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Ferrate promoted oxidative cleavage of sulfonamides: Kinetics and product formation under acidic conditions

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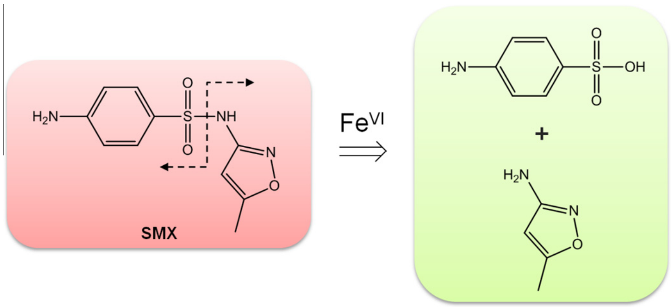
HIGHLIGHTS

- Decrease in rates with increasing pH under both acidic and basic conditions.
- Model considering species-specific reactions describes the trend in rates.
- Oxidative cleavage of S—N bond dominates in acidic medium.
- Hydroxylation appears to be major pathway in basic medium.
- Effective removal of the sulfonamide in presence of humic acid.

GRAPHICAL ABSTRACT



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ABSTRACT

Sulfonamide-based antibiotics are often detected in surface water and secondary wastewater effluent and pose an eminent threat for the development of antibiotic resistance bacteria and genes in aquatic environment. This paper presents the kinetics and stoichiometry of the oxidation of sulfonamides (sulfaguanidine, sulfisoxazole, sulfamethizole, sulfamethoxazole (SMX), sulfamethazine, and sulfadimethoxine) by ferrate(VI) (FeO_4^{2-}, Fe(VI)) in the acidic to basic pH range (2.0–9.6); apparent second-order rate constants (k_{app}, $M^{-1}\ s^{-1}$) decreased non-linearly with increase in pH. The specific rate constants for the individual Fe(VI) species ($H_3FeO_4^+$, H_2FeO_4, $HFeO_4^-$, and FeO_4^-) were determined using acid–base equilibria of Fe(VI) and sulfonamides. The reactivity order of Fe(VI) species with the neutral sulfonamide was $H_3FeO_4^+ > H_2FeO_4 > HFeO_4^-$, which generally explained the pH dependence behavior of rate constants. Detailed studies regarding the resultant oxidized products (OPs) using liquid chromatography–mass spectrometry/mass spectrometry were performed for oxidation of SMX at different molar ratios of Fe(VI) to SMX (i.e., 1.0–15) and at different pH's (i.e., 4.0, 7.0, and 9.0); oxidative degradative products include 3-amino-5-methylisoxazole, and hydroxyl-, hydroxylamine-, nitroso-, and nitro-derivatives of SMX. The possible reaction pathways comprise the S—N bond cleavage, ring-opening of isoxazole moiety, oxidation of aromatic amine, and the hydroxylation of the benzene ring; different OPs formed under acidic, neutral, and basic pH conditions are described. The value of k_{app}, $8.9 \times 10^2\ M^{-1}\ s^{-1}$ at pH 7.0 suggests the oxidative transformation of SMX in seconds by 1 mg L^{-1} K_2FeO_4 and interestingly, the removal of SMX could be achieved at neutral pH by Fe(VI) in the presence of humic acid.

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1. Introduction

Antibiotic-based pharmaceuticals have been reported in aquatic environment worldwide [1] and are responsible for adverse effects on human health and ecosystems due to their biological activity [2]. For example, mixtures of pharmaceuticals even at ng L^{-1} can inhibit cell proliferation [3]. Antibiotics can alter microbial activity and community composition of water-based organisms which lead to antibiotic resistant bacteria and genes in the aquatic environment [4]. Sulfonamides are one of the largest classes of antibiotics which have been widely used in animals and humans with occurrence of these molecules in the environment including wastewater treatment plant effluent, surface water, groundwater, sewage, and drinking water [5,6]. In order to reduce negative impacts of sulfonamide antibiotics in water bodies, it is imperative to treat them via an effective and sustainable treatment technology before their release into the environment.

Antibiotics can be removed by physical methods (e.g., nanofiltration, reverse osmosis, adsorption) [7]. Membrane processes, activated carbon adsorption, and the use of carbon nanotubes can be other options, which may be energy and/or material intensive [8,9]. The use of chemical oxidants is an alternate approach for treating antibiotics in water [10–12]. Chlorine has the potential to remove antibiotics, however, chlorination byproducts may be more toxic than the parent molecules themselves. Chlorine dioxide has also been investigated to oxidize antibiotics, but the transformation of antibiotics under typical ClO_2 disinfection doses may not eliminate the antibacterial activity [13]. Advanced oxidation processes (AOPs) have been successfully demonstrated to eliminate antibiotics from water [14–16]. Aforementioned processes may have limitations in terms of energy requirements.

Among various resources used in treating antibiotics, iron-based materials have garnered more attention in view of their special attributes such as earth-abundant and environmentally friendly nature. This paper pertains to the utility of high-valent iron compound, ferrate(VI) (FeO_4^{2-}, Fe(VI)), which has emerged as a novel oxidant to remove micropollutants in water [17–25]. While several studies have been conducted using Fe(VI), most of them have focused on evaluating the performance of Fe(VI) to remove various contaminants and only trifling effort has been dedicated to the mechanism of ferrate oxidation reactions. Furthermore, hardly any work has been carried out to understand the kinetics and products of the reactions over a wide pH range from acidic to basic [26,27]. The focus of the paper is on oxidation of sulfonamide antibiotics by Fe(VI) under varying pH conditions.

The present paper offers the kinetic measurements for the reactions of Fe(VI) with selected sulfonamides (sulfaguanidine (SFG), sulfisoxazole (SIX), sulfamethizole (SMIZ), sulfamethoxazole (SMX), sulfamethazine (SMAZ), and sulfadimethoxine (SDM)), which comprise a sulfonamide ($—SO_2NH_2—$) group, an aniline moiety, and a five-or six-membered heterocyclic component with the exception of SFG (Fig. 1). The present study fills the void for data under the acidic solutions; study on SFG over the entire pH range has not been performed previously. Importantly, this is the first study that demonstrates the cleavage of S—N bond in SMX by Fe(VI) to produce 3-amino-5-methylisoxazole; identified by high resolution liquid chromatography mass spectrometry/mass spectrometry (LC–MS/MS) technique.

Objectives of the study are: (i) to measure the kinetics of oxidation of selected sulfonamides by Fe(VI) over the acidic to basic pH range, (ii) to apply a kinetic model to explain the trend in rate constants with variation of pH in order to determine the species-specific rate constants, (iii) to compare the kinetics of Fe(VI) oxidation with other oxidants commonly deployed in treating water, (iv) to establish the identity of the oxidized products (OPs) emanating from most widely identifiable entity in water, SMX, at different molar ratios ([Fe(VI)]/[SMX]) and pH, and (v) to determine the influence of organic matter on the removal efficiency of SMX by Fe(VI) at neutral pH.

