Comparative study of degradation of ketoprofen and paracetamol by ultrasonic irradiation: Mechanism, toxicity and DBP formation

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ABSTRACT

The present study comparatively investigated the ultrasonic degradation of ketoprofen (KET) and paracetamol (PCT) in water. Ultrasonic irradiation at 555 kHz achieved rapid degradation of KET and PCT in water, the removal efficiencies of KET (2.5–80 μM) and PCT (2.5–80 μM) reached 87.7%–100% and 50.6%–86.9%, respectively, after 10 min of reaction under an ultrasonic power of 60 W. The degradation behaviors of both KET and PCT followed the Langmuir-Hinshelwood model. KET was eliminated faster than PCT because of its higher hydrophobicity. Acidic media favored ultrasonic degradation of KET and PCT. Organic compounds in water matrices exerted a great negative effect on the ultrasonic degradation rates of KET and PCT major by competing with target compounds with the generated radicals at the bubble/water interfacial region. The effects of anions were species dependent. The introduction of ClO₄⁻ and Cl⁻ enhanced KET and PCT degradation to different extents, while the introduction of HCO₃⁻ posed a negative effect on both KET and PCT. KET and PCT degradation are accompanied by the generation of several transform intermediates, as identified via LC/MS/MS analysis, and disinfection byproducts (DBPs), i.e., trichloromethane (TCM) and trichloronitromethane (TCNM), were found due to chlorination after ultrasonic treatment for both KET and PCT.

1. Introduction

Pharmaceuticals have been excessively used around the world and have side effects on humans and aquatic organisms; therefore, they are one of the main groups of emerging contaminants and thus have attracted great interest around the world in recent years. Among commonly used drugs, nonsteroidal anti-inflammatory pharmaceutical compounds, such as ketoprofen (KET), are often detected in water resources [1]. In addition, paracetamol (PCT) is another pharmaceutical constantly found in aquatic environments [2]. KET is often used as an analgesic and antipyretic for the treatment of muscle pain and inflammation, and certain adverse effects, such as peptic ulcers and diarrhea, are also associated with improper dose [3]. Similar to KET, PCT is also widely employed as an analgesic and antipyretic for relieving pain owing to its few adverse effects and low cost [4]. PCT was reported to cause liver failure due to the formation of a hepatotoxic metabolite (N-acetylindolequinone) [5]. Moreover, some potential deleterious effects of KET and PCT toward aquatic organisms, such as causing metabolic disorders and changing the antioxidant mechanism, have been reported [4,6]. Therefore, it is necessary to remove these pollutants from water and avoid releasing them into aquatic environments.

Among the various methods adopted to remove these pharmaceutical pollutants, advanced oxidation processes (AOPs), which are characterized by the generation of highly reactive hydroxyl (•OH) or sulfate (SO₄•⁻) radicals as the main oxidative species, have attracted great attention as promising methodologies capable of eliminating a wide range of pharmaceuticals from different water matrices [7,8]. UV-based AOPs, electrochemical oxidation, ozonation, Fenton or Fenton-like reactions, and heterogeneous semiconductor photocatalysis are some of the commonly known AOPs. Ultrasonic treatment has long been considered as a promising AOP for removing organic pollutants, including pharmaceuticals, in water [9]. Furthermore, ultrasonic treatment is considered a green technology because it does not require the addition of reagents. Applying ultrasound to water induces the
formation of cavitation bubbles, which will undergo transient collapse events. Three reaction zones, including a hot spot located at the interior of the bubbles, the bubble/water interface, and the bulk solution during the ultrasonic treatment process, are generally acknowledged [10]. At the interior of the bubble, extreme temperatures (>5000 K) and pressures (>500 atm) can be reached during the collapse of the cavitation bubbles. Under such conditions, water and O\textsubscript{2} can pyrolyze to form reactive species, such as \( \cdot \text{OH}, \cdot \text{O}, \text{H} \cdot \) [11]. These reactive radicals produced at the hot spot and bubble/water interface regions may diffuse into the bulk solution. Generally, nonvolatile and hydrophilic compounds were mainly decomposed in the bulk solution via oxidation by radicals, while hydrophobic or volatile compounds more readily diffused into the bubble/water interface or even into the vapor region via decomposition by pyrolysis or radical oxidation. Therefore, the ultrasonic degradation mechanism is highly dependent on the properties of certain compounds, such as the pKa, octanol–water partition coefficient (K\textsubscript{ow}), and Henry’s law constant (K\textsubscript{H}) [12].

