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## Reactivity of unactivated peroxymonosulfate with nitrogenous compounds

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## 14 **Abstract**

15 A recent investigation has demonstrated that peroxymonosulfate (PMS), a peroxide  
16 commonly applied as a radical precursor during advanced oxidation processes (AOPs), can  
17 degrade organic contaminants without the involvement of radicals. However, little is known  
18 about this non-radical reaction mechanism. In this study, the reactivity of PMS with several  
19 nitrogenous compounds was investigated. Fluoroquinolone antibiotics (except for flumequine)  
20 were rapidly degraded by direct PMS oxidation, followed by aliphatic amines (e.g.,  
21 metoprolol and venlafaxine) and nitrogenous heterocyclic compounds (e.g., adenine and  
22 caffeine) at pH 8. The degradation rate of fluoroquinolones followed a second-order kinetic  
23 and was highly pH and structure-dependent. Unlike the radical-based AOPs, the direct  
24 degradation of contaminants by PMS was less influenced by the scavenging effect of the  
25 water matrix. High-Resolution Mass Spectrometry (HRMS) analysis demonstrated that the  
26 piperazine ring of fluoroquinolones was the main reaction site. Results showed that the direct  
27 electron-transfer from nitrogenous moieties (piperazine ring) to PMS can produce amide and  
28 aldehyde compounds. An amide-containing transformation product of ciprofloxacin ( $m/z$  320),  
29 showing the highest signal intensity on HRMS, was previously recorded during ozonation.  
30 Moreover, the hydroxylamine analogue of ciprofloxacin and enrofloxacin *N*-oxide were  
31 tentatively identified, and the formation of the latter was not impacted by the dissolved  
32 oxygen in water. These results suggested that PMS also reacts with nitrogenous compounds  
33 via oxygen transfer pathway. Agar disk-diffusion tests indicated that PMS treatment  
34 efficiently removed the antibacterial activity of ciprofloxacin with the complete degradation  
35 of parent antibiotic, except for the transformation products in an earlier stage, which might  
36 still exert antibacterial potency.

37 **Keywords**

38 Peroxymonosulfate, nitrogenous compounds, high-resolution mass spectrometry, reaction  
39 mechanism

40 **Abbreviations**

41	AOPs	Advanced Oxidation Processes
42	CIP	Ciprofloxacin
43	<i>D</i>	Distribution Coefficient
44	<i>E. coli</i> B	<i>Escherichia. Coli</i> B
45	ENR	Enrofloxacin
46	HPLC	High-Performance Liquid Chromatography
47	HRMS	High-Resolution Mass Spectrometry
48	LC	Liquid Chromatography
49	NOM	Natural Organic Matter
50	PDS	Peroxydisulfate
51	PMS	Peroxymonosulfate

## 52        **1. Introduction**

53    Advanced Oxidation Processes (AOPs) have gained increasing interest in recent years for the  
54    removal of refractory contaminants during water treatment and soil remediation. Hydrogen  
55    peroxide ( $\text{H}_2\text{O}_2$ ), peroxydisulfate ( $\text{S}_2\text{O}_8^{2-}$ , PDS), and peroxymonosulfate ( $\text{HSO}_5^-$ , PMS) are  
56    the commonly used peroxides for AOPs. The activation of these peroxides by energy (e.g.,  
57    UV irradiation) and electron transfer (e.g., transition metal-based catalysis) generates strong  
58    oxidizing species such as hydroxyl radical ( $\cdot\text{OH}$ , 1.9–2.7 V) and sulfate radical ( $\text{SO}_4^{\cdot-}$ ,  
59    2.5–3.1 V) (Neta et al., 1988). Many studies have demonstrated that  $\cdot\text{OH}$  and  $\text{SO}_4^{\cdot-}$  have high  
60    potential to eliminate pharmaceuticals, pesticides, and industrial contaminants (Lutze et al.,  
61    2015; Wols et al., 2015). However, certain water matrix components (e.g., organic matter,  
62    bicarbonate, and halides) are known to reduce the efficiency of AOPs by significantly  
63    scavenging the radicals (Zhang et al., 2013; Yang et al., 2016b). Moreover, the leaching of  
64    heavy metal (e.g., cobalt) can be an important issue during transition metal-based AOPs (Ike  
65    et al., 2018).

66    PMS is commercially available and known as Oxone ( $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ ). It is  
67    relatively stable, thus convenient for storage and transportation. PMS has been applied as a  
68    non-chlorine disinfectant in swimming pools and for delignification in paper and pulp  
69    industry. The electron-transfer from transition metal-based catalysts (e.g., cobalt, copper, iron)  
70    and the cleavage of peroxide bond in PMS by UV irradiation and ultrasound can generate  
71     $\text{SO}_4^{\cdot-}$  and  $\cdot\text{OH}$  (Ghanbari and Moradi, 2017).

72    It has been recently reported that organic contaminants (e.g., carbamazepine,  
73    sulfamethoxazole, chlorophenol) can be decomposed by direct PMS oxidation (i.e., no radical  
74    initiator). Quenching studies and electron paramagnetic resonance spectrometry analysis  
75    confirmed that contaminant transformation was attributed to the direct oxidation by PMS  
76    without the contribution of radicals (Yang et al., 2018). However, little is known about the

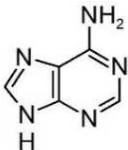
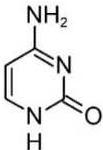
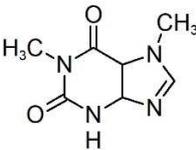
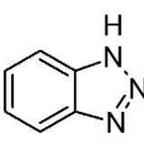
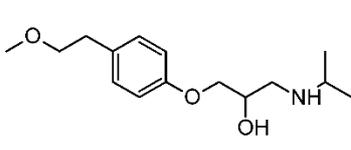
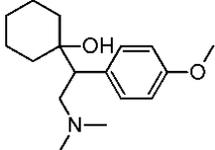
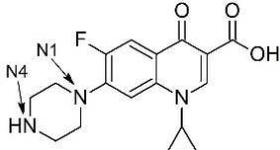
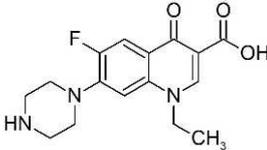
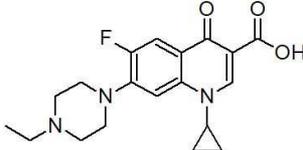
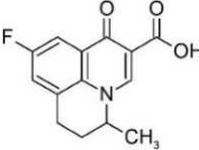
77 reaction mechanism of this non-radical process. Previous studies have reported that sulfur-  
78 containing compounds (thioether sulfur of  $\beta$ -lactam antibiotics) can be substituted by the  
79 oxygen from PMS to produce sulfoxide products (Chen et al., 2018). However, the oxygen  
80 substitution pathway can be affected by steric hindrance, especially for contaminants with  
81 complex structures (Chen et al., 2018).

82 PMS is a strong electron-acceptor with redox potential ( $E^0$  ( $\text{HSO}_5^-/\text{HSO}_4^{2-}$ ) = 1.82  $V_{\text{NHE}}$ )  
83 (Steele and Appelman, 1982). Because of its strong electrophilic character, PMS can  
84 oxidise/degrade contaminants by electron-withdrawing with carbon nanotube as electron-  
85 transfer mediator (Yun et al., 2017). It has been reported that PMS can rapidly inactivate the  
86 disease-associated prion protein. In this process, the amino acid residues of prion protein  
87 were oxidised by PMS through the formation of methionine sulfone and hydroxylated  
88 tryptophan residues (Chesney et al., 2016). The transformation of methionine sulfoxide to  
89 methionine sulfone might be explained by the oxygen transfer mechanism mentioned above.  
90 However, the formation of hydroxylated tryptophan residues suggested that there might be  
91 other reaction pathways for the PMS non-radical process, especially for nitrogenous  
92 compounds.

