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Chain Mechanism in the Photocleavage of Phenacyl and Pyridacyl Esters in the Presence of Hydrogen Donors

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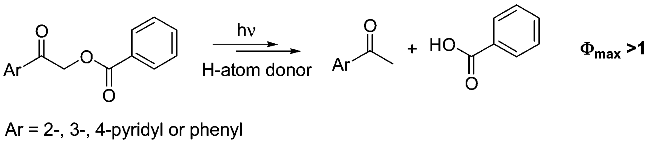

Excited phenacyl and 3-pyridacyl esters of benzoic acid react with an excess of aliphatic alcohols in a chain reaction process involving hydrogen transfer from the ketyl radical intermediates, leading to benzoic acid in addition to acetophenone and 3-acetylpyridine, respectively, as the byproducts. While the maximum quantum yields reached 4 in both cases, the 2- or 4-pyridacyl ester photoreduction proceeded with the efficiency below 100% under the same conditions. The investigation indicates that a radical coupling between ketyl radicals, both formed from the excited ester by hydrogen abstraction from an alcohol, is accompanied by the elimination of benzoic acid from the ester ketyl radical itself. A partitioning between two reactions was found to be remarkably sensitive to the chromophore nature, such as a position of the nitrogen atom in the pyridacyl moiety. The magnitude of a radical chain process is dependent on the efficiency of consecutive steps that produce free radicals capable of a subsequent ester reduction. The driving force of a possible electron transfer from the ketyl radicals to the ester has been excluded on the basis of cyclic voltametry measurements. The observed quantum yields of photoreduction were found to be diminished by formation of relatively long-lived light absorbing transients, coproducts obtained apparently by secondary photochemical reactions. Additionally, it is shown that basic additives such as pyridine can further increase the efficiency of the photoreduction by a factor of 4. A radical nature of the reduction mechanism was supported by finding a large kinetic chain length of an analogous reaction initiated by free radicals generated thermally yet again when phenacyl or 3-pyridacyl benzoate was used. Both phenacyl and pyridacyl chromophores are pronounced to be valuable as the photoremovable protecting groups when high quantum and chemical yields of carboxylic acid elimination are important, but higher concentrations of the hydrogen atom donors are not destructive for a reaction system or are experimentally impractical.

Introduction

In the past two decades, considerable attention has been paid to employment of photoremovable protecting groups (PPG) in organic synthesis, biochemical studies, photolithography, or combinatorial chemistry.[1−12] The phenacyl (PA) moiety has been successfully used as a protecting group, released by chemical reduction, for carboxylic acids and phenols by Hendrickson and Kandall for the first time.[13] Since then, several substituted

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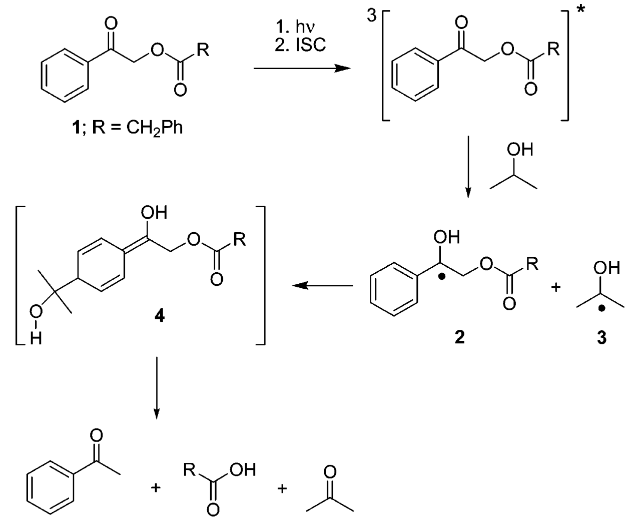
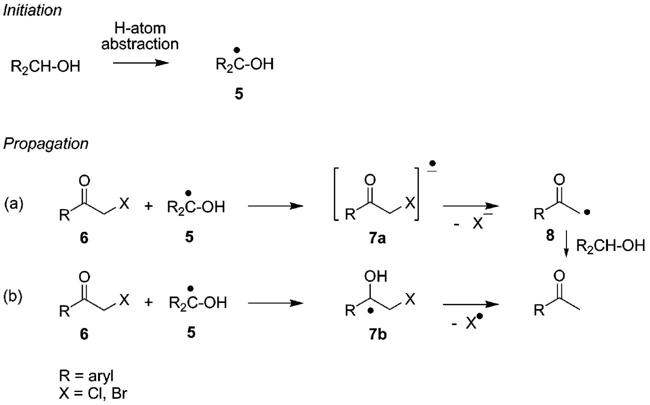
SCHEME 1. Photolysis of Phenacyl Carboxylate in the Presence of Propan-2-ol (According to ref 24)



SCHEME 2. Reductive Chain Dehalogenation of an α-Halogen-Substituted Carbonyl Compound in the Presence of an Alcohol (According to ref 27)



phenacyl chromophores have been established as PPGs, including 4-hydroxyphenacyl,[14−17] 4-methoxyphenacyl,[18] and 2,5-dimethylphenacyl.[19−22]

Sheehan and Umezawa have reported that direct UV irradiation of the 4-methoxyphenacyl esters in 1,4-dioxane solutions yields a free carboxylic acid and acetophenone in good yields.[23] A homolysis of the C−O bond would result in formation of a phenacyl and acyl radicals, which are capable of abstracting the hydrogen atom from solvent molecules to give the corresponding acid and acetophenone. A direct irradiation of phenacyl phenyl acetate, however, did not afford any detectable amount of dibenzyl, an anticipated product of rapid decarboxylation of the phenylacetoxy radical.[24] Banerjee and Falvey performed a laser flash study of photochemical cleavage of phenacyl esters in the presence of the hydrogen atom donors.[24] The proposed mechanism (Scheme 1) involved the hydrogen abstraction from an H-donor by the excited carbonyl group of phenacyl ester (**1**), resulting in formation of a pair of the ketyl radicals **2** and **3**. The ketyl radical **2** decays in a second-order fashion to a relatively short-lived intermediate possibly of structure **4**, a coupling product of two ketyl radicals, and subsequently decomposes to produce acetophenone and free carboxylic acid. Similar metastable coupling species, termed the "light absorbing transients" (LAT) are known to be formed in photoreduction of benzophenone or 3-benzoylpyridine.[25,26]

It is known that various α-halogen-substituted carbonyl compounds can be reductively dehalogenated in alcohols with a chain mechanism.[27−31] Renaud and Scaiano have investigated photochemistry of ring-substituted α-bromoacetophenones (**6**) in alcohols.[32] They suggested that two parallel chain reactions involving hydrogen or electron transfer occur (Scheme 2). Thus, a ketyl radical (**5**) from an alcohol is formed in the initial step, which can transfer either (a) electron or (b) hydrogen to an α-halogen-substituted carbonyl compound. As a result, both radical anion **7a** and ketyl radical **7b** release halide ion or atom, giving rise to a carbonyl compound and regenerating the ketyl radical **5** or halogen atom as the chain carriers.

The goal of the current work was to study photochemistry of a heterocyclic analogue of the phenacyl moiety: pyridinylcarbonylmethyl (pyridacyl; PyA) chromophore as a photoremovable protecting group for carboxylic acids. The course of photochemical and thermal reductive cleavage of three PyA benzoates **9a−c** and phenacyl benzoate **10** in the presence of H-atom donors (Scheme 3) was investigated.

