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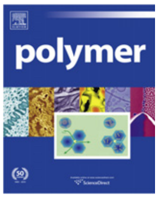

Synthesis of water-soluble homo- and block-copolymers by RAFT polymerization under γ-irradiation in aqueous media

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ABSTRACT

The ambient temperature (20 °C) reversible addition fragmentation chain transfer (RAFT) polymerization of several water-soluble monomers conducted directly in aqueous media under γ-initiation (at dose rates of 30 Gy h^{-1}) proceeds in a controlled fashion. Using functional trithiocarbonates, i.e., *S*,*S*-bis(α,α'-dimethyl-α''-acetic acid) trithiocarbonate (TRITT), 3-benzylsulfanyl thiocarbonylsulfanyl propionic acid (BPATT), and dithioester, i.e., 4-cyanopentanoic acid dithiobenzoate (CPADB), as chain transfer agents, fully water-soluble polymers of monomers such as *N*,*N*-dimethylacrylamide, 2-hydroxyethyl acrylate, acrylamide or oligo(ethylene glycol) methacrylate and stimuli-responsive polymers of monomers such as acrylic acid, *N*-isopropylacrylamide, 2-(dimethylamino)ethyl methacrylate or 2-acrylamido-2-methylpropane sulfonic acid can be obtained over a wide range of degrees of polymerization up to 10,000 with low polydispersity (typically $\overline{M}_w/\overline{M}_n < 1.2$) to near quantitative conversions. Well-defined block copolymers between these monomers, based on several asymmetric macro-RAFT agents, can be obtained, suggesting that the RAFT agents are stable throughout the polymerization process so that complex and well-defined architectures can be obtained.

1. Introduction

Water-soluble polymers are a highly interesting class of materials which have found numerous applications especially in biotechnology [1]. Among them, over the past two decades, delivery of therapeutics [2,3], bioseparations [4,5], or biosensors [6] have been intensively studied. For many purposes, these polymers have to be synthesized via a controlled fashion to obtain targeted molecular weights, narrow molecular weight distributions and well-defined complex architectures. Several techniques can be used to achieve this goal. Anionic polymerization generally gives very good results in terms of molecular weight and polydispersity control [7,8]. However, it is also an experimentally demanding technique, due to the necessity to conduct the reaction with highly pure monomers and solvents. In addition, anionic polymerization cannot be performed directly in water and protic monomers have to be protected first.

Therefore, since the mid-nineties, controlled/living free radical polymerization techniques such as atom transfer radical polymerization (ATRP) [9–13], nitroxide-mediated polymerization (NMP) [14,15] and reversible addition fragmentation chain transfer (RAFT) polymerization [16–19] have received considerable attention due to their relative ease of operation and versatility in synthesizing complex macromolecules with well-defined architectures, controlled molecular weights and low polydispersity. Among these techniques, RAFT polymerization shows particular promise because it possesses significant advantages such as its applicability to a wide variety of monomers (including functional styrenic, acrylate and methacrylate monomers), the performance under a wide array of reaction conditions (e.g. wide range of solvents, including water,

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ambient temperature, UV- or γ-initiation) and processes (e.g. bulk, solution or emulsion). In addition, it allows for the facile preparation of polymers with complex architectures including block, graft and star copolymers [20].

Recently, significant progress has been made in living/controlled free radical polymerization at ambient temperature in aqueous solution, especially via RAFT polymerization. This strategy combines the advantages of working in an environmentally friendly solvent without the necessity to heat the polymerization system. It is also essential in bioconjugate chemistry to work in aqueous systems at low temperature as proteins or viruses require generally mild temperatures ($T \leq 40$ °C) and the absence of organic solvents to avoid denaturation [21–24]. Thus, several strategies have been developed to achieve this goal. For instance, Convertine et al. successfully carried out the aqueous RAFT polymerizations of acrylamide (AAm) and *N,N*-dimethylacrylamide (DMAAm) at 25 °C using *S,S*-bis(α,α′-dimethyl-α″-acetic acid)trithiocarbonate (TRITT) as RAFT agent and 2,2′-azobis[(2-carboxyethyl)-2-methylpropionamidine] (VA-057) as initiator [25]. They obtained well-defined polymers with very low polydispersity (polydispersity index, PDI < 1.1). These authors employed the same process to synthesize thermally responsive poly(*N,N*-dimethylacrylamide)-*b*-poly(*N*-isopropylacrylamide) (PDMAAm-*b*-PNIPAAm) diblock and PDMAAm-*b*-PNIPAAm-*b*-PDMAAm triblock copolymers [26]. In both cases, an azo initiator with a low decomposition temperature was used. Nevertheless, this type of initiator is relatively expensive and difficult to ship and stock due to its inherently low decomposition temperature.

To overcome these disadvantages, other initiating systems were developed. Zhang and coworkers demonstrated that a mixture of potassium persulfate ($K_2S_2O_8$) and sodium thiosulfate ($Na_2S_2O_3$) can be used as redox initiator for RAFT polymerization in aqueous media at ambient temperature [27]. With such a system, these authors were able to polymerize NIPAAm and AAm with good control even at high conversions (>90%). Another possibility of initiation is UV-radiation. Recently Cai's group detailed the RAFT polymerization of *N*-(2-acryloyloxyethyl) pyrrolidone (NAP) and 2-hyroxyethyl acrylate (HEA) monomers in pure water initiated by the photolysis of (2,4,6-trimethylbenzoyl)diphenyl phosphine oxide (TPO) with visible light [28]. Rapid and well-controlled polymerizations were obtained in both cases. Interestingly the reaction exhibited an on/off character: when the irradiation was stopped, the polymerization essentially came to a standstill. Turning on the light again led to another rapid polymerization process with the same kinetics. In addition, Muthukrishnan et al. reported the first RAFT polymerization of acrylic acid (AA) initiated under ultraviolet radiation at a specific wavelength of 365 nm in aqueous solution to achieve PAA with very low polydispersities [29]. In this process, the solution is free of initiator and radicals are generated directly by partial photolysis of the monomer. The chain transfer agent TRITT was used to control the polymerization effectively at conversions as high as 50% with efficient control. However, many RAFT agents, in particular aromatic ones, are UV-sensitive and can decompose under UV irradiation.

Thus, an alternative is initiation by γ-irradiation. Quinn et al. as well as Bai et al. showed that RAFT polymerization can be initiated with γ-irradiation at ambient temperature under full conservation of the control of the polymerization and that the preparation of block copolymers is possible under these conditions [30–34]. This radiation type can initiate most vinylic monomers, such as acrylates, methacrylates and styrenics [35–39]. Barner et al. as well as Barsbay et al. also applied γ-initiated RAFT polymerization to graft polymers from solid surfaces, e.g. polypropylene lanterns [35,40,41] and cellulose [36,42]. Thus, in the past few years, γ-irradiation has been increasingly used in the context of the RAFT process to obtain well-defined (living) polymers [42–45]. Recently, the RAFT polymerization of the water-soluble monomers NIPAAm and AA under γ-irradiation in aqueous media was reported [46]. γ-Initiation was also successfully used to generate a conjugate PNIPAAm–bovine serum albumin via a grafting from approach without any degradation of the protein [47]. It is important to note that while the initiation process under γ-radiation may include a series of species (the initial RAFT agent, the solvent as well as the monomer), a RAFT process is nevertheless in operation (see for example Refs. [48,49]). In here, we describe the generalization of the process to a large variety of water-soluble monomers. We also prove that this technique is an excellent tool to obtain well-defined polymers and block copolymers with very low polydispersity up to full conversion and even for very high degrees of polymerization (DP_n up to 10,000).

