

# Kinetics and Mechanism of Phosphate Photorelease from Benzoin Diethyl Phosphate: Evidence for Adiabatic Fission to an $\alpha$ -Keto Cation in the Triplet State

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**Abstract:** The photodissociation of benzoin diethyl phosphate (**1**, “caged” phosphate) was studied by nanosecond and picosecond laser flash photolysis. The lowest triplet state of **1**, <sup>3</sup>**1**, was identified as the reactive excited state with an absorption maximum around 340 nm and a lifetime of 10–25 ns, depending on the solvent. Two different reaction paths were identified, both of which involve the release of diethyl phosphoric acid from <sup>3</sup>**1** within 25 ns. In addition to a fast cyclization–elimination process leading to 2-phenylbenzofuran (**2**) and diethyl phosphoric acid, heterolytic adiabatic dissociation of <sup>3</sup>**1** yields a triplet cation and diethyl phosphate anion in water, trifluoroethanol, and hexafluoro-2-propanol solutions. The triplet cation (570 nm,  $\tau \approx 430$  ns in water) undergoes intersystem crossing to the singlet ground state before it reacts with the solvent molecules.

## Introduction

Renewed interest in photosensitive protecting groups<sup>1</sup> has arisen due to their application as phototriggers for the spatially and temporally controlled release of biologically active compounds.<sup>2</sup> Examples include the release of calcium ions, nitric oxide, neurotransmitters, nucleic acids, and phosphate esters in biological systems.<sup>3</sup> Photoprotective groups also find applications in photochemical synthesis,<sup>4</sup> solid-phase peptide synthesis,<sup>5</sup> and photolithography.<sup>6</sup> Among the protecting groups used for biological applications, *o*-nitrobenzyl derivatives are the most widely used.<sup>7</sup> However, disadvantages including the highly absorbing and reactive side products as well as the slow release of the active species limit the application of *o*-nitrobenzyl derivatives.<sup>8</sup>

Studies on the photodissociation of benzoin esters were initiated by Sheehan and Wilson.<sup>9</sup> Subsequent studies by these authors showed that the highest yield of benzofuran was obtained on irradiating the 3',5'-dimethoxy-substituted benzoin acetate.<sup>10</sup> Givens and co-workers introduced benzoin phosphate as an alternative to nitrobenzyl phototriggers by demonstrating the efficient photorelease of phosphate esters.<sup>11</sup> These phototriggers are particularly attractive due to their solubility in a wide range of solvents, the rapid rate of photorelease, and the formation of biologically compatible side products. A triplet mechanism was assigned to the reaction based on quenching of benzofuran formation by naphthalene and piperylene. Givens and co-workers subsequently used benzoin esters as phototriggers for biologically active molecules such as cAMP, GABA, and glutamate.<sup>12</sup> Other groups further explored the utility of benzoin phototriggers.<sup>13</sup>

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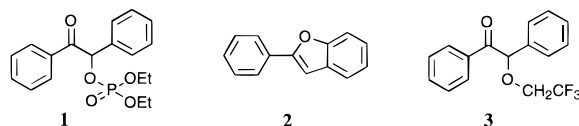
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Several mechanistic studies of related systems by flash photolysis have appeared recently.<sup>14</sup> Here we report the results of nanosecond and picosecond laser flash photolysis studies on benzoin diethyl phosphate (**1**).



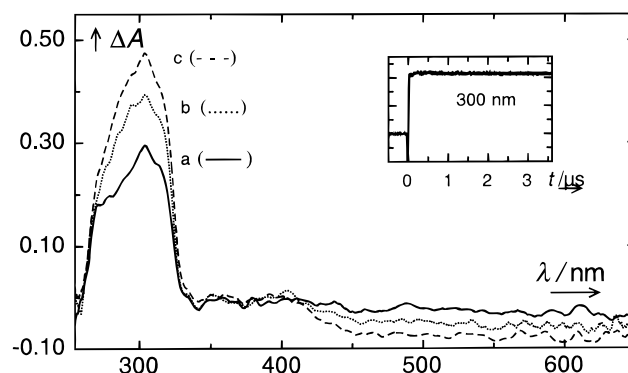
## Results

**Steady-State Photolyses.** Irradiation of benzoin diethyl phosphate (**1**) at 300 nm in acetonitrile, methanol, or benzene solutions was previously reported to give predominantly 2-phenylbenzofuran (**2**) as a primary product; conversion rates were similar in the different solvents, and a quantum yield of 0.26 was determined for the formation of **2** upon 350-nm irradiation in benzene.<sup>11b</sup>

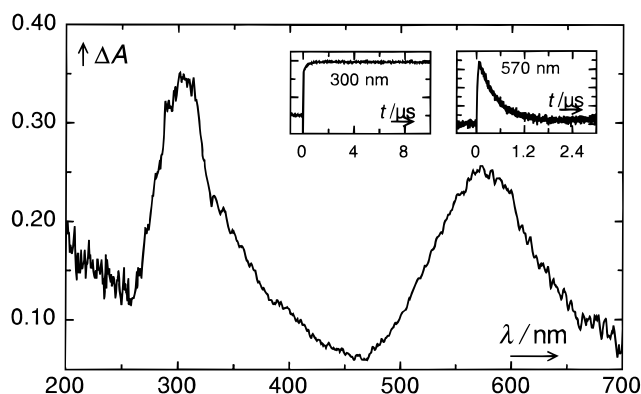
To determine the photoproduct distribution of **1** (ca.  $10^{-4}$  M) in trifluoroethanol, a degassed solution of **1** was irradiated at 365 nm using a Hanovia St-41 medium-pressure mercury lamp equipped with a band-pass filter. In this solvent, the chemical yield of **2** was only about 25%, as estimated from the characteristic UV spectrum of **2** ( $\lambda_{\text{max}} = 302$  nm,  $\epsilon = 32220$  M<sup>-1</sup> cm<sup>-1</sup> in methanol).<sup>11b</sup> GC/MS analysis of the product mixture after evaporation of the solvent showed the presence of another major compound, in addition to **2**. This is assigned to the nucleophilic addition product **3**, based on the molecular mass and fragmentation pattern (Experimental Section). Formation of **3** through a thermal pathway was ruled out on the basis of a blank experiment. In trifluoroethanol containing naphthalene (0.1 M), most of the starting material was recovered after irradiation for the same period. Addition of 0.1 M methanol or of  $10^{-4}$  M 2-propanol to trifluoroethanol did not affect the product distribution, but formation of the nucleophilic addition product **3** was suppressed by addition of 40 vol % methanol (10 M). In addition to the major product **2**, a trace of benzoin methyl ether was present among the minor products.

