# Mechanistic Studies on the Photochemical Deprotection of 3',5'-Dimethoxybenzoin Esters

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## ABSTRACT

Several mechanistic alternatives proposed for the photochemical deprotection of dimethoxybenzoin esters are presented. Both experimental and theoretical evidence suggest the mechanism is heterolysis of the singlet excited state to form a carboxylate and the  $\alpha$ -ketocation. The  $\alpha$ -ketocation has been observed by transient spectroscopy. We propose the  $\alpha$ -ketocation undergoes electrocyclization to an intermediate with extended conjugation, whose deprotonation gives the observed benzofuran product. A Brønsted study of the rates of benzofuran formation with dimethoxybenzoin esters derived from acids of varying  $pK_a$  shows the rate is independent of the basicity of the leaving group. In this multistep reaction, benzofuran formation by a final deprotonation is slower than  $\alpha$ -ketocation generation.

#### INTRODUCTION

Photochemically removable protecting groups play an important role in a variety of technologies in synthetic and bioorganic chemistry. One of the more attractive groups for the protection of acidic functionalities is the 3',5'-dimethoxybenzoin (DMB) ester because it is removed by long wavelength UV light (~350 nm) with a high quantum yield (64%) and high chemical yield, and generates an inert by-product, dimethoxyphenylbenzofuran (Eqn. 1) (1). We have used the DMB group to protect phosphates (2), carbamates (3), and carbonates (4), as have other workers (5–7).



This study focuses on the mechanism by which the DMB group is photochemically deprotected. A general feature of the X group is that it must be acidic, suggesting that a key part of the mechanism involves generation of X-. Several different mechanisms have been proposed for this process. In initial work (1), Sheehan suggested the reaction proceeds through the singlet excited state based on a lack of quenching by neat piperylene. He speculated that the

\*Corresponding author email: michael.pirrung@ucr.edu (Michael Pirrung) © 2006 American Society for Photobiology 0031-8655/06 singlet  $n,\pi^*$  excited state undergoes intramolecular [2+2] cycloaddition and the resulting highly strained intermediate undergoes ring



opening to cation 1 plus a carboxylate.

This cation has played a key role in many of the proposed mechanisms. Sheehan studied benzoin esters with varying substitution on the basic skeleton, observing that substituents strongly affect the efficiency of photochemical deprotection, with *meta*-dimethoxy groups on the non-conjugated ring giving the highest yields.

In our initial studies of benzoin photochemistry, these reactions were hypothesized to occur by photosolvolysis. A number of variants of benzoin acetate substituted in the non-conjugated ring were prepared and the efficiency of their photochemical deprotection examined (2). Besides the 3,5-dimethoxy substitution identified by Sheehan, 2,3-dimethoxy substitution gives very high yields. This observation was consistent with those of Wan, who showed that ortho electron-donating substituents enhance excited state photosolvolysis of simple benzylic alcohols as well or better than meta substituents (8). Comparison of the diethylphosphate and acetate esters of DMB revealed the half-life for loss of the phosphate is about 10% shorter than for the acetate. Additionally, attempts to quench either of these reactions with even relatively high (0.15 M) concentrations of methylnaphthalene failed, again strongly suggesting that the reactive excited state in both DMB phosphates and DMB carboxylates is the singlet. On this basis, we proposed the



Supporting this postulate is the work of Zimmerman on the photochemical meta-effect. His early observations on the photosolvolysis of substituted benzyl acetates showed that electrondonating groups at the *meta*-position were much more effective in promoting singlet excited state solvolysis than when they are in the para-position (9,10). He proposed a heterolytic mechanism for this process. More recent theoretical studies of the ion pairs and radical pairs derived from *m*-methoxybenzyl and *p*-methoxybenzyl acetate have concluded that electron-donating groups are more effective in stabilizing the singlet excited state of the benzylic cation when in the meta-position as compared to the para-position, the opposite of ground state behavior (11).

In studying the photochemical deprotection of unsubstituted benzoin phosphates, Givens initially proposed excited state C-O bond homolysis to form a radical pair, which then undergoes single-electron transfer to generate the ion pair (12,13). Cyclization of the  $\alpha$ -ketocation would generate a cation analogous to 1 as the precursor to 2-phenylbenzofuran. The deprotection of benzoin phosphate is a triplet reaction, as shown by a quenching study. Transient spectroscopy has supported two mechanistic paths for this reaction: direct cyclization to an unobserved intermediate that gives phenylbenzofuran directly, and heterolysis to form the  $\alpha$ ketocation in the triplet state ( $\lambda_{max} = 570$  nm) (14). After undergoing intersystem crossing to the singlet, the  $\alpha$ -ketocation can react with trifluoroethanol to form the corresponding ether. Of course, since this reaction involves a different excited state and leaving group, it is not directly relevant to reactions of DMB esters.

