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Polyphosphonate-Based Macromolecular RAFT-CTA Enables the Synthesis of Well-Defined Block Copolymers Using Vinyl Monomers

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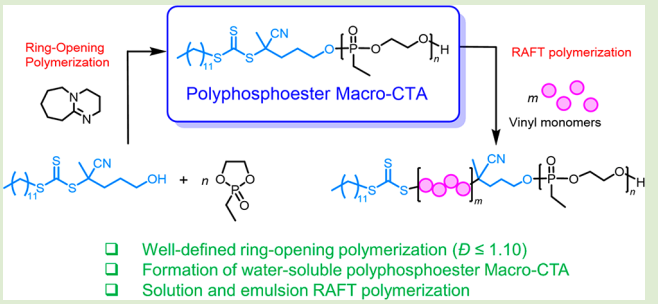
ABSTRACT: Reversible addition−fragmentation chain transfer (RAFT) polymerization has become a straightforward approach to block copolymers using a wide variety of functional vinyl monomers. Polyphosphoester (PPE) macroinitiators from ring-opening polymerization (ROP) of their corresponding cyclic phosphoesters have been previously prepared for atom transfer radical polymerization; however, to date, these biodegradable macroinitiators for RAFT polymerization have not been reported. Herein, a macromolecular RAFT-chain transfer agent (CTA) based on poly(ethyl ethylene phosphonate) was prepared by the organocatalytic ROP of 2-ethyl-2-oxo-1,3,2-dioxaphospholane using 2-cyano-5-hydroxypentan-2-yl dodecyl trithiocarbonate as the initiator and 1,8-diazabycyclo[5.4.0]undec-7-ene as the catalyst. Precise macro-CTAs of degrees of polymerization (DP_n) from 34 to 70 with $Đ \leq 1.10$ were prepared and used in the dioxane solution RAFT polymerization of acrylamide, acrylates, methacrylates, and 2-vinylpyridine to yield a library of well-defined block copolymers. Additionally, the PPE-based macro RAFT-CTA was used as a nonionic surfactant in a typical aqueous emulsion polymerization of styrene to produce well-defined nanoparticles with the hydrophilic PPEs on their surface as the stabilizing agent. This general protocol allowed the combination of polyphosphoesters with RAFT polymerization.



Polyphosphoesters (PPEs) are versatile materials, and they degrade by hydrolysis or enzymatic degradation.[1−3] They are especially important as well-defined water-soluble polymers and potential alternatives to poly(ethylene glycol) (PEG).[1] Although functionalized vinyl monomers with phosphorylcholines or phosphoric/phosphonic acid groups have been explored in radical polymerizations,[4,5] much less has been reported for main-chain PPEs and their combination with commodity vinyl monomers. The combination of radical polymerization with PPEs is an interesting field of research, for example, by the design of macroinitiators or macromolecular chain transfer agents (CTAs) to prepare complex polymeric architectures. Here, we present the first combination of PPEs with reversible addition−fragmentation chain transfer (RAFT) polymerization by a new macro-CTA based on hydrophilic polyphosphonates. The macro-CTA was used to prepare a library of well-defined block copolymers with different vinyl monomers by solution and emulsion RAFT polymerization.

PPEs are interesting as polymeric flame-retardant additives.[6] Further, based on their nucleic acid analog structure and water-solubility, PPEs have been used in promising biomedical applications due to high levels of cytocompatibility, antifouling properties, and the so-called "stealth effect".[7−9] A variety of strategies to access PPEs have been developed, including polycondensation,[10] transesterification,[11,12] enzymatic polymerization,[13] olefin metathesis,[14,15] and anionic ring-opening polymerization (AROP).[7,16] Especially, AROP was used to prepare PPE-containing amphiphilic block copolymers with PEG/polycaprolactone,[17−19] polylactide,[20−22] or side-chain functionalized PPEs as second blocks.[20,23,24] These materials have been assembled into nanoparticles for applications that range from surface protein adsorption[23] and nanocarriers for drug or gene delivery[17,18,21] to antimicrobial nanomedical devices.[20]

