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Thermodynamic and Kinetic Study of Ibuprofen with Hydroxyl Radical: A Density Functional Theory Approach

Ruiyang Xiao,[a] Matthew Noerpel,[a] Hoi Ling Luk,[b] Zongsu Wei,[a] and Richard Spinney*,[b]

Ibuprofen, a frequently detected pharmaceutical in natural and engineered waters, was studied in both neutral and anionic forms using density functional theory at the B3LYP/6-311++G**//B3LYP/6-31G* level of theory in its reaction with hydroxyl radical (•OH). The reaction pathways included •OH addition to aromatic ring, abstraction of a H-atom, and nucleophilic attack on the carbonyl group. The results showed that H-atom abstraction pathways are the most favorable. The free energy change for H-atom abstraction reaction ranges from −37.8 to −15.9 kcal/mol; for •OH addition ranges from −3.85 to −1.23 kcal/mol; and for nucleophilic attack on the carbonyl group is 13.9 kcal/mol. The calculated rate constant between neutral ibuprofen and •OH, 6.72×10^9 $M^{-1}s^{-1}$, is consistent with the experimental value, $6.5 \pm 0.2 \times 10^9$ $M^{-1}s^{-1}$. Our results provide direct evidence for byproduct formation and identification on the molecular level. © 2013 Wiley Periodicals, Inc.

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Introduction

Thousands of tons of pharmaceuticals are consumed or discarded by the public every year.[1–3] These compounds find their way into the water system as pollutants from the pharmaceutical industry, excretory products of medically treated human, and incomplete removal in wastewater treatment plants.[4] The US Geological Survey provided the first overview of the occurrence of pharmaceuticals in water resources across the United States during 1999–2000.[5] The frequency of detection of ibuprofen, a nonprescription anti-inflammatory, was 9.5% among all of the 84 samples, and the median detectable concentration was 0.2 μg/L.[5] A more recent study reported the concentrations of ibuprofen in the range of 10 ng/L to 169 μg/L in an analysis of effluent from wastewater treatment plants in Spain.[6]

Although the detected concentrations are relatively low, they may represent a potential hazard for human health.[7,8] Toxicological studies have shown that exposure of fish and other aquatic organisms to the pharmaceuticals can cause adverse reproductive effects, such as, reduced viability of eggs, sexual disruption, and changes in sperm density.[7,9] In addition, the oxidative metabolites that form in water treatment plants can be more harmful than the parent organic compounds.[10–12]

Therefore, based on precautionary principles, pharmaceuticals in water sources, especially in drinking water resources, should be sufficiently treated to minimize their potential risk to the ecosystem and human health. Efforts have been made to improve the pharmaceutical removal efficiency in water treatment plants. The advanced oxidation processes (AOPs), in which highly reactive electrophilic hydroxyl radicals (•OH) are formed,[13] have been found to be a promising technology, as •OH can nonselectively and rapidly react with electron-rich sites on pharmaceuticals,[14–16] including ibuprofen.[17–19] Packer et al. determined the degradation rate of ibuprofen in both direct photolysis and •OH mediated indirect photolysis.[19] The second-order rate constant of ibuprofen reacting with •OH was measured to be $6.5 \pm 0.2 \times 10^9$ M^{-1} s^{-1} in Milli-Q water. Mendez-Arriaga et al. identified several byproducts of ibuprofen in the photo-Fenton system and found that two major byproducts in their system were decarboxylated and hydroxylated metabolites of ibuprofen.[20] The removal of ibuprofen in water by AOPs has been achieved to some extent. But, it is still unknown how ibuprofen reacts with •OH on the molecular level, what the possible degradation pathways are, and whether the detected metabolites are directly derived from the oxidation of ibuprofen or if they are secondary/tertiary byproducts.

Although the application of density functional theory (DFT) methods[21] in chemical reactivity is slightly controversial,[22,23] numerous studies have reported that the DFT method features an excellent performance-to-cost ratio in predicting reaction mechanisms, byproduct formation, and reaction kinetics.[24–28] For example, Minakata and Crittenden[27] modeled rate constants between •OH and eight organic pollutants, and the estimated rate constants calculated by the DFT approach were within a factor of 5 of the experimental values. Morales-Roque et al. studied •OH oxidation process of phenol in water with DFT method and demonstrated that the ortho position is more readily attacked by •OH compared to para and metapositions.[28] However, modeling pharmaceuticals, especially ibuprofen, with •OH through the DFT method has not been

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explored sufficiently as indicated by the lack of data in the literature.

In this study, the first step of the oxidation reaction between ibuprofen and •OH in water was modeled on the molecular level using DFT approach. Ibuprofen, containing 33 atoms, is a reasonable target compound for the DFT method. In addition, there are some experimental evidence regarding to •OH oxidation of ibuprofen, which can be used to confirm our calculated results. Both thermodynamic and kinetic behavior of the possible reaction pathways were modeled, providing insights into the thermodynamics of product formation, reaction energy profiles, branching ratio, and degradation rate constants. Finally, the reaction between anionic form of ibuprofen and •OH was also studied using DFT method.

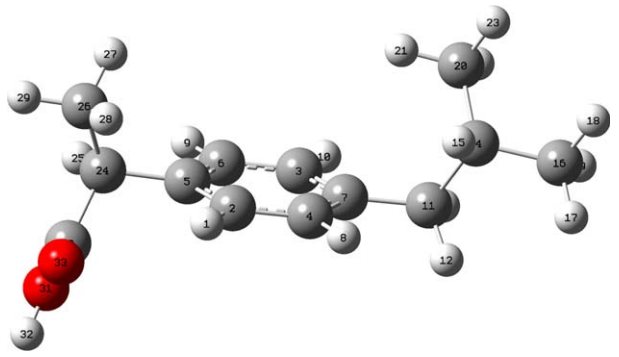


Figure 1. Geometry of neutral ibuprofen was optimized at B3LYP/6–31G* level of theory in gas phase and the single-point energy for the optimized geometry was calculated at B3LYP/6–311++G** level of theory using the IEFPCM water model.

