Permanganate oxidation of diclofenac: The pH-dependent reaction kinetics and a ring-opening mechanism

Hanyang Cheng^{a,b}, Dean Song^{a,b}, Huijuan Liu^{a,*}, Jiuhui Qu^a

^a Key Laboratory of Drinking Water Science and Technology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China

^b University of Chinese Academy of Sciences, Beijing 100039, China

HIGHLIGHTS

- The DCF reactivity with Mn(VII) was found to decrease with increasing pH.
- The anionic DCF has lower reactivity with Mn(VII) than its neutral counterpart.
- Seven degradation products were identified by Q-TOF MS at pH 7.
- The corresponding structures of five products were proposed.
- A detailed ring-opening reaction mechanism of Mn(VII)/DCF reaction was proposed.

GRAPHICAL ABSTRACT

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ABSTRACT

In this work, the fate of diclofenac (DCF) during permanganate (Mn(VII)) oxidation was investigated at environmentally relevant pH conditions (from 5 to 9). The batch experiments showed that the kinetics of the Mn(VII)/DCF reaction follows a second-order rate law with an apparent rate constant of $1.57 \pm 0.02 \text{ M}^{-1} \text{ s}^{-1}$ at pH 7 and 20 °C. The half-value of DCF was calculated to be 37.5 min, when the concentration of Mn(VII) (0.4 mM) was 20-fold excess of DCF. The pH-dependence of the reaction kinetics was investigated, and the DCF reactivity with Mn(VII) was found to decrease with increasing pH. The second-order rate constants were then quantitatively described by incorporating the species distribution of DCF. A lower reactivity of the anionic DCF (DCF^-) in comparison with its neutral counterpart (DCF^0) was most likely attributable to the interaction between the ionized carboxylate group and amine nitrogen position, which can reduce the nucleophilicity of amine nitrogen by inductive and resonance effects. Moreover, a range of degradation products and the corresponding structures were proposed on the basis of the LC-Q-TOF-MS analysis. A detailed ring-opening reaction mechanism was proposed as follows: Mn(VII) acts as an electrophile to attack the amine moiety, leading to the formation of the primary intermediate products 2,6-dichloroaniline and 5-hydroxy-diclofenac, which can be further transformed. The further degradation proceeded through a multistep process including ring-opening, decarboxylation, hydroxylation, and cyclization reactions.

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* Corresponding author. Tel.: +86 10 62849128; fax: +86 10 62849160.

E-mail addresses: owenchy@163.com (H. Cheng), songdean07@mails.ucas.ac.cn (D. Song), hjliu@rcees.ac.cn (H. Liu), jhqu@rcees.ac.cn (J. Qu).

1. Introduction

Pharmaceuticals and personal care products (PPCPs), as emerging micropollutants, have gained increasing attention in recent years (Daughton and Ternes, 1999; Huber et al., 2003; Hu et al., 2011). A representative example is diclofenac (DCF, chemical structure was shown in Fig. 1), one of the most used non-steroidal anti-inflammatory drugs (NSAIDs). As previously reported, the consumption of DCF was as much as 82 tons in Germany (Zhang et al., 2008) and nearly 32.3 tons in Spain (Carballa et al., 2008). Such a large usage could easily lead to the presence of DCF in water. However, due to its poor biodegradability and low adsorption capacity (Ternes et al., 2004; Tauxe-Wuersch et al., 2005; Joss et al., 2006), DCF could not be effectively removed in conventional sewage treatment plants (STPs) (Ravina et al., 2002; Scheurell et al., 2009; Forrez et al., 2010; Nam et al., 2014). The removal efficiency was mainly in the range of 21–40%, and the concentration of DCF in STP-effluent was reported within the scope of 140–1480 ng L⁻¹ (Zhang et al., 2008). Although DCF is susceptible to degradation by natural photolysis (Buser et al., 1998; Zhang et al., 2008), it has also been detected in surface water and underground water in concentrations up to 1.2 µg L⁻¹ and 0.59 µg L⁻¹, respectively (Sacher et al., 2001). Continuous exposure to DCF in the aquatic environment at the low concentration of 5 µg L⁻¹ may lead to renal lesions and alterations of the gills of rainbow trout (Schwaiger et al., 2004; Triebkorn et al., 2004). Mehinto et al. (2010) also pointed out that the exposure of environmental concentrations of DCF is tightly associated with tissue damage in fish. Additionally, DCF has been reported to be associated with some human hematologic diseases, like aplastic anemia, neutropenia, and thrombocytopenia (Eustace et al., 1989; Kim and Kovacs, 1995). More notably, when considering the synergistic effects of various pharmaceuticals in water, the toxic effect may increase enormously (Cleuvers, 2004). Therefore, it is of high significance to better understand the fate of DCF during water treatment processes.

