

Insight into the Mechanism of the OH-Induced Reaction of Ketoprofen: A Combined DFT Simulation and Experimental Study

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ABSTRACT. The OH-induced reactions are the most important reactions for the degradation of pharmaceutical and personal care products (PPCPs) in advanced oxidation process (AOP) systems. In this work, the transformation mechanisms of a typical PPCP, ketoprofen (KP), are investigated in detail by combined density functional theory (DFT) simulations and laboratory experiments. We find that Habstraction pathways are preferred in the OH-initiated reactions, and the influence of the hydrogen bond between the OH radical and the carboxyl group cannot be neglected. The subsequent decarboxylation and decomposition reactions are likely to occur. In addition, under highly acidic condition, the protonation of the carbonyl group in KP or in other benzophenone-like compounds might inhibit the decomposition reactions. Meanwhile, the simulation results are well supported by the Fenton experiments.

Keywords: ketoprofen, advanced oxidation processes, transformation mechanism, decomposition reaction, DFT method

1. Introduction

Pharmaceutical and personal care products (PPCPs) contain a wide and extraordinarily varied group of organic compounds (Zhang et al., 2014; Xiao et al., 2015; O'Brien et al., 2017; Song et al., 2018; Xin et al., 2019). Because of their persistent input and potential threat to the ecological environment and human health, PPCPs have received increasing attention in recent years (Stuer-Lauridsen et al., 2000; Boyd et al., 2003; Hu, 2005; Evgenidou et al., 2015; Papageorgiou et al., 2016). Ketoprofen (KP), which is known as (RS)-2-(3-benzoylphenyl)-propionic acid, is a commonly used non-steroidal anti-inflammatory drug (NSAID) for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, non-rheumatoid diseases and postoperative pain (Cathcart et al., 1973; Tixier et al., 2003; Mirzaei et al., 2017). However, this pharmaceutical contains a benzophenone structure, which experiences photosensitization and causes undesired photo-allergic effects on human skin, such as hypersensitivity and myasthenia gravis. KP can also form an immunogenic complex, which causes an allergic reaction (Tokura, 2000; Musa et al., 2007; Zhao et al., 2020). Thus, type of pharmaceutical is a

potential pollution source without immunogenic complex, which causes an allergic reaction this suitable treatment when it is widely used. An investigation into the removal of this type of PPCP from aqueous environments is greatly needed.

However, PPCPs such as KP cannot be effectively eliminated by conventional wastewater treatment (Rene et al., 2008; Keen and Linden, 2013; An et al., 2016; Hasan et al., 2016). The removal efficiencies of KP in water treatment plant have been reported as 13 and 38% in Finland and Canada, respectively (Vieno et al., 2007; McKie et al., 2016). Advanced oxidation processes (AOPs) have been included in wastewater treatment to either improve the water biodegradability or promote the elimination of contaminants (Zhao, 2016; Lian et al., 2017; Zhang et al., 2019). A study on pilot-scale experiments was conducted by Borikar, Mohseni et al. (2015), and the results revealed that a conventional water treatment plant equipped with AOPs showed a marked improvement in PPCP removal from 26 to 97%. AOPs involve degradation through ozone/UV, UV/H₂O₂, Fenton and Fenton-like oxidation, gamma radiolysis, sonolysis, and electrochemical oxidation. Different AOP techniques are widely used, and the essence of AOPs is based on the formation of a strong oxidant, namely, the hydroxyl radical (OH·). In a sufficient quantity, the OH radicals can affect the chemical degradation of contaminants (Wols et al., 2013; Dewil et al., 2017; Zhang et al., 2019; Huang et al., 2020).

To our knowledge, the studies of KP degradation through AOPs in aqueous environments have been primarily per-

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formed in laboratory experiments. E.G. Illés et al. (2014) evaluated the KP degradation using the combined O₃/UV method, and high mineralization degree of 95% was achieved. In another study, the same authors demonstrated that KP was effectively destroyed by irradiating dilute aqueous solutions, and the products during the degradation were less toxic than KP (Illés et al., 2012). The UV and UV/vacuum-UV (VUV) photodegradation processes of KP and ibuprofen were investigated by Szabó et al., (2011). The degradation of KP was completed in 90 s using the UV/VUV system. In these studies, many by-products were detected, and several plausible degradation pathways were proposed. However, little information about the transformation mechanisms in AOP systems was reported.

Quantum chemical calculations has proven to be a powerful tool to obtain deeper insights into the reaction mechanisms and kinetics. These calculations are not only a valuable complement to experimental studies, but also a cost-effective method to investigate and design the reactions (Shi et al., 2015; Gallego et al., 2017; He et al., 2017; Jing and Chaplin, 2017; Li et al., 2017; Hong et al., 2018; Liu et al., 2018; Xie et al., 2018). For example, Hong et al. (2018) synthesized a series of new iridium catalysts on the basis of the DFT design idea. As far as KP was concerned, the UV-induced decomposition of ketoprofen was investigated using both density functional theory (DFT) and experimental methods (Musa et al., 2007; Martínez et al., 2013; Liu et al., 2019; Yu et al., 2019). Nevertheless, as the most important oxidation reaction, the OH-induced reaction mechanism of KP in AOP systems has not been studied in detail.

