Inorg. Chem. **2007**, *46*, 293–298

Oxidative N-Dealkylation Reactions by Oxoiron(IV) Complexes of Nonheme and Heme Ligands

Kasi Nehru, Mi Sook Seo, Jinheung Kim,* and Wonwoo Nam*

Department of Chemistry, Division of Nano Sciences, and Center for Biomimetic Systems, Ewha Womans University, Seoul 120-750, Korea

Received July 27, 2006

Nonheme and heme iron monooxygenases participate in oxidative N-dealkylation reactions in nature, and high-valent oxoiron(IV) species have been invoked as active oxidants that effect the oxygenation of organic substrates. The present study describes the first example of the oxidative N-dealkylation of *N*,*N*-dialkylamines by synthetic nonheme oxoiron(IV) complexes and the reactivity comparisons of nonheme and heme oxoiron(IV) complexes. Detailed mechanistic studies were performed with various *N*,*N*-dialkylaniline substrates such as *para*-substituted *N*,*N*-dimethylanilines, *para*-chloro-*N*-ethyl-*N*-methylaniline, *para*-chloro-*N*-cyclopropyl-*N*-isopropylaniline, and deuteriated *N*,*N*-dimethylanilines. The results of a linear free-energy correlation, inter- and intramolecular kinetic isotope effects, and product analysis studied with the mechanistic probes demonstrate that the oxidative N-dealkylation reactions by nonheme and heme oxoiron(IV) complexes occur via an electron transfer–proton transfer (ET–PT) mechanism.

Introduction

Metalloenzymes with heme and nonheme iron active sites participate in many metabolically important oxidative transformations by activating dioxygen in biological reactions.[1,2] In the catalytic cycles of dioxygen activation by the enzymes, high-valent oxoiron(IV) species have been invoked as the key intermediates that effect the oxygenation of organic substrates.[1,2] For example, oxoiron(IV) porphyrin π-cation radicals are believed to carry out the oxygenation reactions in cytochromes P450 (CYP 450).[1] Similarly, nonheme oxoiron(IV) species are invoked as the active oxidants in nonheme iron enzymes.[2] In biomimetic studies, reactivities of oxoiron(IV) porphyrin π-cation radicals and oxoiron(IV) porphyrins have been investigated in hydrocarbon oxidations as chemical models of CYP 450.[1,3,4] Very recently, mononuclear nonheme oxoiron(IV) complexes bearing tetradentate N4 and pentadentate N5 and N4S ligands were synthesized and studied in a variety of oxidation reactions, including alkane hydroxylation, olefin epoxidation, and the oxidation of PPh_3, sulfides, and alcohols.[5,6]

The oxidative N-dealkylation of *N*,*N*-dialkylamines by CYP 450 and their model compounds has been intensively

* To whom correspondence should be addressed. E-mail: jinheung@ewha.ac.kr (J.K.), wwnam@ewha.ac.kr (W.N.).

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10.1021/ic0614014 CCC: $37.00
Published on Web 12/02/2006

Scheme 1. Proposed ET−PT and HAT Mechanisms in Oxidative N-Demethylation by $[(Porp)^{+\bullet}Fe^{IV}=O]^{+}$

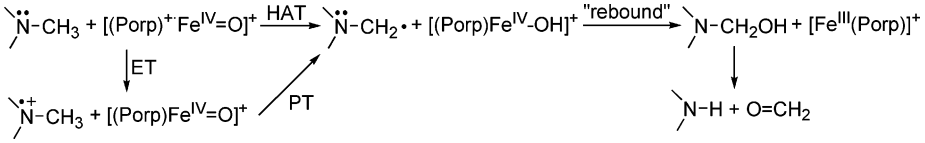
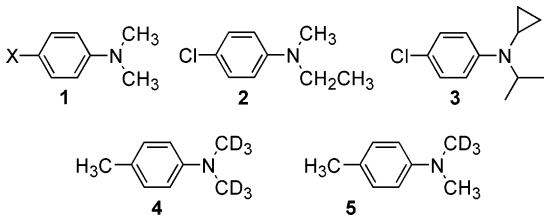


