

Polymer Functionalization by RAFT Interchange

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Cite This: *ACS Macro Lett.* 2023, 12, 1306–1310



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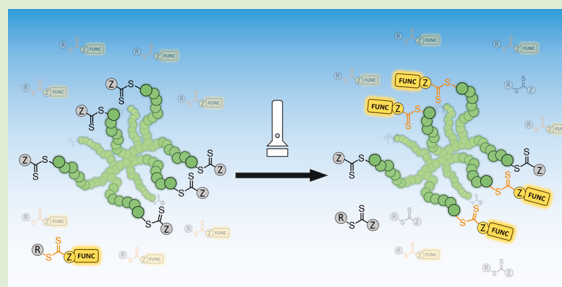
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ABSTRACT: Here, we report a simple approach for end group functionalization of linear polymers and graft copolymers via an interchange process of reversible addition–fragmentation chain transfer (RAFT) polymerization chain transfer agents (CTAs). The high functional group tolerance of the RAFT process allows a library of functionalities to be introduced. Moreover, this approach allows multiple functional groups to be installed simultaneously. Furthermore, as an alternative to end group analysis, we report the utility of the supernatant of the reaction mixture to determine the degree of functionalization.



Polymer end group functionalization is a powerful tool that allows selective site modification for a diverse range of applications such as bioconjugation¹ and surface modifications,² among others.^{3,4} The most common method for introducing end group functionality is using a functional initiator (α -end);⁵ however, this method is not an option with branched architectures where the initiator functions as the branching point. In these cases, ω -end postpolymerization functionalization is often the preferential route for chain end functionalization; this method relies on having a reactive chain end (ω -end) that is specific to the polymerization method employed to construct the branching side chains.⁶ One of the most demonstrated examples is the nucleophilic substitution of a halide end group of a polymer prepared by ATRP, though the allowed functionality is limited to groups that are tolerant to nucleophiles.⁷

Reversible addition–fragmentation chain transfer (RAFT) polymerization has been exploited for designing well-defined polymers,^{8–10} due to its user-friendly nature and versatility. The RAFT process is mediated by exchange of the thiol carbonyl thiol present in chain transfer agents (CTAs), which controls the polymerization and maintains equal growth of propagating chain ends by degenerative chain transfer.^{11,12} Furthermore, the modular nature of the R-group (α -end) and Z-group (ω -end) allows versatility in control over various monomer families and offers facile routes to end group functionalization.^{13,14} Though specific functionality can be introduced via the Z-group, elaborate synthesis would be required to tailor different functionalities on both R- and Z-groups of the CTA. For example, for telechelic α , ω -end functionalization from a RAFT polymerization, typically, a functionality is tethered to the R-group for the α -end functionalization; subsequently, aminolysis of the thiocarbonyl thiol group is carried out postpolymerization to introduce thiol at the ω -end, which can be later reacted by Michael addition (or other reactions) for further functionalization.^{15,16} Although

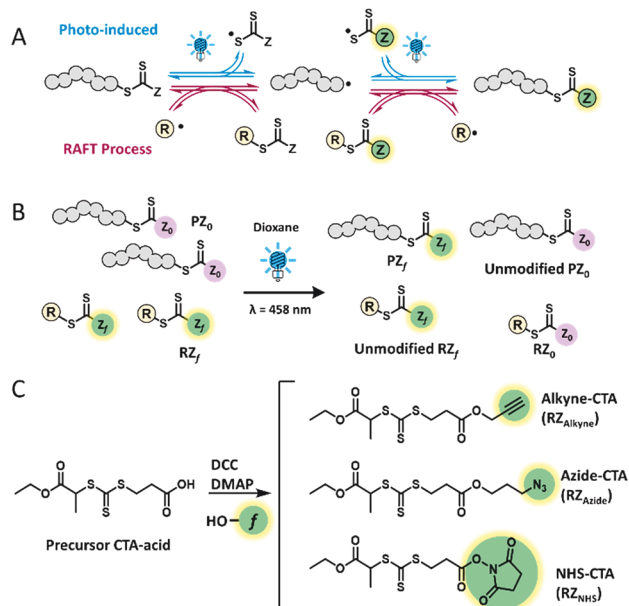
this type of functionalization can be efficient, thiols are prone to oxidation and functional group tolerance is rather limited.¹⁷

