One-Pot Synthesis of Well-Defined Amphiphilic and Adaptative Block Copolymers via Versatile Combination of "Click" Chemistry and ATRP[a]

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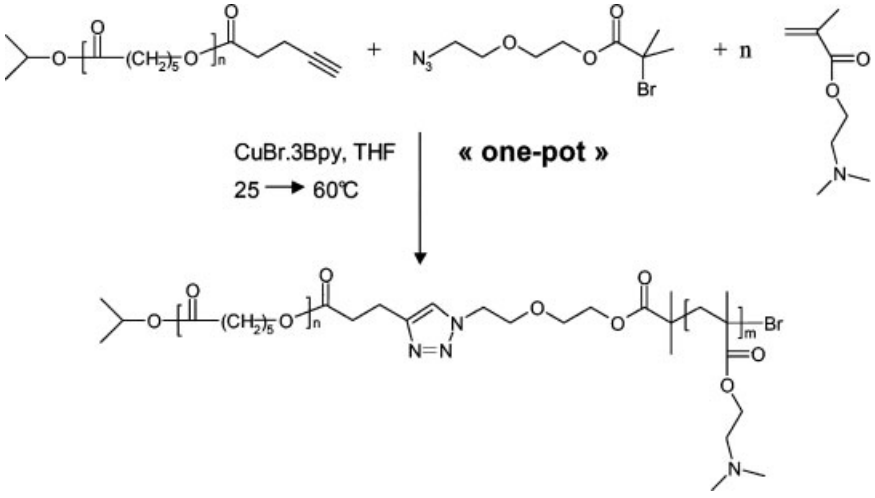
Well-defined amphiphilic PCL-*b*-PDMAEMA block copolymers were successfully synthesized by a combination of ATRP and "click" chemistry following either a commutative two-step procedure or a straightforward one-pot process using CuBr · 3Bpy as the sole catalyst. Compared to the traditional coupling method, combining ATRP and click chemistry even in a "one-pot" process allows the preparation of PCL-*b*-PDMAEMA diblock copolymers characterized by a narrow molecular weight distribution and quantitative conversion of azides and alkynes into triazole functions. Moreover, the amphiphilic character of these copolymers was demonstrated by surface tension measurements and critical micellization concentration was calculated.



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Introduction

"Click" reactions have recently emerged as a powerful and versatile class of chemical transformations. The popularity of these reactions can be attributed to their mild conditions, quantitative yields, absence of by-product formation, and regioselectivity.[1] Click chemistry reactions include the Cu^{I}-catalyzed azide/alkyne cycloaddition,[2] usually known as Huisgen 1,3-dipolar cycloaddition, which has recently been employed to prepare a variety of novel materials including dendrimers,[3] shell-crosslinked nanoparticles,[4] hydrogels,[5] and (co)polymers

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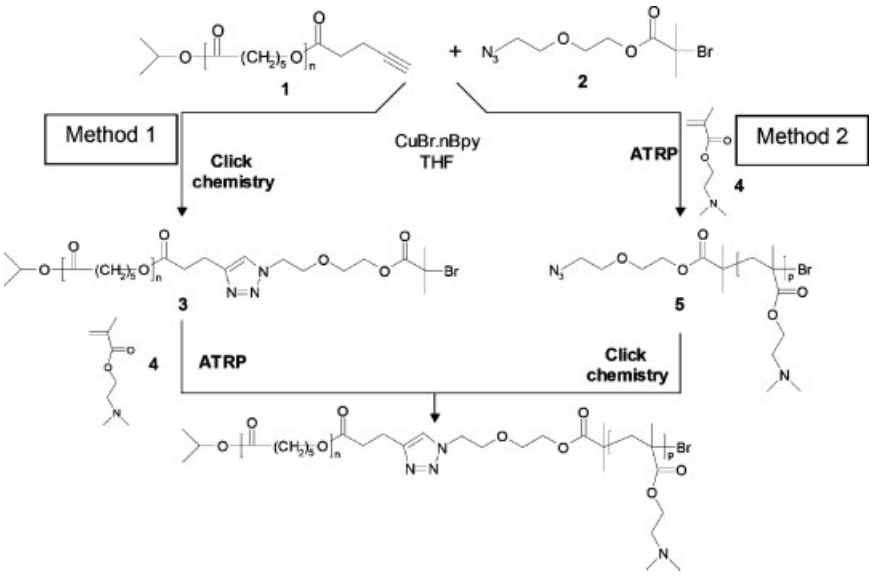
with high degrees of functionalization.[6] This technique is particularly well suitable with polymers prepared by atom-transfer radical polymerization (ATRP) owing to the controlled molecular weight and narrow molecular weight distribution of the resulting polymers as well as the quantitative presence of halogen end groups that can be readily converted into azido functions.[7] Moreover, ATRP shares a number of important features with click reactions including robustness, versatility, tolerance to a wide range of functional groups, and the catalytic use of a ligated transition metal as copper(I) complexes. Interestingly, the combination of these two mechanisms in a multistep,[8] or in a "one-pot" process,[9–11] has already been reported in the literature. Even to date, the one-pot process has been exploited with a moderate success; such a combination may provide a powerful macromolecular engineering tool for the synthesis of well-defined (co)polymer structures exhibiting excellent ability to self-assemble.

