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# All Eyes on Visible Light Peroxyoxalate Chemiluminescence Read-Out Systems

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#### Abstract

Chemiluminescence reactions (CL) have been widely employed and explored over the past 50 years as they offer unique light emission upon a defined chemical stimulus. Herein, we focus on peroxyoxalate (PO) compounds as they feature very high quantum yields tunable over the entire visible spectrum, allowing visible light detection by the naked eye without the necessity for expensive analytical instruments. While analytical methods have been extensively described, PO-CL read-out is a strongly emerging field with ample industrial potential. We explore stateof-the-art PO-CL detection read-out systems for various key analytes. In particular, we detail structural requirements, recent developments of PO-CL read-out probes and current limitations of selected examples. Further, we highlight innovative approaches and synthetic routes to push the boundaries of PO-CL reactions into biological systems. Underpinned by recent contributions, we share perspectives on embedding PO-CL molecules into polymeric materials, which we consider the next step in designing high performance solid phase read out systems.

#### 1. Introduction

The generation of light via a chemical reaction, the phenomenon of chemiluminescence - and more specifically bioluminescence has inspired humanity throughout history. The first reports of natural luminescence are found in poetry from 1500-1000 BC, mentioned in the Thirteen Classics of Confucian Tradition.<sup>[1]</sup> The oldest detailed description dates back to around 350 BC when Aristotle described bioluminescence as "cold light"[2] that he observed in many different organisms such as fungi, fish, and other marine species. Charles Darwin's very first notebook entry<sup>[3]</sup> while aboard the H.M.S. Beagle, described "luminous specks" formed around the vessel when crossing through a field of bioluminescent organisms and the impression held him captive since. Natural luminescence has always been a source for curiosity and mystery but also superstition, leading to many writings about "holy" or "unearthly" lights and even connections to the devil or spirits of departed ancestors.

However, the mysterious light also inspired researchers, such as Robert Boyle in the late 1600s,<sup>[4]</sup> to investigate the origin of chemiluminescence peaking in the discovery of luciferin and luciferase in the late 19<sup>th</sup> century, where the distinguished French physiologist Raphaël Dubois extracted the two chemiluminescent components that we now know are the key for the firefly luminescence.

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During the last decades, the scientific knowledge about chemiluminescence has rapidly expanded and the natural wonders of the firefly luciferin, a bioluminescent bacterium, has been widely studied and explained. The rise of synthetically produced chemiluminescence was enabled by Radziszewski's observations of light emission while percolating oxygen into an alkaline lophine solution.<sup>[5]</sup> With the work of Radziszsewski and Dubois, the history of chemiluminescence had arrived in modern sciences and the search for the chemical origin of the cold light was well underway. In 1963, the first reports of what is today known as peroxyoxalate chemiluminescence (PO-CL) were published by Chandross regarding a simple reaction of oxalyl chloride with hydrogen peroxide  $(H_2O_2)$  in the presence of diphenyl anthracene (DPA), creating a "bluish-white light".<sup>[6]</sup> The vapours of the reaction were described to induce fluorescence of anthracene-impregnated filter paper and a "metastable excited electronic state or some other highly energetic species"[6] present during the reaction was suggested. His hypothesis was largely supported by the work of Rauhut et al., who provided a thorough study of varying substituted oxalate esters, finding oxalate esters bearing electronegatively substituted phenyl groups to be the most effective ones.<sup>[7]</sup> Their conclusions allowed interesting mechanistic insights into the PO-CL and revealed a correlation between the substituent of the phenol and the quantum yield as well as emission lifetime of the corresponding chemiluminescent reaction.

Early experiments of Chandross already indicated one of the key features of PO-CL compared to other luminescent reactions such as luminol or the catalysed CL of phenolate-substituted dioxetanes: the possibility to tune the wavelength of the emitted light by adding different fluorophores to the reaction mixture rather than changing the substitution pattern on the CL molecule.<sup>[6]</sup> In contrast to the intramolecular luminescence of phenolate-substituted dioxetanes, where the wavelength is dependent on the exact substitution of the dioxetane itself, the PO-CL system produces intermolecular luminescence. Thus, the need of such a fluorophore also makes the system more versatile since the emitted wavelength can be tuned on demand by employing a wide variety of different fluorophores, spanning over the complete visible spectrum and even into the infrared area. A detailed mechanistic study of the PO-CL, including the energy transfer to the fluorophore, will be given in the first chapter. Nowadays, the most widely employed oxalate esters are bis(2,4,5-trichlorophenyl-6-carbopentoxyphenyl)oxalate) (CPPO). bis(2,4,6-trichlorophenyl) oxalate (TCPO), and bis-(2,4dinitrophenyl)oxalate (DNPO). Quantum efficiencies for certain phenyl oxalate systems were reported of 30% and more,<sup>[8]</sup> being competitive with their natural counterpart, the luciferin/luciferase system and opening a variety of possible applications. Due to the high sensitivity towards specific activating species, high photon output, and long luminescence lifetimes, PO-CL reactions find widespread application ranging from analytical purposes like the detection of H<sub>2</sub>O<sub>2</sub> in water,<sup>[9]</sup> viable microorganisms in food,<sup>[10]</sup> or blood traces in forensic science,[11] to common everyday objects such as glow sticks or emergency lighting devices.<sup>[12]</sup> In the previous years, CL has gained interest in the fields of nanomaterials, biological imaging, molecular sensors, and in polymer science as will be discussed in more detail in the following chapters.

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Laura Delafresnaye obtained her chemical engineering degree in 2012 and her Ph.D. in Chemistry in 2015 from the University Lyon 1 (France) (Chemistry, Catalysis and C2P2). studied Processes She nanocomposites film-forming latexes with enhanced barrier properties in collaboration with Solvay Belgium. She is currently working a postdoctoral researcher at the as Queensland University of Technology (QUT). Her main research focuses on chemiluminescence particles and photochemistry.

Fabian R. Bloesser received his M.Sc. in pure chemistry from the Karlsruhe Institute for Technology (Germany) in 2017, where he performed his undergraduate studies. He is currently a PhD student under the supervision of Christopher Barner-Kowollik at the Queensland University of Technology (Australia) working on chemiluminescent self-reporting macromolecular transformations.

Katrin B. Kockler obtained her PhD in Chemistry in 2017 at the Karlsruhe Institute of Technology in Germany, where she studied the kinetics of radical polymerisation reactions of a range of acrylate and methacrylate type monomers via pulsed laser polymerisation. She currently works as a postdoctoral researcher at the Queensland University of Technology where she studies chemiluminescence as a light source for chemical reactions.

Christian W. Schmitt received his Master's Degree from the Karlsruhe Institute of Technology (Germany) where he worked on IR-imaging of surfaces and self-reporting drug delivery systems. During his studies, he spent a research stay at the Australian Institute of Bioengineering and Nanotechnology (AIBN) to study the folding behaviour of single-chain nanoparticles Currently, he is a PhD student at the Queensland University of Technology with focus on the surface modification of polymeric micro- and nanoparticles as well as chemiluminescent materials

Ishrath M. Irshadeen received her Bachelor of Science (Distinction) majoring in chemistry and biology from Queensland University of Technology (QUT) in 2018. Her current research interests are in polymers and chemiluminescence. She is currently doing her Honours research in polymer chemistry and chemiluminescence under the supervision of Prof. Christopher Barner-Kowollik and is looking forward to starting a PhD in the near future.