2. Experimental part

2.1. Materials

All chemicals and solvents where purchased from Sigma–Aldrich, Acros and Fluka at the highest available purity and used as received unless otherwise noted. NIPAAm was purified by two recrystallizations in a mixture of *n*-hexane and benzene. AA was distilled under vacuum and used freshly. AAm was purified by two recrystallizations in acetone. 2-Hydroxyethyl acrylate, oligo(ethylene glycol) methacrylate (OEGMA, $M = 526$ g mol^{-1}, ~10 ethylene glycol units) and 2-(dimethylamino)ethyl methacrylate (DMAEMA) were passed through a column of neutral alumina to remove the inhibitor prior to use. The syntheses of the RAFT agents *S,S*-bis(α,α′-dimethyl-α″-acetic acid)trithiocarbonate (TRITT), 3-benzylsulfanyl thiocarbonylsulfanyl propionic acid (BPATT) and 4-cyanopentanoic acid dithiobenzoate (CPADB) have been described elsewhere [50–52]. Poly(ethylene oxide) modified benzylsulfanylthiocarbonylsulfanyl propionate (PEO_{2K}-BPATT) was synthesized according to the following procedure. 8 g (4 mmol) of poly(ethylene glycol) monomethyl ether were dissolved in 40 mL water-free *N,N*-dimethylacetamide (DMAc) in presence of 0.39 mL of anhydrous pyridine (4.8 mmol). The solution was cooled with a water/acetone (1/1 v%) ice bath. 1.396 g (4.8 mmol) of 3-benzylsulfanyl thiocarbonylsulfanyl propionic acid chloride (BPATT-COCl) was then added dropwise under stirring. Details of the BPATT-COCl synthesis have been described elsewhere [51]. The solution was allowed to warm to room temperature and was stirred overnight. The mixture was concentrated under reduced pressure and precipitated in cold hexane. After filtering, the yellow solid (BPATT-COCl) was dried under high vacuum for 24 h prior to use.

2.2. Polymerization procedure

Homopolymers and block copolymers were synthesized following the same procedure described here. Monomers were dissolved with the CTA in pure water or in a mixture of water/organic cosolvent, respectively at the desired concentration. After complete dissolution the stock solution was divided and transferred into glass sample vials, containing approximately 3–4 mL solution. The vials were capped with rubber septa and deoxygenated by purging with nitrogen gas for 15 min each. The samples were placed in an insulated room with a ^{60}Co source at ambient temperature (typically close to 20 °C) at a dose rate of 30 Gy h^{-1}. Samples were taken after pre-selected time intervals to follow the monomer conversion. The conversion of each sample was determined directly from the solution by ^{1}H NMR (in D_2O) from the relative integration of peaks associated with the monomer vinyl group in relation to those associated with the polymer. Subsequently, all samples were freeze-dried and purified by precipitation before SEC measurements or subsequent block extension.

2.3. Characterization

^{1}H NMR spectra were recorded on a Bruker spectrometer (300 MHz) in D_2O (residual peak $\delta = 4.79$ ppm). Depending on the nature of the polymer, *Size Exclusion Chromatography (SEC)* analyses were performed in *N*,*N*-dimethylacetamide (DMAc) (0.03% w/v LiBr, 0.05% BHT stabilizer) at 50 °C (flow rate: 0.85 mL min^{-1}) using a PL50 compact modular system comprising a DGU-12A solvent degasser, an LC-10AT pump, a CTO-10A column oven, and an RID-10A refractive index detector. The system was equipped with a 5.0 μm bead-size guard column (50 × 7.8 mm) followed by four 300 × 7.8 mm linear PL columns (10^5, 10^4, 10^3, and 500 Å). Calibration was performed with low polydispersity polystyrene standards ranging from 500 to 10^6 g mol^{-1}. The polymers were also characterized by SEC using a Gynkotek model 300 pump, a Bischoff 8110 RI detector, a Waters 486 UV detector ($\lambda = 270$ nm), and a 0.05 M solution of LiBr in 2-*N*-methylpyrrolidone (NMP) as eluent. PSS GRAM columns (300 × 8 mm, 7 μm): 10^3, 10^2 Å (PSS, Mainz, Germany) were thermostated at 70 °C. A 0.4 wt % (20 μL) polymer solution was injected at an elution rate of 0.72 mL min^{-1}. Polystyrene standards were used to calibrate the columns, and methyl benzoate was used as an internal standard. Finally GPC in water was also used to analyze some polymers (0.1 mol L^{-1} NaN_3, 0.01 mol L^{-1} NaH_2PO_4, pH = 6.3) at 35 °C (flow rate: 1 mL min^{-1}) using a Gynkotek model 300 pump, an ERC column oven, and a Bischoff 8110 refractive index detector. The system was equipped with a Polymer Laboratories (PL) PLaquagel-OH 8 μm bead-size guard column (50 × 7.5 mm) followed by two 300 × 7.5 mm columns, a PLaquagel-OH mix 8 μm and a PLaquagel-OH 30, 8 μm. Calibration was performed with low polydispersity poly(ethylene oxide) standards ranging from 2000 to 85,000 g mol^{-1}. *Liquid Adsorption Chromatography at Critical Conditions of Adsorption* (LACCC) was conducted on a chromatographic system composed of a degasser ERC 3415R, a pump P4000 (TSP), and an autosampler AS3000 (TSP). Two detectors were used: a UV detector UV6000LP (TSP) with two wavelengths ($\lambda = 230$ and 261 nm) and an evaporative light scattering detector (ELSD) EMD 960 (Polymer Laboratories) operating at 80 °C with a gas flow rate of 6.8 L min^{-1}. Two reversed phase columns C18, 250 × 4.6 mm i.d., with 5 μm average particle size were employed, one with 120 Å (YMC) and the other with 300 Å pore diameters (Macherey–Nagel). The solvents, acetonitrile (ACN) and water (H_2O), were HPLC grade and used freshly. The critical solvent composition for polyethylene glycol monomethyl ether (PEO-OH) determined for this system was ACN/H_2O 38.8/61.2 (v/v) at 23 °C with a flow rate of 0.5 mL min^{-1}. Samples were dissolved in the critical mix at a concentration of 0.2 wt%. Then 20 μL was injected. Modified PEO-OH appeared in adsorption mode due to the low polarity of the end group. To obtain a narrow and well-defined peak, a gradient was used after the elution time of remaining PEO-OH. The composition sequence is detailed here. The critical composition was maintained for 16 min. Then, over 16 min, a linear gradient up to 60% of ACN was realized. This percentage was decreased directly to the critical composition over 1 min also with a linear gradient. Finally, this proportion was kept for 60 min to equilibrate the system before the next measurement.

