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Dual-pathway chain-end modification of RAFT polymers using visible light and metal-free conditions†

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We report a metal-free strategy for the chain-end modification of RAFT polymers utilizing visible light. By turning the light source on or off, the reaction pathway in one pot can be switched between either complete desulfurization (hydrogen chain-end) or simple cleavage (thiol chain-end), respectively. The versatility of this process is exemplified by application to a wide range of polymer backbones under mild, quantitative conditions using commercial reagents.

Controlled radical polymerization (CRP) strategies, including atom transfer (ATRP),[1] nitroxide-mediated,[2] and reversible addition–fragmentation chain transfer (RAFT) processes,[3] are prevalent in both academia and industry for the preparation of well-defined polymers. RAFT polymerization is one of the most versatile CRP methods and can be applied to a comprehensive range of functional monomers under various polymerization conditions (*e.g.*, solution, suspension and emulsion).[3–5] The RAFT process requires the use of a chain transfer agent (CTA), commonly a thiocarbonylthio-based compound, that acts to reversibly cap the reactive carbon-centered radical responsible for chain propagation. While these polymerizations are simple to perform and compatible with a range of monomers, the presence of reactive and colored CTAs at the chain-end of the final product is often detrimental to material performance.[6]

Several protocols have been developed to remove or modify the reactive CTA chain-end. Generally these methods rely on either nucleophilic substitution[7] or thermolysis.[8] For example, the cleavage of CTAs with primary or secondary amines affords a reactive thiol chain-end.[9,10] This approach has been widely utilized for the preparation of surface active polymers,[11] or for further functionalization.[7,12,13] While of great utility for these applications, the thiol chain-ends pose significant challenges due to their reactive nature. For example, thiol end-capped polymers rapidly undergo coupling through the formation of disulfide bonds, limiting their use in applications where molecular weight control is required. To address this reactivity, the conversion of RAFT chain-ends to a simple hydrogen atom has been widely studied.[6] Radical-induced reduction using hypophosphite salts or tin reagents have been demonstrated.[8] However, elevated temperatures and an excess of reagents are required, potentially limiting their use with functional monomers. Owing to the versatility of RAFT polymerizations and challenges associated with their reactive chain-ends, a mild and general protocol for the chain-end modification of RAFT polymers is therefore an important objective. Herein, we report a strategy for the conversion of RAFT chain-ends into either thiol or hydrogen chain-ends with the pathway being dictated by visible light irradiation (Fig. 1). This simple approach is metal-free, mild and utilizes commercial reagents.

In addressing this challenge our attention was drawn to the radical-mediated desulfurization of thiols using tertiary phosphines. This radical-mediated desulfurization has almost exclusively been employed in polypeptide synthesis as a convenient method to convert cysteine residues to alanine, under biologically relevant conditions.[14,15] Interestingly, electron rich tertiary phosphines (*e.g.*, trialkylphosphines) have also been used in conjunction with amines to prevent disulfide formation during the cleavage of RAFT chain-ends to thiols.[16] Given recent interest in light-mediated polymerizations, particularly RAFT,[17–20] the combination of photogenerated

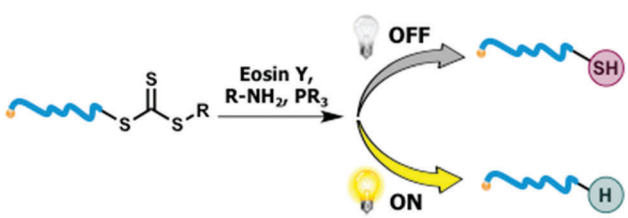

Fig. 1 Selective one-pot conversion of a trithiocarbonate CTA to either the thiol or hydrogen chain-end.

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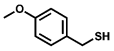
radicals with phosphine-mediated desulfurization presents a unique opportunity to develop a visible light-mediated, dual-pathway reduction of RAFT polymers, where the reaction proceeds through either a traditional nucleophilic pathway, or a sequential nucleophilic/radical photochemical pathway.