Further experimental studies on the mechanism of DMB ester photochemistry were performed by Shi et al. (15). Their work involved  $n,\pi^*$  excitation of four simple DMB esters (including the pivalate) in acetonitrile. The pivalate was expected to reveal any homolytic character of the reaction pathway, since if the pivaloyloxy radical were generated along with 2, it would rapidly decarboxylate. However, no trace of radical-derived products was detected with any of the four reactants, which also gave essentially the same efficiencies. These results in the steady state support the heterolytic mechanism. Shi *et al.* attempted to trap the  $\alpha$ -ketocation by irradiation in 1:1 water: acetonitrile, but observed no dimethoxybenzoin (or related products). Then, using transient spectroscopy in acetonitrile, they identified a species with a 485 nm absorption that appears within the 10 nanosecond rise time of their laser pulse, to which they assigned structure 1. This transient decays at  $10^6$  s<sup>-1</sup>. Addition of small amounts of water led to more rapid loss of the 485 nm species. Shi et al. proposed that the primary step of the reaction is a charge-transfer interaction of the electron-rich dimethoxybenzene ring with the electron-deficient  $n,\pi^*$  singlet excited carbonyl group to form an intramolecular exciplex, which leads to 1 directly. Because of the limited time resolution of this study, they state they had "no direct evidence to rule out the initial formation of the  $\alpha$ -ketocation."

Related studies of Rock and Chan examined bis-(carboxymethoxy)benzoin acetate (4), which was prepared to enhance the water solubility of the simple dimethoxybenzoin group (16). The electronic influence of carboxymethoxy groups on the photochemical reactivity of the benzoin was expected to be similar to methoxy groups. When the irradiation of 4 is performed in aqueous solution, the product is not only the dialkoxybenzofuran, but also the alcohol 5 (Eqn. 3). While this result provided the evidence in favor of the  $\alpha$ -ketocation (and therefore the heterolytic mechanism) that had

been sought by Shi et al., Rock and Chan proposed a quite different mechanism. They disfavored heterolytic cleavage on the basis of the divergent reactivity of the  $n,\pi^*$  state presumed to be involved in the DMB-ester photochemistry and the  $\pi,\pi^*$  excited states of benzyl esters that are known to undergo heterolysis. They instead suggested a radical-based addition of the excited carbonyl to the substituted aromatic, giving 6. Rearrangement of the acetate to the adjacent radical center could provide the closed-shell species 7, which could solvolyze to return 5 or eliminate to give the benzofuran. Rock and Chan also reported (on the basis of kinetic competition experiments) that the intermediate that is trapped by water (which they assign as 7) has a lifetime of  $\sim 5$  ps. The observed products could be more simply explained by direct reaction of a cation analogous to 3 with water. The divergence between the reaction of 4 to give 5 and the lack of formation of dimethoxybenzoin in DMB-acetate irradiation even in mixed organic/aqueous solvent systems may simply be a solvent effect, or





6

R

7

The mechanism of 3',5'-DMB-acetate photolysis has also been considered by ab initio theoretical methods (17). Goddard et al. identified the HOMO as primarily a  $\pi$ -type molecular orbital on the dimethoxybenzene ring, and the LUMO as primarily a  $\pi^*$ -type orbital on the carbonyl group. They suggested that the Franck-Condon excited state is formed by single-electron transfer from the dimethoxybenzene ring to the benzoyl group. Presumably this would generate species 8. Their calculations identify both SOMOs in the resulting open-shell singlet as residing (primarily) at the benzoyl carbonyl group. When the Franck-Condon excited state relaxes, it spontaneously closes to 9. Presumably, further steps are on the ground state surface. Species 8 can be converted to 9 using the electron-pushing formalism shown. Another form 9' can be obtained by an alternative electron-pushing. Species 9 and 9' are not proper canonical forms, but formally are interconverted by an electron transfer. They represent limiting forms of this reactive intermediate; if it is an excited state, both likely contribute. Goddard et al. suggest that 9 is the more accurate depiction of this intermediate and that it loses acetate and a proton to form the benzofuran. Form 9 is analogous to intermediate 6 proposed by Rock and Chan. Goddard et al. state that the determining factor in product formation upon photolysis of benzoin esters is electron transfer from the substituted benzene ring to the benzoyl group. Unclear in this proposal are the exact process by which 9 would be converted to the benzofuran, why an acidic leaving group is required in DMB

photochemistry, and whether any intermediates in this pathway correspond to the 485 nm transient observed by Shi et al.

