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Remote-Controlled Reactivity

Controlling Covalent Connection and Disconnection with Light**

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Dedicated to the centennial of the MPI für Kohlenforschung

Abstract: *The on-going need for feature miniaturization and the growing complexity of structures for use in nanotechnology demand the precise and controlled formation of covalent bonds at the molecular level. Such control requires the use of external stimuli that offer outstanding spatial, temporal, as well as energetic resolution. Thus, photoaddressable switches are excellent candidates for creating a system that allows reversible photocontrol over covalent chemical connection and disconnection. Here we show that the formation of covalent bonds between two reagents and their scission in the resulting product can be controlled exclusively by illumination with differently colored light. A furyl-substituted photoswitchable diarylethene was shown to undergo a reversible Diels–Alder reaction with maleimide to afford the corresponding Diels–Alder adduct. Our system is potentially applicable in any field already relying on the benefits of reversible Diels–Alder reactions.*

Feature miniaturization and the growing complexity of structures used in nanomaterials and nanotechnology demand the precise and controlled formation of covalent bonds on the molecular scale.[1–3] In a conventional dynamic reaction,[4–6] the distribution of products can be controlled by applying different chemical and physical triggers, such as temperature, pressure, or light.[7–9] As light delivers superior spatial, temporal, as well as energetic resolution, photoaddressable molecular switches[10,11] are rendered promising candidates to exploit the typical dynamic covalent reactions available to the organic chemist (such as the reversible formation of imines, hydrazones, oximes, thiols, aldols, boronates, or olefins by metathesis).[12–16] In addition to these transformations, the Diels–Alder (DA) reaction unifies a number of advantageous features: 1) tunable reversibility from endergonic, over highly reversible, to exergonic energy profiles,[17,18] 2) no by-product formation (self-containing nature), 3) catalysis is optional but not necessary,[19] and 4) applicability in solution as well as in gels or the solid state. Furan, in particular, has proved to be a versatile and powerful diene, especially in the field of reversibly cross-linkable polymers[20–23] and the reversible covalent functionalization of sp^2-hybridized carbon allotropes.[24,25] Temperature is the external stimulus for reaction control for the popular furan/maleimide couple, with characteristic reaction temperatures between 25 °C and 50 °C for the forward reaction and above 70 °C to 100 °C for the retro DA reaction. In stark contrast to kinetically controlled, non-dynamic DA reactions, the DA reaction between furan and maleimide is fine-tuned to be controlled thermodynamically and thus exists in a dynamic equilibrium at ambient conditions. It is because of this high reversibility that the temperature-dependent conversion into the adduct is generally not quantitative. Conversely, this dynamic character is the prerequisite for the integration of light as an additional stimulus that offers the possibility to reach a new level of control over this type of reaction.

A number of photochromic molecules exist that could be suitable for this task, with azobenzenes, spiropyranes, and diarylethenes (DAEs) being the most popular representatives.[26,27] However, thermal stability and high fatigue resistance in combination with large optical changes between their ring-open (**o**) and -closed (**c**) forms render DAEs the photochromes of choice for this purpose.[28] Indeed, Branda and co-workers reported a series of photoswitchable DAEs with a diene motif incorporated in their bridge moieties that can undergo DA reactions with various dienophiles and inhibit the retro DA reaction through photochemical cyclization of the adduct.[29–31] However, the intrinsic design margins do not allow for locking the DA reaction to either the side of the starting materials or the products by application of light. This is only possible through choice of different diene–dienophile combinations, as the unreacted diene is photochemically inactive. Having the possibility of using light as a stimulus to switch both the unreacted diene and the DA adduct is thus highly desirable to achieve photocontrol over the formation and scission of dynamic bonds (Scheme 1 a).

Herein we present, to the best of our knowledge, the first method for exerting such photocontrol over the connection and disconnection of dynamic covalent bonds, by employing a DAE as the diene and a maleimide as the dienophile in a reversible DA reaction. The desired ability to photoswitch both the unreacted DAE as well as the DA adduct sets certain demands on the molecular design of the respective target compound. The need to have a photoswitchable system that removes the reactive double bonds in the diene as well as in the adduct upon irradiation with light, thereby preventing either the DA reaction or the retro DA reaction, led us to replace one of the thienyl moieties of a dithienylethene by

