Articles

Combination of Ring-Opening Polymerization and "Click Chemistry": Toward Functionalization and Grafting of Poly(ϵ-caprolactone)

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ABSTRACT: A straightforward strategy is proposed for the derivatization of poly(ϵ-caprolactone) (PCL). First, statistical copolymerization of α-chloro-ϵ-caprolactone (αClϵCL) with ϵ-caprolactone (ϵCL) was initiated by 2,2-dibutyl-2-stanna-1,3-dioxepane (DSDOP). In a second step, pendent chlorides were converted into azides by reaction with sodium azide. Finally, duly substituted terminal alkynes were reacted with pendent azides by copper-catalyzed Huisgen's 1,3-dipolar cycloaddition, thus a "click" reaction. According to this strategy, pendent hydroxyl and acrylate groups and atom transfer radical polymerization (ATRP) initiators were successfully attached to PCL. Similarly, amphiphilic graft copolymers were prepared by cycloaddition of an alkyne end-capped poly(ethylene oxide) (PEO) onto the azide substituents of the copolyester. The dependence of the grafting yield on the experimental conditions of the "click" reaction, i.e., temperature, solvent, and catalyst, was investigated. This strategy is very versatile because a large variety of aliphatic polyesters can be easily synthesized from a single precursor, easily prepared from commercially available compounds, merely by changing the alkyne involved in the Huisgen's 1,3-dipolar cycloaddition. Last but not least, PCL subsituted by azide groups does not have to be isolated after substitution of chlorides by sodium azide, and the "click" reaction can be carried out in a "one-pot" process.

Introduction

For the past decade, steadily increasing attention was paid to environmentally friendly thermoplastics and biomaterials. Aliphatic polyesters, such as poly(glycolide) (PGA), poly(lactide) (PLA), and poly(ϵ-caprolactone) (PCL), combine biodegradability and biocompatibility and are produced at the industrial scale. Nevertheless, lack of pendent functional groups along these polyester chains is a major limitation to a large range of applications.

At the time being, functional groups can be attached onto aliphatic polyesters by two main strategies. In a first approach, PCL is reacted with lithium amides with formation of poly(enolate)s, which are then added with various electrophiles, e.g., benzaldehyde, carbon dioxide, acid chlorides.[1−3] Although this strategy is versatile, the high reactivity of the anionic enolates toward the ester groups makes the chain degradation unavoidable, which is a major drawback. The second strategy relies on the ring-opening polymerization (ROP) of ϵ-caprolactone substituted mainly in the α- or γ-position, by a functional group, e.g., acrylate,[4] olefin,[5] protected carboxylic acid,[6] and hydroxyl protected,[6,7] or not,[8,9] ketal[10] and halide.[11−13] Polymerization of ϵ-caprolactone containing a ketone[14] or a C−C double blond[15−17] was also reported. Nevertheless, the synthesis of functionalized ϵ-CL may be a multistep and thus time-consuming process. Moreover, some functional groups, e.g., hydroxyl and carboxylic acid, are not compatible with the propagating species, such as aluminum or tin alkoxides, and need protection prior to polymerization. The postpolymerization deprotection must be nondegrading, which may be an additional problem.

In order to tackle the limitations inherent to these strategies, they were advantageously combined into a two-step process.[18] Thus, ϵ-caprolactone substituted by a properly selected functional group was first polymerized, followed by derivatization of this substituent into a variety of functional groups, polymeric or not, according to any reaction known in the state of the art. A wide range of aliphatic polyesters could accordingly be made available from a single precursor. For this strategy to be successful, the following criteria must be satisfied: (1) as direct synthesis as possible of the substituted monomer to be first polymerized (one or two steps); (2) compliance of this monomer with controlled (co)polymerization; (3) mild conditions for the envisioned derivatization reactions, such that (i) no chain degradation occurs, (ii) protection/deprotection of the functions to be incorporated is not required, and (iii) reaction is quantitative even at high content of functional groups. In the recent past, prefunctionalized PCL was chemically modified as exemplified by the Michael addition of thiols onto pendent acrylates,[19] atom transfer radical addition of terminal alkenes onto pendent chlorides,[20] addition of amines onto inner ketones,[21] esterification of pendent hydroxyl groups by carboxylic acids,[22] and ring-opening of pendent epoxides by thiols.[23] By far, the Huisgen's 1,3-dipolar cycloaddition is the derivatization reaction that meets more closely the aforementioned criteria.[18]

Since the pioneering work of Sharpless,[24] highly regioselective copper-mediated 1,3-dipolar cycloaddition of alkynes and

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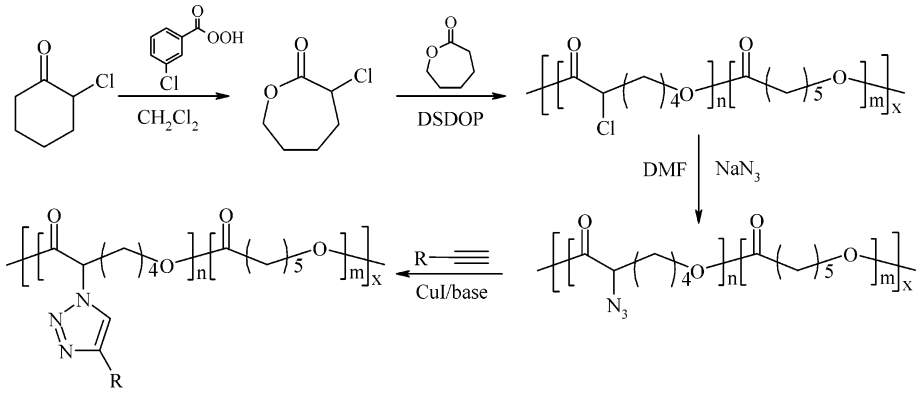
Scheme 1. Strategy for the Chemical Modification and Grafting of PCL by Click Chemistry[37]



azides, known as a "click" reaction,[25] is extensively used in macromolecular engineering.[26−33] When aliphatic polyesters are concerned, star-shaped PCL was prepared by grafting alkyne end-capped PCL onto a multifunctional azide.[34] Emrick et al. reported on the grafting of α-azido-PEO onto alkyne substituents of PCL by Huisgen's cycloaddition.[35] Nevertheless, the experimental conditions used by these authors (water at 80 °C) turned out to degrade PCL, at least in our hands. Moreover, the extension of this strategy to the grafting of low molecular weight organic azides could face safety problems because these compounds are explosive, especially when the number of nitrogen atoms is higher than the number of carbons and when $(N_C + N_O)/N_N < 3$ (with N standing for the number of atoms).[36] The easiest way to overcome this drawback consists of reversing the reaction scheme (Scheme 1),[37] thus reaction of low molecular weight alkynes onto pendent azides of PCL (Scheme 1). For this purpose, α-chloro-ϵ-caprolactone (αClϵCL) was copolymerized with ϵ-caprolactone (ϵCL), followed by reaction of the pendent chlorides with sodium azide. The Huisgen's cycloaddition was then carried out under very mild conditions, thus at 35 °C in an organic solvent (THF) rather than in water. No significant chain degradation was accordingly observed, even when lactide was substituted for ϵ-CL in the copolymer.[37] In addition to ester, amine, and ammonium groups, PEO chains were grafted to PCL with formation of amphiphilic polyϵCL-*g*-polyEO copolymers.

