Mechanism of Photosolvolytic Rearrangement of *p*-Hydroxyphenacyl Esters: Evidence for Excited-State Intramolecular Proton Transfer as the Primary Photochemical Step

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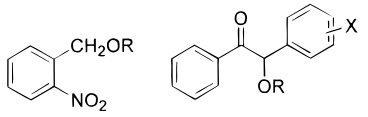
Abstract: The photosolvolytic rearrangement of a variety of *p*-hydroxyphenacyl esters and related compounds **7**−**16** has been studied in solutions with up to 50% aqueous content, using product studies, triplet quenchers, and nanosecond laser flash photolysis. The *p*-hydroxyphenacyl moiety has recently been proposed as a new and efficient photoactivated protecting group in aqueous solution. Practical applications have been demonstrated, but much less is known about the mechanism of photoreaction. Our data support a novel mechanism in which the primary photochemical step from the singlet excited state is formal intramolecular proton transfer from the phenolic proton to the carbonyl oxygen of the distal ketone, mediated by solvent water, to generate the corresponding *p*-quinone methide phototautomer. This reactive intermediate (most likely in its excited state) subsequently expels the carboxylic acid with concerted rearrangement to a spiroketone intermediate, which subsequently leads to the final observed product, *p*-hydroxyphenylacetic acid. An alternative mechanism is deprotonation of the phenolic proton, loss of the carboxylate, and rearrangement to the spiroketone, all in one concerted primary photochemical step from S_1.

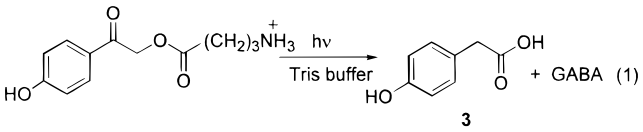
Introduction

Photorelease with near-UV light of biologically relevant compounds has widespread application in physiology and allied areas.[2] The most widely used protecting groups that have been employed to release ("uncage") such compounds are the *o*-nitrobenzyl and benzoin (desyl) groups, illustrated by the simplified generalized structures **1** and **2**, respectively (R =



1 **2** (X = H, OCH_3)

protected functionality).[2a] Recently, Givens and co-workers[3] reported the use of the *p*-hydroxyphenacyl group (e.g., eq 1) as a new phototrigger to release a variety of caged biological effectors (ATP, amino acids, etc.) in aqueous solution, with the



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p-hydroxyphenacyl group being transformed via an overall solvolytic rearrangement to give *p*-hydroxyphenylacetic acid (**3**). The proposed mechanism of reaction[3] involves the triplet excited state of the *p*-hydroxyacetophenone chromophore, and the primary photochemical step was suggested to be C−OCOR bond homolysis to give the radical pair **4**, followed by fast electron transfer to give the corresponding ion pair **5**. Subsequent proton transfer/rearrangement gives spiroketone intermediate **6** which is trapped by water to give **3** (Scheme 1).

Banerjee and Falvey[4] (using laser flash photolysis) have recently studied the photorelease mechanism of phenacyl esters lacking the *p*-hydroxy group and concluded that, in H-atom-donating solvents, the mechanism of photorelease of the carboxylic acid is not via C−OCOR homolysis, but via initial hydrogen abstraction by the acetophenone carbonyl to generate a ketyl radical, which can react further via a long-lived ($\tau > 1$ ms) intermediate of as yet undefined structure, to release the carboxylate. Acetophenone (formal reduction product) is the other product observed via this mechanism. On the basis of solvent isotope effects, Givens et al.[3d] had earlier made a similar mechanistic proposal in the observed photoreduction of *p*-methoxyphenacyl diethyl phosphate ester in MeOH or dioxane. Thus, there is much current interest in the mechanism and potential applications of the phenacyl chromophore.

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(1) (a) University of Victoria. (b) National Institute for Medical Research.

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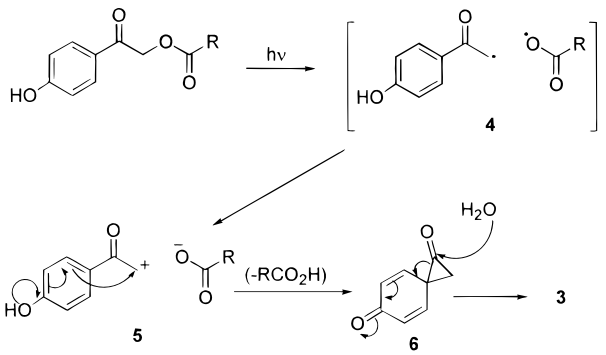
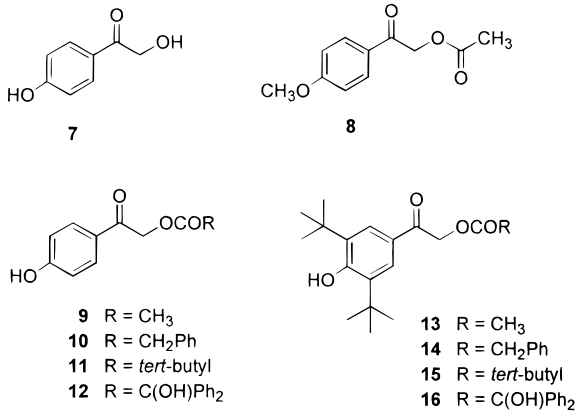
Scheme 1



In recent investigations of the mechanistic photochemistry of a variety of hydroxyaromatic compounds in aqueous solution, we have observed that proton transfer in the singlet state from the hydroxy group (either to solvent or intramolecularly to another basic site of the molecule mediated by a water cluster) is the primary photochemical step which is ultimately responsible for the chemistry.[5] We were therefore intrigued by the possibility that a proton-transfer mechanism might be operative for the reaction shown in eq 1 for these *p*-hydroxyphenacyl esters. Our results indeed show that, for the group of compounds studied in this work, the phenolic hydroxyl group is essential for efficient reaction and that the primary photochemical step is not C−OCOR homolysis but excited-state proton transfer (ESPT), most likely intramolecular proton transfer from the hydroxyl group to the carbonyl oxygen mediated by water (or less efficiently by MeOH). This process photogenerates a reactive *p*-quinone methide (in its ground or excited state) capable of undergoing the remaining steps required for release of the protected functionality. The results offer a rational approach for designing better phototriggers as well as giving insight into the generality of water-assisted excited-state intramolecular proton transfer of hydroxyaromatic ketones from the singlet excited state in aqueous solution.

