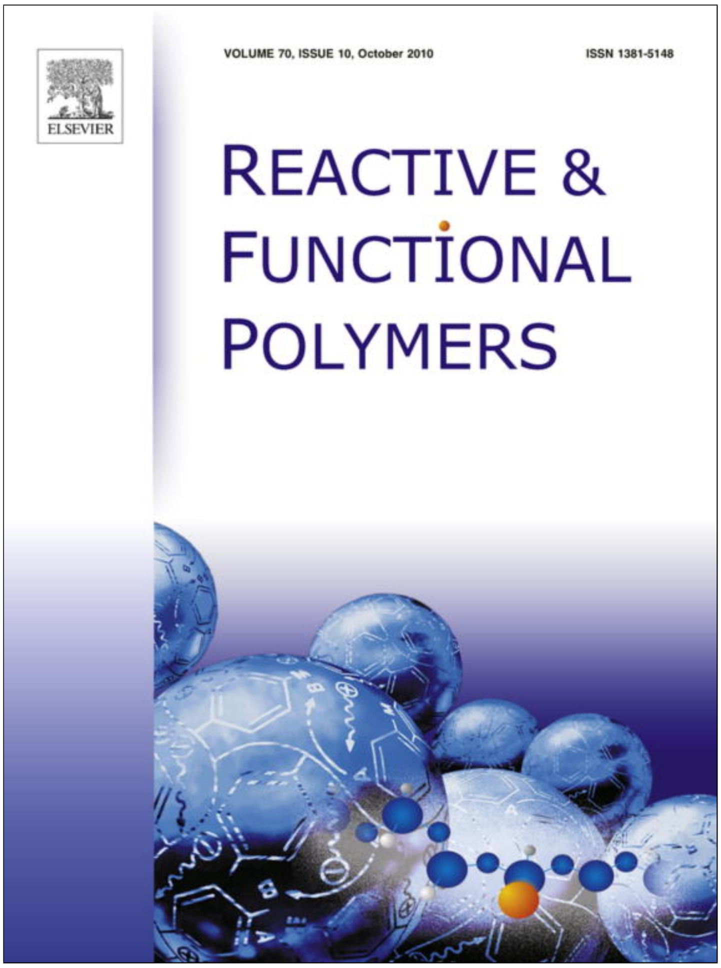
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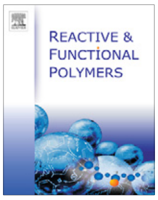

Synthesis of brush-like copolymers using carbohydrates as initiators: Benefits of organic catalysts for the ROP of lactones

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ABSTRACT

New brush-like copolymers have been synthesized using functional polymethacrylate backbones bearing pendant sugars. Ring-opening polymerization (ROP) of L-lactide and ε-caprolactone have been performed using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) carbohydrate residues on the polymethacrylate chains. The latter have been first synthesized by copolymerization of three methacrylate monomers including methyl methacrylate (MMA), α-methoxy, ω-methacrylate poly(ethylene oxide) (MAPEO), and 1,2:3,4-di-O-isopropylidene-6-O-methacryloyl-D-galactopyranose (MAIGP) by atom transfer radical polymerization (ATRP) in toluene at 80 °C using CuBr ligated with 1,1,4,7,10,10 hexamethyltriethylenetetramine (HMTETA) as catalytic complex. The protected sugars have been selectively deprotected using an aqueous solution of formic acid. The molecular characterization of those copolymers was performed by ^{1}H-NMR spectroscopy, FT-IR spectroscopy and gel permeation chromatography (GPC) analysis.

1. Experimental

Materials: ε-Caprolactone (CL, from Acros, 99%) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. L-Lactide (from Galactic, 99%) has been recrystallized three times from toluene and stored under nitrogen. Dibutyl tin dimethoxide ($Bu_2Sn(OMe)_2$) has been distilled under vacuum, diluted in dry toluene and stored in glass ampoules. Triethyl aluminum ($AlEt_3$) in solution in toluene (25 wt.%) from Fluka, has been used as received, diluted in dry toluene and stored in glass ampoule. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been dried over BaO, distilled under vacuum and stored under nitrogen whereas 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) has been dissolved in dried THF and dried over BaO. The latter was filtered off and the solvent was removed to yield dried TBD stored under nitrogen. Methyl methacrylate (MMA, from Aldrich, 99%) and α-methoxy, ω-methacrylate poly(ethylene oxide) (MAPEO, $M_w = {\sim}480\ g\ mol^{-1}$ and $580\ g\ mol^{-1}$, from Aldrich) were purified by filtration on basic alumina and stored under nitrogen at −20 °C. 1,2:3,4-Di-O-isopropylidene-6-O-methacryloyl-D-galactopyranose (MAIGP) has been synthesized prior to use applying previously reported method [1]. Benzoic acid (from Acros, 99%), 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA, from Aldrich, 97%), formic acid (from Aldrich, 98%) and ethyl-2-bromoisobutyrate (E^iBBr, from Aldrich, 98%) were used as received. Copper bromide (CuBr, from Fluka, 98%) was purified in acetic acid for 24 h and recrystallized in ethanol under inert atmosphere until a white powder was obtained. Toluene (Labscan, 99%) was dried by refluxing over CaH_2 and distilled just before use. Dichloromethane (Chemlab, 99%) was dried over CaH_2 and distilled just before use Tetrahydrofuran (THF) (Labscan, 99%) was first dried over molecular sieves (4 Å) for 48 h, then over lithium polystyryl oligomers and distilled under reduced pressure just before use. Chloroform (Chemlab, 99%) has been dried on a solvent purification system MB SPS-800 from MBraun.

