

Generation of Iron(IV) in the Oxidation of Amines by Ferrate(VI): Theoretical Insight and Implications in Oxidizing Pharmaceuticals

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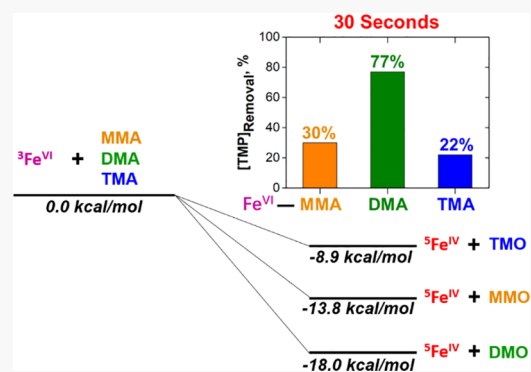
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ABSTRACT: Aliphatic amines are ubiquitously present in natural waters and constitute one of the major moieties in dissolved organic matter and water micropollutants such as pharmaceuticals. This paper presents aliphatic amine {monomethylamine (CH_3NH_2 , MMA), dimethylamine [$(\text{CH}_3)_2\text{NH}$, DMA], and trimethylamine [$(\text{CH}_3)_3\text{N}$, TMA]}-enhanced oxidation of pharmaceuticals (trimethoprim, atenolol, carbamazepine, and sulfadiazine) by ferrate(VI) [$\text{Fe}^{\text{VI}}\text{O}_4^{2-}$, Fe(VI)]. The magnitude of the enhancement varies with amines, and DMA shows the greatest potential to increase the level of oxidation of trimethoprim. The computational approach is applied to describe the trend of an increased level of oxidation by Fe(VI) in the presence of amines. The computation showed that an Fe(VI) /amine solution forms highly reactive Fe^{IV} species as intermediates that react with pharmaceuticals to yield enhanced oxidation. In the rate-determining step of Fe(VI) reactions with amines, TS1, the Fe(VI) is reduced and abstracts an H from N, followed by the transfer of an O atom to N to form a very stable intermediate involving a nitroxide radical. The abstracted H is then transferred back to the N-O group in TS2 to form an H-bonded product complex, which dissociates to the products. The difference in the reactivity of the Fe^{IV} species with the type of amine explains the trend seen experimentally in the enhanced oxidation of pharmaceuticals.

KEYWORDS: high-valent iron, mechanism, density functional theory calculations, transition state, micropollutants, co-contamination



INTRODUCTION

Organic amines are key components in organic synthesis, metalloenzymatic reactions, atmospheric particles, coastal waters, and municipal and industrial wastewater discharges.^{1–5} Amines are widespread in surface water because their moieties are usually found in dissolved natural organic matter and anthropogenic organic contaminants such as pharmaceuticals, personal care products, dyes, and pesticides.⁶ Amines in water resources are of concern because disinfection using chlorine and chloramine results in the formation of potentially toxic disinfection byproducts (DBPs).^{7,8} Many investigators, including our group, are studying an iron-based oxidant, ferrate(VI) [$\text{Fe}^{\text{VI}}\text{O}_4^{2-}$, Fe(VI)], as a preoxidant prior to disinfection by chlorination.^{9–12} The application of Fe(VI) as a preoxidant and subsequent chlorination decrease the levels of chlorinated DBPs (Cl-DBPs) because the oxidation of amine-containing constituents in water and the resulting oxidized products cannot react fully to generate Cl-DBPs.^{9,10,13–15} Amine moieties in pharmaceuticals also play an important role in their oxidation by Fe(VI) in water.^{16–19} For example, in the oxidation of sulfonamides, the amine moieties determined the reaction pathways that yield oxidized products.^{18,20}

The mechanism of oxidation of pollutants, including amine-containing molecules, by Fe(VI) possibly involves iron(IV) (Fe^{IV}), iron(V) (Fe^{V}), or both as the intermediate(s).^{21–27} In

the past, the complexation of ammonia with Fe^{IV} and Fe^{V} has been proposed to describe the observed results for the oxidation of ammonia by Fe(VI) .^{28,29} Recently, we have found that creatinine (2-amino-1-methyl-5H-imidazol-4-one, CRE), an amine-containing major organic constituent of urine, could enhance the degradation of pharmaceuticals by Fe(VI) .³⁰ CRE is known to be a ligand for metal ions, including iron.³¹ The results of kinetic modeling and experimental data suggested the formation of Fe^{IV} to cause enhanced oxidation by Fe(VI) in the presence of CRE. Many researchers, including us, applied a chemical probe molecule, i.e., methyl phenyl sulfoxide (PMSO), to demonstrate the formation of Fe^{IV} / Fe^{V} intermediates during the oxidations by Fe(VI) . Studies did not establish which of the two intermediates dominated during Fe(VI) oxidations.^{24,26} The Fe^{IV} / Fe^{V} species are present at low steady-state concentrations and only for time scales in the range from microseconds to milliseconds.^{30,32,33} Therefore, attempts of spectroscopic

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approaches to identify $\text{Fe}^{\text{IV}}/\text{Fe}^{\text{V}}$ species in an aqueous environment were not successful.^{30,32} The demonstration of the intermediate $\text{Fe}^{\text{IV}}/\text{Fe}^{\text{V}}$ species is restricted to a non-aqueous (or organic) solvent in which the central iron is complexed by bulky organic ligands such as porphyrins and 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane.^{2,34,35} In other words, the direct experimental evidence of the high-valent iron intermediate in the oxidative chemistry of $\text{Fe}(\text{VI})$ requires overcoming of limitations imposed by the inherent instability of $\text{Fe}^{\text{IV}}/\text{Fe}^{\text{V}}$ species and their trapping in aqueous solutions.

