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Phototriggered Release of a Leaving Group in Ketoprofen Derivatives via a Benzylic Carbanion Pathway, But not via a Biradical Pathway

Ming-De Li,^[a] Tao Su,^[b] Jiani Ma,^[b] Mingyue Liu,^[b] Han Liu,^[b] Xuechen Li,^[b] and David Lee Phillips^{*[b]}

Abstract: 2-Acetoxymethyl-2-(3-benzoylphenyl)propionic acid (KP-OAc) was used as a model to elucidate the solvent-mediated photochemistry mechanism of Ketoprofen (KP). In solutions with a low concentration of water, KP-OAc exhibits a benzophenone-like photochemistry, reacting with water molecules through some reaction to form a ketyl radical intermediate. In neutral solutions with a high concentration of water or acidic solutions, KP-OAc undergoes a photodecarboxylation reaction with the assistance of water molecules or with the catalysis of perchloric acid to directly generate a biradical intermediate that cannot induce the phototrigger reaction to release the AcO^- group. Therefore, the

lifetime of the biradical intermediate of KP-OAc is almost same as that of the biradical intermediate formed from KP in the same kinds of solutions. However, the photodecarboxylation of KP-OAc in phosphate buffer solution directly produces the benzylic carbanion intermediate, which can induce the phototrigger reaction to release the AcO^- group. Therefore, the lifetime of the biradical intermediate of KP-OAc is significantly shorter than the lifetime of the biradical intermediate of KP in

Keywords: carbanions • decarboxylation • density functional calculations • photochemistry • radical ions • time-resolved spectroscopy

phosphate buffer solution. Interestingly, the investigation of the photochemistry of KP-OAc not only verifies the solvent-mediated photochemistry mechanism of KP but also provides some new insight into the potential of using this kind of platform for phototrigger applications. The biradical intermediate is not the key species leading to the phototrigger reaction but the benzylic carbanion species is the key reactive intermediate that can mediate the phototrigger reaction of KP-OAc. Therefore, a change in the pH of the solutions can be utilized to switch on and switch off the photorelease reactions of KP derivative phototrigger compounds.

Introduction

After irradiation, Ketoprofen (KP) is known to induce phototoxicity, which hinders its applications as a nonsteroidal anti-inflammatory drug (NSAID).^[1–2] To understand further the phototoxicity of KP, much research has focused on the photochemistry of KP and its derivatives.^[3–11] Laser flash photolysis (LFP) and nanosecond time-resolved resonance Raman spectroscopy (ns-TR³) studies on KP established that the neutral form of KP exhibits a benzophenone-like photochemistry to give rise to the triplet state of KP (³KP), which, in turn, produces a ketyl radical species in nonaqueous solvents such as neat acetonitrile or isopropanol, and in aqueous solutions with a low concentration of water (below

50 %).^[12–16] However, the dissociated form of KP tends to undergo a prompt photodecarboxylation reaction to generate a benzylic carbanion intermediate in phosphate buffered (PB) solutions (pH 7.4) and in basic solutions.^[12–16] Recently, Scaiano and co-workers reported a new phototrigger based on the photochemistry of KP.^[17] KP exhibits interesting features of rapid and efficient photodecarboxylation ($\Phi=0.75$) to give a benzylic carbanion after electronic excitation of KP in PB solution. Subsequently, the benzylic carbanion is rapidly protonated by the solvent ($k \approx 4.9 \times 10^6 \text{ s}^{-1}$) to give 3-ethylbenzophenone.^[17] Derivatives of KP that include an appropriate leaving group sited on the photogenerated carbanion intermediate can release the leaving group in its active form, along with the final product 3-(2'-allyl)benzophenone.^[17] Among these types of derivatives, 2-acetoxymethyl-2-(3-benzoylphenyl)propionic acid (KP-OAc) has a higher efficiency for photorelease that significantly competes with the protonation of the carbanion intermediate. Therefore, the lifetime of the benzylic carbanion of KP-OAc becomes significantly shorter compared with that of the benzylic carbanion formed from KP. Recent ns-TR³ studies on the photochemistry of KP revealed that water molecules or acid can assist the excited triplet state intramolecular proton transfer (ESIPT) from the carboxyl group to the carbonyl group; the neutral form of KP can then also undergo a photodecarbox-

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ylation reaction in neutral solutions with a high concentration of water (more than 70 %) or strongly acidic solutions. The photodecarboxylation reaction causes the ^3KP to transform into a biradical intermediate.^[18] Although we proposed that the benzylic carbanion of KP was not involved in the photodecarboxylation reaction of the neutral form of KP in neutral solutions with a high concentration of water or acidic solutions, compared with a predominant benzylic carbanion intermediate generated from KP in PB solution, there is no unambiguous evidence to support this proposed mechanism. Here, KP-OAc was used as a model to study the highly efficient photogenerated carbanion induced phototrigger reaction in PB solution as well as water- or acid-assisted photodecarboxylation reactions to generate the biradical intermediate directly in neutral solutions with a high concentration of water or strongly acidic solutions. In PB solution, the negative charge located on the benzylic carbanion is the driving force that initiates photorelease of the AcO^- group and this leads to fast decay of the carbanion intermediate. Solvent-mediated ESIPt may shuttle a proton from the carboxyl group to the carbonyl group, which will induce the photodecarboxylation reaction and generate a KP-OAc biradical intermediate. The KP-OAc biradical species is very stable in neutral solutions with a high concentration of water or strongly acidic solutions. The phototrigger reaction to release the AcO^- group is not likely to occur from the KP-OAc biradical intermediate, so the lifetime of the KP-OAc biradical may last for several hundreds of nanoseconds.