Results and Discussion

Photoreduction of Esters in the Presence of Alcohols. Irradiation of PA (**10**) or PyA (**9a−c**) benzoates in the presence of alcohols (methanol, ethanol, or propan-2-ol (IPA)) as H-atom donors at 313 or 366 nm afforded expected[24] products: acetophenone/acetylpyridine and benzoic acid (BA) (Scheme 3). The quantum yields were found to be dependent on the alcohol

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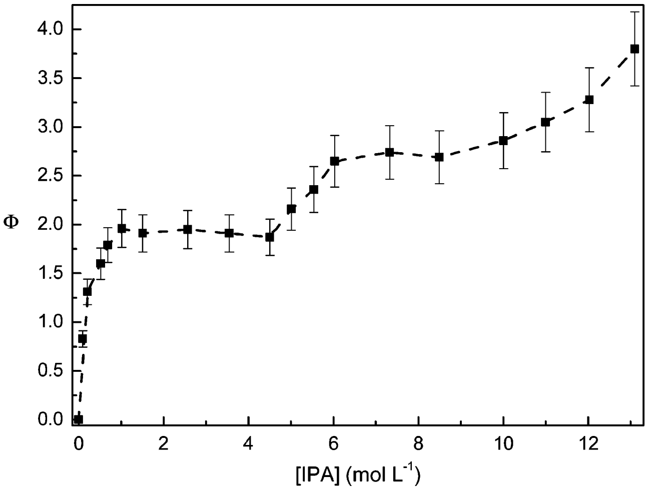
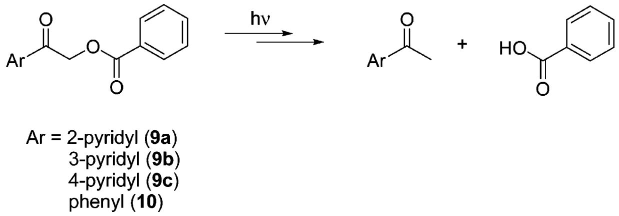


FIGURE 1. Quantum yields of the benzoic acid formation from **10** ($c = 6 \times 10^{-3}$ mol L^{-1}) in acetonitrile as a function of IPA concentration at 20 °C. The reaction conversion was kept below 20%. Error bars represent the relative standard deviation for triplicate measurements.

SCHEME 3. Photolysis of Benzoates 9a−c and 10



concentrations. Figure 1 represents the results obtained for PA benzoate **10** in IPA. The quantum yields considerably increased with an increasing IPA concentration reaching $\Phi \approx 2$ at [IPA] ≈ 1 mol L^{-1}. Further increase of [IPA] had only a moderate effect on Φ, and the maximum quantum yield, $\Phi_{max} = 3.8$, was eventually obtained in neat IPA. An apparent wavelike character of the dependence in Figure 1 at higher IPA concentrations was a characteristic property of the system. The quantum yield was also found to increase with an increasing ester concentration.

Irradiation of esters **9a−c** and **10** in alcohols caused a relatively fast increase of the solution absorbance, mainly in the UV region. The spectral change was not permanent; this absorption largely disappeared within a few days. Furthermore, bubbling the solution with oxygen enhanced the rate of this decay. Such spectral changes are known to occur in similar systems attributing to the formation of an LAT, a relatively long-lived photoinduced intermediate.[25,26] Figure 2 shows the spectral variations following the irradiation of **10** and a differential absorption spectrum with the absorption maximum $\lambda_{max} = 345$ nm, which was assigned to this transient. Relative enhancement of the absorption in the region of 320−400 nm was also substantial in the case of 3-PyA benzoate (**9b**) irradiation, less significant for 2-PyA (**9a**), and insignificant for 4-PyA (**9c**) benzoates (Figure 3a). LAT formed from **9b** had an apparent maximum λ_{max} at 352 nm. Figure 3b shows the spectral variations following the irradiation of **9b** in IPA (not degassed) to a 15% conversion at 313 nm. The half-life was estimated to be approximately 10 h.

Quantum yields (Φ) of BA formation from **9a−c** and **10** in neat solvents are shown in Table 1; they corresponded well to those of ester degradation. However, Φ values of acetophenone/acetypyridine formation were generally lower because of their subsequent photoreduction. Since the Φ values were found to be sensitive to the reaction conversion to some extent, the conversions in all quantum yield measurements were kept below 15% to prevent interference from the photoproducts. Some of the quantum yields were corrected on the LAT formation,

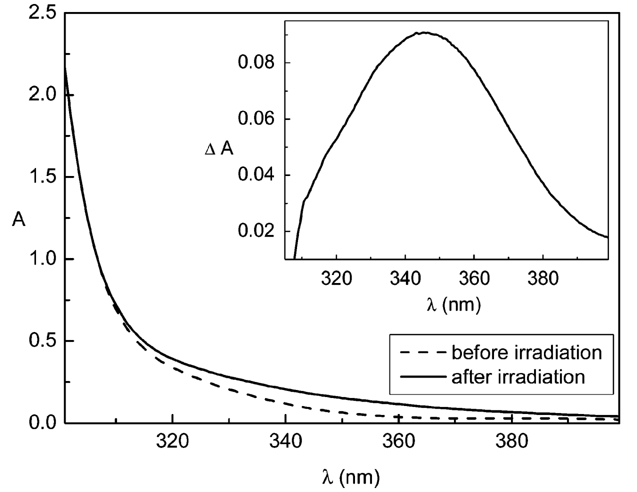


FIGURE 2. Absorption spectra of the solution of **10** in IPA before and after irradiation to a ~15% conversion at 313 nm. The inset displays a differential spectrum of an LAT.

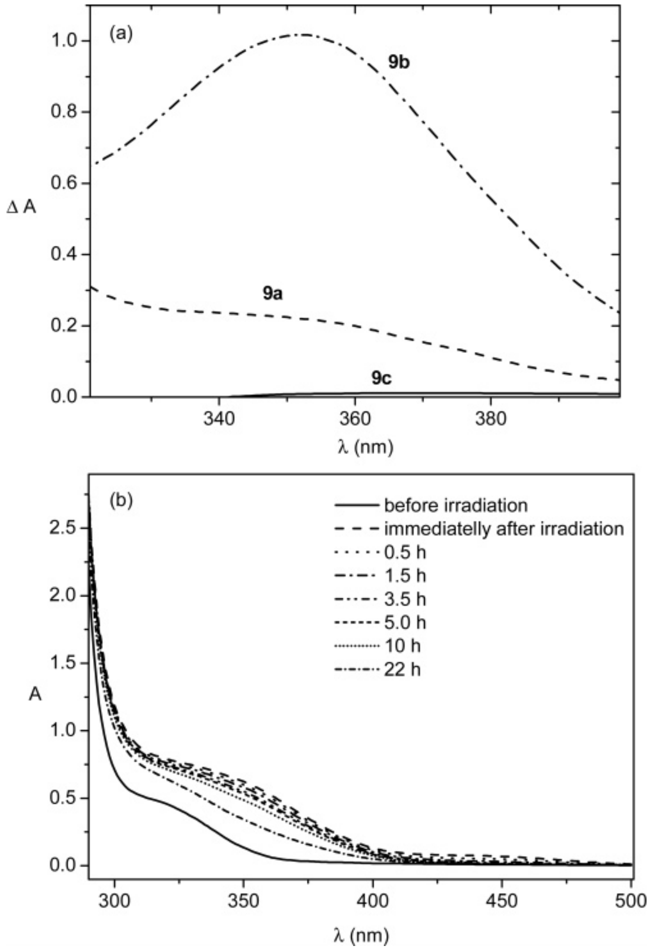


FIGURE 3. (a) Examples of differential spectra of LAT formed by irradiation of **9a−c** to a ~15% conversion at 313 nm. (b) Time course of LAT (formed from **9b**) "dark" decomposition.

TABLE 1. Maximum (Φ_{max}) and Maximum Corrected (Φ_{corr}) Quantum Yields of Benzoic Acid Formation from PA Benzoate (10) and PyA Benzoates (9a−c) ($c = 6 \times 10^{-3}$ mol L^{-1}) in Neat Solvents at 313 or 366 nm (20 °C) in the Absence of Pyridine, and Maximum Quantum Yields in the Presence of Pyridine (Φ_{Py})[a]

ester	solvent	Φ_{max}	Φ_{corr}[b]	Φ_{Py}[c]	chemical yield[e]
10	MeOH	1.2	1.2	n.d.	n.d.
	EtOH	1.6	1.6	n.d.	n.d.
	IPA	3.8	4.0	17.5	99
9a	MeOH	0.5	n.d.	n.d.	n.d.
	EtOH	0.7	n.d.	n.d.	n.d.
	IPA	1.2	n.d.	1.7	99
9b	MeOH	0.6	0.6	n.d.	n.d.
	EtOH	3.1	3.7	9.1 (9.4[d])	n.d.
	IPA	1.7	2.8	1.9 (2.8[d])	99
9c	MeOH	1.0	1.0	n.d.	n.d.
	EtOH	1.2	1.2	n.d.	n.d.
	IPA	0.9	0.9	1.3	99

