Photochemistry

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Reporting the Release of Caged Species by a Combination of Two Sequential Photoreactions, a Molecular Switch, and One Color of Light**

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The use of photolabile molecules to unmask biochemically relevant compounds offers the spatial and temporal control required to assess the effects of particular chemical species on cells and organisms and to potentially release therapeutics on command.[1] Because light can be tuned and focused, it provides the on–off control many other stimuli lack and explains the increased efforts to develop photoresponsive small molecules capable of acting as molecular cages. Representative members of photoresponsive families successfully used for this application include coumarins,[2,3] ketoprofens,[4] 2-nitrobenzyl derivatives,[5,6] *o*-alkylated aryl ketones,[7,8] and molecules containing the benzoin[9,10] and *p*-hydroxyphenacyl groups.[11,12] To date, there are numerous reports describing how these compounds provide on-command control of bond-breaking processes in a variety of end uses ranging from their acting as protecting groups,[2–14] photolithographic agents,[15,16] molecular probes to studying biological processes,[17] and molecular delivery vehicles.[18–21]

Despite their popularity and technological potential, one major limitation of most release systems is their inability to provide information about when and where the uncaging event took place. Molecular delivery vehicles that can both release their payloads and report back to the end user about the event offer significant advantages to biochemical and biomedical research and potentially phototherapy. Most current systems that do report use analytical tools such as UV/Vis absorption,[13,22] fluorescence[4,14,23–27] and ^{1}H NMR spectroscopy,[20,22,28] and HPLC.[29] These methods rely on access to specific instruments and expertise that might limit their application in many working environments where convenience to nontechnical end users is a key requirement. A convenient alternative method is to use a visual readout, such as the changes in colors of solutions or films, which could be a direct and easy way for detection even using the naked eye. Another design feature that would be appealing when developing a system for release and reporting is the ability to tailor the molecular structure with functional groups that allow the end user to decide and differentiate between read-out signals, whether they have different colors or are a combination of colors and more sophisticated signals such as fluorescence, conductivity, and refractive index. The molecular system we describe here perfectly fits this description and is less prone to any structural modifications resulting in reduced photochemical performance.

Herein, we illustrate one of our strategies to develop a relatively universal, visual release-and-report system based on well-known photoreactions. The molecule highlighted herein combines the appealing properties of the dialkoxybenzoin photocage and the diarylethene class of photoswitches (Scheme 1), the former representing an effective photorelease system, the latter being unrivaled as a versatile molecular backbone that has predictable properties.

The hexatriene substructure found in diarylethene photoswitches is responsible for their undergoing ring-closing reactions when exposed to UV light (shown on the left-hand side of Scheme 1).[30–34] This reaction produces a new isomer having a unique set of optoelectronic properties due to the creation of a conjugated π-electron system running through the backbone of the molecule. Visible light triggers the reverse reaction and regenerates the original isomer. The significance of the diarylethene class of photoresponsive compounds lies in the structural diversity and ease of synthesis of systems that can be designed to undergo predictable changes in many specific optoelectronic properties. All diarylethenes undergo changes in their color, which is the focus of this report. They can also be tailored to change the way they fluoresce and phosphoresce,[35,36] rotate polarized light,[37] refract light,[38,39] and undergo electron-transfer reactions.[40] Any one or a combination of these characteristics can be used to provide spatial and temporal information about the release process. In the present example, color is the read-out signal, which is conveniently visible to the naked eye.

The other photoresponsive system we need to introduce is based on dialkoxybenzoins, which undergo bond-breaking reactions when stimulated with UV light and release a wide range of masked compounds including carboxylic acids, carbonates, and carbamates (shown on the right-hand side of Scheme 1). The key feature of interest in this process is the creation of a new carbon–carbon double bond in the benzofuran product because this bond can be used as one of the necessary alkenes in the photoresponsive hexatriene central in the diarylethene photoswitches.

