Biomimetic Oxidation

International Edition: DOI: 10.1002/anie.201509914
German Edition: DOI: 10.1002/ange.201509914

Hydroxylation versus Halogenation of Aliphatic C–H Bonds by a Dioxygen-Derived Iron–Oxygen Oxidant: Functional Mimicking of Iron Halogenases

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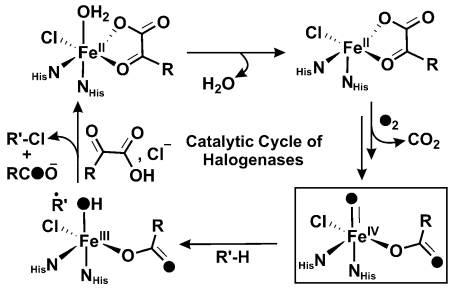
Abstract: *An iron–oxygen intermediate species generated in situ in the reductive activation of dioxygen by an iron(II)–benzilate complex of a monoanionic facial N_3 ligand, promoted the halogenation of aliphatic C–H bonds in the presence of a protic acid and a halide anion. An electrophilic iron(IV)–oxo oxidant with a coordinated halide is proposed as the active oxidant. The halogenation reaction with dioxygen and the iron complex mimics the activity of non-heme iron halogenases.*

Dioxygen-activating non-heme iron enzymes exhibit versatile reactivity, such as halogenation, hydroxylation, desaturation, cyclization, ring-expansion, epoxidation, *cis*-dihydroxylation, and oxo-transfer activity.[1–3] These reactions are essential in the synthesis of important biomolecules and in bioremediation processes. In many of these biological oxidations, high-valent iron–oxo species have been invoked as key intermediates.[4,5] For the four-electron reduction of dioxygen, reducing equivalents required are supplied by organic and/or metal cofactors. The reductants (cofactors) in the non-heme enzyme family include α-ketoglutarate,[2] tetrahydrobiopterin,[6] and ascorbic acid.[7] In α-ketoglutarate-dependent oxygenases, the iron-coordinated α-ketoglutarate cofactor provides two electrons for dioxygen reduction at the iron center, thus resulting in the generation of an active iron(IV)–oxo oxidant, carbon dioxide, and succinate.[1,2,8,9] The iron–oxo oxidant then hydroxylates the C–H bond of substrates. Direct evidence of high-valent iron–oxo intermediates have been found in the enzymatic reactions of several α-keto-acid-dependent oxygenases.[5,10,11]

The non-heme iron(II)/α-keto-acid-dependent halogenases SyrB2 and CytC3 catalyze the chlorination of threonine in syringomycin E biosynthesis and multiple chlorination of the terminal methyl group in L-aminobutyrate, respectively.[12–15] Enzymatic studies have revealed that the α-ketoglutarate-dependent hydroxylases and halogenases involve hydrogen-abstracting iron(IV)–oxo oxidants in the reaction pathway (Scheme 1).[16,17] However, substrate positioning directs the reaction toward halogenation or hydroxylation.[18] Abstraction of a hydrogen atom by a non-heme *cis*-iron(IV)–oxo–halide intermediate followed by rebound of the halide ligand results in a halogenated product through a stepwise radical pathway (Scheme 1).[5]



Scheme 1. Reaction catalyzed by non-heme iron(II)/α-ketoglutarate-dependent halogenases.

Although a number of synthetic models[19,20] of the *cis*-iron(IV)–oxo–halide species observed in non-heme halogenases have been reported, their use in C–H bond halogenation reactions remains unexplored. The involvement of iron(IV)–oxo complexes in electron-transfer reactions with halides has also been documented.[21] However, examples of structural[22,23] and functional mimics of non-heme halogenases are rare.[24–26] Although high-valent iron–oxo species have been proposed[27] to participate in the halogenation of alkanes by biomimetic iron complexes with hydrogen peroxide or alkyl hydroperoxides, there has been no study reported on the use of non-heme iron complexes to mimic the function of iron halogenases with dioxygen as the oxidant.

