PET-RAFT Polymerisation: Towards Green and Precision Polymer Manufacturing

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PET-RAFT Polymerisation: Towards Green and Precision Polymer Manufacturing

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The necessity of sustainable development in chemical industry has continuously drawn attention to find safe, environmental friendly and atom-economic chemical processes which is defined as the 12 principles of green chemistry. Merging photoredox catalysis and reversible addition-fragmentation chain transfer (RAFT) polymerisation, the photoinduced electron/energy transfer (PET)-RAFT process has opened up a new way of performing reversible deactivation radical polymerisation for well-defined polymer synthesis using light as external stimulus. While providing an increased level of control (spatiotemporal, wavelength, and intensity control) over the polymerisation, PET-RAFT has many attractive attributes (abundant catalyst availability, catalyst recyclability, selectivity and oxygen tolerance) to be green and sustainable which is intriguing for precision polymer manufacturing in industry.

Introduction

The past decades have seen rapid growth in developments of reversible deactivation radical polymerisation (RDRP), a form of free radical polymerisation enabling controlled reactions which can be reversibly activated and deactivated. The control afforded by these RDRP methods has enabled polymers of narrow molecular weight distributions to be synthesised, along with the ability to construct well-defined polymer architectures (e.g. block, stars, and brushes, etc). Given the superior capacity of tailoring properties of polymeric materials, they have found potential applications in polymer additives, smart coatings, electronic devices, drug delivery, among others.[1, 2]

The general aims of RDRP include a rapid initiation step and reduction of irreversible termination events.[3] Therefore, nitroxide mediate polymerisation (NMP), atom transfer radical polymerisation (ATRP), and reversible addition-fragmentation chain transfer polymerisation (RAFT) have emerged as major methods of RDRP with diverse mechanisms. NMP as its name implies, is a controlled radical polymerisation exploiting the persistent radical effect by using nitroxides for radical trapping. This is achieved through activation by homolysis of the alkoxyamine to generate the nitroxide and propagating radicals under conditions such as heating, with deactivation by regenerating the bond again through radical coupling, as opposed to termination.[4] Pioneered by Matyjaszewski[5] and Sawamoto,[6] ATRP uses persistent radicals by means of metal complex catalysts. The catalysts undergo oxidation to activate an alkyl halide and generate radicals via electron transfer, and the reverse reaction occurring to deactivate the polymerisation, with polymerisation rates dependent on the equilibrium between the two states. Finally, RAFT operates through a degenerative chain transfer mechanism by utilising thiocarbonylthio compounds, enabling reversible chain transfer in equilibrium through an intermediate state.[3]

Concurrent with progress in RDRP, growing concerns regarding the environmental impact and sustainable development of chemical industrial activities has spawned the concept of green chemistry by Anastas and Warner. This concept outlines approaches to reducing the environmental impacts of chemical activities where possible, which briefly summarised, include waste minimisation, efficient synthesis, and use of benign conditions and reagents.[7] The advances in RDRP towards greener chemistry include the improvement of existing technologies and/or the creation of new methodologies or sustainable polymer materials for real world applications.

Since its discovery by Rizzardo, Moad and Thang,[3] the RAFT technique has evolved into a well-established RDRP method.[8] Previously, the green chemistry potential of RAFT polymerisation had been reviewed by Perrier and co-workers in 2010.[9] This comprised comprehensive coverage of the reaction conditions under which RAFT could be performed, including environmentally benign solvents such as water, supercritical CO_2, and ionic liquids, along with room temperature RAFT polymerisation and applications of enzyme catalysis to increase efficiency while reducing waste through reusability. Degradable polymers and polymer functionalisation of environmentally friendly materials were also noted as being workable with RAFT in a controlled manner. Alternative initiation methods have been sought, including efficient microwave heating[10-12], ionising radiation[13-

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[15], and photopolymerisation. Since 2014, much attention has been drawn to the development of visible light induced RAFT polymerisation, including the photoinduced electron/energy transfer-RAFT (PET-RAFT) technique developed by our group,[16] an approach to initiate polymerisation using visible light which unifies multiple aspects of green chemistry while maintaining the level of control ascertained by RAFT in producing well-defined polymers.

In this feature article, we explore the evolution of RAFT polymerisation towards the emergence of PET-RAFT technique from photoredox catalysis and its status as a versatile and greener approach to satisfy the concepts of green chemistry. We summarise the rapid advances in this area including its suitability to harsh reaction conditions (non-deoxygenation, biological media, etc.), broad compatibility (light sources, photocatalysts, functional monomers, and other synthetic tools) and the limitations in previous implementations of RAFT polymerisation which have been overcome. It is worthy to note that MADIX (macromolecular design via the interchange of xanthates) has the same mechanism as RAFT, but is differentiated by chain transfer agent, and therefore is excluded from the scope of this feature article. However, xanthates as effective mediators are included in the formulation of PET-RAFT system.

From RAFT to PET-RAFT technique through photoredox catalysis

RAFT technique

Introduced to the community by Rizzardo, Moad and Thang in 1998,[3] the RAFT technique joined the arena of controlled/“living” radical polymerisation (CLRP), which brought up a new mechanism to address the challenges of unavoidable irreversible termination in free radical polymerisation. With the introduction of a thiocarbonylthio compound to a conventional free radical polymerisation system as a reversible chain transfer agent, the RAFT process was able to regulate molecular weights at will and control the dispersity of synthetic polymers to 1.2 or less across a wide range of monomers, functionalities, and reaction conditions. The robust livingness, i.e. the effective retention of RAFT end group functionality, also permits the construction of complex polymer architectures, such as block copolymers through multiple chain extension cycles.

Mechanistically, RAFT polymerisation differs from NMP and ATRP which employ persistent radicals.[2, 4] It is understood that

