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Primary Photoreactions of the 3′,5′-Dimethoxybenzoin Cage and Determination of the Release Rate in Polar Media

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3′,5′-Dimethoxybenzoin (DMB) is an important photoremovable protecting group. The primary photoreactions of DMB acetate and fluoride following photoexcitation by a subpicosecond laser flash were investigated by pump−probe spectroscopy. The primary photoproduct is identified as a preoxetane biradical intermediate that decays by different pathways depending on solvent polarity. In polar solvents (acetonitrile, water), the biradical decays by releasing acetate or fluoride with a lifetime of about 2 ns. Thus, DMB is an excellent protecting group for the investigation of fast processes such as protein folding.

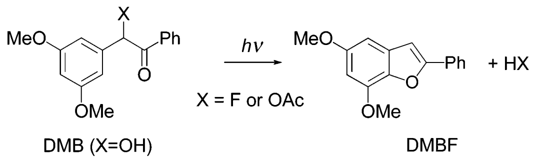
Introduction

3′,5′-Dimethoxybenzoin (DMB) has found numerous applications as a photoremovable protecting group (ppg),[1] e.g., in biochip fabrication,[2] muscle relaxation studies,[3] protein folding,[4] and unfolding,[5] and as a ppg for phosphates,[6,7] alcohols,[2a] and amines.[8] Yet the reaction mechanism is still under dispute (vide infra) and release rates from DMB derivatives are not known.

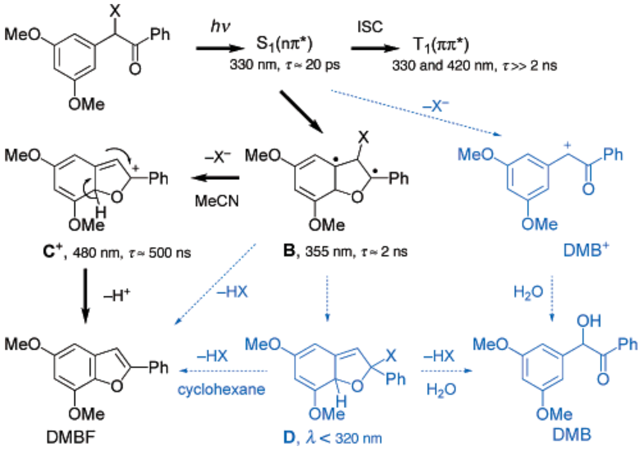
Sheehan and Wilson[9] discovered the photocyclization of benzoin esters in 1964 and anticipated their use for the photorelease of carboxylic acids.[10] They and others[7,8] studied the effect of substitution at the aromatic rings. *meta*-Alkoxy substitution on the nonconjugated phenyl gives the best results: DMB acetate cleanly eliminates acetic acid to yield 2-phenyl-5,7-dimethoxybenzofuran (DMBF) with a quantum yield of 0.64 (366 nm, acetonitrile),[10] Scheme 1. The photoreaction of the parent benzoin compounds proceeds via their lowest triplet state with lifetimes of several nanoseconds.[11,12] In contrast, the photoreaction of DMB ppg's is not quenched by naphthalene nor even in neat piperylene, indicating that the reaction proceeds from a very short-lived excited state, $\tau < 0.1$ ns. Yet, the short excited-state lifetime of DMB's is no guarantee for fast release, because the reaction may proceed via further, longer-lived intermediates that still retain the leaving group.

Several intermediates have been considered as primary photoproducts of DMB derivatives, including a strained bicyclic oxetane intermediate (intramolecular Paterno-Büchi cycloaddition),[10] and the carbocation DMB$^+$ (Scheme 2) formed either directly by heterolytic cleavage[8] of the C−X bond or by homolytic cleavage followed by electron transfer in the radical pair.[7] Shi, Corrie, and Wan observed a transient intermediate, $\lambda_{max} = 485$ nm, $\tau = 1$ μs, by nanosecond laser flash photolysis (LFP) of DMB acetate in acetonitrile and assigned it to the cyclic cation **C**$^+$. They postulated that **C**$^+$ is the primary product formed by intramolecularly assisted heterolytic cleavage of the excited singlet state.[13] Rock and Chan subsequently suggested that attack of the carbonyl oxygen on the dimethoxy-substituted phenyl ring forms a prebenzofuran biradical intermediate **B**.[14]

SCHEME 1: Photoreaction of DMB Fluoride and Acetate



SCHEME 2: Reaction Pathways of DMB (X = OAc, F) in Polar and Apolar Media



Note that the reaction is equally efficient in both polar (acetonitrile, water) and apolar (benzene, cyclohexane) solvents. Heterolytic reactions should be strongly disfavored in apolar solvents. We report a study of DMB fluoride and acetate in various solvents, which provides direct evidence for the forma-

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TABLE 1: Product Distributions after Irradiation of 0.01 M DMB Fluoride in Various Solvents[a]

solvent	DMB fluoride	DMBF	BA[b]	DMB-OCH_2CF_3	DMB
CH_3CN	13	86	1		
CH_3OH	3	93	4		
CF_3CH_2OH	37	29		34	
THF	5	75	20		
C_6H_{12}	3	95			2
CH_3CN/H_2O[c]	12 (9)	73 (71)			15 (20)

[a] Relative yields in % by GC/MS (naphthalene standard), irradiation time 2 h, $\lambda = 350$ nm. [b] 1,3-Dimethoxybenzaldehyde. [c] 1:1 by volume; values given in brackets were determined by H NMR.

