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Direct Observation of Photoinduced Ultrafast Generation of Singlet and Triplet Quinone Methides in Aqueous Solutions and Insight into the Roles of Acidic and Basic Sites in Quinone Methide Formation

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ABSTRACT: Femtosecond time-resolved transient absorption spectroscopy (fs-TA) experiments and density functional theory (DFT) computations were done for a mechanistic investigation of 3-(1-phenylvinyl)phenol (1) and 3-hydroxybenzophenone (2) in selected solvents. Both compounds went through an intersystem crossing (ISC) to form the triplet excited states $T\pi\pi^*$ and $Tn\pi^*$ in acetonitrile (ACN) but behave differently in neutral aqueous solutions, in which a triplet excited state proton transfer (ESPT) process induced by the ISC process is also proposed for 2 but a singlet ESPT process without ISC is proposed for 1, leading to the production of the triplet quinone methide (QM) and the singlet excited QM species respectively in these two systems. The triplet QM then underwent an ISC process to form an unstable ground state intermediate which soon returned to its starting material 2. On the other hand, the singlet excited state QM went through an internal conversion (IC) process to the ground state QM followed by the formation of its final product in an irreversible manner. These differences are thought to be derived from the slow vinyl C-C rotation and the moderate basicity of the vinyl C atom in 1 as compared with the fast C-O rotation and the more basicity of the carbonyl O atom of 2 after photoexcitation. This can account for the experimental results in the literature that the aromatic vinyl compounds undergo efficient singlet excited state photochemical reactions while the aromatic carbonyl compounds prefer triplet photochemical reactions under aqueous conditions. These results have fundamental and significant implications for the understanding of the ESPT reactivity in general, as well as for the design of molecules for efficient QM formation in aqueous media with potential applications in cancer phototherapy.

INTRODUCTION

Excited state proton transfer (ESPT) is an essential biological and chemical process that has been investigated by a large number of researchers.¹ An aromatic molecule containing both acidic and basic positions will typically display greater acidity and basicity upon excitation, respectively and thus afford opportunities for the excited state proton transfer (ESPT) to occur. ESPT reactions can results in the production of tautomers which may be hard to make by thermal methods.²

Quinone methides (QMs) are reactive intermediates of general interest in different areas of chemistry. QMs have been shown to undergo reactions with amino acids³ and DNA,⁴ and QMs can also alkylate and crosslink DNA⁵⁶⁷ which enables them to become powerful agents in cancer therapy. Although QMs may be formed in thermal reactions,⁸⁹¹⁰ the photochemical reactions of some phenols [like photodehydroxylation of hydroxybenzylphenols,¹¹ photoelimination of acetic acid¹² or amines¹³] have appeal due to the milder reaction conditions needed to generate them. Photoinduced QM formation also has potential uses in photodynamic therapy applications. Much effort has gone into the development of new molecular

systems to achieve high quantum yields of QM formation. On the other hand, a number of investigations have been done to examine the photochemical reaction mechanisms of these systems which are important to elucidate how QMs are produced and which processes determine the yields and products made.¹⁴ The accurate identification of the intermediates generated upon irradiation is also necessary to know when these systems are to be used in biological applications.

In some of the molecular systems that are of interest to be used in biological applications, ESPT is sometimes thought to be involved in the reaction mechanisms for QM production. For ESPT reactions previously examined, a typical acidic location may be a phenolic proton, and a typical basic location may be a heteroatom on a heterocyclic ring,¹⁵ or a carbonyl moiety.¹⁶ Remarkably, the carbon atom was recently found to be able to act as a basic group.2 Wan and coworkers reported that the ESPT in3-(1-phenylvinyl)phenol (1) gives the QM species (1QM), which is trapped by water forming a diaryl ethanol product.¹⁷¹⁸The protonation of carbon atoms has been considered to take place slower than the protonation of heteroatoms,¹⁹ and therefore, it was not usually taken into account as a competing excited state pathway with ESPT to H₂O

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or ESPT to heteroatoms. However, theoretical²⁰ and experimental investigations¹⁴ provided pieces of evidence that protonation of carbon atoms can be fast and compete with ESPT.