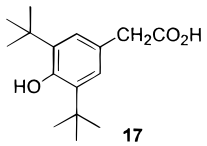
Results and Discussion

Product Studies. Studies reported by Givens and co-workers[3] were restricted to *p*-hydroxyphenacyl phosphates and relatively simple esters. For our mechanistic investigation, we have studied the photosolvolytic rearrangements of compounds **7**−**16** which



include the parent *p*-hydroxyphenacyl alcohol **7**, the *p*-methoxyphenacyl ester **8**, and the *p*-hydroxyphenacyl esters **9**−**12** and **13**−**16,** which differ greatly in the propensity of the corresponding acyloxy radical to decarboxylate (if generated in the reaction mechanism). Pincock and co-workers[6] have shown that differing rates of decarboxylation of the acyloxy radical have a dramatic influence on the ratio of products derived from ionic versus radical intermediates in the photolysis of benzyl and naphthylmethyl esters. Pivalate esters gave the highest yield of radical-derived products, consistent with a very fast rate of decarboxylation for the pivaloyloxy radical [$(CH_3)_3CO_2^{\bullet}$, $k_d = 1.1 \times 10^{10}$ s^{-1}].[6b,c] The reported rate for decarboxylation of the benziloyloxy radical [$(Ph)_2C(OH)CO_2^{\bullet}$, $k_d = (2-8) \times 10^{11}$ s^{-1}][7] is an order of magnitude faster. Thus, if the reaction mechanism involved initial C−OCOR bond homolysis followed by electron transfer (in **9**−**16**), large effects would be expected on the observed product distribution from these substrates.

Photolysis of **9**−**16** was carried out initially in NMR tubes (~10^{-3} M, 1:1 D_2O-CD_3CN, Rayonet photochemical reactor, 300 nm lamps, 10 min) to assess product yields and distributions without the need of workup. All of compounds **9**−**16** gave *p*-hydroxyphenylacetic acid **(3)** (or 4-hydroxy-3,5-di-*tert*-butylphenylacetic acid **(17)**) and the appropriate carboxylic acids



RCO_2H cleanly, with yields of 90−95%, as confirmed by addition of authentic RCO_2H into the product mixture. No reaction was observed if the solutions were not irradiated. There was no evidence for the formation of radical-derived products, which would be attributable to C−OCOR bond homolysis. Only a trace (<5%) of the photosolvolytic product **7** was observed for all of **9**−**12**, even on quantitative conversion of starting material. Preparative photolyses were carried out for **9** and **13** to enable isolation of the corresponding arylacetic acid products **3** and **17**, which were subsequently used for their identification in the NMR photolysis runs. No change was observed in conversion to products for **9** whether solutions were purged by argon or oxygen. Preparative photolysis of **7** also gave *p*-hydroxyphenylacetic acid, although the compound was about 40-fold less reactive than any of **9**−**12**. These observations argue strongly against a mechanism involving initial C−OCOR homolysis. A different primary step must be operative.

Equally informative was the finding that, under the conditions employed for the above compounds (in 1:1 H_2O-CH_3CN, ≤15 min irradiation), the *p*-methoxy compound **8** failed to give any observable reaction (including simple photosolvolysis of the acetate group or its photoreduction to *p*-methoxyacetophenone), showing that the phenolic OH is required for reaction. This observation also argues against a primary step involving simple C−OCOR bond heterolysis (to form an α-acyl carbocation) as the hydroxy and methoxy groups would be expected to have very similar electronic effects in the excited state (as they do in the ground state). We estimate that any reaction with $\Phi >$ 0.02 would be detectable in our experiments, and therefore we

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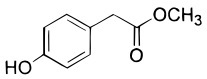
can rule out any substantial photochemistry for **8** in aqueous CH_3CN. However, we cannot completely rule out an inefficient photoreduction or photosolvolytic rearrangement for **8**. Interestingly, Givens et al.[3d] have reported significant photosolvolytic rearrangement and photoreduction for *p*-methoxyphenacyl diethyl phosphate ester in organic solvents in contrast to the lack of reactivity observed for our *p*-methoxy compound **8**. The key difference may lie in the different "leaving groups" employed, phosphate vs acetate, although a more comprehensive investigation comparing the effects of these substituents is required.

Sheehan and Umezawa[8a] reported that a number of *p*-methoxyphenacyl esters including the benzoate were stable to irradiation in benzene but released the corresponding acid on photolysis in dioxane or ethanol. Notably, addition of water to these solutions decreased the yield of cleavage. The *p*-methoxyphenacyl fragment was reduced to *p*-methoxyacetophenone in the reaction. Although no quantum yields were measured, yields were as high as 96%. The mechanism proposed by the authors involves α-cleavage from the triplet excited state, to generate the radical pair, followed by reduction by the solvent. However, the recent report from Banerjee and Falvey[4] would suggest that the mechanism probably involves initial hydrogen abstraction by the carbonyl oxygen to generate a ketyl radical, which subsequently fragments to the enol of *p*-methoxyacetophenone and the acyloxy radical, the latter then being reduced to give the corresponding carboxylic acid.

Anderson and Reese[8b] reported that a variety of *p*-hydroxy- and *p*-methoxyphenacyl halides gave both rearranged and photoreduced products on photolysis in alcohol solvent. Park and Givens[3b] also reported the rearranged product ($\Phi = 0.20$) in addition to the reduction product ($\Phi = 0.07$) for *p*-methoxyphenacyl diethyl phosphate on photolysis in MeOH. In addition, it is well-known[8c−e] that on photolysis a large number of simple arylacyl (phenacyl, naphthacyl) halides undergo α-cleavage followed by a neophyl-like rearrangement similar to that shown in Scheme 1, although in these cases, the rearranged product is an acyl radical which reacts further (via decarbonylation).

The lack of reactivity displayed by the *p*-methoxy derivative **8** observed in this work appears to be difficult to reconcile in view of the above literature reports. However, Banerjee and Falvey[4] have offered a new way to interpret the reactivity of these compounds, viz., the importance of the solvent. In aqueous solution, *p*-hydroxy- and *p*-methoxyacetophenones probably have lowest energy triplet configurations that are mostly π,π^* in character,[8f] making them much less reactive toward hydrogen abstraction or β-cleavage, steps that are necessary for the chemistry described above. Moreover, the organic cosolvent (CH_3CN) used in our studies is a very poor hydrogen donor, further prohibiting radical pathways. Therefore, the observed high reactivity of the *p*-hydroxy derivatives **9**−**16** in aqueous solution strongly suggests that a completely different mechanism must be operative, viz., excited-state proton transfer (vide infra).

