

RAPID COMMUNICATION

Conversion of diols to dithiols via a dehydration polycondensation with a dicarboxylic acid containing a disulfide and subsequent reduction

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Derivatization of compounds often transforms the targeted functional group; however, most of these processes require severe reaction conditions and/or excessive amounts of reagents.¹ These drawbacks frequently occur when transformations of polymer termini are attempted. If we could derivatize the terminal functional groups of polymers easily, we could design new types of polymers with predetermined properties. Transformations of polymer termini have been reported by several groups. A method that uses anionic living polymerization was described by Szwarc.² Cationic living polymerization has also been used to functionalize polymer termini.^{3–5} Müller and co-workers⁵ showed that the thiophene-end-capped termini of a polyisobutylene chain could be transformed. Guillaneuf *et al.*⁶ functionalized the ends of polystyrenes that had been obtained by living radical polymerization techniques, that is, atom transfer radical polymerization or reversible addition and fragmentation transfer. These studies used living polymerizations that required stringent reaction conditions, for example, a very low temperature, a nitrogen atmosphere, a highly reduced pressure, a dry environment and ultrapure reagents.

Recently, Kilbinger and co-workers^{7,8} reported a new method (involving ‘sacrificial synthesis’) to replace a functional group at the end of a polymer produced by ring-opening metathesis. Although this method is revolutionary and therefore interesting, it suffers from low atom economy.^{9,10}

Much attention has been paid to thiol compounds as reactants because they are readily available and usually very reactive; they are often used in addition reactions, nucleophilic reactions, radical reactions and thiol-disulfide coupled reactions; thiol oxidation and disulfide reduction. In particular,

thiol-ene and thiol-yne click reactions^{11–13} have been useful. Application of thiol-related chemistry to polymer synthesis promises to open a new frontier in material design, but first, methods that readily afford a thiol on deprotection must be developed. Martinelle and co-workers¹⁴ described a one-step end-functionalization of poly(ϵ -caprolactone) by a ring-opening polymerization that was catalyzed by *Candida antarctica* lipase B and used mercaptoethanol as the initiator. A transformation of polycaprolactone (PCL) diol to PCL dithiol was reported by Leroux and co-workers,¹⁵ in which PCL diol was condensed with an excess of a dicarboxylic acid that contained a disulfide bond by dicyclohexylcarbodiimide coupling and subsequent reduction.

We have directly polycondensed diols and dicarboxylic acids at moderate temperatures in the presence of rare-earth trifluorometha-

nesulfonate catalysts that afforded aliphatic polyesters with number-average-molecular weights (M_n s) $>1.0 \times 10^4$ (refs 16–24). This polycondensation system made it possible to use thermally unstable monomers that contained a carbon–carbon double bond,¹⁷ a bromine substituent¹⁸ and/or a hydroxyl substituent.^{21,23}

The aforementioned studies, including our own, prompted us to investigate the possibility that the terminal hydroxyl groups of a polymer could be replaced by thiols by a process that included a step polymerization. Such a method would overcome the limitations of the current methods. First, we performed dehydration polycondensations with various diols and the carboxylic acid, 3,3'-dithiodipropionic acid (DTDPA), which contains a disulfide, using scandium(III) trifluoromethanesulfonate ($\text{Sc}(\text{OTf})_3$) as the catalyst. Then we cleaved the disulfides in the

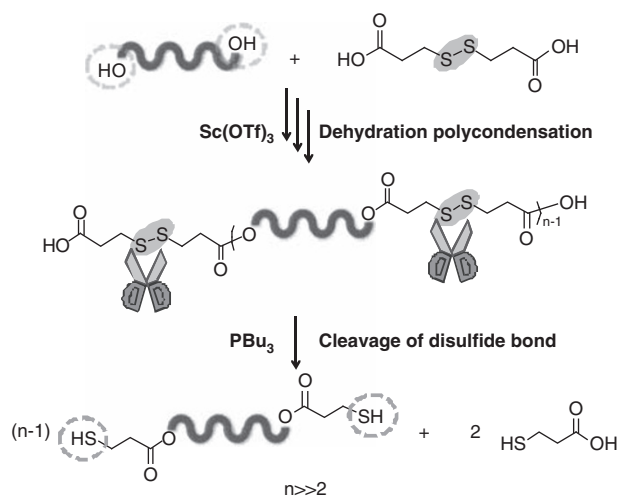


Figure 1 Derivatization of diols by a dehydration polycondensation with a disulfide-containing dicarboxylic acid and subsequent reduction with tributylphosphine.

