Oxidation of cefazolin by potassium permanganate: Transformation products and plausible pathways

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HIGHLIGHTS

- Di-ketone was formed via oxidation of C=C double bond in cycloolefin with Mn(VII).
- Sulfoxide/sulfone was formed via oxidation of thioether in cefazolin with Mn(VII).
- Reaction pathways of cefazolin with Mn(VII) can replay in real surface water matrix.
- Sulfoxide and sulfone products with higher potential risk deserve more attention.

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ABSTRACT

Cefazolin was demonstrated to exert high reactivity toward permanganate (Mn(VII)), a common oxidant in water pre-oxidation treatment. In this study, five transformation products were found to be classified into three categories according to the contained characteristic functional groups: three (di-)sulfoxide products, one sulfone product and one di-ketone product. Products analyses showed that two kinds of reactions including oxidation of thioether and the cleavage of unsaturated C=C double bond occurred during transformation of cefazolin by Mn(VII). Subsequently, the plausible transformation pathways under different pH conditions were proposed based on the identified products and chemical reaction principles. More importantly, the simulation with real surface water matrix indicated that the proposed transformation pathways of cefazolin could be replayed in real water treatment practices.

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1. Introduction

In recent years, numerous concerns have been raised on antibiotics due to their frequent occurrence in the aquatic environment (Bendz et al., 2005). Cephalosporins, as a predominant class of β -lactam antibiotics, are commonly used to treat respiratory diseases of human and livestock (Jiang et al., 2010; Fagerquist et al., 2005).

The production and consumption of cephalosporins have been increased sharply during the past few decades. For example, in China, the annual yield of cephalosporins in 2001 and 2010 was approximately 844 tons and 10,000 tons, respectively (Kümmerer, 2009; Xue and Chen, 2011). Similar to other kinds of antibiotics, cephalosporins cannot be absorbed and metabolized completely by the hosts (Hu et al., 2010). Hence large amount of cephalosporins are excreted via the urine and feces of animals and human beings (Junker et al., 2006). Part of excreted cephalosporins enters into municipal wastewater collection system, and another part in manure is retained by soils and sediments through adsorption, or biotically and abiotically transformed in the environment. However, one report showed that the proportion of biodegradation of cephalosporins could be virtually negligible (Jiang et al., 2010).

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Although cephalosporin antibiotics undergoes hydrolysis ($t_{1/2} = 1\text{--}10$ d at $\text{pH} > 8$ or < 4 at high temperatures ($35\text{--}60^\circ\text{C}$)) in the environment, the hydrolysis rates are quite slow ($t_{1/2} = 10\text{--}18$ d) in common environmental waters ($\text{pH} 7$, 20°C) (Fabre et al., 1984; Deborde and von Gunten, 2008). Therefore, quite a large part of cephalosporins gets access to the surface water by run-off. On the other hand, cephalosporins entering the municipal wastewater collection system could survive in the conventional wastewater treatment practices as well (Dodd et al., 2010; Gulkowska et al., 2008), and have been frequently found in the effluents from wastewater treatment plants (Le Corre et al., 2012; Kümmerer and Helmers, 2000; Kümmerer, 2001, 2010; Heberer, 2001; Sarmah et al., 2006; Leung et al., 2012; Lin et al., 2010). Furthermore, the cephalosporins are discharged with wastewater effluents to surface water which may serve as drinking water sources.

Lots of studies claimed that the residue of antibiotics, including cephalosporins, in aquatic environment was reported to increase bacterial resistance, and plenty of resistant genes have already been detected within ground and lagoon waters (Chee-Sanford et al., 2011; Andreozzi et al., 2004; Batt et al., 2007). Some resistant genes could be partially passed to animals and humans through food chains, which will cause unfavorable impacts on the medical treatments in a long run (Li et al., 2011).

