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Switching in harmony: Tailoring the properties of functional materials with orthogonal stimuli FREE

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ABSTRACT

Bridging the current gap between the precision and efficiency demonstrated by natural systems and synthetic materials requires interfacing and independently controlling multiple stimuli-responsive building blocks in a single platform. The mentioned orthogonal control over material properties (i.e., the ability to selectively activate one stimuli-responsive moiety without affecting another) could pave the way for a multitude of applications, including logic-gated optoelectronics, on-demand drug delivery platforms, and molecular shuttles, for example. In this Review, we highlight the recent successful strategies to achieve orthogonal control over material properties using a combination of stimuli-responsive building blocks and multiple independent stimuli. We begin by surveying the fundamental studies of multi-stimuli-responsive systems, which utilize a variety of stimuli to activate a single stimuli-responsive moiety (e.g., spiropyran, diarylethene, or dihydroazulene derivatives), because these studies lay the foundation for the design of systems containing more than one independently controlled fragment. As a next step, we overview the emerging field focusing on systems which are composed of more than one unique stimuli-responsive unit that can respond to independent stimuli, including distinct excitation wavelengths, or a combination of light, heat, pH, potential, or ionic strength. Recent advances clearly demonstrate how strategic coupling of orthogonally controlled stimuli-responsive units can allow for selective modulation of a range of material properties, such as conductivity, catalytic performance, and biological activity. Thus, the highlighted studies foreshadow the emerging role of materials with orthogonally controlled properties to impact the next generation of photopharmacology, nanotechnology, optoelectronics, and biomimetics.

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INTRODUCTION

During the past several decades, there has been rapid progress in the areas of stimuli-responsive molecular assemblies and materials,

leading to impressive applications, including switchable heterogeneous catalysts,^{1–3} on-demand drug delivery platforms^{4,5} or light-activated field effect transistors.^{6,7} All of these applications rely on the ability to control the macroscopic properties of a material on a molecular level. For instance, switching between aggregated and non-aggregated states (i.e., transitions between insoluble and soluble forms) of molecular catalysts using light as an external stimulus has allowed for facile catalyst recovery and recycling, one of the major breakthroughs for sustainable synthetic chemistry.¹ Likewise, the ability to switch between highly conductive and insulating forms of a material is a pathway to develop the next generation of optoelectronic devices.⁷ As a result, a major focus has been on the development of building blocks which can undergo reversible transformations in response to an applied external stimulus (e.g., light, heat, pH, pressure, or current) and their methods of incorporation into various platforms.^{3–24} For example, integration of stimuli-responsive moieties in relatively large systems (e.g., polymers, supramolecular complexes, or periodic solids) has resulted in the

development of tailorable supercapacitors,²⁵ artificial muscles,²⁶ and multilevel anticounterfeiting and information encryption methods.²⁷

While the majority of artificial systems rely on only one type of stimulus, many natural systems are much more complex and rely on networks of independently controlled processes based on inputs from multiple stimuli.^{28,29} For example, motor neurons, which are responsible for brain and muscle communication, rely on a series of stimuli, including electrical impulses, ion transport, and chemical signaling (i.e., neurotransmitters).³⁰ Without cooperative behavior between each component (e.g., neurons, receptors, muscles, etc.) and the mentioned stimuli, even involuntary motion, such as breathing, would be impossible.^{31,32}

Despite the multitude of elegant examples in nature, a remaining challenge is gaining independent control over synthetic multifunctional systems containing more than one stimuli-responsive building block. This type of orthogonal control relies on the ability to independently activate one stimuli-responsive moiety without affecting a second one, similar to flipping a single switch on a control panel without engaging the others (Scheme 1). Realization of this concept could allow for the development of micropatterned surfaces for optical data storage,³³ DNA nanotechnology,³⁴ or logic-gated optoelectronics,³⁵ for example.

While relatively simple in concept, large molecular assemblies with orthogonally controlled properties are inherently challenging to design and execute for several reasons listed below. For instance, rapid and reversible switching between isomers with distinct properties has been extensively demonstrated using photochromic molecules; however, many of the most commonly studied stimuli-responsive moieties have overlapping absorption profiles in the UV-visible spectrum.³⁶ Consequently, they often require similar excitation wavelengths suitable for their photoisomerization, resulting in a loss of selectivity using light as the only stimulus. At the same time, addressing the issue of spectral overlapping creates further challenges such as selection of building blocks responsive to alternative stimuli other than light. One important consideration in this direction is that the stimulus used to

activate one component should not activate or degrade a second stimuli-responsive unit. After selection of the appropriate responsive moieties, another challenge is associated with their integration into the same platform. Furthermore, these supramolecular host platforms should be suitable and tailorable for the targeted applications, for instance, possess sufficient biocompatibility for drug delivery, high conductivity for optoelectronic device design, or chemical stability necessary for switchable heterogeneous catalysts.

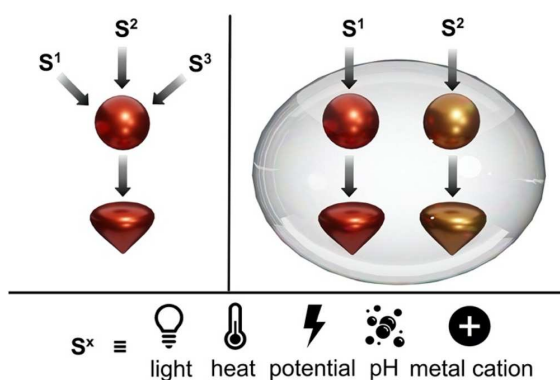
In this Review, we survey the successful strategies for overcoming the mentioned challenges that impede the design of multi-variable systems with properties that can be orthogonally controlled through external stimuli with special attention on application-driven studies. Specifically, we highlight systems and materials that allow for orthogonal control of a defined function, including molecular shuttles, phase transfer agents, and molecular catalysts, for example.^{36–39} The first part of this Review overviews the fundamental studies of multi-stimuli-responsive systems (i.e., systems in which one component can be activated by more than one stimulus) since they lay the foundation for achieving orthogonal switching in materials containing more than one type of stimuli-responsive building blocks. As a next step, we discuss the relatively few known platforms that integrate multiple stimuli-responsive moieties to allow for orthogonal manipulation of material properties. Finally, we shed light on some of the possible avenues that could shift the paradigm of the development of materials with orthogonally controlled properties away from fundamental studies toward the rational design of tunable biomimetic, optoelectronic, and catalytic systems.

SYSTEMS ACTIVATED BY MULTIPLE STIMULI

A cornerstone for the development of stimuli-responsive systems with properties that can be controlled orthogonally is the study of molecular components, which can be activated by more than one stimulus (Scheme 1). For instance, the possibility to utilize a variety of external stimuli, such as light, pH, redox potential, or heat, to control one stimuli-responsive fragment is advantageous because it allows for selection of an appropriate stimulus which would not interfere with a second integrated stimuli-responsive unit. Strategies that involve excitation of a molecule to promote switching between isomers with distinct properties through multiple stimuli ultimately increase the utility of the current library of stimuli-responsive molecules which could be combined in an orthogonal manner.^{38,40–48} For this reason, in this section, we provide the fundamental insights on the design and behavior of multi-stimuli-responsive systems, including those that integrate diarylethene-, spiropyran-, and dihydroazulene/heptafulvene-based molecular switches.

Diarylethene-based systems

Diarylethene derivatives are commonly used building blocks for the development of multi-stimuli-responsive systems because of their rapid isomerization in solution and in the solid state, fatigue resistance, and significant property changes that coincide with molecule isomerization.⁴⁹ For instance, conversion between the “open” and “closed” isomers (Fig. 1) is accompanied by a transition between colorless (non-conjugated) and colored (conjugated) forms.^{40,49} Such isomerization can be triggered by either light or redox potential, allowing for control over multiple states in an orthogonal manner. As a result, many literature reports have evaluated the possibility of integrating diarylethene



SCHEME 1. (Left) A schematic representation of one multi-stimuli-responsive building block undergoing a transformation in response to multiple external stimuli (e.g., light, heat, potential, pH, or metal cations). (Right) A schematic representation of two distinct stimuli-responsive building blocks integrated in one platform and responding to independent orthogonal stimuli (e.g., S^1 and S^2). S^x = possible stimuli used to modulate the properties of a given system.

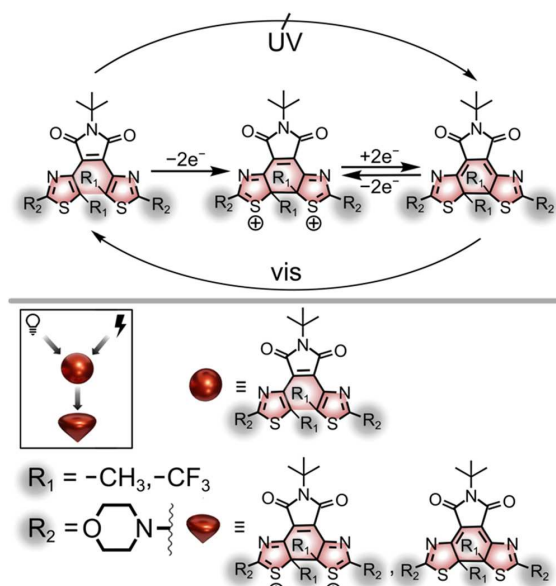


FIG. 1. (Top) Structures of a diarylethene derivative undergoing isomerization between the “open” and “closed” isomers driven by light or redox potential. Isomerization from the “closed” to “open” form can only be achieved upon exposure to visible light. (Bottom) Schematic representation of how light and redox potential can be used to promote switching between “open,” cationic, and “closed” forms of a diarylethene derivative. Adapted with permission from Herder *et al.*, *Chem. Sci.* **4**, 1028–1040 (2013). Copyright 2013 Royal Society of Chemistry.⁴⁰

derivatives for photoelectrochemical control over system properties with applications focused on optical data storage, design of electronic logic gates, and nonlinear optical materials.^{50–52}

