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Photochromic molecular switches

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Chapter 1

Photochromic Switches for Controlling Surfaces: Properties and Function

In this Chapter photochromic switches and their use are described in the context of biological applications. Photochromic switches can be interconverted between two states using light as an external stimulus thereby changing the physical properties of the sample. For example photochromic switches can be used to control the intensity of fluorescence of a fluorophore, which holds great potential for fluorescence microscopy and techniques such as photoactivated localization microscopy (PALM). Molecular switches can also be used as a components of photoresponsive surfaces. Such surfaces hold potential for application in biotechnology, cell biology and medicine. By functionalizing surfaces with monolayers of photochromic switches, the properties of the surface can be controlled, through which surface-cell interactions can be modified.

1.1 Introduction

The Oxford advanced learners dictionary describes switching as; “~(from A to B) a change from one thing to another, especially when this is sudden and complete: a switch of properties”.¹ The most common switch in everyday life is the electrical switch, which can open or close an electrical circuit, thereby switching between an on (A) and an off (B) state (Figure 1.1). A molecular switch is a molecule that can be switched between two states. Like any macroscopic switch, the properties of a molecular switch can be changed between two states (A and B) by applying an external stimulus. Molecular switches can be interconverted by any of a number of stimuli (light, heat, pH, electrical potential and ligand exchange).²

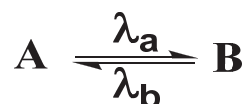


Figure 1.1: Switching from A to B as a result of irradiation.

In this Chapter, the properties of photochromic molecular switches are described in the context of biological applications.³ The properties of photochromic switches can be changed reversibly from state (A) to state (B), upon irradiation at specific wavelengths (Figure 1.1), enabling reversible changes in function. Irradiation of a switch with λ_a results in a distinct change in its absorption spectrum, usually demonstrated by a shift in the absorption maximum. The shift in absorption maximum allows for reversible switching by means of irradiation with a second wavelength (λ_b).

The use of photochromic switches is advantageous as light is a non-invasive stimulus and photochromic switching is reversible and, can exhibit short response times. These properties make photochromic devices widely applicable in smart materials. However, there are other requirements for a molecular switch to be applicable in the field of biomedicine.⁴

- *Selective photo-isomerization*

Photochemical interconversion between the two states should occur at distinct wavelengths and with high quantum yields for the isomerization processes.

- *Non-destructive photo-irradiation*

The wavelength used for photo isomerization should be benign to living cells.

- *Thermal stability*
Thermal isomerization should not occur or be limited over the temperature range of 20 to 40 °C.
- *Change of physical properties*
Isomerization should lead to a substantial change in the physical characteristics of the switch.
- *Fatigue resistance*
Repetitive photoisomerization cycles of the molecular switches should not lead to degradation or the formation of side products.

To date there are many examples of reversible photochromic switches including; stilbenes (1.2.1), overcrowded alkenes (1.2.2.), azobenzenes (1.2.3), thioindigos (1.2.4.), (hemi)thioindigos (1.2.5.), fulgides (1.3.1), spiropyrans (1.3.2) and diarylethenes (1.3.3), several of which will be described in this Chapter. The photoswitchable compounds can be divided into two groups based on the mechanisms of their photo-reactions; *E-Z* photoisomerization (Section 1.2) and photocyclization (Section 1.3).

1.2 Photoisomerization

Alkene (C=C) and azo (N=N) double bonds can exist in two stable states being the *E*- or *Z* geometrical isomer. These isomers are interconverted through isomerization via a 180° rotation around the double bond. An input of energy is necessary to overcome the activation barrier to an isomerization from one form to the other. *E-Z* photoisomerization about a double bond represents one of the simplest ways of converting photon-energy into mechanical motion.⁵

1.2.1 Stilbenes

Stilbenes are an extensively studied class of photochromic switch.^{6,7} The study of stilbene switches has led to insight into C=C bond isomerization. Stilbene switches can exist in either of two states, the *E* and *Z*-isomers, which are interconvertible through photoisomerization around the central double bond (Figure 1.2). Irradiation of *cis*-stilbene can, however, result in 6 π electrocyclicisation resulting in dihydrophenanthrene. In the presence of an oxidant dihydrophenanthrene can undergo, irreversible dehydrogenation yielding phenanthrene. As a result, the application of stilbene switches has been limited.

