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Excited state (formal) intramolecular proton transfer (ESIPT) in *p*-hydroxyphenyl ketones mediated by water

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Abstract

Evidence is presented that show *p*-hydroxyphenyl ketones **6**–**8** undergo excited state intramolecular proton transfer (ESIPT, via the singlet excited state), mediated by water, which formally transfers the phenol proton to the carbonyl oxygen of the ketone. ESIPT was not observed in neat CH_3CN. The ESIPT process in aqueous media generates the corresponding *p*-quinone methides **9**–**11** (and the corresponding conjugate bases (phenolate ions) **12**–**14**), as detected by laser flash photolysis (LFP). It competes effectively with intersystem crossing to the excited triplet state. The respective *p*-methoxyphenyl ketones **15** and **16** failed to undergo the reaction consistent with the expected lack of proton transfer in these systems. Results for the biphenyl ketone **8** indicate that formal ESIPT can also take place over an extended range, suggesting that the process is likely general for all *p*-hydroxyaromatic ketones which opens up the possibility for designing photoswitchable processes based on this general phenomenon. ©2000 Elsevier Science S.A. All rights reserved.

Keywords: Excited-state proton transfer; Quinone methide; Hydroxy ketone

1. Introduction

It is well-known that phenols are much more acidic in the excited singlet state than in the ground state while aromatic ketones are much more basic (in the singlet excited state) [1–3]. Excited state intramolecular proton transfer (ESIPT) occurs due to an enhancement in the acidity and basicity, respectively, of two functional groups on the same chromophore. The close proximity of the phenol and the ketone in *o*-hydroxy aromatic ketones leads to an ESIPT process which has been the subject of extensive study and review [1,2]. The energy wasting back proton transfer in these systems is very efficient, and as such, many molecules of this type have been used as photostabilizers as well as in sunblocks [1,2]. The ESIPT process in the respective *m*- and *p*-isomers has received much less attention. Wolbeis et al. [4,5] employed extensive fluorescence measurements in solutions of varying pH’s to suggest the formation of photogenerated quinone methides (QMs) of 3-hydroxyxanthone (**1**) and 7-hydroxyflavone (**2**). Itoh et al. [6–9] have undertaken studies using two-step laser excitation fluorescence and laser flash photolysis (LFP) to demonstrate the formation of the QMs from **1** and **2** as well as from 7-hydroxyisoflavone (**3**). These studies also showed the photogeneration of the respective anions, formed by excited state proton transfer (ESPT) to solvent (Eq. (1)).

More recently our group has demonstrated the occurrence of formal ESIPT between a phenol and an alkene in two *m*-hydroxystyrenes **4** and **5**, to yield the respective photohydrated products [10,11], via the intermediacy of *m*-QMs (Eq. (2)). The process also takes places for the *p*-isomer of **4**. This study has shown that due to the relatively large separation between the two functional groups undergoing intramolecular proton transfer, the process requires the mediation of several molecules of water. Whether the mediation takes place in a concerted or step-wise manner is open to debate and further study.

Extensive LFP studies have also been conducted on *p*-hydroxybenzophenone (**7**) by several groups [12–16], in order to characterize its triplet excited state in various solvents. All of these studies report the formation of the benzophenone phenolate (albeit only as a weak transient) via the singlet state upon excitation in protic solvents. However, no mention has been made of the possibility of photogenerating the respective *p*-QM under these conditions.

As part of our continuing work on photogenerating QMs, our studies have recently focused on the mechanism of photorelease of protected esters from *p*-hydroxyphenacyl esters [17] which are structurally also *p*-hydroxyphenyl ketones.

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During the course of this work it was hypothesized that ESIPT (from the phenol to the ketone) played a fundamental role in the deprotection mechanism. Based upon these results and the previous studies by Wolfbeis et al. [4,5] and Itoh et al. [6–9] mentioned above, we decided to test the generality of ESIPT in *p*-hydroxyphenyl ketones by studying *p*-hydroxyketones **6–8**. Although most of the previous studies [4–9] relied heavily on fluorescence measurements, all of **6–8** were essentially non-fluorescent (very high intersystem crossing yields), and as such the anticipated ESIPT process must by studied by other methods. We show here that LFP of **6–8** leads to the generation of the respective *p*-QMs and the corresponding phenolate ion thus providing additional evidence that long-range ESIPT via the singlet state in *p*-hydroxyketones is indeed a general process. The observation that it competes effectively with intersystem crossing suggests that it is an efficient process.