Results and Discussions

Ns-TR³ spectra of KP-OAc in neutral solutions with a low concentration of water —formation of a ketyl radical intermediate: Figure 1 A shows the ns-TR³ spectra of KP-OAc obtained in pure acetonitrile (CH_3CN) solvent. At early delay times, one species with its main resonance Raman bands at 966, 1173, 1221, and 1538 cm^{-1} was observed. This first species, seen in the ns-TR³ spectra, is assigned to the triplet state of KP-OAc ($^3\text{KP-OAc}$) for the following reasons. The spectrum of KP-OAc obtained at 0 ns in CH_3CN solvent was in good agreement with that of KP obtained at 5 ns in CH_3CN solvent.^[15] Because CH_3CN is a relatively inert solvent, the intermediate of KP observed on the nanosecond time-scale in pure CH_3CN has previously been assigned as a ^3KP on the basis of femtosecond transient absorption (fs-TA) and ns-TR³ studies.^[19] Thus, the first species of KP-OAc at 0 ns observed in pure CH_3CN can readily be assigned to the $^3\text{KP-OAc}$ intermediate. At later delay times (180 ns), a very weak band appears at 1582 cm^{-1} , which can be attributed to the formation of a ketyl radical, possibly generated from intramolecular hydrogen abstraction on the side chain in KP-OAc.^[15] Figure 1 B displays the ns-TR³ spectra of KP-OAc obtained in a $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 1:1 mixture. At 0 ns, the band in the Raman spectrum at 1538 cm^{-1} has a shoulder at 1582 cm^{-1} . Initially, the observation of the char-

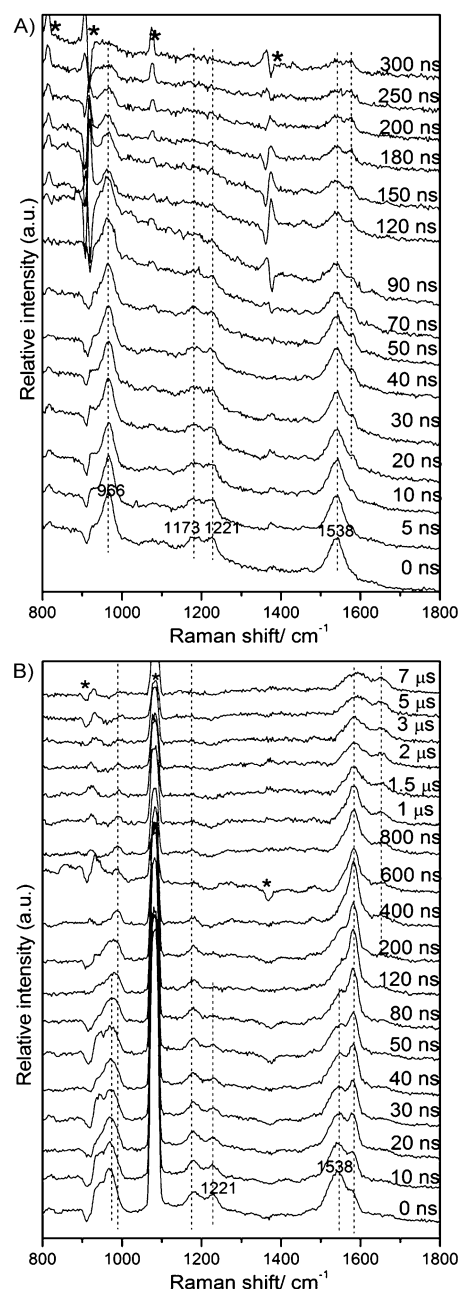


Figure 1. A) Ns-TR³ spectra of KP-OAc in pure CH_3CN and B) in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 1:1 obtained by using 266 nm pump excitation wavelength and 319.9 nm probe wavelength at various time delays indicated next to the spectra. The asterisk (*) marks regions affected by solvent subtraction artifacts and/or stray light.

acteristic Raman band at 1538 cm^{-1} of $^3\text{KP-OAc}$ indicates that $^3\text{KP-OAc}$ is the precursor of the second intermediate. As the $^3\text{KP-OAc}$ species decays, a new intermediate emerges with main Raman bands at 987, 1177, and 1582 cm^{-1} . The latter band is characteristic of the ketyl radical of KP, which indicates that the new species observed following decay of $^3\text{KP-OAc}$ is a ketyl radical produced when the $^3\text{KP-OAc}$ intermediate reacts with the surrounding water molecules, similar to previously observed spectra for KP in analogous solutions.^[16] Subsequently, the KP-OAc ketyl radical may

decay either by a self-coupling reaction or by a cross-coupling reaction with water molecules to form a metastable light absorption transient (LAT) intermediate that can survive hundreds of microseconds.^[1] Therefore, at delay times of more than 1 microsecond the Raman signal at 1592 cm^{-1} and 1648 cm^{-1} is due to the long-lived LAT species.

The triplet state of benzophenone (BP; the parent chromophore of KP-OAc) does not easily abstract hydrogen from CH_3CN , and no Raman signal for the ketyl radical was observed in pure CH_3CN solvent. Only the Raman signal of the triplet state of BP was observed in pure CH_3CN solvent.^[9,20] For BP and KP, Raman spectra apparently due to a ketyl radical-like species can be observed in aqueous solutions on the nanosecond time-scale. Furthermore, for KP, the intensity of the Raman signal of the apparent ketyl radical-like species gradually becomes stronger as the water concentration increases from 10 to 50%.^[9] This suggests that water molecules may play some role in the generation of the ketyl radical-like species after photolysis of KP in aqueous environments. These results indicate that the triplet state of BP and KP neither abstract hydrogen from CH_3CN solvent nor significantly abstract hydrogen from the ground state of BP and KP, even though a higher concentration of samples were used in the ns-TR³ experiments in pure CH_3CN solvent. The observation of the Raman signal of the ketyl radical-like intermediate implies that the triplet state of BP and KP may react with water through some reaction to generate a ketyl radical-like intermediate; however, mechanistic details for its formation are still not clear. Thus, for KP-OAc, the source of the ketyl radical-like species in solutions with a low concentration of water is not clearly understood and further work is required to better understand how it is formed in these kinds of aqueous environments. KP-OAc exhibits a benzophenone-like photochemical behavior in CH_3CN solvent or neutral solutions with a low concentration of water, which is similar to that of KP under corresponding conditions. For the photochemical reaction of KP-OAc in neutral solutions with a low concentration of water, Scheme 1 shows that the singlet excited state of KP-OAc will transform into the $^3\text{KP-OAc}$ intermediate by an ISC process, then the $^3\text{KP-OAc}$ intermediate will undergo some reaction to generate a ketyl radical species.