2. Material and methods

2.1. Reagents

Sulfonamides, sodium borate, and sodium hydrogen phosphate were obtained either from Sigma–Aldrich (St. Louis, MO, USA) or Fisher-Scientific (Austin, TX, USA) with purity higher than 97% and were used as received. High performance liquid chromatography (HPLC)-grade organic solvents of methanol and acetonitrile were purchased from Fisher-Scientific. Solid potassium ferrate (K_2FeO_4) of ~98% purity was chemically synthesized [28]. Fe(VI) solutions were prepared by adding solid K_2FeO_4 to 1 mM $Na_2B_4O_7{\cdot}10H_2O$/5 mM Na_2HPO_4 at pH 9.0; Fe(VI) is stable for conducting experiments in this media. Concentrations of Fe(VI) in the solution were quantified spectroscopically by measuring absorbance at a wavelength of 510 nm ($\varepsilon_{510nm} = 1150\ M^{-1}\ cm^{-1}$) using an UV–visible spectrophotometer (Agilent 8453, Santa Clara, CA, USA). Solutions were prepared using de-ionized water that had been passed through water purification system (18 MΩ cm Milli-Q Millipore, Waters Alliance, Milford, MA, USA). Solutions of sulfonamides were prepared by dissolving the solid compounds in the 10 mM Na_2HPO_4 buffer solution. Solubility of SMX, SIX, and SDM was enhanced by warming up to 50 °C. Once the solution was cooled down to room temperature, no crystals could be detected. The solution pH was adjusted by adding either phosphoric acid or NaOH.

2.2. Kinetic studies

Pseudo-order conditions were used to study the kinetics of the reactions between Fe(VI) and substrates (sulfonamides) wherein the concentrations of substrates were higher than Fe(VI) concentration. A stopped-flow spectrophotometer (SX-18 MV, Applied Photophysics, Surrey, UK) with a photomultiplier detector was used for the kinetic studies. Kinetic traces were collected at a wavelength of 510 nm and data collected from the stopped-flow spectrophotometer were analyzed using the nonlinear least-square algorithm of the SX-18MV Global Software (Applied Photophysics, Surrey, UK). Six replicate runs were performed to obtain averaged rate constant. The pseudo-first-order rate constants for the reactions were obtained by subtracting the observed rate constants from the rate constants determined for Fe(VI) decay with substrates at each studied pH (Sharma, [47]).

2.3. Stoichiometry and products studies

The stoichiometry experiments for the oxidation of SMX by Fe(VI) were carried out by mixing both solutions of 10 mL each, and the pH of the reaction mixtures was maintained at 4.0, 7.0, and 9.0. All the experiments were performed at room temperature. The concentration of SMX was maintained at 0.1 mM and the concentrations of Fe(VI) were varied to attain the ratio of Fe(VI) to SMX from 1:1 to 15:1. The Fe(VI) concentration was monitored using a spectrometer until no residual Fe(VI) was detected. The solutions were filtered using 0.45 μm nylon filters into HPLC vials. The concentration of the SMX in the resulting reaction mixtures was quantified by the use of an HPLC (Waters Alliance 2695, Milford, MA, USA) with a RP-C_{18} column (5 μm; 250 × 10 mm,

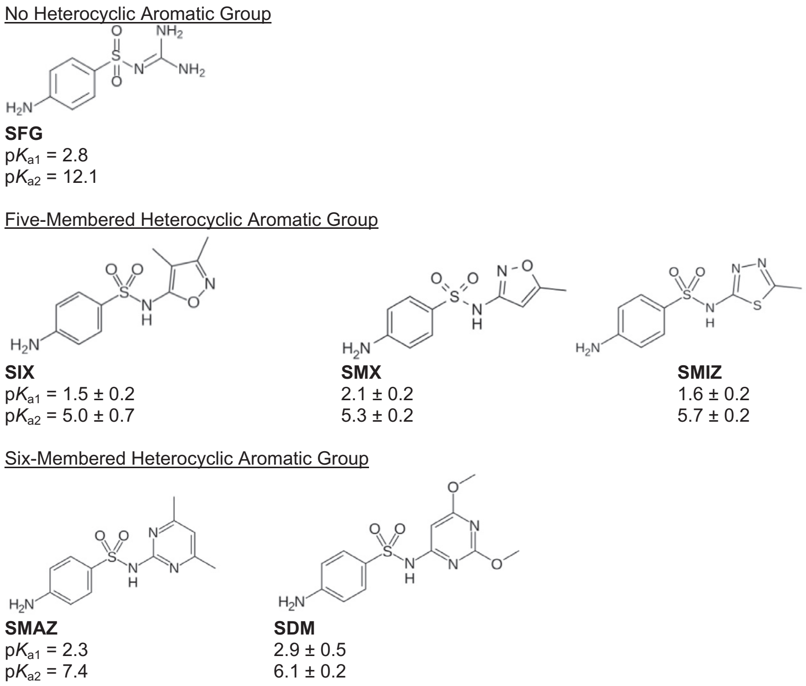


Fig. 1. Structures and dissociation constants of selected sulfonamides.

Alltima, Deerfield, IL, USA) at a wavelength of 292 nm. A binary mobile phase consisting of 35% solvent A (20 mM ammonium acetate) and 65% solvent B (acetonitrile) at a flow rate of 0.5 mL min^{-1} and injection volume of 70 μL were used in an isocratic elution mode.

The products of SMX oxidation by Fe(VI) were analyzed by using LC-–MS/MS. The concentration of SMX was also analyzed using LC-–MS/MS. Instrument had an Accela UHPLC pump and a HTC-PAL autosampler LC system attached to a BenchTop QExactive Orbitrap Mass Spectrometer (Thermo Scientific, San Jose, CA, USA). Chromatographic separation of SMX and its transformation products were achieved on a Hypersil Gold C 18 column (1.9 μm; 50 mm × 2.1 mm, Thermo Scientific, San Jose, CA, USA) using a binary gradient mobile phase of acetonitrile and 0.1% formic acid in water (Table SM-1). For the ionization of analyte molecules, an Ion Max API Heated Electrospray Ionization source was operated in the positive mode with spray voltage of 3500 V, the capillary temperature of 350 °C, and vaporizer temperature of 400 °C. Data were acquired in the full scan mode (i.e., 50–500 *m/z*) for the identification of OPs and MS/MS information on the identified products was obtained in a secondary analysis by isolating the precursor ions detected in the full scan run and by monitoring the product ions produced. Quantitative measurements were carried out in a selected reaction-monitoring mode with three specific transitions.