3. Results and discussion

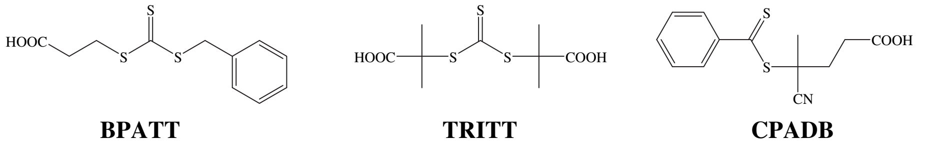
3.1. Homopolymerizations

3.1.1. Polymerization of N,N-dimethylacrylamide (DMAAm)

DMAAm is a very important water-soluble monomer which is widely used [53–55]. DMAAm was polymerized in the presence of two trithiocarbonate CTAs, i.e. BPATT and TRITT (see Scheme 1) at various ratios of monomer to CTA. The results of selected polymerizations are summarized in Tables S1 and S2 and Fig. 1 as well as Figs. S1 and S2 (see Supporting information). Inspection of the kinetic data given in Fig. 1 clearly indicates that TRITT allows for an excellent control of DMAAm polymerization in pure water. This RAFT agent was selected for its good solubility in water, even at high concentration, due to the presence of the two carboxylic moieties. It is also known to allow a good control of acrylate-based monomers [56–58]. With an initial DMAAm/TRITT ratio of 400, the first-order time-conversion plot (Fig. 1A) displays a short induction time, close to 15 min. Such induction phenomena are often observed in the RAFT process [59–62]. After the induction period, the first-order plot is linear up to 90% conversion indicating that the main RAFT equilibrium is rapidly established and an apparent first-order dependence on monomer concentration is operative during the major part of the polymerization. Fig. 1B depicts the evolutions of the apparent number-average molecular weight and the polydispersity index with the conversion. It is obvious that the molecular weight increases linearly with conversion demonstrating the controlled fashion of the process. The difference between the theoretical and the experimental molecular weight can be assigned to the calibration of the SEC on the basis of polystyrene equivalents. The resulting polydispersity indices, PDI, are low (PDI < 1.2) except at the early stage of the polymerization and they decrease throughout the polymerization. Even at high conversions (>95%) the PDI is low (PDI = 1.07) and monomodal molecular weight distributions are observed (results not shown).

The asymmetric CTA 3-benzyl sulfanylthiocarbonylsulfanyl propionic acid (BPATT) was also employed in the γ-radiation initiated polymerization of DMAAm. An added advantage of this CTA is the ability to easily link it via the carboxylic group to surfaces or to small molecules to generate star polymers [42,55,63,64]. However, the main problem of BPATT is its poor solubility in pure water due to the aromatic ring. To dissolve it completely, the addition of a cosolvent is required. Here, the addition of acetone at different volume ratios is used to obtain a homogenous solution. Acetone was chosen due to its low boiling point, which makes it easy to remove by distillation to finally obtain the polymer in pure water.

The fundamental experimental data for BPATT-mediated polymerizations of DMAAm are collected in Table S1 and Figure S1 (see supporting information). As in the case of TRITT, the control of the DMAAm polymerization is very good. When a monomer/CTA ratio of 200 is used, an induction period close to 3 h is observed. Subsequently, the first-order time-conversion plot exhibits a linear relationship during a major part of the polymerization (Fig. S1A). Moreover – as depicted in Fig. S1B – the molecular weight



Scheme 1. RAFT agents employed in the present study. From left to right, 3-benzyl sulfanylthiocarbonylsulfanyl propionic acid (BPATT)), (*S*,*S*-bis(α,α′-dimethyl-α″-acetic acid) trithiocarbonate (TRITT) and 4-cyanopentanoic acid dithiobenzoate (CPADB).

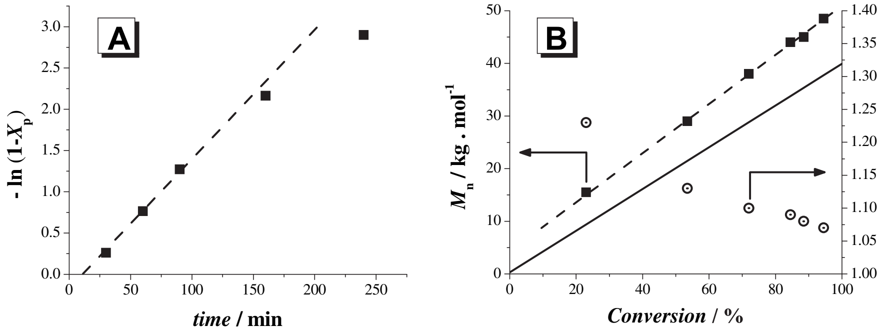


Fig. 1. Kinetics of the RAFT polymerization of DMAAm under γ-radiation (dose rate = 30 Gy h^{-1}) in pure water at ambient temperature using TRITT as CTA for an initial ratio $[M]_0/[CTA]_0 = 400$ with $[M]_0 = 1.5$ mol L^{-1}. (A) First-order time-conversion plot (■), (– –) extrapolation. (B) Apparent number-average molecular weight (■) and PDI (⊙) versus monomer conversion measured by SEC using PS standards, (– –) extrapolation, (—) theoretical number-average molecular weight evolution determined according to the equation $\overline{M}_{n,th} = [M]_0/[CTA]_0 \cdot X_p \cdot M_M + M_{CTA}$.

increases linearly with monomer conversion and the PDI decreases up to 1.05, which indicates the absence of undesired side reactions. Obtaining well-defined blocks of high molecular weight by increasing the monomer/CTA ratio is a considerable challenge. BPATT is an excellent candidate for the RAFT polymerization of DMAAm under γ-radiation to obtain a large variety of chain lengths from $DP_n = 60$ up to 4000 with good control (Fig. S1C and Table S1). The SEC traces and the polydispersity indices indicate good control of the polymerizations even at a very low concentration of RAFT agent up to high conversions. The molecular weight distributions are unimodal except in few cases where a small evidence of termination by recombination of radicals is noticed when the monomer conversion is almost complete.

In addition of being an environmental friendly and cheap solvent, water also improves the kinetics and the control of the RAFT polymerization of DMAAm compared to organic solvents. For the same DMAAm/BPATT ratio (1000/1), kinetic studies were conducted in aqueous media and in 1,4-dioxane. The respective results are summarized in Fig. S2 and Table S2 (see Supporting information). Dioxane is well-known to be a solvent of choice to polymerize DMAAm and other (meth)acrylamide derivatives and good results were already obtained by different research groups [61,65–67]. For instance, Liu et al. used this solvent to synthesize narrowly distributed PDMAAm and PDMAAm-*b*-PNIPAAm [68]. The generated block copolymers were used afterwards for surface modification of multi-walled carbon nanotubes via a *Click* chemistry approach. However, in case of γ-initiation, a long induction period close to 3 h was observed when dioxane was used as can be seen in Fig. S2A. This effect was almost not noticed when the polymerization was conducted in aqueous solution at this high monomer/CTA ratio. Moreover, the apparent rate coefficient associated with the rate of polymerization, k_p^{app} (estimated from the slope of the linear part of the first-order time-conversion plot) exhibits a difference. In dioxane, the polymerization seems much slower in comparison to aqueous media. An apparent rate coefficient of $k_p^{app} = 6.1 \cdot 10^{-5}$ s^{-1} was determined for the organic solvent which is more than 2.5 time lower compared to the one estimated at the same conditions in aqueous media ($k_p^{app} = 16 \cdot 10^{-5}$ s^{-1}). Thus, to reach a monomer conversion of 96%, a reaction time of less than 7 h is needed in aqueous solution while more than 18 h is necessary in dioxane. The low rate of polymerization in dioxane may result from two factors: (i) compared to water, the radical concentration may be lower in dioxane due to a less efficient radiolysis of this solvent compared to water [69] and (ii) protic solvents such as water activate the propagating radical to react faster with monomers present in the media [70,71]. It is also important to note that the control obtained in dioxane is not as good as in aqueous media (Fig. S2B). Low polydisperse PDMAAm samples were obtained in a water-based system with a PDI close to 1.10 even close to full conversion. In dioxane, although the molecular weight increases linearly with the conversion, as in aqueous media, the polydispersity index did not decrease below 1.20. It should be noted that a certain loss of control may be caused by potentially peroxide containing solvents such as tetrahydrofuran and dioxane, which may cause the thio carbonylthio moiety to be oxidized or even removed [72,73].