Earlier studies of DMB ester photochemistry have addressed kinetics only briefly. No suggestions have been offered concerning the rate-determining step in any mechanism. The deprotonation of  $1 (10^6 \text{ s}^{-1})$  may be rate-limiting because 1 does accumulate for observation. Whatever intermediate is attacked by water to give 5 is clearly not involved in the rate-limiting step because of its ~5 ps lifetime.

Major open mechanistic questions in DMB ester photochemistry include whether the reaction proceeds via initial homolysis, direct heterolysis (Eqn. 2), or electron-transfer (Eqn. 4). This type of question appears often in mechanistic chemistry and can be approached in several ways (18). For heterolysis, a correlation is expected between the enthalpy of heterolysis and the  $K_{\rm b}$  of the resulting anion (19). We address this issue for DMB ester photochemistry by a Brønsted study, targeting a family of esters with leaving groups (X-) derived from acids of varying  $pK_a$ . The log of their rate should exhibit a linear free energy relationship with  $pK_b$  if generation of X- is the rate-determining step. Additionally, a pair of reactants was designed to give a common intermediate by cleavage of either a weaker C-S or a stronger C-O bond. Transient spectroscopy of several members of the family permitted observation of a common intermediate in DMB photochemical deprotection that is assigned as the  $\alpha$ -ketocation.



#### MATERIALS AND METHODS

General methods. All purchased starting materials were used without further purification. Dichloromethane was freshly distilled from calcium hydride. THF and diethyl ether were distilled from sodium/benzophenone. DMSO was used without further treatment. Chromatography was performed using silitech 60A silica gel. All NMR spectra were record on



a 300 MHz spectrometer. 3',5'-Dimethoxybenzoin was prepared by the known method.

The derivatives 10a-10e could be prepared by simple acylation of 3',5'dimethoxybenzoin with acid chlorides or anhydrides. The glycine esterhydrochloride 10f was prepared by EDC coupling with Boc-glycine and acid-promoted removal of the Boc group. The benzenesulfinate ester 10g was prepared by an unusual microwave-promoted reaction with the sulfinic acid (21). The thiolester 10h was prepared by displacement of the mesylate 10e. The thionester 10i posed a greater challenge—surprisingly, good solutions for the preparation of even thionobenzoates are not readily available (22). We used the method of Bosnich (23), which gave the target 10i only in low yield (Eqn. 5).



The details are presented below.

3',5'-Dimethoxybenzoin acetate (10a). To a solution of dimethoxybenzoin (1.40 g, 0.005 mol) and pyridine (0.6 mL, 7.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added a methylene chloride solution of acetyl chloride (0.75 mL, 7.5 mmol) over 0.5 h. The reaction mixture was stirred for 2 h at room temperature and washed with H<sub>2</sub>O, dil. HCl, dil. NaOH, and H<sub>2</sub>O. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. After rotary evaporation and recrystallization from methanol, the pure acetate **10a** was obtained as a white crystal in 60% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.94 (d, J = 7.5Hz, 2H), 7.52 (t, J = 7.5Hz, 1H), 7.40 (t, J = 7.5Hz, 2H), 6.76 (s, 1H), 6.59 (d, J = 2.4Hz, 2H), 6.42 (t, J = 2.4Hz, 1H), 3.74 (s, 6H), 2.21 (s, 1H).

3',5'-Dimethoxybenzoin benzoate (10b). Following the same procedure as for **10a**, the known<sup>1</sup> **10b** was obtained as a white crystal in 57% yield, Mp 142.0°C–142.9°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.13 (d, J = 7.5Hz, 2H), 8.01 (d, J = 7.5Hz, 2H), 7.56 (m, 2H), 7.44 (m, 4H), 6.99 (s, 1H), 6.71 (d, J = 2.4Hz, 2H), 6.45 (t, J = 2.4Hz, 1H), 3.78 (s, 6H). UV (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{max} = 237$  nm ( $\epsilon$  2.51 × 10<sup>4</sup>).

