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Influence of ligand architecture in tuning reaction bifurcation pathways for chlorite oxidation by nonheme iron complexes.

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ABSTRACT: Reaction bifurcation processes are often encountered in the oxidation of substrates by enzymes and generally lead to a mixture of products. One particular bifurcation process that is common in biology relates to electron transfer versus oxygen atom transfer processes by high valent iron(IV)-oxo complexes, which Nature uses for the oxidation of metabolites and drugs. In biomimicry and bioremediation an important reaction relates to the detoxification of ClO_x^- in water, which can lead to a mixture of products through bifurcated reactions. Herein, we report the first three water soluble nonheme iron(II) complexes that can generate chlorine dioxide from chlorite at ambient temperature and physiological pH. These complexes are highly active oxygenation oxidants and convert ClO_2^- into either ClO_2 or ClO_3^- via high-valent iron(IV)-oxo intermediates. We characterize the short-lived iron(IV)-oxo species and establish rate constants for the bifurcation mechanism leading to ClO_2 and ClO_3^- products. We show that the ligand architecture of the metal center plays a dominant role by lowering the reduction potential of the metal center. Our experiments are supported by computational modelling and a predictive valence bond model highlights the various factors relating to substrate and oxidant that determine the bifurcation pathways and explains the origins of the product distributions. Our combined kinetic, spectroscopic and computational studies reveal the key components necessary for the future development of efficient chlorite oxidation catalysts.

Introduction.

Iron is ubiquitous in life and has a relatively high abundance. Nature has developed many iron complexes for a multitude of functions ranging from electron transfer and oxygen transport to oxidation catalysis. Therefore, iron enzymes are involved in vital biosynthesis and biodegradation processes in the body.¹ There are two classes, the heme and nonheme iron enzymes. The former have an array of biochemical functions ranging from enzymatic catalysis (monooxygenases, e.g., the cytochromes P450),² and detoxification by peroxidases and catalases,³ to oxygen transport (hemoglobin)⁴ and electron-transfer (e.g., cytochrome c).⁵ Nonheme iron proteins act as dioxygenases in the metabolism of cysteine,⁶ DNA base repair⁷ and biosynthesis pathways,⁸ e.g., hydroxyproline. Finally, metal clusters, such as iron-sulfur clusters, are involved in electron transfer, whereby they relay electrons between a redox partner to a catalytically active site of an enzyme.⁹ Often iron containing biomolecules can react via several possible reaction channels leading to bifurcation pathways of which the product distributions are dependent on the structure and chemical properties of the metal center.

A common approach in mechanistic bioinorganic chemistry is to synthesize a biomimetic model that shares key structural and electronic features and study short-lived intermediates relevant to the enzymatic catalytic cycle,¹⁰ to probe the effects of the protein, the local environment and the nature of the transition metal center.¹¹ A common problem associated with biomimetic oxidants is that they may react via multiple reaction channels leading to bifurcation pathways. In biotechnology, bifurcation often is to be avoided and hence, understanding the chemical origin and nature of bifurcation pathways is essential.

Several examples on modifying bifurcation mechanisms and their corresponding product distributions and regioselectivities have been described. For instance, Fukuzumi and co-workers¹² investigated the electron transfer versus oxygen atom transfer mechanisms of a nonheme iron(IV)-oxo complex and found the former to be enhanced by the addition of perchloric acid. Nam et al¹³ showed that by replacing the axial ligand in an iron(IV)-oxo porphyrin cation radical model, a regioselectivity change from aromatic to aliphatic hydroxylation of ethylbenzene occurred. Clearly, subtle changes to the active oxidant or its environment affect the regioselectivity and bifurcation of the reaction processes and consequently the product distributions.

In recent work, we investigated a biomimetic nonheme iron model, $[\text{Fe}^{\text{II}}(\text{N4Py})]^{2+}$ with $\text{N4Py} = \text{N,N-bis(2-pyridylmethyl)-bis(2-pyridyl)methylamine}$ (Figure 1), and reacted it with terminal oxidants to form the corresponding iron(IV)-oxo and iron(IV)-tosylimido complexes.¹⁴ It was shown that the system reacted by competitive electron transfer or atom transfer with substrates. To gain further insight into bifurcation pathways between elec-

tron and atom transfer processes, we decided to look into an environmentally relevant reaction, namely the detoxification of ClO_2^- in drinking water. Chlorine oxides (ClO_x^-) are used extensively for cleaning and health care purposes with functions ranging from bleaching to disinfection. The high solubility of chlorine oxides in water and their long lifetime in the environment, however, has resulted in major ecological problems, specifically with drinking water. From an environmental perspective the bioremediation of ClO_x^- from water supplies is performed efficiently by perchlorate respiring bacteria. These achieve this reactivity using two enzymes, perchlorate reductase, which catalyzes the conversion of perchlorate to chlorate and subsequently to chlorite, and chlorite dismutase that converts chlorite to chloride (Cl^-) and molecular oxygen (O_2).^{15,16} Chlorite dismutase, however, is an iron-heme enzyme and little is known of nonheme iron centers for the activation of chlorine oxides. Therefore, we decided to investigate nonheme iron complexes and their reactivity with ClO_2^- . To further understand the nature of bifurcation pathways, we used two types of iron(II) precatalysts with N4Py as well as a pentadentate bispidine as ligands (dimethyl 2,4-di(2-pyridyl)3-(pyridin-2-ylmethyl)-7-methyl-3,7-diazabicyclo [3.3.1]nonan-9-one-1,5-dicarboxylate, L^1).¹⁷ We chose the $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ complex because it is known to react efficiently with thioanisoles to form sulfoxides with rate constants considerably faster than those obtained for $[\text{Fe}^{\text{II}}(\text{N4Py})]^{2+}$.¹⁸ Our combined experimental (kinetics and spectroscopy) and computational study using these iron(IV)-oxo complexes shows dramatic differences in electron transfer versus oxygen atom transfer reactivities. These differences are analyzed in detail and approaches are proposed as to how to modify these oxidants further to target specific products. The studies are rationalized with thermochemical and valence bond models.

