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Isoindolinone-based molecular switches†

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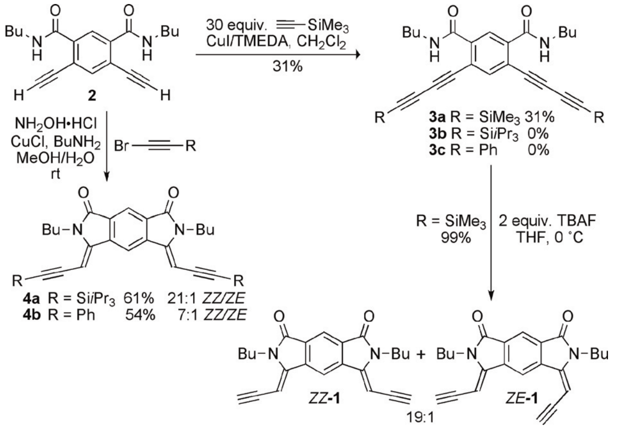
Switches are frequently used to provide external control over the conformation and function of organic and bio-organic molecules. While the use of bistable switches is widespread, multi-stable examples are observed relatively rarely. Reported here is a new class of molecular switch that is capable of forming three stable states of varied geometries, two of which can be induced to interconvert reversibly using either light or acid.

The ability of molecular switches to reversibly alternate between two states is frequently exploited to modulate the structure and function of biomolecules,[1] and organic materials.[2] Dithienylethenes and overcrowded alkenes have been well studied in a variety of systems that display the versatility of these moveable units,[3] but azobenzenes are still the most commonly used switching unit due to their tuneability,[4] and their accessibility through a variety of synthetic transformations.[5] However, among the choices available for incorporation into devices,[6] multi-stable switches are described relatively infrequently,[7] yet a molecule's ability to revolve between many stable conformers/forms has significant implications in applications such as information processing and biomaterials.[8] An ideal multi-stable switch would possess several states that differ in one or more physical and/or electronic properties. It should be possible to interconvert between these states using stimuli, preferably orthogonal, so that each state is produced for a defined length of time; the most desirable time scale would be based on the particular application. The attainment of all of these properties in a single molecule is a considerable challenge.

Isoindolinones (IINs) are a completely unexplored family of molecular switches, despite observation of their photoresponsiveness.[9] In our recent work to develop an efficient synthetic route toward π-extended isoindolinone systems,[10] we further noticed the sensitivity of a few bis-isoindolinone systems, such as compound **1**, to light (Scheme 1). However, the low thermal stability of this carbon-rich molecule due to the lack of protective group on the terminal alkyne, and limited synthetic accessibility of more functionalized structures, hindered our study of the switching aspects of its properties. Our current interest is to exploit and explore the photoswitching of the enyne isoindolinone core of **1** to make multi-stable molecular switches. This general structure has three potential isomeric forms, *ZZ*–*ZE*–*EE*. Switching between these isomers results in changes in end-to-end distances from 2.5 to 6.0 Å, with the alkynyl arms oriented at angles between ~35° and 135°, features that are unique to this isoindolinone motif. Therefore, we describe modifications to our original synthetic route that have allowed the creation of new enyne based isoindolinone derivatives that are more stable than the unprotected derivative; their switching properties were then explored and are described herein.



Scheme 1 Synthesis of enyne bis-isoindolinones.

In our previous studies, terminal diyne **2** was subjected to Hay/Glaser oxidative coupling conditions to produce bis-diyne **3**.[11] Cyclization was then induced with mild base, with concomitant removal of the trimethylsilyl (TMS) groups, to give extended bis-isoindolinone **1** as a 19 : 1 mixture of *ZZ* and *ZE* isomers. Our initial goal was to synthesize derivatives with end-capping groups that would not be removed under mildly basic cyclization conditions.[12] (Triisopropyl)silyl (TIPS) and Ph groups were chosen as these bulky moieties have previously been appended to extended π-conjugated systems to provide stability.[13] However, our initial attempt at making diynes **4** using the same oxidative coupling/cyclization route as for **1** resulted in failure. Butadiynes **3b** and **3c** could not be isolated using these reaction conditions. We then turned to the Cadiot–Chodkiewicz