Irradiation of **7** or **9** in 100% CH_3CN resulted in complete recovery of the substrates. Upon addition of increasing amounts of water to the CH_3CN solution, the compounds became increasingly photosensitive, up to a plateau of reactivity observed at ∼35% H_2O (v/v). Photolysis of **9** in 100% MeOH gave the methyl ester **18**, although an approximately 5-fold



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longer irradiation time was required to achieve the same extent of conversion as observed in 1:1 H_2O-CH_3CN. Thus, the presence of water in the solvent enhances the reaction, consistent with a mechanism involving proton transfer as it is well-known that ESPT from phenols is optimal in aqueous media.[9]

The inference by Givens and co-workers[3] that the triplet excited state is responsible for reaction in these *p*-hydroxyphenacyl systems was based on triplet quenching experiments using sodium 2-naphthalenesulfonate. However, this compound has considerable absorption to 320 nm, very much like the *p*-hydroxyphenacyl chromophore itself, and this inner-filter effect suggests that its use as a triplet quencher for study of *p*-hydroxyphenacyl compounds is problematic. Triplet sensitization is even more difficult as there appear to be no sensitizers that have the required triplet energy (E_T(acetophenone) ≈ 70−74 kcal mol^{-1})[10] and absorb beyond 320 nm. As alternative triplet quenchers that are transparent above 280 nm and therefore do not compete for the excitation light in quenching studies, we have used sodium sorbate, *trans*-piperylene, and 1,3-cyclohexadiene, the former two in 1:1 H_2O-CH_3CN (≤0.1 M quencher) and the latter in 1:1 H_2O-THF (≤0.1 M quencher). All are conjugated dienes and have triplet energies around 50−55 kcal mol^{-1}.[10] They would be expected to quench *p*-hydroxyphenacyl (acetophenone) triplets at diffusion-controlled rates. Reactions taken to partial conversion to avoid secondary photolysis showed only a marginal decrease in yield in the presence of these triplet quenchers (i.e., for product **3** from **9**, from a yield of 40% at zero quencher to a yield of 35% at the maximum quencher concentration used). This small drop in yield of product can be accounted for by the slight opacity of these solutions at high quencher concentrations. The results indicate that the reactive state has a lifetime much below 10 ns that is probably inconsistent with an acetophenone triplet state. Moreover, the suggested operation of an ESPT in the reaction from product studies is more consistent with a singlet-state process.[5,8f,12]

Product Quantum Yields. Since essentially only one product is observed for these reactions (even at 100% conversion), quantum yields for product formation would be identical to quantum yields for disappearance of substrate. The latter can conveniently be measured by UV−vis spectroscopy, since traces for conversion of these compounds to **3** (or **17**) showed a large decrease in optical density at ∼280 nm as the reaction progressed (Figure 1). Using this technique, the absolute quantum yields for product formation (Φ_p) from **9** and **13** measured at pH 7 (1:1 H_2O-CH_3CN; quoted pH is of the water portion) were 0.41 and 0.36, respectively. Subsequently, quan-

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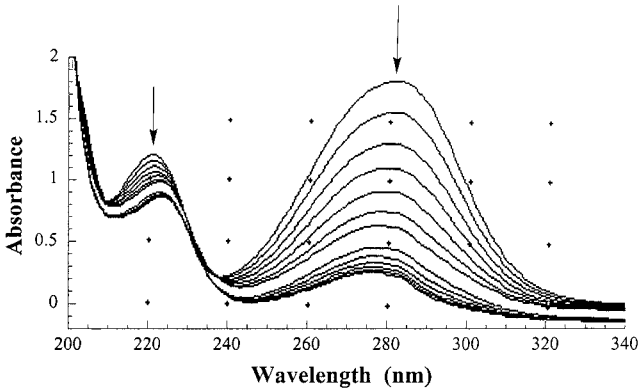

Figure 1. UV−vis traces for the conversion of **9** to **3** on photolysis at 300 nm (in 1:1 H_2O-CH_3CN; argon purged). Each trace represents about 1 min of photolysis time.

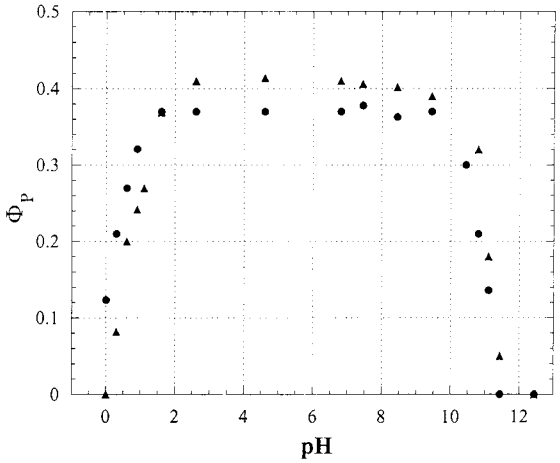

Figure 2. Φ_p vs pH for formation of **3** from **9** (triangles) and **17** from **13** (circles) in 1:1 H_2O-CH_3CN (pH is of the aqueous portion).

tum yields at other pHs for **9** and **13** were measured by ^1H NMR using the value at pH 7 as a secondary reference (Figure 2). The UV−vis method was not used here because of the interference of phenolate produced at high pHs. The plots show that these compound are unreactive below pH $\approx$ 0 and above pH $\approx$ 12. Two titration curves are also apparent in this plot, one for the excited state (pK(S_1) $\approx$ 1) and one for the ground state (pK(S_0) $\approx$ 10.5). Although the latter value is in poor agreement with the known pK_a ($\sim$8) of *p*-hydroxyacetophenone,[11] the discrepancy is readily accounted for by the presence of 50% CH_3CN in the solvent mixture, and was confirmed by UV−vis titration of *p*-hydroxyacetophenone in 1:1 H_2O-CH_3CN, which gave a measured pK_a value of $\sim$11.

A number of control experiments were carried out to ensure that Figure 2 represented the true photochemical behavior of the compounds. For example, control runs showed that, at the lower and higher pHs, no significant (<5%) thermal hydrolysis took place during the time of the experiment (i.e., **9** to **7**), nor was there thermal conversion to **3**. Product studies for the reaction of **7** in 1:1 H_2O-CH_3CN (although 40-fold less reactive than **9**) gave a pH plot that closely resembled that in Figure 2.

