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Enzyme Models

Oxidation of Chloride and Subsequent Chlorination of Organic Compounds by Oxoiron(IV) Porphyrin π-Cation Radicals**

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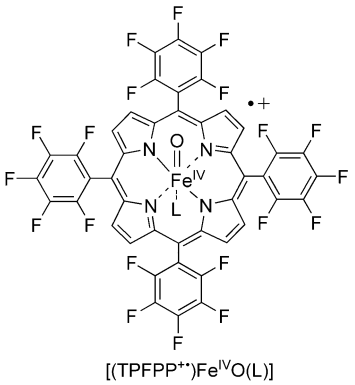
Chloroperoxidase (CPO) and myeloperoxidase (MPO) are the only heme peroxidases that catalyze oxidation of the chloride ion (Cl^-) with hydrogen peroxide.[1] CPO is an enzyme from *Caldariomyces fumago* and catalyzes chlorination reactions in the biosynthesis of chlorine-containing compounds.[2] CPO is also known to exhibit peroxidase, catalase, and cytochrome-P450-like activities.[1b,3] CPO has a thiolate heme axial ligand like cytochrome P450. This makes CPO distinct from other heme peroxidases which have a histidine imidazole as the heme axial ligand.[1] In contrast, MPO is found in the granules of myelocytes (precursors of neutrophils), and works as a major component of the antimicrobial system of neutrophils.[1c,4] MPO belongs to the animal peroxidase superfamily and has an imidazole heme axial ligand.[1b] Numerous biological studies have suggested that an oxoiron(IV) porphyrin π-cation radical species known as compound I is responsible for the oxidation of Cl^- and addition of Cl^- to the ferryl oxygen atom of compound I to produce the transient ferric hypochlorite complex Fe^{III}–OCl.[1,5] The ferric hypochlorite complex is believed to act as a key compound in the reactions leading to chlorination of organic substrates by CPO and antimicrobial activity in MPO. Although the oxidation process has been studied by multi-mixing stopped-flow experiments in which the transiently formed compound I was reacted with Cl^-,[6] the spectroscopic evidence for the formation of the ferric hypochlorite complex has not been obtained and it remains unclear as to how compound I oxidizes Cl^-. Furthermore, the identity of the true chlorinating agent in the subsequent chlorination of organic substrates is not known and more information is needed about the exact roles of the hypochlorite adduct, free hypochlorous acid, and Cl_2.[7]

Synthetic iron porphyrin complexes have been widely used as models of heme enzymes with the aim of gaining an understanding of the details of the enzymatic reaction mechanisms. While extensive studies have been shown to form compound I model complexes from various iron(III) porphyrin complexes and oxidants, such as *m*-chloroperoxybenzoic acid, iodosobenzene, and ozone,[8] there are only a few reports of the formation of an O–X bond between compound I model complexes and halides as models for CPO and MPO.[9] Woggon et al. studied the reactions of iron(III) porphyrin complexes with thiolate axial ligands using either hypochlorite or hydrogen peroxide and Cl^-.[9a–c] Chlorinated compounds were produced by these reactions, but the absence of detailed spectroscopic characterizations has raised questions about the reactive species and the mechanism by which Cl^- is oxidized in these reactions. Groves et al. reported that oxomanganese(V) porphyrin oxidizes Br^- and Cl^- into hypobromite and hypochlorite, respectively.[9d] More recently, Nam, Que et al. reported that an O–I bond is formed between the compound I model complex and phenyl iodide.[9e] Herein we report the direct observation of the oxidation of Cl^- with synthetic compound I model complexes and subsequent reactions leading to chlorination of organic compounds (Scheme 1).

Compound I model complexes, $[(TPFPP^{+\cdot})Fe^{IV}O(C_6F_5CO_2)]$ and $[(TPFPP^{+\cdot})Fe^{IV}O(NO_3)]$ (TPFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin), were prepared by ozone oxidation of the corresponding ferric porphyrin complexes, $[(TPFPP)Fe^{III}(C_6F_5CO_2)]$ and $[(TPFPP)Fe^{III}(NO_3)]$, in dichloromethane at −90 °C and −80 °C, respectively.[10] Spectroscopic data of $[(TPFPP^{+\cdot})Fe^{IV}O(C_6F_5CO_2)]$ and $[(TPFPP^{+\cdot})Fe^{IV}O(NO_3)]$ were consistent with those of oxoiron(IV) porphyrin π-cation radical complexes.[11] Oxidation of Cl^- with $[(TPFPP^{+\cdot})Fe^{IV}O(C_6F_5CO_2)]$ and $[(TPFPP^{+\cdot})Fe^{IV}O(NO_3)]$ were monitored using absorption spectroscopy. Upon addition of 1 equivalent of tetra-*n*-butylammonium chloride (TBACl), the absorption spectrum of $[(TPFPP^{+\cdot})Fe^{IV}O$-