This paper aims at reporting on (i) the synthesis and characterization of azides containing PCL, which was not discussed in the introductive communication,[37] (ii) characterization of the final copolymers prepared by "click" chemistry, and (iii) extension of the "click" strategy to the successful grafting of acrylates, which makes PCL photo-cross-linkable and of activated bromides, which are nothing but initiators of ATRP. An alternative strategy for the synthesis of PCL-*g*-PEO is also discussed. Last but not least, the "one-pot" reaction of pendent chloride containing PCL with sodium azide followed by the Huisgen's cycloaddition of alkynes is documented, which makes this whole process more attractive.

Experimental Section

Materials. Toluene (Chem-lab), tetrahydrofuran (THF; Chem-lab), dichloromethane (CH_2Cl_2; Chem-lab), *N*,*N*-dimethylformamide (DMF; Aldrich), sodium azide (Aldrich), dicyclohexylcarbodiimide (DCC; Aldrich), poly(ethylene glycol) methyl ether (M_W ~750 g/mol; Aldrich), propargyl benzoate (Aldrich), propargyl alcohol (Aldrich), but-3-yn-1-ol (Aldrich), bromoisobutyryl bromide (Aldrich), 3-(dimethylamino)-1-propyne (Aldrich), propargyl acrylate (Aldrich), copper(I) bromide (Aldrich), copper bromide (Aldrich), copper(I) chloride (Aldrich), cupper(II) chloride (Aldrich), sodium ascorbate (Aldrich), 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA; Aldrich), diazobicyclo[5.4.0undec-7-ene] (DBU; Aldrich), and anisole (Aldrich) were used as received. The poly(αClϵCL-*co*-ϵCL) copolymers were prepared as previously reported.[13] 2,2-Dibutyl-2-stanna-1,3-dioxepane (DSDOP) was prepared as reported by Kricheldorf et al.[38] Syntheses of α-chloro-ϵ-caprolactone (αClϵCL)[13] and propargyl bromoisobutyrate[39] were also reported elsewhere. Styrene (Aldrich) and ϵ-caprolactone (Aldrich) were dried over calcium hydride at room temperature for 48 h and distilled under reduced pressure just before use. Toluene was dried by refluxing over a benzophenone−sodium mixture and distilled under nitrogen.

*Synthesis of Poly(*αN_3ϵ*CL-co-*ϵ*CL)*. 5 g of poly(αClϵCL-*co*-ϵCL) (1 equiv of αClϵCL) were dissolved in 15 mL of DMF in a glass reactor, followed by the addition of 1 equiv of NaN_3. The mixture was stirred at room temperature overnight. After elimination of DMF in vacuo, 15 mL of toluene was added, and the insoluble salt was removed by centrifugation (5000 rpm at 25 °C for 15 min). The copolymer was recovered by solvent evaporation in vacuo or by precipitation in heptane whenever it contained less than 20 mol % of αN_3ϵCL units.

Synthesis of α*-MeO,*ω*-(HC≡C-(*CH_2*)*$_2$*-*CO_2*)-poly(EO)*. 1 equiv of α-MeO,ω-HO-poly(EO) (750 g/mol) was dried by repeated (three times) azeotropic distillation of toluene before dissolution in dry CH_2Cl_2. 1 equiv of 4-pentynoic acid, 0.1 equiv of DMAP, and 1 equiv of DCC were added to the polymer solution, which was stirred at room temperature for 36 h. The solvent was evaporated in vacuo, the solid residue was dissolved in THF, and the solution was filtered in order to remove the dicyclohexylurea byproduct and poured in Et_2O. The polymer precipitated at −20 °C overnight. After filtration, it was dried in vacuo at room temperature.

^{1}H NMR ($CDCl_3$): 4.25 (t, 2H, CH_2−O−C(O)), 3.8−3.4 (m, 4H, 2CH_2−O), 2.6 (m, 2H, CH_2−C(O)), 2.5 (m, 4H, CH_2−C≡C) and 1.9 ppm (m, 2H, C≡C*H*)

Typical Click Chemistry Reaction. Poly(αN_3ϵCL-*co*-ϵCL) (1 equiv of azide) was transferred into a THF containing glass reactor. 1.2 equiv of alkyne, 0.1 equiv of CuI, and 0.1 equiv of amine were then added to the reactor. The solution was stirred at 35 °C until the IR absorption of the azide at 2106 cm^{-1} disappeared completely. The copolyester was precipitated in heptane (or methanol), recovered by filtration, and dried in vacuo at room temperature.

Cycloaddition of propargyl alcohol: ^{1}H NMR ($CDCl_3$): 7.8 ppm (1H, s, C*H*═C triazole), 5.3 ppm (1H, s, triazole−C*H*−C(O)), 4.8 ppm (2H, s, CH_2−OH), 4.2−4 ppm (4H, 2 m, 2 CH_2−O−C(O)), 2.3 ppm (2H, t, CH_2−C(O)), and 2−1 ppm (12 H, m, 6 CH_2).

Cycloaddition of 4-butyn-1-ol: ^{1}H NMR ($CDCl_3$): 7.5 ppm (1H, s, C*H*═C triazole), 5.2 ppm (1H, s, triazole−C*H*−C(O)), 4.2−4 ppm (6H, 3 m, 2 CH_2−O−C(O) + CH_2OH), 2.8 ppm (2H, m, CH_2−CH_2−OH), 2.2 ppm (2H, t, CH_2−C(O)), and 2−1 ppm (12 H, m, 6 CH_2).