The data of Figure 2 strongly suggest that ESPT is involved in the reaction mechanism. This is consistent with the titration curve observed over the pH range 0−2, i.e., within the range of many known pK(S_1) values.[12] The titration curve observed at pH 10−12 indicates that excitation of the phenolate form does not result in reaction (or that it is much less reactive). These results are consistent with the fact that **8** is not reactive (lacks phenol) and that an aqueous medium is optimal for reaction for phenols **7** and **9**−**16**. In previous studies of reactions initiated by water-mediated ESPT, we have observed[5b,c] that direct irradiation of the phenolate resulted in a higher quantum yield of reaction. This was not observed for the compounds studied here and indicates that simple proton transfer to solvent is not sufficient to generate the required reactive intermediate. It might be expected that the excited phenolate itself (e.g., **20***) could rearrange to **6** and hence to **3**. This is not observed and suggests that other deactivational pathways for the excited-state phenolate dominate, such as electron ejection to the solvent shell (followed by its efficient return since no net chemistry was observed).

The strong possibility that the mechanism of photosolvolytic rearrangement of these compounds involves ESPT prompted us to measure the solvent isotope effect on reaction for **9** (1:1 H_2O-CH_3CN vs 1:1 D_2O-CH_3CN). We observed essentially no difference in the quantum yields ($\Phi(H_2O)/\Phi(D_2O) = 0.95 \pm 0.05$), which was surprising since a substantial primary solvent isotope effect on the quantum yield would be expected if deprotonation is required in the reaction mechanism. However, some[13a,b] very fast excited-state intramolecular proton transfers (between oxygen and nitrogen) exhibit no observable deuterium isotope effect on rates of transfer, while others[9d,13c] (intermolecular and solvent-mediated intramolecular cases) have rate differences up to 3-fold slower in D_2O. There appears to be no general expectation of what the solvent isotope effect should be in ESPT reactions, although Moog and Maroncelli[13c] have proposed that the proton-transfer mechanism can be modeled by a two-step process of initial solvent reorganization followed by the proton transfer. Systems in which proton transfer is very fast, whereby the rate-determining step is solvent reorganization, would have small solvent isotope effects. Conversely, when proton transfer is much slower than solvent reorganization, substantial solvent isotope effects are expected. In addition, proton transfers which have very early (or very late) transition states would also be expected to exhibit a minimal deuterium isotope effect. Therefore, the lack of a solvent-related primary isotope effect in **9** does not preclude ESPT in the reaction mechanism.

Laser Flash Photolysis and Mechanism of Reaction. Nanosecond laser flash photolysis (LFP, excimer laser, 308 nm, 10 ns, <30 mJ/pulse) of flowing solutions of **9** in neat CH_3CN ($\sim 10^{-4}$ M, N_2 purged) gave a strong absorption with $\lambda_{max} \approx$ 380 nm, which disappeared when the solution was purged with O_2 (Figure 3). The decay trace at 380 nm is single exponential with $\tau = 1.1$ μs. We assign this transient to the triplet excited state of **9**. This assignment is consistent with studies by Banerjee and Falvey[4] and Scaiano and co-workers.[14] Banerjee and Falvey[4] reported the triplet state with $\lambda_{max} \approx$ 340 nm for phenacyl phenylacetate (which contains the parent acetophenone chromophore) in benzene. Scaiano and co-workers[14] assigned a transient observed at $\lambda_{max} \approx$ 380 nm to the triplet state of *p*-hydroxypropiophenone (in wet acetonitrile). Our own LFP studies of *p*-hydroxyacetophenone in neat CH_3CN gave an oxygen-quenchable transient at 360 nm assignable to its triplet state.

LFP studies of **9** in 1:1 H_2O-CH_3CN (N_2 purged) gave a new, strong absorption at 330 nm in addition to the weaker 380 nm absorption. Oxygen quenched the 380 nm transient but had essentially no effect on the one at 330 nm (Figure 4). This

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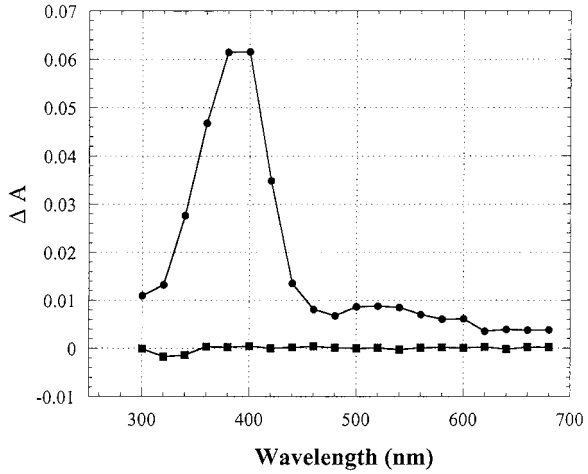


Figure 3. Transient absorption observed on LFP of neat CH_3CN solutions of **9** purged by N_2 (circles) and O_2 (squares).

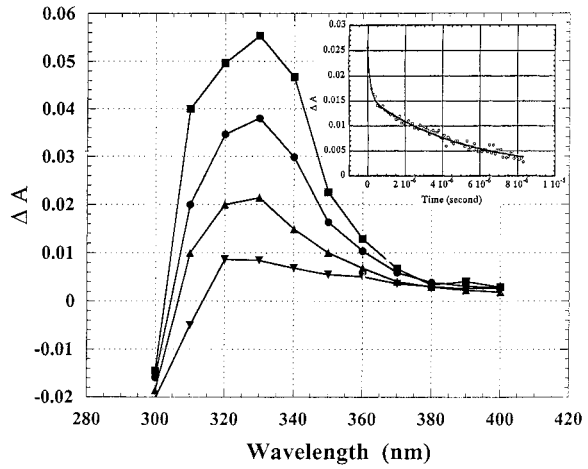
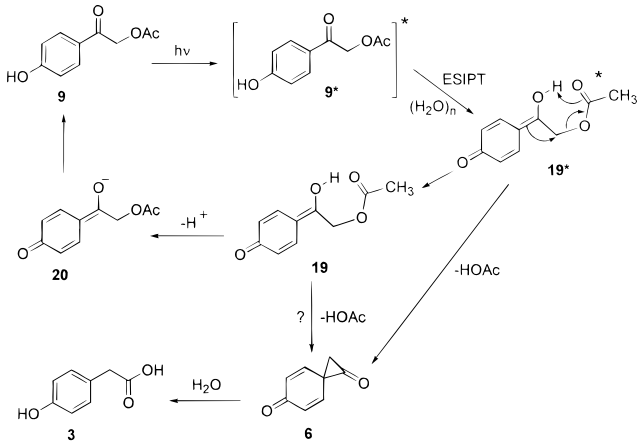