**Nanosecond Laser Flash Photolysis.** Excitation of a solution of benzoin diethyl phosphate (**1**) in degassed acetonitrile using the 248-, 308-, or 351-nm output of an excimer laser produced a permanent absorbance increase,  $\lambda_{\text{max}} \approx 300$  nm. Formation of this absorbance was essentially complete within the laser pulse ( $\leq 25$  ns). An absorption spectrum recorded about 30 ns after laser excitation of an acetonitrile solution of **1** is presented in Figure 1.

Absorption spectra recorded shortly after laser excitation of **1** in water (Figure 2), trifluoroethanol, or hexafluoro-2-propanol exhibited an additional absorption maximum at ca. 570 nm. The 570-nm transient was also formed within the duration of the laser pulse and decayed with a rate constant of  $(2.3 \pm 0.2) \times 10^6$  s<sup>-1</sup> in degassed aqueous solution (Figure 2, inset). Addition of sodium azide or sodium bromide in the millimolar concentra-



**Figure 1.** Difference spectrum recorded ca. 30 ns after laser excitation (248 nm) of a solution of benzoin diethyl phosphate (**1**) in acetonitrile: (a) after one flash, (b) after two flashes, and (c) after three flashes. The spectrum determined prior to irradiation is used as the reference for all three traces. The inset shows a kinetic trace of the absorbance at 300 nm due to the formation of 2-phenylbenzofuran (**2**).



**Figure 2.** Transient absorption spectrum recorded ca. 30 ns after laser excitation (248 nm) of a solution of benzoin diethyl phosphate (**1**) in water containing 4% acetonitrile. The insets show kinetic traces of the absorbances at 300 and 570 nm.

tion range accelerated the decay rate and, at the same time, reduced the amplitude of the 570-nm transient. That decrease is attributed partly to quenching of the triplet state of **1** by the anions, but partly also to decay of the 570-nm transient within the duration of the 25-ns laser pulse. No new transient absorptions or photoproducts (GC/MS) were detected as a consequence of the quenching by these anions. Detection of conceivable halide addition products by GC/MS was not ascertained by controls using authentic compounds, but the starting ester **1** was readily detected despite the fact that diethyl phosphate is a better leaving group than azide or chloride. Moreover, purely physical quenching by the anions is quite consistent with the assignment of the 570-nm transient given below (cf. Discussion).

The decay rate constant of the 570-nm transient observed in aerated aqueous solutions,  $k_{\text{obs}}$ , increased linearly with the concentration of the quencher ions, eq 1, where  $k_0$  is the rate constant for the decay in the absence of the quencher,  $k_Q$  is the bimolecular rate coefficient of quenching, and  $[Q]$  is the concentration of the quencher. Quenching coefficients  $k_Q = (9.9 \pm 0.4) \times 10^9$  M<sup>-1</sup> s<sup>-1</sup> for azide,  $(3.5 \pm 0.1) \times 10^9$  M<sup>-1</sup> s<sup>-1</sup> for bromide, and  $(1.2 \pm 0.1) \times 10^6$  M<sup>-1</sup> s<sup>-1</sup> for chloride ions were obtained from the slopes of these plots (Table 1, Figure 3).<sup>15</sup>

$$k_{\text{obs}} = k_0 + k_Q[Q] \quad (1)$$

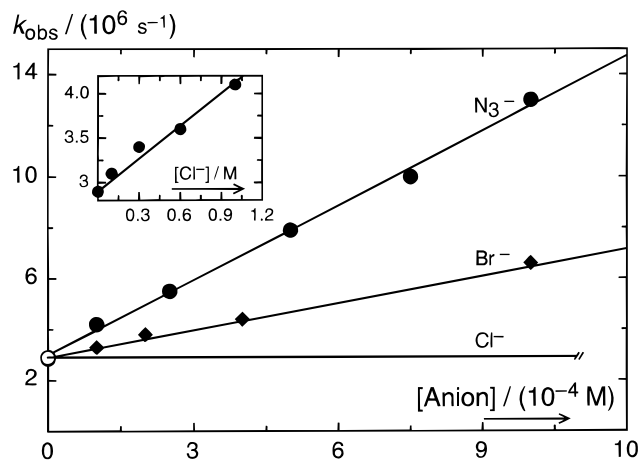
The decay rate of the 570-nm transient was not affected by the addition of sulfuric acid (0.1 M), hydrochloric acid ( $10^{-3}$

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**Table 1.** Rate Constants and Activation Parameters for the Decay of the 570-nm Transient<sup>34</sup>

process	solvent	coefficient
decay (isc)	H <sub>2</sub> O degassed	$k = (2.3 \pm 0.2) \times 10^6 \text{ s}^{-1}$
decay (isc)	CF <sub>3</sub> CH <sub>2</sub> OH degassed	$k = (1.5 \pm 0.1) \times 10^6 \text{ s}^{-1}$
quenching by N <sub>3</sub> <sup>-</sup>	H <sub>2</sub> O	$k_Q = (9.9 \pm 0.4) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$
quenching by Br <sup>-</sup>	H <sub>2</sub> O	$k_Q = (3.5 \pm 0.1) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$
quenching by Cl <sup>-</sup>	H <sub>2</sub> O	$k_Q = (1.2 \pm 0.1) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$
quenching by <sup>3</sup> O <sub>2</sub>	H <sub>2</sub> O	$k_Q \approx 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$
quenching by <sup>3</sup> O <sub>2</sub>	CF <sub>3</sub> CH <sub>2</sub> OH	$k_Q \approx 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$
kinetic solvent isotope effect	H <sub>2</sub> O/D <sub>2</sub> O aerated	$k_H/k_D = 0.97 \pm 0.10$
T-dependence	H <sub>2</sub> O degassed	$E_a = 8.6 \pm 0.2 \text{ kcal mol}^{-1}$ $A = (4.8 \pm 1.4) \times 10^{12} \text{ s}^{-1}$

**Figure 3.** Stern–Volmer plot for the quenching of the 570-nm transient by azide, bromide, and chloride ions. The inset shows the full plot for quenching by chloride. Laser excitation was carried out using the 248-nm output of an excimer laser on solutions of **1** in water containing 4% acetonitrile.

