Oxidation of Sulfonamide Antimicrobials by Ferrate(VI) [Fe VI O 4 2 −] †

ARTICLE *in* ENVIRONMENTAL SCIENCE AND TECHNOLOGY · JANUARY 2007

Impact Factor: 5.33 · DOI: 10.1021/es060351z · Source: PubMed

3 AUTHORS:

Virender K Sharma
Texas A&M University
302 PUBLICATIONS **7,504** CITATIONS
SEE PROFILE

Santosh K Mishra
Missouri University of Science and Technology
10 PUBLICATIONS **273** CITATIONS
SEE PROFILE

Nasri Nesnas
Florida Institute of Technology
20 PUBLICATIONS **682** CITATIONS
SEE PROFILE

Environ. Sci. Technol. **2006**, *40,* 7222−7227

Oxidation of Sulfonamide Antimicrobials by Ferrate(VI) [$Fe^{VI}O_4^{2-}$]†

VIRENDER K. SHARMA,* SANTOSH K. MISHRA, AND NASRI NESNAS

Department of Chemistry, Florida Institute of Technology, 150 West University Boulevard, Melbourne, Florida 32901

Sulfonamide antimicrobials are used in both human therapy and animal husbandry. Sulfonamides are not readily biodegradable and have been detected in surface water and in secondary wastewater effluents. The chemical oxidation of sulfonamides by an environmentally friendly oxidant, ferrate(VI) ($Fe^{VI}O_4^{2-}$, Fe(VI)), was conducted. The sulfonamides used in the oxidation studies were sulfisoxazole, sulfamethazine, sulfamethizole, sulfadimethoxine, and sulfamethoxazole. Kinetics of the reactions were determined as a function of pH (7.0−9.7) and temperature (15−45 °C) by a stopped-flow technique. The rate law for the oxidation of sulfonamides by Fe(VI) is first-order with respect to each reactant. The observed second-order rate constants decreased nonlinearly with an increase in pH and are possibly related to the protonation of Fe(VI) ($HFeO_4^- \leftrightarrow H^+ + FeO_4^{2-}$; $pK_{a,HFeO_4} = 7.23$) and sulfonamides ($SH \leftrightarrow H^+ + S^-$; $pK_{a,SH} = 5.0-7.4$). The activation parameters of the reactions vary with pH due to temperature dependence on the protonation of Fe(VI) and sulfonamides. These results were used to obtain enthalpy of dissociation of sulfonamides. Stoichiometry and products of sulfamethoxazole (SMX) reactions with Fe(VI) were studied in detail using various analytical techniques to evaluate the effect of the oxidation process on the fate of sulfonamides in water. At a stoichiometric ratio of 4:1 (Fe(VI):SMX), complete removal of SMX was achieved. Analyses of oxidation products of the reaction as well as kinetic measurements of substructural models of SMX suggest that the attack of Fe(VI) occurs at the isoxazole moiety as well as at the aniline moiety with minimal preference. The results of the studies reported suggest that Fe(VI) has the potential to serve as a chemical oxidant for removing sulfonamides and converting them to relatively less toxic byproducts in water.

Introduction

In recent years, pharmaceuticals and personal care products (PPCPs) in the aquatic environment have received increased attention due to their occurrence in various waterways (*1*−*3*). Of the several compounds of PPCPs, detection of antibiotics is of concern due to the possibility of increased bacterial resistance (*4*). Antibiotics may also exert other adverse effects on the aquatic ecosystems (*5*−*7*). A combination of pharmaceuticals can significantly inhibit cell growth in vitro (*8*). Sulfa drugs or sulfonamide antimicrobials are among the most frequently detected antibiotics in surface waters (*2*). Sulfonamide antimicrobials consist of synthetic, primarily bacteriostatic, sulfanilamide derivatives (Table 1) and are used in both human therapy and animal husbandry. Disposal of domestic and hospital waste, fields treated with animal manure, and runoff and infiltration from confined animal feeding operation result in the entry of sulfonamides into the environment (*9*). Sulfonamides are not readily biodegradable (*10*) which may lead to the finding of such compounds in groundwater, treated wastewater effluent, landfill leachate, and soils irrigated with reclaimed water (*11*−*13*).

Various chemical oxidation processes can be applied for transformation of sulfonamides in water (*14*−*16*). Though significant transformation of sulfonamide occurs during disinfection of municipal wastewater and drinking water using free chlorine (*14*), chlorination may create and leave disinfection byproducts (DBPs) in treated water. Oxidation of sulfonamide antibiotics by chlorine dioxide has been investigated (*15*). The rates of reactions of sulfonamides with chlorine dioxide were found to be much higher than those with chlorine. Ozonation has shown great potential to remove sulfonamides (*16*). However, ozone can form the potent carcinogenic bromate ion by reacting with bromide present in water. Another advanced oxidation process involves photocatalysis, which transforms sulfonamides on titanium dioxide (*17*). Yet another promising method is the possible application of potassium ferrate(VI) (K_2FeO_4), which can address some of the concerns of currently used methods, in treating sulfonamide antimicrobials.

Ferrate(VI) ($Fe^{VI}O_4^{2-}$, Fe(VI)) is a powerful oxidizing agent in aqueous media with a reduction potential of 2.20 and 0.70 V in acidic and alkaline solutions, respectively (*18*). Under acidic conditions, the redox potential of Fe(VI) ion is the highest of any other oxidant used in wastewater treatment processes (*19*, *20*). Moreover, the spontaneous decomposition of Fe(VI) in water gives molecular oxygen and Fe(III) thus making Fe(VI) an environmentally friendly chemical for coagulation, disinfection, and oxidation for multipurpose treatment of water and wastewater (*19*−*23*). Furthermore, the application of Fe(VI) can improve the removal of natural organic matter or DPBs precursors. Unlike ozone, Fe(VI) does not react with bromide ion; thus the carcinogenic bromate ion would not be formed in the treatment of bromide containing water by Fe(VI).