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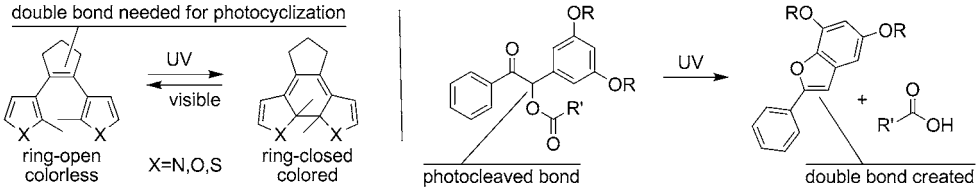
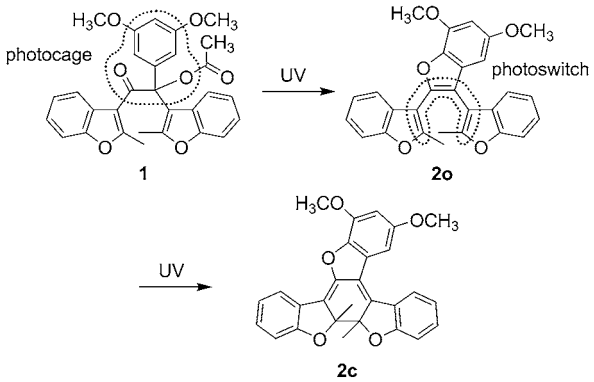


Scheme 1. Diarylethenes undergo reversible ring-closing reactions when exposed to two different colors of light (left). UV light triggers the release of carboxylic acids (and other functional groups) from dimethoxybenzoins to produce benzofuran derivatives (right). The key structural elements for each photoreaction are highlighted.



Scheme 2. UV light triggers both the release of acetic acid from the 2-acetoxy-1,2,2-tri(aryl)ethanone photocage and the ring closing of the resulting diarylbenzofuran photoswitch. The structural components required for each step are highlighted in compounds **1** and **2o**.

Our design principle is shown by compound **1** in Scheme 2 and involves two sequential photoreactions triggered by the same color of light. In the first reaction, the photorelease of acetic acid (eventually other molecules) generates a tris(benzofuran) derivative[41] **2o** bearing all three C=C double bonds in the hexatriene required for subsequent ring-closing (prior to the photorelease, only two of these double bonds are present in **1**). Responding to another photon of the same color, compound **2o** will be converted into its corresponding ring-closed isomer **2c**, which will possess unique, predictable and tunable optoelectronic properties as explained previously. While the visible light-induced ring-opening reaction is not formally involved in the release-and-report process, by being able to toggle the system between two optically unique isomers, it adds the component of time, which provides a better and heightened level of spatial resolution and can potentially distinguish false positive signals.

The synthesis of 2-acetoxy-1,2,2-tri(aryl)ethanone (**1**) is described in the Supporting Information. When an acetonitrile solution of this compound is irradiated with UV light (313 nm),[42] there is an immediate change in its color, from colorless to pink. This visual change in color is consistent with the production of the ring-closed isomers of similar diarylethenes suggesting that the release of acetate followed by ring-closing of the photoswitch occurred (**1**→**2o**→**2c**). This two-step conversion is supported by comparing the changes in the UV/Vis absorption spectra of **1** (Figure 1a) and the ring-open isomer of photoswitch **2o**, which was prepared independently for comparison and undergoes similar changes in its absorption spectrum when exposed to UV light (Figure 1b).[42] In both cases, there is an immediate appearance of a broad absorption band in the visible region of the spectrum (450–550 nm). This band disappears when either pink solution is irradiated with visible light at wavelengths greater than 434 nm, which triggers the ring-opening reaction and generates a solution of **2o**, in both cases.

The differences between these two experiments are the lack of an isosbestic point in the case of **1** (Figure 1a, top plot) and the difference in the rate at which the absorbance at 510 nm increases (Figure 1c) when **1** is compared to **2o**. While the changes corresponding to the ring-closing reaction of the pure photoswitch (**2o**→**2c**) is accompanied by a clear isosbestic point at 285 nm as is expected for this reaction (Figure 1b, top plot), the lack of one for the photolysis of **1** implies that there is more than one species involved in the

