Comparison of photoenolization and alcohol release from alkyl-substituted benzoyl benzoic esters

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Abstract: Photolysis of 1B in argon-saturated solutions yields 4B and releases methanol. Laser flash photolysis of 1B shows formation of biradical 2B, which has a lifetime of ~50 ns and a λ_{max} at 330 nm. Biradical 2B undergoes an intersystem crossing to form photoenols E-3B and Z-3B with a λ_{max} at 390 nm. Laser flash photolysis shows that the lifetimes of E-3B and Z-3B are affected by the solvent. Density functional theory calculations demonstrate that the transition-state barrier for a 1,5-H atom shift from Z-3B to regenerate 1B is affected by the *ortho*-alkyl substituents, whereas the stereoelectronics of the alkyl substituent affect the transition-state barrier of E-3B as it undergoes electrocyclic ring closure to form 4B. The photoreactivity of 1B was compared with its analogous methyl and isopropyl derivatives 1A and 1C, respectively, to better estimate the effect of the alkyl substituent on reactivity.

Key words: photoremovable protecting groups, photoenols, laser flash photolysis, 1,5 H-atom shift, electrocyclic ring closure, intramolecular lactonization.

Résumé : La photolyse de **1B** dans des solutions saturées en argon conduit à la formation de **4B** et à la libération de méthanol. La photolyse éclair au laser de **1B** conduit à la formation du biradical **2B** dont le temps de vie est d'environ 50 ns et un λ_{max} à 330 nm. Le biradical **2B** subit une transformation intersystème avec formation des photoénols **E-3B** et **Z-3B** avec un λ_{max} à 390 nm. La photolyse éclair au laser montre que les temps de vie des isomères **E-3B** et **Z-3B** sont affectés par le solvant. Des calculs selon la théorie de la fonctionnelle de la densité démontre que la barrière de l'état de transition pour un déplacement 1,5 d'atome d'hydrogène à partir de **Z-3B** et conduisant à la régénération du produit **1B** est affectée par les substituants *ortho*-alkyles alors que les effets stéréoélectroniques du substituant alkyle affectent la barrière de l'état de transition de l'isomère **E-3B** lorsqu'il subit une fermeture électrocyclique de cycle conduisant à la formation de **4B**. Dans le but de pouvoir mieux évaluer l'effet d'un substituant alkyle sur la réactivité, on a comparé la photoréactivité de **1B** à celles de ses analogues, les dérivés méthyle (**1A**) et isopropyle (**1C**).

Mots-clés : groupes protecteurs photolabiles, photoénols, photolyse éclair au laser, déplacement 1,5 d'un atome d'hydrogène, fermeture électrocyclique de cycle, lactonisation intramoléculaire.

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Introduction

In the past few decades, various systems have been designed for use as photoremovable protecting groups, phototriggers, and photocaging groups.^{1–7} Photoremovable protecting groups have potential use in a wide variety of applications, such as drug and gene delivery, release of fragrances in household products, and as an aid in multistep synthesis. Furthermore, photoremovable protecting groups have been used to release bioactive compounds in living tissue and thus make it possible to study physiological events such as enzyme activity, muscle contraction by ATP hydrolysis, and ion channel permeability. Because they have potential use in such a wide variety of applications, photoremovable protecting groups with diverse physical properties are desirable. Furthermore, detailed knowledge of the photorelease mechanism makes it easier to determine the best-suited photoremovable protecting groups for each application.

We have shown that ester **1C** releases its alcohol moiety upon irradiation, and that the release is independent of the reaction medium.^{8,9} The release from **1C** is initiated by intramolecular H-atom abstraction by the triplet ketone in **1** to form 1,4-triplet biradical **2C**, which intersystem crosses to E and Z-photoenols **3C**. **Z-3C** is short-lived because it

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decays by a 1,5-H shift to regenerate **1C**. The longer lived **E-3C** undergoes electrocyclic ring closure and intramolecular lactonization to release the alcohol moiety. In comparison, **1A**, which has an *ortho*-methyl group, fails to release its alcohol moiety upon irradiation (Scheme 1), even though transient spectroscopy shows that the major reactivity of **1A** involves intramolecular H-atom abstraction to form **Z-3A** and **E-3A**.¹⁰ It was concluded that the short lifetime of **E-3A** prevented it from undergoing intramolecular lactonization and releasing its alcohol.