Ns-TR³ spectra of KP-OAc in neutral solutions with a high concentration of water or acidic solutions—direct formation of the biradical intermediate: Figure 2 A shows the ns-TR³ spectra obtained in neutral solutions with a high concentration of water. A new Raman band at 1519 cm^{-1} can be observed in the 80% water solution compared with the Raman

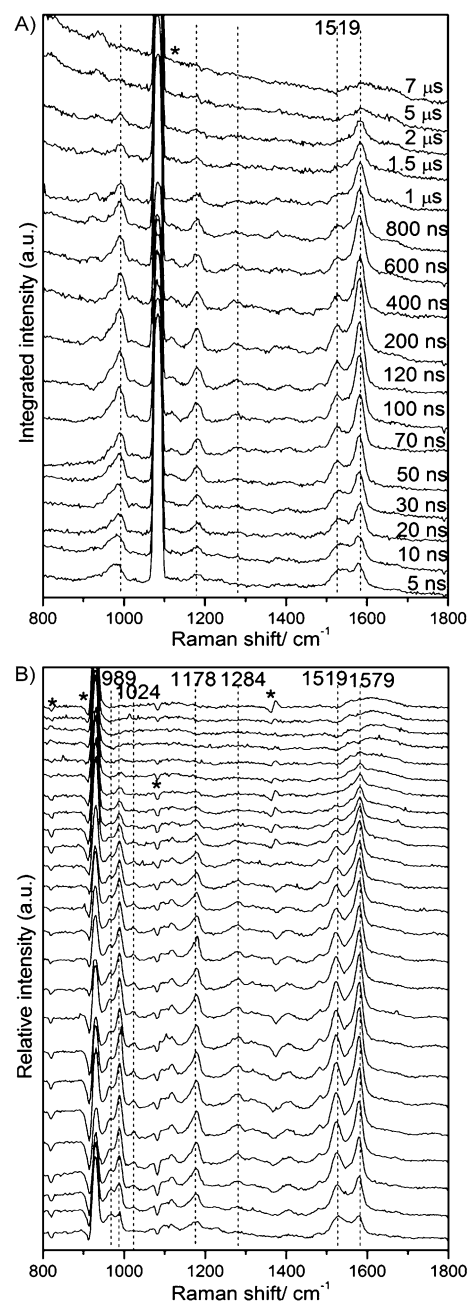
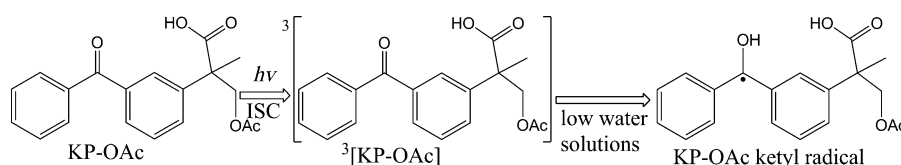


Figure 2. A) Ns-TR³ spectra of KP-OAc in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 8:2 and B) in perchloric acid ($\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 1:1, pH 0) solutions obtained by using 266 nm pump excitation wavelength and 319.9 nm probe wavelength at various time delays indicated next to the spectra. The asterisk (*) marks regions affected by solvent subtraction artifacts and/or stray light.

spectra obtained in the 50% water solution. Previous studies pointed out that the 1519 and 1579 cm^{-1} Raman bands are characteristic of the biradical intermediate of KP and this indicates that some portion of KP-OAc molecules will undergo a photodecarboxylation reaction to generate a biradical intermediate in solutions with a high concentration of water.^[16]



Scheme 1. The proposed photochemistry mechanism of KP-OAc in neutral solutions with a low concentration of water.

In Figure 2A, the intensity of the 1519 cm^{-1} Raman band is weaker than that of the 1582 cm^{-1} band. In the $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 2:8 solution, the photodecarboxylation reaction generating the KP-OAc biradical and the reaction with water, generating the ketyl radical, occur on a similar time-scale so that these two reactions compete. The KP-OAc biradical has a characteristic Raman band at 1579 cm^{-1} and the ketyl radical has a characteristic Raman band at 1582 cm^{-1} , thus these two Raman bands overlap and make it difficult to completely separate them and study their kinetics with this Raman feature. Nevertheless, it appears that the decay times of the 1519 and 1579 cm^{-1} bands are different in the $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 2:8 solution. It should be noted that DFT calculations predicted the Raman spectra of the KP-OAc biradical and indicated that the 1519 and 1579 cm^{-1} Raman bands correspond to the KP-OAc biradical. Further increasing the water concentration will make the photodecarboxylation reaction become the predominant process due to the increasing effectiveness of the water-mediated proton transfer from the carboxyl group to the carbonyl group, which significantly induces cleavage of the C–C bond and the release of CO_2 .^[18] Previous studies concluded that acid can also catalyze a similar photodecarboxylation reaction of KP for which two steps were involved when perchloric acid was used to induce the photodecarboxylation reaction of KP in highly acidic solutions.^[18] For the acid-induced photodecarboxylation, the carbonyl group is first protonated and then the proton of the carboxyl group is transferred to the perchloric anion and simultaneous cleavage of C–C leads to release of CO_2 .

Figure 2B presents the ns-TR³ spectra of KP-OAc obtained in pH 0 aqueous solution. The main Raman bands (966 , 989 , 1024 , 1178 , 1284 , 1519 , and 1579 cm^{-1}) of KP-OAc are essentially the same as those observed for the KP intermediates obtained in an analogous acidic aqueous solution, and this implies that a biradical intermediate is also generated for the KP-OAc molecule. Therefore, KP-OAc can also decarboxylate through catalysis by perchloric acid. In acidic aqueous solution and phosphate buffer solutions, the photodecarboxylation reaction is the predominant reaction. Therefore, the biradical intermediate is the major transient detected, and the 1519 and 1579 cm^{-1} Raman bands have the same decay time because both correspond to the biradical intermediate. As mentioned earlier, the Raman band at 1582 cm^{-1} is assigned to the ketyl radical. The 1519 cm^{-1} Raman band is saliently enhanced compared with that obtained in 80% water solution, which is consistent with the activation energy barrier calculated for the acid-mediated photodecarboxylation reaction of KP being lower than that of the water-molecule-assisted photodecarboxylation reaction of KP.^[18]

