VIP Molecular Switches

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Selective and Sequential Photorelease Using Molecular Switches**

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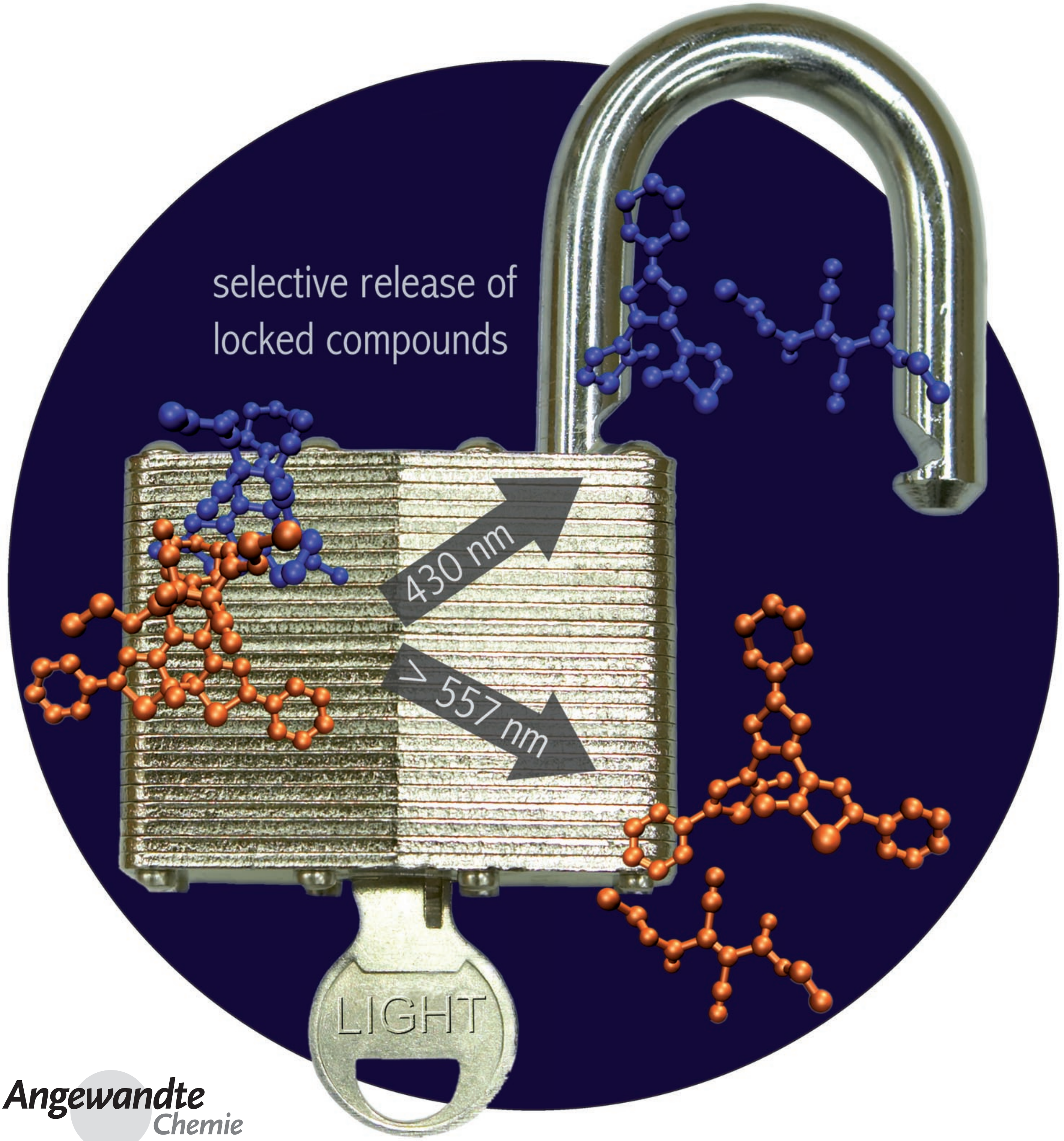
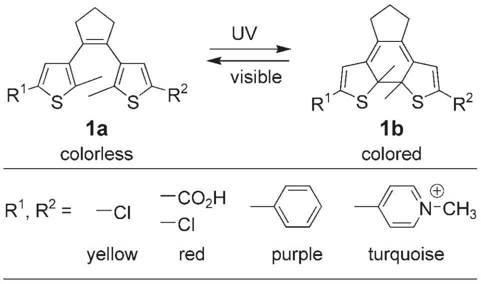