Chart 1



investigated over the past two decades.[1a,7] High-valent oxoiron(IV) porphyrin π-cation radicals are considered as a common oxidant in the N-dealkylation reactions, but two different mechanisms, such as an electron transfer−proton transfer (ET−PT) and a hydrogen atom transfer (HAT) (Scheme 1),[7] have often been proposed on the basis of mechanistic studies using *para*-substituted *N*,*N*-dimethylanilines (**1**),[8] *para*-chloro-*N*-ethyl-*N*-methylaniline (**2**),[9] *para*-chloro-*N*-cyclopropyl-*N*-isopropylaniline (**3**),[10] and deuteriated *N*,*N*-dimethylanilines (**4** and **5**) (Chart 1).[8,9,11] The oxidative N-dealkylation has also been reported in the reactions of nonheme iron enzymes and synthetic nonheme iron complexes.[12,13] For example, the *Escherichia coli* AlkB protein has been known to play an important role in alkylated DNA damage repair, and a nonheme oxoiron(IV) species has been proposed as an active oxidant.[12] In our ongoing efforts to understand the chemical properties of mononuclear nonheme and heme oxoiron(IV) complexes in oxidation reactions,[4,5] we have investigated oxidative N-dealkylation reactions of the aforementioned mechanistic probes[14] with nonheme and heme oxoiron(IV) complexes, such as $[(N4Py)Fe^{IV}=O]^{2+}$ (**6a**),[5b] $[(TMC)Fe^{IV}=O]^{2+}$ (**6b**),[5a] and $(TPFPP)Fe^{IV}=O$ (**6c**)[4] (see Figure 1 for the structures of iron complexes).[15] We now provide experimental evidence that the N-dealkylation of *N*,*N*-dialkylanilines by the nonheme and heme oxoiron(IV) complexes occurs via a rate-limiting ET coupled with a proton transfer (PT) mechanism.

Results and Discussion

The oxidative N-dealkylation reactions were investigated with nonheme and heme oxoiron(IV) complexes generated in situ, and the oxoiron(IV) complexes, **6a**−**c** (Figure 1), were prepared by the literature methods (see the Experimental Procedures). Upon the addition of 20 equiv of *para*-methyl-*N*,*N*-dimethylaniline (*p*-Me-DMA) to the solutions of **6a**−**c** at 15 °C, the intermediates reverted back to their starting iron complexes, showing pseudo-first-order decay as monitored by a UV−vis spectrophotometer (Figure 2a for **6a** and Supporting Information Figures S1a and S2a for **6b** and **6c**, respectively). Pseudo-first-order fitting of the kinetic data allowed us to determine k_{obs} values for the reactions of **6a**−**c** [$k_{obs} = 5.8 \times 10^{-2}$ s^{-1} for **6a** (2 mM), 4.7×10^{-2} s^{-1} for **6b** (2 mM), and 1.1×10^{-1} s^{-1} for **6c** (2×10^{-2} mM)], and product analysis of the resulting solutions revealed that *para*-methyl-*N*-methylaniline (*p*-Me-MA) was produced as a major product with the concurrent formation of CH_2O in all of the reactions (>80% based on the intermediates generated) (eq 1). The pseudo-first-order rate constants increased proportionally with the *p*-Me-DMA concentration, leading us to determine second-order rate constants (Table 1, column of k_2; Figure 2b for **6a**; and Supporting Information Figures S1b and S2b for **6b** and **6c**, respectively). The second-order rate constants indicate that the oxoiron(IV) porphyrin complex, **6c**, is much more reactive than the nonheme oxoiron(IV) complexes, **6a** and **6b**, but that the reactivities of **6a** and **6b** are similar. The latter result implies that the mechanism of the oxidative N-dealkylation is different from that of the oxo transfer from