To date, the only reports on controlled radical polymerization, including PPEs, have used polyphosphates [−P(O)-OR-OCH_2CH_2O−]$_n$ in atom transfer radical polymerization (ATRP). This strategy involved the use of 2-bromo-isobutyryl groups as functional initiators or as part of the cyclic monomer $(CH_2O)_2P(O)OR$ to form macroinitiators for ATRP via ROP of cyclic phosphates followed by the preparation of block or graft copolymers (Scheme 1A,B).[25−28] In contrast, no PPE-containing block copolymers have been reported previously using a RAFT protocol. Besides the well-known PEGylated macro-CTAs,[29,30] other CTAs used mostly hydrophobic polyesters, polyethers, and polycarbonates from ROP to

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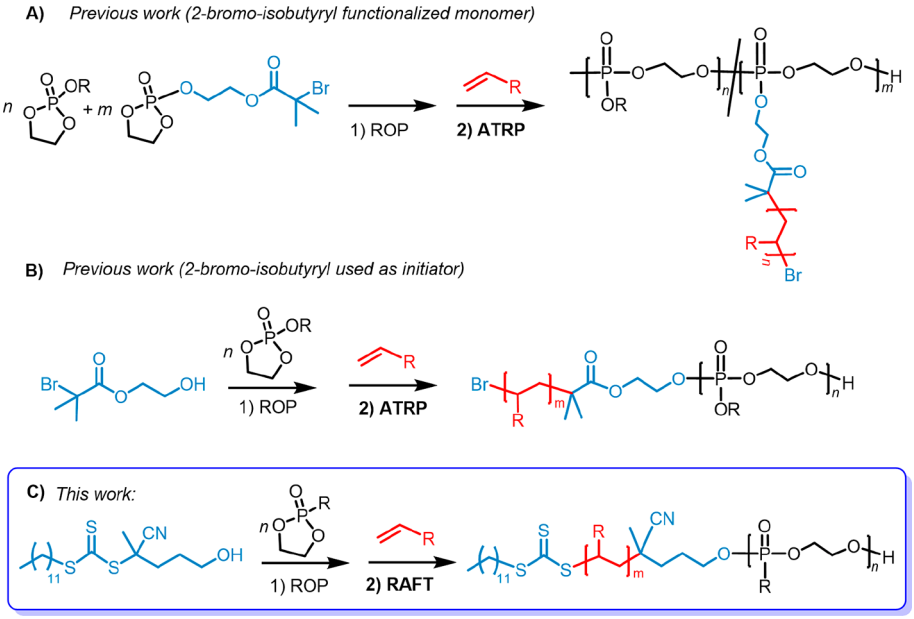
Scheme 1. (A, B) Earlier Reports on ATRP Polymerization Using Phosphates; (C) Preparation of Polyphosphonate-Based Macro-CTA and Subsequent RAFT Polymerization to Block Copolymers