Christopher Barner-Kowollik received his PhD in 1999 from Göttingen University. In 2006 he was appointed Full Professor of Polymer Chemistry at the Centre for Advanced Macromolecular Design at the University of New South Wales in Sydney. In 2008 he became chair for Macromolecular Chemistry at the Karlsruhe Institute of Technology (KIT) and is currently chair for Materials Chemistry at the Queensland University of Technology (QUT) and a group leader at the KIT. In 2016, he was awarded the Erwin-Schroedinger Award of the Helmholtz Association (jointly with M. Wegener and M. Bastmeyer) and in 2017 a



Laureate Fellowship by the Australian Research Council. Christopher Barner-Kowollik is a Fellow of the Australian Academy of Science

### 2. Mechanistic insights

#### 2.1. The Quest for a High Energy Intermediate

The findings of Chandross and Rauhut sparked investigations into the mechanistic details of CL reactions and the search for the high-energy intermediate involved in the production of light. As previously stated, in their comprehensive study of substituted aryl oxalates Rauhut et al. established important relationships between the substitution of the phenols and the quantum yield  $\Phi_{CL}$  on the one hand, as well as a correlation between substitution and emission lifetime on the other hand. With an increasing electronegativity of the substitution, the quantum yields of the PO-CL increased to a total of up to 15%, while the emission lifetimes decreased from several hours to only a few minutes. In agreement with Chandross, Rauhut et al. also found that the CL emission spectra were identical to the fluorescence spectra of the employed fluorophores, except for a minor bathochromic shift that they attributed to small changes in the CL environment caused by H<sub>2</sub>O<sub>2</sub>. Interestingly, infrared spectroscopy (IR) measurements revealed that more than 98% of ester groups have disappeared only four minutes after the addition of  $H_2O_2$ . However, about 75% of the chemiluminescence was observed after these initial four minutes. Subsequently, Rauhut et al. prepared mixtures of DNPO and H<sub>2</sub>O<sub>2</sub> in dimethyl phthalate and added the fluorescent dye with a delay of 27 and 70 minutes, respectively. Although they observed reduced total quantum yields compared to when the fluorescer was initially added, it was evident that a significant amount of CL manifested after no CL was visible anymore in a standard experiment.<sup>[7a]</sup> In order to prove the existence of a high energy intermediate (HEI) as originally suggested by Chandross, they prepared two solutions, one of them containing DNPO and H<sub>2</sub>O<sub>2</sub>, the other one containing DPA or rubrene. When gas streams were passed through the DNPO- H<sub>2</sub>O<sub>2</sub> solution into the fluorescer solution, bright CL with a short lifetime was observed. Based on these results, they proposed 1,2-dioxetane-3,4-dione 1 as the metastable intermediate.<sup>[7a]</sup> Although, direct observation of 1 via IR or mass spectrometry (MS) by Rauhut et al. was unsuccessful, Cordes et al. pioneered the MS investigation of the PO-CL (refer to Scheme 1). By preparing a solution of TCPO and H<sub>2</sub>O<sub>2</sub> in a high boiling point phthalate and its injection into a mass spectrometer, the group was able to detect high intensity signals

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**Scheme 1.** Formation of 1,2-dioxetanedione 1. Oxalyl chloride 2a, aryl oxalates 2b or oxalyldiimidazolide 2c react with H<sub>2</sub>O<sub>2</sub> in a nucleophilic substitution to form oxalic peracid derivative 3. Ring-closure leads to 1,2-dioxetaneous derivative 4, subsequent elimination of HX results in the formation of 1,2-dioxetaneous 1.

at 28, 32 and 44 amu, corresponding to carbon monoxide, oxygen and carbon dioxide, respectively. Moreover, they found peaks at 88 and 60 amu, corresponding to a carbon dioxide dimer (possibly 1,2-dioxetanedione 1) and CO<sub>3</sub>.<sup>[13]</sup> Ab initio nuclear magnetic resonance spectroscopy (NMR) calculations in combination with <sup>13</sup>C and exchange NMR spectroscopy (EXSY) were performed by the group of Barnett.<sup>[14]</sup> In a first set of experiments, <sup>13</sup>C-labelled oxalyl chloride was reacted with H<sub>2</sub>O<sub>2</sub> in d<sub>8</sub>-tetrahydrofuran (THF) in the presence of DPA at -70 °C. On-line <sup>13</sup>C NMR revealed a single carbon species at a chemical shift of 154.5 ppm which was in good agreement with ab initio calculations.[14a] In subsequent <sup>13</sup>C EXSY experiments, detecting chemical exchange and therefore allowing for the identification of reaction pathways, Barnett and co-workers were able to provide evidence for a nucleophilic substitution reaction of  $H_2O_2$  and oxalyl chloride 2a to 2-chloro-2-oxoethaneperoxoic acid 3a and subsequent elimination of HCI and ring-closure to form 1,2-dioxetanedione 1 (refer to Scheme 1).<sup>[14b]</sup> However, as the NMR data have not been directly linked to the CL properties of the system, the presented investigations do not provide clear evidence that dioxetanedione 1 is the previously suggested HEI. In a very elegant experiment, Stevani and Baader attempted the trapping of a cyclic peroxide HEI.<sup>[15]</sup> It has been shown previously that triphenylantimony readily inserts into the O-O bond of tetramethyl-1,2-dioxetane.[16] Stevani and Baader thus synthesised the corresponding triphenylantimony - dioxetanedione adduct via an alternative route and characterised it in order to provide a reference compound. Subsequently, they performed the peroxyoxalate reaction in the absence of a fluorophore and passed a gas stream of N<sub>2</sub> over the reaction mixture that led into a solution of triphenylantimony. Upon contact of the volatile intermediate carried in the gas stream with triphenylantimony, insertion of the antimony species into the O-O bond was anticipated. However, no such reaction was observed. Nevertheless, although no insertion was detected, the property of 1 as HEI has not been disproven, as catalytic degradation of the dioxetane can possibly compete with the insertion reaction.[15-16] In addition to dioxetanedione, a substituted 1,2-dioxetanone has been discussed as a potential HEI.<sup>[17]</sup> Aoyama and co-workers investigated the CL properties of different 2,4,6-trichlorophenyl Naryl-N-tosyloxamates revealing a Hammett relationship between some of the investigated structures. They found reaction constants  $\rho$  of +1.75 for the release of the tosylanilides and +2.66 for the emission of light. These results suggest that formation of a HEI and its decay with an activator is faster than the release of tosylanilides and N-aryl-N-tosyl substituted 1,2-dioxetanones are the reactive intermediate.[17b] Similarly, Murayama et al. provided p-values for the PO-CL reaction of different aryl oxalates with a set of distyrylbenzenes and compared these with the LUMO