Introduction of methyl groups at the 2- and 2'-positions prevents oxidation upon ring closure.⁸

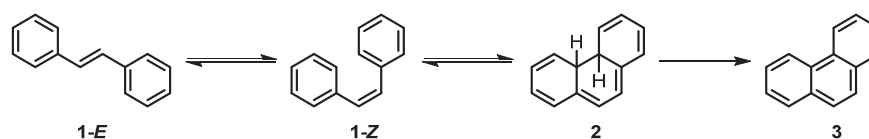


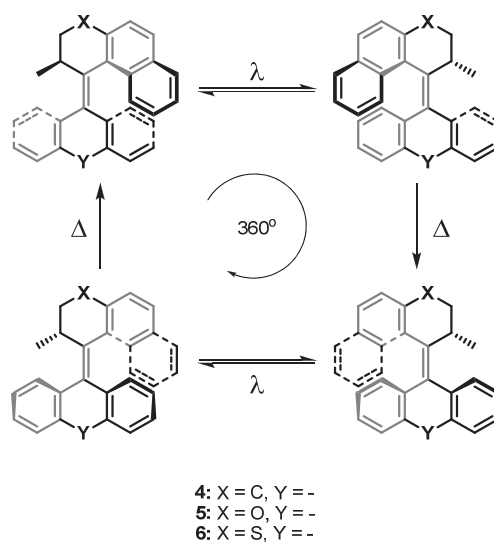
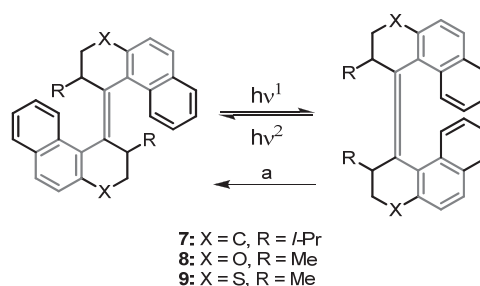
Figure 1.2: Photoisomerization and photocyclisation of stilbene.

1.2.2 Overcrowded alkenes

Overcrowded alkenes are switches that are based on the structure of stilbene switches in which the central double bond is sterically overcrowded by substitution at the *ortho* positions of stilbene core. Typically these switches consist of an unsymmetrical upper-half based on 2,3-dihydrophenanthrene or 2,3-dihydro-1H-cyclopenta[*a*]naphthalene and symmetrical lower-halves based on 9,10-dihydroanthracene or fluorene. The overcrowding of the central double bond causes a distortion out of planarity and as a result these compounds can adopt helical configurations, which can be right (*P*) or left handed (*M*). Interconversion between the two states occurs when the upper- and lower-halves move past each other. The rate of this process is determined by the conformational flexibility of the upper- and lower-halves of the switch.

By introducing a stereogenic centre within the overcrowded alkenes, four states are available stable-*E*-(*P*), unstable-*Z*-(*M*), stable-*Z*-(*P*) and unstable-*E*-(*M*). As interconversion between the states using light and heat is only possible in a sequential unidirectional fashion, these overcrowded alkenes function as molecular rotary motors.

As for stilbene switches, overcrowded alkenes undergo *E*→*Z* isomerization upon irradiation with UV light. As a result of isomerization, not only a bathochromic shift occurs in the UV/Vis absorption spectrum of the compound, but also the helicity of the switch is altered.


Figure 1.3: Photoisomerization of overcrowded alkenes

Table 1.1: Photo and thermal isomerization of overcrowded alkenes 4-8. In which pathway (a) represent the rate limiting thermal isomerization step from unstable to stable.

Switch	λ_{\max} E	PSS $E \rightarrow Z_{\text{unst}}$	$\Delta^\ddagger G^\circ$, $E \rightarrow Z_{\text{unst}}$ (kJ/mol), $t_{1/2}$	λ_{\max} Z_{unst}	PSS $Z_{\text{unst}} \rightarrow E$	$\Delta^\ddagger G^\circ$ $Z_{\text{unst}} \rightarrow E$ (kJ/mol)
4	390	9:91	139, 1376 y	420	-	-
5	391	1:>99	116, 9.4 d	408	1:>99	-
6	410	5:>95	109, 34.5 d	415	-	-
7	338	<1:>99	-	-	-	124 (131)
8	380	9:91	-	410	-	-

The *Z*-isomer is usually strained and thermally unstable and reverts back to the stable *E*-isomer. For molecular motors these steps can be repeated to complete a 360° rotation. The thermal *Z*→*E* isomerization is dependent on several factors amongst which; steric strain in the *fford* region, conformational flexibility of the upper and lower-halves, substituent effects and the size and flexibility of the group at the stereogenic centre.

