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A Case of Fast Photocyclization: The Model of a Downhill Ladder Reaction Pathway for the Bichromophoric Phototrigger 3′,5′-Dimethoxybenzoin Acetate

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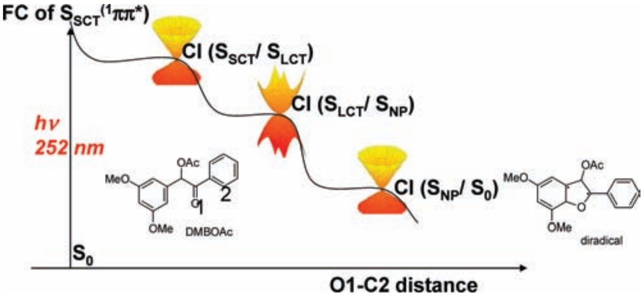
ABSTRACT



A downhill ladder reaction pathway for the bichromophoric phototrigger 3′,5′-dimethoxybenzoin acetate was mapped using ab initio multiconfigurational methods. These computational results explicitly describe a case of fast photocyclization that overcomes two small barriers (<5.0 kcal/mol) and undergoes three internal conversions (ICs) via efficient nonadiabatic relay of conical intersections among long and short distance charge transfer excited states as well as the nπ* excited and ground states. This novel reaction pathway is a consequence of the interaction of the two chromophores.

The 3′,5′-dimethoxybenzoin (DMB) system can function as a highly efficient photoremovable protecting group (PRPG) for the release of a wide range of functional groups such as inorganic phosphates, nucleotides, carboxylates, amines and alcohols.[1] DMB phototriggers have been extensively developed for applications in drug delivery, muscle relaxation studies, lithographic synthesis, biochip fabrication, protein folding and unfolding, and other areas.[2] As illustrated in Scheme 1, the DMB system undergoes photocyclization and deprotection reactions that generate the final products of the corresponding benzofuran (DMBF) and the leaving group. With the presence of a 2-fold *m*-methoxybenzylic substitution, the yield of the photocyclization for DMB acetate

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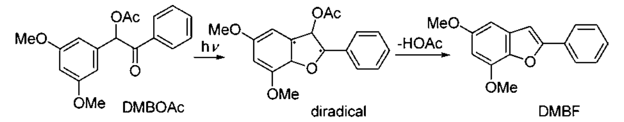
Scheme 1



increases substantially to become $\sim$0.64[3] compared to only $\sim$0.26 for the benzoin acetate phototrigger that does not contain any *m*-methoxybenzylic substitution.[1b] A concerted cyclization−deprotection mechanism mediated by a benzoyl-localized $n\pi^*$ triplet state was proposed for the parent benzoin-based PRPG.[1b,4] In contrast to this, several pieces of experimental evidence from triplet quenching studies and spectral characterization of some intermediates suggest that the deprotection of DMB probably proceeds via a singlet pathway and a number of different intermediates (including a cyclic cation, a carbocation, an intramolecular charge transfer (CT) exciplex, and a diradical species) have been proposed for involvement in the DMB deprotection.[5−10] Recent studies employing femtosecond transient absorption (fs-TA) spectroscopy[10,11] and nanosecond time-resolved resonance Raman (ns-TR^3) spectroscopy[11] concluded that an electronic interaction between the benzoyl (Bz) and dimethoxybenzylic (DMBn) chromophores plays a primary role in initiating a rapid ($\sim 1 \times 10^9 s^{-1}$ rate) stepwise DMB cyclization−deprotection. It was observed experimentally that the DMB cyclization is a very fast process occurring on the tens of picosecond time scale to produce a biradical species as the transient precursor to the subsequent deprotection step of the reaction. The fast cyclization was proposed to arise from a CT exciplex that is produced on an even faster time scale of several picoseconds. The formation of this CT exciplex appears to compete efficiently with the inherently rapid intersystem crossing observed previously in the parent benzoin system and has been considered as the key factor to account for the singlet nature of the reaction mechansim and the very high yield of the DMB PRPG.

The unusually rapid cyclization of DMB has little precedent in the literature. To gain more insight into how this fundamentally important reaction takes place and also to assess the long discussed essential role of a CT species in govening the excited state reaction pathway of aromatic carbonyls,[12] we used quantitative electronic structure calculations here to explicitly describe the nature of the excited states and intermediates involved in the reaction pathway of the DMB cyclization process. We have used a similar approach to obtain insight into the photodeprotection mechanism of *p*-hydroxyphenacyl-caged phototrigger compounds and also predicted a new type of photochemical reaction of a fast photodecarboxylation coupled by ultrafast excited-state intramolecular proton transfer (ESIPT) for some aromatic carbonyl compounds using the high-level ab inito methods of CASSCF and CASSCF/CASPT2.[13,14] By using the same ab initio methods for the excited state computations, we focus here on the particular steps related to the photocyclization of 3′,5′-dimethoxybenzoin acetate (DMBA) and explicitly describe how the photocyclization happens and clarify the uncertainty surrounding the mechanisms of DMB phototrigger compounds.

