Properties and reactivities of nonheme iron(IV)–oxo versus iron(V)–oxo: long-range electron transfer versus hydrogen atom abstraction\textsuperscript{†}

Baharan Karamzadeh\textsuperscript{a}, Devendra Singh\textsuperscript{b}, Wonwoo Nam\textsuperscript{c*,c} Devesh Kumar\textsuperscript{b*} and Sam P. de Visser\textsuperscript{a*}

Recent work of Nam and co-workers [J. Yoon, S. A. Wilson, Y. K. Jang, M. S. Seo, K. Nehru, B. Hedman, K. O. Hodgson, E. Bill, E. I. Solomon and W. Nam, Angew. Chem. Int. Ed., 2009, 48, 1257] on a biomimetic iron complex implicated a mixture of iron(IV)–oxo and iron(V)–oxo intermediates but the latter could not be spectroscopically characterized, hence its involvement was postulated. To gain insight into the relative activity of these iron(IV)–oxo versus iron(V)–oxo intermediates, we have performed an extensive density functional theory (DFT) study on the chemical properties of the chemical system of Nam et al., namely \([\text{Fe(O)(BQEN)(NCCH}_3])^{2+/3+}\) with BQEN = \(N,N^\prime\)-dimethyl-\(N,N^\prime\)-bis(8-quinolyl)ethane-1,2-diamine and their reactivity in hydrogen atom abstraction from ethylbenzene. We show that the perceived iron(IV)–oxo species actually is an iron(IV)–oxo ligand cation radical, similar to cytochrome P450 compound I. Moreover, this intermediate has an extremely large electron affinity and therefore can abstract electrons from substrates readily. In our particular system, this means that prior to the hydrogen atom abstraction, an electron is abstracted to form an iron(IV)–oxo species, which subsequently abstracts a hydrogen atom from the substrate. Thus, our calculations show for the first time how some nonheme iron complexes react by long-range electron transfer and others directly via hydrogen atom abstraction. We have rationalized our results with detailed thermochemical cycles that explain the observed reactivity patterns.

Introduction

Nonheme iron dioxygenases are important enzymes for human health with essential functions that include DNA base repair mechanisms and oxidative cleavage of carotenoids.\textsuperscript{1} In several organisms, natural product biosynthesis is catalysed by nonheme iron dioxygenases, and, therefore, they have important functions in biology as well as in biotechnology. In order to understand enzymatic reaction processes, synthetic model complexes have been developed and designed.\textsuperscript{2} These biomimetic model complexes of nonheme iron oxidants are well studied and many biomimetic high-valent catalytic intermediates have been characterized in recent years.\textsuperscript{3} For instance, to tackle the controversy in Rieske dioxygenases regarding the active oxidant in the reaction process, several biomimetic model complexes with iron(IV)–oxo(hydroxo) as reactive features have been studied and their reactivity patterns established.\textsuperscript{4}

All biomimetic Rieske dioxygenase models contain a hydroxo group in a cis-position of the iron(IV)–oxo group. Only few examples exist of biomimetic iron(IV)–oxo intermediates without this cis-hydroxo ligand and spectroscopic studies gave indirect evidence of its existence.\textsuperscript{5} Thus, McKenzie and co-workers reported the structural characterization of an iron(IV)–oxo species with a monoionic multidentate ligand and found it to react with thioanisole efficiently.\textsuperscript{6} Kim and co-workers used a tetradentate ligand system and formed the corresponding iron(IV)–oxo species by heterolytic cleavage of an iron–acylperoxo intermediate.\textsuperscript{7} They determined kinetic isotope effects (KIE, \(k_1/k_2\)), \(H_2^{18}O\) exchange reactions and measured product distributions. Using a tetraamido macrocyclic ligand, Collins and co-workers studied the sulfoxidation of substrates by an iron(IV)–oxo species and compared the rates with analogous iron(IV)–oxo species.\textsuperscript{8} Finally, Nam and co-workers studied the reaction of \([\text{Fe}(\text{BQEN})^2]^+,\) BQEN = \(N,N^\prime\)-dimethyl-\(N,N^\prime\)-bis(8-quinolyl) ethane-1,2-diamine, with \(\text{CH}_3\text{CO}_2\text{H}\) and found evidence of competing reaction mechanisms originating from...
two oxidants in the reaction mixture that were tentatively assigned as [FeIV(O)(BQEN)]2+ and [FeV(O)(BQEN)]3+. Their studies failed to unequivocally assign the active oxidant in the reaction mechanism, and therefore could not determine the relative reactivity of iron(IV)–oxo versus iron(V)–oxo. In order to resolve this dichotomy and gain general insight into the relative reactivity of iron(IV)–oxo versus iron(V)–oxo with nonheme ligand systems a computational study was conducted using the [FeIV(O)(BQEN)(NCCH3)]2+ (1) and [FeV(O)(BQEN)(NCCH3)]3+ (2) systems, Scheme 1.

Currently, very little is known regarding the catalytic activity of iron(v)–oxo intermediates and to the best of our knowledge, no direct comparison in reactivity between iron(IV)–oxo and iron(V)–oxo has been reported. We present here a DFT study to gain insight into the potential use of iron(v)–oxo with nonheme ligand systems a computational study was conducted using the [FeIV(O)(BQEN)(NCCH3)]2+ (1) and [FeV(O)(BQEN)(NCCH3)]3+ (2) systems, Scheme 1.

To test the effect of the overall charge on the calculations we also performed a set of test calculations on charge neutral complexes, whereby the reactants and rate determining transition states were modified by counter-ions at a fixed distance of 15 Å from the axial nitrogen atom and with an angle of 120 degrees with respect to iron and the axial nitrogen atom. Point charges, Cl− counter-ions and OH− counter-ions were applied, but all results reproduced the solvent optimized results and did not give changes to the charge and spin distributions.

