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Synthesis by RAFT of innovative well-defined (co) polymers from a novel phosphorus-based acrylamide monomer

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The present contribution reports on the synthesis and controlled polymerization of a novel acrylamide monomer containing phosphonated moieties, namely diethyl-2-(acrylamido)ethylphosphonate. This monomer appears to be of great interest due to the phosphonated moieties, which can lead to a wide range of applications, associated with the chemical stability of the acrylamide compared to more common (meth)acrylate monomers. Reversible Addition–Fragmentation Transfer (RAFT) polymerization of this monomer was investigated using two different trithiocarbonate chain transfer agents, and it allowed the synthesis of poly(diethyl-2-(acrylamido)ethylphosphonate) with controlled molecular weight and low dispersity. Additionally, a diblock copolymer was successfully prepared by a similar RAFT procedure using thermosensitive poly(*N*-*n*-propylacrylamide) as a macro-chain transfer agent. A combination of both stimuli-responsive and phosphonated ester or phosphonic diacid (after hydrolysis) containing blocks appears valuable for drug delivery or water treatment, for instance.

Introduction

Phosphorus containing monomers and polymers have gained considerable attention in recent years as phosphorus moieties enabled a wide range of technological applications to be reached. Indeed, phosphonate-based materials were employed for corrosion inhibition[1,2] or for flame retardancy.[3,4] Additionally, phosphorus containing polymers were widely used in the biomedical field[5,6] for drug delivery or tissue engineering, for instance, as well as for their conductivity in fuel cells membranes.[7–9] They also proved to be useful for wastewater treatment[10–12] due to their metal sorption abilities.[13–16] This multiple and specific applications explain the growing interest in the research of new phosphorus containing monomers and polymers. Additionally, another important benefit of phosphonated ester groups is the possibility to easily achieve their hydrolysis to produce phosphonic diacid ones,[17,18] which are able to enhance the properties already mentioned. In this context, the synthesis of phosphorus-based (co)polymers is of great interest, notably with a controlled architecture and, as a consequence, considerable efforts have been made to develop living radical polymerization (LRP) of phosphorus containing monomers. Among the different controlled radical polymerization strategies, Reversible Addition–Fragmentation Transfer (RAFT)/MAcromolecular Design *via* the Interchange of Xanthates (MADIX) polymerizations were successfully used for the controlled polymerization of a very limited number of phosphorus-containing monomers such as vinylphosphonic acid,[19] vinylbenzylphosphonic acid diethyl ester,[20] dimethyl(methacryloyloxy)methyl phosphonate,[21,22] or 3-[2(acryloyloxy)ethoxyl-3-oxopropy](phenyl) phosphinic acid.[23] Another strategy leading to phosphorus-based polymers dealt with the introduction of the phosphonated moieties after RAFT polymerization of an appropriate monomer.[24]

In this contribution, we report for the first time the controlled polymerization of an original phosphorus containing acrylamide monomer, namely diethyl-2-(acrylamido)ethylphosphonate (DAAmEP). To the best of our knowledge, no work has been published to date in the literature on the controlled radical polymerization of a phosphorus-containing acrylamide monomer. The latter is of great interest as acrylamide function is known to be more stable than the corresponding (meth) acrylate which can degrade over time because of the hydrolysis of the ester groups. This can lead to important problems for specific applications.[25] Thus, the use of acrylamide monomers, known for their greater stability, appears as a good alternative to solve this problem.

The RAFT polymerization of the DAAmEP was achieved for various molecular weights using different chain transfer agents: the 2-cyano-2-propyl dodecyl trithiocarbonate (CTA1) and the 2-(dodecylthiocarbonothioyl thio)-2-methylpropionic acid (CTA2),

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allowing the synthesis of phosphonated poly(diethyl-2-(acrylamido)ethylphosphonate) (P(DAAmEP)) homopolymers, and the poly(*N*-*n*-propylacrylamide) (P(*Nn*PAAm)) macro-chain transfer agent, leading to well-defined copolymers. Finally, the hydrolysis of the phosphonated ester into phosphonic diacid groups was carried out and well defined poly(2-(acrylamido) ethyl phosphonic acid) (P(AAmEPA)) moieties were obtained. In the case of P(*Nn*PAAm-*b*-AAmEPA) copolymers, double hydrophilic block copolymers (DHBCs) were afforded below the lower critical solution temperature (LCST) of the P(*Nn*PAAm) block, whereas they became amphiphilic above the LCST. Such well-defined thermosensitive copolymers containing a controlled amount of phosphonic moieties are very promising materials for the aforementioned applications and more specifically for drug delivery or water treatment.

Experimental section

Materials

N-2-(Bromoethyl)phthalimide (Alfa Aesar, 98%), hydrazine monohydrate (Alfa Aesar, 98%), triethylphosphite (Aldrich, 98%), poly(4-vinylpyridine) (Aldrich, 2% cross-linked), acryloyl chloride (Aldrich, 97%), 2-cyano-2-propyl dodecyl trithiocarbonate (CTA1) (Aldrich, 97%), 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (CTA2) (Aldrich, 95%) and bromotrimethylsilane (Aldrich, 97%) were used as received. 2,2′-Azobisisobutyronitrile (AIBN) (Aldrich, 98%) was used after recrystallization in methanol. *N*-*n*-Propylacrylamide (*Nn*PAAm) was supplied by Specific Polymers (Montpellier, France) and was used as received. Specific Polymers commercializes *N*-*n*-propylacrylamide under the reference SP43-0-002 and diethyl-2-(methacrylamido) ethylphosphonate (DMAAmEP) under the reference SP-41-008.

