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Endo and *Exo* Diels−Alder Adducts: Temperature-Tunable Building Blocks for Selective Chemical Functionalization

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Supporting Information

ABSTRACT: The development and application of a novel *endo* furan-protected maleimide building block is reported. The *endo* isomer undergoes deprotection at temperatures ∼50 °C below the *exo* derivative. This enables a simple and powerful approach to quantitatively and selectively introduce functional maleimide groups via temperature modulation.

The development of "click" chemistry has had a profound impact on applications ranging from small-molecule bioconjugation to the synthesis of complex and multifunctional macromolecular systems.[1] Of the myriad of available "click" reactions, maleimides represent one of the most versatile building blocks, as they offer two distinct and highly efficient reaction pathways for secondary functionalization (see Figure 1). The first is a facile [4+2] Diels−Alder (DA)

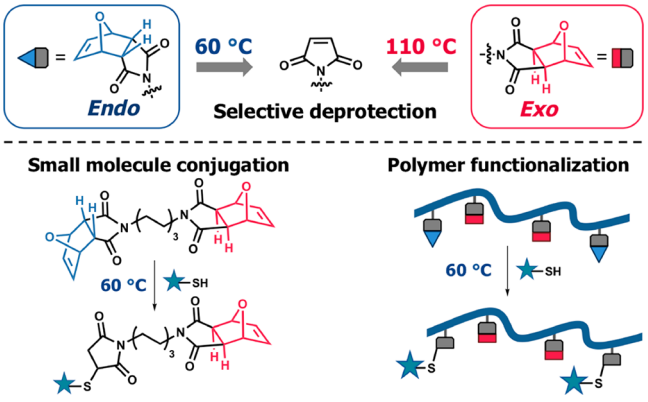

Figure 1. Graphical depiction of *endo* and *exo* isomers of furan-protected maleimide for temperature-dependent deprotection and selective functionalization of small molecules and synthetic polymers.

cycloaddition between electron-deficient maleimides and dienes. The second is a thiol-Michael reaction where a nucleophilic thiol adds across the maleimide double bond.[2] Both pathways proceed quantitatively under equimolar conditions from a wide variety of starting materials. While the high reactivity of maleimides is desirable for post-polymerization functionalization, direct incorporation into polymers prepared through conventional free radical and controlled radical polymerization (CRP) is precluded.[3−5] In previous work, Haddleton and co-workers developed an *exo* furan-protected maleimide atom transfer radical polymerization (ATRP) initiator for incorporation of a masked maleimide moiety at the α chain-end.[6] The furan protecting group could then be removed via a *retro*-DA (rDA) process upon heating at elevated temperatures (∼110 °C). Coupled with facile thiol-Michael addition, this strategy has significantly impacted the preparation of polymer−protein bioconjugates.[7] Maynard and co-workers expanded this work, demonstrating successful incorporation of *exo* furan-protected maleimides in reversible addition−fragmentation chain-transfer (RAFT) polymerization processes.[8] Dove and Sanyal also demonstrated successful utility in ring-opening polymerization (ROP) systems.[9,10] Despite the importance of maleimide incorporation to the field of functional polymer synthesis, only the *exo* isomer has been explored as a functionalization platform. As such, the inherently high deprotection temperature is problematic for thermally unstable systems, such as bioconjugates and supramolecular assemblies.[11] To address this challenge, we hypothesized that the *endo* isomer, which undergoes rDA at considerably lower temperatures[12,13] would afford a new functional building block with the added benefit of temperature tunability.

Our initial exploration focused on a scalable and straightforward synthesis of the *endo* adduct, **1**. Using inexpensive and readily available starting materials (furan and maleimide), a mixture of DA adducts enriched with **1** can be obtained when the cycloaddition reaction is performed at room temperature. From this mixture, the *endo* isomer, **1**, is selectively recrystallized from dichloromethane on up to a 4-gram scale (23% yield, see Supporting Information (SI)). The reaction of **1** with the *exo* isomer, **2**,[14] results in the *endo*/*exo* heterodimer model compound (**3**), which offers the possibility of selective deprotection and separate/successive thiol-Michael addition steps. Significantly, when **3** was heated at 60 °C, only deprotection of the *endo* adduct was observed (see SI). While extended reaction time for complete deprotection is necessary, nucleophilic addition with *n*-dodecanethiol enables exclusive monofunctionalization of the heterodimer to give **3-mono** in good yield (Figure 2). Subsequent deprotection of the *exo*

