Micro- and Opto-Electronic Materials,
Structures, and Systems

Jasper Van Hoorick · Heidi Ottevaere
Hugo Thienpont · Peter Dubruel
Sandra Van Vlierberghe *Editors*

Polymer and Photonic Materials Towards Biomedical Breakthroughs

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Preface

To date, strategies in which photonics, engineering and biomaterials are combined to serve a common purpose have been scarcely reported. Up to now, their cross-fertilization has been mainly limited to the development of photo-responsive polymers for various applications including drug delivery.

One specific example of photo-responsive polymers is are photo-reversible polymers. A photo-reversible polymer can be obtained by introducing functional groups. Which can reversibly dimerize upon irradiation with various wavelengths (see Table 1). The resultant materials combine the benefits of strong covalent interactions with the ease of reversible material manipulation for physically cross-linked materials. In addition, these materials do not require the presence of potentially toxic photo-initiators to result in polymer crosslinking. Common photo-responsive moieties include anthracene, cinnamic acid, thymine, stilbene and coumarin, as they are capable of undergoing photo-reversible dimerization upon applying a suitable UV-induced trigger.

Generally, $[4\pi + 4\pi]$- or $[2\pi + 2\pi]$-cycloadditions occur depending on the applied moiety (see Table 1 and Fig. 1). When applying coumarin, dimerization occurs through the transfer of electrons from one molecule (i.e. the donor) to a second (i.e. the acceptor). This transfer typically occurs from the most energetic electrons in the donor (i.e. the electrons that are present in the highest occupied molecular orbital (HOMO)) to the lowest unoccupied molecular orbital (LUMO) of the acceptor. When light with a wavelength of above 350 nm is applied, an electron can transfer from the HOMO of the alkene in coumarin to the LUMO. However, the development of photo-responsive biopolymers such as gelatin has not received much attention.

Photonics also play a crucial role in polymer processing for photo-responsive polymers. For example, laser-based systems apply photo-polymerization to introduce crosslinks in polymer materials, or to generate polymer chains in a monomer solution. More specifically, stereolithography and the more advanced two-photon polymerization (2PP) method of additive manufacturing (AM) are two well-known examples where polymers and light meet.

Two-photon polymerization is a cutting-edge example of a laser-based technique applying light to initiate the polymerization of a photo-sensitive material, thereby

Table 1 Overview of compounds able to undergo photo-reversible dimerization by application of a suitable UV trigger with (from left to right) stilbene, thymine, coumarin, cinnamic acid and anthracene

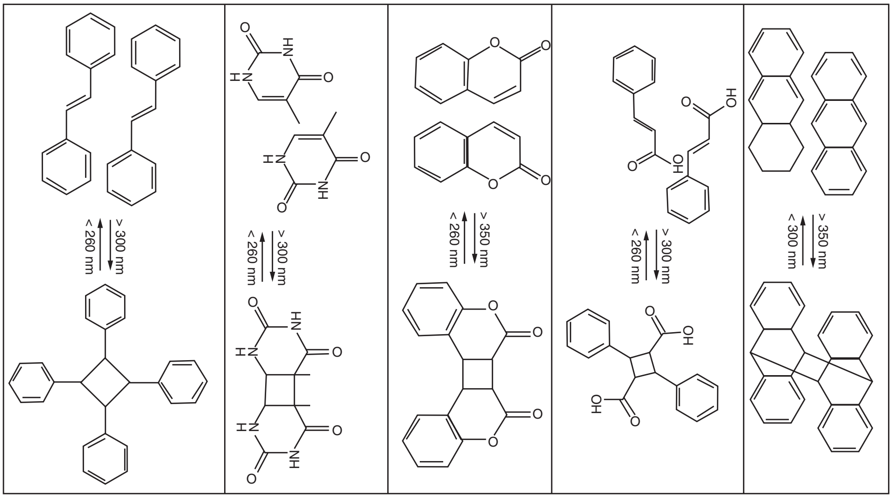
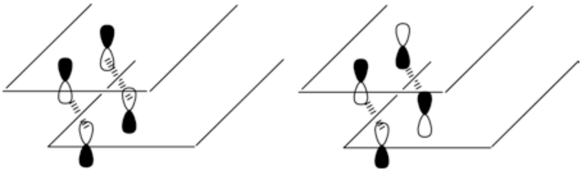


