Versatile functionalization and grafting of poly(ε-caprolactone) by Michael-type addition

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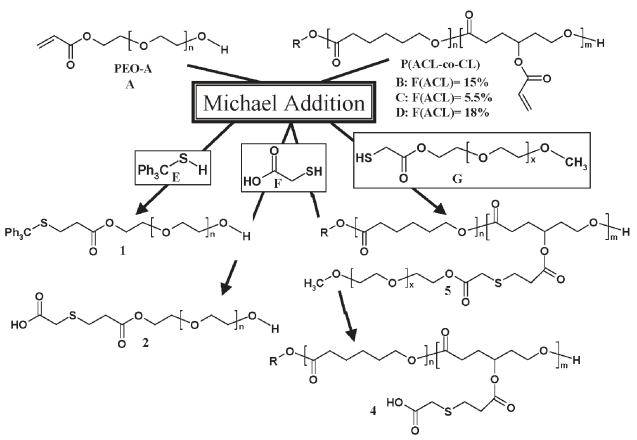
The Michael-type addition of aliphatic (co)polyesters onto γ-acryloyloxy ε-caprolactone units is a very straightforward technique of functionalization and grafting, which is tolerant to a variety of functional groups and does not require intermediate protection/deprotection steps.

Aliphatic polyesters, such as poly(ε-caprolactone) (PCL), have great potential as biomaterials due to a unique combination of biodegradability and biocompatibility. Attaching reactive groups or hydrophilic grafts along these preformed backbones is usually a problem because of the sensitivity of the ester units to nucleophilic attack followed by chain degradation. One strategy to tackle this problem consists of the synthesis of γ-substituted ε-caprolactones and copolymerization with ε-caprolactone. Bromide, activated bromide, (protected) carbonyl, protected hydroxyl and carboxyl groups, and acryloyloxy groups are examples of γ substituents that have been reported.[1–3] Polymerization and copolymerization of these γ-substituted ε-caprolactones are living and permit long chains to be prepared because the γ-substitution does not perturb the reactivity of the cyclic monomer.[1–3] The major drawback of this method is that any protic function reactive towards the metal alkoxides used in (co)polymerization must be protected and that the deprotection has to be carried out under mild conditions. For these specific cases, a more direct functionalization technique is highly desirable.

In this paper, we report on the use of the Michael-type addition[4] to synthesize functional and/or amphiphilic poly(ε-caprolactone) (PCL). The characteristic features of this reaction are (i) occurrence under very mild conditions (preventing the polyester degradation), (ii) tolerance to a wide range of functional groups (avoiding protection/deprotection steps), (iii) no need for metallic catalyst, and thus no contamination that could be a problem for biomedical applications. The easy synthesis and living (co)polymerization of γ-acryloyloxy-ε-caprolactone (ACL) makes it easy to have double bonds distributed along polyester backbones of different architectures[5] and enable Michael-type addition. The addition of thiol derivatives to pendent acrylate groups has been investigated in this paper, as a versatile method of functionalization and grafting of PCL with the advantage of high reactivity and chemoselectivity of the reactants.[6]

The Michael-type addition was first tested with commercially available poly(ethylene oxide) end-capped by an α-hydroxy group and an ω-acrylate group, respectively (PEO-A, M_n = 375 g mol^{-1}, from Aldrich) (Scheme 1, **A**). This preliminary reaction was aimed at optimizing the reaction conditions for the grafting of thiols before being extended to pendent acrylate containing poly(ε-caprolactone) (Scheme 1). The experimental data are reported in Table 1.†

Triphenylmethanethiol (Scheme 1, **E**) was considered first because its strong UV absorption makes quantification of the grafting efficiency quite easy. The reaction was carried out in toluene (a good solvent for poly(ε-caprolactone) that will be used further) at room temperature under nitrogen and in the dark. The effect of three catalysts (Table 1, entries **1**a–c) was compared. Finally, poly(ε-caprolactone) was added to the reaction medium in order to assess its stability under these conditions (GPC analysis before and after reaction). The Michael addition was systematically complete within 5 h (Table 1, entries **1**a–c), and no degradation of PCL was observed whatever the catalyst. Pyridine was selected as a catalyst for the addition of mercaptoacetic acid (Scheme 1, **F**) (Table 1, entries **2**a–e). The reaction was then much slower with only 40% yield after 100 h (Table 1, entry **2**b) even if an excess of thiol (1.5 equiv.) and catalyst (2 equiv.) was used. The higher reactivity of the triphenylmethanethiol might be accounted for by the three phenyl substituents that increase the nucleophilicity and thus the reactivity of this thiol derivative. However, conversion of the acrylate end-group of PEO-A into a carboxylic acid group is quantitative after 75 h in a more polar solvent, such as THF (Table 1, entries **2**c–e) with a large excess of reactant (Table 1, entry **2**e). Once again, PCL that was added to the reaction medium is recovered without any degradation. Similarly, the unprotected hydroxyl end-group of PEO-A remains unmodified, as assessed by ^{1}H-NMR analysis of the reacted PEO-A (spectrum not shown). This reaction is thus a straightforward efficient pathway for