Ns-TR³ spectra of KP-OAc in PB solution—direct formation of the benzylic carbanion intermediate: Based on the ns-TR³ and nanosecond transient absorption studies of KP in neutral solutions with a high concentration of water or acidic solutions and DFT calculations simulating the solvent-assisted ESIPT process, we proposed that KP under-

went a solvent-assisted ESIPT process and then the photodecarboxylation reaction was initiated to generate a biradical intermediate directly in neutral solutions with a high concentration of water or acidic solutions, whereas the KP anion tended to undergo its photodecarboxylation reaction to directly produce the benzylic carbanion of KP with triplet state character in PB solution. In an attempt to verify this proposed mechanism, we chose to use KP-OAc as a model molecule to test the mechanism. Previous studies by Scaiano and co-workers found that KP-OAc was a clear and efficient phototrigger that initiated photorelease of an AcO^- group, and a benzylic carbanion intermediate was formed to mediate the photorelease of the leaving group in PB solution.^[17] Figure 3 A displays the ns-TR³ spectra of KP-OAc obtained in 50% PB solution. The ³KP-OAc intermediate is barely observable in PB solution. A new species is observed at the early delay times of ns-TR³ spectra and this species has its main Raman bands at 989 , 1178 , 1519 , and 1579 cm^{-1} . Due to the observation of the characteristic Raman bands of the biradical intermediate of KP at 1519 and 1579 cm^{-1} , this species is assigned to the KP-OAc biradical intermediate generated by the photodecarboxylation reaction; this intermediate completely disappears after 100 ns. For KP in PB solution, Figure 3 B shows that the Raman intensity of the biradical intermediate is relatively strong and its lifetime is clearly longer than that of the KP-OAc biradical species observed in PB solution.^[16,18]

Interestingly, the results obtained with KP-OAc in the ns-TR³ study coincidentally confirm our initial hypothesis for the reaction mechanism proposed for the decarboxylation of KP under the different aqueous conditions. As expected, the lifetime of the KP-OAc biradical is significantly shortened in PB solution, whereas the lifetime of the KP-OAc biradical intermediate is not affected in neutral solutions with a high concentration of water or acidic solutions. In solutions with a high concentration of water or acidic solution (pH 0), the dynamics of the KP-OAc biradical intermediate is almost the same as that of KP obtained under the same conditions.^[18] For example, the time dependence of the integrated areas of the 1579 cm^{-1} Raman band for the KP-OAc biradical intermediate (closed squares) in a water/ CH_3CN 1:1 perchloric acid (pH 0) solution could be fit by a two-exponential function with a ca. 13 ns growth time constant and a ca. 240 ns decay time constant (see Figure 4). The KP-OAc biradical intermediate could survive with a long lifetime (240 ns decay time constant) that is very close to the lifetime (ca 280 ns) of KP in the same solution.^[18] This implies that a KP-OAc biradical intermediate is directly generated by the photodecarboxylation reaction with the assistance of water or acid. The benzylic carbanion species is not involved in the photochemistry of KP-OAc and KP in solutions with a high concentration of water or acidic solutions. However, the lifetime of the biradical intermediate of KP-OAc and KP exhibits a salient difference in PB solution. Figure 5 presents a comparison of the kinetics of the biradical intermediate for KP-OAc and KP obtained in 50% PB solution. The decay time constant of the KP-OAc biradical intermedi-

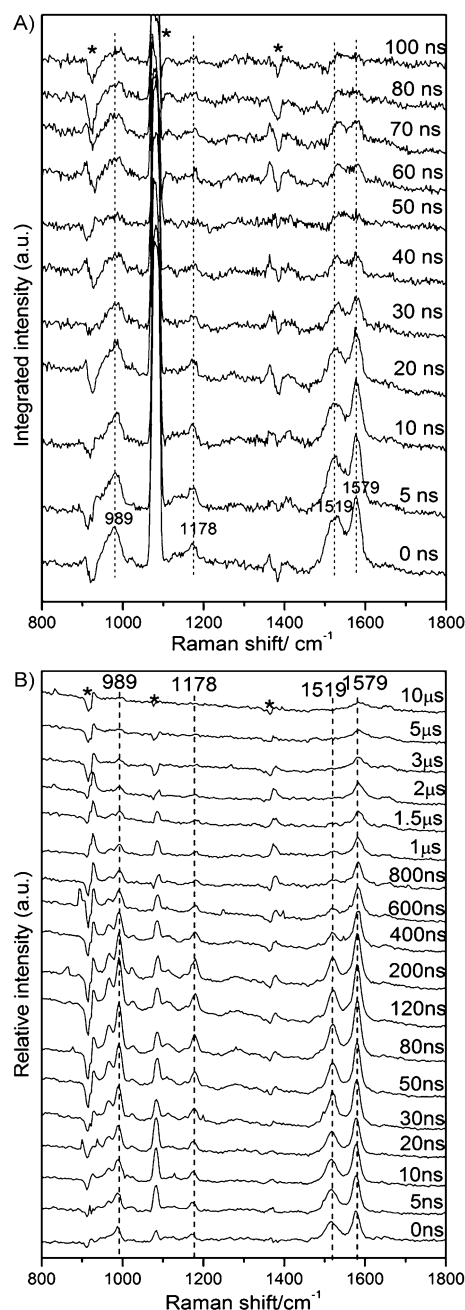


Figure 3. A) ns-TR³ spectra of KP-OAc in PB/CH₃CN 1:1 and B) ns-TR³ spectra of KP in PB/CH₃CN 1:1 obtained by using 266 nm pump excitation wavelength and 319.9 nm probe wavelength at various time delays indicated next to the spectra. The asterisk (*) marks regions affected by solvent subtraction artifacts and/or stray light.

ate in PB solution is only 30 ns, which is dramatically shorter than the time constant of the biradical intermediate for KP in PB solution (780 ns). For KP, the formation process of the biradical intermediate is still readily observed in 50% PB solution, whereas only the decay process of the KP-OAc biradical intermediate is observed for KP-OAc in an analogous PB solution. This result reveals that the benzylic carbanion is directly generated and that the photorelease of the AcO[−] anion will quickly consume the benzylic carbanion

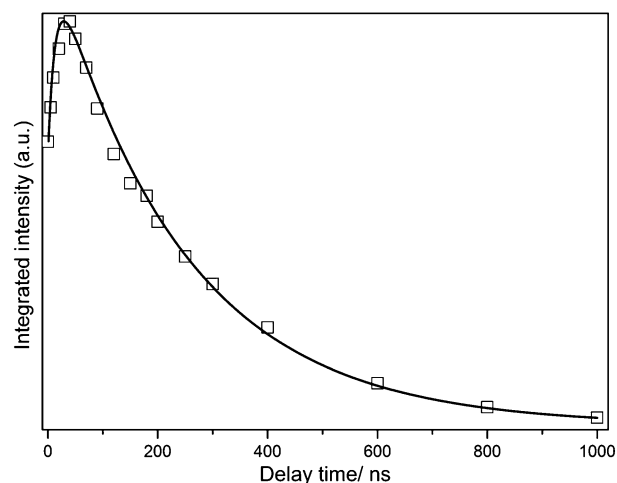


Figure 4. Time dependence of the integrated areas of the 1579 cm^{−1} Raman band of the biradical intermediate for KP-OAc (closed squares) in perchloric acid/(H₂O/CH₃CN 1:1) pH 0 were fit by a two-exponential function with a ca. 13 ns growth time constant and a ca. 240 ns decay time constant.