Recently, this group has initiated the studies on the Fe(VI) oxidation of pharmaceuticals and endocrine disruptor chemicals (EDCs) in water with a particular interest in the kinetics and mechanism of oxidation of sulfonamide antimicrobials by Fe(VI). The kinetic assessments of oxidation of pharmaceuticals, sulfamethoxazole, and ibuprofen were conducted (*24*, *25*). The results showed that Fe(VI) can be effective in removing these drugs. Other workers have performed kinetic measurements as well as removal studies on the oxidation of EDCs by Fe(VI) (*26*−*28*). However, products can be toxic during transformation of pharmaceuticals and EDCs; it is therefore imperative to perform product studies on the oxidations by Fe(VI). There is no such information available in the literature on the products formation during the oxidation of pharmaceuticals and EDCs by Fe(VI).

In this paper, the kinetics of the reaction between sulfonamides and Fe(VI) as a function of pH (7.0−9.7) and temperature (15−45 °C) has been studied using a stopped-

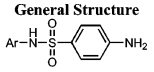
† This article is part of the Emerging Contaminants Special Issue.

* Corresponding author phone: (321)674-7310; fax: (321)674-8951; e-mail: vsharma@fit.edu.

10.1021/es060351z CCC: $33.50
Published on Web 08/11/2006

TABLE 1. General Structure of a Sulfonamide Antimicrobial and Structure of Five Sulfa Drugs Containing a Five- or Six-Membered Heterocyclic Ar Substituent and the Corresponding pK_a Values

General Structure



Sulfonamide	Ar group	pK_{a1}	pK_{a2}	Ref.
Sulfisoxazole		1.5±0.2	5.0±0.7	*33*
Sulfamethazine		2.3	7.4	*34*
Sulfamethizole		2.1±0.2	5.3±0.2	*33*
Sulfadimethoxine		2.9±0.5	6.1±0.2	*35*
Sulfamethoxazole		1.6±0.2	5.7±0.2	*33*

flow technique. The sulfonamides studied are presented in Table 1, and they consist of two moieties, an aniline ring and a five- or six-membered heterocyclic aromatic group (Ar), connected to both sides of the sulfonamide linkage (−NH−SO_2^-) (Table 1). Sulfonamides differ in the N-bound Ar substituent of the sulfonamide linkage. HPLC, IR, ^{1}H NMR, and mass spectrometric detection techniques were applied to identify products formation during the oxidation of sulfamethoxazole (SMX) by Fe(VI). The present investigation aimed to (a) understand the kinetics of the oxidation of sulfonamides, (b) give a plausible mechanism of sulfonamide oxidation, (c) seek complete removal of sulfonamides in water, and (d) learn the nature of byproducts formed during the transformation of sulfonamides by Fe(VI).

Experimental Section

Chemicals. All chemicals (Sigma, Aldrich) were of reagent grade or better and were used without further purification. Solutions were prepared with water that had been distilled and then passed through an 18 MΩ Milli-Q water purification system. Potassium ferrate(VI) (K_2FeO_4) of high purity (+98%) was prepared by the method of Thompson et al. (*29*). The Fe(VI) solutions were prepared by addition of solid samples of K_2FeO_4 to 0.005 M Na_2HPO_4/0.001 M borate at pH 9.0, a pH at which the solutions are most stable. A molar absorption coefficient of $\epsilon_{510nm} = 1150\ M^{-1}\ cm^{-1}$ was used for the calculation of [FeO_4^{2-}] at pH 9.0 (*30*). Sulfonamide solutions were prepared by dissolving solid powder in 0.01 M Na_2HPO_4 buffer solution. Solutions of sulfisoxazole, sulfadimethoxine, and sulfamethoxazole were first warmed to 50 °C and then cooled to room temperature to enhance their solubilities.

Kinetics Study. A stopped-flow spectrophotometer (SX.18 MV, Applied Photophysics, U.K.) equipped with a photomultiplier (PM) detector was used to perform the kinetic measurements under pseudo-first-order conditions with sulfonamides in excess. The concentrations of sulfonamides in the experiments were more than 5×10^{-4} M, while the Fe(VI) concentrations ranged from 0.50 to 0.60 $\times 10^{-4}$ M. Reactions were monitored by measuring the absorbance of Fe(VI) at 510 nm wavelength as a function of time. The temperatures of the reaction media were controlled within ±0.1 °C with a Fischer Scientific Isotemp 3016 circulating water bath. Nonlinear regression analysis of pH dependence of observed constants was conducted using SigmaPlot 2001 software. This program performs analysis of variance in nonlinear regression of the data.

Stoichiometry Study. The stoichiometry of the reaction of sulfamethoxazole (SMX) with ferrate(VI) was carried out at pH 9.0. Equal volumes (0.01 L) of 2×10^{-4} M SMX were mixed with various concentrations of ferrate(VI). High performance liquid chromatographic-ultraviolet (HPLC−UV) method was used to analyze SMX in the reaction mixture. HPLC analysis was conducted on Waters Alliance 2695 Analytical HPLC instrument having a photodiode array (PDA) detector (Model 996). A column used was Atlantis dC_{18}, 4.6 × 100 mm, 5 μm particle size. Analysis was done with two mobile phases (mobile phase A: 0.1% HCOOH and mobile phase B: ACN/0.1% HCOOH (90:10)), injection volume of 70 $\times 10^{-6}$ L, and the separation was carried out using a gradient flow. A flow rate of 10^{-3} L/min was used, and the detection wavelength was set to 300 nm. In dissolved oxygen experiments, 0.01 L of Fe(VI) and SMX solutions were separately purged with N_2 gas for 30 min before mixing. The evolution of oxygen gas in the mixed solution was measured using Thermo Orion O_2 electrode (Model 9708).