M), perchloric acid (0.1 M), or 2-propanol ( $10^{-2}$  M), but increased slightly in the presence of oxygen,  $k_{\text{obs}} = (2.8 \pm 0.3) \times 10^6 \text{ s}^{-1}$  for aerated solutions and  $(3.7 \pm 0.3) \times 10^6 \text{ s}^{-1}$  for oxygen-saturated solutions. Using a value of  $1.39 \times 10^{-3} \text{ M}$  for the concentration of oxygen in water at 20 °C under an oxygen pressure of 1 atm,<sup>16</sup> the second-order quenching constant by oxygen is calculated as  $k_Q \approx 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ . The decay rate constant obtained with aerated solutions of **1** in D<sub>2</sub>O,  $k_{\text{obs}} = (2.9 \pm 0.3) \times 10^6 \text{ s}^{-1}$ , was equal, within the limits of error, to that obtained in aerated water.

For aqueous solutions, formation of the absorbance at 300 nm was largely complete within the laser pulse, but a fraction of about 20% of the growth amplitude was resolved with a rate constant of  $(3 \pm 1) \times 10^6 \text{ s}^{-1}$ . Addition of sodium azide reduced the amplitude of the total increase in absorbance at 300 nm, but did not affect the growth rate of the time-resolved fraction. Stern–Volmer analysis of the growth amplitudes using eq 2,<sup>17</sup> where  $A_Q$  and  $A_0$  are the final absorbances at 300 nm in the presence and absence of sodium azide, respectively, gave  $k_Q\tau_0 = (32 \pm 5) \text{ M}^{-1}$  (14 data points,  $[\text{N}_3^-] = (1.6\text{--}4.0) \times 10^{-2} \text{ M}$ ). Assuming that the quenching rate constant of triplet **1** by azide is the same as that reported for the quenching of triplet acetophenone by azide in a 4:1 mixture of water and acetonitrile,

$k_Q = 3.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ ,<sup>18</sup> the triplet lifetime  $\tau_0$  is calculated to be  $9 \pm 2 \text{ ns}$ .

$$A_0/A_Q = 1 + k_Q\tau_0[\text{Q}] \quad (2)$$

The 570-nm transient was also observed in trifluoroethanol,  $k_0 = (1.5 \pm 0.1) \times 10^6 \text{ s}^{-1}$ , and acceleration of its decay rate by oxygen was more pronounced in this solvent. As the solubility of oxygen in trifluoroethanol is not known, we measured fluorescence quenching of naphthalene by oxygen (eq 2, replace absorbance  $A$  by fluorescence intensity  $I$ ) in this solvent to obtain a reference value for diffusion-controlled quenching, which gave a slope of  $k_Q\tau_0 = 11 \pm 1 \text{ bar}^{-1}$ , where the pressure refers to the oxygen gas pressure. The fluorescence lifetime of naphthalene in degassed trifluoroethanol was determined as  $\tau_0 = 71 \text{ ns}$ , from which  $k_Q = (1.5 \pm 0.1) \times 10^8 \text{ bar}^{-1} \text{ s}^{-1}$  is calculated. Stern–Volmer analysis of the first-order decay rates of the 570-nm transient, eq 1,<sup>18</sup> gave a slope that was an order of magnitude lower,  $k_Q = (1.5 \pm 0.2) \times 10^7 \text{ bar}^{-1} \text{ s}^{-1}$  (6 data points,  $p(\text{O}_2) = 0, 26, 210, 394, 605, \text{ and } 1000 \text{ mbar}$ ). From oxygen solubilities in related solvents<sup>16</sup> we estimate  $[\text{O}_2] \approx 1.5 \times 10^{-2} \text{ M bar}^{-1}$  for the solubility of oxygen in trifluoroethanol. With this value we obtain a rate constant of about  $k_Q \approx 1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$  for quenching of naphthalene fluorescence and  $k_Q \approx 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  for the quenching of the 570-nm transient by oxygen.

No transient absorption was observed at 570 nm after excitation of benzoin phosphate **1** in any of the following solvents: acetonitrile, dichloromethane, trichlorotrifluoroethane, chloroform, tetrahydrofuran, diethyl ether, methanol, ethanol, 2-propanol, and ethyl acetate. A small amount of transient absorption with a decay rate constant of ca.  $8 \times 10^6 \text{ s}^{-1}$  was observed at 570 nm when perchloric or sulfuric acid (both ca. 0.2 M) was added to acetonitrile.

To determine the identity of the permanent product which gave rise to the absorbance change at 300 nm, its absorption and emission spectra were recorded using a gated optical multichannel analyzer. The absorbance change found immediately after the flash (Figure 1) matched well with the persistent changes in the spectrum around 300 nm and the shape of that absorbance was identical with that of authentic 2-phenylbenzofuran (**2**) recorded by the same device. Corroborating evidence that the formation of **2** is essentially complete within 25 ns is provided by the following experiments.

The fluorescence of a solution of **1** in acetonitrile was measured on a conventional fluorescence spectrometer. With a fresh solution of **1**, fluorescence was marginally observable, barely above the solvent background level. After the solution had been exposed to a single laser flash, fluorescence of **2** measured by steady-state excitation was about 100 times stronger than before the flash. On the other hand, the fluorescence emission generated by laser excitation and detected with a diode array was quite strong already during the first laser pulse applied to a fresh solution of **1**, and the spectrum matched well with that of a solution of authentic **2**. A single laser pulse of 150 mJ energy at 248 nm was sufficient to photolyze over 50% of **1** in a  $10^{-5} \text{ M}$  solution (the laser pulse was spread evenly over all of the 5 mL volume in the cell by side-on excitation).<sup>19</sup> The emission intensity obtained by exciting the same solution with a second laser pulse was not much stronger than that observed during the first flash. This proves that the fluorescence arises by re-excitation of the photoproduct **2**, which is formed

(15) The parameters were determined by nonlinear fitting to the logarithmic form of eq 1, for which experimental errors were constant.

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largely within the duration of the first laser pulse. Adiabatic formation of **2** in the excited singlet state is ruled out, because that would have been detected by conventional fluorescence spectroscopy of **1**. Moreover, it would be inconsistent with the triplet mechanism for the formation of **2** that was postulated earlier<sup>11b</sup> and is corroborated by flash photolysis (vide infra).