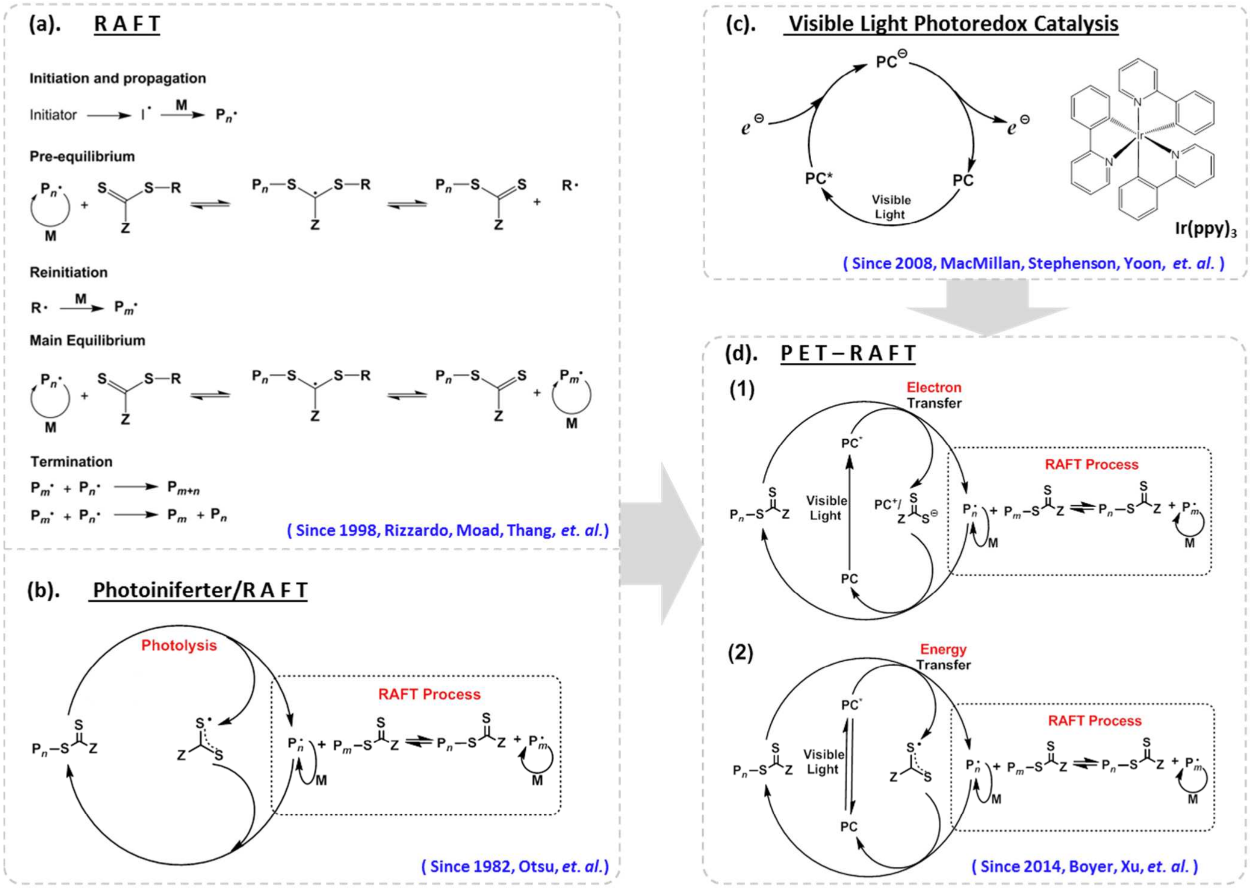

Fig. 1 Progression of PET-RAFT (photoinduced electron/energy transfer - reversible addition-fragmentation chain transfer) polymerisation through the convergence of photoredox catalysis and RAFT technique. The mechanisms for (a) conventional RAFT polymerisation; (b) photoiniferter/RAFT polymerisation; (c) visible light photoredox catalysis and (d) PET-RAFT polymerisation in the presence of photocatalyst: (1) electron transfer and (2) energy transfer mechanism. PC: photocatalyst.

the RAFT process functions by means of degenerative chain transfer (**Fig. 1a)** whereby extremely fast radical addition and fragmentation can occur. When the propagating radical ($P_n\cdot$) transfers to the RAFT agent in the pre- and main equilibrium stages, it results in a dormant species ($P_nSC(S)Z$) in equilibrium with the propagating radical chain ($R\cdot$ or $P_m\cdot$) passing through an intermediate species. This dormant species can then be reactivated by another chain transfer event to continue propagating. The whole process continues until a radical chain without a thiocarbonylthio group terminates irreversibly through combination or disproportionation as observed in conventional free radical polymerisation.[3]

At the time of development, other approaches[17-19] to degenerative chain transfer were known but it was claimed that RAFT had superior control due to the "rapid exchange between dormant and living chains" which resulted in dispersity significantly lower than earlier works. This also means as a requisite, the C=S bond in the RAFT agent must be energetic towards addition of incoming radical species and likewise, the intended leaving group able to easily fragment.

Towards photolytic systems

The approach to earlier examples of RAFT polymerisation largely involved thermally initiated radical sources such as azobisisobutyronitrile, benzoyl peroxide and potassium persulfate which required elevated temperatures to initiate polymerisation.[3] Avoiding heating has brought interest in low temperature polymerisation; radiation of various wavelengths has been investigated as a means of initiating the RAFT process which opened up a wide range of research areas.

Ultraviolet (UV) light can activate RAFT agents through a few different ways. The earliest example was reported in 1982 by Otsu and coworkers,[20] which involved a dithiocarbamate for methyl methacrylate (MMA) polymerisation under UV light irradiation. The thiocarbonylthio compounds function as photoiniferters (**Fig. 1b**) – materials which upon exposure to light, serve as the means of *initiation*, *transfer* and *termination* – as coined by Otsu and later supported in living polymerisation.[21] For more direct initiation, Qiao and co-workers' review in 2016 covered that it was known that other thiocarbonylthio compounds (dithiobenzoate, trithiocarbonate and xanthate, etc) were also responsive to UV light due to the commonly strong UV absorption.[22]

Unfortunately, UV light has inevitable side effects. Davis and co-workers reported feasible polymerisation of styrene and MMA using the chain transfer agents (CTA), 1-phenylethyl phenyldithioacetate (1-PEPDTA) and 1-phenylethyl dithiobenzoate (1-PEDB). However, these two CTAs had shown signs of decomposition under UV light, eventually leading to loss of control and higher dispersity as conversion progressed.[23] Cai and co-workers also posited the lack of desirability of CTAs having high absorbance in the UV region, comparing the CTAs of cumyl dithiobenzoate (CDB) and S-1-dodecyl-S'-(α,α'- dimethyl-α''-acetic acid) trithiocarbonate (DDMAT) and observing that the latter with less UV absorbance was more robust for long wavelength UV RAFT polymerisation.[24] Indeed, while potentially detrimental to control, UV light has also been applied as a useful way of eliminating RAFT end groups by decomposing the thiocarbonylthio functional groups.[25]

Visible light is able to activate RAFT polymerisation through a photoiniferter process, strictly depending on the RAFT agents and light wavelength and intensity applied.[26-31] We investigated the direct photoactivation of specific trithiocarbonates with low C-S bond dissociation energy such as 4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl] pentanoic acid (CDTPA) under blue and green light irradiation, which showed good control of methacrylates.[26, 30, 31] Qiao and co-workers found several trithiocarbonates could be photoactivated to control the polymerisation of a range of acrylates and acrylamides with excellent control but had long induction periods (~ 6 h) under blue light irradiation.[27] A similar system was also reported in which various xanthates were used for the blue light mediated photopolymerisation of the unconjugated monomer vinyl acetate.[28]

Photoredox catalysis

Since the 1980s, there has been continuing interest in utilising metal complex and organic catalysts for highly efficient organic synthesis. The MacMillan,[32] Stephenson,[33, 34] Yoon[35, 36] and König[37] groups proposed the unification of photoredox catalysis and organocatalysis through visible light driven single electron transfer as a powerful tool for organic transformations (**Fig. 1c**). Photocatalysts such as $Ru(bpy)_3^{2+}$ possess high redox potentials with long lived excited states and enable formation of radicals by photoinduced electron transfer (PET) process.[38, 39] The generated radicals were able to initiate various organic transformations including selective oxidations, alkylations, and cycloadditions, among others.[32,40] Likewise, iridium complexes and organic dyes serving as photocatalysts also had similar powerful redox properties which have been covered in several comprehensive reviews.[38, 41-45]

Photoredox catalysed atom transfer radical addition (ATRA)[46] employs the catalysts through a reductive or oxidative quenching cycle to generate radicals from haloalkanes by an atom transfer process to add into alkenes.[38,47] Applying the photoredox concept further to living polymerisation of ATRP, Fors and Hawker used a photoredox cycle with $Ir(ppy)_3$ to polymerise methacrylates[48] and acrylates[49] through generating radicals from alkyl bromides by atom transfer, oxidising the catalyst, and reducing upon deactivation. This process was controlled by switching the light "on/off" to stop and restart polymerisation. Subsequently, a metal free catalyst 10-phenylphenothiazine (PTH) was also found to have similar success with methacrylates, giving the area some green potential.[50] Furthermore, organo-ATRP was developed using advanced computational modelling to design new catalytic systems and establish the structure-property relationship of the photoredox catalysts.[51, 52 53, 54]

PET-RAFT technique

The convergence of developments in photoredox catalysis and photoiniferter properties of thiocarbonylthio compounds

(RAFT agents) eventually culminated in PET-RAFT technology as introduced by our group initially using iridium and ruthenium transition metal complexes as photoredox catalysts. Given the photoredox properties of these catalysts and electron-accepting capabilities of thiocarbonyl compounds, the underlying concepts of photocatalysed ATRP proposed by Fors and Hawker[55] could be applied to the PET-RAFT system (**Fig. 1d(1)**). The excitation of the photocatalyst under visible light irradiation triggers electron transfer to the thiocarbonylthio moiety, reducing it to form radicals (R· or P_n·) which subsequently initiate the RAFT process and also form thiocarbonylthio anion species which are hypothesised to be chemically stable by themselves or otherwise complex with electron-deficient transition metals. Subsequently, the radical may eventually interact with the oxidised photocatalyst to "reset" the system and complete the catalytic cycle.[16] In the case of the energy transfer mechanism expected[56-58] (**Fig. 1d(2)**), the excited photocatalyst transfers energy to the thiocarbonylthio compound to generate propagating radicals for polymerising monomers as well as forming thiocarbonylthio radicals which may quickly recombine to produce dormant RAFT polymer chains.[41] For both mechanisms, the polymerisation control is most likely achieved through a combination of degenerative chain transfer and reversible termination.[59]

With the nature of PET-RAFT polymerisation in mind, an additional level of control is available. Similar to many other photopolymerisation techniques, temporal control can be achieved by controlling the state of the light source, with "off" cycles stopping the reaction temporarily and being able to continue by switching "on" the light.[16, 61] Spatial control can be performed for potential surface patterning. The wavelength of light itself can also be tuned, with selective absorption of photocatalyst/RAFT agent pairs used for orthogonal chemical reactions.

