Transient Intermediates in the Laser Flash Photolysis of Ketoprofen in Aqueous Solutions: Unusual Photochemistry for the Benzophenone Chromophore

L. J. Martínez and J. C. Scaiano*

Contribution from the Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario K1N 6N5, Canada

Received March 13, 1997[⊗]

Abstract: The transient intermediates in the nanosecond laser flash photolysis of ketoprofen, an aryl propionic acid, show the formation of a carbanion in aqueous solutions at pH 7.1. This carbanion incorporates spectroscopic properties from both a ketyl radical anion and a benzylic radical. The ketoprofen carboxylate undergoes biphotonic photoionization, a process that contributes less than 10% to its photodecomposition and leads to a benzylic-type radical after decarboxylation with a rate constant $\geq 1 \times 10^7$ s^{-1}. On the other hand, the carbanion forms monophotonically and the unsuccessful attempts to sensitize the formation of the ketoprofen triplet excited state in aqueous solutions suggest that the carbanion precursor is either an excited singlet state or an extremely short-lived triplet. In organic solvents of lower polarity, the excited triplet state is readily detectable.

Introduction

The photochemistry of aryl ketones in solution and micelles has been extensively studied.[1−6] Aryl ketones find a variety of biochemical applications as site-specific reagents for probing proteins and nucleic acids.[7] They also have pharmacological applications as drugs or sunscreening agents.[8−11] Benzophenone (BP) is probably the best known aryl ketone whose photochemistry is characterized by an efficient intersystem crossing that populates an n,π* triplet state.[2,5,12] In aqueous solutions,[13] benzophenone undergoes biphotonic photoionization and triplet−triplet annihilation involving electron transfer to yield a radical pair.

Ketoprofen (KP) is a non-steroidal anti-inflammatory agent whose chemical structure is basically that of a substituted benzophenone. Product studies of the UV irradiation of KP in aqueous solutions[14,15] point to an efficient photodecarboxylation process of the KP carboxylate (pK_a = 4.7). Two mechanisms have been proposed to account for the photodecarboxylation process (i.e. ionic vs radical).[16,17] Nevertheless, no studies on the transient intermediates produced after excitation of KP in solution have been reported to support either mechanism.[18]

KP
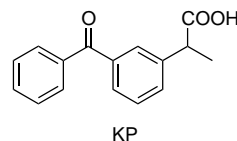
We have employed nanosecond laser flash photolysis techniques to elucidate the photodecarboxylation mechanism of the KP carboxylate in aqueous buffered solutions.

Experimental Section

Materials. Ketoprofen (2-[3-benzoylphenyl]propionic acid), potassium peroxydisulfate (K$_2$S$_2$O$_8$), sodium phosphate monobasic, sodium phosphate dibasic, citric acid, and cysteine were purchased from Sigma Chemical Co. and used as received. Sorbic acid (2,4-hexadienoic acid) and 4-methoxyacetophenone were from Aldrich Chemical Company Inc. 1-azaxanthone was from Lancaster, and phenol was purchased from Fisher Scientific. All solvents were HPLC grade and were used without further purification. Water was purified through a Millipore MilliQ system.

Nanosecond Laser Flash Photolysis. Ketoprofen samples at concentrations ranging from 0.1 to 0.3 mM were prepared in 10 mM phosphate buffer at pH 7.1. All the transient spectra and kinetics were recorded by employing a flow system with a 7 × 7 mm^2 Suprasil quartz cell with a 2 mL capacity. The laser flash photolysis system has been previously described.[19] Briefly, samples were excited with a Lumonics EX-530 laser with a Xe/HCl/Ne mixture generating pulses at 308 nm of ∼6 ns and ≤60 mJ/pulse. For the sensitization experiments we employed either the third harmonic from a Surelite Nd/YAG laser (355 nm, 25 mJ per 8 ns pulse) when exciting 1-azaxanthone or a Molectron UV-24 nitrogen laser for exciting the *p*-methoxyacetophenone at 337

⊗ Abstract published in *Advance ACS Abstracts,* October 15, 1997.