of corresponding 1,2-dioxetanones and eneraies 1.2dioxetanedione 1 based on ab initio calculations. They described a linear dependency of the  $\rho$ -values and the pK<sub>a</sub>-values of the corresponding phenols correlating to the observed CL decay rates. Solely bis(2,6-dichlorophenyl) oxalate and bis(2,4,6tricholorophenyl) oxalate exhibited deviations from the general trend reported, which can be attributed to the para-substitution and its steric hindrance.<sup>[18]</sup> Thus, in agreement with Aoyama,<sup>[17b]</sup> Murayama et al. proposed aryloxy-substituted 1,2-dioxetanones 4b as the HEI. Lindh and co-workers have conducted theoretical studies on the binding energies of 1,2-dioxetanes and 1,2dioxetanones with fluorophores employing naphthalene as a model compound.<sup>[19]</sup> Their calculations showed that unsubstituted 1,2-dioxetanes exhibit a lower binding energy than 1,2dioxetanones, and that binding energies decrease even further upon methylation of the peroxides. Moreover, after formation of the complex, the ground state energy of the cyclic peroxides was found to increase with O-O bond elongation, whereas the energies of the n, $\sigma^*$  and the  $\pi$ , $\sigma^*$  states decrease. This decrease in energy is more pronounced for the unsubstituted 1,2dioxetanone as the carbonyl group provides additional planarity of the molecule.<sup>[19]</sup> Although the presented theory has only been applied to 1,2-dioxetanes and 1,2-dioxetanones, one can speculate about an even more pronounced effect for 1,2dioxetanedione 1, which will be part of their future work.[19] Despite various attempts, to the best of our knowledge, no unequivocal evidence for or against the proposed HEI structures has been provided yet (vide supra).

#### 2.2. Catalysed Degradation of the HEI

Early findings that (i) CL emission spectra were identical to the fluorescence spectra, [6-7, 7c, 20] and (ii) there was no significant CL observed without any fluorescer<sup>[6-7]</sup> led to the assumption that the HEI must somehow interact with the fluorescer in order to produce CL. In a set of experiments, Rauhut et al. reacted oxalyl chloride and H<sub>2</sub>O<sub>2</sub> at constant amounts with varying amounts of DPA. They observed an increase in quantum yield with increasing DPA concentration. Moreover, a linear correlation was found when plotting the guantum yields against DPA concentration in a double reciprocal fashion.<sup>[7c]</sup> This correlation has been supported by the work of various research groups.<sup>[17a, 20-21]</sup> Furthermore, Schuster and co-workers have correlated the bimolecular rate constant of the CL reaction of various organic peroxides with different activators to the oxidation potential of the corresponding activators. The linear dependency of the natural logarithm of the rate constant on the oxidation potential suggests an electron transfer (ET) or at least charge transfer from the fluorophore to the peroxide prior to CL.[20-21] Based on this data, Schuster

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postulated the so-called Chemically Initiated Electron Exchange Luminescence (CIEEL) mechanism, involving an electron transfer and back-transfer (EBT) between organic peroxide and an activator (refer to Scheme 2).[20-21] The group of Baader confirmed that these findings also apply to the HEI of the PO-CL.  $\ensuremath{^{[21c,\,d,\,22]}}$  The CIEEL mechanism involves five key steps: (i) formation of a charge-transfer (CT) complex of an activator with the cyclic organic peroxide within a solvent cage facilitating O-O bond elongation, (ii) electron or at least partial charge-transfer from the activator to the peroxide and almost simultaneous O-O bond cleavage, (iii) concerted cleavage of the carbon-carbon bond (CCC) and release of one equivalent of carbon dioxide, (iv) electron (or charge) back-transfer (EBT) to and singlet excitation of the activator together with the release of a second equivalent of carbon dioxide, and (v) decay of the singlet excited state via emission of light.<sup>[8a, 20-21, 23]</sup> Furthermore, Baader and co-workers correlated the singlet quantum yields of the PO-CL to the change in free energy in the EBT leading to an excited state of the activator.<sup>[21c, d, 22]</sup> Nonetheless, it was unclear whether the two radical ions would remain within a solvent cavity until the EBT step or if they would diffuse away from each other preventing EBT and resulting in low quantum yields of the CL reaction.[20, 24] Adam et al. have studied the influence of solvent viscosity on the CL of a phenyl-adamantyl-substituted dioxetane which follows the CIEEL mechanism in an intramolecular fashion.[25] However, two pathways for the EBT seem feasible. After electron transfer from the phenol moiety to the dioxetane and O-O bond cleavage, pathway one suggests C-C bond cleavage and formation of a phenol radical and an adamantyl anionic radical. While both species are still present within a solvent cage, EBT from the adamantyl species to the phenol occurs intermolecularly. The second route follows C-C bond cleavage and formation of an anionic biradical and adamantanone followed by intramolecular EBT. In case of an intramolecular EBT, the system and therefore the quantum yields should be unaffected by changes in solvent viscosity. In a set of fluoride-triggered CL reactions, Adam et al. have elegantly confirmed the viscosity dependence of the system by employing a range of solvent mixtures of benzene and diphenylmethane (DPM). These experiments therefore support an intermolecular EBT for the CL of phenyl-adamantylsubstituted dioxetanes.<sup>[25]</sup> Baader and co-workers have subsequently investigated the solvent viscosity dependency of the PO system and compared it to the dioxetane system. When gradually changing the solvent from pure toluene to 90% DPM, and thus increasing the viscosity by a factor of 4.6, the CL quantum yields of two different dioxetane systems increased by a factor of 2.2 and 2.6, respectively, whereas the quantum yield of the PO-CL increased by a factor of 9.4. [26] In more polar solvents, however, the effect of solvent viscosity on the CL was less pronounced as a 34-fold increase in viscosity from pure ethyl acetate to pure DPM only resulted in an increase in quantum yields of a factor of five for the PO-CL.[8b] The presented viscosity dependency of both CL systems provides evidence for a rather stable complex within a solvent cage that facilitates EBT before the species can diffuse away. Still, the question has been raised whether the interaction of the organic peroxide with an activator molecule and subsequent decomposition of the peroxide involves an actual electron transfer or if a charge transfer would be more conclusive. In accordance with the Franck-Condon principle, electron transfer and back-transfer are about 100 times faster



**Scheme 2.** Schuster's CIEEL mechanism on the example of 1.2-dioxetanedione 1. Adapted from reference [20].

than that of nuclear motions. Thus, bond breaking and relocating of nuclei would have to happen close-to simultaneously with electron-transfer.<sup>[24]</sup> As this requirement seems highly unlikely, the Charge-Transfer Induced Luminescence (CTIL) mechanism was proposed as an alternative to the CIEEL mechanism. In the CTIL mechanism, a charge at the O-O bond is gradually developed which results in a concerted O-O and C-C bond cleavage. This partial charge-transfer instead of a complete electron-transfer also attributes to the generally high quantum yields of PO-CL.<sup>[27]</sup> Various mechanisms for the PO-CL have been proposed in the past 50 years since its discovery and numerous experiments have been conducted in order to confirm suggested mechanisms and their intermediates. Our group has recently demonstrated the effect of confined environments, which polymers provide, on photochemical single chain nanoparticle folding.<sup>[28]</sup> Similarly, a copolymer consisting of two blocks bearing different fluorophores with distinct emission spectra could provide such a confined environment. If one of the two blocks were to be selectively cross-linked via phenyloxalate moieties and subsequently treated with  $H_2O_2$ , a resulting 1,2-dioxetanedione 1 HEI would be free to diffuse and interact with and produce CL of both fluorophores adjacent to the polymer backbone. On the other hand, if phenyl-substituted 1,2-dioxetanone 4 is the HEI of PO-CL, it would still be bound to the polymer backbone, unable to diffuse freely and only yield the CL of one fluorophore. Thus, we envisage that the confined environments present a key opportunity for further insights into the mechanics of PO-CL.

