Orchestrating Molecular Motion with Light – From Single (macro)Molecules to Materials

David Bléger

The possibility to control molecular systems with light holds much promise for the fields of materials and life sciences. To achieve such control, compounds that are able to reversibly photoisomerize between two states or more can be employed. Several classes of photochromic units are available depending on which properties should be modulated upon isomerization, e.g., electronic gap, polarity, or geometry. The latter class, which is mostly based on E/Z isomerization, is particularly useful to remotely trigger motion at the single molecule level, giving rise to a wide range of applications at all scales after incorporation into the adequate architecture. In this article, recent advances in that direction are highlighted, including our own efforts to optimize the intrinsic properties of azobenzene photoswitches, as well as their integration into oligomers, polymers, and 3D frameworks.

1. Introduction

Organic molecules interplay with light by absorbing photons of suitable frequencies, populating higher energy electronic excited states that eventually deactivate following different possible paths. Some of their most interesting outcomes include the controlled formation of new chemical bonds (photochemical reactions), transferring electrons or energy (photovoltaics, light harvesting), and reversibly transforming their configuration, i.e., photoisomerizing. These different processes are leveraged in Nature for performing tasks of various importance, from the synthesis of vitamin D in the skin to photosynthesis in plants and other micro-organisms. Probably less commonly known, E/Z photoisomerization of dyes confined in exquisitely optimized proteins is also at the origin of several key processes in Nature, such as phototaxis and phototropism in plants, circadian timing, and the most spectacular, visual perception in animals.

Although far from Nature’s sophistication, the development of photoisomerizable compounds—also referred to as molecular photoswitches—and their integration into more complex systems has recently bloomed, with the aim of activating specific tasks on demand as a response to light. In that context, the modification of natural photoswitches has proved to be tremendously useful, in particular with genetically engineered rhodopsins (the proteins responsible for visual perception), which constitute the primary tools of optogenetics. The utilization of artificial photochromic compounds is nevertheless the strategy more generally followed. Diarylethenes, azobenzenes, and spiropyrans are the three most popular classes of artificial photoswitches (see Figure 1A), while several others are routinely used as well.

The choice of the right photochromic compound is dictated by the property that one needs to modulate in order to accomplish a specific function. By definition, photochromic compounds change their color, i.e., their spectral features. The change in geometry and concomitant molecular motion experienced by some photochromic compounds—in particular azobenzenes—upon isomerization can be utilized in...
many different ways, in materials as well as life sciences, and is the main focus of this article. Motion realized at the molecular level can find application from the nano[7] to the macroscopic scale. For the latter, it can be necessary to collect and amplify many local deformation events of individual photoswitching entities. This is usually accomplished via adequate 3D organization within materials,[8] or making use of cascade events such as those operating in signal transduction.

A remarkable application in materials science is the conversion of light into mechanical energy, which can be performed by either photosensitive single crystals[9–11] or polymeric materials[12] A recent example is presented in Figure 1B, where an azobenzene-containing liquid crystalline elastomer (LCE) was shaped by two-photon absorption direct laser writing into a rectangular box, to which four light-insensitive conical “limbs” were attached.[13] By applying green light the incorporated azobenzenes start isomerizing in both directions, inducing a local phase transition (nematic → isotropic) and hence an asymmetry on the top of the object, provoking a reversible 20% contraction of the body. Thanks to the four conical shaped legs, friction forces with the substrate are lowered, while the 45° tilt (see side-view, Figure 1B) creates the adhesion asymmetry necessary for (directional) walking. If three lamellar “legs” were attached to the body instead of the four conical limbs, preventing the object to walk, laser irradiation could induce up to 1 cm (100 body lengths) long jumps, by converting accumulated elastic energy into kinetic energy. The initial ordering of the photoswitches within the LCE material and subsequent local phase transition explains the amplification of the isomerization events, leading to microscopic movements of the entire object.