In real water matrices, different constituents may exert different degrees of effect on the elimination of organic pollutants by AOPs. Thus, it is necessary to comprehensively investigate the impact of different water matrix components on ultrasonic-induced degradation of target compounds. Moreover, several intermediates or products formed during the oxidative degradation processes might be more toxic than their parent compounds [13]. Thus, it is meaningful to evaluate the toxicity of intermediates accompanied by target pollutant decomposition during ultrasonic treatment, which are important pieces of information for risk assessment of ultrasonic treatment application to \textit{in situ} chemical oxidation (ISCO). However, due to their mutual interaction, such as synergistic, antagonistic, and additive effects, it is difficult to evaluate the toxicity of these oxidation intermediates by traditional chemical analysis. \textit{Vibrio fischeri}, a marine photobacterium, is often adopted to assess the toxicity of degradation intermediates in acute toxicity tests [14]. Exposure to KET containing benzophenone would give rise to undesired photoallergic effects on human skin [15]. While PCT can induce damage to liver cells, long exposure to PCT or overdose PCT can affect liver function [5]. In view of the potential side effects of KET and PCT on human beings, it is reasonable to use umbilical vein endothelial cells (HUVECs), instead of bacteria, to evaluate the toxicity of KET and PCT reaction solutions. Another concern regarding AOP treatment of pharmaceuticals is the impact on the formation of disinfection byproducts (DBPs) during subsequent disinfection processes [16]. Considering that pharmaceuticals, including KET and PCT, commonly exist in natural, it is a matter of concern to investigate their transformation as disinfection byproduct precursors (DBPs). Once AOPs, such as ultrasonic treatment, are integrated into drinking water treatment, it is necessary to investigate the impact of ultrasonic treatment on the downstream disinfection process. Generally, under typical water treatment times, there is almost no complete elimination ability toward these compounds, and they may be transformed into intermediates with structural changes rather than complete mineralization [17,18]. Therefore, exploring the variation of DBP formation potential of pharmaceuticals with and without ultrasonic irradiation would also be applicable for water treatment processes.

Thus, in this respect, this study (i) comparatively investigates the degradation performance of KET and PCT during ultrasonic treatment, (ii) identifies major ultrasonic degradation products of KET and PCT, (iii) assesses the toxicity, and (iv) evaluates the influence of ultrasonic treatment on DBP formation from chlorination of KET and PCT.

2. Materials and methods

2.1. Reagents

KET and PCT were purchased from Sigma–Aldrich (USA) and Aladdind Industrial Co. Ltd. (China), respectively. The selected physicochemical properties of KET and PCT are shown in Table S1. Sodium hypochlorite (5% as Cl\textsubscript{2}) and DBP standards were supplied by Sigma–Aldrich (USA). The free chlorine solution was prepared by diluting a certain amount of sodium hypochlorite into pure water, and its concentration was measured by using a HACH method 8021 with a portable spectrophotometer (HACH Pocket ColorimeterTM\textsuperscript{4}, Loveland, USA). Acetonitrile served as the mobile phase and was obtained from J.T. Baker (USA). Sodium acetate and tert-butyl alcohol were obtained from Aladdin Industrial Co. Ltd. Methanol, isopropyl alcohol, ethyl acetate, sodium perchlorate, sodium chloride, and sodium bicarbonate were purchased from Sinopharm (China). Ultrapure water produced from a Millipore purified water system (USA) was used to prepare all the solutions.

2.2. Ultrasonic treatment experiments

The KET and PCT degradation experiments were carried out in a stainless steel reaction vessel (diameter: 70 mm, height: 100 mm), which is directly connected to an ultrasonic transducer. Ultrasound at 555 kHz was emitted from an ultrasonic generator obtained from Shanghai Acoustics Laboratory of Chinese Academy of Science, China. More details of the ultrasonic reactor have been previously described [19]. The actual ultrasonic power was determined through a calorimetric method [20]. The temperature of the reaction solution was controlled at 20 ± 2 °C by submerging the vessel in a water bath. Typically, 100 mL KET or PCT solution was added to the reaction vessel, and the reaction was operated under an air atmosphere. The initial solution pH was adjusted with 1 M NaOH and/or H\textsubscript{2}SO\textsubscript{4}. Reactions were started by turning on the ultrasonic generator. Sample aliquots were collected at predetermined treatment intervals for analysis immediately.