Light is an effective trigger for the release of active chemical and biological species from masked, innocuous forms.[1] It offers the precise temporal and spatial control needed to deliver therapeutics,[2] agents to initiate biological phenomena,[3] and designer reagents for chemical transformations,[4] as well as for photolithography.[4]

The number of classes of molecular structures that can be photochemically cleaved to free a species of interest is relatively small. Most existing systems are based on the photochemical redox reactions of the 2-nitrobenzyl group, with others based on 7-nitroindoline, coumarin, hydroxyphenacyl, and benzoin chromophores.[1,5] Widespread use of these systems in practical applications is limited by a number of factors such as the generation of reactive side products, the need for high-energy radiation sources (200–400 nm), which may lead to undesirable side reactions, and most significantly, the inability to selectively stimulate photocleavable groups in the presence of others due to their absorbing light in the same general spectral range.[1,3,5]

Our goal is to develop a universal photorelease system by using a common photoresponsive molecular scaffold that 1) can be easily tailored to fine-tune its electronic properties without adversely affecting its performance, 2) strongly absorbs long-wavelength light to minimize cellular damage, 3) generates photoreleased products which absorb at wavelengths that are shifted out of the spectral region that triggers the photorelease to minimize side reactions, and 4) is modified using synthetic methods tolerant to a wide range of chemistries.[6] A system that fits this description will offer a means to sequentially release different species by using light of different wavelengths. Here, we report our success in developing a versatile approach to the selective and sequential light-initiated release of an easily functionalized chemical species by using two different thermally bistable dithienylethene (DTE) photoswitches and low-energy visible light of two different wavelengths.

Dithienylethenes are molecular switches, which contain hexatriene architectures, that undergo reversible ring-closing and ring-opening reactions (**1a**⇌**1b** in Scheme 1) when irradiated with UV and visible light, respectively.[7] Scheme 1 also illustrates how the optical properties of the ring-closed forms (**1b**) can be fine-tuned by rationally decorating the two heterocycles on the DTE backbone; an attribute that is central in reports that describe the selective photoreactions of multicolored, multifrequency systems.[8] The same feature makes compounds based on the DTE architecture appealing for use in photodelivery applications.



Scheme 1. Photochemical reactions of the dithienylethene (DTE) architecture. The absorption properties attainable in the ring-closed forms **1b** can be fine-tuned by modifying the groups R^1 and R^2 at the ends of the π-conjugated backbone.

Our use of the DTE architecture as a photocleavable group combines two approaches to integrate chemical reactivity with light (reactivity-gated photoswitching and photogated reactivity) and is based on the Diels–Alder reaction between photostable dienes and a small dienophile to generate photoswitchable DTE derivatives (Scheme 2).[9] In reactivity-gated photoswitching, light does not induce a molecular transformation unless it is preceded by a chemical reaction between two or more species.[9] For example, dithienylfulvenes **2** and **3** are not photoswitchable as they lack the required hexatriene functionality. However, the butadiene portions of the compounds (highlighted in bold) spontaneously undergo thermal Diels–Alder cycloadditions with an electron-deficient alkene **4** to result in the formation of racemic **5a** and **6a**.[10] The rearrangement of the π bonds creates the DTE architecture and renders **5a** and **6a** photoactive. UV light can now be used to convert both DTE derivatives into their thermally stable ring-closed forms, **5b** and **6b**. Thus, the thermal reaction has gated the photochemistry.

In photogated reactivity, light triggers a structural change in the molecule and imparts chemical reactivity unique to each form of the compound. This approach is also illustrated in Scheme 2, where the reverse Diels–Alder reactions can proceed only from the ring-open forms of the compounds because **5b** and **6b** lack the cyclohexene structures required for the fragmentation reactions. UV light has effectively locked the systems in their "armed" states which removes all molecules from the initially established Diels–Alder equilibria. The ring-closed forms can be considered to act as phototriggers as visible light regenerates the cyclohexenes in **5a** and **6a** and allows the thermal Diels–Alder equilibria to be reestablished, spontaneously releasing the dienophile. Thus, the photochemistry has gated the thermal reaction.

