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Synthesis and Functionalization of Thiol-Reactive Biodegradable Polymers

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Supporting Information

In recent years, reactive degradable polymers have gained increased attention due to their widespread application in biomedical and materials sciences. Recent progress in efficient postfunctionalization strategies of polymeric materials have made such reactive polymers a versatile candidate for the design and synthesis of functional polymeric materials.[1] In particular, biodegradable polymeric materials that can be appropriately functionalized with biologically relevant molecules and biomolecules hold immense promise in the area of the design and fabrication of novel drug delivery systems and tissue engineering.[2] The multivalent nature of polymers allows the attachment of multiple targeting units and drugs, thus increasing the efficacy and payload. Furthermore, the degradability of polymers can be applied advantageously to allow controlled release of the drug over prolonged period of time at the disease site.

Aliphatic poly(ester)s obtained via the ring-opening polymerization (ROP) of lactides and lactones have been widely applied in these fields.[3] Such synthetic methodology allows access to poly(ester)s with good control over their molecular weight, polydispersity and end group fidelity. While historically, these polymerizations have been carried out by the ring-opening of cyclic monomers initiated by alcohols in the presence of a metal catalyst at high temperatures, metal-free organocatalytic and enzymatic processes in ROP have emerged as attractive alternatives for the "green" synthesis of polymers that are devoid of any residual metal impurities.[4] Despite the widespread utilization of poly(ester)-based materials for a variety of biomedical purposes, until recently, only a few functionalizable poly(ester)s have been available.[4,5]

Among the recently developed strategies for the synthesis of functional poly(ester)s, those based upon the highly efficient "click" reactions[6] have enabled the synthesis of biodegradable polymers that can be efficiently postfunctionalized. Functionalization of biodegradable polymers using the Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition between azide and alkyne functionalities has been applied by several groups.[7] The presence of residual metal impurities following these manipulations and concerns over polymer degradation during prolonged reaction times, provides motivation for the development of alternative approaches. A wide range of alternative metal-free "click" reactions such as strain promoted azide–alkyne cycloadditions, thiol–ene reactions and Diels–Alder cycloaddition reactions are increasingly becoming a method of choice to synthesize and functionalize polymeric materials.[8] Of these, thiol-reactive biodegradable polymers have immense potential in fabrication of functional degradable materials. Several recent reports have shown that maleimide-containing polymers can undergo mild postfunctionalization modifications.[9] Many polymers that possess a maleimide unit as a core or side-chain functionality have been synthesized due to the effective conjugation of this functional group for biological applications.[10] Notably, the nucleophilic "thiol–ene" Michael addition of thiol-containing molecules to maleimides was also demonstrated to be a highly efficient and selective methodology for the functionalization of degradable polymers in the absence of deleterious side-reactions.[11]

Cyclic carbonate monomers offer versatile methods for the incorporation of functional groups. Over the past years a number of cyclic carbonate monomers containing various pendant functional groups such as benzyl esters,[12] allyl esters,[13] azides,[14] carbamic acid benzyl ester,[15] and photolabile 2-nitrobenzoxycarbonyl groups have been reported.[16] Recently, allyl-functional poly(carbonate)s (obtained by organocatalytic ROP) were shown to be efficiently functionalized with thiol-containing molecules using the thermally initiated thiol–ene reaction in the presence of azobis(isobutyronitrile),[17] and vinyl–sulfone functionalized polymers were obtained by ROP in the presence of stannous octoate. These polymers again were shown to be reactive toward a variety of thiol-containing molecules.[18]

Herein, we describe a novel strategy to synthesize and functionalize maleimide containing thiol reactive biodegradable polymers by the organocatalyzed (co)polymerization of a novel furan-protected maleimide-functional carbonate monomer (Figure 1). Polymers obtained via ROP have pendant groups containing furan-protected maleimide units which, upon subjection to thermal cycloreversion reaction, yields maleimide groups that are ready to react with thiol containing molecules.

The furan-protected maleimide-containing cyclic carbonate monomer was synthesized using the protected diol **1** that was synthesized according to literature procedures.[19] The acetal groups were hydrolyzed using the acidic DOWEX 50W-X2 resin to generate diol **2** before ring-closure using triphosgene yielded the carbonate monomer **3** that could be readily purified either via simple precipitation in diethyl ether or column chromatography using SiO_2 (Scheme 1). The ^1H NMR spectrum (see Supporting Information, Figure S1) clearly shows the presence

