



The Vibrant Interplay of Light and Self-Reporting Macromolecular Architectures

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Inspired by nature, notable efforts have been made towards the exploration of self-reporting polymers within the last decades. Whereas the majority of the previously reported self-reporting polymers deliberately relies on a diverse set of mechanisms triggered via different stimuli (e.g., mechanical, thermal, pH, solvation, light, and chemical amongst others), light plays a ubiquitous role not only as a remote trigger, but also as non-destructive readout signal for the practical applications of self-reporting polymers. Due to the ever-growing interest within the respective field (e.g., load bearing materials, nanotechnology, biomedicine, or theranostics), herein a synthetic overview is presented with the aim to provide an informative perspective on challenges facing the vibrant interplay of light and self-reporting macromolecular architectures.

of responding to exo- or endogenous triggers has been accelerated. Various stimuli-responsive properties ranging from sensing to adoptive behaviors have been envisioned by using biological systems as the benchmark.

One could perhaps argue that the most promising stimuli-responsive behavior is the ability of materials to self-heal;^[4,5] nevertheless, modern science and materials engineering share the view that a new generation of advanced stimuli-responsive polymers, for example, self-reporting (also termed self-sensing or self-monitoring) polymers,^[6,7] will fuel world security (such as against COVID-19 pandemic)^[8] and human welfare. Indeed, self-reporting is an umbrella term used for polymer materials

which are capable of showing a measurable, often visible indication of the conditions they have been subjected to either in bulk or solution. The human skin as a complex natural self-reporter has been used as an inspiration to develop self-reporting polymers that sense and reports changes in their surrounding environment. In fact, polymeric materials with self-reporting (i.e., self-diagnostic) properties^[9] can not only minimize the demolition of resources, but also facilitate an effective and accurate assessment of state-of-health. Accordingly, diverse self-reporting smart materials^[7] with unique operating mechanisms have been developed, which are implicitly indicating the aforementioned transformations in a visible manner by changing color, fluorescence, or chemiluminescence (CL). Notably, the plethora of stimuli responsive triggers is very broad including chemical, electrical, and mechanical stimuli, and thus underpinning the emergence of self-reporting polymers.^[7] While mechano-responsive^[10] and thermally induced^[11] self-reporting polymers are considered as the most established ones, light-triggered transformations are receiving a growing interest. This is attributed to the ideal stimuli mode of light due to its instant input/removal, remote control, wavelength variation, non-invasive excitation with enhanced penetration depths at low energies in the visible light range (400–800 nm), and spatiotemporal control.^[12]

In a similar manner to biological components, which usually serve more than one purpose, light as direct output of a chemical reaction, that is, CL,^[13,14] offers also a self-reporting characteristic. Particularly with high sensitivity resulting from no need of an external light source, CL can reduce light scattering, improve signal-to noise ratio and detection sensitivity, and expand the linear dynamic range.^[15,16] In view of these considerations, this talent article will present a critical literature survey

1. Introduction

Mimicking functions of natural materials is a beneficial endeavor to expand applications in the fields of chemistry and materials sciences.^[1] Indeed, the recent decade has witnessed the development of advanced soft-matter materials^[2] with unprecedented properties, and thus the evolution of technologies towards stimuli-responsive materials^[3] capable

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DOI: 10.1002/macp.202100057

on the interplay between light and self-reporting macromolecular architectures with an inclusive attempt of summarizing recent advancements in synthesis techniques, fundamental and potential properties. Accordingly, polymers that elicit a visible output in a self-reporting fashion upon a defined light trigger will be initially discussed. We subsequently focus on polymers that can radiate light (i.e., CL) as a result of coupling directly to chemically induced reactions (such as oxidations). In each part, the molecular design of the macromolecular architectures and their experimental development in addition to the various strategies for self-reporting process will be described. Finally, current challenges and limitations are highlighted in order to ensure the successful transfer of self-reporting research concept from the laboratory to the real world. Importantly, it is important to note that other aspects of CL, such as those related to mechanochemistry,^[17] are well known and important fields, but they will not be elaborated on herein.

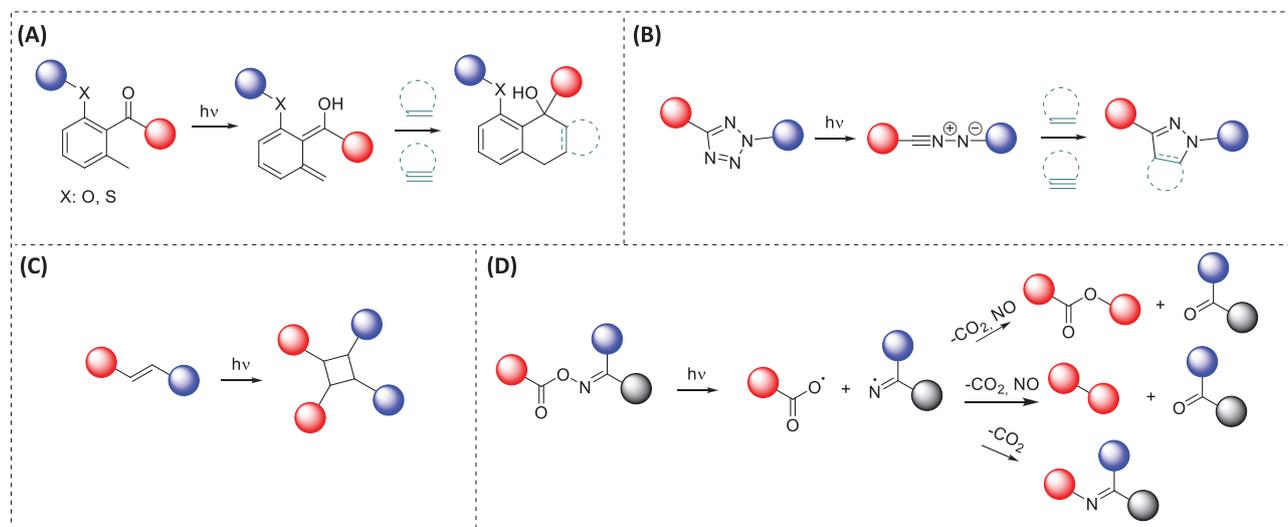
2. Light as a Trigger Toward Self-Reporting Polymers

As previously mentioned, light is a popular choice as exogenous stimulus for chemical transformations over other chemical and biological processes as a result of spatiotemporal control in addition to operational simplicity without the use of toxic metal catalysts and ligands.^[18] Indeed, the interaction of matter with light has fascinated scientists for centuries. Accordingly, the field of polymer science has not been immune to this enchantment. Respectively, the use of light to produce new macromolecular architectures and materials thereof in novel controlled ways is rapidly evolving to more sophisticated systems. In this context, light-induced ligation techniques^[19] are an important class of photochemical reactions^[20] employed not only for macromolecular design,^[21] but also for surface

modification,^[22] fabrication of 3D structures via direct laser writing,^[23] as well as in vivo labeling and tracking.^[24] Consequently, between the numerous available strategies,^[7] light-triggered self-reporting polymer systems have become quite attractive. Whereby the choice of the appropriate technique is driven by the requirements of the specific application, the driving force for the photochemically induced self-reporting behavior of polymer materials can be generally categorized as follows: light-induced i) (cyclo)addition (**Scheme 1A,B**, respectively [4 + 2] and 1,3-dipolar cycloadditions), ii) dimerization based on a [2+2] cycloaddition (**Scheme 1C**), and iii) cleavage (fragmentation, **Scheme 1D**), respectively. A note to the reader: Other useful photoactive transformations, such as the light-induced isomerization of photochromic functional units, inter alia, azobenzene, spiropyrans, spirooxazines, diarylethenes, and fulgides also attracted interest but are beyond the scope of this review.

2.1. Self-Reporting Polymers via Light-Induced (Cyclo)Addition Reactions

Cycloaddition reactions are one notable group of intermolecular bond-forming processes that have been extensively employed in organic and polymer synthesis.^[28] The Diels–Alder reaction (i.e., the [4+2]-cycloaddition) as well as the 1,3-dipolar cycloadditions of nitrile imines (depicted in **Scheme 1 A,B**, respectively) are arguably two of the most studied examples of highly efficient light-induced cycloadditions as handle for self-reporting polymer materials.^[25] On the one hand, the attraction of the former pericyclic process, that is, Diels–Alder reaction, particularly photoenol chemistry, lies in its efficiency as well as in the orthogonality in the presence of other functional groups. A very important advantage of photoenol chemistry is the fact that in vitro generated reactive precursors should not be deactivated



Scheme 1. The photochemically induced techniques that are known to facilitate visible self-reporting behavior of macromolecular architectures: A) the Diels Alder reaction (e.g., exemplary [4 + 2] cycloaddition) of dienophiles with photoenols (i.e., photocaged dienes) which are formed in situ by the tautomerization of *o*-methylphenyl ketones or aldehydes;^[25–27] B) Nitrile imine-mediated tetrazole-ene cycloaddition (NITEC) as exemplary 1,3-Dipolar cycloaddition; C) dimerization based on a [2+2] cycloaddition reaction; and D) an exemplary light-induced fragmentation reaction, that is, the cleavage of *O*-acyl oxime ester derivatives, respectively.