Permanganate (Mn(VII)), one of the most-used oxidants for water treatment, is a promising oxidant for treating some organic pollutants with electron-rich moieties, like phenolic, olefin, amino, and thiol groups (Waldemer and Tratnyek, 2006). Recently, a study demonstrated that Mn(VII) can effectively degrade carbamazepine (CBZ), with an electrophilic attack at the olefinic group in the central heterocyclic ring of CBZ, leading to the formation of a series of ring-opening oxidation products (Hu et al., 2008). In addition to CBZ, the degradation kinetics and mechanisms between Mn(VII) and three other widely used antibiotics were investigated, where the apparent second-order rate constants were reported to be $0.61 \pm 0.02 \text{ M}^{-1} \text{ s}^{-1}$ (ciprofloxacin), $1.6 \pm 0.1 \text{ M}^{-1} \text{ s}^{-1}$ (trimethoprim) and $3.6 \pm 0.1 \text{ M}^{-1} \text{ s}^{-1}$ (lincomycin) at pH 7 and 25 °C (Hu et al., 2010, 2011). Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), a common groundwater contaminant, can be effectively transformed by Mn(VII) at both laboratory and field conditions,

with a second-order rate constant $4.6 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ at pH 7 and 25 °C (Chokejaroenrat et al., 2011). Jiang et al. (2009) examined the oxidation of triclosan in aqueous solution at pH 5–9 and clarified the important roles of ligands during the oxidation process. Additionally, Mn(VII) is an environmental friendly oxidant, because of its insoluble reduction product MnO₂ as a coagulant aids is useful for coagulation or adsorption process, and can be easily removed through sedimentation or filtration process (Ma et al., 1997).

Lately, the oxidation of NSAIDs with Mn(VII) was investigated, suggesting Mn(VII) could significantly degrade DCF along with decrease in the toxicity of degradation products. Mn(VII) concentration was proposed to be the most significant factor on DCF oxidation kinetics, and pH also played an important role in DCF oxidation (Rodríguez-Álvarez et al., 2013). However, there is still a lack of detailed kinetics experiments considering the influence of solution pH and reaction mechanism. The detailed reaction kinetics was investigated at environmentally relevant pH from 5 to 9, and the DCF reactivity with Mn(VII) was found to decrease with increasing pH. Then the effect of pH was quantitatively described by considering parallel reactions between Mn(VII) and two acid-base species of DCF. Moreover, a ring-opening degradation mechanism at pH 7 was proposed on the basis of the degradation products detected by Liquid chromatography–quadrupole–time of flight–mass spectrometry (LC–Q–TOF–MS) analysis.

2. Materials and methods

2.1. Chemicals

Diclofenac was purchased as sodium salt from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China) with purity more than 98%. All the other reagents (KMnO₄, MnSO₄, NaClO₄, CH₃COONa, H₃BO₃, Na₂B₄O₇·10H₂O, NaOH, NaHCO₃, CHOOH, H₂SO₄, CH₃COOH, HClO₄) or solvents (CH₄O), also obtained from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China), were analytical grade or higher. The reaction solutions were prepared with ultrapure water that was produced with a Millipore Water Purification System (Advantage A10, Millipore, Massachusetts, USA). All glassware was soaked in concentrated sulfuric acid and rinsed with ultrapure water several times prior to use.