3',5'-Dimethoxybenzoin dichloroacetate (10c). Following the same procedure as for **10a**, **10c** was obtained as a white crystal in 80% yield (0.78 g from 0.7 g dimethoxybenzoin), Mp 83.4–84.8°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.93 (d, J = 7.5Hz, 2H), 7.55 (t, J = 7.8Hz, 1H), 7.42 (t, J = 7.8Hz, 2H), 6.81 (s, 1H), 6.60 (d, J = 2.1Hz, 2H), 6.45 (t, J = 2.1Hz, 1H), 3.76 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  191.9, 164.2, 161.5, 134.3, 134.1, 129.1, 129.0, 107.0, 101.8, 80.2, 77.6, 77.2, 76.9, 64.1, 55.7. UV (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{max}$  = 248 nm ( $\epsilon$  1.48 × 10<sup>4</sup>). Anal. Calcd. for C<sub>18</sub>H<sub>16</sub>Cl<sub>2</sub>O<sub>5</sub>: C, 56.41; H, 4.21. Found C, 56.85; H, 4.47.

3',5'-Dimethoxybenzoin methanesulfonate (10e). Following the same procedure as for **10a** except that pyridine (4 eq) and CH<sub>3</sub>SO<sub>2</sub>Cl (2 eq) were used, **10e** was obtained as an oil after chromatography in 22% yield (198 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.92 (d, J = 7.8Hz, 2H), 7.56 (t, J = 7.8Hz, 1H), 7.44 (t, J = 7.8Hz, 2H), 6.74 (s, 1H), 6.60 (d, J = 2.4Hz, 2H), 6.45 (t, J = 2.4Hz, 1H), 3.76 (s, 6H), 3.09 (s, 3H). UV (DMSO)  $\lambda_{max} = 260$  nm ( $\epsilon$  1.07 × 10<sup>4</sup>). Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>6</sub>S: C, 58.27; H, 5.18. Found C, 58.16; H, 5.23.

3',5'-Dimethoxybenzoin 4-nitro-benzoate. A methylene chloride solution of 4-nitro-benzoyl chloride (0.47 g) was added to a solution of 0.70 g dimethoxybenzoin and a catalytic amount of DMAP in 0.6 mL pyridine. The reaction was followed by TLC, and after 2 d, it was quenched with water. The organic layer was washed with water several times and dried. Removal of solvent followed by flash chromatography (1:5 ethyl acetate:hexane) gave 0.43 g (41% yield) of the yellow crystalline title compound, Mp 146.4–147.4°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.29 (s, 4H), 7.99 (d, J = 7.8Hz, 2H), 7.57 (t, J = 7.8Hz, 1H), 7.44 (t, J = 7.8Hz, 2H), 7.01 (s, 1H), 6.69 (d, J = 2.1Hz, 2H), 6.47 (t, J = 2.1Hz, 1H), 3.79 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  234.1, 203.9, 192.9, 168.6, 164.4, 161.6, 161.4, 151.0, 135.0, 134.50, 131.3, 129.0, 123.8, 107.2, 101.5, 79.0, 55.7. UV (DMSO)  $\lambda_{max} = 260$  nm ( $\epsilon$  2.77 × 10<sup>4</sup>). Anal. Calcd for C<sub>23</sub>H<sub>19</sub>NO<sub>7</sub>: C, 65.55; H, 4.54. Found C, 65.55; H, 4.75.

3',5'-Dimethoxybenzoin trifluoroacetate (10d). To a solution of dimethoxybenzoin (0.27 g, 1.0 mmol) in NEt<sub>3</sub> (0.14 mL, 1.0 mmol) cooled in an ice bath was added trifluoroacetic anhydride (0.26 mL, 2.0 mmol). After reaction for 1 d, the reaction mixture was evaporated. After flash chro-

 Table 1. Dimethoxyphenylbenzofuran production rate constants for

 10a-10i in DMSO. Allll ester solutions had the same absorptivity at the

 excitation wavelength of 350 nm

Ester	Acid	pK <sub>a</sub>	$k ({ m s}^{-1})$	Concentration (µM)
10e	CH <sub>3</sub> SO <sub>3</sub> H	1.6	$0.0090 \pm 0.0012$	43
10d	CF <sub>3</sub> CO <sub>2</sub> H	3.45	$0.0082 \pm 0.0006$	38
10i	PhCOSH	5.2	$0.0109 \pm 0.0001$	31
10h	PhCOSH	5.2	$0.0119 \pm 0.0005$	25
10c	Cl <sub>2</sub> CHCO <sub>2</sub> H	6.4	$0.0101 \pm 0.0003$	29
10g	PhSO <sub>2</sub> H	7.1	NA	35
10f	+H <sub>3</sub> NCH <sub>2</sub> CO <sub>2</sub> H	7.5	$0.0109 \pm 0.0004$	35
10b	PhCO <sub>2</sub> H	11.1	$0.0104 \pm 0.0005$	27
10a	CH <sub>3</sub> CO <sub>2</sub> H	12.3	$0.0105 \pm 0.0003$	30

