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Combination of ring-opening polymerization and "click" chemistry towards functionalization of aliphatic polyesters

Raphaël Riva, Stéphanie Schmeits, François Stoffelbach, Christine Jérôme, Robert Jérôme* and Philippe Lecomte

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Azide pendent groups of aliphatic polyesters have been derivatized into tertiary amines, ammonium salts and poly(ethylene oxide) grafts. The experimental conditions have been optimized (organic solvent, 35 °C), such that the aliphatic polyesters are not degraded, including even poly(lactide) which is very sensitive to attack by weak nucleophiles.

For the last decade, steadily increasing attention has been paid to biodegradable and biocompatible aliphatic polyesters as substitutes for non biodegradable polymers in environmental and biomedical applications. Altough poly(ε-caprolactone) (PCL) and poly(lactide) (PLA) are produced on an industrial scale, their application in several instances is limited by the lack of pendent functional groups. For instance, polyesters with pendent cationic groups have great potential in making surfaces antibacterial and in gene therapy. Moreover, attachment of drugs or probes onto the chains of these potential biomaterials is also of great interest. Making these aliphatic polyesters hydrosoluble or amphiphilic is another highly desirable target.

Various ε-caprolactones susbstituted mainly in α and γ positions have been prepared and further ring-opened (co)polymerized by aluminium or tin alkoxides into functionalized aliphatic polyesters.[1] Nevertheless, many functional groups, *e.g.*, hydroxyl, carboxyl and epoxides, are not tolerated by the metal alkoxides involved in Ring-Opening Polymerization (ROP), and a protection/deprotection is needed, when possible. In order to bypass cumbersome protection/deprotection reactions, routes should be searched for the direct attachment of unprotected functions onto the aliphatic polyesters so making straightforward the derivatization of a unique precursor into materials with a wide range of properties.

Vert *et al.* reported on the treatment of PCL by lithium amides followed by reaction with an electrophile, *e.g.*, benzaldehyde, naphthoyl chloride, benzyl chloroformate and methyl iodide.[2] Nevertheless, chain degradation during formation of the polycarbanion is a problem. Recently, we reported on the Michaël addition of duly substituted thiols onto pendent acrylate groups of PCL.[3] However, this Michaël addition is not quantitative, and residual acrylic can cause undesired cross-linking. An alternative approach relies on the grafting of non-polymerizable terminal vinyl compounds onto pendent α-chloro substituents of PCL by Atom Transfer Radical Addition (ATRA).[4] Because this reaction is catalyzed by a non-negligible amount of copper bromide, the final aliphatic polyester is contaminated, which is detrimental to biomedical applications. Recently, Emrick *et al.* reported on the grafting of poly(ethylene oxide) (PEO) end capped by an azide group onto pendent acetylenic groups of PCL.[5] These copolymers turned out to be biocompatible.

To date, these strategies have been implemented for the chemical transformation of PCL, which is known to be less sensitive to degradation than PLA. Derivatization of PLA is indeed by far more delicate and, to the best of our knowledge, no satisfactory example has been reported until now. In this respect, chemical transformation by "click" reaction between alkynes and azides is very appealing because of quantitativeness. The aim of this paper is to show that various pendent functional groups, cationic or neutral, polymeric or not, can be attached onto azide containing aliphatic polyesters by "click" reactions of duly substituted alkynes. Our very first objective was to carry out the "click" reaction at low temperature, under non aqueous conditions for it to be applicable to aliphatic polyesters whatever their sensitivity to hydrolytic degradation. A model reaction of grafting of an ester onto PCL was used on purpose. The optimized reaction was then extended to the grafting of tertiary amine, and ammonium salt. Then, this technique was used to prepare amphiphilic aliphatic polyesters bearing both PEO grafts and cationic ammonium groups, never reported until now. Finally, derivatization of PLA by "click" chemistry was successfully carried out.

Our strategy relies on the synthesis of copolyesters bearing α-azide substituents by two different routes based on α-chloro-ε-caprolactone (αClεCL), a monomer very easily prepared by the Baeyer–Villiger oxidation of α-chloro-cyclohexanone, as reported elsewhere (Fig. 1).[6] ROP of αClεCL and εCL mixtures can be initiated by 2,2-dibutyl-2-stanna-1,3-dioxepane (DSDOP) with formation of poly(αClεCL-*co*-εCL) random copolymers, which are then derivatized into poly(αN_3εCL-*co*-εCL) random copolymers by reaction with sodium azide in DMF (room temperature, overnight). This sequence of reactions can however be reversed. Indeed, αClεCL can be reacted with NaN_3 (45 °C, 3 days) and the accordingly formed αN_3εCL monomer can be further copolymerized with εCL by DSDOP into poly(αN_3εCL-*co*-εCL). Synthesis and detailed characterization of these copolymers are beyond the scope of this communication and will be reported in a forthcoming paper. It must be noted that the chloride conversion into azide goes to completeness and that the pendent azide groups are easily identified by IR absorption at 2106 cm^{-1} and by a ^1H NMR chemical shift at 3.8 ppm (CO–C*H*N_3–CH_2–).

