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Comparative Reactivity of Ferric-Superoxo and Ferryl-Oxo Species in Heme and Non-Heme Complexes

Lung Wa Chung,* Xin Li, Hajime Hirao, and Keiji Morokuma*

Fukui Institute for Fundamental Chemistry, Kyoto University, 34-4 Takano Nishihiraki-cho, Kyoto 606-8103, Japan

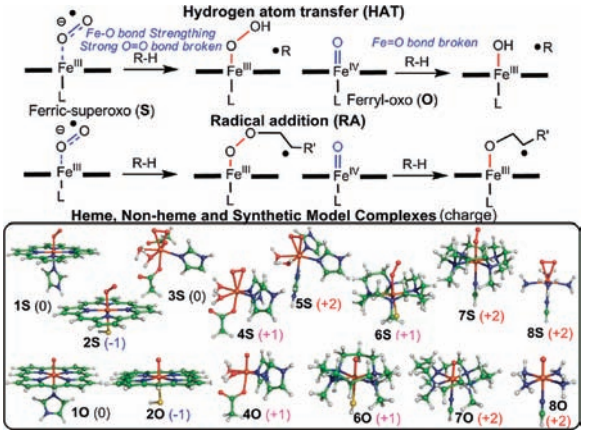
Supporting Information

ABSTRACT: Ferryl-oxo species have been recognized as a key oxidant in many heme and non-heme enzymes. Recently, less-characterized ferric-superoxo species have been found or suggested to be another electrophilic oxidant. Reactivity of several vital ferryl-oxo and ferric-superoxo model complexes was examined by DFT calculations. Reactivity is found to correlate well with thermodynamic driving force and can increase with higher electrophilicity of the oxidant. Reactivity of the ferric-superoxo oxidants generally is not "superior" to the ferryl-oxo ones. Compared to the high-spin non-heme ferric-superoxo, the lower reactivity of low-spin heme ferric-superoxo, seldom utilized in nature, can be attributed to lower electrophilicity and more pronounced quenching of anti-ferromagnetic coupling between the ferric and superoxo parts. The present comparison should shed some light on mechanistic strategies in heme and non-heme enzymes and provide clues to rational design of ferric-superoxo oxidants.

Heme- and non-heme-containing oxygenases and oxidases play vital roles in many selective and efficient biochemical oxidations.[1,2] Several species, including ferryl-oxo, ferric-hydroperoxo, and ferric-peroxy, have been proposed or found to act as oxidants in these enzymes.[1,2] In addition to the well-known high-valent ferryl-oxo species, not-well-characterized lower-valent ferric-superoxo species have recently been suggested or observed as alternative electrophilic oxidants, e.g. in isopenicillin N synthase, hydroxyethylphosphonate dioxygenase, catechol dioxygenases, tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenase (IDO), and nitric oxide dioxygenase (NOD, reaction with $NO^{\bullet}$).[1−6] Furthermore, synthetic ferric-superoxo and other metal-superoxo complexes were recently reported to be capable of catalyzing oxidation, including C−H bond activation.[7] Notably, many non-heme enzymes can use ferric-superoxo species as an oxidant, but only a few heme enzymes (TDO, IDO, and NOD so far) use ferric-superoxo species![4,6] In this regard, we suggested that a neutral porphyrin ferric-superoxo complex could react with neutral π-substrates mainly via radical addition.[4d] In this study, we theoretically and systematically compare reactivity of several key ferric-superoxo and ferryl-oxo model complexes (Scheme 1).