Scheme 1. The proposed QM formation mechanisms of **1** and **2** in neural aqueous solutions include a concerted pathway and a stepwise pathway as illustrated below.¹⁷⁻¹⁸



Although a lot of effort has been out toward the study of **1** and useful information has been obtained, several questions are still left to be answered. First, only the decay of the QM was observed by nanosecond transient absorption (ns-TA) spectra due to the apparent ultrafast formation of the QM species of **1**.¹⁷⁻¹⁸Hence, how the QM species is formed is still uncertain. It could be accomplished by a concerted water-relay ESPT with the phenolic proton transfer to the alkene α -carbon, or by a stepwise ESPT with the phenolic proton ionized first to the solvent and then a fast reprotonation at the alkene α -carbon (Scheme 1). Second, as mentioned above, the carbonyl group is a typical basic site for the ESPT while the carbon atom is viewed as an unusual group to be protonated. However, the fast overall rates and high quantum efficiencies of 1 to generate the OM intermediate observed are surprising. Furthermore, it is reported that the transfer of the proton to a carbonyl group is easily reversible reaction, while the ESPT to a carbon atom is in many cases irreversible that can lead to subsequent reaction to form a reactive QM.²¹²²²³²⁴Third, the generation of the QM intermediate of 1 was reported to take place via a singlet excited state as in many other cases of QM formation. Differently, a facile intersystem crossing (ISC) to the triplet state in benzophenone containing compounds that have a carbonyl group is also well known to occur.²⁵ To clarify the above questions and to unravel the reasons for the efficient QM generation of 1 as well as to illuminate how the carbon atom of the vinyl CH_2 moiety in 1 affects the ESPT process, we have chosen to conduct the ultrafast spectroscopic study for 1, as well as for 3-hydroxybenzophenone (2) (Scheme 1) which contains a more electron-withdrawing oxygen part of the carbonyl moiety and also has the same acidic site of the phenolic proton as found in 1. Our main finding is that waterassisted ESPT takes place in both molecules giving zwitterionic QMs in the excited state, singlet for 1 and triplet for2. However, the ground state zwitterionic structure is only possible in the case of 1, leading to the efficient hydration, and the lack of hydration for 2.

RESULTS AND DISCUSSION

A. fs-TA and DFT Study of1



Figure 1.The fs-TA spectra of **1** in ACN at (a) early, (b) late times after 267-nm excitation, and (c) the comparison of the calculated UV-vis spectra of likely intermediate species with the experimental fs-TA spectra. The calculated UV-vis spectra were calculated at the TD-M062X/6-311+G** (ACN) level of theory using a scale factor of 1.05 and a half-width of 1800 cm⁻¹.

Figure 1 presents the fs-TA spectra of 1 in neat ACN. Upon 267-nm excitation, **1** is excited to a high excited state S_3 as suggested by results from TD-DFT calculations. Then, S₃ proceeds to the lowest singlet excited state $1(S_1)$ with a 333 nm absorption band via an internal conversion (IC) from 0 to 1 ps, as shown in Figure 1a. The clear isobestic feature at 342 nm in Figure 1b indicates a dynamical transformation from $\mathbf{1}(S_1)$ to another species that appears at 376, 480 and 615 nm during the time range from 1.5 ps to 8.4 ps. The new species (denoted as X) is likely the triplet produced via ISC in view of the transformation time scale. From 8.4 ps the species X decayed as the absorbance features at 376, 480 and 615 nm diminished in intensity while the band at 333 nm increased up to the time delay of 2.96 ns, suggesting the generation of another species (denoted as Y). The species Y has prominent absorption bands at 333 and 376 nm. Simulated UV-vis spectra by TD-M062X for $\mathbf{1}(S_1)$, $\mathbf{1}(Tn\pi^*)$ and $\mathbf{1}(T\pi\pi^*)$ (Figure 1c) respectively resemble the corresponding experimental spectra of $\mathbf{1}(S_1)$, X and Y. That is, the species generated in ACN at 705 fs, 2.51 ps and 2.96 ns can be attributed to the $1(S_1), 1(T\pi\pi^*)$ and $1(Tn\pi^*)$ species, respectively. The assignment agrees with Wan and coworkers' work using nanosecond transient absorption spectra that no transients were observed in pure ACN and the formation of QM was excluded under this solution condition.^{17,18}

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Figure 2.The structural parameters (Å) and the corresponding spin distributions of $1(S_1)$, $1(Tn\pi^*)$ and $1(T\pi\pi^*)$ are shown.

