

PET-RAFT Polymerization for the Synthesis of Complex Molecular Architectures

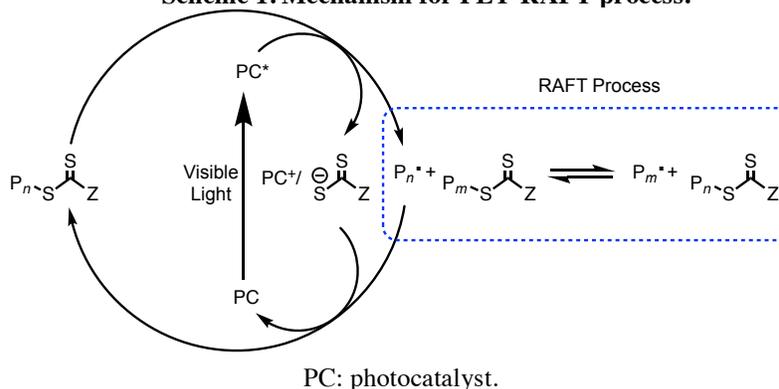
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Since the first report of reversible addition-fragmentation chain transfer (RAFT) polymerization by Rizzardo, Moad, Thang et al. in 1998, it has become one of the most versatile and promising techniques for the controlled radical polymerization of acrylates, methacrylates, acrylamides, and other vinyl monomer species due to its “living” character (in particular, reversibly terminating chain ends and polydispersities less than 1.1) as well as tolerance to a wide range of temperatures and solvent conditions.^{1,2} In the last decade, considerable work has been done to improve upon this technique and afford synthetic chemists control over polymer composition and hierarchical structure comparable to that regularly achieved for natural biopolymers. Photoinduced electron/energy transfer-RAFT (PET-RAFT) in particular maintains the desirable characteristics of traditional RAFT polymerization while providing opportunities for spatial and temporal control.

Scheme 1. Mechanism for PET-RAFT process.



Like RAFT, PET-RAFT operates through the reversible termination of a growing radical polymer chain end by a RAFT agent, typically a dithioate or trithiocarbonate species. However, conventional RAFT activation involves the use of UV light or thermally activated radical initiators to homolytically cleave the RAFT agent from the polymer chain. These activation conditions are often undesirable, as photolysis and thermal degradation of RAFT agents can cause a loss of control and higher dispersities.³ PET-RAFT, by contrast, operates through a photoinduced electron transfer mechanism under much milder conditions.³ The mechanism of PET-RAFT proceeds via the excitation of a photoredox catalyst by visible light, which can then undergo photoinduced electron transfer to the RAFT agent. This species then cleaves mesolytically to generate an anionic thiocarbonylthio adduct and a propagating radical species, which can undergo monomer addition, reversible chain transfer with a different RAFT agent, or interact with the oxidized photocatalyst to restart the catalytic cycle (Scheme 1). Thus, the thiocarbonylthio compound acts as both a chain transfer agent and an initiator, and polymerization occurs only when the system is irradiated with light of a wavelength appropriate

for the excitation of the photocatalyst. Temporal control over the polymerization can be achieved by controlling the light source with alternating “on” and “off” cycles to initiate and reinitiate chain ends or halt monomer conversion, respectively. Studies in the last five years have generated a library of inexpensive photocatalysts with distinct photochemical properties, high efficacies at parts per million concentrations, and selectivities toward particular RAFT agents, offering synthetic chemists greater degrees of control and reaction orthogonality without sacrificing cost or atom economy.^{3,4}

One significant advantage of PET-RAFT over other controlled/living radical polymerization (CRLP) techniques is the fidelity of the thiocarbonylthio chain ends, which allow reactivation of dormant chain ends for successive extensions. Furthermore, since thiocarbonylthio groups are susceptible to activation by a variety of stimuli, multiple polymerization techniques can be used orthogonally or in conjunction with PET-RAFT to generate copolymers. In 2018, Ze Zhang and coworkers demonstrated this versatility through the synthesis of multiblock copolymers using dually switchable polymerization techniques in a single reaction mixture.⁵ It was discovered that trithiocarbonate RAFT agents could selectively polymerize acrylamides through a PET-RAFT mechanism in the presence of an Iridium tris(2-phenylpyridine) photocatalyst, as well as thiiranes through an anionic mechanism at elevated temperatures (> 50 °C). Furthermore, it was found that the polymerization could be reinitiated from dormant chain ends using either heat or irradiation, regardless of the composition of the reinitiating species. Thus, alternately irradiating and heating a reaction mixture containing dimethylacrylamide (DMA) and 2-(phenoxymethyl)thiirane (POMT) monomers, as well as a parts per million concentration of photocatalyst, gave rise to