In this paper, we compare the photoreactivities of methyl, ethyl, and isopropyl benzoyl benzoyl benzoic esters **1A**, **1B**, and **1C**, respectively, in argon- or nitrogen-saturated solutions by performing product studies, transient absorption spectroscopy, and theoretical calculations. The lifetimes of **Z-3** and **E-3** are affected by intramolecular hydrogen bonding, the steric demand, and the stereoelectronic properties of the *ortho*-alkyl groups. The yields of photorelease from **1A**, **1B**, and **1C** depend on the yields of **E-3A**, **3B**, and **3C** and, more importantly, on their lifetimes.

Experiments

Laser flash photolysis

Laser flash apparatus

Laser flash photolysis studies were performed using Excimer¹¹ or YAG lasers.^{12,13} Rate constants were determined by fitting an average of three to eight kinetic traces. Transient absorption spectra were obtained by plotting average absorbance values collected from decays at 10 or 20 nm intervals between 300 and 600 nm.

Sample preparation for laser flash photolysis

Stock solutions of **1A**, **1B**, and **1C** in methanol and acetonitrile were prepared with spectroscopic grade solvents, such that the solutions had absorptions between 0.6 and 0.8 at 266 nm. Stock solutions of **1A**, **1B**, and **1C** in spectroscopic grade benzene and acetonitrile were prepared so that the solutions had absorptions between 0.8 and 0.6 at 308 nm. Typically, about 2 mL of the solutions was placed in 7 mm \times 7 mm Suprasil quartz cells capped with prewashed septa. These solutions were purged with nitrogen or argon for 10 min. The lifetimes of **E-3C** were measured as described earlier.¹³

Preparation of 1B

To a stirred solution of phthalic anhydride (2.29 g, 15 mmol) in a 1:1 anhydrous diethyl ether-toluene mixture was added 2-ethylphenyl magnesium bromide, prepared from 2-bromoethylbenzene (3.0 g, 16 mmol) and magnesium turnings (500 mg, 17.8 mmol) in anhydrous diethyl ether.¹⁴ The resulting mixture was refluxed for 12 h and poured onto ice-hydrochloric acid, and the resulting mixture was extracted with diethyl ether (3 \times 30 mL). The mixture was washed with a 10% NaHCO3 solution, and the aqueous phase was acidified with 10% aq HCl and extracted with diethyl ether (3 \times 30 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated under vacuum to yield 2-(2'-ethylbenzovl)benzoic acid (2.2 g, 8.5 mmol, 56%). Without further purification, the material was dissolved in methanol, concd H₂SO₄ (5 mL) was added, and the mixture was refluxed overnight (16 h). The resulting mixture was cooled to room temperature, neutralized with aq NaHCO₃, and extracted with diethyl ether (3 \times 40 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated under vacuum to yield a yellow residue. The residue was purified by silica gel column chromatography to yield methyl 2-(2'-ethylbenzoyl)benzoic acid ester 1B as a pale yellow oil (2.2 g, 8.2 mmol, 51% yield).

1B: IR (neat, cm⁻¹): 2954, 1725, 1670, 1287, 929, 768. ¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.92 (m, 1H), 7.38–7.62 (m, 5H), 7.13–7.24 (m, 2H), 3.64 (s, 3H), 3.05 (q, *J* = 8 Hz, 2H) 1.34 (t, *J* = 8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, ppm) δ : 198.4, 167.3, 145.8, 142.2, 136.4, 131.9, 131.7, 131.4, 130.4, 130.2, 130.1, 129.7, 128.8, 126.8, 52.6, 27.0, 15.7. HRMS (ESI-MS) *m*/*z* calcd for C₁₇H₁₆O₃Na [M + Na]⁺: 291.0997; found: 291.0983.

Photolysis of 1B in argon-saturated 2-propanol

Ester **1B** (71 mg, 0.27 mmol) was placed in a Pyrex tube and dissolved in 2-propanol (7 mL), and the resulting solution was purged with argon at room temperature for 15 min and sealed with a rubber septum. The solution was irradiated using a 450 W medium pressure mercury arc lamp immersed in a Pyrex well for 28 h at room temperature. The reaction was monitored through thin layer chromatography (10% ethyl acetate in hexane). After the majority of the starting material disappeared, the solvent was removed under vacuum, and the yellow residue was purified with a silica gel column using a 7:93 ethyl acetate – hexane mixture to yield **4B** as a yellow liquid (35 mg, 15 mmol, 56% yield) and recovered starting material (25 mg, 0.09 mmol, 35% recovery).