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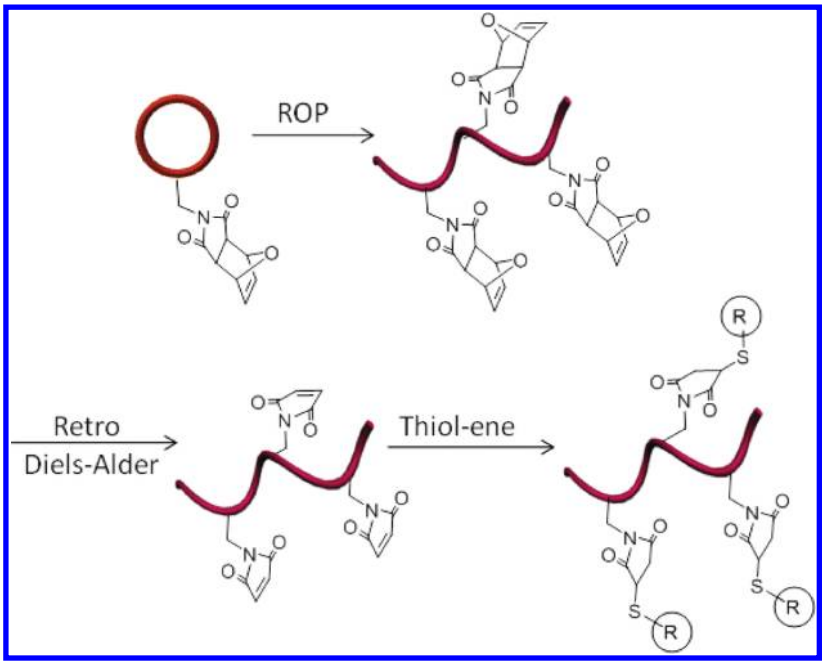

Figure 1. Illustrative scheme outlining the synthesis of maleimide containing polymers.

Scheme 1. Synthesis of Furan-Protected Maleimide-Containing Carbonate Monomer 3 and Unprotected Maleimide-Containing Monomer 4

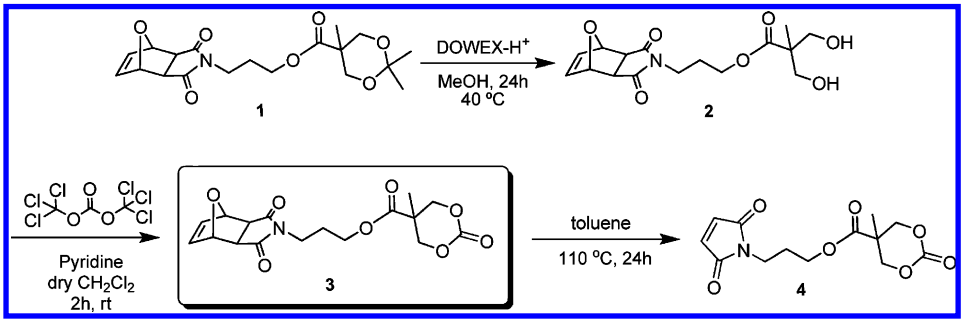

Table 1. Polymerization Conditions and Characterizations of Homopolymers of 3

item	polymer[a]	$[M]_0/[I]_0$[b]	time (h)	convn (%)	$M_{n,GPC}$ (g/mol)	M_w/M_n	$M_{n,theo}$ (g/mol)	$M_{n,NMR}$ (g/mol)
1	P1	20	192	58	5700	1.10	4300	5600
2	P2	20	24	65	2800	1.10	4800	2300
3	P3	20	4	50	2800	1.10	3800	2600
4	P4	20	117	65	3400	1.20	4800	3200
5	P5	40	27	47	5000	1.10	6900	4100
6	P6	100	27	48	5600	1.10	17 600	5000
7	P7	200	18	47	8200	1.10	34 400	8100

[a]Reaction conditions: 2 mol % DBU for **P1**, 20 mol % DBU for **P4** and 10 mol % DBU for all other polymers; all polymerizations were performed in $CDCl_3$ at 25 °C, [**3**] = 0.14 M using benzyl alcohol as the initiator. [b]Targeted degree of polymerization based on [M]/[I].

of the bicyclic unit composed of the furan-protected maleimide unit at δ = 2.84, 5.25, and 6.50 ppm. Additionally, the OCH_2 protons on the six membered carbonate ring appear as two doublets at δ = 4.73 and 4.20 ppm that arise as a consequence of the rigidity of the cyclic structure. The ^{13}C NMR spectrum provides further support of the monomer structure by the observation of three distinct carbonyl peaks at δ = 175.2, 169.8, and 146.6 ppm corresponding to the carbonyl carbons of ester, amide and carbonate groups respectively (see Supporting Information, Figure S2). Subsequent removal of the furan protecting group was possible by heating **3** in toluene at 100 °C for 12 h. The removal of the furan protecting group was evident by examination of the ^1H NMR spectrum of **4**, with loss of the characteristic signals at δ = 5.25 and 2.84 ppm with the concurrent observation of the shift of the vinyl resonances from δ = 6.50 to 6.70 ppm (see Supporting Information, Figure S5).