Fig. 1 Orbital symmetry required to enable suprafacial [2π + 2π]-cycloaddition of two alkenes



enabling 3D structuring. Among others, this technique enables the processing of hydrogels in a very controlled manner. Furthermore, as mild processing conditions are applied to enable crosslinking, a broad range of materials including thermally unstable materials can be processed. The latter opens up perspectives to produce biodegradable and cell-interactive scaffolds, which are functionalized with proteins or other biological compounds. Interestingly, the fabrication of materials encapsulating cells has also been performed in order to improve the cell seeding efficiency.

2PP differs from other laser-based AM techniques because it applies the principle of two-photon absorption for the generation of micro- and nanostructures inside a polymerizable solution. This is made possible by the application of a tightly focused, femtosecond pulsed laser beam. These laser pulses have wavelengths in the near-infrared range as opposed to traditionally applied UV exposure in conventional light based AM techniques. When focused correctly, the 2PP setup enhances the probability for an initiator molecule to simultaneously absorb two or more long wavelength photons. This can result in energy comparable to the absorption of one short wavelength photon and thus induce a polymerization reaction confined to the focal spot. As a result, the technique is described using two-photon polymerization or multi-photon polymerization. This is where technology differs from conventional stereolithographic processes. Conventional methods result in polymerization occurring in the entire area where the laser beam penetrates the solution instead of being confined to the focal spot.

When applying 2PP, the photo-initiator concentration should also be taken into account, as these compounds often show some cytotoxicity, which negatively influences cell viability. However, in general, the unreacted photo-initiator can be removed by incubating the generated structures in an appropriate solvent.

Since 2PP does not operate in a layer-by-layer fashion, it benefits from having nearly no geometrical restrictions when producing a structure. The movement of the focal point through the solution can be easily traced and processed through the solidification of the material, resulting in a 3D drawing. 2PP exhibits a higher resolution than other SFF techniques, even beyond the diffraction limit because of this feature. This is achieved by controlling the number and the energy of the applied laser pulses so that they barely overcome the polymerization energy threshold, which results in nanometer precision.

2PP is able to mimic the extracellular matrix (ECM) to a greater extent than other techniques, which increases cell proliferation.

Similar to other SFF technologies, being able to perfectly control the design of the scaffolds enables them to exhibit regions with varied mechanical properties.

Unfortunately, the 2PP technique possesses a disadvantage when compared to alternative SFF techniques. When constructing large scaffolds, it requires significantly more time, while scaffold dimensions still remain limited to date. Additionally, the technology is still relatively young, resulting in few commercially available set ups and concomitant high associated costs.

The above overview is not exhaustive but highlights the versatile applications that result from the combination of light and materials. This book attempts to overview recent biomedical breakthroughs in which polymers, photonics and their combinations were crucial. In addition, the chemical and engineering aspects accompanying these biomedical breakthroughs have been outlined.

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Part I

Material Development and Processing

Chapter 1
Development and Characterization of Photoresponsive Polymers

Florica Adriana Jerca, Valentin Victor Jerca, and Izabela-Cristina Stancu

1.1 Introduction

Synthetic polymeric materials capable of responding to external stimuli represent one of the most exciting scientific areas of commercially emerging applications. While there are many challenges facing this field, there is a great deal of opportunities in design, synthesis, and engineering of stimuli-responsive polymeric systems, and Mother Nature is an endless supplier of inspiration [1–3]. This book chapter is focused on reviewing the developments made in the field of *synthetic photoresponsive polymers* that undergo physical changes in response to a light stimulus. The control over the physical properties of a polymer system by light is obviously a highly desirable advantage. *Light* is a particularly interesting stimulus that can be controlled spatially and temporally with great ease and convenience from the exterior; therefore, this topic was countless times reviewed [4–8]. The constant scientific interest toward the highly developed experimental techniques in polymer science, which provides today's insight into polymer's structure and optical properties,

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helped to make the photoresponsive materials invaluable assets in everyday life. The field of photoresponsive polymers is a vast domain of research that covers development of polymeric materials for high-tech industry, such as photonics [9–11], biotechnology [12–14], or telecommunications [15]. One obvious example of a practical application of photoresponsive materials relies in the use of sunglasses that darken on exposure to bright sunlight and regain their transparency in darkness or low light intensity. In green high-tech applications, photoresponsive polymers are being used to harvest solar energy and store it for significant amounts of time. Other commercially available products of such polymer systems can be found as toys, cosmetics, and clothing.