4B: IR (neat, cm⁻¹): 2924, 1771, 1465, 934. ¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.03–7.17 (m, 2H), 7.31–7.64 (m, 5H), 7.98–8.00 (m, 1H), 4.31 (q, J = 8 Hz, 1H), 1.28 (d, J = 8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, ppm) δ : 169.8, 146.9, 141.9, 133.5, 131.1, 129.4, 128.7, 126.7, 125.6, 123.4, 123.4, 122.4, 90.3, 50.9, 14.7. HRMS (ESI-

Scheme 2. Photolysis of 1A, 1B, and 1C in argon-saturated benzene.



MS) m/z calcd for $C_{17}H_{16}O_2$ [M + 1]: 237.0916; found: 237.0904.

Quantum yields

Quantum yields for the photolysis of **1B** were determined both for depletion of the starting material and for formation of product **4B**. 2-Propanol was dried over molecular sieves and distilled prior to use. The mole to area ratio response of the GC traces was calibrated for compounds **1B** and **4B** and valerophenone in 2-propanol, which was the actinometer.¹⁵ Irradiation of 0.1 mol/L argon- and nitrogen-saturated 2propanol solutions of **1B** on a merry-go-round apparatus using a 450 W medium pressure mercury arc lamp and potassium chromate filter to isolate the 313 nm line was performed to about 10% conversion. At least three replicates of each sample were irradiated and analyzed with a GC equipped with an FID detector. The results from all three replicates were averaged.

Theoretical calculations

Density functional theory (DFT) calculations were performed using Gaussian03 at the B3LYP level of theory and with the 6-31+G(d) basis set.^{16,17} All transition states were confirmed to have one imaginary vibrational frequency by the analytical determination of the second derivative of the energy with respect to the internal coordinates. Intrinsic reaction coordinate¹⁸ calculations were used to verify that the transition states corresponded to the correct reactant and products.^{19,20} Vertical UV absorption spectra were calculated using time-dependent density functional theory (TD-DFT).²¹⁻²⁵ The effect of solvation was calculated using the self-consistent reaction field (SCRF) method with the integral equation formalism polarization continuum model (IEFPCM) with methanol and acetonitrile as the solvents.26-30

Results and discussion

Product studies

Photolysis of 1B in an argon-saturated solution results in lactone 4B, which is similar to the photoreactivity of 1C (Scheme 2). Irradiation of 1B in solvents such as benzene, toluene, chloroform, and 2-propanol yields 4B in compara-







 Table 1. Quantum yields for depletion of 1 and formation of 4.

Quantum yield for depletion of 1		Quantum yield for formation of 4		
$1\mathbf{A}^{a}$	0.030±0.003	4 A	0	
1B	0.09 ± 0.01	4B	0.07 ± 0.01	
$1C^b$	0.17 ± 0.01	4 C	0.14 ± 0.01	
^a See ref.	10.			

^bSee ref. 8.

ble yields, indicating that the photorelease is not strongly affected by the solvent (Fig. 1). In contrast, we have reported that photolysis of **1A** yields no products in solvents such as benzene and chloroform, which do not have easily abstractable H atoms. However, in solvents with abstractable H atoms, **1A** yields **5** (Scheme 3), presumably from intermolecular H-atom abstraction from the solvent.¹⁰

Quantum yields

The quantum yields for the depletion of 1B and the formation of 4B in 2-propanol are listed in Table 1. The quantum yields for 1C, which have been published previously, are slightly higher than those for 1B and are listed in Table 1 for comparison.