93 In this study, the reactivity of PMS with various nitrogen-containing compounds was  
94 investigated, including nitrogenous heterocyclic compounds, aliphatic amines, and  
95 fluoroquinolones (Table 1). Degradation kinetics experiments (i.e., involving the effect of pH,  
96 and common water matrix components) were conducted on the selected fluoroquinolones due  
97 to their high reactivity with PMS. Fluoroquinolones are among the most consumed antibiotic  
98 classes in the world. Due to their resistance to biodegradation and high adsorption affinity,  
99 fluoroquinolones show long half-life times in the environment (e.g., 10.6 days in surface  
100 water and 580 days in soil). Fluoroquinolones have been detected in wastewater, surface  
101 water, groundwater and sediment/soil at concentrations ranging from ng/L to mg/L (Van

102 Doorslaer et al., 2014). As shown in Table 1, fluoroquinolones are characterized by a core  
103 quinolone ring structure containing a nitrogen atom. Ciprofloxacin, norfloxacin, and  
104 enrofloxacin also have a piperazine ring with two more amine nitrogen atoms. The  
105 transformation products of ciprofloxacin and enrofloxacin after PMS exposure were  
106 tentatively identified by high-resolution mass spectrometry. MS<sup>2</sup> and MS<sup>3</sup> fragmentation were  
107 applied for most compounds for structural identification. Based on the characteristics of the  
108 transformation products, possible reaction mechanisms of PMS reaction with nitrogenous  
109 compounds were proposed. Agar diffusion tests were applied to investigate the residual  
110 antibacterial activity of ciprofloxacin after PMS oxidation.

111 Table 1. Compounds investigated in this study

Adenine	Cytosine	Caffeine	Benzotriazole
			
Metoprolol	Venlafaxine	Ciprofloxacin (CIP) $pK_a=6.2, 8.8^a$	Norfloxacin
			
Enrofloxacin (ENR) $pK_a=6.1, 7.7^a$	Flumequine	1-(2-fluorophenyl) piperazine	
			

<sup>a</sup>  $pK_a$  values were obtained from Jiang et al. (2016)

112

## 113 2. Materials and methods

### 114 2.1 Chemical Reagents

115 All chemicals were of analytical grade or higher and used as received without further  
116 purification. Potassium peroxymonosulfate (available as Oxone<sup>®</sup>), adenine ( $\geq 99\%$ ),  
117 cytosine ( $\geq 99\%$ ), caffeine ( $> 99\%$ ), benzotriazole (99%), ciprofloxacin ( $\geq 98\%$ ), norfloxacin  
118 ( $\geq 98\%$ ), enrofloxacin ( $\geq 98\%$ ), flumequine ( $\geq 97\%$ ), 1-(2-fluorophenyl) piperazine (97%),  
119 metoprolol ( $\geq 98.5\%$ ), venlafaxine ( $\geq 98\%$ ), *tert*-butanol ( $\geq 99\%$ ), and ethanol (pure) were  
120 purchased from Sigma-Aldrich. The Suwannee River hydrophobic acid fraction was  
121 previously isolated (Croué et al., 2000) and used to study the effect of natural organic  
122 matter (NOM) on the degradation rate of ciprofloxacin by PMS. All solutions were prepared  
123 in ultrapure water (18.2 M $\Omega$  cm, Milli-Q, Purelab Classic).

### 124 2.2 Experimental Procedures

125 Experiments were conducted in amber glass bottles at room temperature ( $22 \pm 1^\circ\text{C}$ ).  
126 Predetermined volumes of target compounds and PMS stock solutions were injected into 25  
127 mL of 10 mM phosphate (pH = 6.2–8) or borate (pH = 8.2–11) buffer to obtain the desired  
128 initial concentrations. Samples were periodically collected and quenched with excess  
129 sodium thiosulfate. For most experiments, the initial concentrations used for target  
130 compound and PMS were 5 and 100  $\mu\text{M}$ , respectively. To better identify the transformation  
131 products, high concentrations of ciprofloxacin and enrofloxacin (50  $\mu\text{M}$ ) were treated with  
132 50  $\mu\text{M}$  and 1 mM of PMS. The influence of dissolved oxygen on the formation of  
133 transformation products from enrofloxacin was investigated by purging the solution (before  
134 PMS spiking) with  $\text{N}_2$  until the dissolved oxygen concentration was reduced to 0.21 mg/L.  
135 The solution was kept in  $\text{N}_2$ -purging throughout the experiment (20 min). The concentration  
136 of dissolved oxygen was measured using a WTW Oxi 330 Oxygen meter. For antibacterial

137 activity tests, 5  $\mu\text{M}$  of ciprofloxacin was degraded by 100 and 250  $\mu\text{M}$  PMS. Most  
138 experiments were conducted at least in duplicate.

### 139 **2.3 Analytical Methods**

140 A quantitative analysis of target compounds was conducted with a High-Performance  
141 Liquid Chromatography (HPLC, Agilent 1100) coupled with a Diode Array Detector (DAD,  
142 Agilent 1100) and an XDB-C18 column (5  $\mu\text{m}$ , 4.6  $\times$  150 mm, Agilent). Mobile phase  
143 composition followed various isocratic mixtures of methanol or acetonitrile with 10 mM  
144 phosphate buffer. All compounds were analysed at their maximum UV absorption. Detailed  
145 information on HPLC methods is provided in the supporting information section (Table S1).  
146 The concentration of the residual PMS was determined according to an ABTS colorimetric  
147 method previously published (Zhang et al., 2016). Briefly, 1 mL of sample was spiked into  
148 a mixed solution of 0.5 mL of ABTS (20 mM) and 0.2 mL of  $\text{CoSO}_4$  (20 mM), then allowed  
149 to react for 1 min where a green-colored ABTS radical was formed. Then, 10 mL of  $\text{H}_2\text{SO}_4$   
150 (2%) was immediately added, followed by the spectrometric measurement at 734 nm (Cary  
151 60, Agilent). The transformation products of ciprofloxacin and enrofloxacin were identified  
152 using an Accela 600 Liquid Chromatography system coupled to a High-Resolution Mass  
153 Spectrometry (LC-HRMS, LTQ Orbitrap XL, Thermo Fisher), and fitted with an  
154 Electrospray Ion Source (ESI). Compounds were separated on a kinetex C18 column (2.6  
155  $\mu\text{m}$ , 100 $\times$ 2.1 mm, Phenomenex). Full scan and  $\text{MS}^2$  fragmentation scans were acquired in  
156 positive ionisation mode (+eV).  $\text{MS}^3$  fragmentation was additionally applied for compounds  
157 with major peak areas on LC-HRMS. Details on LC-HRMS parameters are provided in  
158 Table S2.

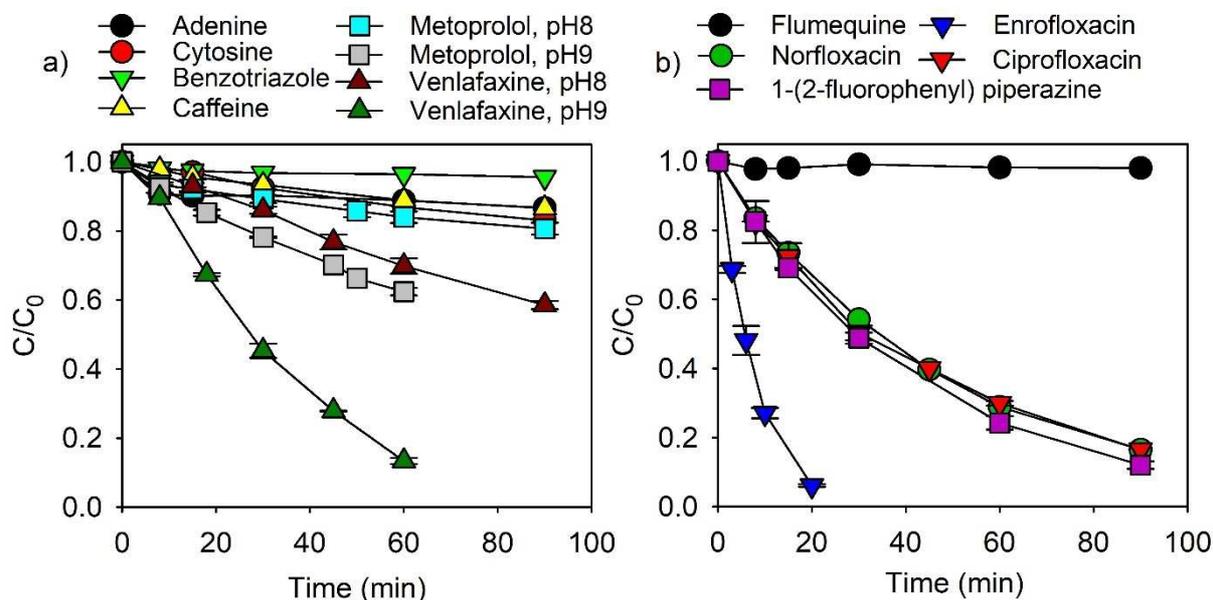
159 The distribution coefficients ( $\log D$ ) of compounds were calculated on a public Web source  
160 developed by ChemAxon (<https://chemicalize.com>, accessed in July 2019).

