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Degradation of ciprofloxacin by manganese(III) intermediate: Insight into the potential application of permanganate/bisulfite process

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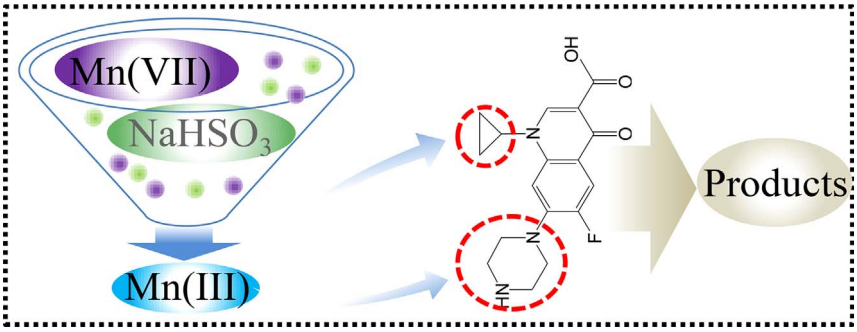
HIGHLIGHTS

- PM/BS process is effective for degrading ciprofloxacin (CPR) over wide pH ranges.
- Background water matrices had little effect on removal of CPR at low concentration.
- Bromate generation and residual Mn (II) removal in PM/BS process were not concerns.
- Piperazine ring and cyclopropyl are the initial attack positions of CPR by Mn(III).
- The products of PM/BS treated CPR showed negligible cytotoxicity and genotoxicity.

GRAPHICAL ABSTRACT



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ABSTRACT

Permanganate could be activated by bisulfite to generate soluble Mn(III) which can oxidize organic contaminants rapidly. However, a lot of concerns need to be addressed for the application of permanganate/bisulfite (PM/BS) process. Taking ciprofloxacin as a target contaminant, the influence of pH, temperature and co-existing solutes on the degradation of organic contaminant in PM/BS process was systematically investigated. The PM/BS process oxidized ciprofloxacin with k_{obs} 2.18–6.27 orders of magnitude larger than other oxidation processes under various reaction conditions and thus stood out. Ciprofloxacin present in real waters can be degraded effectively in the PM/BS process and the co-existing solutes have less inhibiting effect at lower pH and lower ciprofloxacin concentration. Bromate less than 5 μg/L was generated in PM/BS process even in the presence of 1000 μg/L bromide and thus bromate generation in PM/BS process was not a concern. The residual manganese species could be easily removed by aeration from real waters. The degradation products of ciprofloxacin in PM/BS process were identified and the plausible reaction pathways were proposed. Although the quinolone core structure in degradation products remained unattacked, bacterial growth inhibition bioassays and genotoxic experiments showed that the PM/BS treated ciprofloxacin samples displayed negligible cytotoxic and genotoxic potency.

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1. Introduction

The sources, occurrence, fate, effects, and risks of pharmaceuticals in the environment have raised numerous concerns [1,2]. Pharmaceuticals cover a wide range of compounds with substantial variability in structure, function, behavior, and activity and numerous pharmaceutical compounds have been shown to pass through sewage treatment plants and contaminate the aquatic environment [3]. Antibiotics are one of the most important groups of pharmaceuticals [4,5]. The increased use and exposure of antibiotics during the last decades have increased bacterial resistance against them [6]. Moreover, exposure to one compound can lead to resistance against a whole class of antibiotics. Ciprofloxacin, a synthetic fluoroquinolone antibiotic, is widely used for treating human infectious diseases. Within Europe, the most widely prescribed quinolone antibiotic is ciprofloxacin [7]. Like most pharmaceuticals, it cannot be completely metabolized in the body and thus is released into the aquatic environments [8]. Ciprofloxacin is now ubiquitous in aquatic environments, especially those near the megacities with high density of population [9] and receiving effluent from wastewater treatment facilities [8,10]. The presence and accumulation of ciprofloxacin might pose threats to the ecosystem and human health by inducing increase and spread of bacteria drug resistance under long-term exposure, albeit at low concentrations [11].

Various chemical oxidants, such as ozone [12], chlorine [13], chlorine dioxide [14], ferrate [15,16], Fenton reagent [17,18], and manganese oxides (including cryptomelane-type manganese(III/IV) oxides [19], permanganate [20,21], and Mn_3O_4 [22]), can be applied in removing ciprofloxacin in drinking water and wastewater treatment. Recent studies demonstrated the rapid oxidation of various contaminants in the permanganate/bisulfite (PM/BS) process, which was ascribed to the generation of Mn(III) with high reactivity [23–25]. However, there is great knowledge gap on the treatment of ciprofloxacin with soluble Mn(III). Mn(III) can serve as electron acceptors ($Mn^{3+} + e^- \rightarrow Mn^{2+}$) with the standard reduction potential of about 1.5 V [26]. With the negative free energy of reaction (ΔG), soluble Mn (III) is very unstable and spontaneously disproportionate to Mn(II) and MnO_2 [27]. The rate of disproportionation can be slowed by lowering pH, increasing Mn(II) concentration, and decreasing Mn(III) concentration [28]. The equilibrium constant of Mn(III) disproportionation ($2Mn^{3+}(aq) + 2H_2O \leftrightharpoons MnO_2(s) + Mn^{2+}(aq) + 4H^+$) was reported to be 10^7–10^9, depending on the particular MnO_2 phase formed [27]. Previous experiments conducted in perchlorate solutions demonstrated that Mn(III) is considerably hydrolyzed with the hydrolysis constants of $pK_{a1} = 0.08$ [29] and $pK_{a2} = 5.0 \pm 0.1$, as shown in Eq. (1) and Eq. (2), respectively [30].

$$[Mn(H_2O)_6]^{3+} + H_2O \rightarrow [Mn(H_2O)_5OH]^{2+} + H_3O^+ \quad (1)$$

$$[Mn(H_2O)_5OH]^{2+} + H_2O \rightarrow [Mn(H_2O)_4(OH)_2]^{+} + H_3O^+ \quad (2)$$

Considering the significant influence of solution conditions on the properties of Mn(III), it is necessary to investigate the influence of solution chemistry on the degradation of contaminants by Mn(III). The reaction between permanganate and bisulfite may also depend on the solution conditions, including pH, temperature and co-existing constituents. In addition, it still remains unknown whether some by-products of health concerns can be generated or not in the PM/BS process. Therefore, the present study was conducted to assess the feasibility of PM/BS process for the oxidative removal of ciprofloxacin under various conditions. Firstly, new evidence of Mn(III) as the reactive species in the PM/BS process was provided. secondly, the degradation kinetics of ciprofloxacin in the PM/BS process over the pH range of 4.0–9.0 were determined and compared with other processes; Thirdly, the influences of temperature and coexisting constituents were studied to assess the effectiveness of the PM/BS process for efficient elimination of ciprofloxacin in water treatment; Fourth, the formation potential of bromate from bromide in the PM/BS process and removal of residual manganese were investigated. Finally, the degradation products and residual toxicity of ciprofloxacin after treated in the PM/BS process were investigated to gain insight into the degradation mechanisms.