Synthesis of poly(methyl methacrylate-co-α-methoxy, ω-methacrylate poly(ethylene oxide)-co-1,2:3,4-di-O-isoproylidene-6-O-methacryloyl-D-galactopyranose) (P(MMA-co-MAPEO-co-MAIGP)). In a round bottomed flask A were introduced 0.089 g of copper bromide (CuBr, 0.62 mmol) and 0.286 g of 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA, 1.24 mmol). Three freezing/thawing cycles were performed to get rid of the trapped O_2. In a round bottomed flask B were introduced 0.125 g of ethyl-2-bromoisobutyrate (E^iBBr, 0.64 mmol), 1.913 g of 1,2:3,4-di-O-isopropylidene-6-O-methacryloyl-D-galactopyranose (MAIGP, 5.31 mmol), 3 ml of methyl methacrylate (MMA, 27.9 mmol), 12 ml of α-methoxy, ω-methacrylate poly(ethylene oxide) (MAPEO, 27.7 mmol) and 20 ml of toluene. Nitrogen was bubbled through the solution before transferring it into flask A. The polymerization has been led at 80 °C for 3 h then stopped in liquid nitrogen and the polymer was selectively recovered after precipitation in heptane, filtered

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and dried until constant weight at 40 °C. Yield = 81%. The copper catalyst was removed by passing the polymer solution in THF through a basic alumina column. The solvent was then evaporated to yield the pure polymer. ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 0.80–1.17 (m, 3 H, Hb), 1.23–1.56 (m, 12 H, Hj), 1.72–2.12 (m, 2 H, Ha), 3.37 (s, 3 H, Hn), 3.47–3.74 (m, 9 H, Hc + Hl + Hm), 4.00–4.36 (m, 7 H, Hi + Hh + Hg + He + Hk), 4.65 (s, 1 H, Hf), 5.53 (s, 1 H, Hd). M_n SEC = 37,700 g mol^{-1}. M_w/M_n = 1.4.

Synthesis of brush-like copolymers from ε-caprolactone ROP mediated by dibutyl tin(IV) dimethoxide ($Bu_2Sn(OMe)_2$). In a previously flamed and purged round bottom flask equipped with a three way stopcock and a rubber septum were introduced 1.5 g of macroinitiator (P(MMA-co-MAPEO-co-MAGP), M_n = 48,800 g mol^{-1}, 0.03 mmol, 2.17 mmol OH) previously dried by three successive azeotropic distillations with toluene. A solution of $Bu_2Sn(OMe)_2$ (0.09 M, 0.6 ml, 0.05 mmol) was then added and treated by a methanol elimination by two azeotropic distillations with toluene. THF (8 ml) and ε-caprolactone (2.4 ml, 21.7 mmol) were then successively added to the medium. The polymerization reaction proceeded at 25 °C during 3 h and stopped by addition of an acidic aqueous solution. The polymer was selectively precipitated in cold methanol, filtered and dried till constant weight at 40 °C. Yield = 25%.

Synthesis of brush-like copolymers from ε-caprolactone ROP mediated by triethylalumium ($AlEt_3$). In a previously flamed and purged round bottom flask equipped with a three way stopcock and a rubber septum were introduced 1.2 g of macroinitiator (P(MMA-co-MAPEO-co-MAGP, M_n = 48,800 g mol^{-1}, 0.025 mmol, 1.75 mmol OH) previously dried by three successive azeotropic distillations with toluene. Dried dichloromethane (14.6 ml) was then added and the solution was cooled down to −78 °C with a methanol/liquid nitrogen bath. A solution of $AlEt_3$ (0.2 ml, 0.175 mmol) was then added and the ethane release was allowed to evolved with an oil valve. After few minutes, and at −78 °C, the ε-caprolactone (2 ml, 18 mmol) was then added and the solution was allowed to warm up to r.t. The polymerization was allowed to proceed for 145 h and then stopped by adding HCl 1 M aqueous solution. The polymer was recovered by precipitation in heptane, filtered and dried till constant weight at 40 °C. Yield = 41%. Aluminum residues were removed by dissolving the copolymer in chloroform and extracted once with a Na_2EDTA solution and twice with deionized water.

Synthesis of brush-like copolymers using ROP of ε-caprolactone mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In a glovebox, a vial is charged with 0.5 g of macroinitiator (P(MMA-co-MAGP), M_n = 22,700 g mol^{-1}, 0.022 mmol, 0.755 mmol OH) previously dried by three successive azeotropic distillations with toluene. To the macroinitiator, were successively added chloroform (2.7 ml), CL (0.4 ml, 3.6 mmol) and DBU (5.8 mg, 0.038 mmol). The polymerization reaction proceeded at 25 °C during 3 h and was stopped by the addition of benzoic acid. The polymer was selectively precipitated in heptane, filtered and dried till constant weight at 40 °C. Yield = 17%. No characterization, see main text.

Synthesis of brush-like copolymers from L-lactide ROP mediated by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). In a glovebox, a vial is charged with 0.5 g of macroinitiator (P(MMA-co-MAGP), M_n = 22,700 g mol^{-1}, 0.022 mmol, 0.755 mmol OH) previously dried by three successive azeotropic distillations with toluene. To the macroinitiator, were successively added chloroform (2.7 ml), L-LA (0.54 g, 3.75 mmol) and TBD (0.052 g, 0.378 mmol). The polymerization reaction proceeded at 25 °C during 45 min and stopped by the addition of few milligrams of benzoic acid. The polymer was selectively precipitated in heptane, filtered and dried till constant weight at 40 °C. Yield = 99%. ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 0.88–1.03 (m, 3 H, Hb), 1.48–1.86 (m, 5 H, Hn + Ha), 3.32–3.48 (m, 6 H, Hc + Hf), 3.63 (m, 2 H, He), 4.07–4.32 (m, 5 H, Hd + Ho + Hl), 5.00–5.3 (m, 6 H, Hg + Hh + Hi + Hj + Hk + Hm). M_n SEC = 36,500 g mol^{-1}. M_w/M_n = 1.52.

