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Photodecarboxylation of Xanthone Acetic Acids: C–C Bond Heterolysis from the Singlet Excited State

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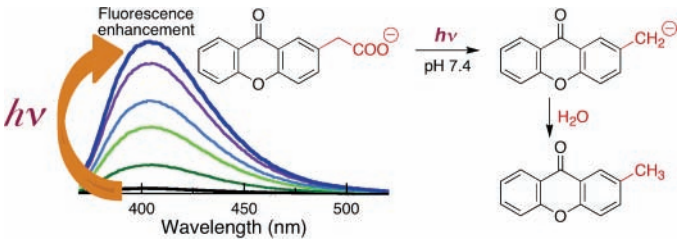
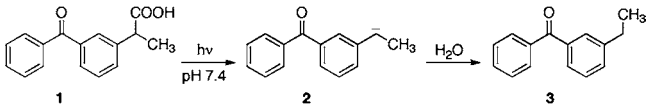
ABSTRACT



Irradiation of 2- and 4-xanthone acetic acid in aqueous buffer (pH 7.4) leads to efficient (Φ = 0.67 and 0.64, respectively) photodecarboxylation to give the corresponding methyl products, consistent with an intermediate benzylic carbanion. Fluorescence and laser flash photolysis (LFP) studies suggest singlet state reactivity, which is unusual for aromatic ketones. 3-Xanthone acetic acid is photoinert under the same conditions. The results suggest that the reactive xanthone acetic acids are promising precursors for carbanion-mediated photocages.

A number of aryl acetic acids possessing electron-withdrawing substituents on the aromatic ring are known to undergo efficient photodecarboxylation in neutral aqueous solution to give benzylic carbanion intermediates, which typically are rapidly protonated to give the corresponding aryl alkane.[1,2] For example, ketoprofen (**1**), a potent nonsteroidal antiinflammatory drug (NSAID), decarboxylates on excitation (in aqueous solution, pH > pK_a) to give carbanion **2**, which is rapidly protonated in approximately 250 ns to give 3-ethylbenzophone (**3**) (Scheme 1) with an overall quantum yield of 0.75, a process that is implicated in some of the drug's phototoxic side effects.[2,3] The photodecarboxylation process appears to be general for other ketoaromatics, although

Scheme 1. Photodecomposition of Ketoprofen in Basic Aqueous Solution



modestly higher reactivities are usually encountered for those with the ketone positioned meta to the acetic acid function when compared to those with a para arrangement.[4] This phenomenon is an example of the "meta effect" that was first proposed by Zimmerman[5] to explain the photoinduced hydrolysis of benzyl acetates and can be readily rationalized with simple MO considerations.

The mechanism of photodecarboxylation from ketoprofen has been a source of interest for almost two decades. Both singlet- and triplet-mediated mechanisms have been proposed.[2] Our own research has favored a singlet pathway,

(1) (a) Budac, D.; Wan, P. *J. Photochem. Photobiol. A: Chem.* **1992**, *67*, 135. (b) Margerum, J. D.; Petrusis, C. T. *J. Am. Chem. Soc.* **1969**, *91*, 2467. (c) Stermitz, F. R.; Huang, W. G. *J. Am. Chem. Soc.* **1971**, *93*, 3427. (d) Krogh, E.; Wan, P. *J. Am. Chem. Soc.* **1992**, *114*, 705.

(2) (a) Martínez, L. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 11066. (b) Monti, S.; Sortino, S.; De Guidi, G.; Marconi, G. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 2269. (c) Cosa, G.; Martínez, L. J.; Scaiano, J. C. *Phys. Chem. Chem. Phys.* **1999**, *1*, 3533. (d) Boscá, F.; Marin, M. L.; Miranda, M. A. *Photochem. Photobiol.* **2001**, *74*, 637.

(3) Borsarelli, C. D.; Braslavsky, S. E.; Sortino, S.; Marconi, G.; Monti, S. *Photochem. Photobiol.* **2000**, *72*, 163.

(4) Xu, M.; Wan, P. *Chem. Commun.* **2000**, 2147−2148.

(5) Zimmerman, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 8988.