In this study, both DFT simulations and Fenton experiments were used to investigate the mechanisms of the OH-induced transformation of KP in AOP systems. All possible initiation pathways of KP with the OH radical were proposed, and their rate constants were calculated. The main subsequent decarboxylation and decomposition reactions were further investigated. Meanwhile, Fenton experiments were performed, and several intermediates were identified by ultra-performance liquid chromatography-mass spectrometry (UPLCMSn). Moreover, the calculated results were compared with the experimental results to verify the accuracy of the computational methods. To the best of our knowledge, this is the first DFT study concerning the decomposition reactions of benzophenone structures in the aqueous phase, which can contribute to a deeper understanding of the reaction mechanisms.

2. Methodology

2.1. Computational Methods

The theorems at the core of DFT state that the energy of a many-electron system in its ground state is fully defined by its electron density distribution. In DFT, the total energy of the particle (typically electrons) system, $E[\rho]$, is calculated by the Kohn-Sham equation:

$$E[\rho] = T_s[\rho] + \int dr v_{\text{ext}}(r) \rho(r) + E_H[\rho] + E_{\text{xc}}[\rho] \quad (1)$$

where T_s is the Kohn-Sham kinetic energy, v_{ext} is the external potential acting on the interaction, E_H is the Hartree (or Coulomb) energy, ρ is the density for an N-particle system, and E_{xc} is the exchange-correlation energy. A detailed description can be found in Kohn and Sham's study (Kohn and Sham, 1965). In this equation, E_{xc} is an empirical parameter, and the exact value cannot be obtained. Thus, choosing proper density functional approximations is crucial for a specific system in practical applications. In the last decade, the M06-2x functional has proven to be one of the best for calculating the main group thermochemistry and kinetic parameters, particularly for studying noncovalent interactions (Zhao and Truhlar, 2008). Numerous studies have shown that the simulation results have a high consistency with the experimental results (Peverati and Truhlar, 2011; Cohen et al., 2012; Medvedev et al., 2017; Sato et al., 2018; Liu et al., 2020; Shen et al., 2020; Yao et al., 2020).

The DFT simulation in this study was performed using the Gaussian 09 package (Frisch et al., 2009). The basis sets were selected according to the accuracy and computational time. The geometrical parameters of reactants, intermediates (IM), transition states (TS), and products were optimized by the M06-2X functional with the 6-311+G(d,p) basis set. The frequencies for the stationary points were obtained at the same level with an optimizing step. Each transition state was verified to connect the designated reactants and products by performing an intrinsic reaction coordinate (IRC) analysis (Fukui, 1981). To accurately obtain the total electronic energies, single-point energies were calculated at more flexible M06-2X/6-311++G(3df,2p) levels. For all energies, the zero-point energy (ZPE) corrections were included (Alecú et al., 2010). The solvent effects were considered in all work by using the SMD continuum solvent models (Marenich et al., 2009). In this article, the potential barriers (ΔE) and reaction heats (ΔH) were calculated as follows:

$$\Delta E = E(TS) - \sum E(Reactants) \quad (2)$$

$$\Delta H = E(IM) - \sum E(Reactants) \quad (3)$$

where $E(TS)$, $E(IM)$ and $E(Reactants)$ are the electronic energy values of TS, IM and the sum of the electronic energies of the reactants, respectively.

Frontier electron density (FED) was calculated based on Fukui's frontier orbital theory in which the sum of each electron $[(C_{ri}^{\text{HOMO}})^2 + (C_{ri}^{\text{LUMO}})^2]$ has the highest density when the electrons are in the HOMO and LUMO (Fukui et al., 1954). According to this theory, the FED can be calculated as:

$$f_r = \sum_i (C_{ri}^{\text{HOMO}})^2 + \sum_i (C_{ri}^{\text{LUMO}})^2 \quad (4)$$

where C^{HOMO} and C^{LUMO} are the orbital coefficients in the HOMO and LUMO, respectively. r is the number of carbon atoms in i: 2s, 2px, 2py, and 2pz orbitals.

The bond dissociation energy (BDE) is a good thermo-

dynamic parameter to predict the bond strength of organic compounds (Vleeschouwer et al., 2008). The BDE in this study was calculated as:

$$\Delta E_{bde}(R-R') = [E(R) + ZPE(R) + E(R') + ZPE(R')] - [E(KP) + ZPE(KP)] \quad (5)$$

where $E(KP)$, $E(R)$ and $E(R')$ represent the energies of KP and radicals R and R', respectively. $Zpe(R)$, $Zpe(R')$ and $Zpe(KP)$ are the corresponding zero-point energies.

