Kurzzusammenfassung / Abstract in German

Gele werden durch einen physikalischen Zustand charakterisiert, der sowohl Eigenschaften von Feststoffen als auch von Flüssigkeiten aufweist. Sie werden aus einem Geliermittel und einer flüssigen Komponente gebildet. Eine wichtige Klasse stellen die Hydrogele dar, die sich aufgrund ihres hohen Wassergehalts und ihrer Ähnlichkeit in mechanischer Zusammensetzung zu natürlichem Gewebe hervorragend für biomedizinische Anwendungen eignen. Fortschritte wurden bei der Entwicklung supramolekularer Hydrogele erzielt, die entweder aus Gelatoren mit niedrigem Molekulargewicht oder Makromolekülen bestehen. Diese arrangieren sich spontan und oft synergistisch durch Selbstorganisation, basierend auf dynamischen, intermolekularen nicht-kovalenten Bindungen. Diese Bindungen setzen sich aus Wasserstoffbrückenbindungen, Metall-Ligand-Koordination, π-π-, Wirt-Gast-, elektrostatischen und/oder Van-der-Waals-Wechselwirkungen zusammen. Die Selbstorganisation und Auflösung von Gelen kann durch verschiedene Parameter wie elektrische Spannung, Ultraschall, pH-Wert oder Licht ausgelöst werden. Letzteres gewinnt immer mehr an Aufmerksamkeit, da es präzise, räumlich und zeitlich kontrolliert, nicht kontaminierend und unabhängig von anderen Einflüssen eingesetzt werden kann. Diese auf Licht reagierenden Hydrogele, auch photochrome Hydrogele genannt, sind mit "photochemischen Schaltern" ausgestattet, die durch Licht reversible molekulare Reaktionen, typischerweise *E*/*Z*-Isomerisierungen oder perizyklische Reaktionen, ermöglichen. In dieser Arbeit wurde eine Reihe von photochromen supramolekularen Hydrogelen untersucht, die aus biokompatiblen zyklischen Dipeptiden mit niedrigem Molekulargewicht bestehen und lichtmodulierte Polarität aufweisen. Es wurde eine Reihe von Azobenzolderivaten verwendet, die hauptsächlich mit sichtbarem Licht schaltbar sind. Insbesondere wurden die bekannten Strukturmotive der tetra-*ortho*-chloro- und dichloro-di-fluor-substituierte Azobenzole, die mit rotem Licht isomerisiert werden, erfolgreich in das Grunddesign des Gelators (DKP-Lys) integriert. Darüber hinaus wurde die unerwartete Entdeckung gemacht, dass tetra-*ortho*-fluorierte Azobenzole (TFABs) – die ursprünglich mit grünem Licht aktiviert wurden – nach der Substitution mit konjugierten ungesättigten Substituenten auch für

rotes Licht empfindlich werden, was das konjugierte TFAB-Chromophor zu einem wertvollen Baustein für die Einbindung in Biomaterialien oder in photopharmakologische Wirkstoffe macht. Eine neue Methode zur Stabilisierung von Hydrogelatoren auf DKP-Lys-Basis wurde durch kooperative Gelierung des basischen DKP-Lys mit dem saurem Polymer Alginat entwickelt. Durch Austausch des photochromen Gelators mit Ca^{2+}-Ionen kommt es zur Bildung ganz natürlicher Hydrogele. Darüber hinaus wurde ein Gelierungsprotokoll entwickelt, das ohne Hitze auskommt, was für die Beladung der Hydrogele mit hitzeempfindlicher Fracht (Proteine, lebende Zellen) wichtig ist. Zuletzt wurde die Wasserstoffbrückenbindungen fördernde peptidische Struktur, die im DKP-Motiv zu finden ist, mit dem Fluorophor Naphthalimid verknüpft, um „AIE-gens“ zu erhalten. Fluoreszenzmessungen zeigten das Potenzial zur Bildung von Nanoaggregaten, vermittelt durch äußere Einflüsse wie z.B. Licht.

Abstract

Gels represent a physical state that exhibits properties of both solids and liquids. They are formed from a gelling agent and fluid component. Their important class are hydrogels, which are suitable for biomedical applications due to their high-water content and their potential compositional and mechanical similarities to native soft tissues. Advances were made in the development of supramolecular hydrogels, formed either by low-molecular-weight gelators or macromolecules in a spontaneous and often synergistic manner by self-assembly through dynamic networks of intermolecular non-covalent bonds. These interactions include π–π stacking, hydrogen bonding, metal-ligand coordination, host-guest, electrostatic and/or van der Waals interactions.