A wide range of organic catalysts have been applied in the ROP of cyclic carbonate monomers and have shown excellent

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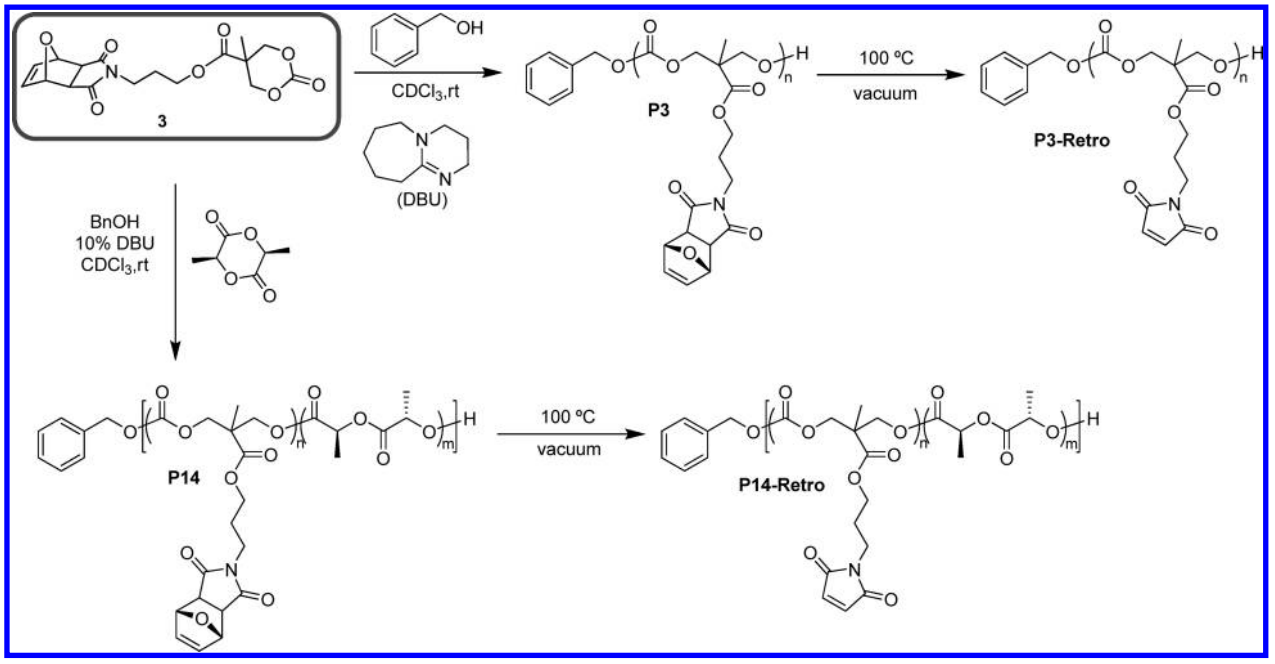
Scheme 2. Synthesis of Maleimide Functional Homo- and Copolymers by ROP and Activation of Maleimide Groups with Retro Diels–Alder Reaction



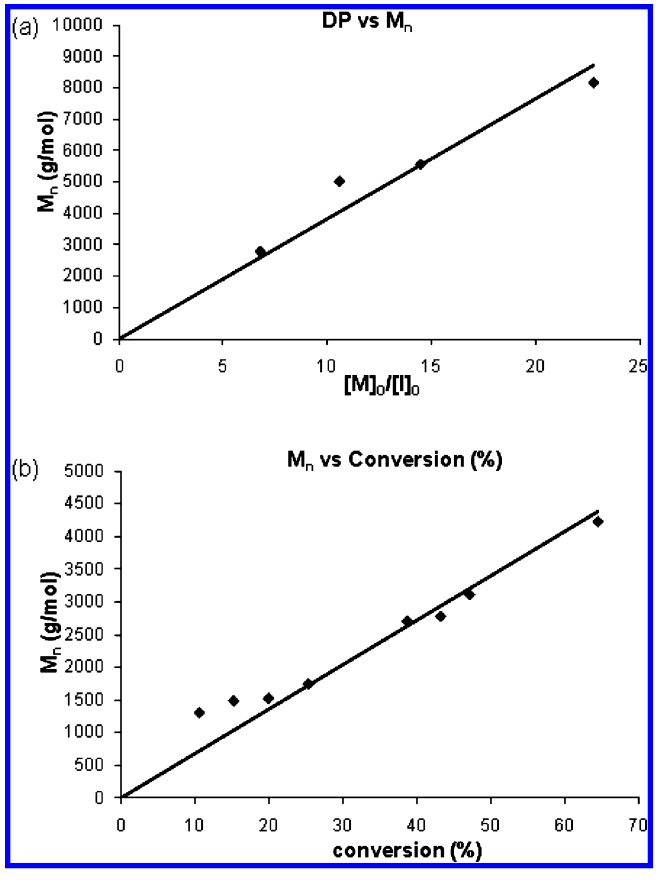


Figure 2. (a) Plot of number-average molecular weight (M_n) vs initial monomer-to-initiator ratio, $[M]_0/[I]_0$, in the ring-opening polymerization of **3**. Conditions: [**3**] = 0.14 M $CDCl_3$ at 25 °C, 10 mol % DBU using benzyl alcohol as an initiator. (b) Plot of number-average molecular weight (M_n) vs % monomer conversion in the ring-opening polymerization of **3**. Conditions: [**3**] = 0.14 M $CDCl_3$ at 25 °C, 10 mol % DBU, $[M]_0/[I]_0$ = 20 using benzyl alcohol as an initiator.