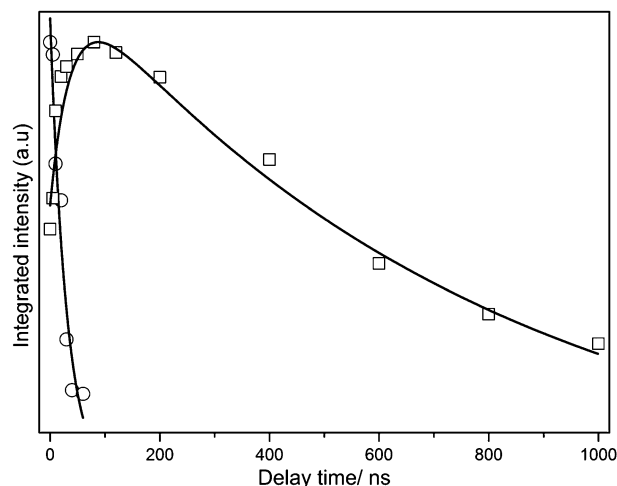
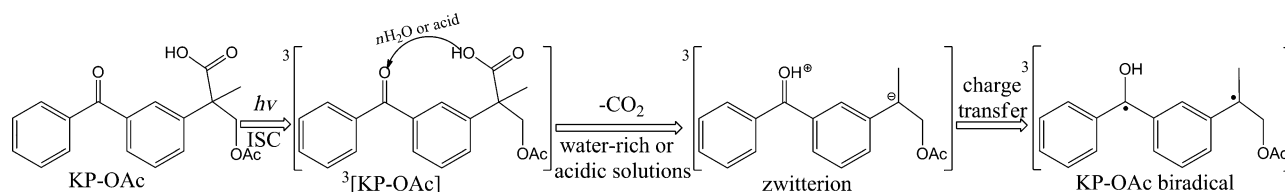


Figure 5. Time dependence of the integrated areas of the 1579 cm^{−1} Raman band for the biradical intermediate of KP-OAc (open circles) in PB/CH₃CN 1:1 were fit by a two-exponential function with a ca. 30 ns decay time constant. Time dependence of the integrated areas of the 1579 cm^{−1} Raman band for the biradical intermediate of KP (open squares) in PB/CH₃CN 1:1 were fit by a two-exponential function with a ca. 37 ns growth time constant and a ca. 780 ns decay time constant.

(see Scheme 3). Therefore, the predominant competitive phototrigger reaction will significantly shorten the lifetime of the KP-OAc biradical intermediate. As for KP, the benzylic carbanion is resonant with the biradical intermediate, which may last for a long lifetime, and then finally the biradical intermediate will undergo a hydrogen shift and intersystem crossing (ISC) to generate the final product.^[8]

Benzylic carbanion switches on and biradical intermediate switches off the photoreleasing reaction of KP-OAc: To obtain direct evidence to confirm that the photodecarboxyl-

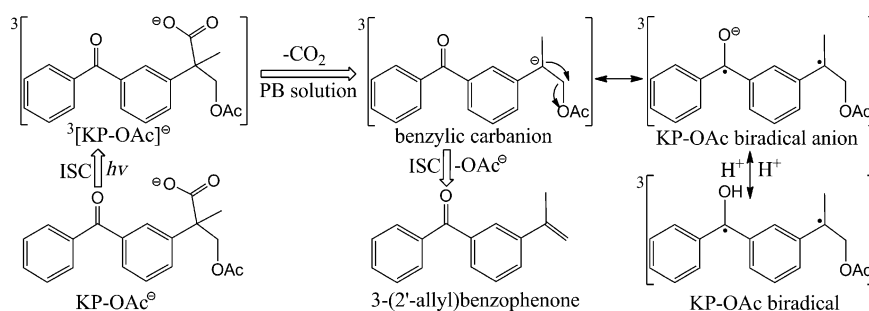


Scheme 2. The proposed photodecarboxylation mechanism of KP-OAc in solutions with a high concentration of water (water-rich) or acidic solutions.

ation reaction is initiated from the $^3\text{KP-OAc}$, femtosecond transient absorption (fs-TA) experiments were conducted for KP-OAc in pure CH_3CN solution, in high water content solution, in acidic aqueous solution, and in PB aqueous solution. In pure CH_3CN solvent, a sharp band (maximum at 334 nm) was first observed, which gradually increased in intensity on the early picosecond time-scale (see Figure 1S in the Supporting Information); this transient was assigned to the singlet state of KP-OAc.^[12,19] Subsequently, the sharp band around 334 nm gradually reduced in intensity and shifted to 325 nm; at the same time, a broad band (maximum at 523 nm) appeared and gradually increased in intensity within 50 ps (see Figure 1S). This process can be assigned to the singlet state undergoing an intersystem crossing (ISC) process to form $^3\text{KP-OAc}$.^[12,19] The $^3\text{KP-OAc}$ is relatively stable in this solvent and does not decay within 3 ns, so that the Raman band at 1538 cm^{-1} , which was assigned to $^3\text{KP-OAc}$, can be clearly observed in the ns-TR³ experiments performed in pure CH_3CN solvent. In solutions with a low concentration of water, $^3\text{KP-OAc}$ slightly reduces in intensity within 3 ns, but can still be observed within 100 ns in this solvent system. In higher water content solution and in acidic solution, a photochemical process similar to that observed in pure CH_3CN solvent and in solutions with a low concentration of water is also observed. First, a sharp band around 334 nm increases in intensity within about 1 ps (see Figure 2S in the Supporting Information); this transient can be assigned to the $\text{S}_1 \rightarrow \text{S}_n$ transition absorption from the S_1 ($n\pi^*$) singlet state. Then the band at 334 nm decreases in intensity and a broad band at 523 nm increases in intensity (see Figure 6 a and b) in a process that corresponds to the singlet state undergoing ISC to form the $^3\text{KP-OAc}$ with high efficiency. The band at 523 nm begins to decrease in intensity with an increase of the delay times in solutions with a high concentration of water and in acidic aqueous solution, which indicates that $^3\text{KP-OAc}$ partly decays through decarboxylation reaction in these types of solutions. With the decay of the band at 523 nm at later times (several ns), a band at 325 nm begins to increase in intensity again, the new band around 325 nm is assigned to the biradical species^[19] and demonstrates that the decay of $^3\text{KP-OAc}$ directly