Characterizations

^{1}H NMR and ^{31}P NMR (δ, ppm): ^{1}H and ^{31}P NMR spectra were recorded using a Bruker Advance DRX 200 (200 MHz) with $CDCl_3$ or D_2O as solvent. For ^{1}H NMR, chemical shifts were referenced to the peak of residual non-deuterated solvents at 7.3 ppm and 4.8 ppm for $CDCl_3$ and D_2O, respectively. ^{13}C NMR spectra were recorded using a Bruker Advance DRX 400 (400 MHz). Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. Mass spectra (positive mode) were measured on a Waters Micromass Q-Tof. *Size exclusion chromatography (SEC)*: size exclusion chromatography in *N*,*N*-dimethylacetamide (DMAc) was performed on a PL-GPC 50 Plus equipped with a RI refractive index detector. PolarGel M was used at 50 °C with a 0.8 mL min^{-1} flow rate of DMAc (+0.1% LiCl weight), calibrated using PS standards. *Lower critical solution temperature (LCST) measurements*: the thermosensitivity of the polymers was estimated by a change in the transmittance through the polymer aqueous solution during a gradual increase of the temperature. The measurement of the transmittance was carried out on copolymer aqueous solutions (5 g L^{-1}) with a Perkin Elmer Lambda 35 UV-Visible spectrometer equipped with a Peltier temperature programmer PTP-1+1. A wavelength of 500 nm was selected. Temperature ramp was 0.2 °C min^{-1} between 15 °C and 30 °C. The thermosensitivity was determined at the sudden slope change in the transmittance curve. The LCST values of the copolymers thus corresponded to the minimum of the derivative curves.

Synthesis of diethyl-2-(acrylamido)ethylphosphonate (DAAmEP) monomer

Triethylphosphite (130.8 g, 787.1 mmol) was added dropwise to the *N*-2-(bromoethyl)phthalimide (A) (40.0 g, 157.4 mmol) at room temperature. The reaction mixture was heated under reflux for 12 hours at 160 °C. Excess of unreacted triethylphosphite was then eliminated by distillation under reduced pressure. Then, the unreacted *N*-2-(bromoethyl)phthalimide (A) was removed by dissolution of the crude material in a water–ethanol mixture (50/50; v/v) followed by filtration. [2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)ethyl]phosphonic acid diethyl ester (B) (39.0 g, yield: 80%) was obtained after removal of the solvent.

^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.83–7.63 (m, 4H, $H_{aromatic}$), 4.16–4.00 (m, 4H, OCH_2), 3.74–3.63 (m, 2H, CH_2N); 2.27–2.10 (m, 2H, CH_2P), 1.30–1.23 (t, 6H, CH_3). ^{31}P NMR ($CDCl_3$, 200 MHz) δ 26.8 (s, 1P, $P(O)(OEt)_2$).

The second step allowed the synthesis of the (2-aminoethyl) phosphonic acid diethyl ester (C). Hydrazine monohydrate (62 g, 1.25 mol) was added dropwise to a solution of B (39 g, 125 mmol) in ethanol (1 L) at room temperature. The reaction lasted for 12 hours at room temperature. Then, the phthalhydrazide precipitate was eliminated by filtration and the solvent was evaporated under reduced pressure. The crude material was dissolved in ethyl acetate and filtration was achieved to remove the remaining traces of phthalhydrazide that were not eliminated by the first filtration. The targeted product (C) (21.1 g, yield: 93%) was obtained after removal of the solvent under reduced pressure.

^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 4.18–4.03 (m, 4H, OCH_2), 2.97–2.83 (m, 2H, CH_2N), 2.15–1.99 (m, 2H, CH_2P), 1.32–1.25 (t, 6H, CH_3). ^{31}P NMR ($CDCl_3$, 200 MHz) δ (ppm): 32.9 (s, 1P, $P(O)(OEt)_2$).

Finally, (2-aminoethyl)phosphonic acid diethyl ester (C) (21.5 g, 118 mmol) and poly(4-vinylpyridine), 2% cross-linked (16 g), were mixed with dichloromethane (160 mL) under nitrogen atmosphere. Acryloyl chloride (14 g, 154 mmol) was added dropwise to the mixture at 5 °C. After 2 hour reaction at room temperature, the reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was chromatographed on a silica gel column using a gradient of ethyl acetate–methanol (AcOEt–MeOH) from 10/0 to 9/1 (v/v) to obtain the 2-(acrylamido)ethylphosphonate (DAAmEP) monomer (14.9 g, yield: 54%).

^{1}H NMR (D_2O, 200 MHz) δ (ppm): 6.10–6.30 (m, 2H, CH_2=, J_{gem} = 3.26 Hz, J_{cis} = 8.31 Hz, J_{trans} = 17 Hz), 5.65–5.95 (m, 1H, =CH), 4.05–4.30 (m, 4H, OCH_2, J = 7.07 Hz), 3.45–3.70 (m, 2H, CH_2N, J = 7 Hz), 2.10–2.35 (m, 2H, CH_2P, J = 7 Hz), 1.25–1.45 (t, 6H, CH_3, J = 7.07 Hz). ^{31}P NMR (D_2O, 200 MHz) δ (ppm): 32.2 (s, 1P, $P(O)(OEt)_2$). ^{13}C NMR (D_2O, 400 MHz) δ (ppm): 168.3

(C=O), 129.7 (H_2C=*C*H), 127.5 (H_2C=CH), 63.3 (O*C*H_2CH_3), 33.1 (NHCH_2), 23.9 (CH_2P), 15.6 (OCH_2*C*H_3). IR υ (cm^{-1}): 3273 (NH), 1661 (C=O), 1626 (C=C), 1240 (P=O). ESI^+ (*m*/*z*): 236.1 $[M + H]^+$.

Synthesis of poly(diethyl-2-(acrylamido)ethylphosphonate) (P(DAAmEP)) by RAFT polymerization

A typical procedure for the synthesis of P(DAAmEP) with CTA1 as a chain transfer agent and a targeted molecular weight of 8000 g mol^{-1} is described here. The [CTA]/[AIBN] ratio was 3/1. CTA1 (34.5 mg, 0.1 mmol), AIBN (5.5 mg, 0.033 mmol) and DAAmEP (1.0 g, 4.25 mmol) were added along with 8 mL of DMSO in a Schlenk tube. Chemically inert 1,3,5-trioxane was added to the reaction mixture as a probe in order to determine the conversion with time during the polymerization. The mixture was degassed by three freeze–evacuate–thaw cycles and then heated at 70 °C under nitrogen atmosphere in a thermostated oil bath. In this particular case, the polymerization proceeded for 230 min (corresponding to a conversion of 77%). The DMSO was first eliminated by cry-distillation. The dry crude material was then dissolved in acetone and precipitated in cold hexane to afford P(DAAmEP) (conversion = 77%, M_n = 6350 g mol^{-1}, $Đ$ = 1.27).