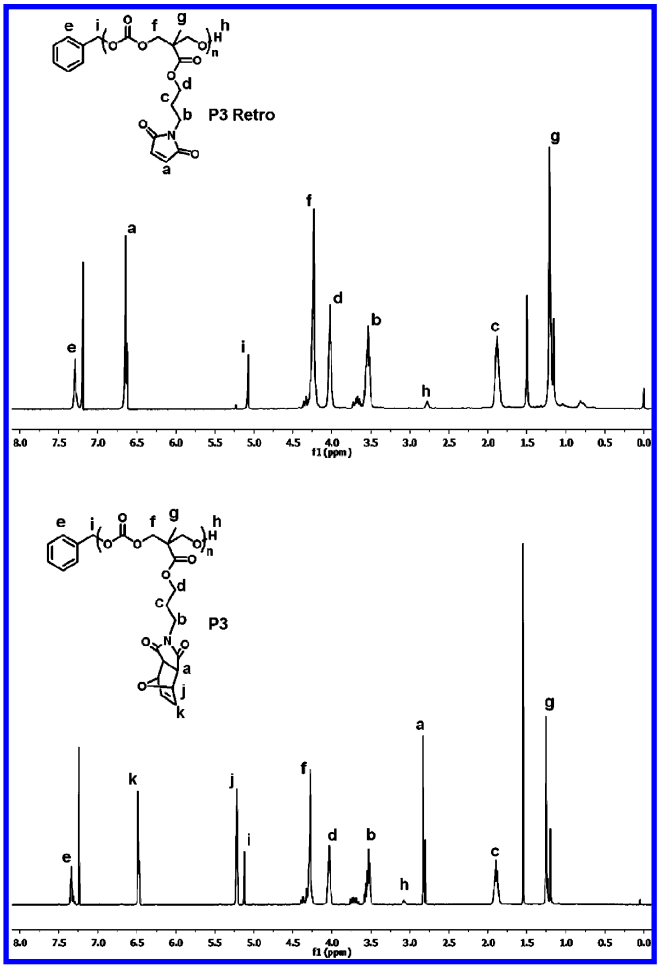


Figure 3. ^{1}H NMR of **P3** (bottom) and **P3-Retro** (top) homopolymers ($CDCl_3$, 400 MHz).

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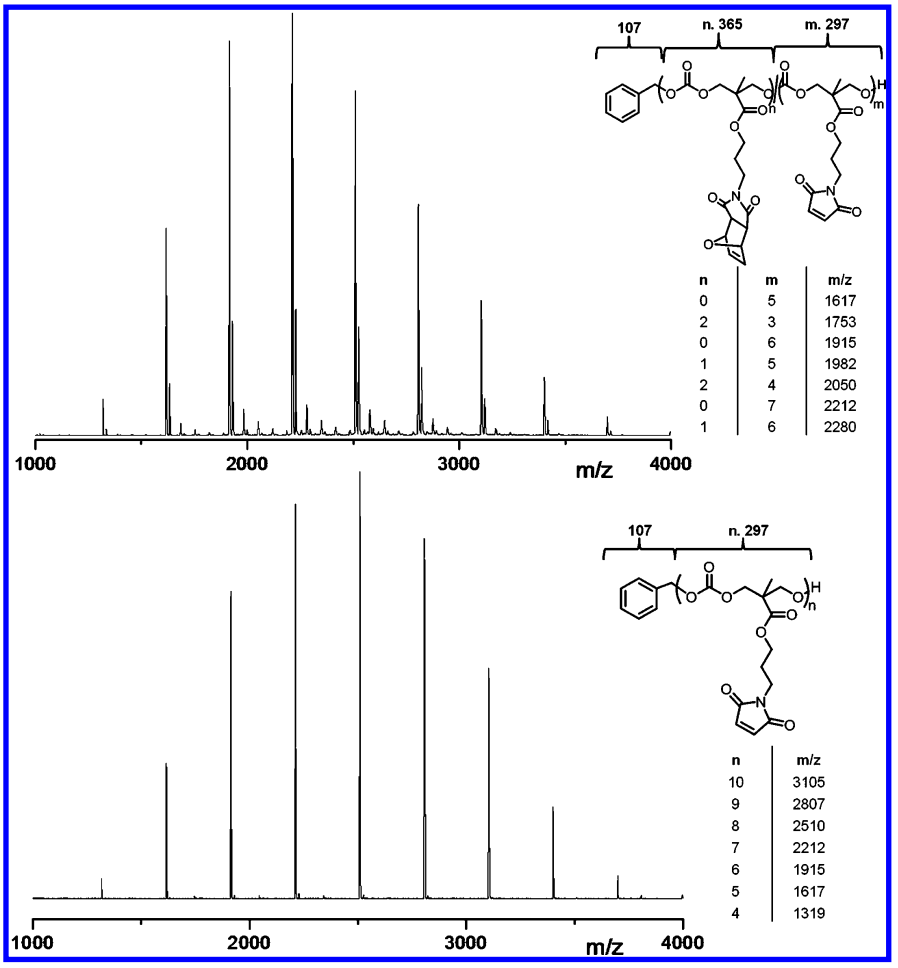

