

# Absolute Rate Constants for Water Protonation of 1-(3-Benzoylphenyl)alkyl Carbanions

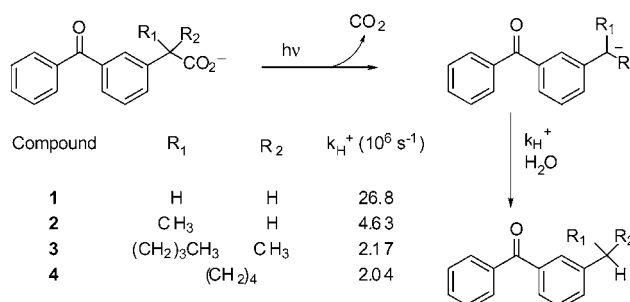
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## ABSTRACT



Efficient photodecarboxylation of (3-benzoylphenyl)alkanoic acids with formation of carbanions has enabled the determination of their protonation rate constants in water; the values obtained show that the reactivity toward protonation is determined by the size of the alkyl groups attached to the carbanion center.

A nonsteroidal antiinflammatory drug commercially known as ketoprofen presents unusual pH-dependent photochemistry.<sup>1–6</sup> In particular, the acid form of ketoprofen behaves as a conventional benzophenone, with high inter-system crossing yields and triplet radical-like behavior.<sup>4,5</sup> In contrast, the carboxylate form undergoes efficient photodecarboxylation within the duration of a nanosecond laser

pulse to yield a carbanion,<sup>4,7,8</sup> which is responsible for the formation of 3-ethylbenzophenone.<sup>9</sup>

This prompt photochemical source of carbanions provides the key to generating very interesting reactive intermediates for mechanistic studies. Thus, beyond their importance as intermediates involved in the photodegradation of a pharmaceutical product, they provide an attractive tool in order to explore the chemistry of carbanions in different systems, in particular, water.

We have thus directed our efforts toward gaining an insight into carbanion reactivity. To that effect we synthesized compounds **3** and **4**, which in combination with the com-

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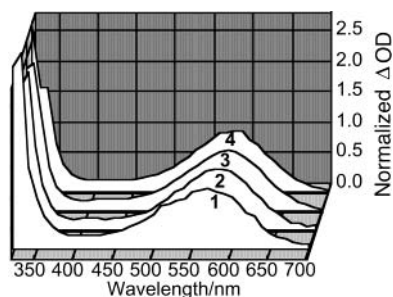
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mercially available analogues **1** and **2** render a complete set of precursors for the generation of primary, secondary, and tertiary 1-(3-benzoylphenyl)alkyl carbanions. These intermediates have been submitted to kinetic and spectroscopic investigation, following light-induced photodecarboxylation of **1**–**4**.

Laser excitation (308 nm) of compounds **1**, **3**, and **4** in 0.1 M KOH aqueous solutions gives rise to transient absorption spectra similar to those observed following laser flash photolysis of ketoprofen (compound **2**).<sup>4,5,7</sup> These spectra, including that of the ketoprofen carbanion, are shown in Figure 1. Note that they have been normalized in the visible region.



**Figure 1.** Normalized transient absorption spectra obtained following 308 nm laser excitation of **1**–**4** in a KOH 0.1 M, 1% v/v MeOH aqueous solution. From front to back: from **1**, 16 ns after the laser pulse; from **2**, 48 ns after the laser pulse; from **3**, 48 ns after the laser pulse; from **4**, 64 ns after the laser pulse. Solutions were equilibrated under N<sub>2</sub>O. Experimental points were acquired at 10 nm intervals.

The visible part of the spectrum is common to all species, with a broad maximum located at ca. 580 nm (see also Table 1). In the case of the carbanion from **1**, a shoulder is

**Table 1.** Quantum Yields of Photodecarboxylation of (3-Benzoylphenyl)alkanoic Acids and Absorption Maxima and Protonation Rate Constants for the Photogenerated carbanions

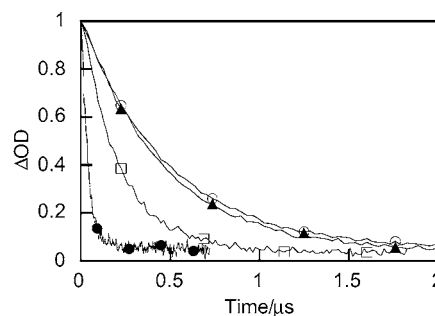
compd	$\Phi_{\text{photodec}}^a$	$\lambda_{\text{max}}/\text{nm}$	$k_{\text{H}^+}/\text{s}^{-1}$
<b>1</b>	0.66 <sup>b</sup>	570	$26.8 \pm 0.3 \times 10^6$
<b>2</b>	0.75 <sup>c</sup>	570	$4.63 \pm 0.04 \times 10^6$
<b>3</b>	0.76	580	$2.17 \pm 0.05 \times 10^6$
<b>4</b>	0.73	580	$2.04 \pm 0.05 \times 10^6$