Studies focusing on light- and redox-responsive diarylethene derivatives attract significant attention due to their utility in light harvesting and energy conversion processes.⁵³ For instance, Hecht and co-workers performed comprehensive mechanistic studies of a thiazole-functionalized diarylethene-based system exhibiting orthogonal responses to light and current.⁴⁰ This report shed light on the design criteria necessary for preparation of fatigue-resistant switches possessing a distinct response to two stimuli (Fig. 1).⁴⁰ In particular, exposure of the diarylethene derivative to redox potential resulted in cyclization from the open to the closed form. In contrast, photochemical pathways allowed for isomerization from the closed to open form upon irradiation with a 436-nm excitation wavelength (Fig. 1). A key component which defines the behavior of the used diarylethene derivatives was the presence of specific electron-donating morpholino substituents on the thiazole rings and an electron-deficient maleimide as the bridging unit [e.g., methylated, trifluoromethylated, and asymmetric bis(morpholinothiazolyl)maleimides]. As shown in Fig. 1, the morpholino substituents facilitated oxidative ring-closure of the diarylethene derivative, while the possibility for photocyclization was hindered due to an intramolecular charge transfer interaction (i.e., formation of a twisted intramolecular charge transfer excited state between the electron donating morpholino substituents and electron

accepting maleimide bridging unit prevented efficient photocyclization).⁴⁰ The authors anticipate that these diarylethene-based systems offer a promising approach not only toward logic-gated devices utilizing photons and electrons as distinct inputs but also can be used for light-energy conversion through photon-driven generation of metastable states with sufficient electrochemical potential to promote redox reactions. Thus, these findings⁴⁰ are the first steps for acquiring fundamental insight required to advance applications in the light-harvesting and energy-conversion sectors.

The studies by Hecht and co-workers illustrate how diarylethene-based systems could be applied in energy storage technologies; however, they could also be used to regulate charge transfer pathways through switching between non-conjugated and conjugated isomers.^{41,42} Modulation of the charge transfer pathways could be achieved through design of molecular assemblies composed of more than one diarylethene unit acting as bridges between metal centers with the possibility to activate only one diarylethene-based unit at a time.⁴³ For example, Rigaut and co-workers demonstrated selective cyclization of either one or two stimuli-responsive molecules in trimetallic Ru-based organometallic complexes containing two diarylethene bridging ligands (i.e., “diarylethene–Ru–diarylethene”) using light and redox potential.⁴³ For instance, irradiation of the diarylethene-bridged Ru complexes with UV light ($\lambda_{\text{ex}} = 350$ nm) resulted in formation of the fully cyclized state (i.e., both diarylethene units underwent photoisomerization from the open to closed forms). In a similar way, the central rings of both diarylethene-based ligands could be reopened by visible light irradiation ($\lambda_{\text{ex}} = 750$ nm). However, access to the intermediate states involving isomerization of only one, but not both, diarylethene ligands from the closed to the open isomers could only be achieved through oxidative cyclization of both ligands to the closed isomers followed by reductive ring opening of a single diarylethene-based unit.⁴³ These stepwise isomerization events (e.g., sequential isomerization of two diarylethene-based ligands) are often mediated by the redox-active metal centers of organometallic complexes. Thus, photoelectrochemical control of such switchable organometallic complexes is a way to achieve on-demand charge storage as well as modulation of electron transfer pathways.⁴³ Access to three different states (i.e., two diarylethene-based ligands in the open form, two in the closed form, or one in the open form and the other in the closed form) via redox-active metal centers in the described multi-stimuli-responsive system could, therefore, be a pathway to design optical, conductive, and nonlinear optical switches which can be integrated into molecular devices, such as single-molecule diodes and rectifiers.⁵⁴

A completely different direction, explored by Chen and co-workers, focuses on the development of optically and electrochemically co-modulated molecular transport junctions (MTJs) based on on-wire lithography (OWL, i.e., lithography performed on one-dimensional nanowires). Research in this area is motivated by the possibility to utilize stimuli-responsive MTJs as modular platforms for exploring molecular electronics, such as rectifiers, junctions, and diodes.⁴¹ The authors prepared nanowires with chemically fabricated nanogaps formed by two gold electrodes connected by two organometallic ruthenium complexes, which were bridged by diarylethene units (i.e., “Au–Ru–diarylethene–Ru–Au”). Using the described OWL system, the Chen group achieved reversible and reproducible conductivity switching in which the changes are orthogonally triggered by the molecular isomerization between a π -conjugated closed state and a

non-conjugated open state of the diarylethene ligands using optical and electrochemical stimuli.⁴¹ Upon 700-nm irradiation, the nano-wires demonstrated photo-triggered switching from a low-resistance state (LRS) to a high-resistance state (HRS) coinciding with isomerization from the colored (conjugated) to colorless (nonconjugated) forms of the diarylethene units. Likewise, a return to the LRS could be induced by exposure to a 365-nm excitation wavelength. At the same time, these transformations could be induced by redox potential (e.g., oxidative ring-closure or reductive ring-opening processes).⁴¹ This study demonstrates the potential for the development of Boolean computing (i.e., binary decisions and logical operators generating “true” or “false” outcomes⁴¹), showcasing two-input OR and three-input AND-OR logic operations.⁴¹ Although a stepwise progression through multiple stimuli-responsive logic gates in one system has not been achieved yet, the mentioned proof-of-concept⁴¹ for the logic gate provides a strong foundation for fabrication of multifunctional molecular devices through optimization of synthetic and operative conditions.

As mentioned above, diarylethene-based systems^{40–43} could provide a pathway to advance various fields focusing on, for instance, optoelectronics or energy storage development.^{40,54} The reported responses of diarylethene derivatives to light and electricity make them a promising class of switches for design of materials for which properties can be orthogonally controlled. Taking into account that they are largely unaffected by other alternative stimuli (e.g., heat or pH) allows one to prepare multi-variable systems containing additional stimuli-responsive building blocks activated by pH or heat (Fig. 1).⁴⁰ Furthermore, the changes in molecular properties (e.g., conjugation) can be readily translated into changes of macroscopic material properties (e.g., conductivity).⁵⁵ Despite the described advantages, diarylethene derivatives have been utilized in a narrow scope of applications so far including molecular computing or single-molecule electronics. These fields can be significantly expanded and advanced through further understanding of intermolecular interactions between diarylethene-based compounds integrated within large assemblies. For instance, incorporation and alignment of a large number of stimuli-responsive units within a single platform would allow for improved data storage capacity.^{40,54,56}

Multi-stimuli-responsive spiropyran-based systems

While spiropyran derivatives have been extensively investigated for their photochromic behavior,^{57–59} they have also attracted significant attention due to the possibility to initiate their isomerization under many orthogonal stimuli. In addition to light, for instance, alternation in pH,^{60–62} presence of metal cations,^{63,64} application of redox potential,⁶⁵ and temperature gradients can be applied to control the properties of spiropyran-integrated systems (Fig. 2).^{66,67} The isomerization process, which can be controlled by any of the mentioned stimuli, is based on switching between the neutral spiropyran and zwitterionic merocyanine forms and coincides with not only a significant geometric rearrangement but also with changes in conjugation, absorbance profile, and dipole moment.⁵⁷

Taking advantage of the possibility to utilize spiropyran derivatives for multifaceted control over material properties, Klajn and co-workers designed rigid porous aromatic frameworks (PAFs) and flexible porous aromatic networks (PANs).³⁸ Incorporation of spiropyran building blocks in PAFs and PANs allowed for light-induced

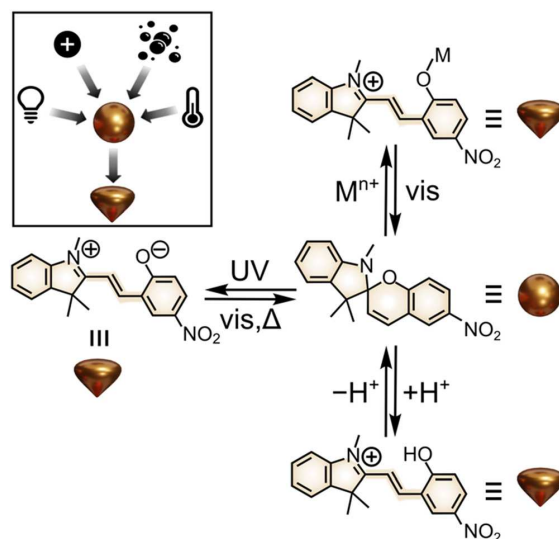


FIG. 2. Structures of spiropyran (gold sphere) undergoing isomerization to the merocyanine form in response to light exposure, temperature gradient, pH alternation, and metal coordination.

metal ion capture by formation of the zwitterionic merocyanine isomer as well as reversible halochromic and solvatochromic behavior. Interestingly, spiropyran-to-merocyanine conversion (Fig. 2) was irreversible in the desolvated flexible PANs, but this process was fully reversible in the desolvated rigid PAFs, highlighting how strategic choice of chromophore and host matrix can affect the overall material performance.³⁸ Photoresponsive PAFs and PANs were probed as light-controlled multifunctional catalysts to promote hydrolysis reactions as well as materials for gas storage, using multiple external stimuli.³⁸ These studies illustrate that the design of the spiropyran derivative and host matrix are important variables for considerations during material preparation for targeted applications spanning catalytic or gas storage and separation systems.