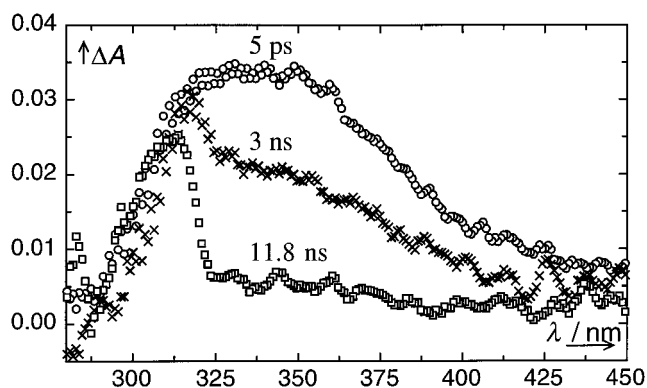
In a control experiment, flash photolysis (248 nm) of benzoin in aqueous solution with kinetic monitoring at 300 nm also produced a transient. However, that absorption decayed with a rate constant of  $3.4 \pm 0.3 \times 10^4 \text{ s}^{-1}$  and **2** was not formed. Laser flash photolysis (308 nm) of benzoin gave no transient at 570 nm. Solutions of **1** in water and trifluoroethanol showed complex transient kinetics around 340–450 nm, which may arise from re-excitation of photoproduct **2** that is formed within the duration of the laser flash (vide infra), but is not fully understood.

**Triplet Energy Transfer.** The triplet state of benzoin diethyl phosphate (**1**) was too short-lived for a reliable determination of its lifetime on the nanosecond laser apparatus and too long-lived for the picosecond setup (vide infra), but it was readily identified by triplet energy transfer to naphthalene ( $E_T = 61$  kcal mol<sup>-1</sup>): benzoin phosphate **1** ( $E_T = 73$  kcal mol<sup>-1</sup>)<sup>11b</sup> in trifluoroethanol was excited by 351-nm laser pulses in the presence of naphthalene, and the amount of energy transfer was monitored by the triplet–triplet absorbance  $A$  of naphthalene at 414 nm at the end of the laser pulse. The triplet absorbance of naphthalene obeyed eq 3, where  $A_{\max}$  is the limiting triplet absorbance reached at high concentrations of naphthalene,  $k_0$  is the rate constant for the decay of triplet **1** in the absence of naphthalene, and  $k_{\text{et}}$  is the bimolecular rate constant for energy transfer. The ratio of these rate constants was found to be  $k_{\text{et}}/k_0 = 88 \pm 5$  M<sup>-1</sup> (9 data points, [naphthalene] = 0.001–0.1 M). The rate constant for triplet energy transfer from acetophenone to naphthalene is diffusion controlled ( $7.7 \times 10^9$  M<sup>-1</sup> s<sup>-1</sup> in benzene solution).<sup>16</sup> Using the viscosity of trifluoroethanol,  $\eta$  (25 °C) =  $1.768 \times 10^{-3}$  Pa s,<sup>20</sup> the rate constant of diffusion in trifluoroethanol is calculated as  $k_{\text{diff}} = 8000RT/(3\eta) = 3.7 \times 10^9$  M<sup>-1</sup> s<sup>-1</sup>. Assuming this value for the unknown rate of energy transfer from triplet **1** to naphthalene,  $k_{\text{et}} = 3.7 \times 10^9$  M<sup>-1</sup> s<sup>-1</sup>, the triplet lifetime of **1** is calculated as  ${}^3\tau = 1/k_0 = 24 \pm 2$  ns in this solvent.

$$A_{\max}/A = 1 + k_0/(k_{\text{et}}[\text{Q}]) \quad (3)$$

Naphthalene had no effect on the decay rate of the 570-nm transient, but its amplitude was reduced due to the quenching of **31** by naphthalene. This finding indicated that **31** is the precursor of the 570-nm transient. Quantitative Stern–Volmer analysis (eq 2) gave a slope  $k_Q\tau_0 = 68 \pm 11 \text{ M}^{-1}$ . Assuming  $k_Q = 3.7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ , as above, gives  $\tau_0 = 18 \pm 3 \text{ ns}$ , in satisfactory agreement with the lifetime of **31** determined above by energy transfer.

**Temperature Dependence.** In an attempt to resolve the formation of 2-phenylbenzofuran (**2**) on the nanosecond apparatus, laser flash photolysis experiments were carried out using cooled solutions of **1** in ethanol and trifluoroethanol. Transient absorption spectra of phosphate **1** in trifluoroethanol solutions at temperatures below  $-40\text{ }^{\circ}\text{C}$  showed absorbance in the 330–430 nm region immediately after the flash, which is attributed to the lowest triplet excited state of **1**. The triplet–triplet absorption spectra of acetophenone<sup>21</sup> and of benzoin<sup>22</sup> are similar



**Figure 4.** Picosecond pump–probe spectra of desyl diethyl phosphate (1) in acetonitrile solution (excitation with a subpicosecond flash at 248 nm): (a) 5-ps delay (○), (b) 3-ns delay (×), and (c) 11.8-ns delay after flash (□).

in shape and position. At about  $-100\text{ }^{\circ}\text{C}$  in ethanol, the formation of the absorbance at  $300\text{ nm}$  was resolved with a growth rate constant of  $1.8 \times 10^6\text{ s}^{-1}$ . The effect of temperature on the decay rate of the absorbance at  $570\text{ nm}$  in water was studied in the range of  $0\text{--}40\text{ }^{\circ}\text{C}$  (five temperatures). Linear regression of  $\ln(k)$  vs  $1/T$  provided Arrhenius parameters for the decay of this transient (Table 1).

**Nanosecond Laser Flash Photolysis of 2-Phenylbenzofuran**

(2). Since the formation of **2** is largely complete within the laser pulse, re-excitation of **2** might contribute to the observed transient kinetics. The following experiments were carried out to probe this possibility. Transient absorption spectra recorded with degassed solutions of **2** in water containing 20% acetonitrile or in acetonitrile showed transient absorptions throughout the near-UV. Kinetic analysis of aqueous solutions at 340 nm showed two components decaying with rate constants of  $k = (2.3 \pm 0.3) \times 10^4$  and  $(4.5 \pm 0.6) \times 10^5 \text{ s}^{-1}$ . In aerated solutions a single decay was observed,  $k = (5.9 \pm 0.6) \times 10^5 \text{ s}^{-1}$ , suggesting assignment of the slower component in degassed solution to the triplet excited state of **2**.