2. Materials and methods

2.1. Materials

A complete listing of reagents is provided in **Text S1**. All chemicals were at least of analytical grade and used as received unless otherwise noted. All solutions were prepared in deionized water.

2.2. Stopped-flow and batch experiments

A stopped-flow spectrophotometer (SFS, Model SX20, Applied Photophysics Ltd., Leatherhead, UK) was used to study the chemical kinetics of fast reactions in solution. The details of stopped-flow kinetic experiments and batch experiments are present in **Text S2**

2.3. Chemical analysis

A Shanghai Leici pH meter with a saturated KCl solution as an electrolyte was used to measure solution pH. The concentration of ciprofloxacin in batch experiments was analyzed with an UPLC (waters ACQUITY UPLC H-Class) and separation was accomplished with an UPLC BEH C18 column. The mobile phase, methanol/0.1% formic acid aqueous solution (40/60, v/v) for phenol and acetonitrile/0.1% formic acid aqueous solution (12/88, v/v) for ciprofloxacin, were run with a flow rate of 0.5 mL min^{-1}. The collected samples in the experiments performed at initial ciprofloxacin concentration of 10 μg/L were analyzed with UPLC-UV following the solid phase extraction (SPE) and the details are described in **Text S3**. Continuous-wave electron paramagnetic resonance (EPR) spectra were recorded on a Bruker X-band EPR system with parallel mode polarizations of the applied magnetic field. Cryogenic temperatures were obtained with liquid helium cryostat. Measurements were carried out for detecting Mn(III) under the following conditions: microwave frequency, 9.393 GHz; microwave power, 1 mW; modulation frequency, 100 kHz; time constant, 20.48 ms; conversion time, 40.96 ms; temperature 2 K. UPLC-QTOFMS was used to detect the degradation products of ciprofloxacin and the details are presented in **Text S4**. Bromate and bromide were detected by ion chromatograph (DIONEX ICS 5000) with the injection volume of 500 μL. The concentration of residual Mn(II) was determined with a spectrophotometer using the periodate method [31]. A novel approach for analyzing MnO_2 was developed in this study and the details are described in **Text S5**. The toxicity of the PM/BS treated ciprofloxacin samples were assessed and the details of the method are provided in **Text S6**.

3. Results and discussion

3.1. New evidence of Mn(III) as the reactive species in the PM/BS process

In this study, parallel-mode EPR spectra were collected to further confirm the presence of active specie of Mn(III) in the PM/BS process. The parallel mode EPR spectrum of synthetic Mn(III)-pyrophosphate (Mn(III)-PP) complex at 2 K shows six well-resolved ^{55}Mn hyperfine lines, as shown in Fig. S1A, similar to that of Mn(III) salen complex at 4.4 K in the presence of either N-methylmorpholine N-oxide (NMO) or (4-phen-ylpyridine-N-oxide) 4-PPNO [32].

To collect the EPR spectrum of the reaction mixture of permanganate and bisulfite, permanganate and pyrophosphate of proper concentration were mixed in the EPR tube before the addition of bisulfite. The EPR tube was then frozen in liquid nitrogen (77 K) before collecting the EPR spectrum at 2 K. To protect the EPR tube from break under low temperature, glycerin must be added into the solution before frozen in

liquid nitrogen. Glycerin could be added to the solution either before the dosing of bisulfite or after the dosing of bisulfite.

The parallel mode EPR spectrum of the reaction mixture with glycerin added after bisulfite application at 2 K was collected and shown in Fig. S1B. This EPR spectrum is indicative of Mn(III)-PP complex. Interestingly, when glycerin was added prior to bisulfite addition, the EPR signal arising from Mn(III)-PP complex disappeared, as shown in Fig. S1C. This phenomenon indicates that Mn(III) formed in the PM/BS process oxidizes glycerin more rapidly than it complexes with PP. The parallel mode EPR spectrum of Mn(II) under low temperature was presented in Fig. S1D for reference.

3.2. Ciprofloxacin oxidation in the PM/BS process

The influence of initial pH on the degradation of ciprofloxacin in the PM/BS process was investigated, and the results are shown in Fig. S2. Over 99% ciprofloxacin was removed at $pH_{ini} \leq 6.5$ while the removal of ciprofloxacin dropped progressively from 92.2% to 59.0% as pH_{ini} increased from 7.0 to 9.0, which should be mainly ascribed to the enhanced disproportionation of Mn(III) with increasing pH [24]. The kinetics of ciprofloxacin degradation in the PM/BS process was investigated with SFS and the results are shown in Fig. 1. The oxidation of ciprofloxacin completed in 0.05–2.0 s, depending on pH_{ini}. There are several obvious trends in the time courses of ciprofloxacin disappearance at different pH_{ini}. Firstly, the initial fluorescence intensity of ciprofloxacin decreased with increasing pH, which should be ascribed to the successive ionization of ciprofloxacin (Fig. S3). Secondly, the lag phase in the pH_{ini} 4.5–7.0 was more prominent at higher pH_{ini}. Moreover, the fluorescence intensity of ciprofloxacin increased in the lag phase at pH_{ini} 6.5–7.0, which should be due to the fact that the increase in the fluorescence of ciprofloxacin arising from pH drop exceeded the decrease in the fluorescence of ciprofloxacin due to degradation during this period (Fig. S4). The drop of pH during the reaction accelerated the reaction between permanganate and bisulfite at $pH < 7.5$, which promoted the generation of highly active Mn(III) and the degradation of organic contaminants [23,24]. Thirdly, the majority of the data could be simulated with pseudo-first-order kinetics after excluding the data points suggesting an initial lag phase, as illustrated by the solid lines in Fig. 1. The k_{obs} of ciprofloxacin degradation fell in the range of 201–9407 min^{-1} (data was shown in Table S1), generally dropped with increasing pH_{ini}.

A Mn(III) generation and utilization model was developed in our previous study to get the second-order reaction rate parameters of benzene oxidation by Mn(III), and then a competition kinetics method was employed to obtain the second-order rate constants of organic contaminant oxidation by Mn(III) [24]. Therefore, the second-order rate constants of ciprofloxacin oxidation by Mn(III) at various pH were obtained by determining the influence of ciprofloxacin on phenol generation from benzene oxidation in the PM/BS process (Fig. S5) and the results are summarized in Fig. 2A. The second-order rate constants of ciprofloxacin degradation by soluble Mn(III) in the pH range of 4.5–8.0 varied from $10^{5.84}$ to $10^{7.31}$ M^{-1} s^{-1} and exhibited a concave shape with the minimum reaction rate obtained at pH 6.5. The influence of pH on the second-order rate constants of ciprofloxacin oxidation by soluble Mn(III) at pH_{ini} 4.5–8.0 was similar to that of benzene, aniline, and bisphenol A in the PM/BS process [24], suggesting that the property of soluble Mn(III) other than the speciation of organic contaminants determined the pH influence.