The most interesting overcrowded alkenes for biological applications are those with a high barrier to the thermal helix inversion, high photostationary states for both the forward and reverse photoisomerization and photoisomerization at a wavelength in the visible region. These characteristics are found in two classes of overcrowded alkenes. 1) Switches based on 2,3-dihydro-1H-benzo[*f*]-chromene or thiochromene upper-halves and fluorene lower-halves (Figure 1.3). 2) Symmetrical overcrowded alkenes based on 2,3-dihydro-1H-benzo[*f*]-chromene, thiochromene or tetrahydrophenanthrene upper and lower halves (Table 1).

1.2.3 Azobenzenes

Azobenzenes⁹ are structurally analogous to stilbenes, however, in azobenzenes *E*-*Z* isomerization takes place around an N=N double bond.¹⁰ Azobenzenes have most widely found application in nanoscale devices amongst the family of photochromic switches. Azobenzenes undergo reversible *E*-*Z* isomerization upon UV irradiation (340–380 nm),¹¹ which is associated with a large change in spatial geometry (3Å) and dipole moment.¹² This photochemical isomerization usually proceeds to a photostationary state (PSS) of 70–90%.¹¹ The *Z*-isomer can be reverted to the *E*-isomer by irradiation using visible light (Figure 1.4) or by a thermal isomerization process. The thermal stability of the *Z*-isomer of azobenzene switches can be regarded as both a disadvantage and an advantage depending on the application the switch is used for.

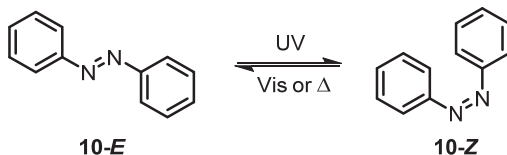


Figure 1.4: Photoisomerization of azobenzene.

The switching characteristics such as absorption, emission, photostationary state (PSS), quantum yield and thermal stability can be controlled through the substituents on the azobenzene.^{13,14} For example substituted azobenzenes, which are bridged at their *ortho* position with an ethylene linker, ensure photoisomerization with near complete

photoconversions ($PSS_{(E \rightarrow Z)}$ 100% at $\lambda = 385$ nm and $PSS_{(Z \rightarrow E)}$ 92% $\lambda = 520$ nm) and relatively high quantum yields of switching ($\Phi_{E \rightarrow Z} = 50\%$ and $\Phi_{Z \rightarrow E} = 72\%$).¹⁵ *Ortho* fluorinated azobenzenes exhibit reversible switching at visible wavelengths ($E \rightarrow Z$ at $\lambda > 500$ nm and $Z \rightarrow E$ $\lambda = 410$ nm).¹⁶ The *Z*-isomer of this switch is thermally stable, with a half-life of ca. 700 days at 25 °C. Addition of electron withdrawing groups (EWGs) at the *para*-position results in high photostationary states ($PSS_{(E \rightarrow Z)}$ 90% and $PSS_{(Z \rightarrow E)}$ 97%). These switching characteristics are attributed to the difference in energy of the $n \rightarrow \pi^*$ bands of each of the isomers. The differences can be controlled by manipulating the energy levels of the *n*-orbitals, EWGs in the *ortho* and *para* positions decrease repulsive interactions between the nitrogen lone pairs in the *Z*-isomer.¹⁶

The physical properties of azobenzenes alter as a consequence of the geometrical change upon photoisomerization. These changes include; length, angle, volume and polarity. Such changes can be exploited for responsive molecular materials and devices. The relatively large change in physical properties, tunability, and the high fatigue resistance¹³ of azobenzenes make them versatile systems and likely candidates for further applications.