2.2. Experimental procedures

To investigate the reaction kinetics between Mn(VII) and DCF, batch experiments were conducted under pseudo-first-order conditions with Mn(VII) in at least a 10-fold excess. The experiments were implemented in a 250 mL glass beaker under dark conditions to avoid direct light degradation. Reactions were initiated by injecting excess Mn(VII) into the prepared DCF solution (0.02 mM) containing 10 mM buffer and 50 mM NaClO₄ as background electrolyte. At predetermined time intervals, samples (1 mL) were withdrawn and quenched with 0.1 mL of MnSO₄ (30 mM). The resulting solutions were filtered (0.22 µm) and then analyzed by HPLC to measure the residual concentration of DCF. The reaction pH was maintained by 10 mM acetate buffer for pH 5–7 and borate buffer for pH 8–9, respectively. Previous experiments showed that phosphate buffer could influence the reaction rate (Jiang et al., 2010). Therefore, acetate buffer was used here to replace phosphate buffer at pH 7, and a small quantity of HClO₄ or NaOH was also used to control the pH if necessary. Unless otherwise stated, all experiments were conducted at 20 ± 1 °C.

In order to identify reaction intermediates and products, a series of higher concentration DCF solutions (0.2 mM) were treated with varying dosages of Mn(VII) (from 0 to 2 mM) at pH 7. These experiments were conducted for sufficient time (more than 24 h)

Fig. 1. Chemical structure of diclofenac (DCF).

to reach completion. The resulting solutions were then filtered and analyzed by LC–Q–TOF–MS.

2.3. Analytical methods

The solution pH was measured by an Orion 720A digital pH meter equipped with a pH electrode acquired from Thermo Scientific Inc (Massachusetts, USA). The concentration of DCF was measured by an Agilent 1260 HPLC/DAD system (High Performance Liquid Chromatography/Diode Array Detector, California, USA) coupled with a C18 column (250 × 4.6 mm, 5 μm). The mobile phase is 0.1% formic acid water–methanol (25/75, v/v) with a flow rate of 1 mL min^{−1}. The detection wavelength was 275 nm and the injected volume was 50 μL for each sample.

Organic reaction products were analyzed by a Waters HPLC/DAD system equipped with a Q-TOF MS (Micromass Q-TOF Micro, Massachusetts, USA). Separation was performed by an Agilent C18 column (150 × 4.6 mm, 3.5 μm) at the flow rate of 0.2 mL min^{−1}. The mobile phase contained A (0.1% formic acid in water) and B (methanol). Gradient elution was as follows: 0–10 min 50% A and 50% B, 10–20 min a linear gradient to 25% A and 75% B, 20–40 min 25% A and 75% B, 40–50 min a linear gradient to 50% A and 50% B, 50–60 min 50% A and 50% B. The MS and MS/MS analysis was conducted with negative electro-spray ionization (ESI[−]) with a mass scan scope of *m/z* 50–1000.

3. Results and discussion

3.1. Reaction kinetics

Fig. 2a shows that the kinetics of DCF degradation follows a pseudo-first-order relationship within the investigated time scales, demonstrating that the reaction exhibits a first-order dependence on DCF concentration. Hence, the rate of the reaction can be described as follows:

$$-\frac{d[\text{DCF}]_t}{dt} = k_{\text{obs}}[\text{DCF}]_t \quad (1)$$

Integration of Eq. (1) gives:

$$\ln \frac{[\text{DCF}]_t}{[\text{DCF}]_0} = -k_{\text{obs}}t \quad (2)$$

where k_{obs} represents the pseudo-first-order rate constant, $[\text{DCF}]_t$ and $[\text{DCF}]_0$ are the DCF concentration at time t and 0 respectively.

The reaction order relative to Mn(VII) was then investigated with varying Mn(VII) concentrations from 0.4 mM to 1 mM at pH 7. Fig. 2b shows that the k_{obs} is proportional to the increasing Mn(VII) concentration, indicating that the reaction is also first-order with respect to Mn(VII) concentration. The reaction order in Mn(VII) concentration was also plot as $\log k_{\text{obs}}$ vs $\log [\text{Mn(VII)}]$ in Fig. S1. The result showed that the slope is 0.97 ± 0.02 , indicating the Mn(VII)/DCF reaction is actually first-order with respect to $[\text{Mn(VII)}]$. Therefore, the Mn(VII)/DCF reaction is of second-order overall. Eq. (2) can be rewritten as Eq. (3):

$$-\frac{d[\text{DCF}]_t}{dt} = k[\text{Mn(VII)}][\text{DCF}]_t \quad (3)$$

where k represents the second-order rate constant, and k_{obs} is equal to $k[\text{Mn(VII)}]$.