3. Results and discussion

3.1. Kinetics

Initially, kinetic experiments were performed on the reaction of Fe(VI) with SFG at pHs 5.5 and 9.0 at 25 °C to determine the rate laws of the reaction in an aqueous acidic and basic medium, respectively. The rate expression for the reaction of Fe(VI) with SFG can be expressed as Eq. (1):

$$-d[\mathrm{Fe(VI)}]/dt = k[\mathrm{Fe(VI)}]^m[\mathrm{SFG}]^n \quad (1)$$

where [Fe(VI)] and [SFG] are the concentrations of Fe(VI) and SFG, m and n are the orders of the reaction with respect to the concentrations of Fe(VI) and SFG, respectively, and k is the overall reaction rate constant. Under pseudo-order conditions with SFG in excess, Eq. (1) can be re-written as:

$$-d[\mathrm{Fe(VI)}]/dt = k_1[\mathrm{Fe(VI)}]^m \quad (2)$$

where $k_1 = k\,[\mathrm{SFG}]^n$. The decrease in absorbance of Fe(VI) as a function of time could be fit to single exponential decays in both acidic and basic pH's, which indicates that the rate was first-order with respect to the concentration of Fe(VI), i.e., $m = 1$. Different values of k_1 were determined at various concentrations of SFG. The values of k_1 increased linearly with [SFG] (Fig. SM-1). The plots of $\log k_1$ versus $\log[\mathrm{SFG}]$ were linear ($R^2 = 0.99$) and slopes were 1.11 ± 0.04 and 0.97 ± 0.04 in acidic and basic pH, respectively (Fig. SM-1). These results indicate that the reaction between Fe(VI) and SFG was first-order with respect to the [SFG] in both acidic and basic media, i.e., $n = 1$ (Fig. SM-1). Kinetic studies were then extended to other sulfonamides at pH 5.5 (Fig. SM-2). Results also showed first-order kinetics with respect to the concentrations of sulfonamides in acidic solutions. Similar kinetics was also observed in basic medium for the oxidation of sulfonamides by Fe(VI) [29]. The rate law for the reaction between Fe(VI) and the sulfonamides (X) can then be expressed as:

$$-d[\mathrm{Fe(VI)}]/dt = k_{\mathrm{app}}[\mathrm{Fe(VI)}][\mathrm{X}] \quad (3)$$

where k_{app} is the apparent second-order rate constant.

Next, the k_{app} ($\mathrm{M^{-1}\,s^{-1}}$) for the reactions of Fe(VI) with SFG and other sulfonamides were determined at various pH's and the results are presented in Fig. 2(a)–(c). Results of sulfonamides, except SFG, at pH ⩾ 7 were taken from our previous study [29]. The kinetics of the reaction of SMX at different pH values was also studied by others in which the formation of a Fe(VI)–SMX intermediate complex was proposed [30]. The formation of the possible intermediate complex from the reaction was explored by performing spectral kinetic studies. The spectra of the reaction, during a reaction time scale of 10–200 s, showed the decay of Fe(VI)

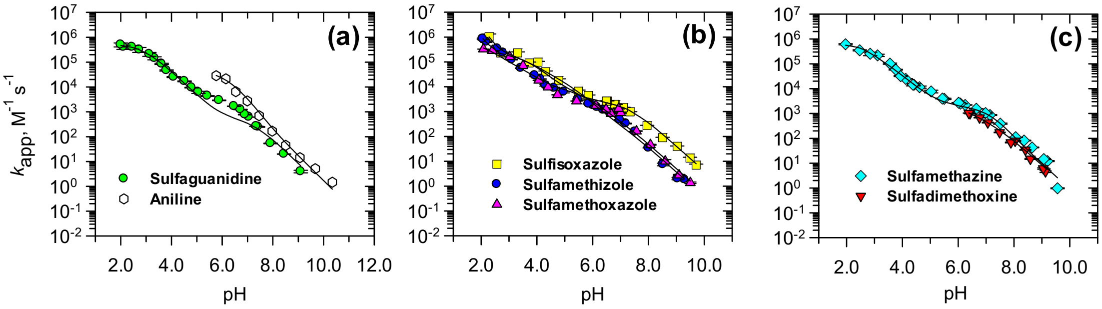


Fig. 2. The apparent second-order rate constants (k, M^{-1} s^{-1}) as a function of pH for the reaction between Fe(VI) and sulfonamides at 25 °C.

without any concomitant growth of the spectrum of an Fe(VI)-intermediate complex (Fig. SM-3). This indicates that no Fe(VI)–SMX intermediate complex formed from the reaction in the time scale of seconds. The results presented in Fig. SM-3 were also supported by Mossbauer spectroscopy measurements on the reaction between Fe(VI) and SMX; no change in parameters of the spectra with and without SMX in the reaction mixture was discerned [31]. The complex formation of Fe(VI) with SMX would have caused changes in Mossbauer parameters or producing a Fe(VI)–nitrido complex through the aniline moiety of the SMX (Sharma et al. [31]). These possible high-valent iron nitride complexes tend to be unstable [32,33] and can attain stability only at very low temperatures (<77 K). Similarly, if the complex in the present study were formed, it would rapidly decompose to give Fe(VI) and SMX to cause non-linearity in the decay of Fe(VI) with the concentration of SMX. However, experiments showed that the decay was linearly dependent on the SMX concentration.

The k_{app} for the sulfonamides oxidation became smaller with increase in pH (Fig. 2). This trend is analogous to the Fe(VI) oxidation of aniline, one of the common moieties in all sulfonamides (Fig. 2a). Values of k for oxidation of aniline were obtained from literature [34]. Furthermore, no deviation in the pH dependence behavior was observed with respect to nature of other moieties present in sulfonamides (aliphatic amine versus heterocyclic moieties) (Fig. 2a–c). Furthermore, magnitude of k did not vary much with respect to various sulfonamides. It appears that the oxidative mechanism of target sulfonamides by Fe(VI) may be occurring through a similar initial step. Other important feature of the pH dependence behavior, shown in Fig. 2, is that it differs from the general trend of variation of k with pH for oxidation of primary (glycine, NH_3CH_2COOH), secondary (dimethylamine, $(CH_3)_2NH$) amines, and β-lactams antibiotics [24]. Generally, the rate constants for these compounds decreased with increase in pH $\geqslant$ 7.5 and then decreased in the acidic media from a maximum at ~pH 7.0. Difference in trends between sulfonamides bearing aliphatic primary and secondary amines also suggests that Fe(VI) possibly initiates the attack via the amine functionality of sulfonamides. More will be discussed in the section of reaction pathways.