With the above thermodynamic information, the reaction kinetics were calculated using the conventional transition state theory (TST) as follows (Tiwari and Mishra, 2016):

$$k(T) = \sigma \Gamma(T) \frac{k_b T}{h} \exp\left(-\frac{\Delta E}{RT}\right) \quad (6)$$

where K_B and h are Boltzmann's and Planck's constants, respectively; ΔE is the potential barrier; σ is the reaction path degeneracy, which accounts for the number of equivalent reaction paths; and $\Gamma(T)$ is the quantum mechanical tunneling factor, which can be obtained from the Wigner transmission coefficient given by (Ng et al., 2013):

$$\Gamma(T) = 1 + \left(\frac{1}{24}\right) \left[1.44 \frac{v_{TS}}{T}\right]^2 \quad (7)$$

where v_{TS} is the imaginary frequency for the corresponding transition state. Considering the limitations of TST on the short-lived intermediates in a multi-step reaction, only the kinetics of the initial elementary reactions (the OH-addition and H-abstraction reactions of KP) were calculated using the TST.

2.2. Materials

KP was purchased from Sigma-Aldrich Co. LLC with a purity greater than 99%. H_2O_2 (30% w/v) and the analytical standard $FeSO_4 \cdot 7H_2O$ were used as Fenton reagents. The pH of the solution was adjusted using H_2SO_4 and NaOH. Glacial acetic acid and acetonitrile were HPLC standard grade and were used for the preparation of the mobile phase for HPLC. All reagents excluding KP were purchased from Tianjin Kemiou Chemical Reagent Co. Ltd.

2.3. Fenton Experiments

The Fenton system is one of the most classical and simplest AOP systems with the least introduced interferences (Mirzaei et al., 2017). Thus, Fenton experiments were selected to represent the AOP system in this study.

The stock solution of KP was prepared at 0.1 M in distilled-deionized water. First, 200 mL of a 0.1 M KP aqueous solution was added to 250 mL reaction vessels, and the pH was adjusted to 3.0 ± 0.1 . Then, the desired dosage of $FeSO_4 \cdot 7H_2O$

/ H_2O_2 was added to initiate the reaction. The mixture was magnetically stirred at 300 rpm at 25°C. At different time intervals, 500 μ L of the sample was removed using an injector. The sample was filtered through 0.22- μ m membranes and subjected to HPLC or UPLC-MSⁿ analysis immediately.

2.4. Analytical Methods

The KP concentrations were determined by high-performance liquid chromatography (HPLC, LC-20AT, Shimadzu, Japan), which was equipped with a UV detector and an ODS-C18 column (5 μ m $\times$ 4 mm $\times$ 250 mm). The mobile phase consisted of 0.1% glacial acetic acid in water and acetonitrile in a 50:50 v/v ratio, and isocratic elution was performed with a wavelength of 260 nm at a flow rate of 0.8 mL/min. A standard calibration curve was constructed using the external standard method based on a signal-to-noise ratio greater than 3, and this curve showed good linearity ($R^2 > 0.999$) between the concentrations of KP and the peak area response.

The transformation intermediates of KP were analyzed using UPLC-MSⁿ with an LCQ Fleet MS (Thermo Fisher Scientific, USA) and a Waters SunFireTM-C18 column (4.6 mm $\times$ 250 mm, 5 μ m). Electron spray ionization (ESI) was used with a spray voltage of 5000 V. The sheath gas flow rate, auxiliary gas flow rate and capillary temperature were set at 30 units, 10 units, and 300 °C, respectively. The mass spectra data were obtained in positive ion mode after scanning from m/z 100 to 400.

3. Results and Discussion

The optimized molecular structures and atom labels for KP are shown in Figure 1. The bond lengths were compared with the crystal experimental values because no experimental values in liquid were found (Table S1) (Vueba et al., 2006). The mean relative deviation of the bond lengths was 1.13%, which was consistent with the experimental values. Furthermore, the effects of KP ionization and protonation are discussed in section 3.3.

3.1. OH-Initiated Reaction Mechanism of KP

The OH-initiated reaction of KP in AOP systems can be divided into two reaction mechanisms: OH addition and H abstraction. For the OH-addition mechanism, OH radicals can be added to atoms with double bonds or the benzene ring, and the subsequent reactions are initiated. For the H-abstraction mechanism, the hydrogen atom of KP is abstracted by the OH radical, and subsequent reactions are generated. KP is a weak acid with a pK_a of 4.7. In most AOP systems, KP anions are more abundant than neutral KP molecules. Therefore, the KP anion was optimized to investigate the reaction mechanisms with the OH radical in this study. Furthermore, the effects of KP ionization and protonation are discussed in section 3.3.

3.1.1. Frontier Electron Density and Bond Dissociation Energy

The frontier orbital theory suggests that the position with

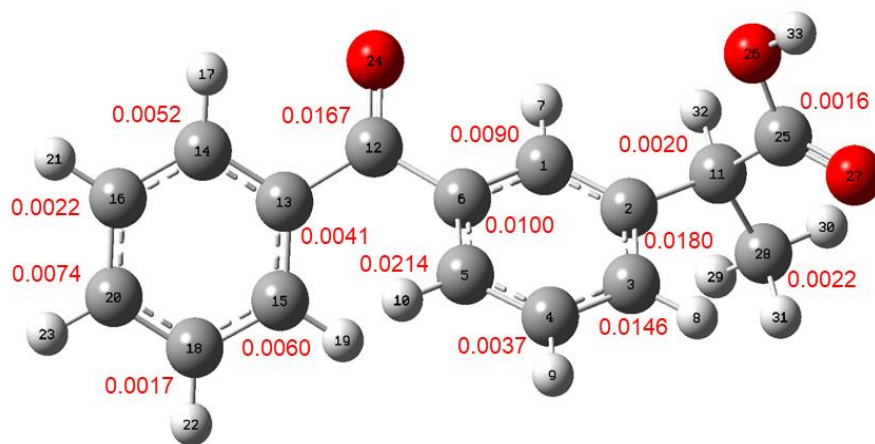


Figure 1. Optimized molecular structure with atom labels and frontier electron densities for KP (M06-2x/6-311+G(d,p)/SMD).

