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pH- and Wavelength-Dependent Photodecarboxylation of Ketoprofen

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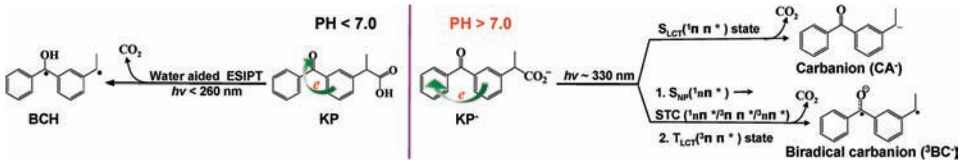
ABSTRACT



The pH- and wavelength-dependent pathways for the photodecarboxylation of ketoprofen (KP) were mapped by CASSCF/CASPT2 computations. The decarboxylation of the basic form (KP$^-$) was found to start from a long-distance charge transfer (CT) excited state when populated by photoexcitation at 330 nm. A short-distance CT excited state populated with photoexcitation at $\lambda < 260$ nm appears to be responsible for the decarboxylation of the acidic form (KP). The H_2O molecules function as a bridge to assist proton transfer in the reactions examined here.

Ketoprofen (KP) and its analogous compounds can rapidly release photolabile protecting groups (PPGs) and are useful in a wide variety of fields such as photolithography, DNA synthesis, microarray fabrication, and solid-state synthesis.[1] The photochemistry of KP has been studied using time-resolved transient absorption spectroscopy to search for the reactive intermediates that are responsible for its release mechanism.[2–9] As illustrated in Scheme 1, the deprotonated form of ketoprofen (KP$^-$) at physiological pH (~7.4) undergoes a rapid and efficient photodecarboxylation reaction ($\phi = 0.75$) to yield a carbanion.[6–9] In contrast, the acidic form of ketoprofen (KP) is generally considered to behave as a conventional benzophenone due to the high efficiency of intersystem crossing to form a triplet radical.[2–9] However, the decarboxylation reaction of the neutral form of KP was recently observed[10] to take place in water-rich concentration solutions under irradiation of a shorter wavelength (~266 nm) in comparison with those used in previous experiments (> 300 nm).[2–9] The water molecules are found to assist an excited-state intramolecular proton transfer (ESIPT) from the carboxylate group to the carbonyl group that triggers subsequent decarboxylation.[10]

This experimentally reproduces the highly efficient photodecarboxylation of *o*-acetylphenylacetic acid that is also triggered by direct ESIPT without the participation of water.[11] Although several possible pathways are proposed to address the photochemistry observed under the different conditions of solvent and excitation wavelength, it is difficult to reach a definitive conclusion due to the strong overlap among the complicated transient spectra.[2] In our

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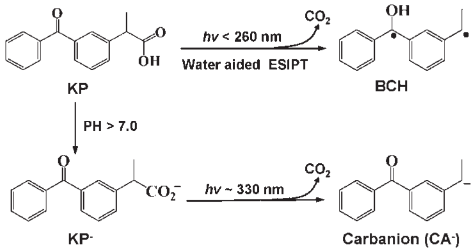
Scheme 1



previous studies, high-level electronic structure calculations can provide detailed information concerning the Franck–Condon (FC) excitation and PES as well as the intermediate and product reaction pathways of PPG compounds that may then be compared in a quantitative manner with experimental observations.[11,12] Therefore, the release mechanisms can be better understood on the basis of calculated reaction pathways. Herein, the same CASSCF/CASPT2 approach (see Supporting Information for computational details) will be used to explicitly describe how the photodecarboxylation of the deprotonated form of ketoprofen (KP^-) occurs and how its mechanism changes when varying the pH value and excitation wavelength.

Table 1. Vertical Excitation Energies (ΔE, kcal/mol), Oscillator Strengths (*f*), Dipole Moments (DM, Debye), at the Franck–Condon (FC) Minimum Geometric Structure for Basic (KP^-) and Acidic (KP) Forms of Ketoprofen and Its Neutral Complex with Two Water Molecules ($KP\cdot 2H_2O$) at the CASSCF(14e/11o)/CASPT2/6-31G* Level of Theory

	transitions	DM	*f*	ΔE
KP^-	S_0	19.66		0.0
	$S_0 \rightarrow S_{NP}(^1n\pi^*)$	18.93	0.004	87.2
	$S_0 \rightarrow S_{LCT}(^1\pi\pi^*)$	12.66	0.029	87.7
	$S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$	11.23	0.258	107.6
KP	S_0	3.31		0.0
	$S_0 \rightarrow S_{NP}(^1n\pi^*)$	2.27	0.003	89.4
	$S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$	5.69	0.153	125.1
$KP\cdot 2H_2O$	S_0	7.43		0.0
	$S_0 \rightarrow S_{NP}(^1n\pi^*)$	8.16	0.005	93.5
	$S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$	2.36	0.238	118.9