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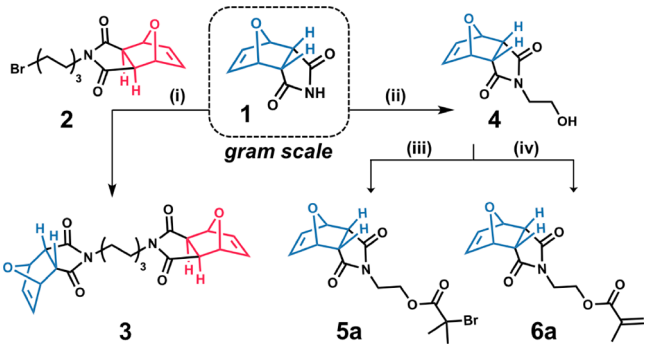
Scheme 1. Synthesis of *Endo*/*Exo* Heterodimer (3) and *Endo* Polymer Building Blocks (5a, Initiator; 6a, Monomer)[a]



[a]Reagents and conditions: (i) K_2CO_3, MeCN, RT, 56%; (ii) 2-bromoethanol, K_2CO_3, MeCN, RT, 73%; (iii) BIBB, Et_3N, DCM, 0 °C to RT, 84%; (iv) methacryloyl chloride, Et_3N, DCM, 0 °C to RT, 80%. For *exo* polymer building blocks (**5b**, initiator; **6b**, monomer) see SI.

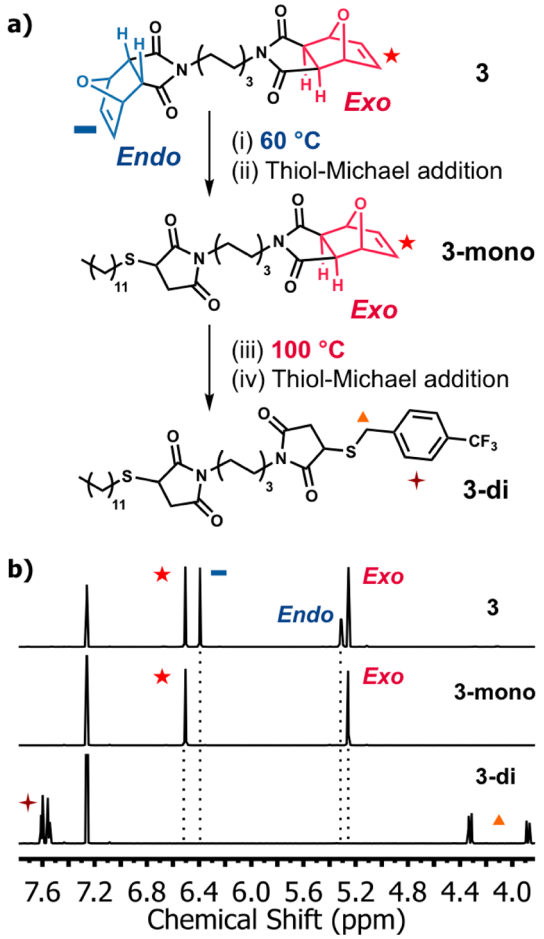


Figure 2. (a) Scheme and (b) ^{1}H NMR overlay of orthogonal deprotection and thiol-maleimide coupling reactions using small-molecule *endo*/*exo* heterodimer, **3**. Reagents and conditions: (i) DMF, 60 °C, 22 h; (ii) *n*-$C_{12}H_{25}SH$, TEA, $CHCl_3$, RT, 15 h, column chromatography, (93%, two steps); (iii) toluene, 100 °C, 17 h, >95% conversion of *exo*; (iv) *p*-CF_3BnSH, TEA, $CHCl_3$, RT, 4 h, column chromatography (81%, two steps).

adduct at 100 °C followed by reaction with 4-trifluorobenzyl mercaptan furnished the final disubstituted compound **3-di** (Figure 2), confirmed by ^{1}H, ^{13}C, and ^{19}F NMR and electrospray ionization mass spectrometry (ESI-MS) analysis (Figures S18–S20).

