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Redox and thiol–ene cross-linking of mercapto poly(ϵ -caprolactone) for the preparation of reversible degradable elastomeric materials†

Benjamin Nottelet,* Guillaume Tambutet, Youssef Bakkour and Jean Coudane

A novel thiol-functionalized PCL (PCL-HDT) was synthesized following a convenient two-step procedure. Taking advantage of the pendant thiol group, degradable elastomeric materials have been prepared from PCL-HDT by redox or thiol–ene reaction. Elastomers were characterized by HRMAS NMR spectroscopy to confirm the formation of disulfide or thioether cross-links. The thermal and mechanical properties of elastomers have been assessed by DSC, DMA and tensile tests. Disulfide containing elastomers (EM_{SS}) and thioether containing elastomers (EM_{TE}) exhibited improved mechanical properties with ultimate strains up to 220%. The stability of the mechanical properties at temperatures close to body temperature was confirmed by DMA with $G' \approx 200$ MPa and $G'' \approx 15$ MPa. Finally, the reversibility of the disulfide formation and breaking has been evaluated, and confirmed the potential of these degradable elastomers as biomaterials.

1. Introduction

Aliphatic polyesters have been widely investigated in recent years for their potential as biodegradable biomaterials for biomedical applications.^{1,2} In particular, degradable elastomeric materials to be used as scaffolds for tissue engineering are highly desirable.^{3–5} However, aliphatic polyesters lack pendant reactive groups, including hydroxyl, amine and carboxylic groups, classically used to enlarge polymer functionalities. Synthesis and polymerization of functional lactones is a strategy of choice to overcome this limitation,^{6–8} but ROP procedures often require severe reaction conditions, which prevents the use of thermally labile functionalized monomers. Post-polymerization reaction represents an interesting alternative. Our group developed, a few years ago, a methodology based on the anionic chemical modification of poly(ϵ -caprolactone) (PCL). This strategy was largely exploited to synthesize various functionalized PCLs bearing lateral small functional groups (iodine, carboxylic acid) or side macromolecular chains [poly(vinylpyrrolidone), poly(dimethylaminoethyl methacrylate), poly(L-lysine), *etc.*].^{9–12}

Considering the potential of thiol groups, it is of great interest to introduce pendant mercapto groups on the PCL backbone. Although some efforts have been made on the preparation of thiol-functionalized polyesters, only a few have been prepared to

date, with mainly end-functionalized polymers used for nanoparticles decoration.^{13–15} In parallel, polycondensations of thiol-containing precursors have also been investigated. For example, the enzymatic polycondensation of dimethyl 2-mercaptosuccinate with hexane-1,6-diol was reported by Matsumura *et al.*¹⁶ However, only low molecular weight polyesters were obtained. Scandium catalysts have also been used for the polycondensation of diols and thiomalic acid to prepare “RAFT-gel”.¹⁷ Both approaches led to polyesters having one mercapto group per repeating unit. In the present work, we were interested in using the anionic chemical modification to generate new PCL derivatives with a few mercapto groups distributed along the polymer backbone, and to use these polyesters for the preparation of degradable elastomeric materials.

Advantageously, the reactivity of thiol groups can be exploited to obtain polymeric cross-linked matrices. First, thiol can react with nonactivated double bonds following the thiol–ene chemistry strategy, which has entered the realm of click chemistry.^{18–20} Secondly, redox reactions can be used to yield disulfide from thiol groups. Cross-linked materials have previously been prepared following these two strategies for biomedical and environmental applications.^{21–24} However, and to the best of our knowledge, only one example of reversible material based on degradable polyester segments bearing thiol groups has been reported so far by Matsumura *et al.*¹⁶

In this paper, we report on the two-step synthesis of a new mercapto-functionalized PCL, namely poly(α -sulfanyl-hexanethiol- ϵ -caprolactone-*co*- ϵ -caprolactone) (PCL-HDT). Redox and thiol–ene conditions are then studied to prepare two types of elastomeric materials from the PCL-HDT precursor. Characterisation of cross-linked insoluble PCL networks was performed by high-resolution magic angle spinning (HRMAS) NMR

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spectroscopy. Finally, as our main objective is to prepare elastomeric materials, mechanical properties of the cross-linked materials are evaluated and the reversibility of the disulfide bonds containing material is investigated.

2. Materials and methods

2.1 Materials

PCL ($\overline{M}_n = 36\,500 \text{ g.mol}^{-1}$, PDI = 1.7), iodine (I_2 , $\geq 99.8\%$), LDA (2 M in THF/*n* heptane/ethylbenzene), 1,6-hexanedithiol (HDT, 99.5%), pentaerythritol triallyl ether (PETAE, 70%) and 2-mercaptoethanol ($\geq 99\%$) were obtained from Aldrich (St. Quentin Fallavier, France). NH_4Cl was obtained from Fluka (St. Quentin Fallavier, France), anhydrous $Na_2S_2O_3$ from Acros Organics (Noisy-le-Grand, France), $MgSO_4$ and potassium carbonate (K_2CO_3 , $>99\%$) from Prolabo (Paris, France), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), toluene and methanol (MeOH) from Riedel de Haën (St. Quentin Fallavier, France). All were used as received. 2,2'-Azobis(isobutyronitrile) (AIBN, 99%) was obtained from Fluka (St. Quentin Fallavier, France) and was recrystallized from methanol prior to use. Tetrahydrofuran (THF) from Acros Organics (Noisy-le-Grand, France) was distilled on benzophenone/sodium until a deep blue color was obtained.

2.2 NMR spectroscopy

1H and ^{13}C NMR spectra were recorded using an AMX300 Brüker spectrometer operating at 300 MHz and 75 MHz, respectively. Deuterated dimethyl sulfoxide or chloroform was used as solvent. Solid ^{13}C spectra were recorded using an AMX300 Brüker spectrometer operating at 75 MHz.

The HRMAS NMR measurements on the swollen networks were carried out on a Bruker Avance III 600 spectrometer, operating at 600.13 MHz for proton and 150.96 MHz for carbon, equipped with a 4 mm $^1H/^{13}C/^2H$ HRMAS gradient probe. The polymers were immersed in a solvent ($CDCl_3$) at room temperature for 24 h. The samples (*ca.* 3 mg) were packed into a 4 mm HRMAS rotor (90 μL sample volume). The spectra were acquired at a temperature of 303 K. In all experiments, the samples were spun at 6 kHz. Gradient selected $^1H/^{13}C$ heteronuclear single quantum coherence (HSQC) spectra were recorded using the topspin Brüker software (topspin 2.1).