In the pursuit of a general ω -end functionalization strategy under mild conditions, we noticed that the RAFT process allows potential interchangeability of chain end functionality through exchange of the thiocarbonyl thio units. In the literature, utility of interchange between two different CTAs was elegantly demonstrated by Whitfield et al., who mixed CTAs with contrasting Z-group reactivity to tailor dispersity of a molecular weight distribution.¹⁸ In an earlier example, addition of a secondary CTA was explored to enhance control over graft copolymerizations by the grafting-from approach.^{19,20} This “Shuttle-CTA approach” enables chain transfer to occur between linear polymers and grafting polymeric side chains, thereby limiting the undesirable intermolecular brush–brush coupling.^{19,20} More recently, Häkkinen et al. further exploited interchangeability of the thiocarbonyl thio units to prepare heterograft copolymer by the “transfer-to” approach, where they demonstrated interchange of grafting polymeric side chains.²¹

Inspired by these works, we envisioned a modular route to end group functionalization of RAFT polymers by the RAFT interchange process (Scheme 1). Here, we prepared a library of trithiocarbonate based CTA tethered with desired functionality on the Z-group through simple Steglich esterification of the precursor CTA-acid (CTA-acid, Scheme 1C, Figures S2–S5).²² In theory, these functionalities tethered to the Z-group (Z_f) can be introduced onto a RAFT polymer postpolymeriza-

Received: August 21, 2023

Accepted: September 11, 2023

Scheme 1. End Group Modification by RAFT Interchange^a

^a(A) Mechanism of the end group exchange by photo-iniferter and RAFT process. (B) Illustration of products from RAFT interchange. (C) Library of functionality appended on the Z-group.

tion via the RAFT exchange process. Once the equilibrium of exchange has been reached, assuming equal distribution of the Z-groups, the amount of the functionalized Z-group (Z_f) introduced onto the polymer (defined as % of polymers functionalized with Z_f, PZ_{f,eq}%) should equal the molar fraction of the initial species (eq 1; see the Supporting Information for detailed derivation):

$$PZ_{f,eq}\% = \frac{[RZ_f]_0}{[RZ_f]_0 + [PZ_0]_0} \quad (1)$$

Here, the Z-group of the initial macro-CTA (i.e., the RAFT polymer) and the functionalized free CTA in the initial feed are referred to as PZ₀ and RZ_f, respectively, whereas the newly formed macro-CTA with functionalized Z-group is denoted as PZ_f and the concomitantly generated free CTA bearing the Z-group originated from the initial macro-CTA is denoted as RZ₀ (Scheme 1B).

It is important to note that characterizing polymer end groups by ¹H NMR can be challenging due to their relative weak signals which can also overlap with the polymer backbone. For this reason, we decided to examine the freely soluble CTAs present in the supernatant after polymer precipitation. In theory, free CTA bearing the Z-group that was originally attached to the polymer will be introduced into the supernatant as RZ₀, following the exchange reaction, together with the remaining (unmodified) RZ_f. By determining the molar fraction of RZ₀ with regard to unmodified CTA (RZ_f), we can calculate the theoretical percentage of functionalized Z-group onto the polymer (PZ_f%) at any arbitrary time point *t* by considering the stoichiometric equivalence *r_f* of RZ_f in the initial reaction mixture (*r_f* = [RZ_f]₀/[PZ₀]₀) via eq 2 (see the Supporting Information for detailed derivation):

$$PZ_f\% = \frac{[RZ_0]_t}{[RZ_0]_t + [RZ_f]_t} \times r_f = RZ_0\% \times r_f \quad (2)$$

Experimentally, we chose to employ polydimethylacrylamide (PDMA) (DP = 80) prepared by traditional RAFT polymerization,²³ as it precipitates well in diethyl ether and hexane where the free CTAs have excellent solubility (Figure 1A). We