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(11) Szczurko, C.; Dompmartin, A.; Michel, M.; Moreau, A.; Leroy, D. *Photodermatol., Photoimmunol. Photomed.* **1994,** *10,* 144.

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(14) Boscá, F.; Miranda, M. A.; Carganico, G.; Mauleón, D. *Photochem. Photobiol.* **1994,** *60,* 96.

(15) Constanzo, L. L.; De Guidi, G.; Condorelli, G.; Cambria, A.; Fama, M. *Photochem. Photobiol.* **1989,** *50,* 359.

(16) Budac, D.; Wan, P. *J. Photochem. Photobiol. A: Chem* **1992,** *67,* 135.

(17) Studies in cellular systems suggest free radical involvement: Chignell, C. F.; Sik, R. H. *Photochem. Photobiol.* **1995,** *62,* 205.

(18) While this manuscript was being reviewed we became aware of similar studies conducted by S. Monti (Monti, S.; Sortino, S.; De Guidi, G.; Marconi, G. *J. Chem. Soc., Faraday Trans.* Submitted for publication).

(19) Other aspects of the system are similar to those described earlier: Scaiano, J. C. *J. Am. Chem. Soc.* **1980,** *102,* 7747. Scaiano, J. C.; Tanner, M.; Weir, D. *J. Am. Chem. Soc.* **1985,** *107,* 4396.
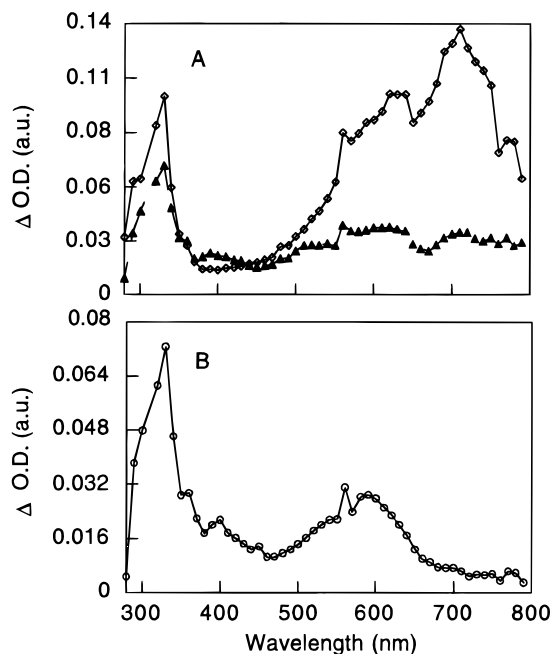
Figure 1. Transient absorption spectra obtained from the 308 nm laser flash photolysis of KP in aqueous buffered solutions at pH 7.1: (A) under N$_2$-saturated ($\diamond$) and O$_2$-saturated ($\blacktriangle$) conditions; (B) under N$_2$O-saturated conditions ($\bigcirc$). All spectra were recorded 72 ns after the laser pulse.

Figure 2. Transient intermediates in the photolysis of KP in aceto-nitrile, 0.72 μs after the pulse ($\bigcirc$), methanol, 0.13 μs after the pulse ($\bullet$), and cyclohexane, 0.32 μs after the pulse ($\diamond$).

Figure 3. Power dependence for the formation of solvated electrons ($\triangle$) and the 600-nm transient ($\blacktriangledown$) observed in aqueous solutions.

nm. The signals from the monochromator/photomultiplier system were initially captured by a Tektronix 2440 digitizer and transferred to a PowerMacintosh computer that controlled the experiment with software developed in the LabVIEW 3.1.1 environment from National Instruments. Samples were purged with the appropriate gas (*i.e.* N$_2$, O$_2$, or N$_2$O) for 30 min before and during the acquisition of the transient spectrum.

Product Studies. Photolysis of ketoprofen solutions at a concentration of 0.5 mM in H$_2$O and D$_2$O was done by using as the excitation source the Lumonics EX-530 308-nm laser. Samples received 100 pulses with an average power of 4 mJ/pulse measured at the sample holder. The solvent was removed under vacuum, and the resulting mixture was analyzed with a Fisons GC/MS 8060 8000 Series equipped with a J&W DB5 30 m × 0.32 mm column.

