

Oxidation of Sulfonamide Antibiotics of Six-Membered Heterocyclic Moiety by Ferrate(VI): Kinetics and Mechanistic Insight into SO₂ Extrusion

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Supporting Information

ABSTRACT: This work presents ferrate(VI) $(Fe^{VI}O_4^{2-}, Fe^{VI})$ oxidation of a wide range of sulfonamide antibiotics (SAs) containing five- and six-membered heterocyclic moieties (*R*) in their molecular structures. Kinetics measurements of the reactions between Fe^{VI} and SAs at different pH (6.5–10.0) give speciesspecific second-order rate constants, k_5 and k_6 of the reactions of protonated Fe^{VI} (HFeO₄⁻) and unprotonated Fe^{VI} (Fe^{VI}O₄²⁻) with protonated SAs (HX), respectively. The values of k_5 varied from $(1.2 \pm 0.1) \times 10^3$ to $(2.2 \pm 0.2) \times 10^4$ M⁻¹ s⁻¹, while the range of k_6 was from $(1.1 \pm 0.1) \times 10^2$ to $(1.0 \pm 0.1) \times 10^3$ M⁻¹ s⁻¹ for different SAs. The transformation products of reaction between Fe^{VI} and sulfadiazine (SDZ, contains a six-membered *R*)



include SO₂ extrusion oxidized products (OPs) and aniline hydroxylated products. Comparatively, oxidation of sulfisoxazole (SIZ, a five-membered *R*) by Fe^{VI} has OPs that have no SO₂ extrusion in their structures. Density functional theory calculations are performed to demonstrate SO₂ extrusion in oxidation of SDZ by Fe^{VI}. The detailed mechanisms of oxidation are proposed to describe the differences in the oxidation of six- and five-membered heterocyclic moieties (*R*) containing SAs (i.e., SDZ versus SIZ) by Fe^{VI}.

INTRODUCTION

Antibiotics have been widely used as human and veterinary medicines to treat infections and to enhance animal growth.^{1–3} The consumption of antibiotics has increased because of an increase in the world population and the aging population in industrialized countries.^{4,5} Significant portions of the antibiotics are excreted in feces and urine without metabolization. An overuse of antibiotics has caused growing concern because their release from hospitals, wastewater treatment plants, and livestock farms into the environment presents potential risks to human health and ecosystems. Among the antibiotics, sulfonamides (SAs) have been extensively used, which may result in ecological health hazards, food contamination, and pollution of drinking water supplies as well as the development of antibiotic resistant bacteria (ARBs) and antibiotic resistant genes (ARGs).^{6–8}

Many investigations have been carried out to treat SAs in water before their release into the environment, such as

biological treatment, adsorption, membrane processes, chlorination, electrochemical means, and advanced oxidation technologies.^{9–18} This current work pertains to the use of the chemical oxidant, ferrate(VI) ($Fe^{VI}O_4^{2-}$, Fe^{VI}), on which several studies on its application to treat micropollutants have appeared in the past decade.^{19–23} Few investigations, including some studies from our laboratory, have been carried out on the kinetics and mechanisms of the oxidation of SAs by $Fe^{VI.24-28}$ SAs contain two aromatic moieties: an aniline ring and a heterocyclic N-containing aromatic ring (*R*) that are joined through a sulfonamide linkage ($-NH-SO_2-$) (Figure 1). The *R* can be either a five- or a six-membered ring. Most of the studies on the oxidation of SAs by Fe^{VI}

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Five-membered Heterocyclic Aromatic Group





Figure 1. Molecular structures of sulfonamide antibiotics (SAs) and their dissociation constants and $log K_{ow}$ values.

sulfamethoxazole (SMX) containing a five-membered R. Products seen were from the attacks by Fe^{VI} on the aniline and the moieties of R.^{24,25,27,28} The research in the present work is stimulated from our recent product analysis on the oxidation of sulfadimethoxine (SDM) by Fe^{VI} that showed extrusion (or release) of SO₂ during the transformation of the parent molecule.^{29'} SDM contains a six-membered R. Comparatively, products identified in the oxidation of SMX by Fe^{VI} showed no extrusion of SO₂ from the parent molecule.^{24,25,27,28} We thus question if the extrusion of SO₂ is related to the heterocyclic ring (i.e., five- or six-membered *R*) of the SAs. To further clarify the mechanisms, we selected sulfadiazine (SDZ) and sulfisoxazole (SIZ), individually containing six- and five-membered R in their structures, respectively, and monitored their transformation products in reactions with Fe^{VI}. We hereby demonstrate for the first time that the extrusion of SO₂ by metal-based oxidant depends on the heterocyclic moiety of the SAs (i.e., R).

The formation of SO₂ extrusion products has been reported during the transformation of SAs with a six-membered *R* by photodegradation,³⁰ sulfate radical-based oxidation,^{9,31,32} horseradish peroxidase,¹⁰ chlorination,³³ and permanganate.³⁴ In these studies, reaction pathways have been given without any mechanistic details on how the oxidant is involved in the reaction steps. This information is available on describing photochemical oxidation of aqueous SAs using theoretical approaches.³⁵ In the current paper, we performed density functional theory (DFT) calculations to elucidate the SO₂ extrusion step of the mechanism via single electron transfer (SET) as an initial step. The obtained transition states (TS) of DFT calculation clearly show the ability of SO₂ extrusion from SAs containing a six-membered *R*. This is the first example of Fe^{VI} inducing SO₂ extrusion, via a single electron transfer initiation step. We also provide an explanation for the absence of SO₂ extrusion in SAs that bear a five-membered ring in the presence of Fe^{VI}. The role of the heterocyclic ring substituent (*R*) of SAs was further elaborated via kinetics studies of the reaction between Fe^{VI} and SAs with varying *R* substituents (Figure 1) as a function of pH (6.5–10.0).

The overall aims of the paper are to (i) determine speciesspecific rate constants (k) of the reactions between Fe^{VI} and SAs, (ii) identify the transformation products of the oxidation of SDZ and SIZ by Fe^{VI} using a high-resolution liquid chromatography-mass spectrometry (HR-LC-MS) technique, (iii) apply quantum chemical calculations and transition state theory to elucidate the SO₂ extrusion mechanism of SDZ by Fe^{VI}, and (iv) compare the oxidation of SAs with fivemembered and six-membered *R* to learn when the formation of SO₂ extrusion products from the SAs is feasible.

MATERIALS AND METHODS

Chemicals and Reagents. Detailed information on the test SAs (sulfisoxazole (SIZ), sulfamethizole (SMIZ), sulfamethoxazole (SMX), sulfathiazole (STZ), sulfapyridine

SAs		pK_{a2}	$k_5 (M^{-1} s^{-1})$	$k_6 (M^{-1} s^{-1})$	R^2	source
five-membered heterocyclic aromatic group	SIZ	5.00 ²⁸	$(1.1 \pm 0.1) \times 10^4$			28
	SMIZ	5.70 ²⁸	$(2.2 \pm 0.2) \times 10^4$			28
	SMX	5.30 ²⁸	$(7.0 \pm 0.5) \times 10^3$			28
	STZ	7.07 ⁴⁵	$(1.2 \pm 0.1) \times 10^3$	$(1.1 \pm 0.1) \times 10^2$	0.938	this study
six-membered heterocyclic aromatic group	SPY	8.56 ⁴⁶	$(2.7 \pm 0.3) \times 10^3$	$(2.1 \pm 0.1) \times 10^2$	0.971	this study
	SDZ	6.28 ⁴⁵	$(1.5 \pm 0.1) \times 10^3$	$(9.0 \pm 0.1) \times 10^2$	0.979	this study
	SM1	6.77 ⁴⁵	$(1.6 \pm 0.1) \times 10^3$	$(9.0 \pm 1.0) \times 10^2$	0.999	this study
	SM2	7.40 ²⁸	$(1.9 \pm 0.1) \times 10^3$	$(2.25 \pm 0.2) \times 10^2$		28
	SMM	6.01 ⁴⁵	$(4.5 \pm 0.2) \times 10^3$	$(6.0 \pm 0.5) \times 10^2$	0.997	this study
	SMP	7.19 ⁴⁷	$(1.8 \pm 0.2) \times 10^3$	$(1.0 \pm 0.1) \times 10^3$	0.954	this study
	SDM	6.10 ²⁸	$(1.88 \pm 0.04) \times 10^4$			24
	SFD	6.01 ⁴⁸	$(5.2 \pm 0.2) \times 10^3$	$(6.5 \pm 0.4) \times 10^2$	0.964	this study