2.3. DBP formation tests

The DBP formation tests were conducted in 40 mL brown glass bottles without headspace in the dark at 25 ± 1 °C. After ultrasonic pretreatment with 20 μM KET or PCT solution, 0.4 mM chlorine was added to initiate the chlorination reaction. Of note, H\textsubscript{2}O\textsubscript{2} was formed during ultrasonic treatment, thus additional chlorine was first added to the treated KET or PCT solution to quench the formed H\textsubscript{2}O\textsubscript{2}. The initial pH of the samples was kept at 7 by using 10 mM phosphate buffer. After reaction for 24 h, ascorbic acid at a concentration twice the initial normality of the chlorine was added to the bottles to quench the residual chlorine before subjecting the solution to DBP analysis.

2.4. Analytical methods

The KET and PCT concentrations were measured using SHIMADZU high-performance liquid chromatography (HPLC). The chromatograph was equipped with a UV detector set at 260 nm for KET and 242 nm for PCT. The mobile phase for KET consisted of 60%/40% (v/v) acetonitrile and Milli-Q water containing 0.1% formic acid at a flow rate of 0.8 mL/min. The mobile phase for PCT consisted of 20%/80% (v/v) acetonitrile and Milli-Q water at a flow rate of 0.8 mL/min. The H\textsubscript{2}O\textsubscript{2} concentration was determined by using the titanium potassium oxalate method [22]. TOC and TN were measured by a Multi N/C 3100 carbon analyzer (Analytik Jena, Germany). Reaction intermediates and products during ultrasonic treatment were determined by LC–MS/MS. The analytical details are presented in Text S1. The concentration of DBPs was measured by using a purge & trap sample concentrator (eclipse4660, OF, USA) and gas chromatography/mass spectrometry (QP2010, Shimadzu, Japan) [23].

2.5. Toxicity analysis

HUVECs were adopted to evaluate the toxicity of KET and PCT reaction solution. A colorimetric microtiter (MTT) assay was used to measure the assay. Concisely, HUVECs (2000 cells/well) were first
seeded on 96-well plates and cultured in Roswell Park Memorial Institute (RPMI) 1640 medium containing 20% Fetal Bovine Serum (FBS) for 24 h. After starvation in serum-free media for 12 h, the HUVECs were treated with KET- or PCT (10 μL)-induced cells or a sovolumetric solvent control (0.1% dimethylsulfoxide (DMSO)) for 24 h. Then, the cell number was measured using a colorimetric assay based on the ability of mitochondria in viable cells to reduce MTT, and the cell number index was calculated as the absorbance of treated cells/control cells × 100%.

All experiments were replicated three times in parallel, and the mean value was reported. The toxicity of KET and PCT as well as their transformation intermediates/products were also evaluated by the quantitative structure–activity relationship (QSAR) method by using the Toxicity Estimation Software Tool (T.E.S.T.).

3. Results and discussion

3.1. Effect of initial concentration

Fig. 1 shows the degradation behaviors of KET and PCT during their sonochemical degradation at 555 kHz, 60 W of actual power and initial concentrations of 2.5, 5, 10, 20, 40 and 80 μM. During this study, the initial degradation rate (μM/min) rather than the pseudo first-order kinetic constant was used to compare sonochemical degradation kinetics under different runs because degradation also depends on the initial concentration of the target compound [24]. Obviously, the extent of degradation for KET and PCT is inversely proportional to their initial concentration, although their initial degradation rate increases with an increase in the initial concentration. For instance, almost complete removal of KET was achieved within 4 min, while the removal rate of KET with an initial concentration of 80 μM decreased to 87.7% at 10 min. However, the initial degradation rate improved from 0.79 to 10.29 μM/min as the initial KET concentration rose from 2.5 to 80 μM. A similar trend was also observed for PCT; after 10 min of sonolysis, the extent of degradation decreased from 86.9% to 50.6%, although the initial degradation rate improved from 0.61 to 5.71 μM/min as the initial PCT concentration rose from 2.5 to 80 μM.

Generally, ultrasonically induced degradation of organic pollutants in water via two mechanisms, (i) direct pyrolysis and (ii) oxidation by the reactive radicals produced during cavitation, and the degradation degree of target pollutants is largely associated with the partitioning of these compounds to the bubble, bubble/water interface and bulk liquid regions [10]. Langmuir-Hinshelwood kinetic model (Eq. (1)) was used to simulate the ultrasonic degradation process of KET and PCT [25].
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Fig. 3. Effect of the initial solution pH on (a) KET and (b) PCT degradation by ultrasonic treatment. Experimental conditions: frequency: 555 kHz, power: 60 W, [KET]₀ = [PCT]₀ = 20 μM.

\[
\frac{1}{t_0} = \frac{1}{k_0 KC_0} + \frac{1}{k_r}
\]

where \( t_0 \) (μM/min) is the initial degradation rate, \( C_0 \) (μM) is the initial concentration, \( k_0 \) (μM/min) is the reactivity constant, and \( k_r \) (μM⁻¹) is the equilibrium constant.