The ab initio calculations were done at the CASSCF level of theory with a total of 10 electrons in 8 active space orbitals (10e/8o) and the 6-31G*, 6-31G basis set. The minimum energy profiles (MEPs) in the $n\pi^*$ singly excited state ($S_{NP}(^1n\pi^*)$) and the short distance CT excited state ($S_{SCT}(^1\pi\pi^*)$) as well as the long distance CT excited state ($S_{LCT}(^1\pi\pi^*)$) were mapped by using two roots state-average multistep optimizations along the fixed O1−C2 distance. To consider the dynamical electron correlation effects for these points, the refined single-point energy was recalculated at the multiconfiguration second-order perturbation theory level (CASPT2) using a four roots state averaged CASSCF (10e/8o)/6-31G zeroth-order wave function. The vertical excitation energies, the corresponding oscillator strengths, and the transition dipole moments for the lowest three excited states of DMBA were found by using the ground state (S_0) CASSCF/6-31G optimizations followed by four roots state average CASPT2 and CASSCF state interaction (CASSI) computations. All of the calculations here were performed by using the Gaussian 03[15] and Molcas[16] program packages. For more computational details see the approriate section of the Supporting Information.

As shown in Table 1, the lowest excited state of the $S_0 \rightarrow S_{NP}(^1n\pi^*)$ transition originates from the promotion of the one electron of the lone pair carbonyl O1 to a π^* orbital that is delocalized along the whole Bz chromophore. The $S_0 \rightarrow S_{NP}(^1n\pi^*)$ transition for DMBA shows a modest dipole moment (0.763 D) and oscillator strength (3.2×10^{-5}). This suggests a "dark" spectroscopic state and a lower charge transfer (CT) character for the $n \rightarrow \pi^*$ transition, which is a common feature for compounds containing the Bz chromophore.[13] Unlike the $n \rightarrow \pi^*$ transition, two other excited

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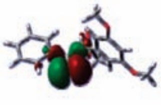
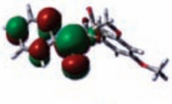
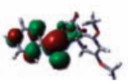
Table 1. Vertical Excitation Energies (ΔE), Oscillator Strengths (f), Dipole Moments (D.M.) at the Franck−Condon (FC) Minimum Geometric Structure for 3′,5′-Dimethoxybenzoin Acetate at the CASSCF(10e/8o)/CASPT2/6-31G Level of Theory, and the Character of Singly Occupied Orbitals for the Different Transitions

Transitions	D.M. (Debye)	Osc. Strength (f)	ΔE (kcal/mol)
S_0	1.66		0.0
$S_0 \rightarrow S_{NP}(^1n\pi^*)$	0.76	0.000032	84.7
$S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$	6.17	0.399	113.4
$S_0 \rightarrow S_{LCT}(^1\pi\pi^*)$	10.83	0.227	118.5
	character of singly occupied orbitals		
$S_0 \rightarrow S_{NP}(^1n\pi^*)$			
$S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$			
$S_0 \rightarrow S_{LCT}(^1\pi\pi^*)$			

states were found for DMBA that have a larger CT character. One electron is initially located in the benzyl ring of Bz to produce the $S_{SCT}(^1\pi\pi^*)$ state. The dipole moment significantly increases from 1.66 D in the S_0 state to 6.18 D in the $S_{SCT}(^1\pi\pi^*)$ state. The $S_0 \rightarrow S_{SCT}(^1\pi\pi^*)$ transition has a large oscillator strength (~0.4) and a vertical excitation energy corresponding to a ~252 nm UV excitation that coincides with the experimental absorption spectra.[11] This transition appears to contribute significantly to the UV light abosprtion of DMB compounds.

Besides the one chromophore (Bz) localized CT state ($S_{SCT}(^1\pi\pi^*)$), another excited state was observed in the FC excitation of DMBA that we denote as a long distance CT state ($S_{LCT}(^1\pi\pi^*)$), which is associated with the two chromophores. As depicted in Table 1, two singly occupied electrons become distributed into the two chromophores, respectively, for the $S_0 \rightarrow S_{LCT}(^1\pi\pi^*)$ transition. Meanwhile, a large dipole moment change of 9.17 D was observed upon this long distance charge transfer excitation. These results provide the first theoretical evidence showing the presence after photoexcitation of electron transport from the DMBn moiety to the Bz chromophore across a long distance in DMB systems. As illustrated in the excited state reaction pathway, this long distance CT state between the Bz and DMBn moieties appears to correlate with the CT exciplex proposed in the previous spectroscopic studies of the DMB cyclization and deprotection.[5,10,11] The present theoretical study provides an intuitive picture of the electronic and conformational features for such a CT character interaction, which can be a general phenomena and play a key role in many other excited state reactions of aromatic carbonyl compounds.[12]

