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Visible Light-Triggered Supramolecular Hydrogel Based on Cyclic Dipeptides Stabilized with Coulomb Interactions

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Amphiphilic cyclic dipeptides are efficient supramolecular hydrogelators. They can be combined with molecular photoswitches to produce light-responsive soft materials, which can be applied in controlled drug delivery. Here it is reported that an arginine-containing cyclic dipeptide decorated with ortho-fluorinated azobenzene forms hydrogels under physiological conditions that can be reversibly liquefied upon exposure to visible light frequencies (green and violet, respectively). The addition of sodium alginate results in composite supramolecular hydrogels with increased gelating capacity supported with Coulombic interactions, which also reversibly dissipate upon irradiation.

1. Introduction

2,5-diketopiperazines (DKPs) are the smallest cyclic peptides. DKPs are ubiquitously occurring in nature[1] as secondary metabolites, or subunits of bioactive products over all domains of life,[2] as well as constituents of food and beverages.[3] Due to their resistance to enzymatic degradation and general biostability, DKPs are therapeutically attractive peptidomimetics.[4] They are known as well for undergoing efficient self-assembly,[5] in particular due to their well-defined conformation and an extensive hydrogen bonding network between the cyclic amide groups. This privileged pre-organization can be used, e.g., in constructing simple enzyme models[6] or biocompatible materials.[7] In particular, DKPs are efficient low-MW supramolecular hydrogelators,[8] applicable as promising drug delivery systems.[9] The mutual interactions between the gelator molecules can be modified by concentration, pH, or temperature changes, and influence the macroscopic properties of the material.

Our group was interested in adding an orthogonal trigger to the available stimuli that influence the macroscopic hydrogel properties. Light is an attractive stimulus: it is biocompatible, easy to control in spatial and temporal manner, and does not permanently contaminate the sample. While numerous photoresponsive hydrogels have been already demonstrated –, e.g., as light-driven drug delivery systems, adaptive surfaces, or soft actuators,[10] the combination of a DKP gelating motif with molecular photoswitches is particularly appealing: due to its higher level of supramolecular pre-organization it is more efficient as a gelator in comparison to linear photoswitchable peptide hydrogelators[11] and synthetically feasible.

Molecular photoswitches are compounds that reversibly convert the energy of light into changes of geometry, polarity, stiffness, and other parameters at the molecular level.[12] They can be implemented into numerous materials and biosystems[13] in order to exert a macroscopic effect[14] or modulate bioactivity.[15] Numerous photochromic systems can operate in aqueous environment,[16] and their biocompatibility increases if they can be bidirectionally isomerized without using highly energetic UV (ultraviolet) light.[17] Azobenzenes are by far the most common photochromic systems with the broadest range of applications.[18] They are complemented with emerging photochromic systems,[19] such as arylhydrazones,[20] indigoids,[21] DASA (donor- acceptor Stenhouse adducts),[22] or hemipiperazines – a DKP-derived motif recently introduced by our group.[23]

Our group has successfully combined the lysine-containing DKP gelator motif with azobenzene photoswitches – initially the unmodified structure which reacts on UV light, and later with ortho-halogenated azobenzenes that can be triggered with green[24] or red light.[25] We obtained gels that reversibly dissipated to non-viscous liquids upon exposure to UV,[26] and later green light.[27] We have also demonstrated a red-light-triggered hydrogel based on ortho-chlorinated azobenzene, which shrinks upon exposure to 660 nm light and acts as "molecular syringe"

