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Facile synthesis of temperature-sensitive ABA triblock copolymers by dispersion RAFT polymerization

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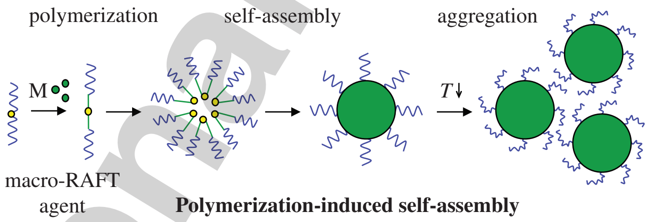
The dispersion RAFT polymerization was applied for the first time to synthesize the well-defined ABA triblock copolymer core–shell nanoparticles of temperature-sensitive poly(*N*-isopropylacrylamide-*co*-acrylic acid)-*block*-poly(*n*-butyl acrylate)-*block*-poly(*N*-isopropylacrylamide-*co*-acrylic acid) and poly(*n*-butyl acrylate-*co*-*N*-isopropylacrylamide)-*block*-poly(*n*-butyl acrylate)-*block*-poly(*n*-butyl acrylate-*co*-*N*-isopropylacrylamide).



Keywords: reversible addition–fragmentation chain transfer (RAFT), RAFT polymerization, dispersion polymerization, self-assembly, block copolymers, temperature-sensitive polymers.

Stimuli-responsive block copolymer nanoobjects have attracted great interest due to numerous potential applications in medicine, electronics, catalysis, coatings, *etc.*[1–3] Block copolymers, in particular stimuli-sensitive block copolymers, are able to self-assemble into nanosized structures of various morphologies, which are controlled by the chemical nature and the length of the blocks as well as environmental conditions (solvent, pH, temperature, *etc.*).[4] Temperature sensitivity seems to be one of the most attractive features of polymers as it can be easily tuned and has advantages in practical applications both *in vitro* and *in vivo*.[5] Among other polymers, poly(*N*-isopropylacrylamide) (PNIPAM) is one of the most frequently used temperature-sensitive polymers due to its lower critical solution temperature (LCST) of 32 °C in water. This value is close enough to the human body temperature, which highlights its promising potential for biomedicine.[6] The incorporation of hydrophobic or hydrophilic monomer units into PNIPAM chain allows one to vary LCST in a controllable fashion.[7]

The development of the methods of reversible-deactivation radical polymerization (RDRP) revolutionized the chemistry of synthetic polymers and made it possible to synthesize a wide range of functional polymers with well-defined molecular structures. In particular, RAFT polymerization is one of the most popular methods due to feasibility under ambient conditions, high tolerance to functional groups and good control over the target molecular weight characteristics of polymers.[8] Previously, block copolymer nanoobjects have been synthesized *in situ* through polymerization-induced self-assembly (PISA).[9–11] Among other RDRP techniques, RAFT polymerization has become the most popular approach in PISA processes as it can be easily applied both in aqueous and organic media.

Recently, we have applied symmetric trithiocarbonates as hydrophilic and amphiphilic macro-RAFT agents for emulsion, dispersion and miniemulsion polymerization of *n*-butyl acrylate to obtain ABA amphiphilic triblock copolymers.[12] RAFT agents of the chosen type have provided the easy formation of symmetric block copolymers. Here, we report the first synthesis of temperature-responsive block copolymers from *N*-isopropylacrylamide (NIPAM), *n*-butyl acrylate (BA) and/or acrylic acid (AA).

Random copolymers of NIPAM and AA containing trithiocarbonate group within the chain were synthesized by RAFT polymerization in 1,4-dioxane (see Online Supplementary Materials).† The composition and the molecular weight characteristics of these copolymers **1**–**3** are given in Table 1.

PISA process includes the polymerization of monomer, either soluble or insoluble in reaction medium, in the presence of a soluble macro-RAFT agent, which mediates the growth of block copolymer.[13] As the length of propagating block increases, the block copolymer becomes insoluble and undergoes self-

Table 1 The composition and the molecular weight characteristics of macro-RAFT agents **1**–**3**.