Computational Methods

As ibuprofen has multiple accessible conformations, a conformational search for a low-energy geometry was conducted using Spartan'10[29] with AM1 as molecular mechanics methods[30] produce an unfavorable high-energy trans-conformation of the acid group. Twelve unique conformers were identified and full geometry optimizations were performed using Gaussian 09.[31] All subsequent geometry optimizations and transition state (TS) searches were performed using Gaussian 09 (Revision A.01).[31] The geometries of the reactants, TS species, and products were optimized at the B3LYP/6–31G* level.[32,33] The B3LYP hybrid functional has been shown to be reliable and in good agreement with experimental data for radical oxidation of organic molecules.[34–39] Single-point energies were calculated for the optimized B3LYP/6–31G* geometries with the same functional but a more flexible basis set, that is, B3LYP/6–311++G**. The solvent (water) effect on the reaction was modeled with the integral equation formalism (IEF) version of the polarizable continuum model (PCM)[40] as part of the B3LYP/6–311++G** single-point energy calculation. The $<S^2>$ values for the various TS structures typically show minimal spin contamination, ranging from 0.75 to 0.80. The nature of all stationary points, either minima or TSs, was determined by calculating the vibrational frequencies at the B3LYP/6–31G* level. Intrinsic reaction coordinates calculations[41,42] were performed for all TS species to confirm that they connect to the anticipated reactants and products on the potential energy surface. The thermal and entropic contributions to the free energies were also obtained from the B3LYP/6–31G* vibrational frequency calculations, using the unscaled frequencies.

The likely sites of reaction can be based on the free radical stability of the resulting carbon radical by comparing bond dissociation energies (BDE),[43] which is defined as the enthalpy change in the reaction of $A-B \rightarrow A + B$.[44] The higher the BDE, the more difficult it is to break the bond. In the case of hydrogen abstraction, the BDEs for benzylic carbons (C11 and C24 in Fig. 1) and tertiary carbon (C14 in Fig. 1) are approximately 85.3 and 95.6 kcal/mol, respectively.[44] However, the BDEs for the primary carbon (C16, C20, and C26 in Fig. 1) are about 100.4 kcal/mol.[44] The lower BDEs for benzylic carbons and tertiary carbons than primary carbons suggests that •OH react more easily at these positions to abstract an H than at a primary carbon position. Therefore, we investigated the hydrogen abstraction reaction at both benzylic and tertiary carbon positions. This is in agreement with experimental data where no oxidation products for the primary carbons were observed, as illustrated in Table 1.[20,45,46] As for the H abstraction mode all possible pathways were calculated, the reaction pathway degeneracy of one was assigned.

In the case of •OH addition, this is most likely to occur at the aromatic ring with its "high" electron density. Addition forms a resonance stabilized carbon radical in the ring and could be expected to be a favorable process. As the two faces of the benzene ring are asymmetric, the thermodynamics of addition to both faces needs to be determined. In Figure 1, •OH addition on the "top" face of the benzene ring is trans to the propanoic acid group and represents an "trans" addition, whereas •OH addition from the "bottom" face of the benzene ring is cis to the propanoic acid group and represents "cis" additions. All possible pathways were calculated for the •OH addition mode, thus the degeneracy of one was also assigned.

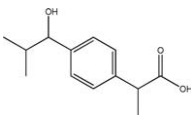
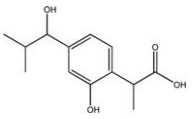
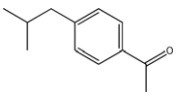
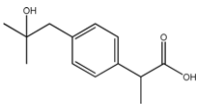
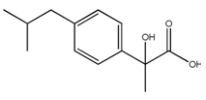
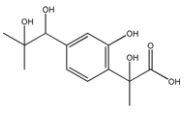
Finally, the carboxylic acid group is susceptible to two modes of attack. First, the •OH could react with the acidic proton and form a water molecule and residual oxygen radical. Second, the •OH could react via a "nucleophilic" attack on C30. All of these processes will be modeled and compared.

The possible pathways for the reactions of neutral ibuprofen with •OH based on these three mechanisms are illustrated in Figure 2. These reactions represent the first step of the oxidative degradation of neutral ibuprofen. Subsequent steps could involve the addition of •OH to the carbon radical or the loss of a second H-atom and formation of a carbon–carbon double bond. Multiple steps would lead to the oxidative products seen by Mendez-Arriaga et al.,[20] Zheng et al.,[45] and Madhavan et al.[46]

Ibuprofen is a weak acid with a pK_a 4.9, thus solution pH determines ibuprofen species distribution (Supporting Information Fig. S1). The reaction of ibuprofen anion and •OH was also studied using DFT approach.