2.3 Size exclusion chromatography

The molecular weights of the polymers were determined by size exclusion chromatography (SEC) using a Viscotek GPCMax autosampler system fitted with two Viscotek LT5000L mixed medium columns (300 \times 7.8 mm), a Viscotek VE 3580 RI detector and a Viscotek VE 3210 UV/VIS detector. The mobile phase was THF at a flow rate of 1 mL min^{-1} and at 30 °C. Typically, the polymer (10 mg) was dissolved in THF (2 mL) and the resulting solution was filtered through a 0.45 μm Millipore filter before injection of 20 μL of filtered solution. \overline{M}_n and \overline{M}_w were expressed according to the calibration using poly(styrene) standards.

2.4 Differential scanning calorimetry

Differential scanning calorimetry (DSC) measurements were carried out under nitrogen at a 5 °C min^{-1} rate on a Perkin Elmer DSC 6000 Thermal Analyser. The samples were heated from 20 °C to 110 °C and the temperature was held for 5 min at 110 °C before cooling to -50 °C. This temperature was then held for 5 min before the final heating ramp to 200 °C. The melting temperature (T_m), glass transition temperature (T_g) and melting enthalpy (ΔH_m) were measured from the second heating ramp while the crystallization temperature (T_c) and enthalpy (ΔH_c) were measured on the cooling ramp.

2.5 Tensile tests and dynamic mechanical analyses

Sample plates were prepared by compression of the polymer in a stainless steel mould for 10 min at 100 °C and 1 ton using a Carver press (4120). For tensile mechanical tests, plates (20 \times 7 \times 1 mm) were analysed at room temperature in an Instron 4444 at a 1 mm min^{-1} crosshead speed rate. Each sample was analysed in triplicate and Young's modulus (E , MPa), ultimate stress (σ_{break} , MPa), ultimate strain (ϵ_{break} , %), yield stress (σ_{yield} , MPa), and elastic limit (ϵ_{yield} , %) were expressed as the mean value of the three measurements. E was calculated using the initial linear portion of the stress-strain curves. Dynamic mechanical analyses (DMA) were conducted on the sample plates (10 \times 5 \times 1 mm). Perkin Elmer DMA7 was used in the temperature or frequency scan mode. Temperature scans were run from 23 to 40 °C at a 1 °C min^{-1} rate, with a 1 Hz frequency, while frequency scans were run from 0.1 to 40 Hz, at 37 °C.

2.6 Synthesis of poly(α -iodo- ϵ -caprolactone-*co*- ϵ -caprolactone) (PCL-I)

Poly(α -iodo- ϵ -caprolactone-*co*- ϵ -caprolactone) (PCL-I) with a 7% iodine content was prepared as described elsewhere.²⁵ Briefly, PCL (70 mmol, 8 g) was dissolved in anhydrous THF (300 cm^3) in a reactor equipped with a mechanical stirrer and kept at -70 °C under argon atmosphere. A solution of LDA (35 mmol, 17.5 cm^3) was injected with a syringe through a septum and the mixture was kept at -70 °C for 20 min. Iodine (35 mmol, 8.9 g) was dissolved in THF before addition and the reaction was carried out for 25 min. The reaction medium was then hydrolyzed with 100 cm^3 of a 4 M aqueous solution of NH_4Cl and the pH was adjusted to *ca.* 7 by using HCl 37%. The copolymer was extracted with dichloromethane (2 \times 100 cm^3). The combined organic layers were washed three times with a solution of $Na_2S_2O_3$, dried on anhydrous $MgSO_4$ and filtered. The solvent was partially evaporated under reduced pressure and the concentrated solution was treated with an excess of cold methyl alcohol. The precipitated copolymer was washed with methyl alcohol and dried under vacuum. PCL-I with $\overline{M}_n = 10\,400 \text{ g.mol}^{-1}$ and PDI = 2.2 was obtained in 80% yield. 1H -NMR spectral data were as follows. 1H -NMR (300 MHz, $CDCl_3$) δ : 4.27 (t, 1H, COCHI), 4.04 (t, 2H, COCH₂), 3.63 (t, 2H, CH₂CH₂OH), 2.28 (t, 2H, CH₂O), 1.98 (q, 2H, CHICH₂), 1.62 (q, 4H, CH₂CH₂CH₂), 1.36 (q, 2H, CH₂CH₂CH₂).

2.7 Synthesis of poly(α -sulfanyl-hexanethiol- ϵ -caprolactone-*co*- ϵ -caprolactone) (PCL-HDT)

In a typical experiment, 7% iodinated PCL-I (1 g, 8.1 mmol) was dissolved in a solution of K_2CO_3 (78 mg, 2 eq. with respect to C–I bonds) in 15 mL of DMF. Argon was bubbled in the medium for 30 minutes with constant stirring. HDT (0.09 mL, 2 eq. with respect to C–I bonds) was added under argon and the reaction was run at room temperature for 24 hours under inert atmosphere. After the reaction, K_2CO_3 residues were filtered before concentration of the filtrate under vacuum. The resulting viscous solution was poured into an excess of cold MeOH to form a white precipitate. The polymer was dried under vacuum (0.87 g). PCL-HDT with $\overline{M}_n = 15\,700\text{ g}\cdot\text{mol}^{-1}$ and PDI = 3.9 was obtained in 92% yield. $^1\text{H-NMR}$ spectral data were as follows. $^1\text{H-NMR}$ (300 MHz, $CDCl_3$) δ : 4.05 (t, 2H, CH_2O), 3.63 (t, 2H, CH_2CH_2OH), 3.18 (t, 1H, $COCHSCH_2$), 2.66 (t, 2H, CH_2CH_2SH), 2.51 (t, 2H, $COCHSCH_2$), 2.28 (t, 2H, $COCH_2$), 1.74–1.55 (q, 4H, $CH_2CH_2CH_2$; q, 4H, $SCH_2CH_2(CH_2)_2CH_2CH_2SH$), 1.50–1.26 (q, 2H, $CH_2CH_2CH_2$; q, 4H, $S(CH_2)_2CH_2CH_2(CH_2)_2SH$).

2.8 Synthesis of a cross-linked PCL-based elastomeric material by redox reaction (EM_{SS})

Poly(α -sulfanyl-hexanethiol- ϵ -caprolactone-*co*- ϵ -caprolactone) was cross-linked according to a procedure described elsewhere.¹⁶ In a typical experiment 370 mg of PCL-HDT were dissolved in 2.5 mL of DMSO in a reaction flask that was placed in a thermostated oil bath at 70 °C. The reaction was carried out for 20 hours under air. An insoluble gel formed and was soaked 5 times in large amounts of CH_2Cl_2 to remove residual DMSO and non-cross-linked polymer chains. After drying under vacuum, 210 mg of a yellow solid was recovered. Cross-linked polymers were characterized by HRMAS NMR spectroscopy.

