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# A Remarkably Long-Lived Benzyl Carbanion

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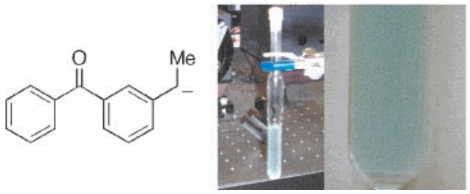
## ABSTRACT



**The photochemistry of ketoprofen, a widely used nonsteroidal antiinflammatory drug (NSAID) has been the subject of several studies as a result of its known phototoxicity. Photolysis of ketoprofen leads to 3-ethylbenzophenone, a process that is mediated by a short-lived carbanion. We have found that under carefully controlled conditions in THF, the lifetime of the carbanion can be extended to several hours, thus providing a powerful tool for studying the mechanism of its formation and subsequent reactions.**

Ketoprofen (**1**) and related benzophenone derivatives have proven to be convenient photochemical sources of carbanions.[1] Carbanion **2** has a lifetime of ca. 200 ns in water and can be readily detected in laser flash photolysis experiments as a result of its characteristic absorption at ∼600 nm.[2] The short lifetime in aqueous solution is not unexpected, since rapid protonation leads to the quantitative formation of 3-ethylbenzophenone (**3**). The carbanion lifetime can be extended by about 1 order of magnitude by isolation in dry zeolites.[3]

Carbanion **2** and related species can also be detected in organic solvents, such as dimethyl sulfoxide, DMSO, which has been employed for mechanistic and kinetic studies.[4] Despite purification and drying efforts, lifetime enhancements in DMSO are marginal. In this communication, we report that the lifetime of **2** in dry, basic THF can be enhanced to many minutes at room temperature, thus allowing a more detailed characterization of this species.

To provide a basic environment, sodium hydride was added to samples of **1** in THF, freshly distilled over metallic sodium. The samples also had a small excess of solid NaH. It is likely that in addition to providing a basic environment (decarboxylation is a characteristic reaction of the carboxylate form of ketoprofen),[2] NaH acted as a sacrificial drying agent for small traces of moisture.

Laser irradiation (355 nm) of solutions of **1** in dry, basic THF led to the formation of a distinct blue coloration in the exposed region. We attribute this color to the formation of carbanion **2**, which under these experimental conditions has a lifetime of several minutes (hours in a freezer at −20 °C). Typical concentrations generated in this manner are in the submillimolar range. It is worth noting that for a $10^{-4}$ M solution of carbanion, 2 ppm of water would be sufficient to destroy it quantitatively. It is possible that **2** may be stabilized by ion-pairing in the nonpolar environment; resonance forms containing a benzyl radical center and a ketyl radical-anion may also contribute to the stability,

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(1) (a) Cosa, G.; Llauger, L.; Scaiano, J. C.; Miranda, M. A. *Org. Lett.* **2002**, *4*, 3083−3085. (b) Borsarelli, C. D.; Braslavsky, S. E.; Sortino, S.; Marconi, G.; Monti, S. *Photochem. Photobiol.* **2000**, *72*, 163−171. (c) Xu, M.; Wan, P. *Chem. Commun.* **2000**, 2147−2148.

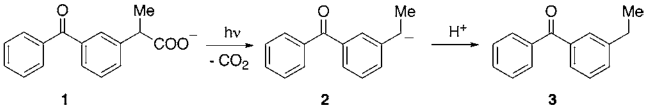
(2) (a) Bosca, F.; Marin, M. L.; Miranda, M. A. *Photochem. Photobiol.* **2001**, *74*, 637−655. (b) Cosa, G.; Martinez, L. J.; Scaiano, J. C. *Phys. Chem. Chem. Phys.* **1999**, *1*, 3533−3537. (c) Martinez, L. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 11066−11070. (d) Monti, S.; Sortino, S.; De Guidi, G.; Marconi, G. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 2269−2275.

(3) Chrétien, M. N.; Cosa, G.; Garcia, H.; Scaiano, J. C. *Chem. Commun.* **2002**, 2154−2155.

(4) Llauger, L.; Cosa, G.; Scaiano, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15308−15312.

10.1021/ol036313r CCC: $27.50

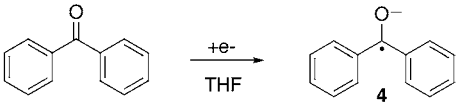
**Scheme 1**



although it should be noted that this biradicaloid form may have a triplet ground state.