Reaction pathways for the anionic form of ibuprofen were limited to the •OH addition to the ortho position of aromatic

Table 1. The experimentally detected byproducts in ·OH oxidation of ibuprofen from the Madhavan et al. study,[46] the Zheng et al. study,[45] and the Mendez-Arriaga et al. study.[20]

Chemical name	Chemical structure	Comment	Reference
2-(4-(1-hydroxy-2-methylpropyl) phenyl) propanoic acid		Monohydroxylated byproduct	[20,45,46]
2-(2-hydroxy-4-(1-hydroxy-2-methylpropyl) phenyl) propanoic acid		Dihydroxylated byproduct	[46]
4-isobutylacetophenone		Decarboxylated byproduct	[20,46]
2-(4-(2-hydroxy-2-methylpropyl)phenyl) propanoic acid		Monohydroxylated byproduct	[20,46]
2-hydroxy-2-(4-isobutylphenyl) propanoic acid		Monohydroxylated byproduct	[20]
2-(4-(1,2-dihydroxy-2-methylpropyl)-2-hydroxyphenyl)-2-hydroxy propanoic acid		Tetrahydroxylated byproduct	[45]

ring (C2 and C6), abstraction of an H-atom at C24, and nucleophilic attack on carbonyl group (C30). Only these pathways were considered as the conformation of the isobutyl group did not change significantly from the protonated form, as well as being too far away from the carboxylate group to have any impact on reactivity. The free energy and enthalpy of the reactions of the anionic form of ibuprofen and •OH for the pathways above were calculated at the B3LYP/6–311++G**//B3LYP/6–31G* level of theory using the IEFPCM water model. The TS for each reaction pathway was located at the B3LYP/6–31G* level of theory and the energy of the TS species was calculated at the B3LYP/6–311++G** level of theory.

The enthalpies (ΔH_R°) and free energies (ΔG_R°) of the reactions corrected by thermal effects at 298 K were calculated using:

$$\Delta H_R^\circ(298\text{K}) = \sum_{\text{products}} (E_0 + H_{\text{corrected}})_{\text{products}} - \sum_{\text{reactants}} (E_0 + H_{\text{corected}})_{\text{reactants}} \quad (1)$$

$$\Delta G_R^\circ(298\text{K}) = \sum_{\text{products}} (E_0 + G_{\text{corrected}})_{\text{products}} - \sum_{\text{reactants}} (E_0 + G_{\text{corrected}})_{\text{reactants}} \quad (2)$$

where E_0 is the total electronic energy at $T = 0$ K, $G_{\text{corrected}}$ and $H_{\text{corrected}}$ are the thermal correction to Gibbs free energy and enthalpy, respectively.

For the TS for each reaction pathway, the relative activation energy, $\Delta G^\ddagger$, was calculated as indicated:

$$\Delta G^\ddagger = (E_0 + G_{\text{corrected}})_{\text{TS}} - \sum_{\text{reactants}} (E_0 + G_{\text{corrected}})_{\text{reactants}} \quad (3)$$

The energy of activation is the minimum amount of energy needed for a reaction to proceed.

Conventional TS theory was used to predict the rate of reaction (M^{-1} s^{-1}) between ibuprofen and •OH at 298 K in water with the standard state 1 M through Eq. (4)

$$k(T) = l\ \Gamma(T) \frac{k_B T}{h} \exp(-\Delta G_0^\ddagger / \text{RT}) \quad (4)$$

where h is Planck's constant, k_B is Boltzmann's constant, and $\Delta G_0^\ddagger$ is the kinetic energy barrier and l is the reaction pathway degeneracy, one for all reactions studied. $\Gamma(T)$, temperature-dependent factor, corresponds to quantum mechanical tunneling and is approximated by the Wigner method[47]:

$$\Gamma(T) = 1 + \left(\frac{1}{24}\right)\left[1.44\frac{\nu_i}{T}\right]^2 \quad (5)$$

where ν_i is the imaginary frequency, whose vibrational motion is the direction of the reaction.

The tunneling correction using the Eckart's approach was also calculated and compared with Wigner's approach for