To explore the generality of ciprofloxacin degradation in various processes, we compiled the kinetic data (in Fig. 2A and B) from previous studies on the second-order rate constants (k_2) and pseudo-first order rate constants (k_{obs}) of ciprofloxacin oxidation (summarized in SI Tables S2–S8). As illustrated in Fig. 2A, the k_2 values of ciprofloxacin oxidation by soluble Mn(III) [24] were much greater than those by the conventional oxidants, including $HClO/ClO^-$ [13], O_3 [33], MnO_4^- [20], ClO_2 [14], and FeO_4^{2-} [16], suggesting the higher reactivity of soluble Mn(III) than these conventional oxidants. Fig. 2B shows the scatter of k_{obs} of ciprofloxacin oxidation in various processes, with the reaction conditions summarized in SI Tables S1–S8. The advanced oxidation processes (AOPs) with ·OH radicals as active oxidants decomposed ciprofloxacin with k_{obs} of $10^{-0.14}$–$10^{-2.3}$ min^{-1}, similar to the conventional oxidation technologies. Although ·OH could oxidize ciprofloxacin with k_2 values of 2.7–4.0 orders of magnitude faster than Mn(III) (Fig. 2A) [33,34], the AOPs were 2.58–6.27 orders of magnitude slower for ciprofloxacin decomposition than the PM/BS process (Fig. 2B). The extremely low steady-state concentration of ·OH [35] lead to the slow degradation of ciprofloxacin in AOPs [36–38]. The PM/BS process oxidized ciprofloxacin with k_{obs} 2.18–6.27 orders of magnitude larger than all the other oxidation processes and thus stood out.

3.3. Influence of temperature on ciprofloxacin oxidation in the PM/BS process

It is well known that temperature plays an important role in the reaction kinetics. As shown in Figs. S6A and S7A, permanganate was reduced by bisulfite in the presence of excess benzene with a greater rate at elevated temperature at pH_{ini} 5.0 and 6.5. It should be clarified that benzene did not react with permanganate or bisulfite while

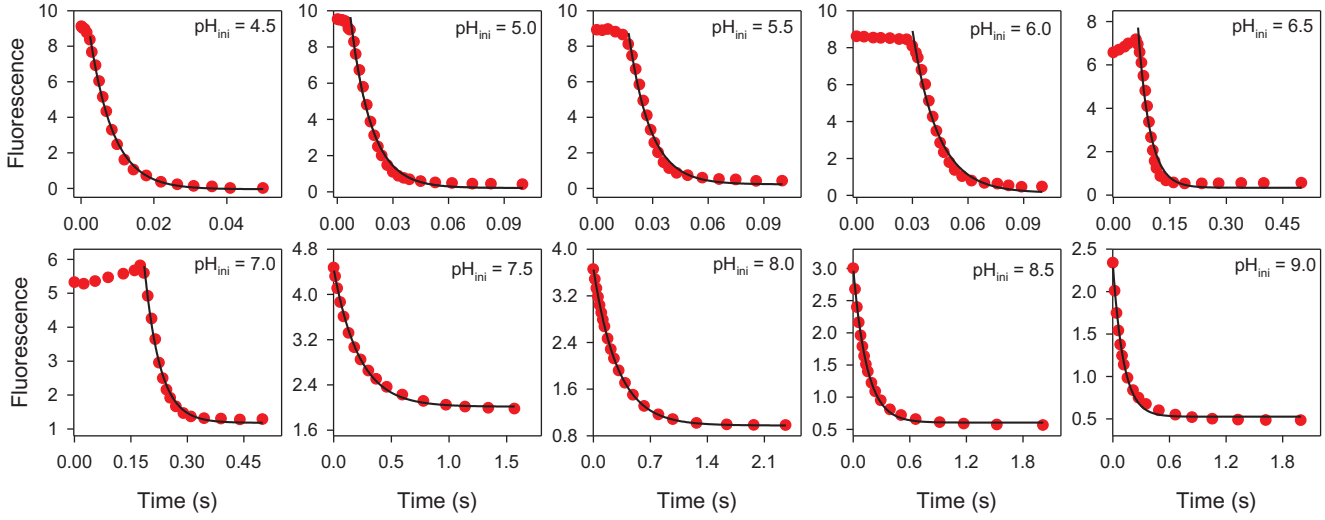

Fig. 1. Disappearance kinetics of ciprofloxacin in PM/BS process at different pH_{ini}. Reaction conditions: $[KMnO_4]_0$ = 50 μM, $[NaHSO_3]_0$ = 250 μM, $[ciprofloxacin]_0$ = 5.0 μM.

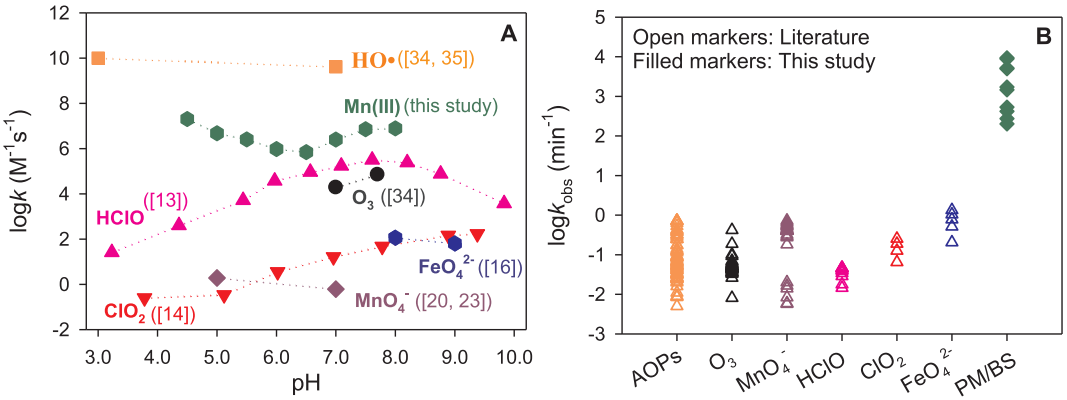

Fig. 2. (A) pH dependent second-order rate constants (k) of ciprofloxacin oxidation by various oxidants. (B) The observed rate constants of ciprofloxacin oxidation in different processes. Literature data used in this plot are summarized in SI Table S1–S8.