Copolymer	Molar ratio of monomers	M_n/g mol^{-1}	$Đ$	D_n/nm	NIPAM molar fraction in copolymer
1	NIPAM : AA = 9 : 1	4400	1.4	2.7	0.89
2	NIPAM : AA = 3 : 1	4700	1.3	3.2	0.74
3	NIPAM : BA = 9 : 1	7100	1.5	5.6	0.91

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† Random copolymers of NIPAM and AA containing trithiocarbonate group within the chain were synthesized as follows. AA was added to a freshly prepared solution of dibenzyl trithiocarbonate, α,α′-azobisisobutyronitrile (AIBN) and NIPAM in 1,4-dioxane. The reaction mixture was polymerized at 80 °C under nitrogen atmosphere until ~100% conversion of monomers. The synthesis of copolymers of NIPAM and BA was performed similarly (Table S1).

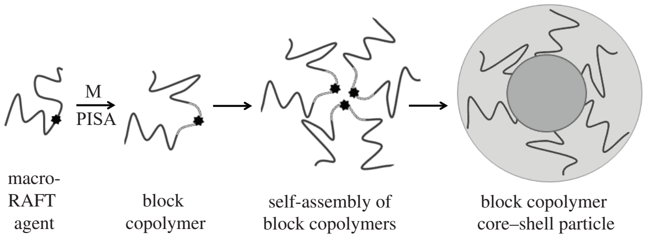

Figure 1 Mechanism of PISA process mediated by symmetric trithiocarbonates.

assembly into core–shell particles (Figure 1). Thus, the solvent plays an important role in PISA process.

The synthesized macro-RAFT agents **1–3** are soluble in water. However, their solubility was lost at temperatures suitable for polymerization. Macro-RAFT agents **1–3** are also soluble in methanol. Their diluted solutions in methanol were analyzed by dynamic light scattering (DLS).[‡] The number-average diameter (D_n) of copolymer particles varied from ~3 to ~6 nm (see Table 1). The effect of the composition of aqueous-organic medium on the solubility of macro-RAFT agents **1–3** was analyzed. In water–methanol mixture, the value of D_n remained constant up to ~30 vol% of water and then rose gradually with increase in water content [Figure 2(*a*)]. The temperature dependence of D_n of macro-RAFT agents **1–3** was analyzed at the water content of 20 vol% [Figure 2(*b*)]. In the case of copolymers **1** and **2**, containing NIPAM and AA units, the D_n value remained nearly constant below 40 °C and increased sharply above this temperature. In contrast, the value of D_n for copolymer **3** was insensitive to temperature change in the range of 10–70 °C. This behavior is typical of temperature-dependent polymers, for which this dependence is frequently used to control their behavior in solutions.[7]

The dispersion polymerization of BA was performed in water–methanol mixture containing 20 vol% of water at BA/dispersion medium ratio of 1 : 7.5 (v/v). The solution containing 3.8 wt% of macro-RAFT agent and 2 wt% of AIBN was prepared in dispersion medium. Then BA was added in two portions as 10 and 90 vol% solutions at 5 min interval under nitrogen atmosphere. Polymerization was conducted at 65 °C with continuous stirring. Experiments in methanol or at BA/dispersion medium volume ratio of 1 : (15 or 3) were conducted similarly.

The dispersion polymerization of BA did not occur in the absence of either macro-RAFT agent or conventional stabilizer (surfactant). With macro-RAFT agent and without surfactant, the dispersion polymerization of BA was fast enough in both organic and aqueous-organic media.[§] The chemical nature of macro-RAFT agent affected the rate of BA dispersion polymerization. For example, in the aqueous-organic medium containing 20 vol% of water the rate values were arranged in the following order of macro-RAFT agents: copolymer **2** > > copolymer **1** ≈ copolymer **3** (Figure 3). Doubling AIBN concentration had slight impact on polymerization rate in the case of macro-RAFT agent **1** and increased monomer conversion in the case of macro-RAFT agent **3** (see Online Supplementary Materials). Regardless of the nature of macro-RAFT agent, the induction period from ~10 to ~20 min preceded the start of the reaction. Notably, the duration of induction period, corresponding to the formation of polymeric/monomeric particles, was higher for the more hydrophobic macro-RAFT agent. Similar results were obtained in methanol or at various volume ratios of BA/dispersion medium.

