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A Mild and Versatile Synthesis for the Preparation of Thiol-Functionalized Polymers

Mikael Trollsås, Craig J. Hawker, and James L. Hedrick*

Center for Polymer Interfaces and Macromolecular Assemblies, IBM Research Division, Almaden Research Center, 650 Harry Road, San Jose, California 95120-6099

Geraldine Carrot and Jöns Hilborn*

Laboratoire de Polymeres, Swiss Federal Institute of Technology Lausanne, CH-1015 Lausanne Switzerland

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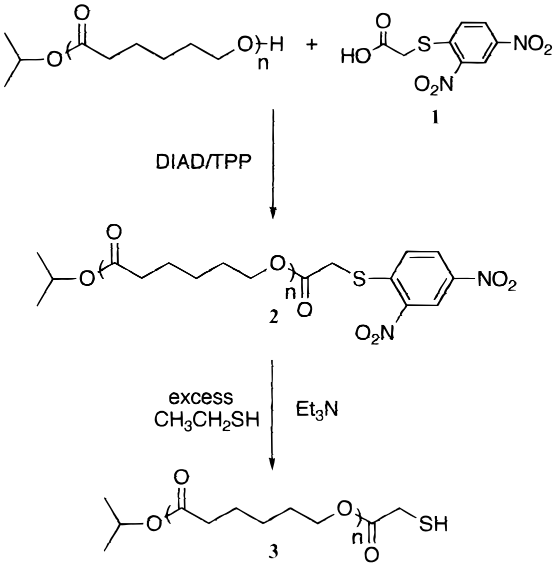
A general synthetic strategy to monothiol-functional polymers has been developed. This method, based on Sangers reagent (2,4-dinitrofluorobenzene), is a mild and versatile procedure which produces thiol-functional polymers in just two steps from chain-end hydroxy-functionalized polymers (Scheme 1).

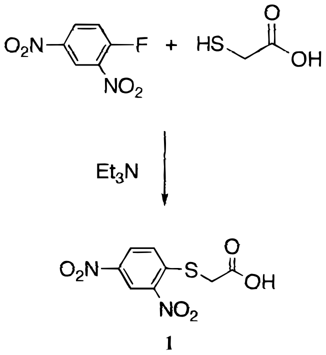
Thiols, known to be strong nucleophiles and good leaving groups, are widely used in all areas of chemistry.[1] In addition, the specific interaction of thiols with metals such as gold, silver, cadmium, etc. has expanded the interest of such compounds into areas ranging from microelectronics to biochemistry.[2] A large number of low molar mass thiols as well as polymers bearing an undefined number of mercapto groups are well-known.[3] These polymers have found use as nanoreactors[3b] as well as scaffolds for the preparation of nanoparticles.[3c] Other examples include their use as photoreactive polymers as reported by Kihara and co-workers.[3g] Although many synthetic routes for the preparation of organic thiols are well-known, only a few examples of well-defined polymers with thiol functionality have been reported.[4−6] The difficulty in preparing thiol polymers is that the typical reaction conditions give only moderate yields with many side products which severely hampers purification in the polymeric case.[3,4] A more controlled procedure for the incorporation of thiol groups at the chain ends or along the backbone is to couple a protected thiol to an already existing functionality of the polymer followed by deprotection. Recently, Tohayama *et al.*[4] reported mercapto functionalized polystyrene and polyisoprene, prepared by the termination of anionic living polymers with alkyl halides containing protected −SH functionalities. Other examples includes the polymerization of vinyl acetate in the presence of thioacetic acid as a chain transfer agent which produces poly(vinyl alcohol) with a thiol end-group after hydrolysis.[5] In addition, mercapto-terminated poly(ethylene oxide) and poly(phenylene sulfide) have been reported.[6] Points in common for these polymer transformations are that they require specific and sometimes severe conditions. These methods leave a need for the development of a mild, quantitative, and general synthetic route for the preparation of thiol-functional macromolecules.