a higher FED is more likely to be attacked by the OH radical. The FEDs of all carbon atoms in KP were calculated and are shown in Figure 1 (values in red). Compared with the C atoms in the side benzene ring, the FEDs of the C atoms in the center benzene ring (C1 to C6) are obviously higher, implying that the C atoms in the center benzene ring are preferentially attacked by OH radicals. However, note that the steric hindrance effect of the side chain might negatively affect the attack of the OH radical on these atoms, especially C2. Additionally, the FED of C12 is very high. The OH-addition reaction with the carbonyl group is favored. Among all the carbon atoms, C2, C5 and C12 have the higher FEDs, and the FED of C5 is the highest, suggesting that these atoms are the first positions that are attacked by OH radical.

The bond dissociation energy is a good thermodynamic parameter to predict the bond strength of organic compounds. A higher BDE indicates a more difficult bond to break. Because benzene C-C bonds are difficult to break, the BDE of these C-C bonds were not calculated in this study. The BDEs of other chemical bonds in KP are provided in Table 1, and all of the calculated BDEs are compared with the experimental values obtained from the Comprehensive Handbook of Chemical Bond Energy (Luo, 2007). The good consistency between the calculated results and the experimental results demonstrates that the calculated thermodynamic data in this study are reliable.

As shown in Table 1, the C11-C28 bond has the lowest BDE of 77.12 kcal/mol, and the C11-C25 bond has the second lowest BDE of 84.24 kcal/mol. The breakage of these two C-C bonds causes the demethylation and decarboxylation of KP, which implies that the groups at the end of the KP side chain are much easier to remove during the degradation process. Meanwhile, for the BDE of the C-H bond, the lowest value of 86.08 kcal/mol belongs to C11-H32. This value is much lower than those from other C-H bonds, indicating that the hydrogen atom at the primary carbon position (C11) might be more readily abstracted by an OH radical. The same finding was observed in ibuprofen in previous studies (He et al., 2014; Xiao et al., 2014).

Table 1. Calculated and Experimental Main Bond Dissociation Energies of KP

Bond position	Calculated BDE*	Experimental BDE*
C1 – H7	113.22	113.50
C3 – H8	111.84	113.50
C4 – H9	112.10	113.50
C5 – H10	111.52	113.50
C11 – H32	86.08	83.50
C14 – H17	112.55	113.50
C15 – H19	111.16	113.50
C16 – H21	111.99	113.50
C18 – H22	112.04	113.50
C20 – H23	111.91	113.50
C28 – H30	102.3	100.40
C2 – C11	92.28	87.60**
C6 – C12	98.67	94.70 ± 4
C11 – C25	84.24	n/a***
C11 – C28	77.12	76.20 ± 2
C12 – C13	99.07	94.70 ± 4

* Energy unit in kcal/mol.

** BDE from Prop-2-enylbenzene.

*** Data not available.

3.1.2. OH-addition Reactions

The OH-addition reactions occur when an OH radical approaches atoms with an unsaturated bond. As shown in Figure 1, KP includes 2 benzene rings and 2 C=O double bonds; thus, fourteen C atom positions can be attacked by the OH radical. Moreover, because of the asymmetry of the KP structure, the OH-addition mechanisms from both the back (α -side) and front sides (β -side) of the benzene ring should be considered. The profiles of the potential energy surface for OH-addition pathways are shown in Figure 2 and S1. Pathway α/β is the reaction between the OH radical and the C α atom from the α/β side.

As illustrated in Figure 2 and S1, all OH-addition pathways are exothermic, and for each TS of the OH-addition reactions on the benzene ring, there is a pre-complex (Pre). The