(SPY), sulfadiazine (SDZ), sulfamerazine (SM1), sulfamethazine (SM2), sulfamonomethoxine (SMM), sulfamethoxypyridazine (SMP), sulfadimethoxine (SDM), and sulfadoxine (SFD)), Fe^{VI}, buffers, and preparation of all reaction solutions is provided in Text S1 of the Supporting Information (SI).

Stopped-Flow Experiments. Experiments were carried out under pseudo-first-order conditions to perform the kinetics of the reactions between Fe^{VI} and seven different kinds of SAs (i.e., STZ, SPY, SDZ, SM1, SMM, SMP, and SFD). Under these conditions, the concentrations of SAs $(5.0-10.0 \times 10^{-4} \text{ M})$ were higher than Fe^{VI} $(5.0 \times 10^{-5} \text{ M})$. The kinetic measurement was performed using a stopped-flow spectrophotometer (SX-20 MV, Applied Photophysics, Surrey, U.K.). Details are provided in Text S2 and Figure S1.

Oxidized Products Experiments. The identification of the oxidized products (OPs) of SDZ $(4.0 \times 10^{-5} \text{ M})$ or SIZ $(4.0 \times 10^{-5} \ \mu\text{M})$ by Fe^{VI} $(2.0 \times 10^{-4} \text{ M})$ at pH 9.0 was conducted by the solid phase extraction-liquid chromatography-high-resolution/accurate mass (HR/AM) spectrometry (SPE-LC–HRMS) technique (Text S2).³⁶ The analysis of OPs by the other oxidants aided us to identify the transformation of SDZ by Fe^{VI.31,32}

Quantum Chemical Calculations. All calculations were performed with the Gaussian 09 program³⁷ using primarily the unrestricted M06 DFT functional³⁸ with the 6-311++G(d,p) basis set. Details are provided in Text S3.

The structure of each species with bond lengths is provided in Figure S2 along with a table of enthalpies and Gibbs free energies (Table S1). The charges and spin densities for all species were calculated with Hirshfeld population analysis^{39–41} and are given in Table S2 and Figures S3 and S4, respectively. Additionally, the atomic labeling of SDZ is provided in Figure S5. The zero-point-energy-corrected Gibbs free energy scale was chosen since the Gibbs free energy of activation can be related directly to the experimental rate constants.⁴²

Eighteen kinds of representative quantum chemical descriptors of all 12 SAs after structural optimization were calculated using the unrestricted M06 DFT functional with the 6-311++G(d,p) basis set to investigate their possible correlations with the observed species-specific rate constants by Fe^{VI}. These parameters included the energy of the highest occupied molecular orbitals ($E_{\text{HOMO-}n}$, n = 0-5), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), the energy difference of E_{HOMO} and E_{LUMO} ($\Delta E (E_{\text{L}} - E_{\text{H}})$), the most negative net charge in the atom of the molecule (q⁻), the most positive net atomic charge on a H atom (qH⁺), dipole moment (μ), average polarizability (α), ionization potential (IP),

electron affinity (EA), hardness (η), softness (S), electronegativity (ζ), and electrophilicity index (ω). The obtained values with the SMD solvent model are presented in Table S3. The correlation analysis was conducted using SPSS software (Version 16.0).

RESULTS AND DISCUSSION

Kinetics. In this study, additional SAs were included to learn the trend of variation of rates with SAs containing *R* of five- and six-membered moieties. An approach used to determine the second-order rate constant (k, $M^{-1} s^{-1}$) of the reaction between Fe^{VI} and SAs was similar to earlier kinetic investigations (eq 1).^{24,25,28}

$$-d[Fe^{VI}]/dt = k[Fe^{VI}][SA]$$
⁽¹⁾

The values of k at different pH were determined from 6.5 to 10.0. Results are presented in Figure S6. Rates were decreased with an increase in pH, and the pattern was similar in the reactions of Fe^{VI} with several inorganic and organic compounds.^{23,43}

The variation in the values of k with pH was interpreted quantitatively using acid—base equilibrium of Fe^{VI} and SAs. In the pH range of the study, only monoprotonated and unprotonated species of Fe^{VI} and SAs (X) are involved (eqs 2 and 3).^{28,44–48}

$$HFeO_4^- \rightleftharpoons H^+ + FeO_4^{2-}, \ pK_{a3} = 7.23$$
 (2)

$$HX \rightleftharpoons H^+ + X^-, \ pK_{a2} = 5.00 - 8.56$$
 (3)

The dependence of k on the pH can thus be modeled by eq 4.

$$-d[X]/dt = k[Fe^{VI}]_{tot}[X]_{tot} = \Sigma k_{ij} \alpha_i \beta_j [Fe^{VI}]_{tot}[X]_{tot}$$
$$i = 1, 2$$
$$j = 1, 2$$
(4)

where $[Fe^{VI}]_{tot} = [HFeO_4^{-}] + [FeO_4^{2-}]; [X]_{tot} = [HX] + [X^{-}]; \alpha_i$ and β_j represent the species fractions of Fe^{VI} and selected SA, respectively; *i* and *j* are each of the species of Fe^{VI} and selected SA, respectively; and k_{ij} is the species-specific second-order rate constant for the reaction between the Fe^{VI} species *i* and the X species *j*. Overall, four reactions could possibly contribute to eq 4.

Equation 4 was applied to empirically fit the kinetic data of the oxidation of SAs by Fe^{VI} in Figure S6. It was observed that only two of the four reactions were needed to reasonably fit the



Figure 2. Proposed transformation pathways of SDZ (a) and SIZ (b) by Fe^{VI} (experimental conditions: $[\text{SDZ}] = [\text{SIZ}] = 4.0 \times 10^{-5} \text{ M}$, $[\text{Fe}^{\text{VI}}] = 2.0 \times 10^{-4} \text{ M}$, pH = 9.0, T = 25.0 °C).

experimental data (see solid lines in Figure S6). These two reactions are presented by eqs 5 and 6.

$$HFeO_4^- + HX \rightarrow products$$
 (5)

$$\text{FeO}_4^{2-} + \text{HX} \to \text{products}$$
 (6)

Values of the species-specific rate constants, k_5 and k_6 , for the reactions 5 and 6, respectively, are given in Table 1. Values of k_5 were found in the range from $(1.2 \pm 0.1) \times 10^3 - (2.2 \pm 0.2) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, while the range of k_6 was from $(1.1 \pm 0.1) \times 10^2$ to $(1.0 \pm 0.1) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. It seems that the variation in k_5 is related to change in R, which influences the aniline moiety, the attacking site by Fe^{VI} in oxidizing SAs. More is discussed in later sections. The reaction between Fe^{VI} and SAs has proton ambiguity, i.e., the reaction of HFeO₄⁻ with X⁻ is involved instead of reaction 6 (i.e., FeO₄²⁻ + HX). The reactivity of protonated Fe^{VI} (or HFeO₄⁻) with X⁻ would be faster than that with HX due to higher electron density on the X⁻. This possibility may occur because FeO₄²⁻ is a weaker oxidant than HFeO₄⁻. However, the kinetics measurements of our study do not fully distinguish which of the two reactions would be preferable.

