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# Photocontrolled Radical Polymerization from Hydridic C−H Bonds

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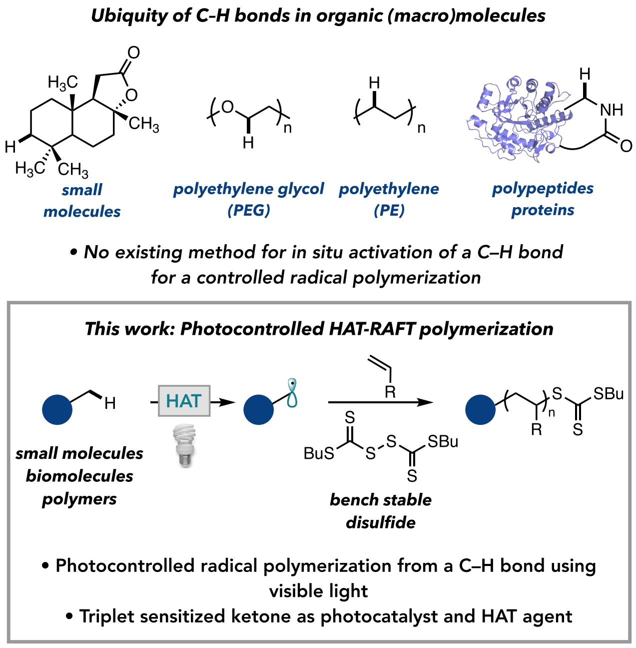
**ABSTRACT:** Given the ubiquity of carbon−hydrogen bonds in biomolecules and polymer backbones, the development of a photocontrolled polymerization selectively grafting from a C−H bond represents a powerful strategy for polymer conjugation. This approach would circumvent the need for complex synthetic pathways currently used to introduce functionality at a polymer chain end. On this basis, we developed a hydrogen-atom abstraction strategy that allows for a controlled polymerization selectively from a hydridic C−H bond using a benzophenone photocatalyst, a trithiocarbonate-derived disulfide, and visible light. We performed the polymerization from a variety of ethers, alkanes, unactivated C−H bonds, and alcohols. Our method lends itself to photocontrol which has important implications for building advanced macromolecular architectures. Finally, we demonstrate that we can graft polymer chains controllably from poly(ethylene glycol) showcasing the potential application of this method for controlled grafting from C−H bonds of commodity polymers.

Reversible-deactivation radical polymerizations (RDRPs) represent one of the most versatile strategies for controlling macromolecular architecture. Numerous synthetic methods have been developed to obtain control over chain length and dispersity. Reversible addition−fragmentation chain transfer (RAFT) has emerged as a powerful tool for controlling radical polymerizations.[1−4] Additionally, photoinduced electron/energy transfer (PET-RAFT) processes have been established as a means to exact temporal and spatial control in these processes,[5−9] finding numerous applications for designing complex 3D architectures.[10] To employ these methods, however, a prefunctionalized initiator/chain transfer agent (CTA) must be installed into a macromolecule, biomolecule, or small molecule for a controlled polymerization. We envisioned a strategy that eliminated the need for the preformation of a CTA and enabled selective grafting of a polymer from hydridic C−H bonds would be an opportunity to streamline macromolecular synthesis (Scheme 1).[11,12] The development of such a strategy would allow the direct formation of protein−polymer bioconjugates or drug−polymer conjugates without prefunctionalization.[13] Furthermore, complex macromolecular architectures could be controllably accessed via grafting from existing polymers in a single step with spatial and temporal control.[14]

Hydrogen-atom transfer (HAT) is a burgeoning synthetic strategy to generate carbon centered radicals from C−H bonds.[15] Benzophenone derivatives have been well demonstrated as hydrogen-atom abstraction agents when excited with visible light, and the resultant ketyl radical acts as an electron donor.[16,17] We hypothesized that radical polymerizations could be initiated using this mechanism.[18−20] Importantly, benzophenone derivatives, in the triplet excited state, can chemoselectively abstract electron-rich, hydridic C−H bonds, which would allow the precise selection of grafting sites.[21] The photogenerated electrophilic oxygen-centered radical has been shown to abstract $\alpha$-oxy, $\alpha$-amino, and hydrocarbon C−H bonds in contrast to $\alpha$-acyl or more acidic C−H bonds. This selectivity will also preclude unwanted C−H abstraction processes from the growing polymer backbone of electron deficient monomers used in controlled radical processes, which could lead to undesirable cross-linking and branching.