Herein we report for the first time the controlled synthesis of amphiphilic block copolymers by the combination of ATRP and click coupling processes in commutative successive steps as well as in a one-pot process using the same and unique catalyst. Practically, two strategies were subsequently studied to produce poly(ε-caprolactone)-*block*-poly(*N*,*N*-dimethylamino-2-ethyl methacrylate) (PCL-*b*-PDMAEMA) block copolymers (Scheme 1, Methods 1 and 2). A straight one-pot process was investigated as well. The first route (Method 1, Scheme 1) relies upon the click chemistry reaction between the α-isopropoxide, ω-pentynoate PCL (**1**) and 2-(2-azidoethoxy)ethyl bromoisobutyrate (**2**, N_3E^iBBr) followed by the ATRP polymerization of DMAEMA monomer **4** as initiated from the alkyl bromide end group. According to the second strategy (Method 2) DMAEMA (**4**) is first polymerized starting from the initiator **2** yielding α-azide PDMAEMA chains **5** able to react with **1** in a subsequent step by click chemistry. Finally those two strategies were merged so as to carry out both ATRP and click reaction in a one-pot process starting directly from compounds **1**, **2**, and **4** using ligated CuBr as the sole catalyst.



Scheme 1. Synthetic routes to PCL-*b*-PDMAEMA block copolymers via commutative combination of ATRP and click coupling reaction.

Experimental Part

General Methods

^{1}H NMR spectra were recorded using a Bruker AMX-300 or AMX-500 apparatus at room temperature (r.t.) in $CDCl_3$ and D_2O (30 mg/0.6 mL). Size exclusion chromatography (SEC) was performed in tetrahydrofuran (THF; polyesters) or THF + 2 wt.-% NEt_3 [(co)polymers-containing amino methacrylate] at 35 °C using a Polymer Laboratories liquid chromatograph equipped with a PL-DG802 degasser, an isocratic HPLC pump LC 1120 (flow rate = 1 mL · min^{-1}), a Marathon autosampler (loop volume = 200 μL, solution conc. = 1 mg · mL^{-1}), 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 and poly(methyl methacrylate) standards were used for calibration. Mass spectrometry measurements were performed on a Waters QToF2 apparatus equipped with an orthogonal electrospray ionization (ESI) source (Z-spray) operating in a positive ion mode. Samples were dissolved in acetonitrile (≈10^{-5} mol · L^{-1}) and infused into the ESI source at 5 μL · min^{-1} rate with a Harvard syringe pump. Typical ESI conditions were capillary voltage 3.1 kV, cone voltage 80 V, source temperature 80 °C, and desolvation temperature 120 °C. Dry nitrogen was used as the ESI gas. The quadrupole was set to pass ions from 100 to 3 000 Th and all ions were transmitted into the pusher region of the time-of-flight analyzer for mass-analysis with 1 s integration time. Data were acquired in a continuum mode until acceptable average data were obtained. Gas chromatography analysis was performed with a GCQ type from Finnigan (Interscience) equipped with an Rtx-5Sil MS column (30 m, 0.25 mm, 0.25 μm) in 5:95 poly(diphenylsiloxane)/poly(dimethylsiloxane). The heating program starts at 60 °C for 1 min, followed by a ramp of 10 °C · min^{-1} until 250 °C and an isotherm at 250 °C for 2 min. Injector temperature was fixed at 250 °C. Helium was used as a mobile phase with a 30 cm · s^{-1} rate. Sample (2 μL) was introduced in the column and the experiment was operated in positive modes EI+ (electronic ionization) and CI+ (chemical ionization) with an electronic energy of 70 eV. In CI+ mode, methane was used as the reac-

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tive gas and the temperature of the source was held at 200 °C. The transfer line was maintained at 260 °C.

Materials

ε-Caprolactone (CL; Acros, 99%) was dried over calcium hydride for 48 h at r.t. and distilled under reduced pressure just before use. Aluminum triisopropoxide [$Al(O^iPr)_3$; Acros, 98%] was molten, distilled under reduced pressure, quenched in liquid nitrogen, rapidly dissolved in dry toluene, and stored under nitrogen. Accurate concentration was determined by back complexiometric titration of Al^{3+} using ethylenediaminetetraacetic acid disodium salt and $ZnSO_4$ at pH = 4.8. DMAEMA (Aldrich, 98%) was passed through a column of basic alumina to remove the stabilizing agents and used immediately. Copper bromide (CuBr; Fluka, 98%) was purified by solubilization of oxidized copper(II) derivatives in glacial acetic acid (Acros), washed by ethanol (Acros) under nitrogen and dried under reduced pressure. Pentynoic acid (Aldrich, 95%), *N,N*-dicyclohexylcarbodiimide (DCC, Aldrich, 99%), *N,N*-dimethylamino-4-pyridine (DMAP, Acros, 99%), 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA, Aldrich, 97%), 2,2′-dipyridine (Bpy, Acros, 99%), sodium azide (NaN_3, Acros, 99.5%), 2-(2-chloroethoxy)ethanol (Aldrich, 99%), and 2-bromoisobutyryl bromide (Aldrich, 98%) were used as received. Triethylamine (Fluka, 99%) was dried over barium oxide for 48 h at r.t. and distilled under reduced pressure. Toluene (Labscan, 99%) was dried by refluxing over CaH_2 and distilled just before use. THF (Labscan, 99%) was previously dried over molecular sieves (4 Å) and distilled over polystyryl lithium complex. Dichloromethane (CH_2Cl_2; Aldrich, 99%) was dried over calcium hydride for 48 h at r.t. and distilled under reduced pressure.