The second-order rate constant at pH 7 and 20 °C was then calculated by Eq. (3) to be $1.57 \pm 0.02 \text{ M}^{-1} \text{ s}^{-1}$. Waldemer and Tratnyek (2006) measured the Mn(VII) oxidation kinetics of some organic contaminants at pH 7 and 20 °C, with values ranging from $9.8 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ to $2.4 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, indicating DCF possesses a relatively high reactivity with Mn(VII) compared with these kinds of reactants. On the other hand, in comparison with other oxidants,

Fig. 2. (a) Pseudo-first-order kinetics plot of DCF degradation at pH 5, 6, 9 ($[\text{DCF}]_0 = 0.02 \text{ mM}$, $[\text{Mn(VII)}] = 0.4 \text{ mM}$, $T = 20 \text{ °C}$); (b) k_{obs} variation along with the change of $[\text{Mn(VII)}]$ at pH 7 and 20 °C.

the Mn(VII)/DCF reaction rate constant is comparable to the chlorine/DCF reaction ($3.89 \pm 1.17 \text{ M}^{-1} \text{ s}^{-1}$) under similar experimental conditions (Soufan et al., 2012).

Additionally, the former studies have shown that alkalinity may have inhibitory effects on compound degradation, such as sonochemical degradation of estrogen hormones process (Suri et al., 2010). While during Mn(VII)/DCF oxidation process, alkalinity appeared to be no obvious effect on DCF degradation (Text S1 and Fig. S2). Therefore, the effect of alkalinity was not considered in the following experiments.

3.2. Effect of temperature

The effect of temperature on the second-order rate constant was then investigated by the Arrhenius equation. As shown in Fig. 3, the $\ln k$ values exhibit a good linearity ($R^2 = 0.99$) with the reciprocal of temperature ($1/T$). The activation energy of the Mn(VII)/DCF reaction was then calculated to be $26.2 \pm 0.4 \text{ kJ mol}^{-1}$, which is comparable to that of Mn(VII)/dichlorvos (29.5 kJ mol^{-1}) and Mn(VII)/microcystins (28.8 kJ mol^{-1}) reactions (Rodríguez et al., 2007; Liu et al., 2009).

3.3. Effect of pH

Fig. 4 shows that the variation of the k value is highly dependent on the pH, with a maximum in slightly acidic media and a minimum in alkaline conditions. A similar pH-dependence of the

Fig. 3. Effect of temperature on the rate constant of Mn(VII)/DCF reaction ($[DCF]_0 = 0.02$ mM, $[Mn(VII)] = 0.4$ mM, pH = 7).

Fig. 4. Effect of pH on rate constants for Mn(VII)/DCF reaction ($[DCF]_0 = 0.02$ mM, $[Mn(VII)] = 0.4$ mM, $T = 20$ °C). The solid line represents the model curve fitted with Eq. (6). Insert shows the calculated species distribution about DCF versus pH ($pK_a = 4.2$).

second-order rate constant was reported during the DCF chlorination process, where the acid-catalyzed reaction between HOCl and DCF were proposed to explain the rapid degradation under acid conditions (Soufan et al., 2012). The rate constants of the biogenic manganese oxides/DCF reaction also increase at decreased pH, which was partly attributed to an altered surface charge of the manganese oxide at neutral pH (Forrez et al., 2010).