Product Study. Various analytical techniques were employed to study the products of the SMX reaction with ferrate(VI). These techniques were thin-layer chromatography (TLC), column chromatography, ^{1}H nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (ESI MS), and infrared (IR) spectroscopy. In a typical experiment, 0.750 L of 2.0×10^{-4} M SMX was oxidized with 0.750 L of 0.001 M Fe(VI) at a pH of 9.0 for 3 h. The reaction mixture was frozen and lyophilized using Freeze Dry System/Freezone 4.5 (Labconco). After lyophilization, the residue was reconstituted in 0.020 L of 1:1 CH_3OH/CH_2Cl_2 and subjected to sonication to ensure homogeneity of the mixture. The organic phase was extracted from the sonicated mixture using 0.010 L of CH_2Cl_2 three times. The organic extract was dry loaded onto a silica gel column and eluted with a 2−3% CH_3OH/CH_2Cl_2 gradient. The fractions were predominately comprised of three main components. They were labeled product A, product B, and product C, and they weighed 5.6, 6.5, and 15.1 mg, respectively. The masses of the products are a reflection of the extraction coefficient of each compound rather than their actual product ratio distribution. The dried reaction product(s) were identified using TLC techniques to ensure proper purification. The following analytical procedures were used to identify products A, B, and C.

Analysis. SMX and products A, B, and C were dissolved in 1 g of CD_3OD before introduction in the AMX-360 IS, a pulse Fourier Transform Nuclear Magnetic Resonance spectrometer with a ^{1}H resonance frequency of 360.13 MHz. The spectra of products A, B, and C were compared with that of SMX for the change in chemical shift of the nonexchangeable protons of the isoxazole and aniline rings. For IR analysis, SMX and the dried reaction products A, B, and C were dissolved in DMSO, and the spectra were taken using Nicolet IR200 FT-IR, which operated on OMNIC 7.1 software. The spectra of the products were compared with that of SMX for the identification of new functional groups. ESI MS was performed on an AccuTOF (JEOL Ltd., Tokyo, Japan) with an ESI ion source.

Results and Discussion

Kinetics. The reactions of Fe(VI) and sulfonamides were determined as first-order with respect to each reactant (text

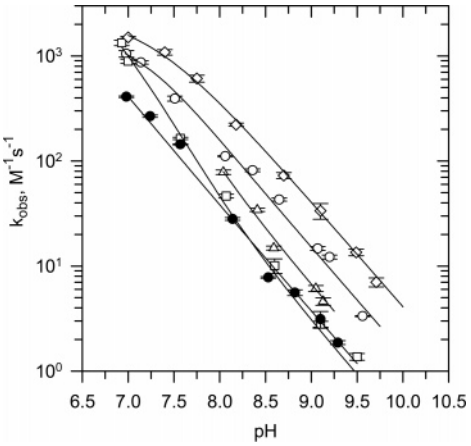


FIGURE 1. The pH dependence of the observed second-order rate constants for the reaction between Fe(VI) and sulfonamides at 25 °C. ([Fe(VI)] = 50−75 × 10^{-6} M; [sulfonamide] = 2.5 × 10^{-3} M; ○, sulfamethazine; □, sulfamethoxazole (data taken from ref *24*); △, sulfadimethoxine; ●, sulfamethizole; ◇, sulfisoxazole).

S1, Supporting Information) and can be described by eq 1

$$-\mathrm{d}\{\mathrm{Fe(VI)}\}/\mathrm{d}t = k[\mathrm{Fe(VI)}]_{\mathrm{tot}}[\mathrm{S}]_{\mathrm{tot}} \quad (1)$$

where k represents the second-order rate constant for the reaction of Fe(VI) with sulfonamide, $[\mathrm{Fe(VI)}]_{\mathrm{tot}}$ represents the total concentration of Fe(VI) species, and $[\mathrm{S}]_{\mathrm{tot}}$ represents the total concentration of each sulfonamide species. The reaction rate constants were determined as a function of pH (7.0−9.7) and are shown in Figure 1. The observed second-order rate constants decreased nonlinearly with increasing pH. Despite structural similarities, the reactivity of sulfonamides varied, and variation is generally more pronounced at higher pH. The pH dependence of k_{obs} can be attributed to the combined speciation effects of Fe(VI) and sulfonamide. Three protonated forms of Fe(VI) have been suggested ($H_3FeO_4^+ \leftrightarrow H^+ + H_2FeO_4$, $pK_{a1} = 1.6 \pm 0.2$ (*31*); $H_2FeO_4 \leftrightarrow H^+ + HFeO_4^-$ $pK_{a2} = 3.5$ (*31*); $HFeO_4^- \leftrightarrow H^+ + FeO_4^{2-}$, $pK_{a3} = 7.3 \pm 0.1$ (*32*)). Sulfonamides have two dissociation constants, one corresponds to protonation of the aniline N ($SH_2^+ \leftrightarrow H^+ + SH$; $pK_{a,SH2} = 1.5-2.9$ (*33*−*35*)) and the other involves the protonation of sulfonamide NH ($SH \leftrightarrow H^+ + S^-$; $pK_{a,SH} = 5.0-7.4$ (*33*−*35*)) (Table 1). In the pH range studied, two forms of Fe(VI), namely, $HFeO_4^-$ and FeO_4^{2-}, react with two forms of sulfonamide (SH and S^-) (eqs 2−5).

$$HFeO_4^- + SH \rightarrow Fe(OH)_3 + \text{product(s)} \quad (2)$$

$$HFeO_4^- + S^- \rightarrow Fe(OH)_3 + \text{product(s)} \quad (3)$$

$$FeO_4^{2-} + SH \rightarrow Fe(OH)_3 + \text{product(s)} \quad (4)$$

$$FeO_4^{2-} + S^- \rightarrow Fe(OH)_3 + \text{product(s)} \quad (5)$$

The rate of disappearance of Fe(VI) is given by

$$-\mathrm{d}[\mathrm{Fe(VI)}]/\mathrm{d}t = k_2[HFeO_4^-][SH] + k_3[HFeO_4^-][S^-] + k_4[FeO_4^{2-}][SH] + k_5[FeO_4^{2-}][S^-] \quad (6)$$

k can be derived into eq 7 considering the equilibriums of Fe(VI) and sulfonamide species

$$k = k_2\alpha_{HFeO_4}\alpha_{SH} + k_3\alpha_{HFeO_4}\alpha_S + k_4\alpha_{FeO_4}\alpha_{SH} + k_5\alpha_{FeO_4}\alpha_S \quad (7)$$

where $\alpha_{HFeO_4} = [H^+]/([H^+] + K_{a,HFeO_4})$; $\alpha_{FeO_4} = K_{a,HFeO_4}/([H^+] + K_{a,HFeO_4})$; $\alpha_{SH} = [H^+]/([H^+] + K_{a2,SH})$; and $\alpha_S = K_{a,SH}/([H^+] + K_{a2,SH})$.