Center for Education and Research on Macromolecules, University of Liège, B6a Sart-Tilman, Liège, B-4000, Belgium.
E-mail: rjerome@ulg.ac.be; Fax: (32) 4-3663497; Tel: (32) 4 3663461

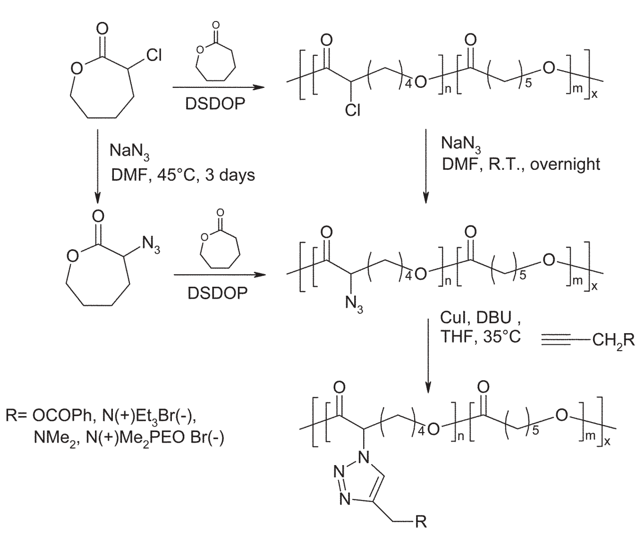

Fig. 1 Derivatization of PCL by combining ROP and "click" chemistry.

In their pioneering work, Emrick *et al.* reported on the grafting of azide end-capped PEO and peptide onto PCL bearing pendent alkyne groups,[5] in the presence of $CuSO_4$ and sodium ascorbate in water at 80 °C, for several hours. Nevertheless, in our hands, when poly(α$\mathrm{N_3}$εCL-*co*-εCL) ($M_{n,SEC}$ = 18 000; M_w/M_n = 1.5, 30 mol% of pendent azide groups) was treated for 4 h, the SEC trace turned bimodal [M_n^1 = 7500 (for the first population); M_n^2 = 1450 (for the second population)], which is the signature of significant intramolecular transesterification (Fig. 2, trace a). So, we addressed the question to know whether the "click" reaction could be carried out in the absence of water and at low temperature (35 °C), in order to restrict the hydrolytic degradation as much as possible. In a model experiment, the efficiency of the "click" reaction was investigated by grafting propargyl benzoate, as a model compound, onto poly(α$\mathrm{N_3}$εCL-*co*-εCL), in THF at 35 °C. Thus, a copolymer containing 30 mol% of α$\mathrm{N_3}$εCL ($M_{n,SEC}$ = 18 000, M_w/M_n = 1.4) units was reacted under these conditions, with 1.2 eq. of propargyl benzoate in the presence of CuI and diazobicyclo[5.4.0]undec-7-ene (DBU) (0.1 eq., each with respect to the α-azide units). The reaction was monitored by IR spectrospcopy. After 2 h, the absorption at 2106 cm^{-1} typical of the azide groups disappeared completely and a new absorption appeared at 1650 and 1611 cm^{-1}, typical of triazoline. Thus, the "click" reaction took place efficiently and was completed within 2 h. The copolymer was then collected by precipitation into methanol for further analysis. The ^{1}H NMR analysis clearly indicated the disappearance of the peak at 3.8 ppm assigned to CO–C*H*N_3–CH_2– and the appearance of a new set of peaks at 8.0, 7.5, 7.4 ppm (–O–CO–C_6H_5), 7.9 ppm (H of triazoline) and 4.2 ppm ($PhCO_2$–CH_2–O–triazoline). The completeness of the reaction was thus confirmed under the mild non-aqueous conditions used. Moreover, $M_{n,SEC}$ (20 000) remained close to the original value, although one may not preclude that the hydrodynamic volume of the chains was modified by the grafting of propargyl benzoate. Nevertheless, symmetry and broadness of the molecular weight distribution remained unchanged. These observations are strong indications that the polyester was not degraded significantly during the "click" reaction. In order to confirm the lack of degradation, poly(α$\mathrm{N_3}$εCL-*co*-εCL) ($M_{n,SEC}$ = 15 000; M_w/M_n = 1, 5, 30 mol% of pendent azide groups) was treated under the same experimental conditions (THF, 35 °C, 0.1 eq. CuI, 0.1 eq. DBU) but in the absence of propargyl benzoate. After 4 h, $M_{n,SEC}$ = 15 000 and M_w/M_n = 1.5 remained strictly identical (Fig. 2, trace b). As a conclusion, the grafting onto PCL by "click" reaction is quantitative in the absence of water and at low temperature (35 °C), conditions are by far less degrading than the ones reported by Emrick. *et al.*