Because the release mechanism is thermally driven and independent of the photochemistry, the photochemical triggers can be tailored to harness a wide range of wavelengths to release the small auxiliary agent, thus offering a relatively universal approach to photorelease technology. Also, the light absorbed by the ring-open isomers, the fulvenes, and the dienophile is significantly higher in energy and lies far outside

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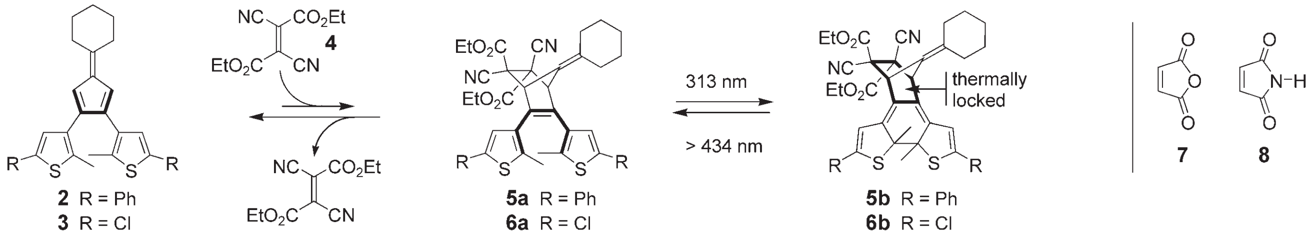
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Reversible Diels–Alder reactions of fulvenes **2** and **3** with dienophile **4** to generate racemic DTEs **5a** and **6a**, which undergo cyclization when irradiated with UV light. The thermally stable "armed" states, **5b** and **6b**, are unlocked with visible light to induce ring-opening, regenerating the cyclohexene necessary for fragmentation. Note that the stereochemistry of **5a**, **6a**, **5b**, and **6b** is arbitrary and does not imply the formation of specific stereoisomers.

the region used to trigger the photochemistry, thus minimizing photochemical side reactions. Another appealing feature is that the two photoisomers of DTE derivatives display a wide range of properties unique to their structure, offering a means to "release and report",[11] that is, to quantify the extent and location of discharge by monitoring a readout signal (color, refractive index, luminescence, or redox chemistry).[12]

We chose the fulvene structure as the Diels–Alder diene component because it undergoes both forward and reverse cycloaddition reactions[13] under milder conditions than those required for other dienes.[14] Dithienylfulvenes **2** and **3** can be prepared from two known DTE derivatives ($R^1,R^2 = Ph$;[15] $R^1,R^2 = Cl$[16] in Scheme 1).[17] As anticipated, compounds **2** and **3** show good photostability and their irradiation with UV or visible light results in minimal degradation.

Dithienylfulvenes **2** and **3** readily undergo Diels–Alder reactions when treated with electron-deficient dienophiles such as maleic anhydride (**7**) and maleimide (**8**; Scheme 2) to afford the bicyclic products in nearly quantitative yields as observed by ^{1}H NMR spectroscopy. The products of these reactions show excellent photoresponsive activity, and irradiating them at $\lambda = 313$ nm[17] leads to an immediate decrease in the intensities of the high-energy absorptions with simultaneous appearance of absorptions in the visible region as is typical for DTE derivatives. These changes are a result of the ring-closing reactions of the compounds, and the solutions are transformed from colorless to pink (when **2** is used) and yellow (when **3** is used). Irradiation of the colored solutions with visible light ($\lambda > 434$ nm) results in ring-opening, regeneration of the original absorption spectra, and bleaching of the solutions.

Although the Diels–Alder products formed using **7** or **8** show excellent photoactivity and are ideal models to characterize the photochemistry of the cycloaddition products, they are not suitable for photorelease applications as their cycloaddition reactions are not significantly reversible at room temperature. The esters of dicyanofumarate are more suitable and establish equilibrating mixtures of starting materials and products under much milder conditions.[18] When solutions of fulvenes **2** and **3** in CD_2Cl_2 are treated with diethyl dicyanofumarate (**4**), reversible reactions are immediately observed and the equilibria between the fulvenes and the racemic, bicyclic products **5a** and **6a** stabilize within 20 minutes (Figure 1a and b) and contain 40–45% of the ring-open products.[19] Equilibrium constants at 22 °C were determined to be $16\,\text{M}^{-1}$ for $\mathbf{2}+\mathbf{4}\rightleftharpoons\mathbf{5a}$ and $13\,\text{M}^{-1}$ for $\mathbf{3}+\mathbf{4}\rightleftharpoons\mathbf{6a}$ from the ^{1}H NMR spectra.