General procedure for the selective removal of isopropylidene protective groups from sugar units. Copolymer (1 g) was dissolved in 50 ml of $HCOOH/H_2O$ (4:1 v/v) and the solution was stirred at room temperature for 48 h. Formic acid was then removed by dialysis against water using a pre-swollen membrane (Spectra/Por, molecular weight cutoff size, 3500D) during 48 h replacing water every four hours. Deprotected copolymer was finally recovered by freeze-drying. Yield = ~95%.

Characterizations: ^{1}H-NMR spectra were recorded using a Bruker AMX-300 apparatus at r.t. in $CDCl_3$ (30 mg/0.6 ml) except for deprotected galactose-based copolymers that were recorded in DMSO-d_6 (30 mg/0.6 ml). Size exclusion chromatography (SEC) was performed in THF at 35 °C using a Polymer Laboratories liquid chromatogram apparatus equipped with a PL-DG802 degasser, an isocratic HPLC pump LC 1120 (flow rate = 1 ml/min), a Marathon autosampler (loop volume = 200 μl, solution conc. = 1 mg/ml), a PL-DRI refractive index detector and three columns: a PL gel 10 μm guard column and two PL gel Mixed-B 10 μm columns (linear columns for separation of MW_{PS} ranging from 500 to 10^6 Da). Polystyrene or poly(methyl methacrylate) standards were used for calibration. FT-IR analysis was carried out with FT-IR spectra were recorded from 4000 to 700 cm^{-1} using a Bio-Rad Excalibur FT-IR spectrometer with a 0.2 cm^{-1} resolution. Spectra were recorded owing to a single reflection crystal system (Split Pea^{TM} from Harrick) and a DTGS detector.

2. Introduction

Since their discovery, amphiphilic copolymers have emerged to be of increasing interest due to their ability to form a wide variety of different supramolecular structures such as micelles, vesicles or bilayers [2–6]. Indeed, during the 50s, studies have highlighted their potential to self-assemble in a selective solvent, thermodynamically favorable for one segment and unfavorable for the other one(s) in terms of solubility [7,8]. The ability of amphiphilic copolymers forming organized nanostructures in aqueous medium has been deeply investigated, thus showing their high potential to be used as carriers and delivering systems for drugs of low solubility in the bloodstream. For this purpose, biomedical applications require a restricted choice of biocompatible polymers. For instance, aliphatic polyesters like poly(ε-caprolactone) or poly(lactide) have been extensively used as hydrophobic core owing to their biocompatible and biodegradable properties while polyethylene oxide has been used as hydrophilic shell to avoid renal excretion and thus increasing the retention time in the bloodstream [9–13]. Complementary, glycopolymers have also attracted much attention in both medical and pharmaceutical fields since widely used in tissue engineering and controlled drug delivery [14,15].

As early as 1969 were already reported the synthesis and characterization of various copolymers containing 1,2:3,4-di-O-isopropylidene-D-galactopyranose (IGP) residues, as well as their deacetonation with aqueous formic acid yielding water-soluble glycopolymers [16]. In the 90's, controlled/"living" radical polymerization has allowed the synthesis of well-defined glycopolymers and amphiphilic block copolymers containing sugar residues from being accessible via various approaches, and more particularly by atom transfer radical polymerization (ATRP) of saccharide-carrying (meth)acrylate monomers conducted both in aqueous and low polarity organic solvents [17–21]. Recent advances in glycoscience have attracted renewed interest in designing well-defined sugar-based polymers with various controlled architectures. For instance, Wulff et al. reported the controlled synthesis of star-shaped amphiphilic poly(ε-caprolactone-b-galactopyranose methacrylate) block copolymers via ATRP [22]. Haddleton prepared amphiphilic block copolymers via metal-mediated controlled radical polymerization using a sugar-derived initiator, which not only form polymeric micelles in water but are also recognized by appropriate lectin [23]. Müller et al. reported on the controlled synthesis of randomly branched glycopolymers using self-condensing vinyl copolymerization of an inimer (i.e., 2-(2-bromopropionyloxy)ethyl acrylate) with isopropylidene-protected sugar-functionalized acrylate via ATRP [24]. Finally, a new route to form multiple morphologies such as spheres, "petal-like" spheres, rods and vesicles, was outlined using amphiphilic graft copolymers based on a short rigid chitooligosaccharide backbone and long hydrophobic poly(ε-caprolactone) grafts [25].

Herein we report on the controlled synthesis of hydrophilic glycopolymer chains via atom transfer radical copolymerization of functional methacrylates such as α-methoxy, ω-methacrylate poly(ethylene oxide) (MAPEO), methylmethacrylate (MMA) and 1,2:3,4-di-O-isopropylidene-6-O-methacryloyl-D-galactopyranose (MAIGP), followed by the deacetonation of protected sugar residues. The tentative initiation of ring-opening polymerization (ROP) of ε-caprolactone (CL) or L-lactide (L-LA) from the as-obtained hydroxyl pending groups is reported using various activators such as dibutyl tin(IV) dimethoxide ($Bu_2Sn(OMe)_2$), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). As emphasized by the Scheme 1, such a strategy gives access to brush-like amphiphilic glycopolymers grafted by poly(ε-caprolactone) hydrophobic segments and poly(ethylene oxide) side chains as hydrophilic counterpart.