Our calculations show that different ferric-superoxo species can adopt different O_2 coordination modes and/or spin states.[8a] For instance, ground-state heme ferric-superoxo complexes ^{1}**1S** and ^{1}**2S** favor low-spin and end-on O_2 coordination, whereas ground-state non-heme or synthetic model complexes ^{7}**3S**, ^{7}**4S**, ^{7}**5S**, and ^{7}**8S** prefer a side-on mode and a high-spin state. Due to steric crowding (large Fe−O−O angle, 139−151°), the 6-coordinate

Scheme 1. Hydrogen Atom Transfer and Radical Addition Reactions with Ferric-Superoxo and Ferryl-Oxo Species



end-on states of ^{7}**6S** and ^{5}**7S** are more stable than the corresponding side-on ones. However, ^{5}**7S** is computed to be similar in energy to less-bulky 5-coordinate complex ^{7}**7′S** (without a NCH ligand) in the gas phase, and ^{7}**7′S** becomes the most stable form in solution ($\Delta\Delta E$ = 3.0 (gas) and −16.5 to −18.0 (acetonitrile, ACN) kcal/mol). Driven further by entropy, the 5-coordinate complex ^{7}**7′S** should be the resting state of the recent not-yet-characterized synthetic model,[7c] whereas the corresponding ferryl-oxo complex was observed to be 6-coordinate.[1b] Recently, a quintet ferric-superoxo species in a non-heme dioxygenase has been shown to be the ground state.[3c] Hence, our B3LYP calculations could overestimate the stability of the septet state.

The ferric-superoxo can be stabilized by anti-ferromagnetic coupling (AFC) between Fe 3d electrons and the superoxo radical in the singlet heme and quintet non-heme complexes, or by ferromagnetic coupling (FC) in the triplet heme and septet non-heme complexes (Schemes 2 and S2). Surprisingly, key electronic structures of **6S**−**8S** are different, in which an out-of-plane $\pi^*(O_2)$ orbital becomes fully occupied and an in-plane $\pi^*(O_2)$ orbital is singly occupied (Figure S13). Additionally, compared to the low-spin heme ferric-superoxo complexes,[2b,4c,d] much smaller coupling was found in the non-heme end-on ferric-superoxo dioxygenase experimentally ($J \approx 6$ cm^{-1})[3c] and in our model complexes. In comparison, the geometry and electronic

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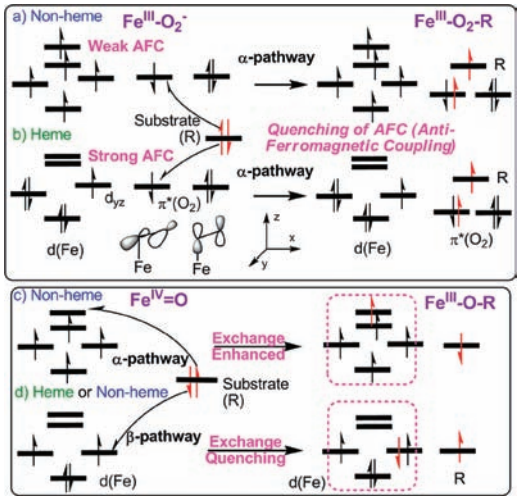
Scheme 2. Schematic Changes of Frontier MOs for Oxidation with Ferric-Superoxo and Ferryl-Oxo Species



configuration of ferryl-oxo complexes are much simpler and generally favor the triplet state.[5,9,10]

Scheme 2 also conceptually illustrates oxidative processes of the ferric-superoxo and ferryl-oxo complexes. For the former, one electron is formally transferred from the substrate to the half-filled $\pi^*(O_2)$ orbital (reduction of superoxo), but not to the metal; thus, a strong $\pi(O_2^-)$ bond is broken and the Fe−O bond is strengthened. Therefore, *the coupling (AFC or FC) between the ferric metal and superoxo part is quenched partly in the transition state and completely in the product*. Since the electronic configuration of the metal does not change, the effect of exchange interactions of the metal on the reaction should be small. In contrast, for the ferryl-oxo oxidants, one electron is formally transferred from the substrate to the ferryl metal (reduction of the metal) to weaken the Fe═O bond via a ferric-oxo transition state.[9,10a] Hence, the reactivity of ferryl-oxo can be affected by changing the exchange interactions in different spin states.[9,10]

