Direct Photolysis of Phenacyl Protecting Groups Studied by Laser Flash Photolysis: An Excited State Hydrogen Atom Abstraction Pathway Leads to Formation of Carboxylic Acids and Acetophenone

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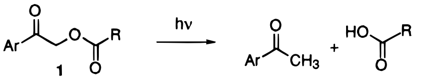
Photochemically removable protecting groups (PRPGs) are molecular entities that can be covalently attached to a functional group of a molecule for the purposes of rendering it inert to some particular set of reaction conditions.[1] The PRPG is then released when the protected compound is exposed to light. Such protecting groups find uses not only in multistep syntheses[2] but also in biophysical studies where they are often called "caged molecules" or "phototriggers".[3,4]

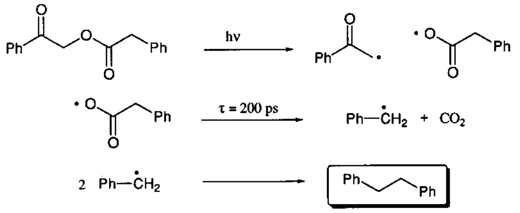
Investigations in several laboratories have focused on various aromatic α-keto groups as PRPGs.[5] Among the earliest α-keto derivatives to be studied were those based on the phenacyl (i.e., the benzoylmethyl, $PhCOCH_2$) chromophore. Sheehan[6] and others[7,8] reported that photolysis of 4-methoxyphenacyl esters in 1,4-dioxane solutions gave good yields of the corresponding acids along with 4-methoxyacetophenone. These workers proposed a mechanism involving excited-state C−O bond homolysis giving phenacyl radical along with an acyloxy radical (Scheme 1). Although elimination of CO_2 from acyloxy radicals ($RCO_2^•$) is an extremely fast process,[9] especially when the product ($R^•$) is a resonance-stabilized species,[10] it was assumed that abstraction of an H-atom was occurring competitively with decarboxylation.

In the course of our studies on the photoinduced electron-transfer behavior of phenacyl esters, we had occasion to undertake direct irradiation of phenacyl phenylacetate **1** in CH_3CN. Assuming the mechanism in Scheme 1, direct homolysis of this compound would lead to phenylacetoxy radical ($PhCH_2CO_2^•$). Pincock[11] has estimated the lifetime of this species to be 200 ps. Consequently, we anticipated rapid decarboxylation would give the benzyl radical ($PhCH_2^•$) which would dimerize to give bibenzyl (1,2-diphenylethane) as a stable product. Contrary to our expectations, we found that photolysis of phenacyl ester gave no detectable bibenzyl (<0.5% by HPLC analysis), but instead high yields of acetophenone and phenylacetic acid (eq 1).[12] Again, when phenacyl (2-methoxyphenyl)acetate was subjected to similar photolysis conditions, acetophenone and the corresponding acid were detected as products.

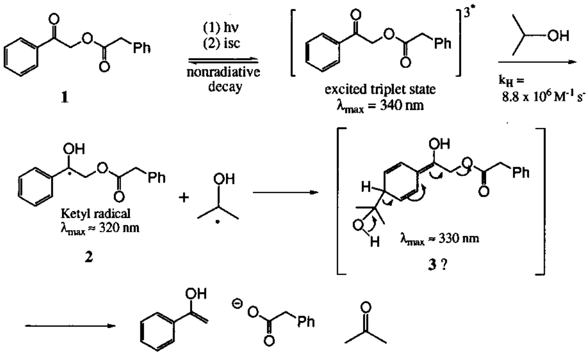


(1)

