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Sulfadiazine oxidation by permanganate: Kinetics, mechanistic investigation and toxicity evaluation

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HIGHLIGHTS

- The reaction kinetics of sulfadiazine with permanganate in aqueous solution was investigated.
- The transformation byproducts were identified and the oxidation pathways of sulfadiazine were tentatively proposed.
- The quantum chemistry calculations were performed to verify the proposed oxidation pathways.
- The toxicity of sulfadiazine and oxidation products was estimated using USEPA EPI suite.

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ABSTRACT

The residues of sulfonamides and their metabolites can not only give rise to the generation of resistant bacterial/gene, but also have negative impacts on both human and ecosystem. In this work, the oxidation of sulfadiazine (SDZ) using permanganate as an oxidizer was comprehensively investigated, including the degradation kinetics, pathways and byproducts toxicity evaluation. In general, the oxidation of SDZ follows the pseudo first-order kinetics with the rate constant of 0.00168–0.498 min^{-1}. The activation energy was calculated to be 58.7 $kJ\,mol^{-1}$ based on Arrhenius equation. Higher SDZ removal rate can be achieved under the lower pH condition, and the removal rate was decreased accompanying with increasing pH from 3.76 to 8.80. The presence of humic acid at low concentration can accelerate SDZ oxidation rate. Six oxidized byproducts were identified and the plausible oxidation pathways were also proposed. The quantum chemistry calculations indicate that S (2), N (14) and C (16) were more likely to be attacked, which were consistent with the proposed pathways. Furthermore, the toxicity evaluation of the oxidation byproducts suggests that the toxicity of three byproducts (i.e. 2-aminopyrimidine, 4-nitro-N-(pyrimidin-2-yl) benzene sulfonamide and 4-(2-iminopyrimidin-1(2H)-yl) aniline) was higher than parent compound. Despite of complete removal by permanganate, the byproducts that generated by SDZ were even more toxic than parent compound. Therefore, more attentions should be paid to application of permanganate to remove sulfadiazine and further risk assessments should be made to transformed byproducts.

1. Introduction

Sulfonamides antibiotics can competitively prevent p-aminobenzoic acid from transforming to dihydropteroate, which is the key pathway for folate synthesis, subsequent purine and DNA synthesis in bacterium [1]. Owning to their inhibiting properties on bacterial pathogens, sulfonamides have been widely administered in humans and livestock to treat diseases causing from bacterial infections [2]. Nevertheless, sulfonamide antibiotics can be frequently discharged into natural environments via many routes, especially for the municipal wastewater treatment plants [3]. Their characteristics of non-biodegradability and continuous input often result in widespread detection in groundwater, treated wastewater effluent and soils irrigated with reclaimed water [4]. The undesirable existence of sulfonamides can bring about the

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formation of antibiotic resistant bacteria/genes and alteration of microbial community composition, which can exert a negative effect on humans, animals and ecosystem [5]. Therefore, it is imperative to develop an alternative method to remove sulfonamides residues before their release to the environment.

In the past few decades, many chemical oxidation techniques, such as ferrate (VI), persulfate, Fenton and ozone, were applied to remove sulfonamide antibiotics in aqueous phase [6–10]. However, the limitations of these methods are quite evident in practical application, involving high cost, secondary pollution and not-easy operation [11]. In comparison, permanganate displays some competitive features, including high efficiency, low cost, high stability, and easy operation [11]. These characters make permanganate become extensively applied in different water treatment practices for the coagulation improvement and cyanotoxins/micropollutants removal [12–14]. Based on the previous literatures, a great diversity of emerging contaminants, including chlorophenol, ciprofloxacin, lincomycin, triclosan, estradiol, bisphenol A and sulfamethoxazole, can be oxidized by permanganate [14–19]. To date, the oxidation of sulfadiazine (SDZ), as one of sulfonamides, by permanganate has not been thoroughly explored.

In this study, the reactions of the sulfonamide antibiotics with permanganate in aqueous solution were investigated using SDZ as a model compound. Influencing factors, including solution pH, permanganate concentration and presence of humic acid (HA), were chosen to exam their effects on SDZ oxidation. The oxidation intermediates and byproducts were identified by rapid resolution liquid chromatography-tandem mass spectrometry (RRLC-MS/MS), and plausible reaction pathways were proposed as well. Frontier electron density (FED) calculations and point charge analysis were also applied to further validate the possible pathways of sulfadiazine oxidation. Furthermore, the toxicity of oxidation byproducts was estimated using USEPA EPI Suite.