Table 1 summarizes the vertical excitation energies, oscillator strengths (*f*), dipole moments of different transitions for the basic (KP^-) and acidic (KP) forms of ketoprofen and its neutral complex with two water molecules, as well as the assignment of excited-state character. The $S_0 \rightarrow S_{NP}(^1n\pi^*)$ transitions of KP^-, KP, and $KP\cdot 2H_2O$ originate from the promotion of one electron of the O2 lone pair to a π^* orbital that is delocalized into the two Ph chromophores (see Figure 1 for the numbering scheme). Their dipole moment changes are −0.73, −1.04, and 0.73 D, respectively, above excitation, which indicates that the $^1n\pi^*$ state has no charge transfer character. The oscillator strengths of the $S_0 \rightarrow S_{NP}(^1n\pi^*)$ transition for the three forms of ketoprofen are 0.003–0.005, 50–60-fold smaller than those of the maximum *f*. This confirms a "dark" spectroscopic character for the transition to $^1n\pi^*$. The vertical excitation energies to the $^1n\pi^*$ state for KP^- and KP are 87.2 and 89.4 kcal/mol, respectively, which are very close to the experimentally observed absorption band at 330–340 nm (86.6–84.1 kcal/mol) with a very low extinction coefficient.[4b,5] In comparison with that of bare KP, the formation of hydrogen bond(s) around the carbonyl O2 leads to a slight increase (~4.1 kcal/mol) of the vertical excitation energy (see Figure 1c for the model including hydrogen bonding).

As shown in Table 1, another dark state $S_{LCT}(^1\pi\pi^*)$ of KP^- ($f = 0.029$) was found to have 87.7 kcal/mol (~326 nm) vertical excitation energy. Considering that the $S_0 \rightarrow S_{LCT}(^1\pi\pi^*)$ transition has a resonance excitation energy and the same magnitude of oscillator strength, one can conclude that the initial population of the $S_{LCT}(^1\pi\pi^*)$ state for KP^- may compete with that of the $S_{NP}(^1n\pi^*)$ state under 330–340 nm excitation. The $S_0 \rightarrow S_{LCT}(^1\pi\pi^*)$ transition originates from a long-distance charge transfer that is associated with the two chromophores. The electronic population shows that the singly occupied electrons are distributed in the moiety of the phenylpropionic carboxylate anion and the benzyl ring, respectively. Approximately, 0.35 electrons is significantly transferred to the moiety of the benzyl ring from the center of a negative charge resulting in a −7.0 D dipole moment change in the FC excitation of $S_0 \rightarrow S_{LCT}(^1\pi\pi^*)$ for KP^-. The elimination of the negative charge that is distributed around the carboxylate anion was found to be the predominant step for photodecarboxylation in our previous study.[11] Therefore, the long-distance CT state of $S_{LCT}(^1\pi\pi^*)$ can function as the precursor state for the photodecarboxylation of the basic form of ketoprofen. Unlike the KP^- form, the long-distance CT state was not found in the FC excitation of the neutral form of KP and $KP\cdot 2H_2O$. This indicates that the carboxylate anion is the internal motivation of the long-distance CT excitation and accounts for why no appreciable decarboxylation reaction was observed experimentally[2–9] in the neutral form of KP upon 330–340 nm excitation.

Like the case of 3′,5′-dimethoxybenzoin[12] and *o*-acetylphenylacetic acid,[11] the short-distance CT state of $S_{SCT}(^1\pi\pi^*)$ was found in both the basic and acidic forms of ketoprofen. The $S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$ transition is localized at one chromophore, where the charge transfer takes place from the aromatic ring of the phenylpropionic carboxylate anion to the C1–O2 carbonyl group, leading to a negative charge center at the carbonyl group that serves as the potential acceptor of proton transfer.[11] As illustrated in Table 1, the vertical excitation energy of $S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$ transition for KP is 125.1 kcal/mol and is similar to the calculated value (123.0 kcal/mol) for *o*-acetylphenylacetic