Figure 1. Oxidants and chemical reactions investigated in this work.

Methods.

Materials. All chemicals were obtained from Aldrich Chemical Co., and were purchased of the best available purity and used without further purification unless stated otherwise. Reactions were carried out and monitored in deionized water purified in a Millipore Milli-Q water purification system. Acetate buffer was prepared freshly by mixing sodium acetate and acetic acid to obtain a solution at pH 5. Sodium chlorite was purchased from Sigma and recrystallized twice from an ethanol/water mixture. The ligands (N4Py, L^1 and L^2 = dimethyl 2,4-di-(2-pyridyl)-3-methyl-7-(pyridin-2-ylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate) were prepared by literature procedures.^{19,20} The corresponding $[\text{Fe}^{\text{II}}(\text{N4Py})(\text{NCCH}_3)](\text{OTf})_2$, $[\text{Fe}^{\text{II}}(\text{L}^1)](\text{BF}_4)_2$ and $[\text{Fe}^{\text{II}}(\text{L}^2)](\text{BF}_4)_2$ were prepared and characterized by purified procedures.^{14a,19,20b}

Instrumentation. UV/vis absorption spectra were recorded on a Hewlett Packard 8453 spectrophotometer equipped with either constant temperature circulating water bath or a liquid nitrogen cryostat (Unisoku) with a temperature controller. Absorption changes were measured as a function of time and enabled us to derive first-order rate constants for the reactions involved. High Resolution electrospray ionization (ESI) mass spectrometry (MS) spectra were recorded on a Waters (Micromass MS Technologies) quadrupole time-of-flight (Q-TOF) Premier mass spectrometer by infusing samples directly into the ion source at a speed of $15 \mu\text{L min}^{-1}$ using a syringe pump.

The spray voltage was set to 2 kV and the capillary temperature at 80°C .

Reactivity studies. Following calibrations described previously,²¹ reactions were run in a 10 mm path length quartz cuvette by monitoring the changes in the spectra of the reaction mixtures over time. Rate constants were determined by fitting the time-dependent change in absorbance of the intermediates under study. First-order rate constants were determined in triplicate with a standard deviation of $<10\%$.

Chlorine dioxide analysis. ClO_2 content was analyzed by extraction of the aqueous solution with diethyl ether and subsequent characterization by negative ion mode ESI-MS (inset of Figure 2a), and by kinetic data (Figure 2b).²² This method was validated by (i) bubbling ClO_2 through an aqueous solution and characterizing the ClO_2 as described above and (ii) extracting a solution of chlorite (NaClO_2 , 8mM) as described above, with the result that no ESI-MS signal at $m/z = 67.14$ was observed since ClO_2^- is insoluble in diethyl ether.

o-Tolidine product analysis. Chlorate content was determined using 3,3'-dimethyl-4,4'-diaminobiphenyl (o-tolidine) as described previously.²³ A typical reaction was carried out with $10 \mu\text{M}$ Fe^{II} oxidant with 4.0 mM NaClO_2 and 1 mM o-tolidine in acetate buffer at ambient temperature. The o-tolidine product was extracted from the aqueous medium into ethylacetate and analyzed by ESI-MS.

Computation. All calculations utilize density functional theory as implemented in Gaussian-09.²⁴ Following extensive benchmark and calibration procedures from the past,²⁵ we used the unrestricted B3LYP method throughout.²⁶ Each structure was subjected to a full geometry optimization and characterized as a local minimum using an analytical frequency calculation at the UB3LYP/BS1 level of theory: BS1 stands for LACVP(Fe) and 6-31G(rest of the atoms).²⁷ This combination of method and basis set was shown previously to reproduce experimentally determined free energies of activation and product distributions well.²⁸ In order to improve the energetics single point calculations were done with a triple- ζ type basis set BS2 (LACV3P+ with core potential on Fe and 6-311+G* on the rest of the atoms). Initially, these single points were done in the gas-phase but later also in a polarized continuum model with a dielectric constant mimicking water. Free energies reported in this work use electronic energies calculated at UB3LYP/BS2//UB3LYP/BS1 and include zero-point, thermal (at 298K), solvent and entropic corrections.