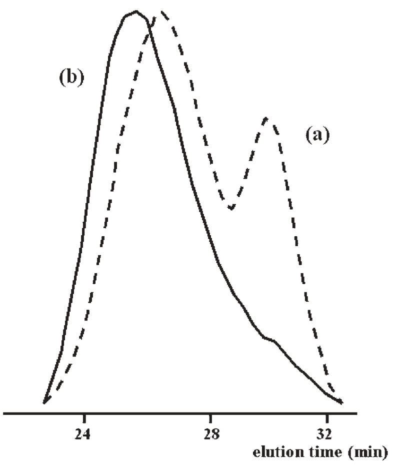

Fig. 2 SEC traces of poly(α$\mathrm{N_3}$εCL-*co*-εCL) after 4 h (a) under Emrick's conditions (water, 80 °C), (b) under our conditions (THF, 35 °C).

In order to extend the range of the grafted functional groups, other alkynes were used in the "click" reaction, *e.g.*, 3-dimethylamino-1-propyne and *N,N,N*-triethylpropargyl ammonium bromide. In all the cases, progress was monitored by IR spectroscopy until the complete disappearance of the absorption of the azide groups at 2106 cm^{-1}. In parallel, the intensity of the IR absorption at 1650 cm^{-1} of triazoline increased. Completeness of the grafting reactions was confirmed by ^{1}H NMR, *i.e.*, the complete disappearance of the peak at 3.8 ppm (CO–C*H*N_3–CH_2–) and the appearance of a new peak assigned to the proton of the triazoline ring. The click strategy is thus an effective tool to modify deeply the properties of the aliphatic polyesters. Water-solubility results from the grafting of *N,N,N*-triethylpropargyl ammonium bromide, and so also might antibacterial properties.[7]

The "click" reaction was extended to the grafting of PEO bearing a *N,N*-dimethylpropargylammonium end-group onto poly(α$\mathrm{N_3}$εCL-*co*-εCL) ($M_{n,SEC}$ = 18 000 containing 30 mol% of α$\mathrm{N_3}$εCL) in THF at 35 °C. After 12 h of reaction, the IR absorption at 2106 cm^{-1} disappeared although not completely. The excess was eliminated by dialysis against water. No proton of terminal alkyne units was observed by ^{1}H NMR (2.85 ppm) of the purified copolymer, whereas the resonance typical of the triazoline units at 7.6 ppm was observed. Composition was calculated from the integrals of the peaks at 4.0 ppm (O-CH_2 of PCL units) and 3.6 ppm (O-CH_2 of PEO units). PCL chains were actually grafted by 10 PEO chains of M_n = 1400. The amphiphilic graft copolymer forms micelles in water, that were analyzed by transmission electron microscopy (TEM) (Fig. 3). It must be noted that the PEO grafts are end-capped by an hydroxyl group, which is available to further attachment of probes or biologically active molecules. Compared to neutral PCL-g-PEO, these PCL-g-PEO chains that contain cationic ammonium groups have the potential

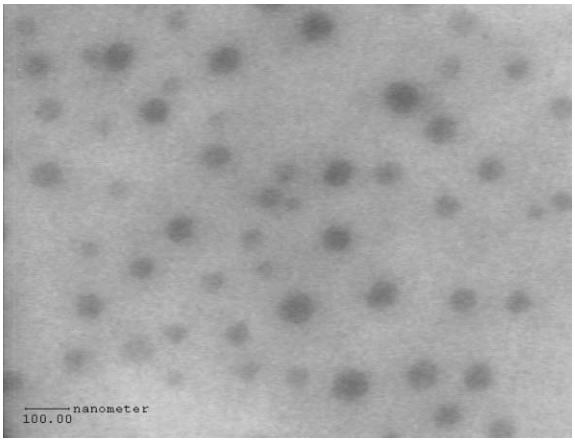

Fig. 3 TEM picture of poly(CL-g-EO) micelles.

to stabilize polyester nanoparticles by electrosteric repulsion, which is under current investigation.