matography with 1:8 ethyl acetate:hexane, **10d** was collected as 260 mg (71% yield) of a yellowish-white crystal, Mp 118.0–119.8 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.92 (d, J = 7.8Hz, 2H), 7.55 (t, J = 7.8Hz, 1H), 7.42 (t, J = 7.8Hz, 2H), 6.86 (s, 1H), 6.61 (d, J = 2.4Hz, 2H), 6.47 (t, J = 2.4Hz, 1H), 3.76 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  190.5, 161.5, 140.9, 134.2, 133.8, 133.6, 129.0, 107.1, 102.1, 99.5, 81.0, 55.8. <sup>19</sup>F NMR (CDCl<sub>3</sub>): –75.019. UV (DMSO)  $\lambda_{max} = 260$  nm ( $\epsilon$  1.00 × 10<sup>4</sup>).

3',5'-Dimethoxybenzoin glycinate hydrogen chloride (10f). To a CH<sub>2</sub>Cl<sub>2</sub> solution of dimethoxybenzoin (0.7 g), Boc-glycine (0.54 g), and a catalytic amount of DMAP was added over 0.5 h a solution of ethyl diethylaminopropylcarbodiimide (EDC, 0.74 g) in methylene chloride. After stirring overnight, the reaction mixture was washed with water, citric acid, sat. NaHCO<sub>3</sub> and water. Removal of the solvent gave ~1 g of crude Boc ester as the only product (91% yield). The Boc group was removed by 1M HCl in acetic acid and the product was recrystallized from CH<sub>3</sub>OH/Et<sub>2</sub>O. Compound **10f** was obtained from 0.158 g of the Boc ester in a 60% yield. <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  8.00 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.2Hz, 1H), 7.45 (t, J = 7.5Hz, 2H), 7.09 (s, 1H), 6.64 (d, J = 2.1Hz, 2H), 6.46 (s, 1H), 4.05 (d, J = 2.7Hz, 2H), 3.72 (s, 6H). UV (DMSO)  $\lambda_{max}$ =260 nm ( $\epsilon$  1.20 × 10<sup>4</sup>).

3',5'-Dimethoxybenzoin benzenesulfinate (10g). Benzenesulfinic acid (0.14 g, 1.0 mmol), dimethoxybenzoin (0.26 g, 0.98 mmol), and 0.4 g silica gel were ground with a mortar and pestle for 1 min. The mortar was placed in a domestic microwave oven for 60 s at full power. CAUTION: The mortar becomes very hot! Microwave treatment was repeated 3 more times for 60 s each, and the reaction mixture was poured into 4 volumes of ether and 1 volume of water. The ether layer was washed with NaHCO<sub>3</sub> solution. Flash chromatography gave **10g** (0.16 g, 40%) as a brownish oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.95 (d, J = 7.5Hz, 2H), 7.30–7.70 (m, 11H), 7.09 (d, J = 2.5Hz, 2H), 6.73 (t, J = 2.4Hz, 1H), 3.80 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  55.7, 107.3, 107.4, 127.4, 128.6, 128.8, 129.3, 129.7, 131.3, 132.8, 188.5, 134.5, 134.7, 136.4,142.7, 160.9, 194.1.

3',5'-Dimethoxybenzoin S-thiobenzoate (10h). To a mixture of **10e** (0.27 g, 0.77 mmol) and NEt<sub>3</sub> (0.17 mL, 1 mmol) in THF was slowly added thiobenzoic acid (0.13 mL, 90%, 0.80 mmol). The reaction mixture was washed with water and the solvent removed by rotary evaporation. Flash chromatography gave **10h** as a brownish oil (0.21 g, 70% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.08 (d, J = 7.8, 2H), 7.96 (d, J = 7.8Hz, 2H), 7.56 (m, 2H), 7.44 (m, 4H), 6.64 (d, J = 2.1Hz, 2H), 6.50 (s, 1H), 6.37 (t, J = 2.1Hz, 1H), 3.76 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 128.9, 127.6, 107.1, 100.7, 55.6, 55.0. UV (DMSO)  $\lambda_{max} = 260$  nm ( $\epsilon$  1.72 × 10<sup>4</sup>). MS: M<sup>+</sup> 392.