Density functional theory (DFT) calculations may be a tool for understanding the mechanism of oxidation by $\text{Fe}(\text{VI})$. There are few studies of the application of DFT calculations to determine the $\text{Fe}^{\text{IV}}/\text{Fe}^{\text{V}}$ involved as intermediate species in reactions of a pollutant (X) with $\text{Fe}(\text{VI})$.^{20,36,37} In the work presented here, we have used DFT calculations to advance our understanding of which of the two intermediates, Fe^{IV} and Fe^{V} , is participating in the initial step of the oxidation of X by $\text{Fe}(\text{VI})$. DFT calculations may determine whether oxygen atom transfer (OAT) [$\text{Fe}^{\text{VI}}\text{O}_4^{2-} + \text{X} \rightarrow \text{Fe}^{\text{IV}}\text{O}_3^{2-} + \text{X}(\text{O})$] or one-electron transfer (SET) ($\text{Fe}^{\text{VI}}\text{O}_4^{2-} + \text{X} \rightarrow \text{Fe}^{\text{V}}\text{O}_4^{3-} + \text{X}^{\bullet+}$) occurs in the initial step of the mechanism to give Fe^{IV} or Fe^{V} , respectively. We selected monomethylamine (CH_3NH_2 , MMA), dimethylamine [$(\text{CH}_3)_2\text{NH}$, DMA], and trimethylamine [$(\text{CH}_3)_3\text{N}$, TMA] as three model aliphatic amines to elucidate mechanisms by $\text{Fe}(\text{VI})$ using DFT calculations. The chosen molecules are primary (1°), secondary (2°), and tertiary (3°) amines, respectively, and the calculations could describe the kinetics of the reactivity with $\text{Fe}(\text{VI})$ with the trend that the reactivity of amines at neutral and alkaline pH conditions [i.e., DMA (2°) or MMA (1°)] was found to be higher than that of TMA (3°).^{16,38}

This work aimed to learn how the trend of the reactivity of different amines influences the magnitude of enhancement of the oxidation of the pharmaceuticals, i.e., trimethoprim, atenolol, carbamazepine, and sulfadiazine, by $\text{Fe}(\text{VI})$. We first determined experimentally the oxidation of the pharmaceuticals in the presence of amines, followed by the DFT calculations on the initial step of the reaction of $\text{Fe}(\text{VI})$ with amines to learn which high-valent intermediate (i.e., Fe^{IV} or Fe^{V}) species as intermediate species cause the enhanced oxidation of trimethoprim (TMP) by the Fe^{VI} –amine system. The implications of the studies of degradation of amine-containing co-contaminants by $\text{Fe}(\text{VI})$ are briefly discussed.

■ EXPERIMENTAL AND COMPUTATIONAL METHODS

Chemicals and Reagents. TMP (>98% purity), amines (i.e., MMA, DMA, and TMA), hydroxylamine, PMSO, methyl phenyl sulfone (PMSO_2), and $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ as well as methanol and phosphoric acid (85%) [high-performance liquid chromatography (HPLC) grade] were acquired from Fisher Scientific (Austin, TX) and used without further purification. A wet chemical synthesis method was applied to synthesize potassium ferrate (K_2FeO_4) at a purity of >95%.³⁹ The stock solutions of TMP, Fe^{VI} , amines, PMSO, and hydroxylamine were prepared in 10.0 mM $\text{Na}_2\text{B}_4\text{O}_7$ at pH 9.0. The concentrations of Fe^{VI} were quantified by measuring the absorbance at 510 nm using an ultraviolet–visible (UV–vis) spectrometer (DR-5000, Hach Co.). An extinction coefficient ϵ_{510} of $1150 \text{ M}^{-1} \text{ cm}^{-1}$ was used.⁴⁰ All solutions were prepared in ultrapure water (resistivity of $>18 \text{ M}\Omega \text{ cm}^{-1}$), obtained from

a Milli-Q water purification system (Millipore, Waters Alliance, Milford, MA).

Oxidation of TMP by $\text{Fe}(\text{VI})$ –Amine Systems. Experiments were performed in 100 mL glass jars under a constant stirring rate (400 rpm) at room temperature in at least triplicate. Different amounts of amine stock solutions (1.0 M for each amine) were pre-added to a TMP solution ($5.0 \mu\text{M}$) before mixing with an Fe^{VI} solution ($100.0 \mu\text{M}$) at an equal volume of 10 mL. The pH of reaction mixtures was maintained at 9.00 ± 0.05 using 10.0 mM borate buffer. After oxidation for 30 s, a $20.0 \mu\text{L}$ hydroxylamine solution (1.0 M) was added to quench the reactions. The aqueous samples were collected and transferred to vials for carrying out analysis. Similar experiments were also conducted using PMSO ($5.0 \mu\text{M}$) as a probe agent of high-valent iron species. To explore the effect of the concentration ratio of Fe^{VI} to amine on the elimination of TMP, the concentration of $\text{Fe}(\text{VI})$ was varied from 50.0 to $200.0 \mu\text{M}$ in the reaction system by keeping the concentration of DMA constant (2.0 mM).