Kinetic isotope effects (KIEs) were calculated for the hydrogen atom abstraction reaction of ethylbenzene by 1 for the replacement of one or more hydrogen atoms of the substrate by deuterium atoms. We initially used the semi-classical Eyring equation (eqn (1)) to calculate KIEE from the difference in free energies of activation (ΔG‡) of the substrate and its deuterium substituted form following previously reported methods.19 Eqn (1) uses the gas constant (R) and the actual temperature (273.15 K).

\[
KIE_E = k_H/k_D = \exp \left\{ \left( \Delta G_{D}^R - \Delta G_{H}^R \right)/RT \right\} \quad (1)
\]

Further corrections due to tunnelling were applied using the Wigner model20 that corrects KIEE with the tunnelling ratio (QH/QD) as described in eqn (2) and (3).

Methods

All studies reported here utilize density functional theory (DFT) methods as implemented in the Jaguar and Gaussian program packages.10 We initially did exploratory gas-phase optimizations on [Fe(O)(BQEN)(NCCH3)]1+/2+ in Jaguar at the UB3LYP level of theory11 and explored the catalytic mechanism of ethylbenzene hydroxylation. However, as most of our chemical systems are multiply charged ions we decided to do a subsequent set of calculations, where the complete project was done using a polarized continuum solvent model included during the geometry optimizations. These studies gave considerable differences from the gas-phase results and therefore we will focus on the solvent optimized calculations mainly. Details of the gas-phase calculations can be found in the ESL. Thus, all geometry optimizations and frequencies were performed with a solvent model included with a dielectric constant mimicking acetonitrile. All local minima are characterized with a frequency calculation and have real frequencies only, whereas the transition states have one imaginary frequency for the correct mode. As transition metal containing complexes give close-lying electronic and spin states,12 we calculated the [Fe(O)(BQEN)(NCCH3)]1+ complexes in the lowest lying doublet, quartet and sextet spin states and the [Fe(O)(BQEN)(NCCH3)]2+ complexes in the singlet, triplet and quintet spin states.

When testing the reproducibility and reliability of the density functional method by applying a range of unrestricted DFT methods, including B3LYP,11 B3LYP-D3,13 B3LYP*,14 and OPBE.15 There is a certain degree of fluctuation observed in the relative energies, spin state ordering and geometric details as commonly observed in nonheme iron complexes.16 However, the results confirmed the assignment of the electron configuration of all complexes and reproduce experimental trends.

All optimizations and frequencies use a triple-ζ quality basis set (BS2) with LACV3P+ on iron and 6-311+G* on the rest of the atoms.17 Previously, we used these methods extensively for the description of nonheme iron complexes and reproduced experimental free energies of activation within several kcal mol−1.18 To test the effect of the overall charge on the calculations we also performed a set of test calculations on charge neutral complexes, whereby the reactants and rate determining transition states were modified by counter-ions at a fixed distance of 15 Å from the axial nitrogen atom and with an angle of 120 degrees with respect to iron and the axial nitrogen atom. Point charges, Cl− counter-ions and OH− counter-ions were applied, but all results reproduced the solvent optimized results and did not give changes to the charge and spin distributions.
KIE\textsubscript{w} = KIE\textsubscript{E} \times Q\textsubscript{H}^2/Q\textsubscript{D}\textsuperscript{2} \quad (2) \\
Q_t = 1 + \frac{1}{24} \left( \frac{h\nu}{k_B T} \right)^2 \quad (3)

In eqn (3), \( k_B \) represents the Boltzmann’s constant, \( h \) is Planck’s constant and \( \nu \) is the imaginary frequency in the transition state.

**Results**

**Isolated reactants 1 and 2**

Our study uses density functional theory (DFT) methods and is focused on the chemical systems of ref. 9 as described in Scheme 1, where we included an acetonitrile solvent molecule in the sixth ligand position of the metal: [Fe(O)(BQEN)(NCCH\textsubscript{3})]\textsuperscript{2+} (1) and [Fe(O)(BQEN)(NCCH\textsubscript{3})]\textsuperscript{3+} (2). These structures have the metal in formal oxidation state iron(IV) and iron(V), respectively. Before we will look into the reactivity patterns of structures 1 and 2 with substrates, we will describe the electronic properties of the optimized geometries of 1 and 2, Fig. 1.

The lowest lying singlet, triplet and quintet spin states of 1 were calculated, but the singlet state was found to be high in energy. Similarly, 2 was investigated in the doublet and quartet spin states only. Fig. 1 displays the molecular valence orbitals of 1 and 2, which are determined by the mixing of the metal 3d orbitals with its ligands. Thus, there are three \( \pi^* \) molecular orbitals (\( \pi^*_{xy}, \pi^*_{yz}, \pi^*_{xz} \)) representing the anti-bonding interactions of the 3d iron orbitals with 2p orbitals on the oxo group. High in energy are two \( \sigma^* \) orbitals for the anti-bonding interactions of the metal with the ligands along the \( xz \)-plane (\( \sigma^*_{xz} \)) and with ligands along the \( z \)-axis (\( \sigma^*_{yz} \)), whereby the \( z \)-axis is defined as parallel to the Fe–O bond. In the iron(IV)-oxo complex, i.e. \( 3\textsuperscript{1}, \) the set of orbitals shown in Fig. 1 is occupied by four electrons, which gives two low-lying solutions with either triplet or quintet spin: 1 has a triplet spin ground state with electronic configuration \( \pi^*_{xy}^2 \pi^*_{xz} \pi^*_{yz} \) (\( 3\textsuperscript{1} \)) that is somewhat lower in energy than the quintet spin state with configuration \( \pi^*_{xy} \pi^*_{xz} \pi^*_{yz} \) (\( 5\textsuperscript{1} \)), vide infra. In both spin states 1 has the metal in formal oxidation state iron(IV). The spin state ordering matches previous studies on hexacoordinated non-heme iron biomimetic model complexes and also supports the experimentally reported absorption band at \( \lambda_{\text{max}} = 740 \text{ nm} \) characteristic for triplet iron(IV)-oxo species and assigned by Nam et al. on [Fe(O)(BQEN)(NCCH\textsubscript{3})]\textsuperscript{2+}.3,9,21