The intention of this paper is to report a mild and versatile synthetic procedure to well-defined thiol-functional macromolecules, allowing sensitive polymers such as poly(ϵ-caprolactone) to be end-functionalized. Hydroxyl-functionalized polymers were chosen as the starting materials due to their ready availability and wide range of possible reactions for coupling with protected thiol moieties, such as mercapto aliphatic acids. 2,4-Dinitrofluorobenzene, known to selectively protect the sulfhydryl group in cysteine in the presence of an amine,[7] was selected as the protecting group for the thiol since it can be quantitatively removed by mercaptoethanol using mild conditions (pH 8).[8] In addition, the coupling of mercapto acetic acid with 2,4-dinitrofluorobenzene is known (Scheme 1).[9] Finally, 2,4-dinitrofluorobenzene provides an excellent handle for characterization of the degree of functionalization by ^{1}H NMR and other techniques.

Scheme 1



Scheme 2



Scheme 1 shows the general synthetic approach exemplified by poly(ϵ-caprolactone). The protection of mercapto acetic acid was performed by a slow addition of acetic acid to a solution of 2,4-dinitrofluorobenzene and triethylamine in $CHCl_3$ (Scheme 2). As the reaction proceeds the color of the solution changes from light orange to reddish. Recrystallization of the crude product from $CHCl_3$ gives **1** as yellow crystals in excellent yield. **1** was then coupled with hydroxyl-terminated poly(ϵ-caprolactone) in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP). This affords the protected thiol polymer, **2**, in excellent yield after purification through precipitation into cold methanol. The extent of functionalization was shown to be 95−100% by a combination of ^{1}H NMR and UV−vis

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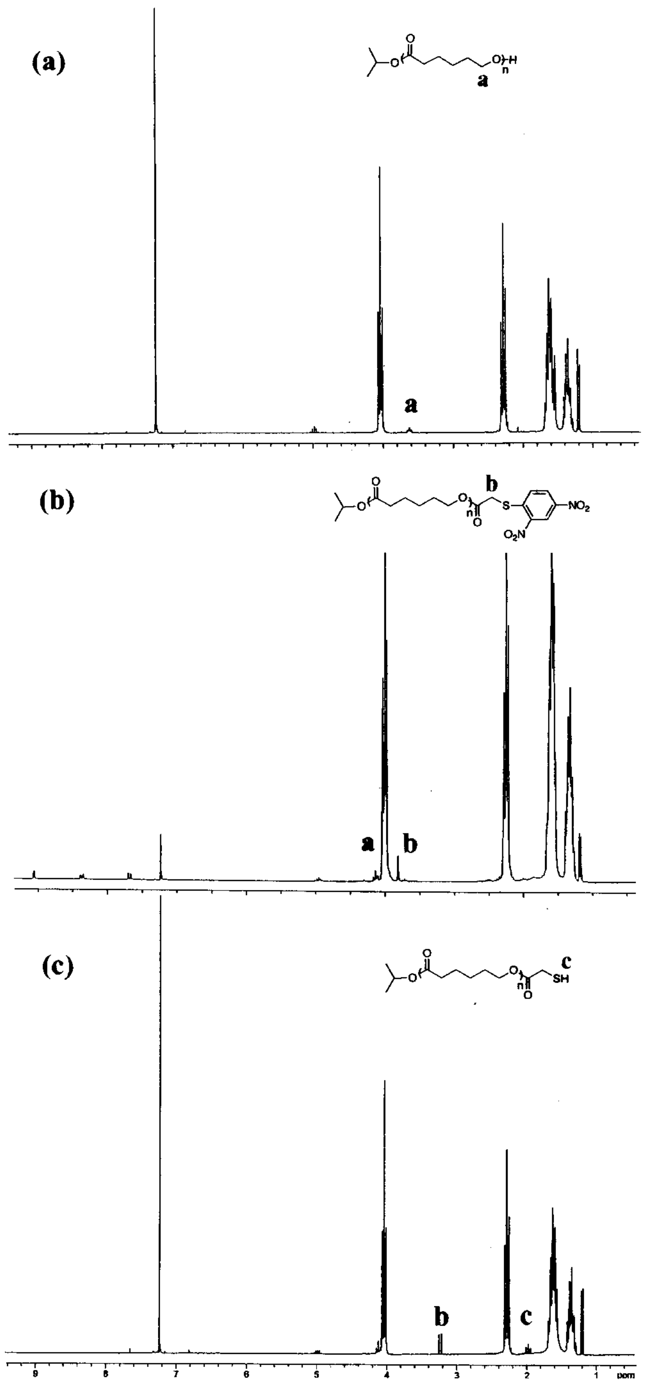