Based on Eq. (1), plots of \( 1/t_0 \) versus \( 1/C_0 \) for KET and PCT are also shown in Fig. 1. The experimental data for both the KET and PCT ultrasonic degradation processes were well fitted by the L-H-based model (R² > 0.99), indicating that the bubble/water interface is the major reaction zone for the ultrasonic degradation of KET and PCT. Two parameters of the L-H model, \( k_0 \) and \( K \), can be determined from the intercept and slope of the fitting straight line. The reactivity constants (\( k_0 \)) were 11.12 and 9.89 μM/min for KET and PCT, respectively, and the equilibrium constants (\( K \)) were 0.033 and 0.021 μM⁻¹ for KET and PCT, respectively. Therefore, the degradation process of the two compounds was associated with the amount of •OH radicals produced and their concentration in the region of the bubble/water interface. Because the steady-state •OH concentration at the bubble/water interfacial region is quite high, •OH self-recombination would be the dominant reaction when the initial concentration of the target pollutant is relatively low, which reduces the degradation rate [26]. In contrast, when the initial concentration of the target pollutant was higher, the chance of •OH radical attack on the target pollutant increased, resulting in an increase in the degradation rate. In addition, the degradation efficiency of KET is higher than that of PCT under various initial concentrations. Generally, strong correlations have been reported between sonochemical degradation rates and various physicochemical properties of the target organic compounds. Organic compounds with higher hydrophobicity more readily accumulate at the bubble/water interface, where the concentration of •OH radicals is higher than that in the bulk solution, which in turn achieves a faster sonochemical degradation rate. KET has a higher log \( K_{ow} \) and Henry’s law constant and lower water solubility than PCT (Table S1); therefore, it is not unexpected that the sonochemical degradation rate of KET is faster than that of PCT.

3.2. Effects of radical scavengers

To further explore the roles of •OH in different reaction regions in the sonochemical degradation of KET and PCT, acetate (AA) and tert-butyl alcohol (TBA) were added during ultrasonic treatment (Fig. 2). AA will reside in the bulk solution and is expected to react with •OH in the bulk solution rather than from the interfacial and vapor phase regions. On the other hand, TBA is a volatile •OH scavenger and expected to scavenge •OH in the vapor and interfacial regions [27,28]. As seen, the presence of AA slightly hindered KET and PCT degradation, and the degradation efficiency of KET and PCT decreased from 97.0% and 69.9% to 93.0% and 52.0%, respectively, as the concentration of AA increased from 0 to 4 mM. However, the presence of TBA largely inhibited KET and PCT degradation, especially PCT. The degradation efficiency of KET and PCT decreased to 34.3% and 3.1%, respectively, as the TBA increased to 4 mM. These results indicated that •OH-induced oxidation of KET and PCT mainly occurred at the gas–liquid interface and, to a much lesser extent, in bulk solution.

3.3. Effect of pH

The effect of the initial solution pH on KET and PCT degradation was examined, and the results are shown in Fig. 3. The sonochemical degradation of KET and PCT is favored under acidic media, and the degradation efficiency decreases as the initial solution pH increases. As stated earlier, both KET and PCT are nonvolatile compounds, and the region of degradation would not be expected at the interior of the cavitation bubble; therefore, the reaction between the generated radicals and KET or PCT would be enhanced if their hydrophobicity is favored because the concentration of •OH at the bubble/water interface was much higher than that at the bulk solution [26]. At low pH values, KET was mainly in its nonionized form, as indicated by its pKa value of 4.45 (Fig. S1). However, at higher pH, KET was mainly in its ionized negatively charged form, which led to the reduction of its hydrophobicity and the tendency of KET to migrate into bulk solution, where a lower concentration of •OH radicals are available, resulting in a slow down on degradation rate. Similarly, since the pKa of PCT is 9.38, its distribution was calculated, as shown in Fig. S1. PCT mainly exists in its ionized form at pH < 9.38, and when pH > 9.38, PCT is in its ionized form. Accordingly, PCT is mostly found in its molecular form at pH 3, 5 and 7, and PCT gradually becomes ionized as the pH further increases. The ionized form of PCT reduced its hydrophobicity, and PCT would degrade in the bulk solution where a lower concentration of •OH radicals are available. Furthermore, at a relatively lower pH, the recombination of •OH is relatively less effective before reacting with the substrate because most target compounds are concentrated at the bubble/water interface [29]. In addition, according to the Nernst equation (\( E_{OH} = E^{\circ}_{OH/H_2O} - 0.059pH \)), •OH in acidic media would expect to exhibit a higher redox potential than in alkaline media [30].
3.4. Effect of organic matter