Potassium permanganate (Mn(VII)) is a strong and active oxidant and has been extensively used in drinking water and wastewater treatment practices for decades (He et al., 2010; Aleboyeh et al., 2009). There have been reports that Mn(VII) could oxidize a wide range of emerging environmental micropollutants, such as chlorophenol, ciprofloxacin, lincomycin, triclosan, estradiol, bisphenol A and sulfamethoxazole (Gao et al., 2014; Liu et al., 2009; Hossain and McLaughlan, 2012; Hu et al., 2011; Zhang et al., 2013; Jiang et al., 2012). On the other hand, researchers have reported the degradation of cephalosporins by UV photocatalysis, ozonation and chlorination (Dodd et al., 2010; Pugazhenthiran et al., 2013; Biçer et al., 2013; Li et al., 2013). However, limited information is available about the removal of cephalosporins by Mn(VII) even though lactam ring, unsaturated double bonds and thioether groups in cephalosporins are susceptible to metallic oxidants such as permanganate.

In this study, cefazolin, a representative of first-generation cephalosporin, was chosen as the target compound due to its widespread occurrence and potential adverse effects. Experiments were conducted to reveal the transformation characteristics of cefazolin during oxidation by Mn(VII). Emphases were laid on identifying chemical structures of the products, and proposing the plausible transformation pathways. What's more, real surface water matrix was used to simulate the transformation characteristics of cefazolin with Mn(VII) in the real environment. Hopefully, the results could elucidate the fate of cephalosporins in the environment and provide some insights for optimizing the current water treatment processes.

2. Materials and methods

2.1. Reagents and solutions preparation

Unless otherwise stated, all the chemicals used in the experiments were of analytical grade reagent. Cefazolin (98%) and formic acid (HPLC grade) were purchased from TCI (Tokyo, Japan) and Acros Organics (Belgium, USA), respectively. Ultrapure water was prepared from Milli-Q purification system (Millipore, Massachusetts, USA). All stock solutions were prepared and diluted with Milli-Q water without adding any organic co-solvents.

2.2. Reaction set-up

The experimental procedures were similar with what has been described previously (Li et al., 2013). Briefly, experiments were performed in 25 mL borosilicate glass bottles with Teflon septa in the absence of light, under constant stirring at $25 \pm 0.5^\circ\text{C}$. Reactions were undertaken in acetate buffer solution (0.2 mM, $\text{pH} 4.6$) and phosphate buffer solution (0.2 mM, $\text{pH} 7.6$), respectively.

Experiments were initiated by adding Mn(VII) stock solution into the 25 mL borosilicate glass bottle containing cefazolin solution. The initial concentrations of cefazolin and Mn(VII) were $10\text{ }\mu\text{M}$ and 6 mg L^{-1} , respectively. The concentration of Mn(VII) in this study is close to the usual dosage used in real water treatment practices. After 30 min (similar to the exposure time in real water treatment process), the reaction solutions were centrifuged at $10,000\text{ r min}^{-1}$ for 10 min. Then the supernatants were filtrated through $0.22\text{ }\mu\text{m}$ nylon membrane twice and analyzed by ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS) immediately. All the experiments were carried out in triplicate.

2.3. Simulation with environmental water samples

The simulation experiment was conducted with a real surface water sample collected from a reservoir in suburban Beijing, China ($\text{NH}_4^+\text{N} = 0.15\text{ mg L}^{-1}$, $\text{DOC} = 4.2\text{ mg L}^{-1}$, $\text{pH} = 8.5$). Firstly, the collected water sample was filtered through $0.7\text{ }\mu\text{m}$ glass fiber membrane (GF/F, Millipore, USA), followed by being spiked with $10\text{ }\mu\text{M}$ of cefazolin and 6 mg L^{-1} of KMnO_4 . The initial concentrations of the reactants and the subsequent procedures were exactly the same as those in the previous experiments with buffer solution.