3.2. Kinetic modeling

The variation of k values with pH was analyzed quantitatively using acid–base equilibria of Fe(VI) and sulfonamides (X) (Eqs. (4)–(8)) [29]:

$$H_3FeO_4^+ \rightleftharpoons H^+ + H_2FeO_4 \qquad pK_{a1} = 1.6 \tag{4}$$

$$H_2FeO_4 \rightleftharpoons H^+ + HFeO_4^- \qquad pK_{a2} = 3.5 \tag{5}$$

$$HFeO_4^- \rightleftharpoons H^+ + FeO_4^{2-} \qquad pK_{a3} = 7.23 \tag{6}$$

$$H_2X^+ \rightleftharpoons H^+ + HX \qquad pK_{a1} \tag{7}$$

$$HX \rightleftharpoons H^+ + X^- \qquad pK_{a2} \tag{8}$$

In the pH range studied for the reaction between Fe(VI) and X, the four species of Fe(VI) (i.e., $H_3FeO_4^+$, H_2FeO_4, $HFeO_4^-$, and FeO_4^{2-}) with the three species of X (H_2X^+, HX, and X^-) could possibly react with one another. The values of pK_{a1} and pK_{a2} for sulfonamides are provided in Fig. 1. The pH dependence can, therefore, be modeled by Eq. (9):

$$dX/dt = k[\mathrm{Fe(VI)}]_{tot}[X]_{tot} = \sum k_{ij}\alpha_i\beta_j[\mathrm{Fe(VI)}]_{tot}[X]_{tot} \quad i = 1,2,3,4, \quad j = 1,2,3 \tag{9}$$

where $[\mathrm{Fe(VI)}]_{tot} = [H_3FeO_4^+] + [H_2FeO_4] + [HFeO_4^-] + [FeO_4^{2-}]$; $[X]_{tot} = [H_2X^+] + [HX] + [X^-]$; α_i and β_j represent the species fractions of Fe(VI) and X, respectively; i and j are each of the species of Fe(VI) and X, 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. There are, thus, twelve possible reactions which could contribute to Eq. (9). In the case of aniline, only eight reactions could be considered because it has only one protonation equilibria ($PhNH_2 \rightleftharpoons H^+ + PhNH^-$, $pK_a = 4.62$, [35]).

The modeling was first carried out on the experimental kinetic data on the oxidation of aniline, an important moiety of SMX, by Fe(VI) [30]. Data could be fitted using the protonation equilibria of $HFeO_4^-$ and $PhNH_2$, with four possible reactions (Eqs. (10)–(13)):

$$HFeO_4^- + PhNH_2 \rightarrow Fe(OH)_3 + \mathrm{Product(s)} \quad k_{10} = (2.8 \pm 0.2) \times 10^5\ M^{-1}\ s^{-1} \tag{10}$$

$$HFeO_4^- + PhNH^- \rightarrow Fe(OH)_3 + \mathrm{Product(s)} \quad k_{11} = (1.1 \pm 0.1) \times 10^3\ M^{-1}\ s^{-1} \tag{11}$$

$$FeO_4^{2-} + PhNH_2 \rightarrow Fe(OH)_3 + \mathrm{Product(s)} \quad k_{12} = (2.5 \pm 0.2) \times 10^5\ M^{-1}\ s^{-1} \tag{12}$$

$$FeO_4^{2-} + PhNH^- \rightarrow Fe(OH)_3 + \mathrm{Product(s)} \qquad k_{13} \tag{13}$$

Only two of the reactions (Eqs. (10) and (11)) were needed to reasonably describe the experimental points (a solid line in Fig. 2a). The reactions of $HFeO_4^-$ with $PhNH^-$ (Eq. (11)) and FeO_4^{2-} with $PhNH_2$ (Eq. (10)) introduce “proton ambiguity”. Hence, the reaction between $HFeO_4^-$ and $PhNH^-$ could be replaced with FeO_4^{2-} and $PhNH_2$. The experimental data could also be described by considering the reaction of $HFeO_4^-$ and FeO_4^{2-} with $PhNH_2$ (Eqs. (10) and (12)). The reaction of protonated species of Fe(VI) ($HFeO_4^-$) is faster than the deprotonated species (FeO_4^{2-}), which is consistent with observations made in other studies [26,27].

Eq. (9) was applied to fit the kinetic data from the oxidation of sulfonamides by Fe(VI). The experimental k_{app} values at different pHs were empirically fit with the consideration of all possible sixteen reactions. A fit using this model was very poor and some of the estimated rate constants had negative values. Therefore, only selected reactions were considered in the model, based on earlier measurements on the oxidation of sulfonamides by Fe(VI) in alkaline medium [29]. It was previously found that the reactions of $HFeO_4^-$ with XH and X^- were able to fit the data to obtain values of k_{app} at pH $\geqslant$ 7.0; hence only these two reactions from the possible four reactions of $HFeO_4^-$ and FeO_4^{2-} with XH and X^- in alkaline medium were used for fitting the data in the entire pH range. It was found that by considering the reactions of $H_3FeO_4^+/XH_2^+$, $H_3FeO_4^+$/XH, and H_2FeO_4/XH^-, experimental values of k_{app} for all of sulfonamides could be fit nicely in acidic medium ($R^2 = 0.98$–0.99; $p < 0.0005$). These reactions were then used to fit the results over the entire pH range. Only two reactions for sulfonamides, except SFG, in acidic medium were considered to fit the values of k_{app} in the acidic pH range. This model of using only four or five reactions was successful in fitting the data over the entire pH range ($R^2 = 0.99$; $p < 0.0001$) (solid lines in Fig. 2a–c). The values of species-specific rate constants are given in Table 1.

The result suggests that the reactions of Fe(VI) with the protonated species of sulfonamides (XH) follow the order of reactivity as $H_3FeO_4^+ > H_2FeO_4 > HFeO_4^-$. This order is the same for the amount fractions of Fe(VI) species with at low pH and can therefore contribute to the overall rates of the reaction between Fe(VI) and sulfonamides; this may be responsible for the increase in the rates of ferrate oxidation of sulfonamides with decreasing pH (Fig. 2). Moreover, density functional theory calculations have shown that the protonated form of Fe(VI) has a larger spin density on the oxo ligands than its unprotonated form, which increases the oxidation ability of protonated Fe(VI) [36]. This is consistent with the observation that faster rates occur for the decomposition of Fe(VI) with a decrease in pH [37].

The reactivity of Fe(VI) with sulfonamides was invariably similar in the acidic pH range while contrasting difference became apparent in the basic medium (Fig. 2). This could be explained by considering species-specific rate constants (Table 1). In the acidic medium, the dominant form of Fe(VI) is deprotonated species (H_2FeO_4), possessing similar rate constants with the neutral species of sulfonamides (XH) thus resulting in comparable rate constants in the acidic medium. Comparatively, in the basic medium, monoprotonated Fe(VI) ($HFeO_4^-$) was the reactive species with XH and the rate constants for this reaction vary with the variety of sulfonamide (Table 1). The sulfaguanidine (SFG), devoid of heterocyclic ring moiety, had the lowest reactivity for the reaction between $HFeO_4^-$ and XH (Table 1); presence of heterocyclic ring in sulfonamides caused increased in reactivity of $HFeO_4^-$ with XH (Table 1) with five-membered heterocycles having higher rate constants than that of the six-membered heterocyclic ring moiety molecules of sulfonamides (see Fig. 1 and Table 1). Overall, the difference in reactivity of sulfonamides in basic medium could be described by considering the reactivity of $HFeO_4^-$ with the neutral species of sulfonamides (XH).