Upon oxidation of 3,5\textsuperscript{1}, however, several possibilities arise for the electronic configuration of 2. Firstly, 3\textsuperscript{1} can lose an electron from \( \pi^*_{yz} \) to give a doublet spin configuration with \( \pi^*_{xy}^2 \pi^*_{xz} \) orbital occupation or lose an electron from the...
doubly occupied $\pi_{sx}$ orbital to give a quartet spin complex with $\pi_{sx}^1 \pi_{sz}^1 \pi_{yz}^1 \pi_{xz}^1$ configuration. These two states have the metal in formal oxidation state iron(IV) and are labelled as $2,4^1$ in Fig. 1. In addition, the oxidation of $1$ can expel an electron from a ligand $\pi$-type orbital, such as $\pi_{BQEN}^*$ and lead to an electronic configuration $\pi_{sx}^2 \pi_{sz}^1 \pi_{yz}^1 \pi_{xz}^1$, whereby the radical on the ligand can be either ferromagnetically or anti-ferromagnetically coupled to the metal-based unpaired electrons in an overall quartet or doublet spin state ($4^1, 2^0$). The latter, therefore, can be seen as an iron(II)–oxo ligand cation radical species with configuration $[Fe^{III}(O)(BQEN^*)](NCCH_3)$ and is reminiscent of compound I of cytochrome P450 enzymes, which was characterized as an iron(IV)–oxo hemc cation radical species, i.e. $[Fe^{III}(O)(heme^*)]$.$^{22}$

Details of the optimized geometries of $3,5^1$ and $2,4^2$ in the gas phase are reported in Fig. 2. In the gas-phase the triplet spin state is the ground state by $\Delta E + ZPE (\Delta G) = 2.0 \ (0.2)$ kcal mol$^{-1}$. Optimized geometries are in line with previously reported structures on non-heme iron(II)–oxo complexes with a short Fe–O bond of 1.66 Å, which implicates a double bond.$^{21,23}$ Group spin densities and charges confirm the orbital assignment of $3,5^1$ as described in Fig. 2 with electronic configuration of $\pi_{sx}^1 \pi_{sz}^1 \pi_{yz}^1 \pi_{xz}^1$ for $1$ and $\pi_{sx}^2 \pi_{sz}^1 \pi_{yz}^1 \pi_{xz}^1 \sigma_{yz}^{-1} \sigma_{xz}^{-1}$ for $3,5^1$.

Nam and co-workers$^{25}$ using absorption and infrared spectroscopy and extended X-ray absorption fine structure (EXAFS) studied the $[Fe(O)(BQEN)(NCCH_3)]^{3+}$ complex experimentally. They identified an iron–oxo bond of 1.67 Å and an average Fe–N distance of 1.97 Å. Our calculated Fe–O distances for $3,5^1$ in Fig. 2 match the experimental values excellently. The experimentally reported Fe–N distances are in good agreement with the triplet spin structures, but not with the quintet spin state structures due to single occupation of the $\sigma_{xz,yz}$ orbital that elongates the distances between the metal and its ligands. Therefore, the computational studies support the characterization of a triplet spin ground state of $1$.

Geometry optimizations of $2,4^2$, however, gives a low-lying solution with two singly occupied $\pi$-orbitals coupled to a radical on the BQEN unit with spin densities of $\rho_{BQEN} = -1.06 \ (0.90)$ in the doublet and quartet spin states. The optimized geometries, therefore, correspond to an electronic state $[Fe^{IV}(O)(BQEN^*)](NCCH_3)^{3+}$, i.e. $2,4^2$ in Fig. 1, rather than the anticipated iron(II)–oxo species. Although we attempted to swap molecular orbitals to generate the iron(II) solution ($2,4^2$) these calculations converged back to $2,4^2$, which therefore is the molecular ground state.

As the complex has a large overall charge of $+3$, we decided to reoptimize these structures using the polarized continuum model mimicking an acetonitrile solution. However, the new model did not affect the spin state ordering and electronic configuration of the ground state and the same electronic state was found. It appears, therefore, that $2,4^2$ is the electronic ground state that can be described as $[Fe^{IV}(O)(BQEN^*)](NCCH_3)^{3+}$ with an iron(II)–oxo group coupled to a ligand radical. As both doublet and quartet spin states represent the same orbital occupation, namely $\pi_{sx}^2 \pi_{sz}^1 \pi_{yz}^1 \pi_{xz}^1 \pi_{BQEN}^*$, we calculate them within 2 kcal mol$^{-1}$. This result is similar to the spin state energies of ferromagnetically versus antiferromagnetically coupled doublet and quartet spin states of compound I of P450, where these spin states were also found to be within a couple of kcal mol$^{-1}$ from each other. Moreover, the energy gap was found to be sensitive to the local environment, including hydrogen bonding interactions to the oxidant as well as solvent effects.$^{24}$ Furthermore, these two spin states result in two-state-reactivity patterns with substrates on competing spin-state surfaces.$^{25}$ Analogously to P450 compound I, the iron(II)–oxo species is an excited state of the molecular ground state with configuration $[Fe^{IV}(O)(BQEN^*)](NCCH_3)^{3+}$. Geometrically $2,4^2$ has metal–ligand bond lengths close to those found for $1^1$, which is also an iron(II)–oxo species.

**Reactant complexes**

Subsequently, ethylbenzene (EB) was added to the model complexes to create a long-range reactant complex (RC) as this was one of the substrates used in the experimental study and we investigated the benzyl hydroxylation processes. The electronic features of $3,5^1RC_4$ or $3,5^1[Fe(O)(BQEN)(NCCH_3) \cdot EB]^{2+}$ and $2,4^2RC_4$ or $2,4^2[Fe(O)(BQEN)(NCCH_3) \cdot EB]^{2+}$ will be discussed prior to the investigation of the catalytic mechanism. Considering that computational modelling occasionally is sensitive to the choice of the density functional used as well as on environmental variables,$^{26}$ some thorough testing of the structures, spin-state energetics and electronic configurations of $3,5^1RC_4$ and $2,4^2RC_4$ using a selection of density functional methods and procedures was carried out. Thus, we performed geometry optimizations of all complexes in the gas-phase at UB3LYP/B31, but also did a full geometry optimization in a dielectric constant mimicking acetonitrile at UB3LYP/B32 and finally a full geometry optimization in a dielectric constant at the UB3LYP-D3/B32. In addition, single point calculations on the UB3LYP/B32 optimized geometries using B3LYP with 15% HF exchange (B3LYP*), UB3LYP-D3 and OPBE were
Table 1  Spin state energies and optimized geometries of reactant complexes as calculated using various DFT methods