**Scheme 1. Design of HAT-RAFT Polymerization**



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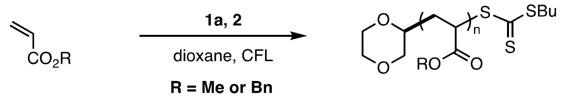
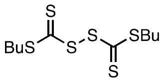
In an approach where we initiate polymerization with C−H abstraction, we envisioned that control over the polymerization could be imbued by a RAFT process via addition of a CTA. However, the $\alpha$-chain end of the final polymer would arise from the chain end of the CTA rather than the C−H bond initiator. Therefore, to achieve efficient grafting we needed to develop a method where the CTA was synthesized *in situ* from the radical formed through C−H abstraction. We hypothesized that the use of a precursor disulfide could effectively generate the CTA *in situ* and provide the desired $\alpha$-chain end (Scheme 1). Additionally, this strategy should allow the employment of multiple monomer classes with a single disulfide precursor without matching designed CTAs to a specific monomer, as a macro-CTA would be generated *in situ*. After formation of the CTA, further generation of radicals via HAT would grow polymer chains controllably. The radical concentration could be controlled by both the photocatalyst and the H atom source loading. This process could also lend itself to photocontrol, as in the absence of light, radical chains would become dormant. Upon generation of radical initiators via the light-gated HAT process, a photocontrolled radical polymerization, initiated from a ubiquitous C−H bond, would be obtained.

We began our studies employing disulfide **1a**, photocatalyst **2**,[16] and dioxane as both the solvent and H atom source. We hypothesized that we could control the radical concentration of this process by simply modifying the concentration of photocatalyst while using the solvent as an H atom source. Methyl acrylate (MA) was efficiently polymerized in the presence of a compact fluorescent lamp (CFL) with a narrow dispersity (Đ) (Table 1, entry 1). The experimental molecular weight ($M_n^{exp}$) showed good agreement with theoretical molecular weight ($M_n^{theo}$), which was calculated such that one disulfide gives one polymer chain. We were able to identify initiation from dioxane as the major chain end by MALDI-TOF (see Supporting Information for more details). In the absence of disulfide, the polymerization is rapid and uncontrolled; however, in the absence of light or H atom source (1,2-dichloroethane used as a solvent), no conversion of MA is observed (see Supporting Information for more details). Additionally, we could effectively target different molecular weights by changing the disulfide to monomer ratio (Table 1, entries 2−5). When CTA **1b** was used in place of the disulfide and in the absence of H atom source, we detected no polymerization (Table 1, entry 6), suggesting that the excited state of the photocatalyst cannot engage in PET-RAFT processes, nor is direct excitation of the CTA responsible for polymerization under standard conditions.[22] Furthermore, when the polymerization was conducted without photocatalyst, no conversion was observed, precluding direct excitation of the disulfide to induce polymerization (Table 1, entry 7). With the optimized conditions, we sought to explore the scope of the method to other monomer classes. Benzyl acrylate (BnA) was efficiently polymerized with good agreement between theoretical and experimental molecular weight with excellent control over molecular weight distribution (Table 1, entry 8). Methacrylates could be polymerized under these reaction conditions, but similar results were obtained in the absence of photocatalyst or HAT source, suggesting a competitive iniferter process.[22,23]

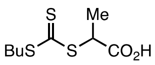
**Table 1. HAT-Mediated Polymerization of Acrylates**



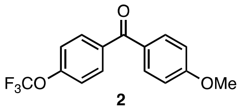
| entry[a] | monomer | [M]:[**1a**]:[**2**] | $M_n^{theo}$ (kg/mol) | $M_n^{exp}$ (kg/mol) | Đ |
|---|---|---|---|---|---|
| 1 | **MA** | 100:1:0.5 | 5.3 | 8.9 | 1.12 |
| 2 | **MA** | 50:1:0.5 | 2.4 | 4.6 | 1.26 |
| 3 | **MA** | 200:1:0.5 | 10.2 | 13.8 | 1.15 |
| 4 | **MA** | 400:1:0.5 | 17.8 | 21.8 | 1.17 |
| 5 | **MA** | 1000:1:0.5 | 54.3 | 51.5 | 1.13 |
| 6[b] | **MA** | 100:1:0.5 | 0.0 | n.d. | n.d. |
| 7 | **MA** | 100:1:0 | 0.0 | n.d. | n.d. |
| 8 | **BnA** | 100:1:0.5 | 16.0 | 19.0 | 1.23 |



**1a**



**1b**



**2**

[a] Monomer (filtered through basic alumina), disulfide **1a**, and photocatalyst **2** dissolved in dioxane (0.04 M in **1a**), degassed and irradiated with a CFL. [b] CTA **1b**, used in place of **1a** and 1,2-dichloroethane used as a solvent.