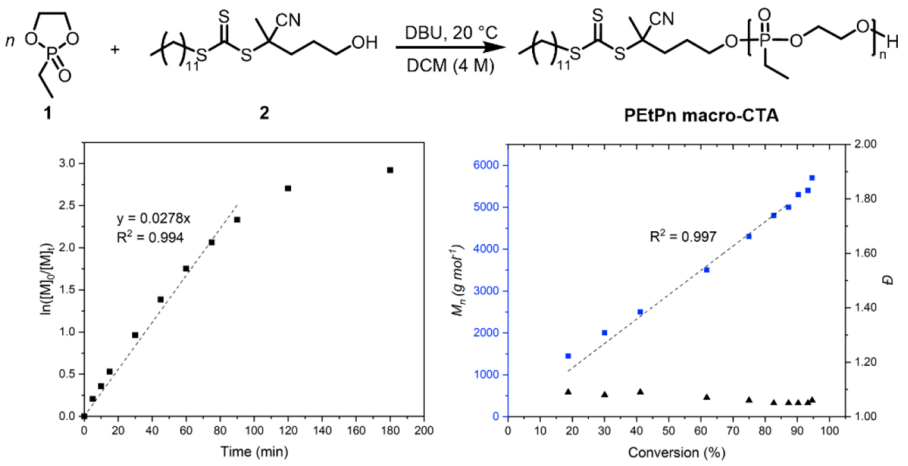


Figure 1. (a) Synthetic scheme for the anionic ring-opening polymerization of **1** using **2** as an initiator. (b) Kinetic studies of AROP of **1**. Plot of $\ln([M]_0/[M]_t)$ vs time and (c) plot on M_n and $Đ$ vs monomer conversion, obtained by a combination of SEC (measured in DMF (0.1 M LiCl) at 60 °C) and ^{31}P NMR spectroscopy.

prepare block copolymers.[31−36] A water-soluble PPE macro-CTA opens up the possibilities of replacing commercial PEGylated CTAs in a broad range of applications, such as drug encapsulation or polymerization-induced self-assembly, for example.[37,38]

We have recently been focusing on one subclass of PPEs, that is, polyphosphonates $[-P(O)R-OCH_2CH_2O-]_n$, which, contrary to polyphosphates, possess a chemically stable P−C bond that is more resilient toward chemical hydrolysis, thermal decomposition, enzymatic degradation, and photolysis and allow that transesterification reactions to be prevented[39] with higher control over molar mass and distributions during AROP.[7,16] AROP of cyclic phosphonates $(CH_2O)_2P(O)R$ was used to prepare well-defined PPEs with controlled molar masses and narrow molar mass distributions ($Đ$ < 1.2).[7,16] In particular, water-soluble polyphosphonates (R = Me, Et, *i*Pr, allyl) are mostly recognized as degradable PEG alternatives.[1,9]

Herein, the AROP of ethyl ethylene phosphonate (EtPn, **1**) by a hydroxy-functionalized trithiocarbonate CTA led to the formation of well-defined and water-soluble poly(ethyl ethylene phosphonate) macro-CTAs (PEtPn macro-CTA; Scheme 1C). This macro-CTA was used in the solution RAFT polymerization to high molar mass block copolymers using acrylates, methacrylates, and acrylamide and also for a less-activated monomer, such as 2-vinylpyridine. As the PEtPn macro-CTA carries a dodecyl chain, it was also used as a nonionic surfactant in the RAFT emulsion polymerization of styrene in water. Well-defined polystyrene nanoparticles stabilized by the water-soluble PPE chains attached to their surface were obtained.

Overall, the herein presented methodology gives fast access to PPE-based and water-soluble macro-CTAs, which can be combined with a variety of vinyl monomers to prepare well-defined block copolymers. This general protocol has the potential to be used in the design of a variety of macro-