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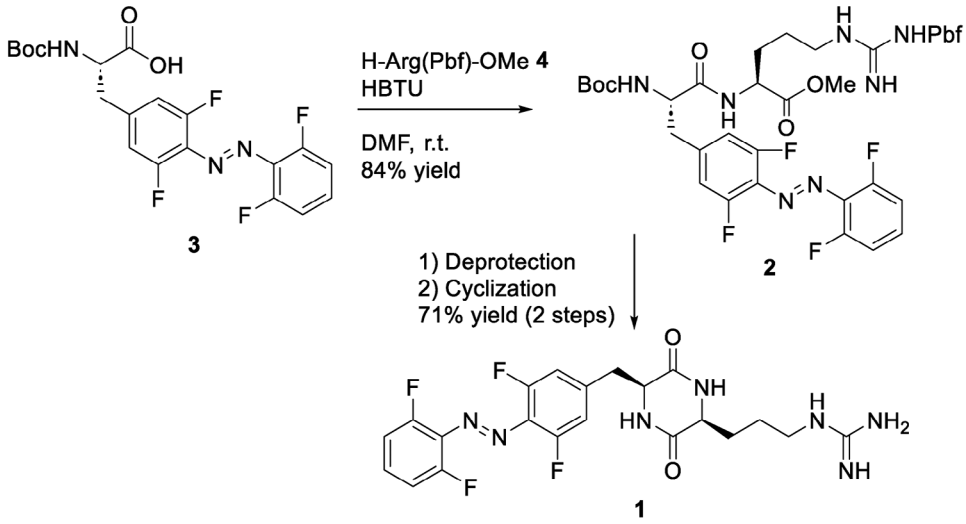

Scheme 1. Synthesis of TFAB-DKP-Arg 1 begins with the formation of a peptide bond between 3 and H-Arg(Pbf)-OMe 4. Subsequently, the dipeptide precursor 2 is deprotected and cyclized to yield the final product 1.

that ejects encapsulated cargo to the environment.[28] We have also demonstrated a composite hydrogel system, where the microscopic structure is stabilized with alginate side chains, and the gel undergoes liquefaction upon UV light exposure.[29]

Consequently, we were interested in expanding the scope of azobenzene-based photochromic DKP gelators beyond lysine-containing cyclic dipeptides. In particular, arginine functionalization has initially drawn our attention, as it is known that oligomers exposing alkylguanidinium chains often penetrate live mammalian cells and have been used as drug delivery vehicles.[30] In this report, we demonstrate that *(S)*-arginine can be also combined with an azobenzene-containing phenylalanine analog, and forms hydrogels that can be reversibly liquefied upon exposure to green light. Moreover, the gelator can also form light-responsive composite material with alginate, which gains additional stabilization from Coulomb interactions.

2. Synthesis and Properties of the Photochromic DKP 1

Synthesis of the gelator **1** has been briefly displayed in **Scheme 1**. It begins with the arginine (Arg) derivative H-Arg(Pbf)-OMe **4** (Pbf- 2,2,4,6,7- pentamethyldihydrobenzofuran-5- sulfonyl group), synthesized from the commercially available Fmoc-Arg(Pbf)-OH (Fmoc- fluorenylmethoxycarbonyl) according to Robertson et al,[31] (see Scheme S2, Supporting Information) and the unnatural tetra-ortho-fluorinated (4-phenylazo)-*L*-phenylalanine (TFAB) derivative **3**, previously synthesized in our lab (Schemes S2–S4, Supporting Information),[27b] which are coupled by a peptide bond to form the dipeptide **2**. Subsequently, the amine and guanidinium group of **2** are deprotected and a final cyclization step yields the product **1**.

Then, we determined the photochromism of the synthesized compound **1**. The fluorinated azobenzene moiety in **1** undergoes reversible photoisomerization upon irradiation with green (523 nm) and violet (407 nm) light (**Figure 1**) in aqueous PBS buffer (pH 7.4) or as solution in MeCN.

Briefly, non-irradiated samples of **1** ("dark state") were measured first – due to the elevated reaction temperature during the final synthetic step of **1**, thermal relaxation yielded nearly pure thermally stable *E*-isomer, which is stable as long as stored in the darkness.

Then, samples were irradiated with green and violet light, until no further change in their absorption spectra could be observed and the wavelength-specific "photostationary state" (PSS) was achieved. For 407 nm, the PSS was reached after 5 min, and for 523 nm – after 10 min (irradiation intensities – see Table S3, Supporting Information). As quantified by HPLC, the photoequilibration at 523 nm (green light) yielded 87% *Z*-**1** in PBS (phosphate -buffered saline) or 89% *Z*-**1** in MeCN (acetonitrile), while violet light (407 nm) produced 80% *E*-**1** in PBS or 86% *E*-**1** in MeCN (Table S4, Supporting Information). A minor solvatochromic effect was observed between the solvents (PBS versus MeCN). Interestingly, this caused significant difference in the result of photoequilibration upon exposure on UV light (365 nm): 64% *E*-**1** in PBS versus 87% *E*-**1** in MeCN – due to strong variation of the relative *E*/*Z* extinction coefficient ratio at that wavelength between both solvents (Figure S2, Supporting Information).