benzene could consume the in situ formed $Mn(III)_{aq}$ generated from the reaction of permanganate with bisulfite, which prevented the drop of pH [24]. The second-order rate constants of bisulfite oxidation by permanganate (k_1) were obtained by fitting the experimental data in Figs. S6A and S7A with pseudo-first order rate law, as bisulfite was in 10-fold excess to permanganate, and summarized in Table S9. The values of k_1 increased progressively from 5.21×10^4 to $1.24 \times 10^5\ M^{-1}\ s^{-1}$ with temperature increasing from 7 to 30 °C at pH_{ini} 5.0. The reaction rates between bisulfite and permanganate at pH_{ini} 6.5 were lower than those at pH_{ini} 5.0 at various temperatures, as listed in Table S9. The activation energies of permanganate reduction by bisulfite at pH_{ini} 5.0 and 6.5 were determined to be 26.93 and 21.91 kJ/mol, respectively, from the Arrhenius plots of ln$k$ versus 1/T (as shown in Figs. S6B and S7B).

To obtain the apparent second-order rate constants (k_{CIP}) of ciprofloxacin oxidation by $Mn(III)_{aq}$ at different temperatures, the previously reported $Mn(III)_{aq}$ generation and utilization model and competition kinetics method were employed [24]. The influence of ciprofloxacin on phenol generation at pH 5.0 and 6.5 over the temperature range of 7–30 °C was shown in Figs. S8 and S9, respectively, and the calculated oxidation rate constants of ciprofloxacin by $Mn(III)_{aq}$ (k_{CIP}) are summarized in Table S9. The rate constants of $Mn(III)_{aq}$ reaction with ciprofloxacin increased with increasing temperature and followed the Arrhenius law (Fig. 3). The activation energies of ciprofloxacin oxidation by $Mn(III)_{aq}$ at pH 5.0 and 6.5 were determined to be 43.6 and 27.5 kJ/mol, respectively. Although the activation energies of permanganate reduction by bisulfite were very similar at pH 5.0 and 6.5, those of ciprofloxacin oxidation by $Mn(III)_{aq}$ at pH 5.0 and 6.5 were very different. Considering that pK_{a1} of ciprofloxacin was 5.9 [39], the dominant species of ciprofloxacin were CPR^+ and CPR at pH 5.0 and 6.5 (Fig. S3), respectively, which may contribute to the large difference in the activation energies of ciprofloxacin oxidation by $Mn(III)_{aq}$ at these two pH levels. Hu et al. reported that the activation energy of ciprofloxacin oxidation by permanganate at pH 7.0 was 54.3 ± 3 kJ/mol [20], much larger than that of ciprofloxacin oxidation by $Mn(III)_{aq}$ at pH 6.5, suggesting the much higher reactivity of $Mn(III)_{aq}$ than permanganate.

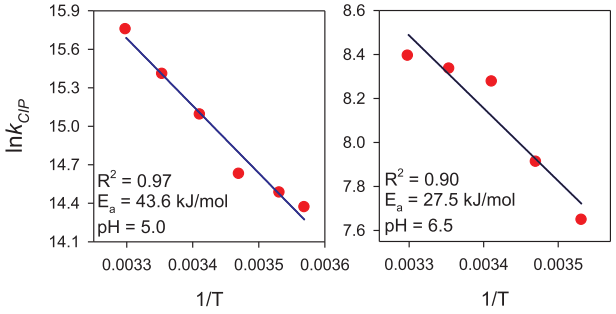

Fig. 3. Arrhenius plots for the reaction between ciprofloxacin and $Mn(III)_{aq}$ at pH 5.0 and 6.5.

3.4. Influence of coexisting solutes on ciprofloxacin degradation in the PM/BS process

The background water matrices, including tap water from our lab, the source water, and the settled water (their characteristics are listed in Table S10), had little effect on ciprofloxacin removal at pH_{ini} 5.0 and 6.5 when the initial concentration of ciprofloxacin was 5.0 μM (Fig. S10). The influence of background water matrices on the removal of ciprofloxacin in the PM/BS process was further determined at ciprofloxacin concentration of 50.0 μM, as illustrated in Fig. 4(A and B). It was found that compared to the removal of ciprofloxacin from Milli-Q water pH_{ini} 5.0, the degradation of ciprofloxacin in the PM/BS process was reduced by < 10% because of the presence of various co-solutes in different background water matrices. However, at pH_{ini} 6.5, the amount of decomposed ciprofloxacin dropped from 15.31 μM in Milli-Q water to 9.13–11.46 μM in different water matrices, indicating that the oxidation of ciprofloxacin in the PM/BS process is more sensitive to the co-existing solutes than that of protonated ciprofloxacin, the dominant species of ciprofloxacin at pH_{ini} 5.0. Further, the strong buffering capacity of real water at near-neutral conditions inhibits the decrease of pH which facilitate the disproportionation of Mn(III), and thus decrease the oxidation of ciprofloxacin [24]. It was interesting to find that the removal of ciprofloxacin in tap water was less than that that in source water and settled water, which needs further study to illustrate the involved interactions. To clarify the major constituents affecting the oxidation of ciprofloxacin in the PM/BS process, the effects of co-existing solutes on ciprofloxacin removal in the PM/BS process at pH_{ini} 5.0 and 6.5 were investigated, as demonstrated in Fig. 4(C and D). The presence of Na_2SO_4, Na_2SiO_3, and $CaCl_2$ decreased the removal of ciprofloxacin only slightly while the removal of ciprofloxacin in the PM/BS process at pH_{ini} 5.0 was inhibited by 11.6–22.6% due to the presence of $FeCl_3$, Na_2CO_3, NaCl, HA, and $MgCl_2$. Their adverse influences on ciprofloxacin removal at pH_{ini} 5.0 increased in the following order: $FeCl_3$ < Na_2CO_3 < NaCl < HA < $MgCl_2$. At pH_{ini} 6.5, all the examined solutes except Na_2SiO_3 and $FeCl_3$ deteriorated the removal of ciprofloxacin by PM/BS process greatly and their inhibiting influence elevated in the following order: Na_2SO_4 < Na_2CO_3 < HA < NaCl < $CaCl_2$ < $MgCl_2$. The influence of these solutes on the reduction of permanganate by bisulfite at pH_{ini} 6.5 was also examined and shown in Fig. S11. Na_2CO_3 lowered the reduction of permanganate by bisulfite, which should be ascribed to the buffering capacity of Na_2CO_3, while all the other solutes had little influence on the reduction of permanganate by bisulfite. Therefore, the inhibiting effect of Na_2CO_3 on ciprofloxacin degradation by PM/BS process should be mainly associated with lower utilization of soluble Mn(III) at elevated pH. The negative influence of HA should be mainly ascribed to the competition of HA with ciprofloxacin for the Mn(III). $CaCl_2$ and $MgCl_2$ depressed