3.3. Comparison with other oxidants

The comparison of the reactivity of different oxidants with SMX is presented in Table 2 [38–42]. Mn(VII) had no significant reactivity [42]. The k_{app} for the oxidation of SMX by chlorine dioxide and O_3 increased with increase in pH increase [38,40]. However, the rate constants for oxidation by chlorine decreased with increase in pH [39], which is similar to oxidation by Fe(VI) (Fig. 2). The order of the reactivity with SMX is O_3 > chlorine > chlorine dioxide > Fe(VI) (Table 2). The half-life ($t_{1/2}$) for degrading SMX by O_3 is $<1\ s^{-1}$. Fe(VI), chlorine dioxide, and chlorine can oxidize SMX in seconds and hence may be suitable for degradation of SMX in water. Rates of Fe(VI) oxidation of SMX, however, are pH dependent. The values of k_{app} for the Fe(VI) oxidation of SMX vary from 1.8×10^4 to $3.0\ M^{-1}\ s^{-1}$ in the pH of 4.0–9.0. Therefore, half-life of SMX would change from less than a second to hundreds of minutes in the same pH range at $1\ mg\ L^{-1}$ as Fe dosage of Fe(VI).

3.4. Stoichiometry

The stoichiometry of SMX with Fe(VI) was extended to acidic pH in the present study. Results of this study and the previous stoichiometric experiments in neutral and alkaline pHs are presented in Fig. 3. The initial stoichiometry for removing half of SMX by Fe(VI) was ~0.25 ([Fe(VI)]:[SMX]), which is similar to that obtained at pH $\geqslant$ 7.0 [29]. However, further removal of SMX in acidic medium required higher amount of Fe(VI) for complete transformation of SMX (Fig. 3). For example, 70% removal of SMX needed five times the amount of Fe(VI), which gives a stoichiometry of 0.2. A complete removal of SMX was observed at pH 4.0 and a stoichiometry of 0.1 (Fig. 3). This is in contrast with observed stoichiometry at pH 7.0 and 9.0, which needed about four times the amount of Fe(VI) for oxidative transformation of Fe(VI). It is known that the self-decomposition of Fe(VI) in water (i.e., without SMX) increased sharply in acidic pH [43] and it is likely that significant amount of Fe(VI) at pH 4.0 reacted not only with SMX, but also with water. Moreover, reactions of Fe(VI) with SMX and their intermediate oxidized products in the reaction mixture have their own pH dependence to demand higher required amount of Fe(VI) to completely oxidize SMX in acidic medium compared to that at neutral and basic medium.

3.5. Identification of OPs

A total of seven oxidative degradation products, OP-98, OP-173, OP-189, OP-267, OP-269, OP-283, and OP-299 were identified at various pH levels (Table 3). Details of mass identifications are specified in Figs. SM-4–10. Peak areas of OPs as a function of pH at various molar ratios of Fe(VI) to SMX are presented in Fig. 4 and discussed individually as follows. Solid lines, shown in Fig. 4, give only general trend of OP formation and disappearance.

OP-98 ($m/z = 99.06$ for MH^+) was identified as 3-amino-5-methylisoxazole (Table 3). This OP has been detected in the oxidation of SMX by ozone, photo-Fenton, TiO_2 photocatalysis, UV photolysis, and permanganate [10,44]. The presence of OP-98 suggests that the cleavage of S—N bond in the SMX by Fe(VI) leads to the formation of OP-98. At acidic and neutral pH, almost complete formation of OP-98 was observed at molar ratios of Fe(VI)

Table 1
The species-specific rate constants for oxidation of aniline and sulfonamides by Fe(VI) at 25 °C.

Sulfonamide	pK_{a1}	pK_{a2}	k ($M^{-1}\ s^{-1}$)				
			$H_3FeO_4^+ + XH_2^+$	$H_3FeO_4^+ + XH$	$H_2FeO_4 + XH$	$HFeO_4^- + XH$	$HFeO_4^- + X^-$
SFG	2.8	12.1	$(4.5 \pm 1.2) \times 10^5$	$(9.0 \pm 0.7) \times 10^6$	$(1.4 \pm 0.2) \times 10^5$	$(5.0 \pm 0.5) \times 10^2$	–
SIX	1.5 ± 0.2	5.0 ± 0.7	$(3.7 \pm 0.2) \times 10^7$	–	$(2.3 \pm 0.3) \times 10^5$	$(1.1 \pm 0.1) \times 10^4$	$(2.4 \pm 0.1) \times 10^3$
SMIZ	2.1 ± 0.2	5.3 ± 0.2	$(6.0 \pm 0.2) \times 10^6$	–	$(2.1 \pm 0.2) \times 10^5$	$(2.2 \pm 0.2) \times 10^4$	$(2.2 \pm 0.3) \times 10^2$
SMX	1.6 ± 0.5	6.1 ± 0.2	–	$(1.4 \pm 0.1) \times 10^6$	$(1.6 \pm 0.2) \times 10^5$	$(7.0 \pm 0.5) \times 10^3$	$(3.0 \pm 0.5) \times 10^2$
SMAZ	2.3	7.4	–	$(5.7 \pm 0.2) \times 10^6$	$(1.1 \pm 0.2) \times 10^5$	$(1.9 \pm 0.1) \times 10^3$	$(5.5 \pm 0.5) \times 10^2$
SDM	2.9 ± 0.5	6.1 ± 0.2	–	–	–	$(2.5 \pm 0.8) \times 10^3$	$(5.0 \pm 0.3) \times 10^2$

Table 2
Second-order rate constants and half-lives for oxidation of SMX by different oxidants at 25 °C.

Oxidant	Species	k ($M^{-1}\,s^{-1}$)	k_{app} ($M^{-1}\,s^{-1}$) pH 7.0	$t_{1/2}$ (s)
Ferrate(VI)[a]	$HFeO_4^-$ (HX)	$(7.0 \pm 0.5) \times 10^3$	7.0×10^2	55
($pK_3 = 7.23$)[f]	FeO_4^{2-} (HX)	$(3.0 \pm 0.5) \times 10^2$		
Permanganate[b]	MnO_4^-	Unreactive	Unreactive	–
Chlorine[c]	HOCl (HX)	1.1×10^3	1.6×10^3	21
($pK_a = 7.54$)[g]	HOCl (X^-)	2.4×10^3		
Chlorine dioxide[d]	ClO_2	7.9×10^3	7.9×10^3	4.3
Ozone[e]	O_3 (HX)	4.7×10^5	5.4×10^5	0.06
	O_3 (X^-)	5.7×10^5		

[a] This study and half-life at dose [Fe] = 1 mg L^{-1} or $[FeO_4^{2-}] = 2.2$ mg L^{-1}.
[b] From [42].
[c] From [39] and half-life at [HOCl] = 1 mg L^{-1}.
[d] From [40] and half-life at $[ClO_2] = 1$ mg L^{-1}.
[e] From [38] and half-life at $[O_3] = 1.0$ mg L^{-1}.
[f] At 25 °C from [46].
[g] At 25 °C from [41].

to SMX $\geqslant 5.0$ (Fig. 4a). In alkaline medium, formation of OP-98 varied with molar ratios and the amount was significantly less than pH $\leqslant 7.0$.