With selective conjugation achieved on a small-molecule heterodimer, our efforts focused on adapting this chemistry to facilitate orthogonal post-functionalization of synthetic polymers. To obtain the necessary polymeric building blocks, a key hydroxyethyl precursor (**4**) was synthesized in one step from **1** (Scheme 1) with single-crystal X-ray analysis confirming the *endo* conformation of **4** (see SI). A traditional ATRP initiator (**5a**) and methacrylate monomer (**6a**) bearing the *endo* isomer could then be obtained from **4** using 2-bromoisobutyryl bromide and methacryloyl chloride, respectively.

Given the lower deprotection temperature of the *endo* isomer and the associated incompatibility with traditional thermally driven radical polymerization techniques, our attention was drawn to ATRP systems that operate under ambient temperatures. Initial investigation of the viability of **5a** for Cu(0) polymerization[15] reveals a bimodal distribution at moderate to high conversions (Figure S23). This is in agreement with previous reports that suggest protected maleimides can still participate in copolymerizations[6] when using Cu-ATRP. To address this issue, we turned to light-mediated CRP techniques, namely metal-free ATRP[16−20] and photoinduced electron transfer-RAFT (PET-RAFT),[21−23] for direct incorporation of temperature sensitive functionalities into polymeric scaffolds. Implementation of metal-free ATRP with purified *endo*- and *exo*-monomers would therefore allow the development of multifunctional polymers that leverage the selective deprotection temperatures of the *endo* and *exo* building blocks (Figure 1a), opening up the range of functionalization chemistries available in synthetic polymer systems. Significantly, metal-free ATRP using Phen-CF_3 yielded a unimodal distribution with low $Đ$ for the *endo*-initiator (Figure 3), while PhenO (see SI) allows **6a** (*endo* adduct) to be successfully copolymerized with **6b** (*exo* adduct), methyl methacrylate (MMA) and benzyl methacrylate (BnMA). The choice of photocatalyst was based on

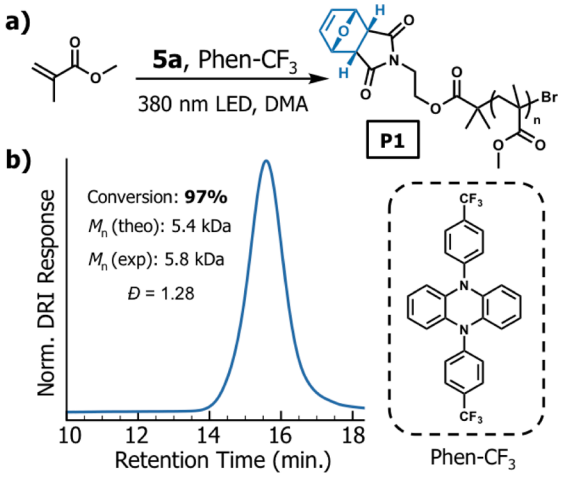


Figure 3. (a) Scheme of metal-free ATRP of MMA using the *endo* ATRP initiator, **5a**. (b) Size exclusion chromatography confirming unimodal distribution with low $Đ$.

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optimal compatibility with the initiator-type as demonstrated in previous reports.[19,20] This represents the first copolymer (**P2**) to contain both *endo* and *exo* isomers (Figure 4a). The