As shown in Figure 1, 252 nm photoexcitation of DMBA takes the system to the FC region of the $S_{SCT}(^1\pi\pi^*)$ state. The wave packet of this excited state rapidly decays to a local minimum that is ~106 kcal/mol above the minimum of the S_0 state when the O1−C2 distance is slightly shortened from 3.24 Å in the FC region of the $S_{SCT}(^1\pi\pi^*)$ state to 3.20 Å. The wave packet of the excited state then overcomes a small barrier of less than ~5.0 kcal/mol to relax to a region of energetic degeneracy ($CI(S_{SCT}/S_{LCT})$) between the S_{SCT} and S_{LCT} excited states. The energy difference was determined to be 1.9 kcal/mol between the two states when the O1−C2 distance shortens further to become 3.1 Å. This energetic similarity allows the propagation of the wave packet of the exctied state to occur in a nonadiabatic manner. Although another local minimum was found at the O1−C2 distance of 2.90 Å, the trends of an uphill energetic curve for the $S_{SCT}(^1\pi\pi^*)$ state prevent further propagation of the wave packet toward a shorter distance in this charge transfer excited state. As shown in Figure 1, the barrier has already increased to become 16.3 kcal/mol in the $S_{SCT}(^1\pi\pi^*)$ surface with respect to local minimum at the O1−C2 distance of 2.90 Å when the reaction coordinate is changed to be 2.2 Å. This implies that the adiabatic channel along the surface of $S_{SCT}(^1\pi\pi^*)$ is an energetically unfavorable process but on the other hand the nonadiabatic pathway of the low-barrier $S_{SCT}(^1\pi\pi^*) \rightarrow S_{LCT}(^1\pi\pi^*)$ coversion via the $CI(S_{SCT}/S_{LCT})$ turns out to be a feasible process for the excited state population. This is in accordance with the recent fs-TA study that observed internal conversion from the photopopulated state (the $S_{SCT}(^1\pi\pi^*)$ here) to the CT exciplex (the $S_{LCT}(^1\pi\pi^*)$ state here) was a very fast process with a ~1.7 ps time constant.[11] The small barrier calculated for this process provides a theoretical interpretation to account for the experimentally observed rapid dynamcis and high efficiency of this process.

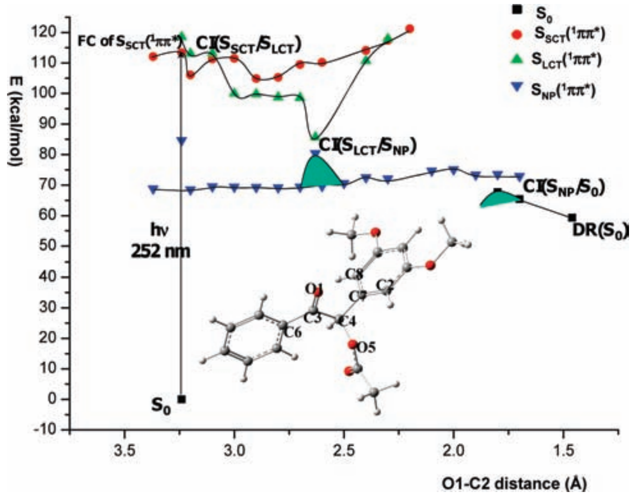


Figure 1. The minimum energy profiles (MEPs) of photocyclization for 3′,5′-dimethoxybenzoin acetate in the S_0, $S_{NP}(^1n\pi^*)$, and $S_{SCT}(^1\pi\pi^*)$, as well as $S_{LCT}(^1\pi\pi^*)$, electronic states along the reaction coordinate (RC) of O1−C2 distance at the CASSCF(10e/8o)/CASPT2/6-31G level of theory.

Once the wavepacket of the excited state population goes to the surface of the $S_{LCT}(^1\pi\pi^*)$ state, the long distance charge transfer starts to predominate the propagation of the wave packet. The dipole moment increases to ~10.0 D in the $S_{LCT}(^1\pi\pi^*)$ state from ~6.0 D in the $S_{SCT}(^1\pi\pi^*)$ state. The downhill curve connects $CI(S_{SCT}(^1\pi\pi^*)/S_{LCT}(^1\pi\pi^*))$ and there is a platform as the O1−C2 distance varies from 2.9 to 2.7 Å. Across this platform, the wavepacket of the excited state goes down to a deep potential well that corresponds to the minimum of the $S_{LCT}(^1\pi\pi^*)$ state with the O1−C2 distance shortened to become 2.63 Å. Further adiabatic propagation of the wave packet on the $S_{LCT}(^1\pi\pi^*)$ surface is hindered by a larger barrier (>~25.0 kcal/mol) along the RC of an increased O1−C2 distance. However, at this point, a second conical intersection between the $S_{LCT}(^1\pi\pi^*)$ and $S_{NP}(^1n\pi^*)$ $(CI(S_{LCT}/S_{NP}))$ states was revealed by the calculation, which may act as an efficient nonadiabatic point to relay the wavepacket to the lower excited state.

