ABSTRACT: Nonheme iron halogenases are unique enzymes in nature that selectively activate an aliphatic C–H bond of a substrate to convert it into C–X (X = Cl/Br, but not F/I). It is proposed that they generate an Fe(II)(OH)(X) intermediate in their catalytic cycle. The analogous Fe(III)(OH) intermediate in nonheme iron hydroxylases transfers OH⁺ to give alcohol product, whereas the halogenases transfer X⁺ to the carbon radical substrate. There remains significant debate regarding what factors control their remarkable selectivity of the halogenases. The reactivity of the complexes Fe(II)(BNPA-BPh₂O)(OH)(X) (X = Cl, Br) with a secondary carbon radical (R*) is described. It is found that X⁺ transfer occurs with a secondary carbon radical, as opposed to OH⁺ transfer with tertiary radicals. Comprehensive computational studies involving density functional theory were carried out to examine the possible origins of this selectivity. The calculations reproduce the experimental findings, which indicate that halogen transfer is not observed for the tertiary radicals because of a nonproductive equilibrium that results from the endergonic nature of these reactions, despite a potentially lower reaction barrier for the halogenation pathway. In contrast, halogen transfer is favored for secondary carbon radicals, for which the halogenated product complex is thermodynamically more stable than the reactant complex. These results are rationalized by considering the relative strengths of the C–X bonds that are formed for tertiary versus secondary carbon centers. The computational analysis also shows that the reaction barrier for halogenation is significantly dependent on secondary coordination sphere effects, including steric and H-bonding interactions.

INTRODUCTION

The formation and synthesis of carbon–halogen bonds are a relatively rare reaction in nature, yet a number of enzymes catalyze this type of transformation, including halogenases and haloperoxidases, and several of those have been identified in recent years. These enzymes are widespread in marine organisms, fungi, plants, and bacteria and are involved in the biosynthesis of natural products that function as deterrents, pesticides, irritants, and for food gathering. Several antibiotics have been found that contain organohalogen compounds, including vancomycin, which is a glycopeptide with the chlorine atom bound to an aromatic ring. One of the first haloperoxidases structurally and functionally characterized was chloroperoxidase, a heme peroxidase in fungi that binds H₂O₂ and forms an iron(IV)–oxo heme cation radical intermediate, called Compound I (CpdI), during its catalytic cycle. CpdI reacts with halides (X = Cl⁻, Br⁻, I⁻) to form the corresponding hypohalide (OX⁻), which then reacts with a substrate to form the organohalogen product. The biosynthesis of hypohalide from H₂O₂ and halide also is catalyzed by the vanadium haloperoxidases and flavin haloperoxidases, but they have a different cofactor and their hypohalide biosynthesis mechanisms are different.

The α-ketoglutarate-dependent nonheme iron halogenases are fascinating enzymes that activate an aliphatic C–H bond of a substrate selectively using molecular oxygen and an α-ketoglutarate (αKG) cosubstrate on an iron center. In many of these enzymes, the overall reaction is highly stereospecific, processes that are still poorly understood. The nonheme iron halogenases contain a nonheme iron(II) center that is bound to the protein via two histidine amino acid groups, see Scheme 1. In contrast to the αKG-dependent nonheme iron hydroxylases, which bind the protein through interactions with two histidine and one carboxylate group of either Asp or Glu, the latter interaction is missing in the nonheme iron halogenases (Scheme 1). Instead, a halogen (usually Cl⁻, but there are also reports with Br⁻) binds the iron(II) center directly. These enzymes use αKG as a cosubstrate and dioxygen to form succinate, CO₂, and a...
high-valent iron(IV)−oxo (FeIV(O)) species. This species was trapped and characterized with spectroscopic methods for the nonheme iron halogenase SyrB2 and shown to react with an aliphatic group of a substrate through hydrogen atom abstraction to give a putative cis-FeIII(OH)(Cl) intermediate and carbon radical (R*), see Scheme 1.31 A halogen "rebound" step then follows, in which the halogen (Cl-) is transferred to the nearby radical to give the halogenated R−Cl product, with concomitant reduction of the metal center to FeII. The reaction is often stereospecific and enables the enantioselective synthesis of halogenated substrates efficiently. Interestingly, the competitive OH- rebound to form alcohol (ROH) does not occur. The overall halogenase mechanism is summarized in Scheme 1.

A range of computational studies on the reaction mechanism of αKG-dependent nonheme iron halogenases have been reported.32−45 The factors that control the key, bifurcation rebound pathway remain controversial, despite much computational and experimental effort. Several possible ideas have been suggested, including substrate positioning,31 oxidant isomerization,32 CO2 attack on iron(III)−hydroxo,33 iron(III)−hydroxo protonation,34 electrostatic interactions of the second-coordination sphere,30 the relative redox potentials of OH− versus X−,42 and energetics of the frontier molecular orbitals.38 Addressing these different hypotheses experimentally is challenging because the putative cis-FeIII(OH)(X) intermediate is too short-lived to be observed directly in the enzymatic system under catalytic conditions.

A few groups have synthesized iron complexes that model aspects of the nonheme iron halogenases, although their reactivity varies dramatically.46−52 Previous efforts by Goldberg and co-workers have led to the synthesis and structural characterization of model complexes of the postulated cis-FeIII(OH)(X) intermediate.53 These complexes, [FeIII(BNPAPh2O)(OH)(X)] (BNPAPh2O = 2-(bis(6-(neopentylamino)pyridin-2-yl)methyl)amino-1,1-diphenylethanolate; X = Cl, Br), see Scheme 2, take advantage of a new ligand with sterically encumbered, second-coordination sphere hydrogen-bonding groups that stabilize the terminal hydroxide ligand. The tetradentate ligand also leaves an open site cis to the OH group for coordination of a wide range of anionic donors, including halogens (e.g., Cl−, Br−). The first study with these cis-FeIII(OH)(X) complexes involved examining their reactivity toward tertiary carbon radical derivatives (p-Y-C6H4)3C* (Y = H, OMe, Cl).53 The reactions led exclusively...
to OH* transfer to give alcohol, and no evidence for halogen transfer was observed. However, the corresponding dichloride complex \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{Cl})_2]\) did react with \((p\text{-Y-C}_6\text{H}_4\text{H}_2\text{Cl})\) through halogen transfer to give \((p\text{-Y-C}_6\text{H}_4\text{H}_2\text{Cl})\) and \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{Cl})]\), indicating that \(X^*\) transfer, with concomitant reduction of \(\text{Fe}^{III}\) to \(\text{Fe}^{II}\), was possible in these systems. The experiments triggered an important question, namely, why do the mixed cis-\(\text{Fe}^{II}(\text{OH})(X)\) complexes react with the 3° carbon radicals to give only hydroxylated products, whereas in the enzymes only halogenation is seen? One possibility is that substrate positioning in the enzymes dominates the selectivity; however, a number of computational studies have suggested that there should be an inherent kinetic selectivity for halogen rebound with cis-\(\text{Fe}^{III}(\text{OH})(X)\) species even in the absence of an enzyme pocket.32–35