$^1\text{H NMR}$ (600 MHz, $CDCl_3$) δ : 4.00 (t, 2H, CH_2OCO), 3.60–3.55 (t, 2H, CH_2CH_2OH), 3.10 (t, 1H, $COCHSCH_2$), 2.60 (t, 2H, $S(CH_2)_5CH_2SS$), 2.50 (t, 2H, $SCH_2(CH_2)_5SS$), 2.25 (t, 2H, $COCH_2$), 1.80 (q, 1Ha, $COCHSCH_2$; m, 2H, $SCH_2CH_2(CH_2)_4SS$), 1.70–1.45 (q, 1Hb, $COCHSCH_2$; q, 4H, $CH_2CH_2CH_2$; q, 4H, $SCH_2CH_2(CH_2)_2CH_2CH_2SS$), 1.45–1.20 (q, 2H, $CH_2CH_2CH_2$; q, 4H, $S(CH_2)_2CH_2CH_2(CH_2)_2SS$).

$^{13}\text{C NMR}$ (150 MHz, $CDCl_3$) δ : 64 (CH_2OCO), 63 (CH_2CH_2OH), 47 ($COCHSCH_2$), 39 ($(CH_2)_5CH_2SS$), 34 ($COCH_2$), 31 ($CHSCH_2(CH_2)_5SS$), 29 ($COCHSCH_2$), 25–28 ($COCH_2(CH_2)_3CH_2O$; $SCH_2(CH_2)_4CH_2S$).

The gel fraction of the cross-linked PCL-HDT was determined from the weight remaining after washing using eqn (1).

$$\text{gel fraction (\%)} = \frac{W_d}{W_0} \times 100 \quad (1)$$

where W_d is the weight of the dried cross-linked sample and W_0 the initial PCL-HDT weight.

The weight swelling ratio at equilibrium (Q_{we}) was calculated based on the initial dry samples weights according to eqn (2).

$$Q_{we} = \frac{W_s}{W_0} \times 100 \quad (2)$$

where W_s is the final weight of the swollen sample weighed at equilibrium, *i.e.* when the solvated weight remained constant

after soaking in CH_2Cl_2 , and W_0 the initial dry weight of the sample. The weight swelling ratio extrapolated to $t = 0$ (Q_{w0}) was obtained by soaking the sample in CH_2Cl_2 for defined short periods of time and extrapolating the plot giving the sample weight as a function of time.

For reversibility studies, disulfide bonds of EM_{SS} were reduced following a procedure described elsewhere.²⁴ In a typical reaction, 0.2 g of EM_{SS} were soaked in 1 mL of CH_2Cl_2 . 0.5 mL of 2-mercaptoethanol was added and the mixture was mechanically stirred at 37 °C for 72 hours.

2.9 Synthesis of a cross-linked PCL-based elastomeric material by thiol-ene reaction (EM_{TE})

Poly(α -sulfanyl-hexanethiol- ϵ -caprolactone-*co*- ϵ -caprolactone) was cross-linked according to a procedure described elsewhere and modified to our systems.²⁰ PCL-HDT (500 mg, 4.1 mmol), PETAE (26 μL , 0.1 mmol, 0.5 eq. with respect to thiol) and AIBN (38 mg, 0.15 mmol, 0.5 eq. with respect to alkene) were added in a Schlenk flask and solubilized in the minimum amount of toluene to solubilize all components. The mixture was degassed *via* three freeze–pump–thaw cycles. The Schlenk flask was heated at 100 °C for 8 hours. An insoluble gel formed and was soaked 5 times in large amounts of CH_2Cl_2 to remove residual toluene, PETAE and non-cross-linked polymer chains. After drying under vacuum, 350 mg of a yellow solid was recovered. Gel fraction and swelling ratio were calculated as described above. Cross-linked polymers were characterized by HRMAS NMR spectroscopy.

$^1\text{H NMR}$ (600 MHz, $CDCl_3$) δ : 5.90 (s, 1H, CCH_2OH), 5.20 (s, 2H, OCH_2C ; s, 2H, CCH_2OH), 4.10 (t, 2H, CH_2OCO), 3.80–3.70 (t, 2H, CH_2CH_2OH), 3.55 (t, 2H, $SCH_2CH_2CH_2O$), 3.30 (t, 1H, $COCHSCH_2$; m, 2H, $SCH_2CH_2CH_2O$), 2.75 (t, 2H, $(CH_2)_5CH_2S$; t, 2H, $SCH_2CH_2CH_2O$), 2.65 (t, 2H, $COCHSCH_2$), 2.40 (t, 2H, $COCH_2$), 1.95 (q, 1Ha, $COCHSCH_2$; m, 2H, $CHSCH_2CH_2$), 1.9–1.6 (q, 1Hb, $COCHSCH_2$; q, 4H, $CH_2CH_2CH_2$; q, 4H, $SCH_2CH_2(CH_2)_2CH_2CH_2S$), 1.50–1.26 (q, 2H, $CH_2CH_2CH_2$; q, 4H, $S(CH_2)_2CH_2CH_2(CH_2)_2S$).

$^{13}\text{C NMR}$ (150 MHz, $CDCl_3$) δ : 71 ($SCH_2CH_2CH_2O$), 70 (OCH_2C ; CCH_2OH), 64 (CH_2OCO), 62 (CH_2CH_2OH), 46 ($COCHSCH_2$), 38 ($(CH_2)_5CH_2S$; $SCH_2CH_2CH_2O$), 34 ($SCH_2CH_2CH_2O$; $COCH_2$), 31 ($CHSCH_2(CH_2)_5S$), 29 ($COCHSCH_2$), 24–28 ($COCH_2(CH_2)_3CH_2O$; $SCH_2(CH_2)_4CH_2S$).