Self-assembly and dissipation of gels can be triggered by various parameters such as electrical voltage, ultrasound, pH, or light. The latter is gaining increasing attention, as it can be applied precisely with spatial and temporal control in a non-contaminating manner and orthogonally to other components of the system. These light-triggered hydrogels, also known as photochromic hydrogels, are equipped with 'photochemical switches'. Such switches give reversible molecular responses, typically in the form of *E*/*Z*-isomerizations or pericyclic reactions, triggered by light.

In this thesis, a collection of photochromic supramolecular hydrogels comprised of biocompatible low-MW cyclic dipeptide gelators with light-modulated polarity was explored. A number of photochromic azobenzene derivatives, mainly switchable with visible light was used. In particular, previously reported tetra-*ortho*-chloro- and di-chloro-di-fluoro-substituted azobenzenes triggered with red light were successfully incorporated into the basic gelator design (DKP-Lys). Moreover, an unexpected discovery was made, that tetra-*ortho* fluorinated azobenzenes (TFABs) – originally activated with green light – upon substitution with conjugated unsaturated substituents become sensitive to red light as well, which makes the conjugated TFAB chromophore a valuable building block for incorporation into biomaterials or into photopharmacology agents.

A new method for stabilization of DKP-Lys-based hydrogelators was provided by composite gelation of the basic cyclic dipeptide with polymeric acidic alginate. There, replacement of the photochromic gelator by equilibration with Ca^{2+} ions leads to all-natural hydrogels. In addition, a gelation protocol without the necessity of heat was developed, which is important for loading the hydrogels with heat-sensitive cargo (proteins, living cells).

Finally, the hydrogen bond-promoting peptidic structure, which can be found in the DKP motif, was linked with the fluorophore naphthalimide to obtain aggregation-induced emission luminogens (AIE-gens). Fluorescence measurement revealed the potential to form nanoaggregates, mediated by external factors such as light.

1 Introduction

1.1 Molecular photoswitches

In the course of the last twenty years, the research interest in 'photochemical switches' highly increased. They react on light, which can be controlled with excellent spatiotemporal precision, yet it is orthogonal towards most elements of chemical and biochemical systems. Light, or specifically photons, do not contaminate the irradiated material.[1] Toxic effects mostly occur only upon irradiation with short-wave UV-light, along with increased scattering of light in the ultraviolet frequencies on cell components.[2] Therefore, light is an attractive trigger to control or study biological function[3] or functional materials[4]. Moreover, the increased interest in photoswitches can be attributed to the emerging field of photopharmacology, in which problems of classical pharmacotherapy such as adverse effects, environmental toxicity, and the appearance of drug resistance can be reduced due to spatiotemporally targeted activation of the drug.[5] An example for the concept of photopharmacology is demonstrated by Wanner *et al.* in 2014 in form of azobenzene derivatives of the mGAT1 inhibitor nipecotic acid. By isomerization of the azobenzene the activity of active membrane transporters was regulated.[6] Another, recently introduced by Pianowski group is an *E/Z*-isomerization of a hemipiperazine photochrome inside plinabulin derivatives, which can increase its cytotoxicity by three orders of magnitude.[7]

The functional core of light-triggered systems discussed in this work are molecular photoswitches. Compounds of this class give reversible molecular responses, typically in the form of *E*/*Z*-isomerizations[8] or pericyclic reactions[9], triggered by light. The former primarily result in distinct structural changes, whereas the latter are characterized by large changes in electronic properties and/or polarity. The transformation between two forms with distinct absorption spectra upon irradiation is also referred to as photochromism and was first described by J. Fritzsche when he observed the reversible photodimerization of anthracene in 1866.[10] Another classification of photoswitches is based on