The values of the individual rate constants of eq 7 were obtained by nonlinear regression of the data. It was determined that reaction 5 was not needed to fit the data of all sulfonamides. Experimental data for sulfisoxazole, sulfamethizole, and sulfadimethoxine could be fit by considering reactions of Fe(VI) species with protonated sulfonamide (eqs 2 and 3). The estimated rate constants for individual reactions are given in Table 2, which fit reasonably well with the experimental data (Figure 1, solid line). The estimated rate constants in Table 2 suggest that the protonated Fe(VI) species reacts faster than the deprotonated sulfamethazine and sulfamethoxazole. Recent density functional theory (DFT) calculations also showed that the $HFeO_4^-$ has a larger spin density on the oxo ligands than FeO_4^{2-}, which increases the oxidation ability of protonated Fe(VI) (*36*). The fraction of $HFeO_4^-$ species (α_{HFeO4}) increases with a decrease in pH and thus contributes to an increase in the rate with a decrease in pH.

Results of Table 2 indicate a faster reaction rate constant of $HFeO_4^-$ with the neutral sulfonamide species (SH) than with the negatively charged ionized species (S^-). This is in contrast with the reactivity of ozone and hydroxyl radical with amines and amino acids in which higher reactivity was observed as a result of deprotonation. Reactivity of ozone and hydroxyl radicals increases with an increase in pH, which is opposite to reactivity of Fe(VI) with sulfonamides. Thus the pH dependence in the present study could be due to electrostatic interaction between Fe(VI) and sulfonamide species. It is expected that the attraction between the Fe(VI) species and SH will be stronger than that with S^-. The fraction of neutral species (SH) (α_{SH}) increases with a decrease in pH, and thus contribution to the overall rates from the reaction between $HFeO_4^-$ and SH would be higher at lower pH.

In a recent study of Fe(VI) with phenolic EDCs (*28*), the results were fitted by assuming that diprotonated (H_2FeO_4) and deprotonated (FeO_4^{2-}) species do not contribute to the overall rate constants, and the reactive species is only $HFeO_4^-$. This kinetic model gave higher rate constants for the reaction between $HFeO_4^-$ and the deprotonated phenolic EDCs than the reaction between $HFeO_4^-$ and the protonated phenolic EDCs. However, the results in their study can also be fitted well by considering reactivity of $HFeO_4^-$ and FeO_4^{2-} with protonated and deprotonated EDCs in which $HFeO_4^-$ would react faster with protonated EDCs than deprotonated EDCs. Interestingly, the pH dependence data in the present study can be empirically fitted by considering interactions of all ferrate species ($H_3FeO_4^+$, H_2FeO_4, $HFeO_4^-$, and FeO_4^{2-}) with only deprotonated sulfonamide (S^-). This fitting approach assumes that reactions between Fe(VI) and protonated sulfonamides (SH_2^+ and SH) do not contribute to the overall rate constants. The assumption does not appear to be good because the proton present in protonated sulfonamide may participate in the reaction as has been demonstrated in the reaction between Fe(VI) and aniline (*37*). Overall, the kinetic model used in the present work is consistent with previous work including the reactivity of Fe(VI) with amino acids (*38*).

The effect of temperature on the reactions of Fe(VI) with sulfonamides was studied at pH 7.0 and 9.1 (Table S1, Supporting Information). The results were used to calculate observed activation energy, E_a, observed activation enthalpy, $\Delta H^{\ddagger}_{\mathrm{obs}}$, and the observed activation entropy, $\Delta S^{\ddagger}_{\mathrm{obs}}$, of the reactions of Fe(VI) with sulfonamides (Table 2 and Figure S1, Supporting Information). The observed activation parameters are different at pH 7.0 and 9.1 (Table 2) because they contain terms due to the effect of temperature on the dissociation of $HFeO_4^-$ ($pK_{a,HFeO_4}$) and sulfonamide ($pK_{a2,SH}$). The values of $\Delta H^{\ddagger}_{SH}$ were determined using a procedure

TABLE 2. Rate Constants and Activation Parameters for the Reactions of Fe(VI) with Sulfonamides

sulfonamide	k (M^{-1} s^{-1}) $HFeO_4^- + SH$	$HFeO_4^- + S^-$, $t = 25$ °C	$FeO_4^{2-} + SH$	pH	$E_{a,obs}$ (kJ mol^{-1})	$\Delta H^{\ddagger}_{obs}$ (kJ mol^{-1})	$\Delta S^{\ddagger}_{obs}$ (J mol^{-1} K^{-1})
sulfisoxazole	$1.10 \pm 0.10 \times 10^4$	$2.42 \pm 0.06 \times 10^3$		7.0	11.0 ± 0.46	8.48 ± 0.47	155 ± 5.83
				9.1	32.3 ± 1.50	29.8 ± 1.41	115 ± 6.70
sulfamethazine	$1.91 \pm 0.04 \times 10^3$	$5.50 \pm 0.10 \times 10^2$	$2.25 \pm 0.20 \times 10^2$	7.0	10.2 ± 2.28	7.72 ± 2.27	163 ± 35.3
				9.1	32.5 ± 3.20	30.0 ± 3.30	123 ± 17.9
sulfamethizole	$2.23 \pm 0.15 \times 10^4$	$2.20 \pm 0.27 \times 10^2$		7.0	-11.3 ± 2.43	-13.9 ± 0.75	238 ± 12.9
				9.1	28.3 ± 3.29	25.5 ± 3.35	150 ± 35.9
sulfadimethoxine	$1.88 \pm 0.04 \times 10^4$	$3.80 \pm 0.40 \times 10^2$		9.1	29.8 ± 2.33	27.2 ± 2.31	138 ± 17.8
sulfamethoxazole[a]	$3.00 \pm 0.13 \times 10^4$	$1.70 \pm 0.20 \times 10^2$	$1.20 \pm 0.10 \times 10^0$	7.0	1.84 ± 0.37	-0.68 ± 0.35	191 ± 35.0
				9.1	38.3 ± 4.25	36.2 ± 4.25	103 ± 15.7