Taking into account all the benefits of using γ-initiation at ambient temperature in aqueous media to polymerize water-soluble monomers by RAFT, a large range of monomers was tested. Selected results are collected in Table 1 and in the Supporting information section (see Table S3–S5 and Figure S3–S6).

3.1.2. *Polymerization of 2-hydroxyethyl acrylate (HEA)*

HEA was polymerized in presence of two CTAs, i.e. TRITT and BPATT. When the polymerization is conducted using BPATT as RAFT agent with an initial HEA/BPATT ratio of 200 in a mixture of water/acetone, good control is reached. The first-order time-conversion plot (Fig. S3A) exhibits linearity up to a conversion higher than 95%, which indicates that the radical concentration is approximately constant over the duration of the polymerization. It also seems that

Table 1
RAFT polymerization under γ-initiation of water-soluble monomers in aqueous media at ambient temperature.

Monomer[a]	CTA	$[M]_0/[CTA]_0$	Acetone %Vol	Time min	x_p[b] %	$\overline{M}_{n,th}$[c] kg/mol	$\overline{M}_{n,exp}$ kg/mol	PDI
HEA	TRITT	400	–	420	91	43	72[d]	1.15[d]
HEA	BPATT	200	25	1440	97	22.8	50[d]	1.12[d]
AAm	TRITT	400	–	300	89	25.6	17[e]	1.19[e]
AAm	BPATT	800	22	2720	>99	57	37[e]	1.19[e]
AA	TRITT	800	–	1200	98	57	87[e]	1.14[e]
AA	BPATT	1200	16	1520	98	85	98[e]	1.10[e]
NIPAAm	TRITT	500	–	180	98	56	74[d]	1.10[d]
NIPAAm	BPATT	1000	15	310	88	100	105[d]	1.12[d]
AMPS	TRITT	800	–	220	90	131	178[d]	1.16[d]
AMPS	BPATT	200	30	1440	96	40	57[d]	1.19[d]
OEGMA	CPADB	100	15	140	16	8.7	10[d]	1.05[d]
OEGMA	CPADB	100	15	240	73	38.7	50[d]	1.07[d]
DMAEMA	CPADB	100	10	240	79	12.7	17.5[d]	1.20[d]

[a] HEA = 2-hydroxyethyl acrylate, AAm = acrylamide, AA = acrylic acid, NIPAAm = *N*-isopropylacrylamide, AMPS = 2-acrylamido-2-methylpropane sulfonic acid, OEGMA = oligo(ethylene glycol) methacrylate, DMAEMA = 2-(dimethylamino)ethyl methacrylate.

[b] Determined by ^1H NMR spectroscopy in D_2O.

[c] $\overline{M}_{n,th} = M_M \cdot X_p \cdot [M]_0/[CTA]_0 + M_{CTA}$.

[d] Measured by SEC using PS standards in *N*,*N*-dimethylacetamide (DMAc).

[e] Measured by SEC using PEO standards in water.

no induction period can be determined by extrapolation of the linear part. Moreover, it is clear from the Fig. S3B that the apparent number-average molecular weight of the polymer increases linearly with the monomer conversion. The linearity, associated with a low PDI which decreases over the polymerization to reach a value close to 1.1, demonstrates the controlled fashion of the process. The SEC traces (Fig. S3C) are monomodal and symmetric at low conversion, yet when a conversion higher than 60% is reached a shoulder can be detected at high molecular weights. This phenomenon can be explained by a possible termination by recombination of two growing radicals. By using TRITT as RAFT agent, it was possible to conduct the polymerization in pure water (see Table S3). Similar results were obtained and a good control was achieved. The first-order time-conversion plot and the apparent molecular weight increase linearly respectively with the time and the monomer conversion (Fig. S4). Again no induction period was detected and the polydispersity index was almost always lower than 1.2 except at low conversion. The obtained low PDIs prove – as for BPATT – that the polymerization of HEA, initiated by γ-irradiation at ambient temperature, proceeds in a controlled manner.

3.1.3. Polymerization of acrylamide (AAm)

The influence of the monomer/CTA ratio was investigated for the RAFT polymerization of AAm mediated by BPATT. Table S4 and Fig. S5 summarize the results. By modifying the monomer/CTA ratio, a large range of targeted degrees of polymerization from 120 to 10,000 was obtained with a good control even at nearly full monomer conversion (>99%). The apparent number-average molecular weight increases linearly with the ratio AAm/BPATT up to 4000 (Fig. S5A). The difference between the theoretical and the experimental molecular weights can be assigned to the calibration of the SEC on the basis of poly(ethylene oxide) standards. It can be also seen that every polymerization exhibits a polydispersity index lower than 1.2. An important reason to explain the low polydispersity is the high dilution (less than 0.5 mol L^{-1}) used when high molecular weight polymers were desired. Indeed, all reactions were performed in a static environment without stirring the solutions. Thus, only Brownian motion allows the monomer and the polymer coils to move. The control of the system is therefore significantly depending on the diffusion of the reactants and on the system viscosity. By using a dilute solution, a reasonably low viscosity was observed and better results were obtained (results not shown). All AAm polymerizations were conducted for a longer time than necessary according to the kinetic results to be sure to reach full conversion. As depicted in Fig. S5B, all molecular weight distributions are monomodal and do not exhibit a shoulder at high molecular weight due to the termination by recombination of growing radicals. Therefore, the RAFT polymerization initiated by γ-radiation is a very useful and versatile tool to obtain well-defined polymers with exactly targeted molecular weight without having a precise knowledge of the polymerization kinetics.

Table 2

RAFT Synthesis of poly(acrylic acid) (PAA) macro-CTAs for the synthesis of block copolymers; γ-initiation at room temperature.

Run	CTA	$[M]_0$/$[CTA]_0$	$[M]_0$ mol/L	Acetone %Vol	Time min	x_p[a] %	$\overline{M}_{n,th}$[b] kg/mol	$\overline{M}_{n,exp}$[c] kg/mol	PDI[c]
B1	BPATT	42	2.5	50	1620	63	2.2	7.9	1.10
B2	BPATT	42	2.5	50	2500	>99	3.4	11	1.08
B3	BPATT	200	2.5	23	1520	>99	14.4	45	1.08
B4	BPATT	500	2.5	20	1520	>99	36.3	87	1.11
B5	BPATT	2000	2.0	15	1520	>99	144	230	1.26

[a] Determined by ^{1}H NMR spectroscopy in D_2O.