resulting polyesters with tributylphosphine to afford the original compounds modified with dithiols that substituted for the hydroxyls and with atom economy. Finally, starting with the polyesterdithiol, and diisocyanate, we synthesized the corresponding polythiourethanes (Figure 1).

RESULTS AND DISCUSSION

We performed dehydration polycondensations that used commercially available low-molecular-weight diols or polymeric diols and DTDPA to produce products that could be converted into dithiols (Details of experimental procedure and some spectra are described in Supplementary Information). The properties of the polyesters produced by dehydration polycondensation are shown in Table 1; the polydispersities of the polyesters are those predicted by Flory's theory,^{25,26} which suggests that they were formed by step polymerization. The dehydration polycondensations that used low-molecular-weight diols were carried out at 80 °C for 6 h under reduced pressure (0.3–3 mm Hg) in the presence of 0.1–0.5 mol% of Sc(OTf)₃ (runs 1–6). After the compounds were dissolved in chloroform (5 ml) and then precipitated using diethyl ether (100 ml), hydrogenetic reduction of the polyesters was carried out using 8-equiv tributylphosphine in CHCl₃ at room temperature for 24 h. The structures of the dithiol

products were confirmed by ¹H-nuclear magnetic resonance (NMR) spectroscopy, the M_n s and M_w/M_n s were evaluated by size exclusion chromatography. The low yields are ascribed to purification procedure (reprecipitation).

As an example of these reactions, 3-methyl-1,5-pentanediol was reacted with DTDPA at 80 °C for 6 h under reduced pressure in the presence of 0.5 mol% of Sc(OTf)₃, and the product had an M_n of 8.4×10^3 and an M_w/M_n of 1.9. The latter value agreed with that calculated using Flory's theory,²⁵ which suggested that the reaction proceeded by step polymerization. After reduction of the disulfides with tributylphosphine, the product, which was the expected dithiol ($M_n=0.76 \times 10^3$, $M_w/M_n=1.1$), was precipitated twice from CHCl₃ with *n*-hexane. According to the ¹H-NMR spectrum of the product (solvent, CDCl₃), 95% of the hydroxyl groups had been converted to the corresponding thiols. For higher conversion, control the polyester end group was performed by polycondensations with 1.05 equiv of DTDPA was carried out at 80 °C to yield polyester having carboxyl end groups based on widely accepted stoichiometric principles of polycondensation.²⁵ Subsequent reduction showed the higher functionalities (runs 2, 4, 5, 6, 8 and 10).

The reaction of PCL diol ($M_n=1.6 \times 10^3$, $M_w/M_n=1.8$, run 9) with DTDPA and 0.5 mol% Sc(OTf)₃ as the catalyst gave

poly(DTDPA-*alt*-PCL) ($M_n=0.94 \times 10^4$, $M_w/M_n=1.3$, run 9). Although the M_n s were $\sim 1.0 \times 10^3$ higher than the prepolymer by the change of the hydrodynamic volume ascribed to terminal transformation from –OH to –OCOCH₂CH₂SH, after reduction of the disulfides the terminal substituents were characterized by matrix-assisted laser desorption/ionization–time of flight spectroscopy (Supplementary Figure S2), which confirmed that the product was the desired PCL dithiol ($M_n=3.0 \times 10^3$, $M_w/M_n=1.3$) and did not show peaks ascribed to monofunctional compounds. By integrating the 3.65–3.73 p.p.m. (alcohol) and 2.69–2.92 p.p.m. (thiol) peak areas in the ¹H-NMR spectrum of PCL dithiol, the extent of derivatization was found to be 93% (Figure 2). The polydispersity of PCL dithiol is narrower than that of PCL diol, which may be because PCL dithiols of low-molecular weights were not recovered upon reprecipitation.