2.4. Identification of transformation products

To facilitate identification of transformation products, UPLC (Ultimate 3000, Dionex, USA) was used to separate the products and subsequently the high resolution QTOF-MS (resolution > 16500 FWHM and $\Delta\text{M}/\text{M} < 2\text{ ppm}$) (microTOF QII, Bruker, Germany) was used to analyze the molecular mass and possible structure. Meanwhile, other indirect evidence obtained from computational chemistry with MOPAC 6.0 was also adopted for the product identification. The operating parameters of UPLC-QTOF-MS and MOPAC 6.0 are available in Text S1 and Text S2.

3. Results and discussion

3.1. Identification of transformation products

A total of five major transformation products, designated as m/z 471a, m/z 471b, m/z 487, m/z 519a and m/z 519b, were detected after the reaction between cefazolin and Mn(VII) by comparing with the total ion chromatography before reaction in Fig. S1. Under acid condition ($\text{pH} 4.6$), products m/z 471a, m/z 487, m/z 519a and m/z 519b were produced, while products m/z 471a, m/z 471b, m/z 487 and m/z 519b were formed under neutral condition ($\text{pH} 7.6$). As shown in Fig. 1, all transformation products were well separated with the optimized gradient elution procedures, and their exact masses were provided by MS^1 spectra in Fig. S2.

Three out of five transformation products, m/z 471a, m/z 471b, m/z 487, have been found in our previous study on chlorination of cefazolin (Li et al., 2013), and their molecular structures have been proposed as shown in Table 1. Products m/z 471a and m/z 471b were identified as sulfoxide compounds in which oxidation of thioether occurred at S2 and S1 atoms, respectively. Likewise, product m/z 487 was the di-sulfoxide in which both thioethers of S1 and S2

Fig. 1. Total ion chromatogram of cefazolin after treatment with Mn(VII).

Table 1

Chemical information of cefazolin and transformation products.

Compound	Chemical formula	Exact mass theoretical (measured)	Structure
Cefazolin	$C_{14}H_{15}N_8O_4S_3^-$	455.0366 (455.0373)	
m/z 471a	$C_{14}H_{15}N_8O_5S_3^-$	471.0322 (471.0328)	
m/z 471b	$C_{14}H_{15}N_8O_5S_3^+$	471.0322 (471.0329)	
m/z 487	$C_{14}H_{15}N_8O_6S_3^+$	487.0271 (487.0290)	
m/z 519a	$C_{14}H_{15}N_8O_8S_3^+$	519.0147 (519.0169)	
m/z 519b	$C_{14}H_{15}N_8O_8S_3^+$	519.0139 (519.0169)	

atoms were oxidized to sulfoxides by Mn(VII). According to the previous report, the standard redox potentials of KMnO_4 and HClO were 1.51 V and 1.48 V under acid conditions, as well as 1.23 V and 1.20 V under neutral solutions (Dash et al., 2009; Xie et al., 2010; Rajasekharan et al., 2007), indicating that the oxidizing ability of KMnO_4 is comparable to that of HClO . Therefore, it was reasonable that these three products that were formed with HClO could also be produced after reaction with Mn(VII).

Apart from three known transformation products, there were two new isomer products, m/z 519a and m/z 519b. It could be seen that the exact masses of these two isomer products were 64 Da larger than that of cefazolin, implying that one of them may be formed by inserting four O atoms in cefazolin molecule. Based on the previous studies, S atoms combine readily with O atoms to form sulfoxides when met with oxidants. There were only three S atoms which were potential to be inserted with O atoms in cefazolin molecule. Considering the strong oxidizing ability of Mn(VII), it was highly likely that the fourth O atom was added on one of the formed sulfoxides to transform into sulfone group. As is known, the reduction potential of thioether is closely dependent on electron density of S atom and the electron density is commonly characterized by electrostatic potential charge (Spry, 1972). Generally, the lower the electrostatic potential charge is, the more easily the oxidation of thioether will be. Hence, the electrostatic potential charges of three S atoms after being oxidized to sulfoxide were calculated with MOPAC 6.0. It turned out that electrostatic potential charge of S1 was the lowest compared to S2 and S3 atoms (shown in Fig. S3). Taking this into account, S1 was most likely to be re-attacked by the fourth O atom to form sulfone group. This has been proved by computational chemistry as well (Jayaraman and East, 2012).