On the basis of the acid dissociation constant ($pK_a = 4.2$) (Huber et al., 2003) of DCF, two major species are present in the aquatic environment, the neutral form (DCF^0) and the anionic form (DCF^-). The fractional distribution of two species is shown in the inset of Fig. 4, where DCF^0 is the major form at pH < 4.2, whereas DCF^- is predominant when pH > 6.0. The pH-dependence of k is related to the acid-base speciation distribution of DCF. Thus we divided the Mn(VII)/DCF reaction into two parallel pathways:

where k_1 and k_2 represent specific second-order rate constants of Mn(VII)/ DCF^0 and Mn(VII)/ DCF^- reactions respectively. The second-order rate constant k can be quantitatively modeled as follows:

$$k = k_1 a_1 + k_2 a_2 \quad (6)$$

$$a_1 = \frac{[H]^+}{[H]^+ + K_a} \quad (7)$$

$$a_2 = \frac{K_a}{[H]^+ + K_a} \quad (8)$$

where a_1 and a_2 are the distribution fractions of DCF^0 and DCF^- . K_a represents the hydrolysis equilibrium constant of DCF, and $[H]^+$ stands for the H^+ concentration in the solution.

The solid line in Fig. 4 is the model curve fitted by Eq. (6) with R^2 of 0.99. The values of k_1 and k_2 acquired were $46.53 \text{ M}^{-1} \text{ s}^{-1}$ and $1.52 \text{ M}^{-1} \text{ s}^{-1}$, respectively. It can be seen that k_1 is several times larger than k_2 , suggesting that DCF^0 is more reactive than DCF^- . Considering the electrophilic property of Mn(VII) (Waldemer and Tratnyek, 2006), it seems reasonable that Mn(VII) should be inclined to attack DCF^- , where the ionized carboxylate group possesses more electron-donating capacity compared with carboxylic acid group (Soufan et al., 2012). However, our result was not consistent with this hypothesis. It is well documented that the pH-dependence of the second-order rate constants between Mn(VII) and a large number of organic compounds generally increased with increasing pH, like phenol and lincomycin (Hu et al., 2010; Jiang et al., 2012), or had no obvious pH-dependence, like ciprofloxacin, carbamazepine, and dichlorvos (Hu et al., 2008, 2010; Liu et al., 2009). An opposite case is trimethopaim (Hu et al., 2010), where the second-order rate constants of the Mn(VII)/trimethopaim reaction decreased with increasing pH like those of the Mn(VII)/DCF reaction. This was attributed by the authors to the protonation of the nitrogen atom adjacent to the reacting site increasing the electron-withdrawing character of the amino group, which can in turn enhance the electrophilicity of the reaction site.

In order to explain the pH-dependence of the Mn(VII)/DCF reaction, the primary reactive site of DCF was analyzed. Previous literature (Pérez-Estrada et al., 2005) suggests the C-5 and C-5' carbons are susceptible to attack, due to their relatively large HOMO (highest occupied molecular orbital) coefficients. The C-5 carbon should be the more attractive one, since the two electron-withdrawing chlorine atom substituents near the C-5' carbon could reduce its electron density (Pérez-Estrada et al., 2005; Sein et al., 2008). On the other hand, Sein et al. (2008) pointed out that the primary reaction site of O_3 addition is the amine nitrogen position rather than the aromatic ring during DCF ozonization, based on calculations of the rate constants between O_3 and different reactive sites. Therefore, the most probable reactive site is the C-5 carbon or amine nitrogen position. Additionally, 2,6-dichloroaniline (the left part of DCF as shown in Fig. 1) with a large peak intensity was detected later as a main degradation product, formed though the cleavage of the C–N bond. In addition, Mn(VII) generally prefers to react with electron-rich sites through several competing mechanisms, including direct oxygen addition to olefins, hydrogen abstraction and electron transfer (Waldemer and Tratnyek, 2006). Hence, we propose that the most probable reactive site for Mn(VII) oxidation is the amine position.

In the alkaline condition, the ionized carboxylate group without the restriction of protons may interact with the amine nitrogen moiety, which can reduce the nucleophilicity of the amine nitrogen by inductive and resonance effects, which in turn decreases the initial reaction rate. Additionally, the negative charge of both reagents could play some role in the slow reaction rate at alkaline conditions (Henbest et al., 1966).

