

Click Polymer Ligation

Light-Induced Modular Ligation of Conventional RAFT Polymers**

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Materials engineering has become one of the most studied areas in contemporary chemistry. Very significant contributions to this ever-expanding field have been made by creatively combining controlled/living polymerization (LP) techniques with a special subset of conjugation techniques, known as click reactions.^[1] Some well-known examples of reactions in macromolecular science, which may fulfill the click criteria, are copper-catalyzed azide–alkyne cycloadditions (CuAAC),^[2] (hetero) Diels–Alder cycloadditions ((H)DA),^[3] oxime ligations,^[4] and nitrile imine tetrazole-ene cycloadditions (NITEC).^[5]

The advantages of click chemistry include mild reaction conditions, practically quantitative conversion and selectivity (i.e., allowing orthogonal reactions to be performed), and the applicability to a wide range of materials. Consequently, click chemistry has proven to be very beneficial for functionalizing polymers as well as generating sophisticated polymeric architectures. Given the utility of click chemistry, it comes as no surprise that there is a continued effort to develop new click-type reactions to expand the toolbox of techniques that can be employed in macromolecular design.

Many of the aforementioned click reactions require functional groups for the controlled polymerization step that are different from those needed for the subsequent polymer–polymer coupling. However, one click reaction that has been employed for a wide range of macromolecular applications^[3b,6] is the RAFT–HDA (reversible additionfragmentation chain transfer–HDA) process, which utilizes a RAFT agent that serves two purposes: The chain-transfer agent mediates polymerization and acts as a reactive endgroup for post-polymerization HDA conjugation.^[3b] RAFT

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polymerization, one of the most powerful LP techniques,^[7] allows for the generation of a great variety of polymeric materials in terms of chemical structure, microstructure, architecture, and properties.^[8] Unfortunately, not every RAFT agent is a suitable reagent for thermally driven HDA chemistry owing to the high activation energy associated with this reaction. The unfavorable reaction energetics stem from the presence of the electron-rich C=S bond of the dithioester, which results in a relatively large highest occupied molecular orbital (HOMO) lowest unoccupied molecular orbital (LUMO) gap for the diene-dithioester pair. Furthermore, only a few dithioesters have been found to allow for both LP and polymer-polymer coupling within an acceptable time frame. Benzyl(diethoxyphosphoryl) dithioformate, benzylpyridin-2-yldithioformate, and benzylphenyl sulfonyldithioformate all bear a highly electron-withdrawing Z group, which lowers the energy of the molecular orbitals and, therefore, reduces the HOMO-LUMO gap between the diene and dienophile (i.e., the RAFT agent). The addition of a Lewis or Brønsted acid can further reduce the frontier molecular orbital gap such that the HDA reaction can proceed in a few minutes at ambient temperature.^[9] Nevertheless, the electron-deficient nature of the aforementioned RAFT agents tends to decrease their ability to mediate and control polymerization and, consequently, limits the selection of monomers that can be polymerized. One possible strategy for overcoming this limitation and, thus, expanding the applications of RAFT polymers in modular macromolecular design is to identify a highly reactive diene that can undergo a HDA reaction with non-activated (i.e., electron-rich) RAFT agents. In this context, photoenols, which represent highly reactive dienes, have recently been employed by us in other DA-based reactions to generate complex macromolecular architectures^[10] and to perform spatially controlled surface grafting.^[11] Photoenols can be generated by irradiating ortho-alkyl-substituted aromatic ketones or aldehydes with UV light.^[12]

Herein, the successful catalyst-free HDA conjugation of a non-activated dithioester, 2-cyanopropyl dithiobenzoate (CPDB), with a reactive photoenol diene at ambient temperature is demonstrated for the first time. CPDB was selected as the dithioester of choice since it can be considered as one of the most universal RAFT agents. Indeed, it is able to control the radical polymerization of most common vinylic monomers (i.e., (meth)acrylates, (meth)acrylamides, styrenics).^[13] In an exploratory study, the HDA reaction between the photoenol precursor 2-methoxy-6-methylbenzaldehyde (**2**) and CPDB-functionalized poly(methyl methacrylate) (PMMA; **1**) was confirmed (Scheme 1). The efficiency of

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Scheme 1. Photo-conjugation of the dithiobenzoate end-capped poly(methyl methacrylate) **1** with 2-methoxy-6-methylbenzaldehyde (**2**), yielding the isothiochroman **3**.

the new conjugation reaction was further evaluated for block copolymer synthesis. Finally, the application of the conjugation technique to photoenol-functionalized poly(ε -caprolactone)s (PCLs) **4** and **5** of different molar masses, as well as to RAFT polymers of different molar masses and monomer composition, shows that the new methodology can be applied to a wide range of polymers.