Scheme 1. Homolytic Bond Scission Mechanism



Scheme 2. Mechanism in Presence of H-Atom Donors



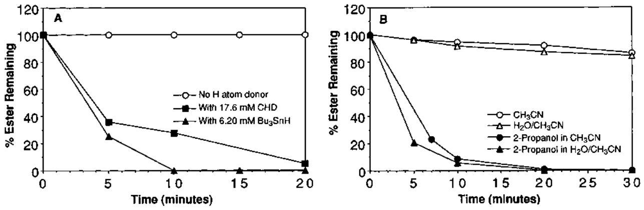


Figure 1. Effect of H-atom donors on the photolysis (150 W Hg−Xe lamp) of **1** (3.5) mM, N_2-purged solutions) in various solvents. Panel A illustrates the effects of adding 6.20 mM *n*-Bu_3SnH to benzene (●) and 17.6 mM CHD to benzene (▲) compared with neat benzene (○). In these experiments the solutions were 10.3 mM in **1**. Panel B illustrates the effect of adding 435 mM 2-PrOH to CH_3CN (●) compared with neat CHCN (○) along with the effect of adding 2-PrOH to H_2O/CH_3CN (ca. 3:2) (▲) compared with the same solvent containing no additives.

These results caused us to reconsider the previously proposed mechanism for phenacyl ester photolysis. The experiments below lead to the conclusion that H-atom transfer,[13] rather than C−O bond homolysis, is the initial photochemical step in the decay mechanism (Scheme 2). The resulting ketyl radical **2** decays through a second-order process, perhaps involving a net disproportionation with the donor radical via a relatively long-lived coupling product of structure **3**.

This conclusion is supported by the following observations:

(1) The quantum yield for decomposition of **1** is greatly increased when efficient H-atom donors (1,4-cyclohexadiene, CHD; tributyltin hydride or 2-propanol) are added to the sample (Figure 1). For example, **1** is stable for over several hours of irradiation in neat benzene, yet it is consumed in <10 min when 6.20 mM *n*-Bu_3SnH was added. This appears to be a general effect that does not require a particular solvent or H-atom donor. Similar increases in photolysis efficiency are observed when CHD is added to CH_3CN and when 2-propanol is added to water. In each case, the only products are acetophenone and the carboxylic acid.

If homolytic bond scission were the first irreversible step in the reaction (i.e., following Scheme 1), then we would expect no

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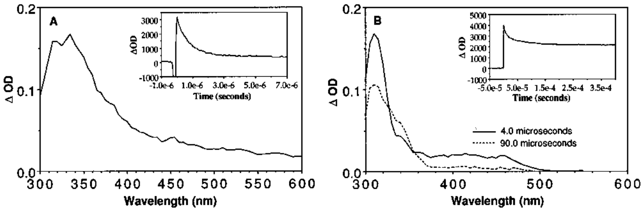

Figure 2. (A) Transient absorption spectrum taken 400 ns after laser flash photolysis (308 nm, 10 ns, 50 mJ) of 10.4 mM solutions of **1** in benzene. The inset illustrates the absorption decay (to 7 μs) at 320 nm. This spectrum is assigned to the excited triplet state of **1**. (B) Transient spectra taken 4.0 and 90.0 μs after pulsed laser photolysis of **1** in N_2-purged 2-propanol. Under the latter conditions, decay of the triplet is rapid and only ketyl **2** and coupling product **3** are detected. The inset illustrates absorption decay (to 450 μs) at 320 nm.

or little dependence of photolysis times on the presence of an H-atom donor. On the other hand, these results follow readily from the mechanism in Scheme 2. In this mechanism, H-atom abstraction competes with photon-wasting nonradiative decay of the excited triplet state of phenacyl ester **1**.

Results from earlier work on similar systems are also consistent with this observation. Sheehan[6] reported that the photolysis of 4-methoxyphenacyl esters was much faster in dioxane (a H-atom donor of moderate reactivity) than it was in benzene. Givens[14] showed a deuterium isotope effect in the photolysis of 4-methoxyphenacyl phosphate esters in CH_3OH. The latter workers also proposed a pathway involving formation of a ketyl radical. In that case they suggested that unimolecular decay of the latter would give an enol along with a phosphate-based radical.