While a prior report of visible light-induced desulfurization of polypeptides utilized a ruthenium-based photocatalyst,[21] our aim was to develop a metal-free and visible light-mediated CTA chain-end reduction strategy. With this in mind, we initially investigated the desulfurization of small molecule thiols using an organic photocatalyst. Our groups have previously had success replacing traditional Ir and Ru based photocatalysts, with metal-free organocatalysts, including Eosin Y and phenothiazine.[22–26] Eosin Y is activated in the presence of visible light and is known to operate under either an oxidative or reductive quenching pathway.[27] As such, we envisioned Eosin Y as an ideal candidate to generate the intermediate thiyl radical *via* a reductive quenching pathway.[28,29] Upon irradiation with 465 nm blue LEDs (Fig. S1, ESI†), dodecanethiol was quantitatively converted to the corresponding alkane in 1 h at room temperature in the presence of hexylamine, tri-*n*-butylphosphine and catalytic Eosin Y. Both ^{1}H NMR (Fig. 2a) and GC-MS (Fig. 2b) confirmed the quantitative conversion of the thiol with concomitant appearance of peaks corresponding to the tri-*n*-butylphosphine sulfide byproduct. Significantly, when the same reaction was attempted in the absence of visible light, no desulfurization was detected. In both reactions, an excess of amine was used to mimic the conditions commonly required for the reduction of a CTA chain-end to the corresponding thiol[30] and as an additional benefit, to facilitate the generation and transfer of thiyl radicals within the system.[12] To illustrate the scope of this reaction, successful desulfurization was also demonstrated with a benzylic thiol (4-methoxy-α-toluenethiol) and a tertiary thiol (adamantanethiol) (Table 1 and Fig. S3 and S4, ESI†). Importantly, this reaction offers a facile, metal-free and visible light-mediated desulfurization of thiols, and should be readily applicable to the biologically relevant polypeptide-based systems previously reported. For example, *N*-acetyl-L-cysteine methyl ester was quantitatively converted to the corresponding alanine in water in 2 h under these desulfurization conditions (Fig. S5, ESI†). These promising small molecule results encouraged us to transfer our method to a synthetic polymer system, utilizing common aminolysis conditions to offer two mechanistic pathways (for an in depth discussion of the mechanism see Fig. S6, ESI†) dependent on the absence or presence of light (Fig. 3).

Table 1 Photochemical desulfurization of small molecule thiols

Substrate	Solvents	Catalyst (eq.)	Lights	Time (h)	Conversion (%)
	DCM	0.10	On	1	>95
	DCM	0.10	Off	1	0
	DCM	0.05	On	16	>95
	DMSO	0.05	On	1	>95
	H_2O	0.05	On	2	>95

Due to reports in the literature outlining key diagnostic NMR signals for CTA and thiol end-capped polystyrene (PS),[31] our investigation began with the synthesis of PS (M_n = 2200 g mol^{-1}, $Đ$ = 1.16) by traditional thermally-initiated RAFT polymerization using 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT) as the CTA. Characterization by ^{1}H NMR revealed a broad signal at 4.7 ppm, which corresponds to the literature value for the benzylic methane proton alpha to the trithiocarbonate chain-end (Fig. 4).[32] Upon subjection of the PS derivative to the conditions developed for small molecule desulfurizations, quantitative removal of the RAFT chain-ends was observed. As shown by ^{1}H NMR, in the absence of light, the signal for the benzylic proton shifted upfield to 3.5 ppm, matching reported values for thiol end-capped PS.[31] This suggests that the presence of Eosin Y does not disrupt the expected aminolysis of the CTA, thus enabling the possibility for a dual-pathway process. Further characterization by gel permeation chromatography (GPC) of the thiol end-capped polymer after purification revealed the appearance of a high molecular weight shoulder, indicative of

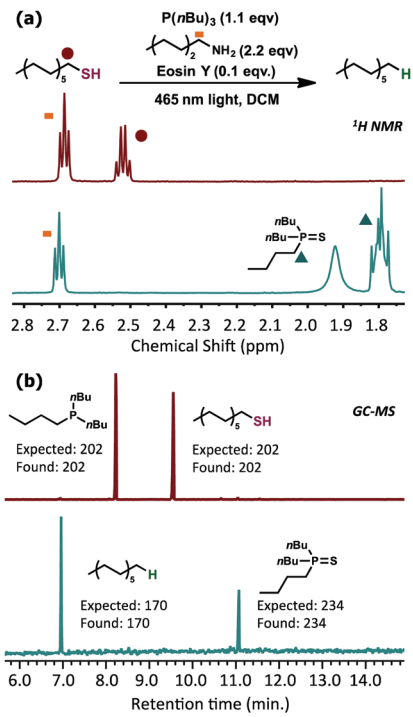


Fig. 2 ^{1}H NMR (a) and GC-MS (b) evidence for the quantitative metal-free and visible light-mediated conversion of dodecanethiol to dodecane using Eosin Y as a photocatalyst.