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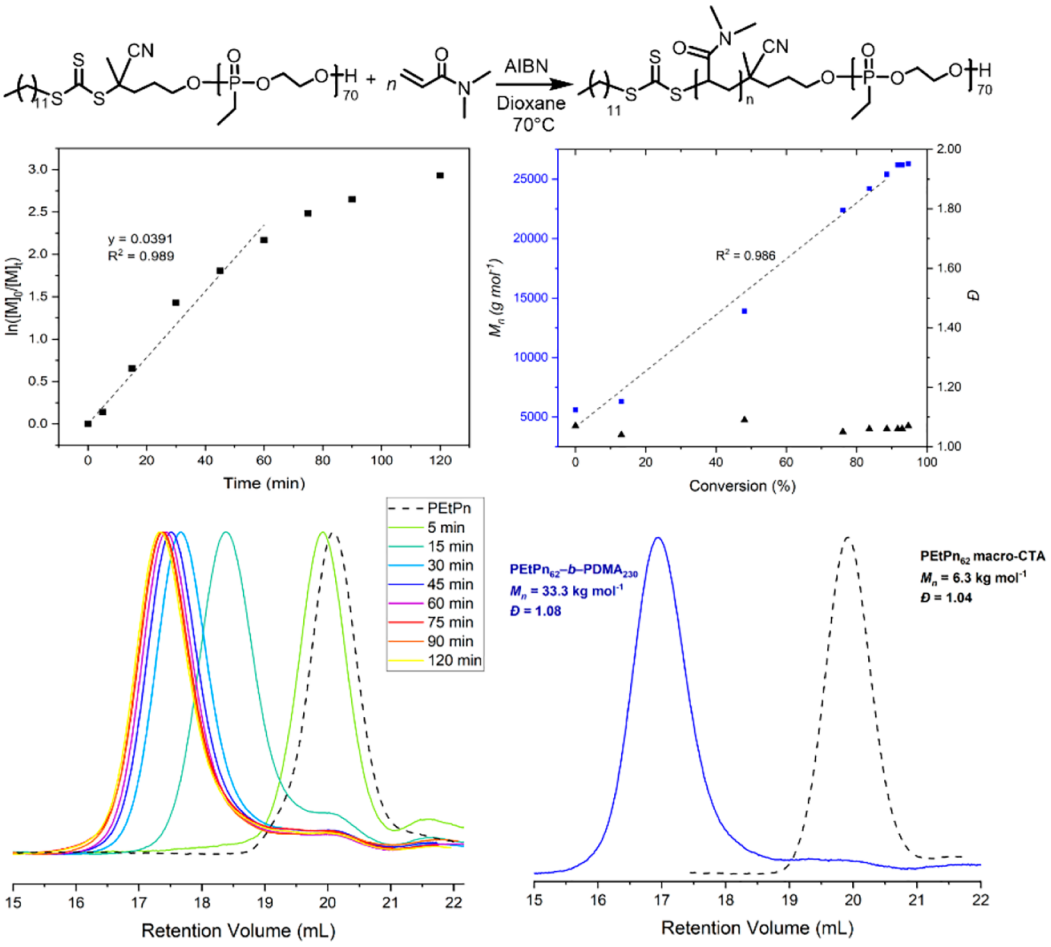

Figure 2. (a) Synthetic scheme for the RAFT polymerization of PEtPn macro-CTA and DMA at 70 °C in dioxane with AIBN. Kinetic studies of RAFT polymerization of PEtPn macro-CTA and DMA. (b) Plot of $\ln([M]_0/[M]_t)$ vs time and (c) plot on M_n and $Đ$ versis monomer conversion, obtained by a combination of SEC in DMF (0.1 M LiCl) at 60 °C and ^{1}H NMR spectroscopy analysis. (d) SEC chromatograms (2 mg mL^{-1}; normalized RI) of PEtPn$_{70}$-*b*-PDMA$_n$ quenched at different reaction times in DMF (0.1 M LiCl) at 60 °C (see Table S3, entries 1−8). (e) SEC elugrams (2 mg mL^{-1}; normalized RI) of isolated PEtPn$_{62}$-*b*-PDMA$_{230}$ (blue, $Đ_m$ = 1.08) and PEtPn$_{62}$ macro-CTA (black, $Đ_m$ = 1.04; measured in DMF (0.1 M LiCl) at 60 °C).

molecular structures with promising applications in the biomedical field and materials science.

Polyphosphonate macro-CTAs were synthesized via organocatalytic AROP polymerization of 2-ethyl-2-oxo-1,3,2-dioxaphospholane (**1**, EtPn) using 2-cyano-5-hydroxypentan-2-yl dodecyl trithiocarbonate CTA (**2**) as the initiator in dichloromethane at room temperature with 1,8-diazabycyclo[5.4.0]-undec-7-ene (DBU) as the catalyst (Figure 1a).

The kinetics of the AROP of **1** with **2** as an initiator was performed as shown in Figure 1 (synthetic details in the SI). High control over the molar mass and its distribution ($Đ$ < 1.09) was achieved under these conditions, reaching 95% conversion in about 180 min, similar to an earlier report using primary alcohols as initiators.[16] A linear relationship between the molar mass M_n and the monomer conversion as well as a linear relation of $\ln([M]_0/[M]_t)$ versus time indicated a well-controlled polymerization (Figure 1b,c). Using these conditions, we prepared a series of well-defined polymers with degrees of polymerization (DP_n) between 34 and 70, which should not be regarded as the limit for this method (see Table S2, entries 1−4). The polymers were obtained as yellow (typical color of trithiocarbonates)[40] and viscous materials at room temperature.