To deeper understand the photophysical pathway(s) for1 in ACN, the structural parameters for $1(S_1)$ and $1(Tn\pi^*)$ were examined and these results are depicted in Figure 2. It is revealed that the C-C bond distances in the two phenyl rings in $1(Tn\pi^*)$ are almost the same in the range of 1.39~1.41 Å, which agrees well with there being no spin distributed on the two phenyl rings. Only the $\pi\pi^*$ transition can occur for the singlet excited state because of there being no n orbital for the ground state 1. Furthermore, the species $1(S_1)$ displays phenyl C-C bonds with more different values of 1.38~1.43 Å which is induced by some spin being distributed onto these two phenyl groups (see spin populations for $1(S_1)$ with a $\pi\pi^*$ electronic configuration shown in Figure 2). The two radicals are distributed parallel as a $\pi\pi^*$ molecular type on the vinyl group for $1(T\pi\pi^*)$, whose energy is 8.1kcal/mol lower than that of $1(S_1)$. Accompanied with the C-C rotation, $1(T\pi\pi^*)$ is transferred to become $1(Tn\pi^*)$ via an IC process and releasing an energy of 31.4 kcal/mol to the solvent. The photophysical process for 1 in ACN can be summarized as $1(S_3) \rightarrow 1(S_1) \rightarrow 1(T\pi\pi^*)$ $\rightarrow \mathbf{1}(Tn\pi^*).$



Figure 3.The fs-TA spectra of **1** in ACN-H₂O (pH 7, 1:1) under 267-nm irradiation are shown.

After characterizing the photophysics of 1 in ACN, we started to explore the photochemical pathways of 1 in aqueous solutions, especially for how QM is generated in aqueous environments which have yet to be determined in the systems of interest here. The fs-TA results for 1 in near neutral aqueous solution are given in Figure 3. The transformation that occurs

at very early time (Figure 3a) is similar to that found in ACN, indicating that the $\mathbf{1}(S_3) \rightarrow \mathbf{1}(S_1\pi\pi^*)$ process also takes place in neutral aqueous solution. After 3.44 ps the absence of the absorption bands at 376, 480 and 615 nm implies that the $1(T\pi\pi^*)$ and $1(Tn\pi^*)$ species detected in ACN were not generated in the neutral aqueous solution. Instead, a new intense band was formed at 405 nm and the initial absorbance at 330 nm was also not decreased significantly from 3.44 ps to 32.4 ps, indicating that the new species (denoted as IM1 hereafter) observed should have two comparable characteristic absorptions at both 330 and 405 nm. As the delay time increased, IM1 transformed soon into another transient species (denoted as IM2) with its absorbance band red shifted from 405 nm to 425 nm, accompanied with the absorbance at 330 nm decreasing in intensity significantly (Figure 3c). Once the species IM2 was fully generated, it then decayed without a new species being observed (Figure 3d) over the time scale accessible to the fs-TA experiment (up to about 3 ns).

Since the ns-TA and final product analysis show the formation of ground state $OM(S_0)$ for 1 in neutral aqueous solutions, ¹⁵⁻¹⁶ TD-M062X calculations were performed for the transient species related with QM formation (see Figure 4a) to help in the assignment of the species IM1 and IM2. It can be found that the experimental spectrum of the species IM1 at 32.4 ps shows reasonable similarity with the calculated UV-vis spectrum of the singlet excited state of $1OM(S_1)$ possessing two comparable bands at 305 and 405 nm, while this is obviously different from the calculated spectrum of the triplet excited state of $1QM(T_1)$ species. The ground state of $1QM(S_0)$ absorbs at 305 nm and 395 nm while the intensity of the band at 305 nm is much weaker than that at 395 nm, which is similar with the experimental IM2 spectrum at 1.48 ns. The assignment of IM2 to $1QM(S_0)$ is consistent with ns-TA and final product analysis study results.¹⁷⁻¹⁸ It is noted that the position of the computed absorption band of $1QM(S_1)$ shows some difference from the experimental spectrum of IM1, which could be due to theM062X/TD-M062X calculation not being highly accurate for this species.



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Figure 4. Comparison of the calculated UV-vis spectra of likely intermediate species (indicated by the red and blue colored lines) with the fs-TA spectra recorded in (a) ACN- H_2O (pH 7, 1:1) and (b) ACN- H_2O (pH 2, 1:1) after 267-nm irradiation. The calculated UV-vis spectra were obtained using TD-M062X/6-311+G** (ACN) with a scale factor of 1.08 and a half-width of 1800 cm⁻¹.