$[(TPFPP^{+\cdot})Fe^{IV}O(L)]$

L = $C_6F_5CO_2$ (pentafluorobenzoate)
L = NO_3 (nitrate)

Scheme 1. The oxoiron(IV) porphyrin π-cation radical complexes used in this study.

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($C_6F_5CO_2$)] changed to a new one having an absorption at $\lambda =$ 552 nm with isosbestic points (Figure 1 a). The new absorption spectrum is similar to that of [(TPFPP)$Fe^{IV}O$].[12] The small peak at $\lambda = 630$ nm and the shoulder peak around $\lambda =$ 500 nm suggest that [(TPFPP)Fe^{III}(X)], where X = $C_6F_5CO_2$ or Cl, is formed concomitantly as a minor product. A similar spectral change was observed even when 50 equivalents of TBACl was added, but the relevant absorption peak of the complex was at $\lambda = 556$ nm (see Figure S1 in the Supporting Information). Since the same complex having an absorption at $\lambda = 556$ nm was obtained when excess Cl^- was added to the compound formed from 1 equivalent of TBACl, the change appears to be due to an equilibrium of the binding of the anions (Cl^- and $C_6F_5CO_2^-$) to [(TPFPP)$Fe^{IV}O$]. [(TPFPP$^{+\bullet}$)$Fe^{IV}O(C_6F_5CO_2)$] was observed to oxidize Cl^- through pathway 1 which is shown in Scheme 2. In contrast, upon addition of 50 equivalents of Cl^- to [(TPFPP$^{+\bullet}$)$Fe^{IV}O$-(NO_3)], the absorption spectrum quickly changed to one having absorptions at $\lambda = 547$ and $\lambda = 687$ nm, and then changed once again to a final spectrum with a peak at $\lambda =$ 561 nm after one minute (Figure 1 b). The peak at $\lambda = 687$ nm was identical to the peak corresponding to [(TPFPP$^{+\bullet}$)$Fe^{IV}O$(Cl)],[13] and the peaks at $\lambda = 547$ and $\lambda =$ 561 nm were similar to those for [(TPFPP)$Fe^{IV}O$] that are observed in the presence of 1 equivalent of NO_3^- and excess Cl^-, respectively. These spectral changes suggest that oxidation of Cl^- through pathways 1 and 2 in Scheme 2 occur at the same time during the initial stage when L is a weakly binding ligand such as NO_3^-. After consumption of [(TPFPP$^{+\bullet}$)$Fe^{IV}O$-(NO_3)], the [(TPFPP$^{+\bullet}$)Fe^{IV}O(Cl)] complex further oxidizes Cl^- to form [(TPFPP)Fe^{IV}O(Cl)].