[a] The relative standard deviation was found below 10% in all measurements. The reaction conversions were always kept below 15%; n.d., not determined. [b] The maximum quantum yields corrected on formation of LAT as an internal optical filter (a lower estimation), calculated for reactions irradiated to a 15% conversion. [c] The concentration of pyridine was ~0.2 mol L^{-1}. [d] The values corrected on formation of LAT. [e] Maximum chemical yields of BA formation (GC) obtained in an exhaustive irradiation at $\lambda >$ 280 nm (a Pyrex optical filter).

because those transients are internal optical filters lowering the quantum efficiency of the reaction. To eliminate its influence, the amount of LAT was estimated by periodical measurement of the absorbance of the solution during irradiation. The light intensity absorbed by LAT was plotted as a function of time, assuming that the absorbance of the starting material did not change significantly at early stages of reaction and that the absorbance increased only because of the LAT formation. The integral of an area beneath a line connecting two neighboring points then provided a lower estimation of the light intensity absorbed by LAT at the corresponding wavelength. The corrected quantum yields (Φ_{corr}) in Table 1 show that the actual values are significantly higher, especially in the case of the **9b** photolysis. Pyridine addition was also found to have an important effect on the quantum yields of benzoic acid formation, the values of which increased approximately by a factor of 4 in the photolysis of **10** in IPA or of **9b** in EtOH, respectively, while the pyridine addition had a negligible effect on Φ in the case of **9b** or **9c** in IPA (Table 1). Figure 4 shows quantum yield variations in the photolysis of **10** in IPA at different pyridine concentrations. A rapid increase of Φ_{Py} with increasing concentration of pyridine leveled off at $c > 0.2$ mol L^{-1}; the maximum quantum yield obtained was 17.5 at this concentration. Moreover, very high chemical yields of benzoic acid formation were observed when ester solutions in IPA were irradiated exhaustively at $\lambda > 280$ nm (Table 1).

In general, the quantum yields higher than 1 in the photolysis of **10** and **9b** may imply that chain propagation in photoinitiated radical or ionic process takes part. Such an amplification of photochemical processes may play an important role in applications where high substrate sensitivity is required, for example lithography, but exceedingly efficient photochemical removal of a protecting group should also be of great interest, especially in biological applications.

The photochemical cleavage of PA or PyA esters shares common features with photoreduction of benzophenone in alcohols.[25,26] Hydrogen atom abstraction by the triplet excited

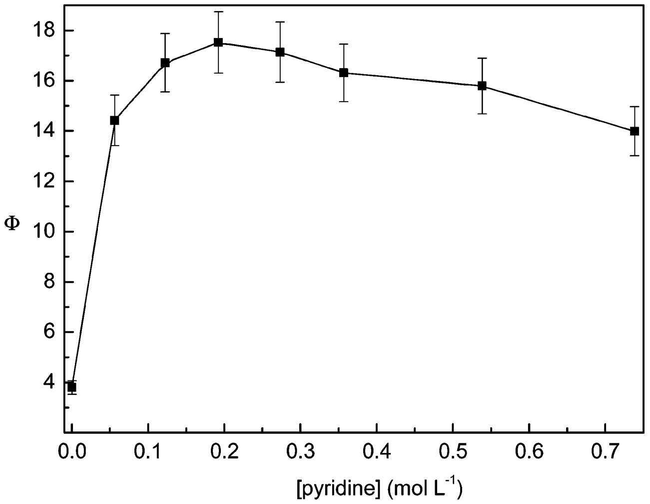


FIGURE 4. Quantum yield variations in the irradiation of **10** ($c = 6 \times 10^{-3}$ mol L^{-1}) in IPA for various pyridine concentrations at 313 nm. Error bars represent the relative standard deviations for triplicate measurements.

phenacyl or pyridacyl[33] chromophore represents the initiation step. An analogy with α-halogen-substituted PA derivatives[32] enables us to discuss the subsequent chain steps in the photoreduction of the esters **9a−c** and **10**. Two different mechanisms involving hydrogen or electron transfer among ketyl radicals and the ester molecules can be accommodated (Scheme 2). Both mechanisms share a common ketyl radical **5** and apparently the same photoproducts. For an *electron transfer* mechanism (analogous to that shown in Scheme 2a), it is necessary that the initial charge-transfer step be exergonic. One way to evaluate the feasibility of such a mechanism is to determine the driving force for this step from the oxidation potential of the donor (E_{ox}) and the reduction potential of the acceptor (E_{red}). The oxidation potential of 1-hydroxy radicals was found to depend strongly on the type of the solvent. E_{ox} of 2-hydroxy-2-propyl radical was reported to be −0.60 V in acetonitrile, −1.1 V in a propan-2-ol/acetonitrile (3:1) mixture, and −1.3 V in water[30,34,35] versus the saturated calomel electrode (SCE), while $E_{ox} = -0.24$ V versus SCE was found for α-hydroxyalkyl radical derived from acetophenone in acetonitrile.[34] The electrochemical reduction of phenacyl benzoate was reported by Falvey et al. to be irreversible; the first reduction peak of the phenacyl benzoate in cyclic voltammogram occurred at −1.89 V versus SCE at 100 mV s^{-1}.[36] The reduction potentials E_{red} of the PA and PyA groups were measured for this work to predict if any of the chromophores are capable of receiving an electron from any of the electron donors present in the reaction system. The voltammograms obtained for all three esters showed two cathodic peaks corresponding to irreversible reduction processes at a slow (100 mV s^{-1}) scan rate (Figure 5), and the relative potentials of the first cathodic peak versus an Ag reference electrode are listed in Table 2. Maximal rates of electron transfer are known to be observed when $\Delta G°$ is

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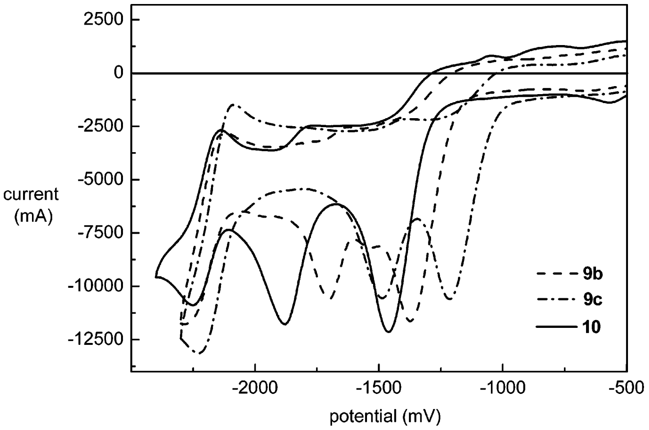


FIGURE 5. Cyclic voltammograms of PA (**10**), 3-PyA (**9b**), and 4-PyA (**9c**) benzoates in acetonitrile. The scan rate was 100 mV s^{-1}.

negative ($\Delta G°$ (kcal mol^{-1}) $\approx -23.06 \times [-E_{ox}^{1/2}$ (donor) $+ E_{red}^{1/2}$ (acceptor)]). Thus, a transfer between the ground-state esters **9a**−**c** or **10** and a ketyl radical should be largely endergonic, and we exclude this mechanism under given experimental conditions.