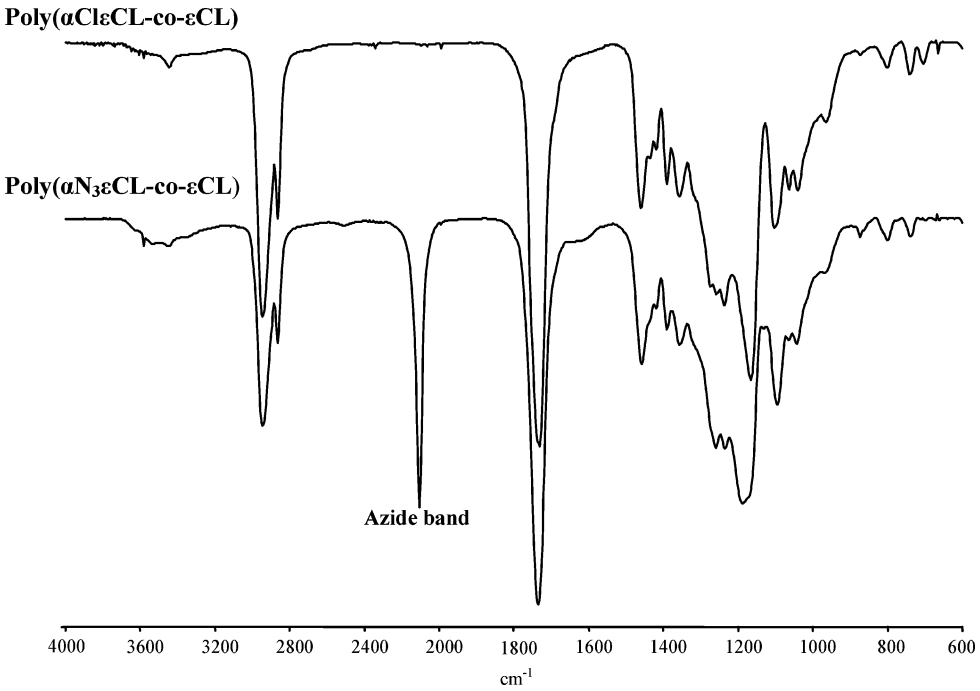


Figure 1. IR spectra of poly(αClϵCL-*co*-ϵCL) and poly(α$N_3\epsilon$CL-*co*-ϵCL).

Cycloaddition of propargyl acrylate: ^{1}H NMR ($CDCl_3$): 7.8 ppm (1H, s, C*H*═C triazole), 6.4, 6.1, and 5.8 ppm (3H, 3 m, C*H*═CH_2 acrylate), 5.3 ppm (3H, s, triazole−C*H*−C(O) + CH_2−O−C(O)−CH═CH_2), 4.2−4 ppm (4H, 2 m, 2 CH_2−O), 2.3 ppm (2H, t, CH_2−C(O)), and 2−1 ppm (12 H, m, 6 CH_2).

Cycloaddition of propargyl bromoisobutyrate: ^{1}H NMR ($CDCl_3$): 7.8 ppm (1H, s, C*H*═C triazole), 5.3 ppm (3H, s, triazole−C*H*−C(O) + CH_2−O−C(O)−C$(CH_3)_2$Br), 4.2−4 ppm (4H, 2 m, 2 CH_2−O−C(O)), 2.3 ppm (2H, t, CH_2−C(O)) 2 ppm (6H, s, 2 CH_3), and 1.8−1 ppm (12 H, m, 6 CH_2).

UV Cross-Linking of Acrylate Containing PCL. 500 mg (0.4 mmol of acrylate) of PCL containing 10 mol % of acrylate was dissolved in 5 mL of toluene. 3.5 mg (0.02 mmol) of benzophenone was added to the solution that was stirred under UV radiation (350−420 nm, 1000 W) at room temperature for 2 h.

Preparation of PolyϵCL-g-polystyrene. 340 mg (0.25 mmol of bromide) of PCL containing 10 mol % of bromoisobutyryl group was dissolved in 4 mL of anisole in a glass reactor. After complete dissolution, 25 mg (0.25 mmol) of CuCl, 4 mg (0.025 mmol) of $CuCl_2$, and 58 mg (0.25 mmol) of HMTETA were added to the reactor. The solution was degassed by bubbling of nitrogen for 15 min. 1.25 mL (12.2 mmol) of freshly distilled styrene was added with a stainless capillary under nitrogen. The solution was stirred at 110 °C for 5 h. The copolymer solution was diluted with THF, before being passed through a silica column in order to remove the catalyst. The copolymer was precipitated into cyclohexane, recovered by filtration, and dried in vacuo.

Synthesis of PolyϵCL-g-polyEO). 200 mg (0.48 mmol of azide function) of poly(α$N_3\epsilon$CL-*co*-ϵCL) containing 30 mol % of α$N_3\epsilon$CL and 360 mg (0.48 mmol) of α-MeO,ω-alkyne-PEO were transferred into a glass reactor containing 7 mL of THF. The solution was stirred until complete dissolution of the polymers. 5 mg (0.048 mmol) of NEt_3 and 9 mg (0.048 mmol) of CuI were added into the reactor. The solution was stirred at 35 °C for 2 h. The graft copolymer was recovered by repeated precipitation in Et_2O in order to eliminate the nongrafted PEO chains.

One-Pot Click Chemistry. 500 mg (1.9 mmol of pendent chloride) of poly(αClϵCL-*co*-ϵCL) containing 50 mol % of αClϵCL was dissolved in 3 mL of DMF in a glass reactor, followed by addition of 150 mg (2.3 mmol) of NaN_3. The mixture was stirred at room temperature overnight. A solution of 10 mg (0.23 mmol) of CuI and 210 mg (2.5 mmol) of 3-(dimethylamino)-1-propyne dissolved in 2 mL of THF was then transferred into the reactor. The solution was stirred at 35 °C for 2 h. After filtration, the polymer was precipitated in heptane and dried in vacuo.

^{1}H NMR ($CDCl_3$): 7.7 ppm (1H, s, C*H*═C triazole), 5.2 ppm (1H, s, triazole−C*H*−C(O)), 4.2−4 ppm (4H, 2 m, 2 CH_2−O), 3.6 ppm (2H, s, CH_2−NMe_2), 2.3 ppm (8H, m, 2CH_3 + CH_2−C(O)), and 2−1 ppm (12 H, m, 6 CH_2)

Characterization Techniques. Size exclusion chromatography (SEC) was carried out in THF at 45 °C at a flow rate of 1 mL/min with a SFD S5200 autosampler liquid chromatograph equipped with a SFD refractometer index detector 2000. PL gel 5 μm (10^5, 10^4, 10^3, and 100 Å) columns were calibrated with either polystyrene or PEO standards. Size exclusion chromatography (SEC) was carried out in DMF at 40 °C at a flow rate 1 mL/min, using a Water 600 autosampler liquid chromatograph equipped with a differential refractometer index detector. Waters gel 5 μm (10^5, 10^4, 500, and 100 Å) columns were calibrated with polystyrene standards. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz in the FT mode with a Bruker AN 400 apparatus at 25 °C. Infrared spectra were recorded with a Perkin-Elmer FT-IR 1720X. The IR samples were prepared by slow evaporation of a copolymer solution, in THF, onto NaCl windows. Thermal gravimetric analysis (TGA) was carried out with a TA TGA Q 500. Differential scanning calorimetry (DSC) was carried out with a TA DSC Q 100 thermal analyzer calibrated with indium. Glass transition and melting temperatures were measured, after a first cooling (−80 °C) and heating (100 °C) cycle. Thermograms were recorded during the second heating cycle at 10 °C/min.