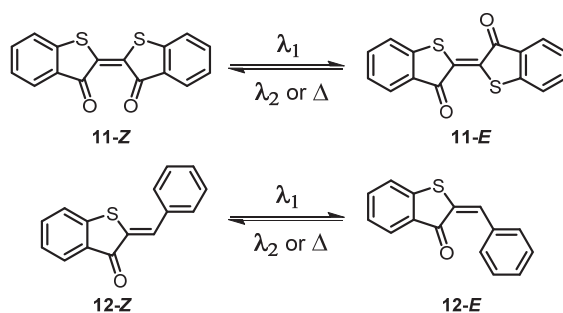


Figure 1.5: Photoisomerization of a) Thioindigo and b) Hemithioindigo.

1.2.4 Thioindigo switches

Thioindigos undergo *cis-trans* photoisomerization upon irradiation at $\lambda \pm 550$ nm (Figure 1.5).¹⁷ The change in conformation is manifested in a hypsochromic shift in their UV/Vis absorption spectra. As for *trans*-stilbene, the *trans*-isomer of thioindigo is fluorescent ($\Phi_f \sim 0.6$), whilst the *cis*-isomer is essentially non-fluorescent.¹⁸ Under irradiation ($\lambda \pm 450$ nm) or standing in the dark the spectral changes revert to recover the original spectrum of the

cis-isomer. Generally the quantum yield for *cis* → *trans* ($\Phi = 0.45$) isomerization is higher than for the *trans* → *cis* isomerization ($\Phi = 0.04$).¹⁹ However, the quantum yield is strongly dependant on the substitution pattern of the thioindigo.

1.2.5 Hemithioindigo switches

Hemithioindigo (HTI) switches are a relatively under studied class of photochromic switches. HTI switches are composed of a thioindigo half and a stilbene half (Figure 1.5b). The central double bond of HTIs undergoes *Z* → *E* photoisomerization upon irradiation (± 405 nm), which results in a bathochromic shift of the long wavelength absorbance in the UV/Vis absorption spectrum.²⁰ As a result photoisomerization from the *E*- to the *Z*-isomer is obtained by visible light (> 480 nm). Generally the *E*-isomer is less stable and reverts to the *Z*-isomer thermally. The speed of the *Z* → *E* photo isomerization and the thermal *E* → *Z* isomerization is dependent on the substituents on both the thioindigo and stilbene half of the molecule. Variations in the substitution of the stilbene half have a strong influence over the rate of *Z* to *E* and *E* to *Z* photoswitching.²¹ Electron donating groups (EDG) in the *para*-position lead to high rates of photoisomerizations. Electron donating groups in the *meta*-position have a negligible effect, as this position is not in direct conjugation with the central double bond. Electron withdrawing substituents (EWG) in the *para*-position have a stabilizing effect on the life time (τ) of the excited state and lead to lower rates of photoisomerization. The effect of the bromo substituent in the *para* position ($\tau_2 = 336$ ps) is minor compared to the effect of the cyano substituent ($\tau_2 = 2650$ ps), whereas a bromo substituent in the *meta*-position led to a substantial stabilizing effect affecting the rates of *Z* to *E* ($\tau_2 = 1480$ ps) and *E* to *Z* photoisomerization. Variations in the substitution of the thioindigo half of the switch also influences the isomerization mainly through inductive effects,²² EWGs (*e.g.* Br) have a less pronounced destabilizing effect and lead to a small decrease in the rate of *Z* to *E* isomerization and the EDG (OMe) led to small increase in the rate of isomerization. Additionally it has been reported that functionalization with fluorine in the *ortho*-position of the stilbene half can lead to ring closure upon photoisomerization.²³ Thermal *E* → *Z* isomerization of HTI switches functionalized with carboxyl group on the indigo half and an EDG in the *meta*-position have half-lives of ca. 47 h in methanol.²⁴ Whereas an EDG in the *para*-position of the stilbene results in half-lives of around 20 h.^{24,25} A more pronounced push-pull system bearing an ammonium chloride salt in the *para*-position exhibits a drastic increase in the speed of the thermal relaxation, and could only be observed by time resolved transient absorption spectroscopy.²⁴ In dichloromethane HTI switches bearing an ester moiety on the thioindigo part show retarded *E* → *Z* isomerization with a $t_{1/2} = 138$ h.