Polyactidediol (PLA diol, runs 11 and 12) was prepared by a ring-opening polymerization that was Sc(OTf)₃ catalyzed in toluene at 80 °C. For the two polymerizations, the M_n s of the PLA diols were 1.4×10^3 and 2.8×10^3 and their M_w/M_n s were 1.3 as measured by size exclusion chromatography with CHCl₃ as the eluent. The ¹H-NMR spectrum of PLA diol (run 11) in CDCl₃ is shown in Supplementary Figure S1. To prepare the polyesters, an equimolar amount of DTDPA was added

Table 1 Derivatization of diols by hydration polycondensation with disulfide-containing dicarboxylic acid^a and subsequent reduction using TBP^b

Run		Diol			Polyester				Dithiol			Functionality ^e (%)
		$M_n^c \times 10^{-3}$	M_w/M_n	Temp. (°C)	Time (h)	Yield (%)	$M_n^d \times 10^{-4}$	M_w/M_n	Yield (%)	$M_n^d \times 10^{-3}$	M_w/M_n	
1	MPD	0.29	—	80	6	86	0.84	1.9	13	0.76	1.1	95
2	1,5-PD ^f	0.28	—	80	6	92	0.63	2.0	31	1.7 ^g	—	99
3	1,6-HexD	0.29	—	80	6	95	1.4	2.3	29	1.9	—	91
4	1,7-HepD ^f	0.31	—	80	6	84	0.67	2.0	11	1.8 ^g	—	94
5	1,8-OD ^f	0.32	—	80	6	86	0.90	2.0	16	1.1 ^g	—	92
6	1,9-ND ^f	0.34	—	80	6	83	1.0	2.0	12	1.0 ^g	—	92
7	TEG	0.35	—	100	14	78	1.1	1.5	14	1.3	1.2	99
8	PCL diol ^f	0.9	1.6	80	12/4	90	1.1	1.9	34	2.2	1.4	93
9	PCL diol	1.6	1.8	80	6	70	0.94	1.3	51	3.0	1.3	93
10	PCL diol ^f	3.4	1.8	80	12/4	79	1.6	1.7	85	4.7	1.4	99
11	PLA diol	1.4	1.3	100/120	12/23	22	1.6	1.2	40	3.6	1.3	>99
12	PLA diol	2.8	1.3	100/120	12/23	44	1.1	1.3	89	4.2	1.3	>99
13	PEG	4.2	1.1	100/120	77/13	99	1.2	1.8	89	6.0	1.4	45

Abbreviations: MPD, 3-methyl-1,5-pentanediol; PCL, polycaprolactone; PEG, polyethylene glycol; PLA, polylactide; SEC, size exclusion chromatography; TBP, tributylphosphine.

^aAll runs were performed as bulk condensations under reduced pressure (0.3–3 mm Hg).

^bReacted at room temperature or 30 °C for 24 h.

^cCalculated values (runs 1–7); determined by SEC (runs 8–13; eluent, CHCl₃; calibrated with polystyrene stands).

^dDetermined by SEC (eluent, CHCl₃; calibrated with polystyrene stands)

^eDetermined by integrating 3.6–3.7 p.p.m. (alcohol) and 2.6–2.9 p.p.m. (thiol) ¹H-NMR peaks (solvent, CDCl₃).

^fPolycondensated using 1.5 equiv of 3,3'-dithiodipropionic acid.

^gDetermined by SEC *in situ* (eluent, CHCl₃; calibrated with polystyrene stands).