In the case of sulfadiazine (SDZ), the kinetics of the reaction with Fe^{VI} were extended to the acidic pH range (Figure S6). This allowed the calculation of the rate constant values of the reaction between diprotonated Fe^{VI} and protonated SDZ (or HX) as $(2.7 \pm 0.5) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. The result suggests that the reactions of Fe^{VI} with the protonated species of SDZ follow the order of reactivity as H₂FeO₄ > HFeO₄⁻ > FeO₄²⁻. Overall, results of different SAs showed that the protonated Fe^{VI} (HFeO₄⁻) reacted faster with SAs than the unprotonated Fe^{VI} (FeO₄²⁻) (i.e., $k_5 > k_6$). It has been suggested that the partial radical character of Fe^{VI} (Fe^{VI} = O \leftrightarrow Fe^V – O[•]) is proton stabilized to yield higher reactivity of protonated species than the unprotonated species of Fe^{VI.49} Furthermore, the oxo ligands in HFeO₄⁻ have larger spin density than in FeO₄²⁻ that result in increased oxidation ability of protonated Fe^{VI.50,S1} The fraction of the HFeO₄⁻ ($\alpha_{\text{HFeO4-}}$) decreased with increase in pH, and hence the overall rate constant of the reactions between Fe^{VI} decreased with increase in pH (see Figure S6).

Understanding of the variation of rates for the oxidation of SAs by Fe^{VI} was attempted by calculating molecular structure descriptors of SAs. A total of 18 kinds of these descriptors were obtained using the unrestricted M06 DFT functional with the 6-311++G(d,p) basis set, which included E_{HOMO-n} (n = 0-5), E_{LUMO} , ΔE ($E_L - E_H$), q^- , qH^+ , μ , α , IP, EA, η , *S*, ζ , and ω (Table S3). A similar approach has been applied in understanding the reactivity of organic pollutants with Fe^{VIS2} and other oxidants.⁵²⁻⁵⁶ The rate constants showed no significant correlation with any individual descriptor (Table S4); therefore, no further evaluation of variation of rate constants of different SAs using the calculated molecular descriptors was performed.

Oxidized Products and Reaction Pathways. In this study, the oxidized products (OPs), generated via the oxidation of SDZ (a representative SA with six-membered heterocyclic group) and SIZ (a representative SA with fivemembered heterocyclic group) by FeVI, were characterized using high-resolution LC-MS (ESI pos). Structural assignments of OPs were performed by product ion scans, based on the corresponding MS/MS spectra and their proposed fragmentation patterns. The detailed data and proposed structures of the OPs and their MS/MS fragments are shown in Table S5 and Figures S7 and S8. Errors of m/z between the experimental and theoretical values errors were mostly <3 ppm. It is necessary to analyze the mass spectrum of the parent compound and the fragment losses generated, which may also be detected in the structural identification of the OPs.^{57,58} For example, SDZ (m/z 251.06027 and Rt at 2.62 min) has four main product ions at 156.01183 and 96.05644, 108.04513, and 92.05033, corresponding to the cleavage of the S-N bond in SDZ, and losses of SO (48 Da from 156.01183) and SO₂ (64 Da from 156.01183), respectively (Figure S7a). Although some MS/MS information regarding the OPs of SDZ and SIZ by $\mbox{Fe}^{\mbox{VI}}$ oxidation is lacking, recent investigations of trans-



Figure 3. Plausible mechanism of Fe^{VI} -catalyzed extrusion of SO_2 from SDZ and other aminopyridine-type sulfa drugs, via initiation of an oxidative single electron transfer from the aniline moiety.

formation products of these two SAs could facilitate the structural identification of these OPs.^{9,10,31-34}

Representatively, OP-187 with a protonated form at m/z187.09831 and chromatographic retention time at 5.22 min was proposed in our study as the product generated from the SO₂ extrusion in SDZ molecule (Table S5 and Figure S7e). This structure was confirmed by six detected product ions at m/z 170.07178, 160.08734, 108.06863, 92.05029, and 65.03954. These MS/MS fragments corresponded to the individual losses of such fragments as NH₃ (17 Da from 187.09831), CN (27 Da from 187.09831), C₃H₂N (52 Da from 160.08734), NH₂ (16 Da from 108.06863), and CN (27 Da from 92.05029), respectively. Similarly, in view of the repeated MS/MS fragments and proposed fragmentation patterns of the OPs of SDZ and SIZ, the individual structures of OP-281, OP-217, OP-201, OP-187, OP-298, OP-282, OP-248, OP-231, and OP-217' were proposed, and the possible fragmentation pathways are shown in Figures S7 and S8. It is difficult to obtain the MS/MS spectra of the OPs with low MS intensity (i.e., OP-267, OP-265, OP-203, and OP-284). Therefore, the structures of such OPs were thus tentatively proposed based on the accurately measured molecular compositions (Table S5) and the possible transformation pathways.

On the basis of the structures of the identified OPs, the proposed transformation pathways of SDZ and SIZ by Fe^{VI} at pH 9.0 are presented in Figure 2. An initial oxidative attack on

the aniline site of SDZ by Fe^{VI} is suggested, which can lead to the two products: the SO₂ extrusion and the hydroxylation of the aniline ring. In pathway I, Fe^{VI} can initiate a single electron transfer oxidative pathway of the aniline ring, resulting in a radical cation and Fe^V. The cation in turn induces the SO₂ extrusion of SDZ leading to OP-187 (Figure 2a). Fe^V has a much higher reactivity than Fe^{VI} and may participate in the oxidation of SDZ alongside Fe^{VI.59,60} The intermediates resulting from a potential Fe^V oxidation would be identical to those resulting from the single electron transfer observed with Fe^{VI}. However, the self-decomposition of Fe^V is fast with a rate constant of order of 10⁷ M⁻¹ s^{-1.49} The competing rate constants of the reaction of Fe^V with SDZ and its selfdecomposition would determine the involvement of Fe^V in the reaction mechanism.

It should be noted that OP-187 is itself not any more oxidized than SDZ, rather, formed as a result an unprecedented catalytic effect of Fe^{VI}. However, subsequent oxidation of OP-187 proceeded by hydroxylation of the aniline ring to form OP-203 with an -NHOH group, which was successively oxidized to generate OP-201 with an -NO group and OP-217 with an $-NO_2$ group (Figure 2a). Pathway II was initiated by hydroxylation in the aniline ring of SDZ, with the resultant product of OP-267. Afterward, similar reaction steps like pathway I after SO₂ extrusion occurred to yield OP-265 and OP-281 (Figure 2a).

In the oxidation of SIZ by Fe^{VI} , pathway I involved ring opening of the five-membered isoxazole ring and hydroxylation taking place on the N atom between the two rings of SIZ (Figure 2b), resulting in the formation of OP-248. Opening of the isoxazole ring has also been suggested during Fe^{VI} oxidation of SMX.^{24,28} This ring opening may involve the $-NH-SO_2-$ group in SMX because isoxazole itself has no reactivity with Fe^{VI} . Theoretical investigations suggested that this step was initiated via nucleophilic attack of Fe^{VI} followed by isomerization, H-bond assisted C–O cleavage and Fe–O bond cleavage.²⁷ With the reaction progressing, further attacks on the heterocyclic ring happened to generate OP-231 and OP-217'. Similar to pathway II of SDZ, OP-284, OP-282, and OP-298 were produced in pathway II of SIZ (Figure 2b). Overall, these identified OPs allowed the enhanced understanding of oxidation of SAs by Fe^{VI} .