Figure 4. MALDI-TOF MS analysis of the polymer **P3** (top) and **P3** after retro DA reaction (bottom).

Table 2. Conditions and Characterizations of Carbonate Monomer 3:L-Lactide Copolymers

item	polymer[a]	time (h)	yield (%)	aimed ratio (3:LA)	obtained incorporation[b] (3:LA)	$M_{n,theo}$ (g/mol)	$M_{n,NMR}$[b] (g/mol)	$M_{n,GPC}$[c] (g/mol)	M_w/M_n
1	P8	120	90	20:80	21:79	17 100	9000	18 500	1.40
2	P9	8	95	5:95	4:96	14 800	11 100	22 000	1.10
3	P10	8	72	10:90	9:91	12 000	10 600	12 300	1.20
4	P11	24	70	25:75	17:83	13 000	7700	9800	1.10
5	P12	48	58	50:50	40:60	14 800	12 500	8300	1.20
6	P13	24	40	75:25	70:30	12 400	6500	8100	1.20
7	P14	24	85	10:90	6:94	14 200	13 300	17 000	1.20

[a]All polymerizations were performed in $CDCl_3$ at 25 °C, 2 mol % DBU, $[M]_0/[I]_0$ = 100 using benzyl alcohol as the initiator. [b]Measured by ^1H NMR spectroscopy . [c]Determined by SEC analysis in THF.

activity and selectivity.[20] DBU-catalyzed ring-opening polymerization of monomer **4** initiated with benzyl alcohol did not yield any homopolymer. Furthermore, attempts to copolymerize this unprotected monomer with L-lactide resulted in formation of a red gel. We propose that this is a consequence of cross-linking by base-catalyzed polymerization of the maleimide functionality that leads to the characteristic red color.[21] As such the furan-protected maleimide-containing carbonate monomer, **3**, was studied to provide access to biodegradable homopoly(carbonate)s bearing reactive maleimide units at their side chains via a protection/deprotection strategy (Scheme 2a). An initial survey of organocatalysts was undertaken to optimize the system with polymerizations carried out at room temperature using benzyl alcohol as an initiator in dry $CDCl_3$.[22] Polymerization using the thiourea/sparteine catalyst system resulted in very slow polymerization of **3**, hence the ROP of **3** catalyzed by 1,8-diazabicycloundec-7-ene (DBU) was studied (Table 1).

Monitoring the monomer conversion with time in the DBU-catalyzed homopolymerization of **3** revealed that the polymerization became severely retarded at ca. 60% monomer conversion,[23,20a] likely a consequence of the ring−chain equilibrium associated with sterically hindered monomers. Thereby, polymerizations were terminated at 50% monomer conversion in order to prevent possible transesterification reactions and obtain reliable data for further characterizations. Until this point, a linear relationship between conversion and molecular weight was observed. Although a discrepancy between targeted and obtained molecular weights was observed due to the