^{1}H NMR (D_2O, 200 MHz) δ (ppm): 4.2–3.9 (OCH_2), 3.7–3.25 (CH_2N), 2.7–2.10 (CH_2P and CH_2–C*H*), 2.10–1.75 (CH_2–CH), 1.75–1.45 (CH_3). ^{31}P NMR (D_2O, 200 MHz) δ (ppm): 31.2 (1P, P(O)$(OEt)_2$).

Synthesis of poly(*N*-*n*-propylacrylamide) macro-chain transfer agent by RAFT polymerization

Poly(*N*-*n*-propylacrylamide) was prepared using CTA2 as a chain transfer agent, for a targeted molecular weight of 10 000 g mol^{-1}. The [CTA]/[AIBN] ratio was 5/1. CTA2 (116.7 mg, 0.32 mmol), AIBN (10.5 mg, 0.064 mmol) and *Nn*PAAm (4.0 g, 35.35 mmol) were added along with 10 mL of DMSO in a Schlenk tube. The mixture was degassed by four freeze–evacuate–thaw cycles and then heated at 70 °C under nitrogen atmosphere in a thermostated oil bath. The polymerization proceeded for 100 min before the product (P(*Nn*PAAm)) was isolated by precipitation in distilled water at 45 °C (conversion = 79%, M_n = 15 100 g mol^{-1}, $Đ$ = 1.25).

^{1}HNMR ($CDCl_3$, 200 MHz) δ (ppm): 3.30–2.90 (CH_2N), 2.25–1.85 (CH_2–C*H*), 1.85–1.30 (CH_2CH_2NH and CH_2–CH), 1.00–0.70 (CH_3).

Synthesis of P(*Nn*PAAm-*b*-DAAmEP) by RAFT polymerization

P(*Nn*PAAm-*b*-DAAmEP) copolymer was synthesized by RAFT polymerization of DAAmEP using P(*Nn*PAAm) as a macro-chain transfer agent. The targeted molecular weight for the second block was 4000 g mol^{-1}. DAAmEP (1.0 g, 4.25 mmol), P(*Nn*PAAm) (2 g, 2 10^{-4} mol) and AIBN (10.8 mg, 6.66 10^{-5} mol) were dissolved in 10 mL of DMSO in a Schlenk tube. Chemically inert 1,3,5-trioxane was added to the reaction mixture as a probe in order to determine the conversion with time during the polymerization. The mixture was degassed by three freeze–evacuate–thaw cycles and then heated at 70 °C under nitrogen atmosphere in a thermostated oil bath. The polymerization proceeded for 100 min (corresponding to a conversion of 83%). The DMSO was first eliminated by cry-distillation. The dry crude material was then dissolved in acetone and precipitated in cold hexane to afford P(*Nn*PAAm-*b*-DAAmEP) (conversion = 83%, M_n = 17 700 g mol^{-1}, $Đ$ = 1.40).

^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 4.40–3.95 (OCH_2'), 3.90–3.40 ($CH_2'N$), 3.35–2.95 (CH_2N), 2.5–1.80 (CH_2–C*H* and CH_2'–C*H*′), 1.80–1.45 (CH_2CH_2N, CH_2–CH, C$H_2'CH_2'$N and CH_2'–CH′), 1.45–1.10 (CH_3'), 1.05–0.80 (CH_3). ^{31}P NMR ($CDCl_3$, 200 MHz) δ (ppm): 29.3 (1P, P(O)$(OEt)_2$).

Hydrolysis of the phophonated ester groups into phosphonic acid ones

The procedure is reported for the hydrolysis of the phosphonated esters of a P(DAAmEP) homopolymer (M_n = 8000 g mol^{-1}). P(DAAmEP) (1.0 g, 4.25 10^{-3} mol of phosphorus moieties) was dissolved in 100 mL of chloroform at room temperature. The reaction media was purged with an inert atmosphere and traces of water were eliminated by azeotropic distillation at 65 °C. After 1 hour, bromotrimethylsilane (0.25 g, 1.7 × 10^{-3} mol, 4 molar equivalents) was added dropwise. The reaction lasted for 12 hours at room temperature under inert atmosphere. Then, the solvent was evaporated under reduced pressure and the polymer was finally dissolved in an excess of methanol. After 2 hours, the solvent was evaporated under reduced pressure leading to P(AAmEPA) (0.91 g, yield = 91%) as the final product.

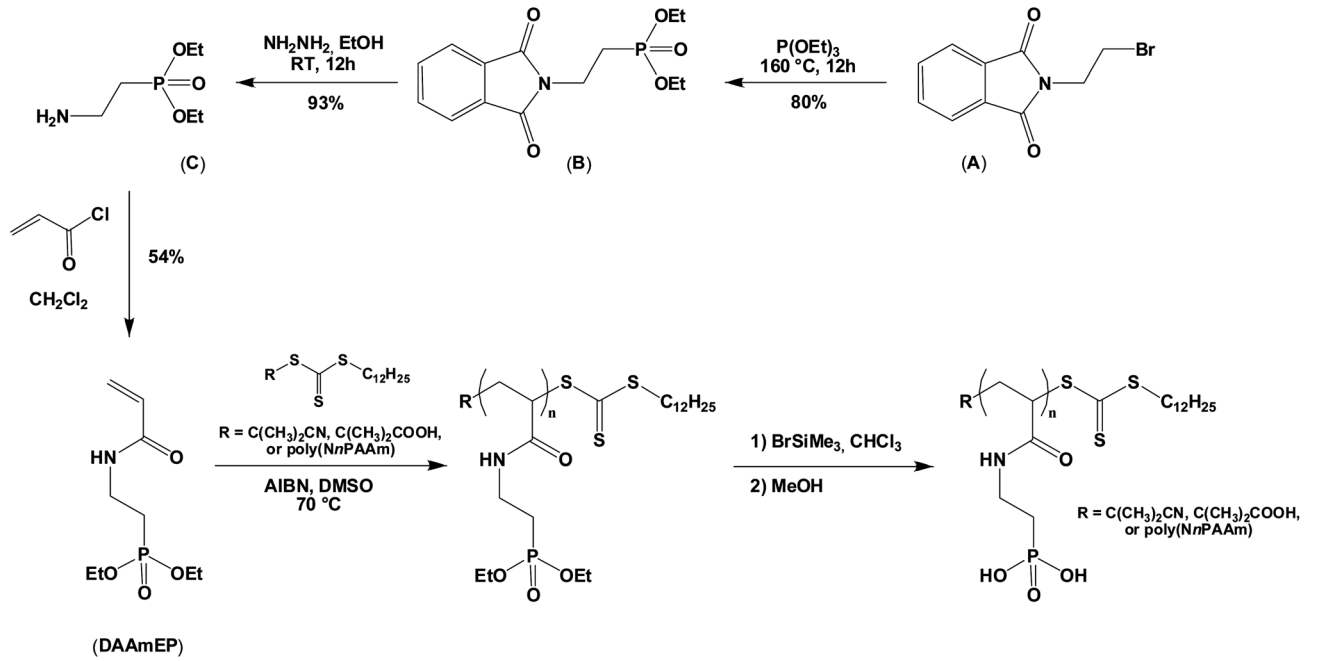
^{1}H NMR (D_2O, 200 MHz) δ (ppm): 3.63–3.22 (CH_2N), 2.46–1.84 (CH_2P and CH_2–C*H*), 1.84–1.43 (CH_2–CH). ^{31}P NMR (D_2O, 200 MHz) δ (ppm): 26.8 (1P, P(O)$(OH)_2$).