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The QM of **1**was thoroughly quenched by water to produce the diaryl ethanol product, that may possibly equilibrate with the carbocation species via protonation.^{17,18} On the other hand, only the carbocation was formed via the acid-catalyzed photoprotonation of the double bond at low pH, as have been ob-served for other aryl alkenes.¹⁷⁻¹⁸ To probe the formation of the carbocation species and to compare with the photochemical reaction of 1 in neutral aqueous conditions, fs-TA spectra were also acquired for 1 in a pH 2 aqueous solution (see Figures 1S and4b).It was found that the first two processes of 1 in acidic aqueous solution (Figure 1Sa and Figure 1Sb) are essentially identical with that detected in the neutral aqueous condition, suggesting the sequential transformation of $1(S_3)$ $\rightarrow \mathbf{1}(S_1)$ and $\mathbf{1}(S_1) \rightarrow \mathbf{1}QM(S_1)$. However, the decay of $\mathbf{1}QM(S_1)$ with the generation of a species IM3 absorbing at 418 nm (Figure 1Sc) indicated that $1QM(S_0)$ was not produced for 1 in the acidic aqueous solution examined. The experimental spectrum for the species IM3 recorded at 2.27 ns (330, 418 and 515 nm) shows a reasonable spectra profile resemblance with the calculated spectrum of the S_1 carbocation species of 1 with characteristic absorption bands at 310, 390 and 485 nm (see Figure 4b). In summary, $1QM(S_1)$ undergoes protonation with the formation of the S1 state of the carbocation species in acidic aqueous solution. Protonation of QM to carbocation in acidic solutions has been reported, however, taking place in the ground state.²⁶



Figure 5.The calculated structures for (a) $1QM(S_1)$ and (b) $1QM(S_0)$ detected in ACN-H₂O (pH 7, 1:1) solution and (c) $1QM(S_1)$ and (d) IM3 detected in ACN-H₂O (pH 2, 1:1) solutions at the M062X/6-311+G** (ACN) level of theory. The numbers refer to the bond distance (Å) between the hydrogen and the *meta*-oxygen atoms.

To explain the different pathways of $1QM(S_1)$ in neutral and acidic aqueous solutions, the structural parameters for $1QM(S_1)$ and $1QM(S_0)$ observed in neutral water solutions, and the two species $1QM(S_1)$ and IM3 (the carbocation) probed in acidic solutions were investigated (see Figure 5). It appears that no hydrogen is bonded to the *meta*-oxygen for both $1QM(S_0)$ and $1QM(S_1)$ in neutral water solution. Somewhat unexpectedly, the hydrogen atom is also not fully connected to the *meta*-oxygen for $1QM(S_1)$ with the atom distance being 1.05 Å in acidic solutions, which should be stabilized by the delocalized two radicals on $1QM(S_1)$. This is consistent with the experimental result that $1QM(S_1)$ was probed for 1 in both neutral and acidic aqueous solutions. On the other hand, the species IM3 was fully formed with the hydrogen atom being bonded to the *meta*-oxygen (bond distance: 0.97 Å) and exhibited a different fs-TA spectra profile from that of $1QM(S_0)$. This indicates 1 undergoes a protonation reaction with the formation of the carbocation IM3 in an acidic aqueous solution after $1QM(S_1)$. Close examination of the spectral profile of IM3 indicates it has some weak but recognizable absorbance around 525 nm (see Figure 4b), which was not seen in the neutral aqueous solution. Therefore, this indicates that the transformation from QM to the carbocation species is negligible for 1 in a neutral aqueous solution.

One may consider the parallel occurrence of the stepwise and concerted reaction of 1 in neutral aqueous solution. To gain more information, fs-TA experiments were performed in alkaline aqueous solutions (see Figure 2S), where QM was also formed based on previously reported studies.¹⁵⁻¹⁶The absorption spectra of 1 in an alkaline solution found a sequential appearance of absorption bands at 333 nm within 197~333 fs, 405 nm within 809 fs~8.75 ps and 425 nm within 341 ps~2.62 ns (Figure 2S), which can be respectively assigned to $1(S_1)$, $1QM(S_1)$ and $1QM(S_0)$. The exception from a neutral aqueous condition is the detection of a signal at 355 nm within 763~809 fs, indicating a new species (denoted as IM4) that appeared between $1(S_1)$ and $1QM(S_1)$. One can expect that an alkaline aqueous solution may facilitate the deprotonation of the phenol group so the experimental spectrum of IM4 was compared to the calculated spectrum for the anion S1species (Figure 3S) and the good resemblance between the experimental and calculated spectra strongly supports the above assignment. From another point of view, the absence of the absorbance at 355 nm in neutral aqueous solution implies that the primary generation reaction mechanism for QM of 1 in a neutral aqueous solution is the concerted water-relay ESPT without participation of the step-wise reaction mechanism.



Figure 6.The potential energy surface profiles for **1** in ACN- H_2O at the M062X/6-311+G** (ACN) level of theory are depicted. The blue line shows the triplet reaction pathway, the red line shows the singlet reaction pathway and the black line shows the ground state reaction pathway.