Calculations

To better understand why 1A, 1B, and 1C react differently, we calculated the stationary points on their energy surfaces. We optimized the gas-phase structures of 1A, 1B, and 1C and their respective first triplet excited states of the ketone. The C=O bond in the T_K of 1 is elongated to 1.311 Å compared with 1.225 Å in the S₀. The progression of the C–O bond stretch fits well with the T_K of 1 having an (n,π^*) configuration.^{31–34} The calculated energies of the T_K s of 1A, 1B, and 1C are ~8 kcal/mol (1 cal = 4.184 J) lower than the measured value for the analogous benzophenone. However, we have previously shown that DFT calculations

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Table 2.	Intramolecular	hydrogen	bonds	in	Z-3	and
E-3 .						

	Bond vibrational frequency	Bond length
Compound	O-H (cm ⁻¹)	C=O H–O– (Å)
Z-3A	3479	1.783
Z-3B	3480	1.782
Z-3C	3459	1.740
E-3A	3506	1.800
E-3B	3504	1.7821
E-3C	3490	1.756

underestimate the energy of triplet ketones with an (n,π^{\ast}) configuration. 35

We optimized the structures of biradicals 2A, 2B, and 2C and found that their lowest energy conformers have intramolecular hydrogen bonding between the O–H group and the C=O ester group. The hydrogen-bonded conformers are ~5– 8 kcal/mol lower in energy than those that do not have intramolecular hydrogen bonding. The calculated O–H and C=O stretches in the hydrogen-bonded conformer of 2A are located at 2996 and 1662 cm⁻¹, respectively, but the corresponding stretches are at 3742 and 1768 cm⁻¹ in a conformer of 2A that does not undergo intramolecular hydrogen bonding. Thus, the calculated IR spectra confirm the intramolecular hydrogen bonding in the lowest energy conformers of 2A, 2B, and 2C.

The structures of **Z-3** and **E-3** with intramolecular hydrogen bonding were also optimized. Enols **Z-3** and **E-3** are between 35 and 40 kcal/mol higher in energy than corresponding ketones **1A**, **1B**, and **1C**. Furthermore, **Z-3** is between 1 and 3 kcal/mol more stable than the corresponding **E-3** molecule. The intramolecular hydrogen bond in **Z-3C** is shorter and has a lower vibrational frequency than that in **Z-3A** and **Z-3B** and is therefore stronger (Table 2). Similarly, the intramolecular hydrogen bond in **E-3C** is found to be stronger than that for **E-3A** and **E-3B**.

We calculated the transition state for the T_K of 1 for the H-atom abstraction to form biradical 2. The transition-state barrier for γ H-atom abstraction of the T_K of 1A is ~8 kcal/mol, whereas the transition-state barriers for the T_K s of 1B and 1C are less by 3 and 4 kcal/mol, respectively. The stationary points on the energy surfaces of 1A–1C are plotted in Figs. 2–4. These plots highlight that the intramolecular H-atom abstraction from the T_K of 1A, 1B, and 1C to form biradicals 2A, 2B, and 2C can be easily achieved at ambient temperature. Even though biradical 2A is a primary radical, it is only ~3 kcal/mol less stable than 2B and 2C, presumably because the radical center on the *ortho*-methylene is stabilized owing to conjugation with the aromatic rings. The driving force for the reactivity of E-3 and Z-3 must be the re-aromatization of the benzene ring.

We calculated the transition states for **Z-3** to reform **1** via 1,5 H-atom shifts (Table 3 and Fig. 5). The transition-state barrier for **Z-3A** to reform **1A** is 7.2 kcal/mol and 6.6 kcal/mol for **Z-3B** to form **1B**. Presumably, the electron-donating effect of the ethyl groups stabilizes the transition state more than the methyl group stabilizes it. In comparison, the steric demand of the isopropyl group, which cannot rotate away as

Scheme 4. Calculated transition state barriers for E-3, 6, and 7.



the ethyl group can, causes the transition-state barrier for the 1,5 H-atom shift in **Z-3C** to increase to 7.9 kcal/mol.

The calculated transition states for electrocyclic ring closure of **E-3** show that alkyl substituents stabilize this transition state (Scheme 4). Thus, the transition-state barrier for **E-3A** is the highest, and the barriers for **E-3B** and **E-3C** are lower. The steric effect of the dimethyl substituents in **E-3C** twists its butadienyl moiety. The torsion angle between the butadienyl moiety in **E-3C** is 44°, but only 33° and 28° in **E-3B** and **E-3A**, respectively. In the electrocyclic ring closures, twisting of the butadienyl moiety to a distorted structure moves the reactant along the potential energy surface towards the transition state's twisted geometry. So the steric effect of the dimethyl substituent in **E-3C** lowers the transitionstate barrier for forming **6C** by twisting the butadienyl moiety.