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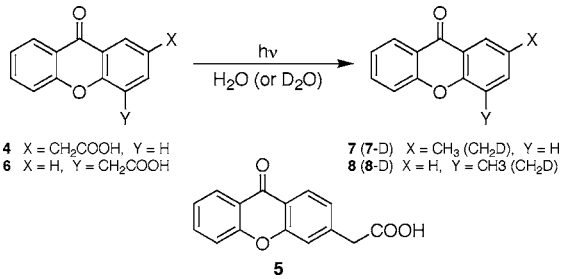
although the research leading to this conclusion was performed in mixtures of organic solvents with water, in contrast with the pure aqueous environment in which most of the ketoprofen reactions have been examined.

A singlet mechanism represents unusual photochemistry for benzophenones, which normally is dominated by triplet processes because of very rapid intersystem crossing (although other examples of singlet-state reactivity are emerging[6]). A major difficulty in unequivocally establishing the multiplicity of the photodecarboxylation of **1** results from the fact that derivatives of benzophenone are not fluorescent, which makes it difficult to gather information on the singlet excited state. To provide insight into the photodecarboxylation mechanism, we decided to study the acetic acids of xanthone, which is structurally very similar to benzophenone but is fluorescent in aqueous solutions (due in part to the much higher oscillator strength of the $S_0 \leftarrow S_1$ transition). To this end, we decided to prepare and study 2-, 3-, and 4-xanthone acetic acids (**4**−**6**, respectively). The differing substitution of the three isomers is expected to provide mechanistic insights: if the mechanism proceeded via direct bond heterolysis (i.e., singlet mechanism), then the reaction efficiency would be expected to be highly dependent on the excited-state electronics at the benzylic position, and derivatives with acetic acids substituted meta to the ketone (**4** and **6**) would be expected to show higher reactivity than at the **5** position. Alternatively, if reaction proceeded by electron transfer as has been proposed for a triplet-mediated mechanism, the substitution should have little effect on the reaction efficiency because both the distance between and the oxidation potentials of the donor and acceptor are similar for the three derivatives.

We are also interested in **4**−**6** as possible new photocage precursors. Recently, we have developed a new type of photoremovable protecting group, or "photocage", based on the ketoprofen structure that can rapidly release a protected moiety (such as a carboxylic acid or alcohol) on irradiation in neutral aqueous solution.[7] The photoprocesses of **4** and **6** reported here suggest that these moieties may have improved spectral properties in relation to their use in photocage design.

We report here the synthesis and photochemistry of 2-, 3-, and 4-xanthone acetic acids (**4**, **5**, and **6**). Very efficient photodecarboxylation is observed for **4** and **6**, and **5** is essentially photoinert (Scheme 2).

Scheme 2. Photodecomposition of Xanthone Acetic Acids **4** and **6**



Derivatives **4**−**6** were synthesized in moderate yield via initial Ulmann coupling between *o*-iodobenzoic acid and *para*-, *meta*-, or *ortho*-hydroxyphenylacetic acid, followed by acid-catalyzed intramolecular acylation.[8] Methyl derivatives **7** and **8** were prepared in the same fashion from 2- or 4-cresol.

Absorption spectra of **4**−**6** in aqueous buffer (pH 7.4) exhibit a desirable improvement over ketoprofen in absorption above 300 nm, as seen in Figure 1 for **6**. The spectra are very

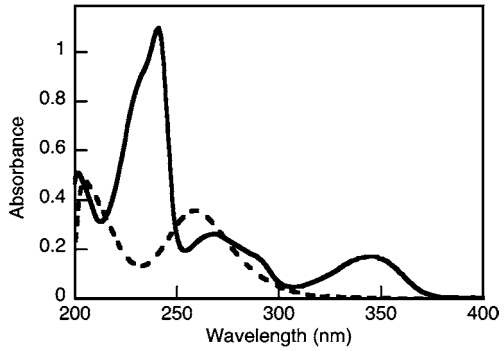


Figure 1. Equimolar (2.0×10^{-5} M) absorption spectra of ketoprofen (dashed line) and **6** (solid line).

similar for the three derivatives, and all show the characteristic $\pi^* \leftarrow \pi$ absorption band with a maximum near 340 nm. The molar absorptivities at their band maxima for **4**, **5**, and **6** are 5600, 7900, and 8100 M^{-1} cm^{-1}, respectively, representing an approximate 40-fold absorption enhancement over **1** (vide infra).