Possible reaction mechanisms of hydroxylation of SDZ (Figure S5) to form OP-267 in pathway II can, in principle, occur on either the aniline N or the sulfonamide N, leading to products of identical masses. In basic pH, the sulfonamide N may become deprotonated and will therefore be more susceptible to oxidation. Hydroxylation of either N atoms can be achieved via two plausible pathways: (i). Sequential two single-electron transfer to Fe^{VI} leading to Fe^{IV} , and subsequent trapping by water and loss of a proton as described in our earlier work on SMX,²⁴ or (ii). A direct oxygen transfer from Fe^{VI} to the N of aniline in SAs, followed by rapid proton transfer from the resulting ammonium salt to the N-oxide leading to hydroxylamine (Figure S9).

Fe^{VI} Oxidation of SDZ—SO₂ Extrusion. Two pathways are proposed in which Fe^{VI} oxidizes either of the two aromatic rings of SDZ via a single-electron transfer leading to Fe^V (Figures 3 and S10). Figure 3 corresponds to single-electron transfer from aniline ring. The electron-transfer from R (pyrimidine ring) of SDZ is another possibility (Figure S10). These mechanistic pathways are unique to SAs containing a six-membered ring with a nitrogen ortho to the amido nitrogen. The presence of the ortho nitrogen heteroatom enables the formation of a five-membered ring intermediate initiated by any number of pathways including oxidative conditions $(SO_4^{\bullet-} \text{ and } Fe^{VI})$ or photochemical excitation to triplet states.^{30,32} The formation of a five-membered ring annihilates the aromaticity of the aniline ring, therefore raising the energy by close to 18 kcal/mol according to our computations. The extrusion of SO₂ then becomes plausible to restore aromaticity (Figure 3), or to generate another intermediate that will itself act as an oxidant to another molecule of the SA leading to a radical cation intermediate and subsequently restoring the aromaticity which leads to the SO₂ extruded product. Although these reactions are occurring in the presence of the strong oxidant Fe^{VI}, the overall extrusion of SO₂ and rearrangement is not a net oxidative pathway, and Fe^{VI} is acting to initiate the catalytic cycle (i.e., chain reactions). This is supported by the observed products discussed in the prior section.

Transition State Calculations. The calculations for the radical cation intermediate support oxidation according to Figure 3 rather than Figure S10. In other words, *R* is not involved in initial oxidation of SDZ by Fe^{VI} (i.e., ruling out the possibility of single-electron transfer as depicted in Figure S10). As stated earlier in the experimental method, C1–C6 are carbon atoms and N17 is N atom of the aniline ring (see Figure S5 for labels). The spin density is almost entirely on the

aniline ring (see Figures S4), indicating that the unpaired electron in the radical resides on that ring. The two largest values are on C5 (0.26) and N17 (0.29). Likewise, the largest positive increase in charge in oxidizing SDZ occurs on the aniline ring, especially the amino N17 (0.1705) (see Table S2). These results suggest that C5 and N17 are likely to be active participants in succeeding steps. Additionally, the diprotonated Fe^{VI} was chosen for transition state calculations since it reacts most readily with SDZ. The optimized structural parameters of all chemical species involved are briefly discussed below.

 $H_2Fe^{VI}O_4$ vs $H_2Fe^{VI}O_4^-$. $H_2Fe^{VI}O_4$ has shorter computed bond lengths, Fe–OH 1.76 Å vs 1.86 Å and Fe = O 1.59 (1.56) Å vs 1.62 Å than $H_2Fe^{V}O_4^-$, as a result of less electron repulsion. The charge on Fe is more positive, +0.55 vs +0.42, and the oxygen atoms are less negative, -0.25 vs -0.42, because there is one less electron. Also, the spin density is lower, 1.68 vs 2.63, on Fe^{VI} because there is one less unpaired electron.

SDZ vs SDZ Radical Cation. The atomic charges on the radical cation are best interpreted by comparison with SDZ (Table S2). The column to the right gives the difference in charge between the cation and SDZ. Notice that there is a much more positive increase on the aniline ring with the largest increase on N17 even though the N17 charge in the cation is only slightly positive (see Figure S5 for the atom numbering). The unpaired electron resides largely on N17 and C5, as indicated by the spin density. The changes in bond lengths are more subtle, with the H17–C2 bond becoming 0.04 Å shorter and the C5–S7 bond stretching by 0.04 Å.

Reactant Complex. An H-bonded complex is formed between the $H_2Fe^{VI}O_4$ and SDZ. The H-bond involves an O-H group on the Fe^{VI} with N17 on SDZ. The primary contribution of the H-bond is to bring the two molecules close enough together that transfer of an electron can occur. The N17-C2 bond and O-H Fe^{VI} bond both increase by 0.03 Å as a result of the H-bond. The charge on N17 is slightly less negative. However, the zero spin densities on SDZ indicate that no electron has been transferred.

TS1. The H-bond involving N17 on SDZ and an O–H group on the Fe^{VI} has broken and a new H-bond is forming, involving N17–H26 on SDZ and an O on the Fe^{VI}. As a result, the charge on N17 has become 0.06 more negative. The spin density indicates no electron transfer at this stage. The principal action is the change in H-bonding.

Radical Cation Complex. The new H-bond has formed between N17-H26 on SDZ and an O on the Fe^{VI}. At the same time, an electron has transferred from SDZ to the Fe^{VI} as indicated by the nonzero spin densities on SDZ, principally 0.32 on N17, 0.25 on C5, 0.19 on C1, and 0.17 on C3 that result from the loss of an electron. Likewise, the spin density on Fe has increased from 1.70 to 2.67 as a result of an additional unpaired electron. After oxidation occurs, there are now three unpaired electrons on the Fe^{VI} and one unpaired electron on SDZ. With a total of four unpaired electrons, one might consider the spin state for the complex to be a quintet. However, much better results were obtained for the triplet spin state, indicating that the unpaired electron on SDZ remains opposite in spin to the added electron on Fe^{VI}. This in turn indicates that the complex is so loose that Hund's rule does not apply. Consistent with the electron transfer, the ${\rm Fe}^{\rm VI}$ has become less positive and the oxygen atoms more negative, and SDZ is overall more positive with the principal changes on N17.

Article



Figure 4. Free energy pathway (kcal/mol) of SO₂ extrusion and rearrangement of SDZ in the presence of diprotonated Fe^{VI} to produce OP-187. Only the organic structures are drawn.

As a consequence of the electron transfer, all the Fe–O bonds have increased. The N17–C2 bond has decreased to 1.32 Å. The aniline ring has become more quinoidal and the C5–S7 bond has increased to 1.79 Å.

SDZ Radical Cation. There is very little geometry change as the complex dissociates to form the radical cation and $H_2Fe^VO_4^-$. There also is no significant change in either the charges or the spin densities. Since the complex has dissociated, the spin states for Fe^{VI} and the SDZ radical cation are now quartet and doublet, respectively.

T52. An intrinsic reaction coordinate calculation (IRC) involving TS2 is very illuminating. As TS2 is approached, the C5–N12 distance decreases while the C5–S7 bond is stretched. The C5–C7 bond is broken shortly after the top of the energy barrier, and after that the C5–N12 bond is formed. Finally, the S7–C10 bond is broken, releasing SO₂. The TS2 structure can be considered to include a five-membered ring although some bond lengths are stretched, especially the C5–N12 distance (1.79 Å vs 1.40 Å in the product radical cation) but also N10–S7 (1.74 Å vs 1.66 Å in SDZ radical cation) and S7–C5 (1.89 Å vs 1.79 in SDZ radical cation).