Our key results for the reactivity of ferric-superoxo and ferryl-oxo oxidants toward a model substrate propene (Table 1, and other substrates (*vide infra*)) are summarized as follows. First, neutral or anionic heme ferric-superoxo and ferryl-oxo oxidants (**1**,**2**) are usually less reactive than non-heme oxidants (**3**−**8**); the reactivity qualitatively increases with increasing positive charge of the oxidants (electrophilicity) and stability of the products (thermodynamic driving force).[11a] Remarkably, a good linear correlation (Figure 1) between the computed barrier and reaction energy (ΔE_{HTS}) of hydrogen atom transfer (HAT) is found for the ferric-superoxo oxidants with different charges and spin states. A similar linear correlation is also observed for the ferryl-oxo oxidants. These correlations suggest that a larger driving force is required to promote the reactivity of the ferryl-oxo species compared to the ferric-superoxo species. Overall, the reactions of the ferric-superoxo and ferryl-oxo species follow the Bell−Evans−Polanyi principle. Second, the lower-valent ferric-superoxo oxidants generally have lower reactivity of HAT and radical addition (RA) than the corresponding ferryl-oxo oxidants, but similar or even higher reactivity was observed for the synthetic ferric-superoxo model complexes **6S**−**8S**. The lower reactivity of the ferric-superoxo oxidant than the ferryl-oxo oxidant in $P450_{CAM}$ was also observed.[5a] Although a polar

Table 1. Energies (kcal/mol, with ZPE, Relative to Isolated Reactants) of Hydrogen Atom Transfer TS (HTS) and Its Product (HP), and Radical Addition TS (ATS) and Its Product (AP), for Fe^{III}-O_2^- and Fe^{IV}═O Species with Propene

	HTS	HP	ATS	AP
$^{3/1}$**1S**[a]	24.4/22.6	15.2/15.2	21.4/19.5	8.6/8.6
$^{3/1}$**2S**[a]	24.6/23.4	15.0/15.0	22.9/21.4	11.2/11.3
$^{5/7}$**3S**[a,b]	19.4/20.0	11.5/11.5	15.4/16.2	6.5/6.6
$^{5/7}$**4S**[a,c]	16.3/17.8	7.7/7.7	11.1/12.8	1.4/1.7
$^{5/7}$**5S**[a]	8.1/8.5	2.9/3.1	1.2/2.8	−6.0/−4.9
$^{5/7}$**6S**[a]	15.8/17.2	8.2/8.3	11.0/12.1	3.2/3.3
$^{5/7}$**7S**[a]	2.7/3.0	−1.3/−0.9	−3.3/−3.1	−9.3/−7.1
$^{5/7}$**7′S**[a]	3.5/3.9	−1.2/−0.3	−2.3/−1.9	−10.3/−7.2
$^{5/7}$**8S**[a]	0.9/0.5	−2.8/−1.0		
$^{3/5}$**1O**[a,d]	17.9/22.5	4.1/7.2	18.3/21.8	2.1/3.3
^{3}**2O**[a]	15.2	3.2	18.5	0.3
$^{3/5}$**4O**[a]	15.8/6.4	1.2/−9.0	17.2/6.6	0.2/−10.5
$^{3/5}$**6O**[a,e]	31.2/15.1	13.4/2.0	35.1/18.7	17.1/5.5
$^{3/5}$**7O**[a,f]	17.8/4.6	3.2/−5.5	9.1/3.7	−0.7/−8.9
^{3}**8O**[a]	2.2	−11.5		
^{2}**HOO**$^{\bullet}$[a]	13.6	4.3		

[a] Superscripts 1, 2, 3, 5, and 7 refer to relative energy in singlet, doublet, triplet, quintet, and septet states, respectively. [b] Energy for $^{3/1}$**HTS** (28.3/26.7), $^{3/1}$**HP** (18.4/18.4), $^{3/1}$**ATS** (25.3/23.8), and $^{3/1}$**AP** (14.6/14.6). [c] Energy for $^{3/1}$**HTS** (22.9/21.9), $^{3/1}$**HP** (12.0/12.0), $^{3/1}$**ATS** (18.0/16.6), and $^{3/1}$**AP** (6.1/6.1). [d] Energy for ^{7}**HTS** (31.2) and ^{7}**ATS** (31.5). [e] Energy for ^{7}**HTS** (28.4) and ^{7}**ATS** (32.2). [f] Energy for ^{7}**HTS** (19.7).