<table>
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<th>Structure</th>
<th>$r_{\text{Fe-O}}$</th>
<th>$r_{\text{Fe-E}}$</th>
<th>$r_{\text{Fe-D}}$</th>
<th>$\Delta E + \text{ZPE}$</th>
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<td>1.633</td>
<td>1.657</td>
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<td>Gas$^{d,e}$</td>
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<td>UB3LYP</td>
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<td>Solv$^{d,e}$</td>
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<td>1.638</td>
<td>1.656</td>
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<td>3.8</td>
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$^*$ UB3LYP/BS1 geometry optimization in the gas-phase. $^2$ Values in Å. $^5$ UB3LYP/BS2 geometry optimization in solvent. $^d \Delta E + \text{ZPE}$ value with energies at the BS2 level of theory in kcal mol$^{-1}$. $^e$ UB3LYP-D3/BS2 geometry optimization in solvent. $^f$ Structure with added point charges that neutralize the system at 15 Å.

Table 1 presents the optimized Fe–O distance and spin-state energies as obtained using these different DFT models and methods. As can be seen all methods, models and optimization techniques give the same spin state ordering, but a certain degree of variation in the relative energies is observed typical for DFT calculated iron complexes. In all cases RC$_1$ and RC$_2$ are characterized as [Fe$(^3)$(O)(BQEN$^*$)(NCCH$_3$)]$^{2+}$ with orbital occupation $\pi_{xy}^2 \pi_{xz}^1 \pi_{yz}^1 \pi_{xz}^1 \pi_{yz}^1 \sigma_{xz}^2 \sigma_{xy}^2$, respectively, in agreement with what was found for structure 3,5,1 above. Regardless of the method and whether the optimization is done in the gas-phase or in solvent, a triplet spin ground state that is well separated from the quintet spin state by 2.4–10.3 kcal mol$^{-1}$ is found. Although this appears to be a large variation in spin state energies, actually for transition metal complexes, and, in particular iron(IV)-oxo complexes a strong variation of the ordering and relative energies is normal in DFT upon changing the density functional method or environmental effects. Nevertheless, all methods give a triplet spin ground state in support of experimental studies.

The situation is dramatically changed when RC$_2$, is investigated with these methods and models. Whereas RC$_2$ was found as the electronic ground state with configuration [Fe$(^4)$(O)(BQEN$^*$)(NCCH$_3$)]$^{2+}$ with two unpaired $\pi^*$ electrons coupled to a radical on the ligand, by contrast, in RC$_2$, we find yet another electronic configuration with two unpaired $\pi^*$ electrons that are coupled to an ethylbenzene radical, i.e. orbital occupation $\pi_{xy}^{2+} \pi_{xz}^1 \pi_{yz}^1 \pi_{BQEN}^2 \pi_{EH}^1$, where the latter orbital is a singly occupied $\pi$-orbital on ethylbenzene. Therefore, addition of an ethylbenzene molecule to RC$_2$, 2,4-dimethylbenzene, is a strong oxidant and can abstract electrons from substrates readily. Most probably this is caused by its extremely large electron affinity, vide infra.

Note that outer-sphere electron transfer upon approach of a substrate onto a metal–oxo species has been calculated before on metal–porphyrins, including a potential intermediate of nitric oxide synthase, where the arginine substrate was found to donate an electron to an iron(IV)–oxo heme cation radical species quickly. Furthermore, approach of a Zn$^{2+}$ ion onto a high-valent manganese(IV)-oxo corrolazine also led to the formation of a manganese(IV)–oxo corrolazine cation radical through valence tautomerization. Finally, studies on the comparative electronic features of the iron(IV)–oxo heme species of cytochrome c peroxidase (CcP) versus ascorbate peroxidase implicated differences in electronic configuration as a result of a bound cation at a distance of 15 Å from the heme. DFT modelling on compound 1 of CcP tested the effect of a point charge with magnitude $Q = -1/1$ on the electronic configuration. It was found that a charge of $Q = +1$ gave an electronic state [Fe$(^4)$(O)(heme$^*$)···Trp$_{191}$], whereas a value of $Q = -1$ resulted in an alternative state corresponding to [Fe$(^4)$(O)(heme)···Trp$_{191}$]. These studies have shown that seemingly small external (but long-range) perturbations can have a major impact on the electronic configuration of the oxidant and consequently on its ability to react with substrates. However, for nonheme metal–oxo species this would be the first example of outer-sphere electron transfer upon substrate approach and is likely caused by the large electron affinity of the ligand. In the following we will describe whether the change in electronic configuration is beneficial or disadvantageous to the catalysis.

Ethylbenzene hydroxylation by 1 and 2

Subsequently, the benzyl hydroxylation of ethylbenzene by RC$_1$ and RC$_2$ was calculated. Fig. 3 displays the calculated reaction mechanism with optimized geometries of the rate determining transition states of the reaction starting from RC$_1$. We calculate a stepwise mechanism with an initial hydrogen atom abstraction from the benzyl position of ethylbenzene via a transition state (TS$_{1A}$) to form a radical intermediate (I) followed by hydroxyl rebound via a transition state (TS$_{1B}$) to form alcohol products (P). In all cases the hydrogen atom abstraction is rate determining and the rebound barriers are small or negligible, so that we will focus on the TS$_{1A}$ pathway only here. Full details of the rest of the mechanism are given in the ESL. In the gas phase very little energy difference between hydrogen atom abstraction from the pro-S versus pro-R site of the benzyl position of ethylbenzene by iron(IV)-oxo complexes was found. Recent computational studies on S-mandalate synthase showed that the shape and size of the substrate binding pocket determines
whether the pro-R or pro-S hydrogen atom can be abstracted. Indeed, site-selective mutations confirmed the computationally proposed hypothesis.