Product Radical Cation. As before, the unpaired electron is almost entirely on the aniline ring, principally N17 and C5. Likewise, the positive charge is located principally on the aniline ring. The most negative charge (-0.29) is on N10, now exo to the diazine ring.

TS3. Only the doublet state is stable, which means that there is still one unpaired electron. Thus, the bond lengths, charges, and spin densities are all very similar to the product radical cation. The major change occurring as TS3 is approached is that the two ring systems are becoming more planar; the dihedral angle between the two planes increases from 136° in the product radical cation to 178° in TS3.

Product. The aniline ring returns from a quinoidal structure to an aromatic structure with nearly equal C–C bond lengths. The C2–N17 and C5–N12 bond lengths have both increased, and the dihedral angle between the two rings has decreased significantly to 111° to minimize steric interaction. The charges on the aniline ring are similar to those in SDZ. Like the product radical cation, the most negative charge (-0.37) is on N10.

The Gibbs free energy pathway for diprotonated Fe^{VI} and SDZ is shown in Figure 4. The diprotonated Fe^{VI} and SDZ form an H-bonded reactant complex involving a hydroxyl H on the Fe^{VI} and the negatively charged N17 on SDZ. Although this H-bond lowers the enthalpy by 4.8 kcal/mol, the entropy loss increases the free energy by 8.2 kcal/mol. The transition state (TS1) involves breaking of the original H-bond and formation of a new H-bond between an amino H on SDZ and an O on Fe^{VI} along with transfer of an electron from SDZ to Fe^{VI}, forming a radical cation complex with Fe^V. This complex dissociates to give the more stable radical cation and Fe^V as separate species. Thus, the sole role of Fe^{VI} is the oxidation of SDZ. The expected large energy required to oxidize SDZ is offset by the difference between Fe^V and Fe^{VI}, $\Delta H = -143.1$ and $\Delta G = -144.4$ kcal/mol (Table S1).

The SDZ radical cation goes through another transition state (TS2) to form the product radical cation, releasing SO₂. It is interesting that while molecular mechanics (UFF) and semiempirical (PM6) calculations predict a stable five-membered ring intermediate as shown in Figure 3, DFT calculations do not. However, TS2 is close to the formation of the five-membered ring. As an azine nitrogen (N12) is forming a bond with C5 to form the five-membered ring, the C5–S7 bond starts to break, followed by dissociation of the N10–S7 bond to release SO₂. Formation of the much more stable final, neutral product is very exothermic with a low barrier (TS3).



Figure 5. Difference in geometries between the five-membered ring of isoxazole in SMX and the six-membered ring of pyrimidine in SDZ. Comparison of their radical cations clarifies the reasoning behind why only SDZ undergoes SO_2 extrusion.

The net oxidation of SDZ to give the product plus SO₂ has a $\Delta H = +7.1$ kcal/mol and $\Delta G = -5.3$ kcal/mol (Table S1).

The oxidation step is rate determining as indicated by TS1 having the highest energy (12.3 kcal/mol) relative to the reactants. This corresponds to a rate constant of $5.7 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ for H₂FeO₄ in good agreement with the experimental value of $2.7 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. Further confirmation of this mechanism is that the TS1 barrier height for HFeO₄⁻ oxidation of SDZ is calculated to be 13.9 kcal/mol, corresponding to a rate constant of $4.0 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$. Both experimental rate constant of $2.0 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. Both experimental rate constants were determined from data obtained over the pH range of 4.0 to 10.0, where the diprotonated and monoprotonated Fe^{V1} are more involved than the non-protonated Fe^{V1}. As further validation, the ratio of the diprotonated/monoprotonated calculated rate constants is 14.3 compared to the experimental ratio of 13.5.

Six-Membered R versus Five-Membered R Containing SAs. Experimental results and theoretical calculations further support our proposed SO₂ mechanism for the oxidation of SDZ by Fe^{VI}, already corroborated by the energy computations for transition states, in that the formation of the five-membered ring transition state TS2, albeit a fleeting transient state, is indeed essential for SO₂ extrusion. It is interesting to note that SO2 extrusion was not observed in SMX and other five-membered ring SAs (see Figures 1 and 2b). Identified OPs showed no extrusion step of the oxidation of SMX by Fe^{VI}, and reaction pathways have been described effectively by DFT calculations.²⁷ In SMX, the five-membered ring of the isoxazole places its N further away geometrically from the aniline ring C holding the S, than a six-membered ring would place the N of the pyrimidine ring. The SO_2N- C=N angle in SMX is about 122.3°, whereas it is 117.2° in SDZ as measured in semiempirical computations (see Figure 5). This is mainly a geometric difference.

Furthermore, the N of the isoxazole in SMX, which is bonded to the O, may have less propensity to curl around forming the "transient five-membered ring TS2" shown in Figure 5. Our DFT results show that the N in the isoxazole of SMX has more electron density (-0.21 atomic charge) than the N in pyrimidine of SDZ (-0.19 charge), plus the overall electronic density of the isoxazole ring in SMX (-0.12 net charge) is richer than that of the pyrimidine of SDZ (+0.05 net charge). This is likely a reason why Fe^{VI} breaks down the isoxazole ring, as seen in our previous work.²⁴ It is therefore plausible that the rate of $-NH-SO_2-R$ oxidation in SMX is faster than the SO₂ extrusion, hence not observed in SMX, but observed in SDZ.

Implications. Previous experimental and theoretical calculations supported no extrusion of SO_2 during the oxidation of SAs containing five-membered heterocyclic

moieties (e.g., SMX) by Fe^{VI} . However, a study of oxidized products and DFT calculations presented herein on the oxidation of SA with a six-membered heterocyclic moiety (e.g., SDZ) by Fe^{VI} indicate that the step of extrusion of SO₂ is involved, forming Fe^{V} and a radical. The presented mechanism of SO₂ extrusion may be possible for structurally similar sixmembered heterocyclic containing SAs.

The species-specific rate constants of the reactions of Fe^{VI} with SAs could describe the experimental second-order rate constants of the oxidation of SAs by Fe^{VI}. The values of *k* at pH 7.0 and 8.0 were used to learn the half-lives $(t_{1/2})$ of the elimination of SAs by Fe^{VI}. If the concentration of Fe^{VI} is in excess over SAs at a dose of $[K_2FeO_4] = 10 \text{ mg L}^{-1}$, as may be expected in practical application, then the $t_{1/2}$ values of the reactions would be short and in the range from 12.52 s (SPY) to 361.20 s (SMIZ) at pH 8.0 and 25.0 °C (Figure S11). Because the values of *k* are pH-dependent, the $t_{1/2}$ values for the removal of SAs by Fe^{VI} would also vary with the solution pH. At pH 7.0, the $t_{1/2}$ values would be much shorter, from 8.14 s (SPY) to 173.74 s (SDM) (Figure S11). Variation in the dose of Fe^{VI} would also change the $t_{1/2}$ to remove SAs by Fe^{VI}.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b06535.

Texts S1–S3, information on chemicals, experimental procedures, and DFT calculations; Tables S1–S4, structural parameters of SAs and their correlation analysis with rate constants; Table 5, analysis data of SDZ, SIZ, and their OPs; Figure S1, self-decay of Fe^{VI} at different pH; Figures S2–S5, DFT calculations; Figure S6, the rate constants of reactions between Fe^{VI} and SAs at different pH; Figures S7 and S8, mass spectra of OPs; Figure S9 and S10, the reaction mechanisms; and Figure S11, the half-lives of the degradation of SAs by Fe^{VI} (PDF)

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Notes

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1	Supplementary Information
2	
3 4	Oxidation of Sulfonamide Antibiotics of Six-membered Heterocyclic Moiety by Ferrate(VI): Kinetics and Mechanistic Insight into SO ₂ Extrusion
5	
6 7 8	Mingbao Feng, [†] J. Clayton Baum, [‡] Nasri Nesnas, [‡] Yunho Lee, [§] Ching-Hua Huang, ^{⊥,*} Virender K. Sharma ^{†,*}
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24	Text: 3.
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27	Total Pages: 35.