3',5'-Dimethoxybenzoin O-thiobenzoate (10i). Thiobenzoylsulfanyl acetic acid sodium salt was synthesized according to the literature and added to a suspension of NaH (0.08 g, 60%, 2 mmol) in 5 mL THF. After initial gas evolution subsided, the reaction mixture was heated to reflux and dimethoxybenzoin (0.27 g, 1.0 mmol) was added. The reaction mixture was heated for another 5 min and stirred at room temperature for 1 d. Flash chromatography gave white crystalline **10i** (10 mg, <2%). This yield was extremely low, but preparation of thionobenzoate compounds is difficult. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.13 (d, J = 7.5Hz, 2H), 8.01 (d, J = 7.5Hz, 2H), 7.55 (m, 2H), 7.43 (m, 4H), 6.98 (s, 1H), 6.71 (d, J = 2.4Hz, 2H), 6.44 (t, J = 2.4Hz, 1H), 3.78 (s, 6H).

Procedures for steady-state photoreactions of 3',5'-DMB esters. Solutions of 3',5'-DMB esters 10 were prepared in DMSO. The concentration of ester 10a in solution was 30  $\mu$ M. The concentrations of the other esters were adjusted (see Table 1) so that all samples had the same absorptivity at 350 nm. Two cuvettes were placed into the UV spectrometer, a blank with DMSO, the other with the prepared solution, and a baseline spectrum was recorded. The cuvette containing the ester was irradiated in a Rayonet reactor with 350 nm lamps for 20 s and the UV absorption was measured. The process was repeated 20 times and a UV absorption curve as the reaction proceeded was obtained.

Caculation of the absorption spectrum of 3. The absorption spectrum of 3 was calculated for a planar geometry in which the aromatic moieties were coplanar using ZINDO-S/RPA and taking into account the first 30 excitations.

Procedures for obtaining transient spectroscopy data. A commercially available tunable femotsecond laser system was used to perform the pumpprobe transient absorption experiments (Spectra Physics/Positive Light). The regeneratively amplified, Ti:Sapphire laser output (120 fs (FWHM), 0.9 mJ/pulse centered at 800 nm, 1 kHz repetition rate) was used to generate the pump beam at 350 nm and probe laser beams at 650, 620, and 490 nm, respectively. These probe wavelengths were selected based on the calculated absorption spectra for 3, vide infra. 80% of output power was used to pump an OPA (Spectra Physics), which generated the 350 nm excitation pulses for the experiments. The remainder of the laser output was used to generate a white light continuum in a thick piece of sapphire, which was then filtered to produce the 650-nm probe pulse. The pump and probe pulses traveled down different optical paths and were then recombined at the sample. The beams were imaged onto the sample to guarantee overlap of the two pulses, and the spot size used was 100 micron. The pathlength of the excitation pulses was varied using a stepper-motor system, which had a resolution of ~0.6 fs/step. All transient optical experiments were performed with a 1 mm quartz flowing cell under the condition of magic angle polarization between the pump and probe pulses. A pulse energy of 100 nJ/pulse was used in all experiments.

Prior to passing through the sample, a 5% reflection of the probe beam was detected by a photodiode. The remainder of the probe beam passed through the sample before being detected by a matched photodiode. The differential signal was detected by a lock-in amplifier and references to the chopping of the excitation beam at  $\sim 100$  Hz. A time constant of 300 ms was used and the time-delay was stepped every 1.5 s. The computer digitized the output from the lock-in amplifier after waiting for 10 times the time constant following the movement of the delay line. The detected probe beam signals (reference and sample) as well as that for the pump beams were directed to A/D converters so that the average power could be monitored over the time course of the experiment. Data analysis was performed using Origin 7.0.

#### RESULTS

The experimental design focused on DMB esters whose acids have known  $pK_{as}$  in organic solvent, relying on the extensive tabulation of  $pK_{as}$  in DMSO developed by Bordwell (20). The acids chosen span 10 orders of magnitude of  $K_a$ . The photochemical reactions of all but one of these compounds in DMSO proceed cleanly and in high yield to the corresponding acid and dimethoxyphenylbenzofuran. For kinetic studies, solutions of 10a-10i were irradiated with 350 nm lamps in a Rayonet photochemical reactor in a cuvette. This enabled the UV absorption of the common benzofuran product at 310 nm, which is significantly greater than that of the DMB esters, to be used to follow reaction progress. Data were taken at 20 s intervals to 1-2 half-lives and analyzed (24) to give rate constants for each reactant. An example of the kinetic data is shown in Fig. 1 for the irradiation of 10c. The rate constants for all molecules studied are given in Table 1 in increasing order of the  $pK_a$  of the conjugate acid of X- in DMSO. The standard deviation of each rate constant is no greater than 5%. The benzenesulfinate ester 10g did not provide well-behaved kinetic data under these conditions and was not further investigated. The invariance of the rate constants for these compounds with exactly the same chromophore and absorptivity at the irradiation wavelength (established by UV spectroscopy) but quite different leaving groups establishes that the chemical



Figure 1. The absorption at 310 nm (probing the benzofuran product) is followed as a function of photolysis time for solutions of 10c. The rate constants determined from such measurements are given in Table 1.

and quantum yields for all of these reactions are similar. The rates would exhibit significance variance if this were not the case.