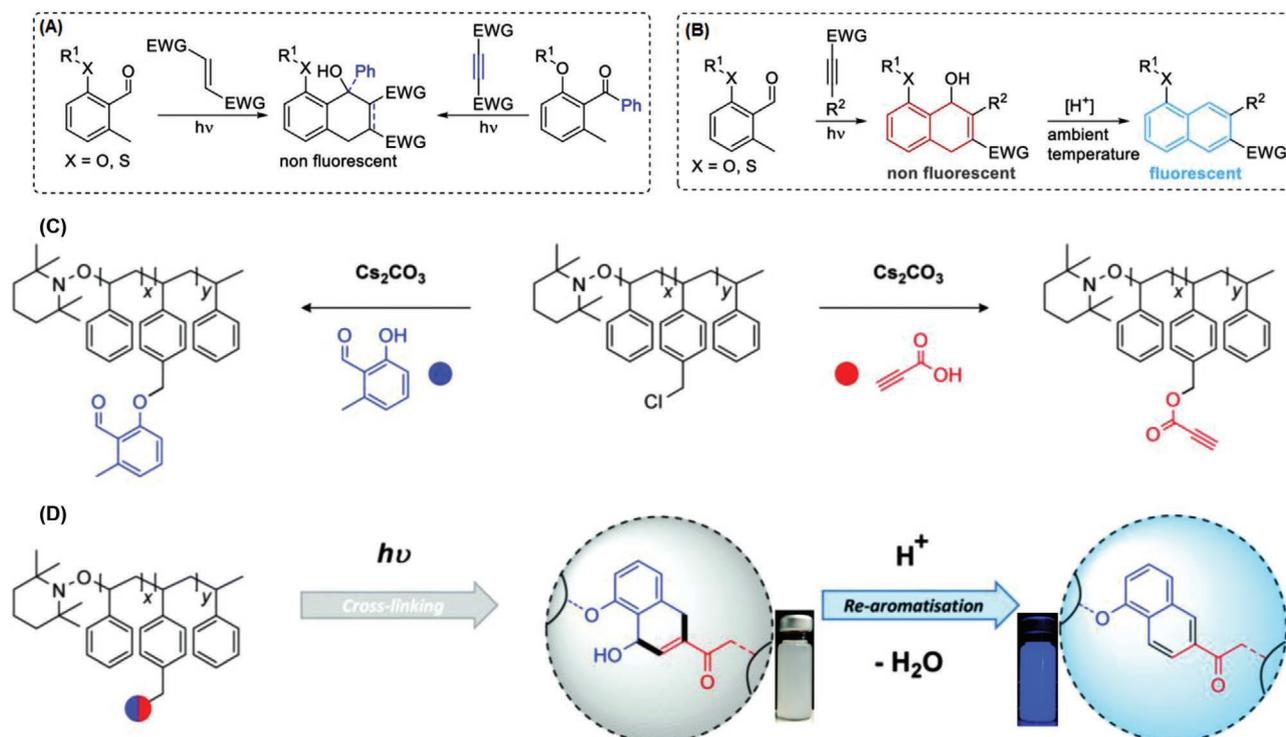


Figure 1. A) Diels–Alder reaction (i.e., the [4+2]-cycloaddition) using *o*-MBAs and electron-deficient alkenes or *o*-methylbenzophenones and alkynes. EWG: electron-withdrawing group. B) Light-induced ligation of *o*-quinodimethane (*o*-QDM) with gated fluorescence self-reporting. C) Synthesis of crosslinkable polymer precursors which are functionalized with the redshifted photocaged *o*-MBA (left, blue color) and electron-deficient terminal, non-symmetric alkyne derivative (right, red color). D) Synthesis of nano- and microspheres (possessing non-fluorescent 1,4-dihydronaphthalene moiety at each crosslinking point) from the functional prepolymers; and the subsequent generation of particles with on-demand acid-gated fluorescence. The photographs show the particles after addition of acid, observed under ambient light (left) and under 365 nm light (right). Reproduced with permission.^[27] Copyright 2020, The Royal Society of Chemistry. (C, D) Reproduced with permission.^[31] Copyright 2020, American Chemical Society.

after the irradiation procedure. The formation of the excited photoenol species is reversible and can be thus transformed into the electronic ground state. In this context, Barner-Kowollik and colleagues reported a light-triggered Diels–Alder reaction (shown in **Figure 1A**) for the conjugation of polymer building blocks containing *o*-methyl phenyl ketone and maleimide functionalities based on the photoinduced generation of photoenols from 2-methylbenzophenones.^[26] Besides, the application array of *o*-methyl benzaldehyde (*o*-MBA) derivatives as a fast and highly efficient tool spans from the spatially resolved surface modifications^[29] to light-triggered step-growth polymer synthesis.^[30] However, the limitation of *o*-MBAs and electron-deficient enes was the lack of a simple visual feedback that reflects the reaction progress and selectivity. Accordingly, a pro-fluorescent Diels–Alder product (i.e., 4-dihydro-1-naphtholes, **Figure 1B**) that converts on demand into a self-reporting fluorescent derivative (e.g., naphthalene) via catalytic dehydrative elimination reaction (in the presence of 10 mmol% *para*-toluenesulfonic acid) was recently developed by the same team, allowing for the fluorometric evaluation of the light-induced cycloaddition reaction.^[27] The conversion to the pro-fluorescent Diels–Alder product was directly followed by the disappearance of the UV–vis $n-\pi^*$ band at 320 nm of *o*-MBA together with the appearance of a new absorption band at 280 nm. Upon the on-demand dehydrative elimination, a new $n-\pi^*$ band at 345 nm and a fluorescence band at 420 nm was detected, corresponding

to the self-reporting fluorescent naphthalene derivative. The fact that the dehydrative elimination can take also place at ambient temperature in aqueous solution (e.g., in a buffer solution at pH 4.2) without the addition of a catalyst was crucially important considering any potential biological applications. Importantly, the fluorescence of the reaction is turned on after the photoligation ($\lambda_{\max} = 385$ nm, 20 min) accompanied with the controlled formation of a fluorophore, whereas previously reported ligation techniques directly lead to fluorescent products. Vitaly, the light absorption of the synthesized fluorophore has not weakened the photoligation via competitive absorption. Notably, no photobleaching or side reactions of the fluorophore were detectable. On the one hand, the introduced system enabled an efficient reaction at concentrations suitable for polymer post-functionalization or bioligation (0.5 to 50 mmol L⁻¹). On the other hand, the method could be of limited use since the synthesis of the essential functional alkyne linkers (particularly the heterobifunctional (nonsymmetric) alkyne substrates) was slightly tedious.

In subsequent work, the strategy was expanded for the development of acid-sensitive profluorescent nano-/microspheres in one step by crosslinking pre-synthesized low molecular weight polymers (e.g., poly(styrene-*co*-chloromethylstyrene) p(St-*co*-CMS) copolymer M_n of 2100 g mol⁻¹) prepared by nitroxide-mediated polymerization (NMP, **Figure 1C**). These were functionalized with the redshifted photocaged

o-MBA (shown in blue color in Figure 1C), which is capable of generating the reactive *o*-quinodimethane (*o*-QDM), and effective to undergo [4 + 2] cycloadditions with suitable dienophiles (e.g., electron-deficient terminal, non-symmetric alkyne derivatives).^[31] Consequently, the photochemically gated particle formation step (at $\lambda_{\text{max}} = 365 \text{ nm}$) yielded a material possessing a reactive, spring-loaded intermediate (i.e., hydroxyl containing 1,4-dihydronaphthalene moiety) at each crosslinking point (Figure 1D). Those moieties, upon exposure to a catalytic amount of acid (such as *para*-toluenesulfonic acid), subsequently underwent a rapid E1 elimination accompanied with dehydration step to yield a fluorescent naphthalene moiety. In similar manner to the preliminary example, the initial polymer did not show any fluorescent properties, and no undesired side reactions took place by competitive photon absorption reactions, while simultaneously the arising fluorescence after the acid addition allowed the self-reporting monitoring of the crosslinking process. Thus, the novel method emphasized, one more time, the power of exploiting modern synthetic photochemistry to impart specific properties, such as self-reporting, to polymer materials in a very sensitive and controllable manner.

On the other hand, the nitrile imine mediated tetrazole ene 1,3-dipolar cycloaddition (i.e., nitrile imine-mediated tetrazole-ene cycloaddition, NITEC, Scheme 1B) as irreversible method proceeds under full conversion of reagents at high reaction rates and without the need of a catalyst or additional reaction to deliver fluorescent cycloadducts (i.e., pyrazolines). Critically, the resulting cycloadduct can be tuned to suit functional needs by the choice of photochemically complementary dipolarophiles. Thus, the NITEC reaction not only ideally lends itself as self-reporting functionalization method due to the formation of a fluorescent product, but also as a photochemically driven polymerization strategy.^[32] Indeed, Yu et al. were the first ones who exploited this unique property and designed photoactivatable fluorescent self-reporting probes based on intramolecular photochemistry.^[33] In a proof-of-concept study, a series of protein-targeting taxoid–tetrazole conjugates were prepared by linking 7- β -alanyltaxol core with a tetrazole unit containing an *O*-allyl overhang at *N*-phenyl ring. Fluorescent pyrazoline adducts with fluorescence turn-on ratios as high as 112-fold for taxoid pyrazoline were formed upon photoirradiation

at 405 nm. Employed in living cells, the photoreaction triggers the fluorescence and the location of the protein-targeting polymer can be monitored in a self-reporting manner. In contrast, Barner-Kowollik and colleagues were the first ones who reported a facile approach for the preparation of self-reporting polymers by employing NITEC based polymerization of nonfluorescent photoreactive monomer systems (either AB^[32] or AA and BB,^[34] where A is a tetrazole unit and B is either maleimide and fumarate ene type unit) with simple visual feedback that allows for monitoring the step-growth polymerization reaction progress. While no fluorescence emission was observed for the initial reaction mixture, the poly(pyrazoline) derivatives exhibited a broad fluorescence emission between 470 and 670 nm (Figure 2). In addition, Delaittre and colleagues^[35] reported the synthesis and characterization of novel intrinsically fluorescent amphiphilic copolymers by utilizing the NITEC polymerization approach of monomers based on an AB structure with fumarate ene-terminated poly(ethylene glycol) (B type) that act as a chain-stopper. Finally, core–shell nanoparticles were prepared by a straightforward nanoprecipitation procedure, which were further elaborated as interesting candidates to generate self-reporting colloidal imaging probes.