The effects of three different organic compounds, methanol (MeOH), isopropyl alcohol (IPA), and ethyl acetate (EA), at different concentrations (1–5 mM) on the KET and PCT ultrasonic degradation rate constants are shown in Fig. 4. All the organic compounds exhibited an inhibiting effect on the degradation of the target compounds, and the inhibition degree increased with increasing organic compound concentration. Furthermore, at any specific organic compound level, the extent of inhibition of the organic compounds followed the order EA > IPA > MeOH. For instance, in the presence of 5 mM EA, IPA and MeOH, the initial degradation rate constant of KET dropped by 85.8%, 75.3%, and 23.3%, respectively, and the initial degradation rate constant of PCT dropped by 97.5%, 93.9%, and 74.8%, respectively.

The negative impact of the organics can be explained as follows. First, organic molecules adsorb onto the bubble/water interface, which is the main region for the decomposition of KET and PCT. Therefore, the presence of organics would compete with KET or PCT for •OH due to the fairly fast reaction rates between these organics and •OH. The reported reaction rate constants between •OH and methanol, isopropyl alcohol, and ethyl acetate were $9.7 \times 10^8$ M$^{-1}$ s$^{-1}$, $1.9 \times 10^9$ M$^{-1}$ s$^{-1}$, and $4.8 \times 10^9$ M$^{-1}$ s$^{-1}$, respectively [31]. Second, these organics, as volatile organic compounds (VOCs), evaporate into the vapor phase within microbubbles and reduce the bubble vapor and interfacial temperatures during transient bubble collapse events by increasing the specific heat capacity of the bubble vapor and consuming energy via the endothermic dissociation of these organic vapors [32]. Third, a previous study indicated that the inhibition magnitude of a certain organic compound on the bubble and interfacial temperatures has a closer relationship with Henry’s law constant, specific heat capacity, and overall endothermic heat of dissociation [33]. Table S2 summarizes Henry’s law constants and the specific heat capacities of the tested organic compounds. Generally, a compound with a higher Henry’s law constant can more readily enter the bubble vapor phase and thus reduce the sites available for the target compound. The presence of organics in the bubble vapor phase with larger specific heat capacities can reduce the maximum bubble and interfacial temperatures created during bubble collapse.

3.5. Effect of anions

The effects of three common anions (1–10 mM), including ClO$_4^-$, Cl$^-$, and HCO$_3^-$, on the degradation rate of KET and PCT are shown in Fig. 5. All the anions exhibited an inhibiting effect on the degradation of the target compounds, and the inhibition degree increased with increasing anion concentration. Furthermore, at any specific anion level, the extent of inhibition of the anions followed the order ClO$_4^-$ > HCO$_3^-$ > Cl$^-$. For instance, in the presence of 10 mM ClO$_4^-$, Cl$^-$, and HCO$_3^-$, the initial degradation rate constant of KET dropped by 97.5%, 93.9%, and 74.8%, respectively, and the initial degradation rate constant of PCT dropped by 100%, 97.5%, and 93.9%, respectively.

The negative impact of the anions can be explained as follows. First, anions adsorb onto the bubble/water interface, which is the main region for the decomposition of KET and PCT. Therefore, the presence of anions would compete with KET or PCT for •OH due to the fairly fast reaction rates between these anions and •OH. The reported reaction rate constants between •OH and ClO$_4^-$, Cl$^-$, and HCO$_3^-$ were $4.8 \times 10^8$ M$^{-1}$ s$^{-1}$, $1.9 \times 10^9$ M$^{-1}$ s$^{-1}$, and $9.7 \times 10^8$ M$^{-1}$ s$^{-1}$, respectively [34]. Second, these anions, as volatile inorganic compounds (VICs), evaporate into the vapor phase within microbubbles and reduce the bubble vapor and interfacial temperatures during transient bubble collapse events by increasing the specific heat capacity of the bubble vapor and consuming energy via the endothermic dissociation of these inorganic vapors [35]. Third, a previous study indicated that the inhibition magnitude of a certain inorganic compound on the bubble and interfacial temperatures has a closer relationship with Henry’s law constant, specific heat capacity, and overall endothermic heat of dissociation [36]. Table S3 summarizes Henry’s law constants and the specific heat capacities of the tested inorganic compounds. Generally, a compound with a higher Henry’s law constant can more readily enter the bubble vapor phase and thus reduce the sites available for the target compound. The presence of anions in the bubble vapor phase with larger specific heat capacities can reduce the maximum bubble and interfacial temperatures created during bubble collapse.
Cl\(^-\), and HCO\(_3\)^- on the KET and PCT ultrasonic decomposition rate constants are shown in Fig. 5. As seen, their effects are different. For example, \(r_0/\bar{r}_{\text{control}}\) decreased with increasing HCO\(_3\)^- concentration, while at 10 mM HCO\(_3\)^-, \(r_0/\bar{r}_{\text{control}}\) dropped by 13.5% and 17.6% for KET and PCT, respectively. In contrast, the degradation rate increased in the presence of ClO\(_4\)^- and Cl\(^-\) to different extents. Specifically, the promoting effect of ClO\(_4\)^- or Cl\(^-\) toward PCT was higher than that of KET at the same anion concentration. At 10 mM ClO\(_4\)^-, the initial degradation rate constants of KET and PCT increased by 4.8% and 25.7%, respectively, while at 10 mM Cl\(^-\), the initial degradation rate constants of KET and PCT increased by 3.2% and 18.0%, respectively.