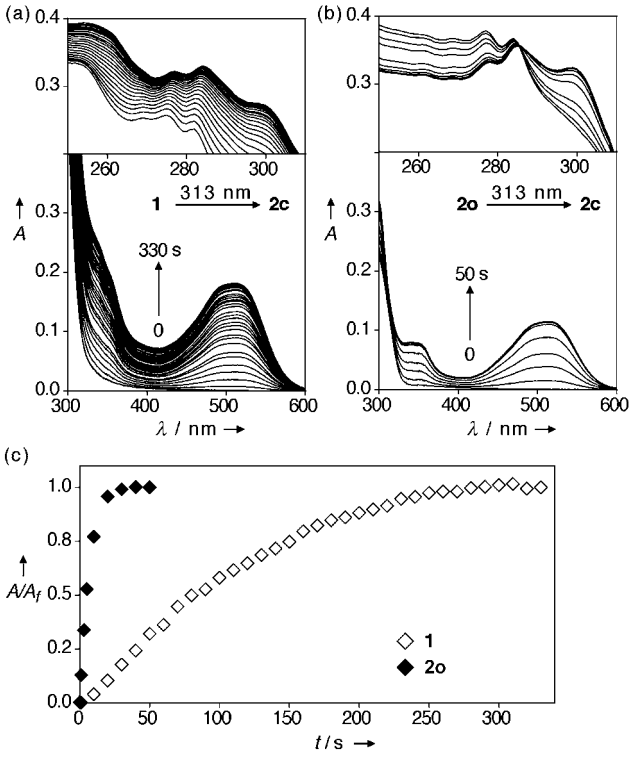


Figure 1. Changes in the UV/Vis absorption spectra of CH_3CN solutions of a) photocage **1** (top: 1.3×10^{-5} M, bottom: 5.1×10^{-5} M) and b) pure photoswitch **2o** (top: 1.6×10^{-5} M, bottom: 1.6×10^{-5} M) as they are irradiated with light of 313 nm. The concentrations for the bottom two plots were chosen to ensure the same absorptivity at 313 nm. The top plot in (a) was measured at lower concentration to show the lack of an isosbestic point. c) Growth of the normalized absorbance bands at 510 nm during the irradiation experiments described in (a) and (b).

photoreaction and supports the conversion of **1** to **2c** through **2o**. This multi-step process is further supported by the fact that a bulk photolysis of a solution of **1** using UV light, followed by exposure to visible light, and subsequent removal of solvent and purification of the residue by column chromatography afforded pure **2o** as characterized by ^{1}H NMR and other spectroscopic techniques.[42]

Figure 1c clearly shows that for the same light source and the same optical density at 313 nm, the pure photoswitch **2o** is converted to its ring-closed counterpart much faster than photocage **1** is converted to **2c**, implying that the first reaction (photorelease of acetate) is the rate-determining step in the entire process.[43] This conclusion is supported by ^{1}H NMR spectroscopy of a CD_2Cl_2 solution of photocage **1** as it is exposed to 313 nm light. When the irradiation is stopped before both photoreactions are complete, the spectra show an equilibrium consisting of all three compounds (**1**, **2o**, and **2c**) as expected. What is important about this equilibrium is the ratio of the integrated peaks corresponding to the ring-open and ring-closed isomers of the photoswitch (66:34), which is the same as for the photostationary state when a solution of **2o** is exposed to the same light source. Given the fact that the photoswitch in both of its isomeric forms (**2o** or **2c**) shows no spontaneous reactivity in the dark (the photoswitch has bistability), the amount of each isomer in these experiments is indicative of a slow photorelease followed by a much faster ring-closing reaction. This is an important feature of the system because it ensures that every release event provides a report signal. If the reverse was true and **1** was converted to **2o** faster than the ring-closing reaction (**2o**→**2c**), the report signal would not accurately represent where and when the release took place.

Laser flash photolysis studies[44,45] with excitation at 266 nm identified transient species in the UV-light photolysis of a nitrogen-saturated CH_3CN solution of compound **1**, having absorption peaks at approximately 340 and 500 nm (Figure 2a). The decay does not return to the baseline indicating the formation of a product with a lifetime longer than 10 μs. Control experiments with **2o** showed the formation of a species (Figure 2b) a long time after the laser pulse having an absorption peak similar to the ring-closed isomer **2c** formed in steady-state irradiation experiments. Therefore, we assign the off-set absorption for compound **1** to the formation of **2c**. The magnitude of the offset absorption for **2c** is not significantly affected by the presence of oxygen.[46]