In this work, a combined experimental and computational approach has been taken to address the factors that may control the selectivity of hydroxyl versus halogen rebound in the cis-\(\text{Fe}^{III}(\text{OH})(X)\) model complexes. One hypothesis is that the nature of the carbon radical influences the outcome of these reactions, and this hypothesis was tested by examining the reactivity of a secondary carbon radical substrate. Detailed computational studies were carried out on these systems analyzing the bifurcated radical rebound pathway, including hypothetical structural derivatives that allowed us to test the influence of hydrogen bonding, steric bulk, positioning (equatorial versus axial) of OH* versus \(X^*\), and the nature of the carbon radical (3° versus 2°) on rebound selectivity. Taken together, the experimental and computational results lead to significant insights regarding the inherent rebound selectivity of these well-defined model complexes.

\[ \text{Fe}^{III}(\text{BNPA Ph}_2\text{O})(\text{Cl})_2 \] crystals (70 mg, 0.10 mmol) were dissolved in CD$_3$CN, and a 1H NMR spectrum was obtained. A second observation was made when 3°-Br was used. The 1H NMR spectrum of \([\text{Fe}^{III}(\text{BNPA Ph}_2\text{O})(\text{Cl})_2]\) crystals dissolved in CD$_3$CN at 38 °C showed only small changes to the structures and energies. Transition states were confirmed by running an analytical frequency calculation that showed a single imaginary mode for the correct transition. Additional intrinsic reaction coordinate (IRC) scans were performed for a selection of transition states and further confirmed their characterization. In particular, the IRCs led to the reactant complexes in one direction and the product complexes in the other direction.

**METHODS**

**Materials.** All structures were synthesized and manipulated in a N$_2$-filled drybox (under an atmosphere with the following conditions: [O$_2$] < 0.2 ppm, [H$_2$O] < 0.5 ppm) or using standard Schlenk techniques under an atmosphere of argon unless otherwise noted. Fluorobenzene, acetonitrile, and pentane were distilled in CaH$_2$. Tetrahydrofuran was dried over Na/benzophenone and subsequently degassed by a minimum of three freeze–pump–thaw cycles and stored over freshly activated 3 Å molecular sieves in the drybox following distillation. All other reagents were purchased from commercial vendors and used without further purification. The ligand BNPAPh$_2$OH was prepared by a literature procedure⁵⁴ and was dried over P$_2$O$_5$ for 12 h under vacuum before metatation. The complexes \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{OH})(\text{Cl})], [\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{OH})(\text{Br})], \) and \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{Cl})]\) were synthesized by previously reported procedures.⁵⁵ The secondary radical precursors \([\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)\text{N}]\text{H}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}\), \([\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}\text{CH}_2\text{Cl}]\), and the chlorinated compound \([\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}\text{CH}_2\text{Cl}]\) were synthesized according to a reported procedure.⁵⁵

**Instrumentation.** The 1H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz or a Bruker 400 MHz NMR spectrometer. Chemical shifts were referenced to reported solvent resonances.⁵⁶

**Reactivity Studies.** \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{OH})(\text{Cl})]\) or \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{Cl})]\) crystals (70 mg, 0.10 mmol) were dissolved in fluorobenzene (4 mL) with stirring. The solution was transferred to a high-pressure vessel and a fluorobenzene solution (2 mL) of \(C_6H_4CH(CH_3)_2N=CH_2\text{CHCl}_2\text{H}_2\) (124 mg, 0.52 mmol, 5 equiv) was added. The reaction mixture was heated at 90 °C for 12 h. The reaction mixture was cooled to room temperature and passed through a silica gel column to remove metal impurities. Purification of the chlorinated product \(C_6H_4CH(Cl)CH_2\) by silica gel column chromatography (2% C$_2$H$_4$OAc/hexane) gave an isolated yield of 40% for \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{OH})(\text{Cl})]\) and 45% for \([\text{Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{Cl})]\). The identity of the product was confirmed by 1H NMR spectroscopy. We attempted the reaction with 1Cl and 2Cl at a lower temperature (~60 °C) but did not see any reaction occur with the iron complex at this temperature.

**Reaction of \(p\text{-Cl-Fe}^{II}(\text{BNPAPh}_2\text{O})(\text{OH})(\text{Cl})\) with \((p\text{-Cl-C}_6\text{H}_4\text{H}_2\text{Cl})\).** Crystalline \(p\text{-Cl}(\text{BNPAPh}_2\text{O})(\text{OH})(10 \text{ mg, 0.016 mmol})\) was dissolved in THF (1 mL). To that solution, excess \((p\text{-Cl-C}_6\text{H}_4\text{H}_2\text{Cl})\)(68 mg, 0.16 mmol, 10 equiv) was added and a color change from red to orange was noted. The reaction was stirred for 5 min and then the solvent was removed under vacuum. The orange residue was dissolved in CD$_3$CN, and a 1H NMR spectrum was recorded. The 1H NMR spectrum shows the complete disappearance of the sharp, paramagnetically shifted peaks corresponding to \(p\text{-Cl}(\text{BNPAPh}_2\text{O})(\text{Br})\). The chlorinated product \(C_6H_5CH(Cl)CH_3\) by silica gel column chromatography (2% C$_2$H$_4$OAc/hexane) gave an isolated yield of 85%.

**Computation.** All calculations were carried out using the Gaussian-09 software package.⁵⁷ The model was created from the crystal structure coordinates of \([\text{Fe}^{III}(\text{BNPAPh}_2\text{O})(\text{OH})(\text{Cl})]\), and hydrogen atoms were added in GaussView.⁵⁵ Geometry optimizations and analytical frequencies were done using the unrestricted B3LYP density functional approach with a basis set containing LANL2DZ (with core potential) on iron and 6-31G on the rest of the atoms: basis set BS1.⁵⁹–⁶⁵ Initially, geometry optimizations were done in the gas phase followed by single-point calculations with a larger basis set (basis set BS2) and solvent included; however, this resulted in low energy barriers that often dropped below the reactant complexes. We, therefore, reoptimized all local minima and transition states and the subsequent frequency calculations with a solvent model included at UB3LYP/BS1 level of theory using the continuum polarized conductor model with a dielectric constant mimicking a tetrahydrofuran solvent.⁶⁶ Basis set BS2 has a triple-ζ quality LACV3P + basis set (with core potential) on iron and 6-31+G* on the rest of the atoms. Some structures were also optimized at UB3LYP/BS2 (Supporting Information, Figure S7); however, this gave only small changes to the structures and energies. Transition states were confirmed by running an analytical frequency calculation that showed a single imaginary mode for the correct transition. Additional intrinsic reaction coordinate (IRC) scans were performed for a selection of transition states and further confirmed their characterization. In particular, the IRCs led to the reactant complexes in one direction and the product complexes in the other direction.