To identify the products resulting from irradiation of **4**−**6**, solutions of each (5 mM in either 0.1 M KOH−H_2O or phosphate buffer, pH 7.4, argon bubbled) were irradiated for 2 min (300 nm) in a merry-go-round apparatus. Each sample, after workup, was characterized by MS and ^1H and ^{13}C NMR. UVA irradiation of **4** for 2 min gave 2-methylxanthone (**7**) in 30% yield as the exclusive photoproduct (Scheme 2), consistent with a mechanism of reaction involving initial photodecarboxylation to give a benzylic carbanion that is subsequently protonated by water to give the observed photoproduct. With exhaustive irradiation, conversion to **7** was complete with no other photoproducts observed. Irradiation of **4** in deoxygenated 0.1 M NaOD−D_2O solution yielded **7** with one of the arylmethyl hydrogen atoms replaced with deuterium (**7**-D, Scheme 2), indicating that the requisite carbanion intermediate receives a proton (or deuteron) from the aqueous solvent and that **7** is not formed via hydrogen abstraction from a radical intermediate, as water is an extremely poor hydrogen atom donor.

Similar photochemistry was observed for **6**; irradiation in deoxygenated phosphate buffer at pH 7.4 (or 0.1 M KOH−H_2O)

(6) Yamaji, M.; Susumu, I.; Nakajima, S.; Akiyama, K.; Tobita, S.; Marciniak, B. *J. Phys. Chem. A* **2005**, *109*, 3843.
(7) Lukeman, M.; Scaiano, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 7698.
(8) Rewcastle, G. W.; Atwell, G. J.; Baguley, B. C.; Calveley, S. B.; Denny, W. A. *J. Med. Chem.* **1989**, *32*, 793.

or in 0.1 M NaOD−D_2O gave **8** or **8**-D, respectively. However, to our surprise, **5** was photoinert under the same conditions, with complete recovery of starting material realized.

Quantum yields for photodecarboxylation from **4** and **6** in aqueous phosphate buffer (pH 7.4) were measured using the photodecarboxylation reaction of ketoprofen ($\Phi = 0.75$ at pH 7.4[9]) as a secondary reference standard. Both derivatives showed high quantum efficiencies of $\Phi = 0.67$ for **4** and $\Phi = 0.64$ for **6** (Table 1), indicating that the xanthone chromophore is able to promote carbanion formation with efficiencies similar to the benzophenone-based derivatives.

Table 1. Photochemical Parameters for **4**−**8**

compound	Φ_R	Φ_F	τ_S (ns)	k_F (ns^{-1})	τ_T (ns)	triplet yield
4	0.67	0.0077	0.079	0.098	5400	0.4
5	<0.01	0.044	0.73	0.061	4500	1.1
6	0.64	0.010	0.10	0.097	6600	0.3
7		0.24	4.8	0.051	9500	1.0
8		0.15	3.9	0.039	6200	(1.0)[a]

[a] Used as a reference for relative triplet yields.

Some xanthone derivatives show fluorescence emission upon electronic excitation; thus, we expected that fluorescence spectroscopy could be a versatile tool in the study of the photodecarboxylation reaction of **4** and **6**. The fluorescence excitation and emission spectra of each compound were recorded for samples of **4**−**6** (absorbance = 0.1 at λ_{ex}) in phosphate buffer (pH 7.4), and each showed a single weak fluorescence band with λ_{max} = 410, 390, and 405 nm, respectively. Brief irradiation of the solution of **4** with a handheld TLC UV lamp (λ_{ex} = 368 nm, 6.2 W m^{-2}, fwhm = 16 nm) led to a drastic increase in the fluorescence intensity and a small shift in the band (Figure 2), presumably resulting from the formation of the more fluorescent photoproduct, **7**. Irradiation of this solution for 1 min gave quantitative conversion to **7**, as evidenced by no further increases in the fluorescence intensity. In all, a ~32-fold increase in fluorescence emission was observed for **4**. Derivative **6** showed similar behavior, with 1 min of irradiation giving quantitative conversion to **8** resulting in a ~15-fold enhancement in fluorescence emission. No fluorescence enhancement was observed for irradiation of the solution of **5**; instead, a small decrease in fluorescence intensity was observed after several minutes of irradiation, probably resulting from inefficient photodegradation of the starting xanthone.