OP-173 ($m/z = 174.02$) and OP-189 ($m/z = 190.10$) represent aniline derivatives after ring-opening cleavage of the isoxazole from the SMX. Although these OPs were also present as impurities in SMX stock solution, they are presented as intermediate products from ferrate oxidation of SMX because of their possible formation and peak area variation with molar ratios of Fe(VI) to SMX (Fig. 4b and c). At neutral and alkaline pH, both of the OPs were completely degraded to undetectable levels at the molar ratio of 15. OP-173 formation was not significant at neutral and alkaline pH for most of the mole ratios. However, significant peak area of OP-173 could be observed at a molar ratio of 10 at pH 4.0. This indicates that OP-173 may not be forming much at pH 7.0 and 9.0 compared to pH 4.0 where higher amount would require additional level of Fe(VI). At the smallest ratio of 1.0 of Fe(V) to SMX, a trace level of OP-173 could be observed at the neutral pH suggesting that any initial impurity of OP-173 could be easily removed with the reaction of Fe(VI). The addition of one oxygen atom to OP-173 would give OP-189 which was present at different mole ratios (Fig. 4c). Undetectable levels of OP-189 at mole ratios of 10 and 15 implies its possible reaction with Fe(VI).

OP-267 ($/mz = 268.04$), OP-269 ($m/z = 270.05$), and OP-283 ($m/z = 284.03$) were identified as nitroso-, hydroxylamine-, and nitro-groups containing SMX molecules (Table 3 and Fig. 4d–f), which were likely produced from the oxidative transformation of aniline moiety of SMX. Other possibilities of the formation of OP-269 would be hydroxylation of benzene ring (OP-269A in Table 3) and ring-opening of isoxazole from the attack of Fe(VI) (OP-269B in Table 3). At pH 4.0 and 7.0, the formation of OP-267 and OP-269 showed initial increase, followed by decrease in peak areas with increasing mole ratios of Fe(VI) to SMX (Fig. 4d and e). At pH 9.0, somewhat similar trend was observed, but amounts of generated OP-267 and OP-269 were low. On the other hand, OP-283 was present at much higher level at alkaline pH than that observed in acidic solution (Fig. 4f). Significantly, amount of OP-283 kept increasing with the increasing molar ratio of Fe(VI) to SMX at neutral and alkaline solutions; indicating that OP-283 has sluggish reactivity with Fe(VI). Furthermore, Fe(VI) reacted with OP-283 at slower rates than with OP-267 and OP-269, which had decreasing peak areas with the increasing molar ratios of Fe(VI) to SMX (Fig. 4f vs. Fig. 4d and e). In the acidic medium, however, almost no formation of OP-283 was observed (Fig. 4f).

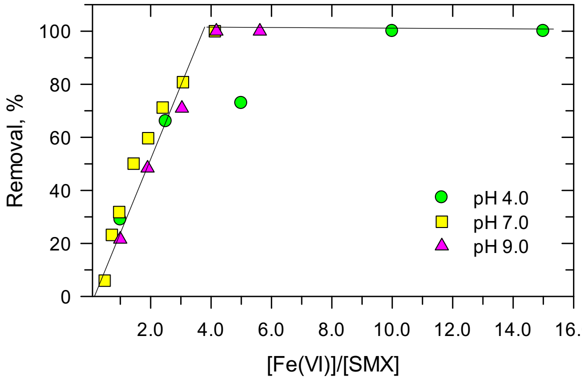


Fig. 3. Stoichiometry of the reaction between Fe(VI) and sulfamethoxazole at different pH.

OP-299 ($m/z = 300.03$), representing addition of one oxygen atom from OP-283, could be safely identified as hydroxylated product (Table 3, Fig. 4g). At pH 9.0, peak areas of OP-299 showed an increasing trend with increasing molar ratios while reverse was observed at pH 4.0 and 7.0 after initial formation of the oxidized product. This suggests that the hydroxylation of benzene ring in SMX was favorable in alkaline solution.

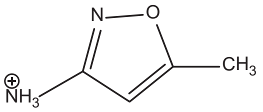
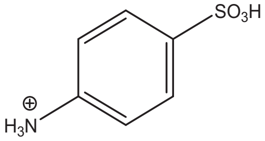
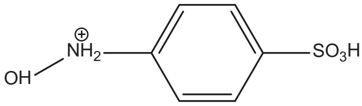
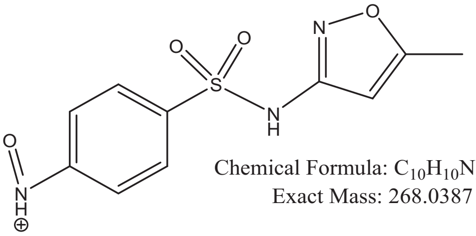
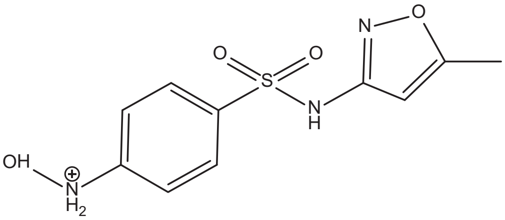
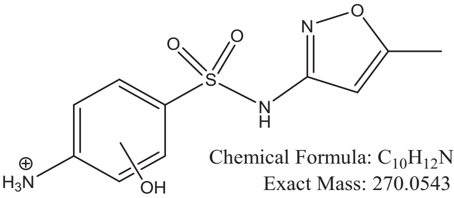
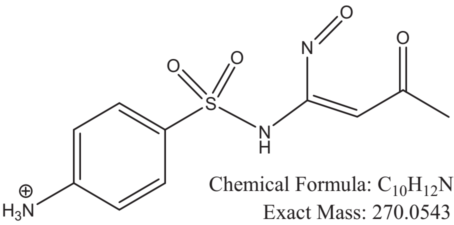
3.6. Reaction pathways

Based on the identified OPs in the acidic to basic pH range, the reaction pathways of oxidation of SMX by Fe(VI) are presented in Fig. 5. The pathways involve oxidation, hydroxylation, and hydrolytic reactions through attacks of Fe(VI) on amine, benzene, sulfonamide, and isoxazole moieties of SMX. Peak areas of Fig. 4 revealed the general trend that could distinguish oxidation pathways under acidic and basic solutions. Fig. 4a suggests that OP-98 is the dominant product of SMX oxidation at pH 4.0 with OP-283 and OP-299 as main oxidized products at pH 9.0 (Fig. 4f and g). Under acidic conditions, the protonated amine group tends to become unreactive towards Fe(VI) as in the case with ozone which had no reactivity with amines/amino acids in acidic solution while amino group showed reactivity in basic solution. Therefore, Fe(VI) might have attacked sulfonic group rather than aniline moiety of SMX. The hydrolytic reaction by Fe(VI) would yield OP-173 and isoxazole (OP-98). Since Fe(VI) almost had no reactivity with isoxazole molecule, therefore, OP-98 as the final product was obtained (Fig. 4a). Further oxidation of OP-173 by Fe(VI) formed OP-190 through oxidation of amino group (Fig. 4b). It appears that OP-189 could be oxidized by Fe(VI) as its concentration decreased to undetectable level with the increase of Fe(VI) concentration (Fig. 4c).