Spiropyran derivatives have also been integrated in polymer matrices to gain control over polymer morphology by using multiple stimuli.⁴⁴ For instance, Zhang and co-workers designed a block copolymer consisting of poly(*N*-isopropylacrylamide)-*b*-poly(*N*-acryloylglycine-*co*-*N*-acryloylglycine spiropyran ester) with the possibility of morphology modulation depending on external stimuli.⁴⁴ The copolymer had a thermo-responsive block [PNIPAM, poly(*N*-isopropylacrylamide)] with a lower critical solution temperature coupled with a second block [P(NAG-*co*-NAGSP), poly(*N*-acryloylglycine-*co*-*N*-acryloylglycine spiropyran ester)] with an upper critical solution temperature that was also responsive to pH and light exposure.⁴⁴ By combining copolymers with distinct responses to temperature, pH, and light, the authors were able to control polymer micellization through post-polymerization modification or by using UV light irradiation, temperature, and pH as variables.⁴⁴ The combination of thermoresponsive polymer blocks with pH- and light-responsive spiropyran moieties allowed for control over the formation of nanospheres and nanolines

with variable morphologies, which could be applied in areas such as high-resolution imaging of biological samples or mechanical stress mapping depending on the selected morphology.^{57,68} Thus, these studies demonstrated that multi-stimuli-responsive block copolymers are a possible pathway to engineer materials with pre-designed morphologies for a broader span of applications including nanoreactors, biosensors, and biomimetic platforms for controlled drug delivery.⁴⁴

While porous frameworks³⁸ and polymers⁴⁴ have been shown to be successful platforms to promote the isomerization of spiropyran derivatives in the solid state, they are not the only possible host matrices to study control of spiropyran photoisomerization through exposure to multiple stimuli (Fig. 2). For example, Guirado, Hernando, and co-workers demonstrated the potential of ionogels (IGs) as platforms for preparing smart materials with integrated multi-stimuli-responsive switches.⁴⁵ In this direction, the authors formulated ionogels by combining a polyfluorinated polymer and an ionic liquid loaded with a photo-, halo-, thermo-, and electrosensitive spiropyran derivative.⁴⁵ When dissolved in an ionic liquid, the spiropyran derivative [i.e., 1',3'-dihydro-1',3',3'-trimethyl-6-nitrospiro[2H]-1-benzopyran-2,2'-(2H)-indole] exhibited the expected photochromic behavior in response to exposure to UV irradiation or addition of acid (Fig. 2). Interestingly, the highly polar environment of the ionic liquid allowed for thermally induced formation of merocyanine (i.e., spiropyran-to-merocyanine isomerization upon addition of heat even without UV irradiation) since the zwitterionic form could be stabilized through electrostatic interactions with the ionic liquid.⁴⁵ Moreover, this behavior could be preserved even in the solid state when the spiropyran derivatives were loaded in the ionogel matrix.⁴⁵ To showcase the possibility to utilize the mentioned spiropyran-loaded ionogels in practical applications, they constructed four spiropyran-functionalized ionogel membranes capable of responding to four different stimuli (i.e., temperature, pH, light, or redox potential) with an integrated microfluidic channel into a flexible electronic device as a proof of principle.⁴⁵ Due to their synthetic accessibility, high ionic conductivities, optical transparency, chemical and thermal stability, and mechanical flexibility, ionogels are highly promising platforms for integration of stimuli-responsive molecules for the development of smart devices in optoelectronic fields like smart displays, sensors, and inks.⁴⁵

As described above, spiropyran derivatives have been integrated into supramolecular hosts to control material properties, but they have also been utilized to control the optical properties of molecular fluorophores.⁴⁶ In this direction, a spiropyran-based functionality has been used to control aggregation induced emission of tetraphenylethylene-based fluorescent probes, which can be applied as labels for biological samples or as components of organic light-emitting diodes.⁴⁶ For example, the Tian group demonstrated that functionalization of a spiropyran core with a tetraphenylethylene derivative resulted in a fluorescent probe that could be switched "on" or "off" based on spiropyran isomerization.⁴⁶ In particular, either irradiation with a 254-nm excitation wavelength or addition of acid induced the spiropyran-to-merocyanine conversion (Fig. 2), resulting in an extension of conjugation throughout the molecule to yield a highly fluorescent chromophore.⁴⁶ Moreover, the emission range could be tailored due to spiropyran photoisomerization, for example, from a maximum emission intensity at 490–615 nm upon merocyanine formation.⁴⁶ As such, photo- and halochromic spiropyran-based chromophores have the potential to

play a role in the next generation of switchable fluorescent sensors and tags to detect and capture, for instance, toxic metal cations.^{69,70}

To summarize, stimuli-responsive spiropyran derivatives are a promising class of switches which could affect diverse platforms such as nanoporous materials, polymers, and ionogels, resulting in materials responsive to various stimuli, including light, pH, temperature, solvents, and electrochemical conditions (Fig. 2). Although integration of spiropyran derivatives offers control through an impressive variety of stimuli, achieving a precise response to an intended stimulus while avoiding unintended activation by a secondary stimulus is a challenge that must be addressed in order to utilize spiropyran-based building blocks for the synthesis of materials for which properties could be controlled orthogonally by multiple stimuli. Overcoming this challenge will undoubtedly yield methods to prepare systems with orthogonally manipulated properties (e.g., switchable and selective fluorescent tags which could be turned on or off by external stimuli) possessing rapid responses toward external stimuli and exhibiting drastic property changes.^{71,72}

Selective activation of dihydroazulene/vinylheptafulvene switches with light and heat

Diarylethene and spiropyran certainly represent two of the most commonly studied classes of multi-stimuli-responsive molecules, but the other less-studied classes also offer distinct advantages in terms of orthogonal switching.^{47,48} For example, isomerization of stimuli-responsive components based on dihydroazulene (DHA)/vinylheptafulvene (VHF) cores can be controlled using light or heat as the stimulus.^{47,48} Control over directional isomerization from the cyclized (closed) DHA to open VHF isomer using two independent stimuli is advantageous since it results in high selectivity and bistability for the system as a whole.⁷³ In this avenue, Setaro, Kreft, and co-workers have designed DHA-based photoswitches for which the forward isomerization process (i.e., DHA-to-VHF isomerization) was exclusively initiated by exposure to a 366-nm excitation wavelength, while the reverse process could only be achieved thermally.⁴⁷ This DHA-based switch was applied to study the effect of molecular dipole moment on the photoluminescence properties of carbon nanotubes (CNTs).⁴⁷ Such studies would be impossible without orthogonal control over the direction of the isomerization process since the excitation wavelength used to probe CNT emission coincided with the typical excitation wavelengths used to promote VHF-to-DHA photoisomerization.⁴⁷ The authors were able to avoid this challenge by selecting between the low dipole moment (DHA) and high dipole moment (VHF) forms of the switch during emission studies of CNTs through either UV excitation or heating. As a result, DHA/VHF switches could be used to demonstrate how the molecular dipole moment of surrounding stimuli-responsive units affects the optical properties of CNTs when they were encapsulated in DHA-functionalized micelles⁴⁷ or when they were coated by DHA-based molecular switches.⁴⁷ Although these studies were conducted as proof-of-principle, the ability to modulate the optical and electronic properties of CNTs has profound impacts in areas like energy storage since CNTs have already been integrated as components of novel lithium-ion batteries, supercapacitors, and organic solar cells.^{74–76}

The foregoing results highlight a wide variety of stimuli that could be employed to control the behavior of stimuli-responsive units integrated in a variety of structural motifs, including organometallic complexes, nanowires, porous frameworks, polymers, ionogels, and

CNTs.^{38,41,43,45,47} In each of the mentioned cases, incorporation of one type of stimuli-responsive unit allowed for tailoring of the whole system's properties and performance, leading to switchable electrical conductivity, photoluminescence, or morphology.^{41,44,47} Given the array of possible stimuli, structural motifs, and properties which could be modulated by stimuli responsive units (e.g., conductivity, fluorescence, morphology, or catalytic performance), it is reasonable to imagine that combining more than one type of stimuli-responsive unit into one cohesive platform could lead to unprecedented control over multiple material properties simultaneously. However, in order to realize this goal, methods for interfacing more than one type of switchable unit, which can be addressed by independent stimuli, must be developed, which is the focus of the discussion below.

ORTHOGONAL CONTROL OF MATERIAL PROPERTIES IN MULTI-SWITCH SYSTEMS

Prior to this section, we have focused on studies of multi-stimuli-responsive building blocks for noninvasive modulation of material properties. As a next step, we consider how the mentioned stimuli-responsive building blocks could be combined within the same platform to design systems comprised of more than one stimuli-responsive fragment which could be activated independently using orthogonal stimuli.^{36,39,66,77} Thus, in the next section of this Review, we highlight some of the possible pathways to interface multiple distinct stimuli-responsive moieties to gain orthogonal control over system properties using a combination of stimuli, such as light, redox potential, heat, pH, or ionic strength.^{36,37,39,66,77–88}

Orthogonal photoswitching

As the first class of orthogonally controlled systems, we focus on those which are activated by light alone using two or more distinct excitation wavelengths. Interest in this area is driven not only by the intriguing fundamental challenges associated with constructing multi-component light-activated assemblies but also by the possibility to

engineer functional smart materials utilizing a spatiotemporally resolved, noninvasive, and nondestructive stimulus.⁸⁹ For instance, significant efforts in the area of orthogonal photoswitching have resulted in platforms to study the mechanisms involved in complex biochemical pathways,⁹⁰ on-demand-activated drug delivery systems,^{80,91} and even methods for controlling gene expression *in vivo*.⁷⁷ Moreover, precise control over light-driven molecular shuttles,³⁷ phase transfer agents,³⁶ and materials for optical data storage^{92,93} are all possibilities given the groundbreaking work done in these directions so far.