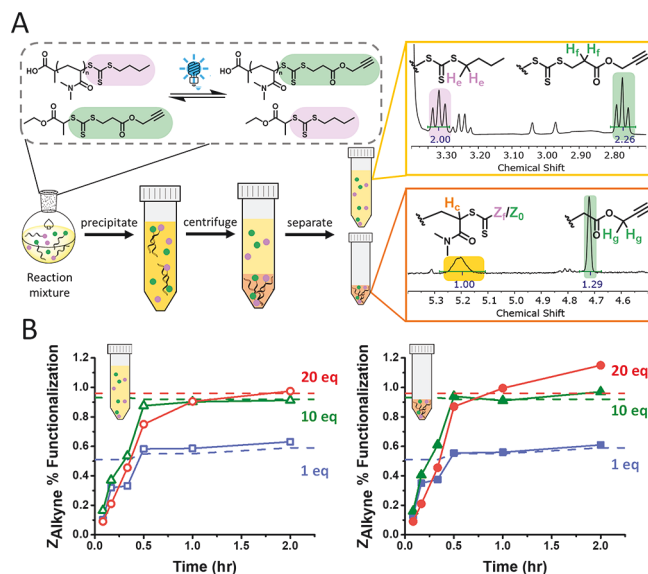


Figure 1. (A) Characterization of end group exchange was achieved by ¹H NMR analysis of the supernatant (yellow) and precipitated polymer (orange). Data shown are from a 1× equivalent of functionalized CTA (RZ_f). (B) Kinetic analysis of end group exchange with 1, 10, and 20 equiv of alkyne-CTA. Degree of functionalization characterized from the supernatant (left) and precipitate (right). The dotted line represents equilibrium limit.

emphasize that a selective solvent–polymer system to ensure complete precipitation of the polymer is necessary to minimize contamination in the supernatant by remaining solvated polymers. Here, we used blue light (λ = 458 nm) to trigger the exchange reaction under catalyst free conditions (Figure S1), which allows direct fragmentation of the (macro)-CTA and RAFT process to occur concurrently to promote RAFT interchange (Scheme 1A). The free CTAs from the supernatant were examined by ¹H NMR after the solvent was removed under reduced pressure.

Additionally, to confirm if our calculations from the supernatant coincide with the yield we observed from the isolated polymers, we first employed alkyne-CTA (RZ_{alkyne}, Scheme 1C). Due to its characteristic CH₂ positioned between the ester and the alkyne at 4.72 ppm by ¹H NMR analysis (H_g, Figure 1A) and using the CH of the terminal monomer unit next to trithiocarbonate at 5.20 ppm as the reference for total polymeric species (H_h, Figure 1A), we were able to calculate the percentage of the polymer that had been functionalized (i.e., directly assessing PZ_f%). For the analysis of the supernatant, we used the CH₂ next to the trithiocarbonate at 3.32 ppm (H_h, Figure 1A) to determine the fraction of the exchanged Z-group (RZ₀) originating from the macro-CTA with respect to the CH₂ next to the carbonyl of the ester group at 2.77 ppm (H_g, Figure 1A) of the unmodified functionalized CTA (RZ_f).

According to eq 1, using 1 equiv of functionalized CTA with regard to the to-be-functionalized RAFT polymer would lead to approximately 50% functionalization (Figures S7–S8). Prior to the exchange reaction, we obtained ^1H NMR spectra to determine the initial molar ratio of macro-CTA (PZ_0) to the functionalized free CTA (RZ_f). From our reaction conditions, equilibrium was reached after approximately 30 min as the degree of functionalized end groups on the RAFT polymer from the precipitated polymers ($\text{PZ}_{\text{alkyne}}\%$, estimated by ^1H NMR of precipitated polymers, Figure 1B) was consistent with theoretical maximum calculated from the molar fraction of the initial reaction mixture, according to eq 1 ($\text{PZ}_{\text{alkyne,eq}}\%$, Table S1). Moreover, the theoretical value of $\text{PZ}_{\text{alkyne}}\%$ from the ^1H NMR analysis of CTAs (RZ_0 and $\text{RZ}_{\text{alkyne}}$) in the supernatant (according to eq 2) at each time point investigated closely matched with the value obtained from the ^1H NMR of the isolated polymers (Figure 1B, Table S1), validating the utility of eq 2. The slight discrepancy between the two methods can be attributed to contamination from incomplete separation during polymer precipitation.