Recent promising advances making use of azobenzene’s E/Z photoisomerization in the context of life sciences[15–17] should be emphasized as well, in particular in the field of photopharmacology (the development of drugs that can be activated by light and possibly autodeactivate over time)[18,19] and for the control of neuronal activity.[20] Several biological targets can be placed under optical control, including enzymes, transporters, receptors, or transmembrane proteins.[21] Figure 1C presents a study where an agonist, in that case glutamate, is covalently tethered to the ligand binding domain...
of an ionic channel via an azobenzene linker. Photoswitching the maleimide-azobenzene-glutamate (MAG) by alternating exposure to UV and green light results in reversible binding of the glutamate. Binding activates the receptor allowing cations to flow, resulting in membrane depolarization. This light-gated glutamate receptors has been used to restore pupillary reflexes and light-avoidance behavior, i.e., visual functions, to blind mice.

These two selected examples illustrate the spectacular possibilities associated with molecular motion performed by geometrical switches based on E/Z isomerization and fueled by light. In the following, our recent efforts in that direction are presented, from the optimization of azobenzenes’ intrinsic photoswitching properties (in particular visible light addressability, see Section 2), to their incorporation within oligomeric/polymeric linear backbones (Sections 3, 4) and 3D frameworks (Section 5).

2. Optimizing Azobenzene Photoswitches

One important prerequisite to extend the scope of photochromic systems is to optimize the tools available, in our case geometric photoswitches. In that regard, the azobenzene moiety, without proper modification, is far from ideal. Although it exhibits excellent fatigue resistance (i.e., many Z/E isomerization cycles are realized without noticeable degradation) and its synthesis is usually straightforward, it still presents several drawbacks: i) the $E \rightarrow Z$ photoconversion is typically high to very high (90–95%), but the reverse $Z \rightarrow E$ photoconversion is often limited to 80–85%; ii) the quantum yields are commonly not higher than 50%; iii) the $Z$ isomer persists up to only a few days in solution; and iv) UV light is normally essential to trigger the $E \rightarrow Z$ isomerization. The last point is critical, since UV light is nonselectively absorbed by all chromophores, can lead to side-reactions, damages cells, and is quickly attenuated in tissues, whereas visible light exhibits a large window of available wavelengths for higher selectivity, is generally harmless, offers good penetration depth, and its predominance in the solar spectrum reaching the surface of the earth makes it advantageous for sunlight conversion.

In order to tackle the issue of UV light activation, and following pioneering work by the groups of Herges and Woolley, we explored the possibility to separate the $E$ and $Z$ isomers’ $n \rightarrow \pi^*$ absorption bands, which usually overlap in azobenzene derivatives (see Figure 2A). We reasoned that introducing electron-withdrawing groups (EWG) ortho to the N=N bond would decrease the electronic repulsion occurring between the N lone pairs in the $Z$ isomer, therefore stabilizing its n-orbital and eventually increasing the n–$\pi^*$ electronic gap of the $Z$ isomer. Encouraged by density functional theory (DFT) calculations (see Figure 2B for the energetic diagram of the $\pi$, n, and $\pi^*$ orbitals, together with the representation of the n orbitals (HOMOs)), we opted for fluorine atoms, which, in addition to being $\sigma$-withdrawing (and $\pi$-donating at the same time), are rather small and therefore do not twist the $E$ isomer around the $N=N$ bond. Planarity is desirable in some cases, especially when an effective conjugation along the $\pi$-system is targeted, or an assembly by $\pi$-stacking is required. As anticipated, the $E$ and $Z$ isomers’ $n \rightarrow \pi^*$ absorption bands of ortho-tetrafluorozobenzene significantly split with a 40 nm separation of the absorption maxima (see Figure 2A). This feature allows for triggering $E/Z$ isomerizations with visible light only (green for $E \rightarrow Z$ and blue for $Z \rightarrow E$). Further EWGs (such as ester groups) introduced para to the N=N work in concert with the ortho-F and lead to a superior photoswitchable compound, which exhibits a 50 nm separation of the n–$\pi^*$ bands. Such a high separation makes possible to address both isomers selectively and as a consequence very high photoconversions (up to 97%) can be reached in both directions. On the contrary, electron donating groups (EDGs) such as N-acyls introduced in para-positions counterbalance the effects of the ortho-fluorine atoms by pushing electron density into the N=N bond. The separation of the n–$\pi^*$ bands is reduced to 22 nm and eventually the two isomers cannot be selectively excited in the visible range, leading to only $\approx 70\%$ $Z \rightarrow E$ photoconversion (when irradiated at 440 nm). Noteworthy, in addition to offering visible light addressability, isomerizing ABs via $n \rightarrow \pi^*$ transitions is also quite efficient (quantum yields of 0.3–0.5 via $n \rightarrow \pi^*$ vs. 0.1–0.2 via $\pi \rightarrow \pi^*$ transitions).