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The potential energy surface profiles of **1** in neutral aqueous solution were mapped employing M062X/6-311+G** (ACN) calculations (see Figure 6). A Stern-Volmer analysis of fluorescence extinguishing of 1 displayed a cubic dependence the concentration of water for the formation of OM.¹⁷⁻¹⁸ Three H₂O molecules were introduced into the calculation system. The species 1 was induced by 267-nm irradiation to take place via the electronic transition from $\mathbf{1}(S_0)$ to $\mathbf{1}(S_3)$. Then the singlet excited route is feasible to overcome a moderate 13.3 kcal/mol energy barrier from $\mathbf{1}(S_1)$ to a transition state $1ts1(S_1)$. and then it goes downhill to $1QM(S_1)$ by a significantly exothermic process (39.6 kcal/mol). $1QM(S_1)$ goes through the IC process to the ground state species $1QM(S_0)$, which is difficult to be produced directly according to the ground state pathway (activation energy: 43.5 kcal/mol). It is interesting the final product cannot realistically be produced by the singlet excited route since it needs a 46.7 kcal/mol activation energy from $1QM(S_1)$ to $1ts_2(S_1)$. The final product should be formed irreversibly by the significantly exothermic pathway which starts from $1QM(S_0)$ that goes through $1ts_2(S_0)$ overcoming a 5.5 kcal/mol activation energy, that agrees well with the final product analysis that QM is totally quenched by water to produce the diaryl ethanol product.¹⁷⁻¹⁸ The photochemical process induced by the triplet species $1(Tn\pi^*)$ seems difficult because of its high energy barrier of 28.4 kcal/mol is required to reach $1ts1(T_1)$ compared with the singlet excited pathway.

B. Ultrafast Study of 2



Figure 7.The fs-TA spectra of **2** in ACN after 267-nm irradiation are shown. A comparison of the calculated UV-vis spectra of likely intermediates with the fs-TA spectra recorded in ACN after 267-nm irradiation is also shown. The calculated UV-vis spectra were determined at the TD-M062X/6-311+G** (ACN) level of theory using a scale factor of 1.13 and a half-width of 1800 cm⁻¹.



Figure 8.The structural parameters (Å) and the corresponding spin distributions of $2(S_1)$, $2(T\pi\pi^*)$ and $2(Tn\pi^*)$ are given.

To compare and contrast with the photoexcited processes of 1, the counterpart 2 was also monitored using similar experimental and calculation methods, and these results are briefly discussed here. Figure 7 presents the fs-TA spectra of 2 in ACN and Figure 8 displays the structural parameters (especially the phenyl C-C bond distances of $1.39 \sim 1.41$ Å in $2(S_1)$ and the corresponding spin distributions of $2(S_1)$ with $n\pi^*$ molecular orbital type, $2(T\pi\pi^*)$ and $2(Tn\pi^*)$. Upon 267-nm irradiation, 2went to a high excited state $2(S_3)$. Then, $2(S_3)$ relaxes to the lowest singlet excited state $2(S_1)$ with an absorption band at 333 nm via an IC process within 1.5 ps (see Figure 7a). The species $2(S_1)$ decayed as the absorbance at 333 nm decreased while the absorbance features at 418, 518 and 578 nm increased in intensity up to 53.7 ps (see Figure 7b), and then decayed without a new species being observed (Figure 7c). Both the calculated UV-vis spectra of $2(Tn\pi^*)$ and $2(T\pi\pi^*)$ contribute to the absorbance in the fs-TA spectra at 53.7 ps, which suggests a mixture of $2(Tn\pi^*)$ and $2(T\pi\pi^*)$ in ACN. This assignment is consistent with DFT calculations that $2(Tn\pi^*)$ and $2(T\pi\pi^*)$ are energetically very close to each other (ΔG : 0.2 kcal/mol) and supported by recent publications.²⁷⁻²⁸2(S₁) goes through the ISC process to 2(T $\pi\pi^*$) with a 10.6 kcal/mol energy gap because the $2(T\pi\pi^*)$ appeared at 578 nm after 1.6 ps, equilibrated with $2(Tn\pi^*)$ after 3.6 ps. It is noted that there is some species generated with an absorbance at 578 nm (see the line recorded at 1.7 ps) between $2(S_1)$ and the mixture of the triplet state species. Based on the calculated energy results, this species should be the $2(T\pi\pi^*)$ produced via an ISC process. The absence of the 418 nm band at 1.7 ps could be caused by a competing pathway from $2(S_1)$ to the ground state via fluorescence which bleached the absorbance of $2(T\pi\pi^*)$ at this wavelength region. The fluorescence of 2 in ACN is depicted in Figure 8S. To sum up, the photophysical process for 2 in ACN can be depicted as $2(S_3)$ $\rightarrow 2(S_1) \rightarrow 2(T\pi\pi^*) \leftrightarrow 2(Tn\pi^*)$