In the alkaline solution, oxidation of aniline and isoxazole moieties of SMX have been suggested by infrared and nuclear magnetic resonance spectroscopy as well as mass spectral analysis of the OPs [29]. The results of Fig. 4d–f confirmed the previous findings of possible oxidation of both aniline and isoxazole moieties in SMX by Fe(VI) at pH 9.0. The opening of isoxazole ring would result in OP-269B. The initial attack of Fe(VI) on NH_2 group would yield hydroxylamine product (OP-269). This attack is favorable in alkaline solution due to increase in electron density on the NH_2 with increase in pH. The resultant hydroxylamine group gave the nitroso product (OP-267), which ultimately was oxidized to nitro product (OP-283). Formation of OP-269 and OP-267 intermediates is supported by their decomposition when additional amount of Fe(VI) in the reaction mixtures was present (Fig. 4d and e). Hydroxylation of the benzene ring of SMX and OP-283 would form OP-269A and OP-299.

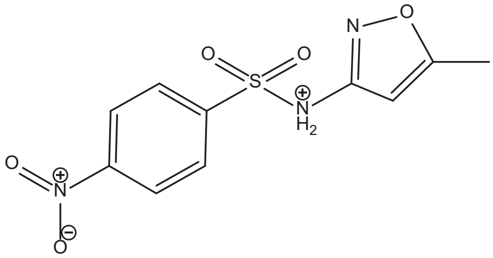
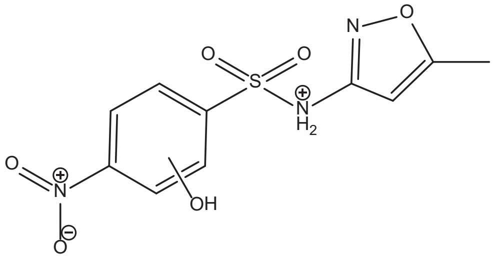
At neutral pH, most of the steps shown in Fig. 5 might be occurring, except one noticeable difference of the hydrolytic pathway.

Table 3
Characteristics of OPs.

OPs	Proposed structure of ion mass	Observed mass[a]
OP-98	 Chemical Formula: $C_4H_7N_2O^+$ Exact Mass: 99.0553	99.056
OP-173	 Chemical Formula: $C_6H_8NO_3S^+$ Exact Mass: 174.0219	174.022
OP-189	 Chemical Formula: $C_6H_8NO_4S^+$ Exact Mass: 190.0169	190.097
OP-267	 Chemical Formula: $C_{10}H_{10}N_3O_4S^+$ Exact Mass: 268.0387	268.039
OP-269	 Chemical Formula: $C_{10}H_{12}N_3O_4S^+$ Exact Mass: 270.0543	270.054
OP-269A	 Chemical Formula: $C_{10}H_{12}N_3O_4S^+$ Exact Mass: 270.0543	
OP-269B	 Chemical Formula: $C_{10}H_{12}N_3O_4S^+$ Exact Mass: 270.0543	

(continued on next page)

Table 3 (*continued*)

OPs	Proposed structure of ion mass	Observed mass[a]
OP-283	 Chemical Formula: $C_{10}H_{10}N_3O_5S^+$ Exact Mass: 284.0336	284.033
OP-299	 Chemical Formula: $C_{10}H_{10}N_3O_6S^+$ Exact Mass: 300.0285	300.028

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[a] Observed in Orbitrap mass spectrometer.

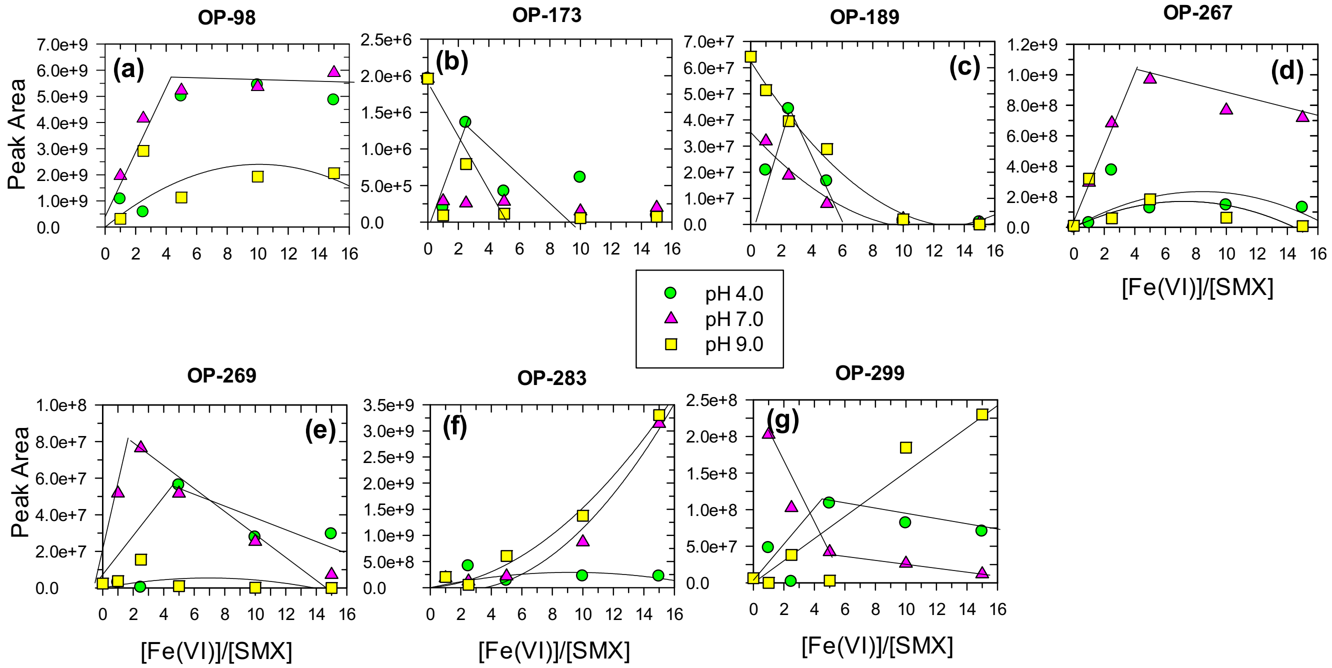

Fig. 4. Peak areas of OPs, obtained under different molar ratios of reactants and pH. (a) OP-98, (b) OP-173, (c) OP-189, (d) OP-267, (e) OP-269, (f) OP-283, and (g) OP-299.

The observed OP-267 is more abundant at pH 7.0 than at pH 4.0 (Fig. 4d). However, peak areas of isoxazole were similar for acidic and neutral solutions (Fig. 4a). This indicates that OP-98 at the neutral pH is formed via a different pathway, possibly by the S—N cleavage of OP-269 (Fig. 5). The sharp decrease of OP-269 with the increase of Fe(VI) concentration supports this proposed pathway (Fig. 4e). In view of the similarities in structures of most of the sulfonamides studied, reaction pathways invariably entails the hydroxylation of aniline ring and cleavage of sulfonamide bond during the oxidation of sulfonamides by Fe(VI).