Analytical Procedures. The residual concentrations of TMP during oxidation by Fe^{VI} with or without amines were determined using an Ultimate 3000 Ultra high-performance liquid chromatography (UHPLC) (ThermoFisher Scientific), coupled with the diode array detector at 271 nm. Chromatographic separation was performed on a RESTEK Ultra C₁₈ analytical column (4.6 mm $\times$ 250 mm, particle size of $5 \mu\text{m}$) at 30°C and a flow rate of 1.0 mL/min. The mobile phase consisted of 0.05% phosphoric acid in water (A, 35%) and methanol (B, 65%), and the sample injection volume was $10.0 \mu\text{L}$. For the measurement of PMSO and PMSO_2 , the HPLC conditions were as follows: A:B, 30:70; flow rate, 1.0 mL/min; detection wavelength, 230 nm (PMSO) and 215 nm (PMSO_2); and injection volume, $10.0 \mu\text{L}$.

Quantum Chemical Calculations. All calculations were performed with Gaussian 09⁴¹ using the unrestricted M06 DFT functional⁴² with an ultrafine integration grid, which gave very good agreement with the experimental geometries of ferrates. For iron, the Wachters–Hay⁴³ all-electron basis set augmented by one f-polarization function was used. The 6-311++G(d,p) basis set was used for all other atoms. During all calculations, solvent effects were accounted for using the SMD⁴⁴ solvation model set to the default dielectric constant for water. Optimized stationary point geometries were obtained with the default Gaussian 09 “Berny” optimization algorithm;⁴⁵ the transition-state (TS) geometries were determined with the QST3 synchronous transit-guided quasi-Newton (STQN) method,^{46,47} where the TS guess was generally taken to be the midpoint between the reactant and product sides. The reactants, products, and intermediates were confirmed by noting that there were no imaginary vibrational frequencies, while for the transition states, each had one imaginary frequency that corresponded to the expected reaction coordinate.

■ RESULTS AND DISCUSSION

Enhanced Oxidation of Pharmaceuticals by $\text{Fe}(\text{VI})$ –Amine Systems. The literature has demonstrated that the reactivity of Fe^{IV} species is higher than that of $\text{Fe}(\text{VI})$.^{36,48,49} This prompted us to explore if Fe^{IV} species could be effective in oxidizing the micropollutants, which otherwise react sluggishly with $\text{Fe}(\text{VI})$ to have degradation of pharmaceuticals in minutes to hours at mild alkaline pH values.⁵⁰ We selected an antibiotic, trimethoprim (TMP), that has slow reactivity

with Fe(VI) ($k = 4.1 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ at pH 9.0).⁵¹ In testing the hypothesis, we mixed Fe(VI) with TMP and added different amounts of amines, and the reaction was quenched in 30 s by adding excess hydroxylamine. In the mixed solution, the molar ratios of amines to Fe(VI) were in the range from 0 to 120. The results are presented in Figure 1a. With no amine

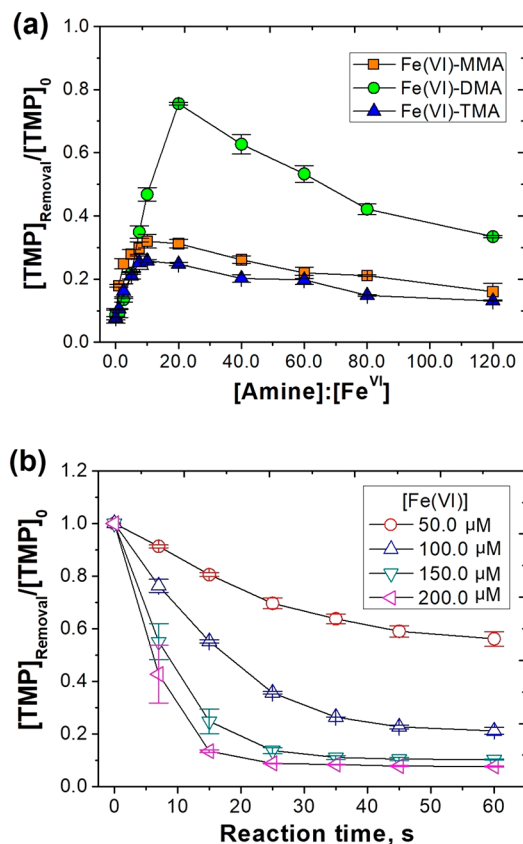


Figure 1. (a) Removal of TMP by Fe(VI) in the presence of different amines (i.e., MMA, DMA, and TMA). Experimental conditions: $[TMP] = 5.0 \mu\text{M}$, $[Fe(VI)] = 100.0 \mu\text{M}$, reaction time = 30 s, and pH 9.0 (10.0 mM borate buffer). (b) Removal of TMP by the Fe(VI)–DMA system at different concentrations of Fe(VI). Experimental conditions: $[TMP] = 5.0 \mu\text{M}$, $[Fe(VI)] = 50.0\text{--}200.0 \mu\text{M}$, $[DMA] = 2.0 \text{ mM}$, reaction time = 60 s, and pH 9.0 (10.0 mM borate buffer).

in the reaction mixture, the level of removal of TMP by Fe(VI) was $\sim 10\%$. However, with amines in the reaction mixture, the level of removal of TMP increased with amine concentration initially, followed by a decrease at higher concentrations of amines.