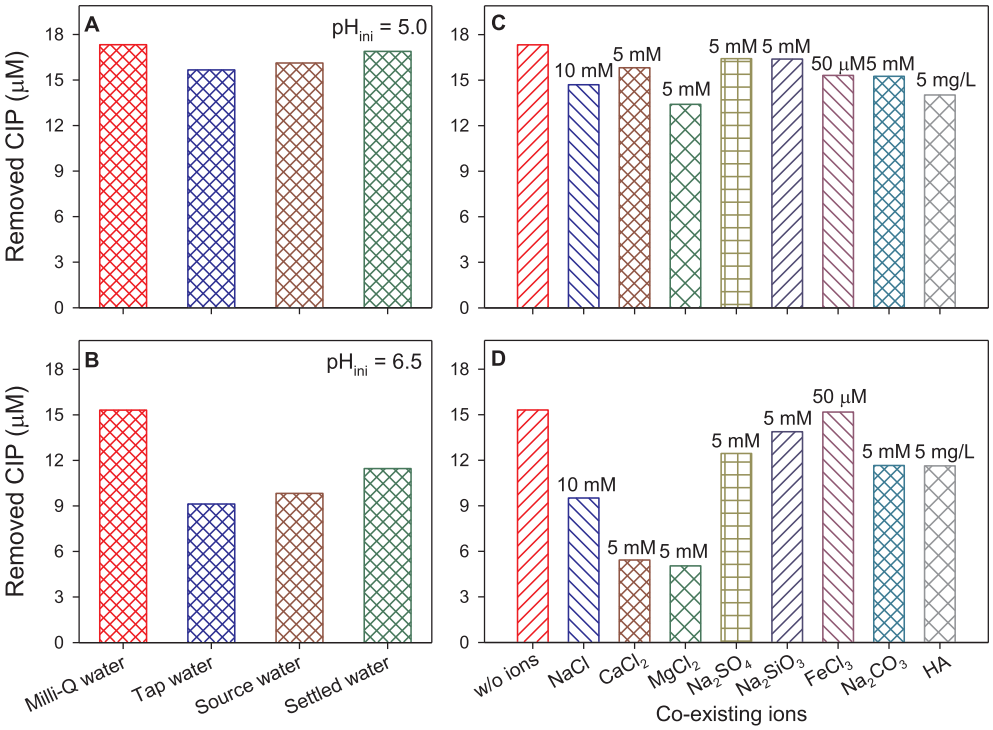

Fig. 4. Removal of ciprofloxacin in PM/BS process in different background water matrices at pH$_{ini}$ 5.0 (A) and 6.5 (B); Influence of co-existing solutes of environmentally relevant concentrations on ciprofloxacin removal in the PM/BS process at pH$_{ini}$ 5.0 (C) and 6.5 (D). Reaction conditions: [$KMnO_4$]$_0$ = 50 μM, [$NaHSO_3$]$_0$ = 250 μM, [ciprofloxacin]$_0$ = 50 μM, Reaction time = 20 s.

ciprofloxacin removal at pH$_{ini}$ 6.5 to a much greater extent than that at pH$_{ini}$ 5.0. $CaCl_2$ and $MgCl_2$ depressed ciprofloxacin removal at pH$_{ini}$ 6.5 to a much greater extent than that at pH$_{ini}$ 5.0, which could be associated with the stronger complexation of Ca^{2+} and Mg^{2+} with ciprofloxacin at higher pH [40,41]. The complexation of Ca^{2+} and Mg^{2+} with ciprofloxacin can change the molecular orbitals and atomic charge distribution of ciprofloxacin and thus has a stabilizing effect on the zwitterionic form of ciprofloxacin [42]. Thus, the more pronounced inhibiting effect of Mg^{2+} on ciprofloxacin decomposition in the PM/BS process compared to Ca^{2+} should be due to the larger stability constant of $Mg(CPR)^{2+}$ ($K_{Mg(CPR)2+} = 1.72 \times 10^5$) than that of $Ca(CPR)^{2+}$ ($K_{Ca(CPR)2+} = 8.84 \times 10^4$) [40]. To identify the influence of Cl^- ions on ciprofloxacin oxidation by Mn(III), the influences of Cl^- and NO_3^- on ciprofloxacin oxidation were compared with Ca^{2+}, Mg^{2+}, or Na^+ as the cation, as shown in Fig. S12. It was found that the degradation of ciprofloxacin was less inhibited when NO_3^- was used instead of Cl^-, regardless of the cations in the solution. The greater inhibitive effect of Cl^- than on NO_3^- ciprofloxacin oxidation by Mn(III) may be ascribed to the consumption of Mn(III) by Cl^- or complex with Mn(III), which needs further verification in future study.

To further verify the feasibility of PM/BS process for effective removal of ciprofloxacin in natural water, ciprofloxacin (10 μg/L) was dosed in a filtrated natural water (pH = 7.2) taken from a reservoir in Yixing, China and was treated by PM/BS process without pH adjustment (Fig. S13). Over 90% of ciprofloxacin could be degraded at permanganate and sodium sulfite dosages of 1.5 mg/L and 7.5 mg/L, respectively. Moreover, pH of the treated water was kept at ~7.2 due to the buffering capacity of the natural water. The effective removal of ciprofloxacin in reservoir water by PM/BS process should be mainly ascribed to the low concentration of ciprofloxacin and the low concentrations of natural organic matter (TOC = 3 mg/L), chloride (~43 mg/L), and hardness (144 mg/L) in this water. Therefore, ciprofloxacin present in real water can be degraded effectively in the PM/BS process without pH adjustment.

3.5. Formation potential of bromate during the PM/BS process and removal of residual Mn^{2+}

Considering the high reactivity of soluble Mn(III), which might lead to the generation of by-products of health concerns in the PM/BS process, the formation potential of bromate in the presence of bromide ion in PM/BS process was investigated. It was found that bromate less than 5 μg/L was generated in the PM/BS process even in the presence of high concentration of bromide (1000 μg/L), as demonstrated in Fig. S14, suggesting that soluble Mn(III) was insensitive towards bromide and bromate generation in the PM/BS process was not a concern. Moreover, 96.8%–99% of dosed Br^- remains unchanged after PM/BS process, indicating that negligible brominated organic products was formed during the oxidation of ciprofloxacin in PM/BS process in the presence of Br^-.