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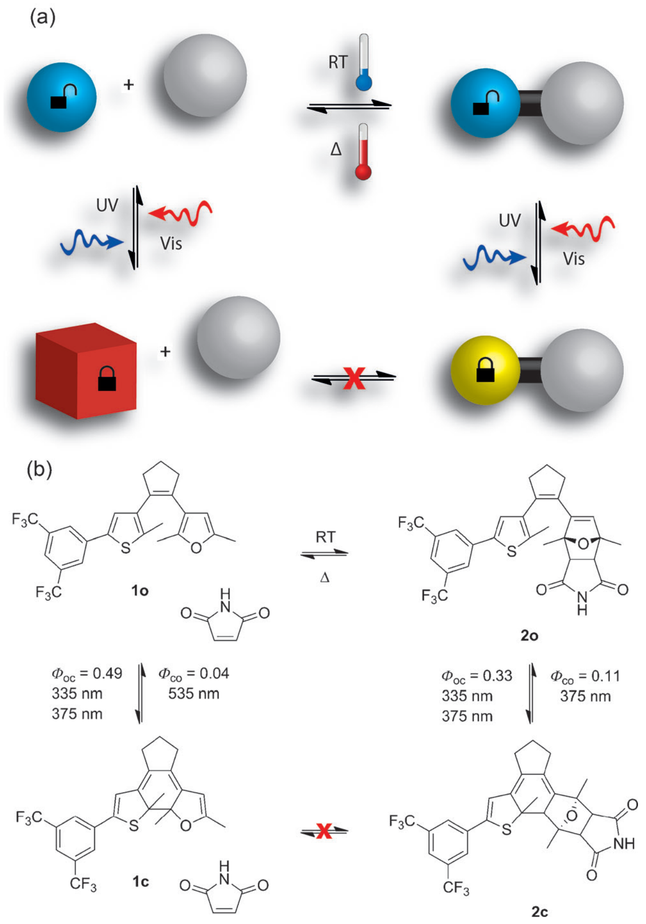

Scheme 1. Photocontrol over the formation and scission of a dynamic bond using photoswitches as locks. a) Concept. b) The different components **1o**, **1c**, **2o**, **2c**, and maleimide in the course of a photocontrolled Diels–Alder reaction, with the respective photocyclization and ring-opening quantum yields measured in toluene as well as the irradiation wavelengths employed for the in situ reaction.

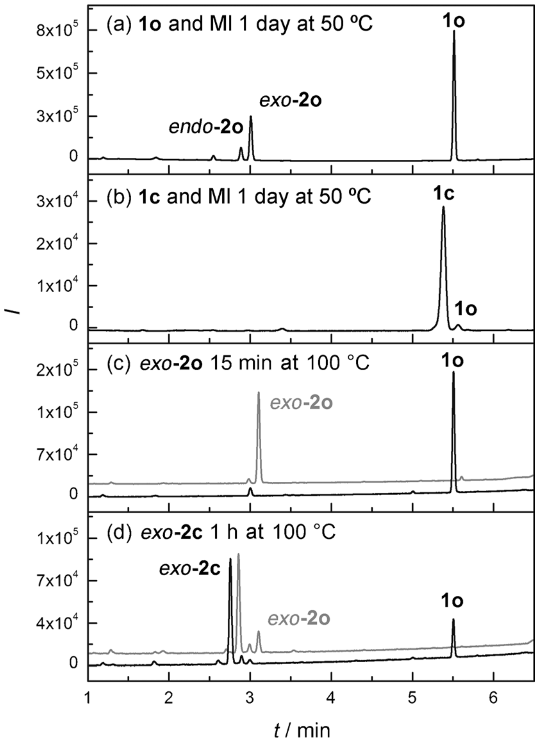

Figure 1. Locking the DA as well as the retro DA reaction with light: UPLC diode array traces of a) the formation of *exo*-**2o** and *endo*-**2o** after heating **1o** and maleimide (MI) at 50 °C for 1 day. b) No adduct formation is visible after heating **1c** and maleimide at 50 °C for 1 day. c) **1o** after heating *exo*-**2o** at 100 °C for 15 min (*exo*-**2o** before heating is shown in gray with offset for comparison). d) No retro DA for *exo*-**2c** is visible after heating a mixture of *exo*-**2o** and *exo*-**2c** at the PSS for 1 h at 100 °C (PSS of *exo*-**2o** and *exo*-**2c** before heating is shown in gray with offset for comparison). The concentration of switches **1o**, **2o**, **1c**, and **2c** was 10^{-5} M, that of maleimide 10^{-2} M.

incorporation of a furyl residue as the reactive diene (compound **1o** in Scheme 1 b).