Results and Discussion

The transient absorption spectra obtained from the 308 nm laser photolysis of 0.1 mM KP in aqueous solutions at pH 7.1 (Figure 1) show absorptions from 280 to 380 nm and from 500 to 800 nm. The broad band in the visible region has contributions from two species that decay almost simultaneously following first-order kinetics ($k_{720\ nm} = 6.1 \times 10^6$ s^{-1}; $k_{600\ nm} = 5.1 \times 10^6$ s^{-1}). The effect of O$_2$ and N$_2$O on these signals (Figure 1) establishes the contribution from the solvated electron (e$^-_{aq}$) and shows clearly the spectrum of another species absorbing at 600 nm. This result indicates that the KP carboxylate photoionizes in aqueous solutions. From the optical density immediately after the laser pulse at 720 nm, and knowing the extinction coefficient of e$^-_{aq}$,[20] we estimate, at most, an 8% contribution from photoionization to the KP photodegradation. In contrast, in solvents of lower polarity such as acetonitrile, methanol, or cyclohexane (Figure 2), photoionization is not observed, but the characteristic triplet−triplet benzophenone-like absorption[21] is readily detectable. In cyclohexane and
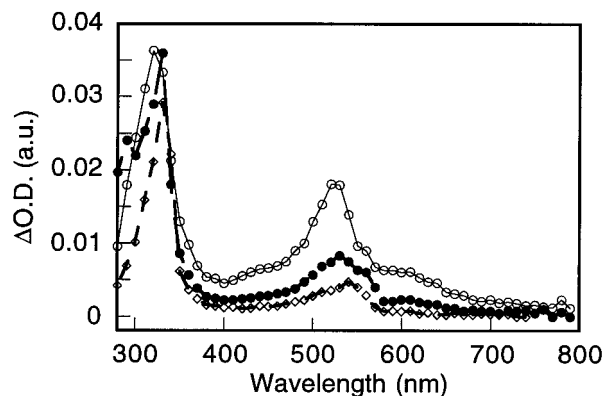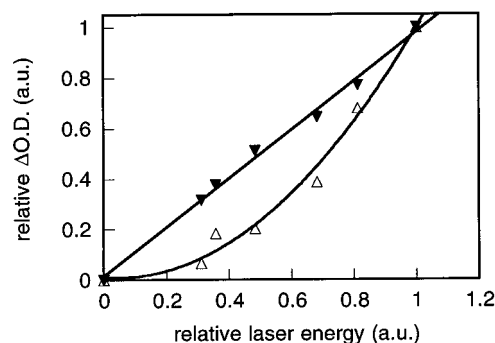
methanol, we also detected the contribution from ketyl radical absorptions to the transient spectra.[22]

To determine if the photoionization of KP is a monophotonic or biphotonic process, the optical density at 720 nm was monitored as a function of laser energy between 0.5 and 4.5 mJ. Figure 3 shows that the e$^-_{aq}$ data are best-fitted by a second-order polynomial, whereas for the signal at 600 nm a linear dependence was obtained. For the 600-nm transient, the linear fit goes through the origin, a requisite for monophotonic processes.[23] Furthermore, a log−log plot (not shown) yields a slope of 0.93 for the 600-nm transient, while a slope of 2.05 was calculated for the e$^-_{aq}$ data. Therefore, the KP carboxylate undergoes biphotonic photoionization in aqueous solutions as reported for benzophenone and other carboxylic acid derivatives.[24,25] As has been previously suggested for benzophenone,[25] the extinction coefficient of the KP triplet at the excitation wavelength (i.e. 308 nm) might be higher than that for the ground state KP at the same wavelength, thus increasing the probability of absorption of a second photon by the KP triplet (reaction 1).

$$^3KP^* \rightarrow KP^+ + e^-_{aq} \qquad (1)$$
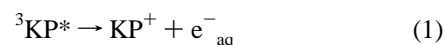
The absorption for the benzophenone radical cation in cyclohexane has a maximum at 850 nm.[26] No such signal was

(20) Hug, G. L. *Optical Spectra of Nonmetallic Inorganic Transient Species in Aqueous Solution*; National Bureau of Standards: Washington, 1981; NSRDS-NBS 69, p 160.