The presence of amines enhances the oxidation of TMP by Fe(VI) (Figure 1a); however, the molar ratio of amine to Fe(VI) determined the magnitude of the enhancement. The maximum level of removal of TMP was at an $[amine]:[Fe(VI)]$ ratio of 20.0. Furthermore, the enhanced oxidation of TMP depended on the type of amines with maximum levels of elimination of 30%, 75%, and 25% for MMA, DMA, and TMA, respectively. This suggests that the formation and nature of the Fe^{IV} –amine complex defined the reactivity with TMP. The formation of the amine complex would be determined by the donating ability of electrons by the amine and its interaction with Fe(VI). TMA is best able to donate electrons to Fe(VI) in the initial step, but steric hindrance inhibits interaction with Fe(VI) to ultimately form the Fe^{IV} –TMA complex. It appears

that the Fe^{IV} –DMA complex is relatively stable to react with TMP to yield the most enhanced removal of TMP (Figure 1a). The results further indicate that, with the addition of an excess of amine [i.e., $[amine]:[Fe(VI)] > 20.0$], the Fe^{IV} –amine complex may be reacting with not only TMP but also amine to cause the decrease in the efficiency of TMP removal by the Fe(VI)–amine system.

The Fe(VI)–DMA system was selected to further enhance the oxidation of TMP. In the Fe(VI)–DMA–TMP system, the concentration of DMA was constant but the Fe(VI) concentration was varied and degradation of TMP as a function of reaction time was monitored (Figure 1b). Notably, $>90\%$ of TMP could be oxidized in 25 s by the Fe^{VI} –DMA system. The level of degradation of TMP increased with Fe(VI) concentration. The reaction of Fe(VI) with DMA has been shown to give formic acid and nitrogen,³⁸ products that are relatively nontoxic.

The formation of Fe^{IV} species was indirectly investigated by using PMSO as a probe molecule. The high-valent iron species converts PMSO to $PMSO_2$, which suggests the existence of high-valent intermediates in the oxidation by Fe(VI).^{24,52} The results of the oxidation of PMSO and the formation of $PMSO_2$ by Fe(VI) and Fe(VI)–DMA systems are shown in Figure S1. No oxidation of PMSO occurred with only Fe(VI) (see Figure S1a). However, the Fe(VI)–DMA system could oxidize PMSO with 100% conversion to $PMSO_2$ (Figure S1b). This suggests the role of high-valent iron intermediates (i.e., Fe^{IV} –amine complex) in accelerating the oxidative transformation by the Fe(VI)–amine system.

Finally, the possibility of Fe^{IV} in enhancing the oxidation of other types of pharmaceuticals and the removal of atenolol, carbamazepine, and sulfadiazine by the Fe(VI)–amine system were tested. The results showed enhanced removal of the pharmaceuticals in Fe(VI)–MMA and Fe(VI)–DMA systems in 30 s (Figure S2). The removal percentages of the Fe(VI)–DMA system were higher than that of the Fe(VI)–MMA system, similar to the oxidation of TMP (see Figure 1a). However, the magnitude of the enhancement differs with the kind of pharmaceutical. This is related to the corresponding rates of the oxidation of the pharmaceuticals by Fe^{IV} species.

DFT Calculations. The first question is whether the oxidation of amines by Fe(VI) proceeds through an initial OAT or SET step. In performing calculations, we used the protonated species ($HFe^{VI}O_4^-$) as the dominant reactive species to react with amines at neutral pH. The computed thermodynamic values are listed in Table S1. The results showed that OAT oxidation of all three amines is exergonic, while SET of the amines is endergonic. This suggests that OAT is the favorable step of the oxidation of amines by $HFeO_4^-$. Next, each of the reactions between $HFeO_4^-$ and the different amines to yield Fe^{IV} via OAT was examined. The results are given below. We have presented DMA first, followed by MMA and finally TMA. The optimized bonds, spins, and charges of the amines, transition states, intermediates, and products are shown in Figures S3–S5. The energy value of the individual starting structures (i.e., Fe^{VI} and MMA, Fe^{VI} and DMA, and Fe^{VI} and TMA) was set as zero, and the relative values of the other structures are given.

Dimethylamine. The computed thermodynamic data for the reactants, transition states, intermediates, and products in the oxidation of DMA by Fe(VI) are listed in Table S2, and the Gibbs free energy pathway is plotted in Figure 2. TS1 is 25.0 kcal/mol higher than the reactants. This is considerably higher