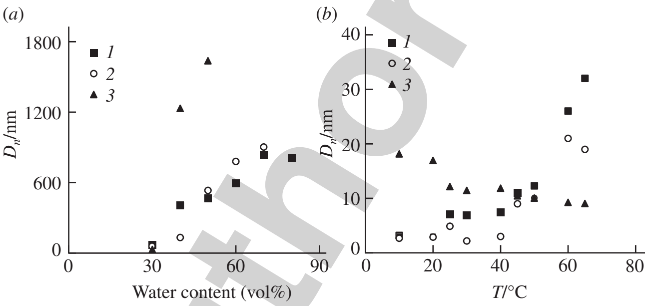

Figure 2 Dependence of D_n of copolymers (*1*) **1**, (*2*) **2** and (*3*) **3** on (*a*) water content in water–methanol mixture and (*b*) temperature in water–methanol (2 : 8, v/v). Copolymer concentration was 1 wt%.

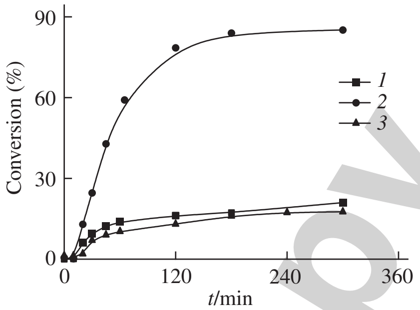

Figure 3 Time dependence of monomer conversion in the dispersion polymerization of BA mediated by macro-RAFT agents (*1*) **1**, (*2*) **2** and (*3*) **3** in water–methanol (1 : 4, v/v) at 65 °C, BA/dispersion medium ratio of 1 : 7.5, macro-RAFT agent concentration of 3.8 wt% and AIBN concentration of 2 wt%.

To confirm the PISA mechanism and the formation of triblock copolymers, the molecular weight distribution (MWD) of polymerization products was analyzed throughout the reaction. The average molecular weight (*M*) and dispersity (*Đ*) were measured by size exclusion chromatography (SEC).[¶] Macro-RAFT agent **2** was consumed during BA dispersion polymerization in aqueous-organic medium to form triblock copolymer poly(NIPAM-*co*-AA)-*block*-poly(BA)-*block*-poly(NIPAM-*co*-AA) [Figure 4(*a*)]. The bimodal MWD curves observed in the wide range of monomer conversion occurred due to the formation of two fractions of triblock copolymers. The low molecular weight fraction corresponds to the block copolymer with the short hydrophobic block of poly(BA) formed during a short induction period. The high molecular weight fraction can be attributed to further grown polymer. A similar phenomenon has been described previously.[14] The MWD curve shifted to the higher *M* with the progress of monomer conversion in accord with the RAFT mechanism.

Indeed, the chain extension of a macro-RAFT agent in the polymerization of BA proceeds *via* a complicated mechanism. The oligoradical of BA ($\mathrm{M}_p^{\bullet}$) appeared due to AIBN initiation reacts with initial macro-RAFT agent P_n–SC(=S)S–P_n, where P_n designates poly(NIPAM-*co*-AA). Diblock copolymer P_n–SC(=S)S–M_p is formed in this reaction while polymeric radical $\mathrm{P}_n^{\bullet}$ is released capable of initiating BA polymerization. Diblock copolymer P_n–SC(=S)S–M_p may continue to participate in the number of reversible chain transfer reactions with

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[‡] DLS analysis was performed using the Malvern Zetasizer Nano-ZS instrument equipped with He–Ne laser (λ = 633 nm, at 173°).

[§] The total monomer conversion was determined by gravimetry taking into account the weight of macro-RAFT agent in the probe.

[¶] The measurements were performed in *N*,*N*-dimethylformamide containing 0.1 wt% of LiBr at 50 °C using the PolymerLabs GPC-120 chromatograph with a refractive index detector and two PLgel 5 μm MIXED B columns for the *M* range from 5×10^2 to 1×10^7 g mol^{-1}. The SEC system was calibrated using narrow-dispersed linear poly(methyl methacrylate) (PMMA) standards. Molecular weight was evaluated from PMMA data using the coefficients in the Mark–Kuhn–Sakurada equation for polyacrylonitrile and PMMA.