<sup>a</sup> Values are means of three independent measurements. <sup>b</sup> From ref 10. <sup>c</sup> From ref 9.

noticeable at ca. 520 nm. This is due to a contribution by absorption from the triplet state of **1**, as determined from time windows monitored at longer times following excitation (data not shown). This is similar to the situation found for ketoprofen following irradiation in basic acetonitrile/water mixtures with  $x_{\text{water}} = 0.13$ .<sup>7</sup>

The time evolution of the transient absorption for the carbanions from **1** to **4**, recorded at 600 nm, is shown in

Figure 2. These traces follow first-order kinetics and lead to the rate constants presented in Table 1.



**Figure 2.** Normalized decay traces ( $\lambda = 600$  nm) for the transients obtained following 308 nm laser excitation of **1**–**4** in a 0.1 M KOH aqueous solution (a few points are shown to assist in the visualization). (●) Starting from **1**; (□) starting from **2**; (▲) starting from **3**; (○) starting from **4**. Solutions were equilibrated under N<sub>2</sub>O.

An analysis of Figure 2 and of the data of Table 1 shows a large effect attributable to alkyl substitution on the decay rate constant of the carbanions. Introduction of a first methyl group in structure **1** increases the lifetime of the resulting secondary carbanion by a factor of 5.

Inclusion of a second alkyl group (structures **3** and **4**) increases the lifetime of the resulting tertiary carbanion by a factor of ca. 10 with respect to the primary carbanion (**1**). The change is not so marked with respect to the secondary carbanion (the lifetime is only twice as long). There is also a slight difference in the lifetime of the carbanions photo-generated from **3** and **4**, the latter being longer lived.

Product studies performed with **1** and other ketoprofen derivatives have demonstrated that the photodecarboxylation pattern characteristic of ketoprofen is in fact a common denominator in (aroylphenyl)alkyl carboxylic acids.<sup>10</sup> Our results obtained with a series of 2-(3-benzoylphenyl)alkyl carboxylic acids further confirm these results. Thus, the transient absorption spectra obtained are independent of the acid employed and in all cases are equal to that of the ketoprofen carbanion. Further, product studies (see also Table 1) reveal that for compounds **3** and **4**, photodecarboxylation and protonation of the corresponding carbanions occur with quantum yields similar to that of ketoprofen.

In the series studied, all the carbanions generated upon photoexcitation can only decay via protonation by water (considering that KOH 0.1 M was employed in these experiments, protonation by free H<sup>+</sup> can be ruled out). Thus, the trends in decay rate constants presented in Table 1 are interesting;<sup>11,12</sup> they show that a primary carbanion reacts

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faster than a secondary one, which in turn is more reactive than a tertiary carbanion. Lower carbanion stabilization is an unlikely explanation for the observed tendency. Such lower stabilization should be accompanied by a bathochromic shift of the carbanion spectra; no such shift is observed when comparing carbanions from **3** or **4** with that from **1**. Further, the carbanion stability order is tertiary < secondary < primary < methyl, given that substitution by electron-donating alkyl groups results in a greater negative charge density at the carbanion central carbon atom.<sup>11</sup> Thus, the trend in protonation is contrary to expectations based on charge stabilization.

Instead, a more satisfactory explanation is that protonation is determined by entropic rather than enthalpic factors. In fact, resonance with the benzoylphenyl group, common to all these carbanions, would account for most of the stabilization effects. This makes negligible the role of alkyl substitution, thus resulting in all these carbanions showing only minor enthalpic differences. Conversely, the reactivity is clearly determined by the size of the alkyl groups attached to the carbanion center, and steric hindrance to protonation appears to control the reactivity with bulkier groups. This would also account for the slight difference observed in the protonation rates of carbanions photogenerated from **3** and **4**, where the cyclopentyl ring existing in the tertiary

carbanion generated from **4** would add an extra constraint compared to the tertiary carbanion from **3**.

While steric effects on solvolysis are not unexpected, absolute rate constants for these processes are generally unavailable. Our studies have shown the possibility of obtaining absolute rate constants for the reactions of carbanions in water. Our results support the data published by Dorfman and co-workers,<sup>13</sup> which to our knowledge are the only reported absolute reactivities of simple benzylic carbanions.

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**Supporting Information Available:** Experimental procedure for compounds **3** and **4** and their HRMS, <sup>1</sup>H NMR, and <sup>13</sup>C NMR characterization, as well as that for their precursors and photoproducts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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