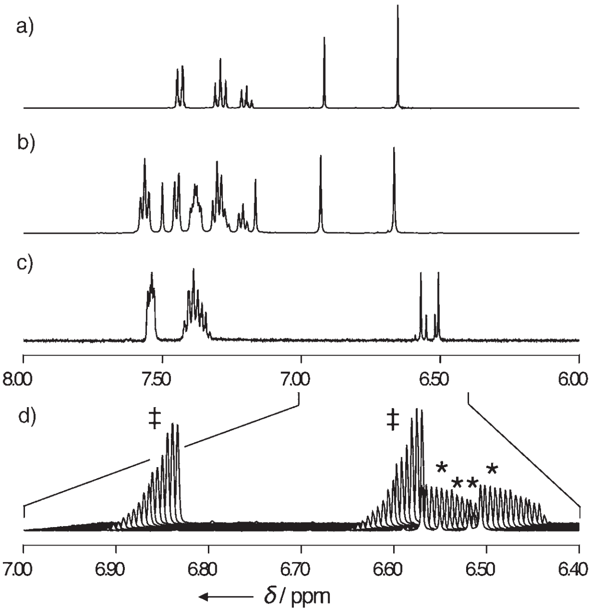


Figure 1. Partial ^{1}H NMR spectra (500 MHz, CD_2Cl_2) showing the peaks corresponding to the aromatic protons in a) fulvene **2**, b) a 1:1 mixture of **2** and diethyl dicyanofumarate (**4**) measured when the equilibrium with racemic **5a** has been reached, c) the isolated mixture of the ring-closed stereoisomers of **5b**, and d) a solution of **5b** periodically irradiated with visible light ($\lambda > 490$ nm) showing the disappearance of the ring-closed compound **5b** (*) and the appearance of fulvene **2** (‡).

The reverse cycloaddition reactions to generate compounds **2**, **3**, and **4** can be prevented by locking the structures in their ring-closed, "armed" forms **5b** and **6b**. Irradiation of solutions containing the fulvenes and fumarate **4** with 313-nm light produces compounds that are thermally stable and can be isolated by column chromatography (Figure 1c). As long as they are kept in the dark, both **5b** and **6b** can be stored with no observable degradation in solution and in the solid state at room temperature. Irradiation of the solutions with light of the appropriate wavelength in the visible range ($\lambda > 557$ nm for **5b** and $\lambda > 434$ nm for **6b**) triggers the ring-opening reactions and subsequent release of dienophile **4** (Figure 1d). In the case of **5b**, only the two starting materials (**2** and **4**) could be observed by ^{1}H NMR spectroscopy by the time a spectrum could be acquired.[20] Under the conditions used to monitor the release reactions by ^{1}H NMR spectroscopy (3×10^{-3} M) and UV/Vis absorption spectroscopy (3×10^{-5} M), there is quantitative release of the fumarate dienophile within the first 3 minutes of irradiation. When the release experiment using compound **5b** is repeated at lower temperatures (−10 to 0 °C), the ring-open isomer **5a** can be briefly observed before it undergoes the rapid thermal fragmentation reaction, illustrating that the photorelease mechanism proceeds through the ring-open isomer **5a** and not by a direct photochemical reaction.

Because **5b** and **6b** absorb different types of visible light, selective and sequential release can be achieved by tuning the light source to trigger the ring-opening reaction of only one of the ring-closed compounds. Figure 2 demonstrates the success of the selective ring-opening using UV/Vis absorption spectroscopy (Figure 2a–d) and the selective release using ^{1}H NMR spectroscopy (Figure 2e–h).[22] An equimolar mixture of compounds **5b** and **6b** could be irradiated at $\lambda = 430$ nm to selectively ring-open only derivative **6b** (Figure 2b), as it absorbs more significantly in this spectral region. Derivative **5b** is more effective at absorbing lower energy light and is virtually unaffected during this irradiation. Fulvene **3** and fumarate **4** are the only new products observed by ^{1}H NMR spectroscopy when the 1:1 mixture in CD_2Cl_2 is irradiated at $\lambda = 430$ nm (Figure 2f). Repeating the irradiation with lower energy light ($\lambda > 557$ nm) selectively ring-opens **5b** (Figure 2c) and releases the fumarate **4** from **5a** (Figure 2g) without affecting **6b**. Both compounds can be triggered to release the dienophile when irradiated at $\lambda >$ 434 nm (Figure 2d and h).

