Oxidation of *N*-Methylanilines by a Nonheme Iron(IV)-Oxo Complex

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High-valent iron-oxo species have been frequently employed in heme and nonheme iron enzymes to carry out catalytic oxygenation reactions.[1-11] In heme-based systems, biological and synthetic oxoiron(IV) porphyrin π-cation radicals are believed to carry out the catalytic oxidations of organic substrates. In the nonheme iron enzymes, oxoiron(IV) intermediates have recently been identified by spectroscopic methods in the catalytic cycle of taurine dioxygenase, and synthetic nonheme oxoiron(IV) species bearing tetradentate and pentadentate ligands were also isolated and characterized.[12-18] In addition, it has been demonstrated that the nonheme oxoiron(IV) species were capable of conducting the conversion of diverse organic subsatrates such as PPh_3, thioanisole, alcohol, and alkanes.[18-20]

The molecular mechanisms of oxidative *N*-demethylation of *N*,*N*-dimethylanilines by heme enzymes such as peroxidases and cytochrome P-450 have been studied for the past twenty years. However, two possible mechanisms, electron transfer followed by proton transfer and hydrogen transfer from α-C-H bonds of the methyl group in *N*,*N*-dimethylanilines, are still under debate. Recently, we also reported the oxidative *N*-dealkylation of *N*,*N*-dialkylanilines and demonstrated that the oxidative *N*-dealkylation reactions occurred *via* a proton-coupled electron transfer process.[21] Meanwhile, secondary amine substrates bearing a cyclopropyl group have been used in the relation to a mechanism-based inactivation of heme enzymes, and the formation of a highly reactive carbon-centered radical was reported in the oxidation of heteroatom-containing cyclopropyl substrates.[22-27] Relatively, a few studies for the oxidation of *N*-methylanilines as substrate were reported using iron, cobalt, and copper complexes.[28-30] However, no detailed mechanistic study in the oxidation of secondary amines with nonheme Fe(IV)-oxo species has been reported until now. Presented in this study is a kinetic examination of the oxidation of *N*-methylanilines with $[(tmc)Fe^{IV}=O]^{2+}$ (tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), which yields *N*,*N'*-dimethyl-*N*,*N'*-diphenylhydrazine formed by the coupling of two *N*-methylaniline molecules. By determining the rate constants for the step of electron transfer from *N*-methylaniline to the iron(IV)-oxo species, we suggest that the oxidation of *N*-methylaniline occurs *via* an electron transfer.

Experimental Procedure

Materials and Instrumentation. All chemicals obtained from Aldrich Chemical Co. were the best available purity and used without further purification unless otherwise indicated. Solvents were dried according to published procedures and distilled under Ar prior to use. $Fe(tmc)(OTf)_2\cdot 2CH_3CN$ was prepared in a glovebox by literature methods.[16,21] *para*-Methyl-*N*-trideuteromethylaniline-d_3(Me-MA-d_3) was prepared by literature methods.[31]

UV-vis spectra were recorded on a Hewlett Packard 8453 spectrophotometer equipped with *Optostat*^{DN} variable-temperature liquid-nitrogen cryostat (Oxford Instruments) or with a circulating water bath. LC-MS spectra were collected on Surveyor Integrated HPLC systems connected with Thermo Finnigan (San Jose, CA, USA) LCQ^{TM} Advantage MAX quadrupole ion trap instrument. Product analysis for the oxidation of *N*-methylanilines was performed either on DIONEX Pump Series P 580 equipped with a variable wavelength UV-200 detector (HPLC) or on Agilent Technologies 6890N gas chromatograph (GC) and a Hewlett-Packard 5890 II Plus gas chromatograph interfaced with Hewlett-Packard model 5989B mass spectrometer (GC-MS). Product analysis for the oxidation of *N*-methylanilines was performed on GC and LC-MS.

Reactions of the Oxoiron(IV) Complex with *p*-Substituted-*N*-methylaniline. In general, reactions were run at least in triplicate, and the data represent average of these reactions. All reactions were followed by monitoring spectral changes of reaction solutions with a UV-vis spectrophotometer. The nonheme oxoiron(IV) complex was prepared by adding 1.2 equiv of PhIO (2.4 mM, diluted in 50 μL of CH_3OH) into an 1-cm UV cuvette containing an iron(II) complex (2 mM), $Fe(TMC)(OTf)_2$ in CH_3CN (2 mL). Then, appropriate amounts of *N*-methylanilines were added into the UV cuvette, and spectral changes of the oxoiron(IV) complex were directly monitored by a UV-vis spectrophotometer. Rate constants, k_{obs}, were determined by pseudo-first-order fitting of the decrease of absorption bands at 820 nm.