PEtPn$_{70}$ macro-CTA (Table S2, entry 4) was used for chain extension via RAFT polymerization of *N*,*N*-dimethylacrylamide (DMA) using AIBN as an initiator ([PEtPn$_{70}$]/[AIBN] molar ratio = 10:1) at 70 °C in dioxane (Figure 2a). The kinetics for the RAFT polymerization of DMA was monitored for a targeted diblock copolymer of the composition: PEtPn$_{70}$-*b*-PDMA$_{200}$, indicating a conversion of >95% after 2 h.

The molar mass M_n of the resulting block copolymer increased linearly with respect to monomer conversion (Figure 2c) and maintained low dispersity values ($Đ$ = 1.04−1.09), indicative of a decent control over the RAFT process. The plot of $\ln([M]_0/[M]_t)$ versus time (Figure 2b) supported these findings with a linear relationship up to 60 min (ca. 88% conversion), indicating pseudo-first-order kinetics consistent with a controlled radical polymerization. Another batch of PEtPn-*b*-PDMA (using a PEtPn$_{62}$ macro-CTA, Table S2, entry 2) was terminated after 60 min with about 87% conversion, and the precipitated polymer showed a monomodal and narrow molar mass distribution with M_n = 33 300 g mol^{-1}; $Đ$ = 1.08 (Figure 2e). The diblock copolymer formation was confirmed by DOSY NMR spectroscopy (Figure S9) as all of the signals appeared at the same diffusion coefficient (D = 1.35 × 10^{-5} cm^2 s^{-1}). By increasing the DMA/CTA ratio, a pair of PEtPn$_{70}$-*b*-PEM$_n$ with different DP_n were deliberately taken to

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Table 1. RAFT Polymerization of Acrylate, Methacrylate, and 2-Vinyl Pyridine with PEtPn Macro-CTA

monomer	$[M]_{monomer}/[M]_{PEtPn\ macro\text{-}CTA}$	conversion[a] (time)	yield (%)	M_n[a]	$M_{n,SEC}$[b]	$Đ$[b]
*t*BuA	200/1	90% (16 h)	33	38 300	29 700	1.12
DMAEMA	200/1	52% (6 h)	36	22 000	13 500	1.28
DMAEMA	200/1	90% (24 h)	47	28 000	12 100	1.47
2VP	200/1	72% (20 h)	71	27 200	16 200	1.31

[a]Calculated by ^{1}H NMR spectroscopy. [b]Determined by SEC in DMF (0.1 M LiCl) at 60 °C.

high conversion (ca. 98%), which resulted in a broadening of the molar mass distribution to 1.39 (Figure S10 and Table S4). ^{31}P NMR spectroscopy proved no degradation of the PPE macro-CTA occurred during the process (see Figure S8).

As the above data shows a high control over the polymerization of DMA using the PPE-based macroinitiator without any degradation or interference of the PPE during the RAFT process, we investigated also other vinyl monomers. Using the same reaction conditions, ethyl methacrylate (EM) was successfully polymerized to well-defined block copolymers and a detailed kinetic study revealed that in 8 h about 79% conversion was reached (Figures S12 and S13). Also, 2-dimethylamino ethyl methacrylate (DMAEMA), *tert*-butyl acrylate (*t*BuA), and the less-activated monomer 2-vinyl pyridine (2VP) were polymerized. The polymer characterization was performed by multinuclear NMR spectroscopy and ^{1}H diffusion-ordered spectroscopy (DOSY) NMR and the molar mass determined by SEC (Table 1; see details in the SI). In the case of PEtPn-*b*-P*t*BuA, after about 16 h, a conversion of about 90% was reached. After precipitation into water, SEC showed M_n = 29 700 g mol^{-1} and molar mass distribution ($Đ$ = 1.12; Figure S21). The purity of the diblock copolymer was confirmed by DOSY NMR spectroscopy analysis as a complement to the SEC characterization. For example, for PEtPn-*b*-P*t*BuA, all of the signals appeared at the same diffusion coefficient ($D = 1.06 \times 10^{-6}$ cm^2 s^{-1}), which is lower than the PEtPn macro-CTA ($D = 3.34 \times 10^{-6}$ cm^2 s^{-1}) used, which proves the successful formation of a pure diblock copolymer with no trace of PEtPn macro-CTA homopolymer impurities (Figure 3).