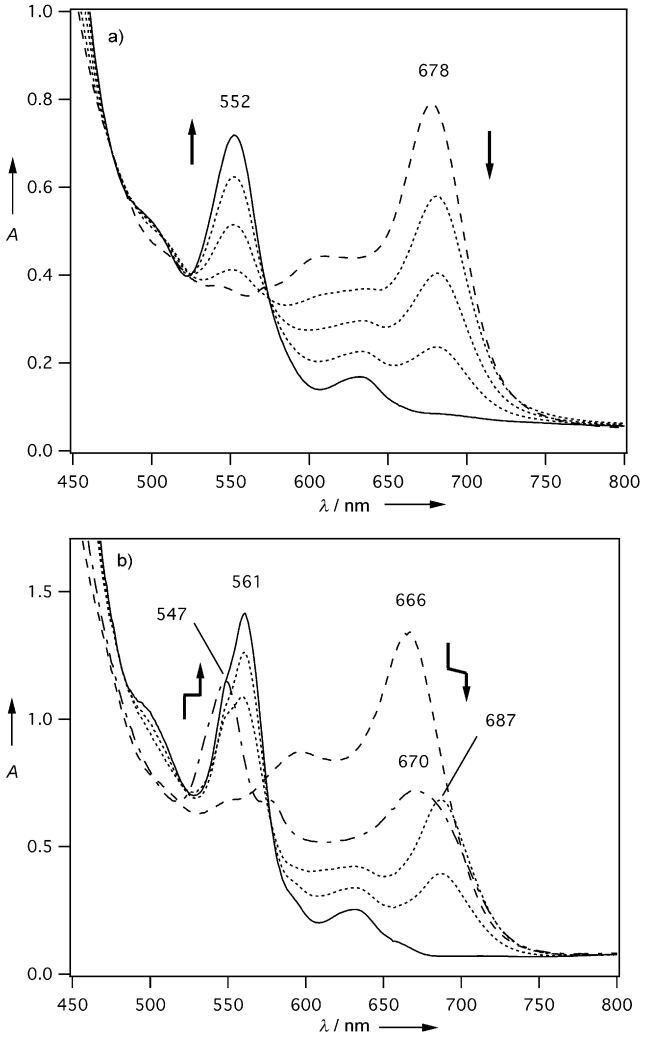
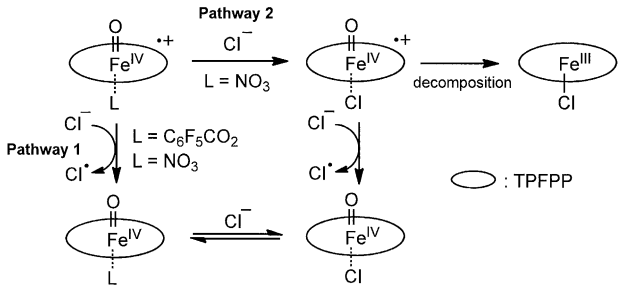


Figure 1. UV/visible spectral changes of [(TPFPP$^{+\bullet}$)Fe^{IV}O(L)] in CH_2Cl_2 observed upon addition of Cl^-. a) [(TPFPP$^{+\bullet}$)$Fe^{IV}O(C_6F_5CO_2)$] (5.0×10^{-4} M) in a 0.1 cm quartz cuvette at −90 °C (-----); after addition of 1 equiv TBACl (•••••); final reaction solution (——). b) [(TPFPP$^{+\bullet}$)$Fe^{IV}O(NO_3)$] (1.0×10^{-4} M) in a 1 cm quartz cuvette at −80 °C (-----); immediately after addition of 50 equiv of TBACl (– – –); after addition (•••••); final reaction solution (——).



Scheme 2. Proposed reaction pathways for the oxidation of Cl^- by [(TPFPP$^{+\bullet}$)Fe^{IV}O(L)].

The formation of the oxoiron(IV) porphyrin species from the oxidation of Cl^- with synthetic compound I model complexes was further confirmed by ^{2}H NMR measurements (Figure 2). The large upfield shift ($\delta = -86.7$ ppm) of the signal for the β-deuterium center of the pyrrole in [(TPFPP$^{+\bullet}$)$Fe^{IV}O(NO_3)$] was consistent with the a_{1u} porphyrin π-cation radical state as reported previously.[11] Upon addition of 50 equivalents of Cl^-, the signal disappeared and a new signal appeared at $\delta = 1.4$ ppm, which is consistent with the formation of [(TPFPP)Fe^{IV}O(Cl)]. The EPR spectrum of [(TPFPP$^{+\bullet}$)$Fe^{IV}O(NO_3)$] showed signals at $g \approx 2$ and 1.7.[14] The final reaction product is an EPR-silent species, consistent with an oxoiron(IV) porphyrin species (see Figure S2 in the Supporting Information). The formation of an oxoiron(IV) porphyrin species for [(TPFPP$^{+\bullet}$)$Fe^{IV}O(C_6F_5CO_2)$] was also supported by ^{2}H NMR and EPR measurements (see Figures S3 and S4 in the Supporting Information).