Considerable widespread research is dedicated to photoresponsive polymers in the form of original research articles, reviews, books, and book chapters, ranging from fundamental studies to emerging applications. There have been reports on photoresponsive polymer systems that convert light into mechanical energy that enables the possibility of bending, flexing, swelling, contraction, and motion [16–20]. However, to start with early developments in this area, the most debated featuring applications of photoresponsive polymers are of course related to the nonlinear optical (NLO) phenomena [11, 21]. A number of several important discoveries made in the 1990s have had a particular impact on the NLO field. These include the surface relief grating (SRG) that can be inscribed on photochromic-based polymers using an interference pattern as a result of photoinduced mass transport [22, 23] and the photochemical phase transition from liquid crystalline (LC) to isotropic (order–disorder) phase because of the perturbation effect arising from the photoisomerization process [24–26]. Most of the research efforts in the 1990s mainly dealt with the physical and optical properties of chromophore-containing polymers and liquid crystals which brought important contribution for the optical signal processing [27], all optical switching to nonlinear optical imaging [28], to reversible optical storage [29, 30].

Today, the research field of photoresponsive polymeric materials remains still extremely active, thanks to important new directions and developments over the last 10 years in the biomedical field, which witnessed exciting progress in cellular biology [31–33], tissue engineering [34, 35], and drug delivery [4, 35–38]. The abundance of research articles in the photoresponsive polymers domain is driven by its enormous potential to contribute to improving health and life quality which are among the most important human priorities in our world. For this reason, it is necessary to reveal the actual challenges that fellow researches need to overcome with the design of the materials, their formulation, and properties and to discuss future research directions. A comprehensive illustration of the existing topographic categories is given in Fig. 1.1, which includes most important and most investigated photoresponsive polymer systems in both biomedical and NLO field.

Although in nature we can find several inspiring examples of how to approach and design functional photoresponsive materials, creating such controllable synthetic systems that respond to a light stimulus in a predictable fashion still represents a great challenge. First of all, it is important that the photoresponsive polymeric-based biomaterials to overcome the restricted mobility within the

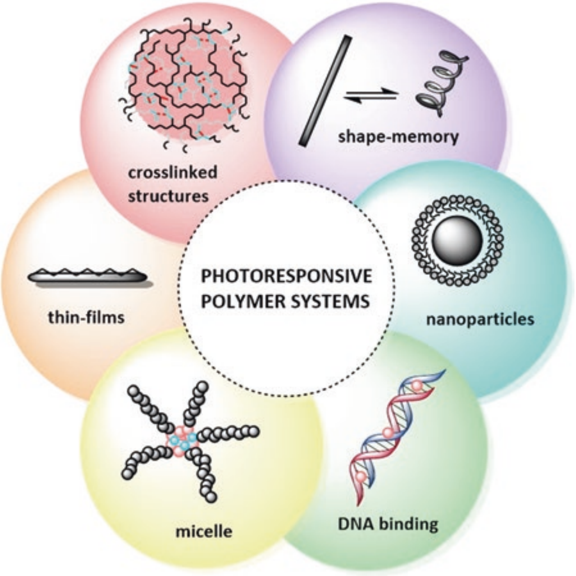

Fig. 1.1 Schematic representation of the dimensional existing variety of structured photoresponsive polymer materials, which range from shape-memory materials [39] to NLO materials (in the form of assemblies in thin films or multilayered films made of different polymers [40]); to crosslinked structures [41], micelles, and particles and their assemblies in solutions for drug delivery [42]; and to DNA/RNA binding for bioactivity [43]

network, while maintaining their mechanical integrity, without imposing limits on obtaining the photoresponsiveness. Another argument in this regard lies in mimicking biological systems where structural and compositional gradients at various length scales are necessary for orchestrated and orderly responsive behaviors. Significantly greater challenges exist when designing polymeric materials to exhibit biocompatibility and biodegradability, whereas the degradation products should be nontoxic. In addition to all these arguments, it is very important to have a highly reproducible composition via synthesis, functionalization or crosslinking when preparing any type of synthetic material.