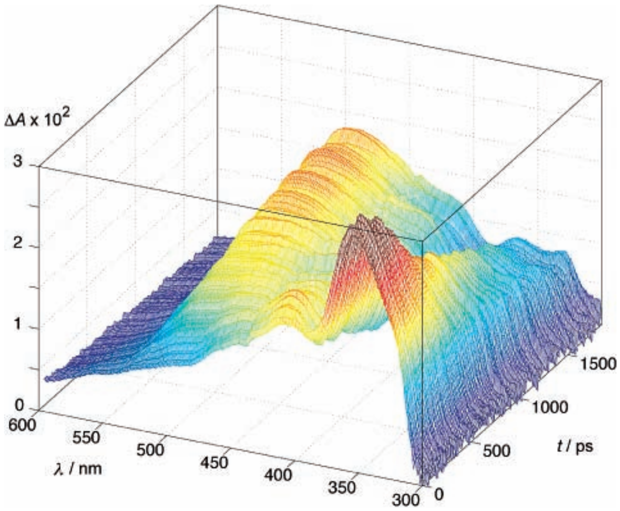

Figure 1. Pump−probe spectra of DMB acetate in acetonitrile.

tion of biradical **B** from the lowest excited singlet state S_1 and the ensuing reactions of this intermediate (Scheme 2).

Results and Discussion

Preparative photolysis of 0.01 M of DMB fluoride[15] at 350 nm gave predominantly DMBF in most solvents used (Table 1). The quantum yield of disappearance of the starting material was determined as $\varphi_r = 0.74 \pm 0.01$ in acetonitrile ($\lambda_{irr} = 350$ nm),[16] similar to that of DMB acetate.[10]

Pump−probe spectroscopy of DMB acetate (excitation with a 200 fs pulse at 260 nm),[17] in acetonitrile produced a set of transient absorbance spectra $A(\lambda,t)$ that were subjected to factor analysis. Three spectral components were required to reproduce the data within experimental accuracy (Figure 1). The lowest n,π* singlet state S_1 of DMB acetate appears within 1 ps of excitation. It exhibits broad absorption throughout the visible region and a pronounced peak at 330 nm. Least-squares fitting of a biexponential function to the reconstructed data matrix covering the time range of 1−1800 ps gave an adequate fit with rate constants $k_1 = (6 \pm 1) \times 10^{10}$ s^{-1} and $k_2 \approx 5 \times 10^8$ s^{-1}.[18] The fast reaction is attributed to the decay of the excited singlet state, which is seen as a decay of the peak at 330 nm and of the extended tail in the visible region. It is accompanied by a rise in absorption at 355 nm.

The transient spectra observed with delays around 50 ps with respect to the pump pulse arise from two species, which are distinguishable by their subsequent reaction kinetics, one with a strong maximum at 355 nm, the other with bands at 330 and 420 nm. The latter is stable up to 1.8 ns, the maximum accessible by the delay line, and is also observable by LFP on a microsecond time scale. It has been identified as the triplet state T_1 of DMB acetate.[13] The decay of the former, $\tau \approx 2$ ns, is accompanied by the growth of a broad absorption band in the visible, λ_{max} 480 nm, which is also observed by LFP of DMB acetate in acetonitrile and has been assigned to the cyclic cation $\mathbf{C}^+$.[13] Our observations support the earlier assignments of T_1 and $\mathbf{C}^+$, but $\mathbf{C}^+$ is not, as claimed, the primary photoproduct. We tentatively assign the precursor of $\mathbf{C}^+$, λ_{max} 355 nm, to the biradical intermediate **B** that Rock and Chan proposed to be the primary photoproduct.[4] Supportive arguments are given below.

Thus, intersystem crossing (ISC) to the triplet state T_1 competes with cyclization to the preoxetane biradical **B**. The triplet decays back to the ground state and does not participate in the reaction.[13] The rate of the primary reaction $S_1 \rightarrow \mathbf{B} + T_1$ is similar ($k \approx (3-6) \times 10^{10}$ s^{-1}) in all solvents, and so is the relative intensity of the transient absorptions by **B** and T_1. Pump−probe spectra determined with solutions of DMB fluoride in acetonitrile are similar to those of the acetate, as expected; the decay of intermediate **B** (X = F) is somewhat slower than that of **B** (X = acetate), $\tau \approx 3$ ns.