Having some experience drying THF over sodium, our first reaction was to assume that the blue color was due to the benzophenone-like radical-anion from ketoprofen, formed photochemically by some unknown mechanism. Benzophenone is frequently used as a dryness indicator, since the formation of blue radical-anion **4** shows that the solvent is dry, Scheme 2.

**Scheme 2**



Our experiments show that the blue color formed upon irradiation of ketoprofen in THF is not due to a radical-anion similar to **4**. The visible spectrum of the species formed upon 355 nm laser excitation of **1** in THF is shown in Figure 1.

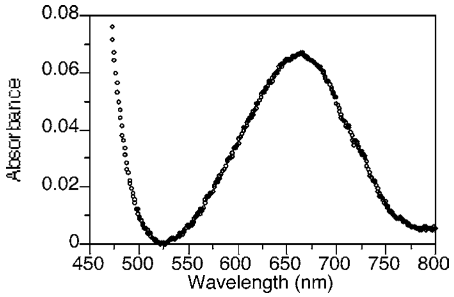


**Figure 1.** Visible spectra, after baseline correction, of a solution of KP in basic THF after irradiation with a 355 nm laser.

The long lifetime of this blue color allowed several reactivity tests that reflect the basic and nucleophilic character of this species. Thus, water, methanol, acetone, and methyl iodide all bleached the blue color immediately following addition to freshly prepared samples.

We note that identical samples that contain benzophenone instead of ketoprofen do not yield the long-lived blue species upon 355 nm laser excitation. This strongly suggests that color formation involves the side chain in ketoprofen, rather that just the benzophenone moiety.

Addition of 1-methylnaphthalene (a well-known triplet quencher) to samples of **1** in THF has no effect on the photoinduced formation of the blue color, although it does have some effect on the transient phenomena observed under these conditions (vide infra). It has been proposed that carbanion formation proceeds from the singlet state of ketoprofen.[2b] Our observations are consistent with this proposal.

Laser flash photolysis of **1** in basic THF yields the characteristic signals from the ketyl radical of the benzophenone-like moiety, with a maximum at ca. ~550 nm (see Figure 2).

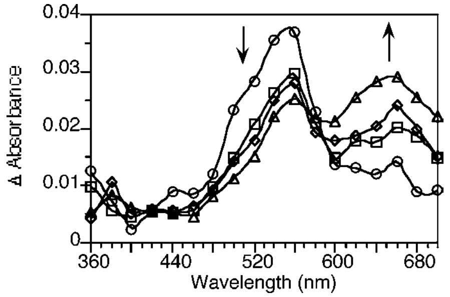


**Figure 2.** Laser flash photolysis with a 355 nm laser, spectra of KP in THF with NaH (○, 2.4 $\mu$s; □ 46.7 $\mu$s, ◇, 78.7 $\mu$s, and △174.7 $\mu$s after the laser pulse).

We attribute ketyl formation to a triplet state reaction, since benzophenone triplet readily abstracts hydrogen from THF. Our results cannot establish if ketyl formation involves the acid or carboxylate forms of ketoprofen. Consistent with this hypothesis, ketyl radical formation is suppressed by addition of triplet quenchers. For example, addition of 0.07 M 1-methylnaphthalene is sufficient to quench completely the formation of ketyl radical signals. The decay of the ketyl radical occurs in the microsecond time scale, as illustrated in Figure 3. These signals are therefore not expected to be detected in the “minute” time scale.

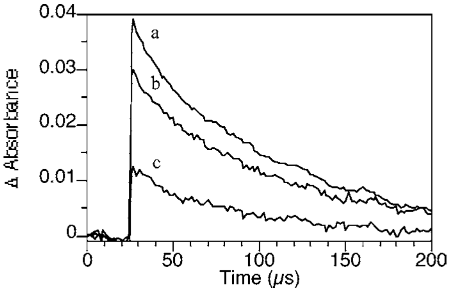


**Figure 3.** Decay of the signal at 550 nm, without (a) and after adding 2.5 mM (b) and 5 mM (c) 1-methylnaphthalene to 9 mM KP in THF and NaH.

When the transient signals are monitored in the 650 nm region, one observes a jump and a distinct growth in the microsecond time scale. This is illustrated in Figure 4.