Results and Discussion

Substitution of the Cl Atoms of Poly(αClϵCL-*co*-ϵCL) by Sodium Azide. According to Scheme 1, the pendent chlorides of poly(αClϵCL-*co*-ϵCL), whose synthesis was previously reported,[13] must be converted into azides by reaction with sodium azide. Poly(αClϵCL-*co*-ϵCL) was thus reacted with 1 equiv of sodium azide in DMF at room temperature overnight. The IR spectrum expectedly shows a new absorption at 2106 cm^{-1} characteristic of the azide (Figure 1).

^{1}H NMR confirms that the conversion of the pendent chlorides into azides is quantitative. Indeed, the resonance peak at 4.25 ppm for the CHCl protons disappears completely in favor of a new peak at 3.8 ppm, typical of the CH−N_3 protons (Figure

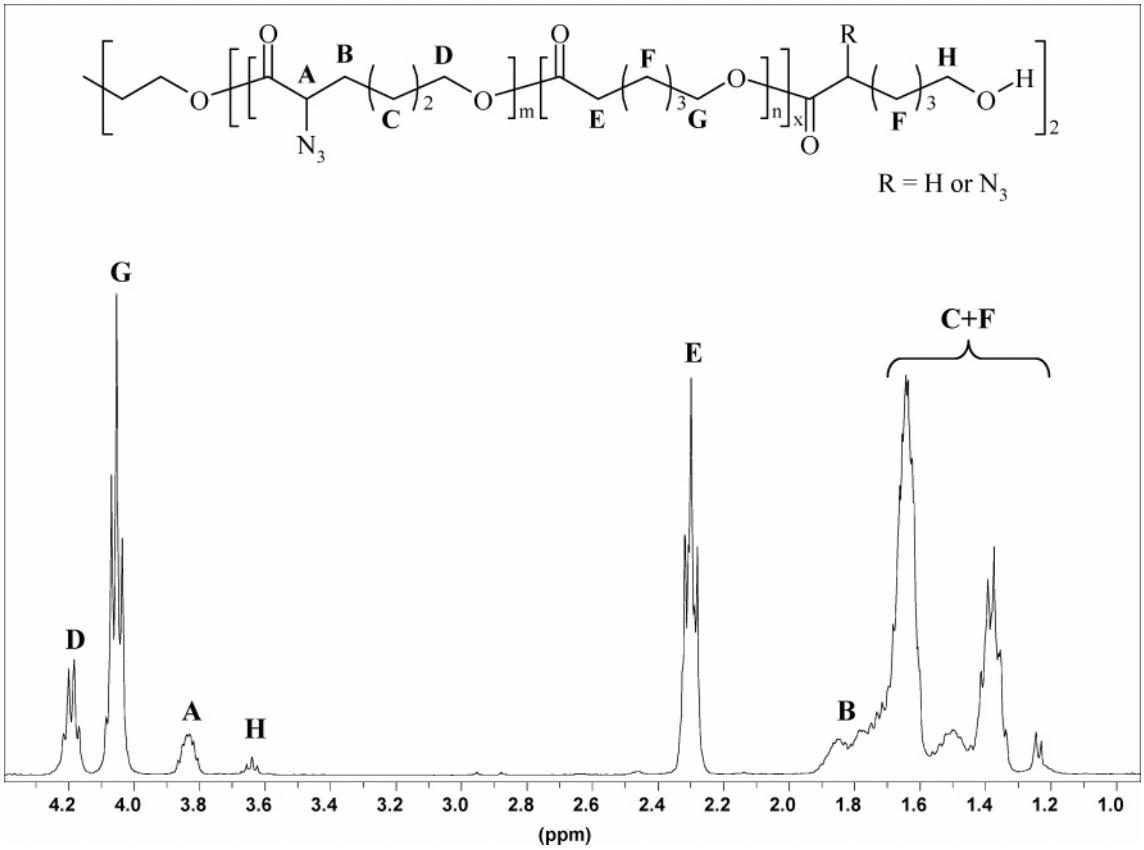


Figure 2. ^{1}H NMR spectrum for poly(αN_3ϵCL-*co*-ϵCL) containing 30 mol % of αN_3ϵCL.

Table 1. Substitution of Chloride of Poly(αClϵCL-*co*-ϵCL) with Different Compositions by Sodium Azide

	poly(αClϵCL-*co*-ϵCL)			poly(αN_3ϵCL-*co*-ϵCL)		
entry	$F_{\alpha Cl\epsilon CL}$ ^{1}H NMR	M_n SEC[a]	M_w/M_n[a]	$F_{\alpha N3\epsilon CL}$ ^{1}H NMR	M_n SEC[a]	M_w/M_n[a]
1	0.10	20 000	1.4	0.10	18 000	1.5
2	0.30	20 000	1.5	0.29	18 000	1.5
3	0.50	20 000	1.6	0.49	19 000	1.6
4	0.70	14 000	1.5	0.70	13 000	1.5
5	1.00	12 000	1.4	1.00	9 000	1.7

[a] Polystyrene standards.

2, peak A). The molar fraction of the α-azide-ϵ-caprolactone units (αN_3ϵCL), $F_{\alpha N_3 \epsilon CL}$, was calculated by integrating the peaks at 2.3 ppm (I_E) (Figure 2, peak E) ($CH_2C{=}O$ protons of the ϵCL unit) and at 3.8 ppm (I_A) (Figure 2, peak A) ($CH{-}N_3$ proton of the αN_3ϵCL unit), respectively (eq 1).

$$F_{\alpha N_3 \epsilon_{CL}} = \frac{I_A}{I_A + I_E/2} \quad (1)$$

The substitution reaction was repeated with poly(αClϵCL-*co*-ϵCL) samples of different compositions. The results are collected in Table 1.

Table 1 shows that the molecular weight of the copolyesters containing up to 70 mol % of αClϵCL is slightly decreased as result of the chloride substitution by azide. This observation is consistent with a small change in the hydrodynamic volume of the copolyester. Importantly, the elution peak remains symmetrical, and no increase in polydispersity is reported, which strongly suggests lack of chain degradation.