3.7. Influence of organic matter

The effect of natural organic matter (NOM) on the removal of SMX by Fe(VI) was tested using humic acid (HA). In this specific experiment, solutions of 10 μg L^{-1} SMX with and without HA

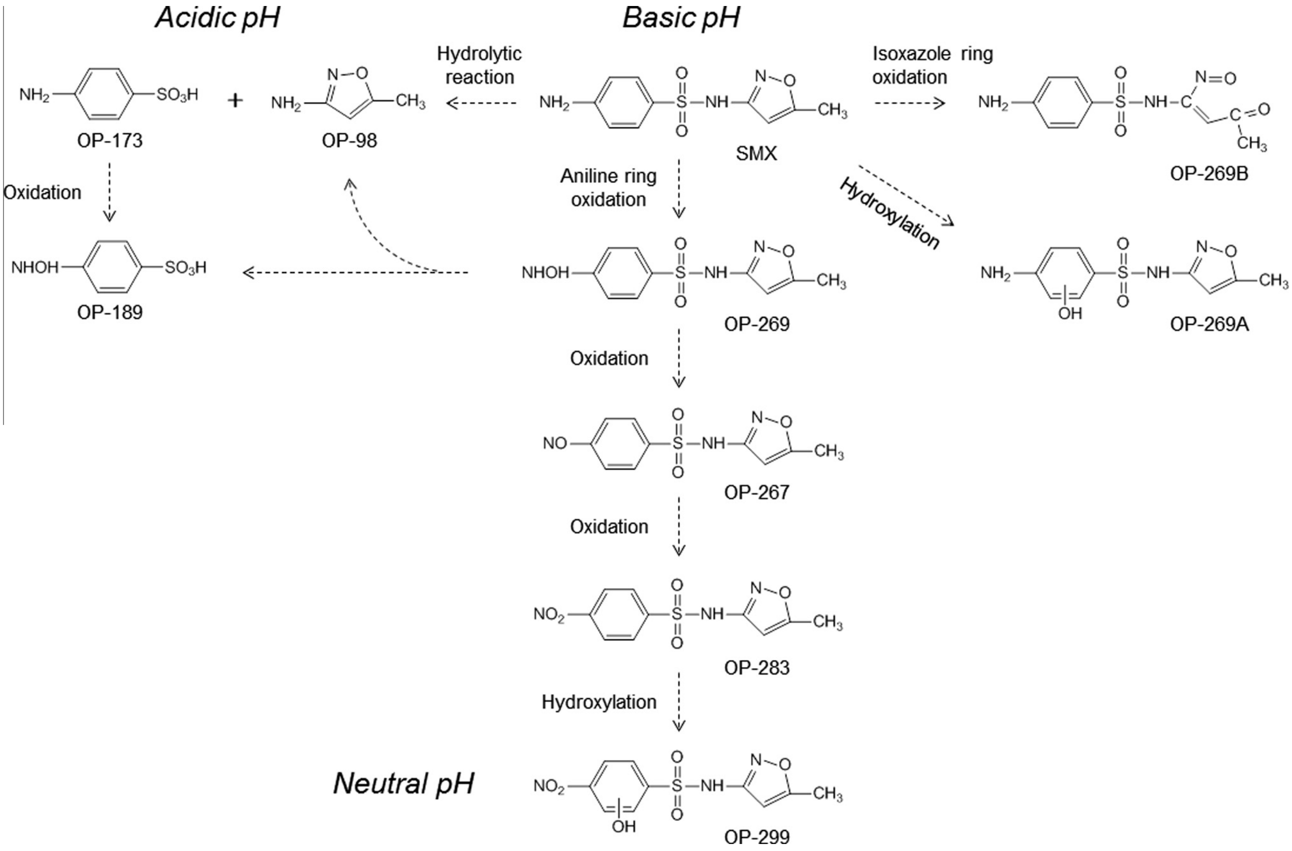

Fig. 5. Proposed reaction pathways of oxidative transformation of SMX by Fe(VI).

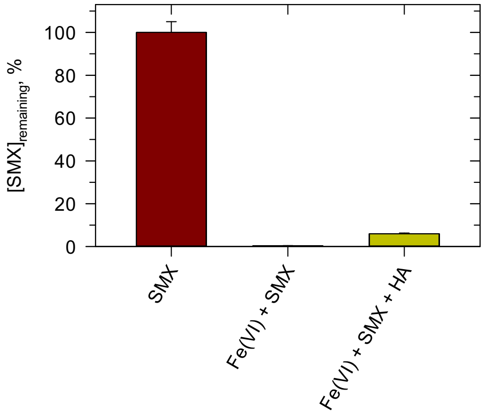

Fig. 6. Removal of SMX by Fe(VI) with and without humic acid at pH 7.0. (Experimental conditions: [SMX] = 10 μg L^{-1}; [HA] = 1 mg L^{-1}; [K_2FeO_4] = 1.0 mg L^{-1}.)

(1 mg L^{-1}) were mixed with Fe(VI) (1.0 mg L^{-1} K_2FeO_4) at pH 7.0. The concentration of Fe(VI) in the reaction mixture was stoichiometry excess (about 15:1 ([Fe(VI)]:[SMX])) while concentration of HA was 100 times more than that of the target micro-pollutant. The results of residual level of SMX as percentage, after the completion of the reaction, are shown in Fig. 6. Without HA in the reaction mixture, SMX was completely removed, which agrees with the stoichiometry of the reaction in water (Fig. 3). More importantly, SMX removal was ~95% in the presence of HA. This suggests that removal of SMX was also possible in NOM containing water. However, higher Fe(VI) amount was understandably needed compared to the case when only SMX was present in deionized water. Consequently, NOM components do compete with SMX to react with Fe(VI), hence some fraction of added Fe(VI) was consumed by NOM. The utilized amount of Fe(VI) by NOM would depend on type and class of components of NOM [45]. Overall, the required amount of Fe(VI) for SMX removal would depend on the concentration and the nature of NOM.

4. Conclusions

- The kinetic modeling involving equilibrium species of Fe(VI) and sulfonamides successfully explained the decrease in oxidation rates of sulfonamides with increase in pH over the acidic to basic pH range.
- The protonated Fe(VI) increased higher reactivity with the neutral species of sulfonamides.
- Based on identified OPs, the oxidative transformation pathways for SMX by Fe(VI) are proposed. The hydrolytic route involving cleavage of S—N bond of sulfonamide in SMX is favorable in acidic medium while oxidation steps were more pronounced under basic conditions. A neutral pH may involve S—N bond break-up of the hydroxylamine derivative of SMX.
- Oxidative transformation of SMX by Fe(VI) could also be achieved in a sample containing humic acid, which was about hundred times more in concentration than the target compound.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cej.2015.04.139.

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