29 Text S1. Chemicals and Reagents

30 Sulfadiazine (SDZ), sulfadimethoxine (SDM), sulfadoxine (SFD), sulfamerazine (SM1), 31 sulfamethazine sulfamethizole (SM2), (SMIZ), sulfamethoxazole (SMX), 32 sulfamethoxypyridazine (SMP), sulfamonomethoxine (SMM), sulfapyridine (SPY), sulfathiazole 33 (STZ), and sulfisoxazole (SIZ), sodium dihydrogen phosphate, and sodium borate phosphate 34 were obtained either from Fisher-Scientific (Austin, TX, USA) or Sigma-Aldrich (St. Louis, MO, 35 USA). The purity of the chemicals was greater than 97%, and they were used without further 36 purification. Organic solvents of methanol and acetonitrile used in the high-performance liquid 37 chromatography (HPLC) were obtained from Fisher-Scientific. Solid potassium ferrate (K₂FeO₄) of ~ 98% purity was synthesized by the wet chemical technique. Solutions of Fe^{VI} were prepared 38 39 by dissolving solid K₂FeO₄ in 1.0 mM Na₂B₄O₇•10H₂O/5.0 mM Na₂HPO₄ at pH 9.0. In this solution, Fe^{VI} is sufficiently stable to perform experiments. Absorbance of Fe^{VI} solutions was 40 41 measured at a wavelength of 510 nm using an UV-vis spectrophotometer. An extinction coefficient, $\varepsilon_{510nm} = 1150 \text{ M}^{-1} \text{ cm}^{-1}$, was used to determine the concentration of Fe^{VI}. All 42 43 solutions were made in water that was obtained from a purification system (18.0 M Ω cm, Milli-44 Q Millipore, Waters Alliance, Milford, MA, USA). In kinetic experiments, the solutions of SAs 45 were prepared by dissolving the solid compounds in a 10.0 mM Na₂HPO₄ buffer-acetone (85:15) 46 solution. The pH of the solution was adjusted by adding either NaOH or phosphoric acid. In the product analysis of the oxidation of SDZ and SIZ by Fe^{VI}, the solutions of these two SAs were in 47 48 the buffer solution at pH 9.0.

50 Text S2. Experimental Section

51 For the stopped-flowed experiments, the kinetic traces were monitored at a wavelength of 52 510 nm. Results from the stopped-flow spectrophotometer were analyzed using the nonlinear 53 least-square algorithm of the SX-20 MV Global Software (Applied Photophysics, Surrey, UK). 54 Six replicate runs were made to determine the averaged rate constants. The pseudo-first-order 55 rate constants for the reactions were corrected by subtracting the obtained first-order rate constants from stopped-flow experiments of reactions between Fe^{VI} and substrates from the rate 56 constants of Fe^{VI} self-decay at each studied pH. The kinetic traces of the self-decay of Fe(VI) at 57 58 different pH are given in Figure S1.

The identification of the oxidized products (OPs) of SDZ (4.0×10^{-5} M) or SIZ (4.0×10^{-5} M) 59 ⁵ μ M) by Fe^{VI} (2.0 × 10⁻⁴ M) at pH 9.0 was conducted using the solid phase extraction-liquid 60 61 chromatography-high-resolution/accurate mass (HR/AM) spectrometry (SPE-LC-HRMS) 62 technique. The operating procedures involved pre-treatment of SPE after the reaction mixture 63 was concentrated on the SPE workstation (Supleco, USA) that had a Waters Oasis HLB cartridge 64 (WAT106202, 6 cc/200 mg). Prior to the extraction procedure, the HLB cartridge was 65 conditioned with 5.0 mL methanol and 5.0 mL water, loaded with 50.0 mL sample, and 66 subsequently dried with purified nitrogen gas for 30 min. The final extracted OPs were obtained 67 by methanol $(2.0 \times 2.0 \text{ mL})$ and then analyzed by the LC-MS technique. The full-scan analysis 68 of OPs was done on a Q Exactive Plus OrbiTrap mass detector (Thermo Scientific, Waltham, 69 MA) coupled to a binary pump HPLC (Ultimate 3000, Thermo Scientific) in a positive ion mode 70 using an electrospray ion (ESI) source. The sheath, aux and sweep gasses were set at 50, 10 and 71 1, respectively, for acquiring data. The spray voltage and S-lens RF were set to 4 kV and 50, respectively. The aux gas heater and capillary temperatures were maintained at 375 and 350 °C. 72

respectively. Full MS spectra were obtained at 70,000 resolution (*m/z* 200) with a scan range of m/z 50–750. Full MS \rightarrow ddMS2 scans were collected at 35,000 resolution (MS1) and 17,500 resolution (MS2) with a 1.5 *m/z* isolation window and a stepped NCE (20, 40, and 60). Before injection, the temperature was maintained at 4 °C for these samples. The injection volume was 10 µL.

Chromatographic separation was carried out on a Hypersil GOLDTM C₁₈ selectivity LC 78 79 column (50 mm \times 2.1 mm, particle size 3 µm), which was at 25 °C using a solvent gradient 80 method. The mobile phase was water (0.3% formic acid) (A) and methanol (B). The gradient 81 method used was as follows: 0-2 min (10% B to 80% B), 2-3 min (90% B to 20% B), 3-26 min (90% B), 26-27 min (10% B), and 27-35 min (10% B). The flow rate was 0.2 mL/min. An 82 83 acquisition of the sample was performed by Xcalibur (Thermo Scientific). Compound Discoverer 84 2.1 software (Thermo Scientific), and online molecular structure libraries (i.e., m/z cloud and 85 ChemSpider) were used to process the high-resolution MS data.

87 Text S3. Quantum Chemical Calculations

88 All calculations were performed with the Gaussian 09 program¹ using primarily the 89 unrestricted M06 DFT functional² with an ultrafine integration grid, which gave very good 90 agreement with the experimental geometries of ferrates. For iron, the Wachters-Hav³ all-electron 91 basis set augmented by one f-polarization function was used. The 6-311++G(d,p) basis set was 92 used for all other atoms. During all calculations, solvent effects were accounted for using the 93 SMD⁴ solvation model set to the default dielectric constant for water. Optimized stationary point 94 geometries were obtained with the default Gaussian 09 "Berny" optimization algorithm;⁵ the 95 reactants, products, and intermediates were confirmed by noting that there were no imaginary 96 vibrational frequencies, while for the transition states, each had one imaginary frequency that 97 corresponded to the expected reaction coordinate.

98 The most stable H-bonded complexes were determined by first freezing the optimized 99 internal coordinates of Fe^{VI} and SDZ species. Next, starting from a variety of initial locations, 100 the location of one molecule with respect to the other was allowed to optimize to the lowest 101 energy. A final optimization was done with all coordinates unfrozen.

It was found that the best transition state (TS) geometries were determined at the unrestricted B3LYP/6-31+G** level^{6,7} in the gas phase. This was accomplished with the QST3 synchronous transit-guided quasi-Newton (STQN) method,^{8,9} where the TS guess was generally taken to be the mid-point between the reactant and product sides. Single-point energy calculations on these optimized geometries at the unrestricted M06/6-311++G(d,p) level with the SMD solvent model for water gave properties that could be compared with the other species.

