

## Commentary

# Thioindigo photoswitches available for the modulation of hydrogels' stiffness by visible light

Fulai Zhao

School of Materials Science and Engineering, Tianjin University, Tianjin 300072, China; jayfly@tju.edu.cn

Chromophore molecules that undergo reversible isomerization under excitation by two different wavelengths of light are commonly referred to as photoswitchable molecules. Through the use of light-induced reversible changes combined with precisely spatial and temporal light control, photoswitchable molecules can be applied in areas such as actuators, optics, molecular motors, and photobiology<sup>[1,2]</sup>.

Thioindigo is a typical photo-switchable material. However, its insoluble properties make it impossible for researchers to study its related applications for a long time. In a recent study published in *Nature Communications*, Walden et al.<sup>[3]</sup> introduced a strategy for the covalent insertion of thioindigo units into polymer main chains, enabling thioindigos to function within crosslinked polymeric hydrogels. Both the thioindigo-containing hydrogels and photoswitching processes are non-toxic to cells, thus offering opportunities for advanced applications in soft matter materials and biology-related research.

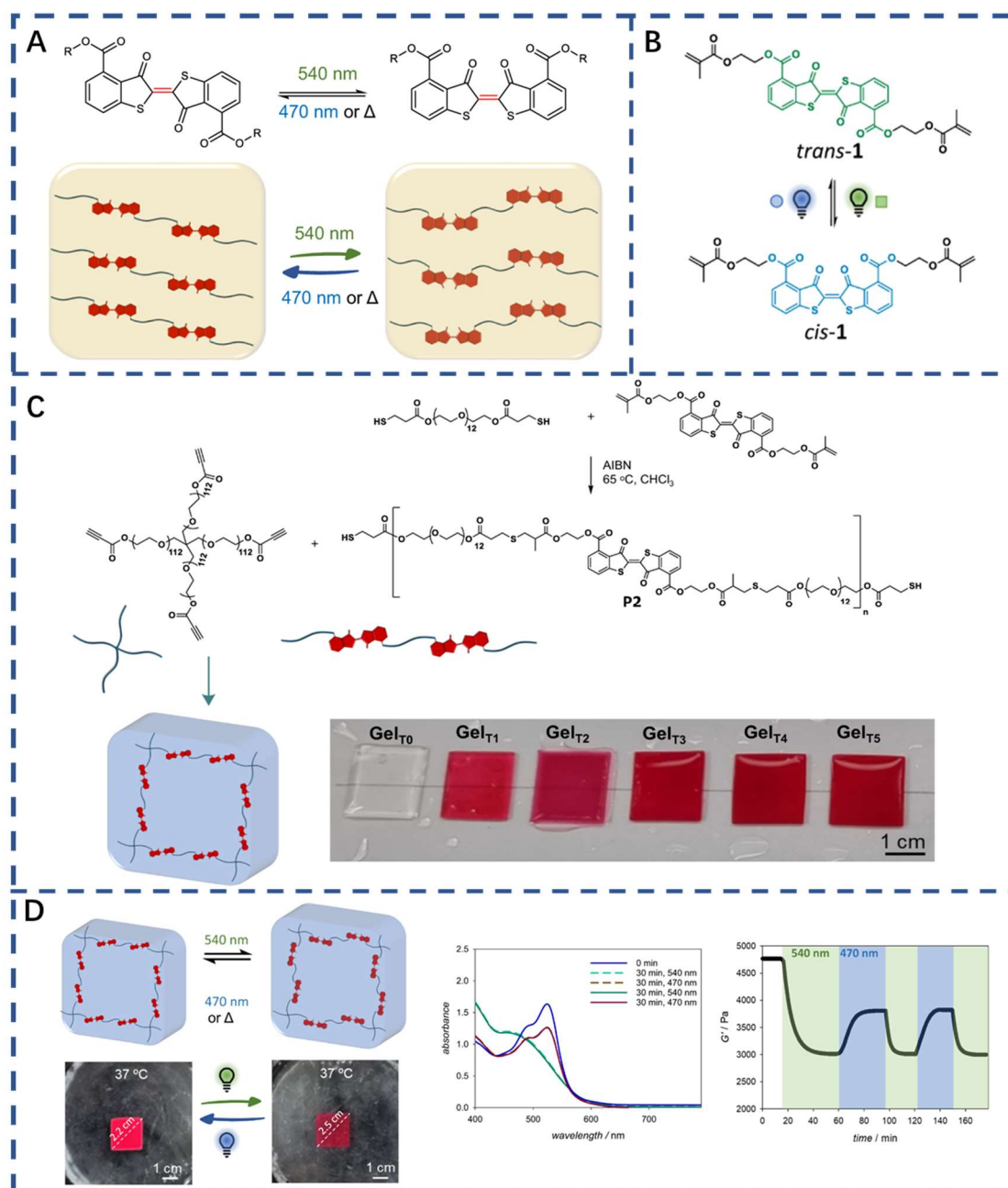
The most widely used chromophores in current optical switching materials are azobenzene, diarylethene, spiropyran, and dithienylethene derivatives<sup>[1]</sup>. In the field of bioscience, azobenzene derivatives are often the preferred choice, primarily because their geometric changes are caused by *trans/cis* isomerization. This molecular motion can lead to substantial conformational changes in their surrounding environment, enabling biologists to discretely and optically modulate mechanical functionality in a biological environment, to study phenomena such as cell-material interactions (mechanotransduction) or the transport of bioactive compounds within a cellular environment<sup>[4]</sup>.