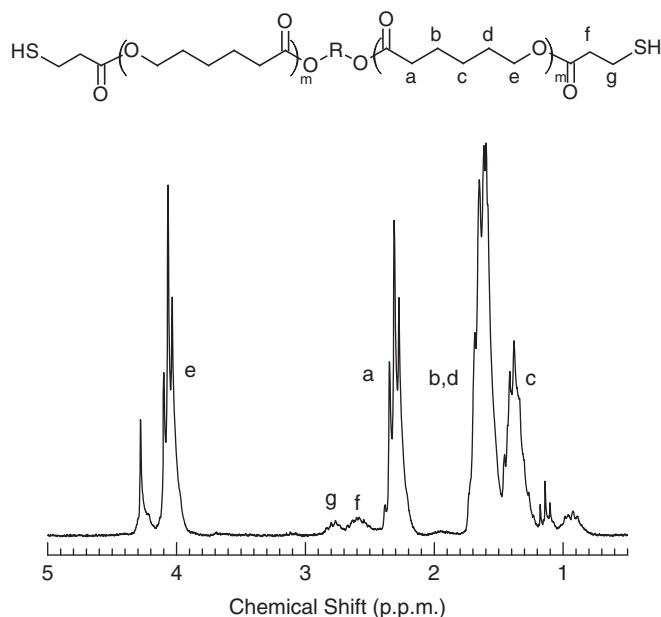


Figure 2 $^1\text{H-NMR}$ (200 MHz) spectrum of PCL dithiol in CDCl_3 (run 9).

into flasks that contained PLA diol in toluene and the reactions were run at 100°C for 12 h and 120°C for 23 h under reduced pressure ($M_n=1.6\times 10^4$, $M_w/M_n=1.2$, yield, 22% (run 11) and $M_n=1.1\times 10^4$, $M_w/M_n=1.3$, yield, 44% (run 12)). A much longer reaction time was required than for PCL diols because the termini of PLA diol are secondary alcohols. After reduction of the disulfides, the expected dithiols were obtained ($M_n=3.6\times 10^3$, $M_w/M_n=1.3$, yield, 40% (run 11); $M_n=4.2\times 10^3$, $M_w/M_n=1.3$, yield, 89% (run 12)). $^1\text{H-NMR}$ proved that the extent of reduction was quite good and we could not observe the peak derived from alcohol which indicated that the derivatization of the diols by a dehydration polycondensation was carried out successfully (Supplementary Figure S3).

We also obtained the poly(DTDPA-*alt*-TEG) (run 7), although a longer reaction time and a higher temperature were required to produce it than were required for the other low-molecular-weight compounds because the scandium catalyst coordinated with the oxygen of the ethylene glycol units.²³ Although the dehydration polycondensations that used polyethylene glycol (100°C , 77 h and 120°C , 12.5 h; $M_n=1.2\times 10^4$, $M_w/M_n=1.8$, yield, 99%) also required longer times and higher temperatures for the same reason, the subsequent reduction afforded the corresponding polyethylene glycol dithiol (run 13, 89% yield, Supplementary Figure S4).

Not only were we able to transform the various diols using this new method, but we could also use the dithiols to synthesize polythiourethanes. For example, the product

of run 1, 3-methyl-1,5-pentane dithiol and triethylamine were dissolved in dimethyl formamide, and then hexamethylene diisocyanate was added under a nitrogen atmosphere. The mixture was stirred for 10 min at room temperature and then for 2 h at 60°C . The product was dissolved in 5 ml of dimethyl formamide and then added 100 ml of diethyl ether. The structure of the product was characterized by infrared spectroscopy and was that expected for polythiourethane ($M_n=3.2\times 10^4$, $M_w/M_n=6.4$). The same method was used for polymerization of PCL dithiol (run 9) ($M_n=8.0\times 10^3$, $M_w/M_n=1.5$). The glass-transition temperatures of the two products are 37 and 17°C , respectively.

In this communication, we demonstrated that terminal diols could be transformed to contain thiols by a dehydration polycondensation with the disulfide-containing dicarboxylic acid, DTDPA, and subsequent reduction of the disulfides to thiols. Both low-molecular-weight diols and polymeric diols, that is, PCL, PLA and polyethylene glycol, could be transformed using this method. The presence of the thiols at the termini was confirmed by $^1\text{H-NMR}$ and matrix-assisted laser desorption/ionization-time of flight spectroscopy. We expect that this transformation process will be used in future polymer material science studies.

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