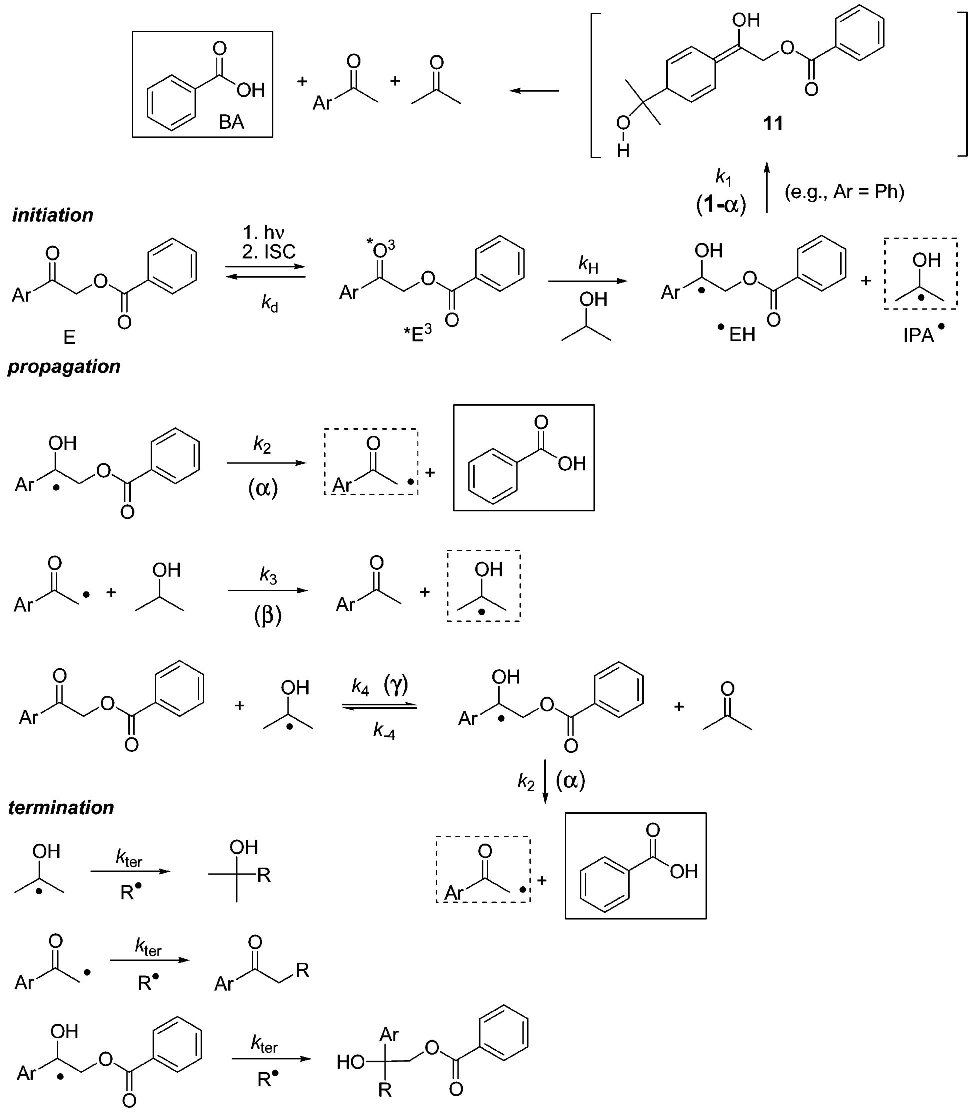
TABLE 2. Relative Potentials E_{red} of the First Cathodic Peak vs an Ag Reference Electrode at a Scan Rate of 100 mV s^{-1}

ester	E_{red} (V)
10	−1.462
9b	−1.374
9c	−1.214

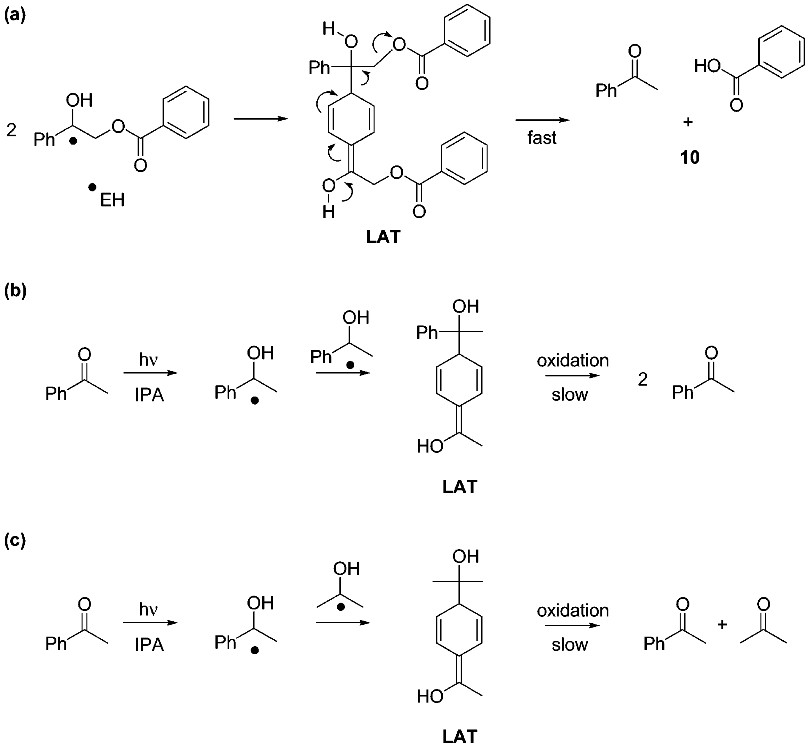
As implied from the mechanism of phenacyl ester photoreduction in the presence of a H-donor proposed by Banerjee and Falvey,[24] the reaction quantum yield should not exceed 100% if the mutual recombination of ketyl radicals formed by hydrogen abstraction is the only reaction mechanism responsible for an acid release. This was not true, however, in most of our experiments when the concentrations of an H-atom donor were high. Direct evidence for termination reactions is formation of the products by cross-coupling of the radicals during photolysis. Only traces of 2,3-dimethylbutan-2,3-diol or other higher molecular weight products were observed, even after exhaustive irradiation of the benzoates in the presence of alcohols.

To discuss the extent of the chain *radical* process, we now propose a tentative mechanism and consider the efficiencies of radical initiation, propagation, and termination steps (Scheme

SCHEME 4. Chain Steps in the Photoreduction of Phenacyl (Ar = Phenyl) or Pyridacyl (Ar = Pyridyl) Benzoic Acid Esters in the Presence of IPA



SCHEME 5. Formation of LAT from 10 or Acetophenone



4). Chain propagation will most probably result from side reactions of the intermediates, the ketyl radicals, formed by the hydrogen abstraction from propan-2-ol (IPA$^•$) or by H-atom transfer to the excited ester. It is well-known that aliphatic 1-hydroxy radicals can reduce ground-state aldehydes and ketones by transfer of a hydrogen atom.[37] Such a transfer is reversible; however, a high thermodynamic stability of the benzyl radicals favors oxidation of an aliphatic radical. Demeter and Berces measured the rate constant (3.6×10^5 L mol^{-1} s^{-1}) for a hydrogen atom transfer from 2-hydroxy-2-propyl radical (IPA$^•$) to benzophenone.[37] The reduction of the ground state of phenacyl benzoate is probably the main decay mechanism of 2-hydroxy-2-propyl radicals in case its concentration is sufficient. As a result, the formation of $^•$EH would lead to either BA elimination (with the efficiency α) and IPA$^•$ recovery in the subsequent step (β) or the recombination (termination) of $^•$EH and IPA$^•$ radicals via a coupling intermediate **11** (1-α) as Banerjee and Falvey[24] suggested. Such a coupling reaction could be enhanced by cage effects since the radicals are produced in a close proximity as the triplet radical pair. Photoreduction of benzophenone, however, is known to exhibit only negligible cage effects. It was reported that formation of a coupling intermediate (LAT) from two diphenyl ketyl radicals was inefficient.[38−40] On the other hand, a significant fraction of reactive encounters between aliphatic and aromatic ketyl radicals can lead to a LAT formation.[25] Although Falvey reports that UV and NMR spectra taken immediately after steady-state photolysis of **10** showed only BA and acetophenone as the products and that **11** is a relatively short-lived transient ($\tau > 1$ ms), we found that irradiation of **10** and **9a−c** in neat IPA did produce a detectable amount of a long-lived LAT characterized by $\tau_{1/2}$ in the order of 10 h (Figures 2 and 3). All differential spectra measured were analogous to those of LAT formed from benzophenone photolysis in IPA with $\lambda_{\max}$ values between 300 and 400 nm for both *o*- and *p*-regioisomers.[25] Furthermore, Albini et al. have reported production of stable LAT in photolysis of 3-benzoylpyridine in the presence of IPA.[26] We propose in Scheme 5a formation of LAT by radical coupling termination of two ketyl radicals obtained from the phenacyl moiety ($^•$EH), which must depend strongly on the lifetime (as well as the concentration) of the ketyl radical and must be proportional to the probability that the radical will collapse to the products (Scheme 4α). It is apparent, however, that such an LAT (analogous to **11**) will be quickly decomposed by releasing a good leaving carboxylic group and cannot be responsible for the LAT absorption observed in this work. In contrast, Scheme 5 demonstrates the possibility that LAT is formed in the photoinitiated *secondary* reaction of acetophenone (and similarly of acetylpyridines) as the primary coproduct of ester photolysis (b and c), which cannot efficiently decompose. LAT concentrations in our experiments increased in the course of the irradiation proportionally with time and eventually leveled off, and their concentrations diminished with time when irradiation was stopped. The LAT, formed from 3-acetylpyridine in degassed samples, for example, decomposed in the dark following single-exponential decay kinetics with the half-life equal to 4.6 h (Figure 6), while the presence of oxygen lowered $\tau_{1/2}$ to 3.7 h. Since photolysis of acetophenone and 3-acetylpyridine in neat IPA provided practically the same differential absorption spectra, with $\lambda_{\max} \approx 340$ and ≈ 350 nm (Figure 6), respectively, as those obtained from the corresponding esters (Figures 2 and 3), pathways b and c represent most probably a rationalization of the internal optical filter effect observed in our experiments.