Figure 1. ^{1}H NMR spectra of (a) the hydroxyl-functionalized, (b) the thiol-protected, and (c) the thiol-functionalized poly(ϵ-caprolactone).

spectroscopy.[10] The same general technique was used for the preparation of thiol functional dendrons and thiol functional poly(ethylene oxide) (PEO). However, for the esterification of the hydroxyl functional dendrons dicyclohexylcarbodiimide (DCC) and ((dimethylamino)pyridyl)-*p*-toluenesulfonic acid (DPTS) were used. In addition, column chromatography was used for their purification. The commercial poly(ethylene oxide) was purified prior to esterification by freeze-drying to remove water which could possibly interact in the condensation reaction. Deprotection of **2** was accomplished through an exchange reaction of the protected chain-end with a large excess of mercaptoethanol in the presence of triethylamine. The desired thiol-functional polymer **3** was recovered by precipitation into cold methanol. This was possible when the molecular weight of the poly(ϵ-caprolactone) was higher than 3000. Otherwise, the precipitation was done in hexane. However, since mercaptoethanol is not soluble in hexane, 1-propanethiol was used due to its solubility for the deprotection of the low molar mass poly(ϵ-caprolactone). In addition, 1-propanethiol was mixed with mercaptoethanol for the deprotection of functionalized poly(ethylene oxide).

