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## COMMUNICATION

## Improving the kinetics and dark equilibrium of donor-acceptor Stenhouse adduct by triene backbone design

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DFT calculations were used to find an optimal substitution site on the triene backbone of a donor-acceptor Stenhouse adduct photoswitch to tune the equilibrium and switching kinetics of DASA without modifying the donor and acceptor groups. Using this approach we demonstrate a new means to tuning DASA based photoswitches by increasing the energy of the closed form relative to the open form. To highlight the potential of this approach a new DASA derivative bearing a methyl substituent on the 5-position of the triene was synthesized and the effects of this substitution was studied using  $^1\text{H}$  NMR spectroscopy, time-dependent UV-Vis and solvatochromic analysis. The new DASA derivative shows a higher dark equilibrium, favoring the open form, and drastically faster thermal recovery than the unsubstituted derivative with the same donor and acceptor.

Control of complex systems by applying a noninvasive stimulus is highly desirable for applications from biology to materials sciences. Compared to other available stimuli, light is a particularly useful noninvasive stimulus due to the availability of inexpensive light sources and the possibility for precise spatial and temporal resolution.<sup>1,2</sup> Of particular interest are photoswitches, which can be transformed from their stable form into a metastable isomer with different properties upon irradiation. The stable form can either be recovered with a separate wavelength (P-type) or thermally (T-type).<sup>3–5</sup> Successful application of photochromic responsive systems is dependent on identifying photoswitching molecules that offer tunable control of light-responsive properties while remaining compatible with a range of materials and biological systems.

Donor-acceptor Stenhouse adducts (DASAs) are a relatively new class of photoswitch discovered by our group in 2014 consisting of an amine donor and a carbon acid acceptor separated by a triene backbone (Figure 1a).<sup>6</sup> Interestingly, while most photoswitches either undergo an *E/Z* isomerization (e.g. azobenzene<sup>7</sup>) or electrocyclicization (e.g. spiropyrans<sup>8</sup>, diarylethenes<sup>9</sup>); the DASA mechanism for switching includes

both a light-triggered *Z/E* isomerization and a thermal  $4\pi$  electrocyclicization to a metastable closed form (see Figure S2), which differs depending on the donors and acceptor groups incorporated into the DASA architecture. This metastable closed form thermally converts back to the open form in the dark. The unique mechanism of DASA derivatives allows for drastic differences in properties (color, size, and polarity) between their open and closed isomers. They have already shown promise for use in drug delivery,<sup>10</sup> self-regulated flow,<sup>11</sup> phase transfer,<sup>12,13</sup> and surface wettability.<sup>14</sup>

Many experimental and computational studies have been undertaken in the past years in an attempt elucidate the full mechanistic picture of DASA based systems.<sup>15–19</sup> Despite significant progress the complete mechanistic picture is still not fully understood and it remains challenging to predict how structural modifications can be used to improve photoswitching properties. Changing the properties of the donors<sup>20–24</sup> and acceptors<sup>25,26</sup> has been explored and proven to dramatically influence DASA photochromic properties, where the properties are closely linked to both the strength and sterics of the donor and acceptor. For example, DASA derivatives with strong donors (i.e., alkylamines) tend to have high equilibrium of the open form in the dark but suffer from poor switching in polar solvents. In contrast, derivatives with weaker donors (i.e., anilines) tend to be less sensitive to the environment but



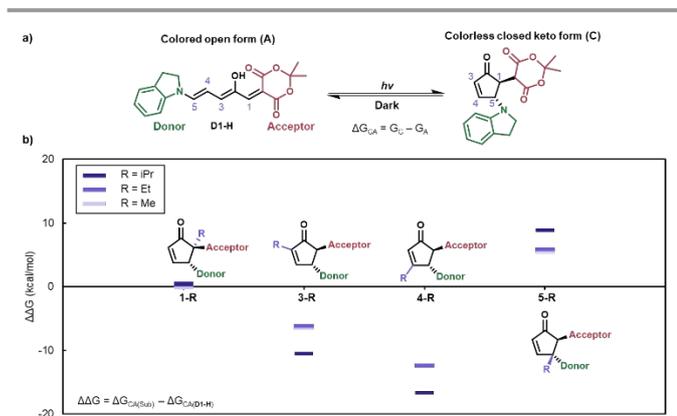
**Figure 1.** a) Schematic highlighting previous work successfully modifying the donor and acceptor to tune the switching kinetics of DASA. In this work we utilize substitutions on the triene to improve switching properties for the first time b) schematic of a DASA with a weak donor and acceptor resulting in a delocalized triene compared to a stronger donor resulting in a triene with alternating single and double bond character. Hybrid DASA derivatives have delocalized charge, while zwitterionic DASA derivatives have alternating single and double bond with more zwitterionic character.