We have also determined thermal stability of the *Z*-**1**. Due to its high stability in comparison to, e.g., non-substituted azobenzene, the measurements at room temperature were inconclusive and had to be performed at 60 °C. At these conditions, thermal half-life $\tau_{1/2}$ of 62.3 ± 1.4 h (60 ± 2 °C in MeCN) has been determined for the *Z*-**1**, which is in agreement with literature (Figure S3 Supporting Information).[27b]

To determine the scope of applicability for the gelator **1** in biological systems, we performed cell viability tests ("MTT assays") using human HeLa cells with increasing concentrations of the *E*-**1** (the "dark" state), as well as with the mixture photoequilibrated with green light that contained >87% of the *Z*-**1** isomer (vide supra). Up to the solubility limit in water (slightly higher for the irradiated mixture), both compositions did not show any significant toxic effect (IC_{50} concentrations could not be determined, we can only state that the IC_{50} (*E*-**1**) > 0.1 mM, and the

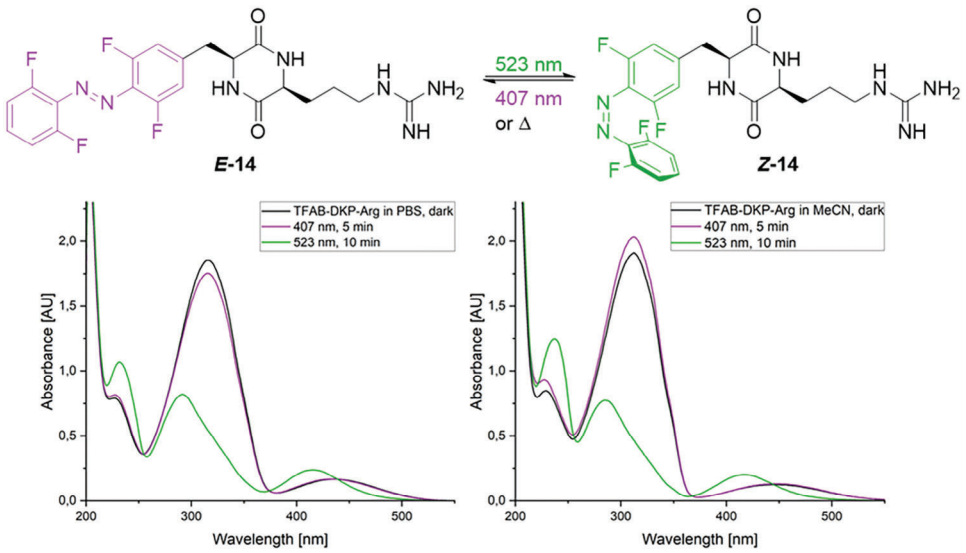

Figure 1. Top: Compound 1 (also abbreviated as TFAB-DKP-Arg) can be reversibly photoisomerized with green (523 nm) and violet (407 nm) light. Bottom: UV-/Vis-spectra of 12.5 µM solutions of 1 in PBS (left) and MeCN (right) were measured for a non-irradiated "dark" sample, as well as after irradiation with green (523 nm) and violet (407 nm) light at their photostationary states.

IC_{50} ($PSS_{523\,nm}$ of **1**) > 1 mM; quantitative data summarized in Tables S6 and S7, Supporting Information), as depicted on the Figure S5 (Supporting Information).