Unlike the energy curves of the $S_{SCT}(^1\pi\pi^*)$ and $S_{LCT}(^1\pi\pi^*)$ states, the energy profile of the $S_{NP}(^1n\pi^*)$ state exhibits a quasiparallel line with respect to the RC. This indicates that further propagation of the wavepacket along the RC may eventually lead to the photocyclization as a fast process with a small barrier. According to the calculation, this barrier appears in the region where the O1−C2 distance is shortened to become ~2.0 Å and has a ~5.4 kcal/mol energy with respect to the stationary point where the wave packet of the excited state initially reaches the surface of $S_{NP}(^1n\pi^*)$ at the O1−C2 distance of 2.63 Å. This barrier is partially responsible for the changes of the redistribution of the singly occupied electrons from the C3−O1 region of the configuration of the $n \rightarrow \pi^*$ transition to the C3 and C8 atoms of the diradical intermediate. The wavepacket in the $S_{NP}(^1n\pi^*)$ state first overcomes this small barrier and then proceeds along the RC rapidly to decay to a region of energetic degeneracy $(CI(S_{NP}/S_0))$ between the $S_{NP}(^1n\pi^*)$ and S_0 states. This third conical intersection $(CI(S_{NP}/S_0))$ was located at 73.5 kcal/mol above the zero level of the S_0 state where the O1−C2 distance is 1.8 Å and the energy difference is 5.8 kcal/mol between $S_{NP}(^1n\pi^*)$ and S_0 (at $CI(S_{NP}/S_0)$). The electronic population analysis concludes that the $CI(S_{NP}/S_0)$ is featured by a diradical configuration in which two singly occupied electrons distribute into the region of the C3 and C8 atoms, respectively. For this configuration, the absorption band with the largest oscillator strength is calculated to lie at ~68.9 to ~75.8 kcal/mol above the zero level of the $CI(S_{NP}/S_0)$. This is very close to the λ_{max} 370 nm[4] (77.3 kcal/mol) and λ_{max} 360 nm[10] (79.4 kcal/mol) transient absorption observed experimentally for the biradical species of photoexcited DMB phosphate and acetate, respectively. It is noted that, although the barrier height for formation of this biradical (5.4 kcal/mol) is similar to that of the initial $S_{SCT}(^1\pi\pi^*)$ to $S_{LCT}(^1\pi\pi^*)$ conversion (5.0 kcal/mol), the former requires the DMB system to undergo extensive nuclei rearrangements such as shortening the O1−C2 distance from 3.20 Å to 1.80 Å. This may impose an entropy associated barrier and account for the slower rate ($\sim 7 \times 10^{10}\ s^{-1}$) of the biradical production compared to the conversion to the $S_{LCT}(^1\pi\pi^*)$ state ($\sim 6 \times 10^{11}\ s^{-1}$).[10,11] This diradical acts as the key reactive precursor to the ensuing leaving group liberation as described in our recent paper.[11]

In this work, we report a case of a very fast photocyclization for a bichromophoric phototrigger compound DMBA that is mediated by a series of excited states and the reaction can be described by a downhill ladder relaxation pathway. This fast photocyclization is initiated by a spectroscopically activated short distance charge transfer state $S_{SCT}(^1\pi\pi^*)$ with the excitation localized in the Bz chromphore. The wave packet of the excited state then overcomes a barrier of less than 5.0 kcal/mol and decays via the conical intersection between the long and short charger transfer states $(CI(S_{SCT}/S_{LCT}))$ to the long distance charge transfer state S_{LCT} that originates from an electron transfer from the DMBn to Bz chromphores. Following this, the $CI(S_{LCT}/S_{NP})$ relays further propagation of the wave packet of the excited state to overcome a ~5.0 kcal/mol barrier leading to cyclization and production of the diradical species which may further decay to its S_0 state via a $CI(S_{NP}/S_0)$. Our computational efforts not only provide a theoretical model for the fast photocyclization from the CT exciplex to a biradical precursor as observed by spectroscopic studies for aromatic ketones[17,18] and phototrigger compounds[10,11] but contribute important implications for synthesis via photocyclization of compounds containing two or more chromophores.

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Supporting Information Available: Computational details and tables of Cartesian Coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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