Fluorescence quantum yields and lifetimes were estimated for **4**−**8**, with values reported in Table 1. Reactive acids **4** and **6** have significantly lower fluorescence quantum yields and significantly shorter fluorescence lifetimes than the nonreactive xanthones, suggesting that an additional deactivational pathway is available to the excited *singlet state* of **4** and **6**, namely, the decarboxylation reaction.

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

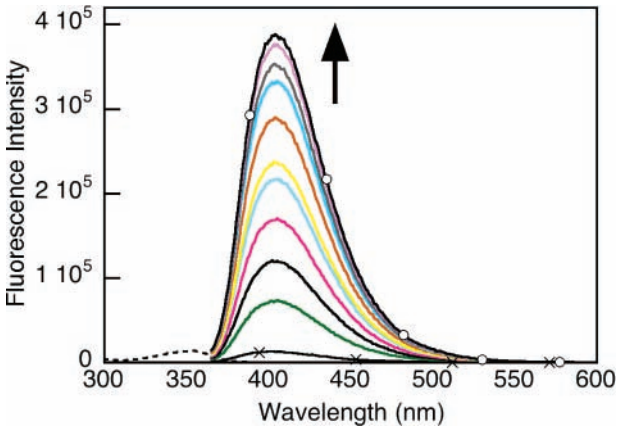


Figure 2. Fluorescence increase with irradiation of **4** (0.02 mM) in pH 7.4 phosphate buffer. Spectra recorded at 0, 2, 4, 6, 8, 10, 15, 20, 25, 35, and 60 s.

The triplet state yields were evaluated using laser flash photolysis. On a first approximation, we assume that the triplet states of **4**−**8** have similar extinction coefficients, and thus, the triplet signal intensities for matched samples can be used as a measure of the triplet yield. These values are shown in the last column of Table 1; they are consistent with the fluorescence data, i.e., molecules **4** and **6**, with highly reactive (decarboxylating) singlets that produce lower yields of the triplet state.

We have had success in detecting and characterizing photogenerated carbanion intermediates from ketoprofen and related derivatives using laser flash photolysis (LFP), so we applied the same approach in an attempt to characterize the transients produced in the photochemistry of **4**−**6**. LFP of nitrogen-saturated flowing solutions of **4**−**6** (λ_{ex} = 355 nm) in either 0.1 M KOH−H_2O or phosphate buffer adjusted to pH 7.4: acetonitrile (80:20) gave rise to transients with broad visible absorption bands with λ_{max} = 580, 600, and 585 nm that decayed with clean first-order kinetics at all wavelengths with lifetimes of 5.4, 4.5, and 6.6 μs (Figure 3). These bands were readily quenched by common triplet quenchers such as oxygen, naphthalene-methanol, and sorbate ions. Because of the similarity of these spectra to the known T−T absorption spectrum of xanthone, as well as the observed quenching behavior, we assign the transients observed for these three species to the corresponding triplet excited state. We hoped to completely supress the T−T absorption for **4** and **6** in an attempt to detect a possible weak signal arising from the proposed carbanion intermediates that might be obscured by the strong signal from the triplet absorption. Although complete supression of the triplet was achieved for both **4** and **6** by employing a 50 mM sorbate (quencher) concentration, no residual signal was detected. This suggests that the lifetimes of the intermediate carbanions are too short lived (τ < 20 ns) to be observed on our nanosecond system.