In general, two synthetic approaches for achieving orthogonal photoswitching have dominated the field thus far.^{36,94,95} The first approach involves incorporation of multiple photolabile protecting groups (PPGs) for either selective release of molecules from a host matrix or activation of reactive functional groups (Fig. 3).^{94,95} In contrast, a second approach involves integration of more than one type of photoswitch (often from different classes of photochromic molecules) into a system in which each photoswitch can be activated by a different excitation wavelength with a distinct outcome (Fig. 3).³⁶ In either case, the inherent challenge lies in selecting two or more light-activated moieties with minimal overlap in their absorbance spectra (i.e., significantly different excitation wavelengths) in order to achieve completely orthogonal switching. Moreover, potential pathways for quenching of optical cycling through aggregation or energy transfer processes must be considered, creating an additional layer of complexity in the design of such systems. While the complexity of these designs has resulted in relatively slow progress up to this point, recent breakthroughs in the field, such as the successful combination of up to five PPGs with distinct excitation wavelengths in one system, will undoubtedly catalyze the rapid growth in the coming years.⁹⁶ Thus, this section surveys the milestone studies first involving orthogonal control of PPGs followed by incorporation of more than one type of photochromic molecule in a single platform.

While studies involving PPGs started in the early 1960s,^{97,98} orthogonal control of the photoresponsive behavior of two PPGs in

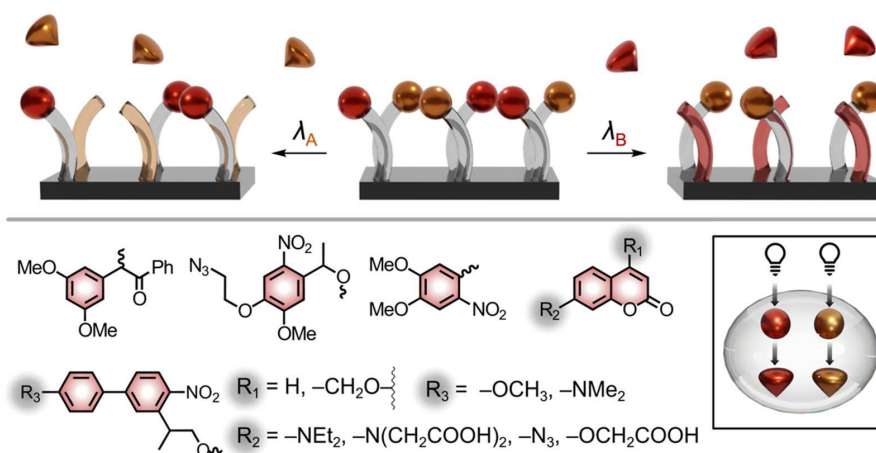


FIG. 3. (Top) Schematic representation of two photolabile protecting groups (PPGs, red and gold spheres) undergoing wavelength-selective cleavage from a host matrix. Cleavage of the PPGs exposes the active sites of the host matrix (red and gold cylinders). λ_A represents one excitation wavelength activating the gold spheres, while λ_B represents a second excitation wavelength activating the red spheres. (Bottom) Structures of the commonly studied PPGs (red or gold spheres) discussed in this Review.

one system through two excitation wavelengths was not accomplished until several decades later when Blanc and Bochet utilized 2-nitroveratryl and 3',5'-dimethoxybenzoin protecting groups (Fig. 3) for diesters and demonstrated selective transesterification based on excitation wavelength.⁹⁵ Since then, the library of PPGs activated by distinct excitation wavelengths has been expanded, allowing for incorporation of up to five PPGs in a single system with independent control over their responses.⁹⁶ These early studies provided a foundation for the more recent application-driven research involving PPGs, which have shown exceptional promise in the areas of biotechnology,⁹⁹ disease treatment,¹⁰⁰ or light-controlled polymerization reactions.¹⁰¹ For example, del Campo, Specht, and co-workers achieved orthogonal light-mediated control over polymerization and photodegradation of polyurethane films by functionalizing the monomers with two different PPGs (e.g., *p*-dialkylaminonitrobiphenyl and methoxynitrobiphenyl groups, Fig. 3).⁷⁸ Furthermore, they incorporated the PPGs into the monomers in two different ways: as terminal groups preventing initiation of the polymerization reaction and as internal groups allowing for light-initiated depolymerization to occur. In other words, one monomer could not be polymerized until irradiation resulting in cleavage of the PPG-end groups, while the other could be polymerized freely in the dark but would undergo photodegradation upon irradiation with a second excitation wavelength. By utilizing excitation wavelength and reaction time as variables, the del Campo group was also able to control the degree of cross-linking or depolymerization of a urethane prepolymer mixture for the preparation of a series of versatile polyurethane films from the same set of precursors.⁷⁸

Demonstrating the versatility of PPGs, similar strategies have been implemented for the control of important biomolecules⁷⁹ and genetic material (e.g., DNA or RNA).⁷⁷ For instance, coupling of proteins to hydrogel networks via photodegradable linkages (PPGs) has been utilized for on-demand delivery of therapeutic proteins in real time by Anseth and co-workers.⁷⁹ In these studies, bone morphogenetic proteins (BMPs) covalently bound to a hydrogel network through nitrobenzyl ether- and coumarin methylester-based PPGs (Fig. 3) could be released with high spatiotemporal resolution in an orthogonal manner. In particular, the BMP bound by nitrobenzyl ether could be released upon irradiation with a 405-nm excitation wavelength, while the BMP bound by coumarin methylester could be delivered after exposure to a 365-nm excitation wavelength.⁷⁹ Thus, these studies⁷⁹ represent a crucial step toward noninvasive control of biological processes which could be applied in targeted drug delivery or other therapeutics.

A different area of interest in the field of orthogonal PPGs is *in vivo* control of genetic information, which would allow for noninvasive manipulation of tissue growth and function.⁷⁷ In this direction, Deiters, Chen, and co-workers utilized caged morpholino oligonucleotides, i.e., functionalized with PPGs, to switch between active and inactive forms of RNA upon light irradiation.⁷⁷ In particular, cyclization of RNA-morpholino oligonucleotide duplexes with PPGs rendered the duplexes inactive. The activity of the RNA duplexes could be restored by photolysis of the PPG.⁷⁷ Integration of two PPGs [e.g., nitrobenzyl ether or [7-(diethylamino)coumarin-4-yl]methyl groups, Fig. 3] allowed for selective silencing or activation of genes related to mesodermal patterning in zebrafish *in vivo* by irradiation with either 365- or 405-nm excitation wavelengths. Thus, these studies represent a pathway for creation of optochemical probes to monitor genetic interactions and methods for dynamically regulating tissue formation and function.⁷⁷

In addition to selective manipulation of genetic material,^{102,103} delivery of proteins¹⁰⁴ and enzymes,³⁹ and biochemical mechanistic studies,⁹⁰ PPGs can also be applied in the field of photopharmacology.¹⁰⁵ For example, Feringa and co-workers developed a system of complementary antibiotics functionalized with two distinct PPGs for treatment of *Escherichia coli* and *Staphylococcus aureus*.⁸⁰ Design of this system was done such that the two antibacterial agents were complementary in function (i.e., each antibacterial agent inhibited the growth of only one bacterial strain) so that activation by removal of the PPGs could be used to promote or inhibit the growth of particular bacteria out of a mixture of microorganisms. For this, fluoroquinolone (a treatment for *E. coli*) and benzylpenicillin (a treatment for *S. aureus*) were functionalized with PPGs, 7-aminocoumarin ($\lambda_{\text{ex}} = 380$ nm) and 7-hydroxycoumarin ($\lambda_{\text{ex}} = 312$ nm), respectively. When both bacterial strains were treated with a mixture of the protected fluoroquinolone and benzylpenicillin derivatives, the growth of *E. coli* or *S. aureus* could be inhibited by irradiation with 380- or 312-nm excitation wavelengths, respectively, without inhibition of the other strain. Therefore, integration of PPGs in antibiotics represents a pathway for orthogonal control of antibacterial treatment and could be used high-precision patterning of complex mixtures of microorganisms in one system.

The studies described above highlight the reasons for the exceptional growth of the field of PPG derivatives over the past several decades, including the transition from fundamental studies of PPG design to their use in complex biochemical applications.^{39,77,79,80} In general, the wealth of studies utilizing PPGs can be attributed to their versatile nature, allowing for relatively facile integration of PPGs through a variety of functional groups (Fig. 3). One of the challenges in this area, however, is that activation of PPGs causes inherently irreversible changes to the system. In other words, after a PPG is removed from a system through light irradiation, it cannot be reintegrated in a noninvasive manner.³⁶ While this is not always problematic for the biochemical applications described above, it does limit the applicability of PPGs in other areas, such as optoelectronics or stimuli-responsive material development. Overcoming the mentioned irreversibility is one of the motivations for studies involving other classes of photochromic molecules with reversible structural or chemical changes, which are the focus of the detailed discussion below.