Synthesis of α-Isopropoxy-ω-hydroxy-poly(ε-caprolactone) (PCL-OH)

Briefly, 30 mL (0.27 mol) of CL was added to 223 mL of toluene in a round-bottom flask under inert atmosphere. Polymerization was initiated at 0 °C by adding 17.5 mL (14 mmol) of aluminum triisopropoxide in toluene solution (0.77 mol · L^{-1}). After 10 min, the reaction was stopped by adding aqueous HCl solution (1 mol · L^{-1}) and the polyester was selectively recovered by precipitation in cold heptane, filtration, and drying under reduced pressure (yield >99%). All residues were removed by liquid/liquid extraction and PCL-OH was recovered by precipitation.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.1 [d, $(\underline{CH_3})_2CH-O-$], 1.3–1.8 [m, $-(CH_2)_3-$], 2.3 (t, $-CH_2-COO-$), 3.65 (t, $-CH_2-OH$), 4.05 (t, $-CH_2-OCO-$), 5.1 [$(CH_3)_2\underline{CH}-O-$].

$\overline{M}_n$ NMR = 2 400 g · mol^{-1}, $\overline{M}_n$ theor = 2 300 g · mol^{-1}, $\overline{M}_n$ ESI-MS = 2 400 g · mol^{-1}, $\overline{M}_n$ SEC = 2 100 g · mol^{-1}, and $\overline{M}_w/\overline{M}_n$ = 1.28.

Synthesis of α-Isopropoxy-ω-4-pentynoate-poly(ε-caprolactone) (PCL–C≡CH)

In a dried and nitrogen purged round-bottom flask, 2.7 g of 4-pentynoic acid (28 mmol) and 2.6 g of DCC (13 mmol) were dissolved in CH_2Cl_2 (25 mL). The mixture was stirred for 6 h at 0 °C to form dipentynoic anhydride. In a second dried round-bottom flask, 14.5 g of PCL–OH (6 mmol, $\overline{M}_n$ = 2 400 g · mol^{-1}) and 0.249 g of DMAP (2 mmol) were dried by three successive toluene azeotropic distillations before adding 25 mL of CH_2Cl_2. These solutions were mixed for 48 h at r.t. and PCL–C≡CH was recovered by selective precipitation in cold methanol, filtration, and drying at 40 °C under reduced pressure. Yield: 87%.

^{1}H NMR (500 MHz, $CDCl_3$) [Figure 1(B)]: δ = 1.1 (d, $6H_g$), 1.3–1.8 (m, $6H_{b,c}$), 1.9 (s, $1H_i$), 2.3 (t, $2H_a$), 2.45 (t, $2H_h$), 2.55 (t, $2H_e$), 4.05 (t, $2H_d$), 5.1 (m, $1H_f$).

$\overline{M}_n$ NMR = 2 700 g · mol^{-1}, $\overline{M}_n$ ESI-MS = 2 665 g · mol^{-1}, $\overline{M}_n$ SEC = 2 600 g · mol^{-1}, and $\overline{M}_w/\overline{M}_n$ = 1.20.

Synthesis of 2-(2-Azidoethoxy)ethanol

In a round-bottom flask surmounted by a reflux column, 20 g of 2-(2-chloroethoxy)ethanol (161 mmol), 52.2 g of NaN_3 (803 mmol), and 80 mL of water were introduced. The mixture was refluxed for 24 h, then cooled down and treated with HCl. The aqueous solution was extracted by EtOAc and the organic solvent was evaporated under reduced pressure. Yield: 92%.

^{13}C NMR (300 MHz, D_2O): δ = 50.96 (N_3-CH_2-), 61.22 ($-CH_2-OH$), 69.75 ($N_3-CH_2-\underline{C}H_2-O$), 72.33 ($O-\underline{C}H_2-CH_2-OH$).

Synthesis of 2-(2-Azidoethoxy)ethyl Bromoisobutyrate (N_3E^iBBr)

In a round-bottom flask, 15 g of 2-(2-azidoethoxy)ethanol (114 mmol), 32 mL of NEt_3 (228 mmol), and 60 mL of THF were introduced. A solution of 15.6 mL of 2-bromoisobutyryl bromide (126 mmol) in 60 mL of THF was added dropwise at 0 °C. After 48 h at r.t., ammonium salts were filtered off and the product in solution was passed through a basic alumina column before evaporation of THF. Yield: 70%.