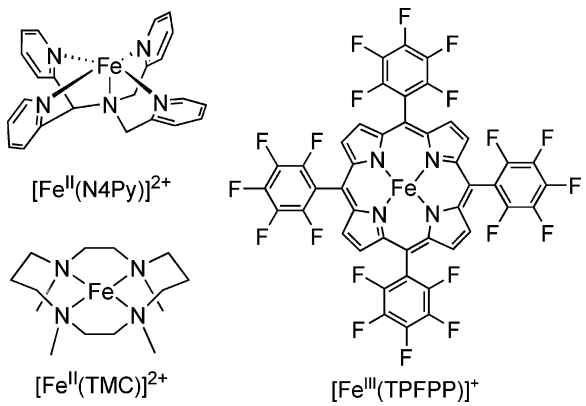


Figure 1. Iron(II) complexes used in this study

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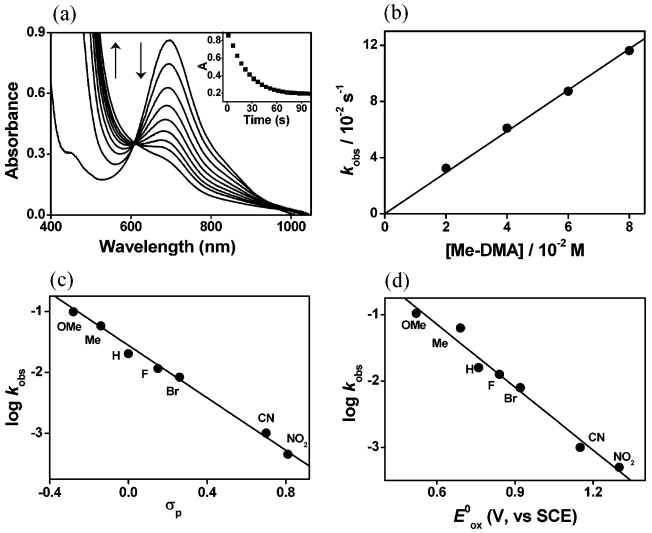
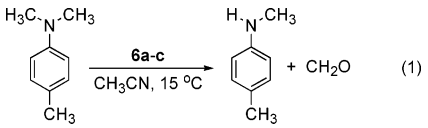


Figure 2. Reactions of $[(N4Py)Fe^{IV}{=}O]^{2+}$ (**6a**) with *N*,*N*-dialkylanilines in CH_3CN at 15 °C. (a) UV−vis spectral changes of **6a** (2 mM) upon addition of 20 equiv of *p*-Me-DMA (40 mM). Inset shows absorbance traces monitored at 695 nm. (b) Plot of k_{obs} against *p*-Me-DMA concentration to determine a second-order rate constant. (c) Hammett plot of log k_{obs} against σ_p of *p*-X-*N*,*N*-dimethylanilines. (d) Plot of log k_{obs} vs E^0_{ox} of *para*-substituted *N*,*N*-dimethylanilines.

nonheme oxoiron(IV) complexes to organic substrates (i.e., 2e$^-$-oxidation reactions) since it has been demonstrated previously that **6a** is a much stronger oxidant than **6b** in the oxygenation of organic substrates such as alkanes, alcohols, and sulfides.[5]



We then investigated the mechanism of the oxidative N-dealkylation by **6a**−**c** with the mechanistic probes, **1**−**5** (see Chart 1). First, the electronic effect of substrates was examined with *para*-substituted *N*,*N*-dimethylanilines (**1**),[8] and we have observed a significant influence of the electron-donating ability of the *para*-substituents on the reaction rates (Table 2). By plotting the rates as a function of σ_p of the *para*-substituents, a good linear correlation was obtained with large negative Hammett ρ values, and all substituents fit the Hammett plot well (Table 1, column of ρ; Figure 2c for **6a**; and Supporting Information Figures S1c and S2c for **6b** and **6c**, respectively). Further, the plot of log k_{obs} against the one-electron oxidation potentials of DMAs (E°_{ox}) afforded a good linear correlation with large negative slopes, such as −3.3 for **6a**, −4.0 for **6b**, and −5.0 for **6c** (Figure 2d for **6a** and Supporting Information Figures S1d and S2d for **6b** and **6c**, respectively). These results indicate that no change of mechanism occurs depending on the electron-richness of

Table 1. Kinetic Data and Product Yields Obtained in Oxidative N-Dealkylation of *N*,*N*-Dialkylanilines by Nonheme and Heme Oxoiron(IV) Complexes[a]

intermediate[b]	k_2 (M^{-1} s^{-1})[c]	ρ[d]	**2a**/**2b**[e]	$(k_H/k_D)_{inter}$[f]	$(k_H/k_D)_{intra}$[g]
6a	1.4 ± 0.1	−2.2	15 ± 2 [88:6]	3.0 ± 0.3	4.9 ± 0.5
6b	1.2 ± 0.1	−2.6	10 ± 2 [80:8]	2.4 ± 0.3	3.6 ± 0.5
6c	(3.0 ± 0.2) × 10^4	−3.3	16 ± 3 [82:5]	2.8 ± 0.3	4.2 ± 0.4