To address all these problems regarding the structural nature, several photoresponsive systems have been developed over time (see Fig. 1.1), with the majority of studies dealing with hydrogel materials [35, 44–46], polymeric solutions, micelles and core–shell particles [4, 47–52], and to some extent polymeric solids [53]. To bring into consideration one of the most significant matter related to the photoresponsiveness of these polymer systems is when using UV irradiation as a stimulus. This stimulus is regarded as a relatively straightforward and noninvasive process to induce light-responsive behavior. However, most biological systems can suffer damage upon this type of irradiation. This is a strong argument which can limit the biomedical applicability of several photoresponsive polymeric systems. Therefore, the constant need to develop new photoactive molecules and improve the existing photoresponsive polymeric systems is imperative. At the "heart" of functional photoresponsive systems underlies the photoactive molecules. They can be incorporated into polymers in various topological configurations, such as side groups of linear polymers, within the backbone of linear macromolecules or as crosslinkers within branched networks. In this book chapter, we aim to approach the present topic from the perspective of the photoactive species that make up the existing variety of photoresponsive polymer systems and to highlight their function in use.

1.2 Photoresponsive Systems based on Photoactive Groups

Photoactive molecules play a pivotal role within photoresponsive systems, being able to capture an optical signal and convert it via a photoreaction, into a useful property change. This chapter's purpose is to cover the wide variety of photoactive molecules and to highlight the photochemical transformations they undergo. Therefore, here are included numerous classes of molecules that respond to light, which are either photochromic molecules or just photoactive, that have been used to trigger the properties of polymeric systems.

Figure 1.2 displays some of the most studied photoactive molecules that have been engineered over time to respond to light, ranging from ultrashort wavelength lasers to near-infrared light, and have been embedded into functional polymeric systems. Before going into detail about the new developments in the biomedical field, a classification of most important photoactive molecules is necessary. The polymer systems incorporating these photoactive molecules become functional and useful depending on the working principle they obey in response to light.

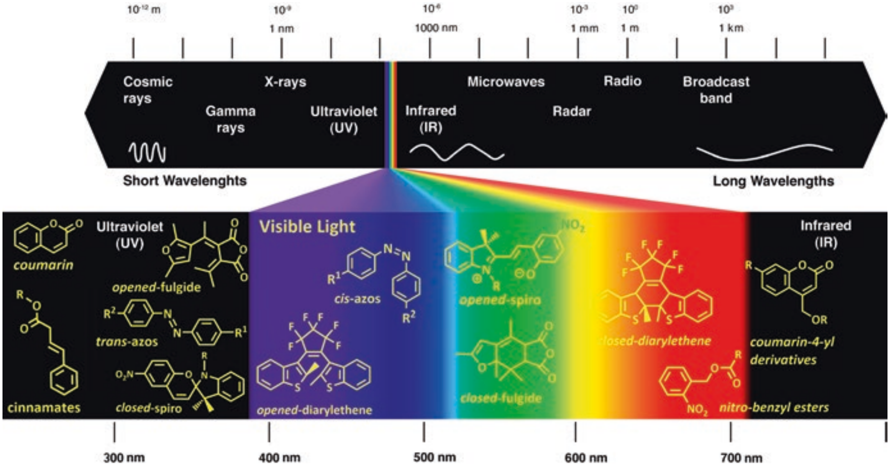

Fig. 1.2 Large-scale view over the variety of photoactive molecules that show typical absorption wavelengths in the broad absorption band that are frequently employed to photoregulate polymeric systems