(2) Laser flash photolysis (LFP) experiments show the excited triplet state of the ester is formed upon direct photolysis. Figure 2A shows the transient UV−vis spectrum obtained following pulsed laser (308 nm, 10 ns, 50 mJ/pulse) photolysis of **1** in benzene. The spectrum consists of a broad absorption band with a maximum near 340 nm. This species decays following clean first-order kinetics fitting to a lifetime of 750 ns (benzene, Ar-purged). This species is assigned to the excited triplet state of the phenacyl group because its lifetime is diminished in the presence of O_2 and because of its resemblance to the excited triplet state spectrum of acetophenone.[15,16]

(3) The excited triplet state abstracts a H-atom from various donors to form the ketyl radical **2**. For example, addition of increasing amounts of CHD to solutions of **1** increases the decay rate of the excited triplet state. A pseudo-first-order analysis of the decays provides second-order rate constants of 5.2×10^8 M^{-1} s^{-1} for CHD, 6.2×10^8 M^{-1} s^{-1} for tributyltin hydride, and 8.8×10^6 M^{-1} s^{-1} for 2-propanol. The latter compares favorably to the reported value of 2.13×10^6 M^{-1} s^{-1} for acetophenone.[17] In addition to quenching the triplet absorption, the H-atom donors cause formation of a new, longer-lived transient species having a maximum near 310 nm and a much weaker tail extending to 425 nm (Figure 2B). Such an absorption spectrum is characteristic of ketyl radicals formed from other acetophenone derivatives.[16] This spectrum is therefore assigned to **2**.

The ketyl radical **2** decays to a long-lived (τ >1 ms) species that absorbs in a similar region of the spectrum as illustrated in Figure 2B. The precise nature of this long-lived transient is still under investigation. However, several facts are relevant. First, **2** decays a second-order fashion (following $d[\mathbf{2}]/dt = k_c[\mathbf{2}]^2$ where $k_c = 3.48 \times 10^5$ ϵ^{-1} s^{-1}). If ϵ_{320} is estimated using the corresponding value for acetophenone ketyl,[16] then $k_c = 7 \times 10^9$ M^{-1} s^{-1}. This value is near the diffusion limit and thus consistent with a radical−radical reaction. Second, the long-lived absorption spectrum differs from that of acetophenone or its enol (270 nm).[18,19] Third, UV and ^1H NMR spectra taken immediately after steady-state photolysis show only formation of $PhCOCH_3$ and $PhCH_2CO_2H$. Thus, the long-lived species is not stable, and moreover, it must decay cleanly to give these products. Finally, extensive photochemical studies on benzophenone in 2-propanol have revealed a metastable species, termed the “light absorbing transient” or LAT.[20−23] This has been assigned to a coupling product where the 2-hydroxy-2-propyl radical binds to the ortho or para ring positon on the benzophenone ketyl radical. By analogy to the earlier work, we tentatively assign the long-lived transient to analogous coupling product exemplified by **3** in Scheme 2.

Unlike the benzophenone LAT, **3** has available to it a facile decay pathway involving elimination of carboxylate from the allylic position of an electron-rich double bond coupled with generation of the oxidized donor species. (For 2-propanol this would correspond to acetone, for CHD, benzene. For n-Bu_3SnH, nucleophilic attack at the Sn atom of the corresoponding adduct would allow for net reduction of **1** and formation of Sn−Nuc. It is also possible that two molecules of **2** would couple in a similar fashion and then disproportionate to give **1** along with the observed products.) While this mechanism is consistent with the available data, further spectroscopic information is necessary to confirm the structure of **3** and to verify the final step in the mechanism. We are currently attempting to generate and characterize **3** at low temperatures. Results from these experiments will be reported in due course.

These experiments identify hydrogen abstraction as an important pathway in the direct photolysis of α-keto protecting groups. It is further argued that direct homolysis occurs inefficiently, if at all. Of course, this does not exclude the existence of other decay mechanisms. Indeed compelling evidence has been presented for a photohomolysis/neighboring group assisted electron-transfer pathway in the decay of 4-hydroxyphenacyl phosphate esters.[24] Likewise, it appears that the benzoin derivatives can decay through a mechanism involving photocleavage coupled with cyclization to form a benzofuran derivative.[14,25,26] The relative efficiencies for each of the possible pathways is undoubtedly controlled by factors such as substitution on the PRPG, the nature of the leaving group, the solvent polarity, and the presence of H-atom donors.[27] Future research directed at understanding how these various factors determine the decay mechanism actually followed will be helpful in designing improved PRPGs.

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