3. Hydrogel Formation from the Photochromic DKP 1 Under Aqueous Conditions

To assess, if the cyclic dipeptide **1** is a low-molecular-weight hydrogelator, we determined its ability for gelation in aqueous media. For this purpose, different amounts of **1** were added to PBS (500 µL) in a 1.5 mL crimp-top vial and subsequently heated at 80 ± 3 °C in a metal heating block for 5–10 min until nearly all solid had dissolved. Brief (<1 min) boiling of this suspension with a heat gun resulted in a clear orange solution of **1**, which was then allowed to cool to room temperature. The samples were then stored overnight in darkness for component equilibration and potentially gelation. The various gelation conditions tested are summarized in Table S5 (Supporting Information). The DKP **1** forms mechanically firm hydrogels at the minimal concentration of 4.0 wt.% at the pH 7.2. At the pH 4.0 (composition in Table S1, Supporting Information), the gelator loading can be decreased to 3.0 wt.%, although the gel formation is longer (2 days vs 2.5 h) and its mechanical stability is reduced. Finally, at the pH of 10.0 (composition in Table S2, Supporting Information) gel formation does not occur due to insufficient solubility of the gelator (Figure S4, Supporting Information).

The gelator **1** likely forms fibers by supramolecular assembly supported by efficient π-π-stacking of the *E*-azobenzene moiety and additional stabilization by hydrogen bonds between the DKP rings.[32] Here, we tested if the gel-to-sol transition process could be achieved upon irradiation with green light, due to the fiber structure destabilization presumably caused by the formation of a significant fraction of polar bent *Z*-azobenzene, which in turn impairs π-π-stacking interactions. For this experiment, the 4.0 wt.% gel was equilibrated overnight in darkness and then irradiated at 523 nm at room temperature for 40 min. After that time, the sample became non-viscous fluid (**Figure 2**). The reverse process of gelation of the sample occurred upon irradiation with violet light (407 nm) for 60 min. and equilibration overnight in darkness. These experiments demonstrated that arginine-based photochromic DKPs can form hydrogels in a similar manner to the previously reported lysine analogs. Yet, the comparison of critical gelation concentrations with the latter ones (1.5 wt.% recorded for the lysine-DKP bearing the same photochromic residue at the PBS buffer under neutral pH[27b]) indicates that the supramolecular self-assembly of **1** is not as efficient. Among the possible reasons one can indicate increased steric requirements of the arginine versus lysine side chains, or diverged charge distribution upon protonation of the side chains under neutral or acidic conditions.

4. Composite Hydrogel Formation from the Photochromic DKP 1 and Alginate

In 2022 our group reported[29] that additional stabilization of a DKP-based photochromic hydrogel bearing UV-light-triggered azobenzene and two symmetrically attached lysine residues is possible upon addition of sodium alginate – a polymer that exposes multiple carboxylic groups on a covalent polysaccharide chain. The additional stabilization was assumed to result from supramolecular "crosslinking" of alginate chains with two protonated alkylamines attached to a single chromophore. That material also underwent reversible UV-light-induced liquefaction, presumably as a result of light-driven geometry changes of the photochromic "crosslinker". The optimal compositions there were based on 0.6 wt.% of the DKP and 0.6–2.4 wt.% of alginate, resulting in hydrogels with T_m ranging from 76–83 °C.

Here, we decided to investigate if the "monodentate" (in terms of basic residues per molecule) hydrogelator **1** can also participate in similar Coulomb interaction-driven stabilization process