#### 3. Application of peroxyoxalate CL read-out

While the application of CL in polymers is still rather limited, CL has found many applications in the small molecules form. CL has been combined with high performance liquid chromatography

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(HPLC) for analytical purposes, employed to detect biological molecules both *in vitro* and *in vivo*, and even combined with nanomaterials recently to expand the range of applications of PO-CL. Herein, we will highlight a selection of PO-CL read-out systems and publications, focusing largely on literature from recent past that have been used in conjunction with the aforementioned analytical applications.

#### 3.1. PO-CL and chromatography

Chemiluminescence has been widely exploited as an analytical tool in the visible spectrum in applications ranging from testing for pollutants in water sources to analysing human serum for a plethora of biological substances.<sup>[29]</sup> This is largely due to the ease of use and reliability of the PO-CL reaction to emit light in response to the presence, or in some cases, the absence, of a diversity of analytes. Its versatility has made the PO-CL reaction a popular analytical tool, which has been extensively employed in combination with HPLC to detect a range of analytes (Table 1). PO-CL/HPLC has been employed to detect traces of H<sub>2</sub>O<sub>2</sub>, compounds that can innately function as fluorophores (e.g. hypericin)<sup>[30]</sup>, compounds that can be derivatised into fluorophores (e.g. aldehydes that are derivatised with 4-(N,N-Dimethylaminosulfonyl)-7-hydrazino-2,1,3-benzoxadiazole to form fluorophores)<sup>[29b]</sup>, and other materials that can act as quenchers (*e.g.* glutathione)<sup>[30]</sup> or enhancers (e.g. 4nitrophenol)<sup>[29a]</sup> for the PO-CL reaction.<sup>[31]</sup>

Compared to fluorescence detection, CL detection does not require photoexcitation. Due to the lack of a photoexcitation source and the baseline error associated with it, CL is often much more sensitive at detecting analytes. PO-CL/HPLC has been employed to detect traces of methamphetamine-based compounds in rat hair roots,<sup>[32]</sup> halofantrine – an anthracene-methanol derivative used to treat malaria – in rat plasma,<sup>[33]</sup> catecholamines in mice brain samples<sup>[34]</sup> and human plasma<sup>[35]</sup> amongst many other applications.

Recently, a novel chromatographic method for detecting low molecular mass aldehydes in human serum via a combination of fluorescence labelling and PO-CL was published by Ali et al. [29b] Cellular oxidative stress can lead to lipid peroxidation of unsaturated fatty acids in cell membranes which produces low molecular mass aldehydes which are cytotoxic and react with DNA.<sup>[39]</sup> The resultant cytotoxic species can lead to a host of degenerative diseases like rheumatic arthritis, diabetes, atherosclerosis, renal failure and cancer. The presented method labels four different serum aldehydes (methylglyoxal, acrolein, crotonaldehyde and trans-2-hexenal) 4-(N,Nwith Dimethylaminosulfonyl)-7-hydrazino-2,1,3-benzoxadiazole via the selective aldehyde-hydrazine reaction. The latter acts as the fluorophore in the derivatised aldehydes. The following PO-CL detection proved to be 10 times more sensitive than fluorescence detection, likely due to the lack of photoexcitation as aforementioned. *Via* this method, relative to healthy people diabetes patients were shown to have enhanced levels of methylglyoxal and acrolein, and for the first time, rheumatic arthritis patients were shown to have enhanced acrolein levels.

#### 3.2 Food analysis

PO-CL is also commonly applied in food analytics, where molecularly imprinted polymers are used to recognise substances in analytes, which then enhance the CL emission. This method was first developed by Li et al. for the determination of ethopabate residues in chicken muscles.<sup>[40]</sup> Further applications were found for the detection of Sudan dyes in eggs<sup>[41]</sup> as well as tetracyclines in milk.<sup>[42]</sup> The vast range of applications of molecular imprinted polymers for sensing and separation reaches further than the scope of this contribution. For further information, we refer to recent reviews on the topic.[43] It was also shown that the PO-CL system could be used to determine the antioxidant activity of common antioxidants in edible oils[44] as well as residual pesticides in water.<sup>[29b]</sup> Here, the analytes are able to scavenge reactive oxygen species (ROS), which are essential for the CL reaction and therefore decrease the emission signal. Christodouleas et al. employed a flow injection analysis device to combine a sample containing olive oil or sunflower oil in isopropanol and the TCPO-H<sub>2</sub>O<sub>2</sub>-catalyst system to measure the attenuation of the chemiluminescence emission in order to determine the antioxidant activity.[44] Indeed, vegetable oils contain phenolic compounds which can scavenge ROS and inhibit the formation of peroxides.[45] In contrast to conventional methods where the emission enhancement is measured, the present work demonstrates an innovative way of utilizing chemiluminescence for quantitative analysis.

#### 3.3 Nanomaterials and PO-CL

A recent critical development in chemiluminescent energy transfer emerged from the usage of nanomaterials such as gold nanoparticles, graphene and quantum dots (QDs) as the final emitting species, quenchers and amplifiers in CL reactions.<sup>[46]</sup> In the field of nanomaterials, the CIEEL mechanism is commonly referred to as CL resonance energy transfer (CRET, in analogy to Förster resonance energy transfer FRET). Energy transfer with traditional small molecule fluorophores is not very efficient, so the advent of nanomaterials with much higher CRET efficiency has paved way to relatively new territory in the area of CL.

QDs can be used in combination with CL in multiple ways in the capacity of a nanomaterial as mentioned above; it can assume the role of the final emitting species, an amplifier,<sup>[47]</sup> or

**Table 1.** Summary of analytical applications in which the PO-CL system has been employed so far. Adapted from reference [31]. DOPO: bis[2-(3,6-dioxaoctyloxycarbonyl)-4-nitrophenyl)oxalate.