### 161 **2.4 Antibacterial Activity Test**

162 Agar disk-diffusion tests were conducted to investigate the antibacterial activity of  
163 ciprofloxacin (5  $\mu\text{M}$ ) after PMS exposure (100 and 250  $\mu\text{M}$ ) using *Escherichia. coli* B (*E.*  
164 *coli* B) as the test microorganism according to the Clinical and Laboratory Standards  
165 Institute (CLSI, 2012). Briefly, lysogeny (LB) agar plates were inoculated with 100  $\mu\text{L}$  of  
166 an overnight culture of *E. coli* B, equivalent to 0.5 McFarland. Then, blank antibiotic  
167 cartridges (approximately 6 mm in diameter) containing the test solutions, were placed on  
168 the agar surface. The diameters of inhibition zones around discs were measured after the  
169 plate was incubated overnight at 37°C. A wider zone of no growth indicates a stronger  
170 antibacterial activity of the test solution. The removal of ciprofloxacin antibacterial activity  
171 after PMS exposure was determined by comparing the diameters of the inhibition zones  
172 from PMS-treated samples of ciprofloxacin and the ciprofloxacin standards with known  
173 concentrations (0.2, 0.5, 1, 2, 3, 4, and 5  $\mu\text{M}$ ). Each sample was tested in triplicates.

174 **3. Results and Discussion**

175 **3.1 Reactivity of PMS with various nitrogen containing compounds**



176

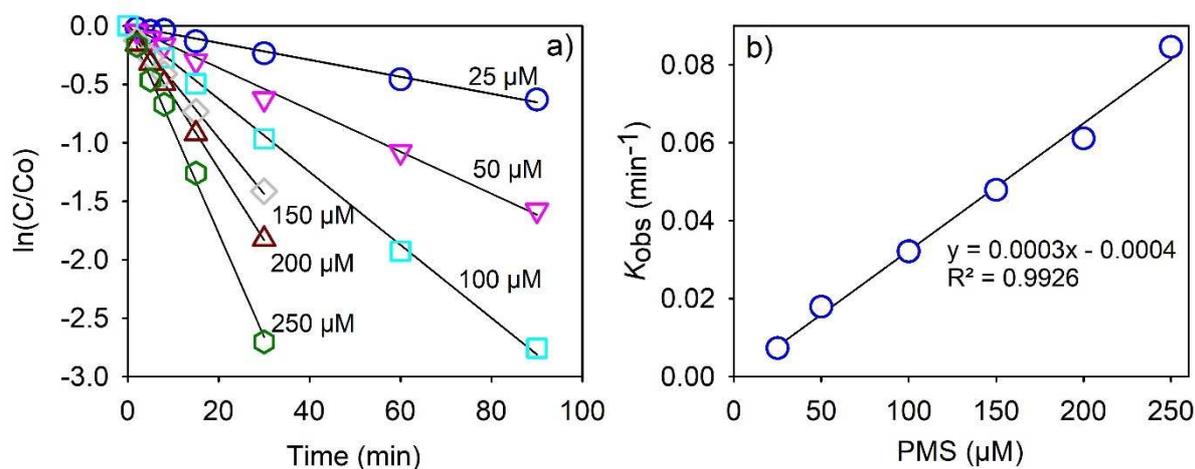
177 **Figure 1.** Relative removal of the selected nitrogenous compounds by PMS (Target  
178 compound: 5  $\mu$ M; PMS: 100  $\mu$ M; 10 mM phosphate buffer at pH 8; Metoprolol and  
179 venlafaxine were also tested in 10 mM borate buffer at pH 9)

180 The degradation of the selected nitrogenous compounds by PMS was individually studied in  
181 the absence of chemical catalysts or UV irradiation. Less than 20% of the selected  
182 nitrogenous heterocyclic compounds (i.e., adenine, cytosine, benzotriazole, and caffeine)  
183 were removed at pH 8 within 90 min (Figure 1a). Approximately 40% of venlafaxine  
184 (aliphatic tertiary amine) was eliminated at pH 8 for the same time frame, which was faster  
185 than metoprolol (aliphatic secondary amine). The degradation of metoprolol and venlafaxine  
186 by PMS was influenced by pH, suggesting that the amine group was likely the main reaction  
187 site. The degradation rates were faster at pH 9 than at pH 8 for both compounds, possibly due  
188 to the higher proportion of deprotonated molecules at higher pH. Venlafaxine was degraded

189 faster than metoprolol in both conditions, revealing that PMS might be more reactive with  
190 tertiary amines than secondary amines.

191 The degradation efficiencies of fluoroquinolones and their related compounds significantly  
192 varied depending on their structural characteristics (Figure 1b). Flumequine, a  
193 fluoroquinolone without a piperazine ring (Table 1), was stable in the presence of PMS in  
194 these experimental conditions, suggesting that PMS does not react with quinolone rings. The  
195 cyclopropane ring of ciprofloxacin (CIP) is substituted by an ethyl group in norfloxacin. 1-(2-  
196 fluorophenyl) piperazine has a fluorobenzene ring instead of the quinolone ring. However,  
197 CIP, norfloxacin, and 1-(2-fluorophenyl) piperazine have the same piperazine ring structure  
198 and exhibited comparable degradation rates toward PMS (80% removal within 90 min).  
199 These results indicated that the piperazine ring was the main reaction site for PMS. This was  
200 further supported by LC-HRMS analyses (section 3.4) from which only piperazine ring  
201 cleavage products were identified after PMS exposure. The N4 (CIP in Table 1 for atom  
202 numbering) in the piperazine ring of enrofloxacin (ENR) is substituted by an ethyl group  
203 (tertiary amine), which differs from CIP (secondary amine). ENR was degraded considerably  
204 faster than CIP, a result that was consistent with the above evidence that tertiary amines were  
205 more susceptible to PMS attack than secondary amines. Overall results suggested that PMS  
206 was more reactive towards fluoroquinolones (except for flumequine) than the selected  
207 nitrogenous heterocyclic compounds and aliphatic amines at pH 8. More detailed experiments  
208 were conducted on CIP and ENR to study the reaction mechanism of PMS with nitrogenous  
209 compounds.