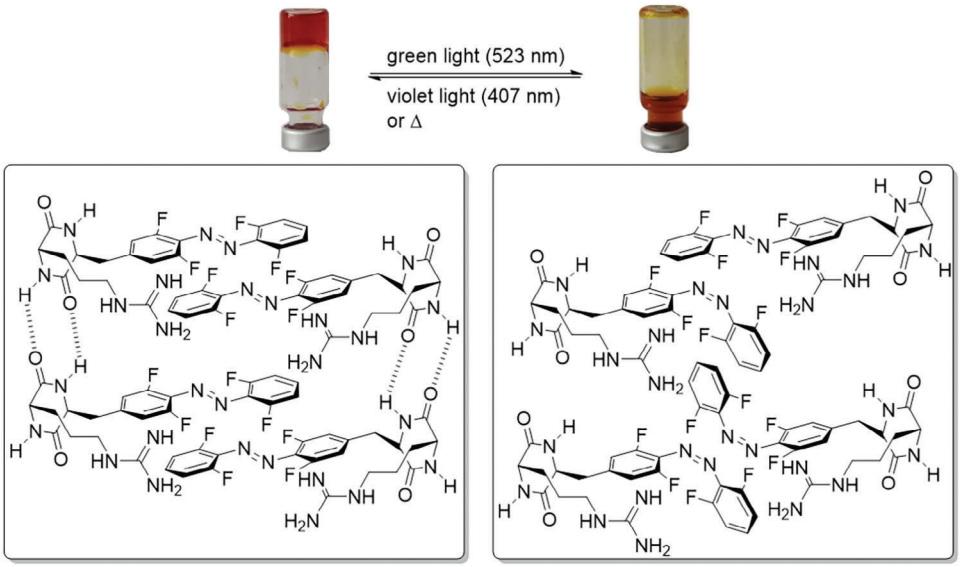

Figure 2. Gel-to-sol transition of TFAB-DKP-Arg 1 was induced by irradiation with green light (523 nm). The hypothesized supramolecular structure of the gel fibers of 1 is destabilized by formation of significant amounts of the *Z*-TFABs.[32] Gelation of the resulting non-viscous solution can be achieved upon exposure to violet light (407 nm) followed by re-equilibration in darkness.

with alginate additive. There, we prepared composite mixtures in PBS buffer pH 7.2 using 0.6 wt.% of **1**. Upon addition of 1.5 wt.% of alginate, we obtained hydrogel with $T_m = 55 \pm 2.5$ °C. Slight increase to 0.8 wt.% of **1** (while retaining the content of 1.5 wt.% alginate) did not significantly change the properties of the resulting gel ($T_m = 55 \pm 3.8$ °C). Both hydrogel samples could be liquefied upon exposure to green light (523 nm) within 105 min, and the resulting non-viscous fluid reconstitutes the hydrogel after 10 min. exposure to violet light (407 nm) followed by overnight equilibration in darkness at room temperature. By further reduction of the alginate content, the composition containing 0.6 wt.% of **1** and 1.2 wt.% of alginate in PBS buffer pH 7.2 ($T_m = 52 \pm 3.4$ °C) can be fully liquefied with green light (523 nm) within 5 min. The reverse process (gelation) is possible upon irradiation of the resulting non-viscous fluid with violet light (407 nm) for 15 min and further incubation in darkness for 30 min (sample in water) (**Figure 3a**).

The T_m values are lower by c.a. 25 °C in comparison to the "bidentate" photochromic cross-linker system (with two lysine side chains linked covalently). Yet, the concentration of gelator **1** is significantly below the critical gelation concentration recorded in the same buffer in absence of the alginate dopant. This suggest two-level stabilization mechanism (Figure 3b) – two (or more) *E*-**1** molecules form a supramolecular aggregate stabilized with $\pi-\pi$ stacking of the flat unpolar *E*-azobenzene residues. These aggregates exhibit multivalent electrostatic interactions via their externally directed protonated arginine side chains with the polyanionic alginate polymers. Irradiation with green light causes photoisomerization to the more polar and bent *Z*-isomer of **1**. There, the hydrophobic stabilization of azobenzene residues is strongly diminished and aggregates fall apart. Thus, the cross-linking of alginate chains is disrupted, the material loses its internal stabilization, and turns into non-viscous fluid. The reverse $Z \rightarrow E$ photoisomerization with violet light reconstitutes the cross-linking DKP aggregates of *E*-**1**, which rebuilds the gel.

We performed rheological investigation of the composite hydrogel in order to quantify its mechanical properties. The elastic modulus G′ exceeds the loss modulus G″ by approximately one magnitude, indicating a predominant elastic response of the material. In addition, G′ is nearly independent of the frequency. Both factors suggest the formation of a physical gel formed through interactions of alginate and the gelator **1**. The gel composed of 0.6 wt.% **1** and 1.2 wt.% alginate in PBS buffer had the $G' = 3 \times 10^3$ Pa and the $G'' = 6 \times 10^2$ Pa (slightly higher values than for the previously demonstrated composite hydrogel liquefied with UV light[29]), depicted on Figure S6 (Supporting Information). The same composition gelated in deionized water was slightly weaker (the $G' = 5 \times 10^2$ Pa and the $G'' = 4 \times 10^1$ Pa, Figure S7, Supporting Information).