Dioxygen activation by non-heme iron(II) complexes in the presence of electron and proton sources has been reported to lead to the formation of different iron–oxygen intermediates.[28–33] The reactivity of iron–oxygen oxidants generated in the reductive activation of dioxygen by an iron(II)–benzilate complex, [(Tp^{Ph2})Fe^{II}(benzilate)] (**1**; Tp^{Ph2} = hydrotris(3,5-diphenyl-pyrazol-1-yl)borate), has been investigated by us (Scheme 2).[34–36] A nucleophilic iron(II)–hydroperoxo species was proposed to form in the oxidative decarboxylation of the iron(II)–benzilate complex. In the presence of a Lewis acid, the complex generates an electrophilic iron(IV)–oxo–hydroxo oxidant, which exchanges its oxygen atoms with water. The electrophilic oxidant performs a range of selective oxidation reactions, such as oxo-atom transfer to sulfides, the *cis*-dihydroxylation of alkenes, and the oxygenation of aliphatic C–H bonds.[36] Computational analyses have previously indicated that the proton-mediated heterolytic O–O bond cleavage of iron(II)–hydroperoxo species has a lower energy barrier than that of iron(III)–hydroperoxide intermediates.[37,38] In analogy to the

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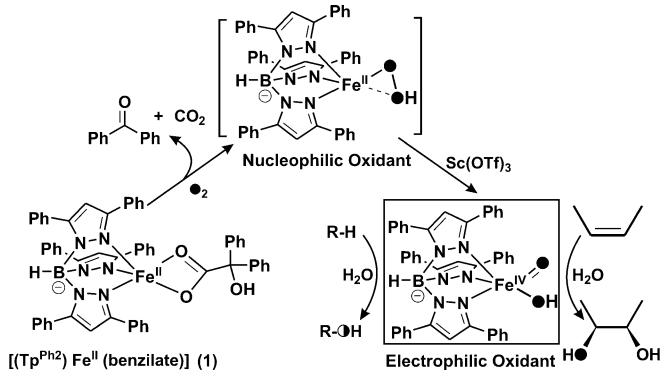
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509914.



Scheme 2. Proposed iron–oxygen oxidants formed in the reaction between complex **1** and O_2.

reactivity of the iron(II)–benzilate complex in the presence of a Lewis acid, it was expected that the nucleophilic oxidant derived from **1** would undergo heterolytic O–O bond cleavage in the presence of a protic acid to generate an electrophilic oxidant. Therefore, the main objective of the present study was to explore the reactivity of complex **1** in the presence of a protic acid and its implications for the halogenation of aliphatic C–H bonds with suitable external halide sources.

The reaction between complex **1** and O_2 in the presence of 2 equivalents of pyridinium perchlorate (or 2 equivalents of lutidinium perchlorate) yielded benzophenone quantitatively along with 90% intraligand hydroxylation in 20 min (Figure 1). The optical spectrum of the oxidized solution showed a broad absorption band at 640 nm attributable to the phenolate-to-iron(III) charge-transfer (CT) transition. The CT band, however, is shifted to lower energy as compared to