2. Experimental details

2.1. General

^{1}H NMR spectra were recorded on a Bruker AC-300 (300 MHz) instrument. Melting points were obtained using a Koefler hot stage microscope and are uncorrected. THF was dried over Na and distilled before use. Chemical ionization mass spectra were measured on a Finnigan 3300 instrument and high resolution mass spectra were taken using a Kratos Concept H (El mode).

2.2. Materials

Ketones **6**, **7**, **15** and **16** were purchased from Aldrich; ketones **6** and **7** were recrystallized before use. All ketones were of >98% purity.

2.2.1. (4′-Hydroxyphenyl)benzophenone (**8**)

Phenyl magnesium bromide was prepared by adding 23.2 ml of PhBr (Aldrich, 220 mmol) dropwise via a syringe to 6.8 g of clean Mg turnings (280 mmol) in 100 ml of dry THF under N_2 at 0°C and allowing the solution to warm to room temperature. After formation of the Grignard reagent the solution was then transferred into a clean, dry three-neck flask purged with N_2. 4-hydroxy-4-biphenylcarbonitrile (Aldrich, 15 g, 77 mmol) in 75 ml of THF was then added dropwise and allowed to stir for 3 h under gentle reflux. During this time, a white solid formed, which was filtered, dissolved in ethanol, and poured into a 250 ml round-bottom flask. To this flask was added 50 ml of 10% HCl, and the mixture was allowed to reflux for 3 h. At the end of the reflux a pale yellow crystalline solid had formed which was filtered and dried on the vacuum pump and shown to be compound **8**. This was then recrystallized from 95% EtOH, yield 20.1 g (95%); m.p. 200–203°C; ^{1}H NMR (($(CD_3)_2CO$)) δ 6.98 (d, 2H, $J = 7$ Hz, ArH), 7.5–7.7 (m, 5H), 7.8–7.9 (m, 6H), 8.6 (s, 1H, ArOH); HRMS calc. for $C_{19}H_4O_2$, 274.0993, obs. 274.0990.

2.2.2. (4′-Methoxyphenyl)benzophenone (**17**)

Crushed KOH (0.4 g, 7.1 mmol) was added to 50 ml of DMSO in a 250 ml round-bottom flask. To this was added 300 mg (1.1 mmol) of **8** and 0.31 g (2.2 mmol) of methyl iodide. After stirring for 45 min, the solution turned into a pale yellow colour. The reaction was then quenched with 50 ml of H_2O, at which point a white solid appeared in solution. This was then extracted twice with 75 ml of CH_2Cl_2. The organic layer was washed four times with 50 ml of H_2O to remove any residual DMSO, dried with $MgSO_4$, and the solvent removed. The product **17** was isolated as a pale yellow solid in 92% yield and was then recrystallized from 95% ethanol, yield 0.29 g (92%); m.p. 169.5–172.5°C; ^{1}H NMR (($(CD_3)_2CO$)) δ 3.86 (s, 3H, OCH_3), 7.07 (d, 2H, $J = 10.3$ Hz, ArH), 7.5–7.9 (m, 11H, ArH); mass spectrum (CI) 289 ($M^+ + 1$).

2.3. Laser flash photolysis (LFP)

All transient spectra and lifetimes were obtained using an excimer laser (Lumonics, <5 mJ, 308 nm) with a pulse width of ∼10 ns. Samples of OD ≈ 0.3 at 308 nm were prepared and irradiated in quartz cells. Flow cells were used for spectra while static cells were used for some lifetime measurements. All solutions were purged with N_2 or O_2 before irradiation. Due to the long lifetimes of the slow decays, it was not possible to obtain a trace that returned to baseline. However, the lifetimes reported for the H_2O/D_2O experiments are the average of several trials, all of which were within 10% of each other.

3. Results and discussion

LFP of **6** (1 : 1 H_2O-CH_3CN, N_2 purged) yielded strong, long-lived transients at 330 nm (fitted to a sum of two single exponential decays) and a shorter lived transient at 340, 400 and 510 nm. The bands at 340, 400 and 510 nm have a lifetime of 700 ns under N_2 purged conditions but disappear under O_2 purged conditions and thus are attributed to the triplet state of **6**. This is consistent with work by Banjaree and Falvey [18] who assigned the triplet state of phenacyl phenylacetate (which has a similar chromophore) in benzene at 340 nm. Similarly, Scaiano and co-workers [19] assigned the triplet state of *p*-hydroxypropiophenone (in wet CH_3CN) to a transient at 380 nm ($\tau = 1.1$ μs). The 330 nm signal was not observed in neat CH_3CN; but upon addition of water, the signal grew in intensity. In 1 : 1 H_2O-CH_3CN, the decay consisted of a sum of two single exponentials ($\tau \sim 1$ and 10 μs) which was unchanged under O_2 and therefore assignable as arising from the singlet excited state (Figs. 1–3).

