p-Hydroxyphenacetyl Phototriggers: The Reactive Excited State of Phosphate Photorelease

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Received March 31, 2000
Revised Manuscript Received July 11, 2000

Fast release of biological stimulants is needed to monitor physiological response in real time.1 p-Hydroxyphenacetyl (pHP) phototriggers meet this requirement. Moreover, the side products of the reactive excited state of pHP phosphates and carboxylates on the basis of quenching experiments.2 In a recent study of pHP esters Zhang et al.3a questioned that evidence and favored a singlet mechanism. Here, we prove that the reactive excited state of pHP diethyl phosphate (1) is a very short-lived triplet state and we provide direct evidence for adiabatic tautomerization of p-hydroxycetophenone and its derivatives in the triplet state.

\[
\text{OH} \quad \text{H}_2\text{O} \quad \text{O}
\]

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

p-Hydroxyphenylacetic acid (2) is the only product detected by GC–MS after irradiation of 1 in wet acetonitrile (AN, H₂O ≥ 5% by vol). Numerous products of higher molecular weight are formed in dry AN. Relative quantum yields of the photoreaction in different media were determined by the permanent bleaching of the absorption by \(\lambda_{\text{max}} = 395 \text{ nm} \) of 3 \(\text{mol} \cdot \text{s}^{-1} \cdot \text{M}^{-1} \). The triplet energy of 3 \(k_{\text{ISC}} = 3.2 \times 10^{-4} \text{ M}^{-1} \cdot \text{s}^{-1} \) is also known. Energy transfer from 3 to naphthalene was again observed.5 Reactions of the triplet state of 3 in aqueous NaOH (0.1 M) at 308 nm gave only the 405 nm bands, which shows that these are due to the triplet state of the anion, 3′.

Apparently, 3′ is re-protonated to form the 350 nm transient in acidic solutions. Thus, the first-order rate coefficient for re-protonation in dilute aqueous acid (HClO₄, \(k_{\text{HClO₄}} = 3 \times 10^{-4} \text{ M}^{-1} \cdot \text{s}^{-1} \)) was proportional to acid concentration, \(k_{\text{HClO₄}} \approx 4 \times 10^{-4} \text{ M}^{-1} \cdot \text{s}^{-1} \). Spectroscopic traces of the equilibrated triplet–triplet absorptions (delay relative to excitation of 3 in aqueous buffer solutions at pH 7) of 3 in aqueous buffer solutions at pH 7 were monitored at \(\lambda_{\text{max}} = 395 \text{ nm} \) for keto (1 M) and 3′ (1 M). The triplet energy of 3 \(E_T = 10.2 \text{ kcal mol}^{-1} \) is well above that of naphthalene. On the other hand, the excitation energy of the quinonoid enol 3′ is expected to be much lower.

Formations of 3′ are equally fast in aqueous AN solvent mixtures \(k_{\text{ISC}} = 2.7 \times 10^{-4} \text{ s}^{-1} \), \(k_{\text{ISC}} = 370 \text{ in dry AN} \), 395 nm with 50% H₂O. Energy transfer from 3 to naphthalene was again observed.5 Reactions of the triplet state of 3 in aqueous NaOH (0.1 M) at 308 nm gave only the 405 nm bands, which shows that these are due to the triplet state of the anion, 3′.

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The observed fast ionization of 3

Self-quenching is attributed to head-to-tail hydrogen abstraction, upon addition of piperylene (0.64.7 kcal mol\(^{-1}\) upon admission of air or oxygen, \(k_0\)). This is consistent with the observed rate of ionization, calculated value is too low. The triplet energy of \(\Delta E\) at of 3 may be calculated as \(p_{k_0} = p_{K_0} = p_{K_0} + E_{a} = 3\).\(3\) at 5% of water, \(k_{\text{obs}} = k_{\text{obs}} + k_{\text{q}} = 0.38, 0.79 s\). The observed fast ionization of 3, followed by diffusional re-protonation of the resulting anion 3 to form enol 3, excludes a concerted, “intramolecular” proton-transfer mechanism through water.

Yet another intermediate, \(\lambda_{\text{max}} = 325\) nm, is formed by LFP of 3 in neutral aqueous solutions. The yield and the lifetime of this transient are not affected by oxygen, and its absorption spectrum is identical with that of the anion 3 in aqueous base, as noted by Wan and co-workers. The main precursor of 3 is the triplet anion 3, a resolved absorbance growth of 3 at 325 nm, \(k_{\text{max}} = 9 \times 10^9\) s\(^{-1}\) in aqueous AN (50% H\(_2\)O): \(K_{a} = k_{\text{obs}} / k_{\text{ef}}\). The observed fast ionization of 3, followed by diffusional re-protonation of the resulting anion 3 to form enol 3, excludes a concerted, “intramolecular” proton-transfer mechanism through water.