The negligible effect of HCO\(_3\)^- on both KET and PCT ultrasonic decomposition is likely due to the reaction between •OH and HCO\(_3\)^- to generate less reactive carbonate radicals (CO\(_3\)^\(\cdot\)), which have been commonly observed to reduce sonochemical degradation [34]. A positive effect of HCO\(_3\)^- was also observed during the ultrasonic degradation process [19,35]. Compared with •OH, CO\(_3\)^\(\cdot\) is a more selective oxidant that can readily react with electron-rich compounds containing aniline, phenolic hydroxyl groups and naphthalene rings [36]. According to Mahdi et al., the self-recombination of •OH would occur when the concentration of the target pollutant is low, and the self-recombination rate of CO\(_3\)^\(\cdot\) (2 \times 10^9 M^{-1} s^{-1}) is far less than that of •OH (5.5 \times 10^9 M^{-1} s^{-1}) [35]. Therefore, although the oxidation ability of CO\(_3\)^\(\cdot\) is lower than that of •OH, a lower recombination rate of CO\(_3\)^\(\cdot\) than •OH can compensate for its oxidation ability to some extent. Therefore, whether HCO\(_3\)^- exhibits an inhibitory effect or an accelerating effect is largely dependent on the initial concentration of the target pollutant as well as its molecular structure.

The promoting effect of ClO\(_4\)^- or Cl\(^-\) may be due to the following: first, the "salting out effect" enables the target compounds to move toward the reactive interfacial region of the cavitation bubble, where more •OH is located; second, the presence of these salts reduces the amount of dissolved gas and therefore reduces bubble coalescence, generating a greater number of small bubbles with higher sonochemical activity [37]. In addition, according to Cheng et al., the presence of ClO\(_4\)^- or Cl\(^-\) would also influence bubble-water interfacial properties, i.e., surface potential and interfacial water structure, which is also beneficial for target compound sonochemical degradation [38].
proposed, as shown in Fig. 6. Studies, the degradation pathways of KET and PCT were tentatively identified. Their mass spectra were provided in Fig. S2-S3. Based on the identified intermediate products and previous ultrasonic system. Seven products of KET and five products of PCT were detected in the SO based system and was also considered to be initiated by decarboxylation, followed by rearrangement and hydroxylation [43]. Fig. 6(b) shows the degradation pathway during ultrasonic treatment of PCT. The intermediate products obtained here are in line with those reported by other OH-based oxidative processes [44,45]. Pathway I arose from the hydroxylation of the aromatic ring of PCT, resulting in the formation of DP1, corresponding to the hydroxylated product of PCT [44]. Then, the cleavage of the aromatic ring of DP1 leads to the formation of a ring opening product, DP2 [45]. Pathway II started from the attack of the •OH on the para position to the phenolic functional group, leading to hydroquinone formation, and successive oxidation of hydroquinone would yield DP3 [45]. Pathway III initiated the attack of •OH on the acetyl-amino group, leading to the formation of DP4, which was then oxidized to DP5 [46].

3.6. Transformation products and pathways

To further clarify the degradation mechanism of KET and PCT, LC/MS/MS was performed to identify the intermediates and products in the ultrasonic system. Seven products of KET and five products of PCT (Tables S3-S5) were identified. Their mass spectra were provided in Fig. S2-S3. Based on the identified intermediate products and previous studies, the degradation pathways of KET and PCT were tentatively proposed, as shown in Fig. 6.