[b] $\overline{M}_{n,th} = M_M \cdot X_p \cdot [M]_0/[CTA]_0 + M_{CTA}$

[c] Apparent number-average molecular weights and PDIs, as measured by SEC using PEO standards in water.

3.1.4. Polymerization of acrylic acid (AA)

Poly(acrylic acid) (PAA) has been intensively investigated for its stimuli-responsive properties. PAA responds in water to changes in pH and ionic strength by changing coil dimensions and solubility. Therefore it finds a vast array of applications, especially in the biomedical area [74–76]. Kinetic details of the RAFT polymerization at ambient temperature in aqueous media under γ-irradiation mediated by TRITT and BPATT have been previously reported by us [46]. Both RAFT agents successfully controlled the polymerization. The first-order time-conversion plot exhibits a linear relationship associated with an absence or only a very short induction period. The apparent molecular weights increase linearly with the monomer conversion and the PDI decreases throughout the polymerization to reach a value close to 1.10. Moreover, the molecular weight distributions are monomodal even at very high conversion, which indicates the absence of undesired side reactions. Finally, we demonstrated the living character of the process by subsequent chain extension. We now investigated the ability of BPATT-mediated RAFT polymerization in aqueous media under γ-irradiation to generate well-defined PAA with very high molecular weight. The results are summarized in Table S5 and Fig. S6. As in the case of AAm, high molecular weight PAA with DP_n up to 10,000 and narrow molecular weight distributions (PDI < 1.20) were obtained via this process. It is also important to note that this technique can be

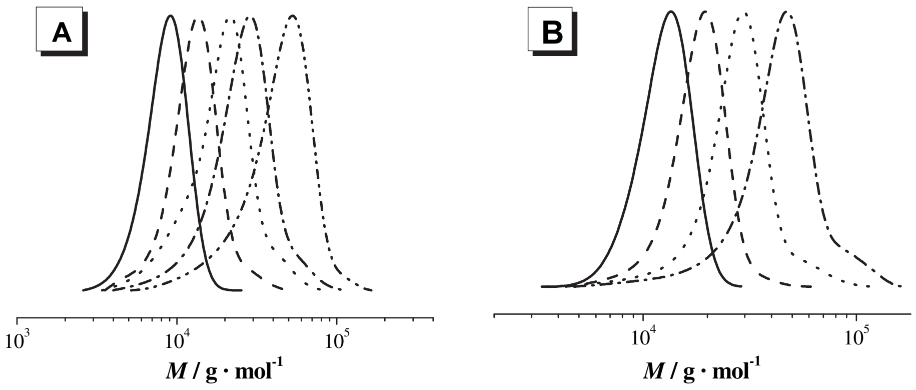


Fig. 2. Dependence of the molecular weight distributions, $w(\log M)$, on the ratio $[AAm]_0/[PAA-CTA]_0$ in the RAFT polymerization of AAm under γ-radiation in water at ambient temperature using PAA macro-CTAs. (A) Using a PAA macro-CTA B1. PAA precursor (—), after chain extension with $[M]_0/[CTA]_0 = 105$ (– –), 205 (• • •), 405 (– • –) and 1000 (– • • –). (B) Using a PAA macro-CTA B2. PAA precursor (—–), after chain extension with $[M]_0/[CTA]_0 = 155$ (– –), 300 (• • •) and 610 (– • –).

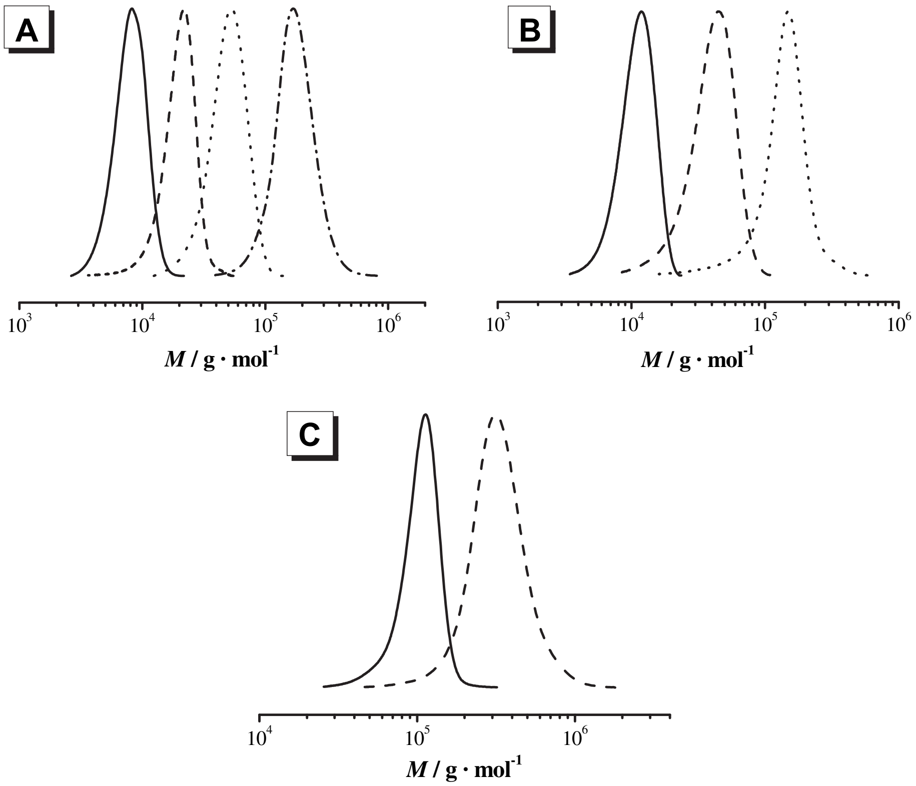


Fig. 3. Dependence of the molecular weight distributions, $w(\log M)$, on the ratio [NIPAAm]$_0$/[PAA-CTA]$_0$ in the RAFT polymerization of NIPAAm under γ-radiation in aqueous solution using PAA macro-CTAs. (A) Using a PAA macro-CTA B1. PAA precursor (——), after chain extension with [M]$_0$/[CTA]$_0$ = 50 (– –), 300 (• • •) and 1000 (– • –). (B) Using a PAA macro-CTA B2. PAA precursor (——), after chain extension with [M]$_0$/[CTA]$_0$ = 200 (– –) and 1000 (• • •). (C) Using a PAA macro-CTA based on B4. PAA precursor (——), after chain extension with [M]$_0$/[CTA]$_0$ = 2000 (– –).

applied over an extremely high range of AA/BPATT ratios from 42 to 10,000 without sacrificing the control. As depicted in Fig. S6A, the apparent molecular weight increases linearly with the initial monomer to CTA ratio up to a *DP* of 300. Afterwards, a deviation is observed which can be attributed to the calibration of the SEC on the basis of poly(ethylene oxide) (PEO) equivalents. Indeed there is a strong difference in behavior between non-ionic PEO and our polyanion PAA during the SEC measurement. However, as can be seen from Fig. S6B, it is clear that all molecular weight distributions are monomodal, symmetric and do not exhibit any visible termination even at nearly full conversion.