3.4. Identification the oxidation by-products

The kinetics experiments suggest that DCF can be rapidly degraded by Mn(VII), yielding a series of degradation products

detected by LC–MS. Fig. 5a shows a representative LC–MS chromatogram of oxidized DCF at pH 7, which contains seven major product peaks in addition to the DCF peak. Most products present greater molecular weights compared with DCF, and some characteristic mass losses like 18 Da ($-\text{H}_2\text{O}$), 28 Da ($-\text{CO}$), 44 Da ($-\text{CO}_2$) and 72 Da ($-\text{CO}-\text{CO}_2$) are observed from the MS fragments, suggesting oxygen insertion into the structure, which may lead to the formation of carboxyl, carbonyl, and alcohol groups (Hu et al., 2008; Jiang et al., 2012).

We formulated these degradation products from P1 to P7 respectively, and proposed possible structures of products P1–P5 on the basis of: (1) the masses of molecular ion peaks and the major fragments of MS/MS spectra; (2) the most probable elemental composition of products; (3) the isotopic distribution characteristics of chlorine atoms and the existence of nitrogen atom in the structure; (4) the information on degradation products from former DCF oxidation processes, including chlorination, UV/ H_2O_2 , ozonization, manganese oxides oxidation, and photo-Fenton oxidation (Miyamoto et al., 1997; Vogna et al., 2004; Pérez-Estrada et al., 2005; Hofmann et al., 2007; Sein et al., 2008; Forrez et al., 2010; Madhavan et al., 2010; Soufan et al., 2012).

The isotopic distribution of ^{35}Cl and ^{37}Cl satisfies the ratio 3:1, which facilitates the identification of the degradation products of DCF (containing two chlorine atoms). The molecular ion peaks of P1–P5 show the isotopic distribution at $M/M + 2/M + 4$ (9:6:1), indicating all these products possess two chlorine atoms in the structures. It is well known that an odd number of nitrogen atom corresponds with an odd molecular weight. These products present the molecular ion peak at m/z 160, 318, 362, 364, 346 in negative mode, suggesting that an odd number of nitrogen atom exists in the structure. Therefore, we deduced that the 2,6-dichloroaniline moiety that contains two chlorine atoms and one nitrogen atom, stayed intact during the oxidation process. The reaction mainly occurs at the nonchlorinated ring of DCF, which is consistent with the former analysis of the primary reactive site. The degradation products of DCF all maintain the 2,6-dichloroaniline moiety during the photo-Fenton oxidation, which is in line with our study (Pérez-Estrada et al., 2005).

DCF: The DCF peak appears at near 37 min as can be seen from Fig. 5a, which is in agreement with the DCF-only case (data not shown). The MS spectrum of DCF shows a strong molecular ion peak at m/z 294 and a weak fragment ion peak at m/z 250. The isotopic peak 294/296/298 with the relative intensity ratio of 9:6:1 indicates the existence of two chlorine atoms in the structure. The fragment m/z 250 (-44) can be attributed to CO_2 loss. The MS/MS spectrum of m/z 294 (Fig. 5b) shows another small fragment at m/z 214, corresponding with HCl loss (-36) compared with m/z 250. Those fragments detected were in accordance with the former studies (Galmier et al., 2005; Soufan et al., 2012).

Product P1: The MS and MS/MS spectra (Fig. 5c) of P1 both show a unique strong peak at m/z 160 without any fragment ion peak, suggesting P1 possesses a relatively stable structure. Additionally, P1 with higher peak intensity was identified as one of the major degradation products, due to the fact that its concentration increased with increasing Mn(VII) dosage (data not shown). Thus we proposed that P1 is 2,6-dichloroaniline, which is easily generated through the cleavage of the C–N bond. 2,6-dichloroaniline was a common degradation product of DCF detected in the former studies (Vogna et al., 2004; Pérez-Estrada et al., 2005).

Product P2–P4: Similar fragmentation patterns and mass differences were observed from the MS/MS spectra of P2, P3, and P4 (Fig. 5d–f), indicating these products may possess analogous structures. The most probable elemental compositions of these products were proposed to be $\text{C}_{12}\text{H}_{10}\text{Cl}_2\text{NO}_5$ (P2), $\text{C}_{13}\text{H}_{10}\text{Cl}_2\text{NO}_7$ (P3), and $\text{C}_{13}\text{H}_{12}\text{Cl}_2\text{NO}_7$ (P4), respectively.