LFP\(^{4}\) of diethyl phosphate 1 in carefully dried, degassed AN showed a strong transient absorbance, \(\lambda_{\text{max}} = 395\) nm, which is assigned to 1. The decay rate of 1 increased linearly with increasing concentration of 1 (0.1–1.5 mM, self-quenching rate constant \(k_{\text{q}} = 8.5 \times 10^9\) M\(^{-1}\) s\(^{-1}\), intercept \(k_0 = 2 \times 10^9\) s\(^{-1}\)). Self-quenching is attributed to head-to-tail hydrogen abstraction, which leads to the radical-derived photoproducts found in dry AN. Energy transfer to naphthalene, \(k_{\text{ef}} = 7.8 \times 10^9\) M\(^{-1}\) s\(^{-1}\), identified 1 as an excited triplet. The decay rate of 1 increased upon admission of air or oxygen, \(k_{\text{q}} = 3 \times 10^9\) M\(^{-1}\) s\(^{-1}\), and upon addition of piperylene (0–1.25 \times 10^{-5} M), \(k_i = 4.5 \times 10^9\) M\(^{-1}\) s\(^{-1}\). The rate constant increased in a parabolic fashion with increasing water content, reaching \(2.8 \times 10^7\) s\(^{-1}\) at 5% of water, and the transient escaped detection by nanosecond LFP at water contents exceeding 10%.

Excellent agreement between the effect of piperylene on the steady-state and time-resolved data establishes that the triplet state is the reactive excited state in the photorelease of diethyl phosphate from 1: the ratio of the quantum yields obtained with (10 mM) and without piperylene in 5% aqueous AN, \(\Phi /\Phi_0 = 0.39\) (vide supra), is equal, within the limits of error, to the corresponding ratio of the lifetimes of the transient intermediate 1, \(\tau_{\text{t}} = k_{\text{obs}} / k_{\text{q}} = 0.38\).

Addition of concentrated HClO\(_4\), (1–100 \times 10^3 M) to AN resulted in a titration plot similar to that shown in Figure 1. Half-protonation was reached at about 4 \times 10^{-3} M acid. The acidic form of the transient is attributed to the quinonoid enol triplet 1. Zhang et al. noted that the quantum yield of the photoreaction of pHP acetate drops in aqueous acid.\(^{26}\) We observe a similar, if less pronounced drop in acidic aqueous (5%) AN, \(\phi /\phi_0 = 0.94, 0.90, 0.84, 0.74\) (1.0). This drop is attributed to protonation of 1 to the neutral enol 1, which is less prone to the release of diethyl phosphate. We could not perform quantum yield measurements in aqueous base, because 1 is quickly hydrolyzed in the ground state. The drop observed at high pH with pHP esters\(^{3}\) may be due to a low quantum yield of ISC. We found that excitation of 3 gives low yields of 3, especially at excitation wavelengths of less than 350 nm.

The sharp increase of the decay rate of 1 with increasing water content in AN is attributed to acceleration of heterolytic phosphate release by water. The spectral evolution seen by pump–probe spectroscopy of 1 in aqueous AN (1:1) is shown in Figure 2. Factor analysis of 79 spectra recorded with time delays of 5–2000 ps required 2 spectral components. Adequate fit to the loading factors was obtained with a dual exponential function, \(k_1 = (3.8 \pm 0.2) \times 10^4\) s\(^{-1}\) (1 to 1) and \(k_2 = (2.4 \pm 0.2) \times 10^4\) s\(^{-1}\) (phosphate release). We believe that phosphate release occurs directly from the neutral 1, but rate-determining ionization to 1 followed by rapid release cannot be excluded.

In summary, the photorelease of diethyl phosphate from p-hydroxyphenacyl diethyl phosphate (1) in neutral aqueous media proceeds via the triplet state, 1, which is formed within a few ps and has a lifetime of 0.4 ns in 1:1 aqueous acetonitrile. The subsequent steps of the rearrangement and hydrolysis to p-hydroxyphenyl acetic acid (2) remain to be elucidated.

Acknowledgment. This work was supported by the Swiss National Science Foundation, Project No. 20-53919.98 (J.W.) and by NSF/OSR-9255223 (R.S.G.).