Results and discussion

Synthesis of diethyl-2-(acrylamido)ethylphosphonate (DAAmEP) monomer

The first step of the work dealt with the synthesis of the diethyl-2-(acrylamido)ethylphosphonate (DAAmEP) acrylamide monomer (Scheme 1). Acrylamide function is known to be more stable than the ester one, in acidic or basic medium, and as a result phosphorus-based acrylamide appears very interesting as it could enhance the chemical stability of resulting materials.

The synthesis of DAAmEP was conducted in three steps. The first two steps were achieved in agreement with the work of Katti *et al.* described in the literature.[26] The first step corresponded to the Michaelis–Arbuzov reaction between *N*-2-(bromoethyl) phthalimide and an excess of triethylphosphite under reflux at 160 °C for 12 hours. Resulting phthalimide (B) was recovered with 80% yield. In the second step, the reaction between the product (B) and hydrazine led to the formation of (2-aminoethyl)phosphonic acid diethyl ester (C) with 93% yield. The final step consisted of the reaction between the acryloyl chloride and the product (C) which was achieved in the presence of poly(4-vinylpyridine), 2% crosslinked to trap the hydrochloric acid produced during the acryloylation. The final DAAmEP monomer was obtained with 54% yield after purification by



Scheme 1 Synthetic pathway for the synthesis and RAFT polymerization of the diethyl 2-(acrylamido)ethylphosphonate monomer (DAAmEP) using three different chain transfer agents 2-cyano-2-propyl dodecyl trithiocarbonate (CTA1), 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (CTA2), and P(*Nn*PAAm).

chromatography on silica gel. All intermediate products were characterized by ^{1}H NMR and ^{31}P NMR. The ^{1}H NMR spectrum of the DAAmEP monomer (Fig. 2) allowed validation of the expected chemical structure and as a consequence the synthetic pathway, notably with the acrylic protons at 6.10–6.30 and 5.65–5.95 ppm and the ethyl group associated with the phosphonated ester function at 4.05–4.30 and 1.25–1.45 ppm for the methylene and the methyl groups, respectively.

Synthesis of P(DAAmEP) homopolymers by RAFT polymerization

RAFT polymerization of DAAmEP was first carried out with two different trithiocarbonate chain transfer agents, namely 2-cyano-2-propyl dodecyl trithiocarbonate (CTA1) and 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (CTA2) (Scheme 1). Three different molecular weights were targeted: 4000, 8000 and 16 000 g mol^{-1}, at 80% conversion. In all cases, the reaction was achieved at 70 °C in DMSO in the presence of 2,2′-azobisisobutyronitrile (AIBN) and the [CTA]/[AIBN] ratio was equal to three.[27] Obtained results are gathered in Table 1. Samples were periodically taken from the reaction mixture to follow the control of the polymerization. Fig. 1 shows (i) the evolution of $\ln([M]_0/[M])$ as the function of time and (ii) the evolution of the molecular weight and the dispersity ($Đ$) as functions of the conversion. The conversion was measured by ^{1}H NMR in deuterated water comparing the signals of the reactive double bond (5.55–5.61 ppm) to the signals of the 1,3,5-trioxane (5.1 ppm). Molecular weights and dispersity were determined by size exclusion chromatography (SEC) in dimethylacetamide (DMAc) at 50 °C.

Table 1 Characteristics of the different (co)polymers prepared by RAFT polymerization of (i) DAAmEP, using CTA1, CTA2 or poly(*Nn*PAAm) as a macro-chain transfer agent, and (ii) *Nn*PAAm, using CTA2

Entry	Monomer	Chain transfer agent[a]	$M_{n,targ}$[b] (g mol^{-1})	Time (min)	Conv[c] (%)	$M_{n,exp}$[d] (g mol^{-1})	$Đ$[d]
1	DAAmEP	CTA1	3850	240	77	2800	1.21
2	DAAmEP	CTA1	7700	230	77	6350	1.27
3	DAAmEP	CTA1	15 600	240	78	9100	1.35
4	DAAmEP	CTA2	3900	230	78	2750	1.28
5	DAAmEP	CTA2	7800	150	78	5400	1.27
6	DAAmEP	CTA2	16 000	200	80	9100	1.34
7	*Nn*PAAm	CTA2	9900	100	79	15 100	1.25
8	DAAmEP	Poly(*Nn*PAAm)	12 370	210	79	18 000	1.27
9	DAAmEP	Poly(*Nn*PAAm)	14 940	210	81	19 370	1.30
10	DAAmEP	Poly(*Nn*PAAm)	19 780	210	79	21 135	1.30

[a] CTA1: 2-cyano-2-propyl dodecyl trithiocarbonate; CTA2: 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid. [b] $M_{n,theo} = ([M]_0/[I]_0 \times M_w$ of monomer $\times$ conv)/100. [c] Determined by ^{1}H NMR. [d] Estimated by PS-calibrated SEC at 50 °C in DMAc (+ LiBr 0.1% weight).