(21) Carmichael, I.; Hug, G. L. *J. Phys. Chem. Ref. Data* **1986**, *15*, 1.

(22) The differences observed in organic solvents could be related to the protonation state of this propionic acid. This is currently under investigation.

(23) Lachish, U.; Shafferman, A.; Stein, G. *J. Chem. Phys.* **1976**, *64*, 4205.

(24) Sauberlich, J.; Brede, O.; Beckert, D. *J. Phys. Chem.* **1996**, *100*, 18101.

(25) Sauberlich, J.; Beckert, D. *J. Phys. Chem.* **1995**, *99*, 12520.

(26) Baral-Tosh, S.; Chattopadhyay, S. K.; Das, P. K. *J. Phys. Chem.* **1984**, *88*, 1404.

observed for ketoprofen. If the radical formed from the photoionization of KP was similar to $BP^{•+}$, it would rapidly react with water yielding a KP-OH$^•$ adduct (i.e. cyclohexadienyl radical). However, the electron is most likely lost from the carboxylate moiety followed by rapid decarboxylation. In N_2O-saturated solutions we detected the absorption of the KP-OH$^•$ radical formed from the reaction with the hydroxy radical generated from reaction 2.

$$N_2O + e^-_{aq} \rightarrow N_2 + HO^• + HO^- \qquad (2)$$

No absorption near 400 nm was detected under N_2-saturated conditions that would confirm the formation of a KP radical of the cyclohexadienyl type.

An experiment using the photolysis of potassium peroxydisulfate ($K_2S_2O_8$) to generate the KP radical formed after loss of an electron showed the formation of a transient absorbing with maxima at 330 and 360 nm. This transient is assigned to the benzylic radical generated from the decarboxylation of the initial aryloxyl KP radical.[27,28]

$$S_2O_8{}^{2-} \xrightarrow{h\nu} 2SO_4{}^{-•}$$

$$SO_4{}^{-•} + KP \longrightarrow SO_4{}^{2-} +$$
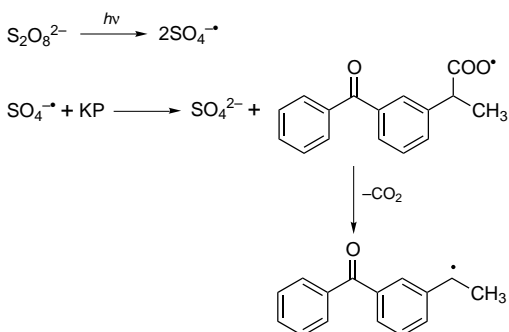
From the growth observed at either 330 or 360 nm, a rate constant $> 1.3 \times 10^7$ s^{-1} was estimated for the decarboxylation process.[29–31] The decay of this radical followed second-order kinetics ($k = 2.1 \times 10^6$ M^{-1} s^{-1}), thus implying that dimerization through a radical recombination process is their principal mode of decay. The direct excitation of KP under N_2-saturated conditions shows a band with maximum at a 330 nm and a small shoulder with a maximum at 360 nm. Thus, the KP radical generated after photoionization and decarboxylation is a benzylic-type radical.

The decay of the e^-_{aq} depends on the initial KP concentration leading to a rate constant of 2.1×10^{10} M^{-1} s^{-1} for electron trapping by KP. This second-order rate constant is slightly

(27) Chatgilialoglu, C. In *Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC Press: Boca Raton, FL, 1989; Vol. II, p 3.