Clearly, the 570-nm transient observed by flash photolysis of **1** in polar solvents (Figure 2) does not arise from re-excitation of **2**. However, part of the weak and complex transient absorbance changes observed in the range of 340–450 nm, as well as the minor, resolved growth in absorbance observed after the sudden rise at 300 nm (Figures 1 and 2), may be attributed to re-excitation of **2** within the laser flash.

**Picosecond Laser Flash Photolysis.** Picosecond experiments were carried out using solutions of benzoin diethyl phosphate (**1**) in acetonitrile, water containing 10% acetonitrile, trifluoroethanol, and several mixtures of water and trifluoroethanol. On excitation by a subpicosecond pulse at 248 nm, all solutions showed a broad transient absorption in the near-UV,  $\lambda_{\text{max}} = 340$  nm. The rise time of this transient in various solvents was in the range of 2–4 ps. Pump–probe spectra covered a time range from 0 to 2 ns for all experiments except those in acetonitrile, where the probe pulse was delayed up to 12 ns (Figure 4). The transient at 340 nm was still detectable at this delay time; hence, the lifetime of this transient must be at least 5 ns. It was necessary to accumulate the data through several hundreds of pulses, and overlapping fluorescence from the accumulating photoproduct **2** made kinetic analysis difficult. Several measurements of the decay kinetics of the 340-nm

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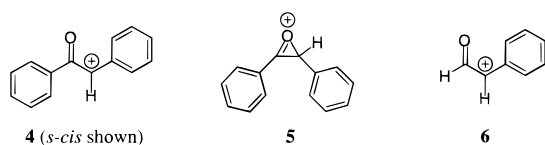
(21) (a) Lutz, H.; Lindqvist, L. *Chem. Commun.* **1971**, 493–494. (b) Lutz, H.; Bréhéret, E.; Lindqvist, L. *J. Phys. Chem.* **1973**, 77, 1758–1762.

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transient with delay times up to 2 ns gave poorly reproducible lifetimes in the range of 2–10 ns, which we do not consider reliable.

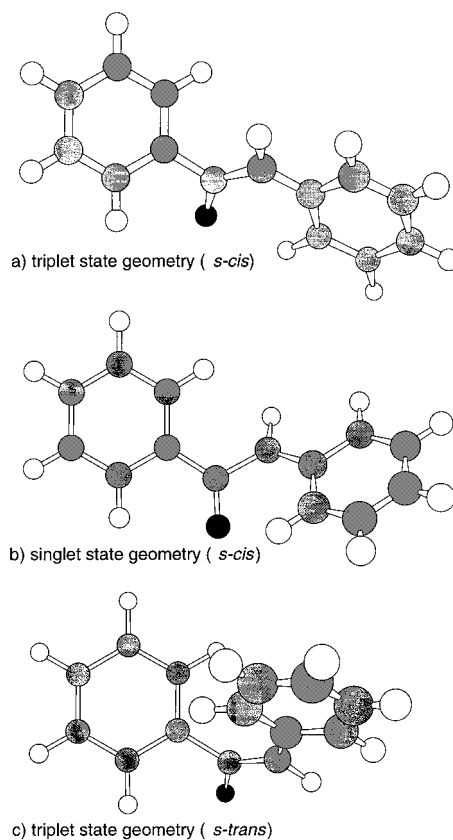
Solutions of **1** in trifluoroethanol showed formation of an additional short-lived absorbance around 470. However, the intensity of this transient at a given time delay was found to increase during data acquisition, which indicated that this absorbance was due to accumulation and re-excitation of the photoproduct **2** in the recycled solution of the flow cell.

**Density Functional Calculations.** Cations **4** and **5** are conceivable intermediates formed by photofission of diethyl phosphate from triplet benzoin phosphate **1**. Energies of the  $\alpha$ -carbonyl cations **4** and **5** and the simpler model compound **6** were carried out with the Gaussian 94 program package<sup>23</sup> using the B3LYP functional and a 6-31G(d) basis set. Energies of the lowest triplet (unrestricted open shell) and singlet states of these cations were calculated. The triplet wave functions were checked for stability.

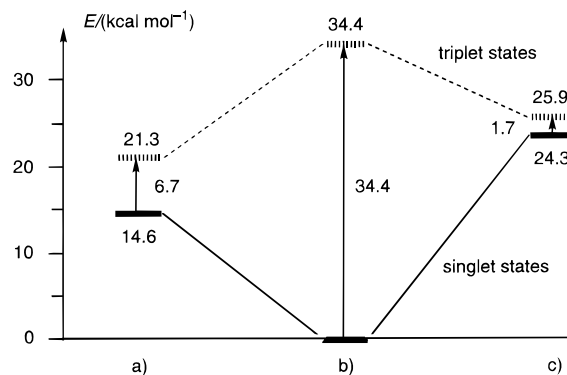


Energies of the cation **4** (*s-cis*) were  $-615.0164633$  hartrees for the triplet and  $-615.0503297$  hartrees for the singlet state, which corresponds to an energy difference  $\Delta E_{ST} = 21.3$  kcal mol<sup>-1</sup> between the two geometry-optimized states, with the singlet state being the ground state of the cation. A secondary minimum with an energy of  $-615.0089808$  hartrees (4.7 kcal mol<sup>-1</sup> above the *s-cis* conformation) was located for an *s-trans* conformation of the triplet cation **4**. The three optimized structures are shown in Figure 5. All structures have two essentially planar moieties; the dihedral angles between these planes are about 40° for the singlet (*s-cis*) structure and 43° (*s-cis*) and 77° (*s-trans*) for the triplet structures. The singlet and triplet structures differ mainly by the conformation of the carbonyl group, which lies in the plane of the adjacent phenyl group in the singlet state, and is coplanar with the benzyl cation moiety in the triplet states. A diagram displaying the relative energies of the singlet and triplet states at these geometries is shown in Figure 6. The vertical triplet excitation energy at the minimum structure of the singlet cation amounts to 34 kcal mol<sup>-1</sup>, but the calculated energy gap is reduced to 1.7 kcal mol<sup>-1</sup> (*s-trans*) and 6.7 kcal mol<sup>-1</sup> (*s-cis*) at the optimized triplet geometries. The energies of the cyclic structure **5** exceeded that for the singlet ground state of **4** by 36.2 (triplet state) and 44.6 kcal mol<sup>-1</sup> (singlet state).