As mentioned before, utilization of two distinct excitation wavelengths in one system is practically challenging since the photoisomerization of the most commonly used photochromic molecules occurs under overlapping excitation wavelengths and, thus, cannot be addressed independently. However, strategic coupling of classes of photoswitches with distinct excitation wavelengths has resulted in very few examples of systems with purely light-driven reversible property changes.³⁶ For example, Feringa and co-workers designed a system containing a donor-acceptor Stenhouse adduct (DASA) and an azobenzene-based photoswitch which could be activated using two excitation wavelengths and functioned as a phase transfer tag for α -cyclodextrin (Fig. 4).³⁶ This system relied on two components: an azobenzene moiety which could bind α -cyclodextrin upon *cis*-to-*trans* isomerization ($\lambda_{\text{ex}} = 430$ nm) and a DASA functionality that promoted transfer from organic to aqueous phases upon cyclization under visible light. As a result, stepwise binding and transfer of α -cyclodextrin could be accomplished by irradiation with a 430-nm excitation wavelength or exposure to white light. These studies demonstrating on-demand binding and phase transfer of molecules are a major step forward for

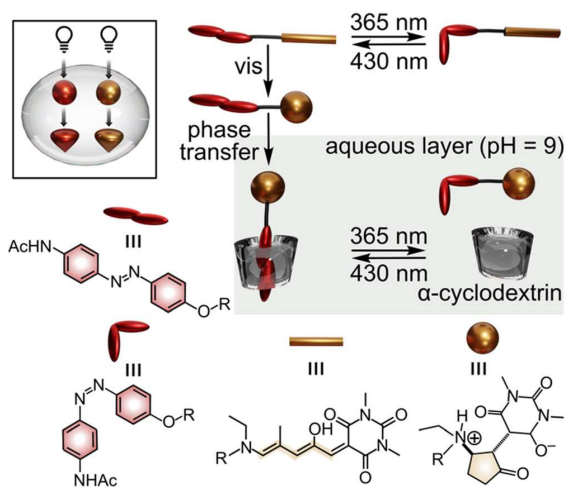


FIG. 4. A schematic representation of the stepwise binding and phase transfer of α -cyclodextrin by the combination of azobenzene and DASA functionalities. Formation of *trans*-azobenzene upon exposure to a 430-nm excitation wavelength promotes binding of α -cyclodextrin, which can be transferred from organic to aqueous solutions upon cyclization of the DASA under irradiation with visible light. Adapted with permission from Lerch *et al.*, Nat. Commun. 7, 12054 (2016). Copyright 2016 Authors licensed under a Creative Commons CC BY License.³⁶

orthogonal control of multifunctional molecular systems and materials integrating multiple stimuli-responsive moieties.³⁶

While the Feringa group utilized the ability of azobenzene to bind α -cyclodextrin to create switchable phase transfer agents, the Wu group utilized two different azobenzene derivatives and two cyclodextrin derivatives to generate micropatterned surfaces capable of alternating between four different states.⁸¹ In this case, parent azobenzene and a tetra-*ortho*-isopropoxy-substituted azobenzene derivative could be used for selective binding of α - and γ -cyclodextrin, respectively.⁸¹ Notably, the two azobenzene derivatives could be activated using different excitation wavelengths. To create programmable micropatterned surfaces, the azobenzene derivatives were microcontact printed on a glass substrate and submerged in a solution of α - and γ -cyclodextrin. Functionalization of α - and γ -cyclodextrin with different fluorescent dye molecules allowed for visualization of the selective binding and release of the fluorescent cyclodextrin derivatives using the two azobenzene moieties.⁸¹ Consequently, four different visual patterns could be achieved upon irradiation with UV, blue, green, or red light.⁸¹ Thus, these studies shed light on a mechanism to use orthogonally controlled photoswitching to create switchable micropatterned surfaces, which are highly desirable for development of cell culture substrates used to study cell proliferation, adhesion, and molecular signaling pathways, for example.¹⁰⁶ Moreover, such micropatterned surfaces could also be applied as strain sensors or as components in flexible electronics.¹⁰⁷

In addition to DASAs and cyclodextrin, azobenzene derivatives have also been used in combination with rotaxanes to construct orthogonally photoswitchable systems.^{37,108} Rotaxanes are composed of macrocycles threaded onto a dumbbell-shaped backbone, leading toward development of molecular shuttles, which are based on the precisely controllable movement of the macrocycle along the rotaxane backbone

(Fig. 5).^{37,108} For instance, Zhang and co-workers prepared novel photochromic rotaxanes containing azobenzene and a naphthalene-derived azobenzene (NP-AB) connected through a 1,5-dioxynaphthalene bridge (Fig. 5). In this system, two macrocycles exhibited preferential binding

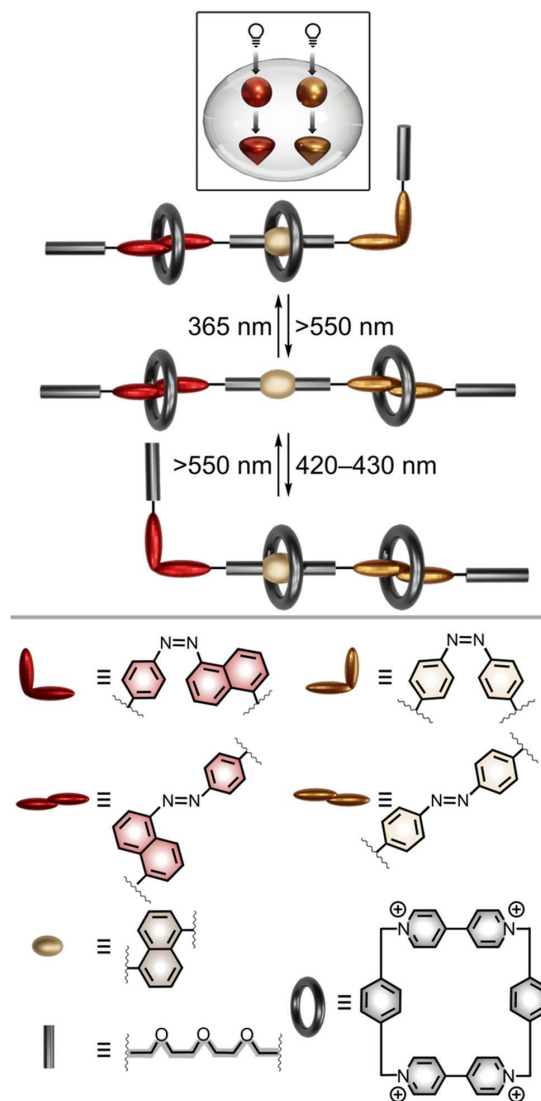


FIG. 5. (Top) Schematic representation of an azobenzene-functionalized rotaxane derivative acting as a molecular shuttle in which the position of macrocycles (gray rings) can be controlled based on azobenzene photoisomerization (red and gold). Presence of *cis*-azobenzene promotes binding of the macrocycle to the naphthalene core (light yellow spheroid). (Bottom) Structures of the *cis*- and *trans*-isomers of two azobenzene derivatives (red and gold) used to promote transfer of macrocycles (gray ring) to and from a naphthalene core (light yellow spheroid). Adapted with permission from Li *et al.*, Org. Chem. Front. 8, 1482–1489 (2021). Copyright 2021 Royal Society of Chemistry.¹⁰⁸

to the azobenzene derivatives in their *trans*-forms.¹⁰⁸ However, irradiation-induced *trans*-to-*cis* isomerization of either azobenzene or NP-AB ($\lambda_{\text{ex}} = 365$ or 420–430 nm, respectively) resulted in migration of the macrocycle to the 1,5-dioxynaphthalene bridge (Fig. 5). Subsequent irradiation with visible light ($\lambda_{\text{ex}} > 550$ nm) caused *cis*-to-*trans* isomerization of both azobenzene and NP-AB, resulting in movement of the macrocycle back to the azobenzene binding site.¹⁰⁸ The authors anticipate that this precise control over molecular motion could be used in the next generation of information storage technologies, which take advantage of rapid and reversible transitions between multiple discrete states.¹⁰⁸

Outside of molecular shuttling and applications in optical data storage, DNA nanotechnology is a different area which will likely see great advancements due to studies of orthogonal photoswitching.³⁹ Many DNA-based nanodevices rely on strand displacement and subsequent rehybridization, which could be accomplished by incorporation of photochromic molecules for which isomerization is accompanied by significant structural rearrangement (i.e., changes in steric bulk upon photoisomerization).³⁹ For instance, switchable DNAzyme-based catalysts have been prepared by Famulok, Valero, and co-workers through the synthesis of the strands of a split horseradish peroxidase enzyme possessing both azobenzene and arylazopyrazole photoswitches.³⁹ Since both of these photoswitches exhibit significant changes in geometry upon photoisomerization and could be activated by two different excitation wavelengths, they could be used for selective control over whether the strands of the enzyme were able to interact and form the active enzyme complex (i.e., the complex formed by three individual strands of the split horseradish peroxidase). As a result, enzymatic activity could be controlled through two independent excitation wavelengths ($\lambda_{\text{ex}} = 365$ or 450 nm). These studies are a starting point for gaining potentially transformative orthogonal control over biological processes using a nondestructive stimulus and foreshadow the use of such systems as multiplexers and encoders for molecular computing *in vivo* since DNA-based technology should be biocompatible.³⁹

To summarize, while there has been significant progress in the area of orthogonal light-activated systems, the design of such systems remains inherently challenging. The relatively few classes of established photochromic molecules, for example, often possess overlapping spectral bands (i.e., operating under a similar set of excitation wavelengths) or their photoisomerization can be quenched through energy transfer processes.^{36,109} Consequently, one of the main goals to advance the field to a different level is to design a more diverse portfolio of photochromic molecules, especially ones that take advantage of a broader range of the electromagnetic spectrum to initiate the photoisomerization process. For instance, photochromic molecules which can be activated by infrared or near-infrared light would be especially useful for diagnostic or therapeutic applications in which typical UV excitation wavelengths could have harmful side effects or have limited penetration depth. Moreover, studies involving two-photon excitation instead of direct excitation of photochromic molecules or PPGs would allow for the current library of photoactive compounds to be utilized in more diverse areas, such as *in vivo* drug delivery or bioimaging.

Orthogonal photoelectrochemical switching

Rather than utilizing two distinct excitation wavelengths to gain control over photoactive molecules and their corresponding properties as described above, other approaches involve combining different types

of stimuli to independently address two or more stimuli-responsive components.^{82,83} For example, combining light and redox potential to regulate material properties is an attractive direction since choice of redox potential as a stimulus is compatible with the fabrication of real devices.⁸² Moreover, the combination of light and redox potential could be employed to modulate the properties of electrocatalytic systems with integrated stimuli-responsive components especially when light alone may not be a sufficient stimulus due to limited penetration depth or poor stability of photostationary states of the photochromic moieties.⁸² Therefore, in this section, we focus on strategies for gaining orthogonal control over system properties through photoelectrochemical activation of assemblies containing both photochromic and redox-active components.