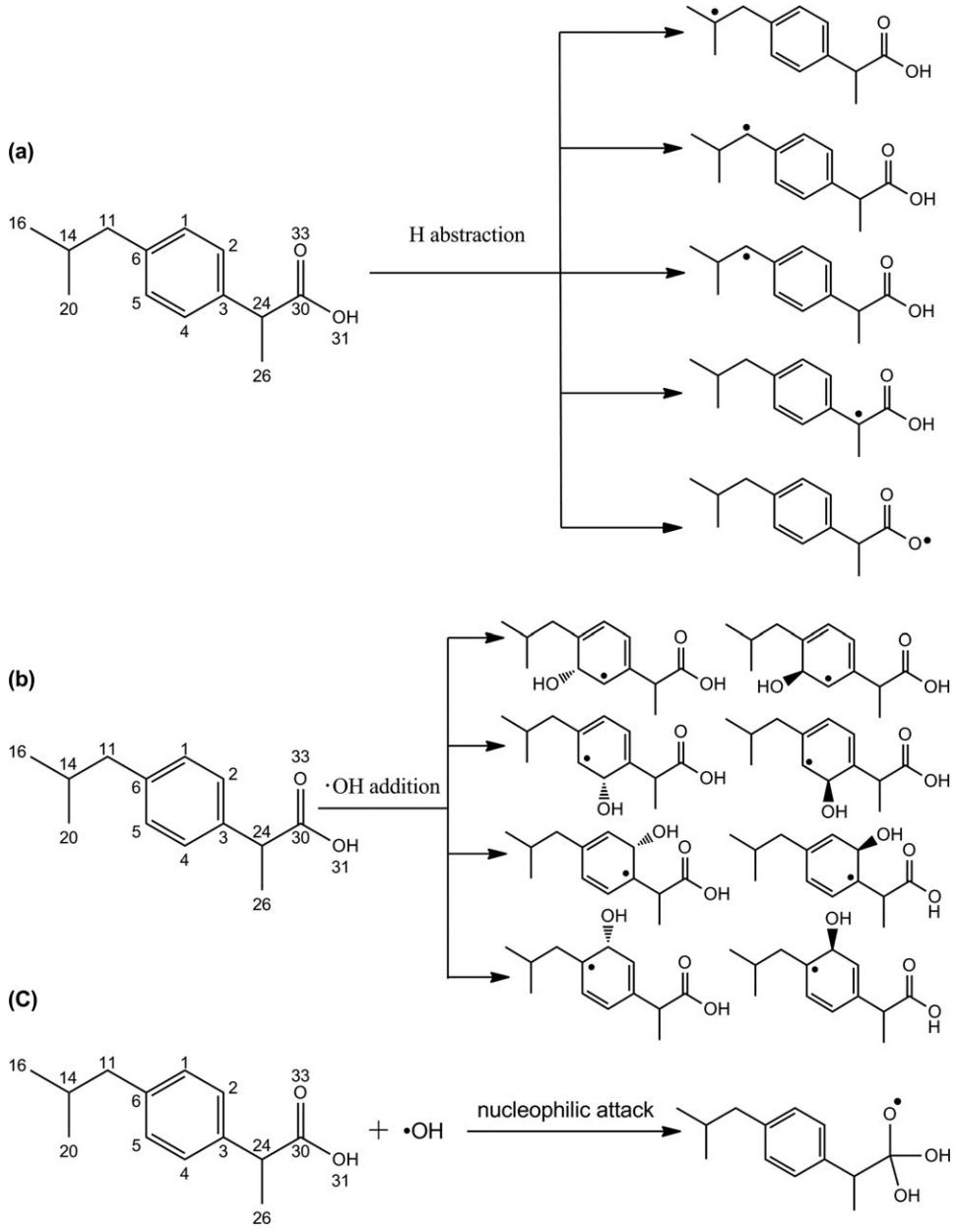


Figure 2. The selected pathways for the reactions of neutral ibuprofen with ·OH based on (a) H abstraction, (b) ·OH addition, and (c) nucleophilic attack.

every reaction channel. The Eckart's approach tunneling factor as function of temperature is calculated as follows[48]:

$$k(T)=e^{\beta\Delta V_1}\int_0^{\infty}k(E)e^{-\beta E}\,dE \tag{6}$$

$$\beta=\frac{1}{k_B T} \tag{7}$$

$$\alpha_1=2\pi\frac{\Delta V_1}{h|\upsilon_{TS}|} \tag{8}$$

$$\alpha_2=2\pi\frac{\Delta V_2}{h|\upsilon_{TS}|} \tag{9}$$

$$\xi=2\pi\frac{E}{\Delta V_1} \tag{10}$$

$$2\pi a=\frac{2\sqrt{\alpha_1\xi}}{\alpha_1^{-0.5}+\alpha_2^{-0.5}} \tag{11}$$

$$2\pi b=\frac{2\sqrt{|\alpha_1(\xi-1)+\alpha_2|}}{\alpha_1^{-0.5}+\alpha_2^{-0.5}} \tag{12}$$

$$2\pi d=2\sqrt{|\alpha_1\alpha_2-4\pi^2/16|} \tag{13}$$

$$\kappa(E)=1-\frac{\cos h(2\pi a-2\pi b)+\cos h(2\pi d)}{\cos h(2\pi a+2\pi b)+\cos h(2\pi d)} \tag{14}$$

where T is temperature (K), ΔV_1 and ΔV_2 are the thermal energy difference between the TS and the reactants and products, respectively, and ν_{TS} is the negative frequency.

Table 2. Calculated dihedral angles (°) and relative conformational energy (kcal/mol) for (*S*)-ibuprofen conformers in neutral form at B3LYP/6-31G* level.

Conformer	$\varphi_{O33=C30-C24-C5}$	$\varphi_{H25-C24-C5-C2}$	$\varphi_{C3-C7-C11-C14}$	$\varphi_{C7-C11-C14-H15}$	Relative E
#1	89.2	−135	104	55.0	1.02×10^{-2}
#2	89.6	10.1	73.9	−55.0	5.52×10^{-3}
#3	89.3	−171	104	54.4	0.00
#4	89.6	−171	74.5	−54.9	2.32×10^{-2}
#5	−97.5	4.3	74.5	−54.9	1.23
#6	−97.6	3.6	104	55.1	1.23
#7	−98.2	−177	76.3	−54.5	1.24
#8	−98.2	−178	104	55.2	1.22
#9	89.2	11.1	90.4	−180	0.987
#10	89.6	−171	90.7	180	0.977
#11	−97.6	3.7	90.2	−180	2.19
#12	−98.3	−176	90.4	180	2.19

Table 3. Calculated dihedral angles (°) and relative conformational energy (kcal/mol) for (*S*)-ibuprofen conformers in anionic form at B3LYP/6–31G* level.

Conformer	$\varphi_{O33=C30-C24-C5}$	$\varphi_{H25-C24-C5-C2}$	$\varphi_{C3-C7-C11-C14}$	$\varphi_{C7-C11-C14-H15}$	Relative E
#1	67.6	11.6	103	54.5	2.94×10^{-2}
#2	67.9	11.5	75.6	−54.5	-2.11×10^{-2}
#3	67.7	−169	105	54.5	0.00
#4	67.6	−169	76.1	−54.8	6.69×10^{-2}
#5	−113	11.5	75.7	−54.5	-2.13×10^{-2}
#6	−114	11.6	103	54.5	2.95×10^{-2}
#7	−114	−169	76.1	−54.8	6.70×10^{-2}
#8	−114	−169	105	54.5	0.00
#9	67.7	11.1	89.4	180	0.944
#10	67.9	−170	90.2	−180	0.938
#11	−114	11.1	89.4	180	0.944
#12	−113	−170	90.2	−180	0.944

Results and Discussion

Ten thousand conformers of the (*S*) enantiomer of neutral ibuprofen, the biologically active form, were examined at the AM1 level to determine the low-energy conformers by rotating dihedral angles, namely, $\varphi_{O33=C30-C24-C5}$, $\varphi_{H25-C24-C5-C2}$, $\varphi_{C3-C7-C11-C14}$, and $\varphi_{C7-C11-C14-H15}$. Twelve low-energy structures were generated and tabulated in Table 2. These structures were optimized in Gaussian 09[31] at B3LYP/6–31G* level and confirmed as a minima by running a frequency calculation. Conformer #3, the global minima, was used in this study (Fig. 1). Vueba et al. investigated the conformational stability of ibuprofen molecule at B3LYP/6-31G* level of theory and found eight geometries to be energy minima.[49] The starting geometry of ibuprofen shown in Figure 1 is consistent with their results for the *R* enantiomer.