As shown in Fig. 6(a), KET was degraded by three routes. As a nonselective oxidant, •OH tends to react with organic compounds via three major mechanisms, namely, hydroxyl addition to unsaturated carbon, hydrogen abstraction, and electron transfer. Therefore, pathway I was characterized by hydroxylation, which was initiated by the attack of •OH on the unsaturated carbon of KET, i.e., aromatic ring of KET, resulting in the formation of a monohydroxylated product, DP1. Further attack by •OH led to an aromatic ring-opening product derived from meta-cleavage. Subsequently, this transformation product yields 2-(3-carboxy (hydroxy)-methyl) phenyl) propanoic acid (DP3). On the other hand, decarboxylation dominates degradation pathway II. First, abstraction of hydrogen atoms from carboxylic groups of KET by •OH leads to the formation of KET•, and then benzylic radicals can be formed after elimination of CO2 [40]. Benzylic radicals can also be formed by UV irradiation via photoionization, which is considered the main transformed intermediate responsible for decarboxylation products [41]. Then, benzylic radicals could transform into 3-ethylbenzophenone (DP4) with the addition of H• [40]. With further •OH attack, 2-(3-(carboxy (hydroxy)-methyl) phenyl) propanoic acid (DP5) and 3-(1-hydroperoxyethyl) benzophenone (DP6) would be formed accordingly [42]. Another degradation product, DP7, showed a mass spectral base peak at m/z 245.08, which was also detected in the SO•• -based system and was also considered to be initiated by decarboxylation, followed by rearrangement and hydroxylation [43]. Pathway III started from the attack of the •OH on the para position to the phenolic functional group, leading to hydroquinone formation, and successive oxidation of hydroquinone would yield DP3 [45]. Pathway II initiated the attack of •OH on the acetyl-amino group, leading to the formation of DP4, which was then oxidized to DP5 [46].

3.7. Toxicity assessment

HUVECs were used to assess the toxicity of the reaction solution. Fig. 7 shows the toxicity changes of intermediates during ultrasonic degradation of KET and PCT. The cell viability of untreated initial KET and PCT solutions were 53.9% and 65.1%, respectively. As the reaction proceeded, the cell viability slightly increased and the toxicity of the solution decreased, which indicated that ultrasonic treatment is capable of controlling the toxicity of the reaction solution. The toxicity of the two compounds as well as their possible degradation products were also evaluated by using T.E.S.T. on the Quantitative Structure-Activity Relationship (QSAR).

Fig. 8(a) shows that products with m/z 211 and m/z 217 exhibited higher toxicity than KET since they have a lower LC50 than that of KET (LC50 represents a concentration that causes 50% lethality to fathead minnows after 96 h). Although m/z 227 has a higher LC50 value than that of KET, it can still be categorized as “very toxic”, which also deserves attention. However, most identified degradation products have higher toxicity than PCT, except for m/z 200 due to the breaking of aromatic rings (Fig. 8(b)). As seen from Fig. 8(c), except for m/z 227 and m/z 211, the bioaccumulation factors of the other degradation products are lower than that of KET. However, the products of PCT with m/z 127, m/z 110 and m/z 140 need to be considered because they have higher bioaccumulation factors than their parent compounds. Although the overall toxicity estimated by HUVECs revealed a decrease in the toxicity of KET and PCT by ultrasonic treatment, the toxicity estimated by T.E.S. T. revealed that the degradation of KET and PCT may form products with higher toxicity; therefore, a higher degree of mineralization is needed to ensure water safety after ultrasonic treatment. Therefore, we should not only pay attention to the elimination of parent organic compounds but also disregard the elimination of their transform intermediates during oxidative processes.

3.8. DBP formation

Fig. 9 exhibits DBP formation from chlorination of the ultrasonically treated KET and PCT solutions. As shown, the trichloromethane (TCM) concentration generated from PCT after 24 h of chlorination was 79.3 µg/L, which was nearly 5.2 times that generated from KET. Generally,
DBP formation mainly depends on the chlorine reactivity of the structure of the target organic matter. Furthermore, organics with low molecular weights are more likely to undergo ring opening reactions and hydrolysis to form DBP via halogenation reactions during chlorination [47]. The amide functional group of PCT increased the electron density of the aromatic ring, making it easily attacked by chlorine through electrophilic substitution. Then, it induces the successive replacement of hydrogen by chlorine and afterward forms TCM through the haloform reaction [48]. The low reactivity of KET toward chlorine was also reported by Noutsopoulos et al. [49]. Since there is no N atom in the molecular structure of KET, no N-DBPs (i.e., dichloroacetonitrile (DCAN) and trichloronitromethane (TCNM)) was expected to be formed from direct chlorination of KET. For PCT, DCAN was also detected from direct chlorination, which is consistent with a previous study [48]. Organic matter containing amino groups (–NH₂ or –NH-) may serve as a precursor of HANs such as DCAN [50]. However, no TCNM was detected from the chlorination of PCT because chlorine can hardly oxidize amine groups in PCT due to the adjacent electron-drawing carbonyl group [51].