Another very attractive feature of F-azobenzenes is the very high thermal stability of the $Z$ isomers. A half-life ($t_{1/2}$) of 2 years was measured at room temperature for F4-azobenzene vs. a few days for the unsubstituted photoswitch (the $E$ isomer of azobenzenes is thermodynamically more stable than the $Z$ isomer, except for some bridged compounds). This effect can be partly attributed to the pronounced stabilization of the n-orbital of the $Z$ isomer (while the n-orbital of the transition state is less stabilized), which eventually leads to a larger barrier for the thermal $Z \rightarrow E$ reaction and as a result place these compounds among the thermally most stable ($Z$)-azobenzenes ever reported. The thermal half-lives of several ($Z$)-ortho-fluoroazobenzenes were measured at 60 °C (see Figure 2C), confirming the general stability of this new class of azobenzene derivatives.

Overall, the high level of thermal bistability combined with the
possibility to isomerize without UV light opens up many perspectives in materials and life sciences. One application based on the integration of such all-visible switches into metal–organic frameworks is presented in the last section of this article.

3. Articulated Rigid-Rod Polymers

The integration of geometric photo-switches within macromolecules has proved to be an efficient strategy for the creation of light-sensitive materials, in particular in the context of photoactuators such as the LCE presented in Figure 1B. Several polymeric architectures have been selected in the past, e.g., dendrimers,[32,33] brush polymers,[34] or more simply linear macromolecules, in which the photoswitches are introduced either as pendant groups[85] or in the main chain.[36–38] The latter design is particularly appealing to obtain polymers able to drastically change their dimensions upon exposure to light.

In order to maximize single (macro)molecules’ photodeformation,[8] geometric switches have to be introduced into stiff polymers. Following this strategy, we have shown that drastic contraction/extension cycles can be induced in poly(para-phenylene) rigid-rods incorporating azobenzenes in the main chain (see Figure 3A). A crucial aspect of the design was the introduction of large twist angles between the azobenzene units to break the electronic conjugation. This point, which was achieved by equipping the backbone with strategically positioned methyl groups, ensures to attain a Z-rich photostationary state (PSS) upon irradiation with UV light, whereas azobenzenes directly connected at their para-positions display very low E→Z photoconversions.[39] The azo-polymers were shown to perform in solution,[40] exhibiting conformational rigid-rod→random-coil transitions accompanied with large changes in hydrodynamic volume.

**Figure 2.** Comparison of electronic transitions and thermal bistability in unsubstituted azobenzene and ortho-fluoroazobenzenes. A) UV–vis absorption spectra in acetonitrile at 25 °C and B) energetic diagram of the π, n, and π* orbitals, and representation of the n orbitals (HOMOs) calculated at the B3LYP/6-31G level of theory (arrows highlight n→π* transitions). C) Thermal half-lifes (τ1/2) of the Z isomers of unsubstituted azobenzene (top-left) vs. some ortho-fluoroazobenzenes derivatives at 60 °C in MeCN. Adapted with permission.[29,30]
(≈ 75%), as determined by light-scattering measurements.