When monitoring the reaction, we noticed an induction period prior to polymerization. After this initial period, $M_n$ increased linearly with conversion, suggesting a controlled radical process (Figure 1a). Unlike traditional radical RAFT processes, we observed a small increase in dispersity over time. We attribute this increase to continued generation of alkyl radical and termination events. We envisioned that the system may be amenable to temporal control, rather than just a photoinitiated process, if a traditional radical RAFT mechanism is invoked. To test this hypothesis, the polymerization was intermittently exposed to light while monitoring conversion (Figure 1b). Gratifyingly, we observed that conversion ceased upon removal from irradiation. Moreover, polymerization continued upon additional irradiation. This process was repeated, including a long “off” period, in which polymerization only occurred in the presence of the CFL.

To test the trithiocarbonate chain end fidelity of our polymers, we isolated a sample of PMA synthesized under our standard polymerization conditions. We then subjected the macro-CTA to a solution of AIBN and BnA monomer in benzene at 65 °C (Figure 1c). We observed efficient chain extension under these conditions, obtaining a PMA-*b*-PBnA copolymer with good matching of $M_n^{theo}$ and $M_n^{exp}$ and narrow Đ. The GPC trace did indicate some remaining PMA macro-CTA, and we attribute the incomplete conversion to reductive termination events during the HAT-RAFT polymerization. Based on GPC data of isolated homopolymer and copolymer, we estimate 78% chain extension.

Given these results, we propose the following mechanism (Figure 1d). Upon excitation with visible light, photocatalyst **2** forms triplet excited state **I**. This diradical will abstract a hydridic C−H bond to form alkyl radical **II**, which will subsequently add to monomer to form a propagating polymer chain. After homolysis with visible light, disulfide **1a** can form two trithiocarbonyl radicals (**III**), one of which can combine with the electrophilic chain end to form macro-CTA (**IV**). Alternatively, the electrophilic chain end can add to disulfide **1a** and generate **III**. The remaining radical (**III**) can be subsequently reduced by the ketyl radical **V** to generate the trithiocarbonic acid and turn over the catalyst. Upon formation

