme and non-heme systems with the same axial ligands.[7,25] Mössbauer studies have shown a positive, large zero-field splitting ($D \approx 30\ cm^{-1}$) for both heme and non-heme Fe^{IV}=O complexes.[14,26,27] Importantly, the calculated geometric and electronic-structure descriptions for the heme and non-heme Fe^{IV}=O species correlate well with experimental data (Table 2).

This comparison of theoretical and experimental data of heme and non-heme Fe^{IV}=O ($S = 1$) complexes demonstrates that the aromatic porphyrin system in the equatorial plane does not significantly change the electronic structure and Fe–O bonding when compared to "innocent", only σ-donating amine-based equatorial ligands, such as the TMC-macrocycle. These Fe^{IV}=O ($S = 1$) heme and non-heme complexes have very similar electronic structures and Fe–O bonding.

This similarity is remarkable, since the e_g set of the porphyrin π system (in idealized D_{4h} symmetry) can interact with the Fe d_{xz}/d_{yz} orbitals (Figure 2, left) and thus affect the Fe–O π bonds, while the amines of the TMC ligand do not have any equivalent orbitals (Figure 2, right).

However, a fragment analysis (see Supporting Information) shows that there is no net π bonding between the porphyrin ring and the iron center.

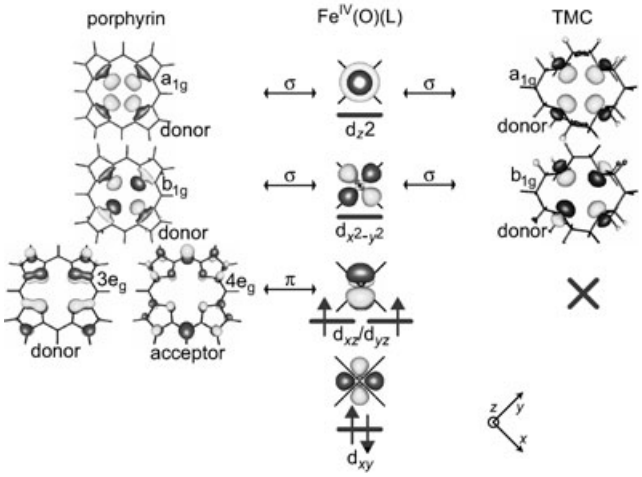

Figure 2. Schematic energy-level diagram for Fe^{IV}=O(L) and possible interactions with the equatorial ligands (labels according to idealized D_{4h} symmetry).

Figure 3 shows an interaction diagram for the three important fragment orbitals in the β-spin manifold. The occupied porphyrin $3e_g$ fragment orbitals only mix into the Fe–O π-bonding orbitals, forming Fe–Por bonding and antibonding

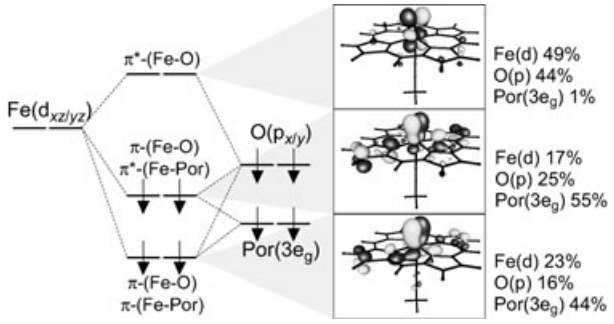

Figure 3. Interactions between β-spin Fe(d_{xz}/d_{yz}), O(p_x/p_y), and Por-($3e_g$) orbitals.

combinations. There is no mixing into the Fe–O π-antibonding orbitals.[28] The very strong and covalent π bond between the close lying iron and oxygen atoms (1.65 Å) dominates the overall bonding and decouples the Fe^{IV}=O unit from the porphyrin π system. NMR spectroscopy studies which show that there is no spin delocalization onto the porphyrin ring support this model.[29,30]

With its conjugated π system in the equatorial plane decoupled from the metal center, the porphyrin system is similar to an "innocent" nitrogen-based σ-donating macrocycle. This situation leads to the similar electronic structures of Fe^{IV}=O ($S=1$) heme and non-heme systems.[31]

The reactivity of these Fe^{IV}=O complexes requires consideration of the electronic structures and FMOs of not only the Fe^{IV}=O reactant, but of the reaction products as well. Herein we consider the hydrogen-atom abstraction reaction of the Fe^{IV}=O ($S=1$) species in heme and non-heme environments resulting in a low-spin Fe^{III}–OH species.[32] As one would expect, both heme and non-heme Fe^{III}–OH (Table 1, Figure 1e and f) have much longer Fe–O bonds than the Fe^{IV}=O complexes. Weakening the Fe–O bond allows the porphyrin π system to interact and covalently mix with the Fe(d_{xz}/d_{yz}) orbitals. As the coefficients in Table 1 show, the porphyrin contribution to these molecular orbitals increases from 4% (Fe^{IV}=O) to approximately 18% in the Fe^{III}–OH heme complex, while in the non-heme complex the contribution of the equatorial TMC ligand, which does not have π interactions, remains low (3–5%). The one-electron reduction and protonation weakens the Fe=O bond and allows the porphyrin π system to couple to the iron center. This delocalization of electron density onto the ligand is observed experimentally in low-spin ferric hemes.[33,34] In contrast to Fe^{IV}=O, for low-spin Fe^{III}–OH, the electronic structures and bonding differ greatly between heme and non-heme complexes.

This difference in the electronic structures of the products will contribute significantly to differences in reactivity between heme and non-heme Fe^{IV}=O complexes. Consequently, for the thermodynamics of the hydrogen-atom abstraction reaction, the greater stability of the Fe^{III}–OH reaction product in a heme environment leads to a less positive reaction free energy (ΔG) by about 10 kcal mol^{-1} (Table 3).

Table 3: Thermodynamics for the hydrogen-atom abstraction reaction by Fe^{IV}=O heme and non-heme complexes.

Ligation	ΔE	+Solvent	ZPCE[b]	$-T\Delta S$[c]	ΔG
TMC_NCCH_3	24.2	−2.7	−1.6	−2.3	17.6
por_NCCH_3	15.4	−3.6	−1.2	−4.4	6.1

[a] All values in kcal mol^{-1}; hydrogen at the tertiary carbon center of 2,3-dimethylbutane abstracted. [b] Zero-point correction energy. [c] Entropy term; for computational details see Supporting Information.

Thus, the electronic structures of the Fe^{IV}=O complexes are dominated by the very strong Fe–O bonding, which decouples the porphyrin π system, leading to similar bonding in heme and non-heme complexes. A weakening of the Fe–O bond in Fe^{III}–OH products of a hydrogen-atom abstraction reaction, however, allows the porphyrin π system to interact with the iron center, stabilizing the heme relative to the non-heme complex and leading to different reactivities.

Received: October 2, 2004
Revised: December 1, 2004
Published online: February 18, 2005

Keywords: bioinorganic chemistry · density functional calculations · electronic structure · high-valent compounds · iron

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[32] Most heme enzymes utilize a Fe^{IV}=O-porphyrin-radical (compound I) to achieve hydrogen-atom abstraction, while mononuclear non-heme iron enzymes utilize a high-spin ($S = 2$) oxo intermediate. In this study we focus on the relative reactivities of heme and non-heme Fe^{IV}=O ($S = 1$) complexes in the same redox and spin states.

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