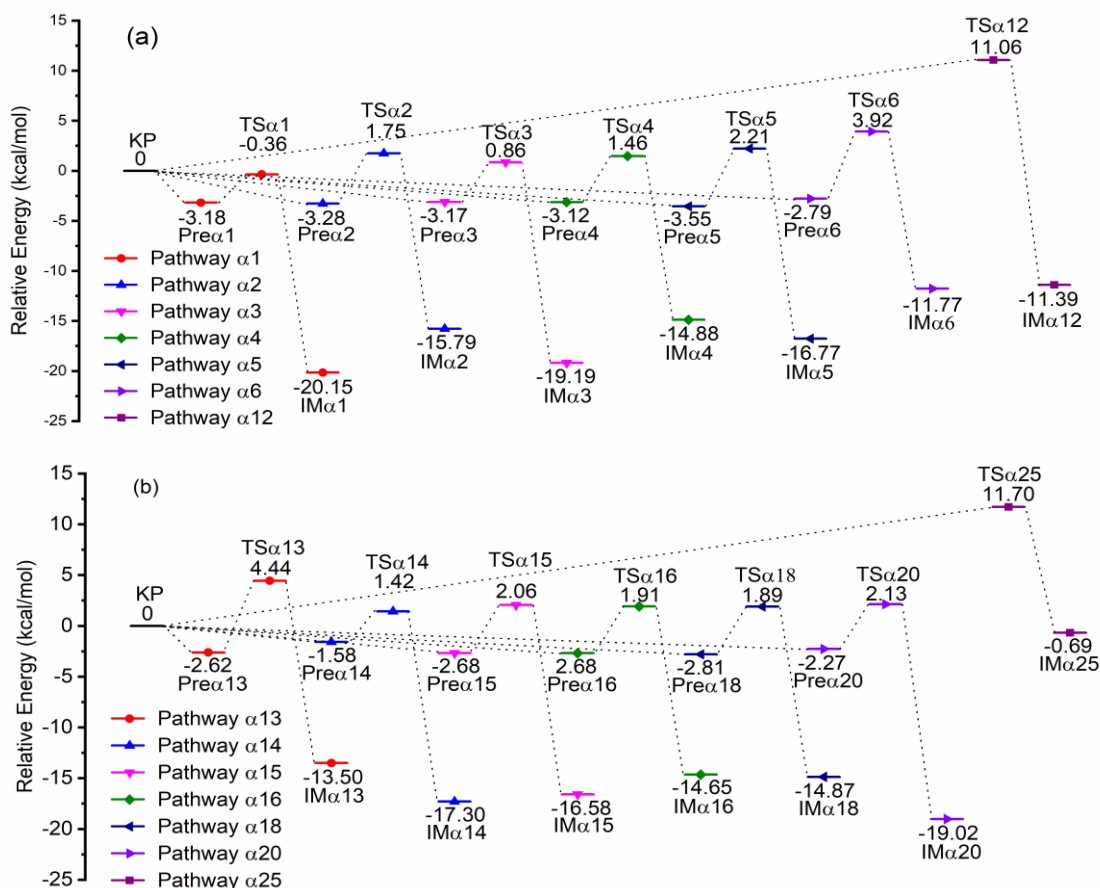


Figure 2. (a) Profile of the potential energy surface for OH-addition pathways on the center benzene ring from the α side, (b) Profile of the potential energy surface for OH-addition pathways on the side benzene ring from the α side.

potential barrier of each pathway is the difference between the pre-complex and transition state. The potential barriers for all OH-addition pathways are 3.00 to 11.70 kcal/mol, and the reaction heat is -0.69 to -23.03 kcal/mol. The OH-addition reactions at the C12 and C25 positions have higher reaction barriers than those on the benzene ring, implying greater difficulty for OH radical addition to the C=O double bond. Meanwhile, lower energies of the pre-complexes are observed from pathways $\beta 1$ to $\beta 6$, which are caused by the hydrogen bond interaction between the OH radical and the carboxyl group. The lower energies of the pre-complexes result in a higher potential barrier. Among all OH-addition pathways, pathway $\alpha 14$ has the lowest potential barrier of 3.00 kcal/mol; thus, it is considered the most thermo-dynamically favorable OH-addition pathway. In addition, because the highest potential barrier is only 11.70 kcal/mol, which is feasible to overcome under natural conditions, all OH-addition reactions are likely to occur in AOP systems.

3.1.3 H-abstraction Reactions

H-abstraction is another primary mechanism for the OH-initiated transformation of KP. There are three types of hydrogen atoms: hydrogen atoms at the primary carbon (C11) and

methyl carbon (C28) and hydrogen atoms on benzene rings. Because there are only slight differences among the three hydrogen atoms at one methyl carbon, only one of them was considered in this study. The profiles of the potential energy surface for all possible H-abstraction pathways are illustrated in Figure 3. Pathway x is the H-abstraction reaction at the C x position.

Nine H-abstraction pathways (pathways 1, 3 to 5, 14 to 16, 18 and 20) at the carbon positions on the benzene rings are observed in Figure 3. The potential barriers and reaction heats of these pathways are in the range of 1.33 to 5.29 kcal/mol and -7.24 to -8.82 kcal/mol, respectively. No obvious difference is found between the reactions on the two benzene rings. Among all these pathways, pathway 3 has a lower potential barrier of 1.33 kcal/mol and a reaction heat of -8.82 kcal/mol. As seen in Figure S4(a), a hydrogen bond is formed between the OH radical and the carboxyl group in TS3, and this hydrogen bond can decrease the energy of the TS. Therefore, the potential barrier of pathway 3 is lower, making this pathway stand out from the other H-abstraction pathways on benzene rings. Thus, in contrast to OH-addition reactions (which increase the reaction barrier), the carboxyl group in KP is considered beneficial for the H-abstraction reaction (because it lowers the reaction barrier).