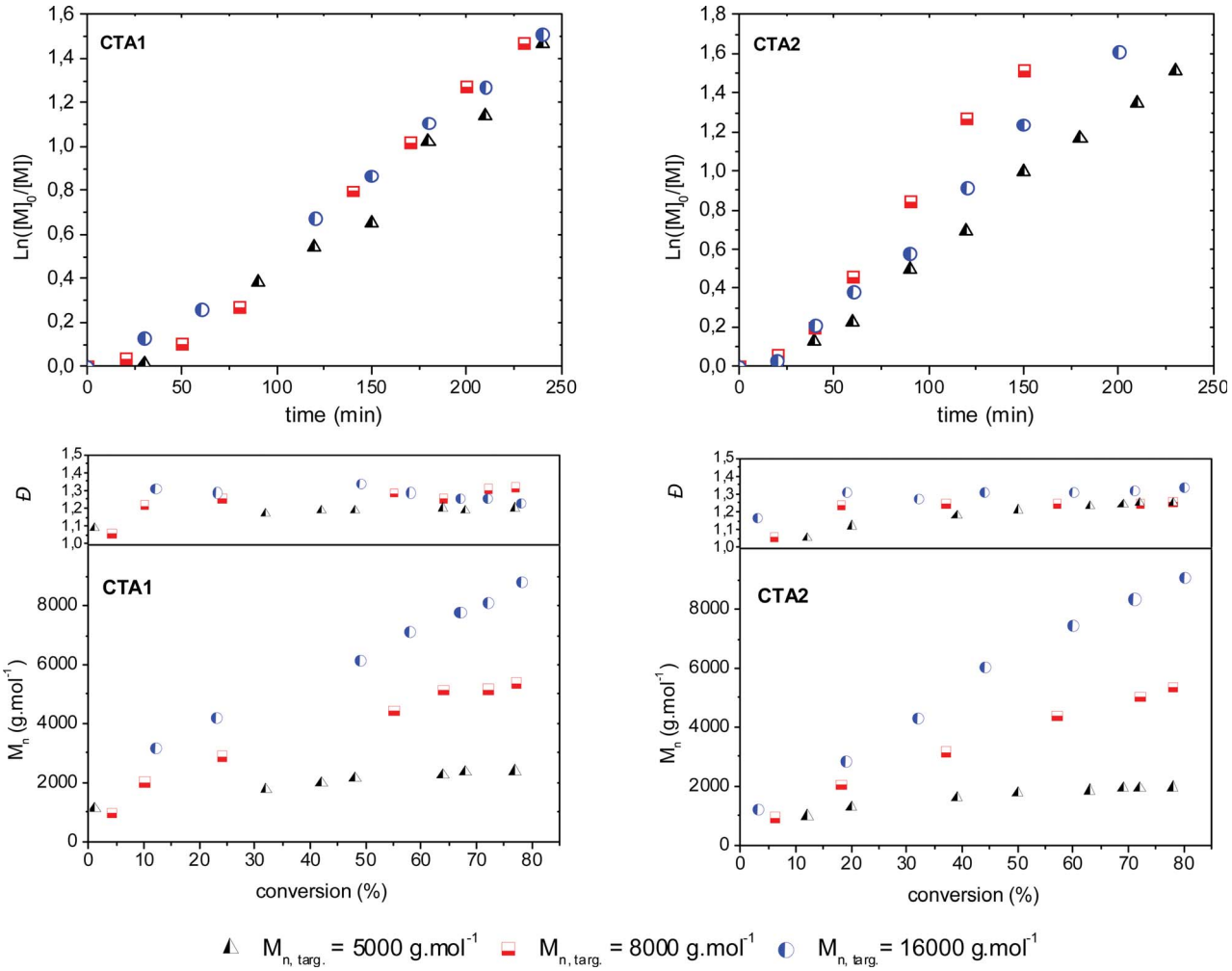


Fig. 1 Kinetic plots and evolution of the molecular weight with conversion for RAFT polymerization of DAAmEP using CTA1 and CTA2 as a chain transfer agent.

RAFT polymerization of the DAAmEP monomer gave first order kinetic plots for both CTAs. An induction period of 25 minutes was measured for all targeted molecular weights. This was explained in the literature by two predominant theories.[28] Barner-Kowollik *et al.* assumed that the intermediate radical obtained during the RAFT process was relatively stable and long-lived (slow fragmentation model).[29] In contrast, Monteiro and de Brouwer proved the presence of cross-termination of the intermediate radical with other free radicals which are in solution (intermediate radical termination model).[30] Both models can also be combined in a unifying model.[31] Linear evolution of the number-average molecular weight (M_n) *versus* conversion was also obtained, showing that no transfer reaction occurred during the polymerization. Additionally, M_n measured by size exclusion chromatography (DMAc, lithium chloride 0.1% weight, 50 °C, PS standard) was under evaluated from the corresponding monomer/chain transfer agent ratio. The observed difference between theoretical and experimental M_n values was attributed to the difference of hydrodynamic volume between the P(DAAmEP) and the PS used for the calibration. Finally, dispersity remained below 1.5 during all the reaction, meaning that all chains grew simultaneously. After purification by precipitation in cold hexane, dispersities were less than 1.35 (Table 1, entries 1–6). From all these results, we concluded that the RAFT polymerization of DAAmEP was controlled.

Results presented in Fig. 1 and Table 1 also show that there were no significant differences between the polymerization of DAAmEP using either 2-cyano-2-propyl dodecyl trithiocarbonate (CTA1) or 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (CTA2). Indeed, the polymerization occurred in similar periods of time and comparable molecular weights and dispersity were obtained with both chain transfer agents.

P(DAAmEP) polymers were characterized by ^{1}H NMR spectroscopy in deuterated water (Fig. 2) which logically showed more broadened peaks in comparison with the monomer. The phosphonated ester group was stable under the polymerization conditions as integrations of the signals attributed to the ethyl groups associated with the ester function at 3.9–4.2 (CH_2) and 1.45–1.75 ppm (CH_3) were in accordance with the one of the methylene in α of the acrylamide group. No residual peaks corresponding to the acrylic protons were noticed, indicating that P(DAAmEP) was pure after precipitation. ^{31}P NMR confirmed the obtaining of a phosphonated-containing polymer with a large signal centered at 31.2 ppm.