High dissolved manganese in drinking water may cause health problem and thus the allowable upper limit of Mn content in drinking water is 0.1 mg/L according to the Chinese Drinking Water Standard. One disadvantage of the PM/BS process is the residual manganese in the solution and thus removing the residual Mn species from water is necessary. Because of the disproportionation of Mn(III), the manganese species after PM/BS process consisted of three parts: (1) colloidal MnO_2, (2) soluble Mn(II) in the solution ($Mn(II)^I$), (3) Mn(II) absorbed in MnO_2 ($Mn(II)^{II}$). The amount of $Mn(II)^{II}$ could be obtained by subtracting MnO_2 and $Mn(II)^I$ from the total manganese dosed to the solution. Since MnO_2 and $Mn(II)^{II}$ are easily separated from the water by filtration or coagulation/sedimentation, we have determined the influence of aeration on the transformation of manganese species after PM/BS process in different water matrixes, with an emphasis on the disappearance of soluble Mn(II).

It should be noted that the concentration of soluble Mn(II) before or after aeration was determined after the samples were filtered. However, the concentration of MnO_2 in the treated samples was analyzed directly with the ABTS method if MnO_2 was in colloidal form. As shown in

Table 1
The concentration of different manganese species.

Sample	Water	Purging air	MnO_2 (μM)	$Mn(II)^{I}$ (mg/L)	$Mn(II)^{II}$ (mg/L)
1	Milli-Q water	Before	14.05	0.249	1.73
2	Milli-Q water	After	13.81	0.086	1.90
3	Tap water[a]	Before	22.55	0.011	1.50
4	Tap water[a]	After	–[b]	0	–
5	Settled water[a]	Before	21.03	0	1.59
6	Settled water[a]	After	–[b]	0	–
7	Source water[a]	Before	21.94	0	1.54
8	Source water[a]	After	–[b]	0	–

Reaction conditions: $[KMnO_4]_0 = 50\,\mu M$, $[NaHSO_3]_0 = 250\,\mu M$, $[ciprofloxacin]_0 = 5\,\mu M$, $pH_{ini} = 6.5$.

[a] The water quality was provided in Table S9.

[b] MnO_2 could not be detected due to the granulation of colloidal MnO_2 after purging air. $Mn(II)^{I}$: soluble Mn(II) in the solution, $Mn(II)^{II}$: Mn(II) absorbed in MnO_2.

Table 1, most of the generated Mn(II) was absorbed on the in situ formed MnO_2. No soluble Mn(II) was detected when source water or settled water was employed as the background. Compared to Milli-Q water, much more MnO_2 was generated in the PM/BS process in tap water, settled water and source water, which may result in very low concentration of soluble Mn(II) or even undetectable soluble Mn(II) because of the adsorption of Mn(II) onto MnO_2. Fortunately, the concentration of soluble Mn(II) in Milli-Q water could meet the drinking water standard of China after aeration for 10 min although its concentration before aeration was far above 0.1 mg/L, the upper limit of Mn content in drinking water in China. Therefore, it was believed that the residual Mn generated in the PM/BS process was not a concern since it could be easily removed by aeration, followed by filtration or coagulation/sedimentation.

3.6. Identification of the degradation products and reduction in the toxicity

Compared to the parent compound of ciprofloxacin, the degradation products might also promote antimicrobial resistance, especially when the active part of ciprofloxacin molecule remains unaltered. Therefore, the degradation products of ciprofloxacin after treatment in the PM/BS process were carefully analyzed with UPLC-QTOFMS (positive ionization mode). Considering the superfast degradation of ciprofloxacin in the PM/BS system, it was difficult to get samples at different time to demonstrate the evolution of degradation products with time. Therefore, we collected the ciprofloxacin samples oxidized by PM/BS process at different permanganate dosages but fixed PM/BS molar ratio and reaction time (3 s) to clarify the degradation pathways of ciprofloxacin by soluble Mn(III).

The total ion current chromatograms of original ciprofloxacin solution and the PM/BS process-treated ciprofloxacin samples are shown in Fig. S15. For the original ciprofloxacin solution, only the peak of ciprofloxacin was observed at ~2.9 min. The intensity of this peak dropped progressively with increasing the permanganate dosage, which was accompanied with the appearance of 8 new peaks with varying intensities. The proposed chemical structure and the QTOFMS scan data of the degradation products are given in Figs. S16–S23.

Based on the fragmentation patterns shown in Fig. S16, the compound with molecular weight (MW) +1 = 306.1254 was identified to be $C_{15}H_{17}O_3N_3F$, which corresponds to the loss of C_2H_2 from ciprofloxacin [12]. The fragmentation products with MW + 1 = 288.1168, 271.0911, 263.0867 and 245.0762 have also been reported in degradation product with *m/z* 306.1254 in the process of ciprofloxacin oxidation by ozone [12], cryptomelane-type manganese(III/IV) oxides [19], TiO_2 photocatalysis [36], chlorine dioxide [14], ferrate [16], and permanganate [43].

The product with protonated form at *m/z* 362.1143 and chromatographic retention time of ~3.6 min was proposed to be $C_{17}H_{16}O_5N_3F$. Its structure, shown in Fig. S17, was supported by the product ions at *m/z* 344.1060 and 332.1417, which have also been reported in the degradation of ciprofloxacin by cryptomelane-type manganese(III/IV) oxides [19], chlorine dioxide [14], and permanganate [43].

The chemical structure corresponding to the product with protonated form at *m/z* 346.1192 was proposed based on its fragmentation products shown in Fig. S18 and following Hu et al. [43], who observed this product during ciprofloxacin decomposition by permanganate. The degradation product with *m/z* 263.0822 (Fig. S19) had been detected in ciprofloxacin oxidation by various oxidants [12,14,16,19,37,43,44]. The products with protonated form at *m/z* 349.0809, 291.0774, 364.0953 and 336.0994 have seldom been reported in the literature. Thus, their structures were proposed upon the basis of the masses of pseudomolecular ions, the major fragments of the MS spectra, and the chromatographic retention times, as demonstrated in Figs. S20–S23. All the detected products exhibited similar fragmentation patterns to that of ciprofloxacin, indicating a similarity in structure and possible conservation of the quinolone core structure. For example, all of the products detected by QTOFMS have the $[M+H\text{-}H_2O]^+$ fragmentation ion which is likely formed by loss of H_2O from the carboxylate group of the quinolone ring [19].