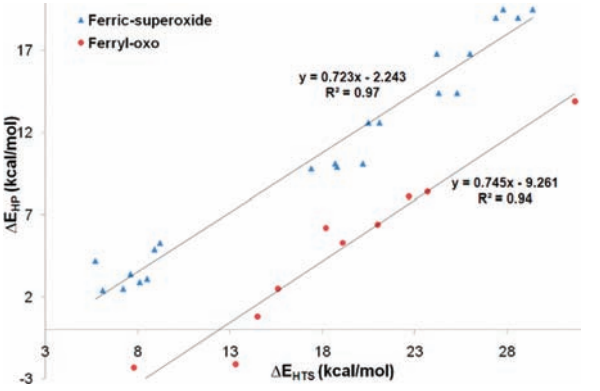


Figure 1. Correlations between the calculated HAT barrier and reaction energy (relative to the most stable reactant complex) for ferric-superoxo and ferryl-oxo species.

ACN solvent normally increases the barrier, cationic oxidants are generally more reactive than heme oxidants, and **7′S** is responsible for the oxidation. Third, the reaction barrier for an intramolecular HAT in **7′S** is high (about 26−30 kcal/mol), and higher than the intermolecular HAT with propene (by 26.0 (gas) and 6.3 (ACN) kcal/mol). Hence, self-decay of **7′S** is less feasible, due to larger strain in the transition state.

As discussed above, the oxidation reactions involve electron transfer from the substrate to the iron oxidants. The more electrophilic complex with a lower-lying electron-accepting orbital[9a] (e.g., the half-filled $\pi^*(O_2)$ orbital of ferric-superoxo complexes, Table S2) can enhance both reactivity and thermodynamic driving force. As shown in Tables 2 and S2, the cationic

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Table 2. Calculated Adiabatic Electron and Proton Affinities of the Key $Fe^{III}-O_2^-$ and $Fe^{IV}=O$ Species (kcal/mol, with ZPE) in the Gas Phase and Acetonitrile Solution[a]

	EA_{ad}	PA_{ad}		PA_{ad}
1S	24.5/75.5[a,b]	−242.8/−14.2[a,c]	**2S**	−317.7/−19.9[a,c]
4S	121.8/94.1[a,b]	−140.2/2.4[a,c]		
7′S	218.8/106.3[a,b]	−52.1/16.5[a,c]		
1O	19.6/63.3[a,b]	−254.1/−22.8[a,c]	**2O**	−338.0/−32.5[a,c]
4O	120.4/93.7[a,b]	−144.2/−3.3[a,c]	**6O**	−155.4/−15.0[a,c]
7O	206.5/103.1[a,b]	−65.8/0.0[a,c]		

[a] DFT(PCM)//DFT. [b] No solvation energy of an electron. [c] $\Delta G_{solv}(H^+)$, −260.2 kcal/mol, was taken from ref 8b.

non-heme complexes have a lower-lying electron-accepting orbital and a higher electron affinity (EA), which can promote the reactivity and driving force, especially for dicationic complexes **7S**, **7′S**, and **7O**. Importantly, even for neutral complexes **1S** and **3S**, the electron-accepting half-filled $\pi^*(O_2)$ orbital for the reactions in ^{1,5}**3S** is lower-lying than ^{1}**1S**. Therefore, the lower reactivity and driving force of the neutral and anionic heme ferric-superoxo complexes are partly attributed to their lower electrophilicity (due to the dianionic π-porphyrin ligand). In this regard, a few non-heme synthetic ferryl-oxo complexes have been found to have a lower reduction potential than heme ferryl-oxo complexes.[12a] Moreover, as discussed before, the more pronounced quenching of AFC in low-spin heme ferric-superoxo complexes than in high-spin non-heme superoxo complexes should further decrease the reactivity and thermodynamic driving force of the heme ferric-superoxo complexes. In fact, the reactive quintet state (for most of the non-heme ferric-superoxo complexes)[5b,c,g] was calculated to have the lowest intrinsic barriers for HAT and RA for **3S** and **4S** (Figures S6 and S7), lower than the singlet state by ∼0.5−3.0 kcal/mol, presumably due to weak AFC.[3c] On the other hand, the higher reactivity should not simply be determined by spin density of the reacting oxygen,[5a] as the spin density for the non-heme superoxo complexes is much smaller than for the heme superoxo complexes.