1.2.1 Origin, Definition of Photochromism, and Basic Operation Principle

The phenomenon of photochromism was first observed by Fritzsche in 1880, who noted a reversible color change in a solution of tetracene upon sunlight exposure, but it took more than 70 years for the scientific community to define this phenomenon and call it photochromism [54]. Photochromic reactions are reversible and unimolecular processes that involve the transformation upon irradiation with light between a thermodynamically stable configuration of a species A to corresponding species B [55]. The species B can return to the ground state through thermal or photochemical processes. If the photogenerated isomers are unstable and revert thermally to their ground state in the dark, then they are termed T-type (thermally reversible type, e.g., spiropyrans and azobenzenes). The photogenerated isomers that are thermally irreversible but photochemically reversible are termed P-type (e.g., fulgides and diarylethenes). In addition to a color change in some cases, the intramolecular ring opening/closing and *cis–trans*-photoisomerization of the two isomeric forms induced by the absorption of light exhibit also a substantial change in the absorption spectra.

The photoresponsive systems typically are composed of a polymeric network and a photoactive moiety, usually a photochromic chromophore as the functional part. The optical signal is first captured by the photoactive molecules. Then, it is converted to a chemical signal through a photoreaction such as isomerization, cleavage, or dimerization, and this processed signal is transferred to the functional part of polymers to tamper with its properties.

1.2.2 Type of Photoactive Molecules and Photoreactions

The numerous photoactive molecules used as a point of origin for polymeric systems include, but are not limited to, azobenzenes [7, 10, 56–60], spiropyrans [61–63], spirooxazines [64–66], fulgides [67], coumarins [68–73], and *o*-nitrobenzylesters [74–79], as outlined in Fig. 1.3. Although all aforementioned classes are light-responsive molecules, not all of them are photochromic molecules. To cover the large availability of photoactive molecules, regardless of their molecular structure, they will be discusses based on the mechanism they obey under irradiation with light. Thus, the photoactive molecules fall in three categories that include photoisomerization reactions, photodimerization reactions, and photocleavage. These dynamic photoreactions have been exploited to generate considerable changes in the optical, chemical, electrical, and bulk properties in the systems that incorporate them.