generates a biradical intermediate. Although $^3\text{KP-OAc}$ already decays to some extent within 3 ns, the triplet state is still observed at the beginning of the nanosecond time delays, and a shoulder Raman band of the 1538 cm^{-1} main Raman band can be observed. In PB solution, with the dramatic decay of the band intensity at 523 nm, a new band appears around 600 nm that is assigned to the benzylic carbanion species.^[12,19] Therefore, in PB solution, $^3\text{KP-OAc}$ cannot be observed in the ns-TR³ experiment. The observation of the ISC process and $^3\text{KP-OAc}$ in higher water content solution, acidic aqueous solution, and PB solution by the fs-TA experiments suggests that the KP-OAc biradical and carbanion species are formed in the triplet state.

Schemes 2 and 3 display the proposed photochemistry mechanisms of KP-OAc in neutral solutions with a high concentration of water, acidic, and PB solutions. After 266 nm



Scheme 3. The proposed photodecarboxylation mechanism of KP-OAc in PB solution.

photoexcitation in neutral solutions with a high concentration of water or acidic solutions, the singlet excited state undergoes intersystem crossing (ISC) to transform into the triplet excited state so that the $^3\text{KP-OAc}$ species is the intermediate first observed by the ns-TR³ experiments, and then the excited triplet state proton transfer from the carboxyl to carbonyl group occurs with the assistance of water molecules or perchloric acid to produce a very short-lived zwitterion intermediate that subsequently undergoes a fast competitive intramolecular charge transfer to evolve into the KP-OAc biradical intermediate, which has a relatively long lifetime. Previous studies showed that acid can also catalyze the photodecarboxylation reaction of KP, for which two steps were involved when perchloric acid was used to induce the photodecarboxylation reaction of KP in the strong acidic solutions.^[18]

For the acid-induced photodecarboxylation, DFT calculations showed that the carbonyl group is protonated first and

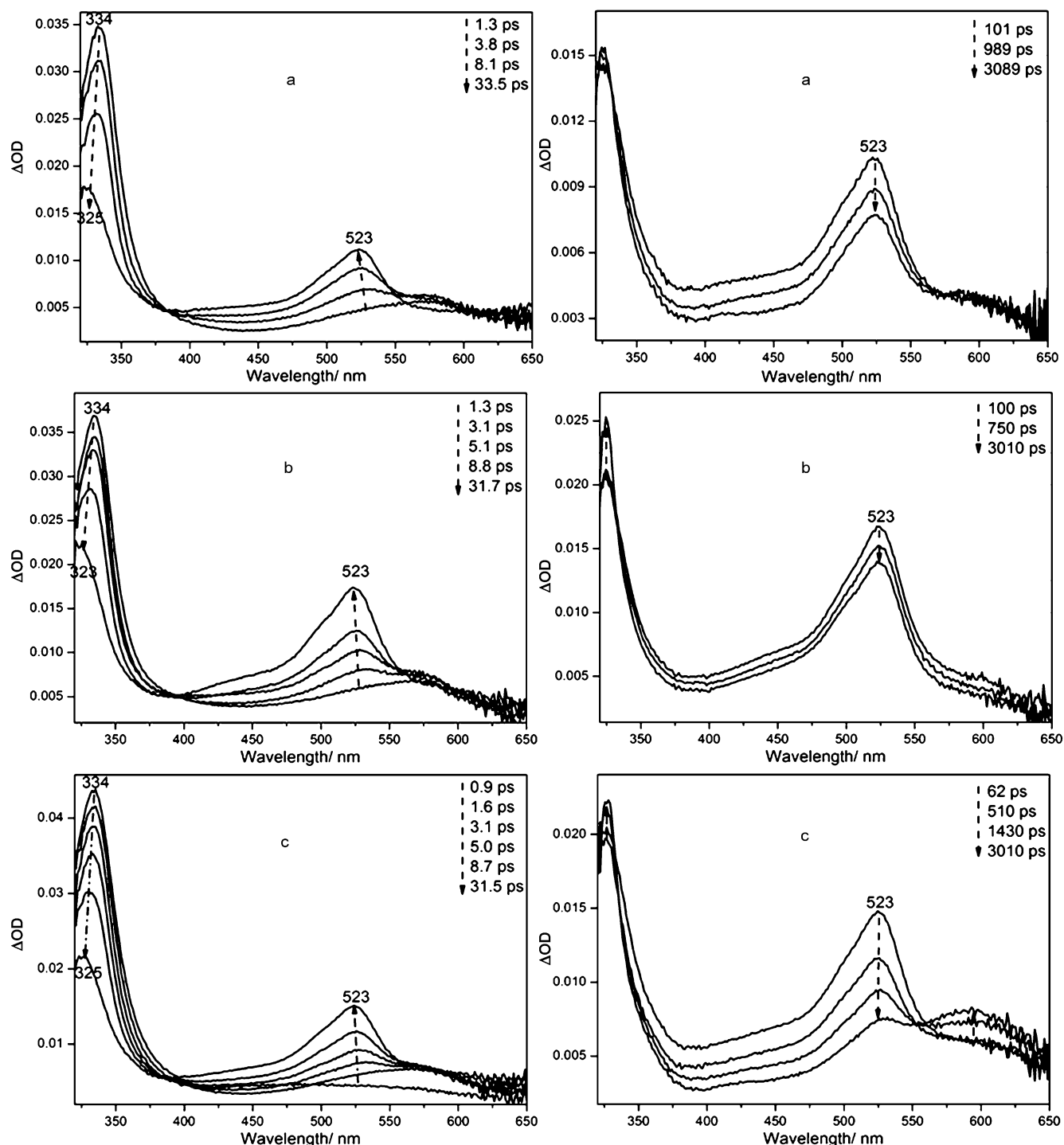


Figure 6. Transient absorption spectra of KP-OAc obtained in a) $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 8:2, b) in acidic $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 1:1, pH 0, and c) in $\text{CH}_3\text{CN}/\text{PB}$ 1:1, pH 7.4.