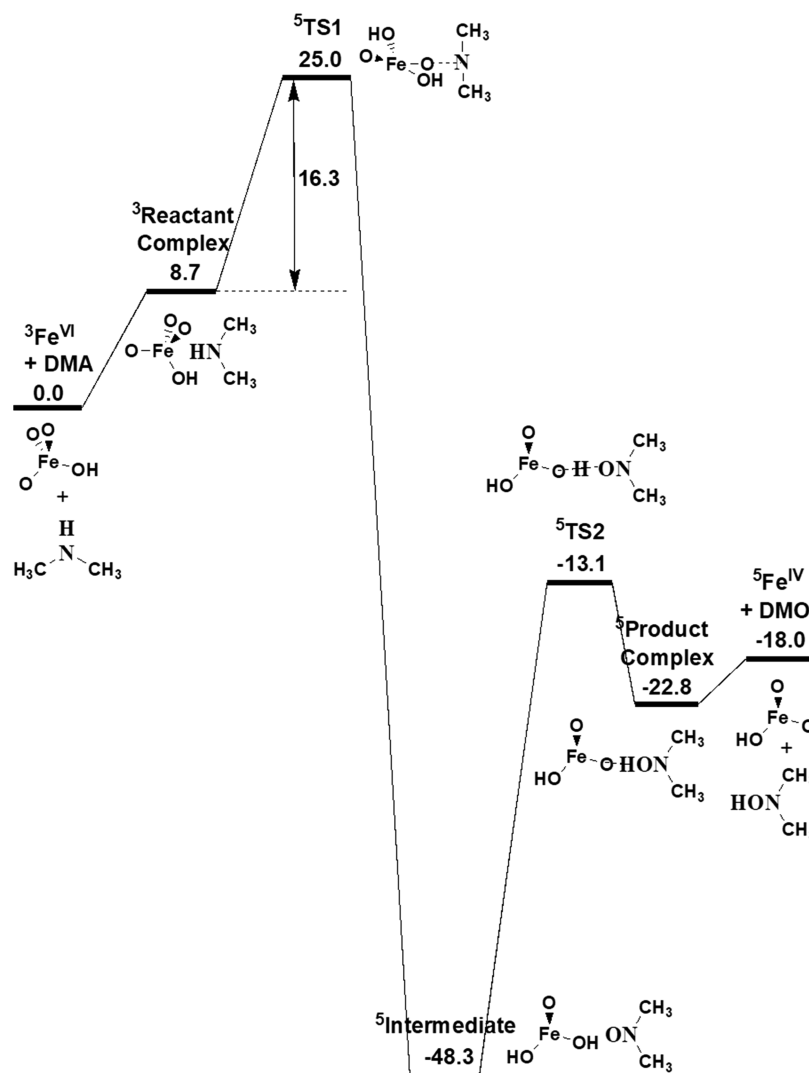


Figure 2. Gibbs free energy pathway (kilocalories per mole) of DMA oxidation by $\text{HFe}^{\text{VI}}\text{O}_4^-$.

than the experimental value of 16.9 kcal/mol based on the measured rate constant.⁵³ However, TS1 is only 16.3 kcal/mol above the reactant complex, very close to the experimental value. This implies the formation of the reactant complex, which may be an intermediate. The formation of the reactant complex is exothermic ($\Delta H = -2.2$ kcal/mol), although a large decrease in entropy leads to a positive ΔG .

$\text{HFe}^{\text{VI}}\text{O}_4^-$ versus $\text{HFe}^{\text{IV}}\text{O}_3^-$. The computed bond lengths of $\text{HFe}^{\text{VI}}\text{O}_4^-$ are shorter than those of $\text{HFe}^{\text{IV}}\text{O}_3^-$ (Fe–OH, 1.80 Å vs 1.84 Å; Fe=O, 1.60 Å vs 1.66 Å) as a result of less electron repulsion. Although the charge on Fe is slightly less positive (+0.38 vs +0.43), the oxygen atom is less negative, −0.40 [−0.35 on O(H)] versus −0.55 on average [−0.48 on O(H)], because there are two fewer electrons. Also, the spin density is lower, 1.57 versus 3.37, on Fe^{VI} because there are two fewer unpaired electrons.

Reactant Complex. There is no geometry change in either of the reactants. There is a slight spin on the DMA atom, all less than 0.00. This indicates slight interaction even though the intermolecular distance is still 3.70 Å. This complex may be an intermediate.

TS1. The triplet TS1 lies 23 kcal/mol above the quintet, so only the quintet was considered. The single imaginary frequency (-415 cm^{-1}) shows the Fe–O stretching as the O

moves to the N and the (Fe)OH bond length decreasing as the H has been transferred from N to ferrate. Therefore, ferrate abstracts an H atom from the NH followed by transfer of the O to N. The TS1 bond lengths reflect this transfer with the N–H distance increased from 1.02 to 2.26 Å and an N–O distance of 1.52 Å. It is interesting that the Fe–O distance has decreased (from 1.80 to 1.41 Å) and the new O–H distance is shorter than expected (0.90 Å vs 0.96 Å). The NCN bond angle has increased from 112° to 180°. Because the overall charge remains −1, it is not surprising that most atomic charges, including Fe (+0.39), remain unchanged. The N does become less negative (−0.22 to −0.08) as does the transferred O (−0.37 to −0.27), while the remaining ferrate oxygen atoms become more negative, especially the remaining Fe=O oxygen (−0.37 to −0.53). The most significant spin change is on Fe (from 1.57 to 3.34), indicating the addition of two unpaired electrons from the surrounding O atoms, which also show increased spin. There is only a very slight spin (−0.03) on N. The negative sign indicates the opposite spin.