Computation of the rotational barrier between the two conformers of **4** would have required excessive effort using density functional theory. An open-shell AM1 calculation gave similar optimized geometries for the two rotational isomers, with the *s-trans* isomer 4.5 kcal mol<sup>-1</sup> above the *s-cis* minimum. The AM1 model predicts a barrier of 13.7 kcal mol<sup>-1</sup> for rotation from *s-cis* to *s-trans* in the triplet state. That would be



**Figure 5.** Optimized geometries (a and c) for the triplet state and (b) for the singlet ground state of the  $\alpha$ -keto cation **4** (cf. caption to Figure 6). The oxygen atom is shown as a solid black ball.



**Figure 6.** Energies of the  $\alpha$ -keto cation **4** relative to the singlet ground state. Density functional calculations (B3LYP, UB3LYP for the triplet state) were done with the Gaussian 94 program package<sup>23</sup> using a 6-31G(d) basis set. Energies shown in the center (b) refer to the geometry optimized for the lowest singlet state, those on the sides (a and c) are geometries optimized for the triplet state. Structures in a–c are shown in Figure 5.

prohibitive on the nanosecond time scale: from an Arrhenius equation with  $\log(A/s^{-1}) = 13$  one obtains a rate constant of  $1 \times 10^3$  s<sup>-1</sup>.

The model compound **6** was used to determine the effect of zero-point energies and thermal corrections on the energy gap. Consideration of the vibrational corrections reduced the energy gap between the singlet and triplet energy minima only marginally, from 26.9 (uncorrected) to 25.2 kcal mol<sup>-1</sup>, with the singlet being the ground state. Optimized geometries of **6** were fully planar in both the singlet and the triplet state, which allowed characterization of the wave functions by symmetry. The triplet state electronic wave function was found to be

(23) Gaussian 94, Revision B.2; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1995.

antisymmetric ( $A''$ ) whereas that of the singlet state was symmetric ( $A'$ ) with respect to the plane of symmetry. This implies strong spin–orbit coupling between the two states.<sup>24</sup>

## Discussion

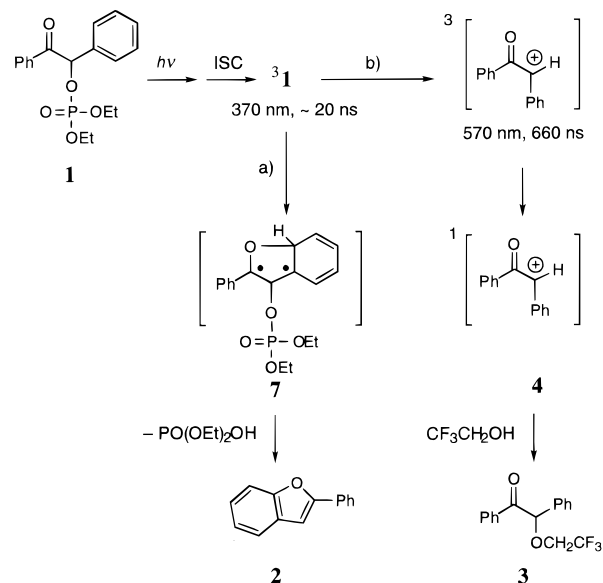
Previous mechanistic work has shown that both the nature of the leaving group and the aryl substituents strongly influence the mechanism and reaction efficiency of benzoin phototriggers. Sheehan and Wilson<sup>9,10</sup> observed that photochemical cyclization of 3',5'-dimethoxybenzoin acetate is not inhibited by piperylene, a triplet quencher, while cyclization of 4'-methoxybenzoin acetate was completely suppressed by it. Later, Pirrung and Shuey<sup>25</sup> confirmed the singlet mechanism for the photocyclization of 3',5'-dimethoxybenzoin phosphates by quenching studies with methylanthracene. Givens and co-workers<sup>11b</sup> have shown by Stern–Volmer analyses of product yields that unsubstituted benzoin phosphates undergo photocyclization through a triplet pathway. Heterolytic dissociation commonly occurs from singlet excited states. The suppression of the photodissociation of 4'-methoxybenzoin acetate<sup>10</sup> and of benzoin diethyl phosphate (**1**)<sup>11</sup> by triplet quenchers was an intriguing observation.

Cameron et al.<sup>26</sup> found that benzoin carbamates undergo efficient cyclization to the benzofuran only when the benzylic aromatic ring was methoxy substituted. Shi et al.<sup>14b</sup> reported nanosecond laser flash photolysis studies of several 3',5'-dimethoxybenzoin esters. They proposed a singlet mechanism involving an intramolecular exciplex and observed a short-lived cationic intermediate as a precursor of the benzofuran product. According to this mechanism, activation of the 2'-position of the benzene ring by the *m*-dimethoxy substituents facilitates the intramolecular cyclization. More recently, Rock and Chan reported the photochemistry of a water-soluble 3',5'-dimethoxybenzoin acetate.<sup>27</sup> The corresponding benzoin was obtained as the major photoproduct and the yield of benzofuran was only 30%. A biradical intermediate that undergoes acetoxy migration to give a cyclic precursor of both the benzoin and the benzofuran products was proposed to explain the mechanism.

In the present study, the lowest excited triplet state,  $^3\mathbf{1}$ , is established as the reactive excited state of **1**. Formation of  $^3\mathbf{1}$  by intersystem crossing was observed to occur within a few picoseconds of excitation by subpicosecond pump–probe spectroscopy (Figure 4). Nanosecond laser excitation of **1** in the presence of naphthalene led to the formation of triplet naphthalene by energy transfer. Lifetimes of 10–25 ns, depending on the solvent, were calculated for  $^3\mathbf{1}$  by various Stern–Volmer analyses.

Two competing reaction paths of diethyl phosphate elimination proceed from the triplet state of **1**, the relative yield of which is strongly solvent dependent (Scheme 1). Reaction path a dominates in most solvents except water and fluorinated alcohols. It generates 2-phenylbenzofuran (**2**) and diethyl phosphoric acid within 25 ns, as indicated by the sudden rise of the characteristic absorption by **2** at 300 nm (Figure 1). Moreover, strong fluorescence of **2** was observed by excitation

## Scheme 1



of pure **1** with a single laser flash, and that is attributed to re-excitation of **2** which is formed within the duration of the laser pulse.