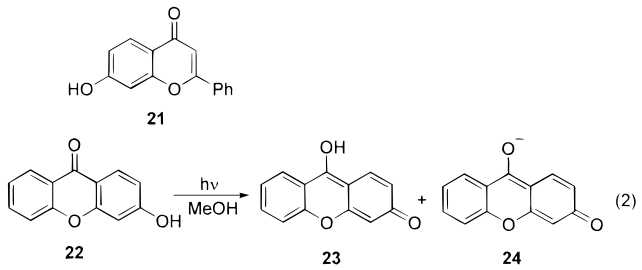
Figure 4. Transient absorption observed on LFP of **9** in 1:1 H_2O-CH_3CN (O_2 purged). Decay trace taken at 400 ns intervals (inset: biexponential decay with a major component of $k_d = 6.3 \times 10^6$ s^{-1} and minor component of $k_d = 1.8 \times 10^5$ s^{-1}). Initial decay taken immediately after the pulse.

indicates that the triplet state is not responsible for the 330 nm transient. At pH 7, the observed decay is best fitted to the sum of two single exponential decays, with a major component (~70%, assuming identical extinction coefficients for the two species at this wavelength) ($k_d = 6.3 \times 10^6$ s^{-1}) and a minor component (~30%) ($k_d = 1.8 \times 10^5$ s^{-1}) assignable to two species with very similar UV absorptions. Kinetic studies at other pHs showed that the proportion of the longer-lived species increased with increasing pH and that it is not observed below pH 6, suggesting that these two species are related by a prototropic equilibrium (although equilibrium is probably not established under our conditions). This is substantiated by rates of decay measured in D_2O, which were about 2-fold slower for both species.

We assign the shorter-lived component to *p*-QM **19** and the longer-lived component to its conjugate base, enolate/phenolate **20**, the latter shown to be unreactive with respect to giving **3** (vide supra) (Scheme 2). Simple *p*-QMs are known to absorb in the 300−350 nm region[15] with rates of decay unaffected by oxygen.[5] Authentic **20** (generated by dissolving **9** in aqueous base) has $\lambda_{max} = 330$ nm. Moreover, Itoh and co-workers[16] have shown by LFP studies that 7-hydroxyflavone (**21**) and 3-hydroxyxanthone (**22**), both of which are also *p*-hydroxy-substituted ketones, undergo excited-state (formal) intramolecular proton transfer (ESIPT) via S_1, assisted by solvent MeOH, to form the corresponding *p*-QMs (e.g., **23**) and their conjugate bases (e.g., **24**) (eq 2), both of which have essentially the same

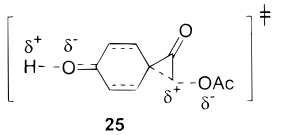
Scheme 2





absorption spectra. LFP studies of the di-*tert*-butyl derivative **13** gave results similar to those for **9** (new transient at 360 nm), indicating that a parallel mechanism is operative for the di-*tert*-butyl compounds. The 30 nm red shift observed for the corresponding *p*-QM is consistent with the presence of two electron-donating *tert*-butyl groups.

LFP of *p*-hydroxyacetophenone in aqueous CH_3CN gave essentially the same 330 nm transient as observed for **9**. Moreover, the transient decays with the same kinetics (sum of two first-order decays) with similar rate constants. The lack of a large difference in the rate constants of decay is inconsistent with the phototautomer **19** being responsible for reaction. Since many simple excited-state proton transfers are adiabatic,[12] it is possible that a significant proportion of the reaction to **6** occurs from photoexcited **19** (i.e., **19***). Such a species would have the required energetics for rearranging to a more strained (but ground state) **6** (Scheme 2). Future experiments using two-laser/two-color LFP are planned to investigate this intriguing possibility. Another mechanistic possibility which we cannot rule out with our data is a concerted deprotonation of the phenolic proton and loss of acetate ion from **9***, via transition state **25**, to generate **6** directly.



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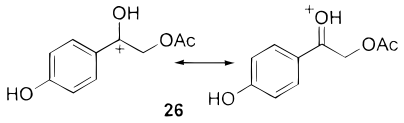
Plots of transient absorption intensity (ΔA) at 330 nm for **9** and at 360 nm for **13** vs pH support the involvement of ESIPT (Figure 5). Significant permanent bleaching of the phenolate was observed above pH 10, making ΔA measurements problematic above this pH. This is presumably due to irreversible photoionization of the phenolate ion, which is only significant under laser photolysis and not in product studies where low-intensity lamps were used. We do not completely understand the "sigmoid" behavior observed in the plots (Figure 5) in the pH 8−10 region. This is made more complex by the fact that 1:1 H_2O-CH_3CN was used as the solvent. As noted earlier, the apparent pK_a value observed in this solvent is about 3 log units higher than that measured in wholly aqueous medium. Thus, the sigmoid behavior observed in the pH 8−10 region suggests a prototropic equilibrium with a pK_a value of about 5−7 in wholly aqueous medium, which is not unreasonable for the deprotonation of the enolic proton of **19**. Formation of **19** via ESIPT is presumably operative throughout the plateau region (pH 4−9) observed in these plots. The progressive decrease in ΔA observed for **13** as the pH decreases from 4 to 1 is further evidence that an ESIPT process is taking place as this is in the region of many known p$K(S_1)$ values of phenols.[12]

Beginning at pH 2 for **9** and at pH 1 for **13**, the intensity of transient signals observed for both **9** and **13** increases as the pH is lowered further (Figure 5). The decays of these transients at low pH are single exponential with $k_d \approx 10^7\ s^{-1}$ (lifetime of about 100 ns), consistent with a single and more reactive species than the proposed *p*-QMs observed at higher pH. We propose that the species observed at low pH are cationic species generated via initial photoprotonation of the carbonyl (i.e., **26** from **9**). A number of benzylic carbocations have been photogenerated by McClelland et al.,[17] who showed that they have absorption maxima at ~320−360 nm. The λ_{max} of the parent protonated acetophenone (generated in concentrated H_2SO_4) is at 335 nm. However, our observed lifetime of about 100 ns in aqueous solution seems to be too long for it to be a simple carbocation of the type **26**. We suggest that the species observed is derived from subsequent reactions of **26** such as electrophilic attack on unreacted substrate or possibly deprotonation of the phenolic proton to generate **19**. However, as these species are not directly relevant to the mechanism of interest, we have not pursued these assignments in detail.