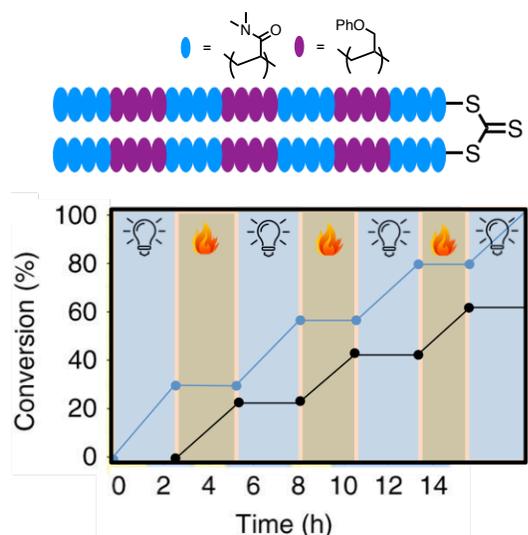


Figure 1. Synthesis of undecablock copolymers via alternating AROP and PET-RAFT polymerization. Adapted from Ref. 5.

multiblock copolymers with acceptable dispersities at low molecular weights ($M_n = 22.3$ kDa, $\mathcal{D} = 1.5$), and block lengths directly proportional to the duration of the stimulus application. In this way, the block lengths could be varied to change the phase behavior of the resultant polymer. Perhaps most significantly, this one-pot approach allowed the formation of undecablock copolymers, which are synthetically intractable by conventional CRLP strategies (Figure 1).⁶ Despite the high dispersities for these polymers, Zhang and coworkers demonstrated the utility of PET-RAFT for the synthesis of complex block copolymers, as well as the potential for control offered by varying external stimuli.

Another recent report from Jiangtao Xu and coworkers further expands on the versatility of PET-RAFT polymerization.⁷ While testing the selective activation of multiple photocatalysts in the same reaction mixture, it was discovered that metallated and non-metallated porphyrinic photocatalysts exhibit selectivity towards different RAFT agents, as well as distinct absorption spectra. Specifically, Zinc tetraphenylporphyrin (ZnTPP) was found via fluorescence quenching experiments to selectively activate trithiocarbonates via PET. This effect was rationalized by a Lewis Acid-Base pairing between the Zinc atom of ZnTPP and the sulfur atom of the

trithiocarbonate RAFT agent, which increases the likelihood of PET by inducing proximity between the donor and acceptor molecules.⁸ Similarly, Pheophorbide A (PheoA) was found to selectively activate 4-cyanopentanoic acid dithiobenzoate due to hydrogen bonding between the acid moiety of the RAFT agent and the pyrrole groups of PheoA. To demonstrate this selectivity, methyl methacrylate was copolymerized with 2-(2-(n-butyltrithiocarbonate)-propionate)ethyl methacrylate (BTPEMA) via irradiation at 690 nm in the presence of PheoA and ZnTPP. It was found that the trithiocarbonate moieties of BTPEMA were not activated, owing to the poor ability of PheoA to undergo PET with trithiocarbonates and the weak absorption of ZnTPP at 690 nm. Subsequent irradiation of the reaction mixture at 530 nm in the presence of methyl methacrylate induced PET-RAFT polymerization from the BTPEMA branching points via selective activation of ZnTPP and trithiocarbonate groups. This result, despite suboptimal dispersities at relatively low overall molecular weight ($M_n = 86.3$ kDa, $D = 1.25$) represents an effective method for the one-pot synthesis of graft copolymers without intermittent purification. The expansion beyond stimulus control to orthogonal reaction control via selective photocatalyst activation affords synthetic chemists yet another means of reaction control unique to PET-RAFT.