Geometrically, the $^{3,5}\text{TS}_{HA}$ structures are quite distinct due to differences in electron transfer processes that happen in these transition states. In the triplet spin state the hydrogen atom transfer is accompanied with electron transfer from the substrate into the $\pi^*_{xz}$ orbital and hence the substrate attacks under an angle ($\alpha_{\text{FeOC}} = 134.2^\circ$) to get ideal orbital overlap between donor and acceptor orbitals. In the quintet spin state the hydrogen atom abstraction is accompanied with electron transfer from the substrate into the vacant $s^*_z$ orbital and hence the substrate attacks from the top with considerably larger FeOC angles ($\alpha_{\text{FeOC}} = 151.1^\circ$), which gives an iron(III)–hydroxo complex with a fully exchange coupled metal 3d system with five singly occupied orbitals that is anti-ferromagnetically coupled to a benzyl radical: $^5\text{I}$ has electronic configuration $\pi^*_{xy} \pi^*_{xz} \sigma^*_{xz} \sigma^*_{yz} \sigma^*_{x^2-y^2} \pi_{xy}^*$. This exchange stabilization makes $^5\text{I}$ considerably lower in energy than the corresponding triplet spin complex. As a consequence, $^5\text{TS}_{HA}$ is stabilized over $^3\text{TS}_{HA}$, although dispersion corrections make them almost degenerate. Nevertheless, the barrier heights on both spin state surfaces are small and implicate an efficient hydrogen atom abstraction process in agreement with experiment. When the enthalpy values from Fig. 3 are converted to a free energy of activation, a value of $\Delta G_{\text{sub}} = 10.8$ kcal mol$^{-1}$ on the triplet spin state surface is found, which is in reasonable agreement with the experimentally reported free energy of activation of Nam et al.

The experimental studies on ethylbenzene hydroxylation by $^{1}\text{RC}_1$ were found to proceed with a kinetic isotope effect (KIE) of 10 for the replacement of hydrogen atoms by deuterium in the substrate. To estimate the isotope effects for replacement of the transferrable hydrogen atom by deuterium in the reaction passing $^{3}\text{TS}_{HA}$ we used the Eyring and Wigner models (see Methods section) to estimate the KIE. Values of $K_{\text{IE}}$ and $K_{\text{IEW}}$ of 4.9 and 5.4 were obtained, whereas these values increased up to 5.1 and 5.7, respectively, when the fully deuterated substrate was used. Our calculated isotope effect, therefore, predicts the same trends as experiment.

We then calculated a reaction complex of $^2\text{RC}_2$ in the gas phase as well as with solvent models included during the geometry optimizations. As mentioned above, the optimized geometry and group spin densities of $^2\text{RC}_2$ characterize the reactant complex as $^3[\text{Fe}^{IV}(O)(\text{BQEN})(\text{NCCH}_3)]^{2+} \cdot \text{EB}^*$. The hydrogen atom abstraction from $\text{EB}^*$ by the iron(IV)–oxo complex then leads to electron transfer from the substrate into the $\pi^*_{xz}$ orbital of the oxidant and spin density changes that are...
very similar to those observed for $^{3}\text{TS}_{\text{HA}}$. Technically, the differences in the hydrogen atom abstraction barrier between $^{3}\text{RC}_1$ and $^{2}\text{RC}_2$ should be very small as both are an iron(IV)–oxo oxidant. However, the outer-sphere electron transfer from the substrate to the oxidant has oxidized the approaching substrate, and hence the differences in barrier heights observed in Fig. 3 and 4 relate to hydrogen atom abstraction of the C–H bonds of EB and EB$^+$/$\text{C}_{15}$, respectively. Previously, it was shown that the hydrogen atom abstraction barrier correlates with the strength of the C–H bond of the substrate that is broken in the process.$^{33}$ Indeed, experimentally determined rate constants of hydrogen atom abstraction reactions by nonheme iron oxidants were shown to correspond to the bond dissociation energy (BDE$_{\text{CH}}$) for the breaking of the C–H bond of the substrate.$^{34}$ We, therefore, decided to calculate the BDE$_{\text{CH}}$ values of EB and EB$^+$/$\text{C}_{15}$ into $\text{C}_6\text{H}_5\text{CHCH}_3$/$\text{C}_{15}$/$\text{C}_1$ and find values of $\Delta E + ZPE + E_{\text{solv}}$ values obtained after a full geometry optimization in solvent at the UB3LYP/BS2 (out of parenthesis) or at UB3LYP/BS2/UB3LYP/BS1 level of theory on a gas-phase optimized geometry.

![Fig. 4 DFT calculated potential energy profile for the hydrogen atom abstraction from EB by $^{2,4}\text{RC}$ with energies given in kcal mol$^{-1}$. Also shown are optimized UB3LYP/BS2(solvent) geometries of $^{4}\text{TS}_{\text{HA}}$ with bond lengths in angstroms, angles in degrees and the imaginary frequency in wave numbers. Relative energies represent $\Delta E + ZPE + E_{\text{solv}}$ values obtained after a full geometry optimization in solvent at the UB3LYP/BS2 (out of parenthesis) or at UB3LYP/BS2/UB3LYP/BS1 level of theory on a gas-phase optimized geometry.](image)

Discussion

Our DFT calculations on $^{3,5}\text{RC}_1$ and $^{2,4}\text{RC}_2$ reported above show that both systems are in the iron(IV) oxidation state and the oxidation
of $2'$ does not oxidize the metal to iron(VI) but rather keeps it at the lower oxidation state of iron(IV) due to electron release from the BQEN macrocycle rather than the metal. Therefore, although $2'$ is perceived as an iron(V)-oxo species, it actually is an iron(IV)-oxo with BQEN cation radical. Moreover, the DFT calculations reported in this work show that approach of a substrate, e.g. ethylbenzene, onto $2'\cdot C_l$, leads to a long-range electron transfer upon formation of the reactant complex $4,2\cdot R_C\cdot C_l\cdot C_l\cdot C_l\cdot C_l$[FeIV(O)(BQEN)(NCCH3)]2+ /C1/C1/C1/C1/C1, Scheme 2. The subsequent hydrogen atom abstraction then gives an iron(III)-hydroxo complex and a C6H5CH+CH3 cation.