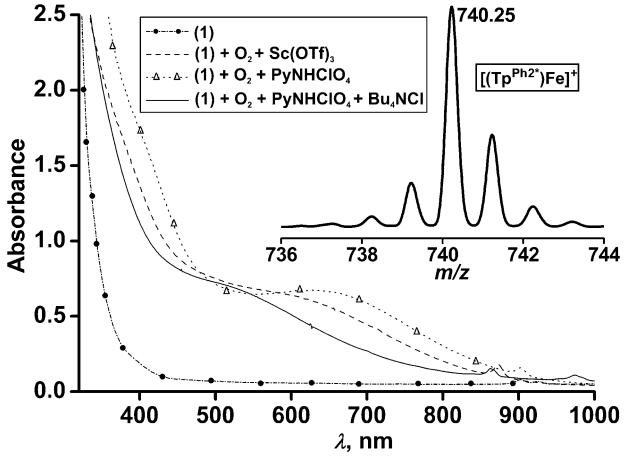


Figure 1. Optical spectra of **1** (0.5 mM in benzene) before the reaction with O_2 (dotted line with circles) and after the reaction with O_2 in the presence of $Sc(OTf)_3$ (1 equiv; dashed line),[36] in the presence of pyridinium perchlorate ($PyNHClO_4$, 2 equiv; dotted line with triangles), and in the presence of $PyNHClO_4$ (2 equiv) and tetrabutylammonium chloride (Bu_4NCl, 2 equiv; solid line). Inset: ESI mass spectrum of the final oxidized solution after the reaction of **1** in the presence of $PyNHClO_4$ (2 equiv) and Bu_4NCl (2 equiv). Tp^{Ph2*} is the modified form of Tp^{Ph2} in which one *ortho* position of one of the phenyl rings is hydroxylated.

that observed in the reaction of **1** with O_2 in the presence or absence of Lewis acids.[35,36]

To probe the nature of the iron–oxygen intermediate formed in the presence of a proton source, we carried out interception experiments with various external substrates. The reaction of complex **1** with thioanisole (1 equiv) and pyridinium perchlorate (2 equiv) afforded thioanisole oxide (36%) as the sole product (see Figure S1 in the Supporting Information), whereby 55% intraligand hydroxylation occurred. However, the amount of pyridinium perchlorate controlled the selectivity for the formation of the sulfoxide versus the sulfone. In the oxidation of thioanisole, about 2 equivalents of pyridinium perchlorate were needed to fully inhibit the formation of sulfones (see Figure S2). In the presence of 10 equivalents of thioanisole, no intraligand hydroxylation was observed, and the yield of thioanisole oxide was found to be 90% (Table 1; see also Scheme S1 in the Supporting Information). A labeling experiment with $^{16}O_2$ and $H_2{}^{18}O$ revealed 24% incorporation of the labeled oxygen atom into thioanisole oxide (Table 1). Hammett analysis with various *para*-substituted thioanisoles showed a ρ value of -1.71, thus supporting the electrophilic nature of the oxidant (Figure 2). Thus, similar to that formed in the presence of a Lewis acid,[36] the iron–oxygen oxidant formed from **1** in the presence of a protic acid has electrophilic character.

The nucleophilic iron(II)–hydroperoxide derived from **1**, whose oxygen atoms do not exchange with water, was previously found to oxidize alkenes to the corresponding *cis* diols in high yields.[35] The electrophilic iron(IV)–oxo–hydroxo oxidant, formed in the presence of a Lewis acid, also efficiently participates in the *cis*-dihydroxylation of alkenes with partial incorporation of the labeled oxygen atom from $H_2{}^{18}O$.[36] Intriguingly, when complex **1** reacted with alkenes in the presence of a protic acid (2 equiv), the oxidant thus formed oxidized alkenes to epoxides instead of *cis* diols (Table 1; see also Scheme S1). With a low concentration of the protic acid, however, a small amount of the diol was observed along with the epoxide. Approximately 2 equivalents of the protic acid (pyridinium perchlorate) were needed for complete inhibition of the *cis*-dihydroxylation of alkenes (see Figure S3). With cyclooctene as the substrate (100 equiv), cyclooctene oxide was formed to an extent of 70% (Table 1; see also Figure S4). The reaction of complex **1** with 1-octene (100 equiv) afforded 1,2-epoxyoctane in 67% yield (Table 1; see also Figure S5). Styrene (100 equiv) was converted into styrene epoxide in 75% yield along with benzaldehyde in 20% yield (Table 1; see also Figure S6). When cyclohexene (100 equiv) was used to intercept the active oxidant, the corresponding products of allylic oxidation, that is, 2-cyclohexenone (35%) and 2-cyclohexenol (22%), were formed along with a trace amount of cyclohexene oxide (5%; Table 1; see also Figure S7).