However, when homopoly(αClϵCL) is concerned, the chloride substitution remains quantitative, but chain degradation cannot be avoided, as witnessed by a substantial increase in the polydispersity index from 1.4 up to 1.7 and possibly by the more important decrease in the apparent molecular weight. As a rule, the homopolymer is more sensitive to degradation than the copolymers.

Thermal Properties of Poly(αN_3ϵCL-*co*-ϵCL). Compared to the poly(αClϵCL-*co*-ϵCL), the poly(αN_3ϵCL-*co*-ϵCL) copolyester that contains 30 mol % of functional counits shows a different TGA profile. Indeed, the thermal degradation starts ∼50 °C earlier as result of the substitution of the chlorine atoms by azides. Moreover, a three-step degradation profile is observed for the azide containing copolyester instead of two for the chloride version. An in-depth analysis is however needed to account for the difference observed in the degradation mechanism.

Poly(αN_3ϵCL-*co*-ϵCL) of different compositions were also analyzed by DSC. They are semicrystalline as long as the αN_3ϵCL content does not exceed 30 mol %. In this composition range, the melting temperature decreases when the azide content increases. This behavior is commonly observed for statistical copolymers of ϵCL.[11] Furthermore, T_g depends linearly on the αN_3ϵCL content, from −60 °C for PCL to −43 °C for poly(αN_3ϵCL) (Figure 3).

Click Reaction of Propargyl Benzoate with Poly(αN_3ϵCL-*co*-ϵCL). This reaction was first catalyzed by copper bromide (CuBr) in DMF at low temperature (40 °C). However, no cycloaddition occurred even after 12 h. Substitution of a combination of $CuCl_2$ and sodium ascorbate for CuBr did not improve the situation. Under more drastic conditions (DMF/MeOH 9:1, 1 equiv of NEt_3, 100 °C overnight), the IR absorption at 2106 cm^{-1} characteristic of the azide completely disappears in favor of a new absorption at 1660 cm^{-1} characteristic of the triazole unsaturations. Nevertheless, the SEC chromatogram was bimodal after reaction, which supported substantial chain degradation with oligomer formation. A small

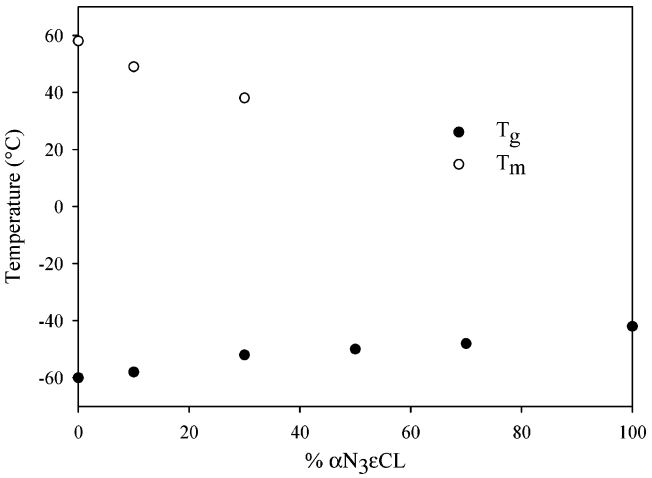


Figure 3. Dependence of T_g and T_m of poly($\alpha N_3\epsilon$CL-*co*-ϵCL) on the molar fraction of $\alpha N_3\epsilon$CL.

amount of methanol, which might be responsible for chain rupture, was actually used because the cycloaddition is commonly carried out in a protic solvent, particularly in water, in which PCL is insoluble.[40] Very recently, Opsteen et al. prepared block copolymers by coupling two populations of polymer chains end-capped by an azide and an alkyne, respectively.[27] The conditions used were very mild: 4 h in the presence of CuI and diazobicyclo[5.4.0undec-7-ene] (DBU) in THF at 35 °C. Under these conditions, propargyl benzoate was grafted onto poly($\alpha N_3\epsilon$CL-*co*-ϵCL). After 2 h, the absorption at 2106 cm^{-1}, assigned to the azide, disappeared completely, and a new absorption appeared at 1660 cm^{-1}.

According to ^{1}H NMR analysis, the cycloaddition was quantitative. Indeed, the peak for the CH−N_3 proton at 3.8 ppm disappeared entirely, and new peaks appeared in the 7.9−8 ppm range. Figure 4 shows the ^{1}H NMR spectrum and the assignment of the signals for poly($\alpha N_3\epsilon$CL-*co*-ϵCL) added with propargyl benzoate. The resonances at 8, 7.5, and 7.4 ppm are typical of the benzoyl protons, and the triazole proton is observed at 7.9 ppm. This assignment was confirmed by ^{1}H−^{1}H cosy 2D NMR analysis. The molar fraction of the addition product, $F_{benzoate}$, calculated by eq 2 (28 mol %), is close to the molar fraction of $\alpha N_3\epsilon$CL in the original copolyester (30 mol %).

$$F_{benzoate} = \frac{I_{G+I}/6}{I_{G+I}/6 + \dfrac{I_{F+C} - I_{G+I}/3}{2}} \qquad (2)$$

The superposition of the SEC curves recorded by refractometry and UV detection (propargyl benzoate) is an additional evidence of the successful cycloaddition. The SEC analysis also confirms that the cycloaddition conditions are mild enough for the chains not being degraded significantly. Indeed, the apparent molar mass is 18 000 instead of 20 000 before the chemical modification, and the polydispersity changes from 1.5 to 1.6 as a result of the cycloaddition.

A more convincing evidence for the nondegrading conditions was provided by adding the catalytic system (10 mol % of CuI and 10 mol % of DBU) to poly($\alpha N_3\epsilon$CL-*co*-ϵCL) containing 30 mol % of $\alpha N_3\epsilon$CL, at 35 °C in THF. Two hours later, the apparent molar mass and the polydispersity did not change at all.