Quenching of the triplet excited state of **4** and **6** by sorbate was extended to steady-state irradiation studies. Two 8 mM solutions of **6** were prepared in 1:1 pH 7.4 phosphate buffer

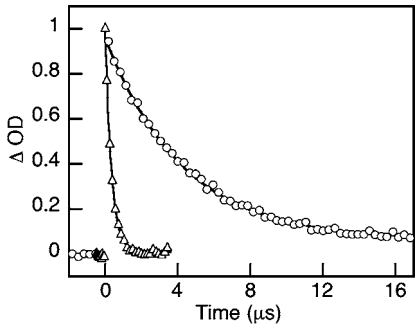


Figure 3. Normalized transient decays for 0.08 mM **5** in deoxygenated pH 7.4 phosphate buffer/acetonitrile (80:20) with (△) and without (○) 1 mM sorbate after 355 nm excitation monitored at 600 nm and fitted with first-order expressions.

and acetonitrile, one solution with 50 mM of sorbate and the other without. Following simultaneous irradiation, ^{1}H NMR analysis showed that the yield of decarboxylation in both cases was 26%, on the basis of ^{1}H NMR quantification. Because we know from the LFP studies that this sorbate concentration will quench >95% of the triplet yield, the absence of quenching in photodecarboxylation argues strongly in favor of a singlet-mediated mechanism.

An additional point of interest in this work is the large disparity in the reactivity of **4** and **6** vs isomer **5**. This appears to be a result of the meta effect, first proposed by Zimmerman, which states that electron-withdrawing and electron-donating substituents attached to the meta position on an aromatic ring have a much stronger influence in the excited state than those substituents substituted at the para position.[5] We propose that the high reactivity of **4** and **6** results from the enhanced electron-withdrawing ability of the ketone that is meta to the benzylic site in both of these isomers, which helps stabilize the carbanion formation. The ketone is substituted para to the benzylic carbon in **5**, so this effect is absent in this case. Instead, the electron-donating ether oxygen is meta to the benzylic site in **5** which would actually destabilize carbanion formation. A similar effect is expected for ortho substituents on an aromatic ring. For this reason, it was initially surprising that **4** and **6** exhibit similar quantum yields despite the electron-donating (deactivating) oxygen ortho to the benzylic position in **6**. Although MO calculations confirm the electronic effect, the longer singlet-state lifetime of **6** (Table 1) actually implies lower reactivity. The rate constant for singlet decarboxylation can be estimated as $k_R = \Phi_R/\tau_S$ (see Table 1) and yield values of $k_R = 8.5 \times 10^9$ s^{-1} for **4** and of $k_R = 6.4 \times 10^9$ s^{-1} for **6**, consistent with MO expectation of a somewhat lower reactivity for **6**.

One drawback associated with the ketoprofenate photocage on which we recently reported[7] is that the absorptivity at wavelengths required for biological applications (>300 nm) is fairly low (Figure 1). For this reason, it is desirable to design analogues which retain or improve on the reactivity of the ketoprofen scaffold but absorb more strongly in the UVA region, minimizing the secondary effects on the biological system induced by light irradiation. Xanthone analogues of the ketoprofen structure hold significant promise for these applications because they retain the electron-withdrawing carbonyl which is believed to be necessary for the initial photodecarboxylation but absorb much more strongly in the UVA region and, as shown in this contribution, undergo decarboxylation as efficiently as ketoprofen. Further, the photochemistry of **6** might also have important medical implications because this compound and related derivatives have shown promise as anticancer drugs.[8]

In summary, a very efficient photodecarboxylation of **4** and **6** occurs in aqueous solution. LFP, fluorescence, and quenching studies all point to a singlet-mediated mechanism. Further, the spectral properties of **4** and **6** are such that they hold promise in the design of new photocages. The readily detectable fluorescence of products from **4** and **6** in aqueous media suggests that photocages based on these moieties may also provide a tool for photorelease mapping; i.e., it should be possible to determine when and where decarboxylation (and thus photorelease) has occurred. This may prove a valuable tool in both *in vitro* and *in vivo* studies.

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Supporting Information Available: Synthetic procedures for **4**−**8**, description of photolysis experiments, absorption extinction coefficients, ^{1}H and ^{13}C NMR of **4**−**8** before and after irradiation. This material is available free of charge via the Internet at http://pubs.acs.org.

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