The fragment m/z 160 is dichloroaniline as proposed before. The fragment m/z 202 of P3 can be attributed to dichloroaniline loss (-160) compared with m/z 362, which is an indirect evidence for the cleavage of the C–N bond. The fragments m/z 218, 244 and 320 also contain two chlorine atoms in their structures according to the chlorine isotopic distribution, suggesting they maintain the dichloroaniline structure as well. The most probable elemental composition of m/z 244 proposed is $\text{C}_{10}\text{H}_8\text{Cl}_2\text{NO}_2$, and the composition of the residual part of this fragment (except for dichloroaniline) is $\text{C}_4\text{O}_2\text{H}_4$, indicating that no other benzene ring exists in this structure. Combined with the former hypothesis of the existence of a series of carboxyl, carbonyl, and alcohol groups, we proposed that some ring-opening products were produced. The fragment m/z 218 of P3 and P4 was attributed to a CHCOOH group ($+58$) addition compared with m/z 160, so we inferred dichloroaniline and CHCOOH groups should be an integral part linked by the C–N bond. Then the residual aliphatic chain of P4 ($\text{C}_5\text{H}_6\text{O}_5$) probably contains two carboxylic groups and one hydroxyl group according to the elemental composition analysis.

Hence, we speculate that P3 (m/z 362) represents a two hydrogen atom loss (-2) compared with P4, mostly attributed to the oxidation of the hydroxyl group to a carbonyl group; and P2 (m/z 318) has a HCOOH (-46) group loss compared with P4 through a condensation reaction between carboxyl and hydroxyl groups, leading to the formation of a five-membered heterocyclic structure. The fragment m/z 244 possibly possesses this relatively stable five-membered heterocyclic structure which corresponds to a loss of a CHOHCOOH group (-74) compared with P2 (m/z 318). The possible structures and detailed fragmentation pathways of these three products are summarized in Fig. 5d–f.

Product P5: The MS chromatogram of P5 shows a molecular ion peak at m/z 346, which is proposed to arise from H_2O loss (-18) compared with m/z 364. Therefore, we deduced that P5 contains a double bond in the structure, which can be further transformed to P4 through hydroxylation. The MS/MS spectrum of P5 (Fig. 5g) shows another two peaks at m/z 328 and m/z 288, corresponding to H_2O (-18) and CHCOOH (-58) group loss compared with m/z 346 respectively.

3.5. Reaction pathway and mechanism

Diclofenac may undergo different degradation pathways depending on different treatment processes. Two possible chloride addition reaction pathways were reported for aqueous chlorination of DCF (Soufan et al., 2012). One is an electrophilic substitution on the aromatic ring leading to the formation of chloro-DCF, and the other one is an electrophilic substitution on the nitrogen atom generating a nitrenium cation, followed by further oxidation to form hydroxylation or dehalogenation products. During the DCF ozonization process, the hydroxyl radical could directly attack the nitrogen position of DCF to form the aminyl radical, which could be further oxidized to generate a series of primary reaction products, including 5-hydroxydiclofenac, diclofenac-2,5-iminoquinone and 2,6-dichloroaniline (Sein et al., 2008). Hofmann et al. (2007) proposed some possible reaction pathways, including hydroxylation, dehalogenation or cleavage of the N–H bridge during heterogeneous catalytic DCF oxidation with H_2O_2 . Therefore, on the basis of the degradation products analyzed and prior literature, a possible ring-opening reaction pathway was proposed as shown in Fig. 6.

The reaction mechanism is in agreement with the kinetics results suggesting that the amine nitrogen position is the primary reactive site. Mn(VII) is inclined to attack the N–H site, leading to the formation of two intermediate products. One is 2,6-dichloroaniline (P1), which was formed from the cleavage of the C–N bond. A similar reaction mechanism was reported during the DCF oxidation processes by photo-Fenton, H_2O_2 , or O_3 (Pérez-Estrada et al., 2005;

Fig. 5. (a) A representative LC chromatogram of oxidized DCF at pH 7 ($[\text{DCF}]_0 = 0.2 \text{ mM}$, $[\text{Mn(VII)}] = 1 \text{ mM}$); (b–g) the MS spectra and proposed fragmentation pathways of DCF and products P1–P5.