The decay of  $^3\mathbf{1}$  was too fast for detection by nanosecond flash photolysis at room temperature, but the formation of **2** from  $^3\mathbf{1}$  could be resolved at reduced temperature. Flash photolysis of ethanol solutions at temperatures below  $-40\text{ }^\circ\text{C}$  initially gave broad transient absorption in the range of 300–440 nm, which is attributed to triplet–triplet absorption by  $^3\mathbf{1}$ . At  $-100\text{ }^\circ\text{C}$  this transient decayed with a rate of about  $2 \times 10^6\text{ s}^{-1}$  to form the final product absorbance by **2**. The apparently single-step transformation  $^3\mathbf{1} \rightarrow \mathbf{2}$ , which occurs within 20 ns at room temperature, is an amazing reaction. We assume that the rate-determining step in the formation of **2** is cyclization of the triplet to biradical **7** (Scheme 1), which eliminates diethyl phosphoric acid so rapidly that it is not observable as an intermediate. There is precedence for rapid addition of  $^3n\pi^*$ -excited ketones to aromatic compounds, e.g., the lifetime of triplet benzophenone is only a few microseconds in degassed benzene solution.<sup>28</sup> Fast release of  $\beta$ -leaving groups from radicals related to **7** is also well substantiated.<sup>29</sup> In particular, fast concerted elimination of diethyl phosphoric acid from a syn-configuration of **7** appears to be feasible in view of very recent calculations,<sup>29e</sup> despite the fact that deprotonation of carbon is usually slow.

We now discuss the evidence for the second reaction shown in Scheme 1, path b. The yield of **2** dropped to about 25% in trifluoroethanol; instead, the nucleophilic substitution product trifluoroethyl benzoin ether (**3**) was formed as a major product on irradiation. The chemical yield of **2** was also substantially lowered in hexafluoro-2-propanol and water. In these three solvents a new transient intermediate absorbing at  $\lambda_{\text{max}} = 570\text{ nm}$  was observed by nanosecond laser flash photolysis at room temperature (Figure 2). Formation of this species was complete

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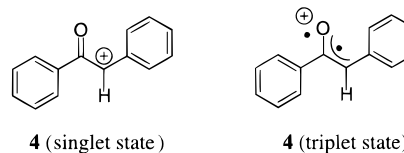
within the laser flash, and its decay observed the first-order rate law with a lifetime of about 500 ns (Table 1). Addition of naphthalene, which does not absorb at the excitation wavelength of 351 nm, reduced the amplitude, but not the lifetime of this transient in trifluoroethanol. At the same time, formation of triplet naphthalene by energy transfer was observed. Stern–Volmer analysis of the reduction of the 570-nm absorbance by naphthalene gave an estimated lifetime of about 18 ns for the triplet donor. Moreover, the quantum yield of both products **2** and **3** was similarly reduced in the presence of naphthalene. Thus, the triplet excited state of benzoin diethyl phosphate (**31**) is established as the common precursor to both benzofuran **2** and the transient observed at 570 nm which is a precursor of product **3**.

Cations **4** or **5** might be considered as possible intermediates for the formation of **3** in trifluoroethanol.<sup>30</sup> However, heterolytic dissociation of **31** to a singlet cation would be a spin-forbidden reaction, and assignment of the 570-nm absorption to a singlet cation may be ruled out by the long lifetime of this transient in aqueous solution (430 ns), which is similar to that in trifluoroethanol (660 ns).<sup>31,32</sup> Also, the absorption maximum is at longer wavelength than expected for a singlet cation of this structure.<sup>33</sup> On the other hand, neither of the other candidate structures that were considered for the 570-nm transient, namely radicals formed by homolytic cleavage of **31**, or a carbene formed by (sequential) *gem*-elimination of phosphate, appeared to be compatible with the observed properties of that species (reactivity, solvent dependence, absorption spectrum).

The decay rate of the 570-nm transient was accelerated in the presence of oxygen (Table 1), which suggested its assignment to a cation in the triplet state. The transient was also quenched by azide, bromide, and chloride ions. The quenching rate constant of chloride was 3 orders of magnitude below that of bromide and azide (Figure 3 and Table 1). Such a large difference in reactivity would not be expected for nucleophilic addition to a cation.<sup>34</sup> On the other hand, the low efficiency of chloride anion as a quencher is consistent with an electron-transfer mechanism. Electron-transfer quenching of excited triplet states by inorganic anions is well-known.<sup>35</sup> The rates of electron-transfer quenching depend on the excitation energy of the triplet state and on the ground-state reduction potential of the anion. The smaller quenching efficiency of chloride may then be attributed to its higher oxidation potential.<sup>36</sup> Dissociation of the geminate radical pairs formed by electron transfer quenching is usually much slower than back electron transfer, although formation of free radicals has been observed in some cases.<sup>37</sup> Back transfer appears to be predominant here, as no new transient absorptions were detected in the presence of halides,

and GC/MS analysis did not indicate the formation of any new products after laser flash photolysis in the presence of bromide or azide.

Density functional calculations were carried out to determine the relative energies of the possible intermediates **4** and **5** and to determine the ground-state multiplicity of these cations. Some earlier theoretical studies of acyl carbonium ions have attributed a lower energy to cyclic structures corresponding to **5**.<sup>38</sup> The present calculations showed the open structure **4** to be lower in energy than the cyclic structure **5** both in the singlet and triplet manifold. The lowest energy was found for the singlet state of **4**; the energy of the lowest triplet state was higher by 21.3 kcal mol<sup>-1</sup>. The density functional calculations predict substantially different structures for the lowest singlet and triplet state of **4**. The carbonyl group was found to be coplanar with the adjacent phenyl group in the singlet state, and with the benzyl cation moiety in the triplet state (Figure 5). Calculated spin densities, bond lengths, and Mulliken charge distributions suggest that the valence structures shown below may be used as simple descriptions of the electronic structure for the singlet and triplet state of **4** (*s-cis* shown).



Thus, we find that the triplet cation **34** is a plausible assignment of the 570-nm transient that is consistent with our observations and calculations. That intermediate may be formed adiabatically by heterolytic dissociation of diethyl phosphate from the  $n\pi^*$  excited triplet state of **1**. The energetics of the heterolytic dissociation in aqueous solution cannot be estimated from the gas-phase calculations available, but in view of the moderately facile  $S_N1$  solvolytic reactions of related compounds<sup>39</sup> there can be little doubt that formation of **34** from the excited triplet state of **1** ( $E_T = 73$  kcal mol<sup>-1</sup>)<sup>11b</sup> is substantially exothermic.