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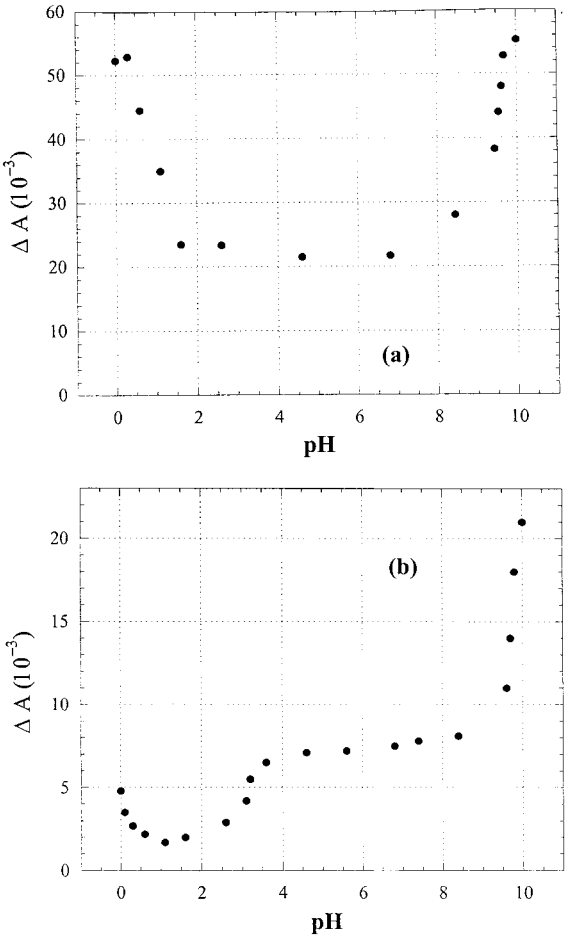

Figure 5. (a) ΔA vs pH observed on LFP of **9** monitored at 330 nm. (b) ΔA vs pH observed on LFP of **13** monitored at 360 nm (both in 1:1 H_2O-CH_3CN; O_2 purged).

Summary

The results presented above are consistent with a mechanism of reaction (via the singlet excited state) involving ESIPT or ESPT as a necessary step which is mediated most efficiently by water. The fact that the di-*tert*-butyl derivatives reacted with quantum yields very similar to those of the parent *p*-hydroxyphenacyl systems implies that the ESIPT (ESPT) process is not hampered by the steric bulk of the two *tert*-butyl groups. Literature precedent for the proposed long-range ESIPT is available in Itoh's studies[16] of **21** and **22**, as well as our recently reported example involving hydroxystyrenes.[5a] The present results suggest that these types of solvent-mediated ESIPT (or ESPT) are much more prevalent and essential for some photoreactions. With respect to applications as a phototrigger, the limiting rate for release of the carboxylate is determined by the rate of reaction of **19*** to **6** (or **9*** to **25**), which is expected to be very fast ($>10^8\ s^{-1}$) due to the fact that both of these are photochemical steps.

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Experimental Section

General Procedures. ^1H NMR spectra were determined on a JEOL FX90Q, Bruker AM 400, or Bruker WM 300 instrument. Silica gel (Merck type 9385) was used for flash chromatography. Low-resolution mass spectra (MS) were taken on a Finnigan 3300 (CI). High-resolution mass spectra were determined on a VG ZAB or Kratos Concept H (EI) mass spectrometer. Microanalyses were performed by MEDAC Ltd., Brunel University, Uxbridge, U.K. Preparative photolyses were carried out in 100 mL quartz tubes in a Rayonet RPR 100 photochemical reactor equipped with 300 nm lamps. IR spectra were recorded on a Bruker IFS25 FTIR spectrometer using a KBr pellet for solid samples. UV−vis spectra were obtained on a Varian Cary 5 spectrophotometer. Melting points (uncorrected) were determined on a Koefler hot stage microscope. Organic solvents were commercially available ACS grades and used as received, except that CH_3CN was dried over CaH_2 (reflux) when required and THF was dried by distillation over sodium. Aqueous solutions of the appropriate pH were prepared by diluting aqueous H_2SO_4 or NaOH stock and used immediately after measurement of their pH on a pH meter.

Materials. 2-(4-Hydroxyphenyl)-2-oxoethyl Acetate (9). On the basis of the method of Alexander et al.,[18] a stirred solution of *p*-hydroxyphenacyl chloride[19] (10.0 g, 58.7 mmol) and glacial HOAc (7.7 mL, 134 mmol) in dry MeCN (200 mL) cooled in an ice bath was

treated dropwise with Et_3N (17.2 mL, 123 mmol) over 15 min and then refluxed for 3 h. The reaction mixture was diluted with ether and washed with aqueous HCl, water, and brine, dried, and evaporated. Crystallization from H_2O gave **9** (5.7 g, 50%), mp 133 °C (lit.[20] mp 133 °C).

2-(4-Hydroxyphenyl)-2-oxoethanol (7). A solution of **9** (1.5 g, 7.7 mmol) in MeOH (33 mL) and 0.5 M aqueous NaOH (33 mL) was stirred at room temperature for 15 min and then acidified with aqueous HCl, and most of the MeOH was evaporated. The residue was extracted with EtOAc, and the organic phase was washed with H_2O and brine, dried, and evaporated. The residue crystallized from H_2O to give **7** (0.79 g, 67%), mp 173 °C (lit.[21] mp 170−172 °C). Under these conditions there was no evidence of a high-melting product as described previously.[21]

2-(4-Hydroxyphenyl)-2-oxoethyl Phenylacetate (10). Compound **10** was prepared as described for **9**, purified by flash chromatography [EtOAc−hexanes (2:3)], and crystallized (EtOAc−hexanes): mp 106−107 °C; ^{1}H NMR δ [90 MHz; $CDCl_3-CD_3OD$ (9:1)] 3.80 (2H, s), 5.30 (2H, s), 6.82 (2H, d, $J_o = 9$ Hz), 7.31 (5H, s), 7.77 (2H, d, $J_o = 9$ Hz). Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.92, H, 5.21.