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S5

109 **Table S1.** Calculated enthalpies and Gibbs energies (kcal/mol) of all species involved in the SO₂

110 extrusion of SDZ.

	Н	G
SDZ	-724263.3	-724300.3
$H_2Fe^{VI}O_4$	-982408.8	-982433.4
radical cation	-724130.9	-724167.8
H ₂ Fe ^V O ₄ -	-982551.8	-982577.8
product radical cation	-379907.1	-379938.5
SO_2	-344227.5	-344245.2
product	-380028.7	-380060.4
reactant complex	-1706676.8	-1706725.5
radical cation complex	-1706689.5	-1706741
TS1	-1706676.2	-1706721.3
TS2	-724115.9	-724150.3
TS3	-379902.19	-379933.7
HFe ^{VI} O ₄ -	-982141.5	-982165.4
mono reactant	-1706407.6	-1706456.5
complex		
mono TS1	-1706405.7	-1706451.8
	Relative H	Relative G
$SDZ + H_2Fe^{VI}O_4$	0	0
reactant complex	-4.8	8.2
TS1	-4.1	12.3
radical cation complex	-17.4	-7.4
radical cation +	-10.7	-12
$H_2 Fe^{v}O_4^{-}$	1.2	-
$TS2 + H_2Fe^{v}O_4$	4.3	5.6
product radical cation	-14.3	-27.9
+ SO ₂ + H ₂ Fe ^V O ₄ -	0.4	22.1
$1S3 + SO_2 + H_2Fe^{V}O_4^{-1}$	-9.4	-23.1
product + SO ₂ +	-136	-149.8
$H_2 Fe^{v} O_4^{-1}$	7 1	5.2
$product + SO_2 - SDZ$	/.1	-5.5
$SDZ + \Pi F e^{-1}O_4$	0	0
mono reactant	-2.7	9.2
complex	0.0	12.0
mono 151	-0.9	13.9

		SDZ	Radical cation	Charge inc	rease
1	С	-0.061906	0.029869	0.091775	*
2	С	0.070879	0.148199	0.07732	*
3	С	-0.058581	0.029474	0.088055	*
4	С	-0.024545	0.009943	0.034488	
5	С	-0.070444	0.025789	0.096233	*

Table S2. Hirshfeld atomic charges of SDZ and its radical cation.

T	U	-0.001700	0.027807	0.071775	
2	С	0.070879	0.148199	0.07732	*
3	С	-0.058581	0.029474	0.088055	*
4	С	-0.024545	0.009943	0.034488	
5	С	-0.070444	0.025789	0.096233	*
6	С	-0.026492	0.008384	0.034876	
7	S	0.44956	0.471953	0.022393	
8	0	-0.386848	-0.35659	0.030256	
9	0	-0.373084	-0.34365	0.029432	
10	Ν	-0.123761	-0.11359	0.010167	
11	С	0.168549	0.173188	0.004639	
12	Ν	-0.188224	-0.17656	0.01166	
13	С	0.062462	0.069624	0.007162	
14	С	-0.051833	-0.04398	0.007858	
15	С	0.061243	0.067479	0.006236	
16	Ν	-0.20285	-0.1962	0.006647	
17	Ν	-0.150569	0.019942	0.170511	**
18	Н	0.059061	0.096322	0.037261	
19	Η	0.059962	0.096544	0.036582	
20	Н	0.062559	0.086807	0.024248	
21	Η	0.05724	0.080459	0.023219	
22	Н	0.159265	0.17133	0.012065	
23	Н	0.067325	0.071587	0.004262	
24	Η	0.07009	0.0735	0.00341	
25	Н	0.066984	0.070545	0.003561	
26	Η	0.151865	0.2147	0.062835	*
27	Η	0.152082	0.214892	0.06281	*
				Sum = 1.0	000

*, ** indicate largest charge increases.

117 **Table S3.** The structural parameters of SAs calculated at UM06/6-311++G(d,p) level with the SMD solvent model. 118

SAs	E _{HOMO}	E _{HOMO-1}	E _{HOMO-2}	E _{HOMO-3}	E _{HOMO-4}	E _{HOMO-5}	E _{LUMO}	ΔE (E _L -E _H)	d.	qH+	μ	α	IP	EA	η	S	ζ	ω
SIZ	-6.499	-7.337	-7.846	-8.328	-8.814	-9.365	-1.124	5.375	-0.384	0.164	8.742	267.714	6.013	-1.244	3.628	0.138	2.385	0.784
SMIZ	-6.567	-7.469	-7.894	-8.128	-8.617	-9.094	-1.334	5.234	-0.381	0.165	10.446	267.280	6.087	-1.681	3.884	0.129	2.203	0.625
SMX	-6.540	-7.544	-7.711	-7.865	-8.971	-9.430	-1.102	5.438	-0.395	0.169	14.841	248.618	6.044	-1.223	3.634	0.138	2.411	0.800
STZ	-6.533	-7.555	-7.904	-8.534	-8.981	-9.375	-2.746	3.787	-0.371	0.169	10.874	250.034	6.046	-3.194	4.620	0.108	1.426	0.220
SPY	-6.525	-6.998	-7.825	-7.909	-8.457	-9.038	-1.101	5.424	-0.402	0.159	13.258	265.832	6.033	-1.476	3.755	0.133	2.278	0.691
SDZ	-6.444	-7.521	-7.709	-7.836	-9.214	-9.298	-1.374	5.070	-0.400	0.161	11.528	253.229	5.963	-1.876	3.920	0.128	2.043	0.533
SM1	-6.521	-7.355	-7.703	-7.836	-8.860	-9.041	-1.273	5.249	-0.399	0.159	10.985	274.614	6.027	-1.768	3.898	0.128	2.130	0.582
SM2	-6.524	-7.289	-7.672	-7.830	-8.737	-8.924	-1.165	5.359	-0.400	0.158	9.871	293.887	6.031	-1.657	3.844	0.130	2.187	0.622
SMM	-6.529	-7.343	-7.837	-8.014	-8.088	-8.885	-1.120	5.409	-0.397	0.166	13.550	281.192	6.034	-1.250	3.642	0.137	2.392	0.785
SMP	-6.531	-7.269	-7.451	-7.844	-8.675	-9.175	-1.722	4.809	-0.397	0.159	9.663	283.960	6.037	-2.190	4.113	0.122	1.924	0.450
SDM	-6.552	-7.146	-7.850	-8.028	-8.141	-8.770	-1.122	5.431	-0.387	0.160	7.561	305.203	6.057	-1.230	3.644	0.137	2.414	0.799
SFD	-6.538	-7.155	-7.765	-7.840	-8.136	-8.949	-1.144	5.394	-0.394	0.159	12.565	304.930	6.045	-1.239	3.642	0.137	2.403	0.793

120 Note: E_{HOMO} , the energy of the highest occupied molecular orbital, eV; E_{LUMO} , the energy of the lowest unoccupied molecular orbital, eV; ΔE (E_L - E_H), 121 the energy difference of E_{HOMO} and E_{LUMO} , eV; q⁻, the most negative net charge in the atom of the molecule; qH⁺, the most positive net atomic charge on 122 a H atom; μ , the dipole moment, debye; α , average polarizability, Bohr³; *IP*, ionization potential (*IP* = $E_{radical cation}$ - $E_{neutral molecule}$), eV; *EA*, electron 123 affinity (EA = $E_{radical anion}$ - $E_{neutral molecule}$), eV; η , hardness, $\eta = (IP - EA)/2$, eV; *S*, softness, S = 1/(IP - EA), eV⁻¹; ζ , electronegativity, $\zeta = (IP + EA)/2$, eV; 124 ω , electrophilicity index, $\omega = \zeta^2/2\eta$, eV.