[a] Reactions were run at least in triplicate, and the data reported represent the average of these reactions. [b] Intermediates were prepared as described in the Experimental Procedures. [c] Figure 2b and Supporting Information Figures S1b and S2b. [d] Figure 2c, Table 2, and Supporting Information Figures S1c and S2c. [e] Product ratios of **2a** to **2b**. Numbers in brackets are percent yields of **2a** and **2b**. [f] The observed k_H and k_D values were determined kinetically in the reactions of *p*-Me-DMA and *p*-Me-DMA-d_6, respectively, and the KIE values were calculated by dividing k_H by k_D. See Supporting Information Figure S5. [g] The KIE values were determined from product analysis of reaction solutions of **5** with LC-ESI MS, and the ratios were calculated by dividing the relative abundance of *para*-methyl-*N*-trideuteromethylaniline (*p*-Me-MA-d_3, **5a**) by *para*-methyl-*N*-methylaniline (*p*-Me-MA, **5b**) (see eq 3 in the text). See Supporting Information Figure S6.

Table 2. Rate Constants Determined in the Reactions of **6a**−**c** with Various *p*-X-*N*,*N*-Dimethylanilines (**1**)[a,b]

			k_{obs} (s^{-1})		
X	σ_p	E°_{ox} (vs SCE, V)[c]	**6a**	**6b**	**6c**
OMe	−0.28	0.52	1.1×10^{-1}	8.8×10^{-2}	nd[d]
Me	−0.14	0.69	5.8×10^{-2}	4.7×10^{-2}	1.1×10^{-1}
H	0	0.76	1.7×10^{-2}	1.6×10^{-2}	nd[d]
F	0.15	0.84	1.3×10^{-2}	1.4×10^{-2}	1.7×10^{-2}
Br	0.26	0.92	7.6×10^{-3}	4.9×10^{-3}	4.7×10^{-3}
CN	0.7	1.15	1.0×10^{-3}	2.6×10^{-4}	1.7×10^{-4}
NO_2	0.81	1.3	5.0×10^{-4}	1.5×10^{-4}	1.5×10^{-4}

[a] Reactions were run at least in triplicate, and the data reported represent the average of these reactions. [b] Rate constants, k_{obs}, were determined by pseudo-first-order fitting of UV−vis spectral changes monitored at 695 nm for **6a**, 820 nm for **6b**, and 547 nm for **6c**. Reaction conditions: substrates (20 equiv to the intermediates) were added to the intermediates (2 mM for **6a** and **6b** and 2 × 10^{-2} mM for **6c**) in CH_3CN at 15 °C. [c] Data are from ref 17. [d] Not determined.

substrates. Further, the large negative Hammett ρ values determined kinetically in the present study are suggestive of a rate-limiting electron transfer from DMA to the oxoiron(IV) species (Scheme 1, pathway ET) (vide infra).[8,16] It should be noted that such a large negative ρ value was observed by the kinetic analysis in the oxidative N-demethylation with a Cu_2^{II}-O_2 adduct,[16] but much smaller ρ values were reported by analyzing products in the oxidative N-demethylation of *para*-substituted DMAs by iron(III) porphyrin complexes and iodosylbenzene (PhIO) under catalytic conditions.[8b,8c] Furthermore, a bell-shaped type dependence of reaction rates on the E°_{ox} of *para*-substituted DMAs and a less sensitive substituent effect on the reaction rates have been observed in the reactions of cumylperoxyl radical and *para*-substituted DMAs, in which HAT rather than ET−PT from substrates to the cumylperoxyl radical was proposed as a rate-determining step.[17] In the CYP 450 model with a rate-limiting electron-transfer step, a large negative

(14) We have observed the polymerization of *N*,*N*-dialkylanilines in some cases. Thus, *para*-substituted *N*,*N*-dialkylanilines were used to avoid the polymerization occurring at the *para*-position: Venkataramanan, N. S.; Kuppuraj, G.; Rajagopal, S. *Coord. Chem. Rev.* **2005**, *249*, 1249.

(15) Abbreviation used: TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane; N4Py, *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)-methylamine; TPFPP = *meso*-tetrakis(pentafluorophenyl)porphinato dianion.