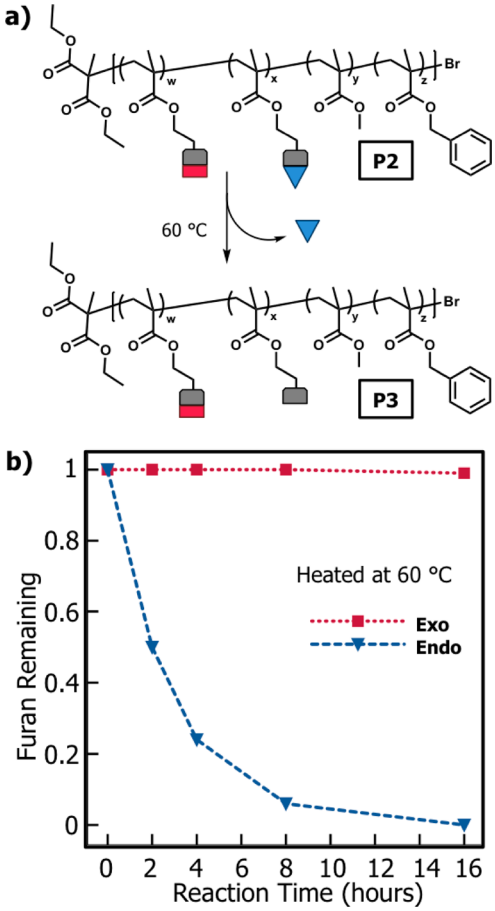

Figure 4. (a) Copolymer **P2** (synthesized using **6a**, **6b**, MMA, and BnMA, with PhenO and 380 nm light) is heated to selectively deprotect the *endo* isomer to yield **P3** (see SI for synthetic details). (b) Plot depicting stability of the *exo* isomer and quantitative deprotection of the *endo* isomer at 60 °C over 16 h.

addition of BnMA serves as a covalently bound internal ^{1}H NMR reference to facilitate reliable determination of the efficiency of selective deprotection. One of the most attractive features of a CRP is the ability to impart site-specific control over a desired functionality. Heating the copolymer in DMF-d_7 at 60 °C results in complete deprotection of the *endo* isomer (Figures 4b and S27). *In situ* addition of 4-trifluoromethyl benzyl mercaptan and characterization by ^{19}F NMR confirmed the fidelity of deprotection to maleimide and the associated reactivity toward thiols (Figures S27–S30). Importantly, subsequent heating to 110 °C after *endo* functionalization resulted in quantitative deprotection of the remaining *exo* isomer to furnish the reactive maleimide (Figures S31 and S33).

We then envisioned the preparation of a multifunctional copolymer, wherein one isomer is incorporated on the chain-end and the other as a pendant group along the backbone. Using **5a**, MMA was successfully copolymerized with **6b** to furnish a functional copolymer (**P5**) with good control (Figure S34). Having successfully demonstrated thiol-Michael addition after selective deprotection of the *endo* isomer, we performed selective deprotection at the α terminus and trapped the *in situ* generated maleimide with an irreversible DA cycloaddition with cyclopentadiene (Cp) end-capped poly(ethylene glycol) (**P4**). Inspired by recent reports from Barner-Kowollik and co-workers, Cp end-capped polymers represent a powerful strategy for highly efficient polymer functionalization.[24−26] Indeed when **P4** (see SI) and **P5** were heated together in solution, a facile and catalyst-free preparation of diblock copolymer (**P6**), with retention of the *exo* functionality, was achieved (Figure 5a,b). While *exo* protected maleimides can undergo deprotection to reveal a reactive maleimide, they can also be used for ring-opening metathesis polymerization (ROMP),[27] radical thiol−ene "click",[28] and inverse electron-demand DA (IEDDA) reactions.[29] The IEDDA reaction with tetrazines has found widespread use in polymer conjugation and chemical biology due to the ability to achieve bioorthogonal, catalyst-free conjugation under mild conditions.[30−32] Significantly, in a one-pot fashion, 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine was added to **P6**, resulting in quantitative consumption of the remaining *exo* isomer as evidenced by ^{1}H NMR and size exclusion chromatography (SEC)−UV analysis (Figure 5b,d). Importantly, in a similar fashion to the dual functionalization of the small-molecule heterodimer (**3**), **P5** can be heated to 60 °C in the presence of *n*-dodecanethiol to give the selective *endo* chain-end functionalized product without deprotection of the pendant *exo* groups (Figure S38). Further heating of the chain-end functionalized polymer at 110 °C in toluene resulted in quantitative deprotection of the *exo*-isomer and the resulting maleimide was reacted with 4-trifluorobenzyl mercaptan in a one pot fashion to yield the dual thiol-Michael addition product (Figures S39 and S40). Analysis of the starting polymer and the final dual addition polymer by SEC-RI indicates no observable change of the molar mass distribution or overall dispersity (Figure S41). Furthermore, the versatility of this method also enables synthetic access to the inverse orientation of **P5**, with the *exo* isomer on the chain-end and the *endo* as pendant groups (**P8**, Figure S42).