Analyte	CL system	Limit of detection	Samples	Ref
Low molecular mass unsaturated aldehydes	CPPO/H2O2/ Imidazole	0.31 - 0.46 μg L <sup>-1</sup>	Human serum	[29b]
Methamphetamine	CPPO/H2O2/ Imidazole	0.001 µg L <sup>-1</sup>	Rat hair roots, shafts and plasma	[32]
Halofantrine	DOPO/H <sub>2</sub> O <sub>2</sub>	1.5 µg L <sup>-1</sup>	Rat plasma	[33]
Catecholamines	TDPO/H2O2/ Imidazole	(0.6-9.1) x 10 <sup>-5</sup> µg	Mouse brain	[34]
Ritalinic acid	CPPO/H2O2/ Imidazole	0.4 µg L <sup>-1</sup>	Rat plasma	[36]
Doxorubicin	TDPO/H <sub>2</sub> O <sub>2</sub> / Imidazole	2.4 x 10 <sup>-6</sup> µg	Rat plasma	[37]
Chlorpheniramine	TDPO/H2O2/ Imidazole	0.14 µg L <sup>-1</sup>	Human serum	[38]

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quencher.[48] In PO-CL, QDs can undergo CRET resulting in prolonged and intensified luminescence processes of up to 100 s of times more than traditional fluorophores.[49] The enhanced luminous output allows for much more sensitive detection of substrates as mere traces can easily be detected due to the highly amplified luminescence. In 2018, Zong et al. synthesised cadmium telluride QDs capped with mercaptopropionic acid which showed highly enhanced CL emission in the QD-TCPO-H<sub>2</sub>O<sub>2</sub> system.<sup>[47]</sup> This system was subsequently used for the highly sensitive detection of carcinoembryonic antigen via an amplified immunoassay with a detection limit of 0.092 ng mL<sup>-1</sup>. The accuracy of the modified QDs in detecting the antigen in seven serum samples of healthy and cancer patients was comparable to the electrochemiluminescence single analyte commercial method. While this method may be expanded to analyse for a host of other antibodies, the authors note that the "flash type" of CL used here may not be practical for clinical applications and a method with longer and more constant emission maybe more suitable.

Chen *et al.* used graphene oxide QDs in combination with the PO-CL reaction and fluorescein to detect the presence of 4nitrophenol in tap and river water samples.<sup>[29a]</sup> 4-Nitrophenol has been listed as a persistent pollutant in water bodies by the US Environmental Protection Agency and, therefore, considerable efforts have been undertaken in detecting its presence in water sources.<sup>[50]</sup> The graphene oxide QDs act as amplifier for the CL signal by increasing the CRET efficiency to fluorescein, but also form hydrogen bonds with 4-nitrophenol increasing the CRET efficiency to fluorescein even further.

Silver nanoparticles were exploited as catalysts in the peroxyoxalate PO-CL reaction to detect 6-mercaptopurine (6-MP), a type of anti-cancer and immunosuppressant drug, with safranin O as a novel small molecule fluorophore.<sup>[51]</sup> 6-MP is suspected to be harmful to pregnant women, hence its detection in a range of pharmaceuticals is potentially vital if they are to be administered to pregnant women. 6-MP competes with safranin O for the high energy dioxetanedione intermediate, thus reducing the chemiluminescent output.

Monitoring biomarkers in human blood serum constitutes one of the most commonly used techniques for early diagnosis of cancer and other diseases.<sup>[52]</sup> Shim *et al.* developed an immunoassay for the determination of thyroid stimulating hormone (TSH) levels in

serum, which is an indicator for thyroid cancer. By immobilizing TSH detection antibodies on fluorescent microspheres, they were able to capture TSH from human blood serum. These TSH conjugated microspheres showed enhanced chemiluminescence emission relative to unconjugated particles when treated with oxalyl diimidazole and  $H_2O_2$ . Thus, they could quantify TSH levels in blood serum more rapidly and sensitively than conventional immunoassays to date.<sup>[53]</sup>

While a range of fluorophores that can be used in PO-CL exist, there always seems to be an interest in finding new and perhaps more efficient small molecule fluorophores. Recently, Kazemi et al. studied the use of hypericin as a novel red fluorophore in PO-CL and the effect of the reductive amino acid glutathione (GSH) on the overall reaction.[30] GSH is one of the most abundant intracellular small molecules and has a thiol group that makes it a potent reducing agent. Hypericin is famous for its many roles including its usage against HIV, cancer and as an antidepressant.<sup>[54]</sup> In this contribution, the quenching effect of GSH in the hypericin-PO-CL reaction was investigated and then used to quantify the amount of GSH found in a tablet. The method seemed robust against many other substances that are commonly found in drugs such as Mg2+, Ni2+, Zn2+ and various amino acids. However, the amino acids cysteine and methionine seemed to interfere severely with the test.

4-Phenylspiro[furan-2(3H),10-phtalan]-3,3'-dione, better known as fluorescamine, is a compound that has been popularly employed in the detection of amino acids at concentrations as low as picomoles.[55] Motoyoshiya et al. have prepared a derivative of fluorescamine bearing a cyano functionality at the meta position of 4-phenyl group.<sup>[56]</sup> The derivatised fluorescamine showed fluorescence output compared to the hiaher original fluorescamine for phenylalanine, alanine, valine, leucine and bovine serum albumin. For the first time, Motoyoshiya also measured the CL output of the fluorescamine derivatised probes by using them as the final emitters of a PO-CL reaction between H<sub>2</sub>O<sub>2</sub> and bis(4-chlorophenyl)oxalate. The CL output was also 2-5 times larger for the cyano derivatised fluorescamine. However, the sensitivity towards the amino acids was lessened to a micromolar level when analysed via CL compared to picomolar level with the fluorescence detection.

Indolizines are a class of compounds that have been explored as potential anti-tumour<sup>[57]</sup> and anti-HIV drugs.<sup>[58]</sup> In a recent study,





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the potential of indolizines to act as the luminophore in a PO-CL reaction and detect the presence of vitamin B6 in pharmaceuticals and bananas was studied.<sup>[59]</sup> The method was very sensitive with a detection limit of  $2.8 \times 10^{-8}$  M for vitamin B6, yet the indolizines exhibited self-absorption behaviour at high concentrations, thus reducing the CL output.