### 210 **3.2 Degradation kinetics of fluoroquinolones by PMS**



211

212 **Figure 2.** a) Effect of the initial concentration of PMS on ciprofloxacin degradation; b)  $k_{obs}$

213 versus initial concentration of PMS (Ciprofloxacin: 5  $\mu\text{M}$ ; 10 mM borate buffer at pH 8.2)

214 The presence of excess ethanol, *t*-BuOH, and  $\text{NaN}_3$  did not affect the degradation kinetic of

215 CIP (Figure S1), which confirmed previous findings that no  $\text{SO}_4^{\bullet-}$ ,  $\bullet\text{OH}$ , and  $^1\text{O}_2$  were

216 involved during the oxidation of fluoroquinolones by PMS (Zhou et al., 2018). The

217 degradation of CIP was promoted by increasing the initial PMS dose (25–250  $\mu\text{M}$ ), following

218 pseudo-first order kinetics ( $R^2 > 0.99$ ) (Figure 2a). The measured rate constants,  $k_{obs}$ , were

219 derived from the slope of  $\ln(C/C_0)$  versus time. As shown in Figure 2b,  $k_{obs}$  exhibited a

220 linear relationship toward the initial PMS dose, suggesting that the overall reaction rate can

221 be described by the second-order kinetic. According to equation 1 and 2, the apparent second-

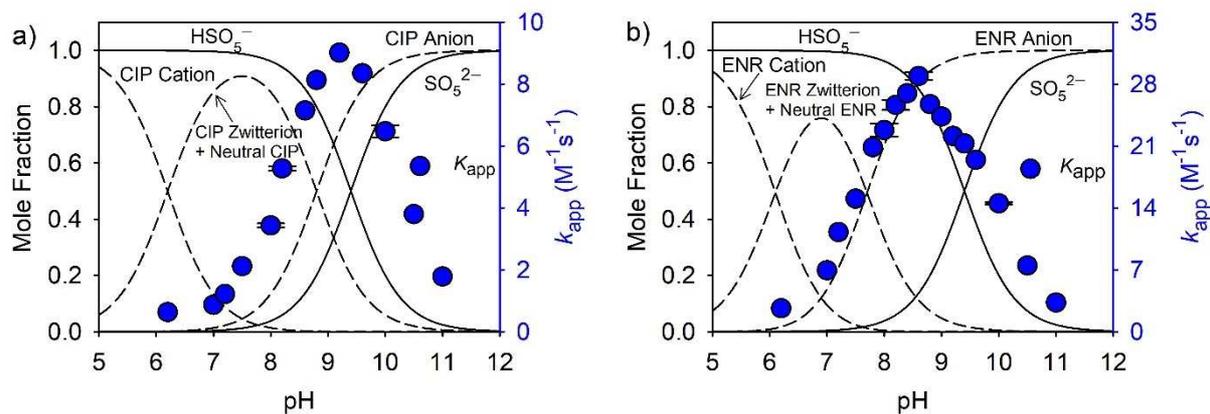
222 order rate constant,  $k_{app}$ , of CIP with PMS was calculated as  $5.28 \pm 0.08$  ( $\text{M}^{-1} \text{s}^{-1}$ ) at pH 8.2,

223 which was comparable with previously reported results by Zhou et al. (2018) ( $\sim 6 \text{ M}^{-1} \text{s}^{-1}$  at

224 pH 8).

225 
$$\frac{d[CIP]}{dt} = -k_{obs}[CIP] \quad (1)$$

226 
$$\frac{d[CIP]}{dt} = -k_{app}[CIP][PMS] \quad (2)$$



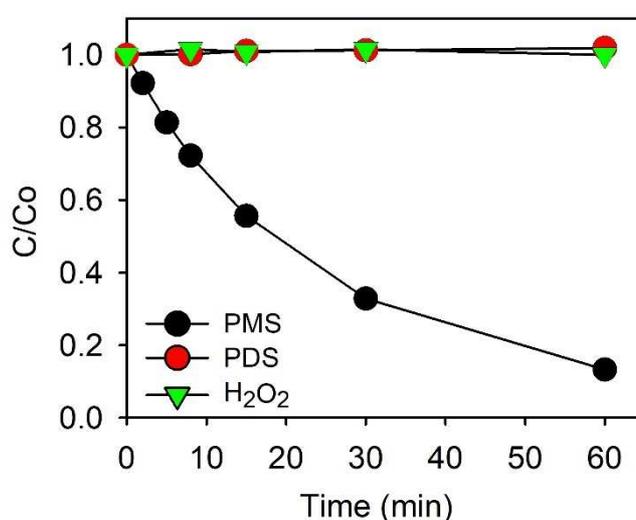
227

228 **Figure 3.** The effect of pH on the distribution of acid-base species of ciprofloxacin (a) and  
 229 enrofloxacin (b), and their apparent second-order constants with PMS. (CIP or ENR: 5  $\mu$ M;  
 230 PMS: 100  $\mu$ M; 10 mM phosphate or borate buffer at pH 6.2–11; The acid-base species of  
 231 ciprofloxacin were shown in Scheme S1 as an example)

232 As illustrated in Figure 3, the degradation efficiency ( $k_{app}$ ) of CIP and ENR by PMS were  
 233 highly pH-dependent. The pH-dependent reactivity of fluoroquinolones was also observed  
 234 with free chlorine (Dodd et al., 2005), manganese oxide (Zhang and Huang, 2005), ozone  
 235 (Dodd et al., 2006), and chlorine dioxide (Wang et al., 2010). The pH-dependence of  
 236 fluoroquinolones degradation can be explained by the change in the distribution of  
 237 fluoroquinolones and PMS acid-base species with pH (Zhou et al., 2018). The  $pK_a$  values of  
 238 CIP and ENR relevant to these experimental conditions were provided in Table 1.  $pK_{a1}$  and  
 239  $pK_{a2}$  were related to the deprotonation of the carboxylic group and the protonation of N4 in  
 240 the piperazine ring, respectively (Scheme S1) (Takács-Novák et al., 1990). PMS dissociated  
 241 into  $SO_5^{2-}$  at alkaline pH ( $HSO_5^- + H_2O \rightleftharpoons SO_5^{2-} + H_3O^+$ ,  $pK_{a2}=9.4$ ) (Ball and Edwards,  
 242 1956). The  $k_{app}$  values of CIP and ENR increased with increasing molar fraction of the  
 243 anionic species (Figure 3), suggesting that the anion forms of CIP and ENR were most  
 244 susceptible to PMS oxidation. In general, N4 in piperazine ring is deprotonated when CIP and  
 245 ENR are present in anionic form, consequently showing a stronger nucleophilic character.

246 The highest  $k_{app}$  values of CIP and ENR were found at around pH 9 and pH 8.6, respectively;  
247 then, it sharply decreased with increasing relative abundance of  $\text{SO}_5^{2-}$ , suggesting that  $\text{SO}_5^{2-}$   
248 is a weaker oxidant compared to PMS.  $\text{SO}_5^{2-}$  was also reported as less reactive than PMS  
249 with  $\beta$ -lactam antibiotics, due to its weaker electrophilic property (Chen et al., 2018). Notably,  
250 PMS showed higher reactivity towards ENR than CIP in all studied pH conditions.

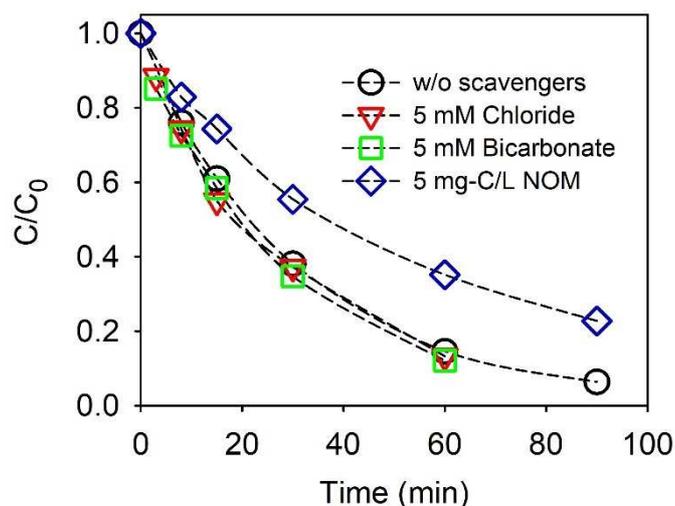
### 251 3.3 Comparison with other peroxides and the effect of the water matrix



252

253 **Figure 4.** Relative removal of ciprofloxacin by PMS, PDS, and H<sub>2</sub>O<sub>2</sub> (Ciprofloxacin=5  $\mu\text{M}$ ;  
254 Oxidants=100  $\mu\text{M}$ ; 10 mM phosphate buffer at pH 8)

255 The reactivity of PMS was compared with other peroxides. Unlike PMS, PDS and H<sub>2</sub>O<sub>2</sub> did  
256 not react with CIP under the same experimental conditions (Figure 4). These results  
257 suggested that PDS and H<sub>2</sub>O<sub>2</sub>, as symmetric peroxides, tend to be more stable; whereas, PMS  
258 is a more efficient electron acceptor, possibly due to its asymmetric structure (Lei et al.,  
259 2016). This is consistent with previous findings indicating that PMS was more efficient  
260 compared to PDS for the removal of organic contaminants during the mediated electron  
261 transfer through carbon nanotubes (Yun et al., 2017; Yun et al., 2018).



