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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.

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 ($t_{1/2}$ = 1–10 d at pH > 8 or < 4 at high temperatures (35–60 °C)) in the environment, the hydrolysis rates are quite slow ($t_{1/2}$ = 10–18 d) in common environmental waters (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 ± 0.5 °C. Reactions were undertaken in acetate buffer solution (0.2 mM, pH 4.6) and phosphate buffer solution (0.2 mM, 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 μM 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 r min^{-1} for 10 min. Then the supernatants were filtrated through 0.22 μm 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 ($NH4\pm N$ = 0.15 mg L^{-1}, DOC = 4.2 mg L^{-1}, pH = 8.5). Firstly, the collected water sample was filtered through 0.7 μm glass fiber membrane (GF/F, Millipore, USA), followed by being spiked with 10 μM of cefazolin and 6 mg L^{-1} of KMnO4. 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 $\triangle$M/M < 2 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 (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 neural condition (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