The photoinduced crosslinking of polymers has been considered as a valuable approach to tune material properties such as solubility, viscosity, and optical properties.^[21] Accordingly, tetrazole ligation chemistry has been applied to visually monitor the formation of polymer networks.^[36] In order to accomplish this, well-defined α,ω -tetrazole-capped polymers were synthesized via reversible deactivation radical polymerization (i.e., reversible addition-fragmentation chain transfer polymerization) and further crosslinked under UV irradiation by a linker (i.e., trimalimide) via NITEC. Due to the precise control over photogeneration of the nitrile imines, the ligation points in the generated network were quantified in a self-reporting manner by monitoring the fluorescence intensity of the cross-linked product. Nonetheless, the latter could only be achieved by cleavage of the insoluble networks into soluble fragments suitable for analytical characterization. Since the initial number of ligation points remains unchanged after the cleavage, this method facilitated the detailed characterization of polymer networks, which so far has been often challenging due to the complexity of the network systems. Specifically, the latter aimed for the adoption of a

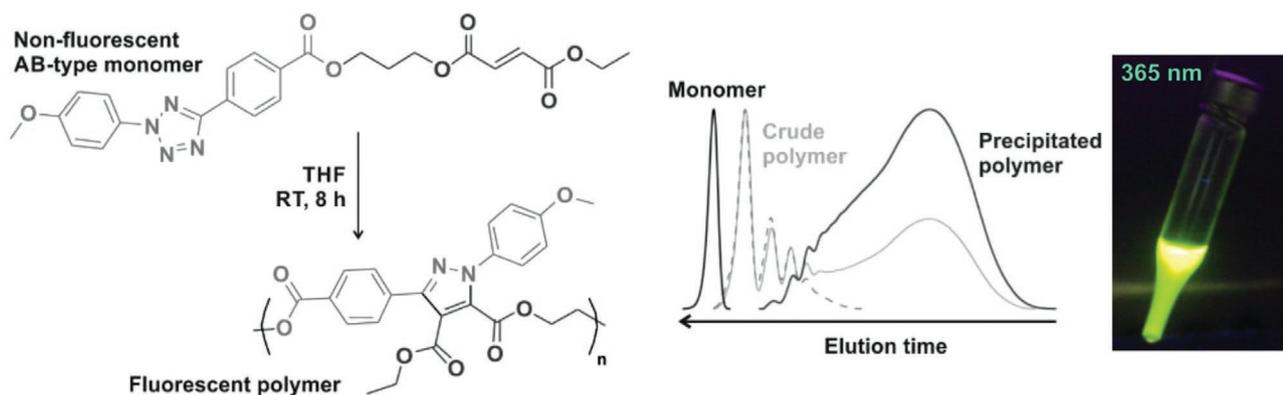


Figure 2. NITEC polymerization using non-fluorescent monomer of AB-type with simple visual feedback that allows for monitoring the step-growth polymerization reaction progress. Reproduced with permission.^[32] Copyright 2020, Royal Society of Chemistry.

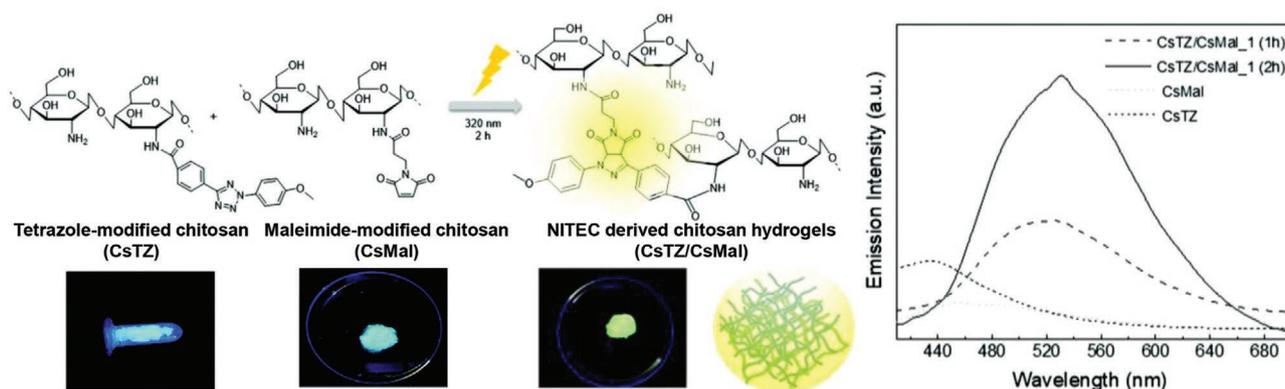


Figure 3. NITEC mediated assembly of tetrazole (CsTZ) and maleimide (CsMal) chitosan derivatives to deliver biocompatible chitosan hydrogels with self-reporting ability. Reproduced with permission.^[39] Copyright 2020, Royal Society of Chemistry.

fluorescence-based methodology enabling the quantification of ligation points in photochemically prepared polymer networks.

NITEC was also successfully used to crosslink complementary tetrazole and maleimide modified cellulose,^[37] nanocellulose,^[38] and chitosan^[39] derivatives into fluorescent hydrogel networks using light irradiation ($\lambda \approx 320$ nm). The fluorescent hydrogel products acted not only as self-reporting species (e.g., with an emission signal at ≈ 530 nm for chitosan-based hydrogels, as shown in **Figure 3**), easing their characterization and assessment of the reaction's efficiency, yet are also used to design traceable materials without the need for additional modification with fluorophores. Indeed, the intermolecular crosslinking process can readily be monitored by fluorescence spectroscopy using an excitation wavelength of 396 nm.

Furthermore, the photochemically induced NITEC reaction was employed to prepare narrow-disperse microspheres from pre-functionalized photoreactive polymers in the absence of stabilizer or initiator,^[40] which are inherently and highly fluorescent. Imaging via confocal fluorescence microscopy allowed confirmation of the uniform and inherent fluorescence of synthesized microspheres, while fluorescence spectroscopy was used to quantify the emission and excitation spectra of the isolated particles with an excitation centered ≈ 400 nm and an emission peak at 540 nm. Unfortunately, since the NITEC mediated crosslinking reaction proceeded via a step-growth mechanism and each individual tetrazole required photon absorption to generate the reactive nitrile imine for crosslinking, the above-mentioned reactions that were performed at high concentrations have become noticeably cloudier, limiting penetration depth of light and thus limiting the reaction medium is irradiated as uniformly as possible. Nonetheless, the advantages of using the highly efficient NITEC reaction are numerous. Thus, aiming to mimic the function of proteins, yet utilizing the synthetic ease of human-made polymers, the NITEC reaction has also been successfully implemented to monitor the intramolecular crosslinking of polymers into single chain nanoparticles (SCNPs).^[41] Generally, folding individual synthetic polymer chains at high dilution by means of multiple intra-chain (reversible or irreversible) bonding interactions produces the SCNPs. In fact, the SCNPs formation was originally carried out under very harsh conditions, still, orthogonal and click-chemistry techniques allowed mild reaction conditions, complex design

strategies, and upscaling of the synthesis.^[42] Nevertheless, due to their ultra-small size (≈ 10 nm in diameter), softness, and internal compartmentalization, SCNPs are highlighted as fundamental ingredient in the field of nanotechnology. While, a wide range of design strategies for SCNPs has been developed to adjust the properties of polymers and particles, notably, the SCNPs prepared via the intramolecular NITEC chemistry featured self-immolative azobenzene motifs, which exhibited redox induced degradability.^[41] This approach constituted a new class of fluorescent and self-immolative SCNPs, which represented a novel technology platform for their use in delivery and imaging applications.

As a note to the reader: Self-immolative systems are based on covalent groups tethered as linkers or spacers within a macromolecular architecture. Those functional groups, upon activation by a specific stimulus, undergo spontaneous intramolecular disassembling, in which they are broken down to their building blocks, and the compound of interest attached to them is released.

In a further case, by employing a pyrene-functionalized tetrazole, the activation of single-chain collapse was shifted into the critical visible light regime using irradiation between $\lambda = 410$ – 420 nm.^[43] In another example, Stenzel and colleagues reported the synthesis of fluorescent glyco-SCNPs from single glyco-polymer chains.^[44] Variable amounts of SCNPs (2.8, 6.0, and 9.3 wt%) were subsequently used for functionalization of nanodiamonds to obtain patchy surface structures. To achieve this, the nanodiamonds modified with fluorescent mannose-SCNPs were incubated with macrophage cells that express mannose receptors, and their successful internalization was observed with confocal fluorescence microscopy in self-reporting manner. In fact, the light sensitivity and lectin binding properties make these fluorescent, nontoxic, and bioactive hybrid particles a good candidate for bioimaging applications.