A labeling experiment for styrene oxidation with $H_2{}^{18}O$ in the presence of pyridinium perchlorate (2 equiv) confirmed about 35% incorporation of labeled oxygen into the epoxide product (Table 1; see also Figure S8). In the case of cyclohexene, a labeling experiment with $H_2{}^{18}O/{}^{16}O_2$ showed the incorporation of 18% labeled oxygen into 2-cyclohexenone, and around 26% incorporation each into 2-cyclohexenol and

Table 1: Reactivity of complex **1** toward various substrates under different conditions.[a]

Substrate	External additive(s)	Product(s)	Yield [%] (^{18}O incorporation from $H_2{}^{18}O$ [%])[b]	Intraligand hydroxylation [%]
thioanisole	$PyNHClO_4$	thioanisole oxide	90 (24)	0
	$PyNHClO_4$ + Bu_4NCl	thioanisole oxide	92	0
cyclooctene	$PyNHClO_4$	cyclooctene oxide	70	20
1-octene	$PyNHClO_4$	1,2-epoxyoctane	67	23
styrene	$PyNHClO_4$	styrene epoxide benzaldehyde	75 (35) 20 (13)	0
cyclohexene	$PyNHClO_4$	2-cyclohexenone 2-cyclohexenol cyclohexene oxide	35 (18) 22 (26) 5 (26)	26
	$PyNHClO_4$ + Bu_4NCl	2-cyclohexenone 2-cyclohexenol 3-chlorocyclohexene	29 15 22	24
adamantane	$PyNHClO_4$	1-adamantanol 2-adamantanol	47 (22) 18 (24)	25
	$PyNHClO_4$ + Bu_4NCl	1-adamantanol 1-chloroadamantane	45 12	31
cyclohexane	$PyNHClO_4$	cyclohexanol cyclohexanone	45 (20) 8 (18)	38
	$PyNHClO_4$ + Bu_4NCl	cyclohexanol cyclohexanone	51 6	33
toluene	$PyNHClO_4$	benzaldehyde benzyl alcohol	37 25	28
	$PyNHClO_4$ + Bu_4NCl	benzaldehyde benzyl alcohol benzyl chloride	26 13 20	32
1,4-cyclohexadiene	$PyNHClO_4$	benzene cyclohexa-2,5-dienol	65 20	7
	$PyNHClO_4$ + Bu_4NCl	benzene cyclohexa-2,5-dienol 3-chlorocyclohexa-1,4-diene	38 18 27	7
2,4,6-trimethylbenzoic acid	$PyNHClO_4$ + Bu_4NCl	2-(chloromethyl)-4,6-dimethylbenzoic acid 5,7-dimethylisobenzo-furan-1(3*H*)-one	15 12	60

[a] Experimental conditions: Complex **1** (0.02 mmol), substrate (10–100 equiv), $PyNHClO_4$ (2 equiv), Bu_4NCl (2 equiv). [b] $H_2{}^{18}O$ (60 equiv with respect to complex **1**) was used for labeling experiments.

cyclohexene oxide (Table 1; see also Figure S9). In interception experiments with alkenes, intraligand hydroxylation to an extent of 20–25% was estimated (Table 1). However, no ligand hydroxylation took place when styrene was used as a substrate (Table 1). With a protic acid, therefore, a different oxidant is generated and carries out olefin epoxidation instead of *cis*-dihydroxylation. This switching behavior bears resemblance to the "chameleonic reactivity" of non-heme iron catalysts reported by Que and co-workers.[39] Moreover, epoxidation reactions have also been reported with high-valent iron–oxo intermediates generated in situ from model complexes of α-keto-acid-dependent oxygenases.[40]

The electrophilic oxidant generated with pyridinium perchlorate oxygenated adamantane (50 equiv) to afford 1-adamantanol (47%) and 2-adamantanol (18%; Table 1; see also Scheme S1 and Figure S10). In the reaction, ring hydroxylation of the Tp^{Ph2} ligand occurred to an extent of 25% (Table 1). Cyclohexane was oxidized to cyclohexanol