The computational methods and approaches follow previous studies from our group and have been previously described and validated against experimental data and were shown to correctly reproduce spectroscopic parameters, product selectivities, and reaction rates.⁶⁵–⁶⁷

**RESULTS AND DISCUSSION**

**Experiment.** The reactivity of 1Cl was previously examined with the tertiary carbon radicals \((p\text{-Y-C}_6\text{H}_4\text{H}_2\text{Cl})\) (Y = Me, H, Cl), resulting in dominant OH* transfer to form the \((p\text{-Y-C}_6\text{H}_4\text{H}_2\text{Cl})\) product with yields >85%.⁵³ By contrast, the dichloro compound, \([\text{Fe}^{III}(\text{BNPAPh}_2\text{O})(\text{Cl})_2]\) (2Cl), reacted through halogen transfer to give \((p\text{-Y-C}_6\text{H}_4\text{H}_2\text{Cl})\) with yields of 75–85%, demonstrating that halogen transfer was feasible. Our hypothesis to explain this selectivity was that the formation of the halogenated product was thermodynamically unfavorable because of the weak nature of the C–Cl bonds in trityl derivatives, in contrast to the C–OH product. To test this hypothesis, we sought a secondary carbon radical that could be reacted directly with 1Cl to give a product in which the C–Cl bond is significantly more thermodynamically stable. This 2° radical might then favor halogen transfer. The phenylmethylmethyl radical was selected for study because of its ease of generation from a diazo precursor.⁶⁸
Reaction of 1Cl with phenylmethylmethyl radical was performed in fluorobenzene and product distributions were measured with $^1$H NMR. As can be seen in Figure 1, the complex 1Cl reacts selectively with phenylmethylmethyl radical to form 1-chloro-1-phenylethane. Although the yield for the halogenated product was only 40%, there was no evidence for the corresponding alcohol or ketone products that would arise from OH$^*$ transfer. The dichloro complex 2Cl was also investigated in a reaction with phenylmethylmethyl radical and gave the halogenated product (45% yield). These results support our hypothesis; changing the substrate from 3° to 2° carbon radical leads to halogenation. One possibility is that the halogenation of the secondary carbon radical arises from a free radical decomposition pathway. The dichloro complex 2Cl is shown on the right-hand side of Figure 2. These are dominated by the metal 3d contribution and labeled $\pi_{xy}$, $\pi_{xz}$, $\pi_{yz}$, $\sigma_{x^2-y^2}$, and $\sigma_{x^2}$; whereby the z-axis is defined along the O–Fe axis. The three $\pi$ orbitals represent the antibonding interactions of the hydroxido ligand and iron atom through the mixing of the atomic 2p orbitals on iron. Higher in energy are the two $\sigma$ orbitals for the antibonding interactions along the z-axis and in the xy-plane: $\sigma_{x^2-y^2}$ and $\sigma_{x^2-z^2}$. Thus, the $\sigma_{x^2}$ orbital represents the interaction of the iron 3d$\pi$ with 2p orbitals on O(alkyl) and N$_{ax}$ while the $\pi_{x^2}$ and $\pi_{y^2}$ orbitals mix the 3d$\pi$ orbitals between iron and N$_{ax}$ and P$_{ax}$ and N$_{ax}$ in the equatorial plane and 3p$\sigma$ orbitals on Fe(III) and OH$.^*$ The decomposition pathways for the 2° carbon radical (e.g., dimerization, desaturation) are much faster than the decomposition pathways for (p-Cl–C$_6$H$_5$)$_2$C$^\bullet$, and these results suggest that there is a kinetic barrier for OH$^*$ transfer that is outcompeted by one or more of the 2° carbon radical decomposition pathways.

**Figure 1.** Top: $^1$H NMR spectra obtained in CDCl$_3$ of isolated $\text{C}_6\text{H}_5\text{CH}(\text{Cl})\text{CH}_3$ from the reaction of 1Cl with $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{N}^\bullet\text{N}^\bullet\text{N}^\bullet\text{CH}_2\text{C}_6\text{H}_5$ (a), from the reaction of 2Cl with $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{N}^\bullet\text{N}^\bullet\text{N}^\bullet\text{CH}_2\text{C}_6\text{H}_5$ (b), and authentic $\text{C}_6\text{H}_5\text{CH}(\text{Cl})\text{CH}_3$ (c). Residual solvent signals are marked with a red asterisk (*). Bottom: Reactivity of 1Cl with tertiary and secondary carbon radicals.

Chlorination of even stronger, aliphatic C–H bonds would be expected if free Cl$^*$ was generated$^{52}$.

With the halogen-transfer results observed for the 2° carbon radical, we questioned whether OH$^*$ transfer could be observed for the same radical if an Fe$^\text{III}$ species were employed that lacks a competitive rebound partner. To address this question, we examined the trflate-ligated [Fe$^\text{III}$($\text{BNPA}^\text{OTf}_{\text{Ph}}$)-OH](OTf)$_2$ (1OTf). No reaction was observed between 1OTf and phenylmethylmethyl radical under the same conditions. On the other hand, reaction of 1OTf with the 3° carbon radical, i.e., (p-Cl–C$_6$H$_5$)$_2$C$^\bullet$, leads to (p-Cl–C$_6$H$_5$)$_2$COH in good yield (Scheme 3).$^5$ The decomposition pathways for the 2° carbon radical (e.g., dimerization, desaturation) are much faster than the decomposition pathways for (p-Cl–C$_6$H$_5$)$_2$C$^\bullet$, and these results suggest that there is a kinetic barrier for OH$^*$ transfer that is outcompeted by one or more of the 2° carbon radical decomposition pathways.

**Scheme 3. Reactions of 1OTf with Tertiary and Secondary Carbon Radicals**

![Scheme 3: Reactions of 1OTf with Tertiary and Secondary Carbon Radicals](image-url)
π**yz** is 10.9 kcal mol\(^{-1}\) higher lying. Therefore, we focused the work on the sextet spin complexes only.

The hydrogen-bonding interactions of the pendant amine groups hold the hydroxo ligand in a tight orientation. The Fe–O distance is relatively long at 1.949 Å for both \(^6\text{I}_{\text{Cl}}\) and \(^6\text{I}_{\text{Br}}\), while the axial ligand distance (Fe–N\(_{\text{ax}}\)) is 2.248/2.252 Å for \(^6\text{I}_{\text{Cl}}/\ ^6\text{I}_{\text{Br}}\). Nevertheless, our calculated values of \(^6\text{I}_{\text{Cl}}/\ ^6\text{I}_{\text{Br}}\) match the crystal structure coordinates and DFT-optimized structures of ref53 well. Most likely, the origin of the long Fe–O distances comes from the hydrogen-bonding interactions in the model as calculations for analogous nonheme iron(III)–hydroxo complexes without these interactions present

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**Figure 2.** UB3LYP/BS1-optimized geometries of the isolated reactants \(^6\text{I}_{\text{Cl}}/\ ^6\text{I}_{\text{Br}}\) as obtained in Gaussian with bond lengths given in Å. Relevant molecular valence orbitals are shown on the right.