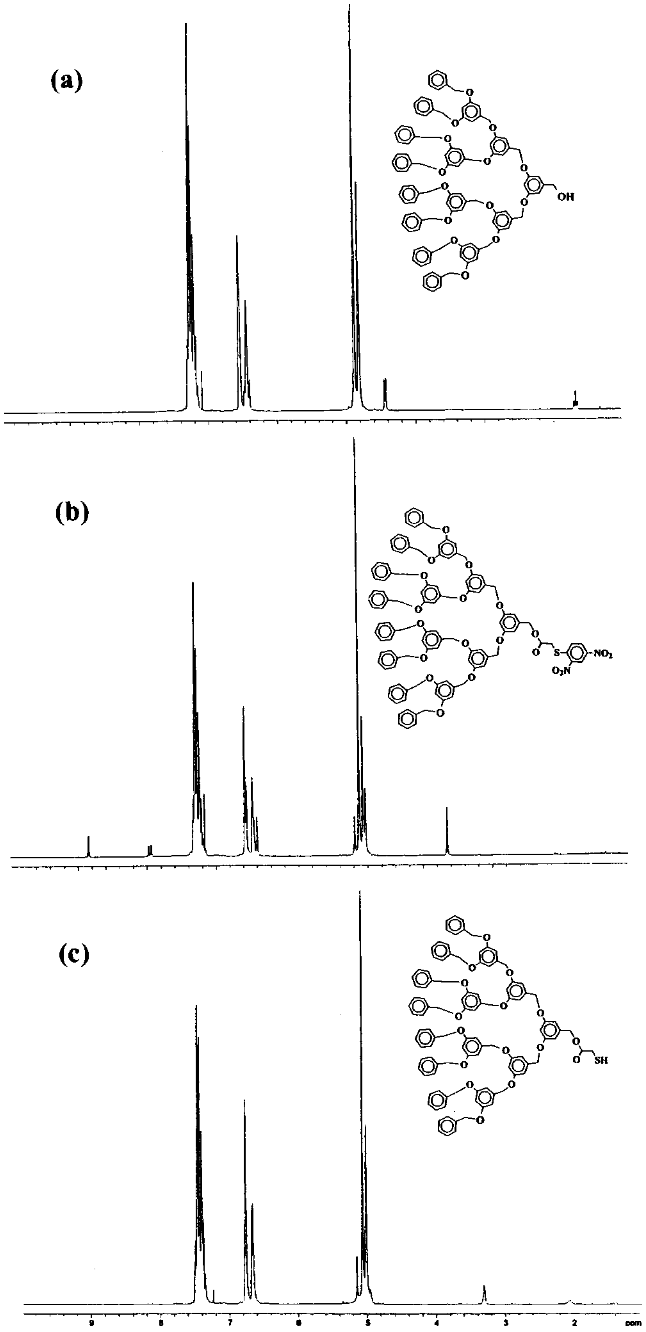

Figure 2. ^{1}H NMR spectra of (a) the hydroxyl-functionalized, (b) the thiol-protected, and (c) the thiol-functionalized dendrimer.

Characterization of the functionalized polymers was performed with ^{1}H NMR spectroscopy. Figure 1a shows the spectrum of hydroxyl-functional poly(ϵ-caprolactone) initiated from $Al(O^iPr)_3$ which shows four large peaks that originate from the repeating units of ϵ-caprolactone. In addition, the spectrum shows one peak (**a**) assigned to the α-methylene protons next to the hydroxyl chain

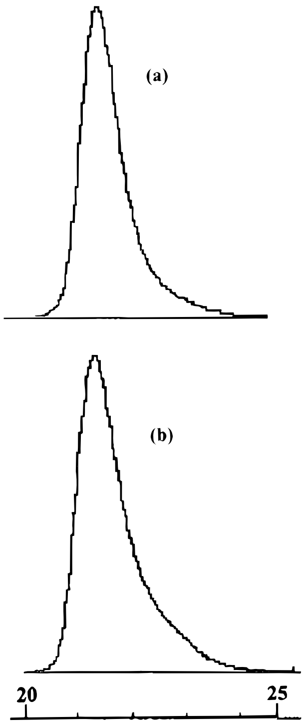

Figure 3. SEC chromatograms from thiol terminated poly(ϵ-caprolactone) (a) before and (b) after deprotection.

end and two peaks from the isopropyl chain end. Upon transformation of the alcohol chain end into an ester, the **a** peak shifts quantitatively and four new peaks appear originating from the protected thiol, Figure 1b. Deprotection of the thiol removes the peaks derived from the protection group, shifts and splits the **b** peak ($-CH_2-$ in mercaptoacetic acid) and generates a triplet (**c**) from the deprotected thiol hydrogen (Figure 1c). The quantitative splitting of the **b** peak and the new triplet (**c**) clearly indicate that the desired thiol is formed. The $-SH$ group formation was further confirmed by Raman spectroscopy, which revealed a $-SH$ stretching at 2600 cm^{-1}. Figure 2 shows the ^1H NMR spectra of the hydroxyl, the protected thiol- and the thiol-functional third generation dendrons. The spectra show a trend similar to the one observed for poly(ϵ-caprolactone). Noteworthy are the dramatic chemical shifts of the benzylic protons upon functionalization with the protected mercapto acetic acid.

Disulfide formation as well as polymer degradation from the synthetic procedure were investigated by size exclusion chromatography (SEC). The SEC chromatograms showed no signs of degradation, nor did they show any signs of disulfide coupling (Figure 3). However, upon standing in THF solution, SEC revealed the slow appearance of a second peak at twice the molecular weight, which can be attributed to the dimeric polymer resulting from disulfide formation. This behavior was more pronounced in the third generation dendron samples than the corresponding fourth generation material and was also clearly observed for PEO (Figure 4).