Aiming to address one current challenge in nanotechnology, i.e., the development of molecular machines performing specific tasks on demand at the smallest scale, we installed our photoshrinkable rigid rods onto an atomically well-defined surface.\[^{41,42}\]

An important requirement to preserve the photoactivity of the polymers was to adequately modify the surface, in that case highly oriented pyrolytic graphite (HOPG), for at the same time orienting the linear macromolecules, isolating them from each other, and decoupling them from the surface (both mechanically and electronically). This was achieved by covering the basal plane of the graphite substrate with an insulating monolayer of octadecylamine. Following this strategy, upon exposure to UV light, the single polymers could all shrink through concerted conformational changes, as visualized by scanning force microscopy. Large contractions and extensions were reversibly induced by alternating irradiation with UV and blue light (see Figure 3B,C), and in some cases the macromolecules were found to "crawl" on the surface (see Figure 3D). While direct visualization of such molecular movements could help providing a fundamental understanding of the behavior governing this family of polymers at different scales, further developments should focus on gaining directionality over the light-induced motion.

Besides the study of isolated photoarticated polymers in solution and on surfaces, those polymeric strands have been assembled in thin layered films, which displayed reversible light-induced disorder of the interdigitated dodecyl side chains along with interesting collective behaviors.\[^{43}\]

Remarkably, fast $E\rightarrow Z$ isomerization ($t = 5$ s) of a small fraction (≈ 20%) of all azobenzene chromophores within the polymer film was sufficient to disrupt the long-range ordering of the dodecyl side chains and to induce a complete amorphization of the films. Various other strategies to self-assemble light-controlled rigid-rod polymers in different environments and take profit of cooperative phenomena are under way.

**4. Light-Induced Modulation of Glycooligomers Binding Affinities**

We have highlighted earlier the exciting opportunities associated with the on-command reversible binding of biological ligands to...
carefully selected receptors using geometrical photoswitches (see Figure 1C). Carbohydrates constitute a promising class of ligands as their molecular recognition underpins many important processes in biology.\[44\] Glycopolymers presenting sugar ligands advantageously positioned along a synthetic main-chain are appealing carbohydrate mimetics, where the multiplicity of the ligands usually assures high binding affinities through simple additivity or, more interestingly, multivalent effects.\[45,46\] Aiming to create glycopolymers whose binding affinities towards specific lectins could be dramatically modulated by light inputs, a series of linear precision oligomers incorporating either one or two azobenzene units in the main chain was prepared\[47\] (see Figure 4A). We reasoned that large photoinduced geometrical changes in the oligomers shape and concomitantly in the sugar ligands accessibility would significantly alter the binding constants and hence possibly inhibit the association. Photomodulating the complexation of such ligands offers potential perspectives for the sensing and adhesion of bacteriological targets on various substrates.\[48,49\] The photoswitchable units were integrated into a synthetic water-soluble polyamide backbone synthesized on solid support\[50\] and post-functionalized with galactose (Gal)-terminated side chains. This stepwise synthetic approach allows for modulating the distance between sugar ligands, hence structure–property correlations and insights into the multivalent binding of glycomimetics can generally be obtained.\[51\]

The tetrameric lectin PA-IL was selected as a receptor. Its crystal structure reveals that the distance between two binding sites is >2.6 nm, which is approximately the length of the photoswitchable oligomers’ repeat unit. Consequently, the distance between two sugar ligands can span the distance of two neighboring binding sites when the switch is in the E-configuration, potentially allowing for chelate binding. Upon E → Z isomerization the sugars’ distance will decrease, which is expected to strongly impact the ligand–receptor binding affinity. This hypothesis was confirmed by surface plasmon resonance (SPR) inhibition/competition assays. The inhibitory concentration at 50% binding (IC\(_{50}\)) value for the divalent (\(n=1\), two Gal units) glycooligomer significantly