As seen, ultrasonic pretreatment significantly influences the formation of DBPs from chlorination of both KET and PCT. Compared with direct chlorination, the DBP species and their concentrations after ultrasonic pretreatment were substantially changed. With increasing pretreatment time from 0 to 15 min, the formation of TCM exhibited an increasing and then decreasing pattern for both KET and PCT. The maximum formation of TCM occurred at 10 min, with concentrations of 290.6 and 171.8 μg/L for KET and PCT, respectively. Our observed phenomenon was consistent with previous related study [21]. The intermediates of KET or PCT contain hydroxylate aromatic structures or ring opening products arising from •OH attack and may become more reactive toward chlorine, thus increasing the subsequent formation of TCM during chlorination. However, another study reported that the UV/H₂O₂ pretreatment process reduced the formation of TCM during the postchlorination of chloramphenicol [52]. Therefore, the impact of peroxidation on the formation of DBPs may depend on the extent of mineralization of the organic matter as well as the structure of the precursors. Of note, it was an interesting finding that ultrasonic pre-treatment enhanced the formation of TCNM during postchlorination. Both KET and PCT exhibited a similar trend for TCNM formation after ultrasonic treatment, and the TCNM concentration increased monotonically with increasing ultrasonic treatment time. The amine groups of PCT may be partially transformed into nitro groups by ultrasonic treatment, which promotes TCNM formation [17]. Special attention should be paid to the formation of TCNM from KET since its structure does not contain an N atom. In fact, in addition to •OH, reactive nitrogen species (RNSs), such as •NO and •NO₂, may also be formed through “nitrogen fixation” in the sonochemistry [53]. These RNSs may lead to the formation of intermediates containing nitrogenous compounds, which could serve as TCNM precursors [54]. The TN for the initial KET and PCT solutions was 0 and 0.33 mg/L, while after 15 min of ultrasonic irradiation, the TN increased to 1.83 and 2.21 mg/L for the KET and PCT solutions, respectively, which also verified that the nitrogen fixation phenomenon occurred during the ultrasonic treatment. Thus, special attention should also focus on the effects of AOPs in actual water treatment processes.

4. Conclusion

The degradation differences of KET and PCT were compared in ultrasonic treatment. Typically, under an actual power of 60 W, both KET and PCT could be rapidly decomposed in water under 555 kHz ultrasonic irradiation. KET exhibited faster degradation than PCT, as
manifested in a greater initial degradation rate, which is associated with its hydrophobicity. Both KET and PCT were mainly degraded via ‘OH oxidation at the bubble/water interface. Acidic media was favored for sonochemical degradation of KET and PCT. The coexistence of organic matter exerted negative effects on KET and PCT degradation, and the inhibition effect followed the order ethyl acetate > isopropyl alcohol > methanol, which is associated with Henry’s law constant and the specific heat capacity of these organics. Both ClO₄⁻ and Cl⁻ slightly enhanced the sonochemical degradation of KET and PCT. HCO₃⁻ has a negative effect on sonochemical degradation. According to the transformation products identified by LC/MS/MS, the degradation pathways of KET and PCT were proposed. Although several transformation products exhibited more toxicity than their parent compounds, as reflected by the T.E.S.T. program; nevertheless, the overall toxicity of both the KET and PCT reaction solutions was decreased, as assessed by HUVECs. Of note, ultrasonic pretreatment may increase the risk of enhancing DBP formation.

Fig. 9. Formation of DBPs derived from (a) KET and (b) PCT during chlorination without and with ultrasonic pretreatment. Experimental conditions: frequency: 555 kHz, power: 60 W, [KET]₀ = [PCT]₀ = 20 μM, [chlorine]₀ = 0.4 mM, chlorination time = 24 h.
during subsequent chlorination. Therefore, its effects on the downstream disinfection process need to be considered when integrating ultrasonic treatment into water treatment.

CRediT authorship contribution statement

Yu-qiong Gao: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. Jia Zhang: Data curation, Formal analysis, Visualization, Writing – original draft. Yan-yan Rao: Formal analysis, Visualization. Han Ning: Data curation, Formal analysis. Jia Zhang: Data curation, Visualization. Jun Shi: Methodology. Nai-yun Gao: Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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