One feasible approach for accomplishing orthogonal photoelectrochemical switching of a system is the coupling of two subsets of azobenzene photoswitches, parent azobenzene (AZ), and *ortho*-tetrafluoroazobenzene (F4) in molecular dimers.⁸² These dimers can be switched through a series of four states: $E_{\text{AZ}}E_{\text{F4}}$, $E_{\text{AZ}}Z_{\text{F4}}$, $Z_{\text{AZ}}Z_{\text{F4}}$, and $Z_{\text{AZ}}E_{\text{F4}}$ conformations, with respect to the *azo* bond of each photochromic moiety. Bléger and co-workers utilized this type of system to demonstrate selective light activation of three of these mentioned modes, while an applied potential could be used to access the fourth mode.⁸² Specifically, switching between the EE_{F4} and EZ_{F4} states could be induced by exposure to visible light ($\lambda_{\text{ex}} > 500$ nm), and the EZ_{F4} -to- ZZ_{F4} transformation was accessible through irradiation with a 350-nm excitation wavelength. However, transitions between the ZZ_{F4} and ZE_{F4} states were only possible through an applied redox potential. The combination of two stimuli resulted in distinct advantages for overall system control. For instance, light as a stimulus allowed for high spatiotemporal resolution with good selectivity, while the electron-induced formation of the fourth state could be performed quantitatively. Therefore, coupling of parent azobenzene and *ortho*-tetrafluoroazobenzene represents a pathway to achieve orthogonal control over the isomerization of azobenzene derivatives using light and redox potential. This combination of stimuli is a relatively uncommon approach for gaining orthogonal control over azobenzene-based materials, but it will definitely expand the current toolset for tuning material properties of these systems.

Rather than coupling two different azobenzene derivatives to achieve orthogonal photoelectrochemical control over the system's properties, a conceptually distinct method is to combine more than one class of switchable molecule within the same platform. For instance, azobenzene could act as a well-established light-responsive entity, while redox-active viologen derivatives could be used as an additional stimuli-responsive moiety (Fig. 6).⁸³ In this direction, Scherman and co-workers investigated orthogonal switching of supramolecular homo- and heteroternary complexes involving a cucurbit[8]uril (CB[8]) host with viologen and azobenzene guests.⁸³ In this system, methylviologen (MV) exhibited binding with CB[8] in either its reduced (MV^{+} , existing as a dimer) or oxidized (MV^{2+}) forms; however, azobenzene could only bind to CB[8] as the *trans*-isomer (Fig. 6).⁸³ As described before, the transition between *trans*- and *cis*-azobenzene can be accomplished using two different excitation wavelengths (i.e., UV and visible light).⁸³ At the same time, transitions between oxidized and reduced homoternary complexes between CB[8] and two methylviologen molecules could be achieved by an applied redox potential. In contrast, formation of a heteroternary complex

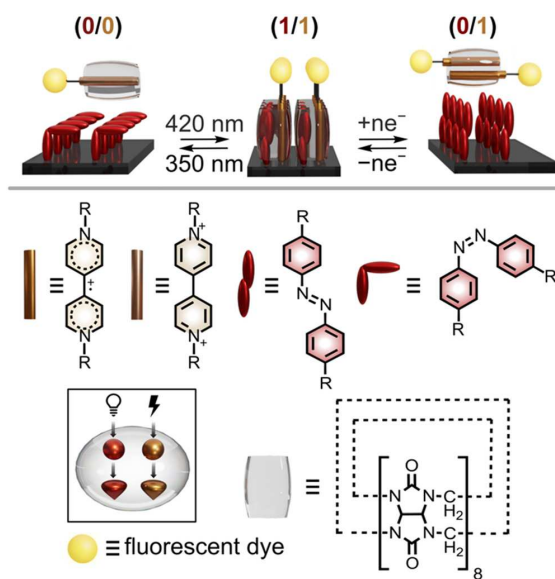


FIG. 6. A schematic representation of SAMs modified with azobenzene moieties (red) for selective binding of a methylviologen-cucurbit[8]uril host-guest complex $[\text{CB}[8](\text{MV}^{2+})]$, gray capsule with gold rods. Irradiation with visible light results in formation of *trans*-azobenzene, which binds to $\text{CB}[8](\text{MV}^{2+})$. Reduction of the methylviologen molecules (gold rods) results in dissociation of the azobenzene- $\text{CB}[8](\text{MV}^{2+})$ complex and formation of $\text{CB}[8](\text{MV}^{+})_2$. Adapted with permission from Tian *et al.*, Nat. Commun. 3, 1207 (2012). Copyright 2012 Springer Nature.⁸³

between $\text{CB}[8]$, methylviologen, and *trans*-azobenzene was induced by irradiation with a 420-nm excitation wavelength to promote *cis*-to-*trans* isomerization of azobenzene and initiate the complexation with $\text{CB}[8]$.⁸³ As shown in Fig. 6, three independent states could then be orthogonally addressed: $\text{CB}[8](\text{MV}^{2+})$, $\text{CB}[8](\text{MV}^{+})_2$, and $\text{CB}[8](\text{MV}^{2+})(\text{trans-azobenzene})$. This orthogonally controlled system was then applied to control the surface wettability of self-assembled monolayers (SAMs) in a logic-gated fashion. By functionalization of the SAMs with azobenzene groups and subsequent submersion in a solution of $\text{CB}[8](\text{MV}^{2+})$, which was coupled with a fluorescent tag for visualization, the water contact angle could be alternated based on formation of the heteroternary $\text{CB}[8](\text{MV}^{2+})(\text{trans-azobenzene})$ complex as a result of the positive charge from MV^{2+} .⁸³ Irradiation with UV light to form *cis*-azobenzene disrupted the complex and restored the original water contact angle of the material. Therefore, photoredox control of supramolecular complexes represents a pathway to amplify external stimuli into macroscopic property changes of a material.⁸³ Notably, coupling of $\text{CB}[8]$ hosts with viologen derivatives and phenylpyridine as guests has also been explored for light- and pH-switchable supramolecular complexes, illustrating the possibility for tailoring supramolecular systems to respond to a variety of stimuli.¹¹⁰

Orthogonal control through alternative stimuli

While light and redox potential are two of the most extensively utilized stimuli for orthogonal control over material properties,

changes in pH, temperature, or addition of metal salts are less studied avenues to explore orthogonal switching capabilities.^{66,84–86} Combinations of the mentioned stimuli in addition to light or redox potential are advantageous since they have been used to demonstrate quantitative switching between states.⁸² That is, addition of stoichiometric amounts of reagent (e.g., acid, base, or metal salts) or heating to a particular temperature can result in a high conversion between two states that cannot always be achieved using light alone.^{66,84–86} Moreover, utilization of alternative stimuli allows for control over stimuli-responsive behavior using experimental setups or reagents that are readily accessible. As a result, studies of pH-, temperature-, or ion-sensitive molecular fragments has yielded switchable ligands for control of the catalytic activity of organometallic complexes,⁸⁴ pH- and light-mediated electronic logic gates,⁸⁵ and polymers exhibiting selective aggregation based on a combination of stimuli.⁸⁶

One of the main and attractive goals in the field of photochromic compounds is to achieve orthogonal control of more than one catalytic process which could be mediated by a single active molecule (i.e., switchable catalysis).^{2,84} A conceptual approach to reaching this goal is the design of molecules with switchable ligating properties allowing for alteration of the environment around catalytically active sites.⁸⁴ For instance, the electronic structure around the metal center could be altered by changing the electron donating ability of redox-active ligands.^{111,112} In addition, interactions between a substrate and a catalytically active metal center can be regulated using stimuli-responsive molecules which undergo significant structural rearrangement upon photoisomerization, thereby altering the sterics of the coordination sphere.¹¹³ Such multifunctional ligands have been prepared by Dielmann, Breher, and co-workers, as shown in Fig. 7.⁸⁴ In their studies, coupling of a redox-active ferrocene-containing ligand with a Brønsted-basic pendant group allowed for switching of catalytic activity through either redox potential or pH alteration.⁸⁴ In particular, a [3]dioxaphosphaferrocenophane ligand was used to explore Rh-catalyzed hydrosilylation of alkynes (Fig. 7).⁸⁴ Remarkably, the catalytic behavior of the Rh-[3]dioxaphosphaferrocenophane complex not only could be controlled orthogonally but also resulted in orthogonal outputs: oxidation of the ferrocene moiety resulted in increased

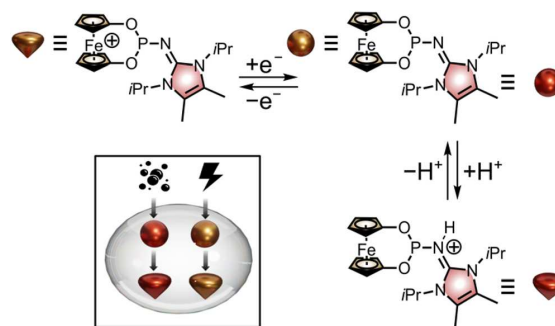


FIG. 7. Structure of a redox- and pH-sensitive [3]dioxaphosphaferrocenophane ligand coordinated to a Rh-based catalyst to promote hydrosilylation reactions. The ferrocene unit (gold) undergoes reduction and oxidation events under an applied potential, and the Brønsted-basic pendant group (red) undergoes reversible protonation upon addition of acid. Adapted with permission from Birenheide *et al.*, Chem. Eur. J. 27, 15067–15074 (2021). Copyright 2021 John Wiley and Sons.⁸⁴

conversion for the hydrosilylation of 1-hexyne, and protonation of the pendant group resulted in a significant change in selectivity of the hydrosilylation reaction. In particular, addition of acid to the reaction mixture resulted in formation of almost exclusively one particular isomer as a product, whereas the same reaction conducted without the addition of acid produced a mixture of three isomers. Therefore, multiple stimuli could be used to tailor different aspects of the same organic reaction, which foreshadows the use of stimuli-responsive ligands for the design of multipurpose catalysts.⁸⁴