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Figure 9.The fs-TA spectra of **2** in ACN-H₂O (pH 7, 1:1) subsequent to 267-nm excitation are presented. A comparison of the calculated UV-vis spectra of likely intermediate species with the fs-TA spectra recorded in ACN after 267-nm irradiation is also shown. The calculated UV-vis spectra were determined at the TD-M062X/6-311+G** (ACN) level of theory using a scale factor of 1.13 and a half-width of 1800 cm⁻¹.



Figure 10.The potential energy surface profiles for **2** in ACN- H_2O at the M062X/6-311+G** (ACN) level of theory are shown. The blue line shows the singlet reaction pathway, the red line shows the triplet reaction pathway and the black line shows the ground state reaction pathway.

Figure 9 shows the fs-TA results of **2** in neutral aqueous solution. The change in the very early time region (Figure 9a) shows the occurrence of the $2(S_3) \rightarrow 2(S_1)$ process. After 2.1 ps

 $2(S_1)$ decayed as the absorption band at 333 nm decreased in intensity whereas that at 578 nm emerged (Figure 9b), which indicates an ISC process from $2(S_1) \rightarrow 2(T\pi\pi^*)$. Thereafter, the spectra profile varies greatly from that observed in ACN, especially with the band at 392 nm generated and the one at 418 nm disappearing (Figure 9c). The species with strong absorbance features at 333, 392 and 515 nm is denoted as IM5, which decays after 110 ps. The potential energy surface profile of 2 in neutral aqueous solution (see Figure 10) also supports an ISC process from $2(S_1)$ to $2(T\pi\pi^*)$. Then the triplet reaction route goes forward to produce the triplet quinone methide $2QM(T_1)$ with a barrier-free and exothermic process. We compare the experimental fs-TA spectrum of the species IM5 which was produced from $2(T\pi\pi^*)$ with the simulated one of $2QM(T_1)$ (Figure 9d). The excellent correlation shown in Figure 9d suggested that IM5 can be attributed to $2QM(T_1)$. The appearance of the species $2QM(T_1)$ at early time (18.8 ps) is also consistent with the calculated results about the fast consumption of $2(T\pi\pi^*)$ so that its characteristic band at 418 nm is not easy to detect. Due to the high energy barrier of 53.3 kcal/mol, the species $2QM(T_1)$ is difficult to overcome the second transition state $2ts_2(T_1)$, while it is more feasible to transfer to the ground state IM6 via an ISC process. The calculation result indicates that IM6 is not $2OM(S_0)$ because the protonation of the carbonyl O atom still did not completely transfer from meta-OH for IM6 (Figure 4S). This indicates that IM6 is unstable and will soon go back to the ground state $2(S_0)$. It is indicated from the ground state energy profile (the black line in Figure 10) that a concerted pathway is proposed for 2 without an intermediate, where the photohydration can be accomplished by the H_2O molecule being split into H^+ and OH⁻ which respectively transfer to the carbonyl O and the C atom without the involvement of the meta-OH. Therefore, no photohydration product can be detected after photoexcitation for 2 in neutral aqueous solutions. It should be noted that photohydration products are unstable, so even if they were formed, they would revert to the starting material.

The above results provide evidence that 1 and 2 go through different ISC processes in pure ACN. That is, the ISC process involves $S_1\pi\pi^* \leftrightarrow T\pi\pi^*$ for 1 while $S_1n\pi^* \leftrightarrow T\pi\pi^*$ for 2. The IC process of $T\pi\pi^* \rightarrow Tn\pi^*$ is the same which respectively involves the vinyl C-C rotation for 1 and the carbonyl C-O rotation for 2. However, fs-TA results indicate there is a significant difference for the bond rotation. It seems that the carbonyl C-O rotation is much faster (from 1.5 ps to 4.2 ps, see Figure 7) than the vinyl C-C rotation (from 1.5 ps to 2.96 ns, see Figure 1). Actually, $2(Tn\pi^*)$ mixes with $2(T\pi\pi^*)$ and can transfer to each other with a fast equilibrium as shown by fs-TA results and their degenerate free energy. However, $1(Tn\pi^*)$ is lower by 31.4 kcal/mol in energy than $1(T\pi\pi^*)$, which in turn accounts for the slow vinyl C-C rotation so that the second triplet state $1(T\pi\pi^*)$ also can be stabilized (energy gap law²⁹) during 1.5 ps to 2.96 ns in ACN. Inspection of the spin distribution for $1(T\pi\pi^*)$ and $2(T\pi\pi^*)$ provides more insight: two radicals localize on the vinyl group for $1(T\pi\pi^*)$ while they delocalize to the substituted phenyl ring for $2(T\pi\pi^*)$. The electronic configuration with the spin delocalization to the substituted phenyl ring is also located for 1 by the TD-M062X method (Figure 5S). However, it is the third triplet excited state, that is higher by 1.7 kcal/mol in energy than $1(T\pi\pi^*)$. These results are explicitly derived from the essential fact that the electron-withdrawing carbonyl O atom can lower the lowest unoccupied molecular orbital (LUMO) of the