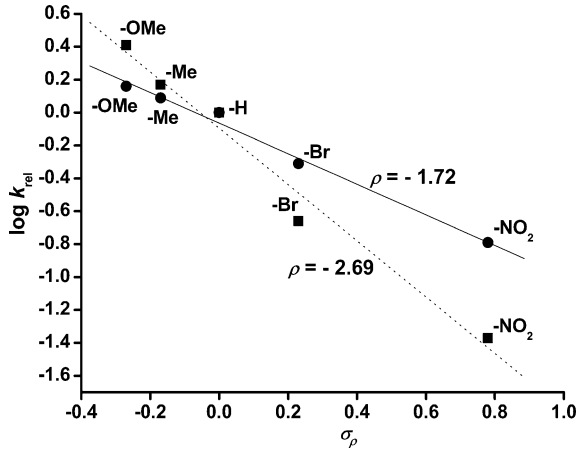
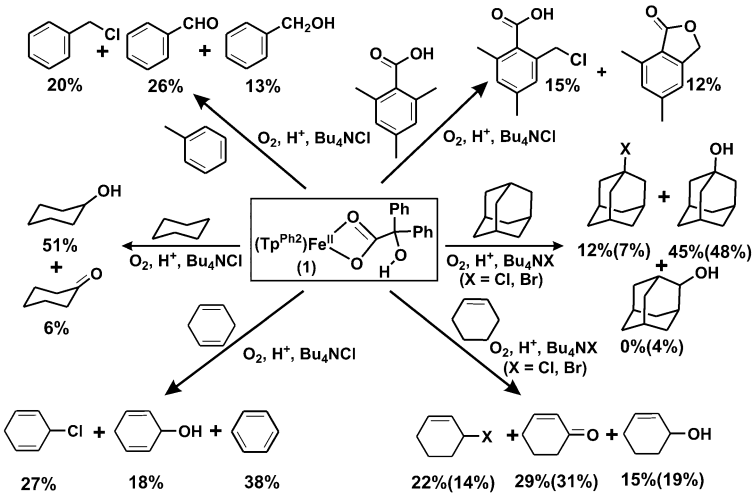


Figure 2. Hammett plots of $\log k_{rel}$ versus σ_p for *p*-X-C_6H_4SMe for the reaction of **1** with $PyNHClO_4$ (2 equiv; straight line) and with $PyNHClO_4$ (2 equiv) and Bu_4NCl (2 equiv; dotted line). The k_{rel} values represent the ratio of the concentration of the product from *para*-substituted thioanisole and the concentration of the product from thioanisole.

The reactivity toward different alkanes and alkenes of the oxidant generated in the presence of halide ions was tested. Interestingly, aliphatic C–H bond halogenation was observed as well as C–H bond hydroxylation (Table 1 and Scheme 3). For substrates such as adamantane, cyclohexene, and toluene, around 25–32% intramolecular ligand hydroxylation took place (Table 1). The reaction of **1** with adamantane (50 equiv), pyridinium perchlorate (2 equiv), and Bu_4NCl (2 equiv) gave 1-chloroadamantane (12%; see Figure S13a) and 1-adamantanol (45%). With toluene (50 equiv), benzyl chloride (20%) was formed (see Figure S13b) along with benzaldehyde and benzyl alcohol. The reaction of cyclohexene (100 equiv) led to 3-chlorocyclohexene (22%; see Figure S13c) along with 2-cyclohexenol and 2-cyclohexenone. When 1,4-cyclohexadiene (100 equiv) was used as a substrate, the corresponding unsaturated chlorinated product (see Figure S13d) was formed along with cyclohexa-2,5-dienol and benzene. The reaction of cyclohexane, which has strong C–H bonds, afforded a mixture of cyclohexanol (51%) and cyclohexanone (6%) without any halogenated product. 2,4,6-Trimethybenzoic acid, which contains both aliphatic (benzylic) and aromatic C–H bonds, was used as a substrate to ensure that the putative iron–oxo–halo oxidant selectively halogenates the aliphatic C–H bonds over aromatic C–H bonds. In the reaction with **1**, 2,4,6-trimethylbenzoic acid formed only the product of halogenation of one of the benzylic C–H bonds (15%; Scheme 3 and Table 1; see also Figure S14). In that case, no aromatic C–H bond halogenation was observed. The steric bulk of the substrate prevents it from coming closer to the oxidant, and thus the oxidant preferentially participates in intraligand hydroxylation (Table 1). Notably, in all cases, the yield of halogenated products was the same if pyridinium chloride was used instead of a mixture of pyridinium perchlorate and tetrabutylammonium chloride.