262

263 **Figure 5.** Effect of the water matrix on the degradation of ciprofloxacin by PMS

264 (Ciprofloxacin: 5  $\mu\text{M}$ ; PMS: 100  $\mu\text{M}$ ; Chloride= Bicarbonate: 5 mM; NOM: 5 mg-C/L; 10  
 265 mM borate buffer at pH 8.2)

266 The water matrix components can compete with the target contaminants to consume radicals  
 267 during AOPs, consequently lowering the treatment efficiency. The effect of the common  
 268 water matrix components (i.e., NOM, chloride, and bicarbonate ions) on the degradation of  
 269 CIP by PMS was investigated. Unlike the radical-based AOPs, the degradation of CIP by  
 270 PMS was not impacted by the presence of 5 mM of chloride and bicarbonate ions (Figure 5).  
 271 PMS was previously reported to oxidize chloride ion into chlorine, which can contribute to  
 272 contaminant degradation (Fortnum et al., 1960). However, the acceleration of the CIP  
 273 degradation rate was not observed in this study upon the addition of 5 mM of chloride. This  
 274 can be explained by the insufficient formation of chlorine due to the low reaction rate  
 275 constant of chloride with PMS ( $1.4 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ ) (Fortnum et al., 1960), which was about  
 276 three orders of magnitude lower than the  $k_{app}$  of CIP with PMS in this study ( $5.28 \pm 0.08 \text{ M}^{-1}$   
 277  $\text{s}^{-1}$  at pH 8.2). The addition of 5 mg-C/L NOM slightly inhibited the removal of CIP,  
 278 suggesting that PMS can react with NOM.

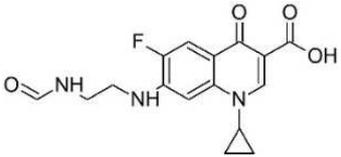
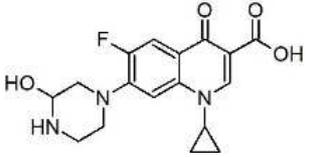
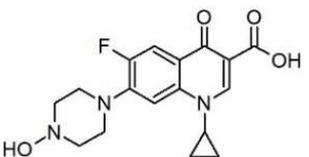
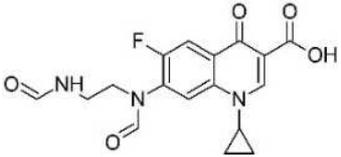
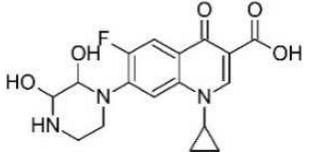
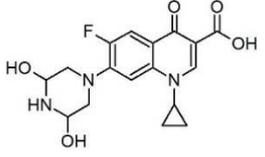
279 **3.4 Transformation products**280 **Table 2.** Transformation products of ciprofloxacin (CIP) detected by LC-HRMS

Compound	RT <sup>a</sup>	Molecular formula	Molecular mass <sup>b</sup>	MS <sup>2</sup> <sup>c</sup> , <i>m/z</i>	Proposed structures
CIP	12.6	C <sub>17</sub> H <sub>19</sub> O <sub>3</sub> N <sub>3</sub> F	332.1404 (-0.169)	314, 288	
P263	16.7	C <sub>13</sub> H <sub>12</sub> O <sub>3</sub> N <sub>2</sub> F	263.0826 (-0.369)	245, 263	
P291	17.4	C <sub>14</sub> H <sub>12</sub> O <sub>4</sub> N <sub>2</sub> F	291.0775 (-0.177)	273, 291	
P306	12.3	C <sub>15</sub> H <sub>17</sub> O <sub>3</sub> N <sub>3</sub> F	306.1248 (-0.183)	306, 288	
P320	18.0	C <sub>15</sub> H <sub>15</sub> O <sub>4</sub> N <sub>3</sub> F	320.1034 (-0.252)	302, 320 MS <sup>3</sup> : 258, 265, 285, 302, 224, 245, 217	
P334a	11.1	C <sub>16</sub> H <sub>17</sub> O <sub>4</sub> N <sub>3</sub> F	334.1198 (-0.750)	316, 317, 314, 306, 296 MS <sup>3</sup> : 296, 245,	

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230, 271, 288

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P334b	17.3	C <sub>16</sub> H <sub>17</sub> O <sub>4</sub> N <sub>3</sub> F	334.1199 (-0.301)	316 MS <sup>3</sup> : 271, 289, 298, 245	
P348a	8.2	C <sub>17</sub> H <sub>19</sub> O <sub>4</sub> N <sub>3</sub> F	348.1348 (-1.841)	331, 287, 304 MS <sup>3</sup> : 287, 273	
P348b	17.3	C <sub>17</sub> H <sub>19</sub> O <sub>4</sub> N <sub>3</sub> F	348.1354 (-0.002)	330, 287 MS <sup>3</sup> : 285, 272, 310, 282	
P362	13.2	C <sub>17</sub> H <sub>17</sub> O <sub>5</sub> N <sub>3</sub> F	362.1143 (-0.985)	344, 362	
P364a	12.4	C <sub>17</sub> H <sub>19</sub> O <sub>5</sub> N <sub>3</sub> F	364.1302 (-0.372)	346, 364 MS <sup>3</sup> : 326, 288, 271	
P364b	16.5	C <sub>17</sub> H <sub>19</sub> O <sub>5</sub> N <sub>3</sub> F	364.1239 (-0.372)	346, 364, 328 MS <sup>3</sup> : 346, 328, 275, 257	

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<sup>a</sup> Retention time (min); <sup>b</sup> Experimental mass for [M+H]<sup>+</sup>; numbers in brackets represent the difference with the theoretical mass of the proposed compound (ppm); <sup>c</sup> MS<sup>3</sup> fragmentation was additionally applied for P330, P334 (a, b), P348 (a, b) and P364 (a, b). The MS<sup>2</sup>/MS<sup>3</sup> spectra of compounds were provided in the supporting

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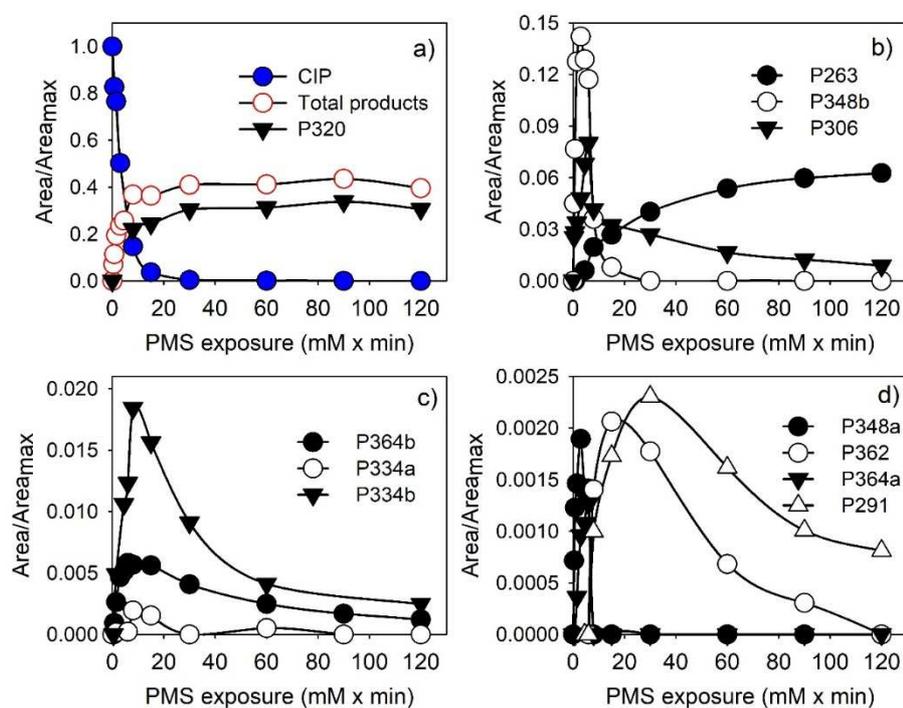
information (Figure S2-S13).