Finally, the non aqueous conditions for the "click" reaction have used in case of PLA. Poly(αN_3εCL-*co*-DL-LA) was prepared by ring-opening copolymerization of αClεCL and DL-LA, followed by reaction with sodium azide (DMF, RT, overnight) as reported for PCL. In order to know whether poly(αN_3εCL-*co*-DL-LA) is degraded under the conditions used for the "click" reaction, this copolymer ($M_{n,SEC}$ = 12 000; M_w/M_n = 1.4, 30 mol% of pendent azide groups) was treated at 35 °C in THF in the presence of 0.1 eq. CuI, 0.1 eq. DBU and 1.2 eq. propargyl benzoate. After 4 h, an important degradation was noted, as shown by the bimodal distribution of the SEC trace (M_n^1 = 6700 (first population); M_n^2 = 1400 (second population)) (Fig. 4, trace b). Because the two hydroxyl end-groups of poly(αN_3εCL-*co*-DL-LA) could be at the origin of backbiting reactions, they were esterified by acetyl chloride ($M_{n,SEC}$ = 11 000; M_w/M_n = 1.3, 30 mol% of pendent azide groups) (Fig. 4, trace a). The same "click" reaction was repeated, and degradation was much less important after 4 h. Finally, substitution of less basic triethylamine (NEt_3) for DBU suppressed basically degradation ($M_{n,SEC}$ = 10 000; M_w/M_n = 1.4). Accordingly, poly(αN_3εCL-*co*-DL-LA) was reacted with propargyl benzoate in THF at 35 °C in the presence of 0.1 eq. of CuI and 0.1 eq. of Et_3N. The "click" reaction proceeded quantitatively as supported by the complete disappearance of both the IR absorption at 2206 cm^{-1} and the ^1H NMR peak at 3.8 ppm typical of the $–CHN_3–$ units. Moreover, the ^1H NMR peak typical of the triazoline unit appeared at 7.9 ppm. The SEC trace ($M_{n,SEC}$ = 12 000; M_w/M_n = 1.6) remained monomodal and no cyclic oligomers was detected (Fig. 4, trace c).

Finally, α-MeO,ω-alkyne-PEO ($M_{n,NMR}$ = 800) was successfully grafted onto poly(αN_3εCL-*co*-DL-LA). The ^1H NMR peak typical of triazoline was reported at 7.55 ppm. The comparison of the integrals of the peaks associated to PLA and triazoline units indicated that the final copolymer contained 3 grafts. Again, no apparent degradation was noted consistent with the symmetrical SEC trace ($M_{n,SEC}$ = 14 000; M_w/M_n = 1.4). For the first time, PLA-g-PEO has been made available by combining ROP and "click" chemistry.

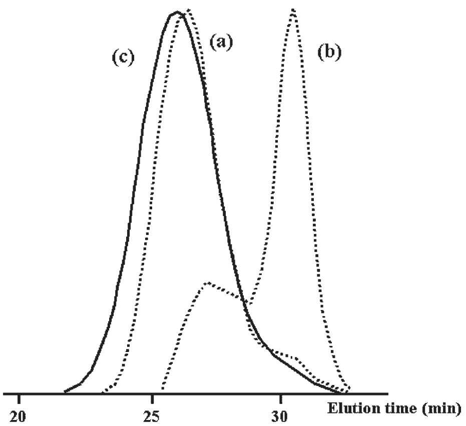

Fig. 4 SEC traces of PLA copolymers: (a) Poly(αN_3εCL-*co*-DL-LA); after "click" by propargyl benzoate (b) unprotected OH groups, in the presence of DBU (c) protected OH groups, in the presence of NEt_3.

Derivatization of aliphatic polyesters by "click" reactions under very mild conditions allows the grafting of a wide range of functional groups, cationic, anionic or neutral, polymeric or not onto PCL without any protection/deprotection reactions. Moreover, an example of derivatization of unstable PLA by "click" chemistry is reported for the first time. The potential of the novel polyesters prepared in this work will be assessed in biomedical applications, *e.g.*, in drug delivery applications and gene therapy.

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