In the following, we explore the features of PET-RAFT polymerisation which make it an easily accessible and green technique and their implications, including use of light sources minimisation of waste, its compatibility with other synthetic approaches, broad availability and recyclability of photocatalysts, selectivity, and oxygen tolerance.

Light source

Light mediated polymerisation as mentioned earlier, is attractive as it allows easy control of reactions by turning the light source on/off. A variety of commercially available light sources with different emission profiles (**Fig. 2**) are suitable including halogen, mercury, xenon and fluorescent lamps, LEDs, laser diodes, and even sunlight.[60, 62] With respect to the environmental aspects, the type of light source has drawn importance mainly due to the consumption of required electricity, and yet the manufacturing materials for the production are also requiring careful consideration to be sustainable. In the earlier examples of photopolymerisation, more energy intensive light sources were considered, in some cases, 500 W xenon lamps were used. [60 63, 64] Towards more efficient light sources, a photoredox catalysed system with trithiocarbonate as RAFT agent using a milder 14 W fluorescent lamp was reported by Johnson an coworkers.[65] As a new generation of light source, LEDs have the advantages of being compact, generally monochromatic and highly efficient (high light output per watt), with experiments applying as little as 1 W for effective activation of polymerisations.[16, 60] They can also be adapted to a variety of forms beyond bulbs with LED arrangements such as strips in setups including light baths[16] and flow reactors[66] to maximise irradiation efficiency. These setups prove themselves durable, bendable, scalable and waterproof, as well as being safe by operating at low voltage and power. Beyond electric light sources, sunlight has potential for further investigation and has been demonstrated for setups including both photo-ATRP and RAFT polymerisation. [28, 59, 67, 68]

Central to PET-RAFT polymerisation is its ease and energy efficiency as it only requires a low energy visible light source and can be performed at room temperature.[16] Suitable wavelengths span the electromagnetic spectrum from blue to red and even to near infrared. The efficiency of a chosen wavelength depends on peak absorbance and molar extinction coefficient of the photocatalyst [16, 66, 69, 70]

Under low energy blue LED irradiation, the initial PET-RAFT studies[16] using $Ir(ppy)_3$ and $Ru[(bpy)_3]Cl_2$ transition metal complexes indicated well-controlled polymerisation as demonstrated by linear molecular weight-conversion relationships with a variety of monomers including MMA,

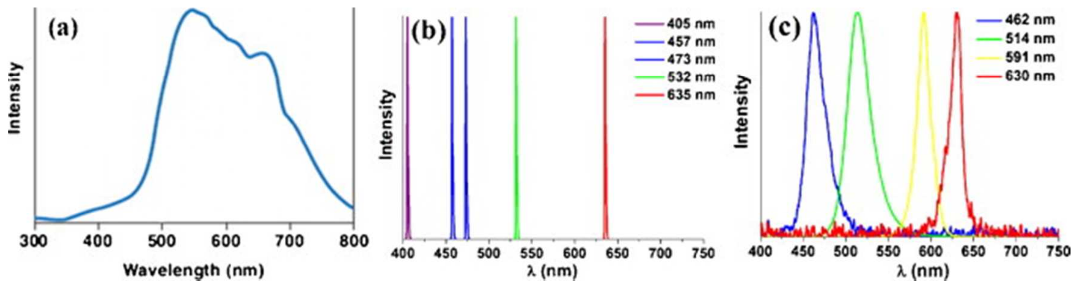

Fig. 2 Emission profiles of various light sources: (a) halogen lamp, (b) laser diodes at 405 nm (purple), 457 nm (blue), 473 nm (blue), 532 nm (green) and 635 nm (red), and (c) household LEDs maximised at 462 nm (blue), 514 nm (green), 591 nm (yellow) and 630 nm (red). Reprinted from reference[60].

methyl acrylate (MA), styrene, and vinyl acetate (VAc) using a wide variety of RAFT agents. The results indicated a generally good control with narrow molecular weight distributions (MWDs) to high conversion (>95%) and with ultrahigh molecular weight (>1,000,000 g/mol) possible.

The flexibility of lighting systems paved the way for diverse reaction setups such as a flow reactor.[66, 71, 72] For the PET-RAFT polymerisation of acrylamides (*N*,*N*′-diethylacrylamide and *N*-isopropylacrylamide) using yellow light at an intensity of 97 W/m^2, the result was reported to have attained 80% monomer conversion within 1 h and a narrow MWD (M_w/M_n < 1.1). The study on varying light intensity also established a linear relationship with an apparent propagation rate constant for the polymerisation of *N*,*N*′-diethylacrylamide.[66] Besides being able to provide monochromatic output, LED setups are also capable of emitting multiple wavelengths in a controlled manner, providing readily available colour control in one source, which provides the ability to tune the effects on polymerisation by wavelength selectivity.[69]

With readily available light sources, the PET-RAFT technique permits simple, environmentally friendly, and precise control of the polymer manufacturing. Consideration does however need to be made for the effects of different wavelengths besides their suitability towards specific photocatalysts (especially with polychromatic sources), noting potential side reactions may occur.

Minimisation of by-products

The minimisation of by-product is achieved by aiming to produce *only* the desired product. Following the principle of green chemistry is the notion that the product should maximise use of participating reactants on an atom basis to minimise waste from side reactions.[73] Visible light photoredox catalysis commands a high degree of atom efficiency, as it presents an effective means of facilitating catalytic processes and selective reactions.[40, 62, 66] The electron generated through the catalysed processes would selectively transfer to specific components which preferentially accept electrons in the reaction mixture. Therefore, the optimal reaction conditions to minimise the waste of reactants is conceivable to achieve through careful design.

Low energy visible light is undoubtedly safer than initiation methods using irradiation in the ultraviolet range or high energy gamma rays. It also reduces the likelihood of side reactions which may be present when using UV and gamma radiation such as undesired initiation of monomers, degradation of RAFT agents,[23, 24] and other damage of chemical bonds and functionalities due to strong absorption.[22] In one example the low energy light has enabled polymerisation of *o*-nitrobenzyl methacrylate by PET-RAFT technique under red and yellow light where the monomer would otherwise degrade under UV light.[74]

By generating radicals directly from RAFT agents, no external radical initiator is introduced, not only reducing the cost but eliminating the complicated decomposed products from radical initiator to contaminate reaction mixture.[75] Although photocatalyst has to be added into the PET-RAFT system, the amount is generally on the ppm scale and the chemical structure of the molecules does not change after polymerisation.

Controlled radical polymerisation of unconjugated monomers is another important area as most of them cannot be polymerised by other methods.[76] Previous reports by Pound and co-workers had identified multiple side products for *N*-vinylpyrrolidone (NVP) polymerisation with xanthates, such as dimerisation of monomer and degradation of the xanthates.[77] This thus had implications of broadened MWD, more dead chains and low end group fidelity using conventional RAFT polymerisation. In contrast, PET-RAFT polymerisation has secured better control with high molecular weights of polyNVP up to 40,000 g/mol and low dispersities (< 1.3), even in bulk conditions or without prior deoxygenation steps. Furthermore, vinyl acetate (VAc) could be polymerised through PET-RAFT process to give the polymers with low dispersities and molecular weights up to 100,000 g/mol without detectable side reactions or degradation of xanthates.[78]

Free of external initiator

The lack of external initiators is linked to atom efficiency benefits of PET-RAFT by means of minimising initiator-derived polymer chains (**Fig. 3**) and potential by-products which would be present in thermally initiated systems.[65, 75, 79] Although it is also noted that initiator-derived polymer chains should form a relatively minor component, careful selection of reaction conditions must be made. During the chain extension, particularly multiple chain extensions, the initiator-derived polymer chains are considerably increasing with the reaction time.[80] Nonetheless, with conventional thermally initiated RAFT polymerisation or ATRP, many groups were still able to synthesise multi-block copolymers of methacrylates, acrylates and acrylamides to moderate dispersities (1.4~1.5). However, only short polymer blocks can be achieved, with a typical molecular weight for each block ranging from 500 to 5000 g/mol.[81-84] In our report of multi-block copolymer preparation,