3. Results and discussion

3.1 Synthesis of PCL-I and PCL-HDT precursors

In designing suitable macromolecular derivatives for evaluating the potential of thiol-functionalized PCLs for the preparation of elastomeric materials, PCL-I was chosen as an intermediate towards PCL-HDT (Scheme 1). As a consequence, the first step consisted of preparing PCL-I by anionic chemical modification under conditions already defined by our group in a previous work.²⁵ Parameters of the activation step with LDA and substitution step with iodine have been optimized to yield polymers with *ca.* 10% molar substitution ratios in a one pot and time saving reaction starting from commercially available PCL. The chemical structure was characterized by $^1\text{H-NMR}$ (Fig. 1a). The substitution degree (SD) was calculated by comparison of the integrals of the resonance peaks at 4.27 ppm, corresponding

to the vicinal proton of the iodine, and at 4.05 ppm corresponding to the non-substituted methylene group as shown in eqn (3).

$$\text{SD (\%)} = \frac{I_{4.27}}{I_{4.05}/2} \times 100 \quad (3)$$

A 7% substitution was obtained. The molecular weight of PCL-I was characterized by SEC analysis in THF. PCL-I with molecular weight $\overline{M}_n = 10\,400 \text{ g}\cdot\text{mol}^{-1}$ and PDI = 2.2 was obtained. These values were compared with the ones of the commercial PCL used as a starting material ($\overline{M}_n = 36\,500 \text{ g}\cdot\text{mol}^{-1}$ and PDI = 1.7) (Fig. 2). A molecular weight decrease between neat commercial PCL and PCL-I was observed, however, it is noteworthy that this is classically observed with the anionic activation of polyester, as a consequence of hydrolysis and back-biting side reactions.²⁶ In the present case, and although remarkable in terms of influence on the final molecular weight, this corresponded to a hydrolysis limited to only 0.87% of the ester groups initially present in the polymer chain.

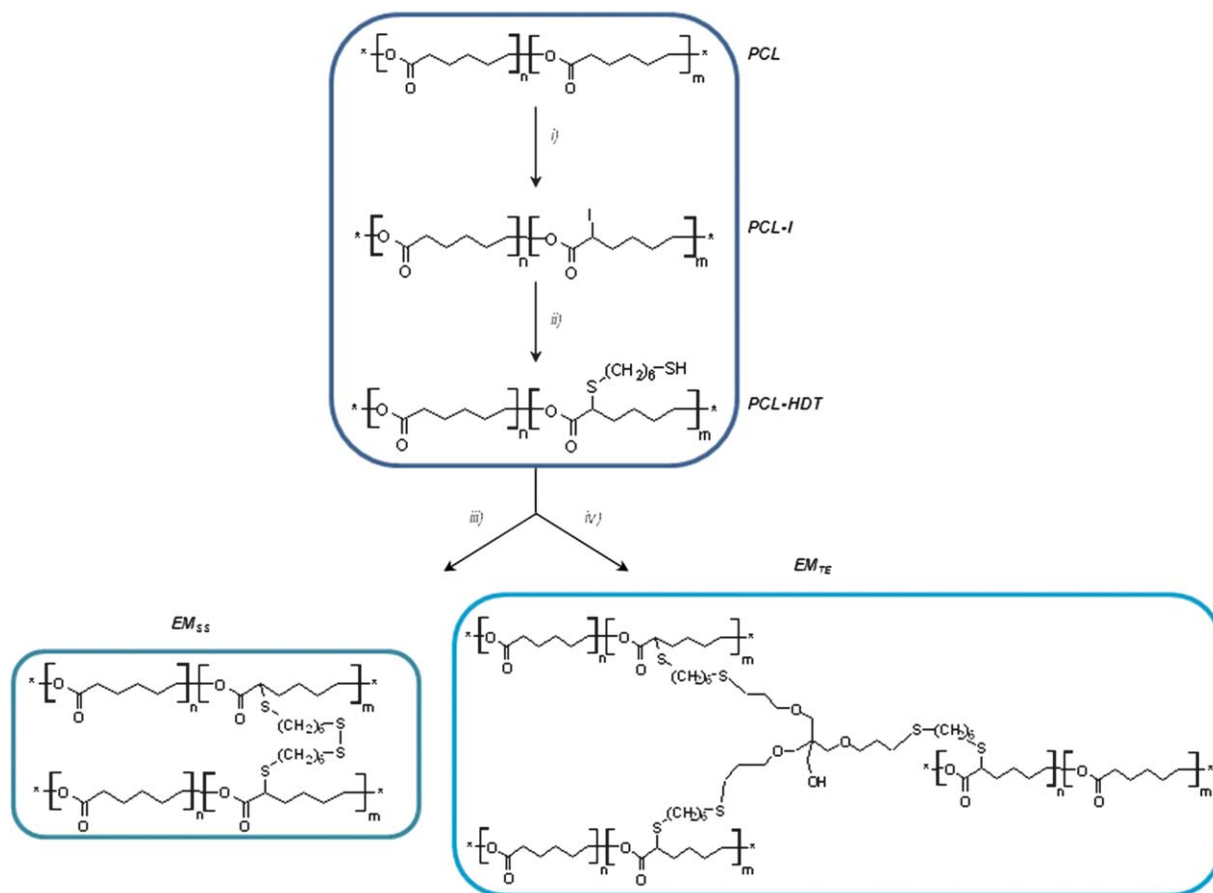
In the second step, PCL-I was reacted with 1,6-hexanedithiol to make the nucleophilic substitution of iodine. PCL-HDT was obtained in a 92% yield. After reaction, the polymer chemical structure was again characterized by ¹H-NMR (Fig. 1b). The substitution degree was calculated by comparison of the integral of the resonance peak at 4.05 ppm corresponding to the non-substituted methylene group on the polymer backbone, and of

the combined integrals of the resonance peaks at 3.47 ppm, corresponding to the vicinal proton of the sulphur on the polymer backbone and between 2.46 and 2.70 ppm corresponding to vicinal methylene groups of the sulphur. Using eqn (4), a 6.5% substitution degree was found, which corresponds to a 90% yield for the reaction.

$$\text{SD (\%)} = \frac{(I_{3.47} + I_{2.46-2.70}/4)}{I_{4.05}} \quad (4)$$

The molecular weight of PCL-HDT ($\overline{M}_n = 15\,700 \text{ g}\cdot\text{mol}^{-1}$ and PDI = 3.9) was characterized by SEC analysis. Taking into account the substitution ratio and the molecular weight of the grafted HDT, no overall change of \overline{M}_n was expected. The observed increase of \overline{M}_n is due to some cross-linking side reaction. Bridging of two PCL-I chains reacting with the same HDT molecule occurs during the substitution reaction, thus leading to both increase of \overline{M}_n and PDI. This is confirmed by the PCL-HDT chromatogram that exhibits small shoulders (Fig. 2). Considering the initial SD and the molecular weight increase, a maximum of 18% of the thiol groups are involved in the cross-linking side reaction. However, it should be noted that despite this limited cross-linking, PCL-HDT is freely soluble in organic solvents such as THF or CH₂Cl₂.