(28) The transient absorption spectra of several benzoyloxyl radicals show broad absorptions covering the visible range. In our case, the quenching and decrease of the initial absorption in the visible region when solutions are gassed with N_2O or O_2 discard the possibility that we are observing similar aryloxyl radicals from KP. Since the lifetime of the transient absorption remaining at 600 nm goes from 5.1×10^6 s^{-1} under N_2 to 1.7 $\times$ 10^7 s^{-1} under O_2 we believe that decarboxylation following the direct excitation of KP occurs within the duration of the laser pulse. (a) Wang, J.; Itoh, H.; Tsuchiya, M.; Tokumaru, K.; Sakuragi, H. *Tetrahedron* **1995**, *51*, 11967. (b) Wang, J.; Tateno, T.; Sakuragi, H.; Tokumaru, K. *Tetrahedron* **1995**, *92*, 53.

(29) The rate of oxidation of ketoprofen with the sulfate radical is quite fast ($k \geq 2 \times 10^9$ M^{-1} s^{-1}). Therefore, we can only provide a lower limit for the decarboxylation process.

(30) The estimate is in line with similar lower limits obtained for other acyl radicals leading to benzylic radical centers: Steenken, S.; Warren, C. J.; Gilbert, B. C. *J. Chem. Soc., Perkin Trans. 2* **1990**, 335.

(31) For phenylacetoxyl radical the rate constant for decarboxylation has been estimated as 5×10^9 s^{-1} (Hilborn, J. W.; Pincock, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 2683). The only absolute measurement corresponds to the radical derived from 9-methylfluorene-9-carboxylate with a lifetime of ca. 55 ps: Falvey, D. E.; Schuster, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 7419.
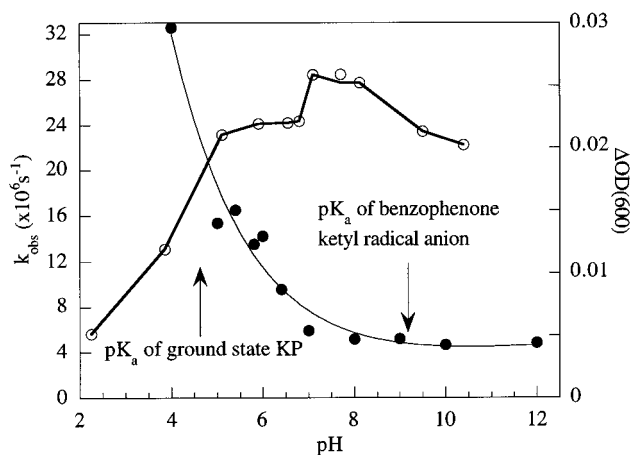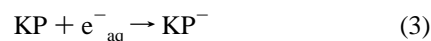
Figure 4. Transient absorption of the 600-nm transient as a function of pH (right) and rate constant of decay of the 600-nm transient as a function of pH (left).

lower than that for benzophenone,[32] as expected for a negatively charged species. The reaction of KP with e^-_{aq} could lead to the formation of KP radical anions (reaction 3). Due to the

$$KP + e^-_{aq} \rightarrow KP^- \qquad (3)$$

nature of the KP chromophore, we expect these radical anions to have absorptions with maxima at 340 and 600 nm just as the ketyl radical anions of benzophenones.[33] The radical anion formed would be rapidly protonated at pH 7.1 to yield a ketyl radical absorbing in the 530-nm region.[34] However, this process is not occurring under the conditions employed in our experiments for three reasons. First, the absorption at 600 nm is still present when solutions where bubbled with N_2O, an efficient e^-_{aq} scavenger. Second, the transient absorbing at 600 nm is produced after absorption of one photon (*vide supra*). If this transient was formed by reaction 3, a biphotonic dependence would have been expected. Third, the formation of ketyl radicals was negligible at the low initial KP concentrations employed. Therefore, we rule out significant contributions to the 600-nm band from reaction 3.