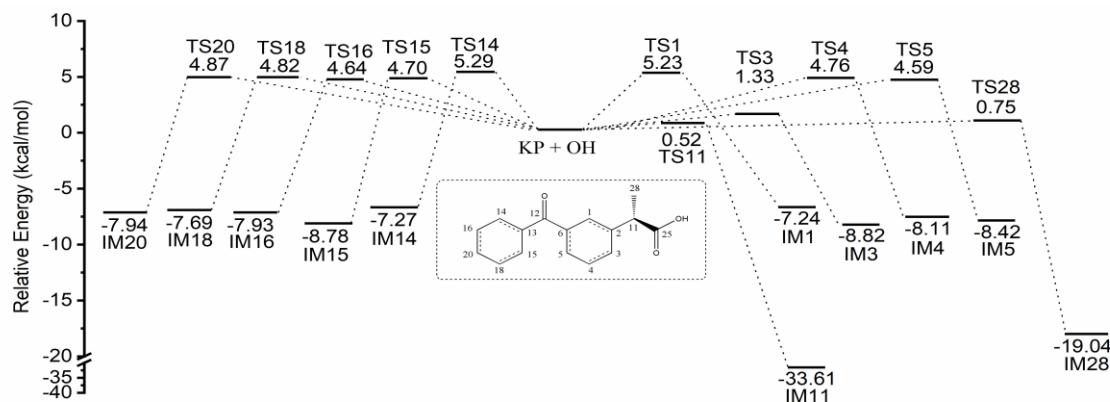


Figure 3. Profile of the potential energy

Pathway 11 depicts the H-abstraction reaction at the primary carbon position, and pathway 28 depicts the reaction at the methyl position. The potential barrier of pathway 28 is 0.52 kcal/mol, which is the lowest among all the H-abstraction pathways. Meanwhile, this pathway releases a much higher reaction heat of -33.61 kcal/mol, meaning that the formed intermediate is the most stable one. Therefore, the H-abstraction reaction at the methyl carbon position is considered the most thermodynamically likely pathway. Furthermore, the potential barrier of pathway 11 is also very low (0.75 kcal/mol), and the reaction heat of this pathway is 19.04 kcal/mol, implying that H-abstraction at the primary carbon position is also thermodynamically favored.

3.2. Kinetics Calculations

To quantitatively evaluate the contribution of each possible pathway and to better understand the KP transformation products in aqueous environments, reaction kinetics studies are performed in a temperature range of 273 to 313 K. The potential barriers (ΔE) and corresponding imaginary frequencies (ν_{is}) of each pathway are listed in Tables S3 and S4.

The rate constants, which are calculated for all pathways, and the overall rate constants (k_{total} ; the sum of the rate constants for all pathways), are provided in Table S5. The values of k_{total} are 1.40×10^{13} , 1.58×10^{13} and $1.70 \times 10^{13} \text{ M}^{-1}\text{s}^{-1}$ at 273, 298, and 313 K, respectively. As shown in Table S5, the rate constants for all pathways and k_{total} increase as the temperature increases. Thus, an increasing temperature promotes the KP transformation by the OH radical. In addition, if the reactions occur so quickly that the reaction rate is the rate of transport of the reactants through the reaction medium (usually a solution), they are diffusion-controlled (Atkins and De Paula, 2010). The diffusion rate constant of the reaction of KP with OH radical was calculated using method from Schone, Schindelka et al. (2014). The diffusion rate constant at 298 K is $1.36 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$, which is 3 orders of magnitude lower than the k_{total} . Hence, the KP transformation reaction in AOP systems is clearly diffusion-controlled over the entire investigated temperature range.

The branching ratios are calculated to understand the contribution of each pathway to the entire reaction and to quan-

titatively predict the generated intermediates. The branching ratios for all pathways in the KP transformation reactions between 273 and 313 K are calculated. The non-negligible pathways (branching ratio > 3%) among them are illustrated in Figure 4. Despite the rising rate constants, no obvious change in the branching ratios is observed as the temperature increases, which can be attributed to the very close relative increasing rates of the dominant pathways. Thus, we suggest that an increasing temperature improves the reaction rate but has a negligible effect on the reaction mechanisms. Among all of the OH-initiated pathways, pathways 28, 11 and 3 contribute the most in the investigated temperature range. The branching ratios for pathways 28, 11 and 3 at 298 K are 60.75, 25.59 and 12.45%, respectively. Other pathways contribute only approximately 1% to the total rate constant. Thus, these three pathways are the dominant routes for the reaction between KP and the OH radical.

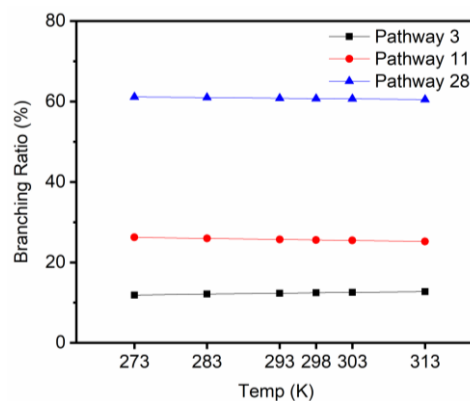


Figure 4. Calculated branching ratios for the main pathways in KP degradation reactions between 273 and 313 K.