It is also noteworthy that the proposed strategy allows the preparation of sulphhydryl functionalized polyesters with molecular weight around $15\,000 \text{ g}\cdot\text{mol}^{-1}$ in a simple two-step strategy



Scheme 1 Synthesis of PCL-based elastomeric materials. *Reaction conditions:* (i) THF, LDA, $-70\text{ }^\circ\text{C}$, 30 min/ I_2 , $-70\text{ }^\circ\text{C}$, 20 min; (ii) DMF, K_2CO_3 , HDT, RT, 24 h; (iii) DMSO, $70\text{ }^\circ\text{C}$, 20 h; (iv) toluene, PETAE, AIBN, $100\text{ }^\circ\text{C}$, 8 h.

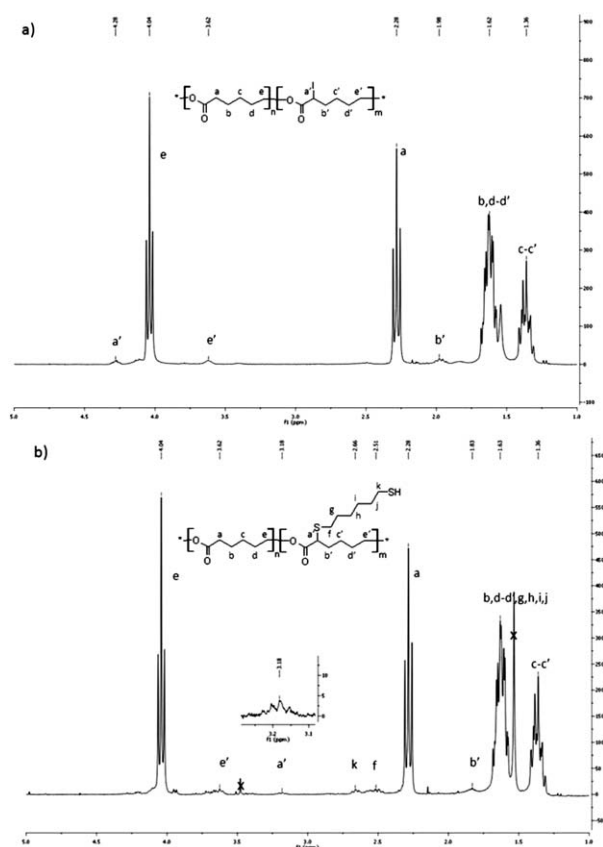


Fig. 1 $^1\text{H-NMR}$ spectra of (a) PCL-I and (b) PCL-HDT (CDCl_3 ; residual water at 1.5 ppm; residual MeOH at 3.5 ppm).

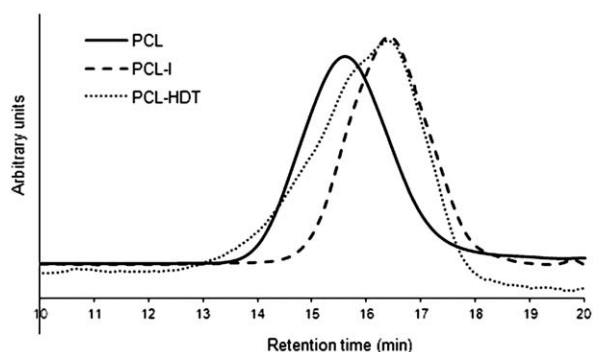


Fig. 2 SEC chromatograms of PCL, PCL-I and PCL-HDT (THF, 1 mL min^{-1}).

and with a commercially available PCL as starting material. This approach presents an interesting and efficient alternative to the strategies described in the literature including enzymatic

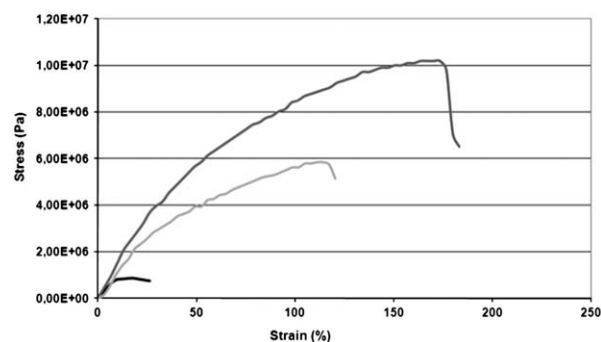


Fig. 3 Typical tensile stress–strain curves for PCL (black line), EM_{SS} (dark grey line) and EM_{TH} (light grey line).

polycondensations or protection–deprotection strategies leading to limited molecular weights ($\overline{M}_n \leq 6000 \text{ g.mol}^{-1}$)¹⁶ or considerable polyester degradation,^{27,28} respectively.

3.2 Synthesis of PCL-based elastomeric materials

PCL-HDT was used to produce elastomeric materials following two strategies. In the first approach, disulfide bonds were targeted. Disulfides are known to be reversibly formed under redox conditions and appeared to be of interest in the frame of designing degradable elastomers. In the second approach, we chose to take advantage of thiol functionalities of PCL-HDT to prepare materials by the thiol–ene strategy which was successfully applied in the past for the preparation of cross-linked polymeric matrices.²¹

A disulfide containing PCL-based elastomeric material (EM_{SS}) was easily prepared by the oxidation of sulphhydryl groups under mild conditions. Thiol pendant groups of PCL-HDT were oxidized to disulfides in air. Although a gel was formed after a few hours, the reaction was maintained for 20 hours. Despite this longer reaction time, the gel fraction was low (56% of cross-linked chains). With PCL-HDT being substituted with 6.5% of pendant thiol groups, intramolecular cross-linking might explain this result. It is our belief that the relatively low thiol content of PCL-HDT, combined with intramolecular cross-linking, are responsible for the observed low gel fraction. This should be compared with the 76% obtained by Kato *et al.* with poly-(hexanediol-2-mercaptosuccinate), which exhibits one thiol per monomer unit.¹⁶ Another explanation is the relatively high molecular weight of the PCL-HDT pre-polymer that decreases thiol accessibility, especially when cross-linking has started, compared to a lower molecular weight and highly substituted polymer used by the later group.