CPDB was synthesized according to a literature method^[14] and subsequently utilized as a chain-transfer agent in the RAFT polymerization of methyl methacrylate. Poly(methyl methacrylate) **1** was obtained with a number-average molar mass (M_n) of 3300 gmol⁻¹ and a polydispersity (PDI) of 1.27. End-group functionalization of **1** with the photoenol precursor **2** was achieved by irradiating a deoxygenated solution of **1** (10 mg mL⁻¹) and **2** (1.1 equiv) in acetonitrile for 3 h at ambient temperature. The photoenol precursor **2** was selected for this reaction because it is the most reactive photoenol tested to date.^[10b] Its high reactivity is believed to originate from the significant overlap of its absorption spectrum ($\lambda_{max} =$ 315 nm) with the emission spectrum of the employed UV lamp (Comedico Arimed B6; $\lambda_{max} = 320$ nm) (Figure S2 in the Supporting Information).

Following irradiation, the product was isolated by precipitation in cold *n*-hexane. The success of the reaction can be qualitatively assessed by comparing the color of the reaction mixture prior to and after irradiation. The initially pink solution became colorless during irradiation, indicating the consumption of the chromophoric dithioester end group. In addition, a control experiment in which a pure solution of 1 was exposed to UV light for an extended period of time revealed the persistence of the pink coloration and suggested that the dithioester is stable under these conditions. Thus, it is reasonable to assume that 1 undergoes a reaction with 2 in the presence of UV light. The nature and success of this reaction were determined by sizeexclusion chromatography/electrospray ionization-mass spectrometry (SEC/ESI-MS), electrospray ionization-collision-induced dissociationmass spectrometry (ESI-CID-MS), ¹H NMR spec-

troscopy, and UV/Vis spectroscopy (Figure 1). UV/Vis spectroscopy was employed to assess the difference in absorbance of the RAFT polymer **1** and the product **3** because the typical strong π - π * and weak n- π * (n = lone-pair electrons) transitions of the thiocarbonyl moiety, which are characteristic for RAFT agents, should be absent in the absorption spectrum of the product if **1** partakes in the desired HDA cycloaddition. Indeed, the absorption maximum at 300 nm



Figure 1. UV/Vis spectra of the RAFT polymer 1 (solid line) and the irradiated mixture of 1 and 2 (dashed line) after precipitation from the reaction mixture.

corresponding to the π - π^* transition is drastically reduced after the reaction compared to that of the starting material. The presence of aromatic substituents in the product can explain the remaining low absorbance in this region. In addition, the absence of a n- π^* transition further indicates that there is no longer any detectable thiocarbonyl functional group present in the product.

SEC/ESI-MS analysis confirmed that the conjugation reaction occured since a comparison of the MS spectra of the starting material and the product clearly reveals that the mass-to-charge (m/z) signal associated with the RAFT polymer **1** is shifted by 149.9 amu, which corresponds very well to the exact mass of **2** (M = 150.07 g mol⁻¹; Figure 2). The SEC/ESI-MS spectrum of the product also reveals the presence of a minor impurity, as well as a trace amount of starting material. Although the presence of starting material would seem to contradict the UV/Vis results, it should be noted that the detection limit of ESI-MS is lower than that of UV/Vis spectroscopy and it is possible that the presence of a small amount of starting material could easily be masked by the absorption spectrum of the product.



Figure 2. SEC/ESI-MS spectra of the PMMA 1 before (top) and after (bottom) the conjugation reaction with **2**. The spectra correspond to the polymer eluted at later retention times (lower molar masses).

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Figure 3. a) ESI-CID-MS spectra of the RAFT-HDA product (bottom) and of the resulting daughter ion (top). The right-hand-side depicts the proposed fragmentation process of the mother ion. b) Structures predicted to result from the fragmentation of the daughter ion. All structures depicted in (a) and (b) are detected as sodium adducts.