1.3 Photocyclization

1.3.1 Spiropyrans

Photoisomerization of the spiropyran family is based on photocleavage of the C-O bond between the pyran-oxygen and the spiro-carbon.²⁶ Photocleavage results in the dearomatization of the phenyl ring of the pyran half of the switch. The quinoid form can exist in either or both of two conformations (*cis-cis* or *trans-trans*) the *trans-trans* isomer being the more stable, due to steric hindrance.²⁷ Rearomatization of the benzene ring leads to a zwitterionic state. Where in the spiropyran switch the two halves are orthogonal, the merocyanine is planar, extending the conjugation between the two halves of the switch.

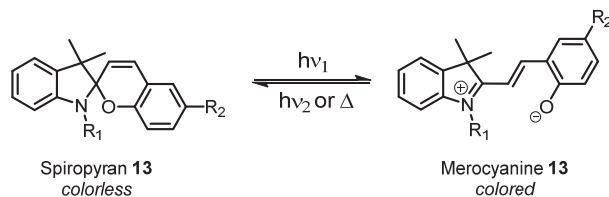


Figure 1.6: Photoisomerization of spiropyran as a result of irradiation.

The merocyanine can be switched back with visible light, however, it also reverts thermally. Although, the poor thermal stability of the merocyanine is a potential drawback, the large change in polarity²⁸ between the two states makes the spiropyran family of switches attractive for application.

Generally spiropyrans have a moderate to large quantum yield for the coloration process (Φ_{col}), for example; for the nitro substituted SP, the Φ_{col} is 0.40 to 0.85 in methylcyclohexane.²⁹ The switching of spiropyrans is, however, solvent dependent. Increasing polarity results in a lower Φ_{col} and higher activation barriers to the reverse process.

1.3.2 Fulgides

Fulgides³⁰ are a class of molecular switches that undergo *Z* → *E* photoisomerization followed by photocyclization to the *C*-form (Figure 1.7), upon irradiation with UV-light, changing in color from the colorless *Z* and *E* isomers to the colored *C*-isomer. Under UV irradiation *E* → *Z* back photoisomerization competes with the forward ring closure.

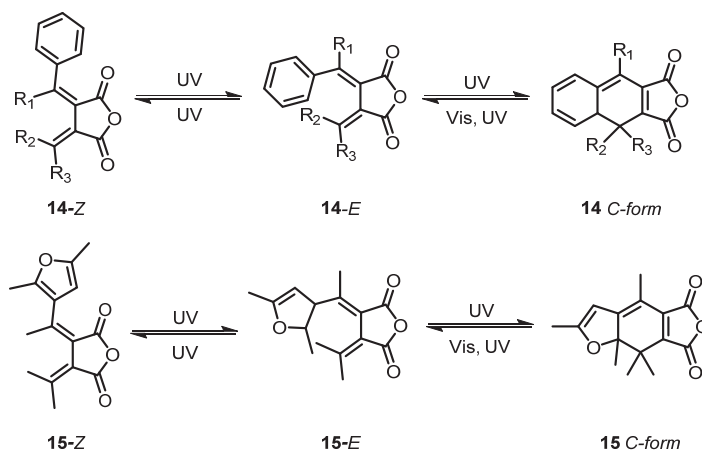


Figure 1.7: Photochemical reactions of fulgide switches.

Aryl substituted fulgide **14** is not thermally stable, however, replacing the phenyl for a furyl group and the substituents (R_1 , R_2 and R_3) by methyl groups render the closed form thermally stable (Figure 1.7, **14**).^{30,31} Quantum yields for the photochemical ring closure ($\Phi_{E \rightarrow C}$ at 366 nm) of aliphatic substituted fulgides are typically between 0.18 to 0.79, while the reverse process is typically less efficient ($\Phi_{C \rightarrow E} = 0.00$ to 0.082) at 366 nm and $\Phi_{C \rightarrow E} = 0.027$ to 0.26 at 492 nm.³⁰ The quantum yield for ring closure ($\Phi_{E \rightarrow C}$) of fulgide switches is enhanced upon increasing the bulk of the substituent R_1 , whereas, $\Phi_{E \rightarrow Z}$ decreases. Exchanging the isopropylidene for an adamantylidene moiety increases the $\Phi_{C \rightarrow E}$ upon irradiation with visible light. The relatively high quantum yields for ring closure and the high thermal stability make fulgides highly attractive switches for nano-scale devices.