It is apparent from the data that the quantum yield is independent of leaving group basicity. The differences in the rate constants are trivial in comparison to the 10 orders of magnitude range in the  $K_b$  of the leaving group. The variance seen here can be compared to the 10% variance we earlier reported for phosphate vs. ester leaving groups (in benzene solvent). One ester was prepared whose data are not included in this Table. The DMB *p*-nitrobenzoate gave an abnormally low rate constant (0.0037 s<sup>-1</sup>), which is attributed to competitive absorption of light and/or intramolecular quenching of the excited state of the benzoin. The comparison of **10h** and **10i** shows no significant difference in reaction rate constant.

The relative independence of these rate constants on leaving group suggested that the DMB-X bond cleavage is not rate-limiting for benzofuran formation in the steady state. In the hope of directly observing DMB-X bond cleavage (production of 2 or 3) and correlating its rate to leaving group basicity, femtosecond transient absorption spectroscopy was applied and the data was analyzed as previously described (25). While it is expected that 3 would absorb to the red of the unsubstituted  $\alpha$ -ketocation (570 nm) observed by Givens and Wirz, the spectrum of the cation has not been determined experimentally. In the absence of experimental data, we calculated the absorption spectrum of 3. For a structure in which the two phenyl rings are coplanar, the lowest energy transition was calculated to be centered at 660 nm. The next highest energy transition is predicted to occur at 490 nm. The calculated ratio of the oscillator strengths for the 490:650 optical transitions is  $\sim$ 5:1. On excitation of 10e with a femtosecond pulse at 350 nm, a transient absorption at 650 nm appears immediately (Figure 2). Similar transient absorption features were observed probing at 620 and 490 nm. The magnitude of the transient signal at 620 nm was an order of magnitude weaker than at 650 nm. The transient signal at 490 nm is at least a factor of 2 larger than that observed for 650 nm. These observations are consistent with the calculated absorption spectrum for 3. Control experiments demonstrate no such transient in pump-probe excitation of pure DMSO solutions, and no transient absorptions were observed probing at 800 nm. Analysis of the decay kinetics at these probe wavelengths give an excited state lifetime of  $13 \pm 2$  ps. Transient spectroscopy was also applied to acetate 10a and thiolbenzoate 10h, which with 10e



Figure 2. Femtosecond pump-probe spectroscopy of a  $4.28 \times 10^{-5}$  M DMSO solution of 10e with 350 nm pump pulse and 650 nm probe pulse. The solid line is a single exponential recovery with a time constant of 13 ps.

represent points throughout the regime of leaving group basicity. Similar transient absorptions and decay constants are observed at 650 nm for **10a** and **10h**. Based on the duration of the pump pulse (~200 fs), the intermediate giving rise to this transient must be formed with a rate constant  $> 10^{12} \text{ s}^{-1}$ .

### DISCUSSION

These studies demonstrate that the quantum yields for conversion of DMB esters to dimethoxyphenylbenzofuran are independent of leaving group for a wide range of leaving group basicities. Therefore, generation of X- cannot be the rate-determining step in benzofuran production. In light of the work of Shi *et al.*, a reasonable suggestion for the rate-limiting step is the deprotonation of 1. If that is true, this work could be considered a Brønsted study of the effect of base strength on the deprotonation reaction rate; if so, that rate is hardly dependent on basicity. Given the significant exothermicity of a reaction that generates an aromatic ring, the transition state must be quite early.

Upon the laser irradiation of several DMB esters, the observation of a transient intermediate with absorptions at 650, 620, and 490 nm that are consistent with the calculated absorption spectrum of 3 supports the heterolysis mechanism. This species decays with a 13  $\pm$  2 ps time constant, comparable to the 5 ps lifetime Rock and Chan determined for an intermediate that reacts with water in their system to produce the benzoin. Their isolation of benzoin rather than benzofuran in the presence of high concentrations of water with kinetics that reflect the high reactivity of the putative  $\alpha$ -ketocation intermediate 3 is consistent with our data. Because we were unable to resolve the growth in the absorption of 3 (this species being generated in less than 100 fs), it was not possible to correlate the rate constant of heterolysis to the basicity of the leaving group. Overall, our data and earlier studies support the stepwise mechanism for DMB ester photolysis given in Eqn. 6. Other evidence bearing on the photochemical reaction pathway for DMB esters includes the lack of decarboxylation product from DMB-pivalate reported by Shi et al., which strongly disfavors the radical mechanism.