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**Figure 4.** Photomodulation of binding affinity in precision glycooligomers. A) Molecular structures of the photoswitchable galactose (Gal)-containing ligands obtained via solid-phase synthesis. B) IC\(_{50}\) values of the two oligomers determined by SPR inhibition/competition assays. C) Structural models of the two oligomers in their E-(left) and Z-(right) configurations bound to the PA-IL lectin. Complexed Gal units are highlighted by dotted circles. Adapted with permission.\[47\] Copyright 2014, Beilstein-Institut.
increases upon exposure to UV light (see Figure 4B), indicating a decrease in binding affinity. However, the trivalent \((n = 2,\) three Gal) glycooligomer shows no change in association constant. This last finding can be rationalized with the help of molecular modeling (see Figure 4C). Both \(E,E,\) and \(Z,Z\)-isomers are able to bind two neighboring sites on the receptor, however using sugars located at different positions on the oligomer: neighboring positions for the \(E,E\)-isomer, but terminal positions for the \(Z,Z\)-isomer (see Figure 4C). Hence, upon \(E,E\rightarrow Z,Z\) isomerization, no significant change in binding affinities can be recorded. Note that the modeling did not take into account possible additional binding modes which might contribute to the multivalent binding of the glycooligomer.

Interestingly, when the oligomers are immobilized at the surface of SPR chips, the opposite trend is observed: no significant photomodulation occurs in the divalent Gal-compound, while the dissociation constant doubles upon (ex-situ) UV irradiation in the case of the trivalent ligand, from \(K_D = 3.3 \times 10^{-6}\) to \(7.4 \times 10^{-6}\) m. This trend reversal most likely arises from the lack of accessibility to the Gal unit located next to the N-terminus attached to the SPR chip. Hence, the divalent compound is reduced to an effective monovalent one, and the trivalent compound to an effective divalent ligand. The latter is therefore expected to show changes in binding behavior similar to those measured for the divalent \((n = 1)\) Gal-glycooligomer in solution, as was indeed observed.

### 5. Photoresponsive Metal–Organic Frameworks

The last part of this article focuses on the integration of \(E/Z\) isomerization-based switches into a class of materials which has attracted a great interest over the past 15 years, i.e., metal–organic frameworks (MOFs). These microporous materials exhibit very high surface areas combined with a great synthetic tailorability via the choice of the linkers and the metallic nodes, which together dictate the architecture and properties of the frameworks. Implementing light sensitivity to MOFs could benefit several fields such as energy conversion,\(^{52}\) optoelectronics,\(^{53,54}\) or nanomedicine,\(^{55}\) to name a few. In particular, the possibility to photoinduce \(E/Z\) isomerization events inside MOFs’ pores has been used to photomodulate the uptake of gas, mainly \(\text{CO}_2,^{56,57}\) and trigger the release of larger molecules.\(^{58,59}\) However, most of these materials require the application of UV light to be activated, which—as explained in the introduction—presents several drawbacks in comparison to visible light irradiation.

In order to create visible-light-responsive materials, \(ortho\)-fluoroazobenzenes (see Figure 2) have been introduced as pendant groups in the walls of carefully selected architectures.\(^{60}\) The terephthalate linker used for that purpose (see Figure 5A) bears two \(ortho\)-fluorines on the same phenyl ring and readily isomerizes in solution upon exposure to green- and blue-light, producing \(E\)-isomers comprising 86% of \(Z\)- and 88% of \(E\)-isomers, respectively. To build MOFs that are stable towards several external factors (water, pressure, temperature), optically transparent, and present pores large enough for the isomerization to take place, we selected the well-described zirconium-based framework UiO-66.\(^{61}\) The resulting new material (F-azo-Uio-66, see Figure 5B) is isomeric to UiO-66 and stable towards UV–Vis irradiation, as confirmed by powder X-ray diffraction (PXRD) measurements.