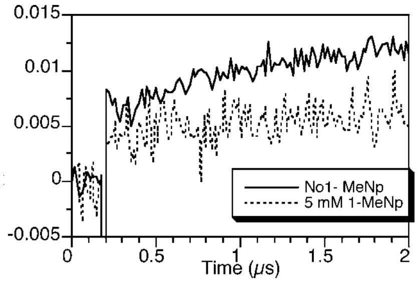
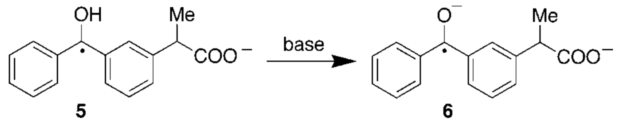


**Figure 4.** Kinetic traces showing absorbance change at 650 nm before and after adding 1-methylnaphthalene (1-MeNp) to 9 mM KP in dry THF with excess NaH.

It is clear that absorption in the 650 nm region would yield a characteristic blue color. Addition of 1-methylnaphthalene results in a reduction and eventually the total elimination of the growth component in the traces recorded at 650 nm (Figure 4). Thus, this observation suggests that the "jump" in Figure 4 is due to a singlet reaction, while the quenchable growth reflects a triplet-mediated process. We believe that the growth component is due to radical-anion formation by deprotonation of the ketyl radical, Scheme 3.

**Scheme 3**



Since **5** is the product of a triplet reaction with the solvent, one anticipates that its formation will be quenched by 1-methylnaphthalene. Thus, the growth component is attributed to formation of a radical anion, while the singlet-mediated "jump" is attributed to carbanion **2**.

While the formation of **6** can be perceived as a complication in the process, in fact it provides a clear distinction between radical anion and carbanion signals. Thus, two blue signals are formed. One, due to the radical anion, can be readily quenched by 1-methylnaphthalene and under our experimental conditions does not survive for minutes. The other, due to carbanion **2**, is singlet-derived, is not quenched by triplet quenchers, and under careful water exclusion it survives for minutes.

Unfortunately, product studies could not be carried out with typical substrates for $S_N2$ reactions (methanol, ketones, alkyl halides) present during the irradiation, since the hydride (present in excess in all samples) readily reacts with them before exposure. However, the decoloration experiments mentioned before confirm not only the reactive nature of the blue species but also its ability to compete with hydride. Further, in the case of methyl iodide as a substrate, the product of carbanion scavenging (3-isopropylbenzophenone) was detected by GCMS; its concentration was about twice as large as that for 3-ethylbenzophenone. The products of trapping by carbonyl compounds have been characterized previously in the case of carbanion reaction in zeolites.[3]

We were surprised by the long lifetimes observed, since both the carbanion and its precursor are carbonyl compounds themselves and therefore possible reactants (i.e., addition to give the carbinol). We rationalize this observation in terms of (a) the submillimolar concentrations involved disfavoring second-order reactions; (b) Coulombic repulsion, since both reactants are negatively charged; and (c) the low dielectric constant of THF (7.6) tending to maximize repulsive interactions. It is also possible that in samples preserved for long times the excess hydride may have consumed some of the initial ketoprofen present.

Product studies were performed following laser or CW exposure (355 or 350 nm) of samples of **1** in basic THF. Both an acid and a basic workup were performed on the samples (see Supporting Information for details). Basic workup followed by extraction in ether eliminates all base-soluble products, retaining only nonpolar products. Under these conditions the major product detected is 3-ethylbenzophenone, consistent with carbanion involvement. Acid workup was followed by treatment with diazomethane in order to produce the methyl ester of products retaining the carboxylic acid. In addition to 3-ethylbenzophenone, these studies revealed the formation of typical photoreduction products, ketoprofen−THF adducts, presumably formed by recombination of radical products. Unfortunately, these products are formed in submillimolar concentration rendering their full characterization difficult. However, their mass spectrum is consistent with the radical reactions observed by laser flash photolysis.

In summary, our studies reveal that under dry, basic conditions the carbanion derived from ketoprofen can have very long lifetimes, presumably unlimited under ideal experimental conditions. This carbanion is produced in a singlet-state reaction, at least in non-hydroxylic media. Its chemistry is in agreement with that anticipated from well-known nucleophilic reactivity patterns.

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**Supporting Information Available:** Experimental procedures and additional graphs and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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