3. Results and discussion

In a first step, sugar-based methacrylic monomers have been copolymerized by ATRP with α-methoxy, ω-methacrylate poly-(ethylene oxide) (MAPEO) ($M_n = \sim 480\ \text{g mol}^{-1}$ as determined by ^{1}H-NMR, $DP_{EO} \sim 9$) and methyl methacrylate (MMA). Methacrylate comonomers polymerization reactions were carried out in toluene at 80 °C using 2-ethylbromoisobutyrate (E^{i}BBr) as initiator and copper bromide (CuBr) ligated with 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) as catalytic complex. Polymers were prepared with a constant molar ratio of sugar monomer of 10% in order to get a good compromise between the ability to characterize the backbone in terms of composition and a reasonable amount of initiation sites for the subsequent lactone ROP taking into account that four hydroxyl groups per sugar moiety will be made available after deprotection. Moreover, overall ratios of 95/1/1/2 and 200/1/1/2, respectively, in monomer/E^{i}BBr/CuBr/HMTETA were chosen while in the case of terpolymers, equimolar molar ratio of MMA and MAPEO was kept constant (45% each). Table 1 summarizes the results obtained for the two polymethacrylate terpolymers. It is worth pointing out that monomer conversions could be readily determined by simply weighing the samples as recovered by selective precipitation in n-heptane. Indeed, no trace of residual monomer or macromonomer (MAPEO) remained in the precipitated samples as evidenced by ^{1}H-NMR spectra, *i.e.*, by the absence of the twin singlets at 5.6 and 6.1 ppm characteristic of the methacrylate group. Conversion could thus be calculated as follows: $\text{Conv.} = (M_{rec} - M_{ini} - M_{cata})/(\Sigma\ M_{comonomers}) \times 100$ where $M_{rec,}$ M_{ini}, M_{cata} are the masses of the precipitated copolymer, initiator and catalytic complex, respectively.

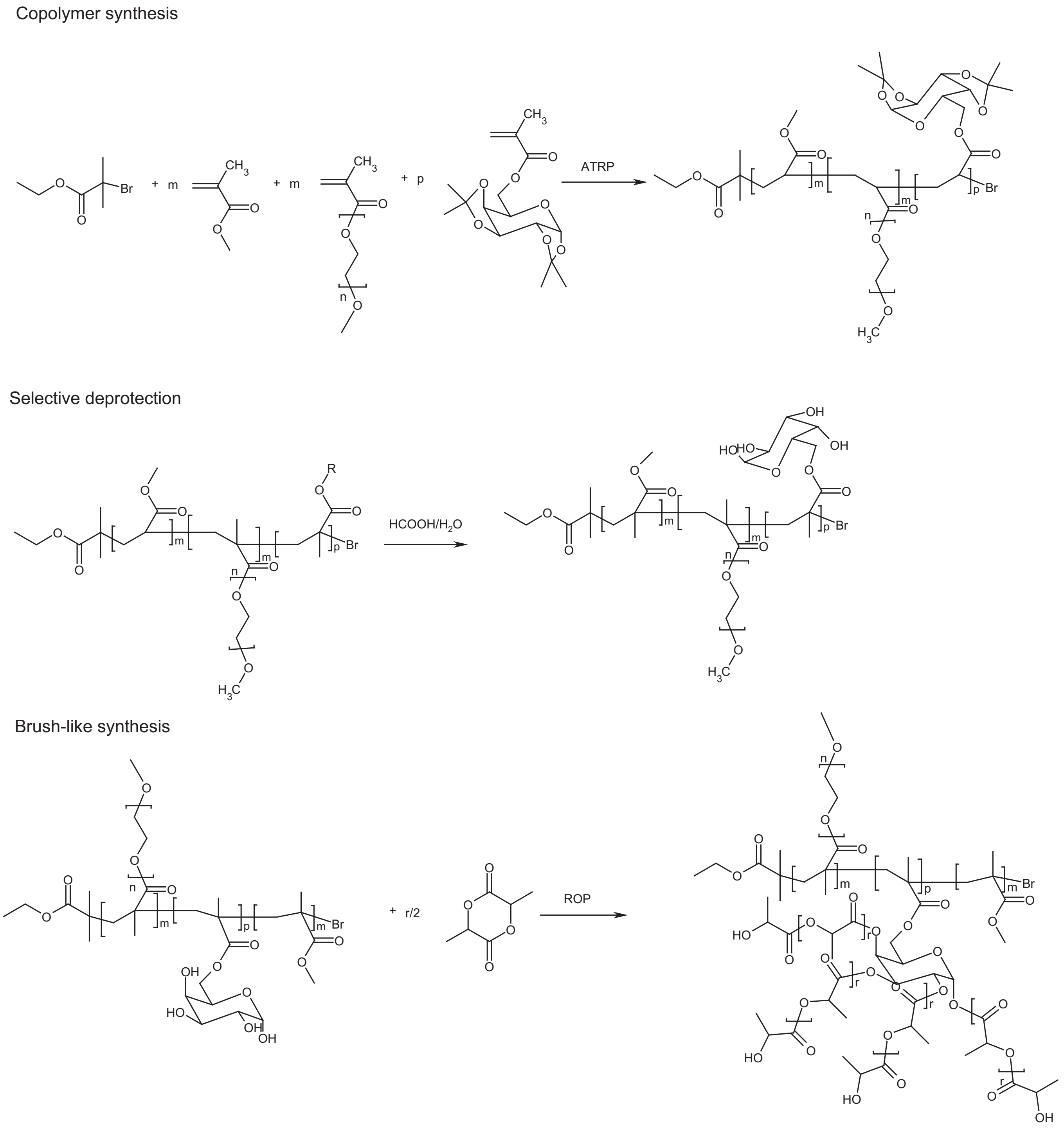
Besides, the MAIGP molar fraction (f_{MAIGP}) has been estimated by ^{1}H-NMR spectroscopy. Fig. 1 shows the ^{1}H-NMR spectrum of a P(MMA-co-MAIGP-co-MAPEO) terpolymer (entry 2, Table 1) for which estimation of f_{MAIGP} requires to compare the intensities of the anomeric proton of protected galactopyranose at 5.55 ppm (H_d) and protons H_b corresponding to repeating methyl groups on the methacrylate backbone. Accordingly, f_{MAIGP} was calculated as follows: $f_{MAIGP} = I_d/[(I_b)/3]$. Similarly, molar fraction of MAPEO (f_{MAPEO}) in the terpolymer can be determined by the following relation: $f_{MAPEO} = I_n/I_b$ where H_n denotes the protons of the methoxy end-group of MAPEO. Regarding the calculated molar fractions values (f), a very good correlation is found for both f_{sugar} and f_{MAPEO} referring initial molar fractions involved in the reaction (F). This ensures the incorporation of a correct amount of PEO chains for the hydrophilicity of the expected amphiphilic copolymers as well as the right amount of sugars for the following ROP process (Section 3). Note that a f_{MAPEO} of 46% corresponds to a weight fraction close to 74%.