The radical mechanism (Scheme 4) produces a ketyl radical $^•$EH, which either couples with the second coproduct IPA$^•$ to **11** (1-α) or eliminates BA (α); a third pathway (a back hydrogen abstraction) could be also considered. As a result, the first

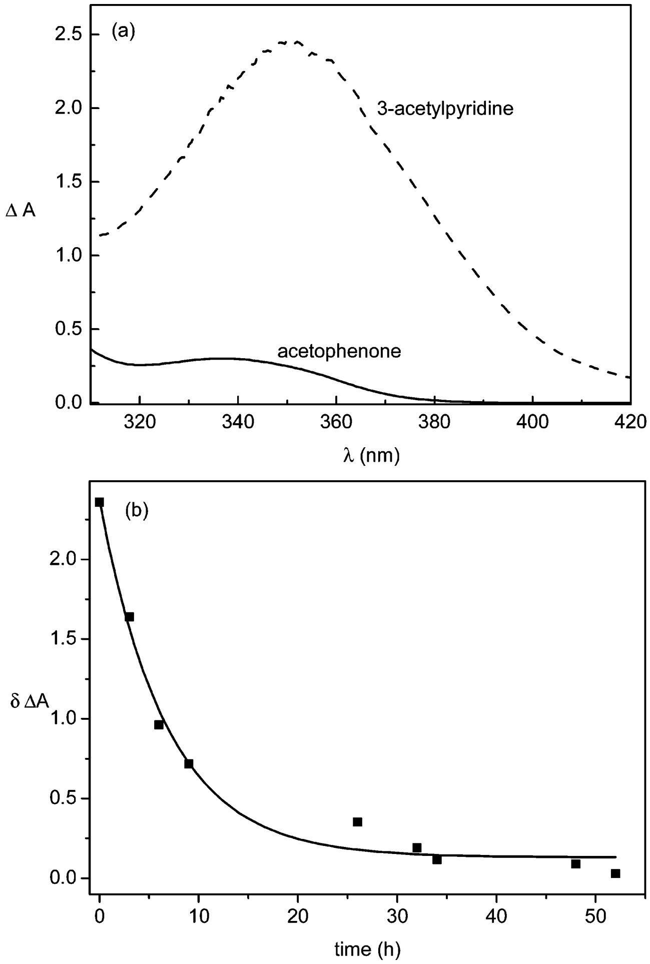


FIGURE 6. (a) Differential spectra of LAT formed during irradiation of acetophenone and 3-acetylpyridine to a ~15% conversion in IPA. (b) "Dark" decomposition of LAT intermediate produced from 3-acetypyridine under argon atmosphere, monitored at 340 nm ($\tau_{1/2} =$ 4.6 h).

process produces radical chain carriers (IPA$^•$ or ArC(=O)CH$_2^•$) in amounts that are dependent on the number of cycles in a chain process. While ArC(=O)CH$_2^•$ can abstract hydrogen from another IPA molecule to form acetophenone/acetylpyridine simultaneously with IPA$^•$ production (β), IPA$^•$ may serve in an exchange process (γ) similar to what was observed in benzophenone photochemistry.[41] The fragmentation of an aromatic ketyl radical $^•$EH into the PhCOO$^•$ radical and acetophenone/acetylpyridine should be more endothermic than the corresponding reaction of the α-halogen- or phenoxy-substituted phenacyl derivatives,[42] and it is not included in our mechanistic considerations.

The corresponding quantum yields of BA formation in radical processes described in Scheme 4 can be calculated according to the following equations. (i) BA produced via termination production of **11**:

$$\phi_t = \phi_T \tau_T k_H[\text{IPA}]P(1 - \alpha) \tag{1}$$

(ii) BA produced from $^•$EH:

$$\phi_0 = \phi_T \tau_T k_H[\text{IPA}]P\alpha \tag{2}$$

(iii) BA produced from IPA$^•$ and the ground-state ester (hydrogen atom exchange):

$$\phi_0' = \phi_T \tau_T k_H[\text{IPA}]P\gamma\alpha \tag{3}$$

(iv) a chain production of BA via elimination of $^•$EH (for an n-th cycle):

$$\phi_n = \phi_T \tau_T k_H[\text{IPA}]P\alpha(\beta\gamma\alpha)^n \tag{4}$$

(v) a chain production of BA via hydrogen atom exchange process (for an n-th cycle):

$$\phi_n' = \phi_T \tau_T k_H[\text{IPA}]P\gamma\alpha(\beta\gamma\alpha)^n \tag{5}$$

The quantum yield of the chain process only (ϕ_{chain}) producing BA is then received by combining eqs 4 and 5:

$$\phi_{\text{chain}} = \sum_{j=0}^{n}\phi_j + \sum_{k=0}^{n}\phi_k' = \phi_T \tau_T k_H[\text{IPA}]P\alpha(1 + \gamma + (\beta\gamma\alpha) + \gamma(\beta\gamma\alpha) + (\beta\gamma\alpha)^2 + \gamma(\beta\gamma\alpha)^2 + \ldots + (\beta\gamma\alpha)^n + \gamma(\beta\gamma\alpha)^n) \tag{6}$$

and the total quantum yield Φ_{BA} can be expressed as:

$$\Phi_{\text{BA}} = \phi_t + \phi_{\text{chain}} = \phi_T \tau_T k_H[\text{IPA}]P(1 + \alpha\gamma + \alpha\beta\gamma\alpha + \alpha(\beta\gamma\alpha)^2 + \gamma\alpha(\beta\gamma\alpha)^2 + \ldots + \alpha(\beta\gamma\alpha)^n + \gamma\alpha(\beta\gamma\alpha)^n) \tag{7}$$

where ϕ_T is the quantum yield of the triplet formation, τ_T is the triplet lifetime, k_H is the rate constant of the hydrogen abstraction, P is the fraction of $^•$EH producing BA that does not undergo back hydrogen transfer, α is the probability equal to the ratio $k_2/(k_2 + k_{\text{ter}})$ (β and γ are expressed correspondingly), and n is the number of cycles of the chain process.

Banerjee and Falvey reported the k_H value for triplet-excited **10** in the presence of IPA to be 8.8×10^6 L mol^{-1} s^{-1} and the following reaction of $^•$EH via **11** with the rate constant near the diffusion limit ($k_1 = 7 \times 10^9$ L mol^{-1} s^{-1}), consistent with a radical−radical termination.[24] While the termination process of $^•$EH is a bimolecular reaction, thus dependent on many variables such as viscosity, its unimolecular decomposition to BA (α) is not. The Hammond steady-state analysis[43,44] of the initial dependence of Φ_{BA} on the IPA concentration (Figure 1) is based on eq $1/\Phi_{\text{BA}} = k_d/\phi_T\alpha k_H[\text{IPA}]$, where ϕ_T is the quantum yield for the triplet formation (in simple phenyl and substituted phenyl ketones, the intersystem crossing quantum yield is unity[45]), and the other constants and variables are defined in Scheme 4. The initial part of a plot of $1/\Phi_R$ versus 1/[IPA] provided a straight line with a slope equal to $k_d/\alpha k_H$. For a unimolecular decay of acetophenone $1/k_d = \tau = 2.3 \times 10^{-7}$ s,[46] the calculated value of $\alpha k_H = 6.1 \times 10^7$ s^{-1} ($\alpha < 1$) is

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well in the order of k_H measured by Falvey. The second part of the dependence in Figure 1 at higher IPA concentrations must reflect a complex interplay among the rate constants of photoinduced and ground-state reduction of the ester.