The decay rate of **34** is governed by triplet–singlet intersystem crossing (ISC), which precedes nucleophilic addition of the solvent. Schuster and co-workers<sup>40</sup> have shown that benzoyl-benzenediazonium salts generate triplet aryl cations upon excitation in trifluoroethanol, and that nucleophilic attack by solvent molecules takes place only after intersystem crossing to the singlet ground state. Cation **34** was not observed in a mixture of methanol (10 M) in trifluoroethanol, and that is consistent with the virtual absence of the nucleophilic addition products **3** or benzoin methyl ether in this solvent mixture. Derivatives of cation **4** have been observed in superacid media<sup>30b,39</sup> and one was even isolated as a solid salt.<sup>39b</sup> These cations rearranged and deprotonated to form the corresponding benzofuran derivatives at elevated temperatures. However, rearrangement of **4** to **2** does not occur in the present situation. Nucleophilic addition of the solvent (fluorinated alcohols or water) to the cation **4** after intersystem crossing to the singlet state is much too fast for cyclization to compete.

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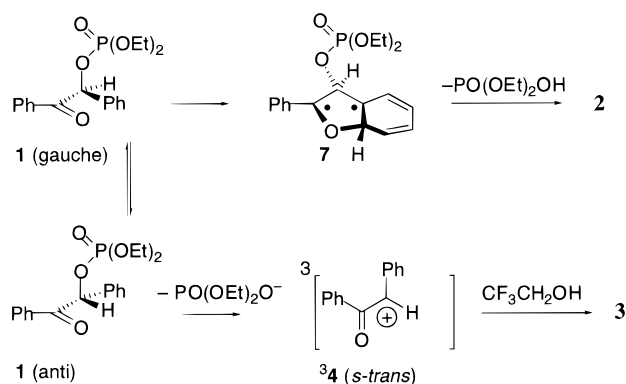
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## Scheme 2



The question remains, why heterolytic dissociation of **31** predominates in fluorinated alcohols and water, but is at best a very minor side reaction in all the other solvents used. One might argue that polar solvents favor heterolytic dissociation, but that would not explain the complete absence of path b in acetonitrile. We propose that the reaction may be driven by the preferred conformation of **1** in the ground state. Ring closure of **31** to diradical **7** requires a conformation in which the carbonyl group and the  $\alpha$ -phenyl group are in close proximity (as shown in the upper “gauche” structure **1** of Scheme 2). Such conformations of **1** may be disfavored for steric reasons in solvents forming strong hydrogen bonds to the carbonyl group (fluorinated alcohols and water). The lower “anti” conformation of **1**, favored by hydrogen bonding, would then yield the *s-trans* isomer of **34** by heterolytic fission.

The calculated triplet excitation energy amounts to only 1.7 kcal mol<sup>-1</sup> at the optimized geometry of the *s-trans* triplet state. It may be speculated that this sequence is reversed in polar solvents, and that may explain the somewhat lower than diffusion-controlled rate observed for quenching of **34** by triplet oxygen and the substantial activation energy of 8.6 kcal mol<sup>-1</sup> that was determined from the temperature dependence of the decay rate of **34**. The preexponential factor of  $A = 5 \times 10^{12}$  s<sup>-1</sup> is remarkably high for a spin-forbidden process, but this is consistent with the calculated electronic structures of the cation's singlet and triplet states.

## Conclusions

The release rate of diethyl phosphoric acid from the lowest excited triplet state of benzoin **1** is on the order of 10<sup>8</sup> s<sup>-1</sup> in polar solvents. The reactive excited state is the triplet state, **31**,

which was identified by transient absorption,  $\lambda_{\text{max}} \approx 340$  nm, and by energy transfer to naphthalene. Two different reactions proceed from **31**. In addition to a cyclization–elimination sequence yielding 2-phenylbenzofuran (**2**) as the major photo-product in most solvents (Scheme 1, path a), **31** dissociates adiabatically to the triplet cation **34** in water, trifluoroethanol, and hexafluoro-2-propanol (path b). The cation **34** is not an intermediate in benzofuran formation. It is trapped by nucleophilic addition of the solvent after rate-determining intersystem crossing to the singlet ground state ( $\tau \approx 430$  ns in water).

## Experimental Section

Acetonitrile (for UV spectroscopy), naphthalene, sodium bromide, sodium chloride, and sodium azide (all from Fluka) and 2,2,2-trifluoroethanol (Aldrich and Fluka) were used as received. All solutions of benzoin diethyl phosphate (**1**)<sup>11b</sup> and 2-phenylbenzofuran (**2**)<sup>11b</sup> in water contained 4% acetonitrile as cosolvent. Stirred solutions of ca. 10<sup>-4</sup> M concentration in 1 cm quartz cells were irradiated for 12–17 h using the filtered output of a Hanovia St-41 stabilized medium-pressure mercury lamp. The temperature of the solutions in the sample chamber was about 30 °C during irradiation, and blank controls were kept in the dark in the same housing for the same period. GC/MS data were recorded on a Hewlett-Packard 5890 series II GC employing a phenylmethylsilicone column (25 m) connected to a Hewlett-Packard 5970A series mass spectrometer. MS of **3** (*m/e*): 294 ( $\text{M}^+$ , 1%), 195 (3%), 189 (55%), 105 (100%), 91 (5%), 77 (45%), 51 (17%). Energy calculations were done by the B3LYP density functional method, using the 6-31G(d) basis set provided in the Gaussian 94 package.<sup>23</sup>

The nanosecond and picosecond laser flash photolysis equipment has been described previously.<sup>41</sup> Nanosecond laser pulses at either 351 or 248 nm were obtained from a Lambda Physik Compex 205 excimer laser (pulse width ca. 20 ns, energy ca. 100–140 mJ) and pulses at 308 nm from a Lambda Physik EMG 101 MSC excimer laser (pulse width ca. 20 ns, energy ca. 50–100 mJ). Picosecond laser flash photolysis experiments were carried out by the pump–probe technique using a 248-nm excitation pulse and a continuum probe pulse, both with subpicosecond lifetimes. Degassing of solutions was carried out by at least 3 freeze–pump–thaw cycles ( $<10^{-2}$  Torr). To study the effect of oxygen on transient kinetics, the solutions were equilibrated with air or oxygen at pressures controlled by a mercury barometer attached to the vacuum line.

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