Although the isomerization of azobenzenes is notoriously difficult in the solid state, thanks to our rational design F-azo-Uio-66 exhibits excellent photochromic properties. The extent of photoswitching was followed by diffuse reflectance UV–Vis spectroscopy, in particular via the position of the \(n\rightarrow\pi^*\) band, which experiences a significant blue-shift upon \(E\rightarrow Z\) isomerization (see Figure 2A for F4-azobenzene in solution). A 1 h cycle of subsequent green and blue light irradiation is shown in Figure 5C, highlighting the possibility to reversibly isomerize within the pores with visible light. Remarkably, \(E\rightarrow Z\) isomerization can be induced much more efficiently with green- than with UV-light, as indicated by the blue-shift of the \(n\rightarrow\pi^*\) band (22 nm with green light vs. 10–13 nm with UV light, see Figure 5D). The better photochromic response obtained with green light is mainly due to an increased penetration depth. Indeed, in the UV region azobenzene’s \(\pi\rightarrow\pi^*\) bands drastically limit the penetration of 310–370 nm light, whereas in the visible the \(n\rightarrow\pi^*\) molar absorption coefficient is rather low. The compositions of the PSSs inside the MOF could be determined by \(^{19}\)F NMR of the digested sample in \(d_6\)-DMSO/\(D_2\)SO mixture. After successive exposure to green- and blue-light, the materials comprise 45% of \(Z\)- and 86% of \(E\)-isomer, respectively. While the \(E\rightarrow Z\) isomerization in the MOF is still limited compared to the free ligand in solution, the back reaction is as efficient and overall the solid-state photoswitching properties are very good (for comparison, see a recent azobenzene-based crystal reporting efficient (ca. 32%) UV light triggered \(E\rightarrow Z\) isomerization in the solid-state\(^{62}\)). It was also proved that the \(Z\) isomers are thermally stable inside the pores, as generally observed for the free \(ortho\)-fluoroazobenzenes in solution (see Figure 2C). Such unique properties open up many possibilities for liquid-phase applications, for
example light-controlled adsorptive separation.

A second MOF incorporating the same ligand and based on the aluminum MIL-53 frame-
work displays interesting photomodulation of CO\textsubscript{2} adsorption capacities upon
green light irradiation. Remarkably, in that case the photoinduced effect is not caused by 
\textit{E/Z} isomerization, but by the suppression of the photonswitching ability due to steric 
congestion inside the 1D channels of the framework. Upon adsorption of green light, the 
confined azobenzenes deactivate by internal conversion, locally generating heat and 
therefore decreasing the amount of adsorbed CO\textsubscript{2} inside the framework. 
This last example nicely illustrates how hindered \textit{E/Z} isomerization, although generally detrimental for 
photochromic applications, may in some cases be the key to interesting light-induced (photothermal) 
effects.

### 6. Conclusions

In this article, the many possibilities offered by the integration of geometrical molecular photon-
switches—in particular azobenzenes—into carefully selected architectures have been highlighted. The recent 
developments dedicated to produce visible-light-responsive systems considerably extend the scope of applications, both in materials and 
life sciences, although research efforts in that direction are still necessary. In particular, bistable 
photonswitches fully addressable in both directions by red or better near-infrared light photons are highly 
desirable but still missing. Implementing nonlinear optical features, in particular two-photon address-
ability, thereby enabling 3D localized switching in one or even both directions, would be highly desirable as 
well. Photonswitchable compounds, which through photoredox catalytic 
cycles can isomerize very efficiently, i.e., where a few photons triggers many switching events, 
are other components of the next-generation systems. Furthermore, addressing photonswitches pre-
senting more than two states—with different wavelengths of light and/or other stimuli such as electrons—will enable to perform more complex tasks via a succession of steps 
selectively activated by orthogonal triggers.

Besides the optimization of the photonswitchable moieties, their clever integration will be key to future applications as well. Choosing suitable and relevant biological tar-
gets is challenging but feasible, as demonstrated by some spectacular results highlighted in the introduction. In the context of materials science, approaches that combine 
rational chemical design with smart molecular engineering and innovative material processing have proved
to be highly successful[13,34,66] Photoswitchable compounds have been known for a long time and have already found several academic uses as well as a few industrial applications, yet their true potential undoubtedly lies ahead!

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