The PEtPn macro-CTA was also used successfully to prepare block copolymers PEtPn-*b*-PDMAEMA. SEC traces with shoulders at lower molar mass regions and the molar mass distribution increased from $Đ$ = 1.28 to $Đ$ = 1.47 (Figures S25−S27) as the conversion to polymer increased from 52% to 90%, respectively, which is indicative of some side reactions after prolonged reaction times. In the case of PEtPn-*b*-P2VP, after 20 h at 70 °C, 72% conversion was observed. After precipitation, a unimodal peak with M_n = 16 200 g mol^{-1} and $Đ$ = 1.31 was measured by SEC (Figure S31).

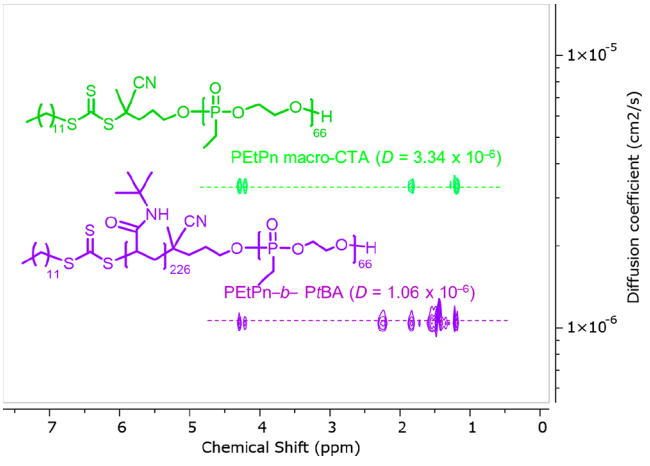

Figure 3. ^{1}H DOSY NMR (600 MHz, $CDCl_3$) spectra of PEtPn macro-CTA (green) and PEtPn-*b*-P*t*BuA (purple).

As poly(ethyl ethylene phosphonate) is a water-soluble polymer with a similar partition coefficient (log *P*) value as PEG,[9] the RAFT process was also investigated in aqueous conditions. With the hydrophobic dodecyl chain, the herein prepared PEtPn-macro CTA resembles a nonionic surfactant, similar to recently prepared PPEs using stearyl alcohol as the respective initiator.[41] We used the PEtPn macro-RAFT agent as a stabilizer for the aqueous emulsion polymerization of styrene as a representative example. With a hydrophilic−lipophilic balance of HLB = 19 (according to the Griffin method, see page S10 in the SI),[42] the PEtPn macro-CTA lies in the range expected for surfactants being capable of stabilizing an aqueous emulsion polymerization, such as previously reported PPE surfactants or the commercial Lutensol AT50.[41] Next, a conventional emulsion polymerization was conducted with the dissolution in water of PEtPn macro-RAFT agent and a water-soluble initiator, that is, 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) and styrene (S) as the monomer. A DP_n of 350 at 20% *w*/*w* solid content was targeted. After stirring for 30 min at 1500 rpm at 20 °C, the emulsion was deoxygenated by bubbling nitrogen for 20 min and placed in an oil bath at 80 °C. After 23 h, a stable dispersion was obtained and an almost quantitative conversion of styrene was observed by ^{1}H NMR spectroscopy. It is notheworthy that the PEtPn macro-RAFT is stable toward hydrolysis under these reaction conditions, as the ^{31}P NMR sprectrum did not present new signals after polymerization (see Figure S33). The PEtPn-*b*-PS diblock copolymer revealed M_n = 35500 g mol^{-1} with $Đ$ = 1.25 by SEC analysis (Figure S35). SEM imaging of the dispersion showed the formation of spherical nanoparticles (Figure 4c) with a mean hydrodynamic diameter of 97 nm with relatively narrow particle size distribution (polydispersity index < 0.10), as determined by dynamic light scattering (Figure 4a).