Finally, monomodal and quite low molecular weight distributions are reached with polydispersity indices around 1.4 for elevated conversions, which is particularly interesting for high molecular weights methacrylate macromonomers such as MAPEO and MAIGP. These results all confirm the control achieved over the radical polymerization in agreement with the "persistent radical" effect taking place in ATRP. Moreover, it seems that both MAIGP and MAIMF behave as conventional alkyl methacrylate monomers [26].

The hydrolysis of protective isopropylidene groups in the aforementioned leading to poly(methyl methacrylate-co-α-methoxy, ω-methacrylate poly(ethylene oxide)-co-6-O-methacryloyl-D-galactopyranose) (P(MMA-co-MAPEO-co-MAGP) terpolymers has been performed by treating the samples with 80% formic acid aqueous solution at room temperature for 48 h according to a previously described procedure [27]. After dialyses against water and freeze-drying, the final products were obtained as a white powder or a gummy solid in an almost quantitative yield (yield ~95%). ^{1}H-NMR spectra recorded in DMSO-d$_6$ all show the complete disappearance of isopropylidene protons initially centered at 1.3 ppm together with the upfield shift of protons in α position of hydroxyl functions (see Fig. S1 in Supporting Information). Moreover no residual formic acid could be detected. The deprotected terpolymers were also analyzed by FT-IR confirming the appearance of a strong absorbance band centered at $\sim 3400\ \text{cm}^{-1}$ assignable to the OH groups of sugar units (Fig. S2). Finally, the presence of the ester carbonyl peak (ν C=O ester $\sim 1725\ \text{cm}^{-1}$) and the absence of OH group from carboxylic acid functions give additional evidence for the selectivity of the reaction and, as a matter of fact, the resistance of the methacrylate ester functions towards hydrolysis reaction in the aforementioned experimental conditions.

The fourth and last step leading to the synthesis of the amphiphilic brush-like copolymers relies upon the ring-opening polymerization (ROP) of dilactones (ε-caprolactone and L-lactide) from the hydroxyl groups of pending sugar moieties all along the main backbone (see Scheme 1). These multifunctional saccharides are D-galactopyranose-type, which has four secondary hydroxyl groups and presenting its anomeric alcohol able to undergo mutarotation in the presence of water. As far as the catalysis is concerned, various promoters well known to polymerize lactones in a controlled manner have been studied here. They include tin (IV) alkoxides, aluminum alkoxides and selected organic catalysts, i.e., amidine and guanidine.

Among organo-metallic catalysts, tin (II), tin (IV) and aluminum-based catalysts are known to be of particular interest regarding the polymerization of ε-caprolactone and L-lactide monomers. In particular, tin(II) bis-(2-ethylhexanoate) also named tin octoate ($Sn(Oct)_2$), proved to behave as a powerful catalyst as already reported [28–30]. Besides, in catalytic amount ($0.02 \leqslant [Sn(Oct)_2]/[OH] \leqslant 0.05$) $Sn(Oct)_2$ has allowed the ROP of ε-caprolactone in toluene from partially silylated dextran thanks to a much faster exchange between the dextran OH groups (remaining not protected) and the in situ generated stannous alkoxides with respect to propagation [31]. Nevertheless, tin octoate did not show



Scheme 1. General synthetic route to access brush-like architecture where *R* represents 1,2:3,4-Di-O-isopropylidene-D-galactopyranose.

Table 1

Molecular characterizations of polymethacrylate terpolymers obtained by ATRP.

Entry	Targeted DP	Time (min)	Conv. (%)[a]	F_{sugar} (%)[b]	f_{sugar} (%)[b]	F_{MAPEO} (%)	f_{MAPEO} (%)[b]	M_{nth} (g mol^{-1})[c]	M_{napp} (g mol^{-1})[d]	M_w/M_n[d]
1	95	120	82	10	11	45	46	23,500	20,700	1.4
2	200	180	81	9	11	48	49	50,400	37,700	1.4

[a] As determined by gravimetry.

[b] F_{sugar} and F_{MAPEO} = initial molar fractions in MAIGP and MAPEO before polymerization, f_{sugar} and f_{MAPEO} = molar fraction in MAIGP or MAPEO, respectively, in the polymers as determined by ^{1}H-NMR (see text).

[c] $M_{nth} = M_{wEiBBr} + (DP_{targeted} \times conv. \times f_{MMA} \times M_{wMMA} + DP_{targeted} \times conv. \times f_{MAIGP} \times M_{wMAIGP} + DP_{targeted} \times conv. \times f_{MAPEO} \times Mw_{MAPEO})$ where Mw_{EiBBr}, Mw_{MMA}, Mw_{MAIGP} and Mw_{MAPEO} are the molecular weights of E^{i}BBr, MMA, MAIGP and MAPEO respectively.