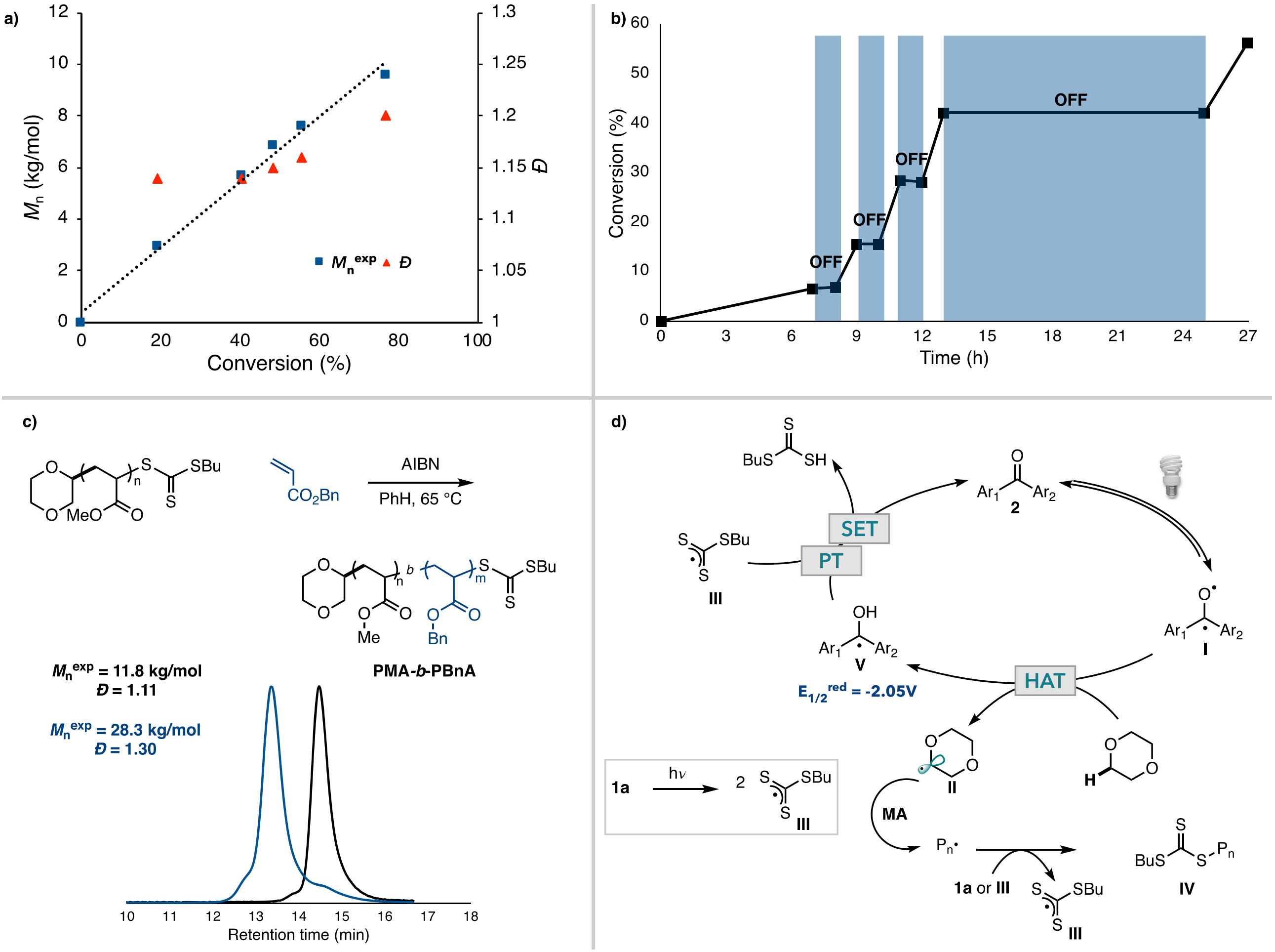


**Figure 1.** (a) Linear growth of molecular weight vs conversion. (b) Temporal control of polymerization with intermittent light. (c) Thermal RAFT chain extension of PMA with BnA. (d) Proposed mechanism; see Figure S47 for a full description of the proposed mechanism.

of **IV**, we propose that additional alkyl radicals are generated from excitation of the photocatalyst to maintain an active RAFT process (see Supporting Information for a full proposed mechanism). In the absence of light, termination events generate an inactive polymerization state, but upon generation of additional radical with irradiation, the RAFT process can be restarted. Termination events include reduction of an active chain end to form an anion which will be rapidly protonated in addition to radical−radical coupling.[24,25]

To apply this method to various applications, such as grafting from an existing polymer or biomolecule, we recognized that using solvent quantities of C−H coupling partner may be inefficient.[16,26−28] We therefore examined a number of C−H initiators in reagent quantities relative to disulfide. In C−H initiators with lower BDEs or more hydridic C−H bonds,[29] radical initiation becomes more facile, and when THF was used as a solvent in a similar manner to that in Table 1, a completely uncontrolled polymerization was obtained. For THF, we found that by reducing the C−H initiator concentration to 20 equiv, we were able to achieve a controlled polymerization (Figure 2). When ethyl acetate was used as the H atom source, even in solvent quantities, no polymerization was detected. Given the lack of hydridic C−H bonds in ethyl acetate, this result is consistent with highly selective HAT processes and suggests that unwanted abstraction from the backbone of the polymer chain can be avoided.[30] Amides also served as C−H initiators, with *N*-methylpyrrolidinone affording similar results to THF, and even Cbz-(L)-proline methyl ester afforded a well-controlled polymerization, suggesting that biomolecules may serve as C−H initiators in bioconjugation. Alcohols were also demonstrated to function as initiators in this chemistry, with benzyl alcohol and ethanol affording well controlled polymerizations.[31] Excitingly, diethylene glycol monomethyl ether, a mimic for poly(ethylene glycol) (PEG) afforded a well-controlled polymerization. Furthermore, cyclohexane, with a C−H BDE of 100 kcal/mol afforded the desired PMA, albeit at higher C−H initiator loadings. Cyclohexane is representative of a polyolefin such as polyethylene and provides future opportunities for grafting from commodity polymers.[14,32]

Lastly, we demonstrated that a PEG polymer could also serve as a C−H initiator (Figure 3). Under slightly modified conditions, we employed 3 equiv of a 2.0 kg/mol PEG-dimethyl ether and obtained well controlled MA polymerizations. With increasing amounts of C−H initiator polymer, we observed increased conversion and molecular weight (see Supporting Information for more details). We also observed that we could achieve graft copolymers of designed molecular weight, 8.3−26.7 kg/mol, by altering the equivalents of monomer. Currently, there are no other examples of *in situ* controlled grafting from a C−H bond of a PEG polymer.[11,12] Excitingly, a signal for PEG was observed in the $^{13}$C NMR of