2. Materials and methods

2.1. Chemicals and solutions preparation

Sulfadiazine was obtained from Aladdin Biochemical Technology Co. Ltd. (Shanghai, China) with the purity of 98% (Fig. S1). Methanol (grade for HPLC) was purchased from Honeywell (Mexico City, USA). The other chemicals employed belong to analytical grade and purchased from Kemiou Chemical Reagent Co., Ltd (Tianjin, China). Ultrapure water (18 MΩ) purified by a Milli-Q system (Millipore, Massachusetts, USA) was administered to solution preparation. The glassware applied was soaked in diluted HNO_3 (10%) for more than 2 h and then rinsed with Milli-Q water for three times before use.

2.2. Experimental procedures

Kinetics experiments were conducted in Erlenmeyer flasks with septum under constant shaking on a rotary shaker at 200 rpm and 25 °C in the absence of light. All oxidation reactions were undertaken in buffer solutions and the total volume of reaction was 30 mL. The solution pH was maintained by 10 mM acetate buffer for 3–7 and 10 mM borate buffer for 7–9. Acetate buffer was used at approximate pH 7 instead of phosphate buffer which was found to affect sulfadiazine oxidation in the pre-experiment. If necessary, NaOH or $HClO_4$ was applied to adjust solution pH. Kinetic experiments were initiated by adding potassium permanganate stock solution into flasks containing a 0.02 mM of SDZ solution. At predetermined time intervals, 0.2 mL aliquots were taken into vials including 0.10 mL of 0.20 M sodium thiosulfate to quench reaction. The collected samples were maintained at 4 °C before analysis. All experiments were carried out in triplicate.

2.3. Chemical analysis

The concentration of SDZ residues was determined by a high pressure liquid chromatography (Agilent 1200). The column (Agilent Zorbax SB-C18, 4.6 × 150 mm, 5 μm) and a diode array detector were used to separate and detect SDZ (mobile phase: 20% MeOH and 80% H_2O, 0.8 mL min^{-1}; detection wavelength: 290 nm), respectively. The final injection volume was 20 μL. The intermediates and products of SDZ in the oxidation process were identified by RRLC-MS/MS (Agilent 1260/Agilent 6460G, USA). The 100 mL reaction solutions containing 0.02 mM SDZ and 0.5 mM permanganate at pH 5.76 (acetate buffer) were concentrated by solid phase extraction (SPE) method with Oasis HLB cartridges (3 cc, 60 mg) (Waters, USA) before mass spectra analysis. The detailed information about mass spectrometer operation conditions was described in Supporting Information.

2.4. Ecotoxicity assessment

In order to evaluate the toxicity change during the process of permanganate oxidation, the acute and chronic toxicity of SDZ and its oxidation byproducts was assessed using the Ecological Structure Activity Relationship (ECOSAR) program in the USEPA EPI suite [20]. The ECOSAR program is proven to be a strong effect predictive tool for evaluating aquatic toxicity [21,22] and has been extensively validated and developed by the USEPA, OECD and EU [23]. In the present study, the acute toxicity to three trophic aquatic organisms was determined based on LC_{50} values (96-h fish and 48-h daphnia) and EC_{50} values (96-h green algae). The chronic toxicity of SDZ and oxidized products to the same organisms was assessed as well.

2.5. Quantum chemistry computation

In order to obtain frontier orbitals and electron densities, quantum chemistry calculations were performed using the Gaussian 09 suite program [24]. The geometry structural optimization of SDZ molecule was carried out at the Becke, three parameters, and Lee-Yang-Parr (B3LYP) level as well as the 6-311 + + G (d, p) basis set. To obtain SDZ with the minimal potential energy surface, a frequency calculation was also conducted. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were determined from Gaussian output files. The Hirshfeld charge can be calculated based on the frequency results and all graphs were plotted by the software Multiwfn 3.4 suite [25].

3. Results and discussion

3.1. Reaction kinetics

It is well known that oxidant concentration can dominate the removal of organic matters in the oxidation process. To determine the effect of permanganate concentration on the oxidation, the oxidation experiments with different initial permanganate concentration (0.01–1.0 mM) were performed. As shown in the Fig. 1a, the removal rate of SDZ is positively correlated with the initial permanganate concentration. After 120 min, SDZ was removed by only 20% at the permanganate concentration of 0.01 mM, but 100% at the concentration of 1.0 mM permanganate.

To clearly illustrate the impact of permanganate dose on SDZ oxidation process, the data were fitted by pseudo first-order equation. The results showed that the oxidation reaction presents a first-order dependence on SDZ concentration. In Fig. 1b, the pseudo-first-order rate constants (k_{obs}, min^{-1}) at various permanganate concentrations are linear with permanganate concentrations. Thus, the oxidation kinetics of SDZ by permanganate can be also described by a second-order rate law:

$$-\frac{d[SDZ]_t}{dt} = k_{obs}[SDZ]_t = k_{app}[Mn(VII)_t][SDZ]_t \quad (1)$$

where k_{obs} and k_{app} are the pseudo first-order rate constant and the