^{1}H NMR (300 MHz, $CDCl_3$) [Figure 1(A)]: δ = 1.9 (s, $6H_a$), 3.35 (t, $2H_e$), 3.65 (t, $2H_d$), 3.75 (t, $2H_c$), 4.3 (t, $2H_b$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 31 [$C(\underline{C}H_3)_2$], 51 (N_3-CH_2-), 56 [$-CH_2-O-C(O)-$], 65.3 [$\underline{C}(CH_3)_2-$], 69.1 ($N_3-CH_2-\underline{C}H_2-O$), 70.5 ($O-\underline{C}H_2-CH_2-$), 171.7 [$O-\underline{C}(O)-$].

Synthesis of α-Isopropyloxy-ω-2-(triazolethoxy)ethyl Bromoisobutyrate-poly(ε-caprolactone) (PCL–Br, First Step in Method 1)

Under inert atmosphere, 0.014 g of CuBr (0.098 mmol), 0.048 g of Bpy (0.31 mmol), 0.251 g of PCL–C≡CH (0.094 mmol), 0.035 g of N_3E^iBBr (0.13 mmol), and 2.6 mL of THF were introduced. After 24 h at r.t., the catalytic complex was removed by filtration of the polymer solution through basic alumina column and PCL-Br is recovered by solvent evaporation. Yield: 95%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.1 [d, $(\underline{CH_3})_2CH-O-$], 1.3–1.8 [m, $-(CH_2)_3-$], 1.95 [s, $C(\underline{CH_3})_2-$], 2.3 (m, $-CH_2-COO-$), 2.7 (t, $-CH_2-\underline{CH_2}-$triazole), 3.0 (t, $-\underline{CH_2}-CH_2-$triazole), 3.7 (t, triazole$-CH_2-\underline{CH_2}-O-$), 3.9 [t, $-O-\underline{CH_2}-CH_2-OC(O)-$], 4.1 [t, $-CH_2-OC(O)-$], 4.3 (t,

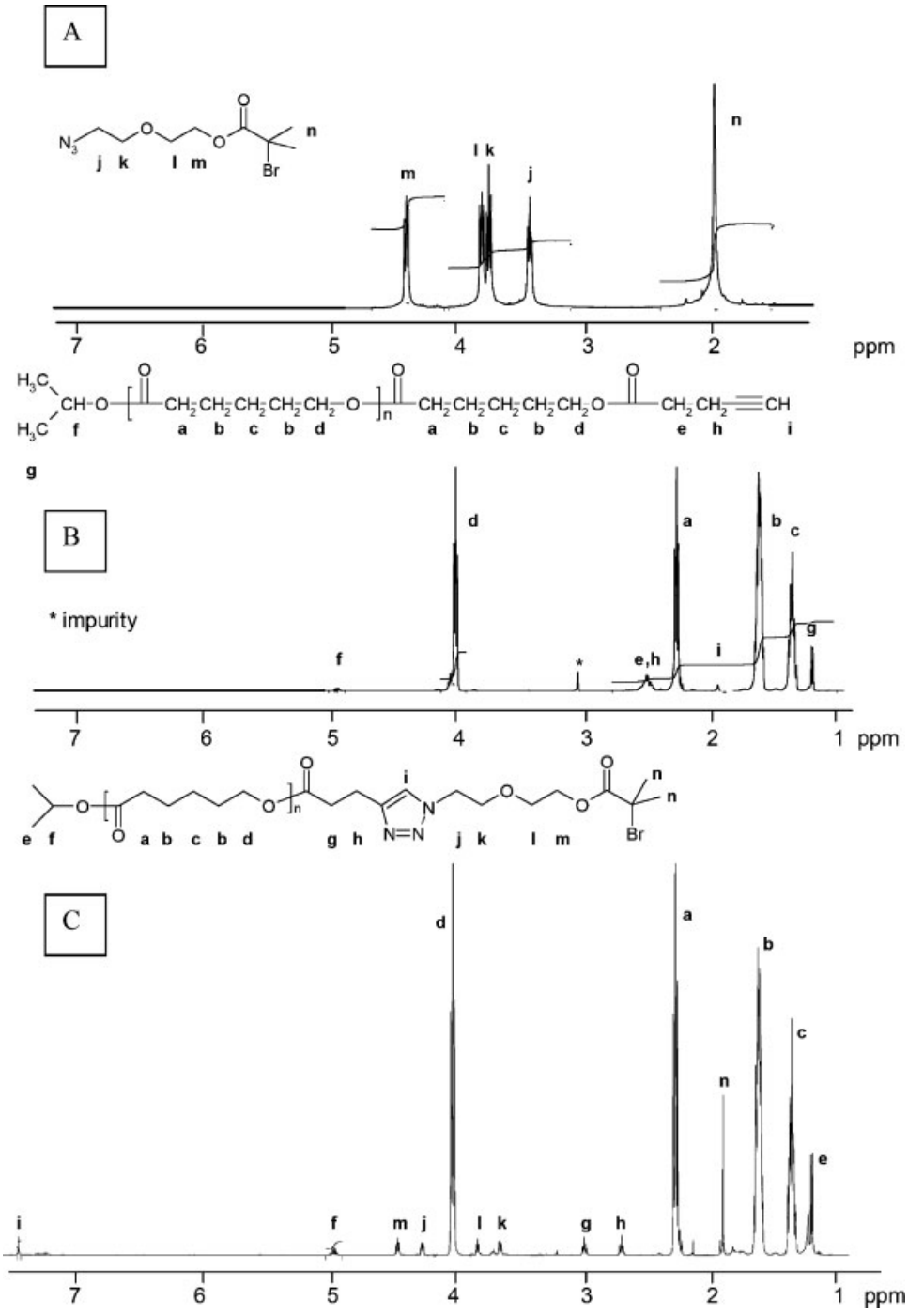

Figure 1. ^{1}H NMR spectra of (A) N_3E^iBBr (**2**), (B) PCL–C≡CH (**1**) precursors, and (C) PCL–Br in $CDCl_3$.

triazole–$\underline{CH_2}$–CH_2–O–), 4.5 [t, –O–CH_2–$\underline{CH_2}$–OC(O)–], 5.0 [m, $(CH_3)_2\underline{CH}$–O–], 7.4 (s, triazole).