In conclusion, we have developed a straightforward and scalable synthesis for an *endo* furan-protected maleimide functional building block and demonstrated its facile incorporation into two distinct systems: a difunctional small-molecule *endo*/*exo* heterodimer and a multifunctional synthetic polymer with control over chain ends and pendant backbone groups. By implementing metal-free ATRP and co-incorporating the *exo* isomer, we highlight key advantages of using mild CRP for the design of materials with tunable functionalities that undergo selective deprotection based on temperature. Furthermore, we have demonstrated the utility of this chemistry through a series of site-specific and quantitative modifications using established and commonly implemented "click" reactions, including thiol-Michael addition, DA, and IEDDA conjugation chemistries. We envision that the ability to selectively introduce functionality based on external temperature regulation will pave new pathways forward for efficient and precision small-molecule and polymer modification. Further development of different functional Diels−Alder derivatives and investigation into additional synthetic polymer applications is currently underway.

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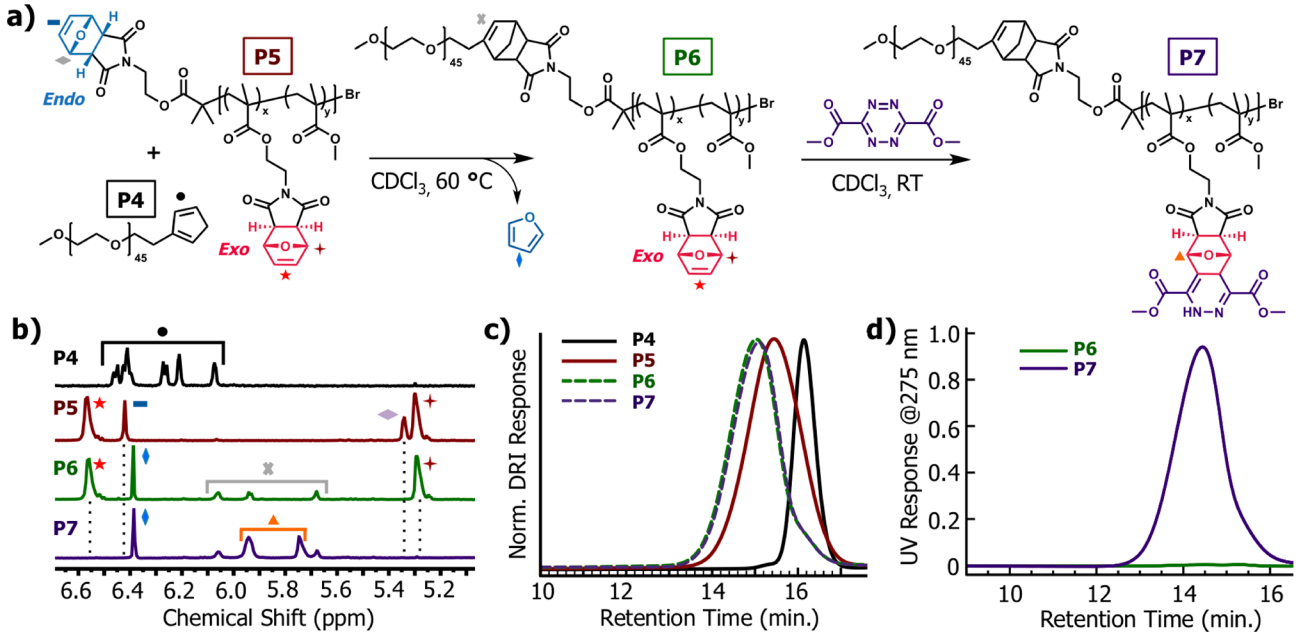

Figure 5. (a) Representative schematic of one-pot selective *endo* deprotection and DA cycloaddition conjugation with PEG-Cp followed by functionalization of remaining pendant *exo* functionality through IEDDA with 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine. (b) Crude ^{1}H NMR overlay confirming successful conversion after each reaction. (c) SEC-RI overlay showing shift to higher molar mass following diblock formation after heating **P4** and **P5** at 60 °C for 18 h. (d) SEC-UV @275 nm overlay of **P6** and **P7** confirming conjugation with bis(methoxycarbonyl)-1,2,4,5-tetrazine after 1 h at room temperature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01544.

X-ray crystallographic data for **1** (also deposited at the Cambridge Crystallographic Data Centre as CCDC 1821820) (CIF)

Experimental details and characterization data, including Figures S1−S42 (PDF)

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Notes

The authors declare no competing financial interest.

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