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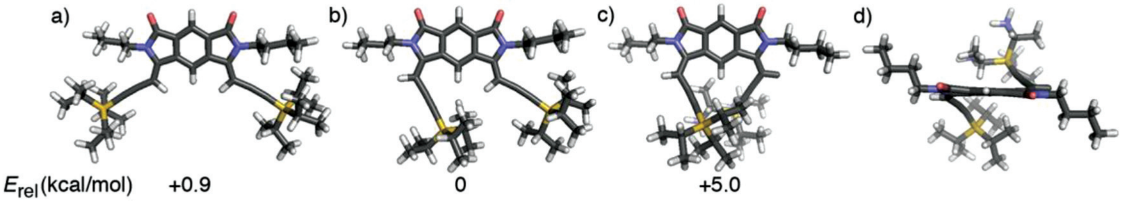

Fig. 1 Computational modelling of (a) *ZZ*-**4a**, (b) *ZE*-**4a**, (c) *EE*-**4a**, and (d) *EE*-**4a**, top view.

coupling, a method that is often used to create unsymmetrical butadiynes.[14] Reaction of terminal acetylene **2** with the appropriate alkynyl bromides provided, in one step, enyne-containing isoindolinones **4a–b** in 61% and 54% yield, respectively. In both cases, the *ZZ* isomers were produced as the main product, as confirmed by NOESY experiments, which showed correlations between the vinyl and the aromatic protons. The *ZE* isomers were observed to be 5% and 13% of the product mixture for the TIPS and phenyl derivatives, respectively.[15]

In preliminary work with terminal diyne **1**, evidence of an *EE* isomer was observed in the ^{1}H NMR spectrum after exposure of the ZZ-**1**–ZE-**1** mixture to 365 nm light.[16] As the presence of the end-capping Ph and Si*i*Pr_3 groups might hinder the formation of this sterically hindered isomer, we carried out some modeling studies to determine the relative stabilities of the isomers of **4a**.[17] Shown in Fig. 1 are the energy-minimized structures of the three possible isomers of **4a** with their E_{rel} values. It was determined that *ZZ*-**4a**-and *ZE*-**4a** are of similar energies, with only a 0.90 kcal mol^{-1} difference. Somewhat surprisingly, the *ZE* form seems to be the most stable. As can be seen in Fig. 1a, the alkynyl moieties on *ZZ*-**4a** are slightly strained and are bent by ~4° due to the bulkiness of the butyl chains on the amide. For *ZE*-**4a**, rotation of one of the alkynyl arms into the *E* conformation allows for relief of strain on that alkyne, which in this isomer results in one completely linear alkynyl unit. It is known that bending of alkynes by up to 20° leads to only minimal increases in strain, explaining the only small difference in energy between *ZZ* and *ZE*.[18] However, it is difficult to confirm that the *ZE* isomer is the thermodynamically most stable isomer using these results, due to the relatively small difference in energy found *via* the calculations.

Not surprisingly, *EE*-**4a** is more strained than both the *ZZ* and *ZE* isomers as a result of steric interactions between the two Si*i*Pr_3 groups. To accommodate the bulk these groups provide, the alkynyl units bend by an average of 7°. As alkynyl groups can bend fairly easily without causing significant increases in energy, and as the *ZZ* and *ZE* isomers also experience slight deformation in this moiety, it is likely that strain caused by the adjacent TIPS groups is accommodated in another way. Shown in Fig. 1d is the top view of the energy-minimized structure of *EE*-**4b**. The isoindolinone backbone is twisted by about 5°, while for *ZZ*-**4a** and *ZE*-**4a** it is completely planar. Considering the rather strained appearance of *EE*-**4a**, it is actually quite surprising that so little a difference in energy, 5 kcal mol^{-1}, is observed between the *EE* and *EZ* isomers of **4a**. However, this small difference in energy was promising for the switching experiments, indicating that the *EE* isomer might be accessible.

A series of photochemical experiments was subsequently carried out, the results of which are summarized in Fig. 2a. Depending on the wavelength of light used, the olefins in structure *ZZ*-**4a** can be isomerized to give an approximately equal mixture of the *ZE* and *EE* forms, which can then be transformed to give 95% of the *ZE* isomer; the *ZE*–*EE* and *ZE* forms can be interconverted reversibly. The isomerisation were carried out as follows. In Fig. 2b is an expansion of the ^{1}H NMR spectrum of the starting mixture of *ZZ*-**4a** (95%) : *ZE*-**4a** (5%); the majority presence of the *ZZ* isomer was confirmed *via* a NOESY experiment. Upon exposure of this mixture to 365 nm light, the vinyl resonance of *ZZ*-**4a** at δ 5.88 ppm gradually diminishes. Correspondingly, two vinyl resonances at δ 5.92 ppm and δ 5.65 ppm appear. After 6 h a state is reached where two isomers that are not *ZZ*-**4a** dominate the mixture, Fig. 2c. In addition to the vinyl peaks, four new resonances also appear in the aromatic region, at δ 9.41, 8.91, 8.26 ppm and 8.25 ppm. The presence of NOESY correlations between the vinyl resonance at δ 5.92 ppm and the