Tanner and co-workers showed that one-electron reduction of **10** causes rapid elimination of BA from $[PhCOCH_2OCOPh]^{\bullet -}$ with the rate constant in the order of 10^8 s^{-1};[47] likewise, elimination of BA from $^{\bullet}EH$ (k_2) could be rapid. The rate constant k_3 of the H-atom transfer is expected to be high. The H-atom exchange rate constants (k_4) are known to be in the order of 10^3 to 10^4 L mol^{-1} s^{-1}, and the equilibrium constants (k_4/k_{-4}) of the exchange process were reported to be on the order of 10−100.[41] If only recombination production of BA occurs, 100% is still an upper limit of the quantum yield (eq 1). If k_2 becomes dominant (eq 2), the subsequent reactions trigger the chain propagation (eqs 3 and 4). Such an event will accompany formation of three chain carriers in the first cycle (two ketyl radicals $IPA^{\bullet}$ and one $ArC(=O)CH_2^{\bullet}$ radical) ($\beta\gamma\alpha$), and each of them is subsequently responsible for further BA production. The partitioning between the initial processes then depends principally on the diffusion efficiency of the two radicals, $EH^{\bullet}$ and $IPA^{\bullet}$, from the solvent cage. Any increase in the IPA concentration will of course affect the efficiency of the H-atom exchange (β). An analysis of eq 7 indicates that the total quantum yield Φ_{BA} is dependent on the term $\phi_T\tau_T k_H[IPA]P$ and on its multiples by the expressions containing α, β, and γ. The α efficiency then plays the most important role in the sum (7) and defines principally the extent of the process.

The quantum yield variations, when three different aliphatic alcohols were used, correlated generally with their hydrogen atom donating ability (Table 1). The Φ values increased in the order of MeOH < EtOH < IPA as the bond dissociation energies decreased from 96 to 91 kcal mol^{-1}, apparently affecting the efficiency of an endothermic hydrogen transfer from the excited ester (E_T values of acetophenone and the 2-, 3-, and 4-acetylpyridines are 74, 70, 71, and 69 kcal mol^{-1}, respectively[48]). The correlation, however, is not straightforward since diffusion as well as abilities of the corresponding radical involved in a radical coupling with $EH^{\bullet}$ are different. Despite the fact that the radical formed from methanol will be more electron deficient than that formed from IPA, the radical coupling must still be a diffusion-limited step.

Although this investigation suggested that the reduction of all esters basically involved hydrogen transfer steps, it can be argued that an electron-transfer mechanism may participate. An enhancement of the ester photolysis quantum yields in the presence of pyridine as a basic additive was shown in Table 1 and Figure 4. The Φ value increased by a factor of ~4 in the case of **10** in IPA, whereas it increased by a factor of 2.5 in the case of **9b** in ethanol. Interestingly, this effect was insignificant for other systems. Bases such as pyridine can interact with the OH group of ketyl radicals via a hydrogen bond. There are two types of ketyl radicals in our system (those of the reduced ketone and those formed by the hydrogen abstraction from alcohols), and the reactivity of both should be affected similarly. A reducing ability of a 1-hydroxy radical can be enhanced when oxidation of the radical is accompanied by deprotonation of the OH group: a proton-coupled electron transfer. It was estimated that the reducing potential of the ketyl radical can increase by ~0.8 V if the electron transfer is coupled with proton transfer to a base such as lutidine.[49] Since the oxidation potentials of $^{\bullet}EH$ and $^{\bullet}IPA$ species will change correspondingly, there must be an increasing probability of the electron-transfer participation in the mechanism. In addition, a hydrogen-bonded complex between $^{\bullet}EH$ and pyridine could facilitate elimination of benzoic acid, thus enhancing the rate constant k_2 at the expense of the termination coupling with $^{\bullet}IPA$. The fact that such an effect was observed in reactions in which a chain propagation dominated advocates the latter concept. We should also note that esters **9a**−**c** contain a pyridine moiety with the same basic site as pyridine.

There is a significant difference in the quantum yields of the photoreduction of esters **9b** and **10** in the presence of H-atom donors, exhibiting signs of a chain propagation, compared to that of **9a** and **9c** (Table 1). The nitrogen atom in the ortho or para positions, in contrast to that of meta, is in a direct conjugation with the carbonyl group. It was shown that the attack of a ketyl radical, such as $^{\bullet}IPA$, to the phenyl ring of a ketyl radical formed from 3-benzoylpyridine is most efficient to the positions ortho and para in respect to the nitrogen atom.[26] Various substituted phenacyl esters were used to study substituent effects on both the redox potential of the phenacyl group and the rate of carboxylate anion elimination.[50,51] It was concluded that there was a tradeoff between the ease of reduction and the efficiency of the elimination. The reduction of a ground-state aromatic ketone by aliphatic 1-hydroxyradical is a favorable reaction. The reactivity of substituted aromatic ketones to 1-hydroxyradicals produced from secondary alcohol correlates with the σ constants, giving $\rho = +1.59$.[52] The higher stability of radicals possessing electron-withdrawing substituents can be explained by captodative stabilization of the ketyl radical site. Additionally, excited 2-acyl-substituted ketones can abstract a hydrogen atom either by oxygen or by nitrogen, and a 1-hydropyridinyl radical can rearrange to a ketyl radical.[53−57] The emissive CIDEP spectrum from the photolysis of 4-acetylpyridine in IPA proved that the hydrogen atom is abstracted by the carbonyl group in the T_1 (mainly n,π*) state.[33] 1-Hydropyridyl radical was also observed, and it was likely produced by secondary reduction of ground-state 4-acetylpyridine by the 2-hydroxy-2-propyl radical. Thus, it is obvious that the position of the nitrogen atom in **9a**−**c** can directly affect the rate constant of BA elimination from $^{\bullet}EH$ (k_2) as well as that of the reduction of the ground-state ester (k_4). While a direct conjugation of the nitrogen atom with the carbonyl group will decrease the efficiency of BA release in the former case, a stabilization of a ketyl radical site of $^{\bullet}EH$ will enhance the ester reduction.

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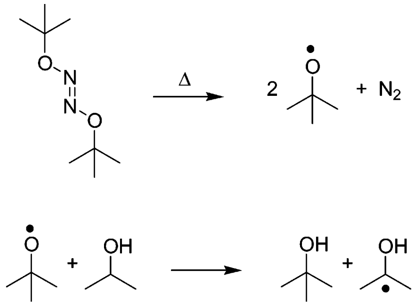
TABLE 3. Maximum Quantum Yields (Φ_{BA}) of Benzoic Acid Formation from Phenacyl Benzoate (10) and PyA Benzoates (9a−c) ($c = 6 \times 10^{-3}$ mol L^{-1})

ester	Φ_{BA}[a]	Φ_{BA}[b]
9a	1.0	0.5
9b	0.6 (2.1[c])	0.5
9c	1.1	0.8
10	0.7	0.7

[a] In the presence of benzophenone ($c = 6 \times 10^{-3}$ mol L^{-1}) in IPA; irradiated at 366 nm. [b] In an acetone/IPA mixture (1:1); irradiated at 313 nm. [c] Corrected on LAT formation.

SCHEME 6



Several experiments in which the ketyl radicals •IPA were generated by reaction of an external initiator with alcohol were performed to clarify the mechanism of ester photoreduction. The methods circumvented a direct self-triggering photochemical excitation of an ester and afforded information about the reactions involved in the propagation steps. The reduction of esters was induced by two different methods: (a) by a selective excitation from a ketone (acetone or benzophenone) present in a large excess and (b) by thermal decomposition of di-*tert*-butyl hyponitrite as a radical reaction initiator.