Although the results from SEC/ESI-MS and UV/Vis spectroscopy both confirm the successful coupling of 1 with 2, these results do not reveal any information about the nature of the chemical bond formed. Therefore, ESI-CID-MS was carried out to determine the chemical structure of the product (Figure 3). The most abundant daughter ion resulting from ESI-CID-MS fragmentation of CPDB end-capped poly-(methyl methacrylate)s contains a terminal double bond resulting from the elimination of benzodithioic acid.^[15] In contrast to the fragmentation pattern of the dithioester-based polymer, the RAFT-HDA product was found to generate no unsaturated fragment. Instead, the primary daughter ion obtained from the fragmentation of the HDA product is a thiol end-capped polymer (m/z 824.38 amu) that results from the cleavage of the S-C bond that was part of the dithioester group. Such a process is only conceivable if the thiocarbonyl group is converted into a thioketal, permitting the generation of two stable fragments (i.e., the polymeric thiol and a cyclic thioether). Additional ESI-CID-MS experiments performed on the daughter ion resulted in a fragmentation pattern that would be expected for methyl methacrylate polymers,^[15a] although an isobaric thiolactone series would also give rise to the same fragmentation pattern. These results support the hypothesis that a polymeric thiol fragment was obtained as the daughter ion of the product.

Finally, the most conclusive evidence for the successful HDA cycloaddition between the non-activated dithioesterterminated polymer **1** and the highly reactive diene precursor **2** was obtained by NMR spectroscopy (Figure 4). The ¹H NMR spectrum of the irradiated solution of **1** and **2** revealed a significant change in the signals between $\delta = 6.5$ and 8 ppm that are associated with the aromatic protons. Specifically, the NMR signals associated with the phenyl protons a-c shift upfield and new resonance signals in the $\delta =$ 6.5 to 8 ppm region emerge, which correlates well with the aromatic protons k', l', and m' of the cycloadduct **3**. In addition, the total integration value for the signals arising from the aromatic protons corresponds to eight protons, which is in perfect agreement with the number of aromatic protons expected for the product. Moreover, the presence of two new resonance signals at $\delta = 5$ ppm and 5.5 ppm further suggests the formation of the desired product since these signals can be attributed to the new protons i' and p' of the isothiochroman.

To assess the scope of the photo-induced HDA reaction, modular formation of block copolymers consisting of a RAFT polymer, (i.e., PMMA **1**, polystyrene (PS), or poly(methyl acrylate (PMA)) and a photoenol-functionalized PCL (**4** or **5**, see Scheme 2) were investigated. Therefore, a ring-opening polymerization (ROP) initiator carrying the photoenol moiety was first synthesized following the synthetic route depicted in Scheme 2.

The ROP of ε-caprolactone was subsequently performed in the presence of the photoenol-functionalized initiator and triazabi-

cyclodecene in toluene under inert gas at ambient temperature for 5 h or 7 h (Scheme 2). Precipitation of the products in cold *n*-hexane resulted in the short PCL **4** (M_n = 2000 gmol⁻¹, PDI = 1.25) and the longer PCL **5** (M_n = 8400 gmol⁻¹, PDI = 1.08), respectively. Quantitative endgroup functionalization was demonstrated by ¹H NMR spectroscopy, through the comparison of the resonance signals corresponding to the aromatic end group protons (δ = 7.35 ppm and 6.8 ppm in CDCl₃) with the characteristic terminal hydroxymethylene proton resonances (δ = 3.64 ppm in CDCl₃).

Polymer conjugations of the different RAFT polymers with the photoenol-functionalized PCLs were performed. A short block copolymer was synthesized from equimolar ratios of PCL **4** and PMMA **1**, determined from the M_n values calculated by ¹H NMR spectroscopy. Larger block copoly-



Figure 4. ¹H NMR spectra of the reactants 2-methoxy-6-methylbenzaldehyde (2) and dithiobenzoate end-capped PMMA 1, as well as the isothiochroman 3 formed after irradiation for 3 h at ambient temperature.



Scheme 2. Synthesis of the photoenol-functionalized PCLs **4** and **5**. Reagents and conditions: a) $K_2S_2O_8$, $CuSO_4$, acetonitrile, 90 °C, 45 min; b) AlCl₃, CH_2Cl_2 , room temperature, 16 h; c) 11-bromo-1-undecanol, K_2CO_3 , DMF, room temperature, 72 h; d) ϵ -caprolactone, triazabicyclodecene, toluene, room temperature, 5 h or 7 h depending on the M_n targeted.

mers were obtained by combining CPDB-functionalized PS or PMA with PCL **5**. SEC and SEC/ESI-MS analyses (Figure S7) of the short block copolymer formed from PCL **4** and PMMA **1** confirmed the success of the conjugation reaction. Owing to the large size of the other block copolymers generated, only SEC analysis could be employed to evaluate the efficacy of these reactions. Representative SEC traces of the individual building blocks and the copolymer products for the PMMA–PCL and PMA–PCL systems are illustrated in Figure 5. The results of the PS–PCL block-copolymer formation are available in the Supporting Information (Figure S8).