[a] From ref *24*.

described in text S2 (Supporting Information) as 21.3 ± 1.1, 39.4 ± 2.4, and 36.9 ± 3.0 kJ mol^{-1} for sulfisoxazole, sulfamethizole, and sulfamethoxazole, respectively. The value of $\Delta H^{\ddagger}_{SH}$ for sulfamethoxazole given in the literature (*39*) using the solubility measurement is 33.76 ± 0.25 kJ mol^{-1} and is in reasonable agreement with the value obtained in the present study. This suggests that a kinetic approach to determine enthalpy of dissociation of sulfonamide is reasonable. A similar calculation could not be performed for sulfadimethoxine (see text S2, Supporting Information). The values of $\Delta H^{\ddagger}_{obs}$ at pH 9.1 were used to calculate $\Delta H^{\ddagger}$ for the reaction of Fe(VI) using the known value of $\Delta H^{\ddagger}_{HFeO_4} = 17.0 \pm 0.4$ kJ mol^{-1} (*32*). The obtained values of $\Delta H^{\ddagger}$ were 46.8 ± 1.0, 42.5 ± 2.4, 44.2 ± 0.4, and 53.2 ± 3.0 kJ mol^{-1} for sulfisoxazole, sulfamethizole, sulfadimethoxine, and sulfamethoxazole, respectively. The $\Delta H^{\ddagger}$ values for these sulfonamides are somewhat similar, which suggest that oxidation of sulfonamides by Fe(VI) may be possibly occurring through a similar activated complex.

Stoichiometry. The results of stoichiometric experiments are presented in Figure S2 (Supporting Information). Slopes of linear relationships between [SMX] and [Fe(VI)] were found to be 0.27 ± 0.02 and 0.24 ± 0.01, respectively, for pH 7.0 and 9.0. The stoichiometry of the oxidation of SMX by Fe(VI) is therefore similar and within experimental error in neutral and basic media. The formation of oxygen was explored, and a slope between Fe(VI) consumed and oxygen formation was found to be 0.23 ± 0.01 (Figure S2, Supporting Information). The addition of potassium thiocyanate to the final reaction mixture gave a characteristic red ferric thiocyanate complex color. This suggests that the final product of Fe(VI) was Fe(III). The oxidation of SMX by Fe(VI) thus follows a stoichiometry of 4:1 ([Fe(VI):[SMX]) which leads to the evolution of one mole of oxygen per mole of SMX, and Fe(III) was the end product of Fe(VI) (eq 8).

$$4HFeO_4^- + SMX \rightarrow 4Fe(III) + O_2 + product(s) \quad (8)$$

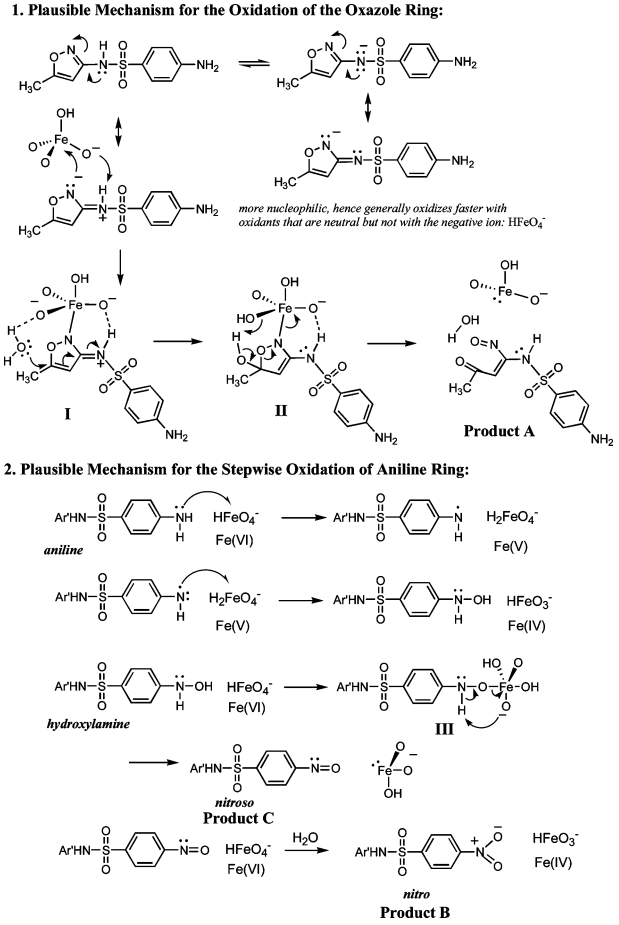
Reactivity of Substructure Compounds. To determine the initial attack of Fe(VI) on SMX, the rate of reaction of the substructural models of SMX viz., sulfanilamide and 3-amino-5-methyl isoxazole (AMI) (Figure S3, Supporting Information), with Fe(VI) were studied at pH 9.0 and 25 °C using a stopped-flow technique. The rate constants were determined under pseudo-first-order conditions (Figure S4, Supporting Information). The slopes of log k_1 versus log[compounds] plots gave values of 0.95 ± 0.04 and 0.88 ± 0.11 for sulfanilamide and AMI, respectively. This suggests that the reactions were first order with respect to each reactant. The rate constants, k, of the reactions of the substructural compounds with Fe(VI) were determined as 6.80 ± 0.27 and 0.78 ± 0.09 M^{-1} s^{-1}, respectively, for sulfanilamide and AMI. Comparatively, the rate constant, k, for the reaction of Fe(VI) with SMX under similar conditions was determined as 2.80 ± 0.20 M^{-1} s^{-1}. It should be maintained that these model structures are the closest mimics for the SMX moieties and that it is understood that they will not be identical in behavior to the SMX subunits. For instance, the AMI amino group is a stronger electron donor than the amide nitrogen of SMX. Although it seems that sulfanilamide reacts faster than AMI, the rate constants are close enough precluding us from making any claims regarding which moieties in SMX react faster. The products, indeed, reflect the comparable nature of the reactivities of the two moieties.