Furthermore, we calculated the transition-state barrier for 6 to undergo lactonization and found that the barrier for lactonization is ~40 kcal/mol, which is considerably higher than the transition-state barrier for E-3 to undergo electrocyclic ring closure. However, it is complicated to compare these transition-state barriers because solvation is expected to affect the lactonization significantly more than the electrocyclic ring closure. The calculated transition-state barriers make it possible to evaluate the effect of the alkyl substituents on these two processes rather than to obtain their absolute values. The steric demand of the dimethyl group in 6C makes the lactonization slightly less feasible than for 6A and 6B.

We calculated the transition states for lactonization of E-3A, 3B, and 3C to form 7. The transition-state barrier is

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Fig. 2. Calculated stationary points on the energy surface for 1A. The energies are in kcal/mol (1 cal = 4.184 J) and are obtained from the singlet- (black) and triplet-optimized structures with zero point energy corrections included. Numbers in parentheses are energies calculated with a polarization continuum model (PCM) model for methanol.



Fig. 3. Calculated stationary points of the energy surface for **1B**. The energies are in kcal/mol (1 cal = 4.184 J) and are obtained from the singlet- (black) and triplet-optimized structures with zero point energy corrections included. Numbers in parentheses are energies calculated with a polarization continuum model (PCM) model for methanol.



~43 kcal/mol for E-3. The calculations demonstrate that the *ortho*-alkyl substituent has minimal effect on the lactonization of E-3. In comparison, the calculated transition-state barrier for 7 to form 4 shows that ring closure of 7A is the least favored as expected, since its butadienyl moiety is less twisted than for 7B and 7C.

Thus, the calculations show that the electrocyclic ring closure of E-3 and 6 are affected by the alkyl substituents, whereas lactonization of E-3 is not. However, the transitionstate barrier for lactonization of 6C is increased by the steric demand of the dimethyl group.

Laser flash photolysis of **1B** in nitrogen-saturated methanol produced a transient spectrum with a λ_{max} at ~330 nm with a lifetime of ~53 ns (Fig. 6) We assign this absorption to triplet biradical **2B** on the basis of its similarity to the transient spectra of the analogous 1,4-biradical **2A**.^{9,10} The TD-DFT calculations support this assignment because the major calculated electronic transition for **2B** is located at 336 nm (f = 0.0871) in the gas phase and at 334 nm (f = 0.1104) in methanol. In oxygen-saturated solutions, the absorption owing to **2B** was quenched. As the absorption band for **2B** decayed, a new transient with a λ_{max} at 390 nm (Fig. 6) formed at the same rate. We assign this absorption to **Z-3B** and **E-3B**, based on comparison with the transient spectra of **3A** and **3C**.^{8,10} The TD-DFT calculations also support this assignment as they revealed that the major absorption bands of **Z-3B** and **E-3B** are located at 426 nm (f = 0.1975) and 437 nm (f = 0.0699) in methanol, respec-

Fig. 4. Calculated stationary points on the energy surface for **1C**. The energies are in kcal/mol (1 cal = 4.184 J) and are obtained from the singlet- (black) and triplet-optimized structures with zero point energy corrections included. Numbers in parentheses are energies calculated with a polarization continuum model (PCM) model for methanol.



Table 3. Calculated transition-state (TS)barriers for the 1,5 H-atom shift in Z-3.

Compound	TS barrier (kcal/mol)		
Z-3A	7.2		
Z-3B	6.6		
Z-3C	7.9		
Note: 1 cal = 4.184 J.			