In summary, amphiphilic PEtPn macro-RAFT agents with a trithiocarbonate chain transfer agent were successfully prepared by AROP of ethyl ethylene phosphonate (**1**). The macro-CTA was used to produce a library of block copolymers with narrow to moderate molar mass distributions via RAFT polymerization of common vinyl monomers (acrylates, methacrylates, and 2VP). The amphiphilic CTA was also used as a stabilizer for an aqueous emulsion RAFT polymerization of styrene and well-defined nanoparticles were obtained. This approach allows the potential formation of amphiphilic well-defined block copolymers to be investigated in the polymerization-induced self-assembly (PISA) which is under current investigation. This protocol affords latex with a minimum of components and in the absence of additional

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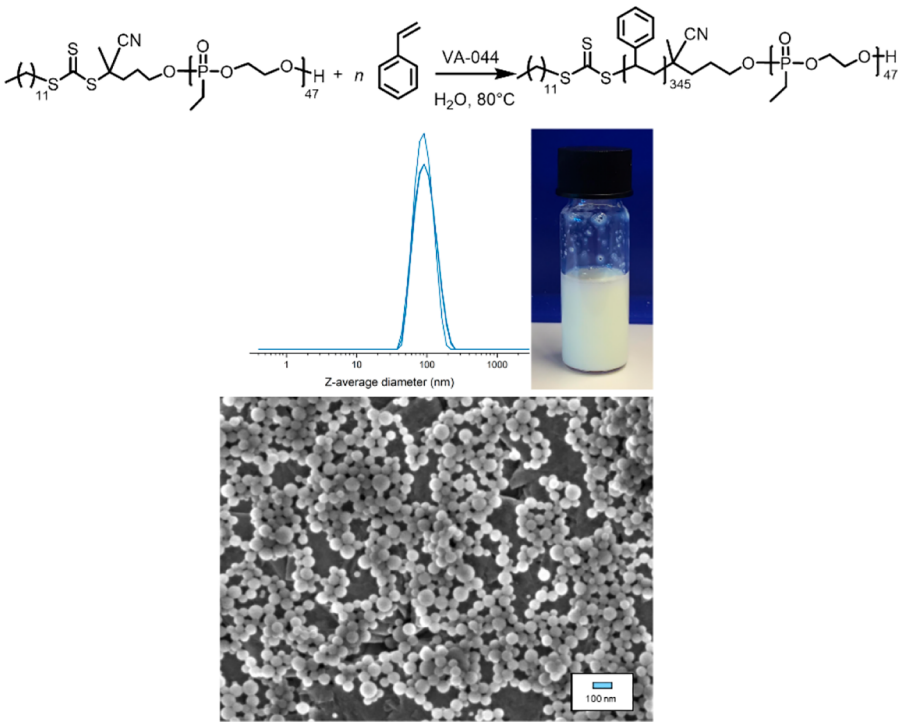

Figure 4. Synthesis of PEtPn-*b*-PS via emulsion RAFT polymerization. (a) DLS (size distribution by intensity, repeated scans) for PEtPn-*b*-PS in water at 20 °C. (b) Photograph of the aqueous dispersion for PEtPn-*b*-PS. (c) SEM image of the well-defined spherical nanoparticles made from PEtPn-*b*-PS (scale bar = 100 nm) prepared from aqueous emulsion polymerization.

surfactant, with the possibility of further degradation of the hydrophilic block.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.1c00564.

General procedures, equipment and reagents, synthesis, and characterization for monomers and polymers, including spectroscopic data and GPC chromatograms (PDF)

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Author Contributions

D.A.R.-L. and F.R.W. conceived and design the experiments. D.A.R.-L. carried out the polymer synthesis and analyzed the experimental results. The manuscript was written and edited by D.A.R.-L. and. F.R.W. The financial support aqcuired for the project leading to this publication was secured by F.R.W.

Notes

The authors declare no competing financial interest.

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