3.1.5. Polymerization of other water-soluble monomers

The polymerization of two other acrylamides and two methacrylate-based monomers were investigated Selected conditions and results are collected in Table 1 and Fig. S7. Poly(*N*-isopropylacrylamide) (PNIPAAm), a thermo-responsive polymer, was already successfully polymerized by us using BPATT or TRITT as RAFT agent via γ-initiation in aqueous media [46]. With both CTAs, narrow distributed polymers were synthesized over a large range of degrees of polymerization. For instance, it can be seen for a polymerization carried out in water with an initial NIPAAm/TRITT ratio of 500 (Table 1), that the reaction reaches a conversion of 98% within 3 h,

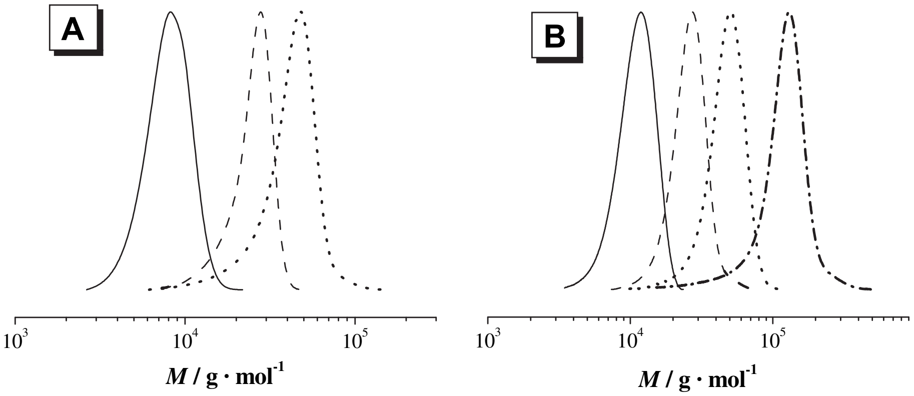


Fig. 4. Dependence of the molecular weight distributions, $w(\log M)$, on the ratio [DMAAm]$_0$/[PAA-CTA]$_0$ in the RAFT polymerization of DMAAm under γ-radiation in aqueous solution at ambient temperature using PAA macro-CTAs. (A) Using a PAA macro-CTA B1. PAA precursor (—), after chain extension with [M]$_0$/[CTA]$_0$ = 100 (– –), 300 (• • •). (B) Using a PAA macro-CTA B2. PAA precursor (—), after chain extension with [M]$_0$/[CTA]$_0$ = 100 (– –), 300 (• • •) and 1000 (– • –).

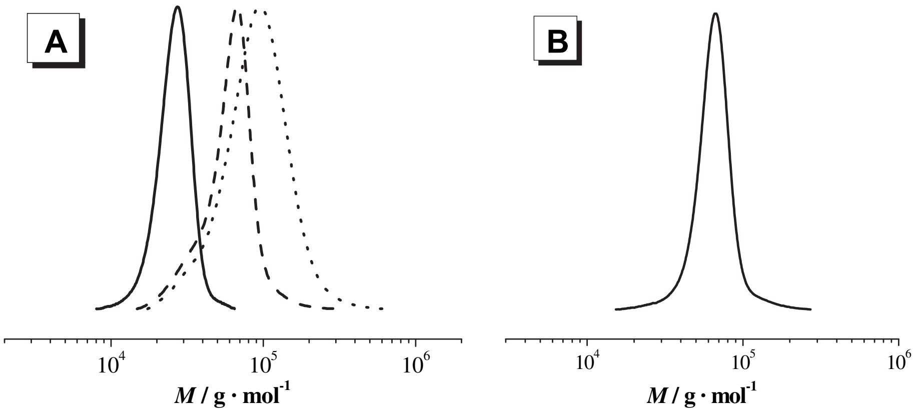


Fig. 5. (A) Dependence of the molecular weight distributions, $w(\log M)$, on the ratio $[\mathrm{DMAAm}]_0/[\mathrm{PNIPAAm\text{-}CTA}]_0$ in the RAFT polymerization of DMAAm under γ-radiation in water at ambient temperature using PNIPAAm macro-CTA. PNIPAAm precursor (—), after chain extension with $[\mathrm{M}]_0/[\mathrm{CTA}]_0 = 400$ (– –) and 1000 (• • •). (B) Molecular weight distribution, $w(\log M)$, of PEO-*b*-PDMAAm synthesized by RAFT polymerization of DMAAm under γ-radiation in aqueous solution at ambient temperature using PEO_{2k}-BPATT macro-CTA.

which highlights the fast character of NIPAAm polymerization in water. However, thanks to the good transfer ability of the RAFT agent, a narrow, a symmetric and monomodal molecular weight distribution was obtained (Fig. S7A). The polymerization of 2-acrylamido-2-methylpropane sulfonic acid (AMPS) also exhibits a good control when BPATT or TRITT is used (Fig. S7B).

Oligo(ethylene glycol) methacrylate (OEGMA) and 2-(dimethylamino)ethyl methacrylate (DMAEMA) cannot be polymerized in a controlled manner when TRITT or BPATT are used. Indeed these RAFT agents are commonly employed for the synthesis of acrylate-based polymers. Due to the low stability of the original radical R• generated from the CTA compared to the growing radical, the fragmentation step of the R group is unlikely. In addition – and more importantly – the propensity of the C═S double bond towards methacrylic radical attack is low. The consequence is a poor control when BPATT or TRITT is used to mediate the polymerization of methacrylates. Therefore, we selected 4-cyanopentanoic acid dithiobenzoate (CPADB) as RAFT agent to polymerize OEGMA and DMAEMA. CPADB has a highly reactive C═S double bond and generates a more stable but reactive tertiary radical R• after fragmentation and allows a good control of methacrylate-based monomers [77–82]. Moreover it features a carboxylic group which allows good solubility in aqueous solution with the use of only a limited amount of organic cosolvent. The RAFT polymerizations of OEGMA and DMAEMA mediated by CPADB showed a good control. Monomodal and narrow molecular weight distribution were obtained in both cases (Table 1 and Fig. S7C and D).

Table 3
Chain extension with acrylamide (AAm) of various poly(acrylic acid) (PAA) macro-CTAs by RAFT polymerization in aqueous media at ambient temperature under γ-initiation.

PAA macro-CTA	$\frac{[\mathrm{M}]_0}{[\mathrm{CTA}]_0}$	$\frac{[\mathrm{M}]_0}{\mathrm{mol/L}}$	$\frac{\text{Ethanol}}{\text{\%Vol}}$	$\frac{\text{Time}}{\text{min}}$	$\frac{x_p}{\%}$[c]	$\frac{\overline{M}_{n,th}}{\mathrm{kg/mol}}$[d]	$\frac{\overline{M}_{n,exp}}{\mathrm{kg/mol}}$[e]	PDI[e]
B1	105[a]	2	40	1620	95	9.3	12	1.14
B1	205[a]	2	30	1620	98	16.4	17	1.25
B1	405[a]	2	22	1620	>99	31	23	1.23
B1	1 000[a]	1.5	20	1440	>99	73.3	37	1.27
B2	155[b]	2	35	1515	97	14.1	17	1.10
B2	300[b]	2	25	1515	99	24.7	25	1.17
B2	610[b]	2	15	1515	>99	46.8	38	1.23

[a] Using asymmetric PAA-macro-CTA B1 of $DP_n = 26$.
[b] Using asymmetric PAA-macro-CTA B2 of $DP_n = 42$.
[c] Determined by ^{1}H NMR spectroscopy in D_2O.
[d] $\overline{M}_{n,th} = M_M \cdot X_p \cdot [\mathrm{M}]_0/[\mathrm{CTA}]_0 + M_{CTA}$.
[e] Apparent number-average molecular weights and PDIs, as measured by SEC using PEO standards in water.