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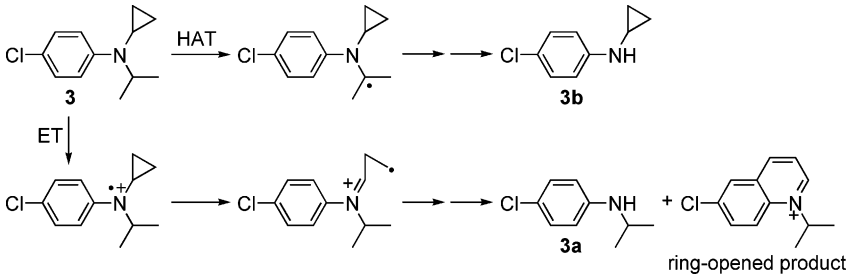
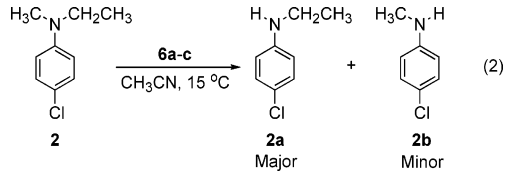
Scheme 2. Products Formed in the ET−PT and HAT Mechanisms

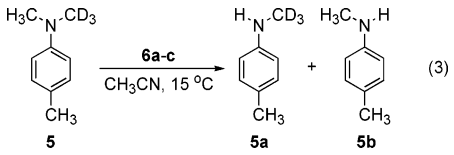


slope (approximately −8) was observed when the reaction rates were plotted against the oxidation potential of *para*-substituted DMAs.[8a]



The rate-limiting ET−PT process was further supported from the N-dealkylation of **2** by **6a**−**c**, in which N-demethylation was greatly favored over N-deethylation (eq 2).[9] The product ratios of **2a** to **2b** were high in all of the reactions (Table 1, column of **2a**/**2b** and Supporting Information Figure S3 for product analysis). The preference of the deprotonation of the methyl group over the ethyl methylene in the step of the proton transfer from the aminium radical to the (L)Fe^{IV}═O species (see the PT step in Scheme 1) was rationalized with a high acidity of the methyl proton as compared to the ethyl one (i.e., pK_a values of *N*,*N*-dimethylaniline and *N*,*N*-diethylaniline are 5.15 and 6.56, respectively).[9] If the N-dealkylation initiates via a HAT mechanism (Scheme 1, pathway HAT), the formation of a deethylated product, **2b**, would be a preferred pathway owing to a weak methylene C−H bond strength (i.e., ∼3 kcal/mol less than the methyl C−H bond strength), and a low product ratio of **2a** to **2b** would be observed (e.g., a ratio of 0.5 in the reaction of a tert-butoxy radical with amines).[18] Consequently, the high ratios of **2a** to **2b** observed in the present study rule out the possibility of a rate-limiting HAT pathway for the oxidative N-dealkylation reactions.

Additional support for the ET−PT mechanism was obtained by carrying out the oxidation of *para*-chloro-*N*-cyclopropyl-*N*-isopropylaniline (**3**) by **6a**−**c**; compound **3a** (and the ring-opened product) is the product(s) of N-decyclopropylation resulting from an ET pathway, whereas **3b** is the product of N-deisopropylation resulting from a HAT pathway (Scheme 2).[10,19] In the present study, we have observed that **3a** was the predominant product with the formation of a trace amount of **3b** in the reactions of **6a**−**c** (∼90% yield based on the intermediates generated) (Supporting Information Figures S4 for product analysis), supporting our conclusion that the N-dealkylation by nonheme and heme oxoiron(IV) complexes proceeds via an ET pathway (Scheme 2, pathway ET).



Finally, the inter- and intramolecular kinetic isotope effect (KIE) values were determined with deuteriated *para*-methyl-*N*,*N*-dimethylanilines such as *para*-methyl-*N*,*N*-di(trideuteromethyl)aniline (*p*-Me-DMA-d_6, **4**) and *para*-methyl-*N*-(trideuteromethyl)-*N*-methylaniline (*p*-Me-DMA-d_3, **5**). The intermolecular KIE values were measured kinetically (Table 1, column of $(k_H/k_D)_{inter}$; Supporting Information Figure S5 showing time traces for the determination of k_H and k_D values), whereas the intramolecular KIE values were obtained by a product analysis method (eq 3) (Table 1, column of $(k_H/k_D)_{intra}$; Supporting Information Figure S6 for product analysis for the determination of k_H/k_D values). The inter- and intramolecular KIE values in Table 1 are fully consistent with the proposed rate-limiting ET−PT mechanism, on the basis of the previous results reported in a number of N-dealkylation reactions by CYP 450 and biomimetic compounds.[8,9,16,19] If the N-dealkylation occurs via a HAT mechanism, a much higher KIE value would be expected.[18,20] Indeed, a KIE value of 50 was reported in both alkane hydroxylation and alcohol oxidation reactions by **6a**, in which a hydrogen atom abstraction from substrates by **6a** was proposed as a rate-determining step.[5b,5e] Further, as we have shown previously, the similar reactivities of **6a** and **6b** exclude the possibility of the HAT mechanism. In addition, the observation that the inter- and intramolecular KIE values are greater than 1 implies that the first ET process is not kinetically isolated but coupled with the following PT process.[9b] In other words, the oxidative N-dealkylation reactions may occur via a concerted proton-coupled electron transfer (PCET) process,[21] but more detailed investigations are needed to establish the PCET mechanism in the oxoiron-

