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Mechanism of 3′,5′-Dimethoxybenzoin Ester Photochemistry: Heterolytic Cleavage Intramolecularly Assisted by the Dimethoxybenzene Ring Is the Primary Photochemical Step

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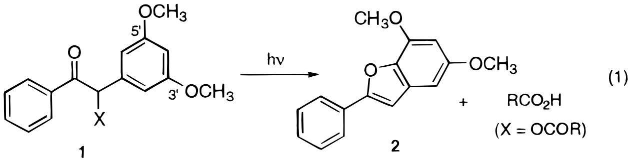
Photochemically removable protecting groups[2] are finding novel applications in the photorelease of biological compounds,[3] in the synthesis of biopolymer arrays,[4] and for photogenerating organic bases.[5] The 3′,5′-dimethoxybenzoin (DMB) system (**1**), and to a lesser extent the 3′-methoxybenzoin system, both orginally studied by Sheehan *et al.*[6a] for carboxylate esters, can efficiently photorelease a variety of functional groups[7] with >300 nm (typically ~350 nm) irradiation. Although photolysis of unsubstituted benzoin derivatives has been described by several groups,[6b,8] the reactions are generally less clean than for the 3′,5′-DMB system. Furthermore, there are significant mechanistic differences, since the photolysis of DMB carboxylates and phosphates is unaffected by triplet quenchers,[6a,7d] whereas unsubstituted benzoins are quenched.[6b,8a,b] The present paper addresses the photolysis of DMB derivatives (eq 1) at wavelengths >300 nm and, hence, exclusively involves n,π^* excitation of the acetophenone chromophore. The photoproduct arising from the DMB moiety is the benzofuran **2**, which is photostable.

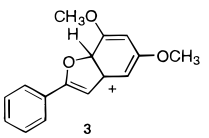


(1)

1 **2**

X = OCOR, OPO(OR)$_2$, OPO$_3^{2-}$, OCONHR, OCO$_2$R, etc.

Sheehan et al.[6a] proposed a Paterno-Büchi reaction of the singlet n,π^* photoexcited carbonyl group of the acetophenone with the 3′,5′-dimethoxybenzene group, resulting in the formation of a strained bicyclic intermediate. Ring opening with the loss of the acetate ion was suggested to give the dimethoxycyclohexadienyl cation **3**, followed by the benzofuran product **2** upon deprotonation. More recent versions of the mechanism have included (a) initial homolysis of the C−X bond of **1** followed by single-electron transfer to generate α-keto-cation **4**, which then reacts to give **3**,[5a] or (b) direct C−X bond heterolysis to generate **4**.[7d] With the growing importance of the DMB system in applied photochemistry, it is appropriate to study the mechanism in more detail, both for the intrinsic interest of the reaction and in order that directions for potential improvements can[9] be pursued. Herein we report the initial results of our mechanistic investigations of several DMB esters **5**−**8** and show by nanosecond laser flash photolysis (LFP) that **3**, which is formed within the laser pulse (~10 ns), is indeed on the reaction pathway. We present evidence supporting a new mechanism involving interaction of the electron-rich dimethoxybenzene ring with the singlet n,π^* excited state of the acetophenone (probably via a singlet exciplex), resulting in C−OCOR bond heterolysis to give cyclohexadienyl cation **3** in the primary photochemical step.



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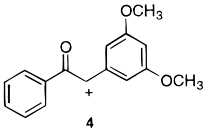

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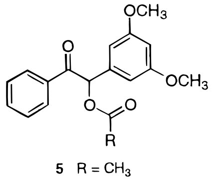

5 R = CH$_3$
6 R = CH$_2$Ph
7 R = Ph
8 R = C(CH$_3$)$_3$

Product studies were carried out for 3′,5′-dimethoxybenzoin esters **5**−**8** differing in structure only at the R group. In studies of benzyl and naphthylmethyl ester photosolvolysis, Pincock and co-workers[9] have shown a remarkable dependence of the ratio of products derived from ionic versus radical intermediates caused by the rate of decarboxylation of the acyloxy radical. In those studies, the pivalate ester gave the highest yield of radical-derived products, consistent with a very fast rate of decarboxylation for the pivaloyloxy radical [$(CH_3)_3CO_2^{\bullet}$, $k_d = 1.1 \times 10^{10}$ s^{-1}].[9a,b]