In previous studies, we showed that the driving force of a hydrogen atom abstraction correlates linearly with the free energy of activation. Therefore, to understand the thermodynamics and kinetics of the reaction mechanisms reported in Fig. 2 and 3 above, we did a detailed analysis of the individual thermodynamic reaction steps for electron and hydrogen atom transfer processes, which are summarized in Fig. 5. Panel (a) in Fig. 5 starts on the top left with $2'\cdot C_l$ and the reaction to the right reflects a one-electron abstraction to form $3\cdot C_l$ and the subsequent one-electron abstraction to form $4,2\cdot C_l\cdot C_l\cdot C_l\cdot C_l$[FeIII(O)(BQEN)(NCCH3)]+ . The vertical arrows reflect the hydrogen atom abstraction processes from both $2'\cdot C_l$ and $3\cdot C_l$. Thermodynamically, the energy for these reactions is associated with the bond dissociation energy of the O–H bond in the metal–hydroxo complex to revert back into the iron–oxo and an isolated H-atom, as defined as BDEOH. The calculated BDEOH values for $2'\cdot C_l$ and $3\cdot C_l$ are virtually the same in the gas phase, which is not surprising as both complexes are iron(n)-oxo intermediates. Therefore, geometrically very little differences in the hydrogen atom abstraction reactions will be obtained. The energy gap between the two BDEOH values widens to 10.2 kcal mol⁻¹ in favour of $2'\cdot C_l$ when solvent, thermal and entropic corrections to the energy are included.

In the case of BDEOH, solvent corrections stabilize the value of $2'\cdot C_l$ over $1\cdot C_l$ by 7.3 kcal mol⁻¹, whereas thermal and entropic
corrections add a further 4.9 kcal mol\(^{-1}\). These BDE\(_{\text{OH}}\) values, therefore, would predict higher reactivity of \(^{2}2'\) over \(^{3}1\) in solvent for hydrogen atom abstraction reactions.

The major differences between \(^{1}\) and \(^{2'}\), however, are related to their electron affinities or reduction potentials. Thus, \(^{2'}\) has a large electron affinity (EA\(_{2}\)) of 316.9 kcal mol\(^{-1}\) in the gas-phase and \(\Delta G_{\text{solv}} = 190.5\) kcal mol\(^{-1}\). It is worth noting that for all calculations we find almost equal values for \(\Delta E + ZPE + E_{\text{solv}}\) and \(\Delta G_{\text{solv}}\), therefore, entropic and thermal corrections to the solvent corrected enthalpies have a negligible effect on the individual reactions studied. The electron affinity of \(^{2'}\) is considerably larger than that found for \(^{3}1\), where values of EA\(_{1}\) = 201.5 kcal mol\(^{-1}\) in the gas-phase and \(\Delta G_{\text{solv}} = 126.0\) kcal mol\(^{-1}\) are found. Consequently, \(^{2'}\) has a \(\Delta G_{\text{solv}} = 63.5\) kcal mol\(^{-1}\) larger electron affinity than \(^{3}1\) and will be more susceptible to react by electron abstraction from substrates.

For completeness we also include in Fig. 6 the thermodynamics for the ethylbenzene substrate for removal of an electron and the C–H bond strengths of the benzyl group of ethylbenzene and the ethylbenzene cation radical. As already mentioned above the ethylbenzene cation radical has a considerably weakened C–H bond strength of \(\Delta G_{\text{solv}} = 35.9\) kcal mol\(^{-1}\) as compared to EB. Consequently, hydrogen atom abstraction from EB\(^{+}\) will have a low barrier.

To find out whether a reaction of \(^{2'}2'\) and \(^{3}1\) with EB would lead to a large thermodynamic driving force for electron transfer, the free energy in solvent for the reactions given in eqn (4) and (5) was calculated. Thus, the electron transfer from EB to \(^{2'}2'\) is calculated to be exergonic by 33.5 kcal mol\(^{-1}\), whereas the one originating from \(^{3}1\) is endergonic by 31.0 kcal mol\(^{-1}\) instead. These two reactions implicate that in a collision between \(^{2'}2'\) and EB the driving force will trigger an electron abstraction from EB, whereas that will not be the case in a collision between \(^{3}1\) and EB. The large EA\(_{2}\) value will, therefore, lead to a large driving force for electron transfer from suitable substrates including ethylbenzene to \(^{2'}\). Moreover, the thermodynamic reaction pathways given in Fig. 5 give further evidence of a likely electron transfer between EB and \(^{2'}\).

\(^{2'}2' + EB \rightarrow ^{3}1 + EB^{+} \quad [\Delta G_{\text{solv}} = -33.5\) kcal mol\(^{-1}\)] \quad (4)

\(^{3}1 + EB \rightarrow [\text{Fe}^{\text{III}}(\text{O})(\text{BQEN})(\text{NCCH}_3)]^{+} + EB^{+} \quad [\Delta G_{\text{solv}} = +31.0\) kcal mol\(^{-1}\)] \quad (5)

Despite the fact that the BDE\(_{\text{OH}}\) values of \(^{1}\) and \(^{2'}\) are virtually the same, actually at the free energy level with solvent included they are separated by about 10 kcal mol\(^{-1}\). However, much more dramatic differences in the electron affinity of both complexes are found. Thus, the bond dissociation energy to break the A–H bond (BDE\(_{\text{AH}}\)) – or hydrogen atom abstraction ability of compound A – can be split into an individual electron and proton transfer via eqn (6), whereby \(\Delta G_{\text{acid}}\) represents the acidity of the weak acid AH, EA\(_{A}\) is the electron affinity of A, and IE\(_{H}\) the ionization energy of a H-atom. The experimentally reported value of IE\(_{H}\) is 13.598 eV.\(^{35}\)

\[
\begin{align*}
A-H & \rightarrow A + H + \text{BDE}_{\text{AH}} \quad (6a) \\
\text{BDE}_{\text{AH}} & = \Delta G_{\text{acid},\text{AH}} - \text{EA}_{A} - \text{IE}_{H} \quad (6b)
\end{align*}
\]