More recent examples of nitrile imine chemistry have taken advantage on the rediscovered reactivity of light derived nitrile imine derivatives with carboxylic acids, thus being essential only to introduce the tetrazole moiety to parent acid-functionalized polymer prior the folding process.^[45] The use of the less sophisticated carboxylic acid derivative instead of electron-deficient enes facilitated not only the preparation of inherently fluorescent SCNPs but also microparticles.^[40]

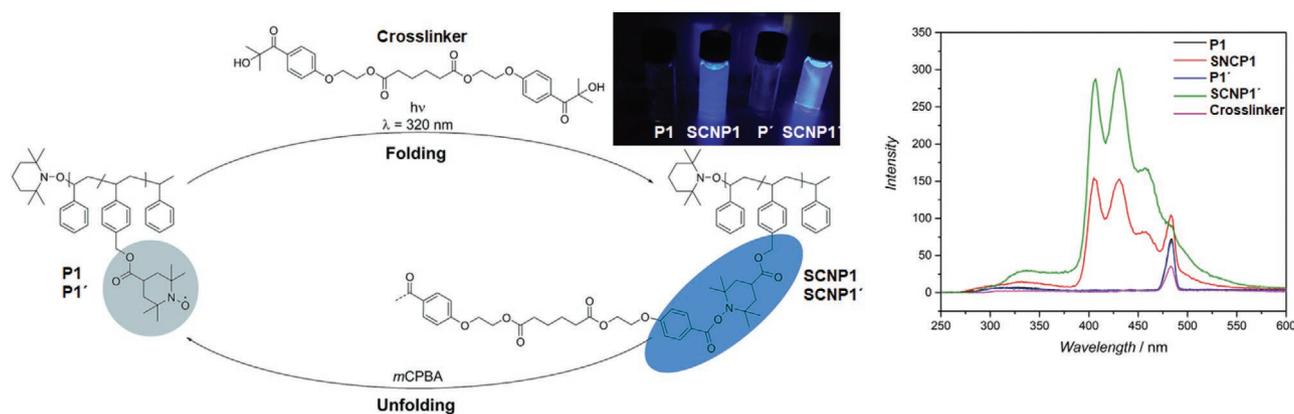


Figure 4. Left: The schematic representation of the self-reporting folding cycle of the nitroxide-containing polymer P1 with the bifunctional crosslinker. The folding is induced by UV-light ($\lambda = 320$ nm) resulting in the intramolecularly folded SCNPs, SCNP1 and SCNP1'. The unfolding of SCNPs was induced by *m*CPBA restoring the initial state. Right: The emission spectra ($\lambda_{\text{exc.}} = 240$ nm) of the polymers P1 and P1' as well as the crosslinker, in addition to SCNP1 and SCNP1', measured in DCM ($c = 0.2$ mg mL⁻¹). Reproduced with permission.^[46] Copyright 2018, Royal Society of Chemistry.

An alternative facile protocol for preparing self-reporting SCNPs was developed by employing the photoaddition of nitroxide radicals with a novel bifunctional crosslinker bearing a photoreactive functionality (i.e., α -hydroxyalkyl phenyl ketone) under mild UV irradiation ($\lambda_{\text{max}} = 320$ nm).^[46] While the nitroxide-containing polymer (M_n of 33 300 g mol⁻¹, \bar{D} of 1.3, P1 and P1' in Figure 4) exhibited no fluorescence in the unfolded state, folding in the presence of the crosslinker into SCNPs (e.g., SCNP1 and SCNP1') led to a broad emission between 380 and 550 nm (Figure 4). Unfolding the SCNPs under oxidative conditions (*meta*-chloroperbenzoic acid, *m*CPBA) resulted in a luminescence switch-off and the reestablishment of the initial precursor polymer. The luminescence of the system was restored by subsequently applying the same photoinduced reaction, resulting in the folding of the single-chain polymer. While, the state of the polymer folding was readily monitored in a self-reporting manner, the process itself required considerably low concentrations of 0.02 mg mL⁻¹, which does not only drastically limit the scalability of SCNPs synthesis, yet critically hinders the online monitoring of the reactions, that in turn is paramount toward improving the understanding of the SCNPs formation process.

2.2. Self-Reporting Polymers via Light-Induced Dimerization

In addition to the abovementioned light induced covalent interactions,^[47] photoinduced dimerization based on a [2+2] cycloaddition reaction (Scheme 1C) is particularly promising because it may form covalent bonds in the absence of a catalyst, while it is still reversible in nature using light.^[48] However, most of the dimerization processes are not compatible to be carried out in biological media, particularly in the presence of living cells, as they require activation by short-wavelength UV-light, and most importantly fail to be self-reporting.^[49] In the search for a reversible photo dimerization which the addition and cleavage can proceed under biologically benign irradiation conditions, Walther and colleagues^[50] introduced modularly

applicable, red-shifted and fluorescence enabled self-reporting photodynamic covalent crosslinker (Figure 5). In other words, a quaternized styrylpyrene (qStyPy) derivative was readily functionalized with (bio)macromolecules (via S_NAr reactions) and the [2+2] cycloaddition outside the harmful UV-regime, for example, with blue light ($\lambda = 470$ nm) in aqueous solution as well as on the material scale to form hydrogel model networks was performed. The kinetic profile of hydrogel formation showed a considerably slower cycloaddition (i.e., 71% of qStyPy was converted into the cycloadduct within 20 h of irradiation) compared to a molecular level reaction setup, which reached a steady state already within 1.5 min. Hence, it was evident that the [2+2] cycloaddition was highly dependent on the mobility of the qStyPy units due to the short-living triplet state. Despite that the system featured a broad emission in the far-red/near-IR (NIR) regime ($\lambda_{\text{em}} = 655$ nm), which in turn enabled to readily track the progress of the cycloaddition in a self-reporting manner, the authors have also underpinned the importance to investigate the potential toxicity of qStyPy units in biomedical applications, as it may intercalate into DNA due to its positive charge and its extended π -system.

Frisch^[51] and colleagues, have developed a green light (λ up to 550 nm) induced [2+2] cycloaddition of a halochromic system based on a styrylquinoxaline (SQ) moiety in solution (Figure 6A). The self-diagnostic phenomena took place by reporting the halochromism of a photoreactive unit that translates into its photoreactivity, allowing to reversibly switch a photoreaction on and off by varying the pH. To reveal the latter, each solution shown in Figure 6B was irradiated with the same wavelength (510 nm) and identical number of photons (1.23×10^{22}) to observe the change in reactivity. The obtained analytical data, for example, size exclusion chromatography (SEC), indicated that at acidic levels (pH 2) the reactivity decreased significantly, whereas it was not affected at higher pH values (pH > 2). In other words, at acidic pH it was possible to switch the reactivity off. Besides, the compact structure of the developed SQ moiety significantly enhances the solubility of the compound in aqueous media. Particularly, when SQ is compared to pyrene units that is usually required for visible light

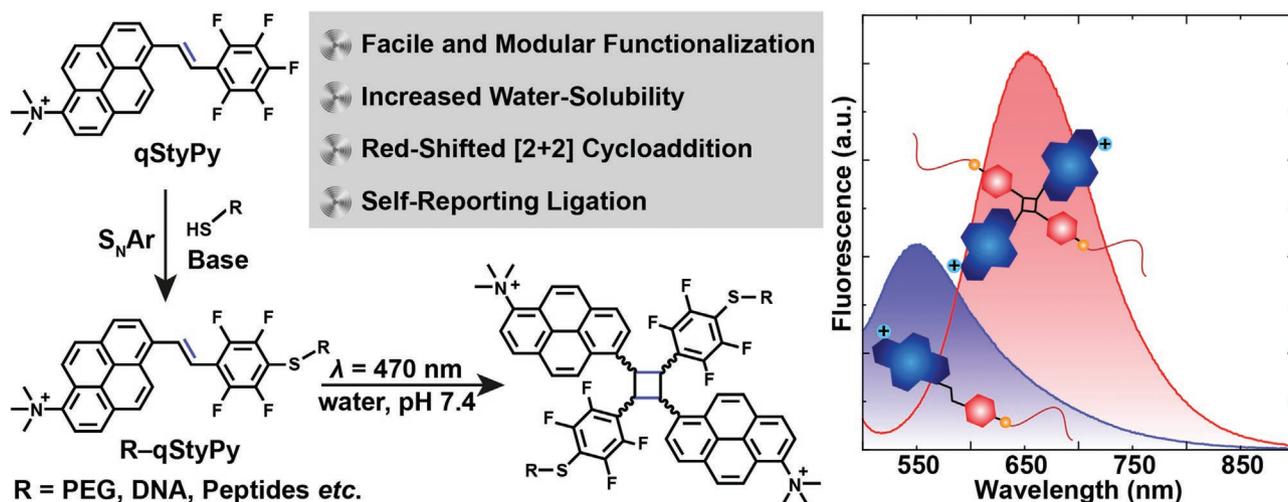


Figure 5. Schematic representation of the synthesis of modularly applicable, red-shifted, and self-reporting photodynamic covalent crosslinker (qStyPy), that performs [2+2] cycloadditions upon irradiation with 470 nm in water. The corresponding fluorescence spectra depicts the clean transformation from the starting material to the cycloadduct in a chemically selective fashion with a new emission maximum at $\lambda_{em} = 655$ nm. Reproduced with permission.^[50] Copyright 2021, Royal Society of Chemistry.

activated [2+2] photocycloadditions. Eventually, a poly(ethylene glycol) decorated with SQ (PEG-SQ, M_n of 3 000 g mol⁻¹, $D = 1.04$) was dimerized in aqueous solution under green light irradiation (400–510 nm with 9.29×10^{22} photons in water, $c = 10$ mg mL⁻¹) for 10 min. The SQ derivative featured a broad emission in the visible light regime ($\lambda_{em} = 450$ nm), whereas new absorbance bands appeared close to $\lambda = 250$ and 325 nm upon the irradiation process (Figure 6C). Such a change in the UV/vis spectrum is well-known to occur upon cyclobutane ring formation between two alkenes, which decreases the extent of the conjugated system. Thus, the presented technology served as a guiding principle to readout the state of cycloaddition reaction. Namely, the parent polymer was capable of emitting light, while in its [2+2] cycloadduct form the luminescence was silenced. The potential applicability of the system was demonstrated in the crosslinking of an 8-arm PEG to form hydrogels (≈ 1 cm in thickness) with a range of mechanical properties and pH responsiveness, highlighting the potential of the system in materials science. In point of fact, the authors envision the extension of the photoligation system to 3D laser lithography, drug delivery, and pharmacology. Particularly, cell-related studies are anticipated, where pH-dependent cellular responses are required to be mapped.