A completely different direction focuses on the use of light and pH as stimuli to control the properties of single-molecule electronics, such as the rectification (i.e., direction of current flow) of molecular diodes and wires.^{85,114–116} For example, Yu and co-workers combined a proton-sensitive pyridinoparacyclophane moiety with a light-activated diarylethene unit to generate a single-molecule AND logic gate (i.e., a positive output resulting from two or more positive inputs).⁸⁵ To construct the AND logic gate, a single molecule composed of diarylethene and pyridinoparacyclophane units was anchored between two gold electrodes. In this logic gate, a high conductivity state could be achieved upon exposure of the prepared electrodes to UV light resulting in formation of the closed (conjugated) diarylethene functionality, and a low conductivity (non-conjugated) state was promoted upon exposure to visible light or acid.⁸⁵ As a result, a series of states with intermediate conductivity values could be accessed through addition of acid without visible light irradiation. The reported ability to transition between multiple states based on input from two stimuli (i.e., light and pH alteration) allowed for construction of a molecular AND logic gate in which two positive inputs (pH and light) resulted in one positive output (conductivity). Specifically, the highest conductive form resulted from exposure to a combination of UV excitation and basic conditions, while the lowest conductive state was achieved upon exposure to visible light and addition of an acid. These studies are very promising steps to advance the area of single-molecule electronics, since construction of molecular memory devices, for example, will likely rely on modulation of electric current for integration in real electronic platforms.⁸⁵

Although spiropyran and diarylethene derivatives have been the subject of several studies involving multi-stimuli-responsive behavior, very little work has been done to incorporate these two classes of compounds within a single system.⁶⁶ The lack of exploration in this direction could be attributed to the similar changes in absorbance profiles upon photoisomerization of these classes and, therefore, similar excitation wavelengths necessary to promote their photoisomerization.⁶⁶ However, the variety of stimuli that could be utilized to control a system containing both spiropyran and diarylethene units makes them promising candidates to achieve orthogonal switching.⁶⁶ In this direction, Shustova and co-workers integrated spiropyran- and diarylethene-based linkers within the same platform, a metal-organic framework (MOF), and demonstrated orthogonal switching promoted through exposure to heat or light as the stimulus.⁶⁶ Both spiropyran and diarylethene moieties could be activated using a 365-nm excitation wavelength, but elevated temperatures in combination with the addition of polar solvents resulted in selective activation of only spiropyran moieties.⁶⁶ In addition to developing the first example of a photothermo-chromic spiropyran- and diarylethene-based framework, these studies shed light on the fundamental interactions between distinct classes of chromophores (e.g., resonance energy transfer modulation),

which will pave the way for better understanding of how to control energy transfer processes in a multi-chromophore system, allowing for the design of stimuli-responsive molecules and platforms with adaptive behavior.⁶⁶

Rather than initiating the isomerization of a molecule through distinct external stimuli as described above, a conceptually different approach is to design monomers or ligands with multiple binding sites which could be selected based on an applied stimulus (Fig. 8).⁸⁶ That is, self-assembly processes could be controlled by external stimuli if the subunits possess more than one possible binding motif (e.g., metal-ligand binding, ion pairing, or π - π stacking). For instance, solvent polarity, temperature, or presence of metal salts could all be used as variables to promote self-assembly through a specific binding mode, resulting in materials with variable morphologies.⁸⁶ For example, Schmuck and co-workers designed a heteroditopic monomer possessing terpyridine and guanidiniocarbonyl pyrrole carboxylate functionalities which could be switched to form cyclic oligomers, globular

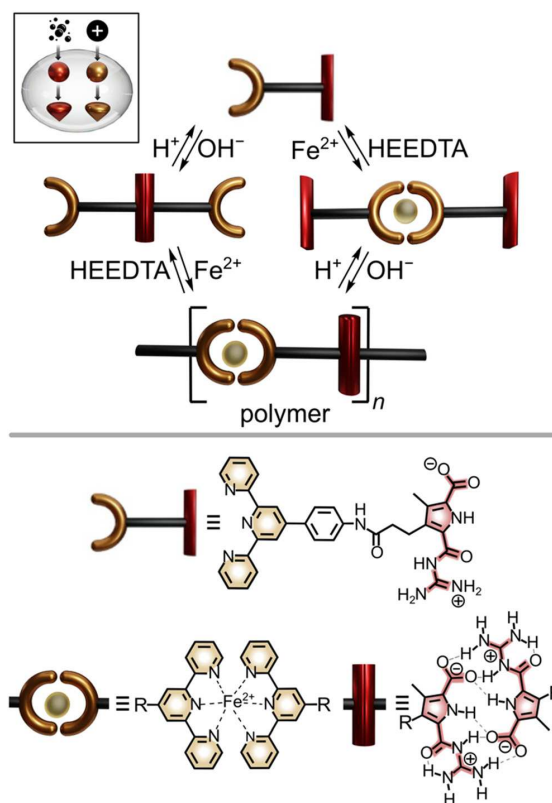


FIG. 8. Self-assembly of a heteroditopic monomer resulting in either cyclic oligomers or linear metallopolymers based on alternation of pH and presence of metal cations. Addition of metal cations promotes metal-ligand binding by the terpyridine functionality (yellow), and changes in pH modulates ion pairing of the guanidiniocarbonyl pyrrole carboxyl groups (red). Adapted with permission from Gröger *et al.*, *J. Am. Chem. Soc.* **133**, 8961–8971 (2011). Copyright 2011 American Chemical Society.⁸⁶

aggregates, or linear polymers by either addition of metal cations or changes in pH (Fig. 8).⁸⁶ In particular, design of the monomer such that it could undergo metal-ligand binding or ion pair formation allowed for selection of the self-assembly process. For example, addition of metal ions to promote the metal-ligand binding mode resulted in formation of a metal complex possessing two monomers as ligands (Fig. 8).⁸⁶ After formation of the metal complex, self-complementary ion pairing of the remaining guanidiniocarbonyl pyrrole carboxylate zwitterions occurred, resulting in linear polymer formation. Moreover, the ion pair formation (i.e., formation of linear polymers) between the guanidiniocarbonyl pyrrole carboxylate zwitterions could be controlled through addition of acid or base to affect the net charge of the molecules. The resulting linear polymers could undergo association in concentrated solutions to form globular aggregates. As a result, the system could be switched through four states, including monomers, cyclic oligomers, linear polymers, or globular aggregates, based on the presence of metal ions, concentration, or pH (Fig. 8).⁸⁶

Orthogonal switching by more than two stimuli

Based on the nature-inspired examples of materials relying on inputs from multiple stimuli (e.g., motor neurons), it is reasonable to project that the next generation of functional materials will utilize more than two independent stimuli at a time.^{87,88} While the majority of studies up to this point focus on only one or two types of stimuli-responsive units which can be switched between two or three states possessing distinct properties, careful design and combination of multiple stimuli could result in systems capable of switching between up to six independently addressable states.⁸⁷ For instance, Samoc, Humphrey, and co-workers developed a binuclear ruthenium alkynyl complex possessing a diarylethene-based bridge exhibiting nonlinear optical properties that could be switched using pH, light, or redox potential through six distinct states (Fig. 9).⁸⁷ To achieve switching between six states, the three components of the studied metal complex (i.e., alkynyl ligands, diarylethene-based bridging unit, and metal centers) were each be regulated based on a unique stimulus. Specifically, addition of acid facilitated conversion between alkynyl and vinylidene ligands. In contrast, exposure to appropriate excitation wavelengths induced photoisomerization of the diarylethene bridge, and an applied potential could cause metal-centered redox events to occur (Fig. 9). The combination of these three switchable components resulted in six total states with distinct features, such as two-photon absorption, saturable absorption, or inactive nonlinear absorption in specific spectral ranges. The mentioned changes in nonlinear absorptivity upon exposure to an appropriate stimulus can be applied in sensing technologies or for the selective modification of the propagation characteristics of laser beams in optical devices.⁸⁷

One of the recurring challenges in the design of systems responding to more than two stimuli is the complex and labor-demanding synthetic routes for both molecular switches and the systems in which they are integrated.⁸⁸ For this reason, single-component systems exhibiting orthogonal responses to multiple stimuli are especially interesting since they offer synthetically accessible and scalable pathways for stimuli-responsive material preparation.⁸⁸ In this direction, carefully designed monomers composed of three stimuli-responsive building blocks have been used to demonstrate orthogonal switching of supramolecular polymers by four independent stimuli: light, temperature, pH, and ionic strength.⁸⁸ In particular, a benzene-1,3,5-tricarboxamide

core facilitated hydrogen bonding interactions that promoted self-assembly or aggregation processes. In order to gain control over the mentioned self-assembly processes, the benzene-1,3,5-tricarboxamide core was decorated with photochromic azobenzene functionalities, thermoresponsive octa(ethylene glycol) chains, and pH- and ionic-strength-responsive C-terminal lysine residues.⁸⁸ As a starting point, the described multi-stimuli-responsive monomers were dissolved in dimethyl sulfoxide, resulting in a homogeneous solution without aggregate formation. Upon addition of water, the hydrogen bonding interactions as well as the hydrophobic nature of the monomer drove the aggregation process to form extended fibers. However, aggregation could then be disrupted due to *E*-to-*Z* photoisomerization of the azobenzene moiety upon exposure to UV irradiation. The degree of aggregation (i.e., fiber length and total number of fibers) could be controlled by temperature since the octa(ethylene glycol) chains exhibited higher hydrophobic character at elevated temperatures, and, therefore, increasing the temperature of the solution resulted in an increased yield of aggregate formation. Furthermore, since the C-terminal lysine residue provided an exposed carboxylic acid and amine group at the periphery of the monomer, aggregation could be controlled through pH or ionic strength to alter the net charge of the monomer. For instance, charge-induced dissociation of the aggregates occurred at either very acidic (pH = 2.2) or basic conditions (pH = 12). As a result, the combination of four stimuli could be used to affect not only whether aggregates formed, but the size and degree of aggregation as well.⁸⁸ Most importantly, the described formation was achieved in a single-component system (i.e., only one monomer composed of multiple stimuli-responsive fragments), which foreshadows an elegant way to mimic the complexity of natural systems without employment of labor-demanding synthetic approaches.