Surprisingly, the lower-valent ferric-superoxo oxidants are calculated to have a higher EA than the high-valent ferryl-oxo species (Table 2). However, besides the electrophilicity of the oxidants, the high-valent ferryl-oxo species is found to have higher proton affinity (and basicity), which also affects the driving force in forming a new O−H bond[11a,12b] and possibly enhances the reactivity, compared to the ferric-superoxo species. The enhanced HAT reactivity of some metal-oxo complexes with a more basic ligand was experimentally attributed to the higher driving force.[12b,c] In addition, an additional gain of the large exchange stabilization for high-spin non-heme ferryl-oxo species further contributes to the higher reactivity and driving force (exchange-enhanced reactivity and thermodynamic driving force).[10] Moreover, compared to similar MO coefficients on the two superoxo atoms in the electron-accepting MO, higher MO coefficients on the oxo ligand could further promote the reactivity.[9a] However, closer contacts between the substrate and equatorial ligands of the ferryl-oxo oxidants may increase the reaction barriers.[9a]

The importance of the driving force on the reactivity and the low reactivity of the heme-superoxo complexes prompt us to investigate effects of substrate, ligand, and metal on HAT. For instance, using cyclohexene, cyclohexadiene, or phenol[7b] as substrate results in higher driving force and reactivity (Figures S22−S24), compared to using propene. On the other hand, the

Table 3. Calculated Bond Dissociation Energy (kcal/mol, with ZPE) Associated with the New O−H Bond Formation

MO_2-H	BDE_{O-H}	MOH	BDE_{O-H}
1S	66.2/65.9[b]	**1O**	78.0
2S	63.9	**2O**	79.4
3S	68.7[c]	Compd **I**	86.8
4S	70.6[d]	**4O**	85.6[e]/77.3[f]
5S	71.2		
6S	70.3	**6O**	77.8[e]/72.1[f]
7S	75.4	**7O**	81.0[e]/76.5[f]
7′S	74.0		
8S	72.5	**8O**	93.4[e]/79.9[f]
1S(Ru)[a]	69.3[b]	tmcsFeO	76.9[e]
1S(Os)[a]	70.1[b]	TauD	87.8[e]/78.7[f]
1S(V)[a]	68.0		
1S(Cr)[a]	65.0	$[MnO_4]^-$	68.8
1S(Mn)[a]	65.6	RuO_4	70.7
1S(Co)[a]	60.8	OsO_4	53.9

[a] Fe in **1S** is replaced by another metal (in parentheses). [b] The SDD basis set and ECP were used. [c] 71.1 kcal/mol for ^{1}**3S**. [d] 73.2 kcal/mol for ^{1}**4S**. [e] Sextet state. [f] Quartet state.

bond dissociation energy of the new O−H bond (BDE_{O-H}) can offer a "qualitative understanding" of HAT reactivity.[11a] Therefore, the BDE_{O-H} values for the key ferric-superoxo, ferryl-oxo (including high-spin ferryl-oxo in TauD and cationic ferryl-oxo in P450), and other common oxidants were evaluated and compared (Table 3) to understand different mechanistic strategies as well as to obtain clues about rational design of reactive heme ferric-superoxo oxidants. BDE_{O-H} is equal to the energy difference between BDE of the new O−H bond (plus the Fe−O bond strengthened in the ferric-peroxy complex) and BDE of the X=O bond (X = O and Fe for the ferric-superoxo and ferryl-oxo complexes, respectively, cf. Scheme 1).