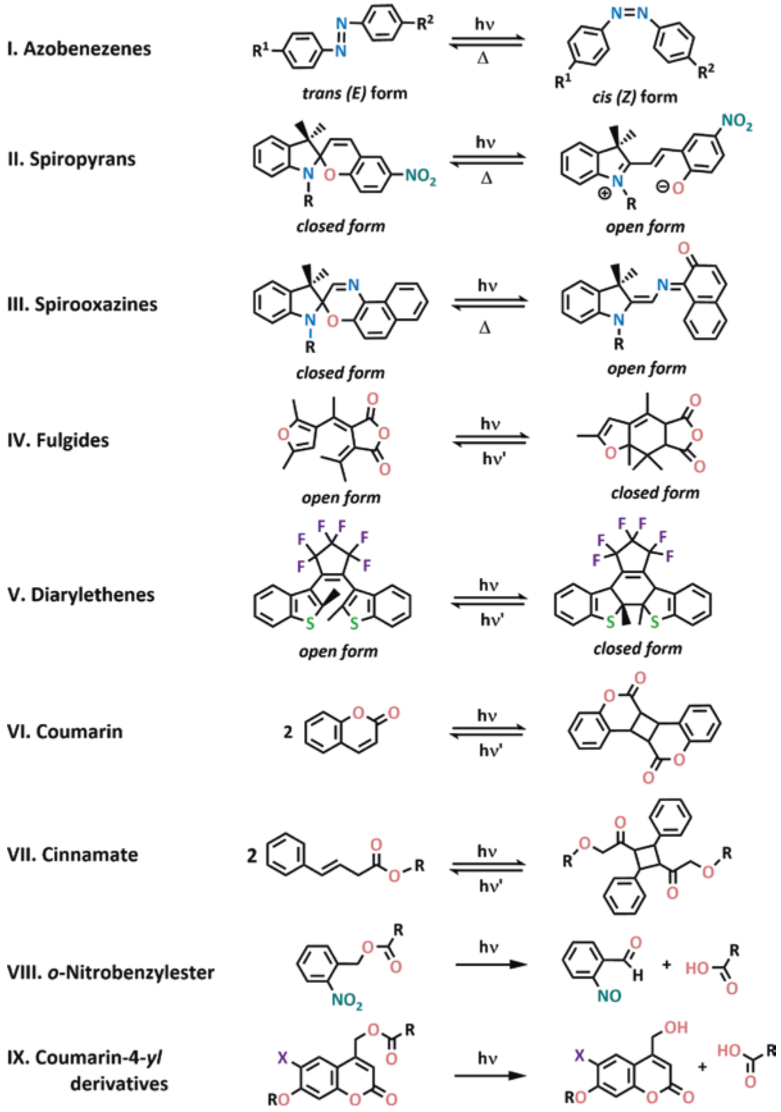

Fig. 1.3 Most widespread photoactive molecules used to control polymer's properties

1.2.2.1 Photoisomerization

The photoisomerization processes are reversible and repeatable and are regarded as the most "clean" photoreactions in chemistry, since only two absorbing species are formed during photoisomerization. This property makes the photochromic molecules very attractive, and thus, photoresponsive polymeric materials are of significant scientific, technological, and commercial interest because photoconversion and photoreversion modulate a multitude of physical properties not just color but also geometrical shape, dipole moment, refractive index, birefringence, conductivity, magnetism, hydrophilicity, hydrophobicity, adhesion, and so forth [1, 7, 8, 58].

The *azobenzene* is perhaps the most investigated photochromic molecule that can undergo a reversible photoisomerization reaction from a stable *trans* to a metastable *cis* conformation. As shown in Fig. 1.3 I, the reversible *trans–cis* isomerization of azobenzenes can be described as a geometrical isomerization. Most of the times their interconversions are not visualized as a distinct color change, as in the case of other photochromic transformations; however, the difference between the isomers is visible by their different $\lambda_{\max}$ values. Due to the numerous reports on this topic, we dedicate an entire chapter to expound the features and particularities of these molecules. The versatility of these photoactive compounds in synthesis and design to address the most recent challenges in the biomedical field will be addressed.

Spiropyran is another well-known photochromic switch. The spiropyran–merocyanine transformation relies on UV-induced (approximately 360 nm) photolysis of the Cspiro–O bond in spiropyran (colorless closed form) to generate the intensely colored open form, merocyanine. Taking advantage of this photochemical transformation, the spiropyran and spirooxazine molecules (Fig. 1.3II, III) were widely used to control the nonlinear optical properties [66], to structure and function biomaterials with light, and to obtain photoresponsive hydrogels and micelles [33, 80, 81]. Similarly, the fulgides and diarylethene derivatives, which are thermally stable (Fig. 1.3IV, V) but photochemically reversible, have also been used for the functionalization of polymers. Both classes have been used in optical memory, photooptical switching, and displays and have been extensively reviewed elsewhere [82, 83].

1.2.2.2 Photodimerization

Light-induced reversible dimerization is another strategy to confer photoresponsive properties to polymeric systems. Dimerization describes the process in which two previously unbound molecules are covalently coupled to each other. Several compounds have been reported having such reversible dimerization properties upon exposure to light including cinnamylidene acetate [84], nitrocinnamate [85], and anthracene [86]. However, cinnamic acid and coumarin derivatives are the most frequently employed molecules that can undergo reversible photodimerization (Fig. 1.3VI, VII). Both have been incorporated as functional components into many types of photoresponsive polymeric systems, such as light-induced reversible crosslinkers for in situ modification of hydrogels [71] or transient stabilization of micelles [87] or used as crosslinking points in photoinduced self-healing materials [88, 89]. Shape memory polymers that can switch between temporary and permanent geometries upon exposure to light were synthesized by incorporation of cinnamate or coumarin groups [90]. Light-induced recovery of permanent geometries in shape-memory polymers using reversible network formation/cleavage via cinnamate-based cross-links represents an orthogonal actuation cue compared to formally temperature changes [17]. Although photodimerization can crosslink and cleave polymer chains using light, some practical biomedical applications remain elusive, due to the UV absorbing reversible process (260 nm) of these structures, which can cause cell damage. Cinnamate- and coumarin-bearing polymers could have more promise when used as photoresists for microelectronic fabrication or as environmentally benign materials that can be decomposed upon light exposure after the expected life cycle of the material.