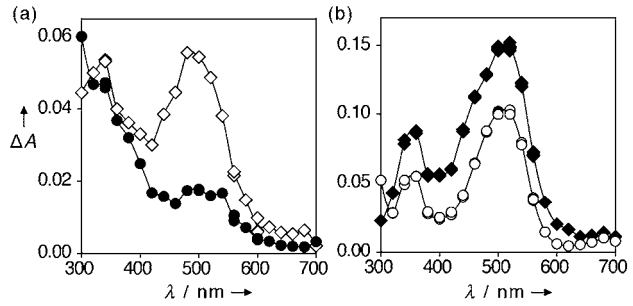
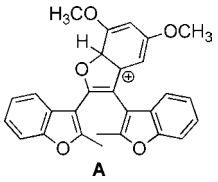


Figure 2. Transient absorption spectra for deaerated CH_3CN solutions of a) **1** (7.2×10^{-5} M) at 0.12–0.17 μs (◇) and 7.54–8.52 μs (●) delay times, and b) **2o** (3.8×10^{-5} M) at 0.12–0.17 μs (◆) and 7.58–8.56 μs (○) delay times. The lines in both plots were included to guide the eye. For delay times in between and decay traces see the Supporting Information.

Photolysis of the ring-open isomer (**2o**) led to the formation of a transient with a lifetime of 2.4 μs, which was shortened in the presence of air. This reactivity is consistent with the formation of the triplet excited state of compound **2o** as has been suggested in other studies.[47,48] The triplet excited state of **2o** is not involved in the formation of its ring-closed counterpart since the offset absorption at long delays is the same when the lifetime of the triplet is shorter in the presence of air. The transient studies with **2o** indicate that **2c** is formed within the laser pulse (15 ns), which is consistent with the femtoseconds to a few picoseconds[47–50] conversion of diarylethene photoswitches from their ring-open to their ring-closed isomers.

The transient decay of photocage **1** to the off-set absorption cannot be fit with random residuals to a mono-exponential function indicating the presence of more than one transient. The transient absorption spectra in the presence of nitrogen and air show the presence of a transient that is not quenched by oxygen with a maximum absorption at 500 nm. In the nitrogen bubbled solutions a new transient appears with broad absorption and a peak at 340 nm. The decay at 500 nm fits well to the sum of two exponentials, with recovered lifetimes of 0.7 and 2.4 μs. A previous report on the photolysis of 3′,5′-dimethoxybenzoin esters showed the formation of a triplet state with a lifetime of approximately 1 μs and absorptions at 330 and 420 nm, and a cationic species with an absorption maximum at 485 nm and a lifetime of 1.0 μs.[51] Our results for compound **1** are consistent with the formation of its triplet excited state and the comparable cationic species **A**. A recent study on the 3′,5′-dimethoxybenzoin photocage suggested that the photochemical pathway involving this cyclohexadienyl cation structure played only a minor role and a faster process could be the predominant pathway.[52] Due to the limitations of our equipment, we were not able to observe any other intermediates prior to generating the proposed cyclohexadienyl cation structure (**A**).



A

We are also assigning a triplet state to cage **1**[51] when it is exposed to UV light because the peak at approximately 340 nm in the transient absorption spectra (Figure 2a) does not appear in an air-saturated CH_3CN solution of the compound. The fact that the rates at which the absorptions corresponding to the ring-closed isomer (**2c**) increase under steady state conditions are almost identical when carried out on aerated and de-oxygenated solutions of **1** and **2o** shows that neither the triplet state effects the bulk photolysis of either compound.[42]

The photocage described in this report is capable of releasing and reporting using the same color of light. We regard this system to be a universal type of release system because a wide range of compounds should be readily unmasked as has already been shown for simpler versions. The diethienylethene architecture provides a high level of

versatility because the choice of read-out signal is not limited to the color, as has been shown by derivatives, the photoisomers of which vary in their emission, refractive index, and charge-transfer properties. Future work will focus on developing derivatives that are compatible with biological environments and release more biomedically relevant species.

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[42] See the Supporting Information for details.
[43] Determining the photolysis quantum yield of compound **1** requires knowledge of the quantum yields for the photolysis of **1**, **2o,** and **2c** because all these species absorb at the excitation wavelength. Such a detailed analysis was not pursued at this time because the qualitative picture is clear—the rate of photolysis for cage **1** is much slower than for photoswitch **2o**.
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