Scheme 1

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Table 1

Entry	Acrylic derivatives[a] (equiv.)	R–SH[a] (equiv.)	Solvent	Catalyst (equiv.)	Reaction time/h	Reaction yield (%)
1a	**A** (1)	**E** (0.5)	Toluene	TBAF (1)	5	100
1b	**A** (1)	**E** (1)	Toluene	NEt_3 (1)	5	100
1c	**A** (1)	**E** (1)	Toluene	Pyridine (1)	5	100
2a	**A** (1)	**F** (1.5)	Toluene	Pyridine (2)	20	<10
2b	**A** (1)	**F** (1.5)	Toluene	Pyridine (2)	100	40
2c	**A** (1)	**F** (10)	THF	Pyridine (15)	30	50
2d	**A** (1)	**F** (10)	THF	Pyridine (15)	50	80
2e	**A** (1)	**F** (10)	THF	Pyridine (15)	75	100
3a	**A** (1)	**G** (20)	THF	Pyridine (25)	25	60
3b	**A** (1)	**G** (20)	THF	Pyridine (25)	60	80
4a	**B** (1)	**F** (10)	THF	Pyridine (15)	30	25
4b	**B** (1)	**F** (10)	THF	Pyridine (15)	50	40
4c	**B** (1)	**F** (10)	THF	Pyridine (15)	75	70
5a	**C** (1)	**G** (10)	THF	Pyridine (15)	80	25
5b	**C** (1)	**G** (10)	THF	Pyridine (15)	150	35
5c	**C** (1)	**G** (10)	THF	Pyridine (15)	300	60
5d	**D** (1)	**G** (10)	THF	Pyridine (15)	80	30
5e	**D** (1)	**G** (10)	THF	Pyridine (15)	150	45
5f	**D** (1)	**G** (10)	THF	Pyridine (15)	300	65

[a] The letters refer to compounds shown in Scheme 1.

the synthesis of α-hydroxy-ω-carboxy-PEO, a macromonomer well-suited to polycondensation with low molecular weight hydroxy-acids.

Finally, an oligomeric thiol, α-methoxy-ω-mercapto-poly(ethylene oxide) (PEO-SH, Scheme 1, **G**), was added to PEO-A. This PEO-SH was synthesized by esterification of MeO-PEO-OH ($M_{n,NMR}$ = 900 g mol^{-1}) with mercaptoacetic acid in toluene in a Dean–Stark apparatus as reported elsewhere.[7] The yield of the Michael addition of PEO-A (**A**) and PEO-SH (**G**) was 80% after 60 h (Table 1, entries **3**a and b), which is quite comparable to the addition of mercaptoacetic acid to PEO-A (**A**).

Thus, under mild reaction conditions, high coupling yields of hydrophilic thiol derivatives (mercaptoacetic acid **F** and PEO-SH **G**) and PEO-acrylate are observed, whereas poly(ε-caprolactone) is not degraded at all. These experimental conditions have been extended to a random poly(ACL-co-CL) copolymer in order to make amphiphilic copolymers available (Scheme 1, **4** and **5**). Synthesis of γ-acryloyloxy-ε-caprolactone has been reported elsewhere,[5] as well as copolymerization with CL.[8] In this work, copolymers with various ACL content (5.5, 15 and 18 mol% ACL; Scheme 1, **B**, **C** and **D**) were reacted with the mercapto-derivative **F** (Table 1, entries **4**a–c) and PEO-SH (**G**) (Table 1, entries **5**a–f), the SH/acrylate and catalyst/acrylate molar ratios being 10 and 15, respectively. In the case of mercaptoacetic acid (**F**) (Table 1, entries **4**a–c), 70% of the pendent acrylates reacted after 75 h providing the hydrophobic polyester with hydrophilicity and water solubility. A comparable grafting efficiency is observed for PEO-SH, but after 300 h (Table 1, entry **5**f). As expected, the size of the hydrophilic thiol (**F** *versus* **G**) clearly has an effect on the kinetics of addition onto the hydrophobic polyester backbone, the reaction between two polymeric partners being unfavourable. Indeed, in the case of graft copolymers, steric hindrance of the first grafts limit further addition. The reaction is then incomplete.