Product Analysis for the Oxidation of *N*-Methylanilines. A reaction solution containing the oxoiron(IV) intermediate (2 mM) was prepared as described above. Then, 20 equiv of

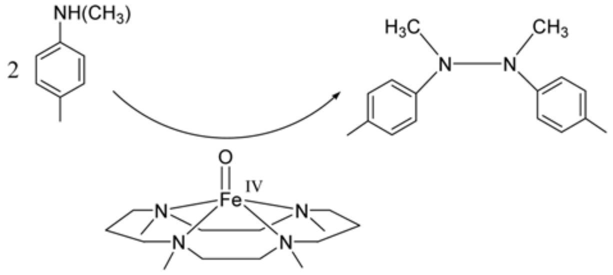
N-methylaniline (40 mM) was added to the reaction solution. Product analysis was performed by injecting reaction solutions directly into LC-MS, GC, and/or GC-MS. Product yields were determined by comparison with standard curves of known authentic samples.

In kinetic isotope effect study by kinetics, Me-MA/Me-MA-d_3 (40 mM) was treated to reaction solutions containing the oxoiron(IV) intermediate (2 mM).

Results and Discussion

The mononuclear nonheme oxoiron(IV) complex, $[(tmc)Fe^{IV}=O]^{2+}$, is prepared in the reaction of their corresponding Fe(II) complex, $[(tmc)Fe(OTf)_2]^{2+}$, by using the method reported previously.[16, 21] In the reaction with 20 equiv *para*-methyl-*N*-methylaniline (*p*-Me-MA), the oxoiron(IV) species reverted back to the starting iron(II) complex at room temp, showing pseudo-first-order decay as monitored by a UV-vis spectrophotometer (Figure 1a). The observed pseudo-first-order rate constants for Fe(IV)=O decomposition increased linearly with *p*-Me-MA concentration, leading us to determine second-order rate constant (k_2) of 1.10 ± 0.05 $M^{-1}s^{-1}$ (Figure 1b). This rate constant is slightly low compared to that observed in the oxidation of *para*-Me-*N*,*N*-dimethylaniline by the same catalyst ($k_2 = 1.2 \pm 0.1$ $M^{-1}s^{-1}$).[21] We then determined activation parameters of $\Delta H^‡$ and $\Delta S^‡$ for the oxidation of *p*-Me-MA by $[(tmc)Fe^{IV}=O]^{2+}$, by determining rate constants at different temperatures ($\Delta H^‡ = 54$ kJ mol^{-1} and $\Delta S^‡ = -81$ $JK^{-1}mol^{-1}$, Figure 1c).

The product analysis of the resulting solutions with HPLC revealed that no *N*-demethylated product was detected and the coupling product of *N*,*N'*-dimethyl-*N*,*N'*-diphenylhydrazine was generated (30%, based on $[(tmc)Fe^{IV}=O]^{2+}$) (Figure 2). In the oxidation of *N*-methylanilines with a synthetic $Fe^{IV}=O$ porphyrin π-cation radical or $CuCl/O_2$, the formation of such coupling products was also reported.[29,30] But other possible coupling products such as benzidine and diphenylamine were not observed, which were predominant pathways for the electrochemical anodic oxidation of *N*-methylaniline.[32-34]



The effects of ring substituents in *para*-substituted-*N*-methylanilines (*p*-X-MAs) were also investigated on the

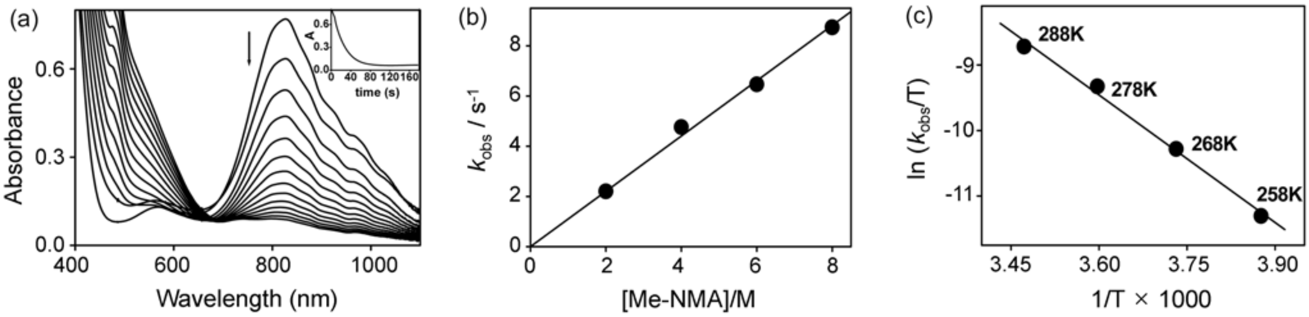


Figure 1. Reactions of $[(tmc)Fe^{IV}=O]^{2+}$ with *N*-methylanilines in CH_3CN at 25 °C. (a) Time-resolved UV-vis spectral changes upon addition of 20 equiv of *p*-Me-MA. Inset shows absorbance traces monitored at 820 nm. (b) Plot of the observed pseudo-first-order rate constant at variable *p*-Me-MA concentrations. (c) Determination of activation parameters by plotting first-order-rate constants determined upon addition of 20 equiv of *p*-Me-MA at different temperatures against 1/T.