Equation 1 also predicts that using 10 and 20 equiv of CTA would allow theoretical degree of functionalization of the RAFT polymer up to 91% and 95%, respectively, once the equilibrium is reached (Figures S9–S12, Table S1). Pleasingly, the experimentally obtained values for the degree of functionalization, calculated from the supernatant (according to eq 2) or estimated from the ^1H NMR analysis of the precipitated polymer, are consistent with the predicted values from the initial molar ratios according to eq 1 (Figure 1B, Table S1). However, at 20 equiv of CTA, we found our experimental estimation for the degree of functionalization, via analyzing the precipitated polymer, to exceed over 100%, due to limitation of end group analysis by ^1H NMR (Figure S11). Therefore, we recommend using the expected value from the initial molar ratio (eq 1) as the maximum degree of functionalization that can be obtained.

We next investigated RAFT interchange with azide functional CTA (RZ_{azide} , Scheme 1C) using the same polymer (PDMA, DP = 80) with 1 equivalence of RZ_{azide} . Here, the CH_2 next to the carbonyl of the ester group at 2.70 ppm (H_f , Figure S14 representing unmodified functionalized CTA (RZ_{azide})) was integrated with respect to the CH peak at 4.72 ppm (H_c , Figure S14) on the R-group (both RZ_0 and RZ_{azide} , representing total CTA species in the supernatant). Pleasingly, the end group analysis of the precipitated polymer (Figure S13), using a terminal monomer unit as a reference, correlated well with the $\text{PZ}_{\text{azide}}\%$ determined from the supernatant (Table S2).

The high functional group tolerance of this RAFT based ω -end group functionalization allows facile installation of sensitive functionalities, which would otherwise be very difficult to directly introduce. For example, NHS-activated esters can be readily introduced using NHS-CTA (RZ_{NHS} , Scheme 1C).²⁴ Similar to the example above, CH_2 next to the trithiocarbonate at 3.36 ppm (H_e , Figure S15) can be used to determine the fraction of the exchanged Z-group (RZ_0) originating from the macro-CTA with respect to the CH_2 next to the NHS-activated ester group at 3.08 ppm (H_f , Figure S15) of the unmodified CTA (RZ_{NHS}) in the supernatant (Table S3).

Furthermore, we envisioned the utility of this method to be advantageous for polymers bearing multiple CTAs such as polymers with CTAs as side chains and graft copolymers that

bear CTAs on the end groups of the grafts.^{25–30} Indeed, polymer chains with multiple sites for functionalization can be desirable for many applications such as drug delivery.³¹ Here, a linear polymer backbone bearing CTA embedded in the repeat unit with the Z-group as side chains was prepared by $\text{A}_2 + \text{B}_2$ RAFT step-growth polymerization following our previous protocol (Figures S17–S19) as the starting point.²⁷

We briefly examined the kinetics of the RAFT interchange with this $\text{P}(\text{M}_2\text{-alt-CTA}_2)$ backbone using 1 equivalence of alkyne-CTA with respect to CTA side chains (Figures 2A and