However, due to the low rotational barrier around the single C-N bond, spatial control exerted by azobenzene is restricted by the widespread geometric shape distribution of the *cis* isomer. This limitation arises from the primary pathway of *trans/cis* isomerization in azobenzene, where the conformational change occurs through rotation of the C-N = N-C dihedral angle rather than the reversal of the C-N = N bending angle within the plane. This limitation is also encountered in other photoswitches derived from fluorinated imide or stilbene.

On the contrary, (thio)indigo derivatives provide unique spatial control over conformational changes, as the molecule switches between its *trans* and *cis* isomers through a 180° rotation around the central C = C bond (**Figure 1(A)**). In comparison to the *trans* isomer, the *cis* isomer exhibits a blue shift in absorption due to non-bonding interactions between sulfur/nitrogen and oxygen atoms, as opposed to the planar-induced distortions and compromised conjugation encountered in azobenzene and stilbene-based light switches. These features make (thio)indigo an excellent candidate for molecular mechanics, providing strong spatial control over attached molecular loads<sup>[5]</sup>.

The light-induced color-changing properties and photoisomerization mechanism of (thio)indigo have been studied for over 100 years. However, their application in soft materials remains a challenging field<sup>[6,7]</sup>. A major limiting factor is their low solubility in almost all conventional organic solvents and water, which hinders their covalent binding or incorporation into polymer materials. Additionally, the rigidity and almost planar structure of both isomers of (thio)indigo drive molecular aggregation, significantly reducing their mobility and reactivity. This severely hinders their application in (bio)materials.

Recently, the research published in *Nature Communications* by Walden et al.<sup>[3]</sup> addressed the key issue by developing a strategy to integrate the functionality of thioindigo into the polymer backbone, enabling evaluating the light exchange of large molecules containing thioindigo in various solvents, including water (**Figure 1(B)**)<sup>[3]</sup>. The method used a polymerizable thioindigo linker that can be easily synthesized at the gram scale. Using a tunable laser system, the optimal wavelength for photoisomerization was revealed, and in-depth studies were conducted on the light switch of small molecules. Most importantly, they developed a strategy to incorporate thioindigo into a biocompatible cross-linked hydrogel structure, demonstrating that thioindigo photoisomerization can be used to modulate the hardness of the hydrogel through visible light.