Grafting of Hydroxyl Group. The grafting of hydroxyl groups onto PCL is an easy way to increase the hydrophilicity of the polyester. However, hydroxyl groups can trigger chain degradation by intra- and intermolecular transesterification reactions. It is the reason why hydroxyl groups are commonly protected before being successfully attached onto PCL. Degradation during deprotection is then a concern.[41−43]

Because "click" cycloaddition can be performed under very mild conditions, hydroxyl groups might be directly grafted onto aliphatic polyesters without chain degradation and need of cumbersome protection/deprotection steps. The grafting of propargyl alcohol onto poly($\alpha N_3\epsilon$CL-*co*-ϵCL) (30 mol % en $\alpha N_3\epsilon$CL) was thus tested under the experimental conditions previously optimized (10 mol % of CuI/DBU at 35 °C). The IR absorption of the azide disappeared completely after 2 h. ^{1}H NMR confirmed the quantitative grafting of the propargyl alcohol (see Experimental Section). Nevertheless, a partial degradation was observed by SEC chromatography. Indeed, the elution peak that was originally monomodal and symmetric was bimodal after reaction as result of oligomer formation (Figure 5). Substitution of DBU by a less basic amine, such as triethylamine, decreased the extent of degradation. A further improvement was reported by increasing the length of the spacer between the hydroxyl group and the alkyne, thus by substituting but-3-yn-1-ol for the propargyl alcohol (10 mol % of CuI/NEt_3 in THF at 35 °C). Although the elution of oligomers persisted, their relative content decreased very significantly (Figure 5).

Grafting of Acrylic Unsaturations. The grafting of acrylate onto PCL is highly desirable for making it photo-cross-linkable. So, cycloaddition of propargyl acrylate was conducted onto poly($\alpha N_3\epsilon$CL-*co*-ϵCL) with 30 mol % of $\alpha N_3\epsilon$CL. After 1 h of reaction, 100% of azide was converted into triazole, as determined by ^{1}H NMR. Nevertheless, the SEC chromatogram of the copolyester after reaction showed a shoulder on the high molecular weight side and a polydispersity index as high as 2.0. This observation was accounted for by the radical coupling of pendent acrylates. Indeed, when propargyl acrylate is added with 10 mol % of CuI and 10 mol % of NEt_3 in THF at 35 °C, polymerization occurs (% conversion less than 5% after 2 h; M_n = 1500 g/mol and M_w/M_n = 1.1). Addition of a radical inhibitor (Tempo or hydroquinone) to the cycloaddition medium could not prevent the coupling reaction from occurring. In contrast, a decrease from 30 to 10 mol % of the azide content of the poly($\alpha N_3\epsilon$CL-*co*-ϵCL) copolyester (M_n = 32 000 g/mol and M_w/M_n = 1.5) was effective in inhibiting this competing reaction. Indeed, the SEC chromatogram remained symmetrical after cycloaddition, and M_n (35 000 g/mol) and polydispersity (1.5) did not change as desired.

Finally, the derivatized copolyester was UV irradiated in the presence of 5 mol % of benzophenone for 2 h. It was then completely insoluble in all the organic solvents, in agreement with the cross-linking of the acrylate containing chains.

Grafting of an ATRP Initiator. In order to prepare graft copolymers of PCL by ATRP, propargyl bromoisobutyrate was successfully grafted onto poly($\alpha N_3\epsilon$CL-co-ϵCL) containing 10 mol % of $\alpha N_3\epsilon$CL. The cycloaddition was complete within 90 min, as shown by the ^{1}H NMR spectrum (Experimental Section).

The copolyester with 10 mol % of bromoisobutyryl groups (M_n(SEC) = 19 000 g/mol; M_w/M_n = 1.5; 9 bromides per chain) was then used to initiate the atom transfer radical polymerization of styrene in anisole with CuCl/$CuCl_2$−HMTETA as catalyst. Several samples were picked out during polymerization and analyzed by ^{1}H NMR and SEC. The ^{1}H NMR spectrum showed new peaks at 7.2 ppm, typical of the aromatic protons of poly(styrene). Their intensity increased with the reaction time. The SEC chromatograms were monomodal and symmetrical until 6 h of polymerization (conversion = 52% (cf. infra)), the

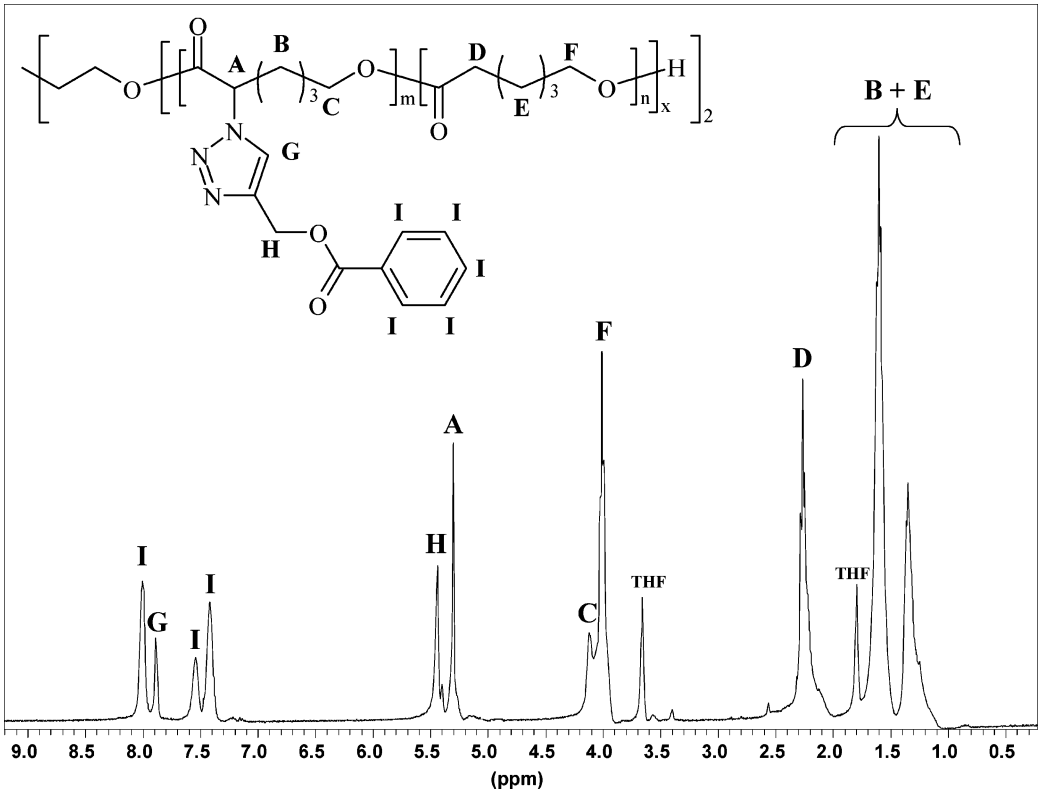


Figure 4. ^{1}H NMR spectrum for the copolyester after the "click" addition of propargyl benzoate.