The electron-transfer mechanism of Goddard et al. can be criticized on the basis of earlier structure-reactivity studies with substituted benzoin acetates (2,6). We apply it to the 2',3'dimethoxybenzoin ester, which we earlier showed has efficiency comparable to the 3',5'-DMB esters. As suggested by AM1 calculations, the HOMO of 2',3'-dimethoxybenzoin acetate is a  $\pi$ type orbital concentrated on the dimethoxybenzene ring, and the LUMO is a  $\pi^*$ -type orbital concentrated on the benzoyl ring, very similar to 3',5'-dimethoxybenzoin acetate. The HOMO-LUMO gap is slightly (2%) larger than in 3', 5'-dimethoxybenzoin acetate. Corrie showed that 3,5,3',5'-tetramethoxybenzoin acetate undergoes photochemical deprotection, but with efficiency about 10-fold lower than 3',5'-DMB esters, due to reduced absorptivity and quantum yield (6). However, MO calculations suggest that tetramethoxybenzoin compounds should be as efficient as 3',5'-DMB esters. The HOMO and LUMO of 3,5,3',5'-tetramethoxybenzoin acetate are topologically very similar to those of the dimethoxybenzoins above, and the HOMO-LUMO gap is  $\sim 1\%$ smaller. Even for these closely homologous reactants, the electrontransfer mechanism seems problematic. Goddard et al. also suggest that their studies could be used as the basis for design of novel groups that can be deprotected with visible or infrared radiation, presumably by decreasing the HOMO-LUMO gap by substitutions on the benzoyl (electron-withdrawing group) or non-conjugated (electron-donating group) rings. In fact, such molecules have already been prepared and studied. We observed a low reaction efficiency for 3'-dimethylaminobenzoin acetate (2). Calculation suggests the LUMO of this compound is similar to the other benzoin esters. The HOMO is higher-lying, but has different topological characteristics. The HOMO-LUMO gap is reduced by  $\sim 6\%$ compared to DMB, which should red-shift the absorption. The presence of the amine might also change the reaction mechanism, though tertiary amines are well-known donors in electron-transfer photochemistry. The ability of the unconjugated ring to transfer an electron to the benzoyl ring cannot be key as claimed by Goddard et al., since reaction efficiency is reduced by increasing basicity in the case of 3'-dimethylaminobenzoin acetate.

Generation of 3 from 10 is conceivably a reversible process. Ion pair return is certainly well-known in ground state solvolysis chemistry. Given that the photochemical process has an overall 64% quantum yield, at most one-third of 3 could return to starting material (that is, if ion pair return were completely responsible for the less-than-quantitative quantum efficiency). A classical method of detecting ion pair return in solvolyses is isotopic labeling of one of the oxygens of an ester, recovery of the starting material after partial reaction, and analysis of positional scrambling between isotopomers. In this study, we had built-in access to compounds for a similar experiment. Compounds 10h and 10i are isomers that might be interconverted by ion pair return, and they are readily differentiated by <sup>1</sup>H NMR spectroscopy on the basis of the chemical shift of the methine adjacent to S or O. Irradiation in  $d_6$ -DMSO to varying conversions revealed no evidence for crossover between 10h and 10i. This is a negative result that did not detect ion pair return, so it cannot prove that it does not occur.

Heterolysis is the only mechanism for DMB ester photochemistry consistent with all experimental data. Given the key involvement of the  $\alpha$ -ketocation in this mechanism, it was investigated by AM1 calculations. Its most stable ground state form has coplanar ketone and phenyl groups and coplanar carbocation and dimethoxyphenyl groups, but the ketone and carbocation are orthogonal. Rotation about the ketone-carbocation bond is necessary for ring closure to occur, which is strongly precedented in the ring closure of an analogous  $\alpha$ -ketocation (Eqn. 7), which was generated from the corresponding acetate by treatment with acid (26–28). Because of this precedent, we attempted to generate **12** photochemically from the acetate (26) to observe its reactivity, but instead observed products of  $\alpha$ -cleavage.



The suggestion by Shi *et al.* that an exciplex may form as a prelude to **3** was reasonable, but the very rapid formation of **3** suggests that no intermediate intervenes between DMB esters and **3**; the excited state is likely completely dissociative. There are significant precedents for similar heterolysis processes occurring on the picosecond time scale (29-32). That a transient we have assigned as the reactive intermediate **3** arises within the 120 fs laser pulse is also confirmatory evidence that the reactive excited state, its precursor, is a singlet.

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