**Figure 3.** Potential energy landscape for halogen versus hydroxyl transfer in complexes \(^6\text{I}_{\text{Cl}}/\ ^6\text{I}_{\text{Br}}/\ ^6\text{I}_{\text{F}}\) as obtained at UB3LYP/BS2//UB3LYP/BS1 level of theory with the solvent and zero-point corrections included. Energies relative to the reactant complexes are in kcal mol\(^{-1}\), while transition-state structures give bond lengths in Å, angles in degrees, and the imaginary frequency in cm\(^{-1}\).
much shorter Fe–O distances are found.\textsuperscript{75,76} Indeed, experimental measurements put Fe–OH distances of biomimetic models in the range between 1.8 and 2.0 Å.\textsuperscript{77–79} The Fe–Cl/Fe–Br distances are 2.463/2.615 Å, respectively, and compare well to the experimentally determined crystal structure coordinates of 2.3945/2.5835 Å.\textsuperscript{83} Overall, the structure observations that only one \(1_{\text{Cl}}\) is observed.

Subsequently, we created a reactant complex containing \(6_{\text{X}}\) (\(\text{X} = \text{Cl}, \text{Br}, \text{F}\)) with 2(p-Cl-C\(_6\)H\(_4\))C\(_3\)Cl, i.e., \(6_{\text{Cl}}\), and ran a geometry optimization. Transition states were located for halogen transfer (\(5_{\text{TS}_{\text{Cl/Cl}}}\)) and hydroxyl transfer (\(5_{\text{TS}_{\text{OH/Cl}}}\)), leading to the iron(II) complexes with either bound \(\text{p-Cl-C}_{6}\text{H}_{4}\)C\(_3\)Cl (\(6_{\text{Pr}_{\text{Cl/Cl}}}\)) or \(\text{p-Cl-C}_{6}\text{H}_{4}\)C\(_3\)O\(_2\)H (\(6_{\text{Pr}_{\text{OH/Cl}}}\)). Generally, nonheme iron halogenases and model complexes typically give an iron(III)–hydroxide intermediate in a high-spin state coupled to a substrate radical with down-spin. In particular, we considered an overall spin multiplicity of quintet state coupled to a substrate radical with down-spin. As such, this intermediate has the metal-type unpaired electrons as up-spin while the radical on the substrate is down-spin. The quintet spin configuration as isolated reactants, although the Fe–OH distance drops by 0.014 and 0.019 Å between isolated reactants and \(6_{\text{Re}_{\text{Cl}}}, 6_{\text{Re}_{\text{Br}}}\) (Supporting Information, Figure S2), respectively. At the same time, Fe–Cl and Fe–Br distances elongate in the reactant complexes to values of 2.561 and 2.719 Å.

The lowest energy group transfer barrier for the reaction of \(6_{\text{Re}_{\text{Cl}}}\) with \((\text{p-Cl-C}_{6}\text{H}_{4})\text{C}_3\)Cl as a substrate is via \(5_{\text{TS}_{\text{OH/Cl}}}\), whereas for \(6_{\text{Re}_{\text{Br}}}\) and \(6_{\text{Re}_{\text{F}}}\) the halogen-transfer barrier is lower. In particular, for \(6_{\text{Re}_{\text{Br}}}\) the two transition states are close in energy with the OH transfer at 23.2 kcal mol\(^{-1}\) above \(6_{\text{Re}_{\text{Cl}}}\) while the chlorine transfer barrier is 24.6 kcal mol\(^{-1}\) above \(6_{\text{Re}_{\text{Cl}}}\). The order of transition states is reversed for \(6_{\text{Re}_{\text{Br}}}, 6_{\text{Re}_{\text{F}}}\) with the lowest one leading to halogen transfer via a barrier \(5_{\text{TS}_{\text{Br/Cl}}}\) of 13.2 kcal mol\(^{-1}\) above \(6_{\text{Re}_{\text{Cl}}}\), while the fluoride transfer barrier is 3.0 kcal mol\(^{-1}\) above \(6_{\text{Re}_{\text{Cl}}}\). By contrast, the OH rebound barriers for these processes are 23.6 and 14.9 kcal mol\(^{-1}\) above the \(6_{\text{Re}_{\text{Br}}}, 6_{\text{Re}_{\text{F}}}\) complexes, respectively. The OH rebound barriers for the reactions of \(6_{\text{Cl}}\) and \(6_{\text{Br}}\) with \((\text{p-Cl-C}_{6}\text{H}_{4})\text{C}_3\)Cl are very similar and an equatorial Cl or Br ligand does not seem to affect the transition-state structure and energetics dramatically.

The transition states for the hydroxylation reactions with \(6_{\text{Cl}}\) and \(6_{\text{Br}}\) have similar electronic configurations and exhibit a large amount of charge transfer from the substrate to oxidant: \(\rho_{\text{sub}} = \rho_{\text{sub}} = -0.27\) in \(5_{\text{TS}_{\text{OH/Cl}}}\) and \(\rho_{\text{sub}} = -0.25\) in \(5_{\text{TS}_{\text{OH/Br}}}\). Much less charge transfer is observed for \(5_{\text{TS}_{\text{Cl/Br}}}\) (\(\rho_{\text{sub}} = -0.40\)), consistent with an earlier transition state on the potential energy surface. The halogen-transfer barriers are significantly lower in energy for 1Cl/1Br than for 1Cl. This trend is seen among a series of S\(_x\)2 reactions for a halide with methanol.\textsuperscript{80} The halogen-transfer barriers are electronically different from the hydroxylation barriers, with a \(\rho_{\text{sub}} = -0.27\) or \(-0.35\) for \(5_{\text{TS}_{\text{Cl/OH}}}\) and \(5_{\text{TS}_{\text{Br/OH}}}\). Generally, transition states with more charge transfer are lower in energy in agreement with what is seen here.\textsuperscript{66}

After the transition states, the systems relax to a product complex of alcohol with the iron(II) complex or the halogenated substrate with iron(II). The halogen-transfer product complexes for \(1_{\text{Cl}}\) and \(1_{\text{Br}}\), however, are higher in energy than the reactant complexes by 5.5 kcal mol\(^{-1}\) (Cl) and 6.0 kcal mol\(^{-1}\) (Br) and consequently have relatively small reverse barriers to return the systems back to the reactant complexes. These calculations are consistent with the reactant \(5_{\text{Re}_{\text{X}}}\) and halide-substituted products \(5_{\text{Pr}_{\text{X}}}\) for \(\text{X} = \text{Cl}/\text{Br}\) being in equilibrium during their lifetime in the solvent cages. The hydroxylation reaction, by contrast, is highly exothermic by \(\sim20\) kcal mol\(^{-1}\) and leads to reverse barriers from products back to reactants of well over 40 kcal mol\(^{-1}\). The latter high-energy barriers are inaccessible at room temperature, making the hydroxylation an irreversible process, while the halogen-transfer step is in equilibrium. Unfortunately, it is not possible to measure experimental kinetics profiles for this system due to the lack of suitable UV–vis absorption bands.