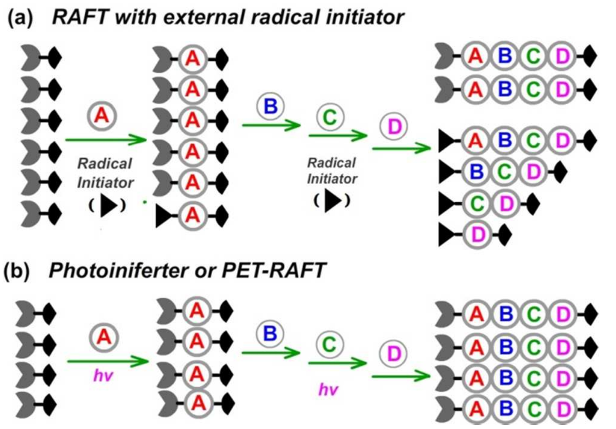

Fig. 3 RAFT polymerisation for preparing block copolymers: (a) with external radical initiator; (b) through photoiniferter or PET-RAFT process.

it was possible to form a decablock polyacrylate towards 80,000 g/mol in which the end group fidelity remained above 90% after 5 cycles of chain extension, indicating low presence of side reactions.[16]

Although the photoiniferter type initiation systems lack external initiators as well, higher energy initiation methods such as UV, gamma rays, and high energy visible light gave rise to potential degradation of reagents. As reported in the examples of thiocarbonylthio iniferter, there was a loss of efficiency attributed to decomposition of the RAFT agents under UV irradiation, with multiple by-products and degradation pathways including cleaving at the C-S bond for the Z-group of RAFT agents.[23, 24]

Compatibility with other synthetic conditions

As a new process developed from RAFT polymerisation, PET-RAFT process has different reaction mechanisms, reaction conditions, formulations and energy sources compared to conventional RAFT polymerisation such as the thermally initiated method. PET-RAFT polymerisation not only has comparable compatibility with conventional RAFT technique, but also more attractive attributes and greener properties in specific cases due to its inherent characteristics. As Perrier and co-workers summarised in their previous review of “green” RAFT polymerisation,[9] it was compatible with a variety of solvents, chemical functionalities and environmentally friendly conditions, along with being able to function in ring-opening polymerisation, enzymatic conditions and dispersion setups. Polymerisation by the PET-RAFT process is feasible in a variety of organic solvents, although better control was achieved in organic polar solvents such as dimethyl sulfoxide (DMSO) and *N*,*N*’-dimethylformamide (DMF) than non-polar solvents such as toluene, tetrahydrofuran and 1,4-dioxane.[16, 66, 78, 85] Aqueous PET-RAFT polymerisation for bioconjugation has also been performed with effective control and retention of living feature as those in other solvents. It is worth noting that the solvents or monomers containing functional groups such as tertiary amines and halogens are expected to interfere with the photocatalysed electron transfer process, and thus possibly distort the results.

Ring-opening polymerisation (ROP) with anionic or cationic chain-growth mechanism is a powerful tool for synthesising biodegradable polyesters and has been demonstrated to be compatible with conventional RAFT polymerisation.[9] Combining ROP with the PET-RAFT technique to prepare block copolymers in a one-pot synthesis, one of beneficial properties introduced by PET-RAFT polymerisation is temporal control using light. The flexibility of how the polymerisation will perform provides opportunities for sequential ROP and PET-RAFT polymerisation in either order, and simultaneous polymerisation without interference and sacrificing chain livingness. This has led to successful preparation of PCL-*b*-PMA diblock copolymer from diphenyl phosphate catalysed ROP of *ε*-caprolactone (CL) and PET-RAFT polymerisation of MA.[86] The simultaneous polymerisation also gave rise to independent behaviour, as the ROP was catalysed through a cationic mechanism and continued in the absence of light, whereas the PET-RAFT process stopped which was useful to control block length. In the case of employing visible light sensitive photoacid as a catalyst to trigger ROP, the one-pot polymerisation with PET-RAFT can be switched between two light wavelengths to afford dual orthogonal reactions. With a photoredox catalyst responsive to red light (635 nm) for the PET-RAFT polymerisation and a photoacid activated under blue light irradiation (460 nm) for ROP, ROP and PET-RAFT polymerisation are able to proceed independently, which sets the way for diblock copolymer (PVL-*b*-PMA) synthesis with both block lengths being controllable.[87]

Photopolymerisation has always had the concerns of light penetration and irradiation homogeneity due to the distance effect, particularly in dispersed polymerisation media. PET-RAFT polymerisation using Ir(ppy)$_3$ as photocatalyst for miniemulsion polymerisation presented a disparity in particle size due to the uneven light exposure and thus nonuniform polymerisation in the system.[88] The other challenge reported was the solubility and partitioning of the Ir(ppy)$_3$ catalyst, which changed over the course of the polymerisation and resulted in reduced rates at later stages as solvent was taken up by the polymer, although the miniemulsion was generally stable due to the surfactant system until particle formation. However, taking dispersed polymerisation further, there was the development of polymerisation induced self-assembly (PISA) by RAFT technique,[89] enabling construction of polymer nanoparticles of various controlled morphologies (micelles, rods, vesicles, etc).[89-91] Extending from RAFT for PISA, PET-RAFT brings to this process its green chemistry properties and degree of controllability by enabling tuning of light exposure time and switching the light source on/off.[92] As applied by our group, there were examples of formation of worm-like micelles by chain extension of poly(oligo(ethylene glycol) methyl ether methacrylate) (OEGMA) to benzyl methacrylate (BzMA) through the PET-RAFT process leading to self-assembly,[93] and further investigating the introduction of singlet oxygen quenchers in a similar system for oxygen tolerance studies.[94] The effects of wavelength on PET-RAFT polymerisation as investigated earlier in homogeneous systems[69] also has implications for PISA, with particle morphology directly controlled by tuning the wavelength. The POEGMA-*b*-PBzMA system was demonstrated to form worm-like micelles under green light, whereas under identical conditions but with blue light, only spherical micelles were produced.[95] Polymer nanoparticles synthesised by PET-RAFT PISA process catalysed by ZnTPP could have application as a singlet oxygen generator for oxidation purposes.[96] Thermally responsive gels prepared by PET-RAFT PISA underwent sol-gel transition on cooling and heating which could see uses in smart materials.[97,93]

Photocatalyst

As a key component of the PET-RAFT technique, photocatalysts play an important role in promoting the green features. With ppm amount of photocatalyst, a broad range of monomers can be polymerised to yield precisely controlled polymers. A great number of photocatalysts are commercially available or can be extracted from abundant natural resources at low costs. More importantly, through effective catalyst immobilisation strategies, catalyst recycling can be practicably achieved.

Broad availability

Numerous photocatalysts, including transition metal complexes,[16, 78, 85, 98-100] metal oxide,[101, 102] metal-free inorganic materials,[103] and organic fluorophores[104] have been demonstrated to be highly efficient for PET-RAFT polymerisation (**Table 1**). In 2014, we launched the PET-RAFT process using transition metal complexes Ir(ppy)$_3$ and Ru(bpy)$_3$Cl$_2$ as photoredox catalysts[16, 85] which have ever been used in photocatalysed organic synthesis and photo-ATRP. Under low energy visible light, various RAFT agents including dithiobenzoates, trithiocarbonates and xanthates have been successfully applied to polymerise a broad range of monomers with excellent control over molecular weights (varying from 10^3 to 2×10^6 g/mol) and narrow molecular weight distributions. Although these transition metal photoredox catalysts are expensive due to the scarcity of iridium and ruthenium in the Earth's crust, they are highly efficient in activating thiocarbonylthio compounds, thus only a small amount of catalyst (e.g. as low as 1 ppm or less for Ir(ppy)$_3$) was needed to achieve high monomer conversion (> 90%). Furthermore, Ru(bpy)$_3$Cl$_2$ was able to activate PET-RAFT polymerisation in aqueous solution or even biological media to accomplish good control.[100] Accordingly, protein-polymer bioconjugates were synthesised through *in situ* polymerisation using bovine serum albumin (BSA) as a model protein without sacrificing its bioactivity.

However, both Ir and Ru-based catalyst mediated polymerisation can only work under blue light irradiation, which also has the suspicious to drive the direct photolysis of specific RAFT agents[26, 27] Therefore, our group attempted to find other inexpensive and completely "green" photocatalysts to avoid the direct photolysis of RAFT agents as well as promote the green features of these catalysts by reducing reliance on transition metal complexes.