A major goal of polymer chemistry in the last decade has been replication of the molecular precision observed in nature for the synthesis of biomolecules. As the versatility of PET-RAFT systems improved, so did opportunities to expand the regime of CRLP into the synthesis of precision polymers and oligomers. As early as 1988, Zard and coworkers reported the generation of macro-RAFT agent adducts via photo-RAFT addition of a single, non-propagating monomer unit to the initiator species.⁹ This single-unit monomer insertion (SUMI) reaction has attracted considerable attention in the last decade as an alternative to protection-deprotection iterative syntheses of discrete, sequence-defined oligomers pioneered by Merrifield,¹⁰ though progress toward its practical application has been hampered by the typical drawbacks of photo-RAFT, such as uncontrolled photolysis and limited monomer scope. SUMI reactions rely on the addition of individual vinyl monomers to a tertiary radical initiator, followed by rapid chain transfer or recombination with the thiocarbonylthio moiety. The C-S bond dissociation energy of the resultant macro-RAFT adduct is accordingly higher, and thus the propensity of these adducts to homopolymerize is low. Zixuan Huang and coworkers, following the work of Jiangtao Xu et al., employed PET-RAFT for iterative SUMI additions to a trithiocarbonate RAFT agent to generate sequence-defined, stereoregular oligomers in acceptable yields (42% overall, Figure 2).¹¹ While a variety of monomer classes have been investigated for potential utility in SUMI reactions, maleimides and indenes are of great interest owing to their demonstrated propensity for alternating copolymerization, a characteristic arising from their differences in polarity and propensity to undergo charge transfer.¹² Furthermore, a library of diverse maleimides can be readily prepared by hydrolysis of maleic anhydride by different amines. Thus, this monomer pair represents an ideal comonomer system for iterative SUMI

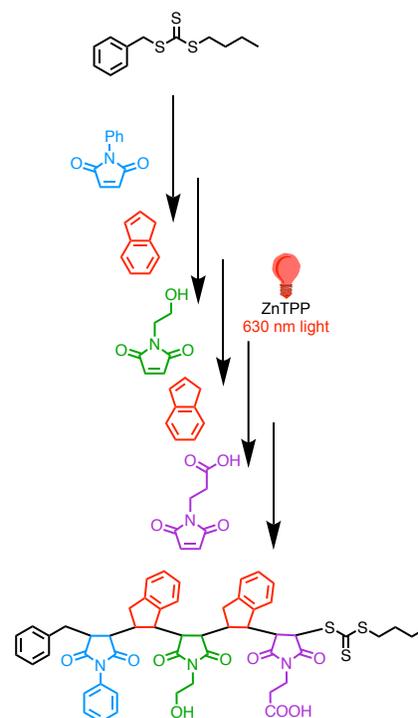


Figure 2. Synthesis of discrete, stereoregular oligomers via iterative PET-RAFT SUMI reactions.¹¹

reactions. Furthermore, it was discovered that the insertion of maleimide and indyl radical species always generates *trans* adducts. This simplifies characterization and offers superior stereoregularity compared to other CRLP syntheses of sequence-defined oligomers.¹³ However, while PET-RAFT SUMI reactions offer considerable control over both the sequence and stereochemistry of products, its monomer scope is currently very limited. Other less-active monomers such as acrylates have a high rate of propagation, and thus tend to homopolymerize. Furthermore, while PET-RAFT offers a considerable advantage over traditional, time-consuming solid-state syntheses, it still requires intermittent purifications. Nonetheless, this work by Huang et al. demonstrates the versatility of RAFT for chain-end functionalization or precise placement of a particular functional group along a polymer chain.

Overall, PET-RAFT is a versatile technique that combines the utility of CRLP with the control of photoredox catalysis. RAFT agents, wavelengths of radiation, photocatalysts, and monomer species may all be varied, offering synthetic chemists multiple experimental handles. However, its compatibility with other polymerization techniques still requires additional study. Furthermore, the industrial application of PET-RAFT is hampered, like other CRLP techniques, by its sensitivity to oxygen. Nonetheless, the preparation of macromolecules with precisely tuned molecular weights and dispersities has been demonstrated in continuous flow reactors without deoxygenation protocols.³ This result points toward the prospective large-scale production of macromolecules via PET-RAFT, though reinitiation strategies, compatibility with other polymerization techniques, and the scope of orthogonal photocatalysts must all be further investigated.

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