In comparison with the SEC curves of each starting material, the chromatograms of the block copolymers are significantly shifted towards higher molar masses. These results clearly indicate the successful coupling of the single blocks. The SEC traces for all the block copolymers indicate that very high conversion is achieved for all of the conjugation reactions because the measured M_n values are found to be in good agreement with the theoretically predicted M_n values for the copolymer (Table 1). Note that the slight differences between the experimental and theoretical values originate from the complex elution behavior of the block copolymers which arises because of the differing properties of each block.^[16]

Although the block copolymer formation was very efficient for all polymer blocks, a very small amount of starting material can be detected in the chromatogram for both the PMA–PCL and PS–PCL systems. The presence of the starting material can be explained by considering that RAFT polymerization usually yields a small fraction of non-thiocarbonylthio functional chains from termination reactions.^[13a,17] Such 'dead' polymer chains are DA unreactive and, thus, an equimolar amount of the PCL polymer block will also remain. Additionally, it is not surprising that more residual starting material is detected for the block copolymer formed from higher molecular-weight RAFT polymers because significantly more dead polymer chains are generated when the RAFT polymerization is conducted for an extended period of time and to higher conversions.



Figure 5. Normalized SEC traces of a) PMMA 1 ($M_n = 3300 \text{ gmol}^{-1}$), PCL 4 ($M_n = 2000 \text{ gmol}^{-1}$) and the block copolymer ($M_n = 5900 \text{ gmol}^{-1}$). An ESI-MS analysis of the PMMA-*b*-PCL is shown in Figure S7 a and Table S1. b) PMA ($M_n = 5400 \text{ gmol}^{-1}$), PCL 5 ($M_n = 8400 \text{ gmol}^{-1}$) and the block copolymer ($M_n = 13000 \text{ gmol}^{-1}$).

Table 1: The M_n values of the homopolymer building blocks and the copolymers prepared.^[a]

| Monomer (RAFT) | M _n RAFT polymer [g mol ⁻¹] | M _n ROP polymer [g mol ⁻¹] | M _n Block copolymer [g mol ⁻¹] |
|---|--|---|---|
| Methyl methacrylate Methyl acrylate Styrene | 3300 5400 5900 | 2000 8400 8400 | 5900 13000 13400 |

[a] The M_n values are generated based on a PMMA calibration curve and the Mark–Houwink constants for PMMA to better compare the M_n values of the single blocks with those of the corresponding block copolymers.

Given the success of the polymer-conjugation technique, the reaction kinetics for the formation of PMA–PCL and PS– PCL block copolymers were investigated (Figure 6 and Figure S9 and S10). Both reactions were found to proceed to completion within 10 min.^[18] Interestingly, the reaction between the photoenol-capped PCL and PS proceeds somewhat slower than the reaction between the same PCL block and PMA, which may be explained by the greater stiffness of the PS backbone compared to that of the PMA backbone. Steric hindrance could also play a role. Nevertheless, the kinetic exploration reveals that rapid photoenol-based polymer–polymer conjugation can be achieved for RAFT polymers of different chemical compositions.



Figure 6. Kinetic study of the block copolymer formation of the PMA– PCL (—) and PS–PCL (----) systems. The dependence of the apparent block copolymer M_n on reaction time is plotted. The fits are a guide to the eye only.

To conclude, a novel polymer conjugation reaction for a non-activated dithioester was established, which is based on a light-triggered HDA reaction with a highly reactive photoenol diene. Near quantitative coupling is achieved within short reaction times at ambient temperature without a catalyst. Coupling of a RAFT polymer with a small photoenol molecule was first verified by ESI-MS. ¹H NMR spectroscopy and ESI-CID-MS techniques were utilized to confirm the isothiochroman linkage formation in the HDA-RAFT product. Furthermore, the applicability of the conjugation technique to the formation of block copolymers from different types and sizes of polymer blocks was demonstrated. The novel polymer-conjugation reaction increases the number of well-defined photo-clickable polymers that can be generated as it can be applied to a conventional RAFT agent, which is suitable for the living polymerization of a wide range of monomers. Therefore, the novel reaction provides a key advantage for synthetic chemists in a variety of applications, such as surface patterning, macromolecular architecture design, three-dimensional network formation, bio-conjugation, and step-growth polymer synthesis. The ability to perform modular ligation on conventional RAFT polymers greatly expands the synthetic toolbox available to macromolecular chemists.

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