Interestingly, the pathway for fluorine transfer from \(5_{\text{Re}_{\text{F}}}\) has a small barrier and is strongly exothermic by almost 20 kcal
Scheme 4. Halogenated and Hydroxylated Product Complexes Showing Feasible Reverse Reactions for Br Transfer and Not for OH Transfer

Scheme 5. Reactions of 2Cl with Tertiary and Secondary Carbon Radicals
from the equatorial (TS_{Cl2,2Cl}) and distal (TS_{Cl3,2Cl}) positions in ^5Re_{2Cl} were located (Figure 4). Transfer of the equatorial Cl ligand via ^5TS_{Cl2,2Cl} has a small barrier of 7.4 kcal mol\(^{-1}\), while the distal Cl ligand transfer barrier via ^5TS_{Cl3,2Cl} is much higher in energy, i.e., at 17.6 kcal mol\(^{-1}\) for the isomerization was calculated for the enzyme.\(^{12}\) For biomimetic models without second-coordination sphere perturbations, barriers of around 12 kcal mol\(^{-1}\) were obtained for the isomerization of changing positions of a hydroxo and halide group to an iron(III) system.\(^{80}\) An isomer of [Fe^{III}(BNPA^{Fe2})(Cl)(OH)], in which the OH and Cl groups have been exchanged in the distal and equatorial positions, ([Fe^{III}(BNPA^{Fe2})(Cl)(OH)], \(2_{OH}\)) was examined computationally. A reactant complex (^5Re_{2OH}) with (p-Cl\(\cdot\cdot\cdot\)C\(_6\)H\(_4\))\(^3\)C\(^•\) was calculated, as well as the chlorine and hydroxyl-transfer transition states (^5Pr_{Cl,2OH} and ^5Pr_{OH,2OH}). In addition, we calculated an isomerization pathway to convert ^5Re_{1Cl} into ^5Re_{2OH} through a constraint geometry scan that fixes the Cl–Fe–N\(_{ax}\) angle and calculates the energies of all structures. The geometry scan for the conversion of ^5Re_{1Cl} into ^5Re_{2OH} through rotation of their halide and hydroxyl groups prior to the reaction with (p-Cl\(\cdot\cdot\cdot\)C\(_6\)H\(_4\))\(^3\)C\(^•\) is shown in Figure 5. The geometry scan shows that the isomerization from ^6_{1Cl} to form ^6_{2OH} costs a considerable amount of energy, i.e., at least 20 kcal mol\(^{-1}\). No change in electronic configuration happens during the scan, but minor steric interactions are seen that affect the energetics.

Figure 4. Optimized geometries of TS\(_{Cl2,2Cl}\) and TS\(_{Cl3,2Cl}\) as obtained in Gaussian. Energies (\(\Delta E + ZPE\)) are relative to the reactant complexes in kcal mol\(^{-1}\), while transition-state structures give bond lengths in Å, angles in degrees, and the imaginary frequency in cm\(^{-1}\).

Figure 5. Potential energy landscape for halogen versus hydroxyl transfer after isomerization of complex 1\(_{Cl}\) into 2\(_{OH}\) as obtained at UB3LYP/BS2//UB3LYP/BS1 level of theory with the solvent and zero-point corrections included. Energies are in kcal mol\(^{-1}\), while structures give bond lengths in Å, angles in degrees, and the imaginary frequency in cm\(^{-1}\). The constraint geometry scan for isomerization from 1\(_{Cl}\) to 2\(_{OH}\) is shown in the inset.
The isomerization is competitive with halogen and hydroxyl transfer in $^5$Re$_{1Cl}$ as $^5$TS$_{1Cl,1Cl}$ and $^5$TS$_{2OH,1Cl}$ are of similar energy (see Figure 3). Note that $^5$Re$_{2OH}$ is less stable than $^5$Re$_{1Cl}$ by 7.8 kcal mol$^{-1}$. The iron(III)–hydroxo(chloride) isomer $^2$OH has favorable OH rebound by 8 kcal mol$^{-1}$ over chlorine transfer, and consequently, hydroxyl rebound in $^5$Re$_{2OH}$ will give dominant hydroxylation products. The OH rebound barrier from $^5$Re$_{2OH}$ is 11.9 kcal mol$^{-1}$, while chlorine transfer has a barrier of 19.8 kcal mol$^{-1}$ above $^5$Re$_{2OH}$, indicating that both $^1$Cl and $^2$OH should give preferential OH rebound over halogenation and dominant (p-Cl–C$_6$H$_4$)COH products. Isomerization therefore does not change the chemoselectivity of the reaction for this biomimetic model complex.

Optimized geometries of $^5$TS$_{1OH}$ and $^5$TS$_{2OH}$ transition states are shown in Figure 5. The halogen-transfer transition state has a very small imaginary frequency of i52 cm$^{-1}$ for the C–Cl–Fe stretch vibration and is productlike with a long Fe–Cl bond of 3.256 Å and short C–Cl distance of 2.230 Å. The substrate approach angle is considerably bent, namely, the Fe–Cl–C angle is 125°. On the other hand, the $^5$TS$_{2OH}$ structure is more reactant-like with a short Fe–O distance of 2.041 Å and a relatively long C–O interaction of 2.300 Å. The substrate approach is much closer to linearity for $^5$TS$_{2OH}$ than for $^5$TS$_{1OH}$ with an Fe–O–C angle of 155°. Taken together, the results from the computational study on the $^2$OH isomer indicate that if the conversion to this isomer were occurring for $^1$Cl, it would not influence the final product selectivity of the reactions with the 3° carbon radicals. Thus, a mechanism involving isomerization in solution for $^1$Cl cannot be ruled out, although there is no evidence to suggest that such a mechanism plays an important role here. It is also interesting to note that the OH rebound barrier is lowered from 23.2 to 11.9 kcal mol$^{-1}$ between model $^1$Cl and $^2$OH, while the corresponding Cl-transfer barriers are similar for the two complexes. These computational results imply that H-bonding has a much stronger influence on OH$^+$ transfer than Cl$^+$ transfer, which does correlate nicely with the stronger H-bond accepting ability of OH$^+$ versus Cl$^+$.