Other than the product containing sulfone group, there was also another possible structure for the isomer products m/z 519. In cefazolin molecule, six-member cycloolefin contains one fully substituted $\text{C}=\text{C}$ double bond consisted of one σ bond and one π bond. Theoretically, when $\text{C}=\text{C}$ double bond meets with moderate oxidants, π bond is broken easily and σ bond remains unchanged, leading to the formation of glycol. However, when oxidized with strong oxidants such as acid Mn(VII), di-ketone group will be formed owing to the cleavage of both π bond and σ bond. Thus, another possibility for the structure of isomer products, m/z 519, is supposed to contain the ketone group.

Although two possible structures for the isomer structures have been proposed, more evidence was needed to distinguish m/z 519a and m/z 519b. Fig. 1 showed that m/z 519a was formed exclusively at acid condition (pH 4.6), while product m/z 519b at both pH 4.6 and pH 7.6. As is well known, oxidizing ability of Mn(VII) under acid condition is significantly stronger than that under neutral condition. This phenomenon showed that the product m/z 519a was inclined to be produced under stronger oxidation condition. On basis of what has been discussed above, among two proposed possibilities, di-ketone product was formed through the cleavage of both σ bond and π bond when meeting with stronger oxidant. Therefore, the product m/z 519a which appeared only at pH 4.6 was the one containing di-ketone group. Additionally, in classic reactions of organic chemistry, $\text{C}=\text{C}$ double bond are inclined to be cleaved into two ketone groups by Mn(VII) under acid condition, which was in well agreement with the speculation in our study (Yan and Schwartz, 1999; Lee and Chang, 1978; Lee and Brownridge, 1974; Lee and Chen, 1989).

Besides, there was other solid evidence to distinguish and verify the proposed structures of m/z 519a and m/z 519b. It was noticed from Fig. 1 that, the retention time of m/z 519a (10.0 min) and m/z 519b (11.5 min) were obviously different. Considering the gradient procedures of UPLC and properties of the reverse phase

chromatographic column used in this study, theoretically, the stronger the polarity of the compounds is, the shorter the retention time will be. In addition, the polarity of one molecule is relevant to its dipole moment. According to basic chemistry principles, larger dipole moment (absolute value) means stronger molecular polarity. Dipole moments of the two products molecules containing sulfone and di-ketone calculated by MOPAC 6.0 were -3.1773 D and 7.3606 D, respectively. This result indicated that the product containing di-ketone had stronger polarity than the sulfone one. Thus, product m/z 519a, which had shorter retention time and larger polarity, was di-ketone product, and the other one m/z 519b was sulfone product.

3.2. Formation mechanisms and transformation pathways

According to the identified chemical structures, five transformation products were classified into two main categories: (1) (di-)sulfoxide or sulfone containing compounds and (2) di-ketone containing compounds. The formation mechanism of (di-)sulfoxide-containing compounds such as m/z 471a, m/z 471b and m/z 487 is shown in Scheme 1. Briefly, in MnO_4^- , the positively charged Mn atom was formed after the electron transfer from the Mn atom to the O atom, followed by being attacked by the reactive nucleophile, the thioether-sulfur atom in cefazolin molecule to form the manganese-sulfur intermediate 1. Subsequently, the donation of an unshared pair of electrons to an empty d -orbital on the Mn atom led to the formation of a coordinate covalent intermediate 2. Eventually, the intermediate 2 underwent a further re-arrangement to form sulfoxide containing product m/z 471b. Furthermore, in the presence of excessive permanganate, the sulfoxide would be oxidized to the corresponding sulfone product such as m/z 519b following the same formation mechanism mentioned above (Lee and Chen, 1991).