2.3. Self-Reporting Polymers via Photocleavage Reactions

Photocleavage reactions offer on-demand spatial and temporal control over system properties for designing tunable platforms, thus numerous applications ranging from deprotection of active substrates to photolithographic patterning of surfaces have been exploited.^[52] Most of the photocleavage reactions mainly rely on a few basic types of photolabile groups,^[53] *o*-nitrobenzyl,^[54] or coumarinylmethyl scaffolds being the most studied. Nevertheless, each type of photocleavable group has specific advantages and limitations for use in a given application. A common feature of these photocleavable scaffolds and

their respective cleavage reactions is that they all require high energy UV-light. However, short-wavelength UV radiation is not compatible with many applications, especially in biology and medicine, because it can induce adverse side reactions. Indeed, visible light labile groups are helpful in overcoming those obstacles by offering a versatile and elegant approach to endow polymers with unique properties for a very wide range of applications. Oxime esters (Scheme 1D)^[55] have long been known as efficient photocleavable scaffolds, whose cleavage occurs on the N–O bond leading to iminyl and acyloxy radicals that can undergo further fragmentation or decarboxylation reactions. Nevertheless, the chemistry of oxime esters has never been evaluated for gated fluorescence response until 2019, when the combination of visible light-induced chemistry and oxime ester derivatives was exploited to induce the formation of self-reporting single-chain folded structures via intrachain radical coupling of carboxyl radicals.^[56] The carboxyl radicals were generated via light-induced ($\lambda = 430$ –435 nm) fragmentation of pyrene-substituted oxime ester moieties along a polymer chain. CO₂ release from the carboxyl radicals leads to highly reactive phenyl radicals as an additional secondary species for chain compaction via homo and hetero-radical coupling events. The concomitant release of pyrene units after the light-induced fragmentation of the oxime ester moieties allowed to “switch on” the fluorescence of the initially non-fluorescent solution under UV irradiation at $\lambda_{exc} = 366$ nm. Whereas limitations such as folding in highly diluted media ($c = 20$ mg L⁻¹) or complex monomer and polymer synthesis need to be overcome for industrial purpose, this platform paves the way toward prospective biomedical, imaging, or sensor applications.

In another complementary example, Tuten^[57] and coworkers incorporated pyreneacyl sulfides via an Ugi four-part multi-component reaction, accessing self-reporting polymer scaffolds decorated with paramagnetic nitroxides (i.e., TEMPO) and profluorescent pyrene moieties (Figure 7). The TEMPO derivatives were placed in direct proximity to the pyrene moieties in order to trigger an efficient fluorescence quenching as

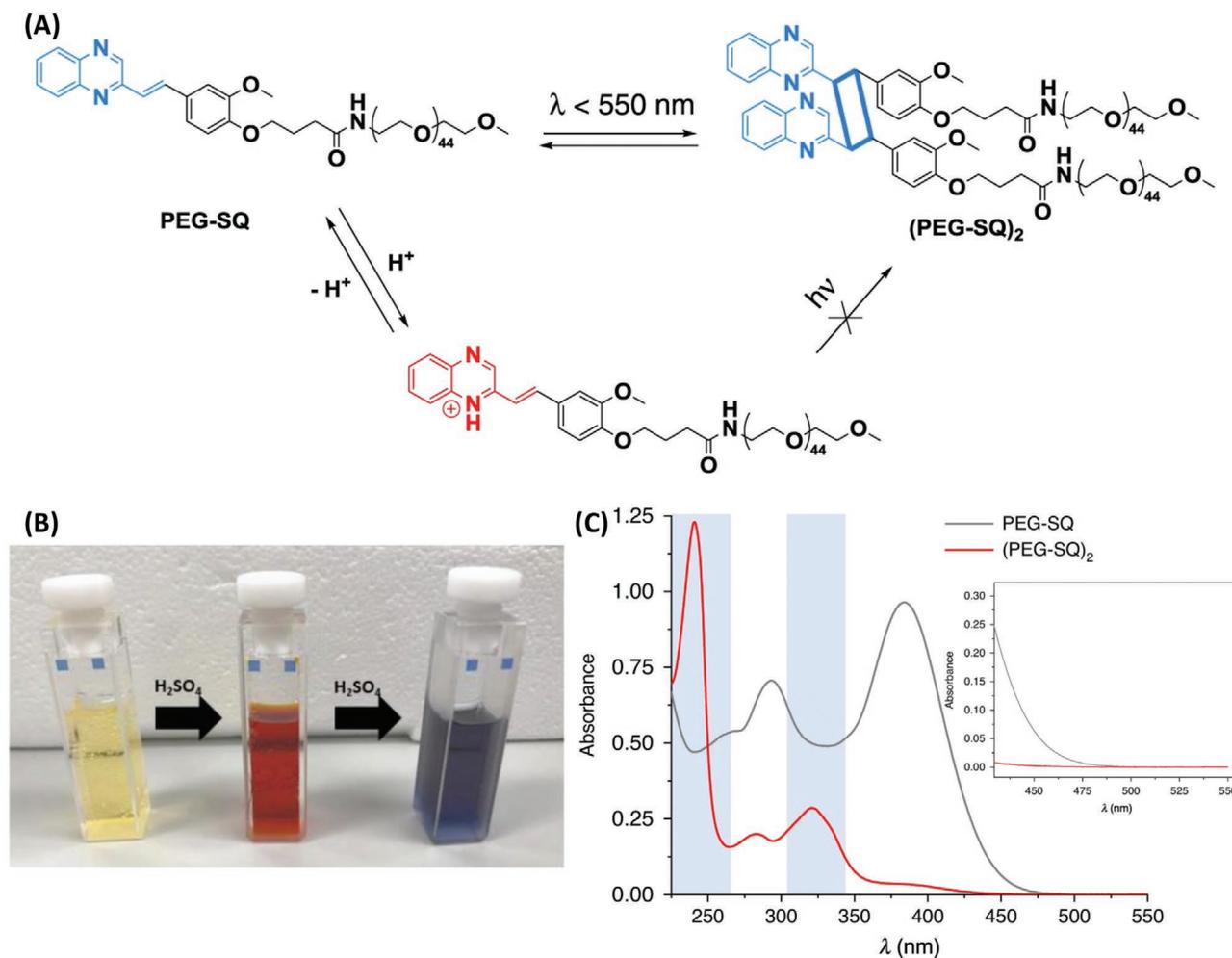


Figure 6. A) Schematic overview depicting the [2+2] photocycloaddition of PEG-SQ, which in turn could be reversibly switched on and off by varying the pH. B) Photographic image showing the self-reporting color change of a PEG-SQ solution ($c = 10 \text{ mg mL}^{-1}$) after addition of 0.1 mL concentrated H_2SO_4 in each step. C) UV/vis spectra of PEG-SQ and $(\text{PEG-SQ})_2$ dimer after irradiation at 510 nm with 9.29×10^{22} photons in water ($c = 10 \text{ mg mL}^{-1}$), with the gray bars showing the appearance of new absorption peaks specific to quinoxaline due to the change in conjugation after irradiation at 510 nm. The insert shows the expanded absorbance spectra between 450 and 550 nm. Reproduced with permission.^[51] Copyright 2020, Springer Nature.

a result of the presence of the unpaired spins. Subsequently, the pyreneacyl sulfide species underwent a Norrish II elimination upon irradiation with visible light (420 nm, at 40 °C

or below under atmospheric conditions) to release an acetyl pyrene derivative (i.e., the profluorescent pyrene moiety), upon which the fluorescence was turned on by over an order of magnitude.

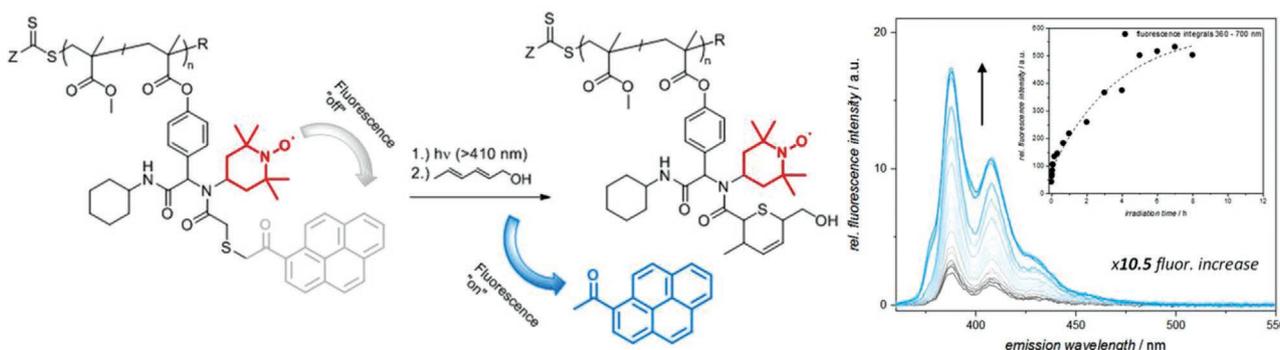
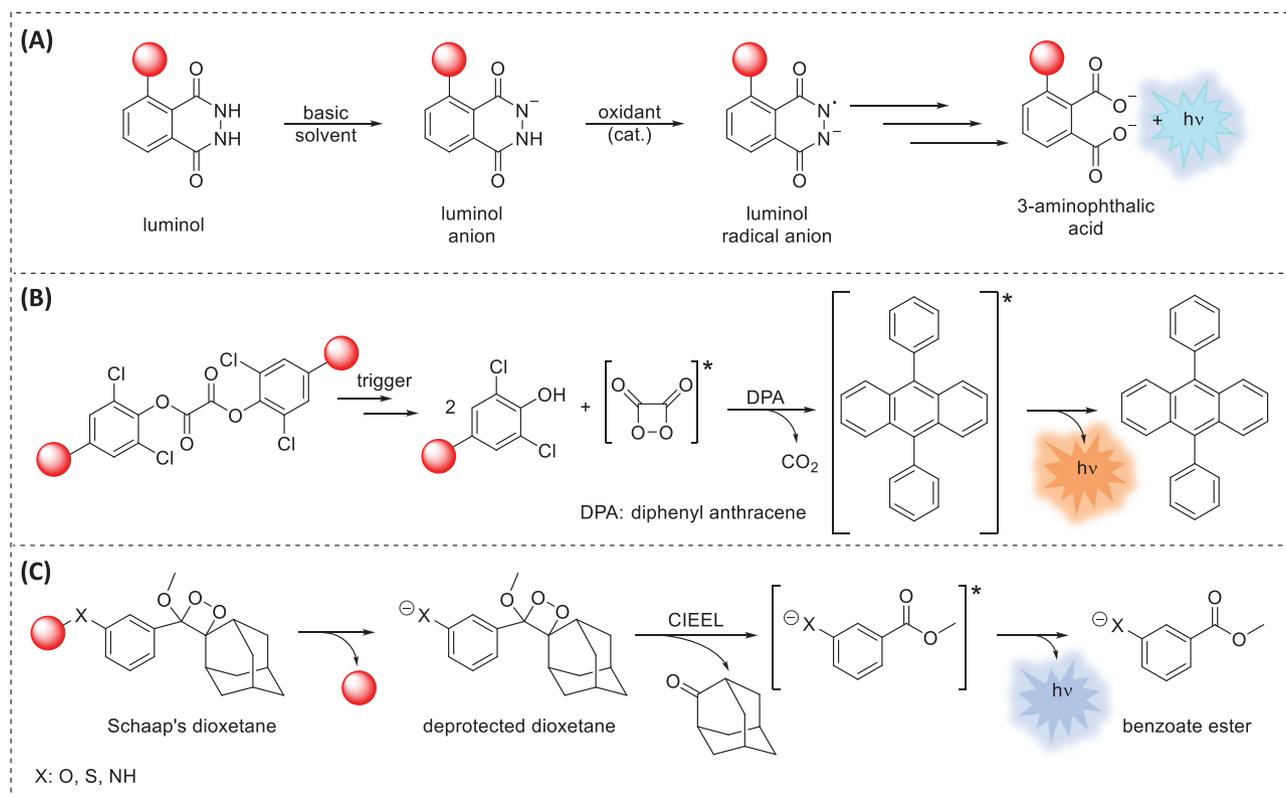