Second-coordination sphere effects on the relative energies of OH versus Cl rebound were examined with a set of calculations on models of $^5$Re$_{1Cl}$ in which the second-coordination sphere substituents were systematically modified. The neopentyl substituents of the amine groups were replaced with a hydrogen atom to give the “no sterics” model (model NS). The amine groups were replaced by CH$_2$ groups to give the “no H-bonds” model (model NH). The combined effects of removing the steric and hydrogen-bonding interactions were examined in a minimal model in which only hydrogen atoms were included on the periphery of pyridine rings, giving the “neither” model (model NE). The reactants, products, and transition states for OH and Cl-transfer were reoptimized for these modified models. The barrier heights with respect to the truncated reactants complexes are shown in Figure 6, while individual structures are given in Figure S3.

As described above, the full model has the OH rebound barrier as a highly exothermic OH transfer, while the Cl transfer is endothermic and inaccessible. This is the same for the product complexes with sterics and/or H-bonding removed. In addition, removal of the neopentyl substituents to the amine groups lowers both OH rebound and Cl-transfer barriers dramatically and makes $^5$TS$_{1Cl}$ the lowest in energy by 4.2 kcal mol$^{-1}$. A similar observation is found for removal of the hydrogen-bonding interactions from the ligand scaffold, and $^5$TS$_{1Cl}$ becomes the lowest transition state by 6.9 kcal mol$^{-1}$. Finally, the removal of all second-coordination sphere perturbations makes the OH rebound barrier the lowest in energy by 2.8 kcal mol$^{-1}$. As such, the halogen-transfer barrier of the three truncated models are close in energy, while a major shift in the barrier is seen for the OH rebound barriers. These calculations show that second-coordination sphere perturbations affect the bifurcation pathways dramatically, leading to hydroxylation or halogenation. Thus, the minimal cluster model with all second-coordination sphere perturbations removed will follow the Bell–Evans–Polanyi principle and give a low barrier and large exothermicity for hydroxyl transfer and a much higher barrier and lesser exothermicity for halogen transfer. The calculations in Figure 6 also show that the Bell–Evans–Polanyi principle can be overruled by second-coordination sphere effects such as hydrogen-bonding interactions to the hydroxo group or steric interactions restricting the substrate approach. This is in line with
calculations reported on nonheme iron halogenase enzymes that reported strong second-coordination sphere effects on the bifurcation pathways of halogenation versus hydroxylation.\textsuperscript{32,35,36,40} Interestingly, the combined perturbations do not favor halogenation but still give hydroxylation, although by a smaller amount than with steric and H-bonding perturbations removed. Clearly, the effect of sterics and hydrogen-bonding interactions restricts and affects the halogen transfer as well. Furthermore, it appears that the combined effect of sterics and H-bonding removal almost linearly affects the hydroxyl transfer, but not the halogen transfer. This is most likely as a result of the fact that we did full geometry optimizations with these perturbations removed. As a consequence, the changes in geometry lead to differences in oxidant–substrate interactions that strongly affect the halogen-transfer pathway.

On the far left and far right-hand side of Figure 6 are given overlays of the OH and Cl-transfer transition states for the reaction of (p-Cl–C\textsubscript{6}H\textsubscript{4})\textsubscript{3}C\textsuperscript{+} with 1\textsubscript{Cl} and truncated models, while Figure S3 gives the individual structures. The four OH rebound barriers are geometrically very similar, and an overlay puts the substrate in approximately the same position in the four transition states. The effect of second-coordination sphere effects on the OH rebound is as expected and leads to a small barrier for the fully truncated model, an increase in the barrier with either the hydrogen bonding or steric perturbations added and a further increase of the barriers with both effects included.

Although the halogen atom that is in the equatorial plane is not directly in contact with the hydrogen-bond donors and steric groups, actually the approach on the halide by a large and bulky substrate such as (p-Cl–C\textsubscript{6}H\textsubscript{4})\textsubscript{3}C\textsuperscript{+} is influenced by the removal of steric and hydrogen-bonding perturbations. Indeed, the position of the substrate in the overlay of the four transition-state structures for chlorine transfer shows the halide and substrate in very different positions in the four transition states. As such, the halide transfer is influenced by these perturbations. Removal of one of the perturbations, therefore, has a much more dramatic effect on the barrier height of Cl transfer than OH transfer. The results displayed in Figure 6 show that the second-coordination sphere has a major effect on the halogenation versus hydroxylation selectivity and, partic-
ularly, the use of a bulky substrate like (p-Cl-C\textsubscript{6}H\textsubscript{4})\textsubscript{3}C\textsuperscript{*} may struggle to optimally reach the halide and form a chemical bond. This is also seen in the dichloro compound 2\textsubscript{Cl}, where the equatorial Cl group is easier to transfer than the distal Cl group by 10.2 kcal mol\textsuperscript{-1} due to lesser steric interactions for equatorial rather than distal approach.

Halogen transfer for Cl/Br appears to be an endothermic, reversible process with the tertiary carbon radical substrates even in the systems with steric and H-bonding interactions removed. These results are consistent with the relatively weak C–X bonds formed in the halogenated products. Moreover, the experimental data shows only hydroxylation products for the 3\textsubscript{°} carbon radical substrates. As the removal of steric and H-bonding interactions from the second-coordination sphere does not lead to halogen transfer, we hypothesized that calculations on 2\textsuperscript{°} carbon radicals may reveal an exothermic process that favored halogen transfer.

Reactions with the 2\textsuperscript{°} carbon radicals diphenylmethyl (C\textsubscript{6}H\textsubscript{5})\textsubscript{2}CH\textsuperscript{*} and phenylmethylmethyl (C\textsubscript{6}H\textsubscript{5})\textsubscript{2}CH\textsuperscript{*} were examined by DFT calculations. The potential energy landscapes for the reactions of \textsuperscript{1}Cl\textsubscript{a} and \textsuperscript{1}Br\textsubscript{a} with these two substrates are shown in Figure 7. Both substrates react with substantially lower halogen- and hydroxyl-transfer barriers as compared to the 3\textsuperscript{°} carbon radical (p-Cl-C\textsubscript{6}H\textsubscript{4})\textsubscript{3}C\textsuperscript{*}, and halogen-transfer barriers are lower in energy than the hydroxyl-transfer reactions. For the diphenylmethyl radical reaction the energy of \textsuperscript{4}TS\textsubscript{Cl,CLPP} is 5.1 kcal mol\textsuperscript{-1} above \textsuperscript{4}Re\textsubscript{CLPP} while the \textsuperscript{4}TS\textsubscript{OH,CLPP} barrier is at 8.1 kcal mol\textsuperscript{-1}. A similar pattern for this substrate with \textsuperscript{4}1Br is seen with barriers for \textsuperscript{4}TS\textsubscript{Br,CLPP} and \textsuperscript{4}TS\textsubscript{OH,CLPP} of 4.4 and 12.5 kcal mol\textsuperscript{-1}, respectively. The same ordering and trends are seen for (C\textsubscript{6}H\textsubscript{5})\textsubscript{2}CH\textsuperscript{*} as a substrate (Figure 7b). These barriers are sufficiently low that they will not compete with the isomerization pathway through flipping of the positions of the hydroxyl and halide groups. Moreover, the results predict chemoselective halogen transfer over hydroxyl transfer for the cis-Fe\textsuperscript{III}(OH)(X) complexes and the 2\textsuperscript{°} carbon radical substrates. They also predict exothermic processes for halogen transfer as anticipated, making the reverse reactions unlikely in these cases. Taken together, the calculations are in good agreement with the experimental results in Figure 1, and indicate that biomimetic cis-Fe\textsuperscript{III}(OH)(X) complexes are able to exhibit halogenase-like activity with appropriate carbon radical substrates.