1.3.3 Dithienylethenes

Dithienylethene (DTE) switches undergo ring closure upon irradiation with UV-light (Figure 1.8).³² The ring closed form is usually thermally stable and can be converted back to the open form by irradiation with visible light. Dithienylethene switches are an important class of molecular switches due to their thermal stability, high fatigue resistance, and wide variety and ease of functionalization.^{32,33} As the structure of the open form is non-planar, there is no conjugation between the two thiophene rings. Ring closure locks the switch in a more planar structure, resulting in conjugation over the entire structure. The difference in conjugation is manifested as a change from colorless to colored.

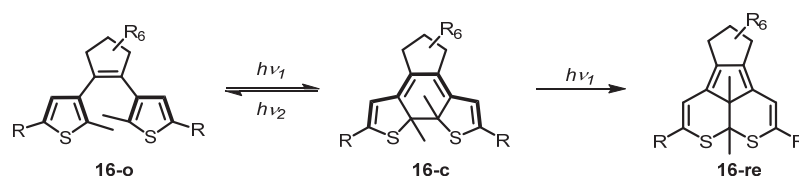
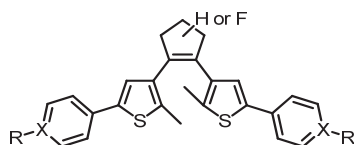


Figure 1.8: Photoswitching of dithienylethene switches. Ring closing upon UV irradiation and ring opening by irradiation with visible light. UV irradiation of the closed form can result in rearrangement of the thiophene units to the condensed 6-membered rings ($R = H$ or F).

As with stilbene switches, ring closure upon irradiation with UV-light is a 6π -electrocyclisation. In DTE switches however, the ring closed form is stable. Irie and co-workers proposed that the thermal stability is dependent on aromatic stabilization in the ring open form.³⁴ The loss of aromaticity upon ring closure, leads to a large difference in ground state energy. Unlike stilbene, DTE switches have two thiophene rings as aromatic units. There are also other variants based on the 1,3,5-hexatriene framework bearing furan³⁵ or pyrrole³⁶ units. The thiophene units have low aromatic stabilization, and consequently the ground state energy is closer to that of the closed form than that of diphenylethenes. In addition DTEs have a larger barrier to ring opening.

As for stilbene switches (Figure 1.2), when the 2- and 2'-positions on the thiophene rings are substituted with methyl substituents, oxidation of the ring closed form no longer takes place. In contrast to stilbenes, the central double bond in DTE switches is bridged, locking the thiophene rings in proximity to each other and preventing competitive *cis-trans* photoisomerization. As a result dithienylethene switches exist in parallel and anti-parallel conformations, of which only the anti-parallel conformation can be switched to the ring-closed form. According to the Woodward-Hoffmann rules such a ring closure can only proceed in a conrotatory fashion.

As a consequence of the two conformations, irradiation of the open form with UV light, results in ring closure with a maximum quantum yield of ca. 50%. However, fast interconversion between the two conformations in the open form allows quantitative ring closure at the PSS. Usually the ring closed form of dithienylethene switches exhibits high thermal stability. This stability is due in part to the fact that it is thermally forbidden for 6π electron systems to open in a disrotatory fashion according to the Woodward-Hoffmann rules. Nevertheless, the thermal properties of the ring opening can be tuned by substitution at the phenyl rings (Table 1.2). Although, many aryl substituted DTE switches have been reported, thermal stabilities have not been reported for all of them. From the limited number of switches in table 1, the following trend can be discerned. EDGs in the *para*-positions of the aryl units in perhydro DTEs, lead to a lower thermal stability (Table 1.2). While the introduction of EWGs leads to an increase in the thermal stability.