Synthesis of PCL-*b*-PDMAEMA (Second Step in Method 1)

Under inert atmosphere, 0.013 g of CuBr (0.093 mmol), 0.039 g of Bpy (0.25 mmol), 0.229 g of PCL–C≡CH (0.086 mmol), 0.026 g of N_3E^iBBr (0.091 mmol), and 2.6 mL of THF were introduced. After 24 h at r.t., the temperature was raised up to 60 °C and 0.7 mL of freshly distilled DMAEMA monomer was introduced. After 220 min of polymerization, the copolymer was recovered by precipitation in cold heptane, filtration, and drying. Yield: 68%. Residual copper catalyst was removed by passing the polymer solution in THF through a basic alumina column and the organic solvent was evaporated.

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^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.7–1.05$ (m, $3H_p$), 1.1 (d, $6H_g$), 1.35 (m, $2H_c$), 1.61 (m, $4H_b$), 1.8–1.95 (m, $2H_q + 6H_n$), 2.3 (t, $2H_a + 6H_t$), 2.6 (t, $2H_s$), 2.75 (t, $2H_h$), 3.05 (t, $2H_e$), 3.65 (t, $2H_k$), 3.9 (t, $2H_l$), 4.05 (t, $2H_d + 2H_r + 2H_j$), 4.50 (t, $2H_m$), 5.0 (m, $1H_f$), 7.5 (s, $1H_i$).

$\overline{M}_n$ theor = 10 520 g·mol^{-1}, $\overline{M}_n$ NMR = 11 700 g·mol^{-1}, $\overline{M}_w/\overline{M}_n = 1.34$.

Synthesis of α-Azido-poly(*N*,*N*-dimethylamino-2-ethyl methacrylate) (N_3–PDMAEMA, First Step in Method 2)

In a round-bottom flask, 0.263 g of CuBr (1.8 mmol), 0.893 g of HMTETA (3.6 mmol), and 15 mL of DMAEMA (89 mmol) were introduced. Three freezing/thawing cycles were performed under vacuum to get rid of trapped O_2. In a second round-bottom flask were introduced 0.5 g of N_3E^iBBr (1.8 mmol) and 2.5 mL of THF previously deprived of its stabilizer by filtration through a basic alumina column. N_2 was bubbled through the solution before transferring it into the first flask. After 22 min at 60 °C, the polymer was recovered by precipitation in cold heptane, filtration, and drying. Yield: 19%. Copper catalyst was removed by passing the polymer solution in THF through a basic aluminum oxide column and the organic solvent was evaporated.

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.7–1.1$ (m, –C–CH_3), 1.6–1.9 [m, –$\underline{CH_2}$–C(CH_3) + –C($\underline{CH_3}$)$_2$], 2.15 [s, N–($\underline{CH_3}$)$_2$], 2.45 [t, N–$\underline{CH_2}$–CH_2–OC(O)], 3.25 (t, N_3–$\underline{CH_2}$–), 3.5 [t, –O–$\underline{CH_2}$–CH_2–OC(O)–], 3.55 (t, N_3–CH_2–$\underline{CH_2}$–), 3.9 [t, –O–CH_2–$\underline{CH_2}$–OC(O)–], 4.1 [t, –O–CH_2–$\underline{CH_2}$–OC(O)–].

$\overline{M}_n$ NMR = 3 600 g·mol^{-1}, $\overline{M}_w/\overline{M}_n = 1.24$.

Synthesis of PCL-*b*-PDMAEMA (Second Step in Method 2)

Under inert atmosphere, 0.014 g of CuBr (0.098 mmol), 0.048 g of Bpy (0.31 mmol), 0.338 g of N_3-PDMAEMA (0.094 mmol; Table 1, entry 2), 0.251 g of PCL–C≡CH (0.094 mmol), and 2.6 mL of THF were introduced. After 72 h at r.t., the reaction medium was diluted, the catalytic complex was removed by passing through a basic alumina column, and THF was evaporated under reduced pressure. Yield ≈99%.

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.7–1.05$ (m, $3H_p$), 1.1 (d, $6H_g$), 1.35 (m, $2H_c$), 1.61 (m, $4H_b$), 1.8–1.95 (m, $2H_q + 6H_n$), 2.3 (t, $2H_a + 6H_t$), 2.6 (t, $2H_s$), 2.75 (t, $2H_h$), 3.05 (t, $2H_e$), 3.65 (t, $2H_k$), 3.90 (t, $2H_l$), 4.05 (t, $2H_d + 2H_r + 2H_j$), 4.50 (t, $2H_m$), 5.0 (m, $1H_f$), 7.5 (s, $1H_i$).