To rationalize the bifurcation pathways and energies and gain insight into the intrinsic properties of the oxidant and substrate that determine the selectivity, we created a valence bond (VB) diagram for C–Cl versus C–OH bond-formation reaction channels, as described in Figure 8. We have used these VB diagrams in a number of cases previously to predict a series of hydrogen atom abstraction and double-bond epoxidation reactions as well as for the bifurcation pathways of desaturation versus hydroxylation and group transfer reactions.\textsuperscript{96–98} Thus, we analyze all molecular orbitals in the reactant and product complexes and determine which orbitals break or form during each reaction pathway. The energies of the breaking and forming of the orbitals that determine the height of the barrier for the reaction are estimated. In the OH transfer reaction, the Fe–O bond is along the molecular z-axis and is based on the three-electron bond resulting from two electrons in the \(\pi_{xz}\) orbital and a single electron in \(\pi_{yz}\). However, when these orbitals break during the OH transfer reaction, one of the electrons pairs up with the incoming radical to form the C–O bond (the \(\sigma_{xy}\) orbital), the second one becomes the 3\textsubscript{d}\textsubscript{z} orbital on iron with one electron, and the third electron is promoted into the \(\pi_{yz}\) orbital. Based on the orbital energies in the reactant structures, we estimated the energy to break the \(\pi_{xz}/\pi_{yz}\) pair of orbitals into atomic orbitals \((E_{\pi_{xz}/\pi_{yz}})\) from the energy gap between the \(\pi_{xz}\) and \(\pi_{yz}\) orbitals. We estimated the \(\pi_{yz} \rightarrow \pi_{yz}^{\ast}\) excitation energy \((E_{\text{exc},\pi_{yz} \rightarrow \pi_{yz}^{\ast}})\) from their orbital energy differences in the reactant complexes. In addition, the OH rebound barrier depends on the bond dissociation energy of the C–O bond (BDE\textsubscript{CO}) that is formed and the driving force for the reaction. The driving force was determined from the difference in energy of the Fe–Cl and C–Cl bonds (halogen transfer) or the difference in energy of the Fe–OH and C–OH bonds (OH transfer) in the reactant and product complexes. As iron complexes sometimes undergo drastic geometric changes when a ligand is removed, we calculated diabatic bond energies for breaking of the Fe–Cl and Fe–OH bonds in \textsuperscript{4}Re\textsubscript{CL} by doing single-point calculations on each of the individual fragments. The bond dissociation energies (BDE) for the C–O bond in the alcohol complex and the C–Cl bond in the halogenated products were determined from a DFT calculation on the isolated products and the optimized geometries of the product with Cl/OH removed. Subsequently, we used the procedure from ref 81 to estimate the OH rebound barriers and summarized in eq 1, whereby the driving force for the reaction is given as \(\Delta E_p\) and the resonance energy \(B\) taken is one-half of the weakest bond that is broken or formed.

\[
\Delta E_{\text{OH,VB}}^p = \frac{1}{4} \left( E_{\pi_{xz}/\pi_{yz}} + E_{\text{exc},\pi_{xz} \rightarrow \pi_{yz}} + \text{BDE}_{\text{CO}} \right) + \frac{3}{4} \Delta E_p - B \tag{1}
\]

In a similar way to the OH rebound barriers, we also estimated the Cl-transfer barriers using our VB approach, see eq 2. As the Fe–Cl bond in the reactant complex is in the equatorial plane, the bond cleavage is not dependent on the \(\pi_{xz}/\pi_{yz}\) pair of orbitals but on the three-electron bond in the equatorial plane with occupation \(\sigma_{a2}^{\ast} \sigma_{a2}^{\ast} \sigma_{a2}^{\ast} \). We determined the energy gap \((E_{\sigma_{a2}^{\ast}/\sigma_{a2}^{\ast} \sigma_{a2}^{\ast}})\) from the orbital energy differences in the reactant complex as well as the excitation energy from \(\sigma_{a2}^{\ast} \) to \(\pi_{yz}^{\ast}\).

\[
\Delta E_{\text{Cl,VB}}^p = \frac{1}{4} \left( E_{\sigma_{a2}^{\ast}/\sigma_{a2}^{\ast} \sigma_{a2}^{\ast}} + E_{\text{exc},\sigma_{a2}^{\ast} \rightarrow \pi_{yz}^{\ast}} + \text{BDE}_{\text{CCL}} \right) + \frac{3}{4} \Delta E_p - B \tag{2}
\]
Based on these electronic values in the reactant and product complexes, we estimated the Cl ad OH transfer barriers with our VB approach and found values of $\Delta E_{\text{Cl}^{+},\text{C}^{+}} = 25.4$ kcal mol$^{-1}$ and $\Delta E_{\text{OH}^{+},\text{C}^{+}} = 23.5$ kcal mol$^{-1}$. These values are in excellent agreement with the DFT calculated barriers in Figure 3 for the same processes. Thus, even though a much stronger C–O bond is formed in the (p-Cl–C$_6$H$_5$)$_2$COH product complex than in the (p-Cl–C$_6$H$_5$)$_2$CCl complex, i.e., $\text{BDE}_{\text{COH}}$ = 59.2 kcal mol$^{-1}$ and $\text{BDE}_{\text{CCI}}$ = 46.2 kcal mol$^{-1}$, this advantage is canceled out by a similar difference of Fe=O versus Fe=Cl bond strengths. The homolytic bond energies of the C–O and C–Cl bonds in the possible product complexes are summarized in Table 1. Furthermore, our diabatic bond energies for the $\text{Re}^{\text{II}}$ complex are BDE$_{\text{FeCO}}$ = 75.0 kcal mol$^{-1}$ and BDE$_{\text{FeCl}}$ = 63.8 kcal mol$^{-1}$. These bond strengths follow the same ordering as those of an $\{\text{Fe}^{\text{III}}(\text{OH})(\text{Cl})\}(\text{TPA})$ complex with TPA = tris(2-pyridylmethyl)amine, although the diabatic bond strengths were much weaker. Therefore, the hydrogen bonding and steric interactions strengthen the Fe–OH bond in 1CI by about 10 kcal mol$^{-1}$. Moreover, the three-electron bond for the interaction of the $\sigma_{2z}$ and $\sigma^*$-$yz$ orbitals appears weaker than the $\pi_{yz}/\pi^*_{yz}$ interaction, and we find the $\alpha$-orbitals separated by 88.8 and 99.2 kcal mol$^{-1}$. Therefore, a weak halogen ligand in the equatorial plane affects the orbitals in the xy-plane.