The conformational search for the global minimum of ibuprofen anion was also performed in the same manner as the conformational search for the neutral form of ibuprofen. The 12 low-energy conformers found in the conformational search were closer in energy than in those of neutral form (Table 3). For the ionic form, the maximal energy difference is 0.96 kcal/mol, as compared to 2.19 kcal/mol for the neutral form. The energy of global minimum for the neutral form of ibuprofen is very similar to that of anionic form (0.02 kcal/mol). Therefore, the starting geometry of ibuprofen anion was the optimized global minimum for neutral ibuprofen without the acid H atom on the carboxyl group.

Thermodynamics

The free energy and enthalpy of the reactions were calculated at the B3LYP/6–311++G**//B3LYP/6-31G* level of theory using the IEFPCM water model. The enthalpies and free energies of the reactions for the three different mechanisms, •OH addition, H-atom abstraction, and nucleophilic attack, are tabulated in Table 4. All of the reactions are thermodynamically favorable processes ($\Delta G^{\circ}_{R} < 0$), except for nucleophilic attack on C30

Table 4. ΔG°_{R}(kcal/mol) and ΔH°_{R}(kcal/mol) for the products involved in the reactions of neutral ibuprofen with ·OH at the B3LYP/6–311++G** level of theory with IEFPCM water model.

Reaction mechanism	Position/atom number	ΔG°_{R}	ΔH°_{R}
OH addition	C2 trans	−1.23	−11.2
	C2 cis	−1.95	−12.6
	C3 trans	−1.68	−12.0
	C3 cis	−2.52	−12.8
	C4 trans	−2.43	−12.1
	C4 cis	−3.85	−13.2
	C6 trans	−2.38	−12.1
	C6 cis	−2.64	−12.8
H abstraction	H12 (C11)	−34.4	−32.6
	H13 (C11)	−34.3	−32.6
	H15 (C14)	−26.8	−24.1
	H25 (C24)	−37.8	−36.4
	H32 (O31)	−15.9	−14.7
Nucleophilic attack	C30	13.9	3.42

Table 5. $\Delta G^{\ddagger}$ (kcal/mol), imaginary frequency (cm^{-1}), rate constants k (M^{-1} s^{-1}), and branching ratio (%) for the transition state species involved in the reactions of neutral ibuprofen with ·OH at the B3LYP/6–311++G** level of theory with IEFPCM water model.

Reaction mechanism	Position/atom number	$\Delta G^{\ddagger}$	Imaginary frequency	k	Branching ratio
OH addition	C2 trans	7.92	288	1.05×10^{7}	0.16%
	C2 cis	8.14	306	7.29×10^{6}	0.11%
	C3 trans	8.30	278	5.46×10^{6}	0.08%
	C3 cis	6.73	293	7.85×10^{7}	1.17%
	C4 trans	7.76	287	1.39×10^{7}	0.21%
	C4 cis	6.53	288	1.09×10^{8}	1.63%
	C6 trans	8.88	350	2.17×10^{6}	0.03%
	C6 cis	7.81	347	1.30×10^{7}	0.19%
H abstraction	H12 (C11)	4.61	257	2.76×10^{9}	41.1%
	H13 (C11)	6.63	358	9.59×10^{7}	1.21%
	H15 (C14)	4.94	137	1.50×10^{9}	22.3%
	H25 (C24)	6.56	679	1.41×10^{8}	2.09%
	H32 (O31)	5.34	1308	2.00×10^{9}	29.7%
Nucleophilic attack	C30	21.1	451	2.74×10^{-3}	0.00%

(13.9 kcal/mol). In addition, all the reactions are exothermic ($\Delta H_R^{\circ} < 0$), except for nucleophilic attack on C30 (3.42 kcal/mol). The activation energy $\Delta G^{\ddagger}$, imaginary vibrational frequencies, rate constants, and branching ratios are tabulated in Table 5. Figure 3 plots the relative TS and product energies for all the reaction pathways.

•OH addition

For •OH addition, the enthalpy change ranges from −13.2 to −11.2 kcal/mol, with a median of −12.4 kcal/mol, whereas the free energy change ranges from −3.85 to −1.23 kcal/mol. The difference can be attributed to a large negative change in entropy as the reaction proceeds from two reactants to a single product.

The activation energy barrier ranges from 6.73 to 8.88 kcal/mol (average: 7.76 kcal/mol). The calculated barrier is consistent with a similar study. Xiao et al.[50] calculated the reaction between ciprofloxacin and •OH in its addition pathway. The activation energy barrier for protonated ciprofloxacin was reported to be 7.29 kcal/mol at the B3LYP/6-31G level of theory.[50] For •OH addition reaction pathway, the energy barrier of ibuprofen is similar to that of ciprofloxacin. However, all addition reactions are less favorable than H-atom abstraction due to the loss of aromaticity in the addition products and unfavorable change in entropy.