Product Identification. The chemical shifts in the ^1H NMR spectra of the different types of nonexchangeable protons in SMX and the products are shown in Figure S5 (Supporting Information). It was observed that for product A there were changes in the chemical shift of the protons of the methyl group and the proton of the isoxazole ring. Both of the shifts were upfield as compared to the chemical shifts of the corresponding peaks of NMR spectra of SMX. This indicates that the isoxazole ring was attacked during oxidation and would have led to the formation of a carbonyl group through a ring opening mechanism (see below). In the case of product B as compared to SMX, the chemical shifts of the protons of the aniline ring were very close and appeared downfield, and the peak due to the amino group and amide linkage could not be found (in nonexchangeable solvents) indicating that the amino group, attached to benzene ring, was oxidized to a nitro in product B or to a nitroso group in product C.

The IR spectra of SMX sample showed peaks due to the presence of the amine N−H stretch, C═N of isoxazole ring, sulfamide linkage, aromatic ring, and CH_3 group (Table S2, Supporting Information). The absence of the C═N signal in the IR spectra of product A suggests the opening of the isoxazole ring. The breaking of the isoxazole ring was further confirmed by the presence of the ketone C═O stretch signal. The methyl C−H stretch signal of product A indicates that the methyl group of isoxazole was not oxidized during the reaction. A N═O signal was observed, suggesting the formation of the nitroso in the opening of the isoxazole. The IR spectra of products B and C did not show any N−H stretch nor any stretch for C═N. However, both products exhibited an amide N−H stretch for the sulfonyl of $NHSO_2$ as well as the amide linkage of $NH-SO_2$ (Table S2, Supporting Information). An absorption reflecting an oxidation at the aniline nitrogen leading to a nitro/nitroso was observed.

Finally, mass spectral analysis, namely ESI MS, of the Fe(VI)-SMX reaction system was employed. An injection of SMX (at 10 μM) was sufficient to generate a readable signal at 276.056 which corresponds to M + Na. A subsequent injection after 10 min of reacting SMX with 5 equiv of ferrate(VI) resulted in a substantial decrease in the 276 peak. After an hour of reaction time, product peaks including

SCHEME 1



292.039 reflect product A + Na (see Figure S6, Supporting Information).

Plausible Mechanism. The products analysis of the reaction suggests the oxidation of both the isoxazole moiety and the aniline unit of SMX by Fe(VI) (Scheme 1). Section 1 of Scheme 1 represents the oxidation of the isoxazole moiety in which the complexation of the Fe(VI) with the resonance form of SMX occurs to give complex I. Entropic calculation of the reaction supports such complex formation (see Table 2). It is proposed that complex I has a trigonal bipyramid geometry. The possibility of this type of geometry in the complex has also been postulated by Kamachi et al. (*36*) through DFT calculations of the Fe(VI) reactions. A water molecule in complex I can be deprotonated by the Fe(VI) to yield intermediate II, which is possibly a result from the attack of water on the β-carbon of the eniminium cation of complex I. Mechanistic arrows depict the collapse of the unstable intermediate II to generate product A. The NMR of the latter shows a clear distinction in the opening of the isoxazole from the chemical shifts of the CH_3 group and the (former) aromatic proton. The chemical shift of the aromatic proton of SMX in CD_3OD is 6.1 ppm, and the CH_3 group on the aromatic isoxazole has the chemical shift of 2.3 ppm, which is well within the expected range for these functionalities. Once the isoxazole ring is disrupted as in product A, the former aromatic ring hydrogen is still fairly downfield (being a vinylic one as well as somewhat withdrawn), but it appears at the expected vinylic position ca. 5.5 ppm (upfield by a significant 0.6 ppm from its aromatic precursor). The CH_3, on the other hand, is a simple acetyl group, and it appears at the expected 2.1 ppm (upfield by 0.2 ppm). The aromatic protons of the aniline ring, in that structure, did not portray any significant shift (as they have in the other products B and C). Moreover, the peak at 292 (product A + Na) in ESI-MS also suggests opening of the isoxazole (Figure S6, Supporting Information).

The oxidation of the aniline moiety is shown in section 2 of Scheme 1. The analysis of the oxidative products indicates the presence of predominantly a nitroso group and a nitro group. It is quite possible that both products go through the hydroxylamine (after a two-electron oxidation of the NH_2 group). The initial attack on the NH_2 group involves a single electron-transfer mechanism as shown by Huang et al. (*37*) in the oxidation of simple aniline by Fe(VI). The resulting hydroxylamine may complex with the Fe(VI) leading to intermediate III, which further collapses to the nitroso group. A potential complexation between the N or the O of the hydroxylamine unit has been suggested in a separate study of the oxidation of hydroxylamines by Fe(VI) (*40*). Since in SMX, the N electrons are somewhat tied up in resonance, being strongly withdrawn by the sulfonamide functionality, it is suggested that the O complexes to the Fe(VI). The nitroso oxidation to the nitro group may occur via electron pair loss to the Fe(VI) after a water molecule's attack on the nitroso (not shown).