#### 3.4. In vivo detection of peroxide species

Since peroxide species play a fundamental role in regulating biological processes and their over expression is often an indicator of serious diseases, the PO-CL reaction has gained more and more interest in the field of bio imaging and online monitoring. However, one of the major drawbacks of peroxyoxalate chemiluminescence, compared to – for example luminol derivatives – is its incompatibility with aqueous systems. In order to enable *in vitro* and *in vivo* applications for the detection of H<sub>2</sub>O<sub>2</sub>, the PO has to be protected from spontaneous hydrolysis in aqueous media.<sup>[60]</sup> There has been a vast range of methods established in recent years to encapsulate PO-CL systems, where the most common approach is the enclosure of a dye and peroxyoxalate in surfactant<sup>[61]</sup> or poly(ethylene glycol)-b-poly(ε-caprolactone)<sup>[62]</sup> stabilised micelles and liposomes.<sup>[63]</sup>

It has also been shown that incorporating oxalates in polymeric materials increases their stability to make them applicable in aqueous media.<sup>[64]</sup> Many improvements have been made over the years to obtain stronger signals and higher spatial resolutions. Most progress was made in terms of the employed fluorophores, for example by using aggregation-enhanced fluorescence or aggregation-induced fluorescence to yield enhanced CL emission and longer lifetimes,<sup>[65]</sup> driven to the point where even normal physiological levels of  $H_2O_2$  could be observed with strong peaks at inflamed tissue sites. This so-called "nano-torch" developed by Singh *et al.* showed an 11-fold stronger signal than to-date state of the art nanoprobes.<sup>[66]</sup>

This class of fluorophores shows emission wavelengths in the farred/near-infrared (FR/NIR) region, which is crucial for in vivo imaging since the wavelength shift decreases the scattering and absorption by biological tissue and therefore increases the light penetration depth.<sup>[67]</sup> Additionally, the efficiency of PO-CL probes was extended by designing surfactant stabilised nano-emulsions of natural oil droplets. The highly hydrophobic oil inside the drop slows down the PO-CL consumption compared to oil-free emulsions, which results in sustained CL signals.[66, 68] In the recent past, several groups have demonstrated the use of photosensitisers for image-guided therapy. Photosensitisers act as FR/NIR emitters, which simultaneously generate singlet oxygen species upon chemical excitation. This effect was observed to efficiently induce tumour cell apoptosis and cell growth inhibition.<sup>[63-64, 68-69]</sup> Mao et al. demonstrated a way to further enhance the chemiluminescence intensity by treating mice with the anti-cancer drug β-phenylethyl isothiocyanate boosting the H<sub>2</sub>O<sub>2</sub> production in tumour tissues and therefore the treatment efficiency (Scheme 3).[68] Moreover, Cho et al. reported simultaneous tissue imaging and therapy via employment of a hydroxybenzyl alcohol-oxalate-copolymer encapsulated in micelles. By scavenging H<sub>2</sub>O<sub>2</sub> from inflamed sites, they were able to yield IR images of the tissue. Concurrently, the degradation of the copolymer released hydroxybenzyl alcohol, which is a common antioxidant that can reduce the level of ROS caused by

inflammation.<sup>[64b]</sup> PO-CL cannot only be used for the *in vivo* detection of peroxides in inflamed or tumorous tissues, but also to track drug-induced oxidative and nitrosative stress in living organisms. Since the liver is the most frequently affected organ from drug-toxicity, and liver failure can cause death, it is highly important to monitor drug metabolism in the liver.<sup>[70]</sup> In a study of Shuhendler *et al.*, a semi conductive polymer doped nanoparticles was modified with galactose moieties to specifically target liver tissue in living mice. The particles were loaded with CPPO and a nitrose-labile fluorescence emitter to independently detect reactive nitrogen (RNS) and ROS generated by drug metabolism.<sup>[69]</sup>

#### 3.5. In vivo detection of glucose

Glucose is a common intermediate in the metabolism of living cells, where tumour cells have a much higher energy consumption and therefore higher glucose metabolism compared to healthy tissue.<sup>[71]</sup> This opens a new platform for the imaging and detection of tumour cells by glucose levels and even further, the patient's response to treatments. However, established methods are only capable of in vitro diagnosis<sup>[72]</sup> and in vivo monitoring of glucose, and were not specific for tumour tissues.<sup>[73]</sup> With the combination of glucose oxidase (GOx) to generate H<sub>2</sub>O<sub>2</sub> and PO-CL, a highly sensitive glucose detection system can be achieved. Shu et al. developed a model platform device for immunoassays utilising the in situ generation of peroxide in combination with digital multimeter readout.<sup>[74]</sup> A more recent example is the work of Li et al., where hydrogels were doped with PO-CL nanoparticles and (GOx) as depicted in Scheme 4. The gel was subsequently used for quantitative in vitro detection of glucose and subsequent in vivo imaging of tumour tissues by injecting the hydrogel into the tumour periphery.<sup>[75]</sup> An alternative method to encapsulate peroxyoxalate was demonstrated by Jie et al. by synthesising hydrophilic mesoporous silica particles doped with CPPO and a dye. The electrostatically adsorbed oxidase catalyses the production of peroxide and further protects the peroxyoxalate from degradation. Upon cell uptake, biomarkers such as glucose, lactic acid, uric acid and ethanol, which are catalytically reacted to H<sub>2</sub>O<sub>2</sub>, were quantified via chemiluminescence emission in living mice (refer to Scheme 5).[76]

a Glucose +  $O_2$  Glucose oxidase (Gox)  $H_2O_2$  + Gluconic Acid



**Scheme 4.** (A) The reaction of glucose oxidised by (GOx) to generate  $H_2O_2$ . (b) The mechanism of chemically ignited fluorescence reaction occurring in PO-CL nanoparticles. (c) Schematic representation of the components of PO-CL nanoparticles and the detection of glucose by PO-CL–GOx–alginate/Ca gel system. Reproduced with kind permission from reference [75].

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**Scheme 5.** The two-step process of a)  $H_2O_2$  generation and scavenging in the peroxisome and b) the peroxisome-like chemiluminescent nano device. c) The fabrication process of the chemiluminescent silica nanodevice (CSN) and its application in intracellular oxidase-catalyzed biomarker detection. Reproduced with kind permission from reference [76].

#### 4. Polymers supported Chemiluminescence

In the current contribution, we have demonstrated that PO-CL is a powerful and versatile tool with applications in a wide range of areas. However, 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. Possible limitations include the difficulty of solubilising monomers, the harsh conditions leading to cleavage, undesired side reactions during the polymerisation process or the necessity of orthogonal post-modification reactions. Since polymers play a ubiquitous role in industry and everyday life due to their tunable properties, chemiluminescent materials represent a promising field. Indeed, polymeric materials can be custom-made to fulfil a wide range of applications by adjusting the composition, structure, inherent chemical and physical properties. As explained above, the PO-CL reaction relies on two components, an oxalate ester and a fluorophore. On the one hand, we will first discuss how to include an oxalate ester in a polymeric backbone and, on the other hand, explore different types of fluorescent polymers. Finally, we will showcase that from elastomers to (nano)particles, polymers have the potential to step up CL reactions to a whole new level.

#### 4.1. Polymer-based oxalate ester

The synthesis of poly(ethylene oxalate) was first reported in 1930, and polyoxalate and copolyoxalate were further developed in the 1970's. Aliphatic polyoxalates are mostly prepared by ringopening polymerization of cyclic oxalates or polycondensation between diols and oxalyl chloride or dimethyl oxalate. Their facile degradability under aqueous conditions and their biocompatibility have raised interest in medical applications such as absorbable sutures<sup>[77]</sup> and drugs delivery, but also as eco-friendly packaging<sup>[78]</sup>. Interestingly, the use of polyoxalate in chemiluminescence has not been extensively studied and only a few examples have been developed aiming at detecting and imaging H<sub>2</sub>O<sub>2</sub>.