then the proton of the carboxyl group is transferred to the perchloric anion and, simultaneously, cleavage of C–C leads to release of CO_2 . The activation energy barriers for perchloric acid assisted proton transfer from the hydroxyl group to the carbonyl group are -0.21 and $-1.32 \text{ kcal mol}^{-1}$, respectively. For those systems with negative reaction barriers, these reactions usually need to overcome the low activation reaction barriers.^[20] Therefore, although the $\text{p}K_a$ of the

acid KP in the S_0 is $4.7^{[1]}$ and the $\text{p}K_a$ of triplet state of BP is 1.5 ,^[21–24] the low activation reaction barriers make it possible that KP-OAc can decarboxylate through catalysis by perchloric acid. However, in PB solution, the deprotonated form initiates the photochemistry of KP-OAc. When KP-OAc is excited at 266 nm , ISC will lead to the generation of the $^3[\text{KP-OAc}]^-$ anion, which will undergo a fast photodecarboxylation reaction on the sub-nanosecond time-scale to

generate a benzylic carbanion species that will induce the phototrigger reaction to release the leaving group AcO^- and subsequently form the final product 3-(2'-allyl)benzophenone. The KP-OAc biradical anion is a resonant structure of the benzylic carbanion, and such a KP-OAc biradical intermediate is also observed in PB solution by the ns-TR³ experiments. Although the zwitterion has a negative charge located at the sidechain of KP-OAc, it must be noted that the zwitterion intermediate does not easily undergo the phototrigger reaction because the lifetime of the KP-OAc biradical is almost the same as that of the KP biradical under analogous conditions. A possible reason for this is that the intramolecular charge transfer is a very fast process, meaning that the phototrigger reaction cannot compete with the intramolecular charge transfer.

DFT computational study on the mechanism of the benzylic carbanion and biradical intermediates mediating the phototrigger reaction of KP-OAc: To gain more insight into the phototrigger reaction mechanism of KP-OAc, DFT calculations were carried out to simulate the benzylic carbanion and KP-OAc biradical intermediates mediating the photorelease reaction. Figure 7 shows the optimized geometries (bond lengths in Å) of reactive complexes (RC), transition

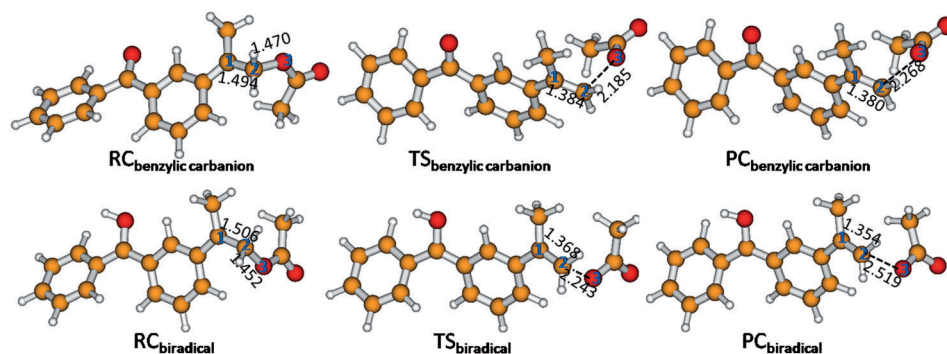


Figure 7. Optimized geometries (bond lengths in Å) of the reactive complex (RC), the transition state (TS) and the product complex (PC) found from the UB3LPY/6-311G** calculations for the phototrigger reactions of the benzylic carbanion and the KP-OAc biradical intermediate.

states (TS), and product complexes (PC) found from the UB3LPY/6-311G** calculations for the phototrigger reactions of the benzylic carbanion and the KP-OAc biradical intermediates. The bond distance between C(2) and O(3) (labeled in Figure 7) is 1.470 Å for the benzylic carbanion, which is somewhat longer than that for the KP-OAc biradical intermediate (1.452 Å). This reveals that cleavage between C(2) and O(3) is more facile for the benzylic carbanion. Additionally, the bond distance between C(2) and O(3) is 2.185 Å in the TS of the benzylic carbanion whereas it is 2.243 Å in the TS of the KP-OAc biradical intermediate. The energy barrier to scan from 1.470 to 2.185 Å for the benzylic carbanion can be expected to be smaller than the energy barrier upon going from 1.452 to 2.243 Å for the KP-OAc biradical intermediate. Figure 8 shows the relative

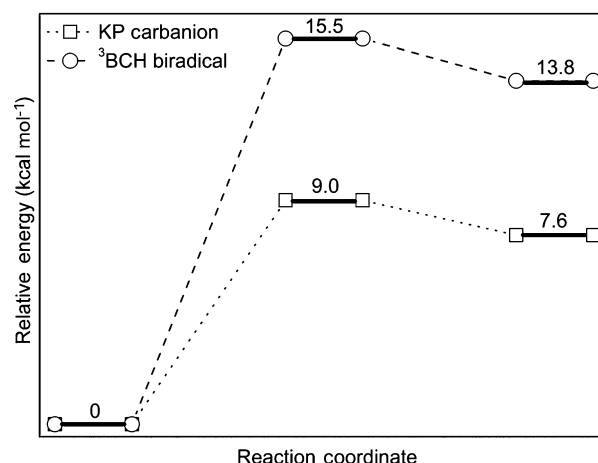


Figure 8. Relative energy profiles (in kcal mol⁻¹) obtained from the UB3LPY/6-311G** calculations for the phototrigger reactions of the benzylic carbanion and the KP-OAc biradical intermediate.

energy profiles (in kcal mol⁻¹) obtained from the UB3LPY/6-311G** calculations for the phototrigger reactions of the benzylic carbanion and the KP-OAc biradical intermediate. The free energy barrier for the phototrigger reaction of the

benzylic carbanion only needs to overcome 9 kcal mol⁻¹, whereas it is 15.5 kcal mol⁻¹ for the biradical intermediate phototrigger reaction. Therefore, the negative charge located on the C(1) atom will greatly promote release of the AcO^- anion. The phototrigger reaction can be expected to easily consume the benzylic carbanion, which provides a basic explanation that is consistent with the experimental observation that the lifetime of the KP-OAc biradical intermediate is very short in PB solution.