The formation mechanism of the di-ketone containing product is described in Scheme 2. The reactive electrophile $\text{C}=\text{C}$ double bond was attacked by the positively charged Mn atom in MnO_4^- . Afterwards, an intermediate 3, cyclic hypomanganate(V) ester, was formed via an activated organometallic complex. Subsequently, the cyclic hypomanganate(V) ester was inclined to be rapidly oxidized to the corresponding cyclic manganate(VI) ester (intermediate 4) with excessively acid permanganate, followed by hydrolysis to form di-ketone-containing product m/z 519a (Lee and Brownridge, 1974; Wiberg and Saegebarth, 1957). This scheme is well supported by the prior reports (Dash et al., 2009; Ogino and Kikuri, 1989).

The transformation pathways of cefazolin with Mn(VII) under pH 4.6 and pH 7.6 were proposed as Fig. 2. In particular, although m/z 471b was not detected under acid pH condition, it was still encapsulated in the pathway (Fig. 2(a)) because it was supposed to be theoretically formed. As shown in Fig. S3, the most negative electrostatic potential charge of S1 indicated that S1 atom was most easily to be oxidized forming m/z 471b atom by Mn(VII). However, m/z 471b was transformed immediately to m/z 487 owing to the strong oxidizing ability of acid KMnO_4 . By contrast, under pH 7.6, the moderate oxidizing ability of neutral KMnO_4 was not able to transform all the m/z 471b to m/z 487 m/z , leading to the remaining m/z 471b that can be detected after reaction.

3.3. Environmental significance

In order to get the transformation characteristics, all the above experiments were conducted in the ideal matrix, buffer solution prepared by Milli-Q water. Yet, in real water treatment practices, the matrix may have an impact on the transformation of micropollutants. For instance, some components in surface water such as natural organic matter (NOM) and other kinds of micropollutants might disturb the transformation behaviors of cefazolin with

Scheme 1. Formation mechanism for sulfoxide product by Mn(VII).

Scheme 2. Formation mechanism for di-ketone product by Mn(VII).

Fig. 2. Transformation pathways of cefazolin with Mn(VII) under (a) pH 4.6; (b) pH 7.6.

Mn(VII). Thus, with the objective of considering the matrix effect, transformation behaviors of cefazolin with Mn(VII) in the real water treatment practices was simulated by using surface water matrix.

It can be seen from Fig. 3 that all transformation products formed in Milli-Q water matrix under neutral condition (pH 7.6) were also found when the surface water matrix (pH 8.5) spiked with cefazolin was treated with Mn(VII). This phenomenon suggested that the transformation of cefazolin in real water treatment followed the pathways proposed in this study as well. More importantly, all these four products formed in real surface water were (di-)sulfoxide or sulfone containing products showed higher genotoxicity than that of cefazolin (Li et al., 2013; Dearfield et al., 1991; Stoewsand, 1995). Thus, this study gave a hint that there was potential ecological risk when treating drinking water or

wastewater containing cefazolin with Mn(VII). It is expected that the present results could provide some insights for optimizing the current water treatment process when treating cephalosporins with Mn(VII).

4. Conclusions

The five transformation products contained two main categories of functional groups (1) (di-)sulfoxide/sulfone via the oxidation of thioether; and (2) di-ketone via the oxidation of C=C double bond. The formation mechanisms and pathways of these two categories of functional groups were proposed based on the identified molecular structures and organic chemistry principles. More importantly, it was found that the proposed transformation pathways could be replayed in real surface water matrix. According to our

Fig. 3. Total ion chromatogram of cefazolin in surface water matrix after treatment with Mn(VII).

previous studies, (di-)sulfoxide and sulfone containing products formed in this study may have potential genotoxicity to animals and human beings. Therefore, all these results elucidated the fate of cefazolin in the environment and alarmed us that more attention should be paid on the ecological risk when cephalosporins antibiotics are treated with Mn(VII).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.chemosphere.2016.01.117>.

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