5. Light-Induced Release of Doxorubicin from the Composite Hydrogel

To demonstrate the applicability of our material for light-induced drug release systems, we have prepared hydrogels composed of 0.6 wt.% 1 and 1.2 wt.% alginate, containing additionally 100 μg of doxorubicin in 500 μL of the gel volume. Doxorubicin is a chemotherapy medication, broadly used to treat numerous human cancers. Due to higher solubility of doxorubicin in pure water, than PBS buffer, these particular hydrogels have been prepared in deionized water. The procedure is described in detail in the section 9 (Supporting Information). Briefly, the gels have been covered with an equal volume (500 μL) of deionized water and incubated for intervals of 5 min. After each interval, the aqueous layer covering the gel has been fully removed with a micropipette, and replaced with a fresh volume (500 μL) of water. The content of doxorubicin in each aliquot has been quantified using HPLC (high performance liquid chromatography) analysis (Table S8, Supporting Information), and the average release from three independent experiments has

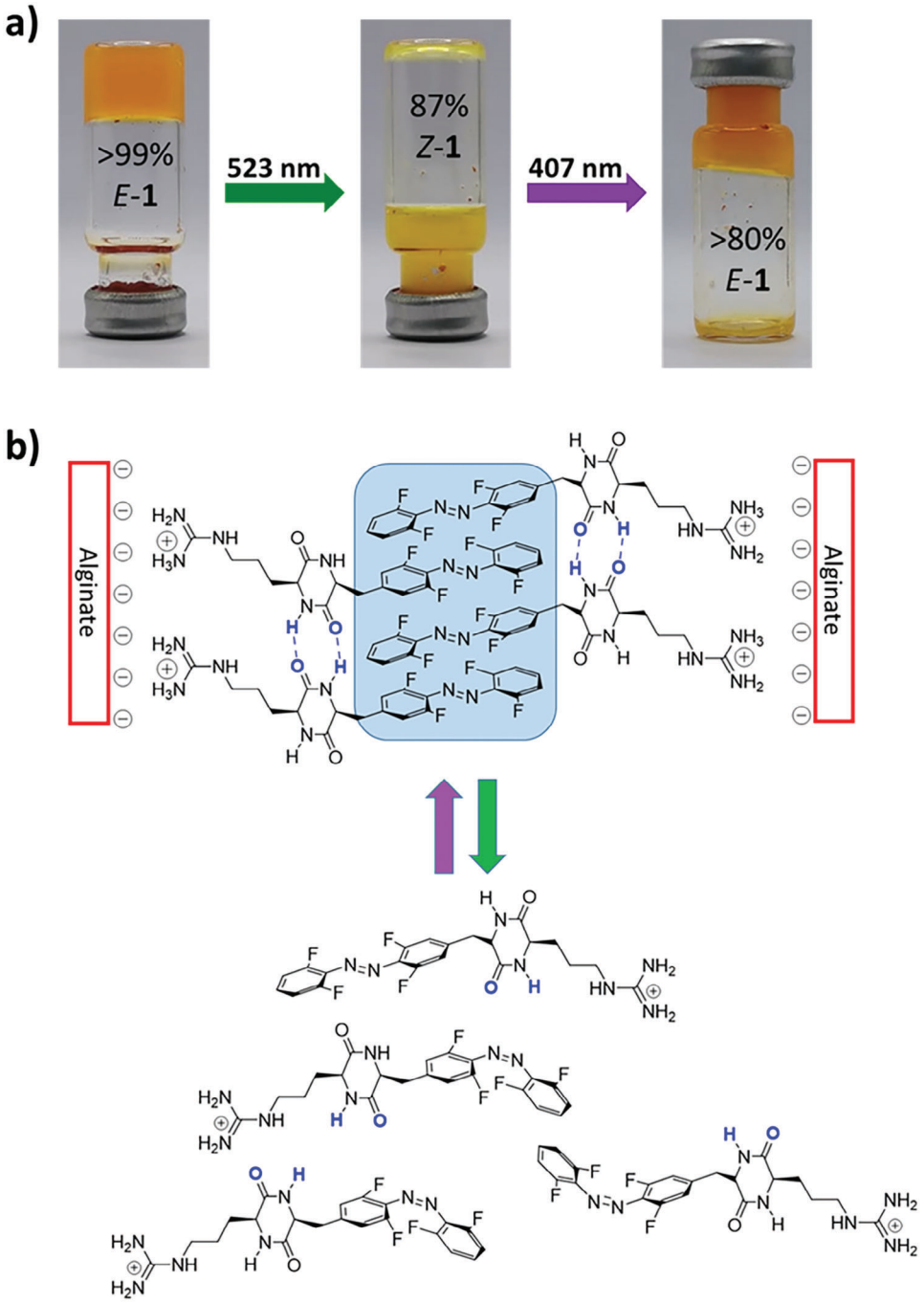

Figure 3. a) The composite hydrogel composed of 0.6 wt.% of 1 and 1.2 wt.% of sodium alginate in PBS buffer pH 7.2 undergoes liquefaction upon irradiation with green light (523 nm, 5 min.). The resulting liquid forms hydrogel again upon exposure to violet light (407 nm, 15 min.) followed by equilibration in darkness for 30 min. (left); b) efficient supramolecular aggregation of the flat and nonpolar azobenzene residues of the *E*-1 presumably stabilizes the composite hydrogel, while the bent and more polar *Z*-1 produced upon green light irradiation cannot support the structure and lead to reversible liquefaction of the material.

been calculated for samples stored in darkness (negative control, Table S9, Supporting Information) or samples under constant irradiation with green light (523 nm) (Table S10, Supporting Information).

The gel exposed to green light undergoes full liquefaction within 25 min of the experiment, which is significantly longer than the same gel composition prepared in the absence of doxorubicin (5 min, vide supra). Both sets of results have been repeated at least three times, and are consistently different. We believe that the cause is significant absorption of doxorubicin in the visible range of light (its aqueous solutions are of intense red color, and efficiently absorb green light).