Fig. 6. Proposed degradation pathways of the Mn(VII)/DCF reaction.

Hofmann et al., 2007; Sein et al., 2008). The other one is 5-hydroxy-diclofenac (Fig. 6), formed through hydroxylation at the C5 position, which possesses a relatively high reaction activity (Pérez-Estrada et al., 2005). 5-hydroxy-diclofenac could be further transformed to diclofenac-2,5-iminoquinone with a quinone-like structure as shown in Fig. 6. This quinone-like intermediate product was first reported by Miyamoto et al. (1997) during the oxidation of DCF with HOCl, myeloperoxidase (MPO), and activated neutrophils. The oxidation of DCF by biogenic manganese oxides was investigated, concluding the formation of 5-hydroxy-diclofenac and diclofenac-2,5-iminoquinone as main degradation products (Forrez et al., 2010). Considering the structural similarities between Mn(VII) and manganese oxides, the formation of these two products was proposed during the Mn(VII) oxidation process as well. Though they were not directly detected in the solution, this was mostly attributed to their further oxidation in the presence of excess Mn(VII).

Diclofenac-2,5-iminoquinone is not stable, and the C3=C4 olefin bond (shown in Fig. 6) can be attacked by Mn(VII) through a 3 + 2 addition or 2 + 2 addition (Yan and Schwartz, 2000; Strassner and Busold, 2001), resulting in hydroxylation products, followed by further oxidation. Further degradation proceeded through a multistep process including ring-opening, decarboxylation, hydroxylation, and cyclation reactions to form a range of products which contain heterocyclic (P2), aldehyde (P3), alcohol (P4) or olefin groups (P5) respectively. Some similar reaction mechanisms for Mn(VII) oxidation were reported previously. The oxidation of 17 β -estradiol with Mn(VII) was investigated by Jiang et al. (2012), suggesting that the phenolic moiety was the primary reactive site and a range of quinone-like and ring-opening products were produced during further oxidation. Zhang et al. (2013) proposed that bisphenol A would undergo a ring-opening reaction when the second hydroxyl was added to the aromatic ring during the Mn(VII) oxidation process.

4. Conclusions

In this work, the detailed kinetics and mechanism were investigated to elucidate the fate of DCF during the Mn(VII) oxidation

process, under environmentally relevant pH from 5 to 9. From a kinetics standpoint, the Mn(VII)/DCF reaction is of second-order overall, first order with respect to each reactant concentration, with the second-order rate constant of $1.57 \pm 0.02 \text{ M}^{-1} \text{ s}^{-1}$ at pH 7 and 20 °C. The reaction activation energy was calculated to be $26.2 \pm 0.4 \text{ kJ mol}^{-1}$. The pH-dependence of the reaction kinetics was obtained, where the DCF reactivity decreased with increasing pH. The apparent second-order rate constants can be quantitatively described by regarding the species distribution of DCF. The individual rate constants between Mn(VII) and two forms of DCF were calculated to be $46.53 \text{ M}^{-1} \text{ s}^{-1}$ (DCF⁰) and $1.52 \text{ M}^{-1} \text{ s}^{-1}$ (DCF⁻) respectively. The amine nitrogen moiety was identified as the most probable primary reactive site, and the lower reactivity of DCF⁻ compared with DCF⁰ was most likely attributable to the interaction between an ionized carboxylate group and amine nitrogen, which can reduce the nucleophilicity of amine nitrogen through inductive and resonance effects. From a mechanism standpoint, seven degradation products were observed and the corresponding structures of five products were proposed at pH 7. Moreover, a detailed ring-opening reaction mechanism was proposed. Mn(VII) should be inclined to attack the amine nitrogen position, leading to the formation of the primary intermediate products 5-hydroxy-diclofenac and 2,6-dichloroaniline. The former intermediate product could be further oxidized through decarboxylation, hydroxylation, or cyclation to form a range of ring-opening products.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.chemosphere.2014.11.062>.

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