(45%) and cyclohexanone (8%; Table 1; see also Figure S11). The reaction of complex **1** with toluene (50 equiv) yielded a mixture of benzaldehyde (37%) and benzyl alcohol (25%; Table 1; see also Figure S12). For cyclohexane oxidation, the labeling experiment revealed (20 ± 2)% incorporation of the labeled oxygen atom from $H_2{}^{18}O$ into both cylohexanol and cyclohexanone (Table 1). In the reaction with adamantane, about (22 ± 2)% incorporation of the labeled oxygen atom into the oxygenated products took place (Table 1; see also Scheme S1). The data from labeling experiments clearly indicate that the oxidant can exchange its oxygen atoms with water.

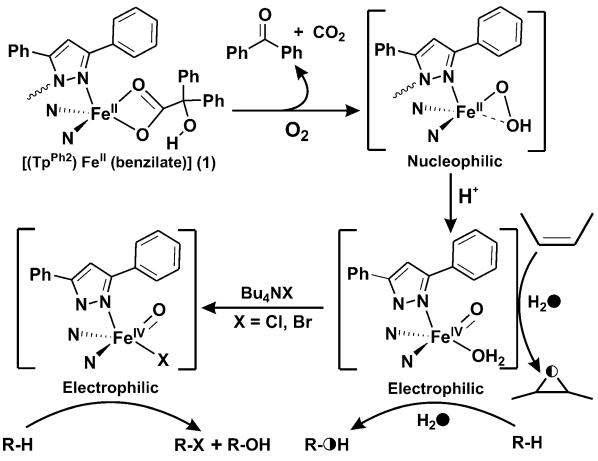
When the reaction of complex **1** was carried out with O_2 and pyridinium perchlorate (2 equiv) in the presence of tetrabutylammonium chloride (2 equiv), benzophenone was formed in quantitative yield. The optical spectrum of the final reaction solution exhibited a charge-transfer chromophore at around 510 nm (Figure 1). The optical spectrum and the ESI mass spectrum ($m/z = 740$) of the final reaction solution support the formation of an iron(III)–phenolate complex of the hydroxylated ligand (Tp^{Ph2*}).[35,36] The observed shift of the CT band to higher energy relative to those of the $Fe^{III}(Tp^{Ph2*})$ complex formed from **1** in the absence of chloride suggests the coordination of a chloride ligand. A Hammett plot for the oxidation of various *para*-substituted thioanisoles gave a ρ value of −2.69, which clearly indicates that the oxidant formed in the presence of protons and chloride anions is much more electrophilic for the oxo-transfer reaction to sulfides (Figure 2). The coordination of a weak donor chloride ligand decreases the electron density at the iron center of the oxidant, thus resulting in higher electrophilicity as compared to that of the electrophilic oxidants formed in the presence of a Lewis acid or protic acid only.



Scheme 3. Halogenation/oxygenation of different substrates with O_2 by complex **1** (0.02 mmol) in the presence of a proton source (2 equiv) and a suitable external halide source (2 equiv). Values in the brackets indicate the yields of products when X = Br.

When tetrabutylammonium bromide was used as the halide source, the corresponding brominated products were formed. However, the yields of brominated products are found to be low as compared to the chlorinated products (Scheme 3). Although the overall yields of halogenated products were low (ca. 25–30%), the iron complex reported herein is the first model system that exhibits halogenase activity with molecular oxygen. Neither the nucleophilic oxidant nor the electrophilic oxidant generated from **1** with a Lewis acid could halogenate aliphatic C–H bonds.