All metal complexes were calculated in the lowest lying spin multiplicities, i.e. doublet/quartet/sextet or singlet/triplet/quintet, but for the calculation of the reaction

energies only the lowest lying spin state of each structure was used. Test calculations with alternative density functional methods (BP86,²⁹ OPBE,³⁰ Mo6,³¹ B3PW91)^{26a,32} predicted the same trends and only gave minor changes to the relative energies. Furthermore, test calculations that included the effect of dispersion³³ were found to give minimal changes to the energetics. Finally, the reproducibility and reliability of the computational methods was tested by calculating the gas-phase electron affinities of ClO, ClO₂ and ClO₃ and compared to those from the NIST database.³⁴ As follows from Table S17 in the Supporting Information the electron affinities of ClO and ClO₃ are reproduced to within 1.2 kcal mol⁻¹. Whenever possible, the experimental values of the electron affinities were used.

In a final set of calculations, we investigated the potential energy landscape for the reaction of the iron(IV)-oxo complex with ClO₂⁻ to form each of the individual products. Firstly, the free energy of activation for electron transfer ($\Delta G_{ET}^\ddagger$) was calculated from the Marcus equations using previously described methods³⁵ from the driving force for the electron transfer reaction (ΔG_{ET} , Eq 1) and the solvent reorganization energy λ_0 . In eqs 1 and 2, N_A represents Avogadro's number, e is the elementary charge and ϵ_0 is the permittivity of vacuum. The static and optical dielectric constants (ϵ_s and ϵ_{op}) were taken from the Gaussian calculation and had values of 78.36 (water) and 1.78, respectively. The hard sphere radii (in Å) of the donor and acceptor molecules of the electron are labelled with r_1 and r_2 .

$$\Delta G_{ET}^\ddagger = \frac{\lambda_0}{4} \left(1 + \frac{\Delta G_{ET}}{\lambda_0} \right)^2 \quad (1)$$

$$\lambda_0 = \frac{N_A e^2}{4\pi\epsilon_0} \left(\frac{1}{\epsilon_{op}} - \frac{1}{\epsilon_s} \right) \left(\frac{1}{2r_1} + \frac{1}{2r_2} - \frac{1}{r_1 + r_2} \right) \quad (2)$$

Finally, the attack of ClO₂⁻ on the iron(IV)-oxo species was investigated through extensive geometry scans initially, whereby either the Cl-O or FeO-O distances were varied in a stepwise manner. In these calculations each geometry step represented a full geometry optimization with fixed Cl-O or FeO-O distance. The maxima of these scans were then subjected to a full transition state search and led to the transition states reported here. Free energies reported here use energies obtained at UB3LYP/BS2//UB3LYP/BS1 with zero-point, thermal, entropic and solvent corrections included at 298K.

To test the effect of solvation on the optimized reactant and transition state structures we ran a full geometry optimization with solvent model included; however, only minor differences in geometry were obtained (Supporting Information).

Results and Discussion.

The disproportionation of ClO_2^- , under the influence of iron(II) complexes, in water was studied with the focus on the product distributions as a function of the ligand structure and electronic characteristics. ClO_2^- can react via any of several reaction pathways, and as such a variety of products can be expected, including ClO_2 and ClO_3^- . We established the reactivities of the iron(II) complexes with ClO_2^- , and subsequently characterize short-lived intermediates formed during the reactions, determine reaction products and identify rate-limiting steps. Computational modeling of the reaction mechanisms and reactivity patterns was performed to rationalize the product distributions and understand the chemical differences between the oxidations.

Figure 2. Spectroscopic and kinetics studies for the reaction of iron(II) complexes with ClO_2^- . (a) Changes in the UV/Vis absorption spectra at a scan interval of 180 s upon the addition of 8.0 mM NaClO_2 to 50 μM $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ in an acetate buffer. Inset shows ESI-MS of products obtained. (b) Second order rate constants obtained for the reaction of ClO_2^- with $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ (black line), $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ (blue line) and $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$ (red line).

Reactivity of iron(II) complexes. The reactivity of sodium chlorite with nonheme iron(II) complexes with pentadentate ligands N_4Py , L^1 and L^2 was investigated in acetate buffer (50 mM) at pH 5.0 at 25 °C (Figure 1). Addition of the iron(II) complexes to solutions of sodium chlorite (NaClO_2), there is an increase in absorbance at 360 nm, characteristic for the formation of chlorine dioxide.³⁶

Figure 2a shows the spectral changes for the reaction of $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ with ClO_2^- , whereas those involving the $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$ and $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ complexes are given in the Supporting Information, Figures S4 and S5, where the same spectral changes are observed. The consumption of chlorite in the process is monitored by the decrease in absorbance at 260 nm ($\epsilon_{260} = 154 \text{ M}^{-1} \text{ cm}^{-1}$) as well as the concomitant formation of ClO_2 as measured through the increase in absorption at 360 nm ($\epsilon_{360} = 1250 \text{ M}^{-1} \text{ cm}^{-1}$).

Negative ion mode ESI-MS of a diethyl ether extract of the reaction mixture (Inset of Figure 2a) shows a signal with an isotopic pattern consistent with ClO_2 formation ($m/z = 67.14$). The reaction reaches a maximum in conversion within 40 min with oxidant loading of 10 μM at 25°C and pH 5.0.