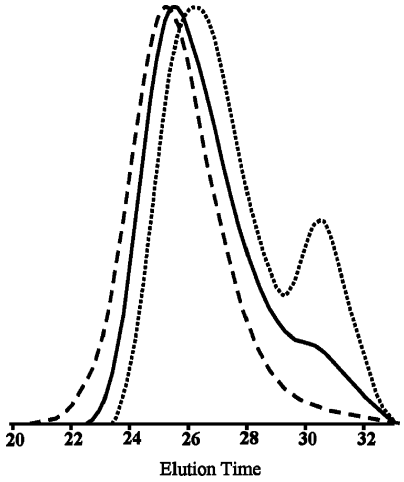


Figure 5. Superposition of the SEC curves for poly(αN_3ϵCL-*co*-ϵCL) with 30 mol % of αN_3ϵCL (- - -) and the copolyesters collected after the click cycloaddition of propargyl alcohol (···), and but-3-yn-1-ol (—).

polydispersity being 1.6. After 6 h, a shoulder appeared as result of parasitic coupling reaction. Therefore, the copolymer was precipitated after 6 h in cyclohexane, a good solvent for poly(styrene) but a very poor solvent for PCL. It was then analyzed by ^{1}H NMR, which showed the resonances typical of PS, thus covalently grafted onto PCL. From the integrals of the proton resonances for PS (7.2 ppm) and PCL (4 ppm), the copolymer composition was calculated as 34 mol % of PCL and 66 mol % of PS.

In order to determine the length of the PS grafts, the polyester backbone was degraded in a mixture of dioxane and HCl (95/5) at 60 °C for 3 days. PS was then collected, precipitated into heptane, and analyzed by SEC. The experimental degree of polymerization was 25 instead 48 in the case of complete conversion. On the assumption that no homoPS was formed, the styrene conversion was 52%. The polydispersity index of the PS grafts was low (1.3). The number of PS grafts was easily calculated from the copolymer composition, M_n PCL and M_n PS. As an average, 9 PS chains were grafted to PCL, thus the same number as the pendent bromide groups (=9) of the macroinitiator, so emphasizing an initiation efficiency close to 100%. This value must be compared to the lower efficiency (60%) observed when ATRP of styrene was directly initiated by poly(αClϵCL-*co*-ϵCL).[13]

Table 2. T_g of Copolyesters Functionalized by "Click" Chemistry

	T_g (°C)
poly(αN3ϵCL-*co*-ϵCL) with 30 mol % of αN3ϵCL	−52
PCL with 30 mol % of acrylate	−40
PCL with 30 mol % of bromide	−43
PCL with 30 mol % of hydroxyl	−50

Thermal Properties of Functional PCL. The copolyesters derivatized by cycloaddition and containing 30 mol % of acrylate, bromide, and hydroxyl are all amorphous with a T_g that depends on the functional group (Table 2). Once again, the functional group dictates the thermal stability of the chains and the degradation mechanism. The polyester is by far more stable when it is substituted by acrylate groups rather than by hydroxyl and bromide groups.

Preparation of PCL-*g*-PEO. A previous communication reported on the synthesis of PCL-*g*-PEO by cycloaddition of an α-alkyne, ω-hydroxyl-PEO, onto poly(αN_3ϵCL-*co*-ϵCL) with 30 mol % of αN_3ϵCL.[37] The alkyne end group resulted from the quaternization of α-(dimethylamino)-ω-hydroxyl-PEO by propargyl bromide. Therefore, the final graft copolymer was carrying a positive charge at each grafting point.

In this work, α-methoxy-ω-alkyne-PEO was prepared by esterification of α-methoxy-ω-hydroxyl-PEO by 4-pentynoic acid in the presence of DMAP and DCC. Because α-methoxy-ω-hydroxyl-PEO is contaminated by α,ω-hydroxyl-PEO, α,ω-alkyne-PEO might be formed, which is liable to cause the cross-

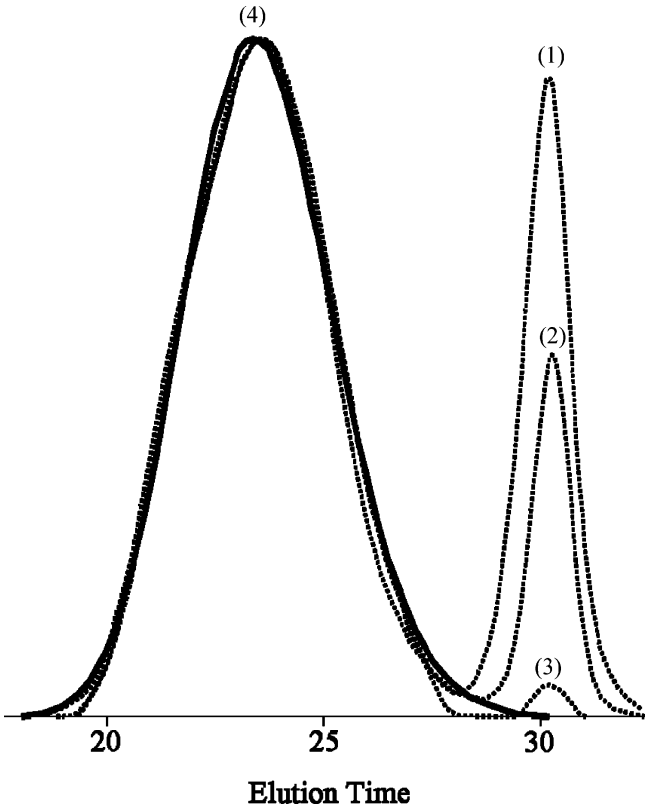


Figure 6. SEC curves of PCL-*g*-PEO before (1) and after repeated precipitation in Et_2O (2, 3, and 4).

linking of the copolyester during the click reaction.[44] Therefore, the hydroxyl end groups of PEO were esterified by 1 equiv of 4-pentynoic acid instead of an excess. 85% of the hydroxyl end groups were actually esterified after 36 h of reaction (NMR analysis).

α-Methoxy-ω-alkyne-PEO was then reacted with poly(αN$_3$ϵCL-*co*-ϵCL) containing 27 mol % of αN$_3$ϵCL in the presence of CuI and NEt_3 in THF for 3 h. The intensity of the IR absorption of the azide decreased, whereas the triazole absorption was observed at 1660 cm^{-1}. The nongrafted PEO chains were eliminated by precipitation of the copolymer in Et_2O. Indeed, α-methoxy-ω-alkyne-PEO was soluble in Et_2O at room temperature, in contrast to the graft copolymer that was insoluble. Repeating the precipitation three times was enough for the copolymer to get rid of homoPEO (Figure 6). The apparent molecular weight of the graft copolymer was 30 000 g/mol (SEC in THF) with a polydispersity index of 1.7.