Photoreduction of Esters in the Presence of Propan-2-ol and an Excess of a Ketone. An ester (**9a−c** or **10**) and benzophenone (the concentration of both was 6×10^{-3} mol L^{-1}) in propan-2-ol were irradiated at 366 nm, where benzophenone absorbs ∼90% of the incident radiation. The excited benzophenone then reacts with IPA, providing two ketyl radicals ($Ph_2C^\bullet{-}OH$ and •IPA), both capable of reducing the ground-state esters (a competing reduction of ground-state benzophenone by •IPA may, however, decrease its concentration). It is highly probable that benzophenone is a propagation retarder by converting •IPA radicals into thermodynamically more stable $Ph_2C^\bullet{-}OH$ radicals. In the second experiment, solutions of esters **9a−c** and **10** in an acetone/2-propanol (1:1) mixture were irradiated at 313 nm, where the optical density of the solution was above 4. Thus, most of the incident light was absorbed by acetone and prevailing photochemical reaction was the formation of two ketyl radicals (•IPA) by the hydrogen atom abstraction from IPA by excited acetone. Unlike the previous arrangement, these experimental conditions assured that a reductive cleavage of esters was triggered by the same type of ketyl radicals. The quantum yields of the BA formation (Table 3) are generally lower than those obtained by direct excitation of the esters in both cases. The fact that the quantum yields are below 1 suggests the absence of chain propagation steps, except, interestingly, in the case of **9b** in the presence of benzophenone, in which $\Phi_{BA} = 2.1$, corrected on a LAT formation, was found.

Photoreduction of Esters in the Presence of Alcohols Initiated by Thermal Decomposition of a Radical Reaction Initiator. A number of chemical probes have been designed to differentiate between a single-step and a multistep reduction.[58,59] For our work, 1-hydroxy radicals can be easily generated by thermal decomposition of di-*tert*-butyl hyponitrite (DBH) in the presence of alcohols. The initiator cleaves into two *tert*-butoxy radicals that are able to abstract the hydrogen atom adjacent to the OH group of an alcohol (Scheme 6). Heating an alcohol solution of PA (**10**) or PyA (**9a−c**) benzoate containing DBH yielded acetophenone/acetylpyridine and benzoic acid, thus the same products as those obtained from photochemical experiments. An anticipated mechanism involved reduction of the ground-state ester by 1-hydroxy radicals and subsequent elimination of benzoic acid, the same steps designated by the efficiencies in the order of γ, α, and β in Scheme 4. Thus, a solution of the corresponding ester and propan-2-ol (IPA) in acetonitrile in the presence of an initiator (DBH) was heated at 60 °C. The kinetic chain length of the transformations was calculated as the R_p/R_i ratio (the rate of propagation calculated from the experimental data to the rate of initiation), where $R_i = fk[DBH]_0e^{-kt}$, f is the efficiency of chain initiation by DBH ($f = 0.6$; vide infra), $k = 2.1475 \times 10^{-4}$ s^{-1} at 60 °C,[60] and R_p was calculated from the experimental data (vide infra). Representative results are shown in Figures 7 and 8, and the maximum values of the kinetic chain length for all esters are listed in Table 4.

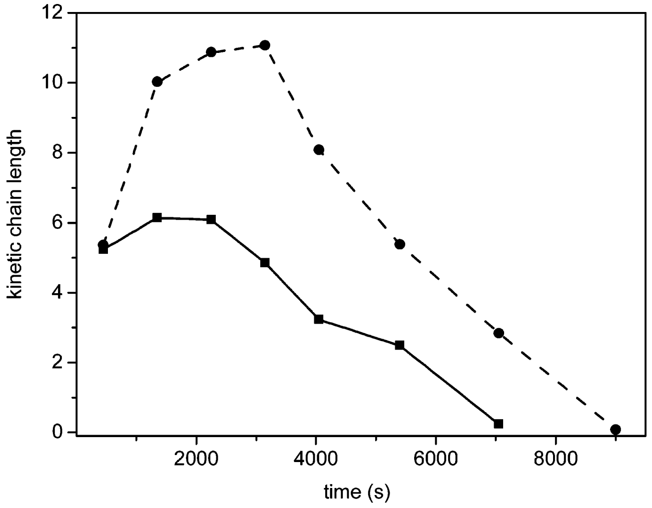


FIGURE 7. Calculated kinetic chain lengths in the course of the heating of **10** ($c = 0.05$ mol L^{-1}) in the presence of IPA ($c = 10$ mol L^{-1}) and DBH at 60 °C (solid line), and in the presence of IPA ($c = 10$ mol L^{-1}), pyridine ($c = 0.4$ mol L^{-1}), and DBH at 60 °C (dashed line).

A time dependence of the calculated kinetic chain length confirmed that the reduction of **10** and **9b**, although under different experimental conditions (i.e., the concentration of phenacyl ester was higher, acetonitrile was used as a cosolvent, and the reactions were carried out at 60 °C), proceeded with a chain propagation, while no or only insignificant chain character of the product formation in the reactions of **9a** and **9c** was observed. An elevated temperature unquestionably enhanced the rate of elimination of benzoic acid from •EH compared to photochemical experiments at 20 °C. A decrease of the kinetic chain length in time (the reaction conversion in the experiments

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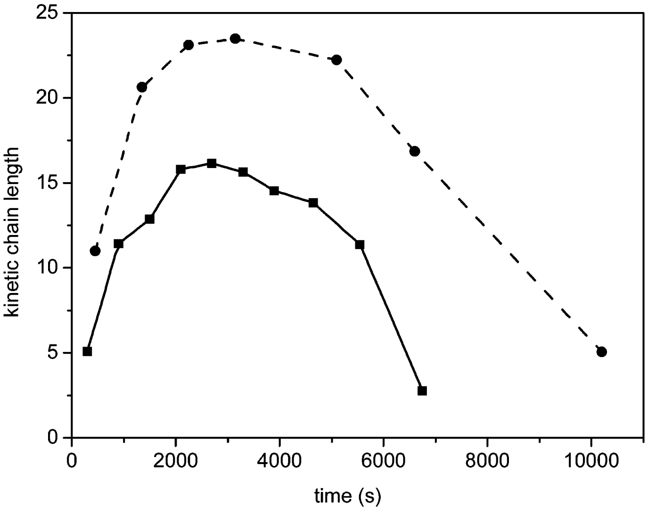

FIGURE 8. Calculated kinetic chain lengths in the course of the heating of **9b** ($c = 0.05$ mol L^{-1}) in the presence of IPA ($c = 10$ mol L^{-1}) and DBH at 60 °C (solid line), and in the presence of IPA ($c = 10$ mol L^{-1}), pyridine ($c = 0.4$ mol L^{-1}), and DBH at 60 °C (dashed line).

TABLE 4. Maximum Kinetic Chain Lengths Found in the Presence of IPA

ester	maximum kinetic chain length
10	6 (11[a])
9a	1.5
9b	16 (23[a])
9c	1

[a] 0.4 mol L^{-1} pyridine addition.

usually reached 60%) can be explained by lowering the concentration of the starting ester, thus lowering the reduction efficiency. The pyridine addition did affect the kinetic chain length values, but not to such an extent as the quantum yields of photoinitiated reductions.

Conclusions

The photoinitiated reduction of phenacyl and pyridacyl esters (**9a**−**c**, **10**) by aliphatic alcohols has been shown to be a kinetically viable process with the chain propagation steps only in the case of two (**9b** and **10**) of four derivatives studied. The elimination of benzoic acid from the esters occurs apparently from two types of the intermediates, ketyl radical $^{\bullet}$EH or radical coupling product **11**. Our results indicate that the partitioning between those two reactions is very sensitive to the chromophore properties, such as a position of the nitrogen atom in the pyridacyl moiety or electron acceptor abilities of the group, in addition to the efficiency of the hydrogen abstraction step controlled by the ketone triplet excitation energies and the C−H bond energies of the alcohols. While formation of the ketyl radical opens the possibility for a chain process, the coupling represents a radical reaction termination. Although two different reaction mechanisms involving hydrogen or electron transfer by the ketyl radicals were considered, the driving force of the ester reduction by the latter mechanism was excluded on the basis of cyclic voltametry measurements. The magnitude of a radical chain process is then dependent on consecutive steps that produce free radicals capable of a subsequent ester reduction. The quantum yields of the photoreduction were found to be diminished by formation of relatively long-lived light absorbing transients, byproducts most likely obtained by secondary photochemical reactions. In addition, it was demonstrated that basic additives such as pyridine increased the efficiency of the photoreduction, which was attributed to an enhanced elimination of BA from the ketyl radical intermediate. The abilities of two esters, **9b** and **10**, to undergo a chain photoreduction was well supported by finding a large kinetic chain length (in the order of 10) of their reduction initiated by free radicals generated thermally.