To study the reaction mechanism, we conducted kinetic studies of the reactions of [(TPFPP$^{+\bullet}$)$Fe^{IV}O(NO_3)$] and [(TPFPP$^{+\bullet}$)$Fe^{IV}O$-($C_6F_5CO_2$)] with Cl^-. The data in Figure 1 a clearly indicates that the reaction of [(TPFPP$^{+\bullet}$)$Fe^{IV}O$-($C_6F_5CO_2$)] with Cl^- is the rate-limiting step of the overall reaction (the first step of the pathway 1 in Scheme 2). The time course of the absorption change for the reaction of [(TPFPP$^{+\bullet}$)$Fe^{IV}O(C_6F_5CO_2)$] was observed to obey first-order kinetics in the presence of excess TBACl and the estimated apparent reaction rate constant is linearly correlated with the concentration of TBACl (see Figure S5 in the Supporting

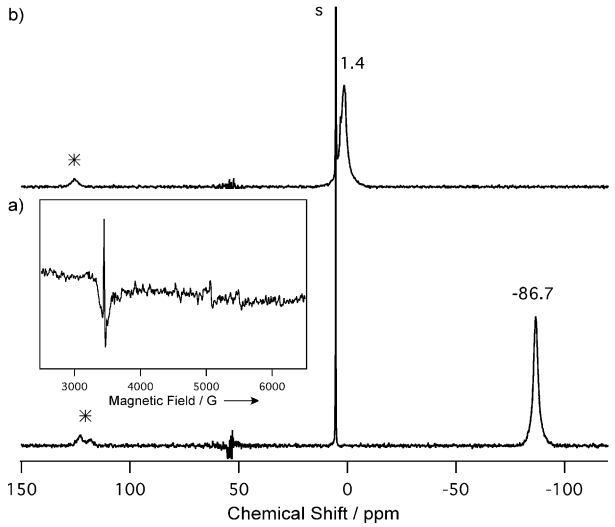
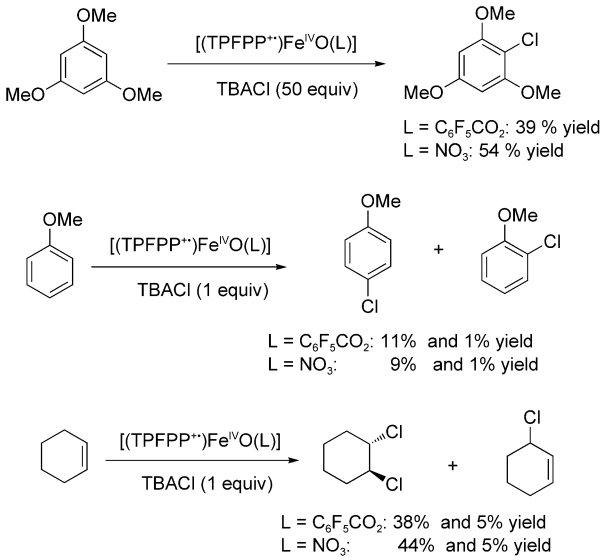


Figure 2. ^{2}H NMR (76.65 MHz) spectra of: a) [([D$_8$]pyrrole-TPFPP$^{+\bullet}$)Fe^{IV}O(NO$_3$)] and b) the solution after addition of TBACl (50 equiv) at −80 °C. The signal (S) of residual $CHDCl_2$ is referenced to $\delta = 5.32$ ppm. Signals denoted by asterisks are due to unoxidized ferric porphyrin complexes. Inset: EPR spectrum of [(TPFPP$^{+\bullet}$)Fe^{IV}O-(NO$_3$)] in dichloromethane at 4 K.



Scheme 3. The chlorination reactions of organic compounds (50 equiv) by [(TPFPP$^{+\bullet}$)Fe^{IV}O(C$_6$F$_5$CO$_2$)] (0.5 mM) at −90 °C and by [(TPFPP$^{+\bullet}$)Fe^{IV}O(NO$_3$)] (0.1 mM) at −80 °C in CH_2Cl_2. The yields are based on [(TPFPP$^{+\bullet}$)Fe^{IV}O(L)].

Information). The second-order rate constant was estimated to be $(7.8 \pm 0.5)\,M^{-1}s^{-1}$ at −90 °C. In contrast, for the reaction of [(TPFPP$^{+\bullet}$)Fe^{IV}O(NO$_3$)] with Cl^-, we could monitor only the reaction of [(TPFPP$^{+\bullet}$)Fe^{IV}O(Cl)] with Cl^- (the second step of pathway 2 in Scheme 2), because the reaction of [(TPFPP$^{+\bullet}$)Fe^{IV}O(NO$_3$)] with Cl^- and the formation of [(TPFPP$^{+\bullet}$)Fe^{IV}O(Cl)] (the first steps of pathways 1 and 2) were too fast to determine the reaction rate constants in the presence of excess TBACl. The reaction rate constant for the reaction of [(TPFPP$^{+\bullet}$)Fe^{IV}O(Cl)] with Cl^- could be determined by the absorption change at $\lambda = 687$ nm, because the oxoiron(IV) porphyrin species does not have an absorption peak at $\lambda = 687$ nm. The apparent reaction rate constant for [(TPFPP$^{+\bullet}$)Fe^{IV}O(Cl)] was also found to be linearly correlated with the concentration of TBACl and the second-order reaction rate constant was estimated to be $(10.8 \pm 0.5)\,M^{-1}s^{-1}$ at −80 °C (see Figure S5 in the Supporting Information). These results clearly indicate that compound I model complexes react with one equivalent of Cl^-.

