Photochromic molecular switches

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Perspectives

In this Chapter the research described in this Thesis is placed in context. Further challenges toward application of molecular switches in functional materials are discussed.

Molecular switches in bio-medical technologies

Building photoresponsive functional units from nanoscale materials has always been intriguing. One of the ultimate applications of molecular switches lies in bio-technologies, especially in real time control of surface chemistry as described in Chapter 2.[1] Photoswitches could be used as responsive probes to gain better understanding of complex dynamic events in biological systems. Switches are a prime candidate for such devices, as nanoscale switches have the ability to modify the properties of a surface[1,2] or proteins[3] completely when they are exposed to external stimuli. The motivation for the majority of the studies described in this Thesis are to further develop the nanoscale toolbox and explore the functioning of photochromic switches, so that they can be better applied to the biological field in the future.

From azobenzene to double azobenzene switches

Cells have the ability to detect and react to subtle changes in their environment. It is therefore not farfetched to think that cells should respond to molecular changes on a SAM surface, and indeed many examples of such behavior are known and reviewed in **Chapter 2**. One of the most elegant systems to date is a surface bound azobenzene bearing an RGD peptide.[4] The cell adhesiveness of the surface can be controlled by the conformation of the switch. In the *E*-isomer cells can freely adhere to the peptide, however, in the *Z*-isomer the peptide is buried in the surrounding non-adhesive OEG-chains making cell adhesion unlikely.

Unfortunately the authors were not able to dissociate adhered cells by using irradiation alone.[4] Auernheimer *et al.* earlier described such a reversible light triggered cell adhesion material using an azobenzene on a PEG polymer.[5] My hypothesis was that one could optimize the length of the surrounding OEG chains with respect to the length of the azobenzene-peptide units and the OEG to peptide ratio in such a way that cells have a minimum adhesion to the surface when the azobenzene is in the *E*-isomeric form. A larger change in binding should be achieved and as a consequence release of the cells should be accomplished.

As so often is the case the focus of a research project adepts over time. During the synthesis of the azobenzene switches, we found a side product which turned out to be a double azobenzene switch. This bis-azobenzene switch was unique in that, its halves were not identical and could be distinguished by ^{1}H-NMR spectroscopy. This difference allowed us to study the kinetic parameters of the thermal *Z* to *E* isomerization of the two halves independently. It was envisioned that isomerization of one of the azo-units might affect the isomerization rate of the other e.g. through field effects. Such an observation would be of importance for development of future complex systems bearing several switching units in proximity to each other. The azobenzene switches, described in

Chapter 3, did not show a dependence on each other's rate of isomerization and function as independent switching units. However, this does not mean that interconnected multiple azobenzene systems in different orientations to each other follow the same behavior. In order to determine if *ortho* or *para* substituted bis-azobenzene switches can influence each other's isomerization rates these switches should be investigated in a similar fashion as described in **Chapter 3**. In addition other bridging units between the two switching units could be considered. For example the bridging unit between two dithienylethene switches is vital to the functioning of the two units. A direct C-C bond,[6] acetylene spacer[7] or a 1,4-bis(ethenyl)benzene unit only show limited photoresponse. However, dimers bridged with a phenyl[8] or dimethylsilyl[9] group undergo complete switching.

Hemithioindigo switches

Even though hemithioindigo switches (HTIs) were first proved decades ago,[10] few studies have been devoted to this class of photochromic switches. These systems are of interest for two reasons: 1) They are a hybrid of two well-studied switches, namely; thioindigos, and stilbenes and 2) they exhibit good switching properties as is described in **Chapter 4** and elsewhere.[10,11] We set out to develop a photo- and electro-chemically responsive hemithioindigo functionalized gold surface. To achieve this goal a series of thioindigo switches were synthesized. The thermal isomerization behavior is one of the most important characteristics of surface attached switches and will for a large part determine its purpose. As there was little information available on the thermal isomerization behavior of HTI switches a series of HTI's were studied in solution. We discovered that HTI switches are sensitive to the polarity of the solvent. This led to a new line of investigation for HTI switches, in which they could eventually be used to sense the polarity of an environment, or the polarity could be used to fine tune the properties of a switch. The polarity effect could also play an important role when HTI switches are employed on a surfaces or in aqueous solution for photoactive pharmalogical compounds.

In the future HTI switches **2**, **4** and **9** (Chapter 4) can be functionalized for surface attachment (Figure 8.1). A surface anchor such as a thiol or silane can be introduced via the bromo, carboxylic ester and the phenol substituent, respectively. To ensure photoswitching on the surface occurs efficiently the switch and surface need to be spaced sufficiently.[12]

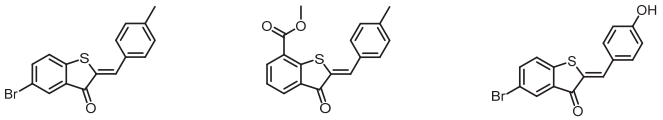

Figure 1: Hemithioindigo switches that can be further developed for surface functionalization.

Even though the electrochemical behavior of stilbene[13] and thioindigo[14] switches is studied extensively, no such studies were reported for HTI switches. The studies described in **Chapter 5** revealed that HTI switches undergo electrochemical reduction followed by a range of subsequent reactions that could not be identified but an overall chemical reversibility is observed. Regardless, electrochemical *Z*-*E* or *E*-*Z* isomerization could not be established. To completely elucidate the electrochemical reduction products, HTI switches should be studied further using techniques such as bulk electrolysis in combination with ^{1}H-NMR spectroscopy and mass spectrometry.