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phenyl ring so that the electron transfer is also favored from the carbonyl group to the phenyl as compared with the carbonyl C-O rotation after the carbonyl photoexcitation. Instead, the poor electron-withdrawing vinyl C atom cannot lower the LUMO of the phenyl group, which induces the vinyl C-C rotation to be much more favorable than spin delocalization to the phenyl ring. It should be emphasized that the polar ACN is an inert solvent that only allows for the photophysical process for 1 and 2. However, the protic solvent water opens the door to photochemical reactions besides only the photophysical process seen in ACN. In neutral aqueous solution, the $1QM(S_1)$ formation promoted by the $\mathbf{1}(S_1)$ is fast enough (energy barrier: 13.3 kcal/mol, see Figure 6) to compete with the vinyl C-C rotation between $1(T\pi\pi^*)$ and $1(Tn\pi^*)$ (from 1.5 ps to 2.96 ns, see Figure 1). As a result, the $1OM(S_1)$ formation but not ISC is the main process for $1(S_1)$. In contrast, the transient ISC process (see Figure 7) and the reactive species $2(T\pi\pi^*)$ (see Figure 10) are favored for the subsequent triplet ESPT process rather than singlet one, which is further corroborated by other aromatic carbonyl compounds reported in aqueous solutions.³ It is wondered why the OM formation for **1** is so efficient while that is not the case for 2. The hydration reaction is very difficult to occur without photoexcitation according to the ground state energy profile for both 1 and 2 (see the black line in Figures 6 and 10), which however, indicate a stepwise pathway for 1 and a concerted pathway for 2. Considering that the excited species must go through the IC process back to the ground state in the halfway or terminal point on the energy profile after photoexcitation, the OM intermediate located by the ground state energy profile is crucial upon irradiation as compared with 2 without a ground state QM species. This difference is obviously correlated with vinyl and carbonyl moieties. The electron rich carbonyl O atom can directly split H₂O to undergo the hydration reaction by one step while the poor vinyl group requires the assistance from the better proton donor of the meta-OH group to achieve the vinyl C protonation, and then the protonated vinyl group enhances hydroxide abstracted from H₂O and the leaving proton returns to meta-O. That is why the ground state energy profile can locate a $1OM(S_0)$ intermediate. It is reasonable to predict that a less basic group than the vinyl group is also disfavored for the photohydration because the proton transfer from meta-OH will become difficult in the singlet excited state, which might turn to the ISC process and the formation of unreactive triplet state (Figure 6). Therefore, the moderate basic character of the vinyl group is crucial for the efficient QM formation of 1.

CONCLUSION

In this contribution we report an ultrafast transient absorption spectroscopic experimental study combined with a computational investigation for **1** in different solvents and directly characterize the excited-states and intermediates involved in the formation of the QM species. The predominant photophysical and photochemical pathway for **1** in neutral, acidic and alkaline aqueous solutions can be depicted in Figure 11 below. The letters and numbers shown next to the chemical structures in Figure 11 are those for the key intermediates also presented in the text. Mechanistic investigations utilizing ultrafast timeresolved spectroscopy and DFT calculation studies can help unravel two distinct pathways for **1** and **2**, leading to the formation of $1QM(S_0)$ but not $2QM(S_0)$, respectively.



Figure 11. The proposed photophysical and photochemical pathways of **1** in neutral, acidic and alkaline aqueous solutions based on the combined fs-TA study and DFT calculations reported here is shown. The letters and numerical values next to the structures are the notations presented in the main text. The absorbance bands of the transient fs-TA detected species are also given.