Using the data from Fig. 5 and the known IE\(_{H}\) value we calculate a \(\Delta G_{\text{acid}}\) of 590.5 kcal mol\(^{-1}\) for [Fe\(^{IV}\)(OH)(BQEN)(NCCH\(_3\))]\(^{3+}\), whereas proton transfer to \(^{1}\) gives the complex [Fe\(^{III}\)(OH)-(BQEN)(NCCH\(_3\))]\(^{2+}\) with \(\Delta G_{\text{acid}} = 515.9\) kcal mol\(^{-1}\). The large difference between EA\(_{A}\) and IE\(_{H}\), therefore, has a direct impact on the acidity of the iron(III)-hydroxo group and makes it considerably more acidic. The origin of the difference in electron affinity of \(^{1}\) and \(^{2'}\) is due to difference in electron transfer processes. Upon reduction of \(^{2'}\) an electron is transferred into the low-lying \(\pi^{*}\)\(_{\text{BQEN}}\) orbital to form a triplet spin \(\pi^{*}\)\(_{xy}\) \(\pi^{*}\)\(_{xz}\) \(\pi^{*}\)\(_{yz}\) \(\pi^{*}\)\(_{\text{BQEN}}^{2}\) configuration.

![Fig. 6 Thermodynamic reaction pathways for electron and hydrogen atom abstraction by [Fe(O)(BQEN)(OH)]\(^{2+}\) and [Fe(O)(BQEN)(OH)]\(^{-}\). All data obtained from a geometry optimization at UB3LYP/BS2. Data (in kcal mol\(^{-1}\)) reported are \(\Delta E + ZPE\) in the gas-phase (\(\Delta E + ZPE\) in solvent) \([\Delta G\) in solvent].](image-url)
On the other hand, reduction of \( ^1 \) leads to filling of the virtual \( \sigma^*_{\text{z}} \) orbital with a single electron. As the \( \sigma^*_{\text{z}} \) orbital is significantly higher in energy than the \( \pi^*_{\text{BQEN}} \) orbital this means the reduction of \( ^1 \) will incur a much smaller electron affinity than adding an electron to \( \pi^*_{\text{BQEN}} \) which is indeed what is found in Fig. 5.

To find out whether the cis-ligand of the metal-oxo group affects the EA and \( \Delta G_{\text{acid}} \) values, we did a further set of calculations on the electron and hydrogen atom transfer reactions for complexes \([\text{Fe}^{IV}(O)(\text{BQEN})^*(\text{OH})]^2+\) and \([\text{Fe}^{IV}(O)(\text{BQEN})(\text{OH})]^2+\), i.e. complexes 2' and 1 that have the acetonitrile ligand replaced by \( \text{OH}^- \). We should note here that replacement of the acetonitrile equatorial ligand by hydroxide does not change the spin state ordering and electronic configuration and these complexes are characterized like 2' and 1 above. Fig. 6 displays the thermodynamic reaction pathways for \([\text{Fe}^{IV}(O)(\text{BQEN}^*)(\text{OH})]^2+\) and \([\text{Fe}^{IV}(O)(\text{BQEN})(\text{OH})]^2+\). Firstly, a very little effect of replacing the acetonitrile with hydroxide is found on the BDEOH values of the complexes. For \([\text{Fe}^{IV}(O)(\text{BQEN})(\text{OH})]^2+\) we find a BDEOH value of 84.0 kcal mol\(^{-1}\), whereas its one-electron reduced counterpart has a \( \Delta G_{\text{solv}} = 75.2 \) kcal mol\(^{-1}\). These values are within 2.5 kcal mol\(^{-1}\) from those obtained with an acetonitrile molecule in the cis-position. The situation, however, changes dramatically for the electron affinities and acidity values of the complexes when the acetonitrile ligand is replaced by hydroxide. Thus, \([\text{Fe}^{IV}(O)(\text{BQEN}^*)(\text{OH})]^2+\) has an electron affinity of \( \Delta G_{\text{solv}} = 150.6 \) kcal mol\(^{-1}\), whereas the much lower value of 82.8 kcal mol\(^{-1}\) is found for \([\text{Fe}^{IV}(O)(\text{BQEN})(\text{OH})]^2+\). These lowered electron affinities with respect to complexes 2' and 1 also mean reduced acidity of the protonated complexes, for which we find values of 548.2 and 471.6 kcal mol\(^{-1}\), respectively.

In addition, a reaction of \([\text{Fe}^{IV}(O)(\text{BQEN}^*)(\text{OH})]^2+\) with ethylbenzene is calculated to give an endergonic electron transfer of 6.4 kcal mol\(^{-1}\) using the data given in Fig. 5 and 6. Therefore, replacing the acetonitrile equatorial ligand in complex 2' with an anion such as a hydroxide will affect the stability and reactivity of the complex and will prevent a long-range electron transfer with substrates like ethylbenzene. The electron transfer from ethylbenzene to \([\text{Fe}^{IV}(O)(\text{BQEN})(\text{OH})]^2+\) is calculated to be even more endergonic (\( \Delta G_{\text{solv}} = 74.2 \) kcal mol\(^{-1}\)) and consequently is not likely to happen.

In summary, we establish reasons for the large thermodynamic driving force for electron transfer from ethylbenzene to 2' as originating from a high electron affinity of the oxidant of \( \Delta G_{\text{solv}} = 190.5 \) kcal mol\(^{-1}\). This implies that the electron transfer to the approaching substrate could be spontaneous for substrates with an ionization potential below 190.5 kcal mol\(^{-1}\) or 8.26 eV. Although, we calculate an ionization energy of 8.54 eV in the gas phase actually in solution the value drops to \( \Delta G_{\text{solv}} = 6.81 \) eV. Therefore, in solution the ionization potential of ethylbenzene is sufficiently low to incur a long-range electron transfer to the oxidant and create \( [\text{Fe}^{IV}(O)(\text{BQEN})(\text{NCCH}_3)]^2+\cdot2\text{EB}^* \).