Subsequently, we took the reactant complexes of truncated models with the (p-Cl–C$_6$H$_5$)$_2$C substrate without H-bonding ($\text{Re}^{\text{II}}$C$_6$H$_5$), with steric removed ($\text{Re}^{\text{II}}$C$_6$H$_5$) and with both sterics and hydrogen bonding removed ($\text{Re}^{\text{II}}$C$_6$H$_5$) and repeated the VB analysis. The analysis shows that little $\sigma_{2z}$-$y$ and $\sigma^*_{2z}$-$y$ orbitals appear weaker than the $\pi_{yz}/\pi^*_{yz}$ interaction, and we find the $\alpha$-orbitals separated by 88.8 and 99.2 kcal mol$^{-1}$. Therefore, a weak halogen ligand in the equatorial plane affects the orbitals in the xy-plane.

Next, using the VB models, we predicted barriers for OH and CI transfer from 1CI to (C$_6$H$_5$)$_2$CH$^*$ and (C$_6$H$_5$)$_2$(CH)$_2$–CH$^*$ radicals. As shown in Table 1, these substrates in a reaction with chlorine lead to stronger C–Cl bonds of 55.4 and 63.7 kcal mol$^{-1}$, respectively. As a result of that, the driving force for CI transfer is lowered and the VB predicted barriers are much lower than with (p-Cl–C$_6$H$_5$)$_2$C$^+$ as a substrate, namely, $\Delta E_{\text{ClVB}} = 16.3$ kcal mol$^{-1}$ for the reaction of 1CI with (C$_6$H$_5$)$_2$CH$^*$ and $\Delta E_{\text{ClVB}} = 7.9$ kcal mol$^{-1}$ for the reaction of 1CI with (C$_6$H$_5$)$_2$(CH)$_2$–CH$^*$. By contrast, the VB predicted corresponding OH rebound barriers for these complexes are 15.1 and 9.4 kcal mol$^{-1}$, respectively. These calculations indeed show that halogen transfer becomes competitive with OH rebound for secondary radicals as the difference in energy between the C–Cl and C–OH bonds is smaller and hence the driving force becomes exothermic. In particular, the VB model as well as the DFT calculations predicts a phenylmethyl radical to react with 1Cl through dominant halide transfer in agreement with experimental observation.

## CONCLUSIONS

The successful synthesis and structural characterization of the nonheme iron complexes Fe$^{\text{III}}$(BNPA$_{\text{Ph}}$O)(OH)(X) (X = Cl, Br) seemed to provide an ideal system to test the preferential reactivity of cis-Fe$^{\text{III}}$(OH)(X) species and carbon radicals, with the aim of modeling the critical rebound step in the nonheme iron halogenases. However, the initial study showed only evidence for hydroxyl transfer to tertiary carbon radicals and no evidence of halogenation. These results fueled speculation regarding what key characteristics might separate our system from the enzymes themselves. Although the lack of an enzyme pocket was an obvious difference, there were a few examples of halogenation mediated by similar nonheme iron complexes that lacked substrate binding pockets. In addition, several computational studies indicated that there was likely an inherent reactivity preference for halogenation over hydroxylation, in contradiction to the Bell–Evans–Polanyi principle, which predicts that the thermodynamically favored hydroxylation process should be kinetically preferred as well. The computational analysis reported in the current study provides a satisfying explanation for the observed reactivity of the tertiary carbon radicals. It predicts a nonproductive equilibrium for the halogenation (X = Cl, Br but not F) pathway, which drives the outcome of the reaction toward the more thermodynamically stable, hydroxylated product. We were pleased to find that this prediction was experimentally verified by showing that back electron transfer occurs between Fe$^{\text{III}}$(BNPA$_{\text{Ph}}$O)(OH) and the alkyl halide (p-Cl–C$_6$H$_5$)$_2$C–Br to give the Fe$^{\text{III}}$(OH)(Br) complex. The calculations also showed that halogenation of an appropriate, secondary carbon radical substrate should not be affected by the same nonproductive equilibrium, at least in part because of the significant stronger C–Cl bond to be formed. These calculations also nicely fit the experimental data: the secondary carbon radical (C$_6$H$_5$)(CH$_2$)–CH$^*$ reacts to give a halogenated product, showing for the first time that an isolated cis-Fe$^{\text{III}}$(OH)(X) complex can selectively transfer the cis-halogen ligand to a carbon radical partner.

The nonheme iron halogenases typically react with substrates tethered to carrier proteins, such as seen in SyrB2. This type of fixed substrate precludes the loss of inherent selectivity for halogenation that might ensue if the enzyme was to operate on different, freestanding substrates. However, a relatively new member of the halogenase family, WelO5, does halogenate a number of freestanding substrates. A recent computational study suggests that controlling the conformation of the active center is crucial for halogenation selectivity in WelO5, where a broad substrate scope is required. In contrast, the substrate in the classical halogenase SyrB2 can provide much of its own, inherent selectivity to favor halogenation. The combined experimental and computational results presented here emphasize the importance of the immediate structure of the radical carbon atom in controlling selectivity. In particular, our work highlights that it will be unlikely for nonheme iron halogenases to activate tertiary C–H bonds, and it would be interesting if this point could be
confirmed experimentally. These results also indicate that substrate structure needs to be carefully considered in the design of any future enzymatic or synthetic halogenation catalysts. The computational results predict that fluorine transfer to aliphatic C−H bonds may be favored for a wide range of carbon radical substrates; however, the iron(III)−fluorine(II) complex has eluded synthetic isolation thus far and this idea requires future testing.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c01375.

All data generated during this study are provided in the Supporting Information. Tables with calculated absolute and relative energies and group spin densities and charges of all complexes discussed in this work; Cartesian coordinates of all structures (PDF)

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**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

The NIH (R01GM119374 to D.P.G.) is gratefully acknowledged for financial support. V.Y. would like to thank JHU for the Gompf Fellowship. E.F.G. and S.P.d.V. thank the BBSRC for funding for a studentship under Grant Number BB/M011208/1. This manuscript is Open Access within the CC-BY agreement.

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**NOTE ADDED AFTER ASAP PUBLICATION**

This paper was originally published ASAP on May 10, 2022. The TOC graphic was revised, and the corrected version was reposted on May 17, 2022.