The first-order rate constants as a function of oxidant concentration (Figure 2b, Table 1) for the reaction of ClO_2^- with $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$, $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ and $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$ were determined. The second-order rate constants of $k_2 = 10 \text{ M}^{-1} \text{ s}^{-1}$ and $32 \text{ M}^{-1} \text{ s}^{-1}$, respectively, for $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ and $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$ (Figure 2b) were determined from the dependence of the rate of generation of ClO_2 on the initial concentrations of the iron(II) complexes. These reaction rates correspond to a maximum yield of 13 and 10% with respect to iron for $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ and $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$, respectively. Our results contradict previous substrate sulfoxidation studies by $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ and $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$, in which the latter was 100 times more reactive, whereas it reacts 40 times faster in hydrogen atom abstraction reactions.¹⁸ In comparison to the bispidine-type complexes, addition of 10 μM $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ to chlorite (4 mM) resulted in the immediate appearance of an absorption band at 360 nm; characteristic of the formation of chlorine dioxide. The absorbance at 360 nm reaches a maximum with a second order rate constant of $1033 \text{ M}^{-1} \text{ s}^{-1}$ and an overall yield of 16% of ClO_2 . As such, the $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ complex reacts with rate constants that are at least 30 times higher than the fastest reacting bispidine complex. The yield of the ClO_2 obtained here is in the line with previous studies of analogous manganese and ruthenium catalysts.³⁷

Table 1 Data for the oxidation of ClO_2^- in aqueous acetate buffer

Complex	$k_2 (\text{M}^{-1} \text{s}^{-1})$	% ClO_2	TON
$[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$	10	13	300
$[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$	32	10	775
$[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$	1033	16	2796

Figure 3. (a) UV/vis absorption spectra of the iron(IV)-oxo intermediate formed during the reaction of 1 mM $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ with 1.2 equiv. of NaClO_2 at 298 K in acetate buffer at pH 5.0. (b) ESI-MS characterization of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$.

Characterization of iron(IV)-oxo intermediates. Identification of the formation of intermediates such as $\text{Fe}^{\text{IV}}(\text{O})$ species could provide insight into the reaction mechanism between the iron(II) complexes with ClO_2^- . Recent studies on the reactivity of nonheme manganese(II) complexes with ClO_2^- showed that oxygen atom transfer occurred to form a manganese(IV)-oxo species and ClO^- . The corresponding iron(IV)-oxo complexes $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$, $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^2)]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ have been characterized previously with UV/Vis absorption, resonance Raman, EPR and mass spectrometric methods.^{38,39}

Figure 3 shows the UV/Vis absorption and mass spectrometric characterization of the iron(IV)-oxo species $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$, and the corresponding spectra for the systems with ligands L^2 and N_4Py are given in the Supporting Information Figures S6 and S7.¹⁸ Addition of 1.2 equiv of NaClO_2 to 1 mM solutions of the iron(II) complexes results in a change in the UV/Vis absorption spectra is observed with a NIR absorption band characteristic of iron(IV)-oxo complexes in near quantitative yields, which was confirmed by ESI-MS analysis: $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$, $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^2)]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ with m/z values close to the theoretical values were observed. Note that under stoichiometric conditions, the iron(IV)-oxo complex is the sole product of the reaction and ClO_2^- is not detected.

The data in Figure 3, therefore, provides evidence that the reaction of the iron(II) complexes with ClO_2^- proceeds through the formation of an iron(IV)-oxo intermediate (Eq 3). This iron(IV)-oxo species was characterized for all three pentacoordinated ligand systems and subsequently reacts with another molecule of chlorite through either electron transfer or oxygen atom transfer to form the final products and hence the overall reaction of two molecules of ClO_2^- per iron center.

Figure 4. (a) UV/Vis absorption spectra of $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ (10 μM , black line) and $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$ (10 μM , red line) after reaction with 4.0 mM NaClO_2 with o-tolidine (40 μM) in acetate buffer. (b) ESI-MS spectra of products obtained from the reaction of NaClO_2 with $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$.

Product distributions from bifurcation pathways.

The reaction of an iron(IV)-oxo species with excess ClO_2^- can lead to products resulting from either electron transfer or oxygen atom transfer, Eq 4 and 5.

The ClO_2 content of the reaction mixture after reaction with $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$, $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$ and $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ was determined by extraction with diethyl ether followed by ESI-MS analysis.

The content of ClO_3^- in the product mixture was determined using o-tolidine, as described elsewhere.²³ It should be noted that o-tolidine reacts with ClO_3^- but not with either ClO_2^- or ClO_2 . Reaction of the iron(II) bispidine complexes with NaClO_2 in acetate buffer in the presence of o-tolidine at ambient temperature results in the appearance of a band at 442 nm corresponding to 3,3'-dimethyl-4-amino-4'-nitrobiphenyl (Figure 4a). The ESI-MS spectrum (after extraction) shows a signal at m/z 242.24 corresponding to the oxidized product. In addition, a signal at m/z = 227.07 corresponding to the partially oxidized nitroso intermediate is observed. The reactions involved and products obtained are summarized in Scheme 1.

Scheme 1. Reaction of o-tolidine with iron(II) complexes.

In contrast, the reaction with $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ did not result in the formation of products associated with the reaction of o-tolidine with ClO_3^- . Instead a peak at 388 nm was observed in the UV/Vis absorption spectrum indicating the presence of ferric species.²³ ESI-MS analysis of the organic extracted phase did not show significant formation of the nitro derivate, which may be a consequence

of subsequent reaction in the oxidation of ClO_2^- . Hence, the bispidine based complexes, $[\text{Fe}^{\text{II}}(\text{L}^1)]^{2+}$ and $[\text{Fe}^{\text{II}}(\text{L}^2)]^{2+}$ (see Supporting Information), react via oxygen atom transfer processes with the formation of ClO_3^- products as the dominant pathway, whereas $[\text{Fe}^{\text{II}}(\text{N}_4\text{Py})]^{2+}$ reacts to yield ClO_2 and related products through a one-electron transfer process.