Target compound **1o** can be synthesized in a straightforward manner on the basis of an established procedure.[32] DAE **1o** can successfully undergo a DA reaction with maleimide to yield the corresponding adduct **2o** as a mixture of *exo* and *endo* stereoisomers, the formation of which are reversible at 100 °C (Scheme 1 b). Although both stereoisomers were isolated and appear to exhibit the same spectral characteristics, only the thermodynamically more stable *exo*-**2o** was employed for thorough analytical characterization and photochemical investigations. Both switches **1o** and *exo*-**2o** show fully reversible photochromism, with suitable photocyclization and ring-opening quantum yields as well as almost quantitative conversion into the ring-closed isomers at their respective photostationary states (PSSs). Further details on the synthesis and spectral characterization are described in the Supporting Information.

Two main aspects can be extracted from Scheme 1 b: 1) Photocyclization of **1o** to **1c** removes the reactive *cisoid* diene functionality of the furyl moiety and thus prevents the molecule from participating in the DA reaction; and 2) ring closure of **2o** to **2c** removes the reactive double bond from the oxanorbonene skeleton, thereby thermally locking the adduct and preventing the retro DA reaction. As can be seen in Figure 1 a, the reaction of **1o** with maleimide results in conversion into adducts *exo*-**2o** and *endo*-**2o** even at very low concentrations. To prove that the forward DA reaction can be inhibited by photocyclization, **1o** was irradiated to the PSS, which consists almost only of **1c**, and then submitted to the same reaction conditions. No apparent conversion into the DA adduct was observed (Figure 1 b). In an analogous manner, Figure 1 c shows the smooth retro DA reaction from *exo*-**2o** to **1o** upon heating. However, heating a mixture of *exo*-**2c** and residual *exo*-**2o** at the PSS clearly reveals that the ring-closed adduct *exo*-**2c** is unreactive and stable under these conditions and only the residual amount of the ring-open isomer *exo*-**2o** can undergo the retro DA reaction (Figure 1 d). Effects caused by thermal ring-opening of the ring-closed forms were ruled out by control experiments in which only **1c** or **2c** were submitted to the same reaction conditions in the dark; this resulted in no notable ring opening being observed.

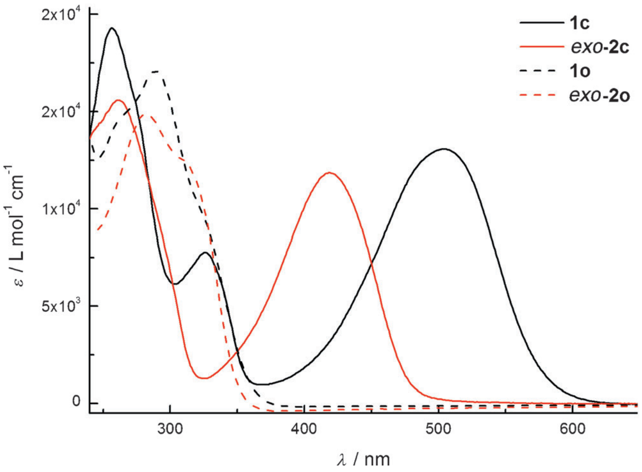

Figure 2. Comparison of the absorption spectra of **1o**, **1c**, *exo*-**2o**, and *exo*-**2c** in acetonitrile at 25 °C. The residual absorbance of *exo*-**2c** above 500 nm is attributed to a minor retro DA reaction taking place during the irradiation process.

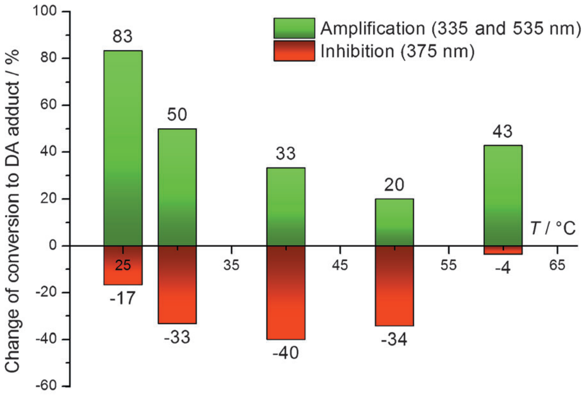

Figure 3. Relative amplification or inhibition of the formation of the Diels–Alder (DA) adduct depending on the illumination wavelength. Changes in the conversion into **2** (**2o**, **2c** *exo* and *endo* combined) on treating DAE **1o** (ca. 10^{-5} M) with maleimide (ca. 10^{-2} M) under irradiation either at 335 nm and 535 nm for 6 h (amplification) or at 375 nm for 24 h (inhibition) compared to the corresponding dark reaction as a function of temperature. See the Supporting Information for absolute values.