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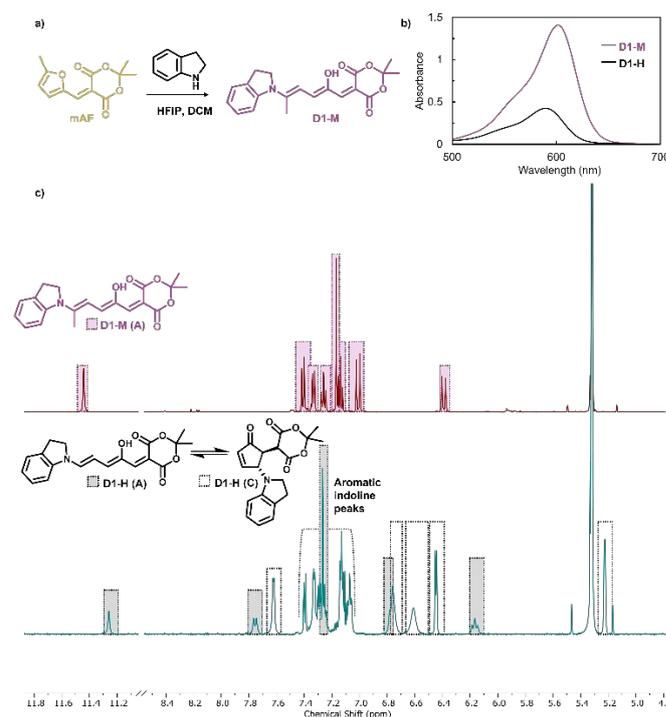
generally suffer from poor dark equilibrium and slow thermal recovery, often too slow to easily observe in nonpolar solvents such as toluene.<sup>19,21,22,24,27</sup> Sensitivity to the environment (e.g. concentration and solvent polarity) is one of the major roadblocks that DASA derivatives face for wide usage.<sup>19,27</sup> Our group has shown that the sensitivity to the environment is closely linked to the zwitterionic nature of the DASA ground state, which can be measured by the solvatochromic shift; the more negative values indicate a more zwitterionic ground state and an increased sensitivity to the environment, while less negative values correspond to a more hybrid (charge delocalized) ground state and decreased environmental sensitivity (**Figure 1b**).<sup>19</sup> Therefore, it is desirable to find a means of tuning the switching properties independent from the strength of the donor and acceptor, and therefore minimize the role the zwitterionic nature of the DASA can play in the photoswitching properties.



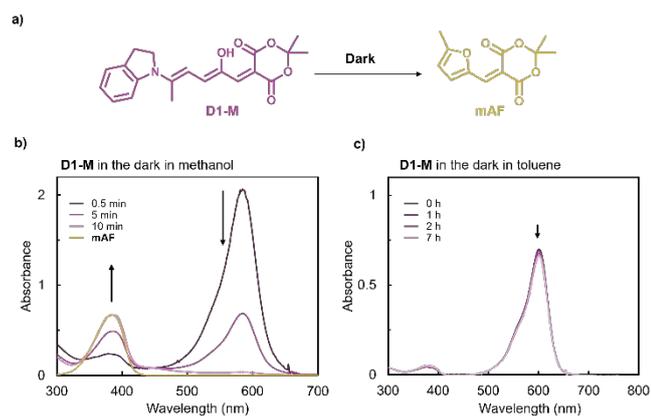
**Figure 2.** a) Model compound **D1-H** with an indoline donor and a Meldrum's acid acceptor resulting in a keto closed form (C) upon irradiation with light and recovers slowly to the open form in the dark b) Free energy difference between the closed keto form and the open form of derivatives with methyl, ethyl, or isopropyl groups substituted on the 1,3,4 or 5-positions of the triene compared to the unsubstituted derivative. A negative value means the C form is stabilized for the substituted derivative compared to the unsubstituted derivative and vice versa. Free energies were calculated using Gaussian 09 software with M06-2X/6-31+G(d,p) in toluene using an SMD solvent model.

To expand our understanding of tuning the performance of DASA based systems, we targeted structural modifications on the triene backbone. Substitution on the 3-position of the backbone has been shown favour the closed form both in donor-acceptor Stenhouse adducts as well as Stenhouse Salts,<sup>28,29</sup> however other substitutions have been largely overlooked. We envisioned that by finding a position on the triene backbone which increases the relative energy of the stable closed form (i.e., destabilize) upon substitution we would be able to improve the dark equilibrium and thermal recovery. This substitution would not change the strength of the donor and acceptor and therefore not significantly increase the zwitterionic character of the DASA. To guide our synthetic efforts, we used DFT calculations to identify an optimal substitution site on the triene backbone, focusing on the role that sterics in the various positions (1,3,4 and 5, **Figure 2a**) play in either stabilizing or destabilizing the closed form of DASA derivatives.