As discussed previously, PO-CL reactions are limited in aqueous media and the reactive molecules have to be confined, e.g. in micelles. In that regard, Lee et al. synthesised polyoxalate polymers by polycondensation of oxalyl chloride with diols and subsequently form CL nanoparticles by adding polyvinyl alcohol as a stabilizer and a dye.<sup>[79]</sup> In vivo imaging was successfully performed in the peritoneal cavity of mice, yet the large size (550 nm) of the nanoparticles limits their further biological use. An interesting avenue is thus to employ amphiphilic copolymers that contain oxalate esters such as poly(norbornenyl peroxalate)poly(norbornenyl ethyleneglycol).[80] Herein, ring opening metathesis polymerisation was employed to allow well-defined amphiphilic block copolymer. The graft copolymer self-assembled into small micelles (33 nm) and sequester the oxalate esters and the fluorescent dye in close proximity within the hydrophobic core. The peroxyoxalate micelles were able to detect H<sub>2</sub>O<sub>2</sub> down to 50 nM and revealed great potential for imaging thanks to the stealth pegylated corona which enhances their circulation lifetime. Recently, Lee and co-workers also developed a new family of biodegradable polyoxalate polymers as potential therapeutic systems in biological applications.[64b] In brief, active drug as well as labile oxalate ester linkages are chemically incorporated into the polymeric backbone. Micelles were then formulated with a biocompatible surfactant and a dye. Thanks to scavenged  $H_2O_2$ , the peroxalate ester bonds cleave and the polyoxalate nanoparticles degrade into small biocompatible compounds, releasing the drug which can be instantaneously monitored by PO-CL. A similar approach has been employed by Höcherl et al. to synthesise self-immolative polyoxalate integrating chemotherapeutic drug via а one-pot step-arowth polymerization.<sup>[81]</sup> The nanoparticles were then loaded with rubrene and the polyoxalate degradation was followed by chemiluminescence as a function of the particle concentration. Based on the above contributions, several synthetic routes have been developed to synthesise polyoxalates with various aliphatic and aryl segments. The next challenge is to incorporate electronegative groups at the 2- or 4-position of the aryl ring to certainly increase the CL efficacy and paves the way to polyoxalate CL systems visible to the naked eyes.

#### 4.2. Fluorescent polymers

Fluorescent polymers can be employed as an energy acceptor and subsequently emit light. While a large range of colours is theoretically accessible employing the PO-CL reaction, the commercially available colours – without mixing dyes – are limited to red, yellow, blue and green. An interesting approach is to copolymerise monomers containing different chromophore moieties. As a prime example, Lee *et al.* prepared series of polyesters<sup>[82]</sup> or polyurethanes<sup>[83]</sup> containing perylene and diphenylanthracene units, respectively a red and blue chromophore. By tuning the copolymer composition, they were able to emit a bright violet light visible to the naked eye. Unfortunately, the anthracene moiety was less resistant to

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peroxide oxidation compared to the perylene moiety and the colour varied a little over time. Additionally, conventional fluorophores are highly conjugated aromatic compounds and they present some limitations due to their insolubility in various solvents, especially in phthalates - the glow-stick solvent. Perylene-containing polyimides as well as the above-mentioned polyesters and polyurethanes showed enhanced solubility in common solvents including dibutylphtalate.

Instead of employing conjugated aromatic compounds that can easily leak and contaminate,  $\pi$ -conjugated polymers can be considered as a suitable alternative because they are normally more stable, tractable, and less toxic. Conjugated polymers are widely employed in polymeric organic light-emitting diodes since the emission colour as well as the quantum efficiency can be readily tuned by adjusting the polymer composition, the nature of substituents, and the regioregularity of the conjugated polymer.<sup>[84]</sup> In theory, shortening the conjugation length of the fluorophore by interrupting the conjugation of the polymer with short intervals of non-conjugated segments - will influence the wavelength of the emitted light and blue-shift the emission. On the other hand, the incorporation of substituents in the backbone such as alkoxy, alkyl or most importantly halogen groups will result in an emission at longer wavelengths.<sup>[85]</sup>

An alternative is to use fluorescent dendrimers as an activator in the PO-CL reaction as this peculiar architecture provides an unusual reaction environment and might provide further mechanistic insights. As such, Koike et al. synthesised poly(benzyl) ether dendrimers having a strong fluorescent distyrylbenzene core.[86] The authors observed a decrease in the fluorescence intensity along with an increase of the generation (up to three generations of poly(benzylether) branches) and they attributed this observation to the dendrimer properties rather than a self-quenching effect. Adding TCPO led to a bright blue light emission, yet the quantum yield decreased concurrently with the dendritic generation. By varying the concentration and generation, the authors proposed that the dendritic structures with large branches act as obstacles between the high-energy intermediate and the fluorescent core. As mentioned in the CIEEL mechanism, the excitation of the fluorophore needs two electronic processes and the steric hindrance of the branches might retard the electronic interaction leading to an insulating effect. Thus, this study showed that by synthesising architecturally well-designed fluorescent dendrimers, control over the light intensity is possible. Furthermore, by employing an amphiphilic triblock copolymer as a polymer matrix, a polyfluorene-based polymer as luminescent reporter, and TCPO as chemiluminescent substrate, Zhen et al.[61] produced chemiluminescent semiconducting polymer nanoparticles via nanoprecipitation. Semiconducting polymer nanoparticles are an emerging class of optical nanomaterials for molecular imaging thanks to their excellent photostability and high brightness. Chemiluminescence spectra were recorded upon addition of H<sub>2</sub>O<sub>2</sub> and confirmed that TCPO is able to chemically excite the semiconducting polymer in close proximity. Interestingly, the authors noted some discrepancy in the ranking of the five polyfluorene-based semiconducting polymer investigated when comparing their fluorescence and chemiluminescence quantum yields and suspected an underlying mechanism. As discussed previously, an intermolecular electron transfer happens between the HEI 1,2-dioxetandione and the fluorophore. After calculation of the energy level between the

highest occupied molecular orbital (HOMO) of the polymer and the lowest unoccupied molecular orbital (LUMO) of the 1,2dioxetanedione, it appeared that the  $\Phi_{CL}$  of the polymers are proportional to this energy interval with the highest HOMO yielding to the highest  $\Phi_{CL}$ . Accordingly, the authors concluded that a minimal energy interval promotes the intermolecular electron transfer and amplifies the light emission. This study is in agreement with Schuster's observation<sup>[87]</sup> and highlights the importance of carefully choosing the fluorophore. Polyfluorene based polymers have shown promising results as their composition was readily adjusted to obtain the maximal light output.