Conclusion

This study investigated the photochemical reaction mechanisms of KP-OAc in solutions with a low and a high concentration of water, acidic, and PB solutions. In neutral solutions with a low concentration of water, ns-TR³ spectra revealed that a ³KP-OAc intermediate was first observed, which then transformed into a ketyl radical intermediate by some reaction with the sidechain of KP-OAc or surrounding water molecules. In neutral solutions with a high concentration of water, KP-OAc underwent a photodecarboxylation reaction with the assistance of water molecules or perchloric acid to directly generate a KP-OAc biradical intermediate that cannot easily induce the phototrigger reaction. In PB

solution, the deprotonated KP-OAc anion underwent a photodecarboxylation reaction to directly produce a benzylic carbanion intermediate that can easily induce a phototrigger reaction to release the leaving group AcO^- . Therefore, the KP-OAc system is a good model molecule with which to examine the proposed photochemistry mechanisms of KP and its derivatives. Water or acid can mediate ESIPT processes that will induce photodecarboxylation reactions of KP in neutral and acidic aqueous solutions. It should be noted that the new insight into the intermediates that more easily undergo phototrigger reactions in the photochemistry mechanisms of KP-based derivatives makes it possible to understand how to modulate the phototrigger reactions of KP derivative compounds and, potentially, other aromatic carbonyl based systems by varying the pH values of the solutions as well as modulating the properties of the key reactive intermediates. When the pH value is increased to a slightly basic solution, the phototrigger reaction will occur mostly from the anionic form of the derivative, in the case of KP-OAc, the phototrigger reaction is switched on, whereas decreasing the pH value in an acidic solution will switch off the phototrigger reaction in the case of KP-OAc. As a consequence, this makes KP-based phototrigger compounds very promising platforms with which to develop new types of phototriggers for utilization in the biological and medical fields.

Experimental and Computational Methods

Materials: 2-Acetoxyethyl-2-(3-benzoylphenyl)propionic acid was prepared by following literature procedures with minor modification. Commercially available 2-(3-benzoylphenyl)-2-methyl propionic acid (Ketoprofen) and other reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer at 400 MHz and 100 MHz, respectively. All NMR data were in accordance with reported data.^[17] Details of the synthetic procedures are presented in the Supporting Information.

Perchloric acid (reagent grade from Aldrich) was used to vary the pH value of the aqueous solutions used in all of the experiments reported here. Spectroscopic grade CH_3CN and deionized water were used as solvents for the experiments presented in this work. In the ns-TR³ experiments, the concentration of the experimental sample of KP-OAc was 1 mM. Unless specified, all of the mixed solvent ratios were of volume ratio.

Ns-TR³ experiments: The nanosecond time-resolved resonance Raman (ns-TR³) experiments were performed with an apparatus and methods discussed in detail previously^[25] and only a brief description will be given here. The 266 nm pump laser pulse generated from the fourth harmonic of a Nd:YAG nanosecond pulsed laser and a 319.9 nm probe laser pulse produced from the third anti-Stokes hydrogen Raman shifted laser line from the second harmonic were used in the TR³ experiments. The two Nd:YAG lasers were synchronized electronically by a pulse delay generator (DG535) to control the time delay of pump and probe lasers, and this time delay between the laser pulses was monitored by a fast photodiode and a 500 MHz oscilloscope. The time resolution for the TR³ experiments was approximately 10 ns. The pump and probe laser beams were lightly focused onto the sampling system and the Raman light was collected using reflective optics into a spectrometer the grating of which dispersed the light onto a liquid nitrogen cooled CCD detector. The Raman signal was acquired for 30 s by the CCD before reading out in the interfaced PC computer and 10 scans of the signal were accumulated to produce a

resonance Raman spectrum. The TR³ spectra presented here were obtained by subtracting the resonance Raman spectrum with a negative time delay of -100 ns (probe-before-pump spectrum) from the resonance Raman spectrum with a positive time delay (pump-probe spectrum). The TR³ spectra in this work were calibrated by using the known Raman bands of CH_3CN solvent with an estimated accuracy of $\pm 5\text{ cm}^{-1}$. In the ns-TR³ experiments, a micropump was employed to push the sample solution, and a 1 mM concentration of KP was used in the ns-TR³ experiments.

Fs-TA experiments: The fs-TA experiments were performed by using apparatus and methods discussed in detail previously.^[19,26] The fs-TA measurements were performed based on a femtosecond Ti:Sapphire regenerative amplified Ti:sapphire laser system and an automated data acquisition system. At each temporal delay, data were averaged for 2 s. For the present experiments, the sample solution was excited by a 267 nm pump beam (the third harmonic of the fundamental 800 nm from the regenerative amplifier). The 50 mL solutions were studied in a flowing 2 mm path-length cuvette with the intensity of absorption 1.0 at 267 nm throughout the data acquisition. The raw spectra obtained for KP-OAc in water solutions contain an overlapping contribution from the sample absorption and solvated electrons produced by the two-photo ionization of the water when 267 nm was used as pump laser. The hydrated electron has a very strong absorption at approximately 600 nm. Therefore, subtraction of the solvent signal should be performed to compensate for the influence of the solvent signal as soon as possible; under these conditions, most of the contribution of the hydrated electron signal will be eliminated. Details of the methods used for this were described previously.^[27]

DFT calculations: Density functional theory (DFT) was used to investigate the phototrigger reaction of the benzylic carbanion and the biradical intermediates for KP-OAc. The optimized geometries, vibrational modes, and the vibrational frequencies for the different species were obtained from (U)B3LYP DFT calculations employing a 6-311G** basis set. No imaginary frequency modes were observed at the stationary states of the optimized structures shown here and only one imaginary frequency was observed for the saddle point transition state structures. All of the reactions have been explored by optimizing the structures of the reactant (RC), transition states (TS), and product complexes (PC). Transition states were located by using the Berny algorithm. Frequency calculations at the same level of theory have also been performed to identify all of the stationary points as minima for transition states (one imaginary frequency). Intrinsic reaction coordinates (IRC)^[28] were calculated for the transition states to confirm that the relevant structures connect the two relevant minima. All of the calculations were performed using the Gaussian 03 program suite.^[29]

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