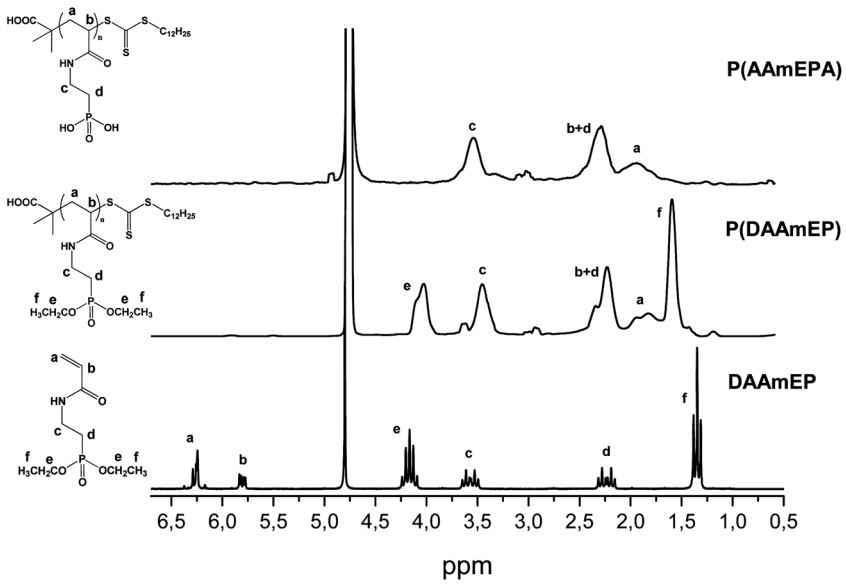


Fig. 2 ^{1}H NMR spectrum of diethyl 2-(acrylamido)ethylphosphonate (DAAmEP), poly(diethyl 2-(acrylamido)ethylphosphonate) (P(DAAmEP)), and poly(2-(acrylamido) ethylphosphonic acid) (P(AAmEPA)) in deuterated water.

Synthesis of P(*Nn*PAAm-*b*-DAAmEP) diblock copolymers by RAFT polymerization

Poly(*N*-*n*-propylacrylamide) macro-chain transfer agent was first synthesized from *N*-*n*-propylacrylamide (*Nn*PAAm) as a monomer, AIBN as a polymerization initiator and DMSO as a solvent. We decided to prepare the P(*Nn*PAAm) thermosensitive polymer with a targeted molecular weight of 10 000 g mol^{-1} (Table 1, entry 7). After precipitation in hot water, the resulting polymer was characterized by size exclusion chromatography in DMAc to determine the number-average molecular weight and the dispersity ($M_{n,exp}$ = 15 100; $Đ$ = 1.25). The ^{1}H NMR spectrum in deuterated chloroform confirmed the obtaining of the targeted structure (Fig. 4). P(*Nn*PAAm) was then used as a macro-chain transfer agent for the polymerization of the DAAmEP monomer in order to prepare well-defined diblock copolymers. For the synthesis of P(*Nn*PAAm-*b*-DAAmEP), the targeted molecular weight of the P(DAAmEP) block was 2500, 5000 and 10 000 g mol^{-1} at 80% conversion (Table 1, entries 8–10). The reaction was carried out using experimental conditions already determined for the homopolymerization of DAAmEP with CTA1 and CTA2: DMSO, 70 °C and a [CTA]/[AIBN] ratio equal to three. 79, 81, and 79% conversion was achieved after 210 minutes for targeted molecular weights equal to 2500, 5000, and 10 000 g mol^{-1}, respectively. Polymerization rates for chain extension were similar in all cases and also equivalent to those obtained for the homopolymerization of the DAAmEP monomer. Kinetic

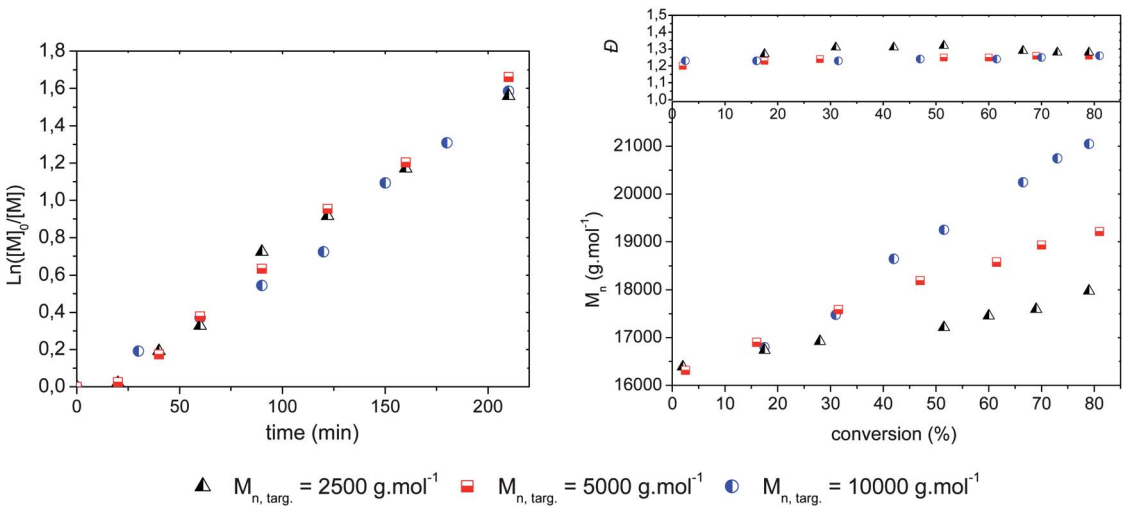


Fig. 3 Kinetic plots (left) and evolution of molecular weight with conversion (right) for the RAFT polymerization of diethyl 2-(acrylamido)ethylphosphonate (DAAmEP) using poly(*N*-*n*-propylacrylamide) (P(*Nn*PAAm)) as a macro-chain transfer agent (M_n = 9900 g mol^{-1}). $M_{n,targ}$ corresponds to the targeted molecular weight for the phosphonated block at 80% conversion.