So far, we only reported PO-CL reaction in solution, but polymeric materials offer a wide range of applications which allow for solidphase CL. In the 1980's, Frei and co-workers<sup>[88]</sup> took this direction and developed a method to immobilise 3-aminofluoranthene on controlled pore glass beads which were subsequently mixed with powdered TCPO in a solid-state flow reactor. This grafting technique permitted to eliminate post-column pump in a highperformance liquid chromatography set-up while efficiently detecting H<sub>2</sub>O<sub>2</sub>. Interestingly, the authors mentioned that the transparency of the beads is rather important to obtain good sensitivity. Based on this research, Pontén et al.[89] compared the PO-CL efficiency of six amino polycyclic aromatic hydrocarbon fluorophores covalently immobilized onto synthetic polymeric materials. As such, non-porous methacrylate beads in the 65 -210 µm range as well as macroporous methacrylate supports were synthesised. The authors outlined that the porous methacrylate particles were more efficient than the non-porous particles of similar composition thanks to a larger surface area and consequently, a higher degree of functionalisation. It is worth noting that similar sensitivity could be reached with the nonporous material but the size should be considerably smaller. The authors also pointed out that the amino aromatics behaved differently in homogeneous solution and immobilised onto the methacrylate particles, thus suggesting that CL efficiency in solution should not be used as a single criterion for the luminophore selection for solid-state. This method is a first step into the realm of solid-phase CL but is still limited by gathering the 3 critical components (PO, fluorophore and H<sub>2</sub>O<sub>2</sub>) in close proximity. Recently, our group synthesised a "2-in-1" fluorescent peroxyoxalate molecule by means of photoligation between a phenyloxalate-maleimide and tetrazole (refer to Scheme 6).<sup>[90]</sup> By carefully selecting the tetrazole, bright blue or yellow light - visible by the naked eyes - is emitted and the tailor-made molecule can be easily incorporated in a wide range of materials. Indeed, a large library of end-group functionality - including acrylate, hydroxyl, and carboxylic acid - has been developed, enabling the tetrazole to be introduced into the polymer backbone or in a postmodification step. As such, poly(divinylbenzene) crosslinked seed particles were first synthesised and a shell of poly(2-hydroxyethyl methacrylate) was further grown to make the particles suitable for polar systems. Functionalization with an acid tetrazole and subsequent photoligation with the phenyloxalate-maleimide led to inherently fluorescent solid microspheres. Addition of H2O2 on the powder triggered the CL reaction and the light intensity was proportional to both the H<sub>2</sub>O<sub>2</sub> and microspheres quantity. This new class of material has the power to unlock the potential of chemiluminescent material and constitutes an innovative alternative to conventional multicomponent CL systems.



Scheme 6. (A) Synthetic pathway for the formation of inherently fluorescent microspheres. (B) Scanning Electron Microscopy (SEM) pictures of the final PDVB - PHEMA - Tz2 - PO. (C-D) Pictures of the PDVB - PHEMA - Tz1 - PO and PDVB - PHEMA - Tz2 - PO particles under a TLC hand - held lamp (365 nm). (E) Kinetics of the light emitted by the microspheres in presence of hydrogen peroxide. Adapted from reference [90].

#### 4.3. Polymers in others chemiluminescent reactions

As very few contributions have been reported on integrating PO-CL reagents into polymeric materials, we will not limit ourselves to the peroxyoxalate reaction and highlight some major advances employing other types of chemiluminescence reactions. For instance, self-immolative dendrimers or polymers are now employed as amplifiers to enhance the signal output of chemosensors.<sup>[91]</sup> Shabat's group - an authority on Schaap's - synthesised self-immolative polycarbonate dioxetanes polymeric chemosensors containing up to twenty monomeric Schaap's dioxetanes and a triggering end group.<sup>[92]</sup> By applying an external stimulus such as fluoride, palladium, or H<sub>2</sub>O<sub>2</sub>, the material disassembled in a domino-like mechanism from head-totail releasing the monomeric dioxetane quinone-methides which subsequently decomposed and emitted light. The authors demonstrated that the CL output and the duration of the light emitted were significantly amplified but also correlated with the polymer length.

In the realm of mechanoluminescent polymers, Sijbesma and coworkers<sup>[93]</sup> introduced a bis(adamantyl)-1,2-dioxetane unit into linear or cross-linked poly(methyl acrylate) backbone. Under mechanical stress, the strained four-membered dioxetane ring cleaved into an adamantanone-excited state which emitted a bright blue light. With a mechanoluminescence intensity being proportional to the number of covalent bond breaks, this approach allows real-time mapping of deformation, chain-scissions, and stress distribution with high temporal resolution. Mechanoluminescent probes provide a direct visualisation of internal bond breaks and have subsequently been explored in thermoplastic elastomers containing soft and hard segments,[94] thermoplastics polyurethanes,<sup>[95]</sup> and polyurethane/siloxane hybrid polymers.<sup>[96]</sup> While no peroxyoxalate has been incorporated into a polymer backbone, fluorescent dyes were covalently linked into a polyurethane-1,2-dioxetane backbone to further improve the light emission and allow tunable emission colours of the material.<sup>[95]</sup> Compared to physical blends, the covalently embedded dyes led to a higher mechanical sensitivity, and thus lowering the force threshold required to trigger the mechanoluminescent events. Indeed, the authors noted that the energy transfer depends on the distance between the donor and acceptor (typically 10 -100 Å) and this proximity was difficult to control by physical blending contrary to a conjugated dye readily incorporated into the polymer main chain. From these examples, we envision that the incorporation of PO and dyes in polymer backbone will result in enhanced brightness, duration, colour, and properties tunability.

#### 5. Summary and Outlook

Chemiluminescence has been intriguing humans ever since they first laid eyes on the natural luminescence and substantial progress has been made in understanding its nature and exploit its unique properties in different scientific areas. The use of peroxyoxalate chemiluminescence in analytical methods has significantly enhanced the detection of even trace amounts of analytes in different media and CL is yet to be utilised to its full potential in the biological and medical fields. Chemiluminescent sensors and internal "molecular flashlights" for photodynamic therapy without external light are just the tip of the iceberg and many new applications are yet to be discovered. To date, the use of PO-CL is mainly limited to small molecules, yet PO-CL holds key potential for future applications in the field of polymer chemistry. Incorporating phenyloxalate moieties in a confined environment such as a single chain nanoparticles or different dyes in a polymer backbone might give further insights into the PO-CL mechanism. The recent development of a fluorescent peroxyoxalate helped bypass the need for multicomponent systems and allowed for solid phase luminescence. Inspired by research undertaken in the field of dioxetane-based self-

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immolative polymers and mechanoluminescence, we envision the design of PO-CL polymeric read-out. Key analytes, material cracks or debonding events could then be straightforwardly visualised employing different colours of light. The preparation of oxalate ester-bearing polymers is challenging and to date is still a barely investigated area, but the results observed in polymerbased luminescence are promising a bright future in the field of chemiluminescent macromolecular materials.

#### **Conflict of interest**

The authors declare no conflict of interest.

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We highlight key recent applications on peroxyoxalate chemiluminescence read-out with a strong emphasis on biological systems and polymer materials in order to inspire research into the polymeric chemiluminescent systems.



Laura Delafresnaye, Fabian R. Bloesser, Katrin B. Kockler, Christian W. Schmitt, Ishrath M. Irshadeen, and Christopher Barner-Kowollik\*

All Eyes on Visible Light Peroxyoxalate Chemiluminescence Read-Out Systems