In addition to the characterization of the iron(IV)-oxo species, ClO_2 and ClO_3^- , we made attempts to characterize additional short-lived intermediates during the reaction process, and in particular focused on the UV-Vis, Infrared and EPR spectra of iron(III)-oxo and iron(III)-hydroxo species. Unfortunately, these species are either not EPR active or the expected signal intensity is below the limits of detection. Furthermore, the UV/vis absorption spectra of such species are not sufficiently intense to be detected at the concentrations employed.

Computational modeling. The differences in the reactivity of chlorite with $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$, $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^2)]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ were investigated by density functional theory (DFT) methods, focusing on the thermochemistry, as well as, barriers to the reaction steps, with the aim of proposing an overall mechanism. Over 20 distinct chemical reactions involving ClO_2 , ClO_2^- , ClO_3^- and ClO^- intermediates were considered including those in which the acetate ions, present in the buffer, are involved (Supporting Information Tables S15 – S17).

Our initial focus was on the formation of the iron(IV)-oxo intermediate, $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$, from the reaction of either an iron(II) complex or a solvent (water) bound iron(II) resting state, $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}^1)]^{2+}$, Figure 5. We took the energy differences for the lowest energy spin state structures, i.e. quintet for the iron(II) complexes and triplet for the iron(IV)-oxo species. The exchange of H_2O with chlorite is exergonic by 6.9 kcal mol⁻¹, which drops to 18.7 kcal mol⁻¹ when the iron(II) complex is pentacoordinated. Whether a solvent molecule is bound to the sixth ligand position of the iron(II) complex has little effect on the formation of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$. Dissociation of $[\text{Fe}^{\text{II}}(\text{ClO}_2)(\text{L}^1)]^{2+}$ into $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$ and ClO^- is also exergonic by 16.2 kcal mol⁻¹; therefore, the $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$ should form readily in a mixture of the $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}^1)]^{2+}$ and ClO_2^- . The overall driving force ($\Delta G_{\text{fi}} + \Delta G_{\text{fz}}$) for the formation of the $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}^1)]^{2+}$ complex from $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}^1)]^{2+}$ is -23.1 kcal mol⁻¹, whereas a value of -37.8 kcal mol⁻¹ is found for the N_4Py complex. Hence, both iron(II) complexes should rapidly form an iron(IV)-oxo species with ClO_2^- . The formation of the iron(IV)-oxo species upon reaction of $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}^1)]^{2+}$ with ClO_3^- requires a highly endergonic displacement of water (ΔG_{fic}), which most probably originates from the fact that HClO_3 is a much stronger acid than HClO_2 and preferentially exists in the ClO_3^- form. Hence although ClO_2^- can react to form an iron(IV)-oxo species, reaction with ClO_3^- by oxygen atom transfer to an iron(II) complex is not ther-

mochemically feasible. A similar result was obtained for the formation of iron(IV)-oxo complexes from hypochlorite and an iron(II)-water complex.⁴⁰

The reactivity of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ with a second molecule of ClO_2^- was considered by two distinct reaction mechanisms; electron transfer (ET) and oxygen atom transfer (OAT), Figure 6. In these reaction steps, aside from the thermodynamic aspects, the kinetics of the reaction are of interest. Barriers to electron transfer were calculated using the Marcus model as described above, with a barrier of $10.1 \text{ kcal mol}^{-1}$ predicted for the reaction of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ with ClO_2^- , whereas for $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ with ClO_2^- a barrier of $17.0 \text{ kcal mol}^{-1}$ is found. These values imply that both $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ are able to react with ClO_2^- by one-electron transfer, whereby the former will react faster than the latter. The free energies of activation for electron transfer are within 2 kcal mol^{-1} of the electron transfer driving forces and hence give only a minor change to the thermodynamically calculated energetics. These electron transfer barriers are in good quantitative agreement with the rate constants reported in Figure 2. Furthermore, the studies imply faster electron transfer for $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ than for $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$. Indeed, the reported $\text{Fe}^{\text{III}}/\text{Fe}^{\text{IV}}$ redox potentials of the L^1 and N_4Py systems confirm that this should be the case.¹⁸ In particular, a slightly higher electron affinity for $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ as compared to $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ by 0.09 eV is calculated, whereas the experimentally reported redox potential difference is 0.08 eV .¹⁸ The calculated free energies of activation for electron transfer imply that these reactions should be rapid as well as spontaneous at room temperature.

Figure 5. Reaction free energies for the individual steps leading to the formation of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ from $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}')]^{2+}$ and ClO_2^- . Free energies given for systems with ligand L^1 are in kcal mol^{-1} and contain entropic, thermal and solvent effects.