Photolysis of **5**−**8** in CH$_3$CN or 1:1 H$_2$O−CH$_3$CN gave only the photocleavage products shown in eq 1 with similar efficiencies for each ester. In contrast to the results of Cameron *et al.*[5a] with the related 3,3′,5,5′-tetramethoxybenzoin system, no trace of radical-derived products for any of **5**−**8** was observed.[10] The rates of decarboxylation of acyloxy radicals RCO$_2$**.** (for **5**−**8**) span

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(10) Conversions were taken to about 40−60% with excellent material balance by ^{1}H (300 MHz) NMR. The molar ratio of products **2** and the carboxylic acid RCO$_2$H is essentially unity as determined by ^{1}H NMR in samples photolyzed in sealed NMR tubes. The quantum yield ($\lambda_{ex} = 366$ nm) for reaction of **5** in 100% CH$_3$CN as reported by Sheehan *et al.*[6a] is 0.64 ± 0.03. Using this value as secondary reference, we have found that all of **5**−**8** react with the same quantum efficiency (100% CH$_3$CN; $\lambda_{ex} = 350$ nm).

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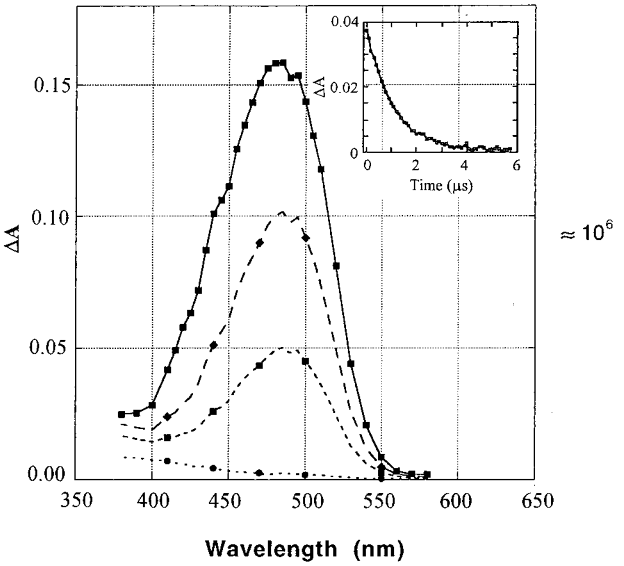
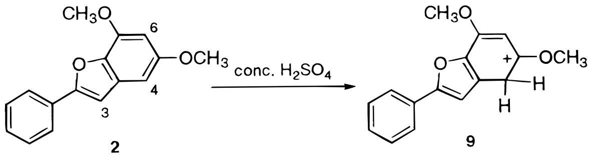


Figure 1. Transient absorption observed on LFP of flowing, oxygen-purged 100% CH_3CN solutions of **5**. Decay traces taken at 300 ns intervals [Inset: single-exponential decay of transient with $k_d = (1.0 \pm 0.1) \times 10^6$ s^{-1}].

4 orders of magnitude[9a,11] and the fact that all of **5**−**8** cleanly gave the same reaction (eq 1) argues against a mechanism involving initial homolysis of the C−OCOR bond, followed by electron transfer.

Nanosecond laser flash photolysis (YAG, 355 nm, <30 mJ) of flowing solutions of each of **5**−**8** in 100% CH_3CN (purged with O_2) gave the same absorption transient at 485 nm, which was formed within the laser pulse (~10 ns) and decayed with first-order kinetics, $k_d = 1.0 \times 10^6$ s^{-1} (Figure 1). Addition of small amounts of water (1−5%) resulted in faster decays of this transient: at 5% H_2O the decay was too rapid to allow its observation after the laser pulse. When **2** was dissolved in concentrated H_2SO_4 (or D_2SO_4), a visible band at 440 nm was observed that had a band shape similar to the 480 nm band observed on LFP. Workup of a solution of **2** dissolved in 2:1 20% D_2SO_4−CH_3CN resulted in >90% exchange at the 4-position (asssigned by NOE studies), the site expected in thermal protonation of **2** (eq 2). We therefore assign the