H abstraction

The hydrogen abstraction reactions can produce two different benzylic carbon radicals at C11 and C24 (H12, H13, and H25, respectively), one tertiary radical C14 (H15), and abstraction of the acidic hydrogen (H32). The benzylic radicals have an enthalpy change ranging from −36.4 to −32.6 kcal/mol (average −33.8 kcal/mol) and free energy change from −37.8 to −34.3 kcal/mol (average −35.5 kcal/mol). The tertiary radical has an enthalpy of −24.1 kcal/mol and free energy change of −26.8 kcal/mol. The acidic hydrogen abstraction has an enthalpy of −14.7 kcal/mol and free energy change of −15.9 kcal/mol. In contrast to the •OH addition reactions, there is a more favorable entropy change for H abstraction as the number of molecules/radicals does not change.

The activation barrier ranges from 4.61 to 6.63 kcal/mol (average 5.93 kcal/mol) for the benzylic radicals. The activation energy barrier for the abstraction of hydrogen at tertiary carbon (C14) and acidic hydrogen (H32) are 4.94 and 5.34 kcal/mol, respectively. Li et al.[51] studied the reaction of eupatilin with •OH in water and they reported the activation energy is 6.3 kcal/mol at the B3LYP/6–311++G(2df,2p) level for H abstraction pathway. Our result is consistent with the activation energy they determined. All hydrogen abstraction products are more thermodynamically stable than the addition products; along with their lower activation barriers

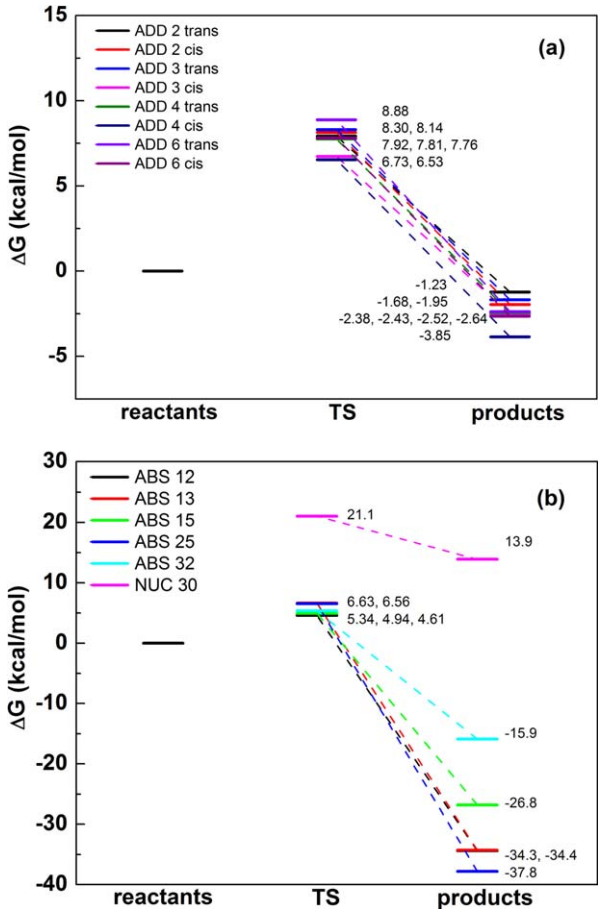


Figure 3. Profile of the potential energy surface [(a) ·OH addition pathway (ADD); (b) H abstraction (ABS) and nucleophilic attack (NUC) pathways] for the reaction between neutral ibuprofen and ·OH at the B3LYP/6–311++G** level of theory with IEFPCM water model.

Table 6. Comparison of the tunneling corrections for every reaction pathway using the Wigner's and Eckart's approach.

Reaction mechanism	Position/ atom number	Tunneling correction using Wigner's method	Tunneling correction using Eckart's method
OH addition	C2 trans	1.080886	1.081721
	C2 cis	1.091224	1.102810
	C3 trans	1.075284	1.076027
	C3 cis	1.083566	1.094409
	C4 trans	1.080222	1.081126
	C4 cis	1.080589	1.090530
	C6 trans	1.118769	1.123621
	C2 cis	1.116897	1.133866
H abstraction	H12 (C11)	1.064072	1.062862
	H13 (C11)	1.124228	1.127530
	H15 (C14)	1.018259	1.017576
	H25 (C24)	1.447476	1.511955
	H32 (O31)	2.665113	5.013903
Nucleophilic attack	C30	1.197617	1.226830

the abstraction reactions would dominate over •OH addition reactions.

Subsequent secondary reaction of the C24 carbon radical could lead to decarboxylation and secondary oxidation leading to a ketone group. For the subsequent decarboxylation reaction, the enthalpy and free energy change are −28.8 and −39.8 kcal/mol, respectively, indicating that the reaction is exothermic. The activation barrier for this reaction is extremely low (1.23 kcal/mol), suggesting that decarboxylation can occur very easily. The decarboxylated product and its further degradation products have been detected as oxidation products of ibuprofen using sonolysis,[46] gamma irradiation,[45] and the photo-Fenton process[20] (Table 1).

Reaction at the carboxylic acid

The final mode of interaction studied was the "nucleophilic" attack of •OH on the carboxylic acid carbon, C30. The enthalpy for this reaction is 3.42 kcal/mol with a free energy change of 13.9 kcal/mol, suggesting the reaction is nonspontaneous. The activation energy is 21.1 kcal/mol, which is highest among all reaction pathways. The high-energy barrier at the carboxylic acid indicates that it is very unlikely to detect this product in the process of oxidation of ibuprofen in water.