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281 Eleven transformation products of CIP after PMS oxidation were detected by LC-HRMS  
282 (Table 2). Their structures were tentatively proposed based on the accurate mass derived from  
283 HRMS and MS<sup>2</sup>/MS<sup>3</sup> fragmentation patterns (Figure S2-S13). The proposed structures  
284 indicated that the degradation of CIP occurred by the hydroxylation and dealkylation of the  
285 piperazine ring, with the subsequent formation of aldehyde and amide moieties. The core  
286 quinolone ring of CIP remained intact and no defluorination or decarboxylation products  
287 were detected, which were the known transformation products of CIP during Fenton  
288 oxidation (Giri and Golder, 2014), SO<sub>4</sub><sup>•-</sup> (Jiang et al., 2016) and photolytic reactions (Paul et  
289 al., 2010). These results were consistent with the fact that flumequine, which does not  
290 incorporate a piperazine ring, did not react with PMS (Figure 1b). Several transformation  
291 products (e.g., P263, P291, P306, P334, P348, P362, and P364) were also obtained during the  
292 oxidative transformation of CIP by manganese oxide (Zhang and Huang, 2005), chlorine  
293 dioxide (Wang et al., 2010), permanganate (Hu et al., 2011), and Ferrate (VI) (Yang et al.,  
294 2016a), revealing that PMS may share a similar reaction mechanism with these oxidants.  
295 However, structural isomers corresponding to CIP with one additional oxygen atom (P348a  
296 and P348b) or two additional oxygen atoms (P364a and P364b) were detected in this study.  
297 Particularly, P348a and P348b shared the same molecular weight, but different MS<sup>2</sup>/MS<sup>3</sup>  
298 spectra (Figure S9 and S10, respectively) and retention time. P348a was proposed as a  
299 hydroxylated analogue of CIP, with a hydroxyl group located on  $\alpha$ -carbon; whereas, P348b  
300 was a hydroxylamine compound. This may be further supported by the calculated distribution  
301 coefficient ( $\log D$ ) at pH 2.3 (pH of LC-HRMS mobile phase). P348b had a higher  $\log D$  (1.15)  
302 than P348a (-2.05), consequently showing a longer retention time on the reverse phase  
303 column. P348b was believed to be rearranged from its *N*-oxide analogue, which is a known  
304 mechanism for primary and secondary amines (Hübner et al., 2015). Most transformation

305 products (except for P263, P306, and P348) were not reported in a previous study on the  
306 oxidation of 20  $\mu\text{M}$  CIP by 0.1 mM PMS (Zhou et al., 2018), likely because higher CIP (50  
307  $\mu\text{M}$ ) was applied in the current study to maximize the formation of by-products. Moreover,  
308 the HRMS signal intensity of most products (e.g., P320, P334, P291) reached their maximum  
309 when the PMS exposure was above 8 (mM  $\times$  min) (Figure 6), which was achieved by initially  
310 applying 1 mM PMS in this study.

311 To the best of our knowledge, the transformation product P320 has only been reported from  
312 the ozonation of CIP (Liu et al., 2012). The MS<sup>3</sup> spectrum (Figure S6b) of P320 exhibited a  
313 dominant ion cluster  $m/z$  258 corresponding to the loss of an amide group ( $-\text{CH}_2\text{ON}$ ) from  
314 the major ion cluster  $m/z$  302 in its MS<sup>2</sup> spectrum (Figure S6a). Thus, the postulated structure  
315 of P320 is an amide moiety formed at the secondary aliphatic amine (N4) of the piperazine  
316 ring.



317

318 **Figure 6.** The evolution of the normalized chromatographic peak areas of ciprofloxacin (CIP)

319 and its transformation products with PMS exposure. Area<sub>max</sub> represents the peak area of

320 ciprofloxacin at t=0 (Ciprofloxacin: 50  $\mu$ M; PMS: 0.05 and 1 mM; 10 mM borate buffer at  
321 pH 8.2)

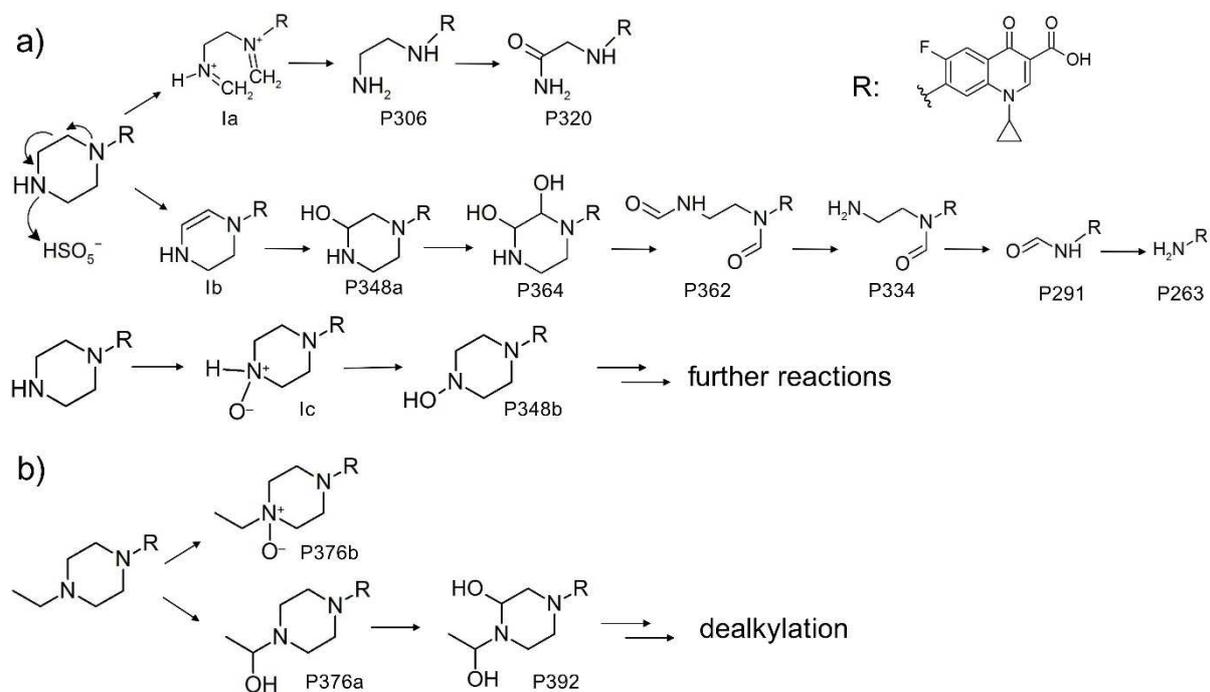
322 Figure 6 presents the evolution of the normalized chromatographic peak areas of CIP and its  
323 transformation products with PMS exposure. P320 exerted the largest peak area among all  
324 identified transformation products (i.e., close to the sum of the peak areas of all  
325 transformation products). P320 was rapidly formed with the degradation of CIP and reached a  
326 plateau. P263, which refers to the complete loss of the piperazine ring, gradually increased  
327 with exposure time. Thus, P320 and P263 were the final products in these experimental  
328 conditions, while all other compounds were intermediates showing a maximum production at  
329 different oxidant exposures. For example, P334b and P362 reached their highest peak areas at  
330 8 and 15 (mM  $\times$  min), respectively, while P320 almost reached a plateau, indicating that  
331 P334b and P362 were unlikely the intermediates of P320.