Fig. 5. Transition state for 1,5 H-atom shift in Z-3A, Z-3B, and Z-3C.



tively. The lifetimes of **Z-3B** and **E-3B** in methanol are 15 μ s and >3 ms, respectively. The lifetimes for each component can be obtained by fitting the decay with a monoexponential function because the decay of **Z-E3** is complete before **E-3B** has decayed significantly (Fig. 7). In acetonitrile, the lifetime of **Z-3B** is reduced to 2.5 μ s, and the lifetime of **E-3B** is >19 ms. This is in agreement with previous reports that show that the Z-photoenols from *o*-methyl benzophenone and *o*-methyl acetophenones are longer lived in solvents that can form hydrogen bonds with the photoenols.^{36,37}

We have reported the laser flash photolysis of **1A** and **1C** previously;⁸ however, in this paper we compare the lifetimes and yields of biradicals **2A**, **2B**, and **2C** and photoenols **3A**, **3B**, and **3C** (see Table 4). The lifetimes of biradicals **2A**, **2B**, and **2C** are similar within experimental error, which fits well with the calculations that predict that these biradicals have similar stabilities.

The ratios of Z-3 and E-3 in benzene (Fig. 7), which can-

Fig. 6. Laser flash photolysis of **1B** in N₂-saturated methanol over (A) a time window of 1 μ s and (B) a time window of 200 μ s.



not form hydrogen bonds with the photoenols, are shown in Fig. 7. The ratios of Z-enol to E-enol were measured from the absorbance at 390 nm by measuring the combined absorptions of Z-3 and E-3 on shorter timescales and the absorption of E-3 on longer timescales. The Z:E ratio was highest for 3A at 1:1.2 and somewhat lower for 3C (3.2:1) and 3B (3.5:1). Thus, by assuming that E-3 and Z-3 have similar absorption coefficients, the quantum yields for enol formation from 1A is only half that observed for 1B and 1C (Fig. 7). The lower yield of photoenols from 1A is a reflection that the intramolecular H-atom abstraction is less favorable in the T_K of **1A** than in that of **1B** and **1C**. However, the Z:E ratio is the lowest for 3A, presumably because intramolecular rotation in 2A is less hindered than in **2B** and **2C**. We have previously shown that restricted intramolecular rotation in analogous biradicals results in less Ephotoenol formation.38

The lifetime of **Z-3C** is the longest in all solvents (Table 4), whereas that of **Z-3B** is only somewhat shorter lived and that of **Z-3A** is considerably shorter. The lifetime



Fig. 7. Decay of E-3 and Z-3 at 390 nm in N_2 -saturated benzene. The kinetic traces are obtained under identical conditions, thus showing relative yields for forming Z-3 and E-3.

Table 4. Measured lifetimes of **2**, **E-3** and **Z-3** in N₂-saturated solutions.

	Lifetime		
Compound	Benzene	MeCN	MeOH
2A	77 ns	57 ns	54 ns
Z-3A	0.09 µs	1.2 µs	6.5 µs
E-3A	1< \u03ct>8 ms	10 ms	162 µs
2B	50 ns	58 ns	33 ns
Z-3B	~0.7 µs	2.5 µs	15 µs
E-3B	1<τ>8 ms	19 ms	>3 ms
2C	70 ns	83 ns	60 ns
Z-3C	1.2 µs	8 µs	17 µs
E-3C	>500 ms	>0.1 s	>0.1 s

of **Z-3A** in methanol is comparable to the analogous Z-enol from 2,4-methyl benzophenone,³⁷ whereas the lifetime of **Z-3A** in benzene is considerably longer. Wagner and co-workers³⁷ showed that the 1,5 H-atom shifts are retarded by intermolecular hydrogen bonding. Thus, we theorize that intramolecular hydrogen bonding also renders **Z-3** more stable towards a 1,5 H-atom shift. The steric factors of the alkyl substituent in **Z-3B** and **Z-3C** also retard the 1,5-hydrogen shift, and thus they are longer lived than **Z-3A**.

The lifetime of **E-3A** was shorter than for **E-3B** in acetonitrile and methanol, whereas the lifetimes in benzene are comparable. **E-3C** is longer lived than both **E-3A** and **E-3B**. Unlike the Z-photoenols, the E-photoenol reketonization is solvent-assisted. Furthermore, in competition with reketonization, **E-3B** and **E-3C** must undergo electrocyclic ring closure and intramolecular lactonization to form **4B** and **4C**, respectively. **E-3A** reketonizes faster than it undergoes electrocyclic ring closure or lactonization. Thus, we theorize that in nonpolar solvents, **E-3B** and **E-3C** decay by electrocyclic ring closure followed by lactonization. Our hypothesis is based on the observation that E-3A does not produce 4A in nonpolar solvent, whereas E-3A has lifetimes that are similar as observed for E-3B and that the transition-state barrier for E-3A to undergo electrocyclic ring closure is larger than that for E-3B and E-3C. In comparison, the calculated transition-state barrier for lactonization of E-3 is not affected significantly by the alkyl substituents.