In addition, the oxygen atom transfer pathway from $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ to ClO_2^- was explored initially by calculation of long range reactant complexes followed by a constraint geometry scan whereby one degree of freedom (the $\text{Cl}-\text{O}$ distance) was fixed and all other coordinates minimized. The maximum of these geometry scans were subjected to a transition state search. A transition state was not found in the triplet spin state and the geometry scan led to a repulsive product state that after optimization fell back to reactants. On the quintet spin state surface a stable OAT transition state $^5\text{TS}_{\text{OAT}}$ at $+11.8 \text{ kcal mol}^{-1}$ above the reactants was obtained, see Figure 6.

The structure is characterized by a low imaginary frequency for the $\text{Cl}-\text{O}$ stretch and $\text{Fe}-\text{O}$ elongation. In the transition state the $\text{Fe}-\text{O}$ bond is relatively long ($2.087 \text{ \AA}$), which matches previous studies on substrate sulfoxidation and aromatic hydroxylation barriers of nonheme iron(IV)-oxo oxidants in the quintet spin state.^{41,42}

In the case of $^3,5[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+} \cdots \text{ClO}_2^-$, the geometry scans led to a maximum with extremely high energy (well over 45 kcal mol^{-1}) and we were unable to characterize its transition state. Probably this has to do with stereochemical repulsions of the approach of the substrate with the bispidine ligand system that prevent the ideal geometry for the transition state. Nevertheless, the geometry scan clearly identifies a high energy pathway for OAT. Indeed, the thermochemistry for OAT gives an overall strongly endergonic reaction for the N_4Py complex ($\Delta G_{\text{OAT}} = 45.3 \text{ kcal mol}^{-1}$), whereas it is only slightly endergonic for the bispidine complex, $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ at $\Delta G_{\text{OAT}} = +8.8 \text{ kcal mol}^{-1}$. The driving forces for the two oxygen atom transfer processes, therefore, imply that it is an energetically accessible process for $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$, but most probably not for $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$, where barriers well in excess of 45 kcal mol^{-1} are expected on all spin state surfaces. These oxygen atom transfer barriers are larger than those anticipated from the experimental rate constants reported above, which may be the result of the lack of polarization or the environment in the calculations.

The studies described in Figure 6 imply that the reaction rates for ET and OAT will be competitive for $[\text{Fe}^{\text{IV}}(\text{O})(\text{L}')]^{2+}$ with similar driving forces and reaction rate constants, whereas $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ at room temperature can only react via one-electron transfer because the driving force for the OAT reaction is substantially greater than that for ET. The reason for this difference in reactivity of bispidine and N_4Py complexes stems from the fact that the N_4Py complexes are weaker oxidants, specifically for oxygen atom transfer reactions, than the ferryl-bispidine complexes. For example, low rate constants for the reaction of $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ with para-substituted thioanisoles were reported.⁴³

Figure 6. Bifurcation pathways for the reaction of ClO_2^- with $[\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ complexes going through electron transfer (pathway to the left) or oxygen atom transfer (pathway to the right). Free energies are in kcal mol^{-1} and contain zero-point, entropic, thermal and solvent corrections. Data out of parenthesis are given for ligand L^1 , whereas values in parenthesis use N_4Py instead. Optimized transition state for OAT is given with bond lengths in angstroms and the imaginary frequency in wave numbers.

Figure 7. DFT calculated free energies of individual reaction steps. All values are in kcal mol^{-1} and contain zero-point, entropic, thermal and solvent corrections. Data outside of the parentheses are associated with the complex of ligand L^1 , whereas data within the parentheses refer to complexes of N_4Py .

A similar bifurcated mechanism was recently found for iron(IV)-oxo versus iron(IV)-imido reactivity with sulfides, where the latter more efficiently performing a two-electron transfer process.²¹ That the N4Py complex reacts preferentially through single-electron transfer pathways, therefore, is not due to an increased electron affinity, but mostly is a result of the destabilization of the OAT pathway. As such, minor differences in ligand structure drive reactions via different pathways and give variations in product distributions. This also means that the ligand system can be modified based on the required product distributions – provided one understands the correlation between structure and reactivity.

The full reaction cycles leading to ClO_2^- deactivation by $[\text{Fe}^{\text{II}}(\text{L}')^{2+}]$ and $[\text{Fe}^{\text{II}}(\text{N4Py})]^{2+}$ were calculated, Figure 7. As discussed above, the reaction is initiated upon displacement of the coordinated solvent of the iron(II) complex by ClO_2^- followed by Cl–O bond cleavage to form an iron(IV)-oxo species and ClO^- with the reaction rate k_f . Note that in an acetate buffer, ClO_2^- can also react with acetate to form peracetate in an almost thermoneutral process, which may be another source for the formation of an iron(IV)-oxo species. Thereafter, the reaction pathway bifurcates into two reaction channels, namely electron transfer (ET, top) with rate constant k_{ET} and oxygen atom transfer (OAT, bottom) with rate constant k_{OAT} . The electron transfer processes forms ClO_2 and $[\text{Fe}^{\text{III}}(\text{O})]^+$, which under acidic conditions is protonated to form an iron(III)-hydroxo complex via a proton-transfer reaction rate k_{PT} . The latter is a highly exergonic reaction step and is not expected to affect the overall reaction rate. The alternative OAT reaction leads to an iron(II)-aqua complex and releases ClO_3^- . The $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})]^{2+}$ complex is converted to the iron(III)-hydroxo product in an electron-transfer reaction with ClO_2 followed by deprotonation via reaction rate k_{CT} .