332 Hydroxylated products (P376 and P392) were the major by-products after PMS oxidation of  
333 ENR (Table S3), which was in accordance with a previous study (Zhou et al., 2018). Like  
334 CIP, two structural isomers of ENR with an additional oxygen atom (i.e., P376a and P376b)  
335 were identified. P376a was proposed as a hydroxylated ENR on  $\alpha$ -carbon, while P376b was a  
336 *N*-oxide analogue of ENR, although further confirmation with analytical standards is needed.  
337 The log*D* value of P376b at pH 2.3 (1.09) was considerably higher than ENR (-1.19) and  
338 P376a (-1.65), consistent with its longer retention time on the LC-HRMS chromatogram  
339 (Table S3). Previous investigations have demonstrated that *N*-oxide analogues of tertiary  
340 amines have higher retention times than their precursors on reverse-phase columns (Merel et  
341 al., 2017). A transformation product of ENR after PMS oxidation was detected on the HPLC-  
342 UV chromatogram (Figure S14), which was eluted after the ENR peak and proposed as  
343 P376b based on an assumption that the eluting order of compounds was comparable on LC-  
344 HRMS and HPLC-UV coupled with similar reverse-phase C18 columns. The HPLC-UV

345 peak area of P376b did not change during the experiments conducted with and without N<sub>2</sub>-  
 346 purged solutions (Figure S15). These results suggested that the dissolved oxygen did not  
 347 contribute to the formation of ENR *N*-oxide. Alternatively, the oxygen likely originated from  
 348 PMS itself. The *N*-oxide formation was also proposed for ENR oxidized by ozone (Dodd et  
 349 al., 2006), manganese oxide (Zhang and Huang, 2005), and permanganate (Xu et al., 2016).

### 350 3.5 Proposed reaction mechanisms

351 **Scheme 1.** Proposed degradation mechanisms of ciprofloxacin (a) and enrofloxacin (b) by  
 352 PMS (Ia, Ib, and Ic are the proposed intermediates)



354 In accordance with the postulated structures of the transformation products and the evolution  
 355 of their peak areas on LC-HRMS chromatograms, reaction mechanisms for the oxidative  
 356 transformation of CIP by PMS were proposed (Scheme 1a). The reaction was initiated by the  
 357 direct electron transfer from the piperazine ring to PMS. In this process, PMS acted as an  
 358 electron acceptor, rather than a radical precursor, to directly oxidize CIP. The N4 atom of  
 359 piperazine ring was the critical site for the electrophilic attack of PMS. The N1 atom is

360 known as less reactive to electrophiles than N4 due to its direct connection to the  
361 fluoroquinolone ring substituted by strong electron-withdrawing fluorine and –COOH (Dodd  
362 et al., 2005; Giri and Golder, 2014). Nevertheless, previous studies have demonstrated that  
363 the piperazine ring should be considered as a whole reaction centre with the contribution of  
364 both nitrogen atoms to electron-transfer (Wang et al., 2010). This could explain the higher  
365 reactivity of PMS with piperazine ring-containing compounds, compared to aliphatic amines  
366 (metoprolol and venlafaxine), as shown in Figure 1.

367 The initial electron transfer from the piperazine ring to PMS produces an imine intermediate  
368 (Ia, Scheme 1a) as proposed by Dodd et al. (2005) and Wang et al. (2010) for the oxidation of  
369 CIP by free chlorine and chlorine dioxide, respectively. The hydrolysis of the imine  
370 intermediate rapidly induced the dealkylation of the piperazine ring to generate P306. The  
371 subsequent electron transfer from the amine group of P306 to PMS was followed by  
372 hydrolysis producing P320. The presence of highly electron-withdrawing carbonyl group  
373 (C=O) in P320 possibly limited the electron transfer from amide-N to PMS. Thus, P320 was  
374 stable in the presence of excess PMS (Figure 6a). The formation of hydroxylated products  
375 P348a and P364 suggested the presence of a similar enamine intermediate (Ib, Scheme 1a),  
376 which has been proposed for the reactions of permanganate (Hu et al., 2011) and Ferrate (IV)  
377 (Yang et al., 2016a) with CIP. The double bond of enamine can be oxidized to aldehyde  
378 moieties (P362, P334, and P291), leading to the complete degradation of piperazine ring.

379 The oxygen transfer from PMS to secondary amine CIP generates *N*-oxide intermediate (Ic,  
380 Scheme 1a), which subsequently rearranged to hydroxylamine compound (P348b) (Lee and  
381 von Gunten, 2016). As shown in Figure 6b, the intensity of P348b reached the maximum at 3  
382 mM (mM × min) and rapidly decreased with PMS exposure, suggesting that P348b was  
383 subjected to further reactions in the presence of excess PMS. The oxygen transfer pathway  
384 might involve the transfer of the distal oxygen in the peroxide bond of PMS to CIP. An

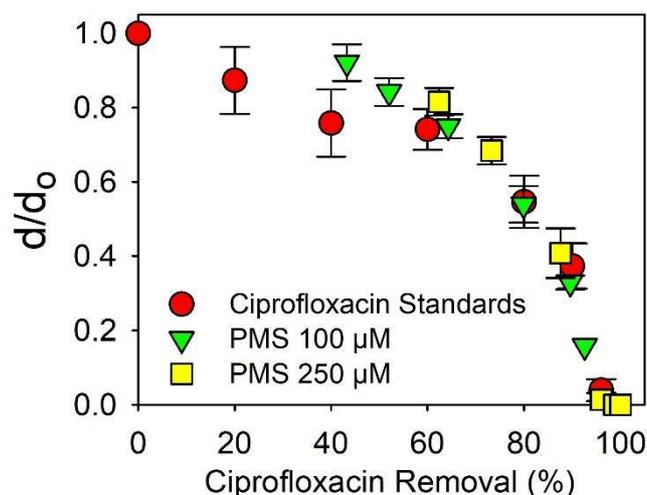
385 oxygen transfer mechanism was also proposed for the oxidation of arsenite As (III) to As (V)  
386 by PMS (Wang et al., 2014). The thioether sulfur of  $\beta$ -lactam antibiotics can be substituted  
387 by the oxygen from PMS to produce sulfoxide products (Chen et al., 2018). The aniline  
388 moieties of sulfonamide antibiotics can be converted to nitroso or nitrobenzene moieties  
389 through PMS oxygen substitution (Yin et al., 2018).

390 PMS was also proposed to react with tertiary amine ENR via oxygen transfer to generate  
391 ENR *N*-oxide, P376b (Scheme 1b). The direct electron transfer pathway also occurred during  
392 PMS oxidation of ENR and led to the hydroxylation on  $\alpha$ -carbon to produce P376a and P392.  
393 Based on the degradation pathway of CIP, it was postulated that the hydroxylated products  
394 P392 might undergo further oxidation, followed by the dealkylation of the piperazine ring.

395 Additional investigation is needed to confirm the major pathway of PMS reaction (electron  
396 transfer *vs* oxygen transfer) with nitrogenous compounds, which might be helpful to explain  
397 the different reaction potential of PMS towards secondary and tertiary amine moieties as  
398 mentioned above.

### 399 **3.6 Antibacterial activity assays**

400 Fluoroquinolones inhibit the bacterial DNA replication by hydrogen binding and charge  
401 interactions with the relaxed DNA. The core quinolone structure would be responsible for  
402 DNA-binding (Dodd et al., 2006), while the fluorine substitute plays an important role in  
403 inhibiting the DNA gyrase and enhancing cell permeation (Serna-Galvis et al., 2017).