3.3. Climate Change Impacts

The hydroxylated KP products are the main intermediate products from the primary reaction and subsequent reactions are initiated from them. Among all the subsequent reactions, the decarboxylation and decomposition reactions are more important for the degradation and transformation of KP.

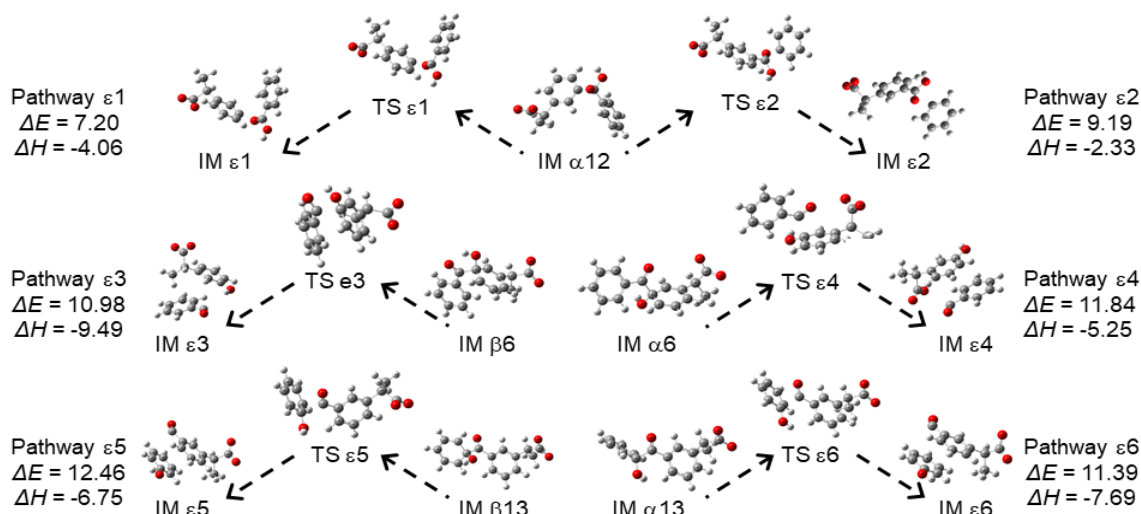


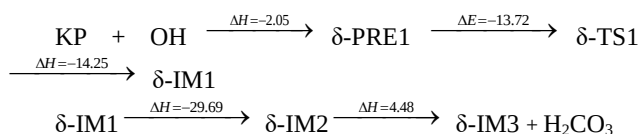
Figure 5. Profile of the potential energy surface for subsequent decomposition pathways.

Note: ΔE is the potential barrier, and ΔH is the reaction heat. The units of ΔE and ΔH are in kcal/mol.

3.3.1 Subsequent Decarboxylation Reactions

In previous studies, the decarboxylation mechanism of KP caused by its deprotonation has been investigated in detail (Martínez, Vilarinho et al. 2013). However, the mechanism was not clear for the OH-initiated decarboxylation reactions. The subsequent reaction of IM25 leads to the decarboxylation of KP. For the subsequent decarboxylation reaction, the reaction barrier and reaction heat are 10.99 and -40.03 kcal/mol (data not shown), respectively, which suggests that decarboxylation likely occurs.

Although the effect of KP ionization is negligible for benzene rings, this ionization causes differences in the decarboxylation mechanisms of KP. Therefore, the reactions of neutral KP with the OH radical at the carboxyl position must be discussed. The decarboxylation pathway of neutral KP is presented as follows:



In this pathway, the OH radical approaches the C25 atom and forms a pre-complex $\delta\text{-PRE1}$, followed by an intermediate $\delta\text{-IM1}$ produced via $\delta\text{-TS1}$. Then, the C25-C11 bond in $\delta\text{-IM1}$ is broken through a barrierless reaction, and $\delta\text{-IM3}$ and H_2CO_3 are formed ($\delta\text{-IM2}$ is the complex of $\delta\text{-IM3}$ and H_2CO_3). The overall reaction barrier of this pathway is 13.72 kcal/mol, and the reaction heat is -35.52 kcal/mol. Compared with the reactions of the KP anion, the overall barrier of this pathway is 2.73 kcal/mol higher, and the products are less stable. Therefore, the decarboxylation of KP has a slight advantage when more ionization occurs.

3.3.2 Decomposition Mechanism of the Hydroxylated Intermediate Products of KP

The decomposition of two benzene ring structures plays an important role in the KP degradation process. All subsequent decomposition reactions are shown in Figure 5.

