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Broadening the Scope of Functional Groups Accessible in Aliphatic Polycarbonates by the Introduction of RAFT Initiating Sites

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The combination of disparate polymerization techniques has attracted considerable attention over the past decade since it allows the generation of materials from monomers that polymerize by fundamentally different mechanisms. Various strategies have been employed including the use of dual initiators, chain-end or pendent group transformations to produce block,[1] graft,[2] brush,[3] star,[4] miktoarm,[5] and cross-linked copolymers.[6] Another approach uses inimers or functional monomers bearing an active initiator as a pendent group.[7] This strategy is particularly attractive for ring-opening polymerization (ROP) as the inventory of cyclic ester and carbonate monomers available are limited. Some of us have demonstrated that 2,2-bis(methylol)propionic acid (Bis-MPA) can produce a six-membered cyclic carbonate ring bearing free carboxylic acid group **1,** which can be readily esterified with a suitable alcohol.[8] New functional polymers bearing hydrophilic, hydrophobic or reactive pendent groups have been successfully prepared by organocatalytic ROP, using basic amine catalysts as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or (−)-sparteine. Both catalyst are known to produce well-controlled polyesters and polycarbonates in mild conditions with the absence of metal contaminants from catalyst residues.[9] Here, we use this approach to enlarge the range of functional cyclic carbonates by introducing a reversible addition−fragmentation chain transfer (RAFT) agent either as initiator **2** or monomer **3** (Scheme 1). RAFT polymerization represents a powerful synthetic tool that allows the polymerization of a variety of functional monomers, including: (meth)acrylates, styrenes, vinylpyridines, and (meth)acrylamides[10] and offering the introduction of pH- and thermo-responsive polymers. Poly(*N*-isopropylacrylamide) (PNiPAAm) represents one of the most investigated thermosensitive polymers owing to its sharp coil-to-globule transition in water at 32 °C, allowing wide potential applications, particularly in biomedical fields.[11]

Since dithiocarbonate-based RAFT initiators are not compatible with primary or secondary amines,[12] the stability of 2-(benzylsulfanylthiocarbonylsulfanyl)ethanol (**2**) was first assessed in organocatalytic ROP of lactide using DBU as the catalyst (Scheme 1).[13] Polymerization of L-lactide (L-LA) was performed in CH_2Cl_2 at room temperature using **2** as initiator with 1 mol % of DBU catalyst for an initial monomer-to-initiator ratio of 50 (Table 1). After a 1 h reaction time, a well-defined PLLA macroinitiator (PLLA−OH; number average molecular weight ($M_{n)}$ = 6,600 g·mol^{-1}, M_w/M_n = 1.15) was obtained with retention of the trithiocarbonate group as evidenced by both the characteristic yellow color of the polymer and ^{1}H NMR spectroscopy, where intensity ratio of methylene protons adjacent to the trithiocarbonate group fits well the theoretical ratio ($I_d/I_e/I_{f+i}$ = 2/2/3) (ESI, Figure S1). Initiation of NiPAAm from the PLLA−OH macroinitiator in dimethylformamide (DMF) at 70 °C using azobisisobutyronitrile (AIBN) as co-initiator (ratio between the chain transfer agent and the initiator was fixed to 10 ([PLLA−OH]$_0$/[AIBN]$_0$ = 10)). As a control, NiPAAm was initiated from **2** with the same experimental conditions described above. The polymerization of NiPAAm was successfully accomplished from both initiators with predictable molecular weights and narrow polydispersities. The effective initiation of NiPAAm from PLLA−OH macroinitiator is clearly observed by the monomodal SEC trace of the diblock copolymer with the absence of any residual PLLA−OH macroinitiator (ESI, Figure S2).