Combining the above information with the degradation products evolution pattern (Fig. 5), the plausible reaction pathways are proposed, as demonstrated in Fig. 6. The initiation step of Mn(III)-ciprofloxacin reaction is suggested to be the oxidative formation of an enamine (intermediated A: *Int. A*) from the aromatic amine group, as reported by Rawalay and Shechter [45]. Hydrolysis of the enamine may lead to the generation of alcohol (*Int. B*) which is subject to oxidation to a ketone group. The species *m/z* 346.1192 was only observed when 5 μM permanganate was applied and it disappeared at higher permanganate dosage, indicating that the piperazine ring is likely the main initial attack position. The concomitant accumulation of the species *m/z* 306.1254 suggests that it is a following product of the species *m/z* 346.1192. The species *m/z* 346.1192 can also be oxidized to a dialdehyde compound (species *m/z* 362.1143), further oxidation of which yields three products *m/z* 306.1254, *m/z* 349.0809 and *m/z* 364.0953. Various pathways of *m/z* 306.1254 formation account for the second increase of species *m/z* 306.1254 concentration, followed by further degradation to species *m/z* 291.0774. Oxidation of species *m/z* 349.0809 and *m/z* 364.0953 is believed to be other sources for the species *m/z* 291.0774. Product *m/z* 263.0822 is formed by subsequent oxidation of species *m/z* 291.0774. The species *m/z* 263.0822 was quite stable in the reaction solution in the process of ciprofloxacin oxidation by cryptomelane-type manganese(III/IV) oxides [19]. Nevertheless, the species *m/z* 263.0822 disappeared at higher PM/BS dosage, implying the powerful reactivity of soluble Mn(III). Another reactive center of ciprofloxacin is suggested to be the cyclopropyl group, which is oxidized to yield carboxylic acid products (species *m/z* 336.0994). The decrease of the species *m/z* 263.0822 and *m/z* 336.0994 concentration indicates that both of them undergo further degradation, which might involve reactive *Int. C*.

Ciprofloxacin is a broad-spectrum antibiotic killing bacteria in terms of inhibiting DNA gyrase which are necessary to separate bacterial DNA [46]. Furthermore, a variety of organic products with the intact core fluoroquinolone group are detected during the oxidation of ciprofloxacin by PM/BS. Therefore, the bacterial growth inhibition and genotoxicity were evaluated by using toxicity bioassays to assess the effects of PM/BS treatment on the toxicity of ciprofloxacin. Fig. 7A shows the measured bacterial growth inhibition curves for untreated and PM/BS-treated ciprofloxacin solutions with various dilution ratios. Bacterial growth in untreated samples is plotted as a function of ciprofloxacin concentration over a serial dilution series. Similarly,

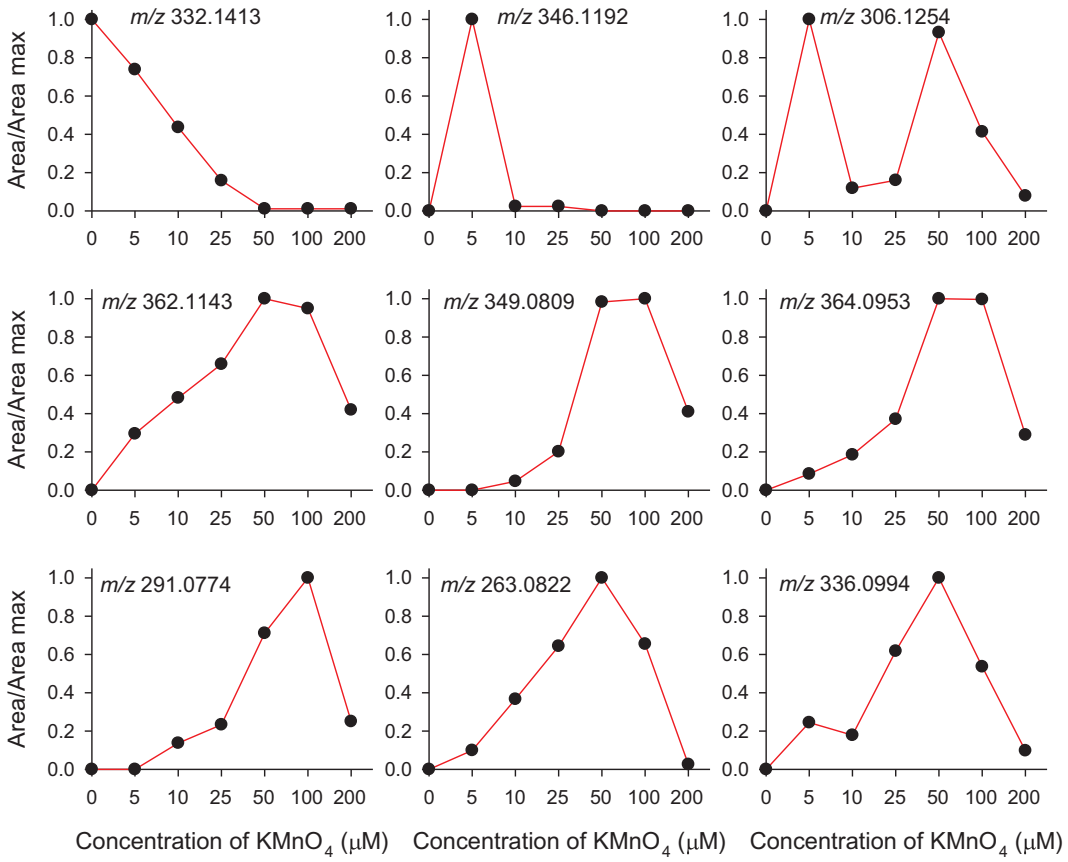

Fig. 5. Evolution of ciprofloxacin and ciprofloxacin degradation intermediates in PM/BS process as a function of permanganate dosage at fixed bisulfite/permanganate molar ratio of 5.0. Reaction conditions: $[ciprofloxacin]_0 = 5.0\,\mu M$, $pH_{ini} = 5.0$.