Porphyrins and metalloporphyrins are important functional molecules with large conjugated ring structures and typically strong absorbance in the visible region of the electromagnetic spectrum which widely exist in nature (chlorophyll, heme, VB$_{12}$, geoporphyrin, etc.) and play essential roles in biological functions. They can be prepared by both biological and laboratory synthesis up to large scales. Porphyrins and their derivatives have received great interest in the last 30 years due to their numerous applications in organic reactions, energy conversion (photovoltaic), photonics[105] and medicine (photodynamic therapy).[106]

Chlorophyll is a group of abundant and naturally occurring metalloporphyrins, being present in all green plants as a light harvesting antenna for natural photosynthesis. We found that it is a promising candidate to replace transition-metal photoredox catalysts in PET-RAFT polymerisation due to its parallel electron transfer mechanism. Chlorophyll *a* (Chl *a*) and bacteriochlorophyll *a* (BChl *a*) were able to activate the PET-RAFT polymerisation of various monomers to yield well-defined polymers.[61] A ppm level (4~25 ppm with respect to monomer concentration) of Chl *a* can perform well as a photoredox catalyst, although the degradation of Chl *a* upon prolonged irradiation has been observed during the polymerisation. The catalyst degradation resulted in a retardation of polymerisation kinetics. However, the degradation behaviour also posed useful as an effective way to eliminate the catalyst after the polymerisation by forming colourless and inactive species under rigorous light irradiation or in the presence of oxidants such as oxygen and carotene derivatives.[107] In the case of BChl *a*, it showed potential in applications in dental curing, coatings, and photolithography attributed to the merits of its strong absorption of long wavelength from red to near-infrared (NIR) and consequently deep light penetration. Given the remarkable feature of NIR light with minimal absorption and scattering between 700 and 900 nm, thus PET-RAFT polymerisation could be performed in the presence of a translucent barrier.[70] Additionally, pheophorbide *a* (PheoA), an organic porphyrin originating from chlorophyll breakdown without metal centre, has also been employed in PET-RAFT polymerisation, presenting high catalytic efficiency with the dithiobenzoate 4-cyanopentanoic acid dithiobenzoate (CPADB).[108, 109]

Inspired by the initial work in chlorophyll, a variety of non-toxic and low cost metalloporphyrins with non-precious metals (ZnTPP, NiTPP, CoTMPP, and FeTMPP) have been investigated for PET-RAFT polymerisation. It was observed that only ZnTPP was able to catalyse the polymerisation to achieve high monomer conversion within several hours at ppm levels (50~100 ppm). Besides its photocatalytic properties, ZnTPP has been demonstrated to have potential applications in photodynamic therapy owing to its ability to effectively convert molecular oxygen into singlet oxygen under visible light irradiation. Polymeric nanoparticles have been synthesised using a ZnTPP-mediated PISA process, in which ZnTPP was simultaneously encapsulated into formed polymer nanoparticles through dialysis in water.[96] In an effort to promote green polymer synthesis and accommodate RAFT photopolymerisation under biologically relevant conditions, we also developed a polymerisation system in aqueous solution using a water-soluble zinc porphyrin photocatalyst (ZnTPPS^{4-}).[110]

Inorganic semi-conducting metal oxides, including TiO$_2$ and ZnO have also been employed as photocatalysts for PET-RAFT polymerisation. These inorganic materials have been widely used as photocatalysis for oxygen reduction reactions and solar cells because of their low cost, broad access, high chemical stability, low toxicity, and easy removal by filtration. PET-RAFT polymerisation of MMA in DMF with TiO$_2$ and ZnO as photocatalyst was demonstrated by You[101] and Wang[102] to achieve high polymerisation rates and well-controlled molecular weights.

To make PET-RAFT polymerisation greener, metal-free photocatalysts are necessary to avoid metal contamination in

Table 1. *Photocatalysts used in PET-RAFT polymerisation.*

Catalyst	RAFT agents[a]	Solvent	Used wavelength	Ref.
$Ir(ppy)_3$	CPADB, BTPA, BSTP, Xanthate	DMSO	Blue	16, 78, 86, 88, 98, 111, 112
$Ru(bpy)_3Cl_2$	CPADB, BTPA, PDS-BTP	DMSO, MeCN, MeOH, water, EtOH	Blue	85, 93, 100, 111
Chlorophyll *a* (Chl *a*)	CPADB, BTPA, CDB, CPD, CDTPA, BSTP	DMSO, DMF, MeCN	Red, blue	61, 107
Bacteriochlorophyll *a* (BChl *a*)	CPADB	DMSO	NIR, far red, red	70
ZnTPP	BSTP, BTPA, CDTPA, CPDTC	DMSO	Red, blue, green, yellow, orange	69, 94, 96, 108, 109, 113-115
$ZnTPPS^{4-}$	$BTPA-PEG_{750}$	Water	Red	110
TiO_2	CPADB	DMF	UV	101
ZnO	CPADB	DMF	>350 nm	102
TPP	CPADB	DMSO	Red	69
TPP-BSTP	BSTP, BTPA	DMSO	Red, green	116
eosin Y (EY)	CPADB, BTPA	DMSO, water, MeCN, DMF	Blue, green	104, 117-119
fluorescein	CPADB	DMSO	Blue	104
Pheophorbide *a*	CPADB	DMSO	Red	108, 109
10-phenylphenothiazine (PTH)	dibenzocyclooctyne (Tetra-DBCO-PEG), bis-azide TTC	MeCN	Blue	65, 120, 121
graphitic carbon nitride ($g-C_3N_4$)	Benzyldodecyl Carbonotrithioate (TTC-1)	DMSO	UV	103

Note: [a]Abbreviation: CPADB: 4-cyanopentanoic acid dithiobenzoate; BTPA: 2-(n-butyltrithiocarbonate)-propionic acid; BSTP: 3-benzylsulfanylthiocarbonylthiosulfanyl propionic acid; Xanthate: methyl 2-((ethoxycarbonothioyl)thio)propanoate; PDS-BTP: 2-(pyridin-2-yldisulfaneyl)ethyl 2-(((butylthio) carbonothioyl)thio)propanoate; CDB: cumyl dithiobenzoate; CPD: 2-cyanopropan-2-yl benzodithioate; CDTPA: 4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl]pentanoic acid; CPDTC: 2-cyano-2-propyl dodecyl trithiocarbonate; BTPA-PEG750: 2-(n-butyltrithiocarbonate)-propionic acid-poly(ethylene glycol)-750.

specific sensitive cases such as biocompatible materials. In researching porphyrin based photocatalysts for PET-RAFT polymerisation, we found that the polymerisation rate using metal-free porphyrin, e.g. 5,10,15,20-tetraphenylporphyrin (TPP), as catalyst was quite slow even at higher catalyst concentrations (~ 500 ppm with respect to monomer).[116] An electron donor-acceptor (EDA) system was designed to increase the collision frequency between the donor (metal-free porphyrin) and acceptor (RAFT agent) and subsequently promote radical generation.[116] With conjugation of electron acceptor (3-benzylsulfanylthiocarbonylthiosulfanyl propionic acid (BSTP) and 2-(*n*-butyltrithiocarbonate)-propionic acid (BTPA)) to electron donor (porphyrin) through covalent bonds with varied spacers, TPP-BSTP, $TPP-C_2-BSTP$, $TPP-C_2-BTPA$ were synthesised. Compared to free porphyrin, the EDA photoredox catalysts were able to significantly increase polymerisation rates, indicating TPP-BSTP gave the best catalytic performance due to the shortest spacer distance between the TPP and thiocarbonylthio moieties in the EDA structure.

Organic dyes and pigments have widespread uses in organic catalysis due to the attractive attributes of low cost and broad commercial availability. For instance, eosin Y (EY) has been demonstrated to be an excellent photocatalyst for a great number of organic transformations as well as free radical polymerisation.[43, 122-126] In our screening of commonly used organic dyes methylene blue, Rhodamine 6G, EY, Nile red and fluorescein for PET-RAFT polymerisation, only EY and fluorescein were able to activate the PET-RAFT polymerisation efficiently.[104] Other dyes showed negligible monomer conversions under identical conditions even if much higher catalyst dosage (500 ppm) was applied. Additionally, the phenothiazine derivative, 10-phenylphenothiazine (PTH), has been employed by the Hawker[50] and Matyjaszewski[127] groups to conduct metal-free photo-ATRP. From these studies, Johnson et al. reported photo-RAFT reactions using PTH as the photoredox catalyst.[65, 120] In the presence of PTH, *N*-isopropylacrylamide was inserted into trithiocarbonate-containing parent polymer networks via photoredox catalysed growth. The composition and the mesh size of the networks could be tuned to obtain daughter gels with altered chemical and mechanical properties, from which a concept of living additive manufacturing was proposed.[120]

A metal-free semiconductor, graphitic carbon nitride (*g*-C_3N_4), was also introduced as a photocatalyst by Qiao and co-workers[103] for PET-RAFT polymerisation, which had been previously used to activate free radical[128] or copper-catalysed RDRP[129] via an electron transfer process. As reported, well-defined polymers with good chain-end fidelities were obtained even without deoxygenation steps. Graphitic carbon nitride possesses high physicochemical stability, low toxicity, high earth abundance, and ease of synthesis,[130] which thus makes a contribution to greener polymer synthesis via the PET-RAFT polymerisation technique.