Comparison to experimental results

The formation of hydroxylated ibuprofen has been detected in several different AOPs systems, such as sonochemical, photochemical, and photochemical-catalytical degradation of ibuprofen. Madhavan et al.[46] sonolyzed ibuprofen at the frequency of 213 kHz with a power output of 55 W/L and identified the structure of sonochemical byproducts with electrospray ionization mass spectrometric technique. They found sonochemical degradation of ibuprofen formed mono and dihydroxylated intermediates (Table 1), thus corroborating our results that the major and first step of ibuprofen reacting with •OH is to undergo H-atom abstraction and then an additional •OH reacts with the ibuprofen radical. Although they did not report the abundance of the decarboxylation byproduct 4-isobutylacetophenone, its formation has been detected, suggesting that it is possible that H-atom abstraction occurs and then decarboxylated from the ibuprofen radical. Mendez-Arriaga et al.[20] studied the photochemical degradation of ibuprofen with TiO_2 and also found the formation of hydroxylated intermediates (Table 1). They indicated that the hydroxylation process can be the first step followed by demethylation or decarboxylation. However, our theoretical results suggest that the first step of •OH oxidation of ibuprofen is more likely via H-atom abstraction pathway at benzylic and tertiary carbon positions. All three benzylic and tertiary hydroxylation products are seen experimentally in Mendez-Arriaga et al.,[20] Zheng et al.,[45] and Madhavan et al.[46] (Table 1).

The •OH addition to ibuprofen is thermodynamically less favorable than H abstraction as it can clearly be seen in Table 4. The ΔG_R° and ΔH_R° for •OH addition is substantially less negative or exothermic than abstraction. One would assume from these trends that the •OH addition should occur less frequently than H abstraction. This is confirmed by experiment where only two •OH addition products were detected.[46]

Kinetics

The TS for each reaction pathway was located at the B3LYP/6-31G* level of theory and the energy of the TS species was calculated at the B3LYP/6–311++G** level of theory. The Cartesian coordinates and geometries for TS species are tabulated and shown in Supporting Information Table S1–S14 and Figure S2, respectively. Relative $\Delta G^\ddagger$, rate constants and imaginary frequency for the TS species involved in the reactions of neutral ibuprofen with •OH in aqueous solution are tabulated in Table 5. The $\Delta G^\ddagger$ for TS species ranges from 4.61 to 21.1 kcal/mol, with a median of 7.24 kcal/mol. Energy profiles for the potential energy surface of the •OH addition, H abstraction, and nucleophilic attack reactions are plotted in Figure 3. Figure 3 shows that the energy barrier height for H abstraction is lower than that of •OH addition and nucleophilic attack pathways, indicating the rate constants for this mode is generally faster than •OH addition and nucleophilic attack. Calculated rate constants for H abstractions range from 9.59×10^7 $M^{-1}s^{-1}$ to 2.76×10^9 $M^{-1}s^{-1}$ (average 1.30×10^9 $M^{-1}s^{-1}$) compared to 2.17×10^6 $M^{-1}s^{-1}$ to 1.09×10^8 $M^{-1}s^{-1}$ (average 3.00×10^7 $M^{-1}s^{-1}$) for the addition reactions. Calculated rate constant for nucleophilic attack is 2.74×10^{-3} $M^{-1}s^{-1}$, suggesting this reaction is very unlikely to occur. The sum[25,26,52] of calculated rate constants for all three pathways is 6.72×10^9 $M^{-1}s^{-1}$. In comparison with the experimental rate constant, Packer et al.[19] monitored the degradation of ibuprofen in purified (Milli-Q) water in the Fenton reaction system and measured its second-order rate constant with •OH to be $6.5 \pm 0.2 \times 10^9$

Table 7. ΔG_R° (kcal/mol), ΔH_R° (kcal/mol), $\Delta G^\ddagger$ (kcal/mol), imaginary frequency (cm^{-1}), and rate constants k (M^{-1} s^{-1}), for the reaction of anionic form of ibuprofen with ·OH at the B3LYP/6–311++G** level of theory with IEFPCM water model.

Reaction mechanism	Position/atom number	ΔG_R°	ΔH_R°	$\Delta G^\ddagger$	Imaginary frequency	k
OH addition	C2	−7.51	−18.4	4.88	473	2.00×10^9
	C6	−7.92	−18.9	2.03	467	7.40×10^9,[a]
H abstraction	H25 (C24)	−37.1	−36.1	-7.67×10^{-2}	857	7.40×10^9,[a]
Nucleophilic attack	C30	11.5	0.527	19.5	380	3.88×10^{-2}

[a] k was calculated by the simplified version of the Roman Smoluchowski equation.

$M^{-1}s^{-1}$, which is consistent with the calculated result in this study.

The tunneling correction using the Wigner's and Eckart's approach was compared and tabulated in Table 6, The tunneling corrections calculated by the Wigner's and Eckart's methods are quite similar, except for abstraction reaction occurring at H32. The Eckart tunneling correction is 1.87 times higher than that of Wigner's method at this channel. The corresponding rate constant using Eckart tunneling correction is 8.48×10^9 $M^{-1}s^{-1}$, which is 30.5% higher than the experimental value. It is reported that the Eckart method is often found to overestimate the tunneling corrections.[53–55] The calculated rate constant using Wigner's method is in a good agreement with the experimental value.

Although the DFT approach exhibited good performance for the calculation of the rate constant between ibuprofen and •OH, characteristics (i.e., dissolved organic matter, dissolved oxygen, etc.) of waters are variable.[16,56] In addition, there may be coexisting pollutants, which should be also taken into considerations when AOPs are applied in water treatment plants. These coexisting pollutants will compete for •OH, thus resulting in reduced degradation kinetics.