For initial DFT calculations, a model DASA with an indoline donor, Meldrum's acid acceptor and unsubstituted triene (**D1-H**) was investigated. This DASA derivative was chosen since it exhibits many of the drawbacks we sought to improve. For example, in toluene it has a low dark equilibrium of 29% open form and the thermal recovery from the closed to open form is too slow to observe via time dependent UV-Vis.<sup>22</sup> Importantly, however, it also has properties we wish to retain, such as a low solvatochromic shift of -7 nm which corresponds to a hybrid ground state and therefore being less sensitive to the environment. With this in mind, we calculated the free energy difference between **A** (open form) and **C** (closed form) isomers ( $\Delta G_{CA}$ ) with methyl, ethyl, and isopropyl substitutions on the 1, 3, 4, and 5-positions of the triene using M06-2X/6-31+G(d,p) in toluene using an SMD solvent model and compared the results to **D1-H**. The differences between the  $\Delta G_{CA}$  of the substituted and unsubstituted derivatives are plotted as  $\Delta\Delta G$  in **Figure 2b**, where a positive value means that the substitution destabilizes the closed form, and a negative value means the substitution stabilizes the closed form relative to the unsubstituted derivative model DASA **D1-H**. Substitution in the 1-position seem to show little effect. The  $\Delta\Delta G$  between DASA derivatives with substituents in the 3- and 4-position compared to the unsubstituted derivative show a stabilization of the closed form in line with previously published results.<sup>29</sup> In contrast, we found that  $\Delta\Delta G_{CA}$  is increasingly positive when steric bulk is introduced



**Figure 3.** a) Synthesis of **D1-M** from a methylated Meldrum's acid activated furan (**mAF**) after treating with indoline in the presence of HFIP in DCM b) UV-Vis of 10 $\mu$ M solutions of **D1-M** (purple) and **D1-H** (black) in toluene with 5% dichloromethane for solubility equilibrated in the dark (1 h for **D1-M** and 7 d for **D1-H**) showing that the solution of **D1-M** has a higher absorbance than **D1-H** due to the higher equilibrium c) <sup>1</sup>H NMRs of **D1-M** (top) and **D1-H** in deuterated dichloromethane highlighting that **D1-M** exists predominantly in the open form while **D1-H** has a large amount of closed form (unfilled boxes) compared to the open form (filled boxes)



**Figure 4.** a) UV-Vis data of a solution of **D1-M** dissolved in methanol sitting in the dark for 10 minutes compared to the absorbance of **mAF**, the DASA starting material (**Figure 1c**) showing that **D1-M** reverts to the starting material when sitting in methanol in the dark b) UV-Vis data of a solution of **D1-M** dissolved in toluene sitting in the dark for 7 hrs, showing that the absorbance only drops by approximately 5% in 7 hours in toluene.

to the 5-position due to steric interaction between the methyl and donor group (**Figure S15**). We suspected that this difference would lead to a higher dark equilibrium of the open form as well as faster thermal recovery from the closed form to the open form.

To experimentally test the effect of substitution on the 5-position of DASA, we synthesized **D1-M** (**Figure 3a**). We confirmed by  $^1\text{H}$  NMR and UV-Vis spectroscopy that a substitution on the 5-position with a methyl group **D1-M** showed a drastic improvement in the equilibrium (>95 % open form for **D1-M**; 29 % open for **D1-H**; **Figures 3, S4-S7** in both toluene and deuterated dichloromethane). This simple synthetic modification effectively converts **D1-M** into a derivative with a high dark equilibrium in toluene, typically only seen in derivatives with strong donors or acceptors (i.e., zwitterionic ground state). Despite this advance, introduction of a methyl group at the 5-position also leads to a side reaction. Monitoring the dark equilibrium via  $^1\text{H}$  NMR spectroscopy and UV-Vis revealed that over time the **D1-M** undergoes a retro-reaction resulting in the release of the amine and recovery of the activated furan **mAF** (**Figure 4, S9**). This side reaction appears to be dependent on solvent polarity, as **D1-M** fully reverts to the starting materials in methanol within 10 minutes, but only loses 5% of the maximum absorbance of an equilibrated sample in toluene over 7 hours. Future studies are underway to better understand this unexpected side reaction and to determine the generality of this reaction for other DASA derivatives.

Encouraged by the improved dark equilibrium properties, we investigated the effect of the substitution at the 5-position on the switching properties via time-dependent UV-Vis using a 617 nm red LED for irradiation (**Figure 5a**). Due to the relative stability in toluene, we chose to use toluene with 5% dichloromethane (to help with solubility) for the UV-Vis studies comparing the photoswitching properties of **D1-H** and **D1-M**.