Recyclability

One of the green chemistry principles is to minimise waste. The photocatalyst in photopolymerisation is one of the components which could be minimised in use and maximised in recovery due to its high efficiency and intact chemical structure after polymerisation. A straightforward strategy is to immobilise the catalyst onto a solid support, which could effectively facilitate removal and recycling of the catalyst from the product. In RDRP, different methods have been reported for catalyst immobilisation in ATRP, including physical adsorption,[131-133] covalent binding,[132, 134, 135] and reversible hydrogen-bonding attachment.[136]

For PET-RAFT process, we were able to immobilise the zinc metalloporphyrin (ZnTPP) on a solid support and smoothly achieve easy separation and recycling of the catalyst. The solid support material plays an essential role for catalyst immobilisation. Following the selection criteria of green chemistry, cellulose is an excellent candidate support material as it is the most abundant natural polymer and has been extensively studied in supporting matrices for the immobilisation of nanoparticles, proteins, antibodies, anticancer drugs, and heparin. In PET-RAFT polymerisation studies, celluloses in the forms of fibrous cotton and porous sponge were chosen as the supporting materials for the immobilisation of ZnTPP (**Fig. 4**).[114] These immobilised catalysts were able to mediate PET-RAFT polymerisation of various monomers with good control over molecular weights and molecular weight distributions. Separation and recycling of the catalyst can be realised by simply squeezing and washing the material after each polymerisation cycle. These catalysts were reusable for at least three cycles without sacrificing the catalytic efficiency. More recently, silica nanoparticles were modified with EY on the surface through covalent attachment to prepare a novel heterogeneous catalytic system for PET-RAFT polymerisation.[118] The EY conjugated silica nanoparticle (EY-SNP) was found to efficiently catalyse polymerisation of hydrophobic and hydrophilic monomers to reach high monomer conversions with narrow molecular weight distributions in a range of different solvents, including water, DMSO, and *N*-methyl-2-pyrrolidone. Additionally, the EY-SNP was elegantly recovered via centrifugation at the end of the polymerisation and was reused to perform multiple polymerisation cycles.

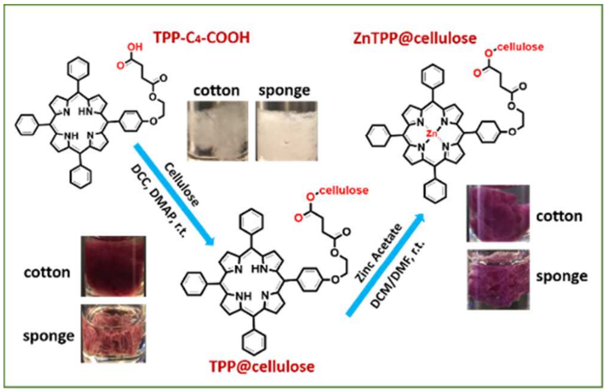

Fig. 4 General procedure for catalyst immobilisation on fibrous cotton and porous sponge. Reprinted from reference[114].

Selectivity

In general, selectivity of a chemical reaction is seen as the result of favouring one product or pathway over the other. In the context of green chemistry, greater selectivity towards desired products means increased atom efficiency, reduced chemical waste and higher yield. In PET-RAFT technique, an innovative concept of selective photoactivation (**Fig. 5**) was developed for advanced organic and polymer synthesis, which can be applied into two different processes: (1) a precise single unit monomer insertion (SUMI) process; (2) an orthogonal photoactivation by RAFT agent/photocatalyst pairs.

Firstly, a precise single unit monomer insertion (SUMI) process was demonstrated by the selective activation of a highly efficient photocatalyst, PheoA, to CPADB (**Fig. 5a(1)**).[108] With the SUMI reaction proceeding in the presence of monomers such as acrylates, acrylamides, or styrene, the R-group of CPADB transitions from a tertiary carbon to a secondary carbon, resulting in a considerable increase in the C–S bond dissociation energy. As a result, the initial RAFT agent (CPADB) can be activated for further reactions whilst the mono-adduct (CPADB-M) cannot be activated any more.

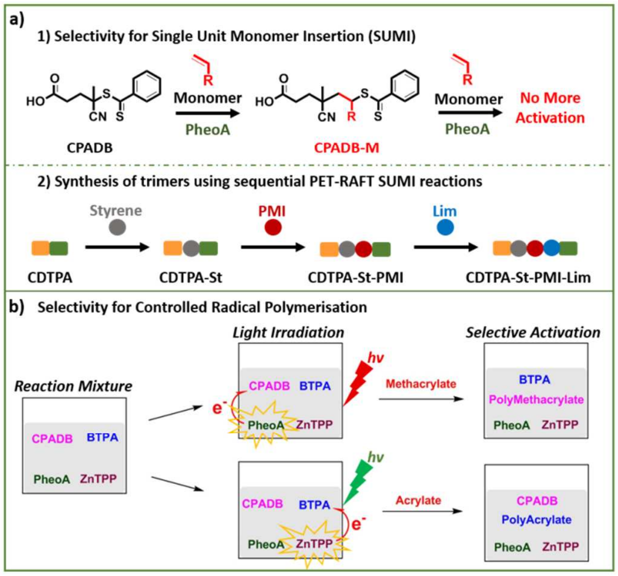

Fig. 5 Two processes of selective photoactivation: (a) Selective activation of initial RAFT in the presence of macro-RAFT adduct (1) and its application for the Synthesis of trimers using sequential PET-RAFT SUMI reactions (2); (b) Selective activation of specific RAFT agent by photoredox catalyst under orthogonal light irradiation.

Consequently, pure mono-adducts can be prepared in high isolated yield (> 97%), with low catalyst concentration (as low as 1 ppm) and without (or with minimal) purification in a single step.

Extending this PET-RAFT SUMI process, a modular strategy was proposed to prepare discrete oligomers by utilising the high selectivity provided by PET activation to develop efficient and sequential SUMI into RAFT agents (**Fig. 5a(2)**).[137] Therefore, a series of single unit adduct, dimers and trimers were synthesised in very high yield under mild conditions. Moreover, a uniform hexamer can also be prepared by *N,N'*-dicyclohexylcarbodiimide (DCC) mediated coupling reaction of the trimer with diol linker and these functional trimers can then be used as building blocks for the construction of higher order precise polymer architectures. Another study was followed to prepare discrete oligomers using a catalyst-free methodology of PET-RAFT SUMI combining with thiol-ene click chemistry.[138] The synthetic procedure comprised of three consecutive PET-RAFT SUMI reactions and two intermediate esterification and thio-ene steps.

Secondly, we found that PheoA could selectively activate CPADB for controlled radical polymerisation of methacrylates in the presence of trithiocarbonate (such as BTPA). Meanwhile, ZnTPP was found to selectively activate trithiocarbonates with higher efficiency than dithiobenzoates (**Fig. 5b**). By combining the unique selectivity of ZnTPP and PheoA, a model graft copolymer ((PMMA-*r*-BTPEMA)-*g*-PMMA) was prepared via a one-pot, two-step process and simple light switching. In this polymerisation, two RAFT agents (CPADB and BTPA) and two monomers (MMA and BTPEMA (2-(2-(*n*-butyltrithiocarbonate) propionate)ethyl methacrylate)) were initially introduced into the reaction mixture containing two catalysts ZnTPP and PheoA. The first step pf polymerisation led to the formation of linear methacrylate copolymers catalysed by PheoA under red light. Upon reaching complete monomer conversion, MA was then introduced into the reaction pot followed by a switch to green light to activate trithiocarbonate by ZnTPP and grow the side chains through the trithiocarbonate sites. Consequently, a graft copolymer with polymethacrylate backbone and polyacrylate graft chains was synthesised through a process of two orthogonal reactions. This one-pot synthetic strategy has been applied in the synthesis of PCL-*b*-PMA block polymers in which diphenyl phosphate (DPP) catalysed ROP and PET-RAFT polymerisation were combined.[86, 87]

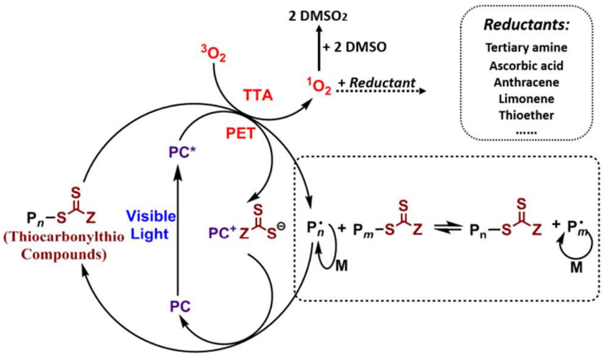

Fig. 6 The mechanism of oxygen-tolerant PET-RAFT polymerisation. PC: photocatalyst.