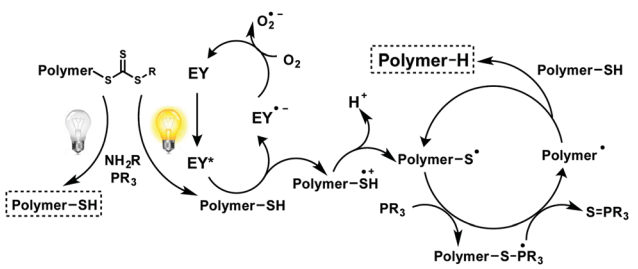


Fig. 3 Proposed mechanisms in absence and presence of light.

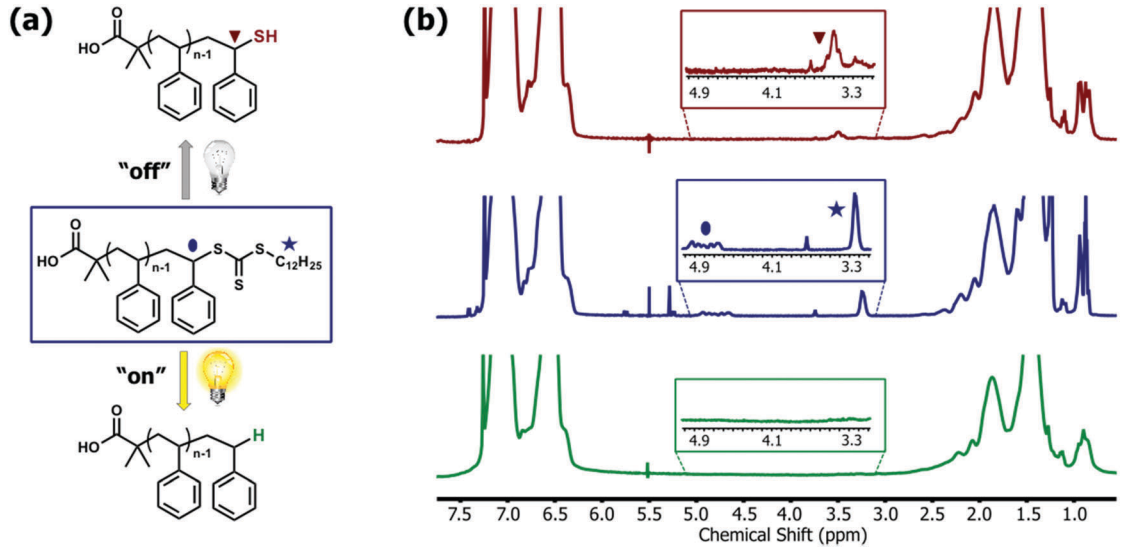


Fig. 4 (a) Chemical scheme of dual-pathway reduction of PS-CTA (M_n = 2200 g mol^{-1}). (b) ^{1}H NMR showing corresponding chain-end signals.

undesired disulfide coupling (Fig. S7, ESI†). In contrast, when the reaction mixture was irradiated with visible light, the complete disappearance of signals in the region from 3.0 to 5.0 ppm was observed, suggestive of quantitative removal of the CTA and introduction of a hydrogen chain-end. Significantly, GPC analysis of the irradiated product showed negligible change in peak shape and dispersity from the starting material, further supporting successful desulfurization (Fig. S7, ESI†). Notably, this desulfurization could also be achieved using natural sunlight (Fig. S8, ESI†). Control experiments in the absence of Eosin Y and/or irradiation resulted in complete conversion to the thiol chain-end, confirming the requirement for both light and a photocatalyst to obtain the hydrogen chain-end (Fig. S9, ESI†). Additionally, subjection of the purified thiol end-capped PS to our desulfurization conditions resulted in quantitative conversion to the hydrogen chain-end (Fig. S10, ESI†). To provide further evidence for the installation of a hydrogen chain-end, d8-polystyrene was synthesized using thermally-initiated RAFT polymerization. The presence of deuterated repeat units facilitates enhanced identification of the chain-end units. In this case, subjecting the deuterated polymer to Eosin Y and light revealed the emergence of a broad signal at approximately 2.5 ppm in the ^{1}H NMR, which can be attributed to successful introduction of a hydrogen chain-end (Fig. S11, ESI†).