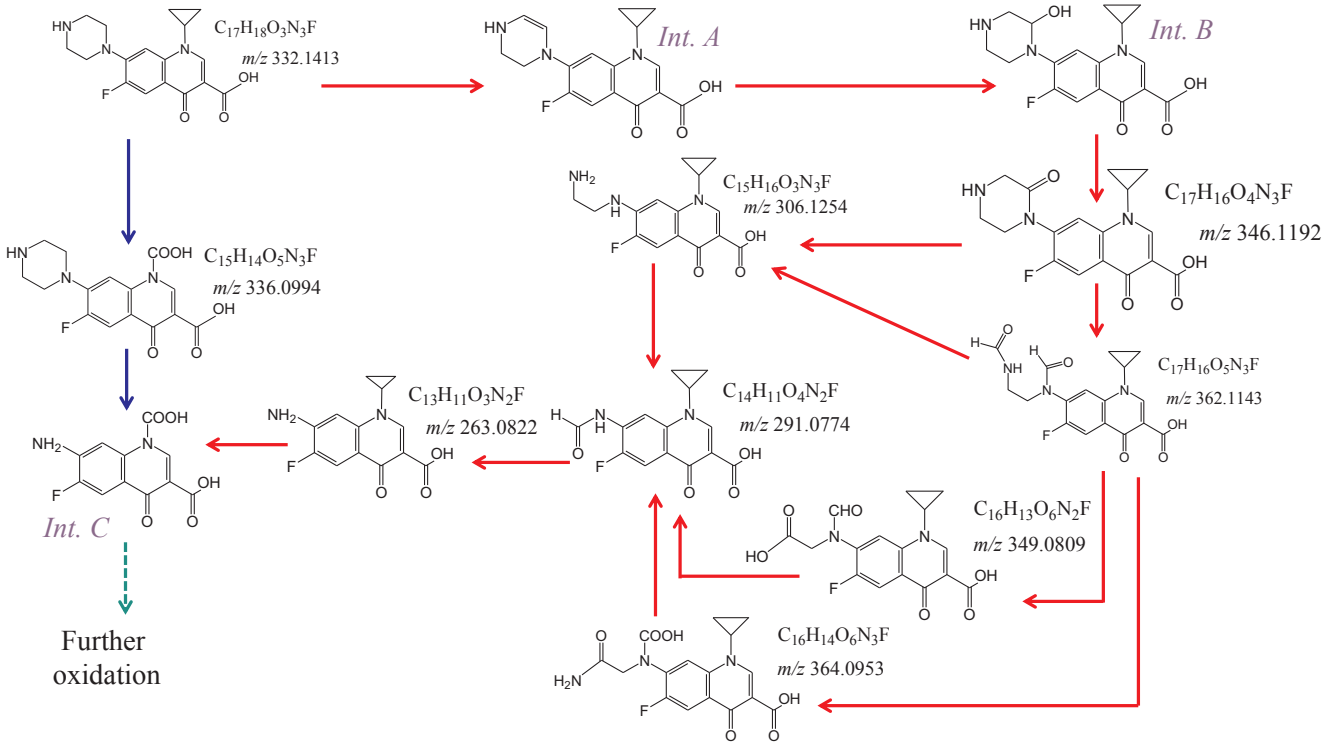

Fig. 6. Proposed degradation pathways of ciprofloxacin in PM/BS process.

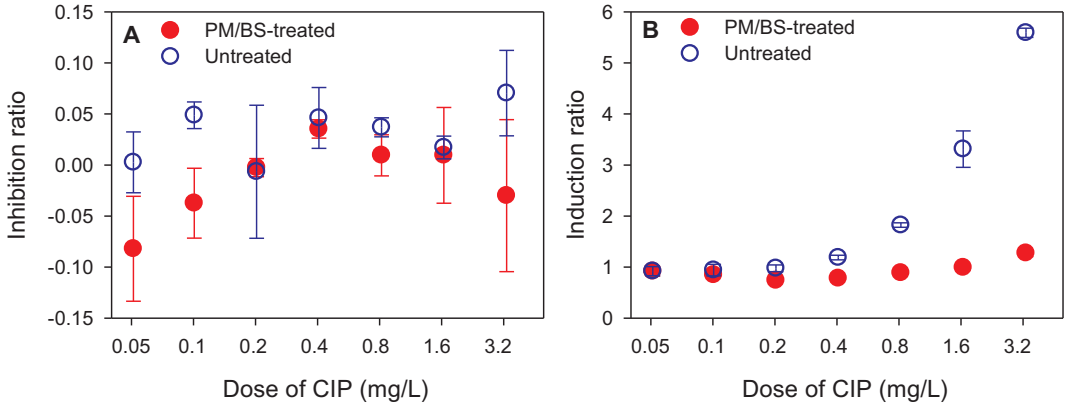

Fig. 7. The inhibition ratio (A) and induction ratio (B) of untreated and PM/BS-treated ciprofloxacin on *E. coli* K12. Reaction conditions: $[KMnO_4]_0$ = 50 μM, $[NaHSO_3]_0$ = 250 μM, $[ciprofloxacin]_0$ = 10 μM. Ciprofloxacin was oxidized at pH_{ini} 6.0, and then the pH of reaction solution was adjusted to 7.0 for toxicity assessment.

bacterial growth in the PM/BS-treated samples is also plotted with the same dilution series. As can be seen from Fig. 7A and Table S11, the measured growth of *E. coli* K12 in the presence of untreated and PM/BS-treated ciprofloxacin showed negligible influence of 10 μM ciprofloxacin on the bacterial growth inhibition. Fig. 7B showed the measured induction ratio curves for untreated and PM/BS-treated ciprofloxacin solutions with various dilution ratios. The measured induction ratio in the presence of untreated ciprofloxacin samples indicated the strong genotoxic potency of parent ciprofloxacin (Fig. 7B and Table S11). Comparing the measured induction ratio of untreated ciprofloxacin, the PM/BS treated samples displayed negligible genotoxicity, indicating that the genotoxic potency of oxidation products of ciprofloxacin can be mainly attributed to the parent compound (Fig. 7B and Table S11). The degradation products analysis showed that core fluoroquinolone structure in many degraded products of ciprofloxacin remains intact after treatment in the PM/BS process, suggesting the significant role of substituents in the toxic potency of ciprofloxacin. These finding showed that the incomplete degradation of ciprofloxacin in PM/BS process was sufficient to eliminate the genotoxic potency of waters.

4. Conclusions

This study demonstrated the extraordinarily fast oxidation of ciprofloxacin in the PM/BS process, along with the elimination of ciprofloxacin toxicity, suggesting the potential application of PM/BS process in degrading antibiotics in water treatment. The residual manganese after PM/BS process can be easily removed from the water by aeration to meet the drinking water standard of China. Although bisulfite was applied exceeding the stoichiometric ratio of permanganate reduction by bisulfite [23], no residual bisulfite was detected after the reaction, which should be mainly associated with the rapid oxidation of bisulfite by dissolved oxygen catalyzed by manganese species in PM/BS process [47]. Due to the combined application of permanganate and sulfite, the colorimetric problem introduced by permanganate of high concentration can be avoided. The low formation potential of bromate and brominated organic products suggests that the PM/BS process is an environmental benign one. The experiments conducted in real waters further prove the feasibility of the PM/BS process for decomposing ciprofloxacin in water treatment.

In our lab, the efficiency of the PM/BS process for sequestering various organic contaminants under different conditions is being systematically investigated and the preliminary results are shown in Fig. S24. It was found that more than 95% of selected pollutants could be removed in the PM/BS process except benzotriazole and caffeine, indicating that the PM/BS process is a potential broad-spectrum destruction technology for organic pollutants. The performance of the PM/BS process for different kinds of pollutants in real water will be compared with that of some advanced oxidation processes (e.g., catalytic ozonation by strong reductants) in the near future. In sum, the PM/BS process has the potential to be employed as a pre-oxidation technology in drinking water treatment process as long as the residual manganese species can be easily removed in the following coagulation and sedimentation processes.

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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.2018.01.131.

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