We also monitored the pH dependence for the decay of the 600-nm transient in an attempt to determine its pK_a (Figure 4). At pH values close or below the ground state pK_a of KP other species contribute to the absorption at 600-nm, such as the KP triplet (*vide infra*). In addition, the nature of the absorbing species changes from the carboxylate to the neutral acid, thus only a pH-dependence half-wave curve could be obtained. Nevertheless, our results based on signal amplitude suggest that the pK_a of this transient must be around 6.9, while the kinetics indicate a pK_a between 4.5 and 7.0, indicating that its acidity constant is about two orders of magnitude lower than for the benzophenone ketyl radical. The presence of a propionic acid side chain at the meta position should not affect dramatically the properties of a ketyl radical anion derived from a benzophenone-like chromophore since delocalization of the electron density through resonance cannot occur. If a biradical-type structure dominated, one would expect the ketyl moiety to behave essentially the same way as in a monoradical.[35–37]

(32) Ross, A. B.; Mallard, W. G.; Helman, W. P.; Bielski, B. H. J.; Buxton, G. V.; Cabelli, D. A.; Greenstock, C. L.; Huie, R. E.; Neta, P. *NDRL/NIST Solution Kinetics Database: Ver. 1,* 1.0 ed.; NIST, U.S. Department of Commerce: Gaithersburg, MD, 1992.

(33) Hayon, E.; Ibata, T.; Lichtin, N. N.; Simic, M. *J. Phys. Chem.* **1972**, *76*, 2072.

(34) The pK_a of the benzophenone ketyl radical anion has been reported to be 9.2 (see ref 28).

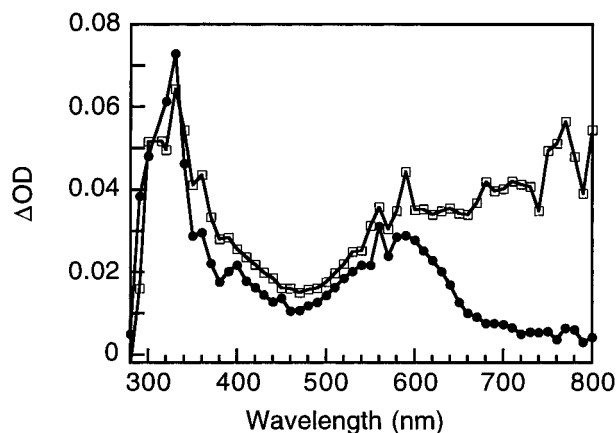(35) Small, R. D.; Scaiano, J. C. *J. Phys. Chem.* **1977**, *81*, 828.

Figure 5. Transient intermediates in the 308 nm laser flash photolysis of KP in aqueous solutions at pH 7.1 under N_2O-saturated conditions (to remove contributions from the solvated electron) (□) and under N_2-saturated conditions with 1 mM sorbic acid (●). Spectra were recorded 64 ns after the laser pulse.

Scheme 1

Caldwell et al.[37] have determined the pK_a for the biradical from γ-phenylbutyrophenone as 10.2 in water; the value is directly relevant to the KP case since the biradical also has a ketyl and a benzylic site. Clearly the 600-nm transient from KP is not a typical biradical with a ketyl radical anion site.

In solvents other than water, the KP triplet (^{3}KP*) absorbs with maxima at 320 and 520 nm. A large red shift (i.e., 80 nm for the longer wavelength maximum) for the triplet in a polar solvent like water would not be expected as the T−T absorption maximum for benzophenone is not solvent dependent.[21] An experiment with sorbic acid (a conjugated diene and excellent triplet quencher and e^-_{aq} scavenger) showed no effect on the transient absorption at 600 nm (Figure 5), indicating that it does not correspond to ^{3}KP*; further, its precursor is either not a triplet or a remarkably short lived triplet.