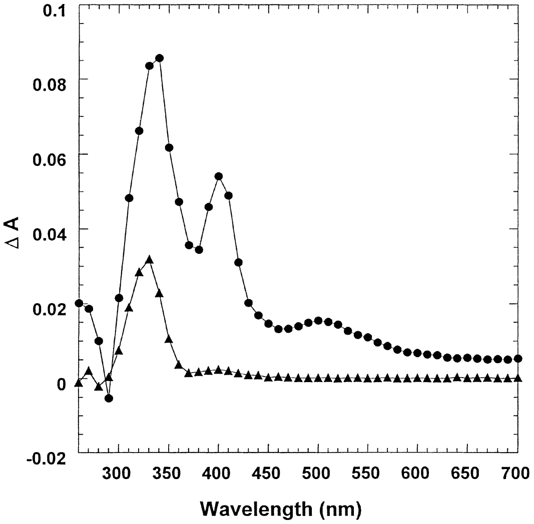


Fig. 1. LFP spectra of transients observed for *p*-hydroxyacetophenone (**6**) in 1 : 1 H_2O-CH_3CN. Triangles: O_2 Purged; Circles: N_2 Purged.

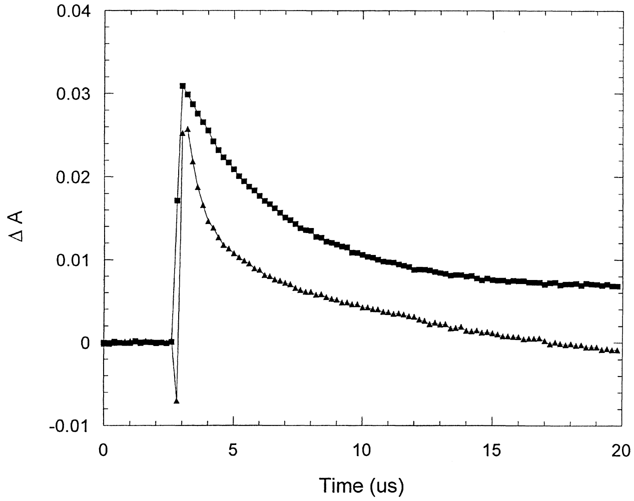


Fig. 3. Representative transient decays fitted to a sum of two single exponential decays observed in LFP experiments in 1 : 1 H_2O-CH_3CN (O_2 purged) at 330 nm (**6**, triangles) and at 380 nm (**8**, squares).

LFP of **7** as above (N_2 purged) yielded a transient which is best fitted to the sum of two single exponentials with lifetimes of ~3 and 65 μs, both at 350 nm (Fig. 2). These signals remain unchanged under O_2 purged conditions, and hence are attributable to intermediates arising from the singlet excited state. No signals were observed in neat CH_3CN (under O_2). The fact that this transient remains at essentially the same intensity under both N_2 and O_2 purged conditions is indicative that reaction via the singlet manifold is preferred over intersystem crossing to the triplet state.

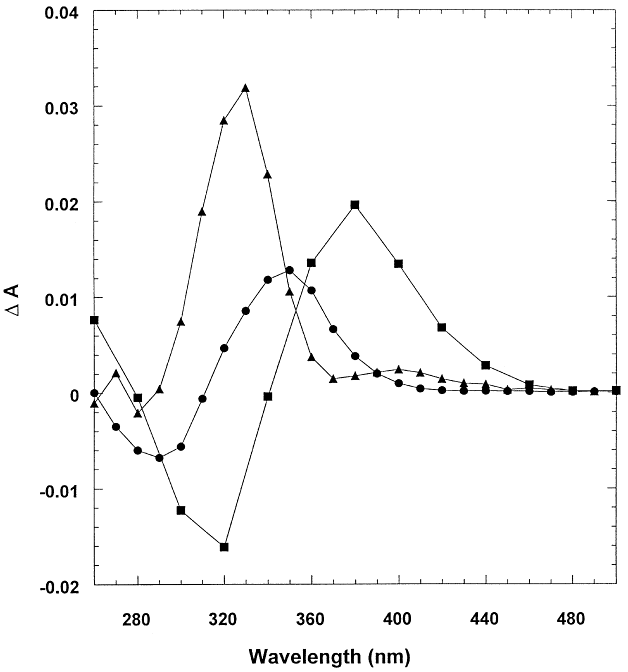
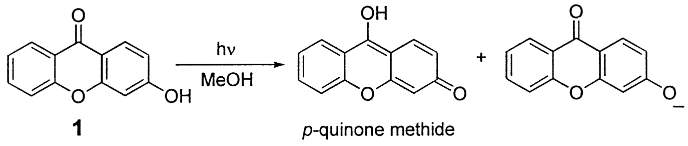


Fig. 2. LFP spectra of transients observed for **6** (triangles), **7** (circles) and **8** (squares) in 1 : 1 H_2O-CH_3CN, O_2 purged. The bleaching of signal seen in the spectra at shorter wavelengths is attributed to the decrease in absorption of the ground state material, due to formation of excited triplet states/reactive intermediates on laser excitation.