[d] Apparent molar masses and polydispersities as determined by size exclusion chromatography (SEC) in THF at 35 °C using PMMA standards.

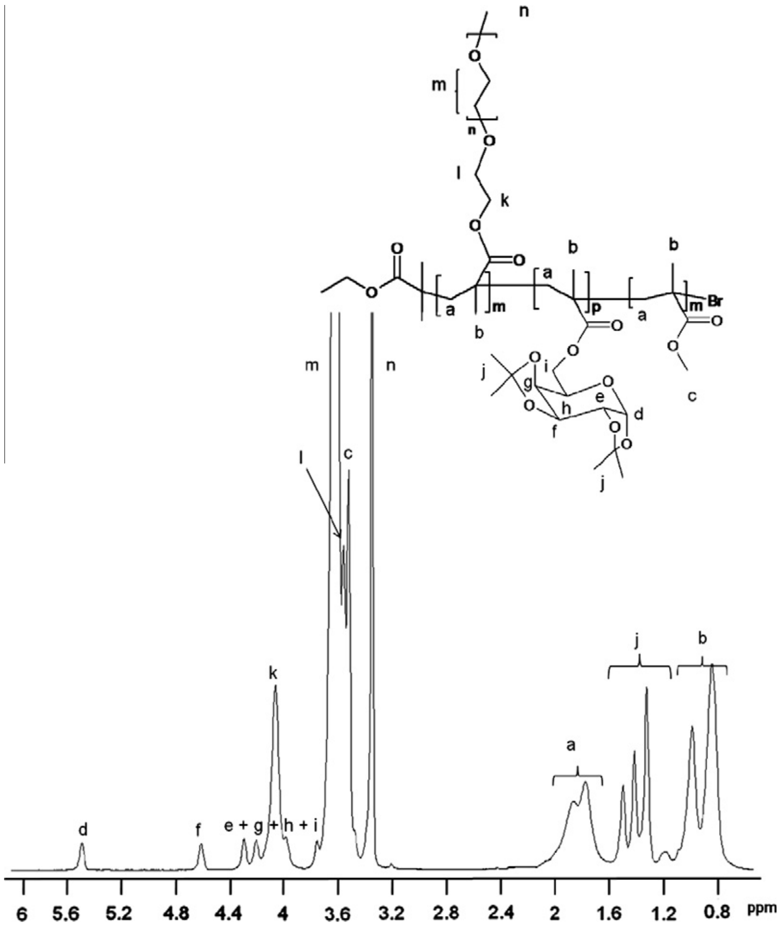
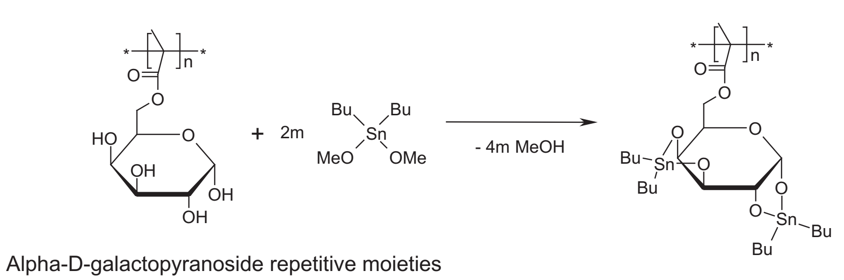


Fig. 1. ^{1}H-NMR spectrum of a P(MMA-co-MAIGP-co-MAPEO) terpolymer (entry 2 of Table 1) in $CDCl_3$.

any high efficiency for the present system as the D-galactose moieties were proved to undergo degradation at the working temperature of tin octoate, (i.e., 80 °C) as determined by thermogravimetric analysis (TGA) due to the presence of the reactive anomeric alcohol. Polymerizations in THF with such activator being particularly slow, the multihydroxylated initiator tends to undergo degradation before initiating the polymerization.

Therefore, dibutyltin dimethoxide ($Bu_2Sn(OMe)_2$) and triethyl aluminum have been studied thanks to the catalytic activity tin(IV) and aluminum-based alkoxides allow at room temperature. As far as dibutyltin dimethoxide is concerned, polymerizations of CL reached quantitative conversion after several hours depending on the initial monomer/catalyst molar ratio [32]. Kricheldorf et al. reported successful polymerizations of CL as initiated from several glycosides such as α-D-methyl glucopyranoside and β-D-methyl glucopyranoside [33]. At first, dibutyltin dimethoxide reacts with the four alcohol groups of the sugar ring yielding tricyclic dibutyl tin alkoxide derivatives upon methanol elimination. The resulting stable and isolable structures are thus composed of four tin alkoxide active groups on the sugar ring. Similarly we studied the polymerization of CL from α-galactose-based tricyclic dibutyltin alkoxide derivatives, thus pending along the polymethacrylate backbone (Scheme 2). Indeed, the choice of α-D-galactose seemed judicious as the formation of the tricyclic structure leads to less strained five-membered rings with apparent structure of diisopropylidene protected galactose. Besides, triethyl aluminum ($AlEt_3$) also proved of high efficiency as the reactive aluminum alkoxides may be generated by the reaction of alcohols with triethyl aluminum (after elimination of ethane as the byproduct). The use of triethyl aluminum has already been reported for the polymerization of lactones from partially silylated dextran [31].



Scheme 2. Synthesis of tricyclic dibutyltin alkoxide derivatives from pending D-galactose as multifunctional macroinitiators for ROP of CL.

Table 2
Molecular characteristics of the copolymers obtained via ROP of CL from deprotected P(MMA-co-MAPEO-co-MAIGP) (entry 2, Table 1) using $Bu_2Sn(OMe)_2$ or $Al(Et)_3$ as active species promoters.