Fig. 1 shows the ^{1}H-NMR spectra for P(ACL-co-CL) (Scheme 1, **D**) (M_n = 24 000, $F_{ACL,H-NMR}$ = 18%) before (Fig. 1a) and after reaction (Fig. 1b) with PEO-SH ($M_{n,H-NMR}$ = 900 g mol^{-1}).

The PCL-g-PEO comb-like copolymer was purified by precipitation in water, followed by dialysis against water and recovery by ultracentrifugation. The methylene protons (**x** and **y**, see Fig. 1b) adjacent to the sulfur atom are observed at 2.6 ppm (proton **y**) and 2.9 ppm (proton **x**). Moreover, the intensity of the acryloyloxy protons (5.8–6.4 ppm) is much lower. From the relative intensity of the protons **x** and **e** + **e**′, the copolymer composition was calculated. As an average, one PEO graft is attached to PCL every 10 units ($PCL_{0.9}$-g-$PEO_{0.1}$).

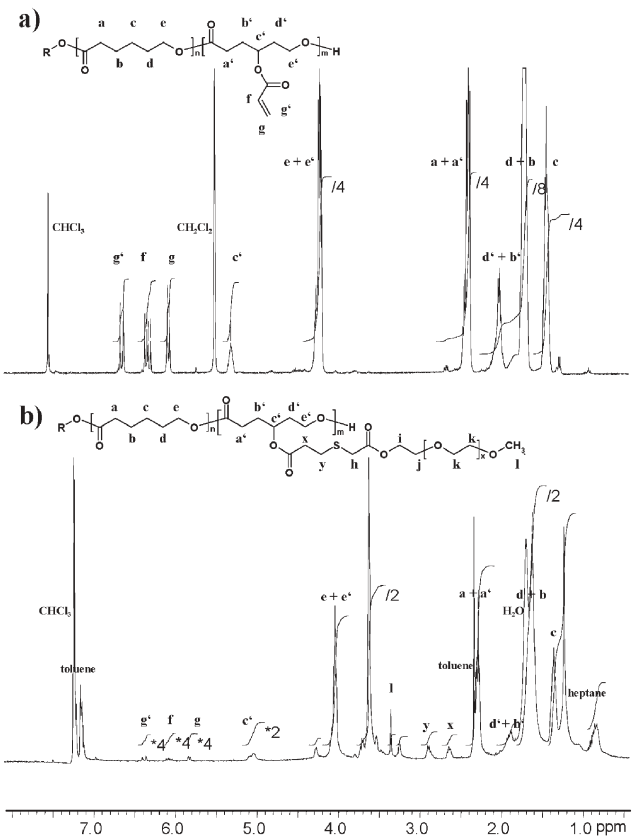

Fig. 1 ^{1}H-NMR spectra for P(ACL-co-CL), $F_{ACL,H-NMR}$ = 18%, a) before, b) after reaction with PEO-SH (Table 1, **5**f).

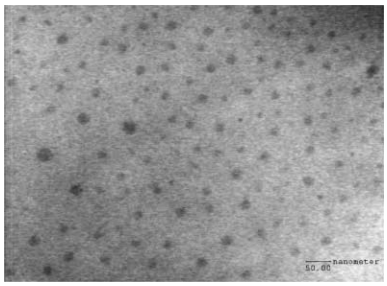

Fig. 2 TEM picture of PCL-g-PEO self-assembled in water (**5**f).

Success of the grafting was confirmed by TEM observation of the copolymer self-associated in water. When one drop of an aqueous solution was evaporated on a TEM grid, micelles with an average diameter of 20 nm were observed, as shown in Fig. 2.

These preliminary experiments have shown that the Michael-type addition is a straightforward, effective and versatile reaction for the functionalization and grafting of PACL and copolymers, so making an originally biodegradable and biocompatible polyester reactive and amphiphilic. The incompleteness of the reaction with PEO-SH leads to few remaining pendant acrylic functions on the graft copolymers that can be reacted further with small size thiols to avoid cross-linking and bring additional functionality. Tolerance of the Michael addition to urea or protic functions, such as carboxylic acid and alcohol, should be noted. This allows the grafting of α-biotinylated-ω-mercapto PEO onto PCL and ultimately the targeting of specific organs based on biotin–avidin complexation.[9] Similarly, the α-hydroxy group of the grafted ω-mercapto-PEO could be used to attach molecules with biological activity, *e.g.*, in diagnostics, sensoring devices, *etc.*

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Notes and references

† The kinetics of the Michael addition were monitored by ^{1}H-NMR analysis of protons characteristic of the addition products (**x** and **y** at 2.2–3.0 ppm) and protons of the reacting acryloyloxy groups (5.8–6.4 ppm). After reaction and before analysis, the copolyesters were purified by dialysis against water in order to eliminate any excess of the thiol compounds.

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