Conclusion

The product studies show that 1B and 1C release their alcohol moiety upon irradiation via photoenolization and form 4B and 4C, whereas 1A also undergoes photoenolization, but both Z-3A and E-3A decay back to the starting material. Laser flash photolysis shows that 1A, 1B, and 1C all undergo H-atom abstraction to form 2, which intersystem crosses to form E-3 and Z-3. The yields of the photoenols are similar for **1B** and **1C** and slightly less for **1A** in benzene. The calculations further support this because stationary points on the energy surface of these esters are very similar. The lifetime of E-3A is significantly shorter in methanol than that of both E-3B and E3C. Thus, E-3A does not react to release its alcohol moiety but rather regenerates 1A. In comparison, the lifetime of E-3A is considerably longer in benzene and acetonitrile, however, because the electrocyclic ring closure for E-3A is less favorable than for E-3B, it reketonizes faster than it undergoes electrocyclic ring closure. Thus, in designing photoprotecting groups based on intramolecular photoenolization, it is important to consider the effect of the alkyl substituent on electrocyclic ring closure and lactonization.

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References

- Sankaranarayanan, J.; Muthukrishnan, S.; Gudmundsdottir, A. D. Adv. Phys. Org. Chem. 2009, 43, 39. doi:10.1016/ S0065-3160(08)00002-6.
- (2) Herrmann, A. Angew. Chem. Int. Ed. 2007, 46 (31), 5836. doi:10.1002/anie.200700264.
- (3) Ellis-Davies, G. C. R. Nat. Methods 2007, 4 (8), 619. doi:10. 1038/nmeth1072.
- (4) Mayer, G.; Heckel, A. Angew. Chem. Int. Ed. 2006, 45 (30), 4900. doi:10.1002/anie.200600387.
- (5) Bochet, C. G. Pure Appl. Chem. 2006, 78 (2), 241. doi:10. 1351/pac200678020241.
- (6) *Dynamic Studies In Biology*; Goeldner, M.; Givens, R., Eds. Wiley-VCH: Weinheim, 2005.

- (7) Pelliccioli, A. P.; Wirz, J. Photochem. Photobiol. Sci. 2002, 1 (7), 441. doi:10.1039/b200777k.
- (8) Pika, J.; Konosonoks, A.; Robinson, R. M.; Singh, P. N. D.; Gudmundsdottir, A. D. J. Org. Chem. 2003, 68 (5), 1964. doi:10.1021/jo0261193.
- (9) Pika, J.; Konosonoks, A.; Singh, P.; Gudmundsdottir, A. D. Spectrum (Bowling Green, OH) [Online] 2003, 16 (4), 12. http://www.bgsu.edu/departments/photochem/assets/pdf/ spectrum/winter2003spectrum.pdf.
- (10) Konosonoks, A.; Wright, P. J.; Tsao, M.-L.; Pika, J.; Novak, K.; Mandel, S. M.; Krause Bauer, J. A.; Bohne, C.; Gudmundsdottir, A. D. *J. Org. Chem.* **2005**, *70* (7), 2763. doi:10.1021/jo048055x.
- (11) Muthukrishnan, S.; Sankaranarayanan, J.; Klima, R. F.; Pace, T. C. S.; Bohne, C.; Gudmundsdottir, A. D. Org. Lett. 2009, *11* (11), 2345. doi:10.1021/o1900754a.
- (12) Liao, Y.; Bohne, C. J. Phys. Chem. **1996**, 100 (2), 734. doi:10.1021/jp951697r.
- Mitchell, R. H.; Bohne, C.; Wang, Y.; Bandyopadhyay, S.;
 Wozniak, C. B. J. Org. Chem. 2006, 71 (1), 327. doi:10. 1021/j0052153g.
- (14) Wijtmans, M.; Rosenthal, S. J.; Zwanenburg, B.; Porter, N. A. J. Am. Chem. Soc. 2006, 128 (35), 11720. doi:10.1021/ja063562c.
- (15) Wagner, P. J. J. Am. Chem. Soc. 1967, 89 (23), 5898. doi:10. 1021/ja00999a028.
- (16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision A.1. Pittsburgh, PA: Gaussian, Inc., 2003.
- (17) Becke, A. D. J. Chem. Phys. 1993, 98 (7), 5648. doi:10. 1063/1.464913.