	$\log k_{\rm HFeO4}$.	Еномо	E _{HOMO-1}	E _{HOMO-2}	E _{HOMO-3}	E _{HOMO-4}	E _{HOMO-5}	E _{LUMO}	ΔE (E _L -E _H)	q	qH+	μ	α	IP	EA	η	S	ζ	ω
$\log k_{\rm HFeO4-}$	1.00																		
E _{HOMO}	-0.39	1.00																	
E _{HOMO-1}	0.11	-0.09	1.00																
E _{HOMO-2}	-0.46	0.19	0.02	1.00															
E _{HOMO-3}	-0.15	-0.14	0.350	0.63	1.00														
E _{HOMO-4}	0.42	-0.37	0.70	-0.26	0.12	1.00													
E _{HOMO-5}	0.20	-0.45	0.68	-0.10	0.37	0.81	1.00												
E _{LUMO}	0.49	0.01	0.46	0.04	0.62	0.38	0.43	1.00											
$\Delta E (E_L - E_H)$	0.52	-0.02	0.47	0.03	0.61	0.41	0.46	0.99	1.00										
q-	0.31	-0.17	-0.41	-0.55	-0.90	-0.10	-0.32	-0.64	-0.61	1.00									
qH^+	0.20	0.06	-0.70	-0.42	-0.62	-0.23	-0.56	-0.38	0.37	0.58	1.00								
μ	-0.21	0.06	-0.13	-0.02	0.30	-0.02	-0.21	0.15	0.14	-0.39	0.36	1.00							
α	0.22	-0.26	0.68	0.14	0.35	0.76	0.84	0.38	0.41	-0.22	-0.63	-0.40	1.00						
IP	0.49	-0.60	0.15	-0.29	-0.24	0.48	0.30	-0.07	-0.02	0.45	0.24	-0.07	0.27	1.00					
EA	0.62	0.00	0.44	-0.09	0.48	0.49	0.41	0.96	0.97	-0.48	-0.22	0.16	0.40	0.03	1.00				
η	-0.60	-0.03	-0.43	0.07	-0.49	-0.47	-0.39	-0.97	-0.97	0.50	0.23	-0.17	-0.39	0.02	-0.99	1.00			
S	0.62	0.04	0.41	-0.12	0.44	0.48	0.37	0.94	0.95	-0.45	-0.17	0.18	0.28	0.00	0.99	-0.99	1.00		
ζ	0.65	-0.03	0.45	-0.10	0.46	0.52	0.42	0.96	0.96	-0.45	-0.20	0.16	0.42	0.08	1.00	-0.99	0.99	1.00	
ω	0.67	-0.01	0.43	-0.18	0.37	0.54	0.39	0.91	0.92	-0.37	-0.12	0.18	0.40	0.10	0.99	-0.98	0.99	0.99	1.00

126Table S4. The complete correlation analysis (r) between the values of log $k_{\rm HFeO4-}$ and the structural parameters of SAs.127

Table S5. Accurate mass measurements of SDZ, SIZ and their transformation products by Fe^{VI} , which were determined by LC-MS/MS (ESI pos).

132

Compound	$R_{\rm t}$	Formula	Experimental mass	Calculated mass	Error
	(min)	$[M + H]^{+}$	(m/z)	(m/z)	(ppm)
SDZ	2.62	$C_{10}H_{11}N_4O_2S$	251.06027	251.06027	0.00
OP-281	4.81	$C_{10}H_9N_4O_4S$	281.03458	281.03445	0.46
OP-267	4.80	$C_{10}H_{11}N_4O_3S\\$	267.05502	267.05519	-0.64
OP-265	5.05	$C_{10}H_9N_4O_3S$	265.03913	265.03954	-1.55
OP-217	5.29	$C_{10}H_9N_4O_2$	217.07259	217.07255	0.18
OP-203	5.22	$C_{10}H_{11}N_4O$	203.09241	203.09329	-4.33
OP-201	5.22	$C_{10}H_9N_4O$	201.07750	201.07764	-0.70
OP-187	5.22	$C_{10}H_{11}N_4$	187.09831	187.09837	-0.32
SIZ	4.80	$C_{11}H_{14}N_3O_3S$	268.07556	268.07559	-0.11
OP-298	5.14	$C_{11}H_{12}N_3O_5S$	298.04987	298.04977	0.34
OP-284	5.20	$C_{11}H_{14}N_3O_4S$	284.07059	284.07050	0.32
OP-282	5.20	$C_{11}H_{12}N_3O_4S$	282.05481	282.05485	-0.14
OP-248	2.97	$C_8H_{14}N_3O_4S$	248.07040	248.07050	-0.40
OP-231	3.02	$C_8H_{11}N_2O_4S$	231.04381	231.04395	-0.61
OP-217'	4.56	$C_7H_9N_2O_4S$	217.02934	217.02830	4.79



Time, s Figure S1. The self-decay of Fe^{VI} (50.0 μ M) at the wavelength of 510 nm at different pH values,

137 determined by the stopped-flow instrument.



142 Figure S2. Bond lengths (Å) of structures. (continued on next page)







151

Product Radical Cation





TS3

153

154



156

155

Product









 $H_2Fe^{VI}O_4$

SDZ



















Figure S3. Charges on structures. (continued on next page)









SDZ



194

195

Reactant Complex













211

Product









Figure S5. Structure of SDZ with atom labels.



Figure S6. Dependence of second-order rate constants (k_{obs} , M⁻¹ s⁻¹) on pH for the oxidation of SAs by Fe^{VI} at 25.0 °C. 225 226 227



230 231 **Figure S7.** Product ion spectra of SDZ and its degradation products by Fe^{VI}, measured by LC-

MS/MS (ESI pos), and their proposed fragmentation pathways at pH 9.0 and at 25.0 °C. (continued on next page)



236 237

Figure S7. Product ion spectra of SDZ and its degradation products by Fe^{VI}, measured by LC-MS/MS (ESI pos), and their proposed fragmentation pathways at pH 9.0 and at 25.0 °C. (continued on next page)



- Figure S7. Product ion spectra of SDZ and its degradation products by Fe^{VI}, measured by LC-
- 244 MS/MS (ESI pos), and their proposed fragmentation pathways at pH 9.0 and at 25.0 °C.



Figure S8. Product ion spectra of SIZ and its OPs by Fe^{VI}, measured by LC-MS/MS (ESI pos), and their proposed fragmentation pathways at pH 9.0 and at 25.0 °C. (continued on next page)



252 253 Figure S8. Product ion spectra of SIZ and its OPs by Fe^{VI}, measured by LC-MS/MS (ESI pos),



Figure S8. Product ion spectra of SIZ and its OPs by Fe^{VI}, measured by LC-MS/MS (ESI pos), and their proposed fragmentation pathways at pH 9.0 and at 25.0 °C.



Figure S9. Plausible mechanism for oxygen transfer to N in SDZ or SIZ; could occur on either N and will give the same MS peak for hydroxylated products (i.e., OP-267 for SDZ; OP-284 and

- and will give theOP-248 for SIZ).
- 265



Figure S10. Plausible mechanism of Fe^{VI}-catalyzed extrusion of sulfur dioxide from SDZ and other aminopyridine-type sulfa drugs, via initiation of an oxidative single-electron transfer from the pyrimidine moiety.







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Figure S11. Half-lives $(t_{1/2})$ of the oxidation of SAs by Fe^{VI} at pH 8.0 (a) and 7.0 (b) with a dose of K₂FeO₄ of 10 mg L⁻¹ and 25.0 °C.

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