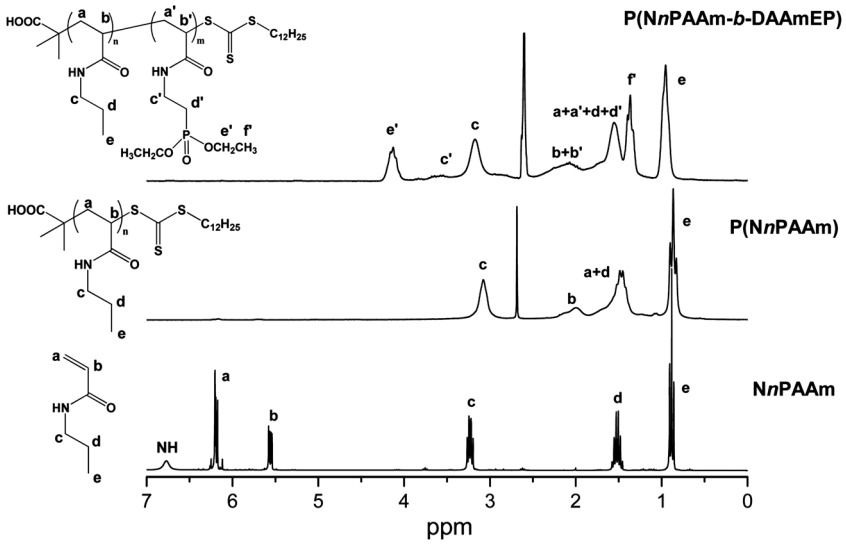


Fig. 4 ^{1}H NMR spectrum of *N*-*n*-propylacrylamide (*Nn*PAAm), poly(*N*-*n*-propylacrylamide) (P(*Nn*PAAm)) (Table 1, entry 7) and poly(*N*-*n*-propylacrylamide)-*b*-(diethyl 2-(acrylamido)ethylphosphonate)) (P(*Nn*PAAm-*b*-DAAmEP)) (Table 1, entry 9) in deuterated chloroform.

results (Fig. 3) show the linearity of both curves representing (i) the evolution of the $\ln([M]_0/[M])$ as the function of time and (ii) the evolution of the molecular weight *versus* conversion. Additionally, the dispersity ($Đ$) remained low during the whole polymerization process. Once again, an induction period of 25 minutes was measured.

Diblock copolymers were precipitated in cold hexane. The comparison between ^{1}H NMR spectroscopy of P(*Nn*PAAm) and P(*Nn*PAAm-*b*-DAAmEP) (Fig. 4) demonstrated that the synthesis of the diblock copolymer was successful. Indeed, all the signals corresponding to both blocks were found, notably those associated with the methylene of the phosphonated ester group of the P(DAAmEP) and to the methyl of the P(*Nn*PAAm), at 3.95–4.40 and 0.8–1.05 ppm, respectively. The presence of the phosphorus atom was confirmed by ^{31}P NMR analysis with a broad signal centered at 29.3 ppm.

The copolymers were finally analyzed by size exclusion chromatography in order to confirm that the DAAmEP-based second block had grown on the P(*Nn*PAAm) macro-chain transfer agent. SEC shows monomodal peaks (Fig. 5) and a lower elution time was obtained for the P(*Nn*PAAm-*b*-DAAmEP) diblock copolymer compared to the P(*Nn*PAAm) macro-chain transfer agent, concomitant with an increase of the molecular weight. In all cases, dispersity of the diblock copolymers was lower than 1.30.

From all these results, we concluded that the polymerization was controlled and that it was possible to prepare well-defined copolymers with a phosphonate-containing polyacrylamide moiety. Finally, it was also possible to hydrolyze the phosphonated ester of P(DAAmEP) homopolymers and P(*Nn*PAAm-*b*-DAAmEP) copolymer into phosphonic diacid groups, leading to more hydrophilic (co)polymers.

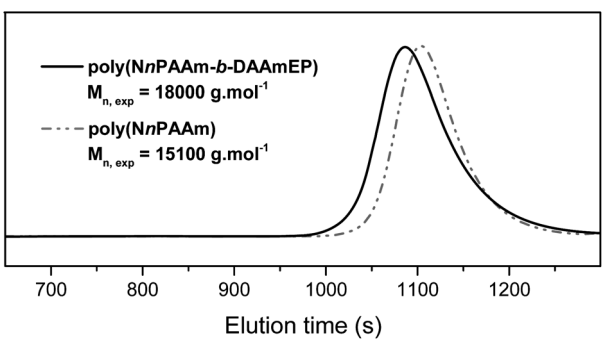


Fig. 5 Size exclusion chromatograms of the poly(*N*-*n*-propylacrylamide) (P(*Nn*PAAm)) macro-chain transfer agent (Table 1, entry 7) and the poly(*N*-*n*-propylacrylamide)-*b*-(diethyl 2-(acrylamido)ethylphosphonate)) (P(*Nn*PAAm-*b*-DAAmEP)) diblock copolymer (Table 1, entry 8) (DMAc eluent + LiCl 0.1% weight at 0.8 mL min^{-1}, with PS standards at 50 °C).

Phosphonated ester hydrolysis of P(DAAmEP) homopolymers and P(*Nn*PAAM-*b*-DAAmEP) copolymer

Well-defined polymers bearing phosphonated ester groups are of real interest for application as flame retardancy or anti-corrosive materials. Nevertheless, properties can be improved and other applications can be considered for such polymers when changing the phosphonated ester groups into phosphonic diacid groups. Indeed, diacid phosphonic moieties are often more reactive than their corresponding ester derivatives. For instance, phosphonic diacid groups provided attractive properties for proton conduction in fuel cell membranes.[7] Additionally, going from phosphonated esters to phosphonic diacid enabled us to enhance the polymer solubility in water which appeared as a great opportunity for applications such as drug delivery or water treatment. Besides, such active groups have also shown higher sorption properties for metallic cations in comparison with corresponding phosphonated ester ones. Thus, the hydrolysis of the phosphonated ester of P(DAAmEP) is of great interest and was carried out on both P(DAAmEP) and P(*Nn*PAAm-*b*-DAAmEP) homo- and copolymers. The hydrolysis

was performed using bromotrimethylsilane and then methanol at room temperature, as already reported in the literature.[32] Resulting poly(2-(acrylamido)ethylphosphonic acid) (P(AAmEPA)) and poly((*N*-*n*-propylacrylamide)-*b*-(2-(acrylamido) ethylphosphonic acid) (P(*Nn*PAAm-*b*-AAmEPA)) were characterized by ^{1}H NMR spectroscopy. For better clarity, the spectrum reported in Fig. 2 corresponds to the P(AAmEPA) homopolymer. Both signals corresponding to the phosphonated ester of P(DAAmEP) (between 3.8 and 4.2 ppm and between 1.1 and 1.35 ppm, for the methylene and methyl groups, respectively) disappeared in the ^{1}H NMR spectrum of P(AAmEPA), proving that the hydrolysis was effective. Additionally, the comparison between the chemical shifts of the phosphorus in ^{31}P NMR spectroscopy demonstrated a shift of the signal from 31.2 ppm for P(DAAmEP) to 26.8 ppm for P(AAmEPA) which confirmed the change of chemical surrounding the phosphonated moieties. Same conclusions were deduced concerning the hydrolysis of P(*Nn*PAAm-*b*-DAAmEP), as characterization by ^{1}H and ^{31}P NMR permitted us to prove the disappearance of signals corresponding to the phosphonated ester moiety in favor of phosphonic diacid groups.