Figure 7. Left: Schematic overview depicting the polymer decorated with paramagnetic nitroxides (i.e., TEMPO) and profluorescent pyrene moieties. Followed by visible light activation, acetyl pyrene is released via a Norrish type II mechanism and fluorescence is activated. Right: The comparative emission spectra depicting the visible light activation of the parent polymer demonstrating over ten times fluorescence increase. Reproduced with permission.^[57] Copyright 2018, Wiley-VCH.



Scheme 2. CL reaction pathways of A): luminol;^[60] B): POs in the presence of a fluorophore;^[61] and C): Schaap' dioxetane probe.^[62]

Importantly, the fluorescence activation could also be monitored with the naked eye. Thus, the introduced visible light-induced self-reporting release system was postulated as a critical step in remotely and mildly activating as well as monitoring payload release.

3. Light as a Direct Read-Out of Chemically Responsive Self-Reporting Polymers

The discussion in the previous section has revealed the importance of light as trigger for self-reporting properties, nevertheless, it is of critical importance to emphasize that light is not only functioning as trigger; it may also be the self-reporting characteristic upon chemically induced process. In fact, CL, that is, light as direct output of a chemical reaction, entails several benefits ranging from high sensitivity to simultaneous real-time monitoring over a wide dynamic range without the need of sophisticated equipment.^[58] Indeed, CL is recognized as a useful tool beyond that of glow sticks and at criminal scenes by forensic scientists. CL reactions have received interest in diverse fields, for example, biomedical or analytical applications, with ongoing research for persistent advances.^[59] Most CL probes (luminol^[60] and peroxyoxalates (POs)^[61] shown in **Scheme 2A,B**) deliver light emission upon reaction with an oxidizing agent (such as H_2O_2), besides 1,2-dioxetane (**Scheme 2C**)^[62] derivatives that are specifically activated by a chemical of interest (reactive oxygen species, ROS, or enzyme derivatives). Generally, the former two classes of probes undergo an oxidation step

to form an unstable strained peroxide, which in turn rapidly decomposes to generate an emissive species in its excited state that decays to its ground state through emission of light. Inevitably with the development in organic synthesis and polymer chemistry, recent research into common luminophores which are similar to the naturally occurring luciferin-luciferase systems have been developed. Critically, CL has been developed into a self-reporting method with specific advantages over fluorescence, since irradiation by an external light source is not required; thus, the background signal is extremely low and the sensitivity is high. Below, the characteristics of CL probe derivatives based on luminol, POs, and dioxetanes that led to the development of a plethora of advanced self-reporting CL polymer systems^[7] will be briefly discussed.

3.1. Luminol-Based Self-Reporting Polymers

Luminol (3-aminophthalhydrazide, **Scheme 2**) and its derivatives enable a broad range of applications from analytical chemistry^[63] to biotechnology^[64] and forensic science^[65] as an efficient CL agent, since its first utilization by Specht to analyze a crime scene.^[66] The most essential and relevant information regarding the chemical features, CL, clinical, and nonclinical applications along the future uses of luminol and its small molecule derivatives have been reviewed comprehensively.^[67] Nevertheless, it is important to mention that the reaction mechanism is complex, and requires an alkaline medium to provide luminol monoanion (LH^-) along diverse intermediates such as a radical form of

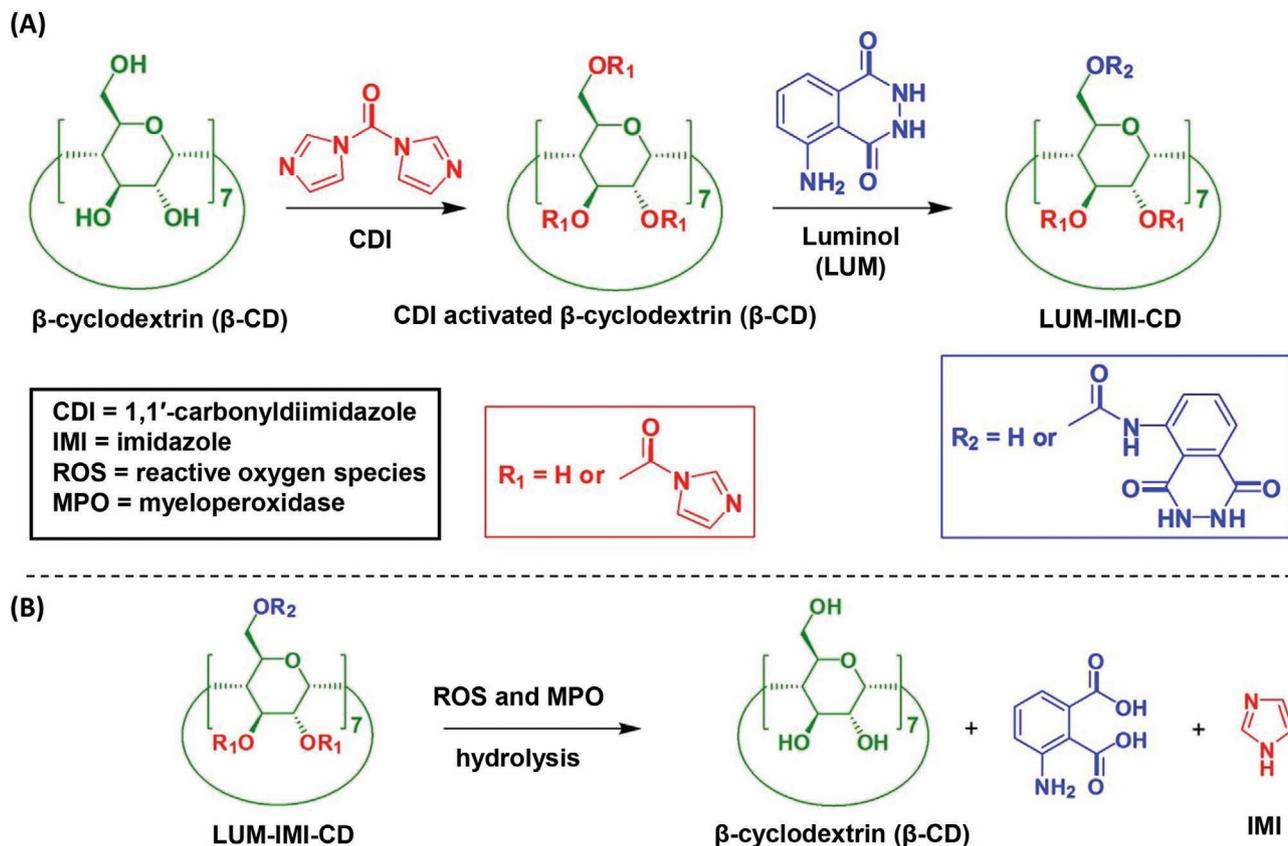


Figure 8. Schematic illustration of: A) the synthetic route of MPO-responsive luminescent material, LUM-IMI-CD, by functional modification of β -cyclodextrin; and B) hydrolysis of the luminescent cyclodextrin material into the parent cyclodextrin compound with self-illuminating read-out. Reproduced with permission.^[72] Copyright 2017, Elsevier Ltd.