The branching ratios, referring to the contribution of each reaction pathway to the overall degradation, for the products through different pathways are also tabulated in Table 5. H abstraction at H12, H15, and H32 are dominant compared to other positions, suggesting that the decarboxylated and hydroxylated products that were experimentally detected[20,45,46] is the secondary/tertiary byproducts in the process of oxidation of ibuprofen.

Reaction between ibuprofen anion and •OH

ΔG_R°,ΔH_R°, relative $\Delta G^\ddagger$, rate constants k, and imaginary frequency for the reaction of ibuprofen anion with •OH in aqueous solution are tabulated in Table 7. Similar to the energy profile for the reaction of neutral ibuprofen with •OH, all the selected pathways for the reaction of ibuprofen anion and •OH are thermodynamically favorable processes ($\Delta G_R^\circ < 0$), except for nucleophilic attack on C30 ($\Delta G_R^\circ = 11.5$ kcal/mol). However, the energy barrier for H25 abstraction for ibuprofen anion (-7.67×10^{-2} kcal/mol) is significantly lower than that for neutral ibuprofen (6.56 kcal/mol). This very low activation barrier results from an intermolecular hydrogen bond which forms with the deprotonated hydroxyl group as the •OH approaches the H25 (Fig. 4). The intermolecular hydrogen bond also lowers the activation energy for •OH addition on C6 (Fig. 5), which does not occur to the neutral form of ibuprofen. This low activation barrier would explain the ortho addition products seen by Madhavan et al.[46] (Table 1). The metaproduct is not seen as the activation barrier, without hydrogen bonding, is too high.

As the conventional TS theory fails to calculate the reaction with low barrier heights, especially when $\Delta G^\ddagger < 3$ kcal/mol,[57,58] TS theory is not applicable for H25 abstraction and •OH addition on C6 pathways. Therefore, the simplified version of the Roman Smoluchowski equation was used to predict the diffusion controlled rate constant,[59] calculated in Eq. (15)

$$k_D = 4N_A\pi(r_{OH} + r_{IBU})(D_{OH} + D_{IBU}) \quad (15)$$

where N_A is the Avogadro constant; r_{OH} and r_{IBU} are radii for •OH and ibuprofen, respectively. D_{OH} and D_{IBU} are the diffusion coefficients for •OH and ibuprofen, respectively. The second-order rate constant for the reaction is calculated to be 7.40×10^9 $M^{-1}s^{-1}$. In this case diffusion theory would give a better

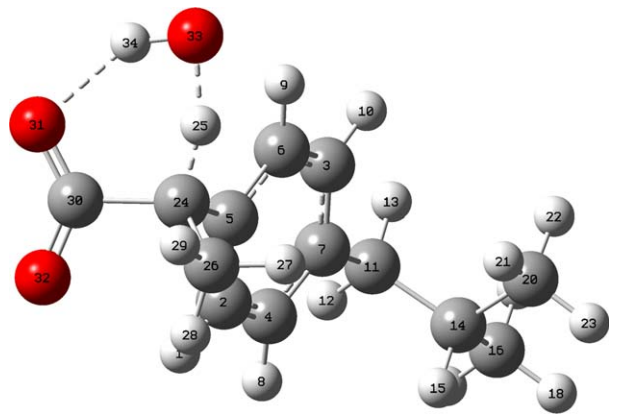


Figure 4. TS species of H25 abstraction on the anionic form of ibuprofen with hydrogen bonding significantly lowering the activation energy.

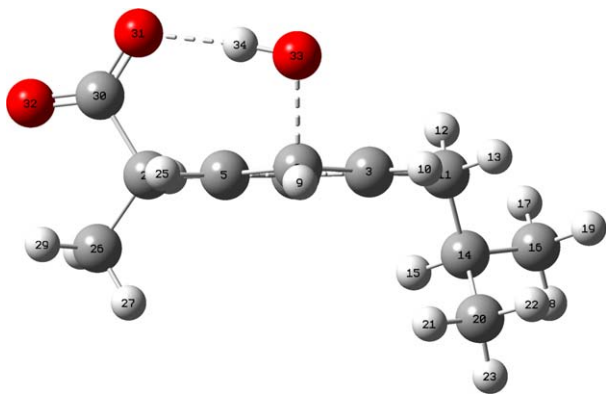


Figure 5. TS species of ·OH addition to C6 on the anionic form of ibuprofen with hydrogen bonding significantly lowering the activation energy.

approximation, although likely an over estimation of the rate constant.

Conclusions

In this study, the conformational search of (*S*)-ibuprofen in both neutral and ionic forms was analyzed and the first step of the oxidation of the resulting global minimum conformation of ibuprofen with •OH in water was calculated. We proposed three possible pathways for •OH oxidation of ibuprofen, •OH addition, H abstraction, and nucleophilic attack on carbonyl group. The calculated second-order rate constant of neutral ibuprofen with •OH using B3LYP functional and the Wigner's tunneling correction is in good agreement with the reported value, 3.5% error. This suggest that the Wigner correction for a B3LYP/6–311++G**//B3LYP/6-31G* DFT method is a valid means to calculate rate constants. The high distribution of H-abstraction products suggested that the experimental detected decarboxylated and hydroxylated products are the secondary/tertiary byproducts in the oxidation reaction chain. For the reaction of the anionic form of ibuprofen with •OH, the reaction pattern is different from that of neutral form of ibuprofen. Its reaction kinetics is controlled by diffusion with second-order rate constant 7.40×10^9 $M^{-1}s^{-1}$. Our results provide theoretically calculated direct evidence for byproduct formation and identification in •OH oxidation of ibuprofen on the molecular level.

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Keywords: ibuprofen · ibuprofen anion · hydroxyl radical-density functional theory · H-atom abstraction · thermodynamic and kinetic study

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