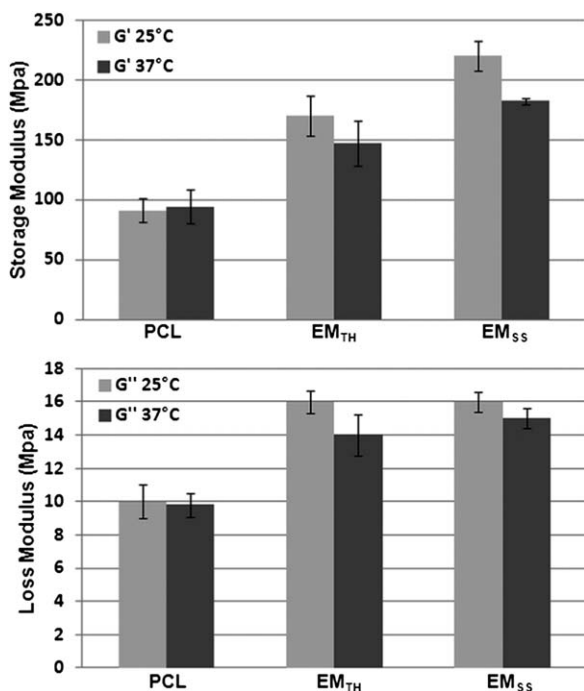
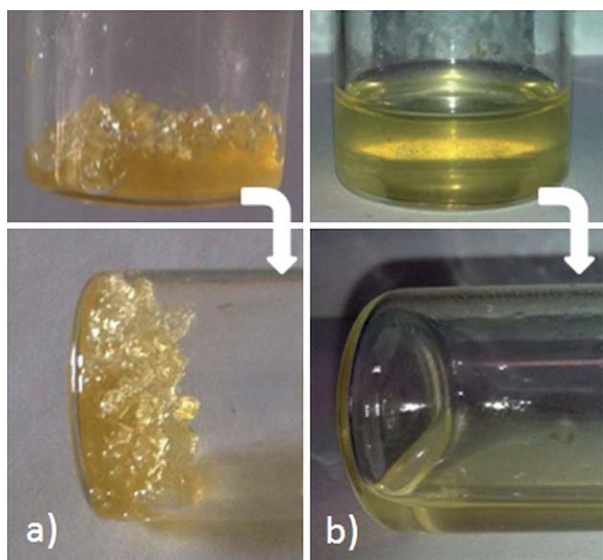
A PCL-based elastomeric material obtained by thiol–ene reaction (EM_{TH}) was prepared by the reaction of the pendant

Table 1 Physico-chemical characterization of PCL-based materials

Sample	Substitution (%)	$\overline{M}_n \text{ g.mol}^{-1}$	PDI	$\overline{M}_{c,\text{theo}} \text{ (g.mol}^{-1}\text{)}$	$\overline{M}_{c,\text{exp}} \text{ (g.mol}^{-1}\text{)}$	$T_m/\Delta H_m \text{ (}^\circ\text{C/J.g}^{-1}\text{)}$	$T_d/\Delta H_c \text{ (}^\circ\text{C/J.g}^{-1}\text{)}$	$T_g \text{ (}^\circ\text{C)}$
PCL-I	7	10 400	2.2	/	/	/	/	/
PCL-HDT	6.5	15 700	3.9	/	/	50/66	25/–68	–46
EM_{SS}	/	/	/	1720	1550	49/31	19/–35	–47
EM_{TH}	/	/	/	1720	1500	48/35	23/–38	–44

Table 2 Mechanical properties of PCL-based materials

Sample	Young's modulus (E , MPa)	Elastic limit (ϵ_{yield} , %)	Ultimate stress (σ_{break} , MPa)	Ultimate strain (ϵ_{break} , %)	Storage modulus (G' , MPa)		Loss modulus (G'' , MPa)	
					25 °C	37 °C	25 °C	37 °C
PCL	50 ± 5	6.5 ± 1	0.8 ± 0.3	22 ± 3	91 ± 10	94 ± 14	10.0 ± 1.0	9.8 ± 0.7
EM _{SS}	135 ± 7	28 ± 2	9.0 ± 1.4	223 ± 35	220 ± 13	182 ± 3	16.0 ± 0.6	15.0 ± 0.6
EM _{TH}	110 ± 14	23 ± 3	6.6 ± 0.7	130 ± 25	170 ± 17	147 ± 19	16.0 ± 0.7	14.0 ± 1.3

**Fig. 4** Storage and loss moduli of PCL, EM_{SS} and EM_{TH} at 25 °C (light grey bars) and 37 °C (dark grey bars).**Fig. 5** Reversibility of EM_{SS} swollen in CH₂Cl₂ (a) before reduction and (b) after reduction.

thiol groups with the PETAE triene. The reaction was carried out under classical conditions in the presence of AIBN as radical precursor and led after 8 hours to an insoluble gel. The gel fraction was calculated and found to be equal to 70%.

Weight swelling ratios at equilibrium (Q_{we}) and extrapolated at $t = 0$ ($Q_{\text{w}0}$) were evaluated for both materials. Using eqn (2), Q_{we} of 4900% and 3100%, and $Q_{\text{w}0}$ of 226% and 225% were calculated for EM_{SS} and EM_{TH}, respectively. These values were further used to calculate the molecular weight between cross-links ($\bar{M}_{\text{c,exp}}$) according to the Flory–Rehner equation (eqn (5)),

$$\bar{M}_{\text{c,exp}} = \frac{V_{\text{so}} \times d_{\text{p}} \times \left(\frac{F_{\text{p}}}{2} - F_{\text{p}}^{1/3} \right)}{\ln(1 - F_{\text{p}}) + F_{\text{p}} + \chi F_{\text{p}}^2} \quad (5)$$

where V_{so} is the molar volume of the solvent (64.341 mL·mol⁻¹ for CH₂Cl₂), F_{p} is the volume fraction of the polymer in the swollen gel equal to $1/Q_{\text{w}0}$ and χ is the Flory solvent–polymer interaction parameter ($\chi \approx 0.64$).²⁹ $\bar{M}_{\text{c,exp}}$ of 1550 g·mol⁻¹ and 1500 g·mol⁻¹ were calculated for EM_{SS} and EM_{TH}, respectively. These values are in good agreement with the theoretical molecular weight between cross-links $\bar{M}_{\text{c,theo}} = 1720$ g·mol⁻¹ calculated by taking into account the molecular weight of the polymer precursor and the substitution degree (Table 1).