**Table 1.2:** Thermal stability of DTE switches.

Number	Substitution	DTE(perhydro) ($t_{1/2}$)	DTE(perfluoro) ($t_{1/2}$)
17	R = H	66 h ^a	432 h ^b
18	R = Me	n.a.	- ^c
19	R = OH	n.a.	167 h ^d
20	R = OMe	40 h ^a	<2% after 14h
21	R = CN	100 h ^a	<2% after 14h
22	X = N, R = :	- ^e	f
23	X = N ⁺ , R = Me	n.a.	4.1 h ^d

a) at 100°C in toluene,³⁷ b) at 100°C in crystalline solid,³⁸ c) in crystalline solid, coloration remained unchanged till melting temperature (133°C),³⁹ d) at 60°C in acetonitrile,^{40,41} e) thermally stable for several hours at 80°C,⁴² f) no detectable ring opening after 15 days at 60°C in benzene.⁴¹

Perfluoro-DTE switches generally are more thermally stable and have higher fatigue resistance than their perhydro-counterparts.⁴³ However, the thermal stability of the closed form is affected by replacing the aryl ring for a pyridine and is further lowered by the formation of a dimethyl pyridinium cation. Thermal instability in the latter switch is attributed to weakening of the photogenerated C–C bond by the electron withdrawing effect.³² Interestingly, perfluoro-DTE switches bearing strongly electron EWGs on the thiophene rings, display thermal ring opening (R = CHC(CN)₂, $t_{1/2}$ = 3.3 min at 60°C).³² Exchanging the methyl groups at the 2- and 2'-positions for *iso*-propyl groups dramatically lowers the thermal stability of the ring closed form ($t_{1/2}$ = 20 min at 100 °C).

Switching fatigue of DTE switches usually entails the formation of endoperoxides in samples containing oxygen,³² or the formation of by-product 16-re as a result of irradiation of the closed form in the absence of oxygen.⁴³ The resistance to switching fatigue can be dramatically increased by the addition of methyl groups to the 4- and 4'-positions of the DTE switch, preventing rearrangement of the thiophene rings.⁴³

1.4 Conclusions

To date there are a large number of photochromic switches available to chemists and physicists for the development of novel nano-scale responsive systems. The properties of the various families of photochromic switch can be utilized for diverse applications. This chapter describes the key properties of photochromic systems required to be used in biomedical or biology samples. These properties include; selective photoisomerization, non-destructive photoirradiation, thermal stability, change of character and fatigue resistance. This chapter, can serve as a guide to choose the most appropriate switch for a particular application.

1.5 Thesis outline

This Thesis has two parts; in the first (Chapters 3 to 5) the aim is to explore the properties photochromic switches in terms of, high thermal stability and facile readout. Towards this goal the photochemical and thermal switching characteristics of several families of photochromic switches have been studied. The second part (Chapters 6 and 7) describes the synthetic efforts towards photoresponsive fluorescent tags based on a dithienylethene photochromic switch and explore if such switches can potentially be used to obtain fluorescence images in living cells; opening the door to photo activated localization microscopy, which allows images to be obtained with a resolution beyond the diffraction limit.

In Chapter 2 the state of the art in dynamic control over the cell adhesive properties of self-assembled monolayers is reviewed. Several external stimuli such as photochemical, electrochemical and supermolecular control over the cell adhesiveness to SAMs are also discussed. The SAMs described in this chapter have primarily been used to pattern cells on surfaces and their sequential release from their confinement on-demand.

Chapter 3 describes the kinetic analysis of a double azobenzene system, in which the two azobenzene switching units are positioned *ortho* with respect to each other. As photo-responsive molecular systems become ever more complex (bearing several functional units), the proximity of another photochromic unit might have an effect on the characteristics of the individual switching units.

Chapter 4 describes the photochemical and thermal properties of a series of new hemithioindigo switches. Special attention is given to solvent and functional effects on the photochemical switching and the thermal relaxation of these switches. The investigation of

HTI switches is continued in Chapter 5. In this Chapter the electrochemical properties of HTI switches are explored under oxidative and reductive conditions using cyclic voltammetry (CV). It was hypothesized that HTI switches could exhibit electrochemical switching much like their stilbene and thioindigo analogous, which would make them a attractive new family of redox controlled switches.

In Chapter 6 progress towards a photoactivated localization microscopy (PALM) probe based on a dithienylethenes switch is described. The properties of dithienylethenes make them excellent switching units for molecular PALM probes. The probe described in this chapter was specially designed to functionalize and visualize small gold nanoparticles in mammalian cells.

In Chapter 7 the development of a new method for the exchange from *t*-Bu thioethers to thio-acetates mediated by TiCl_4 is described; this methodology is highly relevant for self-assembly of thiol-functionalized molecules on Au-surfaces, and was discovered during the synthesis of the dithienylethenes switches for self-assembly described in Chapter 6.

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