As shown in Figure 5, pathways ϵ_1 and ϵ_2 are decomposition reactions that are initiated from $IM \alpha_{12}$, which is the intermediate of the OH-addition reaction at the carbonyl position. For pathway ϵ_1 , after the OH-addition reaction, the C12-C6 bond is broken through a transition state ($TS \epsilon_1$); then, a molecule of benzoic acid and a 2-phenylpropionic acid radical form. For pathway ϵ_2 , the C12-C13 bond is broken, and a 3-(1-carboxy-ethyl)-benzoic acid and a benzene radical are produced. The potential barriers of pathways ϵ_1 and ϵ_2 are 7.20 and 9.19 kcal/mol, respectively. Pathways ϵ_3 to ϵ_6 are decomposition reactions that originate from $IM \beta_6$, $IM \beta_6$, $IM \beta_{13}$ and $IM \beta_{13}$. The reaction barriers of these four pathways are 10.98 to 12.46 kcal/mol. From the IRC analysis, it is clearly observed that pathways ϵ_3 and ϵ_5 are generated because the C12-C13 bond breaks, and pathways ϵ_4 and ϵ_6 are generated owing to the breakage of the C12-C6 bond.

Among all the decomposition reactions, pathway ϵ_1 has the lowest reaction barrier of 7.20 kcal/mol, which indicates that the subsequent decomposition of KP is preferably generated by the breakage of the C6-C12 bond in $IM \beta_{12}$. The intermediate products in this pathway are benzoic acid and 2-phenylpropionic acid/hydroxylated 2-phenylpropionic acid.

It is commonly accepted that the carbonyl group is easily protonated under highly acidic conditions to form KPH^+ . To investigate the influence of KP protonation on the decomposition mechanisms, all of the decomposition reactions are calculated for KPH^+ . First, note that the protonation of the O atom leads to the high positive electricity of C12, making it react more easily with an OH radical. This idea is supported by our calculation result in which the potential barrier of the OH-addition reaction to the C12 atom decreases from 11.06 to 7.46 kcal/mol (data not shown). Then, all the decomposition path-

ways for KPH^+ are given in Figure S5. From Figure S5, an interesting finding is observed in which, contrary to KP, all of the decomposition pathways for KPH^+ are endothermic. The reaction heat values range from 3.75 to 15.34 kcal/mol, which implies that the protonation of KP inhibits its degradation in aqueous environments. This finding might be applicable to other benzophenone-like compounds since they have similar structures.

3.4. Identification of the Degradation Products

Fenton experiments are performed to investigate the OH-initiated degradation mechanisms of KP and to avoid the photo-induced decarboxylation reactions. Degradation samples were taken for the MS^n analysis when $82.6 \pm 4.1\%$ KP was removed. The transformation products of KP, which were identified by the UPLC- MS^n analysis, are listed in Figure 6, and their MS^n information is given in Table S6.

As shown in Figure 6, KP is identified at an m/z of 253. The decarboxylation product (3-ethyl-phenyl)-phenyl-methanone is found with a prominent protonated molecular ion peak at m/z 209. Benzoic acid is identified at m/z 121, which implies that the decomposition reactions of KP might experience the cleavage of the C6-C12 bond. This finding is consistent with our calculated pathway ϵ 1. The decomposition product at m/z 149 is identified as hydroxylated 3-ethyl-benzaldehyde instead of 2-phenyl-propionic acid because the hydroxyl group is identified by further MS^n -MS analysis. The occurrence of hydroxylated 3-ethyl-benzaldehyde indicates that the decomposition reactions through the C12-C13 bond breakage are also feasible.

The (3-Ethyl-phenyl)-phenyl-methanone is a decarboxylation product of KP, which is identified at m/z 209. The identified compounds at m/z 225 and 269 are the hydroxylated products of (3-ethyl-phenyl)-phenyl-methanone and KP. The other compounds in Figure 6 (the values in black) are the further hydroxylated products, which contain 2 to 8 hydroxyl groups.

As mentioned, the experimental findings are quite consistent with our calculation results in which hydroxylated KP is the main transformation product. The OH-initiated decarboxylation reaction is also likely to occur, which causes the formation of (3-ethyl-phenyl)-phenyl-methanone and its hydroxylated products. Furthermore, although subsequent decomposition reactions prefer to cleave the C6-C12 bond, the breakage of the C12-C13 bond is also feasible.

4. Conclusions

In this study, the transformation mechanism of KP in AOP systems is revealed by using DFT and Fenton experiments. The H-abstraction pathways are preferred, and the OH-initiated decarboxylation reaction of KP is likely to occur. The decomposition reactions of KP are preferably generated by breaking the C6-C12 bond in IM β 12. A high consistency between the DFT simulations and the experiments is achieved.

In addition, two interesting findings should be highlighted in this article:

a) The hydrogen bond that is formed between the OH radical and the carboxyl group negatively affects the OH-addition reaction but promotes the H-abstraction reaction of KP.

b) In the primary reactions, the protonation of KP decreases the potential barrier of the OH-addition reaction at the carbonyl group, thus facilitating the reaction. However, in the subsequent steps, our finding suggests that the change in the reaction heats above can inhibit the decomposition reactions due to the change in the reaction heat values. Meanwhile, this finding can also be applied to other benzophenone-like compounds.

Different from the experimental studies, which consume large amounts of materials and depend on many large-scale instruments, this study offers a cost-effective method to probe the transformation mechanism of KP in AOP systems. Further efforts can focus on investigating the quantitative structure-activity relationship/quantitative structure-property relationship (QSAR/QSPR) for related PPCPs in AOP systems.

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