Intermediate. The intermediate is very stable compared to the reactants (−49.6 kcal/mol). The N–O bond has formed (1.28 Å) as well as the new ferrate O–H bond (0.96 Å). The Fe–O bond lengths have all increased by 0.05 or 0.07 Å. The charge on Fe has decreased from +0.39 to +0.25, and the

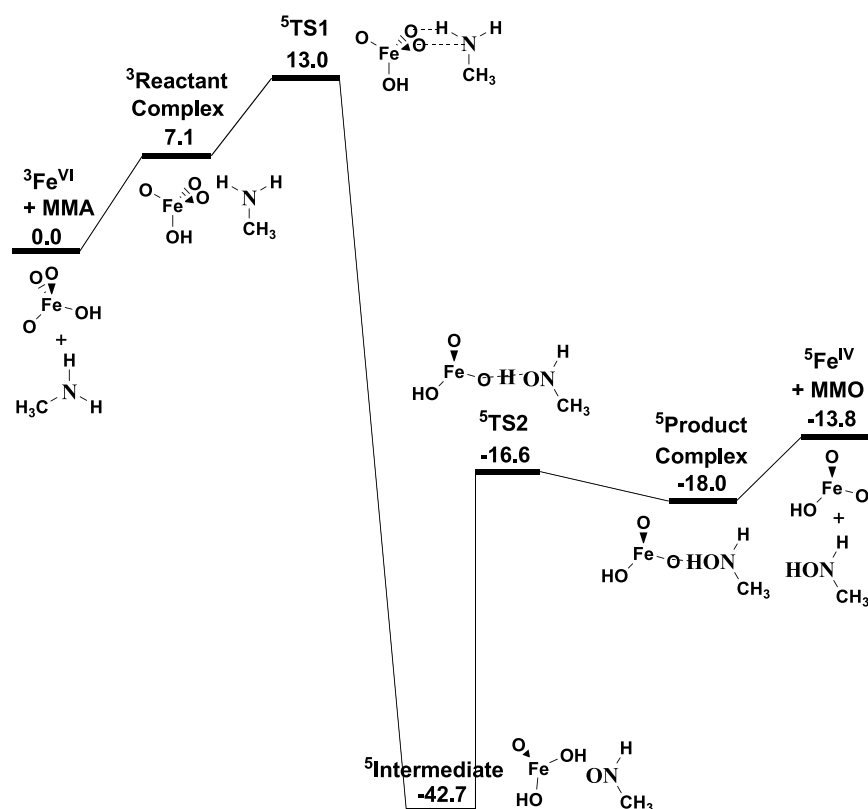


Figure 3. Gibbs free energy pathway (kilocalories per mole) of MMA oxidation by HFe^{VI}O₄⁻.

ferrate O atom is more negative (−0.27 to −0.48) upon formation of the FeO–H bond. The charge on N is now positive (+0.08) upon formation of the N–O bond. There are significant changes in the spins on the amine moiety, specifically −0.44 on N and −0.26 on O with slight negative spins on the other atoms, so the total spin on the nitroxide is −0.83 (opposite spin to ferrate). This is consistent with its description as a nitroxide radical. The Fe spin has increased from 3.34 to 3.97 with smaller increases on the other ferrate atoms for a total ferrate spin of 4.83 (five unpaired electrons).

TS2. The single imaginary frequency (−1732 cm^{−1}) shows the H atom being transferred back from a ferrate O atom to the amine NO oxygen. The H atom is located midway between the O atoms on ferrate and the amine oxide. The N–O bond is longer (1.37 Å vs 1.28 Å in the intermediate) as the H atom is transferred, and the ferrate bond lengths are close to that of the final product. The only change of note is a more negative charge on N (−0.07 vs +0.08 in the intermediate). The net spin on the nitroxide is −0.28, indicating some remaining radical character, and the spin on Fe is now 3.72 (total of 4.26 on the ferrate).

Product Complex. The transfer of the H atom results in a stable H-bonded complex, 4.8 kcal/mol below the final products. The internal geometries are essentially the same as the individual products, discussed below. The charges are slightly different than in either TS2 or the products (dimethyloxime, DMO). For example, the Fe atom charge is +0.33 versus +0.47 (TS2) or +0.43 (DMO) and the N atom charge is −0.04 versus −0.07 (TS2) or −0.10 (DMO). There is a slight spin (0.10) on the N atom, indicating slight interaction between the two products.

Products. In Figure 2, Fe(IV) and DMO represent the products. Relative to TS2, the Fe–O(H) bond length

decreases (from 1.73 to 1.67 Å) as the H atom is transferred back to the amine moiety. Likewise, the O–H distance decreases (from 1.14 to 0.96 Å) as that bond is formed in the amine along with an increase in the N–O bond length (from 1.37 to 1.43 Å). The ferrate O(H) charge becomes more negative (−0.45 to −0.57) once the H atom is completely transferred back to the amine. The changes in the amine charges are slight. The DMO spins are zero because there are no unpaired electrons and the ferrate(IV) spins are as described above.

Monomethylamine. The computed thermodynamic data for the reactants, transition states, intermediates, and products are listed in Table S3, and the Gibbs free energy pathway is plotted in Figure 3. The energy of TS1, the rate-determining step, is 13.0 kcal/mol higher than the reactants (5.9 kcal/mol relative to the reactant complex). This is lower than the experimental value of 17.1 kcal/mol based on the measured rate constant.³⁸ It also is qualitatively incorrect in predicting the oxidation rate for MMA is faster than for DMA. However, a variety of computations (e.g., explicit inclusion of water molecules) failed to produce better results and the overall mechanisms for the two amines are consistent with one another.