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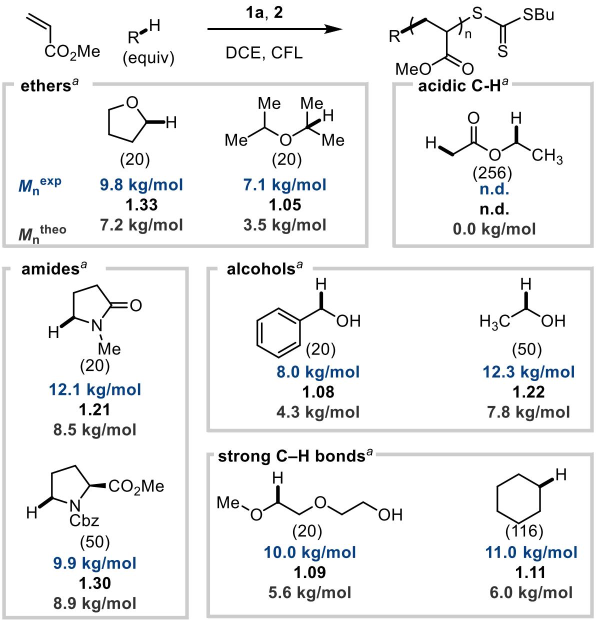

**Figure 2.** Examples of C−H initiators to mediate HAT-RAFT polymerization. ^a^MA (100 equiv, filtered through basic alumina), disulfide **1a** (1 equiv), **2** (0.75−1.0 equiv) and C−H coupling partner (20−116 equiv) dissolved in DCE (0.04 M in **1a**), degassed and irradiated with a CFL.

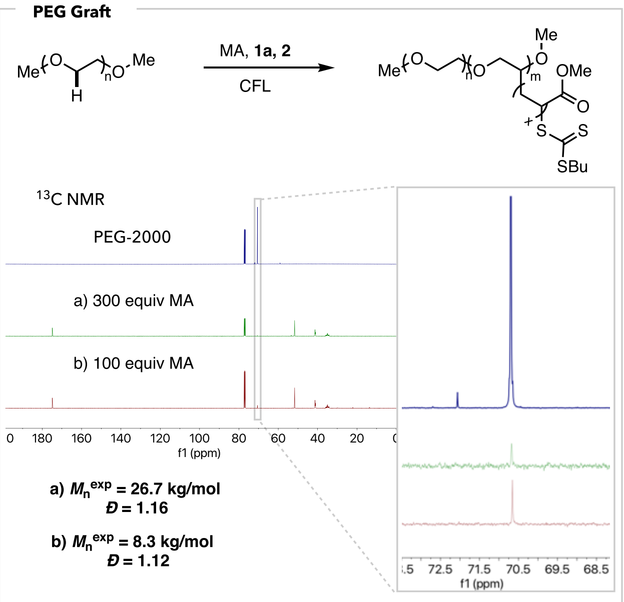

**Figure 3.** MA (100 or 300 equiv), poly(ethylene glycol) dimethyl ether (3 equiv, MW = 2.0 kg/mol), **1a** (1.0 equiv), **2** (1.0 equiv), degassed and irradiated with a CFL.

the precipitated graft copolymer after removel of the remaining PEG macroinitiator, which was confirmed by GPC analysis.[33] Furthermore, no PEG degradation was detected via GPC analysis, highlighting the advantage of our method for functionalizing PEG, where the installation of thiocarbonyl compounds results in PEG decomposition.

We demonstrated that ubiquitous C−H bonds can serve as radical initiators for controlled radical polymerizations via use of a benzophenone derivative and visible light. We can access a controlled polymerization by employing a RAFT process, which can be accessed via an inexpensive and easily modifiable disulfide. We have highlighted future applications of this method in controlled polymerization from biomolecules as well as commercial or commodity polymers.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c00287.

> Reagent and analytical information, general procedures, and additional studies (PDF)

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### Notes

The authors declare no competing financial interest.

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(30) We conducted experiments on macro-CTAs to test for branching in the polymer backbone and observed no considerable polymerization, suggesting that abstraction from the backbone is not a major pathway. See the Supporting Information for more details.

(31) Benzyl alcohol chain ends are identified by $^1$H NMR; see the Supporting Information for more details.

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(33) See the Supporting Information Figures S48 and S51 for GPC chromatograms.

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