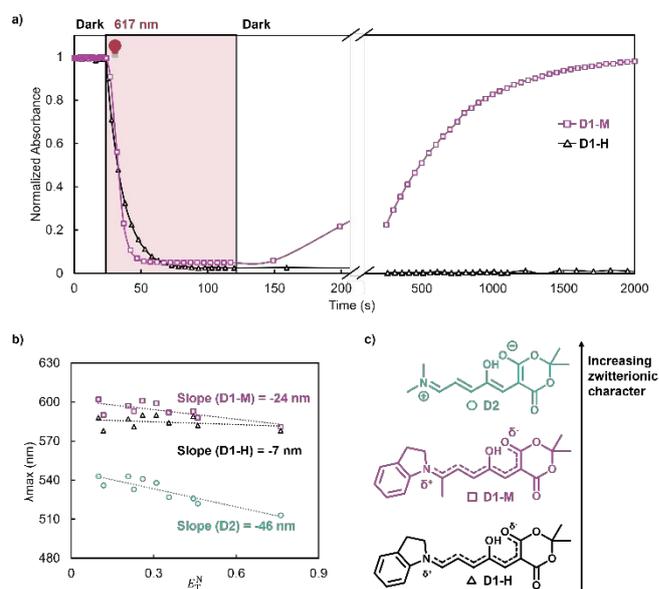
**Table 1.** Photophysical Properties of Compounds in Toluene with 5% Dichloromethane

	$\lambda_{\text{max}}$ (nm)	Dark eq. (% open)	PTSS <sup>a</sup> (% open)	Recovery (%)	$t_{1/2}$ (s)
<b>D1-H</b>	590	29	<1	n.d. <sup>b</sup>	n.d. <sup>b</sup>
<b>D1-M</b>	609	95	5	99	136

<sup>a</sup>Photothermal stationary state (PTSS) is dependent on both the temperature and intensity of light used, here calculated by multiplying the percent open in the dark by the percent that switched to give the total percent open during light exposure <sup>b</sup>Not determined due to limited recovery over 2,000 s in toluene with 5% dichloromethane.

Both fully isomerize to the closed form within 95 s of irradiation. **D1-H**, as previously reported, shows very little recovery in toluene as the sample is monitored over 2,000s (see **Figure S10** for more details). In contrast, the simple substitution of a methyl in the 5-position results in full recovery of **D1-M** within 2,000 s (**Table 1**). This result is consistent with the prediction based on our DFT results.

Given this dramatic improvement in reversible switching properties, we investigated how the electronics of the ground state were impacted by the introduction of the methyl group using solvatochromic analysis.<sup>19</sup> **D1-M** has a more negative solvatochromic slope than **D1-H** (-24 nm compared to -7 nm), indicating that it has a slightly more zwitterionic ground state. However, the solvatochromic slope remains much lower than DASA derivatives with strongly donating amines and/or strongly



**Figure 5.** a) Time dependent UV-Vis data of **D1-H** (black triangles) and **D1-M** (purple squares) in toluene with 5% dichloromethane for solubility. 25 measurements were taken at 1 s intervals prior to irradiation, followed by irradiation with a 617 nm LED with spectra taken at 1 s intervals for 95 s. Recovery was monitored in the dark for 1500 s with spectra taken every 10 s. Every 5 timepoints after the start of irradiation are averaged for clarity. The normalized absorbance is plotted at 590 nm for **D1-H** and 609 nm for **D1-M**. b) Solvatochromic analysis of **D1-H** (black), **D1-M** (purple), and **D2** (green) in acetone, acetonitrile, chloroform, dichloromethane, diethyl ether, dimethyl sulfoxide, ethyl acetate, methanol, tetrahydrofuran, and toluene showing that **D1-M** has a higher solvatochromic shift than the unsubstituted derivative but remains significantly lower than the more zwitterionic compound **D2** c) **D2**, **D1-M**, and **D1-H** drawn with increasing zwitterionic character from **D1-H** to **D2**, based on their solvatochromic shifts.

withdrawing carbon acid acceptors, such as **D-2**, which has a solvatochromic slope of -46 nm (**Figure 5c**). Importantly, these results support that substitution to the 5-position of the triene provides a new design element to tune the equilibrium and switching kinetics separately from modifying the strength of the donor and acceptor groups.

In conclusion, we used DFT to discover that substitution on the 5-position disfavours the closed form isomer of a DASA derivative and provides a handle to tune the photoswitching properties. To highlight this potential, a new DASA derivative with a methyl in this position was prepared with a higher dark equilibrium and faster thermal recovery than the unsubstituted analogue. Importantly, the faster thermal recovery than typical derivatives with weak donors and acceptors results in a more functional photoswitch while remaining less zwitterionic in nature than typical derivatives with strong donors or acceptors. Unfortunately, while these results are promising, we also discovered that the substitution favours a thermal reversion to the starting materials over time. We are currently conducting further investigations to substitute this position without resulting in the thermal reversion to the starting materials.

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