Although the carbon atom of the vinyl group in 1 is more difficult to be protonated than the oxygen atom of the carbonyl group in 2, the formal ESPT for 1 with efficient generation of the QM species revealed a particularly fascinating aspect of these photochemical reactions. The results here can aid researchers in the design of new precursors for the efficient photogeneration of QM intermediates. For instance, the greater acidity of the phenol group in S_1 in these kinds of molecules is viewed to be required for QM formation as previously described. 31323334 Our work here clearly points out that the basic site is of equal importance for the design of QM precursors. Besides, the comparison between 1 and 2 applies fundamental and essential information for a deep understanding of the photophysical and photochemical behaviors of aromatic compounds, like, a small change of the skeleton with one atom leads to distantly different destinations for the reaction. It should be noted that, these two compounds are meta substituted and the intermediates via the photohydration reaction only have "non-Kekulé" structures, which may be of interest to computational chemists. Furthermore, the distinct characterizations and assignments of all the key intermediates and transients in the pathways of the QM formation furnish important knowledge for further insight and future work into the photoinduced QM reactions with DNA and amino acids in cancer therapy. We also note that phototoxicity is an important aspect when evaluating the biological and clinical use of a cancer agent. The totally different behaviors of 1 in water containing solutions or not containing water (eg. the ACN solution results) conditions may potentially be exploited as a new and useful tool to study the dynamics of solvent-assisted reactions in biological systems.

EXPERIMENTAL AND COMPUTATIONAL METHODS

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3-(1-phenylvinyl)phenol was prepared using literature methods (see the supporting information with the ¹H NMR and ¹³C NMR spectra shown as Figure 6S and Figure 7S, respectively).^{17,18} Its pKa is determined to be 9.56 ± 0.03 (see the details in Figure 9S, Figure 10S and Figure 11S). 3hydroxybenzophenone was commercially acquired and used as-is. Deionized water and spectroscopic grade acetonitrile were employed to make samples with. perchloric acid and sodium hydroxide used as needed to adjust the pH of the solvent (before addition of the sample compound). Taking the alkaline sample solution for instance, the solvent, ACN-H₂O (1:1, v:v), was brought to pH 10.0 by addition of sodium hydroxide. Then, a certain amount of compound 1 was added until the absorbance reached 1 at 266 nm. After the addition of the compound 1 the pH of the solution was around 8.0 which is below the pKa (9.5) of **1** (see the details given in Table 1S). That is, the species existing in the alkaline aqueous solution for the fs-TA experiments is the ground state of the neutral form of 1, rather than the phenolate form. Fs-TA experiments were done with a femtosecond regenerative amplified Ti:Sapphire laser apparatus. The 120 fs oscillator output seeded the amplifier. About 5% of the amplified 800 nm production was employed to make the probe pulse320 nm to 700 nm white-light continuum via a CaF₂ crystal. Two portions of the probe beam were used in the experiments with one directed to a reference spectrometer and the other going through the sample. 40 ml sample solutions were passed through a cuvette with a 2 mm path-length that a 267 nm pump beam excited. The experiments used sample solutions made so that they had an absorbance of 1 at 267-nm.

M062X method DFT calculations were performed for the ground state and triplet state with a 6-311+G** basis set. The MO62X method is thought to be reasonably reliable to predict the chemical behavior of main groups by several other groups.³⁵ Frequency calculations using the identical method and basis set were done to determine that the geometries were at local minima (with all-real frequencies) or at transition states (containing one imaginary frequency only). The transition state character was found by examining the movement by the eigenvector connected with the imaginary frequency. Intrinsic reaction coordinates³⁶ were calculated to determine that the pertinent transition state structures connected the two pertinent minima. TD-M062X/6-311+G** computations were used to compute the singlet excited state and the UV-vis spectra. The second and the third triplet state for compound 1 in ACN solvent were also optimized by TD-M062X. The effect of solvent polarity on the stability of the relevant species was examined with structural optimization calculations done using the integral equation formalism polarizable continuum model (IEFPCM) in ACN (ε = 35.688) on the gas-phase structures in which the nonelectrostatic terms and the radii used the universal solvation model (SMD) developed by Truhlar and coworkers.³⁷ The Gibbs free energy G_{solv} was used in the discussion of most of the results. However, the electronic energy Ewas used if the singlet excited state was involved. All the computations were done with the Gaussian 09 program.

ASSOCIATED CONTENT

Supporting Information. Figures and tables giving the fs-TA spectra for the reported species, optimized geometries of the RC, TS, and PC, the reaction energy profile obtained from the M062X /6-311+G** calculations and the excited state energies and oscil-

lator strengths from TD-DFT (M062X /6-311G**) calculations for the transient species, and Cartesian coordinates, total energies, and vibrational zero point energies for the optimized geometry from the M062X /6-311G** calculations for the compounds and intermediates considered in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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