In cyclohexane, the lifetime of intermediate **B** (X = acetate) is about 1 ns, but none of the cation intermediate $\mathbf{C}^+$ is formed. Thus, an alternative pathway for the reaction of **B** to the final product DMBF must exist, which could either be reaction via **D** as proposed by Rock and Chan, or a direct, concerted elimination of HX. Fast release of leaving groups from radicals related to **B** has precedent[11] and is supported by theory.[19]

The mechanism of DMB photolysis in aqueous solutions is of particular interest, because that is the preferred medium for biophysical investigations. DMB's are only sparingly soluble in water, but a water-soluble DMB derivative has been synthesized.[4] We investigated DMB acetate in aqueous acetonitrile containing up to 60% (v/v) water. As observed previously by LFP,[13] the cation $\mathbf{C}^+$ is trapped by water. The decay rate of $\mathbf{C}^+$ increases linearly with increasing water content, until it escapes detection by LFP at a water content >2% (1 M). The slope of this plot gives the second-order rate constant for the reaction of $\mathbf{C}^+$ with water, $k_w = (5.7 \pm 0.2) \times 10^6$ M^{-1} s^{-1}. The amplitude of the $\mathbf{C}^+$-transient does not change up to this concentration.

Assignment of the primary photoproduct to the preoxetane biradical **B** nicely accommodates the fact that it is formed with comparable efficiencies and rates both in polar and apolar solvents and both from DMB acetate and fluoride. Moreover, the absorption spectrum of **B**, λ_{max} 355 nm, is consistent with the α-oxy-substituted, planar benzyl radical chromophore contained in structure **B**.[20] Finally, preparative photolyses (Table 1) and results available in the literature[2,3,8,10] suggest that the quantum yield φ_r of HX elimination hardly depends on the leaving group X or on the solvent. This is readily rationalized by assuming that the formation of biradical **B** is equally efficient and irreversible in all solvents, so that the quantum yield for formation of **B** is equal to that of the photoreaction, $\varphi_r \approx 0.64$, whereas ISC to the triplet state accounts for the rest, $\varphi_{ISC} = 1 - \varphi_r \approx 0.36$.

Rock and Chan observed only a 30% yield of DMBF by irradiation of their water-soluble DMB acetate in wholly aqueous solution.[4] Formation of the corresponding DMB derivative accounted for the reduced yield of DMBF. We also found major amounts of solvent addition products upon photolysis of DMB fluoride in trifluoroethanol or in aqueous acetonitrile (Table 1). We cannot exclude that solvent addition takes place via intermediate **D**, as proposed by Rock and Chan,[4] but reaction via DMB$^+$ seems more likely (Scheme 2).[7,8]

The dichotomy between the parent benzoin derivatives (reaction predominantly from the triplet state)[11] and the DMB derivatives studied here (reaction predominantly from the lowest excited singlet state) is remarkable. Singlet−triplet ISC of the parent benzoin compounds occurs within a few picoseconds and is at least an order of magnitude faster than that of the DMB derivatives, $k_{\text{ISC}} = \phi_{\text{ISC}}/{}^1\tau \approx 0.36 \times 6 \times 10^{10}\ \text{s}^{-1} \approx 2 \times 10^{10}\ \text{s}^{-1}$. Thus, fast ISC apparently precludes efficient reaction from the singlet state in benzoins. The triplet state of the DMB derivatives, on the other hand, is long-lived and nonreactive. This might be due to energy transfer to the nonconjugated DMB moiety; available reference data[21] suggest that the triplet energy of the latter is somewhat below that of the benzoyl chromophore (73 kcal mol^{-1}).[12]

Conclusion

The primary intermediate, $\lambda_{\max} = 355$ nm, that is formed within 50 ps from the nπ^* excited singlet state of DMB fluoride or acetate is assigned to the prebenzofuran biradical intermediate **B**. In polar solvents, heterolytic dissociation of the leaving groups X^- from **B** yields the cation $\mathbf{C}^+$, $\lambda_{\max} = 480$ nm, with rate constants of about $5 \times 10^8\ \text{s}^{-1}$. Thus, DMB is an excellent ppg that provides fast release with high quantum yields in acetonitrile or water.

The present results do not unambiguously define the release rate for HX in apolar solvents, where biradical **B** decays with a rate constant of about $1 \times 10^9\ \text{s}^{-1}$. The product formed from **B** does not absorb significantly in the visible region. Reaction of **B** to the neutral intermediate **D** was proposed by Rock and Chan.[4] The release of HX might then occur on a longer time scale.[22] Alternatively, a concerted elimination of HX from **B** is conceivable in apolar solvents (Scheme 2).

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