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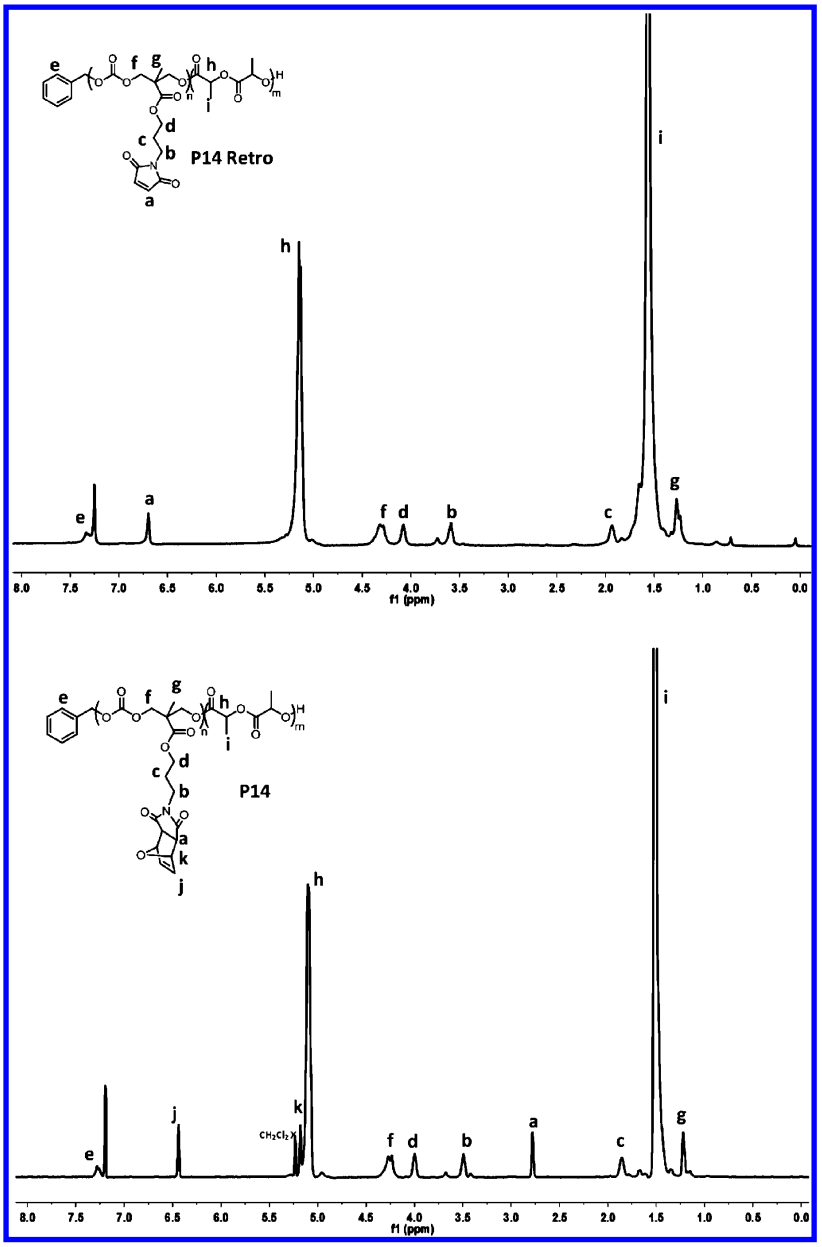

Figure 5. ^{1}H NMR spectrum of **P14** (bottom) and **P14-Retro** copolymers (top) ($CDCl_3$, 400 MHz).

extremely slow propagation of the polymer, a linear relationship between DP and obtained molecular weight was maintained (Figure 2).

The homopolymer **P3** was subjected to the retro Diels–Alder reaction by heating to 100 °C in a vacuum oven to unmask the maleimide groups to their reactive forms. Quantitative deprotection of the maleimide functional groups by elimination of furan was evident from the disapperance of the proton resonances in the ^{1}H NMR spectrum at δ = 2.82, 5.23, and 6.47 ppm resulting from the removal of the bicyclic core, and the appearance of a new proton resonance at δ = 6.65 ppm belonging to the active double bond protons of the maleimide unit (Figure 3). As expected, a slight decrease in the molecular weight of the polymer **P3** after the retro Diels–Alder step was observed by SEC analysis (**P3**, M_n = 2800 g·mol^{-1}, PDI = 1.10; **P3-Retro**, M_n = 2700 g·mol^{-1}, PDI = 1.10). More importantly, both ^{1}H NMR and SEC analysis of the resultant polymers show that no chain scission or other side reactions occurred during this activation step (see Supporting Information, Figure S3).

The homopolymers before and after the retro Diels–Alder reaction step were also analyzed by MALDI-ToF mass spectrometry (Figure 4). The MALDI–ToF MS of the parent homopolymer **P3**, displays peaks that correspond to polymer chains that contain the deprotected maleimide functionality alongside those expected for polymer **P3** with furan protecting groups retained. These data indicate that the retro Diels–Alder reaction partially occurs upon ionization by the laser as previously observed.[11b] The MALDI-ToF spectra of the homopolymer **P3-Retro** obtained after the retro Diels–Alder step consisted solely of the polymer with the reactive maleimide side chains.