MMA versus DMA. The most obvious difference is the presence in MMA of two sites (N–H bonds) to initiate oxidation. Additionally, the second methyl group in DMA sterically hinders access to the N atom. There are no significant differences in the bond lengths (e.g., N–H, 1.02 Å vs 1.01 Å). The additional methyl group reduces the negative charge on N slightly (−0.22 vs −0.28).

Reactant Complex. The closest approach involves a weak H-bond with an O–HN distance of 2.90 Å. The geometries,

atomic charges, and spin densities of the two reactants are unchanged.

TS1. The quintet transition state converged with one imaginary frequency of -629 cm^{-1} that shows an O atom being transferred from ferrate to MMA while an H atom has already been transferred from the N atom to ferrate and the newly formed O–H bond is shrinking. The N atom charge has decreased from -0.28 to -0.14 . There has been a transfer of an electron from MMA to ferrate, resulting in an unpaired electron on MMA with significant spin density (0.71) on the N atom. The spin density on Fe has increased from 1.57 to 2.83 with the addition of an electron. Note that the O atom being transferred has the only negative spin (-0.20).

Intermediate. The intermediate is very stable (-42.7 kcal/mol) compared to the reactants. The N–O distance has decreased from 2.33 to 1.26 Å as the N–O bond has formed. Likewise, the new ferrate O–H bond is 0.96 Å (reduced slightly from 0.97 Å in TS1). The Fe–O distances are all longer (1.72 , 1.90 , and 1.91 Å vs 1.63 , 1.84 , and 1.86 Å) than in TS1, or in Fe^{VI} or Fe^{IV} . The N atom charge is now positive ($+0.06$); the H(N) is also more positive ($+0.04$ to $+0.17$), while the Fe charge has decreased from $+0.37$ to $+0.26$. The remaining O(Fe) has become more negative (-0.47 to -0.70). The spin density on Fe has increased further from 2.83 to 3.96 as have those of the other ferrate atoms, while the spin density on the MMA species is now negative with the value on N being -0.43 . In contrast to that of DMA, this is a two-stage process. In MMA, the second electron is transferred to the ferrate when the transfer of the O atom to MMA has reached completion, which occurs after TS1. The net spin density (-0.82) on the MMA species is consistent with the formation of a nitroxide radical, and the ferrate has been reduced to Fe^{IV} .

TS2. There is one imaginary frequency at -868 cm^{-1} that involves the transfer of an H atom from ferrate back to the MMA species. The H atom is close to the midpoint, 1.34 Å from the ferrate oxygen and 1.10 Å from the MMA oxygen. The N–O bond length has increased from 1.26 to 1.39 Å , and the Fe–OH bond length has decreased from 1.91 to 1.73 Å . The charges are closer to those in TS1, -0.06 on N, $+0.39$ on Fe, and -0.54 on O(Fe). The spin density on the MMA species goes to zero as the H atom is transferred to form the oxime.

Product Complex. A stable (-4.2 kcal/mol with respect to the products) H-bonded complex is formed from TS2. The O–HO distance is 1.78 Å ; the N–O bond length has increased slightly more (1.42 Å), and the Fe–O bond is now slightly shorter (1.69 Å). There are no significant changes in the charges or the spin densities.

Products. In Figure 3, $\text{Fe}(\text{IV})$ and monomethyl oxime (MMO) represent the products. There are no further changes to the internal properties of the ferrate or oxime once the H-bond in the complex is broken.

Trimethylamine. The computed thermodynamic data for the reactants, transition states, intermediates, and products are listed in Table S4, and the Gibbs free energy pathway is plotted in Figure 4. There is no H atom bonded to nitrogen in TMA, so the only transition state involves the transfer of an O atom from the ferrate to TMA. Consequently, no intermediate is formed. The energy of TS, the rate-determining step, is 19.5 kcal/mol higher than that of the reactants (15.9 kcal/mol relative to the reactant complex). This is reasonably close to the experimental value of 18.2 kcal/mol based on the measured rate constant.⁵³ It is also correctly higher than the experimental

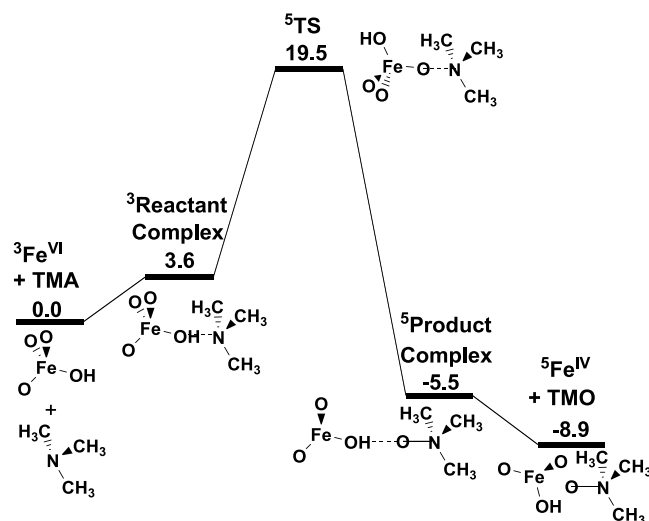


Figure 4. Gibbs free energy pathway (kilocalories per mole) of TMA oxidation by $\text{HFe}^{\text{VI}}\text{O}_4^-$.

and predicted results of MMA and DMA (with DMA measured relative to its reactant complex). The mechanism also is consistent with those of MMA and DMA. Probably because the transition state is simpler, involving only the transfer of the O atom, the agreement with the experiment is best without having to invoke the reaction complex equilibrium as in the case of DMA.