Entry	Catalyst/activator	$[Catalyst]_0/[OH]_0$	$[CL]_0$ (mol L^{-1})	Time (h)	Yield (%)[a]	M_{napp} (g mol^{-1})[b]	M_w/M_n[b]	Comments
1	$Bu_2Sn(OMe)_2$	0.04	2	1	10	36,500	1.5	SEC bimodal
2	$Bu_2Sn(OMe)_2$	0.04	2	2	6	34,700	1.7	SEC bimodal
3	$Bu_2Sn(OMe)_2$	0.04	2	3	25	36,500	1.6	SEC bimodal
4	$Bu_2Sn(OMe)_2$	0.04	2	16	33	36,200	1.6	SEC bimodal
5	$AlEt_3$	0.1	2	/	/	/	/	Gelation
6	$AlEt_3$	0.25	2	/	/	/	/	Gelation
7	$AlEt_3$	0.1	1	145	41	15,100	5.2	SEC bimodal
8	$AlEt_3$	1.1	1	18	2	/	/	Gelation after 18 h

[a] As determined by gravimetry.
[b] Apparent molar masses as determined by size exclusion chromatography (SEC) in THF at 35 °C using PS standards.

As depicted in Table 2 (entries 1–4), no controlled ROP could be achieved with dibutyltin dimethoxide since size exclusion chromatography shows bimodal distributions for each sample. Unfortunately, initiation still seems to proceed heterogeneously, meaning that the tin alkoxide derivatives either suffer from a lack of activity or a too high steric hindrance around the alkoxide species, preventing monomer to access to the active sites.

As for aluminum-based, various initial $[Al]_0/[OH]_0$ molar ratios were investigated. For entries 5 and 6 in Table 2, the monomer concentration has been set to 2 M. However, gelation occurred either instantaneously at −78 °C or when reaching room temperature, thus preventing polymerization to proceed. This observation has been already achieved with partially silylated dextrans where triethyl aluminum reacted with more than a single alcohol to form intermolecular di- and trialkoxides leading to cross-linked and swelling networks [29]. Accordingly, the medium has been diluted to 1 M in CL. Catalytic to stoechiometric aluminum/alcohol ratios have been studied. At $[Al]_0/[OH]_0 = 0.1$, the polymerization proceeded very slowly with the formation of a viscous solution. Again, a bimodal chromatogram has been recorded by SEC with no evidence of significant PCL grafting onto the macroinitiator while the presence of a second peak at higher elution volume indicated the formation of free PCL in the sample. Finally, a stoechiometric amount of triethyl aluminum relative to the hydroxyl functions has been attempted in order to promote the formation of Al mono-alkoxides. As evidenced (entry 8, Table 2), gelation nevertheless occurred after 18 h resulting in a very low recovering yield (<5%). Although triethyl aluminum has been proven unable to promote the grafting of small PCL chains from the terpolymer backbones, its use has highlighted the availability of the hydroxyl functions attached on the pending sugar rings, by the crosslinking of the system upon $AlEt_3$ addition, meaning that other parameters, such as steric hindrance or alkoxide activity have to be taken into account.

Accordingly we attempted to promote the polymerization of CL (and L-LA) from the investigated multifunctional terpolymers, using amidine and guanidine based catalysts. Indeed, such “super base” catalysts have recently been reported as powerful structures for the ROP of CL and LA. The main advantage of TBD and DBU relies upon the fact that they act as bifunctionnal catalysts activating both monomers and alcohol initiator. Comparing to tin (II and IV) or aluminum-based catalysts, no covalent bonds are never formed between the hydroxyl groups and the organic catalysts avoiding then steric hindrance. In particular, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) are used depending on the monomer, the former is better suited for the polymerization of L-LA while TBD is preferred for CL at room temperature [34]. Three representative polymerization reactions (overall DP in lactones ~10) are listed in Table 3. Regarding the CL ROP, rather limited monomer conversions were determined even after 7 h at room temperature. As a result and even if the samples show PCL typical resonance peaks by ^{1}H-NMR, no significant shift to higher molecular weights is observed in size exclusion chromatography while keeping chromatograms monomodals

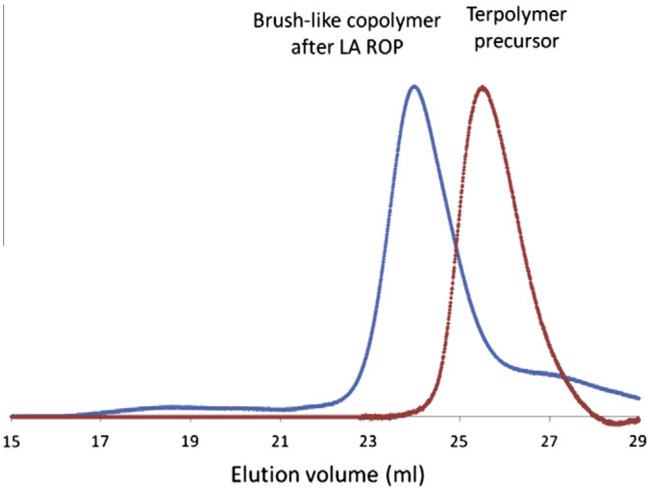


Fig. 2. GPC traces of P(MMA-co-MAPEO-co-MAGP) (red curve) and the brush-like copolymer after ROP of L-LA using DBU as catalyst (blue curve) (entry 3, Table 3). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Molecular characteristics of copolymers obtained after ROP of CL or L-LA from the deprotected P(MMA-co-MAPEO-co-MAIGP) (entry 2, Table 1) using either DBU or TBD as catalysts.