To both overcome the limitations of poor monomer polymerizability and to enable the synthesis of maleimide-functional poly(lactide)s, copolymerization of **3** with L-lactide was studied by DBU-catalyzed ROP (Scheme 2b). A range of comonomer

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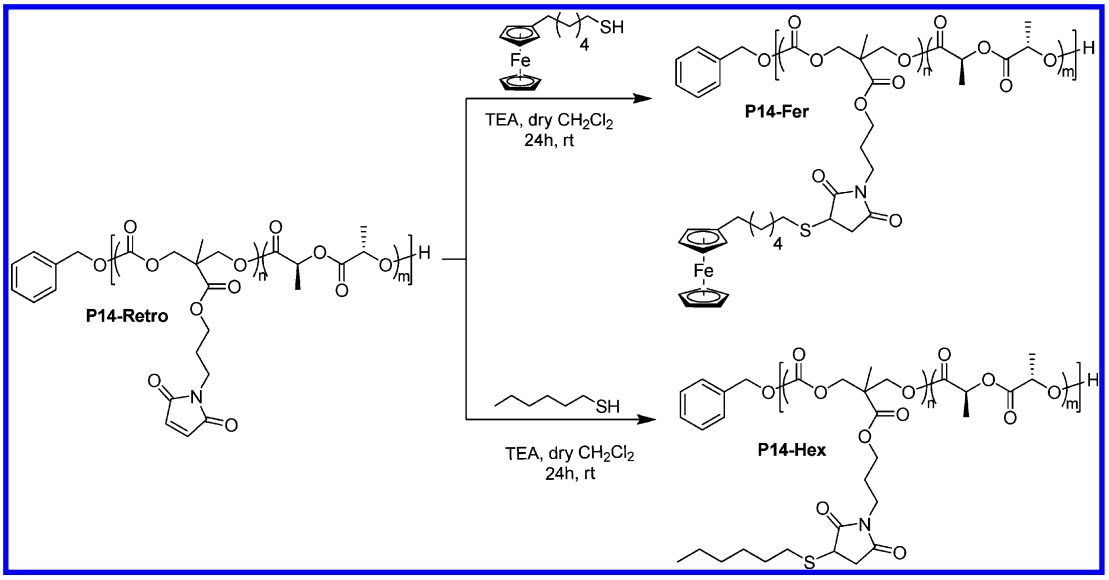
Scheme 3. Functionalization of Polymers via the Thiol−Ene Reaction



feed ratios were investigated (Table 2) with good correlation between feed ratio and comonomer incorporation being observed up to between 10 and 20% feed ratio of **3**. At higher feed ratios of **3**, lower incorporation of the carbonate comonomer into the poly(lactide) chain is observed (in comparison to that anticipated from the monomer feed ratios) which suggests that at higher overall monomer conversions the copolymers may be more accurately considered as tapered blocky copolymers, consistent with the higher rates of homopolymerization of lactide in comparison to **3**. Nonetheless, excellent control over the molecular parameters of the polymers is maintained. Following exposure of the furan-protected copolymers to high vacuum at 100 °C, the efficiency of the rDA reaction was clearly evident from the ^{1}H NMR spectra of the polymers observing a complete disappearance of the resonances at δ = 6.48, 5.28, and 2.83 ppm and appearance of a new resonance at δ = 6.69 ppm corresponding the unsaturated maleimide vinyl protons (Figure 5).

Analysis of the copolymers by thermogravimetric analysis (TGA) was also performed to probe the activation step via the rDA cycloreversion. Removal of the furan units is clearly observed between 60 and 180 °C and, as expected, different polymers containing higher maleimide incorporation displayed an increased weight loss (see Supporting Information, Figure S4).

To evaluate the efficiency of Michael type additions of thiol-containing molecules to the maleimide-functional polymers, functionalization studies were performed using two different thiols with the polymer **P14**, namely 6-(ferrocenyl)hexanethiol and 1-hexanethiol (Scheme 3). These thiols were chosen as representative examples which demonstrate the functionalization efficiency with 6-(ferrocenyl)hexanethiol providing a readily observable NMR handle as a consequence of the metalated cyclopentadienyl rings. Quantitative conjugation of thiol containing small molecules to the maleimide side chains was achieved at room temperature by using 2-fold excess of thiols per maleimide group. Using one equivalent of thiol per maleimide group led to a maximum conversion of 81%. Therefore, a thiol to maleimide ratio of 2:1 equiv was used for conjugations in order to achieve quantitative derivatization.

Examination of the ^{1}H NMR spectra of the polymer functionalized with 6-(ferrocenyl)hexanethiol revealed that the characteristic maleimide double bond resonance at δ = 6.69 ppm had disappeared and resonances corresponding to the protons on the ferrocene rings appeared at δ = 4.01 and 4.08 ppm. The proton resonances from the newly formed succinimide ring and the alkyl chain are also clearly assignable. Similarly, disappearance of maleimide proton resonances and appearance of expected proton resonances were also observed for the 1-hexanethiol conjugation reaction (see Supporting Information, Figure S7). SEC analysis of the functionalized polymers also confirmed the addition of thiol-containing species to the polymer backbones indicated by the decreased retention time in comparison to the maleimide-functional polymer precursor which indicates a change to the hydrodynamic volume of the polymer in solution as may be expected by an increase in molecular mass or a change in the polymer structure commensurate with the successful addition of thiol-containing species (Figure 6). Importantly, a narrow PDI is preserved in the polymers thus demonstrating that maleimide−thiol conjugation chemistry is an efficient method for functionalization of the copolymers without degradation of the polymer backbone.