To confirm the formation of a reactive chlorinating agent, we examined a chlorination reaction of organic compounds (see the Experimental Section). The results are summarized in Scheme 3. These were single-turnover reactions, so the product yields were based on compound I model complexes. When 1,3,5-trimethoxybenzene was added to the reaction mixture of [(TPFPP$^{+\bullet}$)Fe^{IV}O(NO$_3$)] and [(TPFPP$^{+\bullet}$)Fe^{IV}O-(C$_6$F$_5$CO$_2$)] with 50 equivalents of Cl^-, a chlorinated product, 1-chloro-2,4,6-trimethoxybenzene, was produced in 54 % and 39 % yield, respectively.[15] No other products (such as 1-chloromethoxyl-3,5-dimethoxybenzene, a main product of a reaction with chlorine radical), were detected.[16] The chlorination reactions of anisole and cyclohexene were also examined under the same conditions. As shown in Scheme 3, anisole was chlorinated to form 4-chloroanisole and 2-chloroanisole in 9 % and 1 % yield, respectively when using [(TPFPP$^{+\bullet}$)Fe^{IV}O(NO$_3$)], and 11 % and 1 % yield respectively, when using [(TPFPP$^{+\bullet}$)Fe^{IV}O(C$_6$F$_5$CO$_2$)]. The production of the *para* and *ortho* isomers from the compound I model complexes were similar to the isomers produced by the CPO reaction, but their regioselectivity for the compound I model complexes were better than the regioselectivity of the CPO reaction or the reaction with free hypochlorous acid in acidic aqueous conditions.[16] The chlorination of the methoxy group was also not observed for anisole. Cyclohexene was chlorinated to form *trans*-1,2-dichlorocyclohexane, a typical addition product under ionic conditions, in 44 % yield using [(TPFPP$^{+\bullet}$)Fe^{IV}O(NO$_3$)] and 38 % yield using [(TPFPP$^{+\bullet}$)Fe^{IV}O(C$_6$F$_5$CO$_2$)]. A small amount (5 %) of 3-chlorocyclohexene was also formed from these reactions. 4-chlorocyclohexene and *cis*-1,2-dichlorocyclohexane (possible free-radical chlorination products), and 2-chlorohexanol[17] (an expected product from a reaction with hypochlorous acid), were not detected in these chlorination reactions.

To further confirm the formation of a reactive chlorinating agent in the reaction mixture, we added tetra-*n*-butylammonium iodide (TBAI) as a reducing agent. Excess TBAI was added to the solution after the reaction of [(TPFPP$^{+\bullet}$)Fe^{IV}O-(NO$_3$)] with Cl^- at −80 °C. The absorption spectrum of the reaction mixture was not significantly changed upon addition of TBAI (see Figure S6 in the Supporting Information). [(TPFPP)Fe^{IV}O(Cl)] was not reduced by TBAI in the absence of protons. However, 1-chloro-2,4,6-trimethoxybenzene was not detected at all by GC/MS measurements when 1,3,5-trimethoxybenzene was added after addition of TBAI. Only the reactive chlorinating agent was reduced at −80 °C by TBAI. These results clearly indicate that a reactive chlorinating agent was formed in the reaction mixture by the oxidation of Cl^- with [(TPFPP$^{+\bullet}$)Fe^{IV}O(L)].

In addition, we examined participation of an oxoiron(IV) porphyrin complex in the chlorination reaction. We added cyclohexene to the solution after the reaction of $[(TPFPP^{+\bullet})Fe^{IV}O(NO_3)]$ with Cl^- at −90 °C and the reaction mixture was stirred for 1 hour at −80 °C.Meanwhile, $[(TPFPP)Fe^{IV}O(Cl)]$ was not decomposed significantly (see Figure S7 in the Supporting Information). After reduction of $[(TPFPP)Fe^{IV}O(Cl)]$ and the remaining chlorinating agent with TBAI and trifluoroacetic acid at −80 °C, the reaction mixture was analyzed by GC/MS. Even with these reaction conditions, *trans*-1,2-dichlorocyclohexane and 3-chlorohexene were formed in 27% and 4% yields, respectively. This indicates that the oxoiron(IV) porphyrin complex is not responsible for the chlorination reaction.