**Figure 1.** Thioindigo derivatives and thioindigo-containing polymer and hydrogels, and their photoisomerization mechanism and visible light-induced switching. (**A**) Schematic overview of photoswitching. (**B**) Photoisomerization of a polymerizable thioindigo linker. (**C**) Thioindigo-containing hydrogels. (**D**) Visible light-induced switching of hydrogels stiffness<sup>[3]</sup>.

The solution to the solubility problem of thioindigo is a crucial advancement in enabling this material to be applied to soft materials. The thioindigo bismethacrylate developed by Walden et al.<sup>[3]</sup> not only overcomes the solubility issue of thioindigo, but more importantly, the linker can undergo a radical-initiated thiol-ene reaction for step-growth polymerization, thus generating polymers containing indigo (**Figure 1(C)**). This opens up new possibilities for the application of thioindigo in soft materials, overcoming the limitations of existing materials and methods.

A suitable solubilization strategy is crucial for establishing the utility of thioindigo in the water environment, paving the way for its application in chemical and mechanical biology and intelligent soft materials. The thioindigo bismethacrylate developed by Walden et al.<sup>[3]</sup> has two advantages: one is easy to synthesize at the gram level, and the other is that it can participate in free radical thiol-ene addition through step growth polymerization and covalently insert into the main chain of the polymer. The study of photoisomerization mechanism shows that the ideal wavelengths for *trans*- to *cis*-isomerisation and *cis*- to *trans*-isomerisation are 540–550 nm and 450–470 nm, respectively. When bound to the main chain of poly(ethylene glycol) (PEG) polymer, the thioindene units exhibit reversible photoisomerization under green and blue light, similar to the photoisomerization of the monomer compound. This optical switching behavior can be observed in a series of organic solvents.

It is interesting that at physiological temperature (37 °C), the self-assembly of the thioindigo moiety induced physical interactions, resulting in the gelation of thioindigo-linked PEG in water. Furthermore, reversible photoisomerization further allows modulation of the modulus of the hydrogel by alternating green and blue light irradiation, i.e., the hardness of the hydrogel can be decreased or increased by green or blue light irradiation, respectively. In other words, the insertion of the thioindigo unit into the covalently cross-linked PEG hydrogel altered the optical and physical properties of the hydrogel (**Figure 1(D)**).

Finally, Walden et al.<sup>[3]</sup> also demonstrated that the PEG hydrogel containing thioindigo chain segment and the photoswitching process are harmless to live cells, paving the way for further cell studies with this hydrogel scaffold. These findings demonstrate the potential application of the thioindigo photoswitches in polymer materials. Especially in the context of biological research, it provides enormous potential for personalized disease models and opens up avenues for a deeper understanding of the impact of hardness changes on disease progression. However, although the authors have solved the insolubility problem of thioindigo, in addition to polymers containing thioindigo chain segment, they have not investigated the specific application of the photoswitching behavior of these soluble thioindigo monomer molecules. Researchers should have made more efforts in this regard.

Based on these findings, there are many potential research areas for the innovative application of thioindigo photoswitches. Firstly, further research and development of novel thioindigo photoswitchable molecules can be carried out to achieve higher photoresponse performance, faster switching speed, and longer stability. This may involve designing and synthesizing new photosensitive molecular structures, or improving the performance of existing photoswitching materials through nanotechnology and material engineering. Secondly, thioindigo photoswitching materials are expected to be applied in a wide range of fields, such as optical devices, information storage, sensor technology, and wearable devices. In addition, combining the needs of biology and medicine, the application of photoswitching materials in biological imaging, drug delivery, tissue engineering, and biosensing can be explored<sup>[8–11]</sup>. This will require interdisciplinary collaboration to develop photoswitching materials that are biocompatible and bioactive, and to study their interactions with living organisms. Finally, with the increasing demand for sustainable and environmentally friendly materials, future research on photoswitching materials may focus more on renewable materials, biodegradable materials, and green synthesis methods to reduce their impact on the environment.

Overall, the future development in the field of photoswitching materials should include materials optimization for various performances, extending its application to various sustainable areas, which will bring more innovation and development to the research and application of photoswitching materials.

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## Conflict of interest

The author declares no competing interests.

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