1.2.2.3 Photocleavage

Photocleavage of photoactive protecting groups is another interesting approach to induce photoresponsiveness in polymers. The concept of incorporation photolabile groups into polymer systems originates from a study that aimed to engineer selective biological activity in signaling molecules [91]. To restore the native biological function of the small molecule, light-induced cleavage of photoactive groups was used [92]. The *o*-nitrobenzyl group is one of the most useful photolabile compound for photoresponsive polymeric systems used for biomedical purposes (Fig. 1.3VIII). The biocompatibility of the *o*-nitrobenzyl moiety has been demonstrated for the natural endothelium [93]. However, some studies show that upon photoirradiation, the cleavage of the *o*-nitrobenzyl group yields a cytotoxic nitrosobenzaldehyde derivative, which significantly inhibits the proliferation of cells under standard in vitro conditions [94]. Despite of this drawback, this molecule affords by substitution to adjust polymer’s photochemical properties, such as red shifting the wavelengths for photolysis, quantum yield, absorbance maximum, and extinction coefficient [95]. Thus, this photocleavage reaction has been used extensively to fragmentize side chain, main chain, or end groups in numerous polymer architectures in an ordered fashion and to control supramolecular interactions by changing the chemical properties of interacting molecules [75, 96–98]. Another interesting characteristic of the *o*-nitrobenzyl photoactive derivatives is that they can be tailored to undergo cleavage through a nonlinear optical process that requires simultaneous absorption of two photons [99]. Since the two-photon process can be achieved with near-infrared (NIR) radiation which is less absorbed by the living tissues than UV radiations, it is beneficial for in vivo applications. Two-photon absorption provides a very promising path for preparing photoresponsive polymers with three-dimensional microstructures used in regenerative medicine and controlled release [47, 79].

Coumarin-4-ylmethyl (Fig. 1.3IX) and its derivatives can also serve as protective groups for selective photocleavage and have been showed to exhibit larger two-photon absorption cross section compared to *o*-nitrobenzyl derivatives [34, 100]. Alcohols [101], phenols [101], and amino acids [102] have been conjugated with coumarin-4-ylmethyl through photolabile bonds to give photoresponsiveness to the polymeric system incorporating them. Exhibiting a higher penetration depth compared to the *o*-nitrobenzyl derivatives, the risk to damage the cells and tissues is diminished. Also, coumarin derivatives are well known for their biocompatibility and natural biodegradability, therefore, they are more suitable candidates for the biomedical field [73].

Photolysis of *p*-hydroxyphenacyl groups [103], acetal–ketal protecting groups [104], and triphenylmethane derivatives [105] have also been used in the related fields to confer photoresponsiveness to polymeric systems.

1.3 Figures of Merit for Photoresponsive Azobenzenes

Azobenzene, with its two phenyl rings separated by the azo bond, is the point of origin for a broad class of aromatic azo-derivatives. The most interesting property of these azo compounds is the induced and reversible isomerization of the azo bond between the thermally stable *trans* configuration and the *meta*stable *cis* form. Most azobenzenes can be optically isomerized from *trans* to *cis* with light, anywhere within the broad absorption band. Once formed, *cis* isomers will thermally reconvert back to the stable *trans* state within a timescale dictated by the substitution pattern, which depends greatly on its interaction with the surrounding medium. This "clean" photochemistry is the most important feature of azobenzene and offers a reversible control over a variety of chemical, electronic, and optical properties [7, 27, 106]. This light-induced interconversion is accompanied by a large geometrical transformation from the extended *trans* configuration to the three-dimensional and more compact *cis* isomer, which allows to alter the natural structural order of systems incorporating them to substantially tune up the strength of the host–guest interactions [57, 107].