The trend in computed BDE_{O-H} is consistent with the above-discussed reactivity and driving force (Tables 1 and 3). The less reactive heme oxidants have smaller BDE_{O-H} than non-heme oxidants (even for low-spin ^{1}**3S** and ^{1}**4S**). Also, the ferric-superoxo oxidants intrinsically give smaller BDE_{O-H} than the ferryl-oxo oxidants, presumably due to the strong $\pi(O_2^-)$ bond broken and quenching of AFC in the former ones, and the exchange stabilization gain for the latter ones. Comparatively, a very reactive cationic low-spin ferryl-oxo oxidant (Compound I) employed in P450 heme enzymes is driven by the very large BDE_{O-H} (86.8 kcal/mol). On the other hand, the extra exchange stabilization gained in the high-spin ferryl-oxo oxidants in TauD or synthetic complexes increases the BDE_{O-H} (81.0−87.8 kcal/mol) and, thus, increases the reactivity.[10] The highest-valent metal-oxo oxidants $[MnO_4]^-$ and MO_4 (M = Ru or Os) have rather small BDE_{O-H} (53.9−70.7 kcal/mol), explaining why stepwise HAT is less favorable than the concerted [3+2] pathway.[11b] As to the heme ferric-superoxo, replacing Fe in **1S** by other first-row transition metals gives only a smaller or similar BDE_{O-H}, while using Ru or Os affords a slightly higher BDE_{O-H}. We finally used a monoanionic 21-oxaporphyrin ligand to generate a cationic heme-like ferric-superoxo complex $\mathbf{1S_{oxa}}$. We are pleased to find that $\mathbf{1S_{oxa}}$ gives a lower HAT barrier with propene (19.3 vs 24.2 kcal/mol for **1S**, Figure 2), and higher BDE_{O-H} (70.4 kcal/mol).

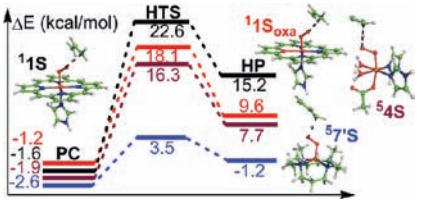

Figure 2. Energy profiles of HAT reaction for **1S** (black), $\mathbf{1S_{oxa}}$ (red), **4S** (dark red), and **7′S** (blue) with propene in the gas phase.

In summary, the reactivity of several key ferric-superoxo and ferryl-oxo model complexes is found to correlate well with the driving force and can be enhanced by using more electrophilic complexes. Moreover, ferryl-oxo complexes with higher driving force are usually more reactive than ferric-superoxo ones. *Compared to non-heme ferric-superoxo oxidants, the lower electrophilicity and more pronounced quenching of the anti-ferromagnetic coupling in the heme ferric-superoxo complexes lower the reactivity*. In addition, the non-heme Fe center is often coordinately unsaturated and flexible: the substrate can be directly activated through ligation for intramolecular reactions (and even forms a strong C═S or C═O bond after HAT[2a,5b−d,g]). This may be why nature prefers to use transient non-heme ferric-superoxo species for oxidation to a larger extent than the heme superoxo species. The latter may be tailored to function mainly as oxygen storage or carrier, and be activated by electron and/or proton transfer.[1,4] Having various oxidants with different reactivity in nature, the milder ferric-superoxo oxidants should render oxidations more selective with reactive substrates and atomically economic. The reactivity and driving force of the ferric-superoxo could be further enhanced in enzymes by stronger electrostatic interactions with reacting (more charged and polar) O−H moieties. Quenching of the coupling may affect reactivity of other bioinorganic systems. Our comparative results may help design more reactive ferric-superoxo oxidants or artificial heme enzymes.

■ ASSOCIATED CONTENT

Supporting Information. Computational details, complete ref 4a, tables, schemes, figures, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
chung@fukui.kyoto-u.ac.jp; morokuma@fukui.kyoto-u.ac.jp

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