The formation of oxoiron(IV) porphyrin complexes from the oxidation of Cl^- with oxoiron(IV) porphyrin π-cation radical complexes can be explained by direct one-electron oxidation or formation of an iron(III) hypochlorite complex, with subsequent homolysis of the O–Cl bond. The direct one-electron oxidation mechanism seems to be quite different from the mechanisms proposed previously for CPO and MPO.[1–5] Cl^- must come close to the oxo ligand of compound I to make a bond between the oxo ligand and Cl^-. The negative net charge of the oxo ligand prevents Cl^- from closely approaching the oxo ligand because of electrostatic repulsion. Thus, the one-electron transfer occurs from Cl^- to compound I in the model system. In CPO and MPO, protein matrices form a cationic environment on the distal side of the heme pocket and keep the Cl^- close to the oxo ligand of compound I. In fact, previous studies reported that Cl^- binds to CPO and MPO.[18] The formation of an iron(III) hypochlorite complex as a transient species may also be a reasonable reaction mechanism. The observed first-order kinetics for Cl^- can be explained when $[(TPFPP^{+\bullet})Fe^{IV}O(L)]$ forms an equilibrium with $[(TPFPP)Fe^{III}OCl]$ and the small amount of $[(TPFPP)Fe^{III}OCl]$ formed from the equilibrium decomposes to $[(TPFPP)Fe^{IV}O]$ by homolytic cleavage of the O–Cl bond. The homolysis of the O–Cl bond has been proposed for the *meso* chlorination of heme in peroxidase.[19] In addition, the solvent effect would also affect the reaction of compound I with Cl^-. A protonation of heme-bound hypochlorite may be essential for the two-electron oxidation of Cl^-. Additional studies will be required to reveal the oxidation mechanism.

In summary, we report here the first examples of the oxidation of Cl^- and subsequent chlorination of organic substrates using synthetic compound I model complexes. The compound I model complexes oxidize Cl^- to form oxoiron(IV) porphyrin complexes and chlorine radical by either a direct one-electron oxidation or an iron(III) hypochlorite intermediate, with subsequent homolysis of the O–Cl bond. A reactive chlorinating reagent formed under this set of reaction conditions can chlorinate various organic compounds.

Experimental Section

Instruments and materials are shown in the Supporting Information.

A typical procedure for oxidation of Cl^- and a subsequent chlorination reaction: $[(TPFPP)Fe^{III}(C_6F_5CO_2)]$ (0.5 mM) was prepared in a 0.1 cm UV cuvette in a low-temperature chamber set within a UV absorption spectrometer in CH_2Cl_2 at −90 °C. Ozone gas was bubbled into the solution with a gastight syringe. After confirming the formation of $[(TPFPP^{+\bullet})Fe^{IV}O(C_6F_5CO_2)]$, the excess ozone was removed by bubbling argon gas through the mixture. For $[(TPFPP)Fe^{III}(NO_3)]$, 0.1 mM sample in CH_2Cl_2 was prepared in a 1 cm UV cuvette and the ozone oxidation was carried out at −80 °C. Tetra-*n*-butylammonium chloride (1 or 50 equiv) was then added to the solution with stirring at −80 or −90 °C and the reaction was monitored by recording the changes in the absorption at fixed time intervals. 1,3,5-trimethoxybenzene (50 equiv) was added to the solution at −80 or −90 °C after confirming completion of the oxidation of Cl^-. The reaction mixture was stirred for 2 min at the same temperature and then warmed to room temperature. After addition of undecane (0.5 equiv) as an internal standard, the reaction products and their yields were determined by GC/MS. The reaction products were identified by comparing retention times and mass patterns with those of authentic samples. The yields were determined with calibration lines prepared with authentic samples and undecane. The product yields were based on the compound I model complex.

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[15] When 1 equiv of Cl^- was used, the yield of 1-chloro-2,4,6-trimethoxybenzene from $[(TPFPP^{+\cdot})Fe^{IV}O(NO_3)]$ and $[(TPFPP^{+\cdot})Fe^{IV}O(C_6F_5CO_2)]$ was reduced to 23% and 33%, respectively.

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