3.2. *Synthesis of block copolymers with acrylic acid*

3.2.1. *Synthesis of poly(acrylic acid) macro-CTAs*

To further demonstrate the retention of the RAFT functionality and the controlled nature of the above discussed polymerizations, several block copolymers were synthesized. Selected results are summarized in Table 2 and Figs. 2–5. A number of PAA macro-CTAs were synthesized using BPATT under γ-irradiation. Since BPATT is an asymmetric CTA, it allows the generation of AB diblock copolymers. After purification, these macro-CTAs were used to polymerize various monomers.

3.2.2. *Block copolymers with acrylamide (AAm)*

Two different PAA CTAs were used to polymerize acrylamide at different AAm/PAA ratios of up to 1000. The results are given in Table 3 and Fig. 2. For all ratios good control was found. Monomodal molecular weight distributions were obtained even at high conversion and no remaining PAA precursor was observed in the SEC traces as inspection of Fig. 2A reveals. However, the distributions are not completely symmetric and a tailing towards low molecular weights can be noticed. Such a phenomenon may be associated with the slow establishment of the pre-equilibrium

Table 4
Chain extension with NIPAAm of various PAA macro-CTAs by RAFT polymerization in aqueous media (50 Vol% dioxane) at ambient temperature under γ-initiation.

PAA macro-CTA	$\frac{[\mathrm{M}]_0}{[\mathrm{CTA}]_0}$	$\frac{[\mathrm{M}]_0}{\mathrm{mol/L}}$	$\frac{\text{Time}}{\text{min}}$	$\frac{x_p}{\%}$[f]	$\frac{\overline{M}_{n,th}}{\mathrm{kg/mol}}$[g]	$\frac{\overline{M}_{n,exp}}{\mathrm{kg/mol}}$[h]	PDI[h]
B1	50[a]	1	1440	81	6.8	17.5	1.14
B1	100[a]	1	1440	89	12.2	24	1.12
B1	200[a]	1	1440	98	24.5	38	1.12
B1	300[a]	1	1440	99	35.8	50	1.14
B1	1000[a]	1	1440	>99	115	130	1.20
B2	200[b]	1	1440	98	25.6	38	1.15
B2	1000[b]	1	1440	>99	116	102	1.30
B3	2000[c]	0.6	1440	>99	241	217	1.24
B4	2000[d]	0.5	1440	>99	262	254	1.28
B5	1000[e]	0.4	1440	>99	257	343	1.40

[a] Using asymmetric PAA-macro-CTA B1 of $DP_n = 26$.
[b] Using asymmetric PAA-macro-CTA B2 of $DP_n = 42$.
[c] Using asymmetric PAA-macro-CTA B3 of $DP_n = 200$.
[d] Using asymmetric PAA-macro-CTA B4 of $DP_n = 500$.
[e] Using asymmetric PAA-macro-CTA B5 of $DP_n = 2000$.
[f] Determined by ^{1}H NMR in D_2O.
[g] $\overline{M}_{n,th} = M_M \cdot X_p \cdot [\mathrm{M}]_0/[\mathrm{CTA}]_0 + M_{CTA}$.
[h] Apparent number-average molecular weights and PDIs, as measured by SEC using polystyrene standards in *N*,*N*-dimethylacetamide (DMAc).

Table 5

Chain extension with DMAAm ($[M]_0 = 1$ mol L^{-1}) of various PAA macro-CTAs by RAFT polymerization in aqueous media at room temperature under γ-initiation.

PAA macro-CTA	$[M]_0$/$[CTA]_0$	Acetone %Vol	Time min	x_p[c] %	$\overline{M}_{n,th}$[d] kg/mol	$\overline{M}_{n,exp}$[e] kg/mol	PDI[e]
B1	100[a]	17	2540	>99	12.1	23	1.09
B1	200[a]	13	2540	>99	22	31	1.10
B1	300[a]	10	2540	>99	32	38	1.16
B2	100[b]	13	2540	>99	13.4	25	1.08
B2	200[b]	10	2540	>99	23.3	32	1.12
B2	300[b]	4	2540	>99	33.2	41	1.11
B2	1 000[b]	4	1440	>99	102.5	88	1.31

[a] Using asymmetric PAA-macro-CTA B1 of $DP_n = 26$.
[b] Using asymmetric PAA-macro-CTA B2 of $DP_n = 42$.
[c] Determined by ^{1}H NMR spectroscopy in D_2O.
[d] $\overline{M}_{n,th} = M_M \cdot X_p \cdot [M]_0/[CTA]_0 + M_{CTA}$.
[e] Apparent number-average molecular weights and PDIs, as measured by SEC using PS standards in *N*,*N*-dimethylacetamide (DMAc).

between the PAAm growing radicals and the PAA macro-CTA. Very well-defined block copolymers PAAm$_x$-*b*-PAA$_y$ were synthesized even when a PAA macro-CTA obtained at full monomer conversion was employed. According to the SEC traces, no residual PAA seems to be present and only a small amount of recombination was observed at extremely high conversion (>99%) for the diblock copolymers. These experiments show that RAFT polymerization under γ-irradiation is a simple process to generate well-controlled block copolymers in aqueous solutions. Due to the extremely low amount of bimolecular termination or other side reactions, precursors and extended polymers can be polymerized up to full conversion which allows a precise control of the targeted DP_n over a wide range.

3.2.3. Block copolymers with N-isopropylacrylamide (NIPAAm)

AB block copolymers were synthesized from PAA precursors. Selected results are collected in Table 4 and Fig. 3. PNIPAAm-*b*-PAA responds to both temperature and pH and it is known to form hydrogen bonds between the carboxylic groups of the acrylic acid unit and the amide groups of NIPAAm [83]. When the polymerizations were carried out in pure water, the complexation leads to a full collapse of the block copolymers which results in a loss of control. To avoid this loss, an organic solvent dioxane was added in the media to prevent the aggregation.

Two low molecular weight PAAs with a degrees of polymerization of 26 and 42, respectively were used to generate different block copolymers over a very large range of NIPAAm/macro-CTA ratios of up to 1000. In all cases, the obtained polymers were narrowly distributed (PDI ≤ 1.20). The SEC traces did not exhibit any traces of residual precursor as evident from Fig. 3A and B. Moreover, the molecular weight distributions are symmetrical and even at high conversion no termination by coupling was detected. Three further PAA macro-CTAs produced at near quantitative monomer conversions and having DP_n's of of 200, 500 and 2000, respectively, were also used to generate high molecular weight PNIPAAm-*b*-PAA block copolymers. As previously observed for the short chain PAA, well-defined block copolymers were obtained in all cases. A clear shift of the molecular weights and an absence of residual macro-RAFT agent were found for the molecular weight distributions for the samples prepared with the PAA$_{196}$ and PAA$_{500}$ as depicted in Fig. 3C, which demonstrate the possibility to generate very high molecular weight block copolymers (up to 250 kg mol^{-1}) with this technique.