Due to their cross-linked nature, the chemical characterization of the elastomeric materials could not be done *via* classical solution NMR. Instead, we took advantage of the high-resolution magic angle spinning (HRMAS) technique which has proved to be pertinent for gels.³⁰ In this way, a ¹H NMR line-width similar to liquid samples can be reached. ¹H and ¹H/¹³C HSQC HRMAS confirmed the formation of disulfide and thioether bonds as a result of the cross-linking (ESI, Fig. S1–S3†). In particular, ¹H/¹³C spectra showed coupling of peaks at 2.60/39 ppm and 2.50/31 ppm for EM_{SS} corresponding to the vicinal methylenes of the disulfide ((CH₂)₅CH₂SS) and of the thioether (CHSCH₂(CH₂)₅SS) groups. The same was observed for EM_{TH} with couplings at 2.75/38 ppm and 2.65/31 ppm. The ¹³C chemical shift from *ca.* 25 ppm for the starting CH₂-SH hexanethiol to *ca.* 38 ppm for CH₂-S-S and CH₂-S-CH₂ confirms the cross-linking reaction.

3.3 Thermo-mechanical properties and reversibility of PCL-based elastomeric materials

3.3.1 Thermal properties. Thermal properties were investigated by DSC. Typical thermograms are given in the ESI, Fig. S4† and the results are listed in Table 1. Thermograms vertical scales have been adjusted for clarity reasons. PCL is a semi-crystalline polyester with a glass transition temperature (T_{g})

around $-60\text{ }^{\circ}\text{C}$, a melting temperature (T_m) around $60\text{ }^{\circ}\text{C}$ and a melting enthalpy ΔH_m around 80 J.g^{-1} .³¹ As a result of the lower molecular weight and of the long alkyl chains of the pendant thiol group, PCL-HDT has a lower T_m ($50\text{ }^{\circ}\text{C}$). The presence of few cross-links in PCL-HDT, as discussed in Section 3.1, induced an increase of the glass transition to $-46\text{ }^{\circ}\text{C}$ and ΔH_m was found to be equal to 66 J.g^{-1} . After cross-linking, whatever the strategy used, elastomeric materials still were semi-crystalline with $\Delta H_m = 31\text{--}35\text{ J.g}^{-1}$. This lower value indicates a decrease of crystallinity, as expected for cross-linked polymers whose chains have less mobility for crystalline rearrangement. However, small PCL chains between cross-links, with $\bar{M}_{c,\text{exp}} \approx 1500\text{ g.mol}^{-1}$ are still long enough to induce crystallization. PCL oligomers with low molecular weight ($\bar{M}_n = 1200\text{ g.mol}^{-1}$) are known to crystallize.³² In the present case, this crystallization results in semi-crystalline materials with for EM_{SS} $T_m = 49\text{ }^{\circ}\text{C}$ and $T_g = -48\text{ }^{\circ}\text{C}$ and for EM_{TH} $T_m = 48\text{ }^{\circ}\text{C}$ and $T_g = -44\text{ }^{\circ}\text{C}$ (hardly visible). Considering a melting enthalpy of 142 J.g^{-1} for a 100% crystalline PCL,³³ PCL-HDT, EM_{SS} and EM_{TH} have crystallinities of 46%, 22% and 25%, respectively. To summarize, cross-linking did not induce significant changes of T_m and T_g for the elastomeric materials but was accompanied with a decrease of crystallinity by a factor 2.

3.3.2 Tensile mechanical properties. Mechanical properties have been evaluated on plates obtained by compression. Tensile mechanical tests have first been carried out to evaluate the elastomeric character of the cross-linked materials. Typical stress-strain curves are given in Fig. 3. For comparison, a commercial PCL with a molecular weight $\bar{M}_n = 12\,700\text{ g.mol}^{-1}$ and PDI = 1.7 was used as a control. This PCL was chosen for its molecular weight similar to the one of the PCL-I and PCL-HDT precursors. As expected, cross-linking had drastic effects on the mechanical properties of the PCL-based materials. Young's modulus was doubled from 50 to *ca.* 110–130 MPa, but more interestingly, the elastic limit was increased from 6.5% for PCL to *ca.* 25% for the elastomeric materials (Table 2). One should note that, considering the strict ASTM definition of elastomers, our materials, with a uniaxial elastic limit of 25% (inferior to 100%), cannot be labeled as elastomers. However, even if improper, this denomination is largely accepted in the literature and, with this comment in mind, will be further used in this work for clarity reasons. Ultimate stress and strain were also strongly increased with a 10 fold increase for σ_{break} passing from 0.8 to *ca.* 6.6–9 MPa, and a 6 to 10 fold increase for ϵ_{break} reaching up to 220% for EM_{SS}. When comparing the elastomeric materials, no significant differences can be found between EM_{SS} and EM_{TH}. Only a higher ultimate deformation for EM_{SS} should be noted with 220% compared to 130% for EM_{TH}. This difference probably results from the nature of the cross-linking with EM_{SS} having bimolecular disulfide cross-links compared to the trimolecular cross-links expected in EM_{TH}.

3.3.3 Dynamic mechanical properties. Beside tensile mechanical tests, the materials have also been assessed by dynamic mechanical analyses. As PCL is degradable and widely used in the biomedical field, we were interested in evaluating the PCL-based materials under two temperature conditions including room temperature and physiological temperature.

Temperature scans were carried out at 1 Hz between $23\text{ }^{\circ}\text{C}$ and $40\text{ }^{\circ}\text{C}$ (see ESI, Fig. S5–S6† for typical curves). As can be seen in Fig. 4, the loss modulus (G'') was similar for the two elastomeric materials with values around 15 MPa and a limited 10% decrease when increasing the temperature from $25\text{ }^{\circ}\text{C}$ to $37\text{ }^{\circ}\text{C}$. The differences were more pronounced for the storage modulus (G') with values of 220 MPa for EM_{SS} and 170 MPa for EM_{TH} at $25\text{ }^{\circ}\text{C}$. As expected, raising the temperature to $37\text{ }^{\circ}\text{C}$ decreased G' for both materials with a 20% decrease for EM_{SS} (180 MPa) and a 12% decrease for EM_{TH} (150 MPa) (Table 2). To complete this study, frequency scans were also run at $37\text{ }^{\circ}\text{C}$ in the range 0.1 Hz to 40 Hz. However, no significant change of moduli was observed in this range (data not shown). Similarly to the Young's modulus, the storage modulus of EM_{SS} was *ca.* 20–30% higher compared to the one of EM_{TH}. This difference may be due to the higher mobility of the 3 ether bonds in EM_{TH} compared to the mobility of the single disulfide bond in EM_{SS}.