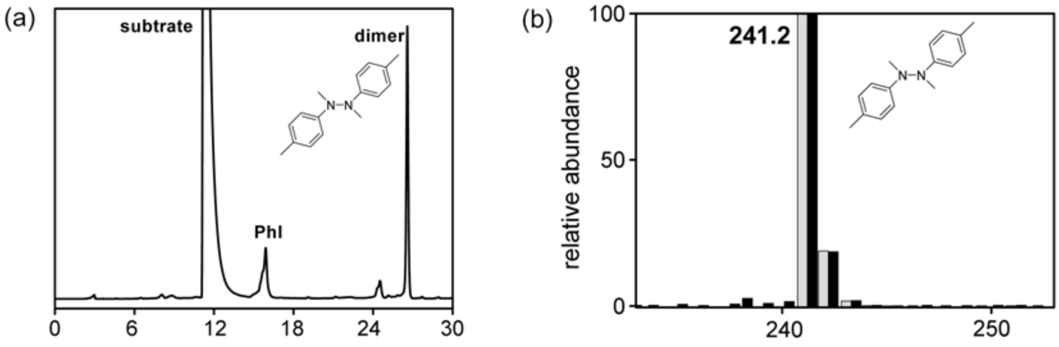


Figure 2. (a) A representative high performance liquid chromatogram for the oxidation of *para*-methyl-*N*-methylaniline by $[(tmc)Fe^{IV}=O]^{2+}$. The retention time for *N*,*N'*-dimethyl-*N*,*N'*-diphenylhydrazine is 26.6 min. (b) LC-ESI MS spectrum of *N*,*N'*-dimethyl-*N*,*N'*-diphenylhydrazine.

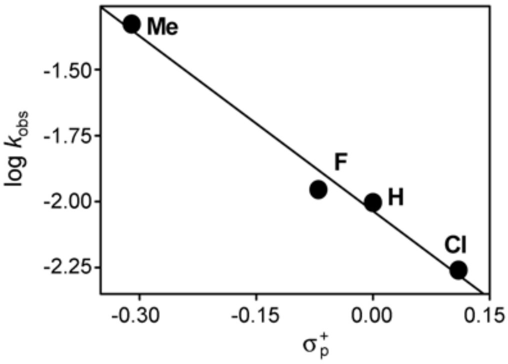
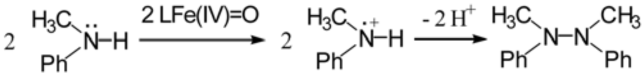


Figure 3. Correlation of the Hammett substituent constant (σ_p) and the pseudo-first-order rate constants in the presence of excess *p*-X-MA.



Scheme 1

rates of decomposition of $[(tmc)Fe^{IV}{=}O]^{2+}$. As shown in Figure 3, the decay rates for the Fe(IV)=O species correlate with Hammett σ_p values to give large negative ρ values (−1.96) for $[(tmc)Fe^{IV}{=}O]^{2+}$. Hence, increasing the donating ability of *p*-X-MAs diminishes the stability of the Fe(IV)=O species, as previously observed for the alcohol and *N*,*N*-dimethylaniline oxidation by $[(tmc)Fe^{IV}{=}O]^{2+}$.[19,21] This strongly suggests that the *para*-substituents affect the positively-charged transient state intermediate of $[(tmc)Fe^{IV}{=}O]^{2+}$ by the inductive effect during the first event of oxidation of MAs. It should be noted that such large negative values were observed by the kinetic analysis in the oxidation of *para*-substituted-*N*,*N*-dimethylanilines with Cu^{II}-μ-peroxo species[35] and in the oxidation of *para*-substituted-anilines by (salen)-$Cr^{V}{=}O$,[36] in which the rate-limiting electron transfer process was also proposed.

The additional hint for the reaction mechanism of *N*-methylaniline oxidation by $[(tmc)Fe^{IV}{=}O]^{2+}$ was obtained from kinetic study in the experiments with a deuterium-labeled substrate. Kinetic isotope effects (KIE) obtained following the decay of the absorption bands of $[(tmc)Fe^{IV}{=}O]^{2+}$ with *para*-methyl-*N*-methylaniline and *para*-methyl-*N*-trideuteromethylaniline turned out 1.1, which strongly supports that only the electron transfer reaction from MA to the oxoiron(IV) intermediates is involved in the primary rate-determining step and the rate-determining electron transfer step not coupled with the following proton transfer.

The oxidation of *N*-methylanilines by the Fe(IV)=O species used in this study may proceed by one-electron oxidation at the nitrogen atom (Scheme 1) to generate an anilinium radical ion. The anilinium ion then combine with another ion to form a stable dimer of hydrazine after losing two protons.

Conclusion

We have carried out the reaction of a nonheme $Fe^{IV}{=}O$ species with *N*-methylanilines by the spectral, kinetic, and product analysis studies. These experimental results show that the nonheme $Fe^{IV}{=}O$ species achieves *N*-methylaniline oxidation through the rate-determining electron transfer.

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