In conclusion, a novel procedure to thiol-functional polymers has been developed that offers the advantage of mild reaction conditions and compatibility with a variety of polymeric structures. The technique allows reactive hydroxyl-functional polymers such as poly(ϵ-caprolactone) to be converted into thiol functionality in only two steps with only minimal purification required. In addition, it was shown that the technique works with a large number of macromolecular structures including convergent dendrimers. The extension of this technique to the use of **1** and its derivatives as initiators for living ring-opening polymerization of PCL as well as for living free radical polymerization (ATRP), to produce telechelics with thiol functionality at one chain end, is currently under investigation

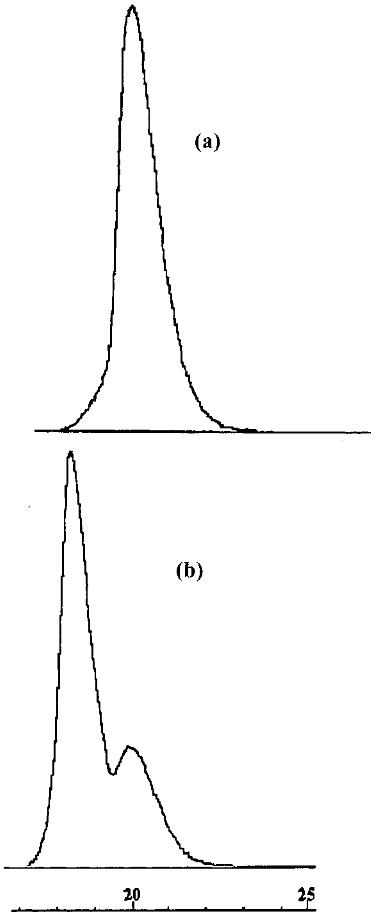

Figure 4. SEC chromatograms from thiol-terminated poly(ethylene oxide) (a) directly after deprotection and (b) upon standing in THF.

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(11) ^{1}H NMR spectra were recorded in CDCl$_3$ solution, on a Bruker AM 250 (250 MHz) apparatus with the solvent proton signal for reference. ^{13}C NMR spectra were recorded at 62.9 MHz on the same instrument using the solvent carbon signal as a reference. The molecular weights and the molecular weight distributions were determined by size exclusion chromatography (SEC) using a Waters chromatograph connected to a Waters 410 differential refractometer and an UV-detector. Four 5 mm Waters columns (300 × 7.7 μm) connected in series in order of increasing pore size (100, 1000, 10^5, 10^6 Å) were used with THF as the solvent at 25 °C. Poly(styrene) standard samples were used for calibration.

(12) ((Dimethylamino)pyridyl)toluenesulfonate (DPTS), poly(ϵ-caprolactone) and the different dendrimers were synthesized according to literature procedures.[10,13] The used polymers had molecular weights ranging from 3000 up to 10000 and molecular weight distributions between 1.06 and 1.20. All other chemicals were purchased from Aldrich and used as delivered.

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(14) *2,4-Dinitrophenylthioacetic acid* (1):[9b] 5.00 g (26 mmol) of mercaptoacetic acid dissolved in CHCl$_3$ (20 mL) was slowly added to a solution of 2.47 g (26 mmol) of dinitrofluorobenzene and 8.14 g (81.0 mmol) of triethylamine in CHCl$_3$ (30 mL). The reaction mixture was stirred for 15 h at room temperature before it was extracted with 1 M HCl and 2× with water. The organic phase was separated and filtered to yield yellow crystals which were recrystallized from CHCl$_3$. Yield: 6.1 g (94%). Mp: 171 °C. ^{1}H NMR (CDCl$_3$): $\delta = 3.76$ (s, 2H, $-$SCH_2COOH), 7.75 (d, 1H, $-$Ar, $J_o = 9.0$ Hz), 8.27 (dd, 1H, $-$Ar, $J_m = 3.0$ Hz, $J_o = 9.0$ Hz) 9.06 (s, 1H, $-$Ar, $J_m = 3.0$ Hz).

(15) *A general procedure for polymer functionalization with the protected thiol*: DIAD (1.5 equiv) was added to a stirred solution of poly(ϵ-caprolactone), **1** (1.3 equiv), and TPP (1.5 equiv) in THF (10 mL). After 24 h the solution was precipitated into cold MeOH. The functionalized polymer was filtered and dried to give a yield of 95%.

(16) *A general procedure for the deprotection*: Triethylamine was added to a solution of the functionalized polymer in mercaptoethanol or propanethiol, until the pH was 8. After 15 h of stirring at room temperature, the reaction mixture was precipitated into cold MeOH to yield the polymer in 95% yield.

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