In conclusion, a new maleimide-containing cyclic carbonate monomer has been synthesized and its homopolymerization and copolymerization behavior with L-lactide has been investigated using organocatalytic ring-opening polymerization. The side chains of these polymers were activated by retro Diels−Alder reaction to obtain reactive maleimide groups for further conjugations. Michael-addition "thiol−ene" conjugations were used to modify the pendant maleimide groups in a quantitative fashion without any noticeable degradation of the parent polymers. Further study of the copolymerization behavior of these monomers and subsequent fabrication of the resultant functional materials using this novel class of reactive polymers is underway and will be reported in due course.

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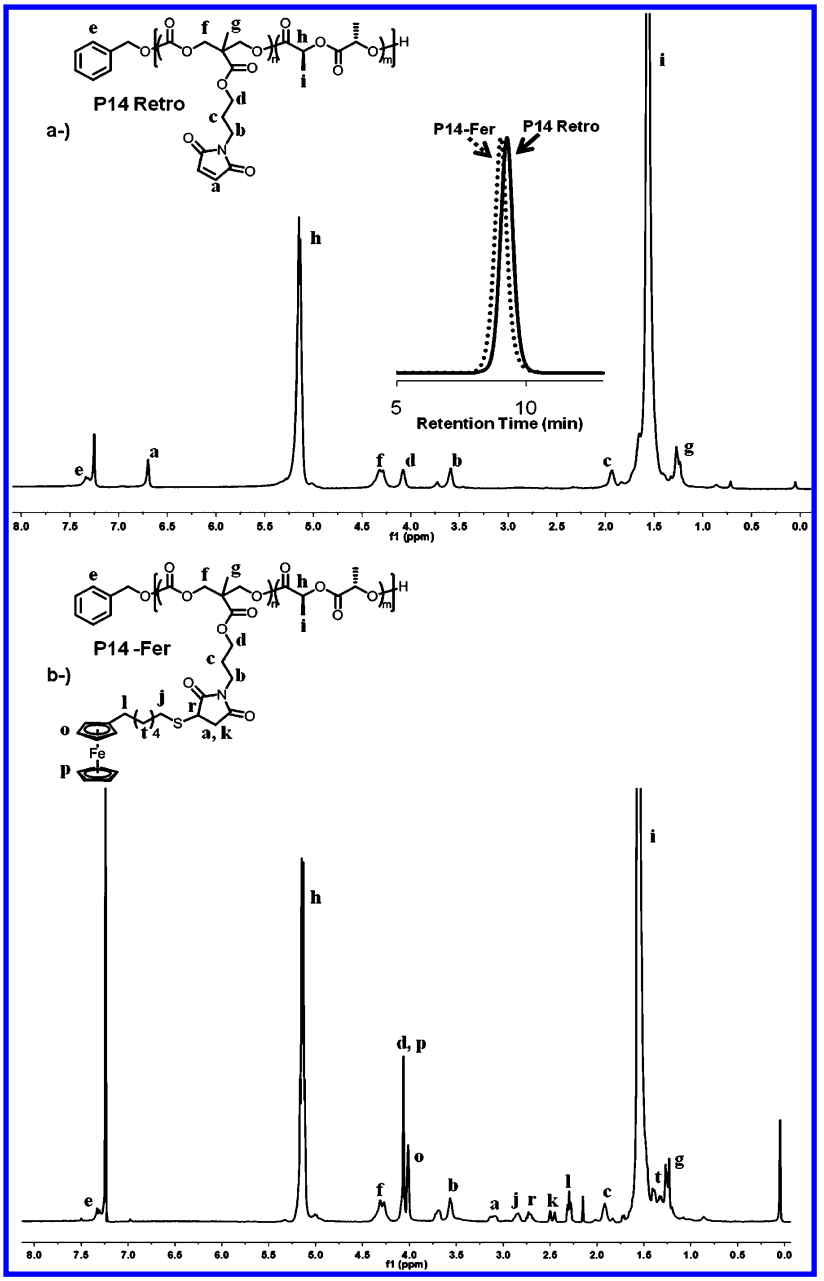

Figure 6. ^{1}H NMR in $CDCl_3$ of (a) **P14-Retro** (b) ^{1}H NMR of in $CDCl_3$ 6-(ferrocenyl)hexanethiol functionalized polymer (**P14**-Fer) and SEC traces before ($M_{n,SEC}$ = 17.0 kg/mol, M_w/M_n = 1.20) and after thiol functionalization ($M_{n,SEC}$ = 18.4 kg/mol, M_w/M_n = 1.20).

■ ASSOCIATED CONTENT

Supporting Information

Experimental section and ^{1}H and ^{13}C NMR spectra, GPC traces, and TGA thermograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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