^{1}H NMR analysis confirmed the grafting of PEO by a typical CH_2-O resonance at 3.6 ppm and that one of the triazole link at 7.5 ppm (Figure 7). The total number of EO units in the copolymer (DP_{PEO},total) was calculated from the integrals of the peaks assigned to the CH_2-O protons of PEO (3.6 ppm) and PCL (4 ppm), respectively (eq 3).

$$\frac{I_{1H,PCL}}{I_{1H,PEO}} = \frac{DP_{PCL}}{DP_{PEO},total} \quad (3)$$

The number of PEO grafts per chain (*N* graft) was calculated by eq 4, where DP_{PEO},graft is the number of EO units in the PEO chains.

$$N\ \text{graft} = \frac{DP_{PEO,}total}{DP_{PEO,}graft} \quad (4)$$

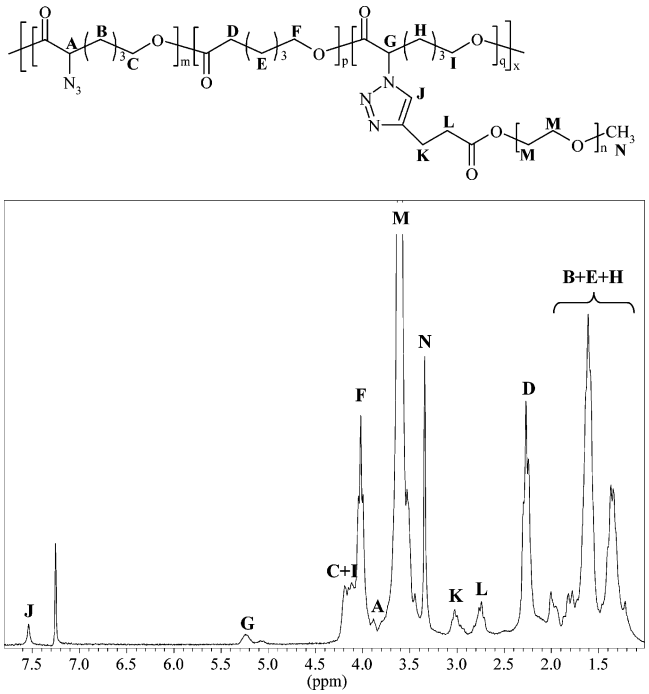


Figure 7. ^{1}H NMR spectrum of PCL-*g*-PEO.

As an average, 10 PEO chains were grafted onto poly(αN$_3$ϵCL-*co*-ϵCL) that contained 24 αN$_3$ϵCL units. The grafting efficiency was thus 40%. M_n of the grafted copolyester was 17 500 g/mol as calculated by eq 5.

$$M_n,\text{PCL-}g\text{-PEO} = M_n,\text{backbone} + (N \times M_n\,\text{PEO graft}) \quad (5)$$

The 14 azide groups that were unreacted remained available to further grafting by another alkyne. Indeed, the PCL-*g*-PEO copolymer was reacted with propargyl benzoate in the presence of CuI/NEt_3 in THF at 35 °C. The IR absorption of the azide disappeared completely after 2 h. The ^{1}H NMR spectrum of the copolymer previously precipitated in methanol showed the resonances characteristic of the aromatic protons of the benzoate at ∼7.5 ppm. The grafting of benzoate was quantitative, which is a strong incentive to have a variety of functional groups grafted onto the polyester backbone of PCL-*g*-PEO. In the future, this strategy will be extended to the grafting of functional groups onto the backbone.

One-Pot Synthesis. Because of the well-known unstability of azides,[36] their handling should be restricted as much as possible. Therefore, the implementation of the reaction Scheme 1 in a "one-pot" process is highly desirable in order to bypass the intermediate isolation and purification of poly(αN$_3$ϵCL-*co*-ϵCL). In this respect, poly(αClϵCL-*co*-ϵCL) with 50 mol % of αClϵCL was reacted with 1.2 equiv of NaN_3 in DMF overnight. The pendent chlorides were quantitatively converted into azides as supported by the complete disappearance of the CHCl protons at 4.25 ppm and the observation of the CHN_3 protons at 3.8 ppm. The molar fraction of αN$_3$ϵCL in the copolyester was 49% as expected within the limits of experimental errors. Then, a solution of 1.1 equiv of 3-(dimethylamino)-1-propyne and 0.1 equiv of CuI in THF was added into the reactor, and the temperature was increased to 35 °C. The IR absorption of the azide disappeared after 2 h, and the azide content was 48%, thus close to the theoretical value (^{1}H NMR; see Experimental Section). The polydispersity index of the copolyester (1.2) remained unchanged. The tertiary amine grafted PCL precipitated when a solution in THF was poured into distilled water.

Nevertheless, when the pH of water was decreased by addition of HCl, the copolyester was soluble in the aqueous medium although the content of amine was only 50 mol %. The "one-pot" procedure is thus a very efficient and convenient method for grafting functional groups (polymeric or not) onto PCL by the Huisgen's 1,3-dipolar cycloaddition.

Conclusions

Substitution of the pendent chlorides of poly(αN_3ϵCL-*co*-ϵCL) random copolymers by sodium azide, followed by the Huisgen's 1,3-dipolar cycloaddition of alkynes (functional and/or polymeric), is quite a valuable technique for grafting a variety of substituents onto PCL. This strategy has the advantage of being implemented under very mild conditions that preserve the length of the polyester chains. Last but not least, all the reactions can be carried out in the same reactor, without need of isolating and purifying intermediate compounds, such as the azide containing PCL. Such a "one-pot" process is time-saving and restricts the handling of unstable products. In addition to hydroxyl groups, acrylates can be quantitatively grafted onto PCL, thus making the polyester photo-cross-linkable. The grafting of an ATRP initiator is also quite feasible, which opens the way to graft copolymers, the synthesis of PCL-*g*-PS being exemplified in this work. In addition to the "grafting from" technique, the "grafting onto" strategy can also be contemplated as illustrated by the grafting of preformed PEO end-capped by an alkyne. The versatility of the reaction pathway shown in Scheme 1 is currently exploited in our laboratory in the frame of the macromolecular engineering of aliphatic polyesters.

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Supporting Information Available: Figures showing the (i) superposition of the SEC curves for poly(αClϵCL-*co*-ϵCL) and poly(αN_3ϵCL-co-ϵCL); (ii) TGA curves for the poly(αClϵCL-*co*-ϵCL) and poly(αN_3ϵCL-*co*-ϵCL) copolyesters containing 30 mol % of functional counits; (iii) ^{1}H−^{1}H cosy 2D NMR spectrum of the copolyester after the click addition of propargyl benzoate; (iv) comparison of the SEC profiles of PCL-*g*-PS and the PS grafts collected after degradation of the PCL backbone; and (v) the TGA curves of PCL functionalized by click chemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

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