404

405 **Figure 7.** Antibacterial activity removal of ciprofloxacin (CIP) during PMS treatment.  $d_0$   
 406 represents the diameter of the inhibition zone in agar plate formed by 5  $\mu\text{M}$  of CIP standard  
 407 solution (CIP standards: 0.2, 0.5, 1, 2, 3, 4 and 5  $\mu\text{M}$ ; for PMS treatment, initial concentration  
 408 of CIP:5  $\mu\text{M}$ , PMS: 100 and 250  $\mu\text{M}$ , 10 mM borate buffer at pH 8.2)

409 Based on LC-HRMS results, the transformation products of CIP after PMS treatment still  
 410 retained the core quinolone structure, raising concerns about the residual antibacterial activity.  
 411 Thus, agar diffusion assays were conducted with *E. coli B* as an indicator. As shown in  
 412 Figure 7, the antibacterial activity of the solution gradually reduced with the removal of CIP  
 413 during PMS treatment. However, after 40 to 50% removal of CIP with 100  $\mu\text{M}$  of PMS, the  
 414 sample resulted in a larger inhibition zone in the agar plate than CIP standard solutions. This  
 415 result indicated that the transformation products at an earlier stage (e.g., hydroxylamine  
 416 product P348b, Figure 6b) might still exert antibacterial potency. The residual antibacterial  
 417 activity was efficiently removed with the complete degradation of CIP, suggesting that the  
 418 major final products P320 and P263 showed negligible antibacterial activity compared to CIP.  
 419 The structural modifications on the piperazine ring alter the acid-base speciation and  
 420 significantly affect fluoroquinolones cell permeation (Paul et al., 2010). Although the amide  
 421 and aldehyde moieties produced after PMS exposure kept the core quinolone structure in this

422 study, their physicochemical characteristics might be significantly different from those of CIP,  
423 consequently reducing their uptake by bacteria cell and binding to DNA. The current results  
424 were in agreement with previous findings reporting that the photolytic transformation  
425 products of CIP retaining the quinolone ring significantly diminished the antibacterial  
426 potency of the parent antibiotic (Paul et al., 2010).

#### 427 **4. Conclusion**

- 428 • PMS can efficiently degrade the selected fluoroquinolones (except for flumequine),  
429 followed by aliphatic amines and nitrogenous heterocyclic compounds. The common  
430 water matrix components (e.g., bicarbonate and chloride ions) did not impact the  
431 degradation rate of CIP by PMS. The electron transfer from the piperazine ring of CIP  
432 to PMS induced the dealkylation and hydroxylation of the molecule and led to the  
433 formation of amide and aldehyde moieties. PMS was also proposed to react with CIP  
434 and ENR via oxygen transfer to produce hydroxylamine analogue of CIP and ENR *N*-  
435 oxide, respectively.
- 436 • PMS efficiently removed the antibacterial activity of CIP. However, the  
437 transformation products in earlier stages of the reaction still exerted antibacterial  
438 potency. A complete elimination of the parent compound, as well as its transformation  
439 products, is required during the fluoroquinolone treatment by PMS.

440 The findings of this study suggested that the direct PMS oxidation can be selectively applied  
441 for the removal of nitrogenous compounds (e.g., fluoroquinolones). However, some  
442 persistent transformation products (e.g., *N*-oxides) can be formed, which are inert to the  
443 biodegradation (Hübner et al., 2015). Unlike radical-based processes, this treatment can  
444 maintain its efficiency in complex water matrixes. However, NOM slightly inhibited the  
445 degradation of CIP by PMS. Therefore, additional studies are needed to investigate the

446 reactivity of PMS with NOM fractions of different characteristics to optimize the PMS dose  
447 for its best treatment efficiency. Because environmental components (e.g., nitrogen and  
448 sulfur-containing organics) (Chen et al., 2018; Yang et al., 2018) are susceptible to react with  
449 PMS, the non-radical pathway might hinder the formation of radicals during PMS-activated  
450 AOPs, consequently limiting the removal of the targeted hazardous compounds. The electron  
451 and oxygen transfer pathways proposed in this study assist in understanding the non-radical  
452 reaction mechanism of PMS with organic contaminants and in predicting the formation of  
453 potential transformation products. Similar mechanistic studies and screening of  
454 transformation products can be extended to other oxidants used during water treatment,  
455 which also have similar peroxide bond and asymmetric structure to PMS, such as organic  
456 peracids (Luukkonen and Pehkonen, 2017).

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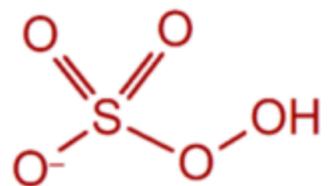
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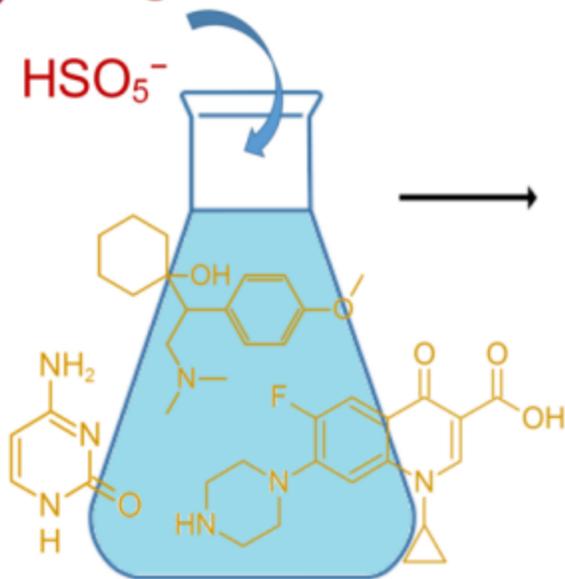
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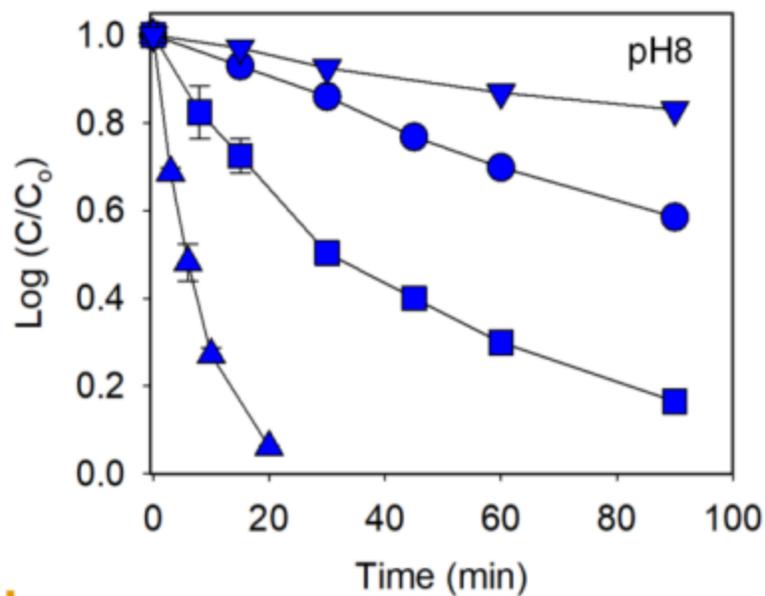


$\text{HSO}_5^-$

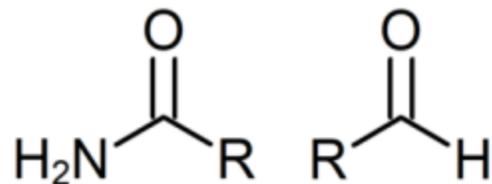
Kinetics: Piperazine moiety > Aliphatic amines  
> Nitrogenous heterocyclic compounds



**Nitrogenous Compounds**



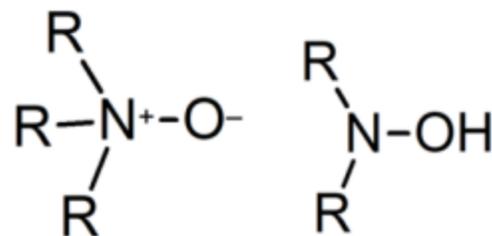
HRMS



$\text{R-NH}_2$

electron transfer

oxygen transfer



**Transformation Products**