- (18) Wilson, R. M.; Hannemann, K.; Heineman, W. R.; Kirchhoff, J. R. J. Am. Chem. Soc. **1987**, 109 (15), 4743. doi:10.1021/ ja00249a060.
- (19) Gonzalez, C.; Schlegel, H. B. J. Chem. Phys. 1989, 90 (4), 2154. doi:10.1063/1.456010.
- (20) Gonzalez, C.; Schlegel, H. B. J. Phys. Chem. 1990, 94 (14), 5523. doi:10.1021/j100377a021.
- (21) Parr, R. G.; Weitao, Y. Density Functional Theory in Atoms and Molecules; Oxford University Press: Oxford, UK, 1989.
- (22) Denisty Functional Methods in Chemistry; Labanowksi, J. K.; Andzelm, J. W., Eds. Springer-Verlag: New York, 1991.
- (23) Stratmann, R. E.; Scuseria, G. E.; Frisch, M. J. J. Chem. Phys. 1998, 109 (19), 8218. doi:10.1063/1.477483.
- (24) Bauernschmitt, R.; Ahlrichs, R. Chem. Phys. Lett. 1996, 256 (4-5), 454. doi:10.1016/0009-2614(96)00440-X.
- (25) Foresman, J. B.; Head-Gordon, M.; Pople, J. A.; Frisch, M. J. J. Phys. Chem. 1992, 96 (1), 135. doi:10.1021/j100180a030.
- (26) Tomasi, J.; Persico, M. Chem. Rev. 1994, 94, 2027. doi:10. 1021/cr00031a013.
- (27) Cramer, C. J.; Truhlar, D. G. Chem. Rev. 1999, 99, 2161. doi:10.1021/cr960149m.
- (28) Tomasi, J.; Mennucci, B.; Cammi, R. Chem. Rev. 2005, 105
 (8), 2999. doi:10.1021/cr9904009.
- (29) Mennucci, B.; Cances, E.; Tomasi, J. J. Phys. Chem. B 1997, 101 (49), 10506. doi:10.1021/jp971959k.
- (30) Cancès, E.; Mennucci, B. J. Chem. Phys. 2001, 114 (10), 4744. doi:10.1063/1.1349091.
- (31) Srivastava, S.; Yourd, E.; Toscano, J. P. J. Am. Chem. Soc. 1998, 120 (24), 6173. doi:10.1021/ja981093b.
- (32) He, H.-Y.; Fang, W.-H.; Phillips, D. L. J. Phys. Chem. A 2004, 108 (25), 5386. doi:10.1021/jp0377351.
- (33) Fang, W.-H.; Phillips, D. L. J. Theor. Comput. Chem. 2003, 2 (1), 23. doi:10.1142/S0219633603000355.
- (34) Fang, W.-H.; Phillips, D. L. ChemPhysChem 2002, 3 (10), 889. doi:10.1002/1439-7641(20021018)3:10<889::AID-CPHC889>3.0.CO;2-U.
- (35) Muthukrishnan, S.; Mandel, S. M.; Hackett, J. C.; Singh, P. N. D.; Hadad, C. M.; Krause, J. A.; Gudmundsdottir, A. D. J. Org. Chem. 2007, 72 (8), 2757. doi:10.1021/jo062160k.
- (36) Scaiano, J. C.; Wintgens, V.; Netto-Ferreira, J. C. *Tetrahedron Lett.* **1992**, *33* (40), 5905. doi:10.1016/S0040-4039(00) 61085-7.
- (37) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* 1977, 60
 (8), 2595. doi:10.1002/hlca.19770600813.
- (38) Muthukrishnan, S.; Sankaranarayanan, J.; Pace, T. C. S.; Konosonoks, A.; De Michiei, M. E.; Meese, M. J.; Bohne, C.; Gudmundsdottir, A. D. J. Org. Chem. **2010**, 75 (5), 1393. doi:10.1021/jo9021088.