The polymerization of methylcarboxytrimethylene carbonate-2-(benzylsulfanylthiocarbonylsulfanyl) ethanol ester **3** was accomplished by ROP using either DBU or (−)-sparteine[9,13] with *N*-(3,5-trifluoromethyl)benzyl-*N*′-cyclohexylthiourea (TU) as a cocatalyst initiated from benzyl alcohol (Bz−OH) in CH_2Cl_2 (2 mol·L^{-1}). The less basic (−)-sparteine/TU cocatalyst combination polymerized **3** with a better control than DBU, as assessed by the narrowly dispersed products. In order to space the RAFT initiating sites from each other, **3** was copolymerized with methylcarboxytrimethylene carbonate ethyl ester **4**, which forms random copolymers.[14] The copolymerization (10 mol % in **3**) was carried out in the presence of (−)-sparteine/TU cocatalyst and using benzyl alcohol as the initiator (targeted DP = 100). We found that decreasing the initial monomer concentration from 2 to 1 mol·L^{-1} produced well-defined and narrowly dispersed copolymers (Table 2). The effective initiation was demonstrated by initiating the copolymerization from either 4-pyrene-1-butanol or a poly(ethylene oxide) monomethylether (PEO−OH, M_n = 1900 g·mol^{-1}, M_w/M_n = 1.02). Comparing gel permeation chromatography (GPC) traces (Figure 1) from the refractive index (RI) with UV−vis (300 nm) detectors demonstrates the complete incorporation of the 4-pyrene-1-butanol initiator in the polymer chain and the narrow molecular weight distribution. The copolymerization of **3** and **4** initiated from PEO−OH was successfully achieved as the GPC chromatogram shows clean chain-extended block-copolymer free from any unreacted macroinitiator (M_w/M_n = 1.27, Figure 1). The polymerization of *N*-isopropylacrylamide (NiPAAm) (targeted degree of polymerization (DP) of 40) was performed by RAFT from the trithiocarbonate moieties available along the polycarbonate backbone. The reaction was conducted in DMF (3 mol·L^{-1}) at 70 °C for 8 h using AIBN as co- initiator[15] (chain transfer agent-to-initiator molar ratio = 10) (Scheme 1). A conversion of 94% was obtained