luminol (L^-), azaquinone (AQ), and finally the light-emitting species aminophthalate (AP^*). Luminol undergoes CL reactions with a range of oxidants, such as hydrogen peroxide (H_2O_2), oxygen, potassium permanganate, ferricyanide, tetravalent cerium ion, lead dioxide, and oxygen-free radicals being the most common ones. Whereas, the CL process is feasible both in aqueous solutions and organic solvents, such as dimethyl sulfoxide, the CL emission generated during the oxidation of luminol is of relatively low intensity due to its low quantum yield. Therefore, in order to enhance the inherent CL emission, it has become crucial to exploit the luminol in macromolecular systems. Accordingly, our team has investigated a guanidine-based superbases as an efficient booster for the CL emission output of the luminol oxidation.^[68] In contrast to conventional bases, organic superbases (such as 1,5,7-triaza-bicyclo-[4.4.0]dec-5-ene, TBD) allow the synthesis of monomers for the implementation within multi-functionalized polymers and have paved the way for the development of polymer self-reporting CL-systems.^[16] Indeed, the limited number of synthetic methodologies that have been developed for preparing luminol containing polymers^[60] has restricted the application of polymer luminol derivatives as self-reporting materials for long time. Consequently, a copolymer possessing luminol and the superbases was synthesized via sequential free radical polymerization of pentafluorophenyl acrylate (PFPA) and 4-vinyl benzylchloride (VBC) in the presence of methyl methacrylate, and subsequent orthogonal post-polymerization modifi-

cation. The PFPA segment reacted selectively in an orthogonal manner with luminol as a result of the high reactivity of acrylate PFP-ester derivatives toward aromatic amines,^[69] and the VBC moiety was substituted with TBD, which, as aforementioned, is the essential coreactant for the CL response of luminol. The superbases-driven luminol concept^[68] was expanded by constructing supramolecular assemblies based on the luminol-TBD-polymer with a tailor-made supramolecular host-molecule (such as methylated derivative of β -cyclodextrin, Me- β -CD) in order to construct self-reporting CL system. Indeed, β -CD derivatives are recognized as efficient booster for the CL of luminol.^[70] Moreover, the guanidine-moiety in the essential amino acid l-arginine,^[71] which is analogue of the guanidine functional unit in TBD, is known to facilitate selective host-guest inclusion complexes with β -CD derivatives. Upon the addition of ROS (i.e., 0.1 mL of 1.0 M H_2O_2), the host-guest-interactions with the self-assembly were broken. The subsequent oxidation of the luminol to 3-aminophthalic acid (3-APA) generated striking blue light emission of the polymer system that was detectable by the naked eye in addition to 1D and 2D NMR spectroscopy (particularly nuclear overhauser enhancement spectroscopy (NOESY) experiment), dynamic light scattering (DLS), UV/Vis spectroscopy and CL measurements. In similar manner, a β -CD derivative, which was post-modified with luminol, was employed as CL material for real-time imaging of acute and chronic inflammatory diseases (Figure 8).^[72,73] Activation of β -CD via 1,1'-carbonyldiimidazole

(CDI), followed by conjugation of luminol units on β -CD delivered biodegradable polymer materials in which one luminol and three imidazole units were covalently linked to each β -CD molecule. These novel post-modified materials displayed amphiphilic properties since the covalently linked luminol units were relatively hydrophilic and the remained imidazole moieties were hydrophobic. Nanoprecipitation/self-assembly of those amphiphilic polymers resulted in spherical nanoparticles with a mean diameter of 228 ± 19 nm ($n = 15$), as observed by transmission electron microscopy (TEM) and DLS. The nanoparticle based on this functional material displayed notably high and sustainable CL read-out (with $\lambda_{\text{max}} \approx 440$ nm) upon triggering by inflammatory conditions with abnormally elevated ROS (i.e., at 1.0 mM H_2O_2) and myeloperoxidase (MPO). The CL response mechanism was simply based on hydrolysis with the respective release of luminol and imidazole derivative. Furthermore, those spherical nanoparticles self-illuminated alcoholic liver injury and acute liver failure under diseased conditions.^[74]

From the abovementioned examples, it is clear that the field has remained in its infancy as a result of the limited number of synthetic methodologies that have been developed for preparing luminol containing polymers. Thus, we postulate that the toolbox of the numerous opportunities to apply the concepts of classical and modern polymer chemistry to prepare self-reporting macromolecules based on luminol derivatives (with useful properties) is still not fully explored.

3.2. Peroxyoxalate-Embedded Self-Reporting Polymers

The first reports of what is today known as peroxyoxalate chemiluminescence (PO-CL, Scheme 2B) date back to 1963. Accordingly, Chandross disclosed the formation of “bluish-white light” from the reaction of oxalyl chloride with H_2O_2 in the presence of diphenyl anthracene.^[75] Mechanistically, the PO readily reacts with H_2O_2 via the [2+2] addition to form 1,2-dioxetanedione which is further degraded into carbon dioxide. The intermediate 1,2-dioxetanedione chemically excites the loaded fluorescent dyes. By taking advantage of this property, diverse PO compounds, which feature very high quantum yields (30% or higher for certain oxalate phenyl systems) tunable over the entire visible spectrum have been developed. Importantly, those PO-CL derivatives also allow for visible light detection by the naked eye without the necessity for expensive analytical instruments. The state-of-the-art and the current limitations of PO-CL detection read-out systems for various key analytes have been recently summarized.^[61] In addition, the innovative approaches and synthetic routes to push the boundaries of PO-CL systems into diverse application fields have been collated in a comprehensive review.^[61] Therefore, the below mentioned examples are selected with the idea to underpin the potential of PO-CL decorated polymer materials as high-performance self-reporting CL read-out systems. It is of critical importance to mention that the PO-CL reaction relies on two components, an oxalate ester and a fluorophore. Therefore, we will explicitly discuss the polymers systems in which oxalate ester derivatives were tethered either in the backbone or as side (pendent) chain.

The synthesis of poly(ethylene oxalate) is known since 1930;^[76] nevertheless, their use as CL read-out systems has not

been extensively studied, and only a few examples have been developed aiming at detecting and imaging H_2O_2 . It took more than 70 years until Lee et al. reported the synthesis of polyoxalate polymers by step-growth polymerization of oxalyl chloride with diols, which in turn formed CL nanoparticles in the presence of polyvinyl alcohol (as a stabilizer) and a dye.^[77] The PO-CL nanoparticles showed tunable wavelength emission (460–630 nm) and excellent specificity for H_2O_2 over other ROS with detection limit of 250 nM. Appealingly, at 10 μM H_2O_2 , PO-CL nanoparticles revealed a CL intensity of 1.3×10^6 RLU^[78] s⁻¹, which is 50 times higher than with either tert-butyl peroxide or the hydroxide radical itself. Subsequently, Höcherl et al. synthesized nanoparticles containing a self-immolative PO linker and a chemotherapeutic hormone directly into the polymer backbone.^[79] The PO-based prodrug nanoparticles were loaded with a dye to monitor the ROS-initiated degradation in real-time by CL. The above-mentioned self-reporting systems has revealed multicomponent nature (i.e., peroxyoxalate, fluorophore, H_2O_2), and inevitably has implied the need of an additional fluorophore for the CL reaction, which in turn could be seen as limitation. Thus, Barner-Kowollik and colleagues developed a method which facilitates to readily adjust the emission wavelength from the UV/Vis to the NIR spectral range on demand by carefully choosing the fluorophore, rather than modifying the luminophore in a tedious synthesis strategy. Accordingly, the successful combination of the PO-moiety and the fluorophore in one material was reported to enable solid-phase CL read-out. Inherently fluorescent microspheres (based on poly(divinylbenzene)^[80] or polystyrene^[81]) that undergo PO-CL were synthesized by employing a PO linker (i.e., maleimide PO) that can subsequently react with nanoparticles decorated with tetrazole derivatives (e.g., Tz1 and Tz2, respectively) under UV-light range to form a fluorescent pyrazoline adduct via the NITEC reaction. Note for the reader, the employed tetrazole derivatives display emission wavelength of 525 nm for Tz1 and 475 nm for Tz2 ($\lambda_{\text{ex}} = 390$ nm), respectively. Subsequently, the particles were degraded on demand by addition of hydrogen peroxide that cleaved the PO linking points, and disintegrated the particles (**Figure 9**). Degradation of the microspheres was readily monitored by the light emitted during the peroxyoxalate chemiluminescent reaction process in a self-reporting manner.

The effectiveness of the PO-CL platform was further expanded by incorporating a drug (aspirin) into a copolymer as a pendant group via peroxyoxalate ester linkages.^[82] The drug-loaded nanoparticles reacted with the high concentrations of H_2O_2 at the pathogenic sites, and degraded into biocompatible compounds to release the drug with CL self-reporting read-out.

In similar manner to luminol based self-reporting macromolecules, peroxyoxalate read-out systems have only been limited to small molecules and very few applications have exploited PO-CL molecules in combination with polymeric materials. As explained above, possible limitations may include the harsh reactions conditions that are employed while incorporating phenyloxalate moieties in a polymer backbone, which in turn might lead to cleavage and undesired side reactions. Nevertheless, inspired by the recent research development in the field of synthetic polymer chemistry, explicitly by the results observed in polymer-based luminescence, we envision the design of PO-CL polymeric read-out systems.

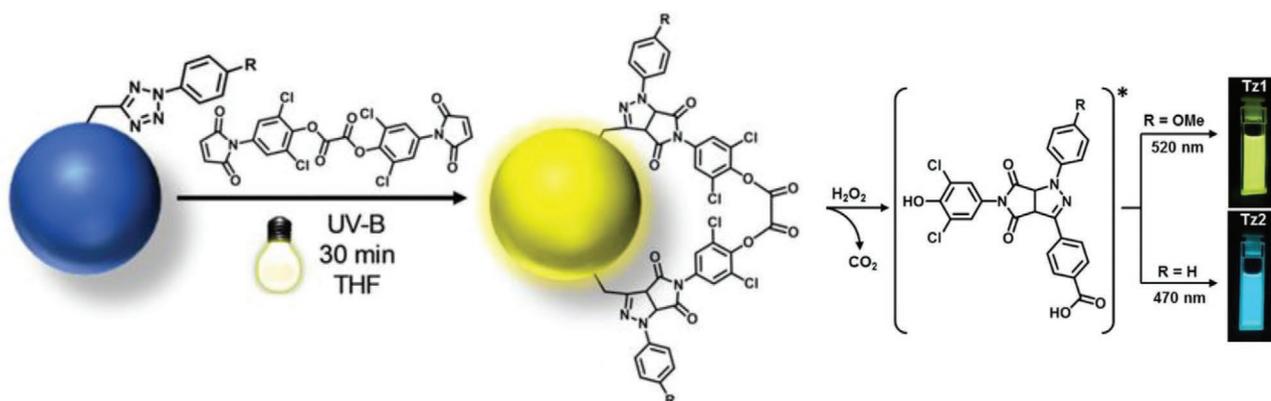


Figure 9. Synthetic pathway for the formation of inherently fluorescent microspheres, and the simplified CL activation pathway of the microspheres. The pictures of the samples after addition of H_2O_2 are displayed next to the corresponding tetrazole (e.g., Tz1 and Tz2, respectively). Reproduced with permission.^[80] Copyright 2019, Wiley-VCH.