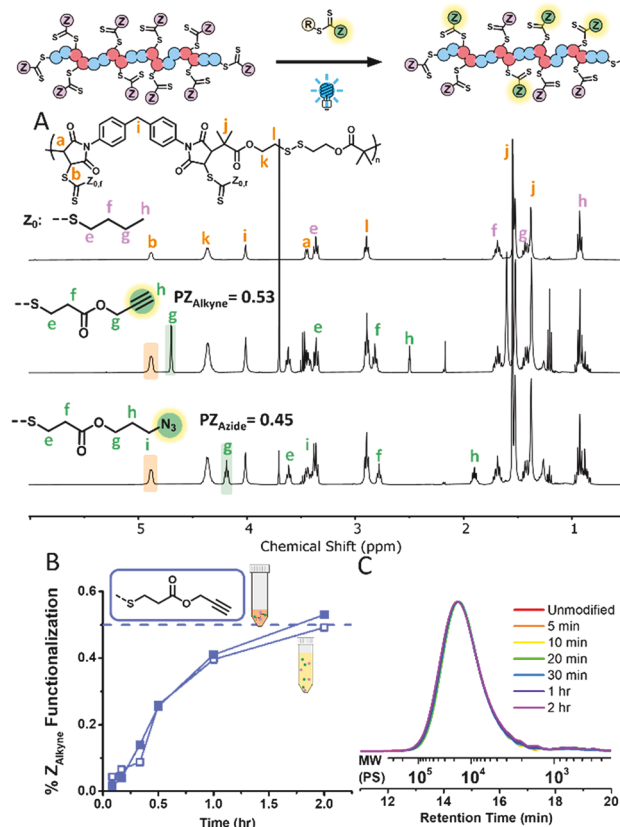


Figure 2. (A) Stacked ^1H NMR spectra of $\text{P}(\text{M}_2\text{-alt-CTA}_2)$ before and after RAFT interchange with azide and alkyne CTA. (B) Kinetic analysis of Z-group exchange of $\text{P}(\text{M}_2\text{-alt-CTA}_2)$ with azide-CTA and (C) its unchanged molecular weight distribution from SEC analysis.

(S20–S21). Because of the large amount of CTA side chains (two per repeat unit), a relatively higher mass of the exchanging CTA is required. Interestingly, compared with the earlier exchange reaction (Figure 1B), this exchange reaction took longer time (~ 2 h) to reach equilibrium (Figure 2B). Nonetheless, after 2 h, approximately 50% functionalization was confirmed from ^1H NMR of the precipitated polymer and the supernatant (Figure 2B). In addition, we also successfully demonstrated a similar degree of functionalization with azide-CTA under the same reaction conditions (Figure 2A). Moreover, in contrast to the end group analysis, characterization of the side chains provides signals that are relatively higher in intensity as determined by ^1H NMR spectroscopy (Figure 2A). In addition, despite the functionalization occurring through radical intermediates, SEC analysis did not reveal signs of possible cross-linking from bimolecular combination (Figure 2C).

Lastly, we explored the end group functionalization of graft copolymers via this new method. Using poly(*N*-acryloylmorpholine) (PNAM) graft copolymer, which was prepared by grafting from P(*M*₂-*alt*-CTA₂) backbone (Figure S22) and under the same reaction conditions as above, we were able to achieve simultaneous end group exchange with azide-CTA (RZ_{azide}) and alkyne-CTA (RZ_{alkyne}) with the PNAM graft copolymer (Figures 3 and S23–S25). We applied a