3.2.4. Block copolymers with N,N-dimethylacrylamide (DMAAm)

Block copolymers with *N*,*N*-dimethylacrylamide (DMAAm) were also generated by RAFT using γ-irradiation to initiate the process. Again different PAA precursors were used. Selected results are highlighted in Table 5 and Fig. 4. When short PAA macro-CTAs based on BPATT were employed, the following results were obtained. The SEC traces of the block copolymers depicted in Fig. 4A and B exhibit a clear shift in molecular weight compared to the macro-RAFT agent. The molecular weight distributions are monomodal and narrowly distributed (PDI generally below 1.15). It should be noticed that often a small tailing can be observed in the range of the low molecular weight. This phenomenon, also observed in the case of PAA-*b*-PAAm, may find its origin in a slow fragmentation of the original macro-CTA where the PAA macroradical is found to be less stable than PDMAAm or the PAAm macroradical, respectively. However this phenomenon plays a minor role and well-defined polymers were produced at the end. Finally, all the block copolymers were synthesized at almost full monomer conversion and no or only very minor termination was observed.

3.3. RAFT synthesis of PNIPAAm-b-PDMAAm

PNIPAAm was also evaluated as macro-RAFT agent to generate PDMAAm-*b*-PNIPAAm diblock copolymers. The obtained results are summarized in Table 6 and Fig. 5A. The syntheses were carried out in pure water due to the solubility of all components in this solvent at ambient temperature. Both reactions were carried out close to full conversions and present rather low polydispersities. However, the SEC traces depicted in Fig. 5A indicate some residual PNIPAAm precursors, may be due to a slow establishment of the RAFT equilibrium compared to propagation.

3.4. RAFT synthesis of PEO-b-PDMAAm and PEO-b-PAA

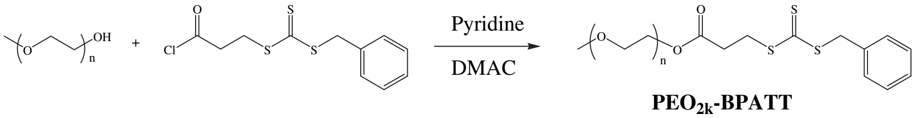
Finally, other types of block copolymers were synthesized using a poly(ethylene oxide)-based CTA (PEO$_{2k}$-BPATT). The synthetic access to the RAFT agent is outlined in Scheme 2. A monohydroxy-

Table 6

Chain extension with DMAAm or AA of poly(*N*-isopropylacrylamide) (PNIPAAm) and poly(ethylene oxide) (PEO$_{2k}$-BPATT) macro-CTAs by RAFT polymerization in aqueous media at ambient temperature under γ-irradiation.

Monomer	CTA	$[M]_0$/$[CTA]_0$	$[M]_0$ mol/L	Acetone %Vol	Time min	x_p[c] %	$\overline{M}_{n,th}$[d] kg/mol	$\overline{M}_{n,exp}$ kg/mol	PDI
NIPAAm	BPATT	200	1.5	25	1440	76	17.5	25[e]	1.07[d]
DMAAm	PNIPAAm[a]	400	1	–	2540	>99	57	55[e]	1.15[d]
DMAAm	PNIPAAm[a]	1000	1	–	1440	>99	116	78[e]	1.27[d]
DMAAm	PEO$_{2k}$-BPATT[b]	600	1.7	20	2500	>99	62	62[f]	1.09[d]
AA	PEO$_{2k}$-BPATT[b]	600	1.7	20	2500	>99	45.5	69[f]	1.15[e]

[a] Using asymmetric PNIPAAm-macro-CTA of $DP_n = 152$.
[b] Using asymmetric PEO-macro-CTA of molecular weight 2000 g mol^{-1}.
[c] Determined by ^{1}H NMR in D_2O.
[d] $\overline{M}_{n,th} = M_M \cdot X_p \cdot [M]_0/[CTA]_0 + M_{CTA}$.
[e] Apparent number-average molecular weights and PDIs, as measured by SEC using PS standards in 2-*N*-methylpyrrolidone (NMP).
[f] Apparent number-average molecular weight and PDI, as measured by SEC using PEO standards in water.



Scheme 2. Synthesis of a PEO-based macro-RAFT agent.

functional PEO (PEO_{2k}-OH) with $DP = 45$ was reacted with an acyl chloride-modified BPATT in anhydrous dimethylacetamide in the presence of pyridine to generate PEO-BPATT. To characterize this macro-CTA, liquid adsorption chromatography under critical conditions (LACCC) was performed. This method has been successfully used to analyze PEO end-capped with a RAFT agent [84]. LACCC is one of the few techniques that are exclusively sensitive to modifications of the end group of a polymer molecule when keeping the side groups or repeating units unreacted [85–87]. Fig. S8 displays the LACCC traces of two hydroxyl-functionalized PEO of 2000 and 5000 g mol^{-1}, under the critical conditions of PEO (acetonitrile/water 38.8/61.2 at 23 °C); both traces overlay perfectly. By end-capping BPATT onto PEO-OH with 2000 g mol^{-1}, a clear shift in the elution volume is observed. The reaction is quantitative and no remaining unmodified PEO_{2k}-OH can be detected. In addition, the presence of only one peak proves that no side product is generated during the synthesis of the PEO_{2k}-BPATT.

The PEO_{2k}-BPATT macro-CTA was used as precursor to generate PEO-*b*-PDMAAm and PEO-*b*-PAA. Acetone was added, especially for PEO-*b*-PAA, to minimize the formation of hydrogen bonding complexes between the acrylic acid and the ethylene oxide units during the reaction. Strong aggregation of the block copolymer was observed in pure water which leads to an uncontrolled polymerization. When a PEO with a longer block is utilized, the hydrogen bonding is more pronounced and block copolymers were synthesized in pure organic solvent (results not shown). For both PEO-*b*-PDMAAm and PEO-*b*-PAA, monomodal and narrow distributions were obtained after polymerization (see Fig. 5B) and no traces of unreacted PEO was detected by SEC, congruent with the LACCC measurements. The traces are symmetric and no undesired termination was detected even at high conversion, which underpins the high efficiency of this process to generate well-defined block copolymers. All these examples prove the excellent ability of RAFT polymerization initiated under γ-irradiation to generate a large variety of block copolymers in term of monomers composition and molecular weights.

4. Conclusions

We have demonstrated that RAFT polymerization of several water-soluble acrylic monomers can be carried out in aqueous media under γ-radiation. Under these conditions, the controlled/living characteristics are proven for three CTAs, i.e., TRITT, BPATT, and CPADB (Scheme 1) for a large range of monomer/RAFT agents ratios. For most of the monomers, monomodal distributions and the virtual absence of termination or side reaction was observed even near to quantitative conversion. These specifications allow for the synthesis of precisely tailored block copolymers. Moreover, associated with the benefit of using an environmentally friendly solvent, the polymerization rates in aqueous media are higher and better controlled than in organic solvents, as demonstrated in the case of DMAAm. The living character of the generated macro-RAFT agents was confirmed by subsequent chain extension with various acrylamides. During the block formation process the polydispersity remained low and well-defined block copolymers are generated. Side reactions and bimolecular termination were observed to a very minor extent. The presented polymerization technique thus constitutes a powerful tool for the straightforward preparation of complex macromolecular architectures constituted of smart polymers.

Acknowledgements

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.polymer.2010.07.017.

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