It is proposed that four molecules of Fe(IV), produced in the reactions, would self-decompose to give oxygen ($4HFeO_3^- + 6H_2O \rightarrow 4Fe(OH)_3 + O_2 + 4OH^-$). This is consistent with the stoichiometric results in which one mole of oxygen is produced from the consumption of four moles of Fe(VI). Furthermore, no Fe(II) formation was observed, which would otherwise be likely produced from the reaction of Fe(IV) with SMX and/or intermediate(s). This possibility would give less mole consumption of Fe(VI) per mole of SMX than observed in the present study. The analysis of products did not give any azo compounds as has been observed in the oxidation of aniline by Fe(VI) (*37*, *41*). This is not surprising because azo compounds are formed when aniline concentration is more than Fe(VI) in the reaction mixture. The present study used nearly stoichiometric amounts of reactants and gave the expected nitro products of the reaction.

In summary, potassium ferrate(VI) exhibits good potential to be an efficient oxidant for the removal of sulfonamides in water. If one uses excess Fe(VI) concentration (10^{-5} M or 2 mg L^{-1} K_2FeO_4) relative to the sulfonamides in water, the half-lives of the reactions using observed rate constants in the present study would be within 5 min at pH 7.0 for most of the sulfonamides. The reaction rates are pH dependent; thus, so are the half-lives of the reactions. An important aspect of the oxidation process by Fe(VI) is the destruction of the aromatic ring (e.g. isoxazole ring), which will undoubtedly render the oxidized product a differing biological binding property. It is expected that an oxidation of the amino group and/or an oxidation of the isoxazole ring (which leads to its potential opening/destruction) will change its binding properties sufficiently rendering it less of a mimic for the important *p*-aminobenzoic acid. The latter is necessary in the synthesis of the essential vitamin: folic acid. Thus Fe(VI) not only removes sulfonamides in water but also produces byproducts that are expected to be less toxic.

Acknowledgments

This paper was improved from the comments of three anonymous reviewers.

Supporting Information Available

Text (S1 and S2), tables (S1−S3), and figures (S1−S6). This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Jones, O. A. H.; Voulvoulis, N.; Lester, J. N. Human pharmaceuticals in the aquatic environment a review. *Environ. Technol.* **2001**, *22*, 1383−1394.