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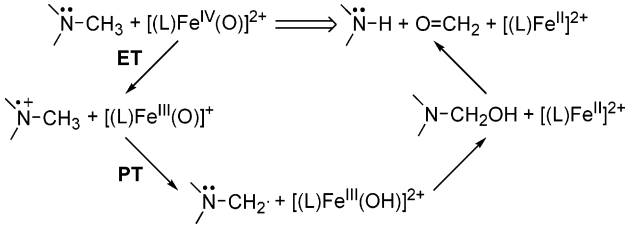
Scheme 3. Proposed Mechanism in Oxidative N-Demethylation by Nonheme Fe(IV)-oxo Intermediates



(IV) reactions. In the CYP 450 model system, the observation of high KIE values in a rate-limiting ET−PT mechanism was interpreted that there is a competition between back electron transfer from (Porp)Fe^{IV}═O to the nitrogen radical cation (i.e., a reverse reaction of the ET step in Scheme 1) and H-atom transfer from the nitrogen radical cation to (Porp)Fe^{IV}═O (i.e., the PT step in Scheme 1).[8a]

In summary, we have reported the first example of the oxidative N-dealkylation of *N*,*N*-dialkylanilines by nonheme and heme oxoiron(IV) complexes generated in situ. Mechanistic studies performed with various probes such as *para*-substituted *N*,*N*-dimethylanilines, *para*-chloro-*N*-ethyl-*N*-methylaniline, *para*-chloro-*N*-cyclopropyl-*N*-isopropylaniline, and deuteriated *N*,*N*-dimethylanilines (see structures in Chart 1) provided strong evidence that the N-dealkylation reactions proceed via a rate-limiting ET followed by a PT process (Schemes 1 and 3 for mechanisms of heme and nonheme oxoiron(IV) reactions, respectively). The relative reactivities of nonheme and heme oxoiron(IV) complexes were briefly discussed in the present study, but more detailed investigations are needed to understand the exact role of ligand structures in controlling the reactivities of nonheme and heme oxoiron(IV) complexes in the oxidative N-dealkylation reactions.[22]

Experimental Procedures

Starting Materials. All chemicals obtained from Aldrich Chemical Co. were the best available purity and used without further purification unless otherwise noted. Solvents were dried according to published procedures[23] and distilled under Ar prior to use. Iron(II) complexes such as Fe(TMC)$(OTf)_2$·$2CH_3CN$ and Fe(N4Py)-$(ClO_4)_2$·CH_3CN were prepared in a glovebox by literature methods.[5a,24] Iodosylbenzene was prepared by a literature method.[25] *m*-Chloroperbenzoic acid (*m*-CPBA) was purified by washing with phosphate buffer (pH 7.4) and then water, followed by drying under reduced pressure. Fe(TPFPP)Cl and CD_3I were obtained from Aldrich. *para*-Methoxy-*N*,*N*-dimethylaniline was prepared by reacting *para*-anisidine with *para*-formaldehyde followed by sodium cyanoborohydride reduction.[26] *para*-Chloro-*N*-ethyl-*N*-methylaniline (**2**) was obtained by coupling *para*-bromochlorobenzene with *N*-ethylmethylamine in the presence of $Pd_2(dba)_3$ and BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) as catalysts.[27] *para*-Chloro-*N*-cyclopropyl-*N*-isopropylaniline (**3**) was prepared by condensing *para*-chloro-*N*-cyclopropylaniline[28] with acetone, followed by sodium cyanoborohydride reduction.[29] *para*-Methyl-*N*,*N*-di(trideuteriomethyl)aniline (*p*-Me-DMA-d_6, **4**) and *para*-methyl-*N*-(trideuteriomethyl)-*N*-methylaniline (*p*-Me-DMA-d_3, **5**) were prepared by alkylating either *p*-toluidine or *N*-methyl-*p*-toluidine with CD_3I.[11b] The purities of the compounds were checked with ^1H NMR spectra.