2-(4-Hydroxyphenyl)-2-oxoethyl 2,2-Dimethylpropanoate (11): mp 178.5 °C (EtOAc−hexanes); ^{1}H NMR δ [90 MHz; $CDCl_3-CD_3OD$ (9:1)] 1.29 (9H, s), 5.25 (2H, s), 6.84 (2H, d, $J_o = 9$ Hz), 7.78 (2H, d, $J_o = 9$ Hz). Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 65.75; H, 6.78.

2-(4-Hydroxyphenyl)-2-oxoethyl 2,2-Diphenyl-2-hydroxyacetate (12). Aqueous NaOH (1 M) was added to a suspension of benzilic acid (2.28 g, 10 mmol) in water (10 mL) to adjust the pH to 6.7. *p*-Hydroxyphenacyl chloride (0.85 g, 5.0 mmol) and sodium iodide (0.15 g, 1.0 mmol) were added, and the mixture was refluxed for 3.5 h. The cooled mixture was extracted with ether, and the organic extract was washed with water, 250 mM pH 5.5 NaOAc buffer, and brine, dried, and evaporated. Flash chromatography [EtOAc−hexanes (2:3)] gave **12** as an amorphous solid (from hexanes) (0.69 g, 38%): mp 155−156 °C; ^{1}H NMR δ [90 MHz; $CDCl_3-CD_3OD$ (9:1)] 2.88 (1H, s), 5.39 (2H, s), 6.82 (2H, d, $J_o = 9$ Hz), 7.19−7.66 (10H, m), 7.77 (2H, d, $J_o = 9$ Hz); FAB-MS, *m*/*e* $(M + Na)^+$ calcd for $C_{22}H_{18}O_5 +$ Na 385.1040, found 385.1052.

2-Bromo-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethanone. This compound was obtained by a modified procedure of Karhunen et al.[22] A solution of 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethanone[23] (10.0 g, 40.32 mmol) in EtOH (350 mL) was treated with bromine (2.6 mL, 50.4 mmol) in one portion, and nitrogen was bubbled continuously into the stirred mixture. After 30 min the nitrogen flow and stirring rate were both increased. After a further 2 h the solution was concentrated to ∼50 mL and kept overnight at 4 °C. The title bromide (9.56 g, 73%) was filtered and dried: mp 107.5−108.5 °C (from hexanes); ^{1}H NMR δ (90 MHz; $CDCl_3$) 1.44 (18H, s), 4.37 (2H, s), 5.82 (1H, s), 7.87 (2H, s). Calcd for $C_{16}H_{23}BrO_2$: C, 58.72; H, 7.08. Found: C, 58.48; H, 6.98.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-oxoethyl Acetate (13). On the basis of the method of Park and Givens,[3b] a solution of 2-bromo-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethanone (1.31 g, 4.0 mmol) and glacial HOAc (0.3 mL, 5.2 mmol) in dry toluene (52 mL) was cooled to 0 °C, and DBU (0.78 mL, 5.2 mmol) was added in one portion. The solution was stirred in ice for 1 h and then overnight at room temperature and diluted with Et_2O. The solution was washed with H_2O and brine, dried, and evaporated, and the residue was crystallized (MeOH) to give **13** (0.96 g, 79%), mp 103−105 °C (lit.[24] mp 103−105 °C).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-oxoethyl 2-Phenylethanoate (14). Compound **14** was prepared as for **13** and the crude product flash chromatographed [EtOAc−hexanes (14:86)] and crystallized (EtOAc−hexanes) to afford a 58% yield: mp 63−63.5 °C; ^{1}H NMR δ (90 MHz, $CDCl_3$) 1.43 (18H, s), 3.80 (2H, s), 5.30 (2H, s), 5.75 (1H, s), 7.31 (5H, s), 7.75 (2H, s). Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.64; H, 8.01.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-oxoethyl 2,2-Dimethylpropanoate (15). Compound **15** was prepared as for **13** and the crude product flash chromatographed [EtOAc−hexanes (7:93)] and crystallized (EtOAc−hexanes) to afford a 70% yield: mp 134−135.5 °C; ^{1}H NMR δ (90 MHz, $CDCl_3$) 1.30 (9H, s), 1.45 (18H, s), 5.29 (2H, s), 5.76 (1H, s), 7.78 (2H, s). Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.16; H, 9.40.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-oxoethyl 2,2-Diphenyl-2-hydroxyacetate (16). Compound **16** was prepared as for **13** and crystallized (EtOAc−hexanes) to afford a 69% yield: mp 151−152 °C; ^{1}H NMR δ (90 MHz, $CDCl_3$) 1.45 (18H, s), 4.16 (1H, br s), 5.43 (2H, s), 5.80 (1H, s), 7.24−7.68 (10H, m), 7.76 (2H, s). Calcd for $C_{30}H_{34}O_5$: C, 75.92; H, 7.22. Found: C, 75.84; H, 7.23.

Product Studies. Preparative photolyses were carried out with samples (20−100 mg) dissolved in the appropriate solvent (40−100 mL) and transferred to a quartz tube. The solution was irradiated at 300 nm with continuous cooling (by a coldfinger) and purging by a stream of argon for approximately 15 min before and continuously during irradiation (via a long stainless steel needle). Photolysis times ranged from 3 to 30 min, depending on the conversion desired, the efficiency of the reaction, and the size of the sample. After photolysis, aqueous samples were worked up by extraction with CH_2Cl_2 after addition of NaCl. Direct evaporation of the organic solvent was used when samples were irradiated in wholly organic solvents.

Analytical photolysis runs were carried out by direct photolysis of samples in NMR tubes. A solution was made by dissolving 2−3 mg of substrate in ∼2 mL of 1:1 D_2O-CD_3CN. The solution was then purged by argon for 10 min, and transferred to an NMR tube. This NMR tube was subsequently placed in the middle of a Rayonet RPR 100 photochemical reactor and irradiated at 300 nm. An internal fan in the reactor was used to cool the sample during the photolysis. Photolysis times ranged from 1 to 10 min, depending on the number of lamps used, the conversion desired, the efficiency of the reaction, and the size of the sample. ^{1}H NMR spectra were taken directly after the photolysis without further treatment. Typical experiments are described below.