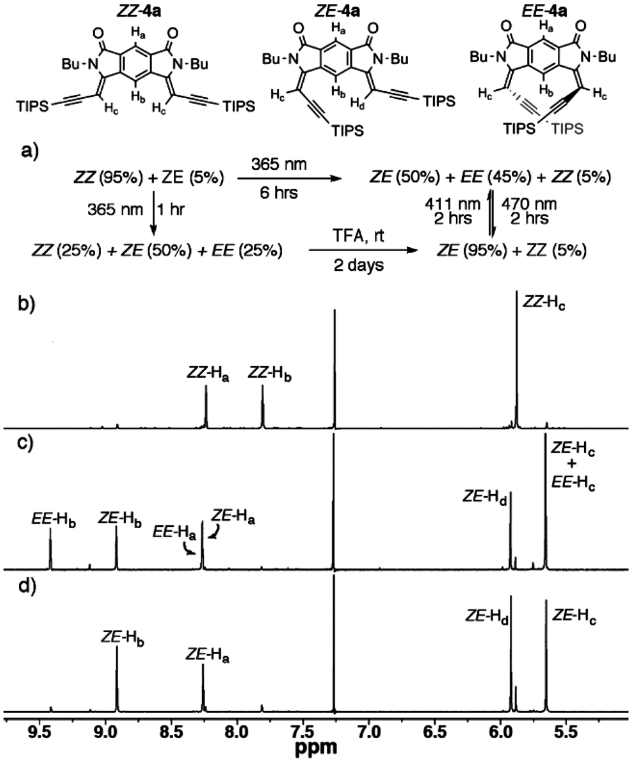

Fig. 2 Switching properties of IIN-**4a** as monitored by ^{1}H NMR in $CDCl_3$. (a) Scheme summarizing switching properties, (b) *ZZ* (95%) isomer, (c) mixture of *ZE*–*EE* and traces of *ZZ* after exposure to 365 nm light for 6 h, (d) primarily *ZE* isomer after exposure to 470 nm light for 2 h.

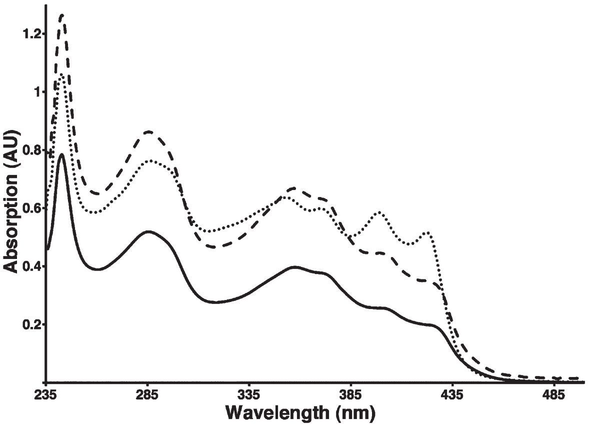

Fig. 3 UV-Visible absorption spectra of *ZZ–ZE–EE* isomers of **4a**. *ZZ*-dotted line (······), *ZE*-solid line (—), *ZE–EE*-dashed line (– – –).

aromatic resonance at δ 8.91 ppm, in addition to the correlation between the vinyl resonance at δ 5.65 ppm and the methylene group at δ 3.78 ppm, confirmed that *ZE*-**4a** is produced. No correlation was observed between the new vinyl resonance at δ 5.65 ppm[19] and the aromatic resonance at δ 9.41 ppm, which was assigned to the aromatic proton *ortho* to the vinyl group of *EE via* an HMBC experiment. However, after continued exposure of the approx. 50 : 50 mixture to 365 nm light, no further changes were observed, indicating the achievement of a photostationary state. Irradiation of the mixture in Fig. 2c with 470 nm light for 2 h did lead, though, to further changes in the isomer ratio.