As illustrated by the studies described above, strategic design of multicomponent assemblies which can be controlled through several external stimuli is a pathway to construct functional molecules and materials for diverse applications, including platforms for sequential diagnostic and therapeutic techniques,⁷⁹ programmable nanoscale electronic devices,⁸¹ “shape-shifting” polymers for soft robotics,⁴⁵ switchable catalysts,⁸⁴ and micropatterned surfaces for data encryption.^{33,81} The realization of these concepts, however, depends on the fundamental studies of multi-stimuli-responsive molecular switches and orthogonal control over more than one stimuli-responsive moiety in a single platform. For this reason, in our Review, we outlined the successful approaches toward achieving orthogonal material behavior utilizing more than six different classes of stimuli-responsive molecules (e.g., diarylethene, spiropyran, azobenzene, viologen, dihydroazulene, and various photolabile protecting groups) integrated in a variety of molecular and supramolecular host systems. The highlighted studies are the first steps toward achieving noninvasive control over material properties including conductivity,⁸⁵ fluorescence,⁴⁶ morphology,⁴⁴ nonlinear optical behavior,⁸⁷ host-guest binding interactions,⁸³ and surface wettability.⁸³ Furthermore, on-demand removal of protecting groups to expose reactive functional groups or catalytically active sites has resulted in tunable polymerization reactions,⁷⁸ selective treatments against bacterial infections,⁸⁰ and tailorable DNA-based catalysts.³⁹

The highlighted studies uncovered numerous design principles that have aided in the development of materials with orthogonally controlled properties; however, there are still fundamental questions to be answered and practical challenges to be addressed before these

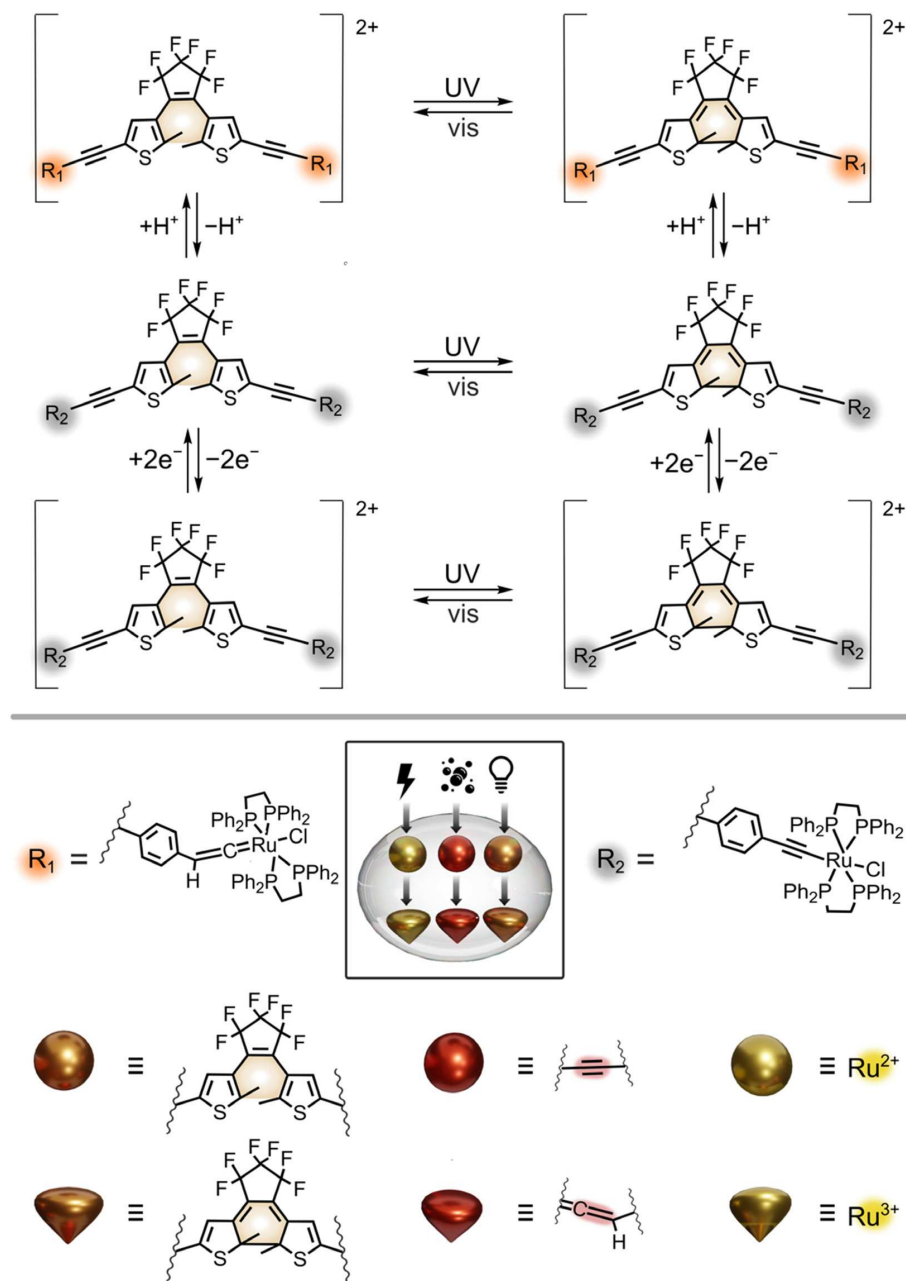


FIG. 9. (Top) Structures of a diarylethene derivative bridging two Ru-based organometallic complexes. Exposure to UV irradiation causes photoisomerization of the diarylethene core to the closed form. Addition of acid causes conversion between alkynyl and vinylidene ligands, while an applied redox potential can be used to control the metal oxidation state. (Bottom) Structures of the alkynyl- and vinylidene-containing Ru complexes (gray and orange, respectively). The different forms of the diarylethene core, alkynyl ligand, and Ru metal center before and after exposure to the appropriate stimulus are shown in gold, red, and yellow, respectively. Adapted with permission from Green *et al.*, *Angew. Chem., Int. Ed.* **48**, 7867–7870 (2009). Copyright 2009 John Wiley and Sons.⁸⁷

materials can be integrated into real, accessible devices. For example, the successful combination of more than one stimuli-responsive molecule into one platform is based on acquiring a fundamental understanding of how the selected molecules could interact with each other or with the host matrix and how such interactions could affect the molecules' switching ability. Studies of these interactions will require both theoretical modeling and experimental techniques to shed light on switching mechanisms of integrated stimuli-responsive moieties, which could be highly sensitive to the molecular environment or could result in a loss of selectivity if interactions occur (e.g., energy or charge transfer between stimuli-responsive molecules). Moreover, systematic tuning of the molecular switches themselves must be done to ensure high photostationary states (i.e., a high conversion from one state to another upon exposure to a particular stimulus) in order to achieve truly significant and controllable changes in material properties. Understanding the behavior of integrated stimuli-responsive moieties is especially important for studies involving multiple excitation wavelengths, redox potential, changes in pH, or elevated temperatures that could be utilized for orthogonal control of the system properties. Furthermore, the design of systems that harness the potential of coupling less frequently studied external stimuli such as mechanical stress^{117,118} with any of the aforementioned stimuli could significantly broaden the pool of practical applications for materials with orthogonally controlled performance. Recent advances utilizing mechanical force in combination with an excitation wavelength to promote isomerization of widely studied classes of photochromic molecules, such as stilbene¹¹⁷ or diarylethene¹¹⁸ derivatives, provide a promising foundation for designing materials with properties that could be orthogonally controlled through pressure and light, for instance.^{117,118} In particular, the coupling of distinct mechanochromic and photochromic units could be a pathway toward selective stress sensors, mechanical data encryption methods, or molecular hinges, which are intriguing directions to pursue.^{117,118} In addition to the discussed fundamental questions, practical challenges including the production of stimuli-responsive thin films on a scale suitable for device fabrication must be addressed. In this direction, filling the current gap between chemistry and engineering is a critical step.

Thus, this Review only highlights the exciting directions in the relatively young and rapidly expanding field of materials with properties that can be controlled through orthogonal stimuli while pointing out the gaps in fundamental knowledge that will certainly be filled through upcoming studies. The efforts of inorganic, organic, and physical chemists combined with the achievements of materials scientists and engineers will continue to forge new pathways to utilize orthogonal stimuli to impact existing and new areas including photopharmacology,^{80,105} nanotechnology,^{41,81,85,119} optoelectronics,^{55,87} and biomimetics.^{39,77,120} While the full potential of orthogonal switching is largely unexplored today, the aforementioned studies outlined the scientifically exciting directions that will continue to grow with time to bridge the synthetic and natural realms.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Grace C. Thaggard and Buddhima K. P. Maldeni Kankanamalage contributed equally to this work.

Grace C. Thaggard: Visualization (supporting); Writing – original draft (equal); Writing – review & editing (equal). **Buddhima K. P. Maldeni Kankanamalage:** Visualization (equal); Writing – original draft (equal); Writing – review & editing (supporting). **Kyoung Chul Park:** Visualization (supporting); Writing – original draft (supporting); Writing – review & editing (supporting). **Johanna Haimerl:** Visualization (equal); Writing – review & editing (supporting). **Roland Fischer:** Supervision (equal); Writing – review & editing (supporting). **Natalia B. Shustova:** Conceptualization (lead); Funding acquisition (lead); Project administration (lead); Supervision (equal); Writing – original draft (equal); Writing – review & editing (lead).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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