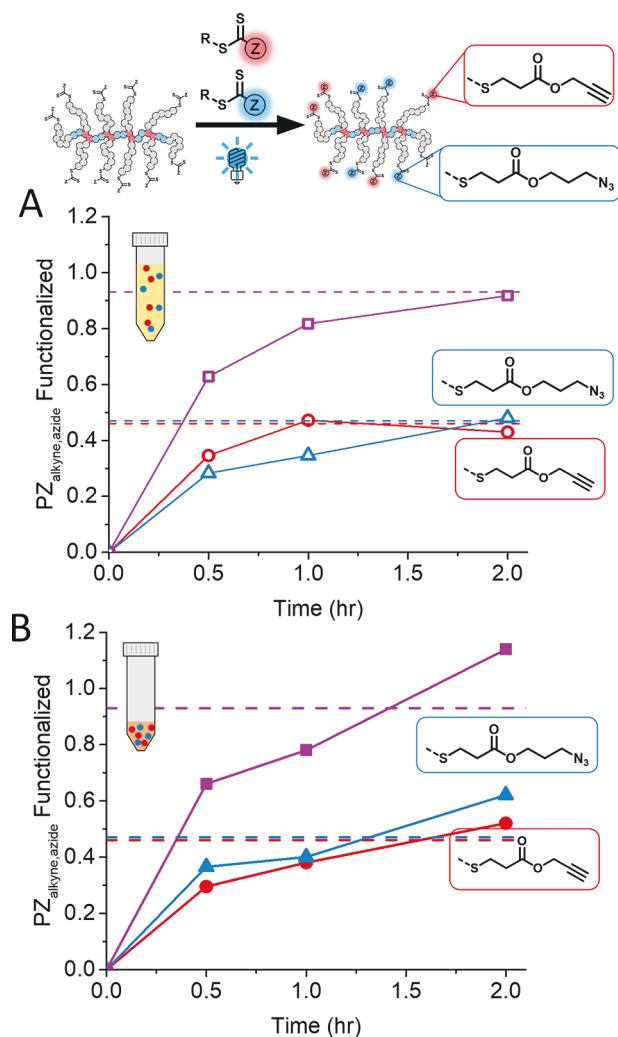


Figure 3. Simultaneous Z-group exchange with azide (blue trace) and alkyne (red trace) CTAs on graft end groups of P(M₂-*alt*-CTA₂)-g-PNAM). The dotted line represents the equilibrium limit of exchange. The purple trace shows the combined degree of functionalization. (A) Kinetic analysis from supernatant characterization. (B) Kinetic analysis from precipitated polymer.

stoichiometric ratio (r_{alkyne} and r_{azide}) of 5 each with respect to the end group CTA (PZ₀) to target approximately 91% degree of functionalization (or 45% of each, Table S4). Despite the additional complexity of introducing a second functionalized CTA in our system, we can determine the theoretical degree of functionalization from the supernatant by considering the initial stoichiometric ratio (r_{alkyne} and r_{azide}) (see the Supporting Information for further details). In contrast to directly characterizing the graft copolymer end group, where a clear overestimation of the degree of functionalization was apparent (Figures 3B and S24, Table S4), analyzing the

supernatant seemingly gave a more reliable degree of functionalization (Figures 3A and S23, Table S4).

We emphasize that, while this methodology is generally applicable for functionalizing graft copolymers with CTA end groups, the effect of radical termination is an inherent limitation that needs to be taken into consideration, especially with an increasing number of grafts bearing CTA end groups. In our earlier preliminary experiments, we found brush–brush coupling to occur at lower equivalence of RZ_f (1 equiv) at longer reaction times (4 h, Figure S26). This effect can be minimized by employing higher equivalences of RZ_f and stopping the reaction right after the equilibrium has been reached. It is also conceivable to optimize reaction conditions by reducing the generation of radical species through modulating the light source (distance/intensity/wavelength).

By taking advantage of the rapid equilibrium of the RAFT process, we demonstrate a unique end group functionalization with robust functional group tolerance. The degree of functionalization can be determined from the supernatant, allowing alternative means to end group characterization. Though this approach allows a predictable degree of functionalization from the initial feed ratio of the functional CTA, it is important to note that the yield is limited by the nature of the equilibrium; consequently, this may not be an ideal route for end group functionalization of a linear polymer if quantitative conversion is desired. Nonetheless, we anticipate the utility of this methodology in functionalizing polymers that contain multiple CTAs, such as graft copolymers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsmacrolett.3c00495>.

Experimental details and characterization data (Figures S2–S26, Tables S1–S4); derivation of the equations used for characterization (eqs S1–S46) (PDF)

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Author Contributions

S.P. initially conceived the idea of end group functionalization of graft copolymers by RAFT exchange.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge the initial study conducted by Dr. Joaquin Sanchis-Martinez and Erny Sagita at the Monash Institute of Pharmaceutical Sciences. This work was financially supported by the National Science Foundation (NSF) under Award CHE-2108670. A Bruker AVANCE III Nanobay 400 MHz NMR spectrometer was supported by the National Science Foundation under Grant No. CHE-0922858. The authors thank Dr. Marc A. ter Horst from the University of North Carolina's Department of Chemistry NMR Core Laboratory for the use of the NMR spectrometers.

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