Entry	Monomer (*M*)	Catalyst	$[Catalyst]_0/[OH]_0$	Time (h)	Yield (%)[a]	$M_{n\ SEC}$ (g mol^{-1})[b]	M_w/M_n[b]
1	ε-CL (2)	TBD	0.05	3	17	12,100	1.37
2	ε-CL (2)	TBD	0.05	7	15	10,800	1.45
3	L-LA (1)	DBU	0.5	0.75	~99	36,500	1.52

[a] As determined by gravimetry.
[b] Apparent molar masses and polydispersities as determined by size exclusion chromatography (SEC) in THF at 35 °C using PS standards.

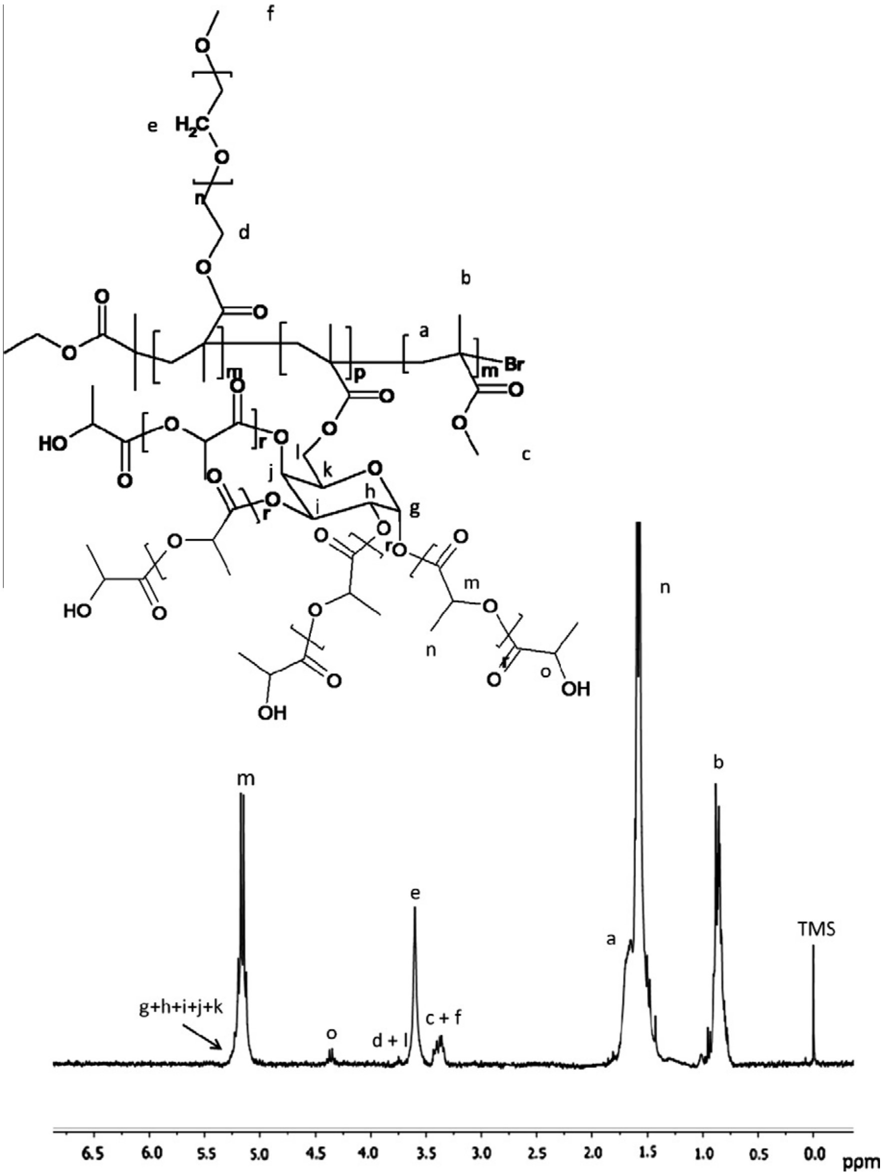


Fig. 3. ^{1}H-NMR spectrum ($CDCl_3$) of brush-like copolymer resulting in the ROP of L-LA from the pending D-galactopyranose residues (entry 3, Table 3).

(entries 1 and 2). It is worth noting that PDI are slightly increasing when the CL ROP reaction time goes from 3 to 7 h without any evolution of the associated molecular weight. This observation tends to point out that possible back-biting processes are competitively involved during the propagation process. Comparatively from LA ROP catalyzed by DBU, a clear shift is observed compared to the initial backbone (entry 3) as shown by Fig. 2 indicating the efficiency of the L-LA polymerization as initiated from the hydroxyl groups of the D-galactose rings pending along the polymethacrylate backbone. Besides, ^{1}H-NMR evidenced the presence of L-LA repetitive moieties as shown in Fig. 3. However, some clear contamination of the expected brush-like copolymer can be observed, affecting for the efficiency of the copolymerization by ROP by a rather limited control over the molecular parameters.

4. Conclusions

This study has highlighted the controlled synthesis of terpolymers based on methyl methacrylate (MMA), α-methoxy, ω-methacrylate poly(ethylene oxide) (MAPEO), and 1,2:3,4-di-O-isopropylidene-6-O-methacryloyl-D-galactopyranose (MAIGP). The synthetic strategy relies upon a two-step approach with a first step as the ATRP reaction followed by selective deacetonation of pendant sugar moieties. As a second step, ring-opening polymerization of ε-caprolactone (CL) or L-lactide (L-LA) from the as-obtained free-hydroxyl groups pending along the polymethacrylate backbone has been studied under different experimental conditions by varying the type of catalyst in order to cope with the different problems encountered, mostly the availability of initiating hydroxyl groups and the catalyst activity. We finally highlighted the possibility to promote the ROP from the secondary alcohols of grafted sugar moieties thanks to DBU metal-free catalyst.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.reactfunctpolym.2010.06.001.

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