TMA versus MMA and DMA. There is no H atom bonded to nitrogen in TMA. The same tetrahedral structure (CNC bond angles of 110°) and the same N–C bond lengths are present. The third methyl group further reduces the negative charge on N slightly to -0.17 .

Reactant Complex. The closest approach involves a strong H-bond ($\Delta H = -7.4\text{ kcal/mol}$ vs -1.7 kcal/mol for MMA and -2.2 kcal/mol for DMA) with an O–HN distance of 1.79 Å and a resulting smaller ΔG because the entropy decreases are similar for all three amines. The geometries, atomic charges, and spin densities of the two reactants are unchanged, except that the N atom charge has decreased to -0.10 .

TS. The quintet transition state converged with one imaginary frequency of -572 cm^{-1} that shows an O atom being transferred from ferrate to MMA. At the maximum, the O atom is nearly midway (Fe–O, 1.79 Å ; O–N, 1.96 Å). The CNC bond angles have increased to 115° . The TMA is more positively charged with N = $+0.02$, and the Fe charge has decreased from $+0.36$ to $+0.26$. In contrast to DMA, where both electrons have been transferred to Fe in TS1, the spin density on Fe has increased only from 1.61 to 2.72 with the addition of one electron. There is significant spin density on the O atom being transferred (0.35) and the N atom (0.32), which indicates that the second electron has not yet been transferred completely. The two-electron transfer is not complete until after the transition state. This may explain why the energy of TS1 in DMA is so much higher than that in MMA and TMA. In MMA, with the lowest-energy TS1, the spin density on the N atom is 0.71 , indicating most of the second electron is still on the amine. In TMA, more of the second electron has been transferred (0.32 on N), whereas in DMA, with the highest TS1 energy, the second electron has been completely transferred (-0.03 on N).

Product Complex. A strong H-bond is formed with an O–HO distance of 1.78 Å . However, it is unstable with respect to

the products by 3.4 kcal/mol because of the large entropy decrease. The O atom has fully transferred to form the trimethyl oxime (TMO) with an O–N bond length of 1.39 Å. The C–N bond lengths have slightly increased from 1.45 to 1.49 Å. There is a return to the tetrahedral structure (CNC bond angles of 109°). The charge on the oxime O is –0.40; the N has become slightly negative (–0.09), and the C atoms have become slightly positive (+0.03). On the ferrate, Fe is more positive (+0.42) with slight changes on the remaining atoms. The second electron has completely transferred with no spin density remaining on the oxime and an increase on the Fe atom from 2.72 to 3.37 with smaller increases on the remaining O atoms.

Products. In Figure 4, Fe(IV) and trimethyl oxime (TMO) represent the products. There are no further changes to the internal properties of the ferrate or oxime once the H-bond in the complex is broken.

CONCLUSIONS

The investigated aliphatic amines (MMA, DMA, and TMA) in combination with Fe(VI) showed enhanced oxidation of pharmaceuticals, and the magnitude of the increase compared to that with Fe(VI) depends on the molar ratio of amines to Fe(VI). Among the amines, DMA had the highest increase at a molar ratio of ~20:1. Quantum chemical calculations could describe the trend of enhancement by different amines. The calculations indicated the formation of the Fe^{IV} species during the oxidation of amines by Fe(VI). The computed relative stabilities of the formed Fe^{IV}–amine complex in the reaction mixture (see Figures 3 and 4 and Table S1) agree with these experimental results. The experimental and computational results suggest amines in water may be beneficial in treating recalcitrant pharmaceuticals with Fe(VI). The role of amines would depend on the kind of amines (i.e., 1°, 2°, or 3° moiety). The amines in surface water are present in the form of dissolved organic nitrogen from wastewater discharges, algal blooms, and agricultural runoff activities. Amines as co-contaminants with pharmaceuticals would enhance and accelerate the oxidation of the target contaminants by Fe(VI), for example, the enhanced efficiency of the oxidation of pharmaceuticals in the presence of creatinine in hydrolyzed urine.³⁰ However, this effect of amines depends on the concentration of amines compared to that of Fe(VI) because the formation of the Fe^{IV}–amine complex and its enhanced performance depend on the molar ratio of amine to Fe(VI). Furthermore, the oxidation of amines will eliminate one of the precursors in water that generate DBPs during chlorination;^{12,15,54} therefore, the amount of chlorinated DBPs would decrease in the use of Fe(VI) as a preoxidant before chlorination. Fe(VI) has been demonstrated to be an effective disinfectant and coagulant.^{33,55–59} Therefore, application of Fe(VI) has a potential to have multiple advantages in treatment processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsestwater.1c00156>.

Information about the thermodynamic comparison of SET versus OAT of amines by HFe^{VI}O₄[–] and calculated enthalpies and Gibbs energies of all species involved in the oxidation of amines by HFe^{VI}O₄[–] (Tables S1–S4),

data for the oxidation of PMSO by Fe(VI) and Fe(VI)–DMA at pH 9.0 (Figure S1), data for the oxidation of other pharmaceuticals by Fe(VI), Fe(VI)–MMA, and Fe(VI)–DMA (Figure S2), and bond lengths, spins, and charges on the structures of all species involved in the calculations (Figures S3–S5) (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to Professor J. Clayton Baum, who was the leader of this work.

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