Attempts to sensitize triplet formation in water with *p*-methoxyacetophenone as a sensitizer lead to signals that could be identified neither as triplet KP nor as the 600-nm transient mentioned above, in spite of extensive (>90%; $k = 2.4 \times 10^9$ M^{-1} s^{-1})[38] triplet quenching by KP. In contrast, sensitization in acetonitrile leads to the readily detectable KP triplet. The absence of the 600-nm signal in water is not particularly significant, since the highest concentration of KP that could be employed was limited by its competitive absorption of the excitation beam. The shortest triplet lifetime for *p*-methoxyacetophenone achieved under these conditions was ca. 200 ns, i.e. longer than the 600-nm signal from KP.[39] Similarly, in another experiment where we used 1-azaxanthone to sensitize the formation of the KP triplet, we were unable to detect any transient that would correspond to ^{3}KP* even at KP concentrations that would quench ≥75% of the 1-azaxanthone triplets and lead to 1-azaxanthone triplet lifetimes of 250 ns. Interestingly, we detected the formation of the 1-azaxanthone ketyl radical anion ($k \geq 2.7 \times 10^7$ s^{-1}), thus suggesting that electron
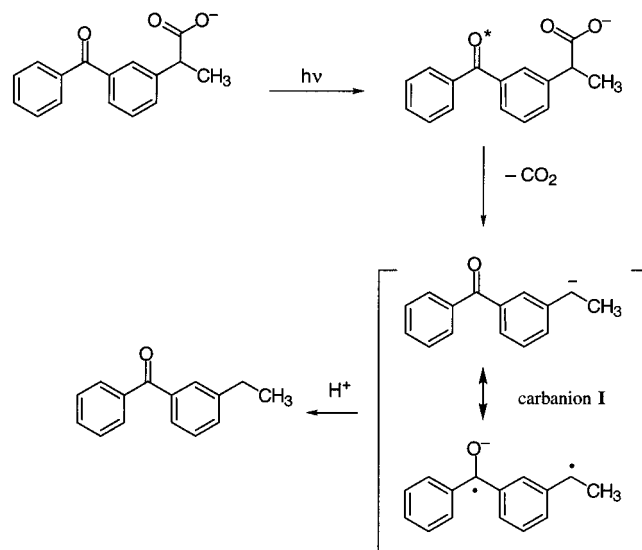
transfer from the ^{3}KP* had occurred.[40,41] This mechanism would explain the lack of singlet oxygen sensitization reported by Constanzo and co-workers.[15] The efficient electron transfer from the KP triplet state in polar environments would decrease the amount of KP triplets available for energy transfer reactions to oxygen.

The product studies reported by Bosca and co-workers[14] in aqueous solutions showed an almost quantitative conversion of the ketoprofen carboxylate to the 3-ethylbenzophenone under anaerobic conditions. Additional evidence for an ionic pathway in the photodecomposition of KP comes from deuterium incorporation at the benzilic position of the major photoproduct (*i.e.* 3-ethylbenzophenone). We performed an experiment using the 308 nm laser excitation of ketoprofen in aqueous solutions and in D_2O at pD > pK_a. Incorporation of deuterium was quantitative, as revealed by mass spectrometric analysis of the product (data not shown).

The time-resolved results mentioned above and published product studies[14,15] are consistent with the assignment of the transient intermediate absorbing with maxima at 330 and 600 nm to a carbanion that incorporates spectroscopic features reminiscent of a ketyl radical anion and a benzylic radical (see Scheme 1).[42] This carbanion is quenched by oxygen, cysteine ($k = 3.0 \times 10^9$ M^{-1} s^{-1}), and phenol (1.04×10^8 M^{-1} s^{-1}). Only with cysteine were we able to detect absorptions with maxima at 330 and 545 nm, indicative of the generation of ketyl radicals. This is not surprising due to the known H-atom donating ability of cysteine, and it exemplifies the biradicaloid nature of this intermediate (*vide infra*).[43] The reaction with phenol does not involve electron or hydrogen atom transfer since we did not detect the formation of phenoxy radicals even at the highest concentrations of phenol employed.

Budac and Wan[16] proposed that intramolecular electron transfer in the triplet state could lead to the formation of a carbanion having as precursor a biradical-like species. We

(36) Small, R. D., Jr.; Scaiano, J. C. *J. Phys. Chem.* **1977**, *81*, 2126.

(37) Caldwell, R. A.; Dhawan, S. N.; D. E., M. *J. Am. Chem. Soc.* **1985**, *107*, 5163.

(38) The rate constant is below diffusion control, but somewhat faster than comparable isoenergetic triplet energy migration as expected for a slightly exothermic transfer: Encinas, M. V.; Scaiano, J. C. *Chem. Phys. Lett.* **1979**, *63*, 305.