In the case of $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}')^{2+}]$, the reaction with ClO_2^- to form a stable iron(IV)-oxo species is exergonic with a driving force of 23.1 kcal mol⁻¹. The bifurcation pathways results in competition between ET and OAT, which have barriers within 1.5 kcal mol⁻¹ and therefore a mixture of products can be expected. The iron(III)-oxo species formed after electron abstraction from substrate is protonated to form an iron(III)-hydroxo complex with large exergonicity and is converted back into an iron(IV)-oxo species by reaction with another molecule of ClO_2^- and H_3O^+ . The overall reaction stoichiometry for the electron transfer pathway is given in Eq 6 and yields ClO_2 as well as Cl^- products. However, as shown previously,⁴⁴ and also confirmed by DFT here, ClO^- reacts with another iron(II) complex to form an iron(IV)-oxo species and Cl^- . Therefore, a reaction pathway that follows the electron transfer channel will use two molecules of ClO_2^- to form two molecules of iron(IV)-oxo and a Cl^- . Each iron(IV)-oxo reacts with one molecule of ClO_2^- to form ClO_2 . As such a max-

imum yield of 50% can be achieved for the reaction shown in Figure 7.

The alternative reaction after OAT has a high endergonicity for charge transfer from $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}')^{2+}]$ to ClO_2^- . Instead, the $[\text{Fe}^{\text{II}}(\text{H}_2\text{O})(\text{L}')^{2+}]$ will react with ClO_2^- to form another iron(IV)-oxo complex. The overall reaction stoichiometry for the process involving the OAT pathway is essentially disproportionation of ClO_2^- into ClO^- and ClO_3^- catalyzed by an iron(II) center, Eq 7. Indeed, the disproportionation reaction is calculated to have a driving force of $\Delta G_{\text{disproportionation}} = -14.3 \text{ kcal mol}^{-1}$.

The computational modelling shows that multiple products are expected from the reaction of ClO_2^- on iron(II) centers. In particular, $[\text{Fe}^{\text{II}}(\text{L}')^{2+}]$ is expected to give a mixture of products due to competition between the barriers to each pathway and yield ClO_2 , ClO^- , ClO and ClO_3^- products, whereas $[\text{Fe}^{\text{II}}(\text{N4Py})]^{2+}$ will give products through the k_{ET} process only and not ClO_3^- . The thermochemical analysis from Figure 7 is in good agreement with the product distributions in Figure 4, where a significant amount of ClO_3^- was obtained for the bispidine complex but none for $[\text{Fe}^{\text{II}}(\text{N4Py})]^{2+}$.

The reactivity differences and the reason the bispidine complex reacted via multiple reaction channels, in contrast to the N4Py complex, were rationalized through a valence bond curve crossing diagram, Figure 8. These diagrams have been used previously to establish the intrinsic properties of the oxidant and reductant that determine reaction processes and, for instance, enabled us to predict reactivity trends and rate constants.⁴⁵

The VB diagrams start on the bottom-left with the reactant configuration, which in this case is the iron(IV)-oxo species and ClO_2^- . The iron(IV)-oxo species is in a triplet spin ground state with orbital occupation $\pi_{\text{xz}}^2 \pi_{\text{yz}}^2 \pi_{\text{xy}}^* \pi_{\text{xz}}^* \pi_{\text{yz}}^*$. Slightly higher in energy is a quintet spin state with $\pi_{\text{xz}}^2 \pi_{\text{yz}}^2 \pi_{\text{xy}}^* \pi_{\text{xz}}^* \pi_{\text{yz}}^* \sigma_{\text{zz}}^*$.⁴⁵ Panel (a) in Figure 8 gives a mechanism for single electron transfer from ClO_2^- to iron(IV)-oxo species and lead to the electron-transfer products ClO_2 and $[\text{Fe}^{\text{III}}(\text{O})]^+$. The two VB curves for reactant and product cross and lead to an avoided crossing and a transition state for electron transfer. Generally, the curve crossing energy is a fraction of the excitation energy in the reactant complex from the reactant electronic configuration to the product electronic configuration. As such the electronic differences between the reactant and product wave functions determine the height of the reaction barrier.

Figure 8. Valence bond curve crossing diagrams explaining the differences for the ET and OAT reaction steps.

Therefore, the one-electron transfer process will simply be determined by the ionization energy of ClO_2^- ($\text{IE}_{\text{ClO}_2^-}$) and the electron affinity of the iron(IV)-oxo complex (EA_{FeO}), Eq 8. We calculated the electron affinities of the two iron(IV)-oxo complexes as well as the ionization energy of ClO_2^- and find diabatic values of $\Delta E + \text{ZPE} + E_{\text{solv}} = 121.7 \text{ kcal mol}^{-1}$ ($\text{IE}_{\text{ClO}_2^-}$), and 90.1 and 81.8 kcal mol^{-1} for the EA of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L})]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$, respectively.