In terms of the selectivity of ZnTPP to trithiocarbonates, it is not a common phenomenon. In our previous studies, we demonstrated that CPADB is easily activated as it presents a higher reduction potential (−0.4 V versus standard calomel electrode (SCE)) than BTPA (−0.6 V versus SCE). However, ZnTPP investigated in this study is an exception to this rule as activation of BTPA is carried out more efficiently than CPADB, which suggests an unusual selectivity possibly due to an interaction between the ZnTPP and BTPA.

Oxygen tolerance

Oxygen is well known to be radical scavenger, inhibiting radical polymerisation by reacting with propagating radicals to form peroxy species and thus terminating the radical chains.[139,140, 141] To overcome these problems, several strategies have been proposed to remove molecular oxygen from reaction mixtures, including degassing and blanketing with inert gases (nitrogen or argon) before polymerisation,[142-144] repetitive freeze-pump-thaw cycles,[145] and addition of sacrificial agent to react with or reduce oxygen.[145, 146] Although these methods have been demonstrated to be efficient in oxygen removal, inherent drawbacks still exist, especially concerning the green features of the polymer synthesis. The use of expensive inert gases or other deoxygenation methods increase the costs, cause loss of volatile reagents, and are also difficult to operate in manufacture, thus hindering potential industrial applications. Addition of sacrificial agents can consume oxygen efficiently; however, there are concerns in the separation of the introduced reagents, thereby limiting process efficiency and purity of desired products. Construction of an oxygen-free environment could also be challenging for specific applications of polymerisation systems in which the polymerisation media has to be exposed to atmospheric oxygen.[147-150] Although it is possible to use the radical initiator itself to consume oxygen in traditional RAFT polymerisation, it requires a relatively large amount (~2,000 ppm with respect to monomer) as well as elevated temperature (~100 °C) to minimise the inhibition period.[151, 152]

The development of the PET-RAFT technique is promising in solving the problems described above in terms of practicality, cost, and green potential. With the addition of less than 50 ppm photoredox catalyst (Ir(ppy)$_3$ or ZnTPP), oxygen tolerance can be accomplished in PET-RAFT polymerisation conducted in ambient conditions (room temperature). Generally, oxygen tolerance in PET-RAFT polymerisation is attributed to the following processes: (1) conversion of the molecular oxygen into singlet oxygen by intermolecular triplet-triplet annihilation (TTA) of energy transfer from excited photoredox catalyst to molecular oxygen;[16, 78, 85, 104, 153, 154] (2) reaction of singlet oxygen with the solvents (DMSO and so on) or other added reducing agents (tertiary amine, ascorbic acid, and anthracene, limonene, thioether, etc) (**Fig. 6**).[104, 137]

In the PET-RAFT polymerisation using Ir(ppy)$_3$ and Ru(bpy)$_3$Cl$_2$ as photoredox catalysts, induction periods up to several hours were observed, in which consumption of oxygen occurred during light irradiation. Surprisingly, in the system mediated by ZnTPP no induction periods were observed and the polymerisation rates did not show obvious differences between the reactions in the presence and absence of oxygen. We hypothesised that ZnTPP is an excellent singlet oxygen generator, which could be extremely fast to convert molecular oxygen to singlet oxygen; and singlet oxygen was then trapped by DMSO to form the corresponding sulfone, dimethyl sulfone (DMSO$_2$).[66] Furthermore, the addition of reductant can consume the oxygen, resulting in oxygen-tolerant reaction systems. For instance, triethylamine and ascorbic acid have been utilised as singlet oxygen quencher to facilitate the PET-RAFT polymerisation without the deoxygenation procedure.[104, 110,155]

Applications of oxygen tolerance

Oxygen tolerant dispersed systems

We have applied the oxygen tolerant property to polymerisation-induced self-assembly (PISA) to prepare well-defined polymeric nanoparticles.[94, 97, 113, 117] For example, benzyl methacrylate was polymerised to chain extend a POEGMA macro-RAFT agent under ethanolic conditions without inert gas sparging in the presence of ascorbic acid or 9,10-dimethylanthrancene, after which polymer nanoparticles of various morphologies (spheres, worm-like micelles, and vesicles) were obtained.[94] In the other study, 2-(methylthio)ethyl methacrylate, a functional monomer bearing thioether moieties, capable of quenching singlet oxygen to form sulfoxide,[156] was used as a core-forming monomer in a methanolic PISA formulation to prepare nanoparticles with different morphologies in the presence of air.[113]

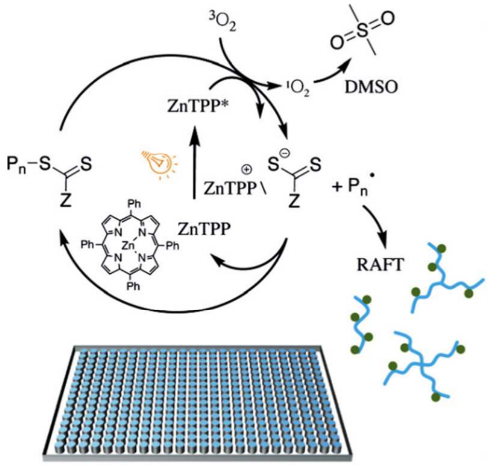

Fig. 7 Ultralow volume PET-RAFT polymerisation for various polymer architectures without prior deoxygenation step.

Polymerisation for ultralow volumes

A remarkable advantage of this oxygen tolerant property is seen in PET-RAFT polymerisation with ultralow volume reaction mixtures, in which deoxygenation is difficult to perform. Although several research groups[157,158,159] have demonstrated that the addition of an oxidase enzyme can be utilised to enable the photoinitiated PISA process without prior deoxygenation, its applicability may be limited by the stability of the enzyme under different conditions particularly in the presence of organic solvents or at elevated temperatures. We reported a photopolymerisation approach using a 96-well microtiter plate (20 uL) for the synthesis of a range of homopolymer and diblock copolymers with the assistance of ascorbic acid.[117] The ability to perform multiple parallel polymerisations in low volumes without deoxygenation has the potential to increase the efficiency at which different reaction parameters can be synthetically screened with less reagents, solvent, and energy. For instance, investigations on the effect of polymer structure on protein binding (lectin concanavalin A) were conducted using this method.[115] In particular, ZnTPP was employed to make clickable polymer libraries with linear, 3-arm, and 4-arm stars which were functionalised with mannose, thus enabling the screening of structure-activity relationships (**Fig. 7**).

Most recently, another application of oxygen tolerant PET-RAFT polymerization was the high throughput synthesis of anti-microbial polymers. In this study, the synthesis of 32 linear copolymers with variety of functional side groups (aminoethyl, phenylethyl, and hydroxyethyl) and block sequences was rapidly achieved in the presence of oxygen in a one-pot synthetic approach.[160] The antimicrobial effects of monomer distribution within these copolymers were comprehensively investigated. Interestingly, the specific placement of these monomers in the polymer chain resulted in different anti-microbial activities.