LFP experiments were also conducted on **8**, to examine the effect of having the phenol and ketone moieties separated over a longer distance. LFP of **8** (N_2 purged) yielded a strong signal at 380 nm again consisting of the sum of two single exponential decays with lifetimes of ~3 and 27 μs and a broad weak signal from 430–700 nm. The latter signal disappeared under O_2 purged conditions, while the former remained unchanged; hence the 380 nm signals is assigned as arising from the singlet state (Fig. 2), while the broad 430–700 nm band is attributed to the triplet excited state. As observed with 7, the above data is consistent with a scheme in which reaction from the singlet excited state of **8** predominates over intersystem crossing in 1 : 1 H_2O-CH_3CN.

Kinetic studies of the 350 nm transient of **7** were carried out in both 1 : 1 D_2O : CH_3CN and 1 : 1 H_2O : CH_3CN (O_2 purged), to help in the assignment. The lifetime of the faster decay increased by about 20% (2.9 vs. 3.5 μs in H_2O vs. D_2O), while the lifetime of the slower decay increased by a factor of 2 (65 vs. 135 μs in H_2O vs. D_2O). Similar results were observed for **6** (in H_2O vs. D_2O). The faster decay remains essentially the same (τ ~1 μs in H_2O vs. D_2O), while the lifetime of the slower decay is twice as long in D_2O (20 vs. 10 μs).

LFP experiments were also conducted using the respective *p*-methoxy compounds **15–17**, as the methoxy group is expected to have similar electronic effects as hydroxy, but lack an acidic proton. LFP of these compounds (1 : 1 H_2O-CH_3CN) yielded strong transients under N_2 which were completely quenched under O_2, thereby indicating that only triplet-derived processes were occurring. These results show that the *p*-hydroxy group is required for the formation of the transient species observed above. LFP experiments were also conducted using *m*-hydroxybenzophenone in



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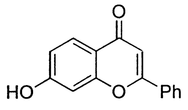

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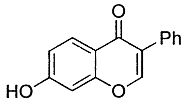

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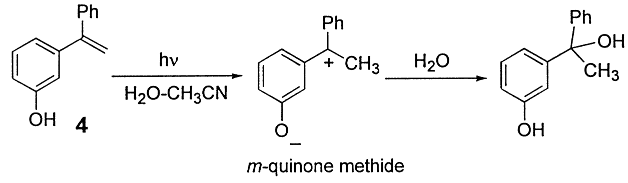

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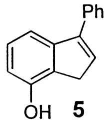

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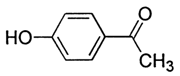

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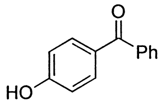

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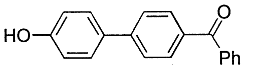

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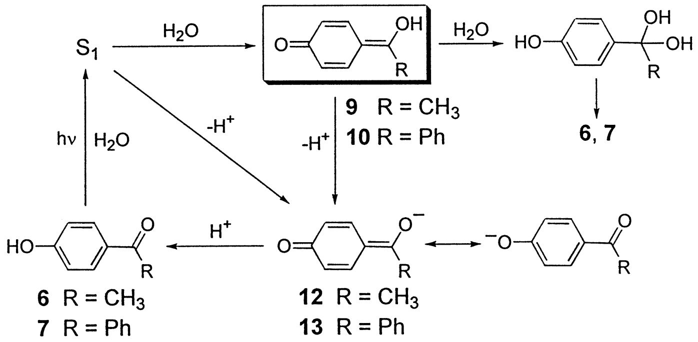
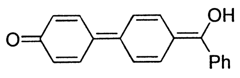


Scheme 1.