The ability to lock **1o** as well as **2o** by converting them into **1c** and **2c**, respectively, with UV irradiation is remarkable and offers manifold possibilities to employ these switch prototypes as photocontrollable locks. However, the true value of the system arises from the ability to selectively induce the reverse photoprocesses so as to unleash either the reactive diene or DA adduct by choosing the proper irradiation wavelength. Comparing the absorption spectra of the two ring-closed forms reveals a considerable spectral separation ($\Delta\lambda_{max} = 86$ nm) between the absorption maxima of **1c**, which absorbs in the green region, and *exo*-**2c**, which absorbs in the blue region (Figure 2). Thus, and despite the fact that **1c** absorbs slightly in the region where *exo*-**2c** is addressed, this allows for almost independent initiation of ring-opening reactions while irradiating a mixture of the two ring-closed derivatives—the key to achieving control over a dynamic system with light.

Indeed, irradiation of a mixture of **1o** and maleimide with light enables in situ control over the outcome of the DA reaction. Although thermal reactions of **1o** (at low concentrations of 10^{-5} M suitable for optical spectroscopy) with maleimide to form **2o** occur with conversions of 18–35 % after 24 h, depending on the applied temperature, the formation of the DA adduct and subsequent formation of the respective ring-closed isomers can be amplified or inhibited by irradiation with light of the appropriate wavelength (Figure 3). Irradiating a mixture of **1o** and maleimide with light at a wavelength of 335 nm and 535 nm induces cyclization of both ring-open isomers **1o** and **2o**, but ring-opening of **1c** only (Figure 2). This effectively leads to an enrichment of **2c** in the reaction mixture and an amplification of DA adduct formation, compared to the dark DA reaction, after 6 h (green bars in Figure 3). The heating time was reduced, as prolonged irradiation and heating result in degradation. The same method, but using different wavelengths, can also be applied to bias the DA reaction in favor of adduct inhibition. Using light with a wavelength of 375 nm cyclizes **1o** to **1c** as well as **2o** to **2c**, but simultaneously addresses the visible band of the ring-closed adduct **2c**, thereby also inducing ring-opening to give **2o** (Figure 2). According to Le Châtelier's principle, diene **1o** is removed from the dynamic DA equilibrium by conversion into **1c** and thus the reaction is effectively inhibited compared to the dark—that is, solely thermal—DA reaction (red bars in Figure 3).

In addition to the applied irradiation wavelength, the amount of amplification or inhibition is strongly dependent on the applied temperature (Figure 3). However, rationalization of the process is difficult, since the overall outcome is a result of a superposition of thermal and photochemical equilibria in the ground as well as in the excited states. Elevated temperatures, for example, not only promote the retro DA reaction but also increase the ring-opening quantum yields, which noticeably affects the composition at the PSS.[33] Furthermore, amplification works best at temperatures typically unfavorable for the DA reaction (i.e. in the highly reversible regime), while inhibition works best at temperatures that already result in high conversion in the dark. This indicates that the possibility for amplification and inhibition are greatest when the reaction rate constant for the thermal DA reaction at a given temperature favors the opposite direction.

We have been able to selectively either amplify or inhibit a DA reaction by illumination with light of different wavelengths, thus broadening the repertoire of DCC. In addition to this general approach of manipulating the formation and scission of a covalent chemical bond by light, our prototypic DAE has tremendous potential for a variety of possible applications, ranging from reversibly cross-linkable polymers to the reversible covalent functionalization of sp^2-hybridized carbon allotropes, such as graphene and carbon nanotubes.

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Remote-Controlled Reactivity

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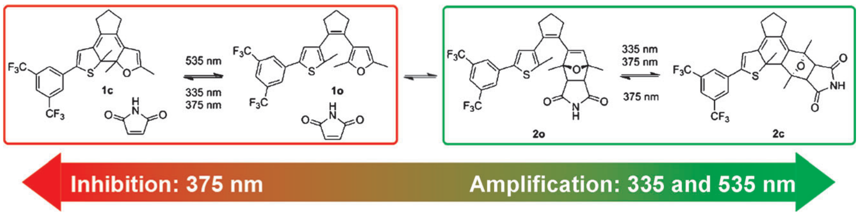
Controlling Covalent Connection and Disconnection with Light



Remote-controlled equilibrium: Gating both sides of a reversible covalent Diels–Alder reaction by a photoswitch allows control over the connection and disconnection of two chemical entities and shifting of their equilibrium by light. This approach should prove particularly powerful when designing dynamic cross-linked polymers and for reversible covalent functionalization of sp2-hybridized carbon allotropes, such as graphene and carbon nanotubes.