Polymer bioconjugation

Oxygen tolerance may facilitate the synthesis of polymer bioconjugates that may be difficult to prepare in large quantities.[100, 161, 162] Synthesis of protein-polymer bioconjugates, using BSA,[100, 163] lipase,[164] or lysozyme[161] have been reported. Recently, Hawker and co-workers functionalised the yeast cell surface with chain transfer agent and then conducted the PET-RAFT polymerisation in phosphate-buffered saline (PBS) in the presence of EY and triethylamine (TEA) (**Fig. 8a**).[165] Within 5 minutes, polymer-modified cells were obtained at room temperature without any significant damage to the cells. More importantly, cell aggregation and assembly could be controlled. With the addition of tannic acid (TA), cytocompatible polymer coatings can actively moderate cellular aggregation via interaction between TA and cell surface grafted polymers. This methodology was applied to mammalian cells, which are more fragile and sensitive due to the lack of cell wall. Therefore, covalent binding of RAFT

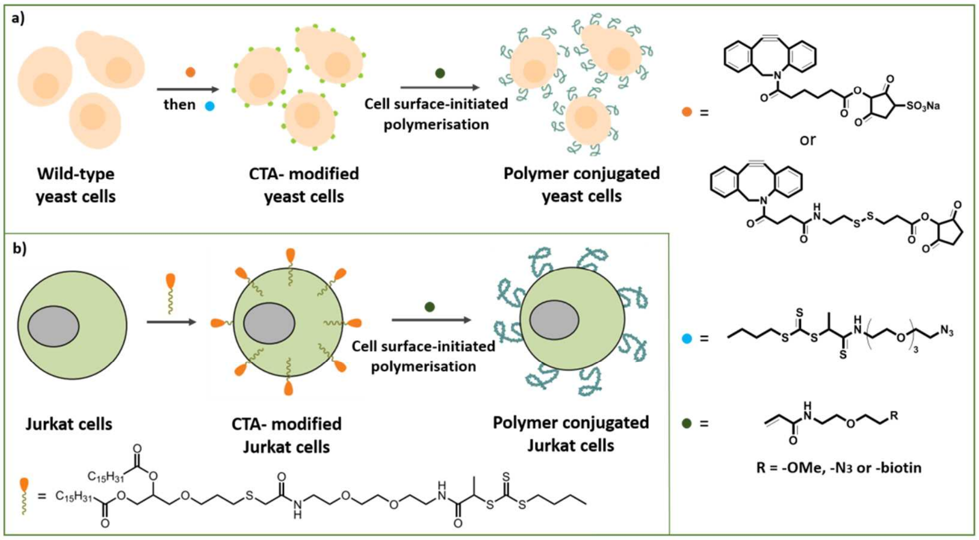

Fig. 8 Polymer grafting on cell surfaces through PET-RAFT polymerisation. Cell surface-initiated polymerization on (a) yeast cells; (b) Jurkat cells. Reprinted from reference[165].

agent will induce excessive cellular stress, resulting in poor cell viability after cell surface-initiated polymerisation. To address this problem, a lipid analogue bearing a RAFT head group, a hydrophilic spacer, and a non-charged 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE)-mimicking C16 tail, was synthesised and then inserted (non-covalent) into Jurkat cell membranes. Afterwards, well-defined graft polymer chains grew from the cell surface without compromising cell viability (**Fig. 8b**).[165]

Polymerisation in flow

An exceptional application of a system with such oxygen tolerance is to upscale the process through flow polymerisation. In 2011, Hornung and coworkers reported the first solution-phase RAFT polymerisation in a continuous flow capillary reactor in which steel tubing was used to prevent quenching of the radical process by oxygen.[166] Later, a variety of controlled radical polymerisation processes using continuous flow reactors have been described by various research groups, including Moad, Junkers and others.[166-171] However, deoxygenation protocols were needed, hindering the industrial potential where large volumes of reaction mixtures are processed. A flow reaction system for PET-RAFT polymerisation was introduced to prepare various macromolecules with tuneable molecular weight distributions on a large scale with outstanding consistency and control (**Fig. 9**). The polymers produced in our flow reactor without prior deoxygenation all presented narrow and unimodal molar mass distributions.[66, 172] Reaction conditions were otherwise extremely mild in terms of the energy source (low intensity yellow and green light) and the temperature (ambient temperature). Therefore, this polymerisation system showed excellent advantages for prospective production of controlled macromolecules regarding cost, practicality, and the sustainability in polymer manufacturing.

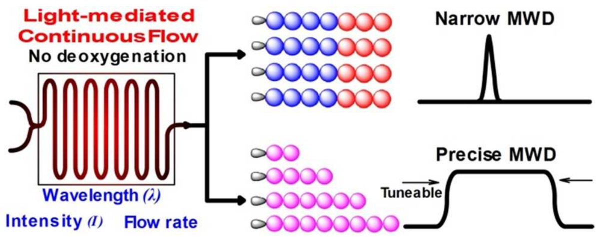

Fig. 9 Advanced polymer synthesis through visible light-mediated continuous flow process in the presence of oxygen.

Other opportunities: Converting oxygen into radicals

By exploiting the oxygen tolerant system in the presence of ascorbic acid, we proposed a novel energy storage system to mimic the photosynthesis in green plants in which the light harvesting cycle and the Calvin-Benson cycle (dark cycle) are included. *In situ* production of hydrogen peroxide from molecular oxygen was achieved after a brief period of visible light irradiation in the presence of photo-organocatalyst (rose bengal) and ascorbic acid. Hydrogen peroxide is slowly consumed by ascorbic acid to generate HO·, which initiates RAFT polymerisation. With irradiation periods as short as 5 minutes, polymerisation could be sustained for several hours in the dark to achieve high monomer conversions (> 70%).[173] This process offered a solution for the challenge of much deeper penetration in photopolymerisation, without sacrificing the temporal control.

Conclusions

PET-RAFT polymerisation possesses attractive features which satisfy principles of green chemistry while carrying the benefits of RAFT polymerisation and maintaining its capability for precision polymer synthesis. The living polymerisation properties of RAFT are retained, limiting irreversible termination and producing well-defined polymers of low dispersity, with the ability to continue polymerisation through chain extensions and create precise polymer architectures. Likewise, finer control techniques can be easily applied in PET-RAFT such as selective SUMI and spatiotemporal control while maintaining high reaction efficiency. Accordingly, further progress in one-pot synthesis is possible with the abilities such as wavelength dependent orthogonal activation enabling very precise control of polymer composition.

By exploiting the RAFT technique mediated by thiocarbonylthio compounds and the versatility of photoredox catalysis, PET-RAFT polymerisation arose as a powerful tool of synthesising polymers under environmental benign conditions. By eliminating the external initiator, end groups of polymer chains can be retained with the same structure of the RAFT agents. Compared to photoiniferter/RAFT polymerisation which generally involves UV or high energy visible light, PET-RAFT technique requires low energy visible light which is safer to handle. Being receptive to a wide range of wavelengths also opens the door to new levels of control over organic reactions and polymerisation, with controlled reaction rates on photocatalyst selection and tuneable nanoparticle morphologies in PISA system.

Auxiliary components such as photocatalysts can be derived from nature, are potentially degradable, and possess a similar degree of compatibility with common monomers and other synthetic techniques. Only sparing amounts of photocatalyst at ppm levels are necessary due to their high efficiency, thus minimising use of resources.

The issue of photocatalyst separation and recycle from polymer products was solved through immobilisation of photocatalyst to a natural abundant substrate. The successful polymerisation exposed to air also highlights the benefits of the area of oxygen tolerance, with simplification of low volume synthesis as concerns of monomer loss during degassing are avoided; time is also saved on possibly larger scale polymer production because heavy duty of degassing techniques can be bypassed.

However, there are still limitations to both the capabilities of PET-RAFT process and its green chemistry features which may be overcome in the future. The development of efficient and selective photocatalyst systems is still required to design a high degree of control over reaction orthogonality. Computational modelling is necessary to understand the underlying catalytic mechanism and structure-property relationship of photocatalysts.

The oxygen tolerance of PET-RAFT polymerisation comes at a cost as while polymerisation proceeds, by-products can be generated and inhibition of polymerisation occurring to some extent. Similar to conventional RAFT polymerisation which is limited in its selection of RAFT agents with monomer compatibility, PET-RAFT polymerisation must make comprehensive consideration of the compatibility of both RAFT/monomer and RAFT/photocatalyst since photoactivation is not universal.

There may still be some time for development before PET-RAFT polymerisation sees uses beyond research, with approaches such as the flow reactor setup pointing to its potential in scaling up to a practical level. We are keen to see in future the polymers produced from these techniques being used in industries such as medicine, drug delivery, and advanced materials. As an area of interest, it carries the benefits of both being green and improving on existing methods by reducing possible costs through minimising waste, providing better reaction control, and allowing for new ways in which existing challenges can be tackled. It should be kept in mind that green chemistry is not an end, with constant improvement occurring and it is hoped that eventual applications can incorporate these principles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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