Thermosensitive behavior of P(*Nn*PAAm-*b*-DAAmEP) and P(*Nn*PAAm-*b*-AAmEPA) block copolymers

One of the important characteristics of the polyacrylamides is their thermo-responsive behavior which makes them suitable for many applications, notably in the biomedical field.[33,34] Water-soluble thermosensitive polymers undergo coil-to-globule phase transitions when the temperature is increased above the lower critical solution temperature (LCST). LCST value of the P(*Nn*PAAm), around 22 °C,[35] can be influenced by experimental conditions (pH, ionic strength, *etc.*). Another possibility to modulate the LCST is the synthesis of diblock copolymers combining one thermosensitive block and either a hydrophilic (increase of the LCST) or a hydrophobic (decrease of the LCST) moiety. We first measured the LCST of the P(*Nn*PAAm) with a number-average molecular weight equal to 15 100 g mol^{-1} by UV at a 500 nm wavelength, following the changes in the transmittance through the copolymer aqueous solution during a gradual increase of the temperature (Fig. 6). The temperature ramp was 0.2 °C min^{-1} between 15 °C and 30 °C. The LCST was equal to 22.2 °C, which was coherent with the value usually given in the literature for P(*Nn*PAAm) polymers (22 °C).

The measurement of the thermosensitive behavior of P(*Nn*PAAm-*b*-DAAmEP) and P(*Nn*PAAm-*b*-AAmEPA) diblock copolymers was then achieved in order to evaluate the influence of the second block on the thermosensitivity. Concerning the P(*Nn*PAAm-*b*-DAAmEP), the measured LCST was equal to 21.7 °C which was equivalent to the LCST of the homopolymer. This indicated that the DAAmEP block did not influence the hydrophobic or the hydrophilic characters of the copolymer compared to the P(*Nn*PAAm) homopolymer. On the reverse, the LCST of the P(*Nn*PAAm-*b*-AAmEPA) was higher, as it was measured at 23.6 °C, due to the presence of hydrophilic phosphonic acid groups which provided stronger polymer–water interactions. Finally, to conclude on thermo-responsive behavior, both copolymers proved to be temperature-dependent. Below the LCST, they are fully soluble in water as we have a double hydrophilic block copolymer (DHBC) whereas above the LCST, the P(*Nn*PAAm) moiety becomes insoluble, leading to amphiphilic character.

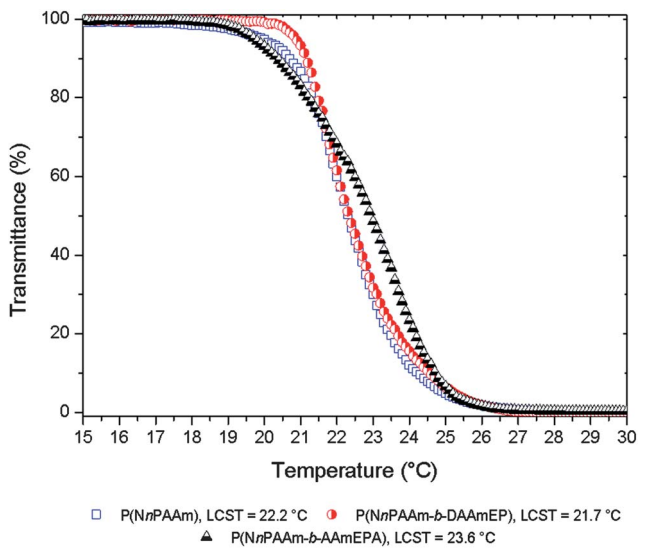


Fig. 6 Plot of transmittance as a function of the temperature for aqueous solution (5 g L^{-1}) of poly(*N*-*n*-propylacrylamide)-*b*-(diethyl 2-(acrylamido)ethylphosphonate)) (P(*Nn*PAAm-*b*-DAAmEP)) and poly(*N*-*n*-propylacrylamide)-*b*-(2-(acrylamido)ethylphosphonic acid)) (P(*Nn*PAAm-*b*-AAmEPA)). Ramp temperature: 0.2 °C min^{-1}, from 15 to 30 °C.

Conclusions

A new phosphorus containing monomer, namely diethyl-2-(acrylamido)ethyl phosphonate (DAAmEP), was synthesized and polymerized by RAFT with two different trithiocarbonate chain transfer agents. Polymerization was controlled and P(DAAmEP) with various molecular weights was prepared, with low dispersity. No noticeable difference was observed between both CTAs. Additionally, P(*Nn*PAAm-*b*-DAAmEP) diblock copolymers were also synthesized using a poly(*N*-*n*-propylacrylamide) thermosensitive polymer as macro chain transfer agent. Once again, RAFT polymerization was perfectly controlled. Then, hydrolysis of the phosphonated ester into phosphonic acid was achieved, leading either to the P(AAmEPA) homopolymer or to the (P(*Nn*PAAm-*b*-AAmEPA)) diblock copolymer. Finally, thermosensitive behavior of the copolymers was studied. We demonstrated that adding the phosphonated block to the first thermosensitive P(*Nn*PAAm) one permitted us to increase the LCST value, due to the hydrophilicity of the phosphonic diacid groups. In this case, LCST value was logically higher for the copolymer.

To conclude, this contribution highlights the synthesis of innovative phosphonated polyacrylamide based polymers and copolymers with a well defined architecture which provide new and chemically very stable materials suitable for a wide range of applications.

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