3.3. 1,2-Dioxetane-Based Self-Reporting Polymers

Schaap's CL probe (Scheme 2C), described in 1987,^[83] is based on a thermally stable adamantylidene 1,2-dioxetane bearing a hydroxyl group with an analyte responsive protecting group (such as phenol derivative) at the meta position. Upon removal of the protecting group (as recognition unit), an active species is generated that undergoes decomposition to generate an electronically excited (EE) derivative through a process occurring via a chemically initiated electron exchange luminescence mechanism. The decay of EE compound delivers a blue CL output in organic solvent media. While, it is of fundamental importance to depict the development of triggerable small-molecule dioxetanes as chemiluminescent probes for enzymes and chemical analytes, this topic is beyond the scope of the current talent article, and hence, the reader is referred to recent expansive publications.^[58,84] Herein, we will focus on the recent progress in the field of chemiluminescent activatable polymer scaffolds that trigger their CL in the presence of chemical of interest. Indeed, with hydroxyl group that can be relatively easily functionalized, various kinds of polymer CL platforms based on Schaap's dioxetane structures have been synthesized, which have paved the way toward infinite possibilities for self-reporting materials. For instance, Shabat's^[85] group has synthesized self-immolative polymers based on polycarbonate backbones that contains one trigger group at the chain termini (**Figure 10**). Importantly, Schaap's adamantylidene-dioxetane turn-ON CL probe was incorporated into each monomer unit via unique para-hydroxymethyl appendage. Cleavage of the trigger by an analyte (e.g., fluoride) triggered domino-like depolymerization of the polymer that releases a number of dioxetane quinone-methides through multiple eliminations and decarboxylation reactions. Upon trapping of the quinone-methide by water, a phenolate-dioxetane was generated that spontaneously decomposed by a chemically initiated electron-exchange process to generate an excited state benzoate and adamantanone. The CL output signal ($\lambda_{\text{max}} \approx 499 \text{ nm}$) occurred as the benzoate decayed to the ground state. Importantly, the domino-like fragmentation mechanism of the self-immolative polymer was confirmed by ^1H NMR and monitoring the kinetics of CL.

In another example, Akkaya^[86] and coworkers used an AB_2 -self-immolative dendron bearing two molecules of Schaap's dioxetanes for the detection gateway of two different analytes (e.g., fluoride and hydrogen peroxide). While, silyl ether was used as the trigger for fluoride ion detection, hydrogen peroxide was used as analyte for phenyl boronic ester. A single cleavage event of the trigger initiated a double quinone-methide elimination to release the two phenolate-dioxetane species. With such molecules a moderate signal amplification (two-fold) of the CL signal was obtained. Therefore, with the presented examples, the quinone – methide elimination has been recognized as a common, efficient self-reporting gateway to deliver functional self-immolative polymer CL systems. Thus, we believe that further studies in this direction will lead to CL probes with even higher light emission efficiency than that of the luciferin/luciferase system in the near future.

4. Conclusion and Outlook

The aim of this talent article was to provide the reader with a digest of the diverse recent applications of self-reporting macromolecular architectures. While, current approaches toward self-reporting polymers are mainly focused on the introduction of mechanochromic molecules, excimer-forming dyes or microcapsules, representative examples of implementation of polymers that elicit a visible output in a self-indicating way upon light trigger have been discussed. In addition, selected examples on polymer materials that can radiate light (i.e., CL) as a result of coupling directly to chemically induced oxidation reactions have been mentioned.

Indeed, this overview has revealed that the design of self-reporting processes in polymer materials is a far from being universal even when well-established synthetic pathways are applied; especially, as side products (for instance generated as a result of the intercalation of qStyPy units into DNA)^[50] and side reactions (e.g., dimerization of tetrazole during the NITEC process)^[32] may adversely impact the main reaction method.

Although the last decade has offered a number of new discoveries that significantly enhanced our limited understanding of self-reporting macromolecular architectures, which take

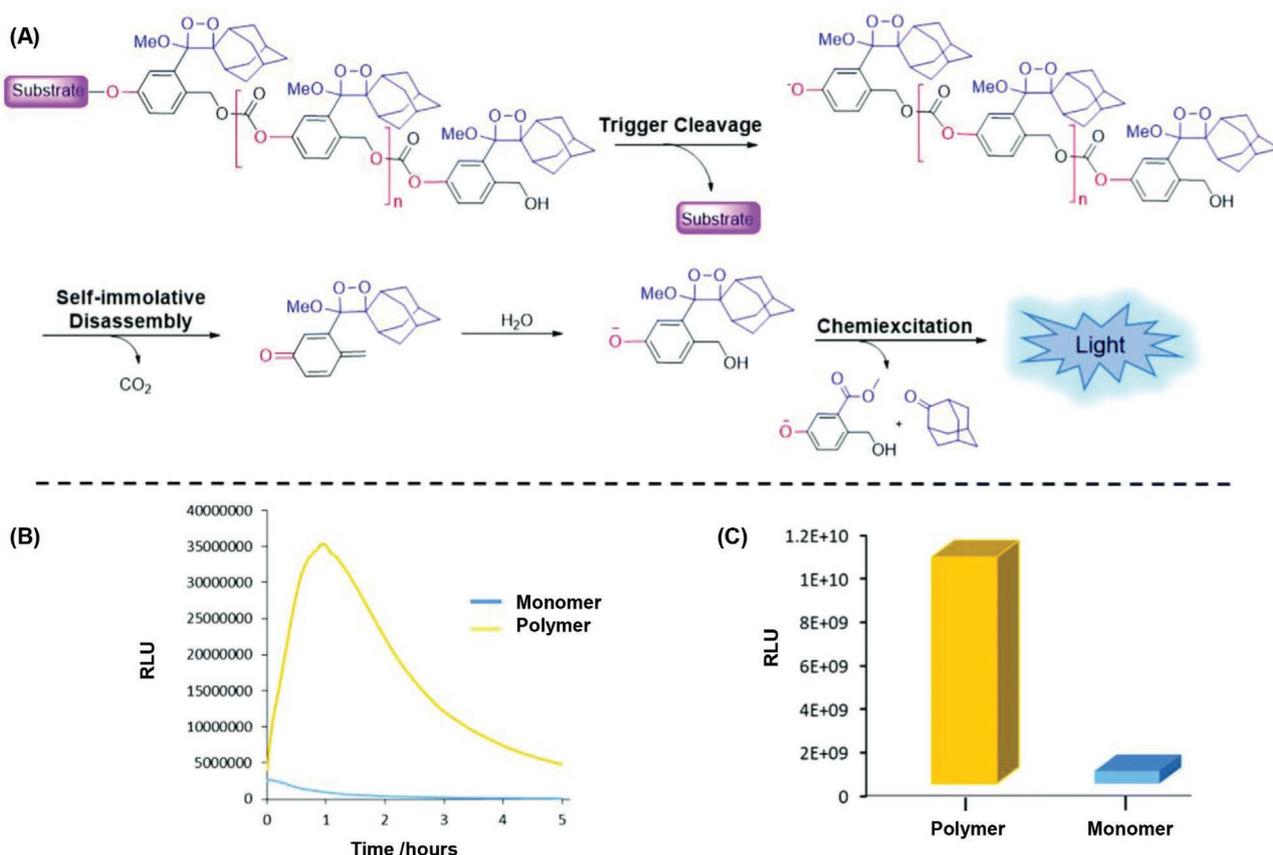


Figure 10. A) Molecular structures and activation mechanisms of CL self-immolative polymers; B) CL kinetic profiles of self-immolative polymer and its monomer after activation by an analyte (e.g., fluoride); C) Total light emitted from the polymer and monomer, respectively. RLU: Relative Light Unit. Reproduced with permission.^[85] Copyright 2017, American Chemical Society.

advantage of light either as the trigger or reporting function, there are still many unanswered questions. For instance, it is intriguing to consider whether the light responsive self-reporting components should be chemically attached to a polymer backbone or physically dispersed in a polymer matrix; and further how intrinsic properties (physical/chemical compositions and concentrations, density, elasticity, etc.) will determine the ability to report. Nevertheless, we admit that the future progress in self-reporting polymers will depend upon the discovery of advanced chemistries (such as multi component reactions) which offer rapid, controlled and facile reporting to deliver polymer materials with the intrinsic intelligence to self-diagnose.

Accordingly, we can postulate that from a view of material applications, opportunities could also arise from the following aspects: i) combining with modern fabrication techniques and nanoscience, such as 3D printing, micro-/nano-patterning techniques can lead to polymers and flexible devices that increase the efficiency of CL and broaden its application scope; ii) remodeling of chemical bonds accompanied with the destructive luminescent process. Instead of destructive, if the applied trigger for CL could be productive in use, reporting and healing bond scission in polymers will be realized in situ. Thus, it is envisioned that advances in understanding and control of the self-reporting properties of polymers will increasingly stimulate the development of novel materials with precise spatiotemporal

control of their properties, as well as advanced tools for accurate modulation of biological systems. In other words, inevitably, the vibrant interplay of light and self-reporting polymer materials will fuel a new age of exploration in polymer chemistry and materials science in many years ahead.

Acknowledgements

H.M. acknowledges Prof. P. Theato (KIT) and Prof. C. Barner-Kowollik (Queensland University of Technology (QUT)) for their ongoing sponsor- and mentorship.

Open access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

chemiluminescence, cycloadditions, light, real-time feedback, self-reporting polymers

Received: February 11, 2021

Published online:



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