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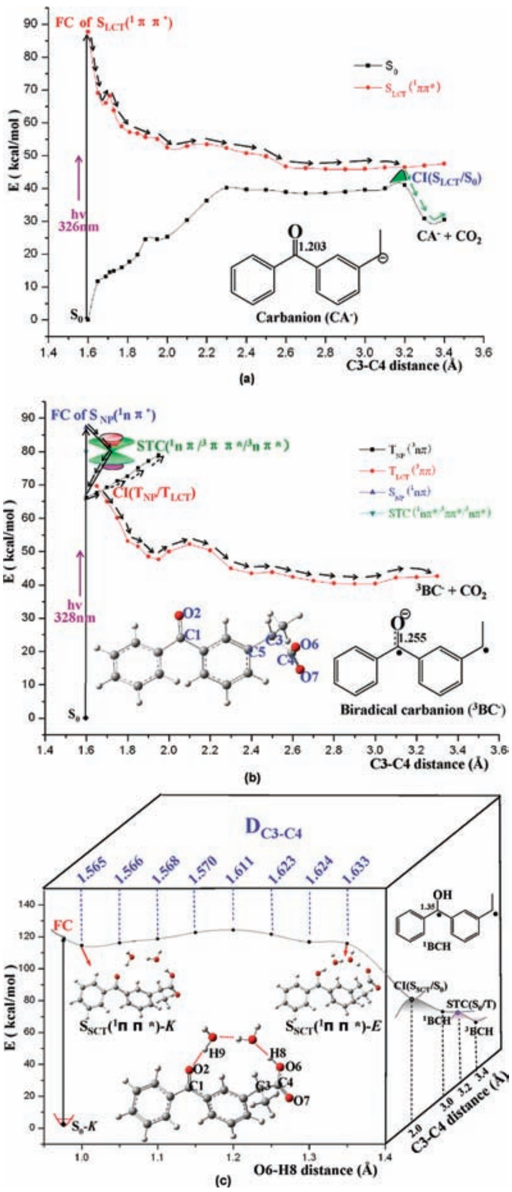

Figure 1. Minimum energy profiles (MEPs) of decarboxylation along the reaction coordinate of C3–C4 distance for KP^- photoinitiated by ~326–328 nm light: competitive long-distance CT (a) singlet $S_{LCT}(^1\pi\pi^*)$ and (b) triplet $T_{LCT}(^3\pi\pi^*)$ state reactions. (c) MEP of decarboxylation triggered by water-aided ESIPT for $KP\cdot 2H_2O$ under < 260 nm excitation. All MEPs were obtained by multi-optimizations along a fixed corresponding reaction coordinate at the CASSCF/CASPT2/6-31G* level of theory.

acid.[11] The formation of a hydrogen bond around the carbonyl O2 leads to a decreased energetic level of 118.9 kcal/mol in $KP\cdot 2H_2O$. It should be noted that the present model for the hydrogen bonding is simplified and more hydrogen bonds surrounding the C1–O2 carbonyl group are expected to exist in the actual water environment, thereby leading to a much lower vertical energy to the $S_{SCT}(^1\pi\pi^*)$ state for the ketoprofen–water complex calculated here. As shown in Table 1, the short-distance charge transfer state of $S_{SCT}(^1\pi\pi^*)$ for ketoprofen in its different forms has maximum oscillator strength over other transitions, and this confirms the nature of the "bright" spectroscopic state for compounds containing an aromatic carbonyl chromophore.[11,12] Therefore, the $S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$ transition is responsible for the $\lambda < 260$ nm UV excitation observed in experimental absorption spectra[10] of ketoprofen.