(39) Naturally, the precursor process (sensitization) needs to be faster than the decay of the intermediate of interest for this species to be detectable. For the 600-nm transient this would require such high concentrations of KP that selective excitation of the sensitizer would be impossible. The experiments do show the absence of KP triplet in the time scale available through sensitization.

(40) The 1-azaxanthone triplet is a much better electron acceptor than the electron rich triplet of 4-methoxyacetophenone.

(41) Alternatively, the KP carbanion could be the species involved in the electron transfer reaction. It is well documented that carbanions that are not resonance stabilized can transfer an electron to photoexcited aromatic hydrocarbons. Budac, D.; Wan, P. *Adv. Carbohydr. Chem.* **1996**, *2*, 147.

(42) A seminal study of the carbanion derived fron *p*-nitrophenyl acetate has been reported: Craig, B. B.; Weiss, R. G.; Atherton, S. J. *J. Phys. Chem.* **1987**, *91*, 5906.

(43) Thiols were among the earliest reported biradical scavengers: Wagner, P. J.; Kelso, P. A.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7480.
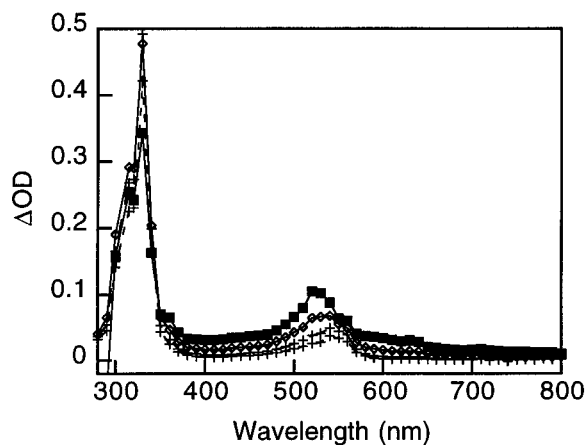
Figure 6. Transient absorption spectra for the ketoprofen ethyl ester in a 1:1 MeOH/H_2O mixture: (■) 72 ns, (○) 0.32 ms, (◇) 0.79 ms, and (+) 1.47 ms after the pulse.

propose that the decay of the KP carbanion is due to protonation by the solvent (*i.e.*, water) with a lifetime of 150 ns. This lifetime was independent of buffer concentration at least in the 5−60 mM range. The monophotonic dependence for its formation and the lack of triplet absorption agree with the mechanism proposed. The decay kinetics for this carbanion show a small isotope effect ($k_H/k_D = 1.2$). A small isotope effect has also been reported for the benzyl carbanion.[44] Preliminary AM1 calculations show that the KP carbanion would have a biradical-like structure in which part of the electron density is shared with the carbonyl group in the benzophenone chro-

mophore. Our results are consistent with carbanion formation, either directly (Scheme 1), or following excited state electron transfer through a 1,5-biradical intermediate. We presume that the biradical would be the most stable electronic configuration in the triplet manifold, while the carbanion structure will be preferred in the singlet state.

Additional evidence for this mechanism comes from the studies with the KP ethyl ester (Figure 6). The transient intermediates observed for the KP ethyl ester corresponded to the triplet state (λ_{max} at 320 and 520 nm) and to ketyl radicals (λ_{max} at 330 and 545 nm). Esterification of KP shuts down the intramolecular electron transfer process in the excited singlet or triplet state and allows the detection of transients characteristic of the benzophenone moiety. This is also in agreement with the results from the photolysis of the KP free acid (pH 3.2) showing the formation of e^-_{aq}, KP triplets, and ketyl radicals.

In conclusion, the ketoprofen carboxylate undergoes biphotonic photoionization. The formation of a carbanion as intermediate has been confirmed, indicating that the photodegradation of ketoprofen in aqueous solutions proceeds mainly ($\approx90\%$) through an ionic mechanism involving either the singlet state or a very short lived triplet.

(44) Bockrath, B. a. L. M. D. *J. Am. Chem. Soc.* **1974**, *96*, 5708.