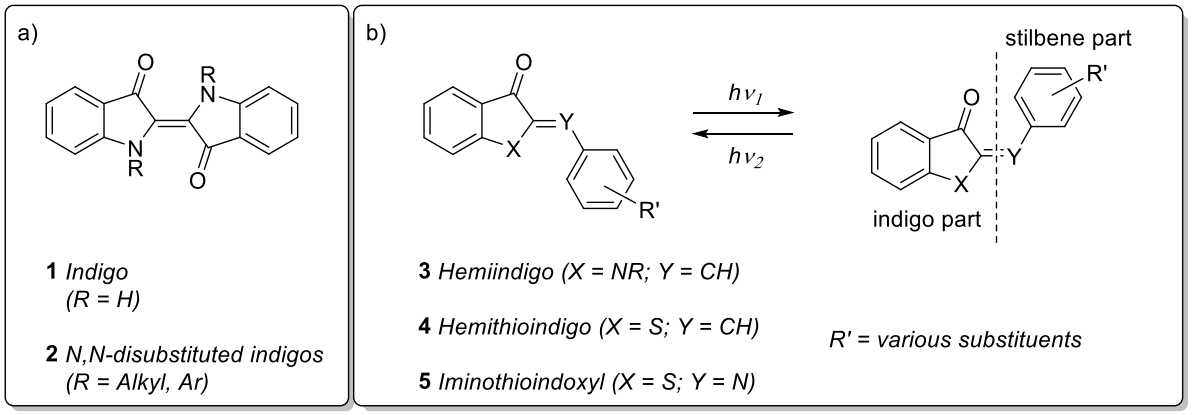
their back reaction to the thermodynamically stable form after initial excitation: In T-type switches this process is driven thermally, whereas in P-type switches it is exclusively photochemically.[9] Furthermore, in the context of T-type switches we distinguish between the positive photochromism - when the color of the switch fades in the absence of light - or the negative photochromism - when the color reversibly fades upon light irradiation and is restored in the dark.[11] These characteristics classify photoswitches as valuable tools for optical manipulation of various materials with spatiotemporal precision, thereby allowing for a wide variety of applications.

1.1.1 Most commonly used photoswitches

A plethora of photoswitchable molecules were developed over the last decades. Some of them have become firmly established and are frequently applied due to the extensive knowledge about them. The following chapter describes a selection of the most commonly used photoswitches.

Indigoids

The structure of indigoids is derived from the dye indigo (ἰνδικόν, ancient Greek for “blue dye from India”) which is one of the oldest known pigments (Scheme 1 a)). Initial production was by extraction of the glycoside indican from the leaves of *Indigofera tinctoria*, followed by fermentation to indoxyl and final oxidation to indigo on air[12]. *E*/*Z*-photoisomerization of the double bond in unsubstituted Indigo (**1**) is not possible because of excited-state proton transfer[13] (ESPT), though after the discovery of hemiindigo (**3**) photoisomerization in 1999[14], a large spectrum of indigo derivatives was synthesized and investigated. Still, the photochemistry of parent hemiindigo (**3,** Scheme 1 b)) is constraint by unwanted side reactions such as [2+2] cycloadditions or triplet generation.[15] ESPT in the parent indigo (**1**) inhibits photoisomerization[13], consequently disubstitution of the indigo NH (**2**) paves the way to new indigo derived visible light switches. The properties of these compounds are highly tunable depending on the substituents.



Scheme 1: Indigoid photoswitches. a) the structures of non-photochromic indigo **1** and it's *N*,*N*-disubstituted photochromic derivatives. b) Related photochromic compounds originating from the indoxyl and thioindoxyl core, the *E/Z*-photoisomerization is demonstrated.

Tremendous improvement was achieved in 2017 by the group of DUBE through the generation of push-pull systems *via* donor substitution, with the indigo carbonyl assuming the acceptor part.[16] These new hemiindigo (**3**) derivatives are characterized by high bistability of up to 83 years for some derivatives at room temperature, solvent-independent visible light photoswitching and high photostationary states (PSS).

Hemithioindigos (**4**) - the combination of thioindigos and stilbenes (Scheme 1) can be isomerized with visible light if strong donors are installed in *para* position on the stilbene unit.[17] The problem of low thermal stability of these derivatives is solved by additional donor-*para*-substitution related to the sulfur in the thioindigo part.

Iminothioindoxyls (**5**) are the hybrid of thioindigos and azobenzenes and are characterized by rapid isomerization, a short thermal half-life in the range of milliseconds, and photoisomer band separation of over 100 nm. They stand out for switching in solid state and high solvent tolerance, rendering them suitable for various applications.[18]

Unlike most photoswitches, indigoids are characterized by high photostability and have the advantage that their core structure absorbs light in the visible region of the spectrum. Furthermore, their fast and efficient photoreaction be-