$\overline{M}_w/\overline{M}_n = 1.50$.

One-Pot synthesis of PCL-*b*-PDMAEMA

Under inert atmosphere, 0.013 g of CuBr (0.090 mmol), 0.039 g of Bpy (0.246 mmol), 0.229 g of PCL–C≡CH (0.086 mmol), 0.026 g of N_3E^iBBr (0.091 mmol), 0.7 mL of DMAEMA (4.15 mmol), and 1.8 mL of THF were introduced. After 24 h at r.t., temperature was raised up to 60 °C for 6 h to promote DMAEMA polymerization. The reaction medium was diluted, the catalytic complex was removed by passing through a basic alumina column, and THF was evaporated under reduced pressure. Yield ≈95%, monomer conversion ≈99%.

^{1}H NMR (500 MHz, $CDCl_3$) [Figure S1]: $\delta = 0.7–1.05$ (m, $3H_p$), 1.1 (d, $6H_g$), 1.35 (m, $2H_c$), 1.61 (m, $4H_b$), 1.8–1.95 (m, $2H_q + 6H_n$), 2.3 (t, $2H_a + 6H_t + 6Ht'$), 2.6 (t, $2H_s + 2Hs'$), 2.75 (t, $2H_h$), 3.05 (t, $2H_e$), 3.65 (t, $2H_k$), 3.90 (t, $2H_l$), 4.05 (t, $2H_d + 2H_r + 2H_j$), 4.1 (t, $2H_{r'}$), 4.50 (t, $2H_m$), 5.0 (m, $1H_f$), 5.6–6.15 (d, $2H_{u,v}$), 7.5 (s, $1H_i$).

$\overline{M}_n$ theor = 11 000 g·mol^{-1}, $\overline{M}_n$ NMR = 13 800 g·mol^{-1}, and $\overline{M}_w/\overline{M}_n = 1.31$.

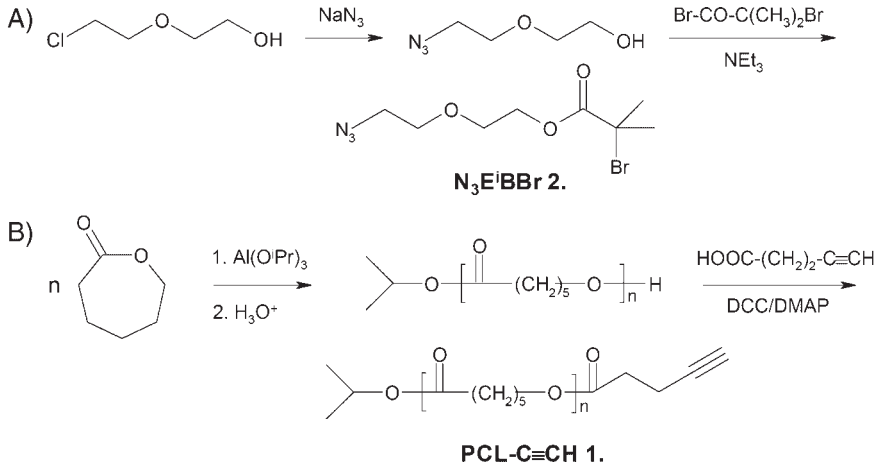
Results and Discussion

The key point of all studied synthetic routes relies on the use of the azido-functionalized ATRP initiator **2** obtained via a two-step reaction involving the nucleophilic substitution of chloride from 2-(2-chloroethoxy)ethanol by NaN_3 and the esterification of the azido-alcohol intermediate with 2-bromoisobutyryl bromide [Scheme 2(A)]. The effective formation of **2** was confirmed by ^{1}H NMR spectroscopy [see Figure 1(A)] while its purity was fully attested by GC-MS. In agreement with "Method 1", N_3E^iBBr (**2**) was first coupled by click chemistry to PCL–C≡CH (**1**), which was previously synthesized by ring-opening

Table 1. Molecular characteristics of PCL (**1**), PDMAEMA (**5**), and PCL-*b*-PDMAEMA block copolymers as-obtained through Method 1, Method 2, and one-pot process.

Entry	Polymer sample	Synthetic route	Conv. $_{DMAEMA}$ [a]	Conv.$_{triazol}$ [b]	$\overline{M}_n$	$\overline{M}_w/\overline{M}_n$ [e]
			%	%	g·mol^{-1}	
1	PCL (**1**)	ROP	–	–	2 700[c]	1.2
2	PDMAEMA (**5**)	ATRP	–	–	3 600[d]	1.25
3	PCL-*b*-PDMAEMA	Method 1	>99	>99	12 300[d]	1.35
4	PCL-*b*-PDMAEMA	Method 2	–	97	6 300[d]	1.5
5	PCL-*b*-PDMAEMA	One-pot	95	>99	12 700[d]	1.3

[a] Conversion of DMAEMA monomer as determined by ^{1}H NMR (in $CDCl_3$); [b] Conversion of azide and alkyne functions into triazole group as determined by ^{1}H NMR (in $CDCl_3$); [c] Calculated by ESI-mass spectrometry; [d] Determined by ^{1}H NMR in $CDCl_3$; [e] Molecular weight distribution as determined by SEC in THF + 2 wt.-% NEt_3.