As there are few studies on HTI switches many potential fields of study remain for the future. It would for example be interesting to develop a new chiroptical switch based on HTI switches by introducing a chiral group to one of the halves of the HTI switch. Linking two such chiral switches could possibly form helical structures of which the form of the supramolecular structure can be altered by irradiation.

Dithienylethene switches as PALM probes

A report of fluorescent amphiphilic dithienylethene switches,[15] for which the fluorescence could be reversibly switched on and off inside mammalian cells stimulated interest in this field. A report by Leifert *et al.* on the cytotoxicity of gold nanoparticles[16] highlighted difficulties in visualizing small (± 2 nm) gold nanoparticles in cells. Our initial idea was to use dithienylethene switches as fluorescent probes to image small nanoparticles in cells. The advantage of using dithienylethene switches over regular fluorescent probes is that they can potentially be used as novel small molecular photoactivated localization microscopy (PALM) probes. Towards this goal a fluorescent dithienylethene switch was synthesized and the characterized of this system is described in **Chapter 6**. The switching fatigue of the dithienylethene switch in **Chapter 6** is one of the main challenges encountered. Using a per-fluoro dithienylethene instead should lead to a more fatigue resistant probe, fatigue resistants of switching can be further increased by addition of methyl groups to the 4- and 4'-positons of the DTE switch (Figure 2a).

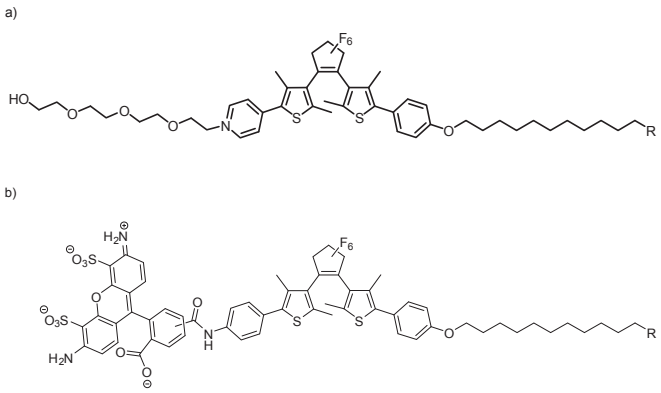

Figure 2: Possible structures of improved photoswitchable fluorescent probes. a) A per-fluoro DTE switch bearing methyl groups in the 4- and 4'-positons. b) DTE switch bearing an Alexa fluor 488 fluorophore.

Using a more efficient fluorephore *i.e.* a fluorophore with a high quantum yield $\Phi > 0.90$ and a high extinction coefficient (ε) should lead to probe with a high brightness, among such suitable fluorophores is Alexa fluor 488 (Figure 8.2b). For fluorescent quenching to take place the emission spectrum of the donor and the absorption spectrum of the acceptor need to overlap (Figure 8.3). In **Chapter 6** a thiol-group was introduced to anchor the probe to a gold surface. In addition, other anchoring groups could be introduced during the synthesis of the probe.

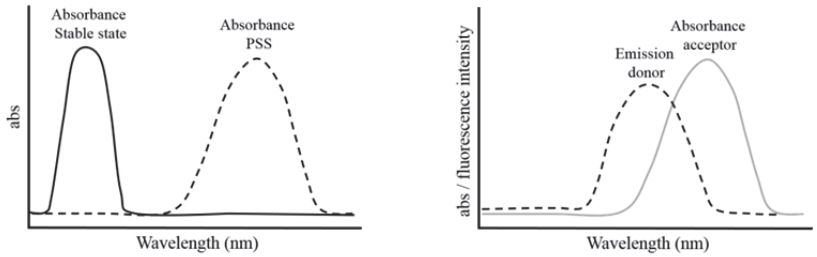

Figure 3: Schematic representation of a) Change in UV/Vis absorption spectrum as a result of photoswitching. b) Donor emission and acceptor absorbance bands for fluorescence quenching by a photoswitch (acceptor).

A new method for substituting protection groups

Balancing the order of reactivity during the synthesis of the switches in **Chapter 6** proved challenging. The crux of the synthesis was predominantly centered around the order of protection and deprotection steps of the thiol-functionality. Protecting groups such as acetyl and trityl were discarded during the synthesis, however the *t*-butyl

protecting group was found to be robust enough to withstand the conditions of the key steps in the early stages of the synthesis. Nevertheless the deprotection of the *t*-butyl-thioether was thought to be too harsh to be left in the final product. Therefore, the *t*-butyl group was exchanged for an acetyl protecting group during the final stages of the synthesis. This method has previously been used during the synthesis of aromatic thiols that can self-assemble on a gold surface and deprotection wass achieved using BBr_3.[17] The use of $TiCl_4$ in this reaction turned out to lead to a serendipitous discovery, achieving higher reaction rates, greater functional group tolerance and higher yields (**Chapter 7**). It seems that the *t*-buty/acetyl exchange proceeds through a Friedel-Crafts acylation, in which the acylium ion is formed by the addition of the $TiCl_4$. However, more detailed mechanistic studies should be undertaken to determine the exact mechanism through which this reaction operates.

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