From the above experimental results, it is evident that the electrophilic oxidant generated from **1** in the presence of protons and halide anions is distinctly different from the electrophilic iron(IV)–oxo–hydroxo intermediate intercepted in the presence of a Lewis acid. The experimental results in the present study unambiguously prove that protons can facilitate heterolytic O–O bond cleavage to generate an electrophilic oxidant. To cleave the O–O bond of iron(II)–hydroperoxo species, 1 equivalent of the proton source should theoretically be sufficient. However, our experimental results reveal that 2 equivalents of pyridinium perchlorate are required to fully inhibit the formation of the sulfone in the oxidation of thioanisole and to fully inhibit the formation of the *cis* diol in the oxidation of alkenes. The additional proton might be involved in polarizing the protonated hydroperoxide species through a second-sphere interaction leading to heterolytic cleavage of the O–O bond to form an iron(IV)–oxo–aquo species (Scheme 4). The shift in the absorbance maxima of the final oxidized solution of **1** in the presence of a protic acid to 640 nm from 600 nm (Figure 1) is in line with our proposal. Protonation of the hydroxide-coordinated $Fe^{III}(Tp^{Ph2*})$ complex forms the corresponding water-coordinated complex, thus resulting in the observed lower-energy CT band.[36] The electrophilic iron(IV)–oxo–aquo oxidant thus formed can exchange its oxygen atoms with water and performs various oxidation reactions. In the presence of halides, the iron(IV)–oxo–aquo species is converted into an iron(IV)–oxo–halide oxidant. However, in contrast to enzymatic systems, the halide is proposed to bind after the heterolytic O–O bond cleavage mediated by a proton. The putative iron(IV)–oxo–halo species then participates in the halogen-transfer reaction as well as C–H bond-cleavage reactions. Complex **1** is capable of carrying out the aliphatic C–H bond halogenation of substrates such as adamantane, toluene, cyclohexene, 1,4-cyclohexadiene, and 2,4,6-trimethylbenzoic acid, but not that of cyclohexane. Enzymatic halogenation reactions are controlled by positioning the reactive C–H bond of the substrate closer to the halogen atom of the oxidant.[18] Although a halogenation reaction would be expected to occur preferentially,[14] the C–H bond of cyclohexane is probably directed away from the halogen atom of the proposed iron(IV)–oxo–halide oxidant.



Scheme 4. Mechanistic proposal for the formation of the electrophilic iron–oxygen oxidant derived from **1** and O_2 and its role in aliphatic C–H bond halogenation.

In summary, we have investigated the reactivity of a biomimetic iron(II)–benzilate complex supported by a tris-(pyrazolyl)borate ligand in the presence of a protic acid. Mechanistic studies suggest the in situ formation of an electrophilic iron(IV)–oxo–aquo oxidant from the iron(II) complex in the presence of a proton source. The electrophilic oxidant participates in epoxidation reactions instead of the *cis*-dihydroxylation of alkenes. It also activates the strong C–H bonds of alkanes. The formation of halogenated organic products from substrates containing aliphatic C–H bonds supports the in situ generation of an iron(IV)–oxo–halo intermediate in the presence of an external halide source. Although there is no direct experimental evidence for the proposed intermediates, indirect evidence for the formation of such species has been obtained from interception experiments with external substrates. Unlike non-heme iron halogenases, which use a α-keto-acid cofactor, the biomimetic system presented herein utilizes an α-hydroxy acid for dioxygen reduction and the subsequent generation of a metal-based oxidant to carry out the halogenation of aliphatic C–H bonds. The reactivity of the model complex provides new insight into the development of bioinspired catalysts for the oxidative halogenation of aliphatic C–H bonds.

Acknowledgements

T.K.P. acknowledges the Council of Scientific and Industrial Research (CSIR) for financial support (Project File No. 01(2776)/14/EMR-II). S.C. thanks the CSIR for a fellowship.

Keywords: dioxygen · electrophilic oxidants · halogenation · iron · protic acids

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 7717–7722
Angew. Chem. **2016**, *128*, 7848–7853

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Received: October 23, 2015
Published online: January 28, 2016