Since elimination of a carboxylic acid from the phenacyl and pyridacyl chromophores was found to occur with very high chemical and quantum yields, they are pronounced to be useful photoremovable protecting groups in applications when higher concentrations of the hydrogen donors are not destructive for a reaction system or experimentally impractical.

Experimental Section

Materials and Methods. NMR spectra were recorded on a 300 MHz spectrometer. ^{1}H and ^{13}C NMR data were measured in $CDCl_3$ with tetramethylsilane as an internal standard. Gas chromatography was performed on a gas chromatograph equipped with a 15-m column (5% diphenyldimethylsiloxane). Mass spectra were recorded on a spectrometer in positive mode with EI. UV spectra were obtained with matched 1.0-cm quartz cells. Cyclic voltametry measurements were carried out on an instrument using a three-electrode cell with Pt or Au working electrodes, a Pt counter electrode, and an Ag wire as a reference electrode. All CV measurements were performed in 0.1 mol L^{-1} solution of Bu_4NBF_4 in acetonitrile.

All solvents were purified by distillation before use. Pyridine (p.a.) was dried with KOH and distilled before use. Acetylpyridines (>97%) were purchased and used as received. Di-*tert*-butyl hyponitrite (^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 18 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.0, 81.4) was prepared from *tert*-butyl bromide (>97%) and sodium hyponitrite (hydrate) according to Mendenhall's procedure.[61]

The pyridacyl esters (**9a**−**c**) were prepared from the corresponding acetylpyridines according to the literature.[62] In a typical procedure, bromine (2.65 g, 16.6 mmol) was added to a solution of acetylpyridine (2.01 g, 16.6 mmol) in carbon tetrachloride (80 mL). The resulting mixture was then gently refluxed under argon for 1 h. The orange precipitate of α-bromoacetylpyridine hydrobromide was filtered off, washed several times with diethyl ether, and dried at ambient temperature. Benzoic acid (2.03 g, 16.6 mmol) and triethylamine (13.43 g, 133 mmol) were then dissolved in dry acetonitrile (100 mL), a suspension of α-bromoacetylpyridine hydrobromide in acetonitrile (100 mL) was added while stirring, and the mixture was stirred for 2 h. Acetonitrile was removed under reduced pressure, water (50 mL) was added, and the mixture was extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed successively with 5% aqueous Na_2CO_3 (50 mL), water, and brine and dried with $MgSO_4$. The solvent was removed under reduced pressure, and a crude ester was purified using silica gel flash chromatography with ethyl acetate/hexane mixtures as mobile phases.

2-Pyridacyl Benzoate (9a):[63] Overall yield 15%; white solid; mp 105.6−106.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 2H), 7.46−7.63 (m, 4H), 7.88 (dd, $J_1 = 7.6$ Hz, 1H), 8.07 (d, $J = 7.6$ Hz, 1H), 8.17(d, $J = 7.3$ Hz, 2H), 8.71 (d, $J = 4.6$ Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 67.3, 121.9, 128.0, 128.4, 129.8, 129.9, 133.2, 137.1, 149.1, 151.7, 166.2, 193.3. MS (EI, 70 eV) *m/z* 242, 241 (M^+), 182, 136, 105, 78, 77.

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3-Pyridacyl Benzoate (9b): Overall yield 32%; white solid; mp 105.2−107.2 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.49 (s, 2H), 7.31−7.39 (m, 3H), 7.50 (t, $J = 7.3$ Hz, 1H), 8.02 (d, $J = 8.3$ Hz, 2H), 8.13 (d, $J = 8.0$ Hz, 1H), 8.71 (d, $J = 4.6$ Hz, 1H), 9.10 (s, 1H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 66.3, 123.8, 129.1, 129.6, 129.8 (overlap of two peaks), 133.4, 135.2, 149.1, 154.1, 165.8, 191.5. MS (EI, 70 eV) *m*/*z* 241 (M$^+$), 213, 183, 136, 119, 106, 105, 78, 77.

4-Pyridacyl Benzoate (9c): Overall yield 35%; white solid; mp 118.8−119.6 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.45 (s, 2H), 7.36 (dd, $J_1 = 7.6$ Hz, $J_2 = 7.3$ Hz, 2H), 7.49 (t, $J = 7.3$ Hz, 1H), 7.62 (d, $J = 5.8$ Hz, 2H), 8.01 (d, $J = 7.6$ Hz, 2H), 8.71 (d, $J = 5.8$ Hz, 2H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 66.4, 120.6, 128.4, 129.0, 129.8, 133.5, 140.0, 151.0, 165.7, 192.2. MS (EI, 70 eV) *m*/*z* 242, 241 (M$^+$), 213, 211, 183, 135, 119, 106, 105, 78, 77.

The phenacyl benzoate **10** was prepared from α-bromoacetophenone and benzoic acid according to the literature.[50]

Quantum Yield Measurements. The experiments were accomplished on an optical bench consisting of a high-pressure 200 W Hg lamp, a $^1/_8$-m monochromator with grating 200−1600 nm set to 313 or 366 nm, and a 1-cm quartz cell containing the sample solution (degassed by bubbling with argon). The light intensity was monitored by a Si photodiode detector (UV enhanced) with a multifunction optical power meter.

Since quantum yields depended on the ester concentration, the concentration of all solutions was adjusted to approximately 6×10^{-3} mol L^{-1}, if not stated otherwise. A solution of valerophenone (0.025 mol L^{-1}) in hexane was used as an actinometer ($\Phi = 0.30$ for acetophenone formation[64]). The irradiated samples were analyzed using gas chromatography; a 5%-diphenyldimethylsiloxane chromatographic column was found most suitable for the determination of BA concentrations. Hexadecane was used as an internal standard. The relative standard deviation for triplicate samples was found below 10% in all measurements.

Determination of the Chain Length. The chain length is a ratio of the rate of propagation (R_p), calculated from the experimental data, to the rate of initiation (R_i). Concentrations of benzoic acid released were followed during the course of the reaction and then plotted as a function of time. A linear interpolation between two neighboring data points was performed, and the slope of the resulting line was taken as a derivative at the midpoint. Thus, $R_d = ([\mathrm{BA}]_{t2} - [\mathrm{BA}]_{t1})/\Delta t$, where $[\mathrm{BA}]_{t1}$ and $[\mathrm{BA}]_{t2}$ are the BA concentrations at the corresponding reaction time ($\Delta t = (t_2 - t_1)/2$). For di-*tert*-butyl hyponitrite (DBH), it was possible to calculate R_i from the literature data according to the equation $R_i = fk[\mathrm{DBH}]_0 e^{-kt}$, where $k = 2.1475 \times 10^{-4}$ s^{-1} at 60 °C[60] and f is defined below. Thermal kinetic studies were performed with a solution of the corresponding ester (0.05 mol L^{-1}) in a solution of propan-2-ol (10 mol L^{-1}) in acetonitrile. The presence of this solvent was essential to enhance the solubility of an ester in alcohol. The reactions were initiated by 20 mol % of the initiator. Hexadecane was added to the solution as an internal standard. The solution was bubbled with argon to remove oxygen that significantly slows down the reaction process. The mixture was kept at 60 ± 0.5 °C for several hours. Sample aliquots were withdrawn periodically from the reactor and subsequently analyzed by GC.

Determination of the Factor *f*. The reduction of acetophenone (AP) by propan-2-ol initiated by di-*tert*-butyl hyponitrite was used to estimate the *f* value. A solution of acetophenone (0.05 mol L^{-1}) and IPA (10 mol L^{-1}) in acetonitrile, containing approximately 20 mol % of the initiator, was purged with argon and then maintained at 60 °C for at least 10 h. The GC analysis revealed the consumed amount of acetophenone. Only reduction products of AP were detected; there was no observable amount of 2,3-dimethylbutan-2,3-diol (a coupling product between two aliphatic IPA-derived ketyl radicals). The factor *f* was calculated using the equation $f = \Delta[\mathrm{AP}]/[\mathrm{initiator}]$, and it was found to be equal to 0.6. The value reported in the literature, $f = 0.8$,[65] was calculated for neat alcohol as a solvent only.

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