As shown in Figure 1a, photoexcitation of KP^- at 326 nm takes the system to the FC region of the $S_{LCT}(^1\pi\pi^*)$ state. The wavepacket from this excited state rapidly decays to a local minimum that is ~66.0 kcal/mol above the S_0 minimum in energy. Meanwhile, the C3–C4 distance is elongated from 1.59 Å in the FC region of the $S_{LCT}(^1\pi\pi^*)$ state to 1.69 Å in the local minimum, while the O6–C4–O7 angle is increased from 130.0 to 136.0°. The potential well of this local minimum is extremely shallow where only ~2.0 kcal/mol barrier is encountered, leading to a downhill relaxation pathway. Evolution of photoinduced charge transfer from the moiety of the phenylpropionic carboxylate anion to the benzyl ring causes the wavepacket to go down to a flat valley of energy ranging from 52.5 (at the C3–C4 distance of 2.0 Å) to 46.5 kcal/mol (at the C3–C4 distance of 3.2 Å). Meanwhile, the energetic gap between the $S_{LCT}(^1\pi\pi^*)$ and S_0 states is gradually decreasing and finally reaches a degenerate region of $CI(S_{LCT}/S_0)$ at the C3–C4 distance of 3.2 Å. The $CI(S_{LCT}/S_0)$ conical intersection is 41.2 kcal/mol below the FC point of the $S_{LCT}(^1\pi\pi^*)$ state in energy. As shown in Figure S3 in Supporting Information, the negative charge is totally transferred from the moiety of O6–C4–O7 to benzophenone in the relaxation from the FC of $S_{LCT}(^1\pi\pi^*)$ to $CI(S_{LCT}/S_0)$. Accordingly, the O6–C4–O7 angle and C–O bonds in the $CI(S_{LCT}/S_0)$ structure become ~176.0° and 1.140 Å, while they are ~130.0° and 1.237 Å in the FC of $S_{LCT}(^1\pi\pi^*)$, respectively. These findings indicate that the formation of neutral CO_2 is almost completed in the $CI(S_{LCT}/S_0)$ by efficiently taking the photoinitiated charge transfer from the COO^- moiety to the benzophenone. The conical intersection of $CI(S_{LCT}/S_0)$ functions as an efficient nonadiabatic relay to funnel the wavepacket of $S_{LCT}(^1\pi\pi^*)$ to the ground state, producing the carbanion (CA^-) intermediate that has 30.7 kcal/mol of energy with respect to the zero level of S_0. The absorption band with the largest oscillator strength is calculated to lie ~56.5 kcal/mol above the zero level of CA^-. This is very close to the λ_{max} 580 nm (49.3 kcal/mol) transient absorption observed experimentally for the carbanion.[6–9]

The crossing of the $^1n\pi^*/^3\pi\pi^*/^3n\pi^*$ was repeatedly verified to be commonly found in aromatic carbonyl compounds, and this allows an efficient intersystem crossing (ISC) leading to photochemical reactions in the triplet state in many systems.[13] As excepted, the three surface crossings of STC $(^1n\pi^*/^3\pi\pi^*/^3n\pi^*)$ for KP^- are found to locate at ~80.0 kcal/mol above the zero level of the S_0. The most striking changes of the structure of STC $(^1n\pi^*/^3\pi\pi^*/^3n\pi^*)$ are associated with an elongated

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carbonyl C1−O2 and four elongated and two shortened C−C bonds in the moiety of the benzene ring in comparison with those in S_0. As illustrated in Figure 1b, STC($^1n\pi^*/^3\pi\pi^*/^3n\pi^*$) relays the wavepacket of $S_{NP}(^1n\pi^*)$ ISC to a local minimum of the $T_{NP}(^3n\pi^*)$ state that is ~66.0 kcal/mol above the zero level of the S_0 state. A sharply increased energy curve of $T_{NP}(^3n\pi^*)$ hinders the continuous propagation of the wavepacket in the $T_{NP}(^3n\pi^*)$ state in an adiabatic manner along an increasing C3−C4 distance. As an alternative nonadiabatic relaxation channel, the wavepacket decays to the long-distance CT triplet state of $T_{LCT}(^3\pi\pi^*)$ via a conical intersection of CI(T_{NP}/T_{LCT}), where there is a ~2.0 kcal/mol barrier above the $T_{NP}(^3n\pi^*)$ minimum at the C3−C4 distance of ~1.65 Å. With the occurrence of the above nonadiabatic transition, the dipole moment of KP^- rapidly decreases to ~15.0 D in the $T_{LCT}(^3\pi\pi^*)$ state from ~20.0 D in the $T_{NP}(^3n\pi^*)$ state, which confirms the CT characteristic of $T_{LCT}(^3\pi\pi^*)$. Driven by the long-distance charge transfer from the moiety of the phenylpropionic carboxylate anion to the benzyl ring, KP^- decays to a local minimum of $T_{LCT}(^3\pi\pi^*)$ at the C3−C4 distance of 1.95 Å. The local minimum of $T_{LCT}(^3\pi\pi^*)$ is 47.6 kcal/mol above the zero level of S_0 followed by a 4.6 kcal/mol barrier at the C3−C4 distance of 2.1 Å. When this small barrier was overcome, the triplet state wavepacket reaches a flat valley of energy that is similar to the situation seen for the $S_{LCT}(^1\pi\pi^*)$ state and finally gives rise to a biradical carbanion ($^3BC^-$) intermediate and CO_2. The two singly occupied electrons in the configuration of $^3BC^-$ are found to distribute in the region of C1 and C3, while its negative charge is calculated to mainly localize in the C1−O2 carbonyl group, resulting in the negative center around O2 with about −0.64 charge. The triplet intermediate of $^3BC^-$ is ~10.0 kcal/mol less stable than the singlet one (CA^-). This allows the negative center around O2 of $^3BC^-$ to abstract a proton from the solvent matrix and form a much more stable ^{3}BCH product.[14]