Scheme 2. Schematic illustration of precursor synthesis: (A) N_3E^iBBr (**2**) and (B) PCL–C≡CH (**1**).

polymerization (ROP) of CL monomer using $Al(O^iPr)_3$ as the initiator at 0 °C in toluene, followed by an esterification reaction of the hydroxyl end group with 4-pentynoic acid activated by DCC in the presence of DMAP [Scheme 2(B), Figure 1(B), and Table 1, entry 1].[12] Practically, the click coupling reaction was carried out at 25 °C in THF and catalyzed by CuBr complexed by three equivalents of Bpy under nitrogen atmosphere. The initial azide-to-alkyne ratio was fixed to 1 ($[\mathbf{2}]_0 = 0.03$ mol·L^{-1}). After 24 h reaction, an aliquot was withdrawn from the reactive medium whereas the temperature was increased up to 60 °C, and freshly distilled DMAEMA (**4**) was injected in the polymerization medium to get a $[\mathbf{4}]_0/[\mathbf{3}]_0/[CuBr]_0/[Bpy]_0$ molar ratio fixed to 50:1:1:3. ^{1}H NMR analysis performed on the aliquot reveals a quantitative conversion of azide functions into 1,2,3-triazole groups by the disappearance of both the α-N_3 and α-alkyne methylene protons from the starting materials. Furthermore, the relative intensities of the protons adjacent to the triazole junction between the polyester **1** and initiator N_3E^iBBr (**2**) fit well the expected ratios ($I_i/I_f/I_h/I_k/I_l/I_m = 1:1:2:2:2:2$)[†]. An additional confirmation was brought by ESI-MS by the exclusive and expected apparition of doubly charged ω-(triazole ethoxy)-**2**-ethyl bromoisobutyrate PCL chains **3** [M+2Na$^+$] centered at *m/z* 1228.3[†]. Therefore, it can be assumed that **4** is exclusively initiated by a bromo-terminated PCL macroinitiator. Actually an initiation efficiency (f) as high as 0.85 has been determined. As seen in Table 1 (entry 3), the combination of click reaction with ATRP following the route depicted in Method 1 yields well-defined block copolymers as attested by SEC, where a clear-cut shift of the copolymer trace toward lower retention volume (with respect to **1**) is observed while the molecular weight distribution remains narrow [$\overline{M}_w/\overline{M}_n = 1.35$, Figure 2(a)].

According to "Method 2" approach, the controlled radical polymerization of DMAEMA (**4**) was first initiated by using CuBr complexed by HMTETA in THF at 60 °C.[13] Initial monomer concentration was set up at 5 mol·L^{-1} for an initial $[\mathbf{4}]_0/[\mathbf{2}]_0/[CuBr]_0/[HMTETA]_0$ molar ratio of 50:1:1:2 and polymerization time was limited to 22 min. The number-average molecular mass of N_3-PDMAEMA (**5**) was determined by ^{1}H NMR from the relative intensity of terminal azido methylene protons at 3.3 ppm and amine methyl protons of the repeat units at 2.15 ppm ($\overline{M}_n = 3\,600$), assuming that each polymer chain is end-capped by a N_3E^iBBr group. Compared to the theoretical molar mass expected, assuming both a living process and initiation from every N_3E^iBBr (**2**) (i.e., $\overline{M}_{n,theor} = ([\mathbf{4}]_0/[\mathbf{2}]_0) \times conv. \times \overline{M}_w\mathbf{4} + \overline{M}_w\mathbf{2}$), a quite low initiation efficiency was found ($f = 0.26$). Such a low initiation efficiency has already been observed by others[14] when using an azido-containing initiator even if the origin of which remains unclear.

In a second step, N_3-PDMAEMA (**5**) was coupled to PCL–C≡CH (**1**) by click reaction in THF at r.t. using CuBr·3Bpy catalytic complex. Initial concentrations in both azide and alkyne functions were maintained at 0.03 mol·L^{-1} while great care was taken to ensure exact stoichiometry ($[\mathbf{1}]_0/[\mathbf{5}]_0 = 1$). Such a condition allows reaching near complete click coupling reaction (97%; Table 1, entry 4) at least within the accuracy of ^{1}H NMR spectroscopy. The SEC trace of the resulting block copolymer was again monomodal and shifted toward a lower elution volume attesting for the formation of macromolecular species with a higher molecular weight [Figure 2(B)]. Nevertheless, the polydispersity index appeared quite broad ($\overline{M}_w/\overline{M}_n = 1.50$), which might be attributed to the presence of some residual polymer precursors.