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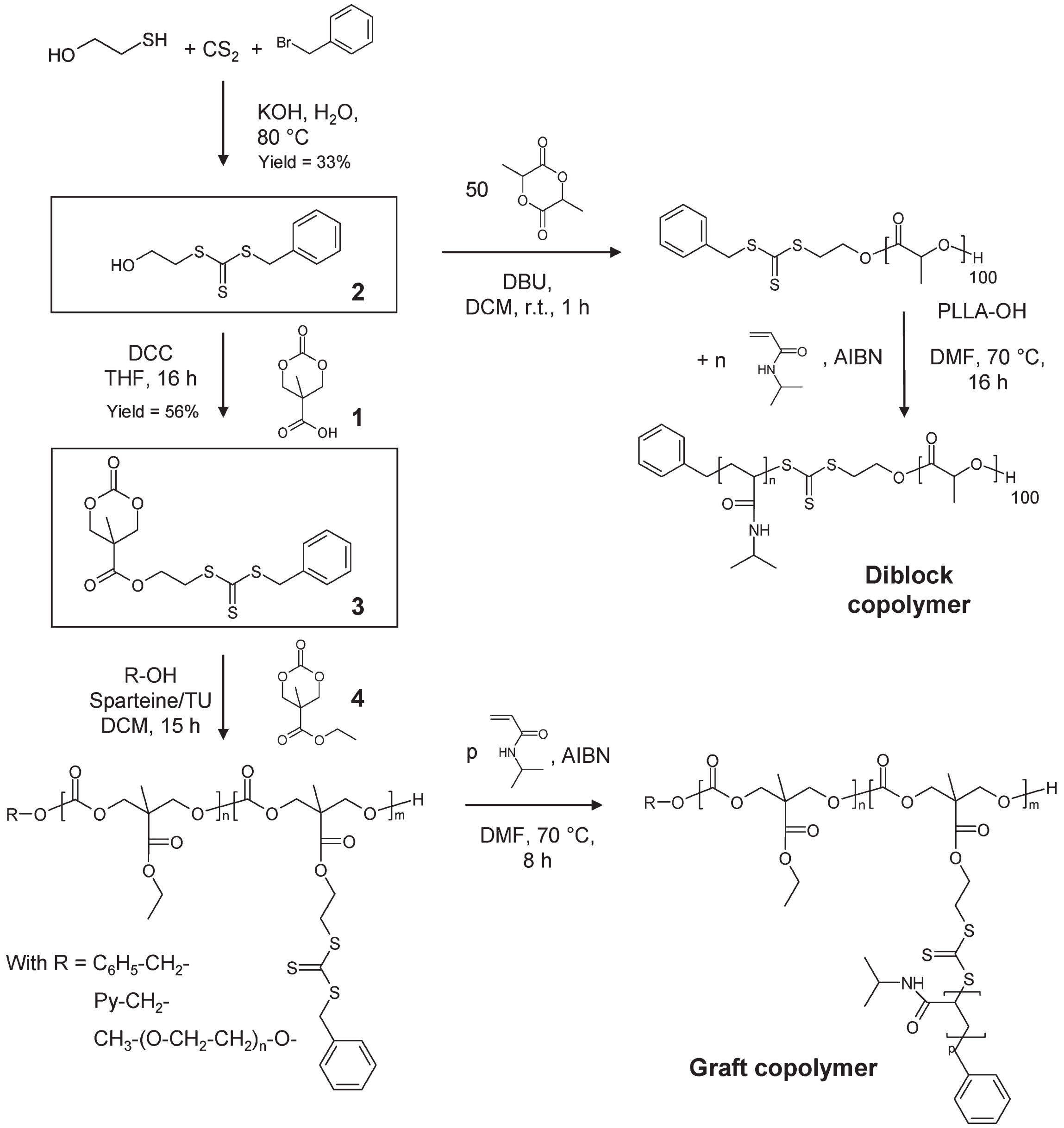
Scheme 1. Development of the Carbonate Inimer Concept for the Easy Preparation of Environmentally Sensitive Graft Copolymers[a]



[a] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TU = *N*-(3,5-trifluoromethyl)benzyl-*N*′-cyclohexylthiourea, DCC = *N*,*N*-dicyclohexylcarbodiimide, AIBN = azobisisobutyronitrile, DCM = dichloromethane, and THF = tetrahydrofuran.

as determined by ^{1}H NMR spectroscopy from the relative intensity of acrylate protons at 5.5 ppm and amide methine protons from the repetitive units at 3.9 ppm. A narrow polydispersity of 1.25 was recorded by SEC, attesting for the control over the RAFT polymerization.

Table 1. Initiation of *N*-Isopropylacrylamide (NiPAAm) from 2-(Benzylsulfanylthiocarbonylsulfanyl)ethanol) (2) and Poly(L-lactide) (PLLA−OH) Macroinitiator in Dimethylformamide (DMF) at 70 °C, $[\mathrm{NiPAAm}]_0$ = 3 M, Targeted DP = 100, and AIBN 10 mol % to Initiator

initiator	convn[a] (%)	M_n(th)[b] (g·mol^{-1})	M_nSEC[c] (g·mol^{-1})	M_w/M_n[c]	yield[d] (%)
2	>99	11 600	26 000	1.16	>99
PLLA−OH	>99	18 200	42 700	1.19	>99

[a] As calculated by ^{1}H NMR spectroscopy in $CDCl_3$. [b] M_n(th): theoretical molecular weight as calculated from the conversion. [c] Number average molecular weight (M_n) and polydispersity index (M_w/M_n) determined by GPC in DMF at 80 °C, relative to PS standards. [d] Gravimetrical yield.