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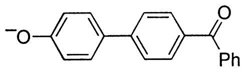

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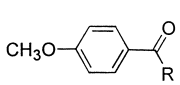
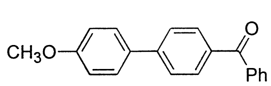


15 $R = CH_3$
16 $R = Ph$



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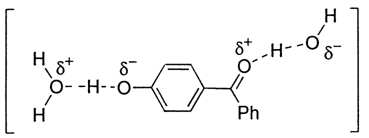

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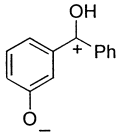

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1 : 1 H_2O-CH_3CN (O_2 or N_2 purged). However, only very weak signals were observed and further studies on the meta isomers were not pursued.

The proposed mechanistic scheme which accounts for the observed results is shown in Scheme 1 (for **6** and **7**). The transients observed only in aqueous solution for all three ketones **6–8** (at 330, 350 and 380 nm, respectively) are essentially identical to the UV–VIS spectra of the corresponding authentic phenolate ions (generated at high pH) of these compounds (i.e., **12–14**, respectively). However, the biexponential decays indicate that there are two species involved, with very similar absorption spectra. We propose that the other species formed are the corresponding *p*-quinone methides **9–11**, which are expected to have similar absorption spectra as the corresponding phenolate ions above. This proposal is consistent with results of Wolfbeis et al. [4,5] and Itoh et al. [6–9] who have proposed the formation of similar species for **1–3**. The *p*-quinone methides **9–11** are formed via the singlet excited state, presumably via assistance of water, as shown in transition state **18**. In addition, simple proton transfer to water from the excited singlet state to generate **12–14** probably also occurs although it is difficult to estimate the extent of this process. The fact that only very weak signals were observed for *m*-hydroxybenzophenone would suggest that initial ESIPT is required for formation of the phenolate ions, via subsequent deprotonation.

The primary mode of decay for phenolates **12–14** is simple reprotonation on the phenol oxygen, to regenerate starting ketone. The primary mode of decay for *p*-quinone methides **9–11** is probably nucleophilic attack by water at the exocyclic vinyl carbon, as shown for a variety of other photogenerated quinone methides in aqueous solution [20,21]. For **9–11**, such an attack generates the corresponding ketone hydrates which will readily revert to starting ketone. Another mode of reaction for **9–11** is deprotonation of the enolic proton to generate **12–14**. Unfortunately, the relative contributions of these two modes of decay could not be estimated since we were unable to design any successful product study experiments. Any simple nucleophile which can attack **9–11** would give a tetrahedral intermediate that would readily expel the nucleophile, to regenerate substrate. Attempts at using hydride were problematic due to efficient thermal reaction.

One would expect a substantial primary solvent (water) isotope effect upon reprotonation of the phenolates **12–14**, but not with nucleophilic attack (by water) on the vinyl carbon of *p*-quinone methides **9–11**. Based on this expectation in solvent isotope effects for the decays of the two species in our LFP data, we have assigned the slower decay to that of the phenolate and the faster decay to the p-quinone methide. These assignments are also consistent with the assignments made by Itoh et al. [6–9] for **1** and **2**.

The question remains as to the possibility that the above formal ESIPT process can occur for the meta isomers. We have shown that *m*-quinone methides can be photogenerated efficiently from suitable precursors and that they have lifetimes that are measurable using nanosecond LFP [10,11,20,21]. However, all of the *m*-quinone methides detected so far have only one decay pathway, viz., nucleophilic attack by water at the benzylic carbon (e.g., Eq. (2)). LFP studies of *m*-hydroxybenzophenone gave only very weak signals; they appear at the same wavelength as the corresponding phenolate generated in basic solution. Therefore, it is possible that some phenolate is photogenerated but no evidence was available indicating formation of the corresponding *m*-quinone methide **19**. Indeed, Bhasikuttan et al. [12] have assigned a transient with similar intensity at 360 nm to this phenolate (photogenerated in MeOH). A more detailed examination of the structure of **19** would indicate that the main pathway for reaction of this species is deprotonation of the hydroxyl group since the corresponding conjugate base (the ketone) is a very weak base. The rate of such a deprotonation, assuming Eigen-like behavior, would be very fast ($>10^9\ s^{-1}$). Therefore, if such an intermediate is formed, it would not be observable by nanosecond LFP. It seems clear that more kinetic studies are warranted to fully understand ESPT and ESIPT processes for hydroxyaromatic ketones. Our initial results above indicate that much more remains to be explored in their excited singlet state chemistry which may have been inadvertently neglected in the past.

4. Summary

Formal ESIPT (and ESPT) was found to occur in hydroxy aromatic ketones **6**, **7** and **8,** to yield the corresponding *p*-quinone methides as well as the respective phenolates, suggesting that this is a general process for all such ketones. The ESIPT process was found to take place via the singlet manifold and requires water (or another protic solvent) to mediate the process.

Acknowledgements

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