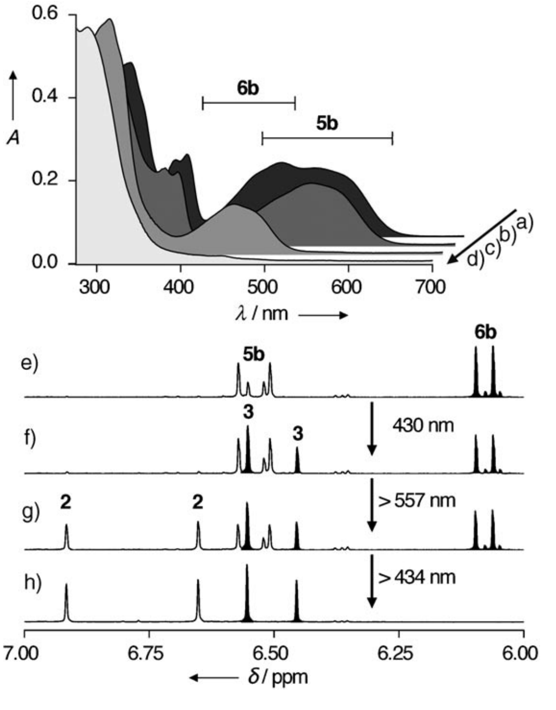


Figure 2. a–d) UV/Vis absorption spectra of a 1:1 mixture (in CH_2Cl_2) of the ring-closed compounds **5b** and **6b** (a), after irradiating the solution at $\lambda = 430$ nm (b), after irradiating a similar 1:1 sample at $\lambda > 557$ nm (c), and after irradiating either sample at $\lambda > 434$ nm (d). e–h) Partial ^{1}H NMR spectra (500 MHz, CD_2Cl_2) of a 1:1 mixture of **5b** and **6b**[20] (e), after irradiating the solution at $\lambda = 430$ nm to partially ring-open compound **6b** (f), after irradiating the same sample at $\lambda > 557$ nm to partially ring-open compound **5b** (g), and after irradiating the same sample at $\lambda > 434$ nm to fully ring-open both compounds (h).

In summary, we have presented a new approach to deliver chemical species based on combining reactivity-gated photochemistry and photogated reactivity. The light used to trigger the release reaction is in the visible range, leading to the dual advantages of limiting biological damage and increasing the penetration depth. In addition, the DTE substructure will facilitate the monitoring of the release events by using a wide range of physical properties, such as the absorbance or emission of light, or electrochemical properties which are unique to the "armed" and "released" systems. The economical size and chemistry of the fumarate auxiliary implies that it can be modified with various chemical species without significantly interfering with the role of the component of interest, thus offering a great potential for practical applications.

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[10] The stereochemistry of **5a**, **6a**, **5b**, and **6b** is arbitrarily drawn in Scheme 2. Compounds **5a** and **6a** are produced as racemates, while **5b** and **6b** are produced as a mixture of enantiomers and diastereomers. See Supporting Information for details.

[11] For a recent account of "release and report" using fluorescence, see: J. R. R. Majjigapu, A. N. Kurchan, R. Kottani, T. P. Gustafson, A. G. Kutateladze, *J. Am. Chem. Soc.* **2005**, *127*, 12458–12459.

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[19] To obtain measurable equilibria at the concentrations used for the experiment ($1–7\times10^{-2}$ M), 4 equivalents of **4** were added to the solutions of the fulvenes. The same results were obtained when dimethyl dicyanofumarate was used.

[20] The thermal release of **3** and **4** was significantly slower, and appreciable amounts of the ring-open isomer **6a** could be observed by ^{1}H NMR spectroscopy.

[21] Derivative **5b** was purified as a mixture of stereoisomers by column chromatography. Derivative **6b** was further purified by recrystallization (hexanes), which resulted in the enrichment of specific stereoisomers.

[22] Selective ring-opening was pushed almost to completion using different samples (Figure 3a–d) to demonstrate the high level of selectivity. In the case of the release experiments (Figure 3e–h), the same NMR sample was used to show sequential release. Irradiation of each compound was stopped after partial release for easy comparison of the spectra.