Photolysis of 9 in 1:1 H_2O-CH_3CN. Compound **9** (20 mg) was dissolved in 1:1 H_2O-CH_3CN (40 mL), and the solution was irradiated for 3 min by eight lamps using the procedure for preparative photolysis. After workup and evaporation of the solvent, ^{1}H NMR of the photolyzate showed that conversion to photoproduct **3** was 40% (the remaining was starting material **9**). Separation by preparative TLC (silica, 10:1 CH_2Cl_2-EtOAc) gave the pure photoproduct, *p*-hydroxyphenylacetic acid (**3**). Conversion was 90−95% when a sample was photolyzed for 10 min. ^{1}H NMR δ ($(CD_3)_2CO$) 3.48 (2H, s), 6.76 (2H, d, $J = 9$ Hz), 7.10 (2H, d, $J = 9$ Hz); mp 148−150 °C (lit.[25] mp 149−151 °C); MS (CI) *m*/*z* 153 $(M^+ + 1)$. Compound **9** was also studied by the procedure for analytical runs, as for **10**−**12** (see below).

Photolysis of 9 in CH_3OH. Using the procedure for preparative photolyses, solutions of **9** (20 mg) dissolved in neat CH_3OH (40 mL) were irradiated by eight lamps for 15 min. Conversion to methyl *p*-hydroxyphenylacetate was 40%, which was separated by preparative TLC (silica, 2:1 hexanes−EtOAc): ^{1}H NMR δ ($(CD_3)_2CO$) 3.48 (2H, s), 3.61 (3H, s), 6.0 (1H, s, exchangeable with D_2O), 6.76 (2H, d, $J =$ 9 Hz), 7.10 (2H, d, $J = 9$ Hz); this spectrum is identical to that reported for the authentic sample;[25] mp 55−56 °C (lit.[25] mp 59 °C); MS (CI) *m*/*z* 167 $(M^+ + 1)$.

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Photolysis of 10−12. These esters were studied only in analytical runs. A solution of **10** (2.5 mg) dissolved in 1:1 D_2O-CD_3CN (1.6 mL) was irradiated for 10 min. Conversion to photoproduct **3** was ∼95%. The ^{1}H NMR of the photolyzate showed a 1:1 mixture of **3** and phenylacetic acid (δ 3.95 (2H, s), 7.6 (5H, m)) and a trace (<5%) of **7**. The presence of both phenylacetic acid and **7** was confirmed by addition of authentic samples into the photolyzed mixture, which enhanced the readily assignable methylene protons of these substrates. Esters **11** and **12** were studied in the same way. In each case, conversion to the photoproduct **3** was ∼95%. The ^{1}H NMR spectra of the photolyzates showed (for **11**) a 1:1 mixture of **3** and pivalic acid, which has a distinctive singlet at δ 1.52 (9H), or for **12** a 1:1 mixture of **3** and benzilic acid (δ 7.8, 10H, m). Addition of authentic pivalic or benzilic acid as appropriate confirmed the identifications, by enhancement of the specific signals noted above.

Photolysis of 13 in H_2O-CH_3CN. Using the procedure for preparative photolysis, solutions of compound **13** (30 mg) dissolved in 1:1 H_2O-CH_3CN (40 mL) were photolyzed for 3 min. Conversion to pure photoproduct **17** was 36% as indicated by ^{1}H NMR of the photolyzate. Photolysis for 10 min gave photoproduct **17** with ∼95% conversion. Pure **17** was obtained by preparative TLC (silica, 10:1 CH_2Cl_2-EtOAc): ^{1}H NMR δ ($(CD_3)_2CO$) 1.40 (18H, s), 3.48 (2H, s), 6.0 (1H, s, exchangeable with D_2O), 7.10 (2H, s); mp 151−153 °C (lit.[26] mp 154−156 °C); IR (cm^{-1}) 3630, 2958, 1698, 1432, 1309, 1233; MS (CI) *m*/*z* 265 ($M^+ + 1$); HRMS (EI), calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1726. Compound **13** was also studied by the procedure for analytical runs which showed essentially quantitative conversion to **17** and acetic acid.

Photolysis of 14−16. In addition to preparative runs, these esters were also studied in analytical runs. Solutions of substrate (3 mg) dissolved in 1:1 D_2O-CD_3CN (1.6 mL) were irradiated for 10 min. Conversion to photoproduct **17** was ∼90−95% for each. The ^{1}H NMR (D_2O-CD_3CN) of photolyzates showed a 1:1 mixture of **17** and the appropriate carboxylic acid. The latter was confirmed by addition of an authentic sample of the acid, as described for esters **10**−**12**.

Quantum Yield Measurements. Absolute product quantum yields (Φ_p) were measured in 3.0 mL Suprasil quartz cuvettes on an optical bench utilizing an Oriel 200 W Hg-arc lamp in conjunction with an Applied Physics monochromator set at 254 nm with 4 nm slits. Solutions were irradiated at ambient temperature and purged with argon. Before and immediately after photolysis, the UV−vis absorption was measured at the monitoring wavelength (λ_{mon}) and the conversions were kept below 20% to avoid the interference from the photoproduct. The extinction coefficients in 1:1 H_2O-CH_3CN are 15 700 M^{-1} cm^{-1} for **9** at 279 nm (λ_{mon}) and 8400 M^{-1} cm^{-1} for **13** at 284 nm (λ_{mon}). The light intensity was determined by using potassium ferrioxalate as a chemical actinometer.[10] UV traces reported in Figure 1 were obtained by photolysis of solutions in UV cuvettes using a merry-go-round apparatus placed inside a Rayonet reactor (300 nm lamps).

Triplet Quenching Experiments. Compound **9** was photolyzed under identical conditions described above for product studies (preparative photolysis), but with an added triplet quencher in the solutions. Experiments with sodium sorbate or *trans*-piperylene as quenchers were performed in 1:1 H_2O-CH_3CN, and 1:1 H_2O-THF was used when the triplet quencher was 1,3-cyclohexadiene because of its poor solubility in 1:1 H_2O-CH_3CN. The concentration used for all these triplet quenchers was 0.01−0.1 M. Conversions to **3** were measured by ^{1}H NMR (on the photolyzate) and compared to those of runs without triplet quencher.

Laser Flash Photolysis. A Spectra-Physics excimer laser (308 nm, ∼10 ns, <30 mJ/pulse) was used for excitation, and signals were digitized with a Tektronix TDS 520 recorder. Samples of OD ≈ 0.3 at 308 nm were prepared and irradiated in quartz cells. Static cells were used for the kinetic studies of samples, and flow cells for all other studies. Samples in flow cells were continuously purged with a stream of N_2 or O_2. Samples in static cells were purged with N_2 or O_2 and then sealed prior to photolysis.

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