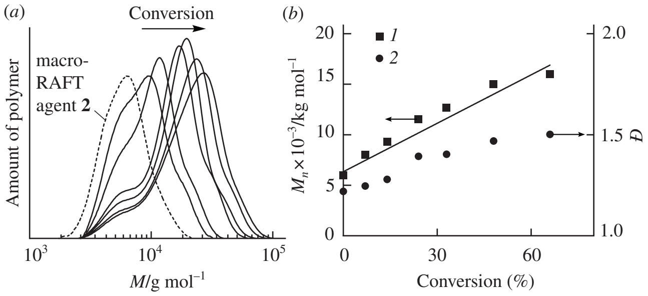

Figure 4 (*a*) MWD curves normalized by unit area for the polymers formed at various monomer conversion during BA dispersion polymerization mediated by macro-RAFT agent **2**. (*b*) The dependence of (*1*) M_n and (*2*) Đ on monomer conversion for triblock copolymers formed during BA dispersion polymerization mediated by macro-RAFT agent **2**. Experimental conditions were similar to those mentioned in Figure 2.

propagating radicals giving rise to the formation of final triblock copolymer. The detailed mechanism of this process was described elsewhere.[15] The repetitive reactions of reversible chain transfer and propagation result in the successive increase of number-average molecular weight (M_n) with the progress in monomer conversion [Figure 4(*b*)]. Simultaneously, Đ of the block copolymer increases slightly throughout the reaction due to the formation of part of the chains *via* the conventional radical termination.[16]

The synthesized products demonstrated a single glass transition temperature which was typical for the block copolymers with relatively short blocks corresponding to the initial macro-RAFT agent.[12] Its value depended on the ratio of the block lengths. For example, it was –48, –45 and –42 °C at the volume ratio of BA/methanol of 1 : 15, 1 : 7.5 and 1 : 3, respectively, according to an increase in the length of poly(BA) block in triblock copolymer. These values differ from the glass transition temperature of the homopolymer of BA[17] due to surrounding with the more rigid short blocks of initial macro-RAFT agent **3**.

The values of D_n for the triblock copolymer particles synthesized with macro-RAFT agents **1** and **2** in aqueous-organic dispersions were 2.3–3.5 μm, *i.e.* large enough, which indicates that the poly(NIPAM-*co*-AA) blocks have a poor ability to stabilize the particles, which leads to their aggregation. This result agrees with the above-mentioned analysis of the temperature sensitivity of copolymers **1** and **2** in the medium investigated. The similar situation was observed after the transfer of dispersions into water *via* dialysis. Nevertheless, these dispersions kept their stability under storage for several months.

However, after BA dispersion polymerization in methanol, the D_n values of particles were remarkably lower. For example, in the case of macro-RAFT agent **3**, the D_n value did not exceed 20 nm at 65 °C. Lowering the temperature to 45 °C increased D_n to 80 nm and resulted in a slight clouding of the mixture independently of the volume ratio of BA to methanol (1 : 15 or 1 : 7.5). The further decrease of the temperature to 25 °C led to the growth of D_n up to 2 μm. The photographs of methanol dispersions at different temperatures are given in Figure 5. After replacing methanol with water by dialysis at 65 °C, D_n values increased to 37 and 48 nm at BA/methanol ratio of 1 : 15 and 1 : 7.5 (v/v), respectively. Decreasing the temperature resulted in the same regularities, and all the dispersions were milky opaque at 25 °C.

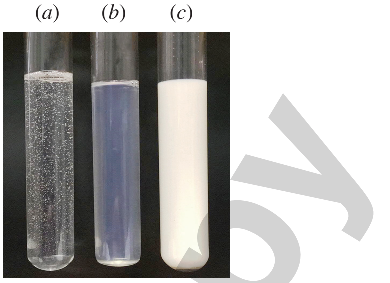

Figure 5 The photographs of triblock copolymer dispersions formed in methanol in the presence of macro-RAFT agent **3** at BA/methanol ratio of 1 : 7.5 (v/v) and temperature of (*a*) 65, (*b*) 45 and (*c*) 25 °C.

Thus, the prepared dispersions of triblock copolymer particles exhibited the temperature sensitivity.

In conclusion, the new approach to the synthesis of temperature-sensitive triblock copolymers from NIPAM, BA and AA monomers was developed. In organic or aqueous-organic medium, these copolymers self-assembled into the particles exhibiting temperature-sensitive properties.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.014.

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