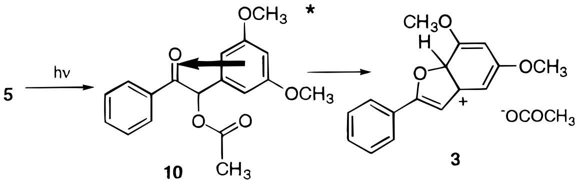
(2)

440 nm band to cyclohexadienyl cation **9**. The band at 485 nm observed in LFP is assigned to **3**, the cyclohexadienyl cation precursor to **2** in the photoreaction. The longer λ_{max} of **3** may be qualitatively explained by its more extended simple polyene-type π-conjugation, whereas **9** may be regarded as an allyl cation conjugated to a furan ring.

LFP studies of **5** in N_2-purged CH_3CN solutions gave an additional transient with $\lambda_{max} = 330$ and 420 nm and $k_d \approx 10^6$ s^{-1}. Introduction of air resulted in faster decay of this transient without affecting the 485 nm transient assigned to **3**. We therefore assign the 330, 420 nm transient to the triplet state of **5**.[12] Because the 485 nm transient assigned to **3** is formed in the presence or absence of oxygen with similar yields, the reaction of **5**−**8** most likely proceeds via their singlet excited states. This is further supported by the observation that chemical yields for formation of **2** from **5**−**8** were also not affected by the presence of oxygen.

The results described to this point do not give any direct information as to the pathway for photogenerating **3**, the only intermediate observable by ns LFP. We have no direct evidence to rule out initial formation of the α-keto cation **4**, although if it is formed, it would have to rearrange to **3** within 10 ns, which is not unreasonable. α-Keto cations are highly reactive carbocations, and those with an α-phenyl group (e.g., **4**) are known to rearrange to the corresponding benzofuran or undergo nucleophilic attack by solvent.[15] However, we have not observed any trace of the corresponding nucleophilic trapping product **1** (X = OH) in photolyses of **5**−**8** carried out in 1:1 H_2O−CH_3CN, which suggests that **4** is either not formed or rearranges very quickly to **3**.[16]

We propose a new mechanism for 3′,5′-dimethoxybenzoin photosolvolysis. The primary step is a charge-transfer interaction of the electron-rich dimethoxybenzene ring with the electron-deficient oxygen of the n,π^* singlet excited acetophenone, to form an intramolecular exciplex **10** (eq 3), which can return to **5** or react to give **3**. The *m*-dimethoxy substituents strongly activate the 2′-position of the benzene ring toward bonding to the carbonyl oxygen, giving rise to cation **3** in the primary photochemical step. This explains why such a substitution pattern of methoxy groups gives rise to the highest yields in benzoin ester photosolvolysis and photodeprotection. This mechanism also explains why no solvent-substitution or radical-derived products are observed in 3′,5′-dimethoxybenzoin photochemistry. More rational approaches to improving the photochemical efficiency of benzoin photodeprotection can now be pursued.



(3)

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Supporting Information Available: Preparation of esters **6**−**8**, representative photolyses, thermal deuterium exchange of **2**, representative absorption spectra of substrates, and a description of the laser flash photolysis experiments (7 pages).

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[12] The acetophenone moiety is the essential chromophore of these benzoins at 350 nm excitation. The triplet state of a variety of acetophenones has been reported to have absorptions in the 330−455 nm region[13] and for acetophenone itself has a triplet lifetime of ~0.1−0.2 μs,[14] which is readily quenchable by dissolved oxygen.

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[16] Pirrung and Shuey[7d] and Cameron *et al.*[5a] have suggested that **4** is formed in the primary photochemical step since the 3,5-dimethoxy-substitution pattern on the nonbenzoyl ring (both *meta* to the benzylic position) is known to enhance heterolytic cleavage at the benzylic position, (Zimmerman's *meta*-effect[17] (more correctly *meta-ortho* effect)[17a]). However, since only the acetophenone moiety is electronically excited at λ_{excit} >300 nm and energy transfer from acetophenone to dimethoxybenzene is prohibitive (E_s = 79 and 95 kcal mol^{-1}, respectively),[13] it is not clear how Zimmerman's *meta*-effect can operate here.

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