As such, the VB curve crossing diagram predicts a $G_{\text{ET}} = 31.6$ and $39.9 \text{ kcal mol}^{-1}$ for the bispidine and N4Py complexes. In general, the barrier height is one third of the promotion gap,⁴⁷ and, therefore, the VB diagram predicts electron transfer barriers of $\Delta E^\ddagger = 10.5$ and $13.3 \text{ kcal mol}^{-1}$ for the reactions involving the bispidine and N4Py ligated systems, respectively. These values are in good quantitative agreement with the relative barrier heights discussed above in Figures 5 and 6.

$$G_{\text{ET}} \propto \text{IE}_{\text{ClO}_2^-} - \text{EA}_{\text{FeO}} \quad (8)$$

Figure 8b shows the VB curve diagram for the oxygen atom transfer from iron(IV)-oxo to ClO_2^- , which shows resemblance to schemes rationalizing substrate sulfoxidation by iron(IV)-oxo complexes.⁴⁸ This process is a concerted reaction where a Cl-O bond is formed in a single elementary step. Thus, ClO_2^- is first ionized to ClO_2 and the unpaired electron on the Cl atom forms a bond with an electron in a 2p orbital on the oxygen atom. However,

at the start of the reaction the oxygen 2p orbitals are hybridized with 3d orbitals of the metal. Therefore, one of the sets of π_{xz}/π_{xz}^* or π_{yz}/π_{yz}^* pairs of orbitals will split back into atomic orbitals to give a singly occupied 2p orbital on the oxygen atom and a doubly occupied 3d orbital on the metal, i.e. $3d_{xz}^2 2p_x^1$. Upon oxidation of ClO_2^- , however, one electron will move to the iron that is reduced from iron(IV) to iron(III). Consequently, the promotion gap for the oxygen atom transfer process will depend on the ionization energy ($\text{IE}_{\text{ClO}_2^-}$) of ClO_2^- as well as the reduction of the iron(IV)-oxo to iron(III)-oxo, EA_{FeO} , Eq 9. Additional energy costs incurred in this process relate to the breaking of the π_{xz}/π_{xz}^* orbitals (E_{π/π_{xz}^*}), but also energy will be released due to the formation of the Cl-O bond.

$$G_{\text{OAT}} \propto \text{IE}_{\text{ClO}_2^-} - \text{EA}_{\text{FeO}} + E_{\pi/\pi_{xz}^*} - \text{BDE}_{\text{Cl-O}} \quad (9)$$

The π_{xz}/π_{xz}^* and π_{yz}/π_{yz}^* energy gaps at UB3LYP/BS2+solvent are 70.6 and 74.0 kcal mol^{-1} for $[\text{Fe}^{\text{IV}}(\text{O})(\text{L})]^{2+}$, whereas values of 102.0 and 103.1 kcal mol^{-1} are found for $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$. The diabatic ionization energy of ClO_2^- is 121.7 kcal mol^{-1} , while the vertical electron affinity of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L})]^{2+}$ and $[\text{Fe}^{\text{IV}}(\text{O})(\text{N4Py})]^{2+}$ are 90.1 and 81.8 kcal mol^{-1} , respectively. Based on these numbers and the calculated Cl-O bond strength of 56.7 kcal mol^{-1} we estimate a value of G_{OAT} that is 24 kcal mol^{-1} lower in energy for the reaction of $[\text{Fe}^{\text{IV}}(\text{O})(\text{L})]^{2+}$ with

ClO_2^- than the one where $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ is involved in. Therefore, a difference in OAT barrier height of about 8 kcal mol⁻¹ between the two oxidants is predicted, which would correspond to a rate enhancement of well over 700,000. Indeed, as shown above in Figure 6 and in agreement with the experimental data, $[\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}$ does not react via oxygen atom transfer, but preferentially through one-electron transfer. The VB diagram shows that this is due to increased π_{xz}/π_{xz}^* energy splitting and a decreased electron affinity. As such the VB curve crossing diagram gives an explanation what the driving force for electron transfer versus oxygen atom transfer is and how the oxidants can be further modified to obtain the required product distributions.

Conclusion.

In summary, we present the first experimental and computational study of the selective oxidation of chlorite to chlorine dioxide. We show that the reaction can proceed via competing pathways, whereby the nature of the ligand system and the binding affinity for ClO_x^- substrates determines the driving force and activation barriers to each reaction step. The proposed mechanisms were validated experimentally and the high-valent iron(IV)-oxo intermediate formed in situ was characterized experimentally.

ASSOCIATED CONTENT

Supporting Information. Details with additional experimental data, UV/Vis absorption spectroscopic and mass spectrometric data focused on the characterization and reactivity of iron(IV)-oxo complexes. Computational data including absolute and relative energies, group spin densities and charges as well as calculated reaction energies and Cartesian coordinates of optimized structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ABBREVIATIONS

N_4Py = N,N-bis(2-pyridylmethyl)-bis(2-pyridyl)methylamine;
 L^1 = dimethyl 2,4-di(2-pyridyl)3-(pyridin-2-ylmethyl)-7-methyl-3,7-diazabicyclo [3.3.1]nonan-9-one-1,5-dicarboxylate;
 L^2 = dimethyl 2,4-di(2-pyridyl)-3-methyl-7-(pyridin-2-ylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate; ET = electron transfer; OAT = oxygen atom transfer; DFT = density functional theory; ESI-MS = electrospray ionization-mass spectrometry.

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For Table of Contents only: This paper describes a novel mechanism of chlorite oxidation by iron(II) complexes and it is shown that two competing pathways for either oxygen atom transfer or electron transfer participate depending on the nature of the ligand system.