3.3.4 Reversibility of E_{ss}. Cleavage of disulfide bonds under reductive conditions is well known especially for proteins containing cysteine moieties. In the present work, we were interested in checking the capacity of our disulfide containing EM_{SS} to be reversible. Reduction was done *via* the reductive agent 2-mercaptoethanol (ME) as it was found to be effective on disulfide containing cellulosic materials.²⁴ The reaction was carried out at $37\text{ }^{\circ}\text{C}$ for 72 hours. Contrary to what was observed for cellulosic material, after 24 hours no change was observed despite a lower disulfide bonds concentration. The reduction time was increased to 72 hours and a gel-sol transition was observed (Fig. 5). SEC analysis of the resulting polymer chains was carried out to evaluate the molecular weight of the isolated chains after reduction. No degradation of the PCL backbone was observed: $\bar{M}_n = 19\,000\text{ g.mol}^{-1}$ and PDI = 2.3 instead of $\bar{M}_n = 15\,700\text{ g.mol}^{-1}$ and PDI = 3.9 for the starting PCL-HDT (see ESI, Fig. S7†). This slight molecular weight increase can be attributed to a few residual uncleaved disulfide bonds. These findings confirm the capacity of disulfide elastomeric materials to be reversibly cleaved under redox conditions, without degradation of the PCL backbone, which might be of interest for future applications.

4. Conclusions

Two types of degradable PCL-based elastomeric materials have been obtained from the new PCL-HDT precursor. This thiol-functionalized PCL was readily prepared from PCL in two steps, thanks to an initial anionic activation simple strategy. Redox and thiol-ene reactions were conducted with this precursor to yield disulfide (EM_{SS}) and thioether (EM_{TH}) containing elastomeric materials. HRMAS NMR spectroscopy confirmed the chemical structure of the cross-linked compounds. All mechanical properties of the cross-linked polymers were increased compared to neat PCL, with doubled Young's moduli and four fold increases of the elastic limits. EM_{SS} was found to be superior for all properties when compared to EM_{TH}. In addition, the demonstrated reversibility of the disulfide bond in EM_{SS} might be an advantage for future applications as biomaterial.

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Notes and references

- 1 L. S. Nair and C. T. Laurencin, *Prog. Polym. Sci.*, 2007, **32**, 762–798.
- 2 H. Seyednejad, A. H. Ghassemi, C. F. van Nostrum, T. Vermonden and W. E. Hennink, *J. Controlled Release*, 2011, **152**, 168–176.
- 3 B. G. Amsden, *Expert Opin. Drug Delivery*, 2008, **5**, 175–187.
- 4 A. Harrane, A. Leroy, H. Nouailhas, X. Garric, J. Coudane and B. Nottelet, *Biomed. Mater.*, 2011, **6**, 065006.
- 5 M. C. Serrano, E. J. Chung and G. A. Ameer, *Adv. Funct. Mater.*, 2010, **20**, 192–208.
- 6 V. Darcos, S. Antoniacomi, C. Paniagua and J. Coudane, *Polym. Chem.*, 2012, **3**, 362–368.
- 7 S. Blanquer, J. Tailhades, V. Darcos, M. Amblard, J. Martinez, B. Nottelet and J. Coudane, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 5891–5898.
- 8 S. El Habnoui, V. Darcos and J. Coudane, *Macromol. Rapid Commun.*, 2009, **30**, 165–169.
- 9 S. Gimenez, S. Ponsart, J. Coudane and M. Vert, *J. Bioact. Compat. Polym.*, 2001, **16**, 32–46.
- 10 B. Nottelet, A. El Ghzaoui, J. Coudane and M. Vert, *Biomacromolecules*, 2007, **8**, 2594–2601.
- 11 B. Nottelet, M. Vert and J. Coudane, *Macromol. Rapid Commun.*, 2008, **29**, 743–750.
- 12 B. Nottelet, J. Coudane and M. Vert, *Biomaterials*, 2006, **27**, 4948–4954.
- 13 G. Carrot, J. G. Hilborn, M. Trollsas and J. L. Hedrick, *Macromolecules*, 1999, **32**, 5264–5269.
- 14 C. Hedfors, E. Ostmark, E. Malmstrom, K. Hult and M. Martinelle, *Macromolecules*, 2005, **38**, 647–649.
- 15 I. Javakhishvili and S. Hvilsted, *Biomacromolecules*, 2009, **10**, 74–81.
- 16 M. Kato, K. Toshima and S. Matsumura, *Biomacromolecules*, 2009, **10**, 366–373.
- 17 K. Yamamoto and A. Takasu, *Macromolecules*, 2010, **43**, 8519–8523.
- 18 H. Durmaz, A. Sanyal, G. Hizal and U. Tunca, *Polym. Chem.*, 2012, **3**, 825–835.
- 19 C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad and W. Van Camp, *Angew. Chem., Int. Ed.*, 2011, **50**, 60–62.
- 20 L. M. Campos, K. L. Killips, R. Sakai, J. M. J. Paulusse, D. Damiron, E. Drockenmüller, B. W. Messmore and C. J. Hawker, *Macromolecules*, 2008, **41**, 7063–7070.
- 21 A. E. Rydholm, C. N. Bowman and K. S. Anseth, *Biomaterials*, 2005, **26**, 4495–4506.
- 22 A. B. Lowe, *Polym. Chem.*, 2010, **1**, 17–36.
- 23 A. F. Luo, X. S. Jiang, H. Lin and J. Yin, *J. Mater. Chem.*, 2011, **21**, 12753–12760.
- 24 D. Aoki, Y. Teramoto and Y. Nishio, *Biomacromolecules*, 2007, **8**, 3749–3757.
- 25 B. Nottelet, V. Darcos and J. Coudane, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 5006–5016.
- 26 S. Ponsart, J. Coudane and M. Vert, *Biomacromolecules*, 2000, **1**, 275–281.
- 27 C. G. Overberger and H. Aschkenasy, *J. Am. Chem. Soc.*, 1960, **82**, 4357–4360.
- 28 C. G. Overberger and H. Aschkenasy, *J. Org. Chem.*, 1960, **25**, 1648–1651.
- 29 H. Eser and F. Tihminlioglu, *J. Appl. Polym. Sci.*, 2006, **102**, 2426–2432.
- 30 W. P. Power, *Annu. Rep. NMR Spectrosc.*, 2010, **72**, 111–156.
- 31 S. El Habnoui, S. Blanquer, V. Darcos and J. Coudane, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 6104–6115.
- 32 H. L. Chen, L. J. Li and T. L. Lin, *Macromolecules*, 1998, **31**, 2255–2264.
- 33 H. Tsuji and T. Ishizaka, *Macromol. Biosci.*, 2001, **1**, 59–65.