In summary, we demonstrated that the RAFT-based carbonate monomer is an interesting starting building bock for the preparation of well-controlled polycarbonate structures as obtained by combination of RAFT and metal-free ring-opening polymerization. This concept can be successfully extrapolated to the preparation of cross-linked materials presenting challenging properties as biodegradability and biocompatibility as well as pH- and thermo-responsiveness and will be the topic of a forthcoming paper.

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Table 2. Homo- and Copolymerization of Methylcarboxytrimethylene Carbonate-2-(benzylsulfanylthiocarbonylsulfanyl)ethanol Ester (3) with Methylcarboxytrimethylene Carbonate Ethyl Ester 4 Using either 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) or (−)-Sparteine and *N*-(3,5-Trifluoromethyl)benzyl-*N*′-cyclohexylthiourea (TU) as Catalytic System, in CH_2Cl_2 at Room Temperature

catalyst	DP **3**	DP **4**	$[M]_0$ (mol·L^{-1})	initiator	time (h)	convn of **3**^{d} (%)	convn of**4**^{d} (%)	M_n(th)^e (mol·L^{-1})	M_w/M_n^{f}
DBU	50		2	BzOH	2	90.6		17 600	2.02
(−)-sparteine^a/TU^b	50		2	BzOH	2	35.3		6900	1.11
DBU	10	90	2	BzOH	2	> 99	99.4	20 800	1.71^g
(−)-sparteine^a/TU^c	10	90	2	BzOH	9	> 99	94.3	19 900	1.78
(−)-sparteine^a/TU^c	10	90	1	pyrene/BuOH	15	98.1	94.4	20 000	1.27
(−)-sparteine^a/TU^c	10	90	1	PEO−OH	15	97.2	93.1	21 400	1.21

[a] 5 equivalents to BzOH. [b] 10 mol % to monomer. [c] 5 mol % to monomers. [d] Conversion determined by ^{1}H NMR spectroscopy in $CDCl_3$. [e] Theoretical molecular weight calculated from conversion(s). [f] Polydispersity index (M_w/M_n) obtained by GPC in tetrahydrofuran (THF). [g] Multimodal.

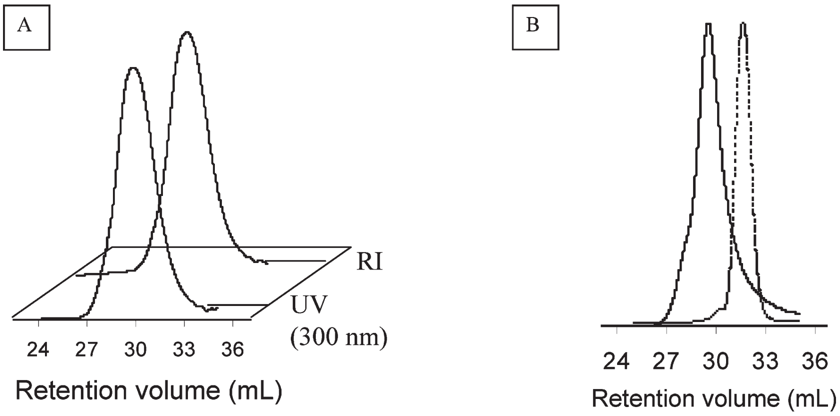

Figure 1. (a) Gel permeation chromatography (GPC) traces from RI and UV detectors (300 nm) in tetrahydrofuran (THF) showing the incorporation of the UV-responsive 1-pyrenebutanol initiator into the copolymer and (b) the SEC trace in THF of the copolymer after chain-extension from a poly(ethylene oxide) monomethyl ether (PEO−OH) macroinitiator.

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Supporting Information Available: Figure S1, showing the ^{1}H NMR spectrum of the crude RAFT end-capped PLLA−OH in $CDCl_3$, and Figure S2, SEC trace of the diblock copolymer and PLLA−OH polymer precursor. This material is available free of charge via the Internet at http://pubs.acs.org.

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