Interestingly enough, direct synthesis of PCL-*b*-PDMAEMA copolymers was carried out starting from a mixture of **1**, **2**, and **4** using CuBr·3Bpy as the sole catalyst and applying a temperature gradient from 25 to 60 °C. The initial $[\mathbf{4}]_0/[\mathbf{1}]_0/[\mathbf{2}]_0/[CuBr]_0/[Bpy]_0$ molar ratios were fixed to 50:1:1:3 ($[\mathbf{2}]_0 = 0.03$ mol·L^{-1}). After 24 h at 25 °C, the temperature was increased to 60 °C for 220 min to promote the ATRP of DMAEMA. Then, the reaction mixture was diluted in THF, the catalytic complex removed by filtering the solution through basic alumina column and the copolymer was recovered by precipitation in cold heptane. ^{1}H NMR analysis (see Supporting Information) performed

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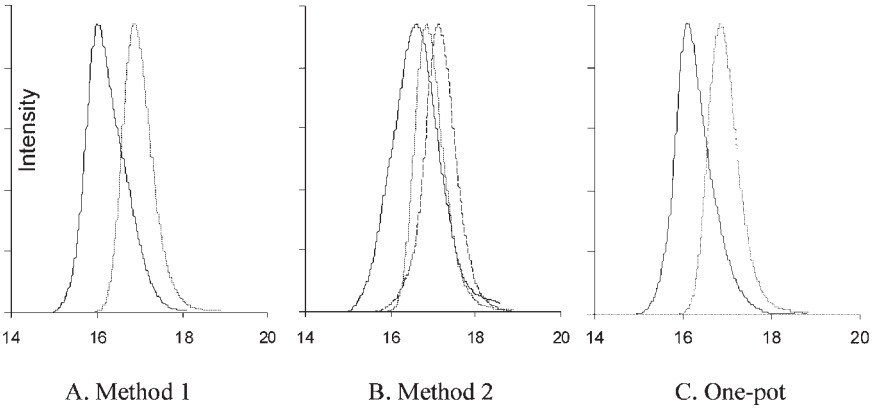

Figure 2. SEC traces of PCL-*b*-PDMAEMA block copolymer (solid line) and the related homopolymers (**1**, short dashed line and **5**, long dashed line) before the click reaction using CuBr · 3Bpy as a catalyst and following (A) Method 1, (B) Method 2, and (C) one-pot synthetic route.

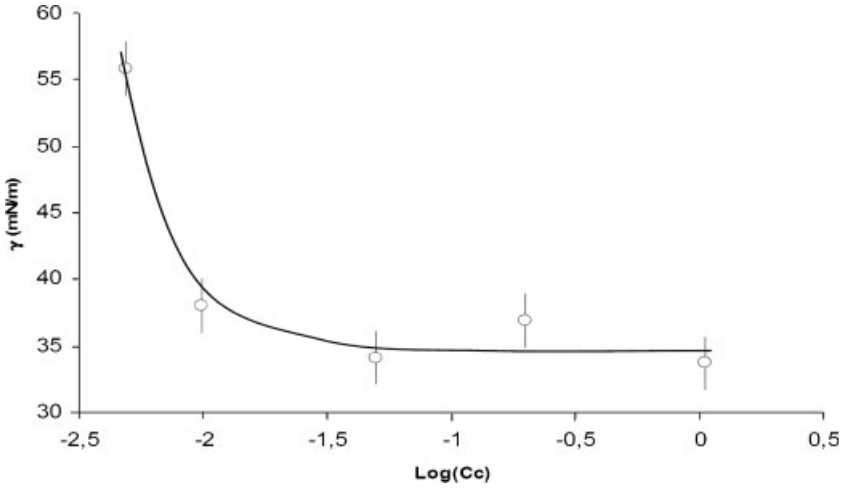

Figure 3. Semilogarithmic plot of the surface tension (γ) versus the concentration in $g \cdot L^{-1}$ in acetic buffer of the PCL-*b*-PDMAEMA block copolymer obtained by the one-pot process.

on the crude product reveals quantitative DMAEMA monomer conversion. Moreover, no more azido methylene protons could be detected at 3.3 ppm attesting for the complete click reaction conversion. Knowing the number-average molar mass of PCL-C≡CH (**1**), the molecular weight of the polymethacrylate block could be calculated from the relative intensity of the α-amino methylene protons at 2.6 ppm and compared to the theoretical value assuming a living process. It provides a higher initiation efficiency ($f \approx 0.8$) compared to the value obtained for the homopolymerization of DMAEMA initiated from N_3E^iBBr (using CuBr · 2HMTETA as catalyst). This shows that CuBr · 3Bpy is an efficient catalyst not only for the click reaction but also for the ATRP of DMAEMA. SEC trace of the diblock copolymer is monomodal and narrow and shows a clear shift of the copolymer trace toward lower elution volume with respect to **1** [Figure 2(C)].

The amphiphilic character of the PCL-*b*-PDMAEMA block copolymers has been highlighted by preliminary surface tension measurement in an acetic buffer ($C_c = 0.5$ M, pH = 4.8, Figure 3). For the block copolymer synthesized via the one-pot process (see Table 1, entry 5), a critical micellar concentration (CMC) of ca. 0.01 $g \cdot L^{-1}$ has been measured.

Conclusion

In conclusion, amphiphilic diblock copolymers have been successfully synthesized by combining controlled ROP, ATRP, and click coupling reaction. A one-pot approach involving only one catalytic complex is reported leading to well-defined tensioactive and adaptative copolymers, the self-assembling properties of which are expected to be pH and temperature dependent.[15]

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