Upon full liquefaction of the gel samples (25 min, 5 aliquots), we recovered in total at least 65% of the previously encapsulated doxorubicin in the soluble form. Yet, summary quantification of the aliquots collected at the surface of the same gel composition stored in darkness demonstrated that the doxorubicin release ("leaking") under these conditions was lower than 2% of the overall input (Figure S9, Supporting Information). Overall, these results indicate that our composite material is well-suited for selective light-driven drug release.

6. Conclusion

We have demonstrated that the azobenzene-decorated DKP **1** bearing an arginine side chain efficiently forms hydrogels under physiological conditions. Such hydrogels can be dissipated to non-viscous fluids upon exposure to green light, and gelated again with violet light, due to the reversible photoisomerization of the ortho-fluoroazobenzene component. Both photoisomers of **1** show negligible cytotoxicity – a good prerequisite for in vivo applications. We have also demonstrated that hydrogels based on **1** can gain additional stabilization via Coulombic interactions with sodium alginate. The *E*-**1** likely forms supramolecular aggregates that enhance the stabilization effect, but reversibly dissipate upon photoisomerization to the *Z*-form. This new composite material can be rapidly switched (within 5 min.) between gel and sol using visible light frequencies, and thus is more biocompatible than previously reported UV-light-triggered compositions. To demonstrate the practical applicability of our material, we have demonstrated rapid and selective green-light-induced release of strong anticancer drug doxorubicin previously physically encapsulated in the hydrogel. The cargo leaking in darkness was negligible. In the future, we will explore the possibility of applying azobenzenes triggered with red light, in order to fit to the "therapeutic window" (630–900 nm), as well as other anionic components of the composite. Particularly appealing is the possibility of using polyanionic DNA or RNA (e.g., therapeutic oligonucleotides) and investigation of cell penetration ability of such arginine-rich supramolecular aggregates, also below the critical gelation concentrations.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in Supplementary Information of this article.

Keywords

fluorinated azobenzenes, photochromic cyclic dipeptides, photoresponsive materials, supramolecular hydrogels

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