As discussed above, an acceptor for the proton transfer is immediately generated around O2 with −0.60 charge once the acidic (KP) form of ketoprofen is taken in the FC of the short-distance CT excited state of $S_{SCT}(^1\pi\pi^*)$ after photoexcitation by $\lambda < 260$ nm UV light. However, the direct ESIPT is disallowed due to a large spatial distance (5.5 Å) between the donor H8 and acceptor O2. Therefore, two water molecules are introduced to function as a bridge to assist the proton transfer. With a slight deviation (0.01 Å) of the O6−H8 distance from that of FC, the excited-state wavepacket of $S_{SCT}(^1\pi\pi^*)$ of $KP\cdot 2H_2O$ rapidly decays to the local minimum that has 114.5 kcal/mol energy with respect to the zero level of S_0 (see Figure 1c). A maximum appears at the 1.20 Å O6−H8 distance and is 9.9 kcal/mol above the minimum of the keto form of $S_{SCT}(^1\pi\pi^*)$-*K*. This barrier is larger than that of a barrierless ESIPT without water participation for *o*-acetylphenylacetic acid that has a closer distance between the donor and acceptor.[11] Like observations in the ESIPT for *o*-acetylphenylacetic acid, the C3−C4 distance (D_{C3-C4}) is simultaneously elongated with the evolvement of the proton transfer, leading to a partial breaking of the C3−C4 bond with a distance of 1.63 Å in the enol form of $S_{SCT}(^1\pi\pi^*)$-*E* (O2−H9 distance is ~1.0 Å).[11] Once the enol form of KP is formed, the excited-state wavepacket rapidly reaches an energetic degenerate region between $S_{SCT}(^1\pi\pi^*)$ and the ground-state CI(S_{SCT}/S_0) that has 62.0 kcal/mol energy at the C3−C4 distance of 2.0 Å. When the C3−C4 distance and evolution of charge transfer from the COO^- moiety to other parts of KP is further increased, the singlet-state intermediate of ^{1}BCH with biradical configuration is finally generated at the C3−C4 distance of 3.0 Å with an O6−C4−O7 angle of ~180.0°. The ^{1}BCH is energetically ~7.7 kcal/mol lower than CI(S_{SCT}/S_0) and ~8.4 kcal/mol above the triplet-state intermediate of ^{3}BCH at the C3−C4 distance of 3.4 Å. Obviously, ^{1}BCH is easy to decay to ^{3}BCH by spin inversion of the two singly occupied electrons via singlet−triplet crossing STC(S_0/T).

In this work, we report efficient photodecarboxylation pathways of ketoprofen in its different forms, which are revealed to be dependent on the pH value of the aqueous solution and the wavelength of photoexcitation. At pH > 7, KP exists mainly in its basic form (KP^-). Photoexcitation at ~330 nm results in the basic KP^- form in the long-distance CT state of $S_{LCT}(^1\pi\pi^*)$. From the $S_{LCT}(^1\pi\pi^*)$ state, it is very easy for the KP^- form to relax into the CI(S_{LCT}/S_0) region, where the $S_{LCT} \rightarrow S_0$ nonadiabatic decay is accompanied with formation of CO_2. This is the most probable pathway of decarboxylation observed experimentally for ketoprofen at a physiological pH condition. The $S_{NP}(^1n\pi^*)$ state can be populated upon photoexcitation of the KP^- form at 328 nm. Through STC($^1n\pi^*/^3\pi\pi^*/^3n\pi^*$) and CI($T_{NP}/T_{LCT}$), the wavepacket can be propagated nonadiabatically to the $T_{LCT}(^3\pi\pi^*)$ state, where decarboxylation occurs with considerable efficiency. During irradiation of KP in acidic aqueous solution at $\lambda < 260$ nm, the KP molecule is excited to the short-distance CT excited state of $S_{SCT}(^1\pi\pi^*)$. Then, the decarboxylation from this state is triggered by water-bridge-aided ESIPT, which overcomes a moderate barrier of 9.9 kcal/mol, producing a triplet-state intermediate of ^{3}BCH. The present computational efforts together with our previous results[11,12] provide benchmarks for understanding the release mechanism of compounds containing photolabile protecting groups.

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Supporting Information Available. Computational details, tables, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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