Finally, the thermodynamics values of Fig. 6 and 7 also enable us to predict the hydrogen atom transfer driving force in complexes RC\(_2\) and RC\(_1\). As described above, RC\(_2\) undergoes a long-range electron transfer and converts to \([\text{Fe}^{IV}(O)(\text{BQEN})(\text{NCCH}_3)]^2+\) and EB\(^*\). This complex reacts via hydrogen atom transfer via eqn (7) with a free energy change of \(-40.4 \) kcal mol\(^{-1}\). The DFT calculations for this process, see ESI\(^\dagger\) implicated a free energy change of \( \Delta G_{\text{solv}} = -42.4 \) kcal mol\(^{-1}\) for the formation of the radical intermediate \(^2\) and therefore its calculated value is in good agreement with the value estimated from our thermodynamic cycles.

\[
[\text{Fe}^{IV}(O)(\text{BQEN})(\text{NCCH}_3)]^2+ + \text{EB}^* \rightarrow [\text{Fe}^{III}(OH)(\text{BQEN})(\text{NCCH}_3)]^{2+} + \text{C}_6\text{H}_5\text{CH}^+\text{CH}_3 \quad [\Delta G_{\text{solv}} = -40.4 \text{ kcal mol}^{-1}] \quad (7)
\]

By contrast, if we do the same for complex RC\(_1\) and take the difference in free energy between the BDE\(_{\text{CH}} \) and BDE\(_{\text{OH}} \) values of oxidant and substrate, we find an almost thermoneutral hydrogen atom abstraction reaction, eqn (8). Indeed, the DFT calculations above predict a radical intermediate with an exergonicity of 6.9 kcal mol\(^{-1}\) with respect to the reactant complex in good agreement with the thermodynamically estimated value.

\[
[\text{Fe}^{IV}(O)(\text{BQEN})(\text{NCCH}_3)]^{2+} + \text{EB} \rightarrow [\text{Fe}^{III}(OH)(\text{BQEN})(\text{NCCH}_3)]^{2+} + \text{C}_6\text{H}_5\text{CH}^+\text{CH}_3 \quad [\Delta G_{\text{solv}} = -1.2 \text{ kcal mol}^{-1}] \quad (8)
\]

To test whether the electron transfer observed here in our reactant complexes is a general feature that could be found in alternative iron(v)-oxo complexes as well, we also decided to investigate the well-studied \([\text{Fe}^{IV}(\text{TPA})(\text{OH})]^2+\), TPA = tris-(2-pyridylmethyl)amine, system of Costas and co-workers.\(^\text{10b}\) Previously, \([\text{Fe}^{IV}(\text{TPA})(X)]^2+\) with X = halide or \( \text{OH}^- \) has been used in studies of the cis-effect on substrate activation by metal-oxo species, but also as a model for non-heme iron halogenases. Technically \([\text{Fe}^{IV}(\text{TPA})(\text{OH})]^2+\) is an iron(v)-oxo complex as indeed confirmed by DFT calculations.\(^\text{38}\) The question, of course, arises whether the oxidation state of the complex stays in the iron(v) state upon approach of an ethylbenzene molecule. Thus, we optimized the reactant complex \([\text{Fe}^{IV}(\text{TPA})(\text{OH})\cdot\text{EB}]^2+\) in the doublet and quartet spin states at UB3LYP-D3/B2S level of theory and show the structures and group spin densities of the complexes alongside those of \(^2\)RC\(_2\) in Fig. 7.

The results in Fig. 7 show that upon approach of an ethylbenzene molecule to an iron(v)-oxo center, a long-range electron transfer takes place from substrate to oxidant. Therefore, the group spin densities of \(^2\)RC\(_2\) and \([\text{Fe}^{IV}(\text{TPA})(\text{OH})\cdot\text{EB}]^2+\) both refer to an iron(v)-oxo complex with a nearby EB\(^*\) ion. Both complexes have a doublet spin state with \( \pi^*_z \) configuration,
i.e. a triplet spin iron(ν)-oxo complex with a nearby doublet cation radical ethylbenzene. By contrast the quartet spin state configurations of these complexes have orbital occupation π*yz
π′x2
π′y2
σz1
σ′x1
configuration with the ethylbenzene radical anti-ferromagnetically coupled to three unpaired electrons on the iron(ν)-oxo complex. Note that without ethylbenzene the [FeO(TPA)(OH)]2+ complex converges to an iron(ν)-oxo species and no ligand radical is found. The TPA ligand, therefore, has much lower lying molecular orbitals than a BQEN ligand and as a result the πBQEN orbitals become competitive with the π′x2/π′y2 orbitals on the FeO group. As a result of this [FeO(BQEN)(NCCH3)]3+ has an electronic configuration representing an iron(ν)-oxo coupled to a ligand radical, whereas [FeO(TPA)(OH)]2+ is an iron(ν)-oxo species.

Conclusions

In summary, we present here the first comparative study on the reactivity patterns of nonheme iron(ν)-oxo versus iron(ν)-oxo intermediates. Upon approach of the substrate to the iron(ν)-oxo ligand cation radical it abstracts an electron from the substrate readily, and thereby creates an iron(ν)-oxo ligand cation radical species. The perceived reactivity of the iron(ν)-oxo species, therefore, is due to the activity of the iron(ν)-oxo ligand cation radical instead. We also show that oxidation of ethylbenzene weakens the C–H bond strength of the substrate and thereby lowers the hydrogen atom abstraction barriers and leads to higher reactivity. This is an example of how outer-sphere (long-range) electron transfer may be a common feature in transition metal catalysis, but further research will be needed to find more examples of this type of reactivity patterns.

Acknowledgements

SdV thanks the Royal Society for an International Exchanges with Korea grant. The National Service of Computational Chemistry Software (NSCCS) is acknowledged for cpu time. DK acknowledges Department of Science and Technology (New Delhi) for a Ramanujan Fellowship. The research at EWI was supported by NRF of Korea through CRI (NRF-2012R1A3A2048842) and GRL (NRF-2010-00353).

Notes and references


10 (a) Jaguar, version 7.9, Schrodinger, LLC, New York, NY, 2011; (b) Gaussian-09, Revision C.01, Gaussian Inc., Wallingford CT, 2010.


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