As shown in Fig. 2d, the presence of *ZE*-**4a** now dominates the ^{1}H NMR spectrum. Irradiation of the *ZE* isomer with 411 nm light for 2 hours again produced the *ZE–EE* mixture in Fig. 2c. Alternating between 470 and 411 nm light led to cycling between the primarily *ZE* mixture, Fig. 2d, and the approx. 50 : 50 mixture of *ZE–EE*, Fig. 2c.[20] This result is comparable to what is observed with many commonly used switches, which reach photostationary states before full conversion. Ten cycles were performed on **4a** with 470/411 nm light and no fatigue was observed.

Cycling back to the *ZZ* isomer proved to be difficult. As can be seen in Fig. 3, the UV-Visible spectra did not provide much help in this endeavor due to the broad absorption throughout the 235 nm to 450 nm range of all isomers, making it difficult to target a particular absorbance in a single isomer. The ability to convert the *ZE–EE* mixture in Fig. 2c to the primarily *ZE* isomer in Fig. 2d with 470 nm light is likely due to the high wavelength absorption tail that appears in the UV-Visible absorption spectrum in the ≥460 nm region of the *ZE–EE* mixture, Fig. 3 (dashed trace). This low-energy tail is not present in the UV-Visible spectra of just the *ZZ* and *ZE* isomers, dotted and solid trace, respectively, and therefore must belong to the *EE* form. Correspondingly, the *ZZ* and *ZE* structures do not respond to light ≥460 nm. Interestingly, when a mixture of all three isomers, produced by exposure of the *ZZ* isomer to 365 nm light for 1 h, is treated to the equilibrating conditions of trifluoroacetic acid (TFA), only the *ZE* isomer is produced, indicating that this isomer is the thermodynamic minimum, Fig. S1.†

The phenyl-substituted **4b**, similarly to **4a**, responds to a range of wavelengths. However, this derivative does not operate as a switch in the same way as **4a**. As shown in Fig. S2,† 365 nm light can be used to switch the primarily *ZZ* mixture of **4b**. After 6 h of exposure at this wavelength, a photostationary state is reached with a 1 : 5 : 5 mixture of *ZZ–ZE–EE*-**4b**, Fig. S2.† Despite the observance of some light sensitivity in this mixture, cycling between the *ZE* and the *ZE–EE* mixture was not possible. Although the energy-minimized structures of **4b** share similar features to **4a**, Fig. S3,† namely small deformations in the alkynyl bond angle in the *ZZ,ZE* and *EE* isomers, and twisting of the isoindolinone backbone in the *EE* form, there are no significant differences in energy between the three isomers of **4b**. In addition, the UV-Visible absorption spectrum of **4b**, Fig. S4,† shows that the *ZZ* isomer and the 1 : 5 : 5 mixture of *ZZ–ZE–EE*-**4b** share very similar broad absorption features, possibly explaining the lack of individual response to light. In addition, prolonged exposure of **4b** to TFA resulted only in decomposition, not isomerisation to one isomer, as for TIPS-protected **4a**. In this case, extension of the conjugation and removal of the bulky TIPS groups appear to be detrimental to the switching properties.

Molecular switches that involve photo-isomerisation between *Z*/*E* isomers often experience thermal conversion to the thermodynamic minimum at rt. In our case, we observed that the *ZZ*, *ZE* and *EE* forms of compound **4a** are stable indefinitely at rt when protected from light; we have yet to observe changes in isomer ratios under these conditions. In addition, the mixture of isomers shown in Fig. S1† was heated to 60 °C for 24 h in $CDCl_3$ with no change in isomer ratio, Fig. S5.† Heating to 120 °C for 24 h in DMF, however, minimally altered the product ratio toward a decomposition product. The observed thermal stability is a surprising result due to the thermal responsiveness of hemi-thioindigo,[6] which shares structural features with the isoindolinone switch presented here.

Conclusions

A new molecular switch has been realized using an isoindolinone motif. These structures are available in a few steps and given proper substitution can reversibly alternate between two isomeric forms using either light or acid. All isomers are thermally stable at rt and at elevated temperatures. Future studies will focus on a full photophysical examination and fine-tuning to provide a fully reversible tri-stable switch.

Acknowledgements

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19 This resonance is overlapping with the *E*-vinyl resonance of the *ZE* isomer. Integration indicates the presence of two vinyl resonances from *EE* and one vinyl resonance from *ZE*. Any *EE* vinyl-alkyl correlation is buried under the same correlation for the *ZE* isomer.

20 Due to the broad absorption of **4a** in the UV-Visible region, it was not possible to target a specific absorption. Hence, **4a** was exposed to a number of wavelengths in the 300–470 nm region. 470/411 nm provided the best results.