To demonstrate the versatility of this approach, CTA-terminated poly(methyl acrylate) (PMA) was synthesized using 2-cyano-2-propyl dodecyl trithiocarbonate under thermal RAFT conditions (M_n = 4800 g mol^{-1}, $Đ$ = 1.09). Characterization by matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-ToF-MS) was diagnostic in identifying the chemical nature of the chain-ends. As expected, analysis of the starting material yielded a single set of molecular ions corresponding to the trithiocarbonate chain-end. Upon irradiation with visible light, complete loss of the original molecular ions was observed, with the appearance of a set of peaks for the hydrogen terminated PMA (286 gmol^{-1} difference in m/z between the trithiocarbonate and hydrogen chain-ends) (Fig. 5). In direct contrast, analysis of the non-irradiated sample resulted in multiple sets of molecular ions, most likely due to the high reactivity of the thiol chain-end. Modulation of this reactivity by *in situ* capping of the thiol chain-end by Michael addition to butyl acrylate, resulted in molecular ions corresponding to the expected thioether chain-end (Fig. S12 and S13, ESI†).[33–35]

Additionally, a water soluble and higher molecular weight polymer, CTA-terminated poly(*N*,*N*-dimethyl acrylamide) (PDMA) was synthesized using 2-(*n*-butyltrithiocarbonate)-propionic acid (M_n = 25 000 g mol^{-1}, $Đ$ = 1.10). Under aqueous conditions, PDMA was subjected to chain-end modification using tris(2-carboxyethyl)phosphine (TCEP) and butylamine. ^{1}H NMR analysis of the isolated polymers with and without irradiation showed quantitative removal of the CTA, with GPC-UV traces confirming its disappearance in both cases (Fig. S15, ESI†). The change in reactivity of the chain-end was clearly illustrated using a refractive index (RI) detector of the irradiated polymer (Fig. 6c), which shows a single peak with low dispersity, nearly identical to that of the starting CTA-terminated polymer (Fig. 6a). However, as previously observed in the case of PS, the GPC-RI trace for the non-irradiated sample showed a prominent high molecular weight shoulder, indicative of undesired disulfide coupling. To further confirm disulfide

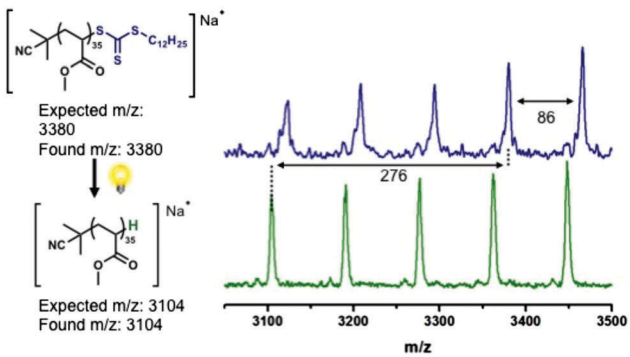


Fig. 5 Scheme and enlarged MALDI-ToF-MS spectra of a sample of PMA, before and after photo-induced desulfurization.

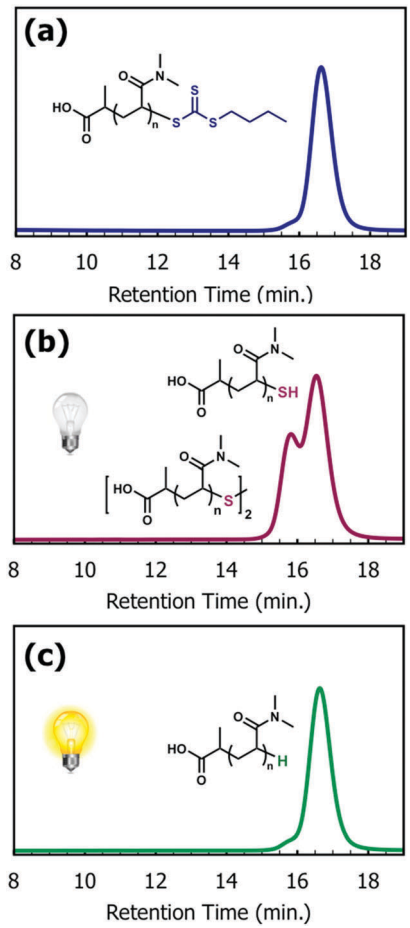


Fig. 6 GPC-RI traces of PDMA before (a), and after subjection to the dual-pathway conditions, with (c) and without (b) visible light irradiation.

formation, addition of TCEP resulted in a reduction of the high molecular weight shoulder (Fig. S16, ESI†).

In conclusion, we have developed a versatile, metal-free desulfurization strategy with broad applicability to RAFT polymers. This approach allows a standard set of conditions for the preparation of polymers with either a hydrogen (visible light) or thiol (no light) chain-end, representing a mild and inexpensive alternative to current approaches for RAFT chain-end modification. The full scope and versatility of this system is currently under investigation.

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