Caution: Perchlorate salts are potentially explosive and should be handled with great care.

Instrumentation. 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-ESI MS spectra were collected on a Finnigan Surveyor Integrated HPLC systems (PDA detector and LC pump) connected with Thermo Finnigan (San Jose, CA) LCQ Advantage MAX quadrupole ion trap instrument. The separation of products was achieved by on-column injection to a Hypersil GOLD column (5 μm, 4.6 × 250 mm) using a CH_3CN/H_2O (3:1) eluent at a flow rate of 1 mL/min, at the spray voltage 4.8 kV and the capillary temperature at 250 °C. All products *m*/*z* correspond to $[M + 1]^+$. Product analysis for the oxidation of *N*,*N*-dialkylanilines was performed on DIONEX Pump Series P580 equipped with a variable wavelength UV-200 detector (HPLC). GC and GC-MS analyses were with an 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). ^1H NMR spectra were recorded on a Bruker 250 spectrometer. All spectra were recorded in $CDCl_3$ using TMS as an internal standard.

Reactions of Nonheme and Heme Oxoiron(IV) Complexes with *N*,*N*-Dimethylanilines. 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. Nonheme oxoiron(IV) complexes, **6a** and **6b**,[5a,5b] were prepared by reacting Fe(N4Py)$(ClO_4)_2$ (2 mM) with excess solid PhIO and Fe(TMC)-$(OTf)_2$ (2 mM) with 1.2 equiv of PhIO (2.4 mM, diluted in 50 μL of CH_3OH), respectively, in a 1 cm UV cuvette in CH_3CN (2 mL) at ambient temperature. Oxoiron(IV) porphyrin, **6c**, was prepared by adding 4 equiv of *m*-CPBA (8 mM, diluted in 10 μL of CH_3CN) into a solution containing Fe(TPFPP)Cl (2 mM) and H_2O (3 μL) in a solvent mixture (0.1 mL) of CH_2Cl_2 and CH_3CN (1:3) at ambient temperature,[4] and then the resulting solution was diluted with CH_3CN. The final concentration of **6c** was 0.02 mM. Then, appropriate amounts of *N*,*N*-dialkylanilines were added into the UV cuvette, and spectral changes of the oxoiron(IV) complexes were directly monitored with a UV−vis spectrophotometer. Rate constants, k_{obs}, were determined by pseudo-first-order fitting of the decrease of absorption bands at 695 nm for **6a**, 820 nm for **6b**, and 547 nm for **6c**.

Product Analysis for the Oxidation of *N*,*N*-Dialkylanilines by Oxoiron(IV) Complexes. Reaction solutions of oxoiron(IV) intermediates (2 mM) were prepared as described above. Then, 20 equiv of *N*,*N*-dialkylanilines (40 mM) was added to the reaction solutions. Product analysis was performed by injecting reaction solutions directly into HPLC, LC-ESI MS, GC, and/or GC-MS (see Figures S3 and S4). Product yields were determined by comparison with standard curves of known authentic samples.

In the reaction of *para*-methyl-*N*-(trideuteriomethyl)-*N*-methylaniline (*p*-Me-DMA-d_3, **5**), *p*-Me-DMA-d_3 (40 mM) was added

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to reaction solutions containing oxoiron(IV) complexes (2 mM). After 30 min, the resulting solutions were passed through a short silica-gel column. Product analysis was then performed with HPLC for product yields and LC-ESI MS for product ratios. The deuterium compositions in *para*-methyl-*N*-methylaniline were analyzed by the relative abundances of $m/z = 122$ for *para*-methyl-*N*-methylaniline and $m/z = 125$ for *para*-methyl-*N*-(trideuteromethyl)aniline (see Figure S6).

Acknowledgment. This research was supported by MOST/KOSEF through the Creative Research Initiative Program (W.N.), the Korea Research Foundation (KRF-2005-217-C00006 to M.S.S.), and the SRC/ERC program of MOST/KOSEF (R11-2005-008-00000-0 to J.K.).

Supporting Information Available: Additional kinetic and spectroscopic data and product analysis (Figures S1−S6). This material is available free of charge via the Internet at http://pubs.acs.org.

IC0614014