(2) Kolpin, D. W.; Furlong, E. T.; Meyer, M. T.; Thurman, E. M.; Zaugg, S. D.; Barber, L. B.; Buxton, H. T. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999−2000: A national reconnaissance. *Environ. Sci. Technol.* **2002**, *36*, 1202−1211.
(3) Ternes, T. A.; Joss, A.; Siegrist, H. Scrutinizing pharmaceuticals and personal care products in wastewater treatment. *Environ. Sci. Technol.* **2004**, *20*, 393A−399A.
(4) Gould, I. M. A review of the role of antibiotic policies in the control of antibiotic resistance. *J. Antimicrob. Chemother.* **1999**, *43*, 459−465.
(5) Kummerer, K. Significance of antibiotics in the environment. *J. Antimicrob. Chemother.* **2003**, *52*, 5−7.
(6) Cleuvers, M. Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. *Toxicol. Lett.* **2003**, *142*, 185−194.
(7) Snyder, S. A.; Westerhoff, P.; Yoon, Y.; Sedlak, D. L. Pharmaceuticals, personal care products, and endocrine disruptors in water: implications for water industry. *Environ. Eng. Sci.* 2003, 20, 449−469.
(8) Pomati, F.; Castiglioni, S.; Zuccato, E.; Fanelli, R.; Vigetti, D.; Rossetti, C.; Calamari, D. Effect of a complex mixture of therapeutic drugs at environmental levels on human embryonic cells. *Environ. Sci. Technol.* **2006**, *40*, 2442−2447.
(9) Gao, J.; Pedersen, J. A. Adsorption of sulfonamide antimicrobial agents to clay minerals. *Environ. Sci. Technol.* **2005**, *39*, 9509−9516.
(10) Ingerslev, F.; Halling-Sorensen, B. Biodegradability properties of sulfonamides in activated sludge. *Environ. Toxicol. Chem.* **2000**, *19*, 2467−2473.
(11) Holm, J. V.; Ruegge, K.; Bjerg, P. L.; Christensen, T. H. Occurrence and distribution of pharmaceutical organic compounds in the groundwater downgradient of a landfill (Grindsted, Denmark). *Environ. Sci. Technol.* **1995**, *29*, 1415−1420.
(12) Pedersen, J. A.; Soliman, M. A.; Suffet, I. H. Human pharmaceuticals, hormones, and personal care product ingredients in runoff from agricultural fields irrigated with treated wastewater. *J. Agric. Food. Chem.* **2005**, *53*, 1625−1632.
(13) Miao, X.; Bishay, F.; Chen, M.; Metcalfe, C. D. Occurrence of antimicrobials in the final effluents of wastewater treatment plants in Canada. *Environ. Sci. Technol.* **2004**, *38*, 3533−3541.
(14) Dodd, M. C.; Huang, C.-H. Transformation of the antibacterial agent sulfamethoxazole in reactions with chlorine: kinetics, mechanisms, and pathways. *Environ. Sci. Technol.* **2004**, *38*, 5607−5615.
(15) Huber, M. M.; Korhonen, S.; Ternes, T. A.; Gunten, U. V. Oxidation of pharmaceuticals during water treatment with chlorine dioxide. *Water Res.* **2005**, *39*, 3607−3617.
(16) Huber, M. M.; Goebel, A.; Joss, A.; Hermann, N.; Loffler, D.; McArdell, C. S.; Ried, A.; Siegrist, H.; Ternes, T. A.; Gunten, U. V. Oxidation of pharmaceuticals during ozonation of municipal wastewater effluents: a pilot study. *Environ. Sci. Technol.* **2005**, *39*, 4290−4299.
(17) Calza, P.; Medana, C.; Pazzi, M.; Baiocchi, C.; Pelizzetti, E. Photocatalytic transformation of sulfonamides on titanium dioxide. *Appl. Catal. B: Environ.* **2004**, *53*, 63−69.
(18) Wood, R. H. The heat, free energy, and entropy of the ferrate-(VI) ion. *J. Am. Chem. Soc.* **1958**, *80*, 2038−2041.
(19) Sharma, V. K. Potassium ferrate(VI): an environmentally friendly oxidant. *Adv. Environ. Res.* **2002**, *6*, 143−156.
(20) Jiang, J.-Q.; Lloyd, B. Progress in the development and use of ferrate(VI) salt as an oxidant and coagulant for water and wastewater treatment. *Water Res.* **2002**, *36*, 1397−1408.
(21) Sharma, V. K.; Kazama, F.; Jiangyong, H.; Ray, A. K. Ferrates (iron(VI) and iron(V) as environmentally friendly oxidants and disinfectants. *J. Water Health* **2005**, *3*, 42−58.
(22) Sharma, V. K.; Burnett, C. R.; Yngard, R.; Cabelli, D. E. Iron(VI) and iron(V) oxidation of copper(I) cyanide. *Environ. Sci. Technol.* **2005**, *39*, 3849−3854.
(23) Eng, Y. Y.; Sharma, V. K.; Ray, A. K. Ferrate(VI): Green chemistry oxidant for degradation of cationic surfactant. *Chemosphere* **2006**, *63*, 1785−1790.
(24) Sharma, V. K.; Mishra, S. K.; Ray, A. K. Kinetic assessment of the potassium ferrate(VI) oxidation of antibacterial drug, sulfamethoxazole. *Chemosphere* **2006**, *62*, 128−134.
(25) Sharma, V. K.; Mishra, S. K. Ferrate(VI) oxidation of ibuprofen: a kinetic study. *Environ. Chem. Lett.* **2006**, *3*, 182−185.
(26) Jiang, J. Q.; Yin, Q.; Zhou, J. L.; Pearce, P. Occurrence and treatment trials of endocrine disrupting chemicals (EDCs) in wastewater. *Chemosphere* **2005**, *61*, 544−550.
(27) Li, C.; Li, X. Z.; Graham, N. A study of the preparation and reactivity of potassium ferrate. *Chemosphere* **2005**, *61*, 537−543.
(28) Lee, Y.; Yoon, J.; Gunten, U. V. Kinetics of the oxidation of phenols and phenolic endocrine disruptors during water treatment with ferrate (Fe(VI)). *Environ. Sci. Technol.* **2005**, *39*, 8978−8984.
(29) Thompson, G. W.; Ockerman, L. T.; Schreyer, J. M. Preparation and purification of potassium ferrate VI. *J. Am. Chem. Soc.* **1951**, *73*, 1379−1381.
(30) Bielski, B. H. J.; Thomas M. J. Studies of hypervalent iron in aqueous solution: radiation-induced reduction of iron(VI) to iron(V) by CO_2^-. *J. Am. Chem. Soc.* **1987**, *109*, 7761−7764.
(31) Rush, J. D.; Zhao, Z.; Bielski, B. H. J. Reaction of ferrate(VI)/ferrate(V) with hydrogen peroxide and superoxide anion- a stopped-flow and premix pulse radiolysis study. *Free Rad. Res.* **1996**, *24*, 187−198.
(32) Sharma, V. K.; Burnett, C. R.; Millero, F. J. Dissociation constants of the monoprotic ferrate(VI) ion in NaCl media. *Phys. Chem. Chem. Phys.* **2001**, *3*, 2059−2062.
(33) Boreen, A. L.; Arnold, W. A.; McNeill, K. Photochemical fate of sulfa drugs in the aquatic environment: sulfa drugs containing five-membered heterocyclic groups. *Environ. Sci. Technol.* **2004**, *38*, 3933−3940.
(34) Lin, C. E.; Chang, C. C.; Lin, W. C. Migration behavior and separation of sulfonamides in capillary zone electrophoresis III. Citrate buffer as a background electrolyte. *J. Chromatogr., A* **1997**, *768*, 105−112.
(35) Boreen, A. L.; Arnold, W. A.; McNeill, K. Triplet-sensitized photodegradation of sulfa drugs containing six-membered heterocyclic groups: identification of an SO_2 extrusion photoproduct. *Environ. Sci. Technol.* **2005**, *39*, 3630−3638.
(36) Kamachi, T.; Kouno, T.; Yoshizawa, K. Participation of multi-oxidants in the pH dependence of the reactivity of ferrate(VI). *J. Org. Chem.* **2005**, *70*, 4380−4388.
(37) Huang, H.; Sommerfeld, D.; Dunn, B. C.; Lloyd, C. R.; Eyring, E. M. Ferrate(VI) oxidation of aniline. *J. Chem. Soc., Dalton Trans.* **2001**, 1301−1305.
(38) Sharma, V. K.; Bielski, B. H. J. Reactivity of ferrate(VI) and ferrate-(V) with amino acids. *Inorg. Chem.* **1991**, *30*, 4306−4310.
(39) Martinez, F.; Gomez, A. Thermodynamic study of the solubility of some sulfonamides in octanol, water, and the mutually saturated solvents. *J. Solution Chem.* **2001**, *30*, 909−923.
(40) Johnson, M. D.; Hornstein, B. J. The kinetics and mechanism of the ferrate(VI) oxidation of hydroxylamines. *Inorg. Chem.* **2003**, *42*, 6923−6928.
(41) Johnson, M. D.; Hornstein, B. J. Unexpected selectivity in the oxidation of arylamines with ferrate-preliminary mechanistic considerations. *Chem. Commun.* **1996**, 965−966.

Received for review February 15, 2006. Revised manuscript received June 14, 2006. Accepted July 3, 2006.

ES060351Z