Depending on the absorption wavelength, the azobenzene chromophores were divided into three general classes, as described by H. Rau early in the literature [108]. The azobenzene- type molecules which absorb in the UV (330–370 nm) range and their *cis* configuration can be stable for days in the dark, the amino-azobenzenes that have an intermediate lifetime and a slight red shift of the *trans* absorption band, and the pseudo-stilbenes which exhibit a very fast thermal reconversion and a far-red-shifted maximum of absorption. These features gives the azobenzene class a significant advantage over the previously enumerated photoactive compounds in Fig. 1.3, as the chemical substitution pattern has a large effect on the photophysical properties [58, 59, 109, 110]. In addition, azobenzenes can be photoisomerized on a timescale of microseconds down to sub-nanoseconds, reversibly 10^5–10^6 times without exhibiting side reactions.

The recent contributions in the photochemistry of azobenzenes show just how versatile it is the nature of this class in design and synthesis. In Fig. 1.4 are illustrated two classical examples of azo-molecules, the parent azobenzene and Disperse Red 1 (DR 1), by comparison with the latest designs. While DR 1 brought large contribution in the photochemistry of azobenzene, exhibiting exceptionally high nonlinear optical activity [107, 111], the other azo-derivatives were synthesized to face the present requirements in both NLO and biomedical field [58]. Based on

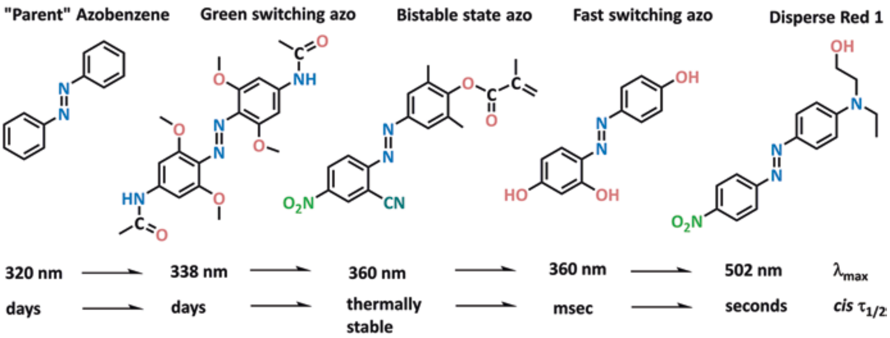

Fig. 1.4 Examples of azobenzene derivatives tailored over time to meet specific photophysical requirements. Ranging from the UV absorbing "parent" azobenzene to an aminoazobenzene with two electron-donating groups that isomerize to *cis* with visible light for biomedical purposes, to a thermally two-state azobenzene derivative for optical storage data, to fast photoswitching azo-derivative for real-time information-transmitting data, and to a strong electron push–pull pseudo-stilbene DR1, which possess a strong red-shifting absorption that is visibly useful in nonlinear optical imaging

rational design, azo-derivatives that *trans–cis* isomerize under green light irradiation have been reported by Woolley's group [60]. New azo-derivatives were designed to exhibit fast relaxation times, based on solvent interactions for molecular photoswitching by Velasco's group [112]. Elegant examples of thermally stable *cis* configurations in azo-derivatives were reported by Jerca's group [56, 113]. The incorporation strategy is the key to exploiting azobenzene unique behavior, and one of the most attractive methods for incorporating azobenzene into functional materials is covalent attachment to polymers. The resulting materials will benefit from the inherent stability, rigidity, and processability of polymers, in addition to the target photoresponsive behavior of the azo moieties. However, there have been increasing efforts toward the development of new diverse functional materials and azo-derivatives, and the last 10–15 years witness emerging applications other than information storage and switching. In the next subsections, a brief description of azo-derivatives contribution to photopharmacology and to biological systems will be made.

1.3.1 Azobenzenes in Photopharmacology

One of the most important area in the biomedical field that witnessed important progress is the *photopharmacology*, which has been formulated by Feringa group as a viable alternative to optogenetics [114]. Photopharmacology is a complementary branch of research of photoresponsive drugs whose activity can be regulated with light in the so-called near-infrared phototherapeutic window (650–900 nm). However, Erlanger and coworkers pioneered the concept of *photopharmacology*